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Original research

Gender differences in high-risk modifiable sexual practices: insights from a student population

Isabel Noemi-Torres[a], María Jimena Barroso-Alverde[a], Emilio Moreno-González[a], Antonio Ibarra[a,b,1*]

[a] Universidad Anáhuac México, Centro de Investigación en Ciencias de la Salud (CICSA), Facultad de Ciencias de la Salud, Estado de México.
[b] Secretaria de la Defensa Nacional, Escuela Militar de Graduados en Sanidad, Ciudad de México, Mexico.

ID ORCID:

[1]https://orcid.org/0000-0003-2489-4689

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ABSTRACT

Introduction: Sexually transmitted infections (STIs) are on the rise, particularly in vulnerable groups with limited sexual education and healthcare access. In Mexico, high rates of STIs underscore the need for effective public health strategies and sexual education. **Objective:** Investigate gender differences in high-risk sexual practices among students aged 18-25 in a private University in Mexico City, focusing on modifiable behavioral risk factors for STIs. **Materials and Methods:** This research performed a cross-sectional observational design, surveying students from a private university. A z-score test was performed, with a 95% confidence interval and a 5% error. **Results:** A difference of 30% (95% CI, p=0.003) between the male and female participants that received health education was identified (80% female vs 50% males). A difference of 25% (95% CI, p=0.0122) between females and males (67.5% females vs 42.5% males), reported discussing STI status before sexual activities. Regarding the use of barrier methods, a difference of 25% (95% CI, p=0.0122), (70% females vs 45% males) reported the consistent use of such methods. **Conclusion:** These findings underscore the urgent need for targeted sexual health education, particularly for men, to address the substantial knowledge gaps and risky behaviors. Comprehensive and accessible education programs, coupled with community engagement and policy support, are critical to fostering a culture of sexual health responsibility among young adults.

Key words: sexually transmitted infections; sexual education; gender; prevention; sexual protection.

* *Corresponding Author:* Antonio Ibarra. Universidad Anáhuac México, Centro de Investigación en Ciencias de la Salud (CICSA). Address: Av. Universidad Anáhuac núm. 46, Lomas Anáhuac, 52786. Huixquilucan, Estado de México, México. Tel.: +52 55 5627 0210 ext. 8524. Email: jose.ibarra@anahuac.mx

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RESUMEN

Introducción: las infecciones de transmisión sexual (ITS) son mayores en grupos con educación sexual y atención médica limitadas. En México, las altas tasas de ITS demuestran la necesidad de mejores estrategias de salud pública y educación sexual. **Objetivo:** investigar las diferencias de género en prácticas sexuales de alto riesgo, entre estudiantes de 18 a 25 años de una universidad privada de la Ciudad de México, enfocándose en factores de riesgo conductuales modificables para ITS. **Materiales y métodos:** la investigación fue realizada mediante un diseño observacional transversal, se encuestaron a estudiantes de una universidad privada. Se realizó una prueba de puntuación z, con un intervalo de confianza del 95% y un margen de error del 5%. **Resultados:** se identificó una diferencia del 30% (IC 95%, p=0,003) entre los participantes masculinos y femeninos que recibieron educación sexual, el 80% de las mujeres recibieron educación sexual mientras que el 50% de los hombres la recibieron. Se identificó una diferencia del 25% (IC 95%, p=0,0122), donde el 67,5% de las mujeres indicaron discutir el estado de las ITS antes de las actividades sexuales, comparado con el 42,5% de los hombres que indicaron hacer lo mismo. En cuanto al uso de métodos de barrera, se identificó una diferencia del 25% (IC 95%, p=0,0122), donde el 70% de las mujeres afirmaron utilizar siempre protección, mientras que el 45% de los hombres indicaron lo mismo. **Conclusiones:** estos hallazgos resaltan la necesidad de brindar educación sexual específica, especialmente a los hombres. Abordar las lagunas de conocimiento y los comportamientos de riesgo. Los programas educativos integrales y accesibles, junto con la participación comunitaria y el apoyo político, son esenciales para promover una cultura de responsabilidad en materia de salud sexual entre los jóvenes.

Palabras clave: infecciones de transmisión sexual; educación sexual; género; prevención; protección sexual.

INTRODUCTION

Sexually transmitted infections (STI) are defined as a group of diseases acquired by sexual contact (skin-to-skin, oral, vaginal or anal) caused by bacteria, parasites, viruses or fungi.[1] The Center for Disease Control and Prevention (CDC) has studied epidemiologic behavior of STIs for the last ten years, with an increasing incidence and prevalence of STIs, especially in vulnerable groups that have limited sexual education, low income and non-accessible health services.[2] Currently, STIs are a threat to public health, short and long-term complications have a serious impact on patients quality of life and an economic burden to healthcare systems.[3] The World Health Organization estimates that 1 million STIs are acquired every day, for 2020, there was a world incidence of 374 million infections, being the most common chlamydia, gonorrhea, syphilis and trichomoniasis. Genital herpes, VPH and Hepatitis B are also among the most common STIs.[4]

In the context of STIs, key risk factors include early initiation of sexual activity, engaging with multiple sexual partners, co-infection with other STIs, and facing both biological and social challenges. The absence or inconsistent use of contraception, particularly condoms, significantly elevates the risks associated with STIs. Substance abuse can precipitate unprotected sexual encounters, while coercive sexual experiences can also play a pivotal role. Limited access to comprehensive sexual education and healthcare services, coupled with social determinants such as socioeconomic status and education level, further exacerbates the issue. According to the World Health Organization's 2006 definition, sexual health is defined as a state of physical, emotional, mental, and social well-being in relation to sexuality.

In this context, risk factors have been identified that include early initiation of sexual activity, engaging in sexual relations with multiple partners, being co-infected with other STIs, and encountering both biological and social challenges. Furthermore, the absence or inconsistent use of contraception, particularly condoms, can serve to elevate these risks. Substance abuse may lead to unprotected sexual encounters, while coercive sexual experiences can also play a role. Additionally, limited access to comprehensive sexual education and healthcare services, as well as societal determinants like socioeconomic status and education level, contribute to this phenomenon.[5] In accordance with the World Health Organization's 2006 definition, sexual health can be defined as a state of comprehensive well-being across the physical, emotional, mental and social dimensions in relation to sexuality.[6]

The elevated risk of contracting STIs among teenagers is attributable to both their behavioral proclivities and biological characteristics.[7] The CDC indicates that young individuals are more susceptible to contracting STIs for a variety of

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reasons. From a behavioral perspective, many of them engage in high-risk sexual activities, such as having multiple partners, which serves to further increase their vulnerability.[8] Furthermore, not all individuals pursue recommended STI screenings, and many find the process of discussing their sexual history with healthcare professionals to be challenging. These factors collectively highlight the heightened susceptibility of young people to STIs in comparison to adults.

Mexico is confronted with the challenge of managing a diverse range of STIs, with a particularly high incidence of infections such as chlamydia, gonorrhoea, syphilis and human papillomavirus (HPV).[9] In Mexico, the overall prevalence of Chlamydia ranges from 1.1% to 31%, with an average of 14.4%. Of particular concern is the prevalence of gonorrhea among high-risk groups, such as sex workers. The prevalence of syphilis in the general population is estimated to be between 0.1% and 1.5%. HPV affects up to 31% of women and 43% of men.[10] The implications of these infections extend beyond individual health, impacting the broader healthcare infrastructure and underscoring the need for comprehensive strategies to tackle their proliferation.[11,12]

The available evidence suggests that there are significant differences in the way that sexual and reproductive health education is provided to males and females, which are shaped by cultural norms and societal expectations.[13] It is common practice to provide girls with education that is focused on menstruation and pregnancy prevention, whereas boys are more likely to learn about sexually transmitted diseases. These discrepancies are indicative of traditional gender roles and sexual behavior expectations.[14]

HYPOTHESIS

A greater propensity for engaging in high-risk behavior is observed among male students aged 18-25 in comparison to their female counterparts.

OBJECTIVE

The objective of this study is to analyze and compare the modifiable behavioral risk factors leading to STIs in male and female students aged 18-25, with a view to highlighting any gender-specific differences and commonalities.

MATERIAL AND METHODS

Study design and sample size

A cross-sectional observational study was conducted at Universidad Anahuac México Norte, targeting a population of university students, with the objective of identifying risk factors associated with the contraction of STIs. The study population comprised currently enrolled students, aged between 18 and 25 years, who were either male (n = 40) or female (n = 40), and who were sexually active and had provided informed consent to participate in the study. The study excluded students who did not consent to participate, were not sexually active, were under the age of 18 or over 25 years of age.

The data were collected over a period of three months. Participation was entirely voluntary, and respondents were guaranteed anonymity. The survey was conducted online via a secure platform to facilitate a broad reach and ensure the confidentiality of respondents' identities.

As this was an exploratory study, the sample size was determined by the feasibility of recruitment using convenience sampling. A sample of 80 students (40 per group) was established. This sample size is sufficient to detect an effect size of 0.1 or larger.

Evaluation of the reliability of questionnaire

The survey instrument comprised a series of questions designed to elicit data on sexual habits and the level of education regarding contraceptive methods. The instrument was developed following an extensive review of the literature, a process of validation by professional experts, and a pilot test on a small cohort to ensure comprehensibility and relevance. The reliability of the questionnaires was evaluated using internal consistency measures, specifically Cronbach's alpha. All the questionnaires demonstrated a Cronbach's alpha value of 0.95 or above. The survey employed a series of closed-ended questions to facilitate the collection of quantitative data.

Ethical considerations

Prior to their participation in the study, all subjects provided electronic informed consent. The research was conducted

in accordance with the ethical standards set forth in the Declaration of Helsinki and the official Mexican Standard NOM-012-SSA3-2012. To ensure the anonymity of patients, a consecutive number was provided on confidential files.

RESULTS

The 80 volunteers included in the study had a mean age of 23, with an age range of 18 to 25 years. Of these volunteers, 40 (50%) were female and 40 (50%) were male. All 80 participants were sexually active. As illustrated in Table 1.

Table 1. General characteristics of the population studied. The table **displays the data divided into male and female subcategories and total students interviewed**

General population characteristics	Females	Males	Total
Total students interviewed	40	40	80
Mean Age	22.5	23.7	23.6
Sexually active	40	40	80

Positive sexual behaviors

The responses to the survey, which are also presented in Table 2, Figure 1, were obtained. About the question of whether they had received formal education on STIs and safe sexual practices, including the identification of various types of STIs and their modes of transmission, it was confirmed by 32 women (80%) and 20 men (50%) respectively that they had received such education.

Regarding the question of discussing a partner's STI status prior to engaging in sexual activity, 27 women out of 40 (67.5%) and 17 men out of 40 (42.5%) reported that they had indeed discussed the matter.

In terms of consistent condom or other barrier method use during sexual intercourse, 27 women (67.5%) and 17 men (42.5%) indicated that they always use protection.

Table 2. Question responses. Data obtained **in the survey, expressed in percentages, divided into females and males**

Questions	Received formal education about STIs	Use consistently condoms or barrier methods	Inadequate condom use	Discussing STIs before sexual activity	Had sexual activity without protection in long-term relationships	Used protection in oral sex or other types of sexual activity	Have had past diagnosed STIs	Had unprotected sexual intercourse with someone with multiple partners
Females (n=40)	80%	70%	15%	67.5%	62.5%	30%	12.5%	25%
Males (n=40)	50%	45%	55%	42.5%	60%	25%	15%	62.5%

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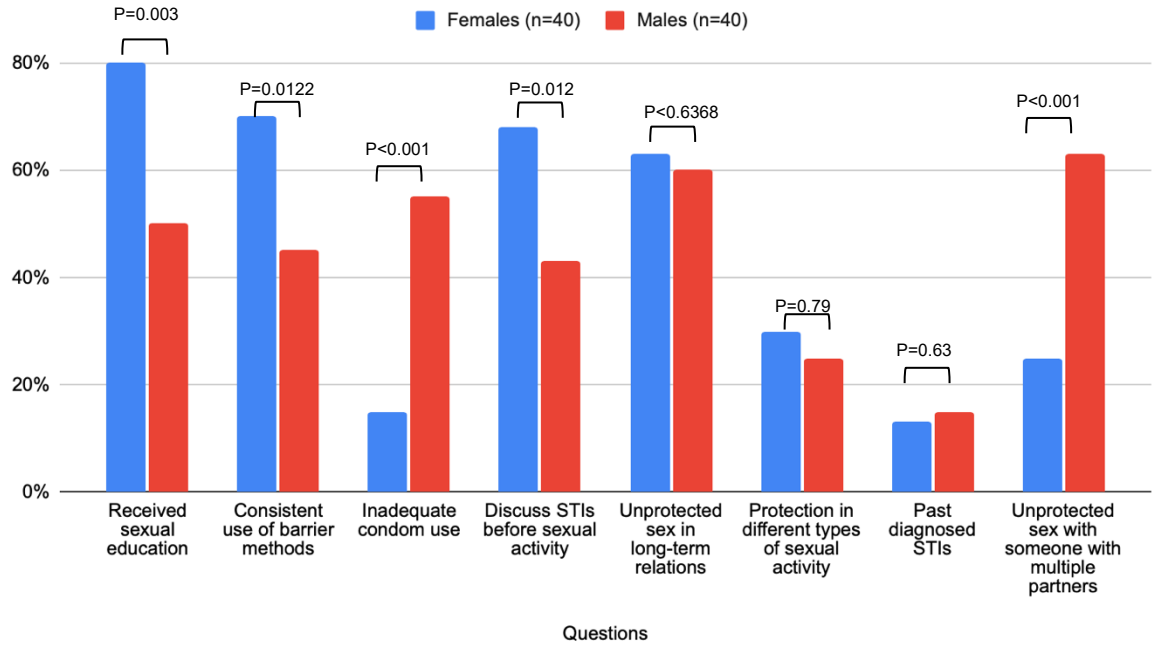

FIGURE 1. STD questionnaire answers in bar graph. The graph depicts the comparative frequencies of high-risk sexual behaviors and STI knowledge between male (red) and female (blue) college students, expressed in percentages.

High-risk sexual behaviors

In relation to inadequate condom use, such as storing condoms in locations that could expose them to extreme temperatures (e.g., car glove compartments, wallets), reusing condoms for multiple sexual encounters or use of expired or damaged condoms, 6 women (15%) and 22 men (55%) acknowledged doing so.

Concerning engaging in sexual activity without any form of protection due to being in a long-term relationship, 25 women (62.5%) and 24 men (60%) confirmed that they had engaged in such behavior.

In relation to the utilization of barrier methods (e.g. dental dams) during oral sex or barrier protection for specific types of sexual activity, 12 women (30%) and 10 men (25%) confirmed the use of such methods.

In relation to engaging in unprotected sexual intercourse with someone known to have multiple partners, 10 women (25%) and 25 men (62.5%) admitted to having engaged in such activity (Figure 1).

Past sexually transmitted infections

In terms of past diagnoses of STIs, among the 40 female respondents, five (12.5%) reported a previous diagnosis of an STD. Among the 40 male respondents, six (15%) also reported a previous diagnosis of an STD (Figure 1).

DISCUSSION

Following the analysis of the data collected from the college student cohort, the initial hypothesis was confirmed, revealing a clear trend. This indicated that males within the group exhibited riskier sexual behaviors more frequently than their female counterparts and possessed significantly less knowledge regarding the appropriate use of contraceptive methods.

About positive sexual behaviors, specifically sexual education, a statistically significant difference was observed between males and females, with a proportion of 30% (95% CI, p=0.003). The foundation of sexual health education

appeared to be significantly weaker among males. Only half of the male respondents reported receiving formal education on STIs and safe sexual practices, compared to 80% of females. This educational gap is likely to contribute to other risky behaviors observed in the survey. A lack of awareness of these issues can lead to delayed identification and treatment of STIs, which in turn can exacerbate health risks.

In the context of sexual activity, a notable discrepancy was observed in the discourse surrounding STIs. Specifically, 42.5% of male participants engaged in open dialogue about their partner's STI status prior to sexual intercourse, whereas 67.5% of female participants did so (95% CI, p=0.0122). This discrepancy suggests that women may be more inclined to proactively address sexual health risks with their partners. Notwithstanding these risky practices, there were areas where behaviors exhibited by the two genders were similar.

About the utilization of contraceptive methodologies, a discrepancy of 25% (95% CI, p=0.0122) was discerned in the deployment of protective measures between women (67.5%) and men (45.5%). This indicates that women are more likely to utilize protective measures during sexual intercourse than men. A 40% difference was identified in the analysis of high-risk sexual behavior, specifically inadequate condom use (95% CI, $p < 0.001$). Furthermore, the utilization of condoms is indicative of this proclivity towards risky behaviors. A greater proportion of men (55%) than women (15%) stored condoms in locations susceptible to extreme temperatures, such as glove compartments in vehicles or wallets. Such conditions can impair the integrity of the condom. Furthermore, the utilization of expired or compromised condoms was significantly more prevalent among male participants, which suggests a deficiency in knowledge or disregard for proper condom usage among the male respondents.

No statistically significant difference was identified between the two groups (95% CI, p=0.6368) about the utilization of contraceptive methods in long-term relationships. Both genders engage in unprotected sexual intercourse in this type of relationship.

No statistically significant difference was identified between males and females about the utilization of barrier methods across a range of sexual encounters (95% CI, p=0.7912).

The evidence indicates that men engage in a greater number of sexual encounters with multiple sexual partners than women (95% CI, $p < 0.001$).

It is noteworthy that practices that directly contribute to the higher incidence of STIs, such as not using a condom or misusing it, were observed among this group. A series of questions were posed to ascertain the number of women and men who had received sexual education, the prevalence of high-risk behavior, and the final question addressed the occurrence of past STIs. It is reasonable to conclude that the discrepancy in educational attainment is a significant contributing factor to the subsequent behavioral risks. The lower awareness of STI symptoms among males may result in a delay in the recognition and treatment of these infections, thereby prolonging the transmission risk to others. In contrast, female respondents demonstrated a high level of engagement with sexual education and a proactive approach to STI awareness. It is evident that males are engaging in sexual behaviors that are more likely to result in the transmission of STIs, which may be attributed to deficiencies in their knowledge and awareness of sexual health. Addressing these deficiencies in educational provision could facilitate more informed decision-making and safer sexual practices, which would ultimately serve to reduce the risks of STIs and unintended pregnancies. The following bar graph presents the percentage differences between males and females in a clear format.

A recent study conducted by Faludi and Rada[14] examined the gender-based disparities in sexual and reproductive health outcomes among young adults. The study revealed that women were more likely to engage in sexual health discussions than men. Furthermore, it was established that women had received consistent guidance from their families regarding the importance of cautious sexual activities and the adverse effects of unprotected sexual intercourse. However, male participants were less engaged in sexual education conversations. The qualitative component of the study revealed that the frequency and nature of sexual health discussions were significantly shaped by gender roles and sexual desire. This evidence lends support to the findings of the study and provides further insight into the sociocultural aspects of sexual education, particularly in relation to the negative perceptions often associated with it in the context of women.[14] Even though women sexual education's is sustained by the social stigma about sex, this allows women to be well-informed regarding STIs, have less high-risk sexual activities and consequently less incidence of STI's.

Another study conducted recently by Burrell et al,[15] identified that women are more knowledgeable about sexual health than men, supporting the hypothesis and results. One of the most significant findings of Burrell's research was that women are more inclined to seek urgent care or clinical guidance when confronted with sexual health concerns or uncertainties. Furthermore, this study emphasizes the discrepancy between the sexual maturation of males

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and females and proposes that the sexual education provided should consider the disparate maturation processes of the two genders. This may explain the discrepancy observed between male and female education, as current programs lack specific gender-based requirements for sexual advice based on sexual maturation times.[15]

There is a clear indication that men are engaging in higher-risk sexual behaviors, potentially due to gaps in knowledge and awareness about sexual health. Addressing these educational shortcomings could lead to more informed decisions and safer sexual practices, ultimately reducing the risks of STIs and unintended pregnancies. Percentual differences are presented in the following bar-graph, with a clear comparison between males and females.

The data analysis revealed that men engage in riskier behaviors and demonstrate a lack of knowledge regarding the appropriate use of contraceptive methods, thereby confirming our initial hypothesis. By identifying this high-risk group and the lack of gender-specific sexual education, it is possible to suggest the creation of targeted educational programs designed to promote sexual health in men. The destigmatisation of this topic must commence at an early stage of sexual education and be reinforced throughout the lives of young adults. Despite the identification of a higher level of sexual education, method use and lower incidence of high-risk behavior among women, a proportion of this group has not received this type of education and engages in high-risk sexual activities. It is imperative that efforts to promote sexual guidance consider the specific needs of both men and women.

CONCLUSION

The survey data not only reveals significant gender disparities in sexual health behaviors, with male students demonstrating a greater proclivity for high-risk behaviors than their female counterparts, but also serves to underscore a broader issue: the enduring prevalence of risky sexual practices among young adults. These findings emphasize the pressing necessity for comprehensive and accessible sexual health education that encompasses not only the mechanics of STI transmission and prevention but also the socio-cultural factors that influence behaviors.

The persistence of such risky behaviors among young adults is indicative of the necessity for a multi-faceted approach that combines education, accessible healthcare services, community engagement and policy support to create an environment conducive to informed sexual health decisions. By addressing these needs, it is possible to work towards a reduction in the incidence of STIs and the fostering of a culture of sexual health responsibility and empowerment among young people.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Original research

COVID-19 host-genetics: Known and novel variants in an admixed population

Vanessa Gonzalez-Covarrubias[a1*], José Luis Cruz-Jaramilllo[b2], Willebaldo García-Muñoz[b3], Lourdes Anzures-Cortés[b4], Lorenza Haddad-Talancón[b5], Sergio Sánchez-García[c6], María del Carmen Jiménez Martínez[d7], Edgar Pérez Barragán[e8], David Koepsell[f9], Alejandro Nieto-Patlán[g10], José Darío Martínez-Ezquerro[c11], Kenneth Rubio-Carrasco[a12], Nancy Vara Gama[h13], Laura del Bosque-Plata[a14], Mauricio Rodríguez-Dorantes[a15], Gabriela Mellado-Sánchez[i16], Sonia Mayra Pérez-Tapia[i17]

[a]Instituto Nacional de Medicina Genómica, Ciudad de México, México.
[b]Laboratorio de Genotipificación, Código 46, Cuernavaca Morelos, México.
[c]Centro Médico Nacional Siglo XXI, Unidad de Investigación Epidemiológica y en Servicios de Salud, Área Envejecimiento, Ciudad de México, México.
[d]Universidad Nacional Autónoma de México, Facultad de Medicina, Departamento de Bioquímica. Unidad Periférica "Conde de Valenciana"-UNAM, Departamento de Inmunología, Ciudad de México, México.
[e]Hospital General de Zona no. 48, IMSS, Ciudad de México, México.
[f]Texas A&M, College Station, Texas, USA.
[g]Texas Children's Hospital, Center for Human Immunobiology, Department of Allergy, Immunology and Rheumatology, Houston, TX, USA.
[h]Universidad Nacional Autónoma de México, Facultad de Química, Ciudad de México, México.
[i]Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Unidad de Desarrollo e Investigación en Bioterapéuticos, Ciudad de México, México.

ID ORCID:

[1]https://orcid.org/0000-0003-2072-2847, [2]https://orcid.org/0009-0004-3103-3793, [3]https://orcid.org/0000-0003-2418-1419, [4]https://orcid.org/0000-0001-5769-4849, [5]https://orcid.org/0000-0002-8747-9186, [6]https://orcid.org/0000-0001-5648-7223, [7]https://orcid.org/0009-0005-7433-7612, [8]https://orcid.org/0000-0002-3839-1567, [9]https://orcid.org/0000-0001-7250-8928, [10]https://orcid.org/0000-0002-8668-6853, [11]https://orcid.org/0000-0002-2609-4207, [12]https://orcid.org/0000-0002-0601-3051, [13]https://orcid.org/0009-0005-5277-7772, [14]https://orcid.org/0000-0003-3224-378X, [15]https://orcid.org/0000-0003-4249-7222, [16]https://orcid.org/0000-0002-8299-5958, [17]https://orcid.org/0000-0002-2818-8522

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ABSTRACT

Introduction: The investigation of host gene variants associated to COVID-19 has led to causal relationships and potential therapeutic targets, but most of these studies have taken place in individuals of European descent. **Objective:** Here, we aimed to confirm allele frequency differences in host genetic variants previously associated to COVID-19 in admixed individuals i.e., Mestizos from Mexico. Genes studied included those previously reported and replicated including, *ABO, CCR2, CCR9, CXCR6,*

* *Corresponding Autor*: Mirelle Vanessa Gonzalez Covarrubias. Instituto Nacional de Medicina Genómica (INMEGEN). Address: Periférico Sur 4809, Arenal Tepepan, Tlalpan, 14610, Ciudad de México, México. Email: vgonzalez@inmegen.gob.mx

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DPP9, FYCO1, IL10RB/IFNAR2, LZTFL1, OAS1, OAS2, OAS3, SLC6A20, TYK2, and *XCR1*. **Methods**: DNA from 106 COVID-19 patients and 2677 individuals were genotyped using the Illumina GSA array. Variants not probed in the array or that did not pass quality controls were imputed for these 14 genes using the 1000G phase 3 hg19 as reference following current standard protocols. Allele frequencies were computed and compared between COVID-19 patients and the general population. **Results:** We confirmed allele frequency differences for *ABO* rs657152, *DPP9* rs2109069, *LZTFL1* rs11385942, *OAS1* rs10774671, *OAS1* rs2660, *OAS2* rs1293767, and *OAS3* rs1859330 p<0.03. In addition, we identified over 100 SNVs with significant allele frequency differences (p-value <10 -2). Of these, there were four variants on *ABO, OAS1/2* and *FYCO1* with a high functional impact assessed in-silico. **Conclusions:** our observations confirm allele frequency differences in genes associated to COVID-19 in an admixed population and prompts for the development of metanalyses to validate local and geographical patterns of COVID-19 severity and infection associated to genetic variation.

Key words: COVID-19; host genetics; gene variation; admixed population.

RESUMEN

Introducción: Las variantes genéticas asociadas a la COVID-19 son indicadoras de genes causales y potenciales blancos terapéuticos. Desafortunadamente, la mayoría de estos estudios se han realizado en individuos de ancestría europea y desconocemos la presencia de éstas en otras poblaciones. **Objetivo:** Identificar y confirmar la frecuencia alélica de variantes relacionadas con la COVID-19 en población mexicana mestiza en los genes *ABO, CCR2, CCR9, CXCR6, DPP9, FYCO1, IL10RB/IFNAR2, LZTFL1, OAS1, OAS2, OAS3, SLC6A20, TYK2,* and *XCR1*. **Métodos**: El ADN de 106 pacientes y 2677 individuos sin infección previa y al momento de la entrevista fueron genotipados mediante microarreglo e imputación. Se determinó la frecuencia alélica y esta se comparó entre pacientes versus la población general. **Resultados:** Se confirmaron diferencias en la frecuencia alélica para las variantes ya reportadas, *ABO* rs657152, *DPP9* rs2109069, *LZTFL1* rs11385942, *OAS1* rs10774671, *OAS1* rs2660, *OAS2* rs1293767, y *OAS3* rs1859330 p<0.03. También reportamos más de 100 variantes con diferencias en la frecuencia alélica entre pacientes y la población general (p-value <10-2), se determinó el impacto funcional in-silico de éstas identificando 4 variantes con un impacto alto en *ABO, OAS1/2* and *FYCO1*. **Conclusiones:** Se confirman diferencias en la frecuencia alélica entre pacientes con COVID-19 y la población general en mestizos mexicanos, para genes previamente asociados con COVID-19, validando estudios previos, y fomentando el desarrollo de metaanálisis que validen y complementen la información genética relacionada con la infección y severidad a la COVID-19.

Palabras clave: COVID-19; genética humana; variantes genéticas; población mestiza.

INTRODUCTION

The World Health Organization (WHO) announced the COVID-19 pandemic as a world health emergency on January 30th, 2020, following the confirmation of 7,818 cases across 18 countries. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection develops with a wide range of symptoms, from asymptomatic, to mild, to severe manifestations, and lethality related to respiratory failure, septic shock, and multiple organ dysfunction. Different factors including clinical biomarkers, anthropometric, and demographic parameters have been associated to COVID-19 outcomes highlighting the heterogeneity of these components linked to SARS-CoV-2 infection. Parallel to the method development for the identification of SARS-CoV2 strains we have been witnessing much progress in the characterization of the host genetics and its association with disease symptoms and clinical outcomes.[1]

The host genetics of COVID-19 has been intensively studied showing that several variants can impact immunity, inflammation through the cytokine cascade, severity, and susceptibility to SARS-CoV-2.[2,4] A consistent set of genetic variants have been associated to COVID-19 including some for the virus receptors *ACE2*, *TMPRSS2*, immune components *IFNAR1/2*, *TYK2*, interleukins IL6, antiviral genes OAS1-3, toll-like receptors of innate responses, *TLR3/4/7*, *HLA* genes, *APOE* and the locus 3p21.31 (several genes including, *SLC6A20*).[3,5] At the time of this study there are about 22 genome wide association studies (GWAs) for COVID-19 adding to the collection of variants that link, in part, disease risk, severity, and susceptibility mostly in populations of European descent.[6,7] Several of these have been

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confirmed in more than one study and these consistently include variants on genes, ACE2, ABO, OAS1-3, and the 3p21.31 locus that holds 6 genes, *SLC6A20*, *LZTFL1*, *CCR9*, *FYCO1*, *CXCR6*.[8,9] It is important to mention that there is still ongoing research in the field including the development of associations between the host genome and a myriad of clinical characteristics and outcomes that have been reported during SARS-CoV-2 infection, these might include key endpoints as mentioned above, and specific symptoms such as headache, pharyngalgia, dyspnea, diarrhea, myalgia, vomiting, sputum production, anxiety, chest pain, fatigue, nausea, anorexia, abdominal pain, rhinorrhea, runny nose, nasal congestion, dizziness, chills, systemic pain, mental confusion, hemoptysis, asthma, taste disorder, smell disorder, belching and tachycardia, with or without fever and normal, or dry cough, accentuating the complexity of these genetic associations.[10] The current literature indicates that up-to 15% of COVID-19 patients evolve to a severe disease[11] which can be in part due to gene variants that favor COVID-19 infection, susceptibility, respiratory failure, inflammation, immune exacerbated reactivity, and death.[12-16] Initial reports of the COVID-19 pandemic identified male and older age as risk determinants for increased severity, respiratory stress, and death.[17,18] This prompted to the creation of collaborative research groups such as The Sex, Gender and COVID-19 Project, that attempted to explain why more males were hospitalized compared to women.[19] T. Takahashi et al. reported that females show a more robust T cell activation while immune cytokines, associated with a worse progression, are higher in males.[20] Other hypotheses revolved around variation on the X chromosome such as a hypercoagulation karyotype, and genetic variation on *TLR7* and *ACE2* on the X chromosome.[21-23] Today it is still no clear whether sex differences have a genetic basis. Nevertheless, a faulty adaptive and innate immune system can partly explain the cytokine storm and the inability of the immune system to efficiently fight against SARS-CoV-2[24] and over 100 genetic variants on genes related to the immune function have been associated to exacerbated responses and immune-related death after SARS-CoV-2 infection including variants *on IFNAR1*, *IL6*, *OAS1-3*, and *TYK2*. Of all these studies only 2 were performed in non-Europeans, showing the lack of completion of the collection of genetic knowledge associated to COVID-19 for all world populations. The coverage of this paucity in genetic information could be of relevance to explain discrepancies of epidemiological studies which have shown that people from non-white ethnic backgrounds are at higher risk of infection and of severe COVID-19.[7] Research on COVID-19 host genetics provides an opportunity to fill the population knowledge gap, to determine whether genetic differences might be relevant risk factors for COVID-19, and if these associations are population independent. Up-to August 2023, twenty-two GWAS have identified relevant genetic variation associated to COVID-19 with 15 variants confirmed by more than one research group including, The COVID-19 Host Genetics Initiative,[9] The UK based Genetics of Mortality in Critical Care (GenOMICC),[6] and The Severe COVID-19 GWAS Group.[25,26] Results from these investigations motivated the development of models to predict the risk of severe COVID-19 and in March 2021, G. Dite et. al. published a validated model to assess the risk of COVID-19 for participants of the UK Biobank. The model included genetic variants from previous research, new variations from The COVID-19 Host Genetics Initiative, and variants from P. Castineira *et al.*[6,27,28] The final prediction model showed that 7 out of 116 variants, rs112641600, rs10755709, 118072448, rs7027911, rs71481792, rs112317747, rs2034831, can partially predict COVID-19 severity.[28] These predictions were based on 22 studies of which only two were performed in non-Europeans, one in China and another with East Asian participants.[7] This points towards the need to expand and replicate risk model assessments in different populations including those admixed and from Latin-America. Here, we sought to investigate allele frequencies of COVID-19 associated variants in Mexican individuals of mixed ancestry according to previously published GWAs that were available at the onset of this investigation.[1,6,29-31]

MATERIALS AND METHODS

Study population

One-hundred and six COVID-19 patients and 2677 non-infected individuals were recruited by three different institutions in Mexico City: Hospital General de Zona 48, Instituto Politécnico Nacional (IPN, ENCB), Código 46, and Instituto Mexicano del Seguro Social (IMSS). All participants signed informed consent, protocols followed the principles of the declaration of Helsinki, and were approved by the Committees of Research, Ethics and Biosafety at INMEGEN No. CEI2017/04 and IMSS No. 23/2016/I. SARS-CoV-2 infection was confirmed in 106 patients by a nasal PCR or an antigen test (Table 1). DNA was extracted from a blood sample using the Puregene blood kit (Qiagen). The comparison group was defined as the general population consisting of 2677 individuals (Table 1) with no COVID-19 infection confirmed by a PCR test (N=803, 30%), an antigen test (N=900, 34%) or a follow-up call (N=977, 36%).

Table 1. Population characteristics

	COVID-19	General Population
N	106	2677
males*	64	1148
age y	42 (17 – 73)	58 (17 -97)
BMI kg/m²*	28(20 – 31)	33 (17 - 55)
T2D*	85	1832
Hypertensive*	76	1272
Hospitalized	14	none
COVID antigen confirmed	44	803
COVID PCR confirmed	72	900
Severe COVID	16	none
Moderate COVID	43	none
Asymptomatic	47	none

Mean (range); *denotes differences between group comparisons; T2D: type-2 diabetes, HT: hypertension, Hosp.: hospitalized, PCR and antigen tests refer to COVID-19 diagnostic laboratory tests; * indicate significant differences, p-value<0.05.

Genetic analyses

Genotyping was performed with the Infinium GSA microarray v.1.0 (Illumina) focusing on genes previously associated to COVID-19, *ABO, CCR2, CCR9, CXCR6, DPP9, FYCO1, IL-10RB/IFNAR2, LZTFL1, OAS1, OAS2, OAS3, SLC6A20, TYK2,* and *XCR1* with special interest in variants with consistently reported allele frequency differences, *ABO* rs657152, rs8176747, rs41302905, *CCR9/LZTFL1, CXCR6, FYCO1, XCR1* Locus 3p21.31 (lead rs11385942), *DPP9* rs2109069, *IL10/IFNAR2* rs2236757, OAS1-3 rs10774671, rs2660, rs10735079, rs1293767, rs1859330, rs2285932, *SLC6A20* rs2742396, and *TYK2* rs1108572, rs74956615 (Table 2).[27,32]

Table 2. Single nucleotide variants previously associated with COVID-19 variants replicated in this admixed population

Gene, rs AF reported for Latin America	AF COVID-19	AF General Pop.	p-value	Ref.
ABO rs8176747, AF:0.064	0.0425	0.0579	NS	European (8,32)
ABO rs41302905, AF:0.009	0.0100	0.0139	NS	
ABO rs657152, AF:0.239	0.3600	0.244	7.50×10^{-5}	
DPP9, AF:0.238	0.3208	0.2462	1.35×10^{-2}	Multiple ancestries (4,11,16)
IFNAR2 rs2236757, AF:0.454	0.4380	0.4563	NS	
OAS1 rs10774671, AF:0.224	0.1840	0.2748	2.71×10^{-2}	British, Multiple (3,11,39)
OAS2 rs2660, AF:0.194	0.1085	0.1806	3.10×10^{-2}	
OAS3 rs10735079, AF:0.213	0.1274	0.1950	1.41×10^{-2}	
OAS3 rs1859330, AF:0.211	0.1462	0.2762	2.90×10^{-2}	
OAS3 rs2285932, AF:0.184	0.1040	0.137	NS	

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SLC6A20 rs2742396, AF:0.398	0.2123	0.4449	1.80×10^{-11}	European (3,39)
TYK2 rs1108572, AF:0.102	0.0047	0.0003	3.75×10^{-3}	
LZTFL1 rs11385942, AF:0.039	0.0094	0.0383	2.92×10^{-2}	Italy/Spain (3,39)

AF: Allele frequency, Gral Pop.: general population, Latin America AF from GnomAd and the ALFA project from https://www.ncbi.nlm.nih.gov/snp/. *TYK2* rs74956615 and *OAS2* rs1293767 were not detected.

Statistical and bioinformatic analyses

Variants that were not probed by the Infinium GSA array or did not pass microarray quality controls we imputed according to standard protocols with the software MACH v.1.0 and recommendations for human genetic imputation.[33,34] Public data from the 1000G phase 3, and the human genome assembly hg19 were included in the imputation protocol.[35] Allele frequency comparisons were performed using PLINK for variants that passed imputation bioinformatic quality controls.[33,36] Population admixture was calculated with 56,663 microarray variants using a model-based likelihood estimation with the program ADMIXTURE 3.0 (Supplemental Figure 1).[37] The selection of the informative ancestry variants was based on allele frequency of the minor allele (MAF > 0.05) between the four main parental groups; variants were excluded if they were in linkage disequilibrium ($r2 \geq 0.1$) or within a predefined physical distance of at least 500 kb.[21,22] COVID-19 samples and the general population showed very similar genetic ancestry proportions and did not impact allele frequency differences. All patients were admixed Mexicans from the metropolitan area showing on average, 45% Native, 34% Caucasian, 12% Asian, and 8% African ancestral proportions determined by comparing their genotypes with continental populations. Northern Europeans from Utah (CEU), Chinese Han from Beijing (CHB) and Yoruba Ibadan from Nigeria (YRI) from the 1000 genomes data base. No individual showed exclusively Native or European ancestries, no differences in admixture proportions between study groups were detected and admixture observations were in accordance with previous reports (Supplemental Figure 1).[38,39] In addition, kinship and inbreeding analyses using PLINK and an IBD proportion <0.5 showed that individuals were not related in first or second degrees, on average the population showed an inbreeding proportion similar to average populations between 10-15%. Allele frequency differences between groups were determined using a Chi-square test considering a p-value<0.05 as significant, calculations were computed using the Software R v4.0.5 and PLINK.[36,40]

Variant functional impact assessment

The functional impact of novel variants was determined in-silico using the Ensembl Variant Effect Predictor (VEP v.111). Variation was annotated according to the GRCh37.p13 genome assembly. VEP assessed functional consequences across coding and noncoding regions by comparing each variant to its corresponding transcript in the ENSEMBL/GENCODE 19 database matching the transcript location of the variant with molecular consequences computed and reported using the Sequence Ontology nomenclature. Here, we report the last iteration of this functional analysis, which represents the variant to the closest gene, and the one with the highest precision from all iterations performed.

It is important to mention that the differences in sample size between study groups did not allow for the development of association models, but future studies with additional COVID-19 samples may incorporate different covariates such as genetic ancestry to better account for population stratification.

RESULTS

Available clinical information for COVID-19 patients is presented in Table 1. On average individuals were 42 years old, 50% were diabetic and 70% hypertensive and showed an average BMI of 28 kg/m^2. The general population was on average 58 years of age, showed a BMI of 33 kg/m^2, 68% were diabetic and 48% hypertensive.

Genomic analyses and descriptive statistics

We genotyped and imputed single nucleotide variants (SNVs) on genes previously associated with COVID-19, only variants that passed bioinformatic quality controls for microarray and imputation processes were considered for further analysis. We detected most previously reported

variants including, *ABO* rs657152, rs8176747, rs41302905, *CCR9/LZTFL1, CXCR6, FYCO1, XCR1* Locus 3p21.31 (lead rs11385942), *DPP9* rs2109069, *IL10/IFNAR2* rs2236757, OAS1-3 rs10774671, rs2660, rs10735079, rs1293767, rs1859330, rs2285932, *SLC6A20* rs2742396, and *TYK2* rs1108572, rs74956615, but *TYK2* rs74956615 and *OAS2* rs1293767 known to impact COVID-19 outcomes, were not identified here; either because these did not pass bioinformatic quality control, they were not found in this population, or due to imputation limitations. Supplemental Table 1 lists all variants identified on these genes with an allele frequency ≥0.01%.

Allele frequency differences in COVID-19 associated variants

We confirmed allele frequency differences in 9 of the 13 detected SNVs (Table 2 and Figure 1), these were on *ABO* rs657152 p-value=7.2x10-5, *DPP9* rs2109069 p-value=0.014, *LZTFL1* rs11385942 p-value=0.029, *OAS1* rs10774671 p-value=0.0035, *OAS1* rs2660 p-value=0.007, *OAS2* rs1293767 p-value=0.00501, and *OAS3* rs1859330 p-value=2.9 x10-5. Allele frequencies in this admixed population were compared with that of ancestral populations, CEU, YRI, CHB based on data from the 1000 Genomes database, as mentioned above. Most allele frequency (AF) values were similar when compared to continental populations, but some apparent differences were detected for key variants including, *FYCO rs200040076, CXCR6 rs113318190, XCR1 rs181118021, ABO rs56390333,* and *OAS3 rs2072134*. Figure 1 shows AF key differences; for example, *FYCO* rs200040076 in COVID-19 patients showed an AF of 0.014, but it was almost absent in other populations. Similarly, *CXCR6* rs113318190 and *XCR1* rs181118021 showed an allele frequency around 0.10 in COVID-19 samples and were significantly less frequent in all other continental groups including admixed Mexicans (AF:0.0002). A more common variant was *OAS3* rs2072134 which showed an allele frequency of 0.10 in COVID-19 patients similar to that reported for CHB, but with an AF of 0.008 in this admixed population, and absent in other continental groups, potentially hinting towards the ancestral line that led this variant to Mexico (Figure 1). Intriguingly, *ABO* rs56390333 was present in COVID-19 patients and in individuals with YRI ancestry (AF: 0.080 and 0.050), but absent in other populations. We also found interesting differences in allele frequencies on *CXCR6 rs113318190, XCR1 rs181118021, and OAS3 rs2072134* between Mexicans from Los Angeles (MXL) from the 1000 Genome database and Mexicans from this study. The *OAS3 rs2072134* variant was present as a heterozygous only showing a low allele frequency <0.001, but these variants, *CXCR6 rs113318190, XCR1 rs181118021, and OAS3 rs2072134*, were absent in MXL likely due to the small group representing MXL. This highlights the importance of studying admixed populations in larger sample sizes.

Novel variation on COVID-related genes

We identified over 100 SNVs, not previously reported, with apparent and significant allele frequency differences between COVID-19 patients and the general population. The most relevant were listed in Table 3 and Figure 1, all showing the presence of the alternative allele more frequently in COVID-19 patients compared to the average population. Genes with the largest number of variants showing significant allele frequency differences between groups were *ABO (8 SNVs)*, *FYCO1 (5 SNVs),* and *XCR1 (5 SNVs)*, (p-value<10^{-50}).

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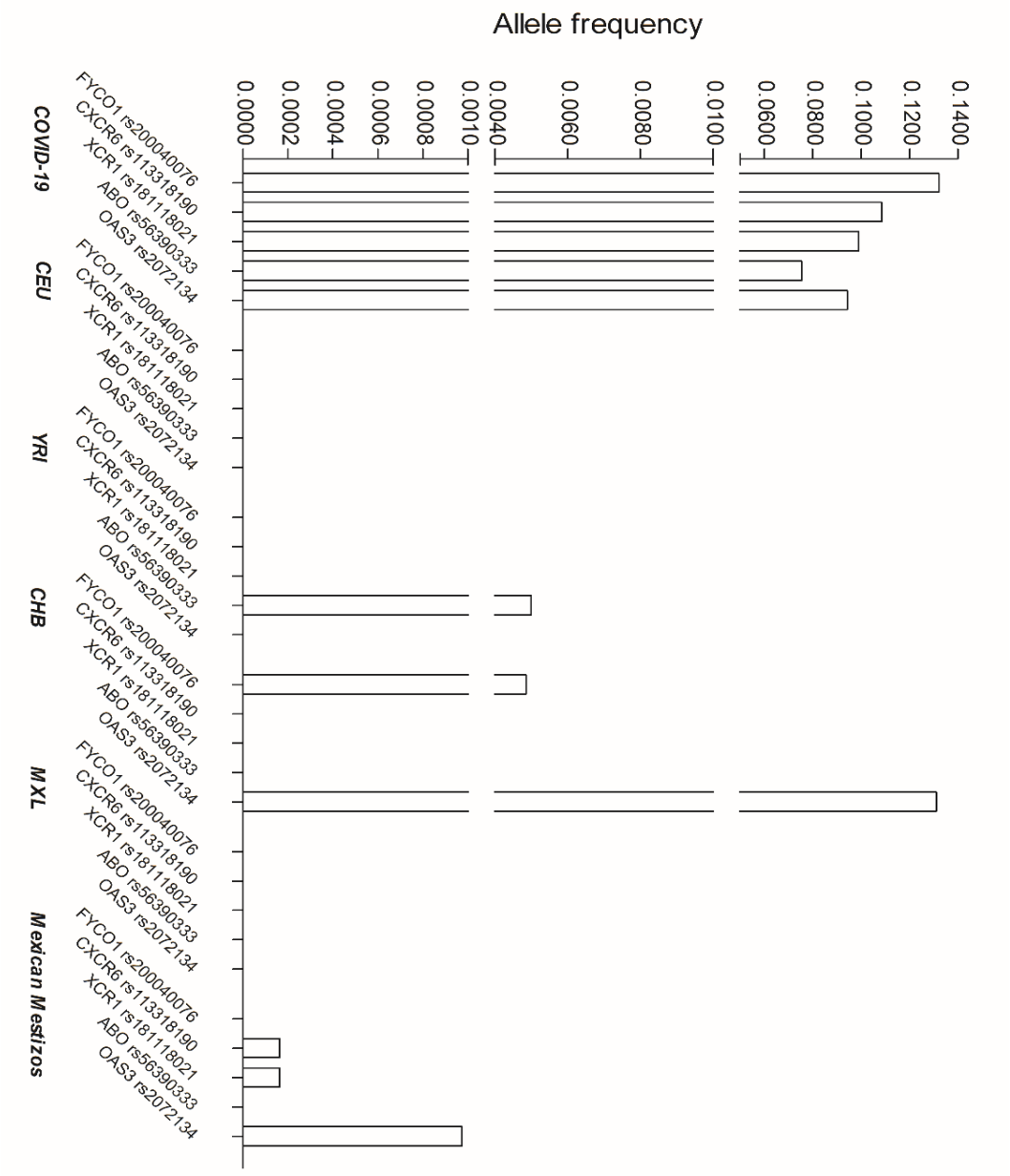
Table 3. Top novel variation of allele frequency differences in COVID-19 samples

Gene	rs identifier	allele	AF COVID-19	AF Gral Pop	p-value
FYCO1	rs200040076	C>T	0.1321	0	$1.14\ 10^{-179}$
CXCR6	rs113318190	G>A	0.1085	0.00016	$2.30\ 10^{141}$
XCR1	rs181118021	G>A	0.0991	0.00016	$1.15\ 10^{-128}$
ABO	rs56390333	G>A	0.0755	0	$2.47\ 10^{-103}$
OAS3	rs2072134	G>A	0.0943	0.00097	$1.40\ 10^{-97}$
ABO	rs35494115	G>A	0.0802	0.00049	$1.86\ 10^{-92}$
OAS3	rs16942374	G>A	0.066	0.00016	$2.54\ 10^{-84}$
DPP9	rs118149076	G>A	0.0708	0.00081	$1.23\ 10^{-71}$
ABO	rs371569951	G>A	0.0613	0.00049	$8.44\ 10^{-68}$
ABO	rs200932155	G>A	0.066	0.00097	$3.07\ 10^{-62}$
DPP9	rs75191837	T>C	0.0755	0.00227	$7.01\ 10^{-53}$
ABO	rs8176716	G>A	0.1179	0.00796	$7.28\ 10^{-49}$
SLC6A20	rs184655598	G>A	0.033	0	$3.50\ 10^{-46}$
CCR9	rs41289608	G>A	0.2264	0.03313	$9.74\ 10^{-46}$
IFNAR2	rs144511372	C>T	0.0283	0	$7.91\ 10^{-40}$
CCR9	rs79006711	G>A	0.1981	0.0302	$2.70\ 10^{-38}$
TYK2	rs35018800	G>A	0.0613	0.00276	$1.79\ 10^{-34}$
ABO	rs9411372	G>A	0.0377	0.00065	$1.81\ 10^{-34}$
ABO	rs61736301	G>A	0.0283	0.00016	$5.14\ 10^{-34}$
CCR9	rs6775854	G>A	0.2028	0.03556	$1.76\ 10^{-33}$
CCR9	rs7648467	C>A	0.2028	0.03556	$1.76\ 10^{-33}$
FYCO1	rs141064206	C>T	0.0236	0	$1.80\ 10^{-33}$
FYCO1	rs141476300	G>A	0.0236	0	$1.80\ 10^{-33}$
FYCO1	rs7619256	G>A	0.1934	0.03264	$2.24\ 10^{-33}$
CCR9	rs17078408	T>G	0.2028	0.03573	$2.65\ 10^{-33}$
ABO	rs1053878	G>A	0.2028	0.03654	$1.95\ 10^{-32}$
FYCO1	rs140002692	G>A	0.0377	0.00081	$1.09\ 10^{-31}$

AF: allele frequency, NS, not significant.



Bars indicate the allele frequency of each genetic variant, note the scale in the Y axis for low and higher allele frequencies. COVID-19: patients from this study, CEU: Europeans, YRI: Africans South of the Sahara, CHB: Chinese Han from Beijing, MXL: Mexicans from Los Angeles from The 1000G database, Mexican Mestizos: individuals from this study.

Figure 1. Allele frequency differences on genes associated to COVID-19 compared to continental populations. COVID-19 refers to patients from this study, CEU, YRI, CHB and MXL data were taken from the 1000G database, Mexican Mestizos refers to the general population data from this study.

We also identified genetic variation exclusive of COVID-19 samples including, 43 SNVs with a null allele frequency in the general population but present in COVID-19 samples. Of these, *ABO* rs56390333 (AF=0.076) and *FYCO1* rs200040076 (AF=0.132) were the most common (Table 3).

Other genes also showing variation exclusively in COVID-19 samples were, *CCR9* (9 SNVs), *OAS2* (3 SNVs), *LZTFL1* (12 SNVs), *SLC6A20* (8 SNVs), *IFNAR2*, *DPP9*, and *IL10RB*, statistical significance ranged from p-value < 10-8 (Supplemental Table 1).

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In-silico functional impact of genetic variants

The functional impact of these variants was assessed in-silico using the Ensembl Variant Effect Predictor (VEP) algorithm as mentioned earlier.[41,42] Table 4 and Figure 2 list and depict the functional impact of the top 100 novel variants most of these were either upstream (26%) or non-coding (22%). We also detected 9% of missense variants (N=17), 4 on *ABO*, 6 on *FYCO1*, 3 on *OAS3*, 2 on *TYK2*, and one on XCR1 and LZTFL1, all of them showing a moderate impact on protein function.

Table 4. Summary of the functional impact analysis of newly reported variants

Gene variant	AF difference, p-value	Functional impact
ABO rs56390333	$2.47\ 10^{-103}$	moderate/intron
FYCO1 rs200040076	$1.14\ 10^{-179}$	moderate/intron
OAS3 rs2072134	$1.40\ 10^{-97}$	moderate/intron
TYK2 rs35018800	$1.79\ 10^{-34}$	moderate/intron
XCR1 rs181118021	$1.15\ 10^{-128}$	moderate/intron
OAS1 rs2660	$7.00\ 10^{-03}$	high/stop codon
OAS1 rs10774671	$5.00\ 10^{-02}$	high/stop codon
OAS2 rs15895	$1.63\ 10^{-04}$	high/stop codon
FYCO1 rs13079869	$1.00\ 10^{-02}$	high/stop codon
ABO rs2014439325	$1.50\ 10^{-02}$	high/stop codon

The first five variants represent those with the largest differences in AF between COVID-19 samples and the general population. The latter five refer to those variants with the highest functional impact by VEP analysis, but they all have a lower statistical significance.

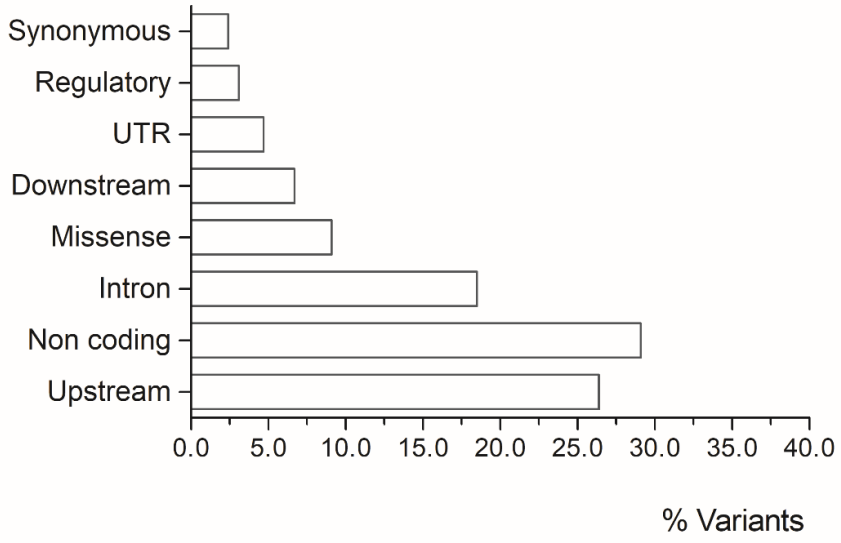

Figure 2. *In-silico* functional impact of top 100 variants with allele frequency differences.

DISCUSSION

Infection with SARS-CoV-2 presents an unpredictable course which can go from asymptomatic, to serious complications many of which have been associated to metabolic diseases.[10,43] According to the WHO and the Institutional Repository for Information Sharing (IRIS), Mexico showed a 18 – 25-fold higher COVID-19 risk compared to other countries.[44] It is known that within the country's demographic and geographical regions there are clusters of genetic variation with apparent differences meaningful for biomedical traits.[38] Moreover, Z. Yildirim et al. noted that for certain populations a higher COVID-19 incidence is seldom explained by behavior, environment, vitamin D levels, socioeconomic status, or cardiovascular risk, which prompts for the identification host genetic variants.[45] In this study we confirmed and expanded the list of COVID-19 associated gene variants in an admixed population from Mexico, below we discuss the relevance of these observations in the scope of what it is currently known about these loci.

Variation on the ABO gene

Initial reports on the host genetics of severe COVID-19 linked results almost immediately to blood type. Several research groups have reported ABO variants, rs8176747, rs657152, and rs41302905 which enhance the activation of the complement increasing COVID-19 severity.[46-48] Significant allele frequency differences in *ABO* rs657152 and rs8176747 (Table 2) were confirmed here (Table 2 and Supplemental Table S1). Here, we listed 157 additional COVID-19-associated variants on the *ABO* gene of which rs56390333 was the most significant and rs2014439325 showed a high detrimental impact in-silico, predicting a stop codon (Table 4). These observations expanded the relevance and variation of this gene in relation to COVID-19.

Variation on the OAS1-3 genes

Variation on *OAS1-3* may alter the proteins antiviral properties as their products trigger viral mRNA degradation.[29] *OAS3* rs1859330 reported here is a missense variant with a moderate impact on protein function, rs10735079 is located in a UTR region with an in-vivo functional impact not yet clear, rs10774671 and rs2660 showed an in-silico high detrimental impact as stop codons (Table 4). All *OAS1-3* variants here reported showed a lower allele frequency in COVID-19 samples compared to the general population (Table 3) supporting the notion that certain *OAS1-3* variation, putatively inherited from Neanderthals, may confer protection against severe COVID-19.[49]

Variation on the SLC6A20 gene

SLC6A20 is a glycine transporter needed for cytokine deployment during COVID-19 infection,[8] it is associated with T2D, and its product, SIT1, co-expresses and may interact with the SARS-CoV-2 receptor, ACE2. It is still not known if SIT1 affects the recognition of ACE2 by SARS-CoV-2,[50] but it may influence the proinflammatory cytokine secretion after SARS-CoV-2 infection.[8] Allele frequency differences on *SLCO6A20* rs2742396 were confirmed here (Table 3), and even though the *in-silico* functional analysis predicted it as a modifier variant, its actual impact on its product and its relation to COVID-19 has yet to be clarified.

Variation on the TYK2 gene

TYK2, tyrosine kinase 2 is part of the effector cascade of activated interferon receptors, its presence increases susceptibility to microbial infections and has been suggested as a drug target to treat COVID-19.[1] *TYK2* was first associated with severe COVID-19 by Pairo-Castineira et. al, and *TYK2* rs1108572 and rs35018800 were confirmed here, both predicted as modifier variants in-silico and more frequently present in COVID-19 patients (Table 3). Their clear role in COVID-19 severity is not evident, *TYK2* rs1108572 and rs35018800 are intron and missense variants so, it is possible that *TYK2* genetic variation alters the cytokine storm observed in severe cases.[6,51]

Variation on the DPP9 gene

DPP9 codes for the dipeptidyl peptidase, also known as CD26, is mainly responsible for T cell activation. Variants DPP9 rs13015258 and rs2109069 have been associated with severe COVID-1912,45 through its impact on the disease's immunogenetics52. We confirmed previous reports regarding *DPP9* rs2109069 by identifying significant a higher allele frequency o *DPP9* rs118149076, and rs75191837 in COVID-19 samples (Table 3, Supplemental Table S1). These variants were intronic or located on untranslated regions with a modifier impact in-silico, its causal association to COVID-19 remains to be investigated.

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Variation on the LZFTL1 gene

LZFTL1 rs11385942 is an intron variant with a modifier *in-silico* effect on the protein function, linked to the activation of the complement in individuals with severe COVID-19,[25] and more recently to a weakened airway viral clearance,[12] *LZFTL1* rs11385942 was confirmed here with a 4-fold lower allele frequency in COVID-19 patients (Table 3) supporting previous results.[53]

LZFTL1 codes for leucine zipper transcription factor like 1 and this variant did not show a relevant functional prediction *in-silico* analysis. Other variants here observed on *LZFTL1* seemed to have a modifier impact in protein function (Figure 2, Supplemental Figure SF2, and Supplemental Table ST2).

In-silico functional impact analysis of all 400 variants revealed five SNVs with a high functional impact, these were on *ABO, FYCO1, OAS1*, and *OAS2*, all affecting the stop codon and showing allele frequency differences between COVID-19 samples and the general population (Table 4 and Supplemental Table ST2). Future studies may seek to uncover its relevance in COVID-19 severity and clinical outcomes.

As COVID-19 research continues more variants will be identified as potential causal targets. For example, a recent multicenter metanalysis identified 113 variants associated to COVID-19 mortality most of them related to the modulation of the immune response directing more studies into regulating gene expression in immunity and lung function pathways.

Moreover, translational research has started to look into hindering the entrance of the virus by targeting the lipid platform needed for its entry i.e., inhibiting acid sphingomyelinase.[54] Minnai et al. have identified several drug candidates for inhibiting acid sphingomyelinase including the known drugs, amiodarone and astemizole.[55] Consequently, it is only logical to hypothesize that by increasing genetics and omics research the scientific community will complete the collection of genetic variation that may lead to identifying individuals at risk with a mechanistic explanation.

To summarize, our study confirmed allele frequency differences in genes previously associated with COVID-19 on *ABO, OAS1-3, SLC6A20, TYK2,* and *DPP9*. In addition, we provide a list of over 100 variants on these genes with significant allele frequency differences between COVID-19 patients and the general population that have not been previously reported. It is important to mention that the available clinical information and small sample size of the COVID-19 patients limited our statistical analyses for the development of association models.[25,29] Mexico is within the top fifteen countries with the highest number of COVID cases and 4th in COVID-related deaths. Infection and mortality rate are not consistent nor in proportion with population density highlighting the relevance of investigating all potential factors including genetic variation that may explain infection and mortality. Therefore, it is of relevance to continue genetics research related to COVID-19 to complement biomedical parameters that would possibly lead to the identification of populations at risk and therapeutic targets.

CONCLUSIONS

COVID-19 host genetic variation is slowly being completed and current endeavors are focused on quantitatively identifying individuals or populations at risk for all world populations. Our results confirm and complement previous reports on host gene variation in an admixed population. As more research becomes available it will be possible to validate the impact of host genetic variants on SARS-CoV-2 infection susceptibility, disease severity and treatment efficacy for all countries. Metanalyses considering admixture will enable the development of prediction models to discern if the impact of genetic variation for COVID-19 is population independent.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

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SUPPLEMENTAL MATERIAL

All supplemental information is consolidated in a pdf and includes Supplemental Table 1. Allele frequencies of all

genotyped variants; Supplemental Table 2. In-silico functional impact of all observed variants; and Supplemental Figure 1. Population admixture.

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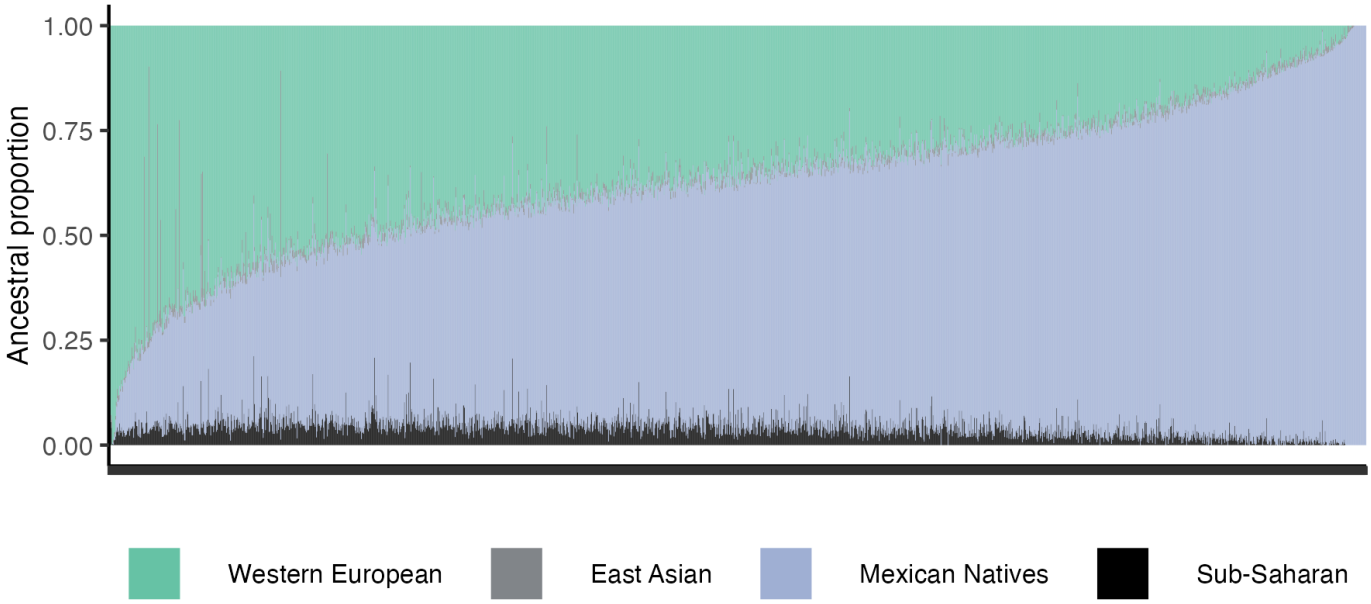
ALLSUPPLMATS COVID

Figure S1. Study population admixture proportions



Supplemental Table S1. Allele frequency on genes associated with COVID-19

SNP	CHR	GENE	Reference alelle	Alternative allele	Alternative allele frequency in General population	Alternative allele frequency in COVID-19 patients
rs56390333	9	ABO	A	G	0	0.07547
rs35494115	9	ABO	C	T	0.0004872	0.08019
rs371569951	9	ABO	A	G	0.0004872	0.06132
rs200932155	9	ABO	A	G	0.0009743	0.06604
rs113318190	3	CXCR6	A	G	0.0001624	0.1085
rs118149076	19	DPP9	A	G	0.000812	0.07075
rs200040076	3	FYCO1	C	T	0	0.1321
rs181118021	3	NRBF2P2	C	G	0.0001624	0.09906
rs16942374	12	OAS3	T	C	0.0001624	0.06604
rs2072134	12	OAS3	T	C	0.0009743	0.09434
rs7466899	9	ABO	T	C	0.0009743	0.03302
rs8176739	9	ABO	A	G	0.005196	0.07075
rs1053878	9	ABO	T	C	0.03654	0.2028
rs8176716	9	ABO	C	G	0.007957	0.1179
rs9411372	9	ABO	A	C	0.0006496	0.03774
rs8176705	9	ABO	G	A	0.004547	0.07075
rs61736301	9	ABO	C	A	0.0001624	0.0283
rs543040	9	ABO	G	A	0.2335	0.5708
rs613534	9	ABO	A	T	0.2442	0.5708
rs544873	9	ABO	C	G	0.2442	0.566
rs545971	9	ABO	A	G	0.2335	0.5519
rs612169	9	ABO	T	C	0.2335	0.5519
rs597988	9	ABO	C	T	0.2332	0.5519
rs597974	9	ABO	T	C	0.2332	0.5519
rs576123	9	ABO	G	C	0.2332	0.5519
rs8176663	9	ABO	C	A	0.2335	0.5519
rs491626	9	ABO	C	A	0.2332	0.5425
rs492488	9	ABO	A	T	0.2332	0.5425
rs493246	9	ABO	G	C	0.2332	0.5425
rs494242	9	ABO	G	A	0.2439	0.5519
rs495203	9	ABO	T	C	0.2332	0.5425
rs582118	9	ABO	A	G	0.2161	0.5142
rs582094	9	ABO	C	T	0.217	0.5425
rs79006711	3	CCR9	A	G	0.0302	0.1981
rs41289608	3	CCR9	T	C	0.03313	0.2264
rs6775854	3	CCR9	C	T	0.03556	0.2028
rs7648467	3	CCR9	G	A	0.03556	0.2028
rs17078408	3	CCR9	T	C	0.03573	0.2028

https://doi.org/10.36105/psrua.2024v4n8.02

rs75192040	3	CCR9	A	G	0.03621	0.1792
rs113305890	19	DPP9	G	A	0.02273	0.1321
rs73539528	19	DPP9	T	C	0.02192	0.1321
rs75894880	19	DPP9	G	A	0.01786	0.1321
rs57034092	19	DPP9	A	G	0.02209	0.1321
rs74840661	19	DPP9	T	C	0.01007	0.09434
rs78788550	19	DPP9	G	T	0.01056	0.09434
rs16992502	19	DPP9	G	A	0.01185	0.09434
rs79945697	19	DPP9	C	T	0.01056	0.09906
rs75191837	19	DPP9	C	G	0.002273	0.07547
rs114625537	19	DPP9	T	G	0.01056	0.09434
rs60431156	3	FYCO1	T	G	0.01559	0.1038
rs564601460	3	FYCO1	A	G	0.001949	0.04245
rs146554934	3	FYCO1	CT	C	0.002111	0.04245
rs114548859	3	FYCO1	A	G	0.002111	0.04245
rs141155944	3	FYCO1	A	G	0.001949	0.04245
rs150785981	3	FYCO1	A	G	0.001949	0.04245
rs140002692	3	FYCO1	T	C	0.000812	0.03774
rs77896301	3	FYCO1	A	G	0.002111	0.04245
rs75726990	3	FYCO1	A	G	0.002111	0.04245
rs145828326	3	FYCO1	T	A	0.000812	0.03774
rs181518477	3	FYCO1	C	G	0.001949	0.04245
rs140228956	3	FYCO1	T	C	0.001949	0.04245
rs189847748	3	FYCO1	T	G	0.001949	0.04245
rs141064206	3	FYCO1	G	C	0	0.02358
rs141476300	3	FYCO1	T	C	0	0.02358
rs7619256	3	FYCO1	C	T	0.03264	0.1934
rs3947589	3	FYCO1	G	T	0.06772	0.2406
rs144511372	21	IFNAR2	C	T	0	0.0283
rs61732395	12	OAS3	T	C	0.001462	0.03774
rs184655598	3	SLC6A20	A	G	0	0.03302
rs35018800	19	TYK2	A	G	0.002761	0.06132
rs55882956	19	TYK2	T	C	0.0203	0.1415
rs569981396	9	ABO	A	C	0	0.004717
rs10901251	9	ABO	A	G	0.1431	0.3208
rs34266669	9	ABO	T	C	0.05278	0.1274
rs199969472	9	ABO	C	G	0.05278	0.1274
rs35184739	9	ABO	C	G	0.05261	0.1274
rs7849280	9	ABO	T	C	0.05294	0.1274
rs9411475	9	ABO	C	T	0.04449	0.1179
rs13291798	9	ABO	G	A	0.0354	0.1085
rs34085694	9	ABO	T	C	0.06073	0.1792
rs4962113	9	ABO	AT	A	0.4209	0.3349

rs111590440	9	ABO	T	C	0.01104	0.0283
rs73660468	9	ABO	C	T	0.008282	0.04717
rs7870156	9	ABO	C	T	0.01023	0.04245
rs62574565	9	ABO	T	C	0.4638	0.5613
rs58081338	9	ABO	G	C	0.4729	0.6274
rs62574567	9	ABO	T	C	0.4729	0.6274
rs60484807	9	ABO	G	A	0.4688	0.3255
rs12554580	9	ABO	A	G	0.4688	0.3302
rs12554336	9	ABO	A	T	0.4726	0.6274
rs12554339	9	ABO	G	T	0.4657	0.5755
rs10901253	9	ABO	G	A	0.4726	0.6274
rs10751502	9	ABO	A	C	0.4657	0.3208
rs11244052	9	ABO	T	C	0.4657	0.5755
rs11244053	9	ABO	T	C	0.4726	0.6274
rs4962114	9	ABO	A	G	0.4726	0.6274
rs4962115	9	ABO	T	C	0.4726	0.6274
rs4962116	9	ABO	A	C	0.4726	0.6274
rs8176757	9	ABO	G	C	0.4696	0.3302
rs111207633	9	ABO	C	G	0.00682	0.0283
rs11244054	9	ABO	T	C	0.3157	0.2264
rs530909128	9	ABO	A	G	0.0003248	0.004717
rs7469795	9	ABO	C	A	0.4701	0.3255
rs7466519	9	ABO	T	C	0.00682	0.0283
rs8176748	9	ABO	C	T	0.4657	0.5802
rs8176745	9	ABO	A	G	0.4662	0.5802
rs201439325	9	ABO	A	C	0.0004872	0.004717
rs56116432	9	ABO	G	T	0.0006496	0.004717
rs557530257	9	ABO	A	G	0	0.004717
rs7855255	9	ABO	A	C	0.06642	0.1085
rs8176735	9	ABO	C	A	0.04027	0.009434
rs8176733	9	ABO	A	G	0.06642	0.1085
rs2073823	9	ABO	A	C	0.06642	0.1085
rs8176730	9	ABO	G	A	0.06642	0.1085
rs8176729	9	ABO	T	C	0.04027	0.009434
rs8176725	9	ABO	T	C	0.0669	0.1085
rs111310794	9	ABO	T	C	0.06155	0.01415
rs45610939	9	ABO	A	G	0.009256	0.02358
rs4962040	9	ABO	G	A	0.2092	0.1509
rs138164693	9	ABO	A	G	0.008769	0.02358
rs8176710	9	ABO	C	T	0.0669	0.01415
rs183228393	9	ABO	A	T	0.008769	0.02358
rs8176702	9	ABO	C	G	0.2082	0.1321
rs8176698	9	ABO	C	G	0.00406	0.01415

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rs8176696	9	ABO	C	G	0.00406	0.01415
rs687621	9	ABO	G	A	0.233	0.3019
rs687289	9	ABO	C	G	0.2319	0.3019
rs150372066	9	ABO	A	G	0.00341	0.0283
rs143174772	9	ABO	G	A	0.009419	0.06604
rs151155628	9	ABO	A	G	0.009419	0.06604
rs8176694	9	ABO	C	T	0.2186	0.1368
rs150326069	9	ABO	G	A	0.0001624	0.004717
rs8176692	9	ABO	C	G	0.01072	0.06604
rs145090216	9	ABO	C	G	0.009419	0.06604
rs8176691	9	ABO	A	G	0.2134	0.1415
rs8176687	9	ABO	T	G	0.06479	0.01415
rs8176684	9	ABO	A	C	0.007957	0.04717
rs147279040	9	ABO	T	C	0.0112	0.0566
rs657152	9	ABO	T	C	0.2436	0.3632
rs8176682	9	ABO	G	A	0.2135	0.1274
rs139568229	9	ABO	A	G	0.01072	0.0566
rs149756392	9	ABO	A	G	0.01072	0.0566
rs145595975	9	ABO	AG	A	0.01072	0.0566
rs148824570	9	ABO	A	G	0.01072	0.0566
rs146458069	9	ABO	C	T	0.01072	0.0566
rs181170522	9	ABO	A	G	0	0.004717
rs141515001	9	ABO	T	C	0.01072	0.0566
rs8176679	9	ABO	A	G	0.06479	0.01415
rs587736740	9	ABO	A	G	0.01072	0.05189
rs138313692	9	ABO	C	T	0.0003248	0.01415
rs149567216	9	ABO	G	T	0.01072	0.0566
rs8176676	9	ABO	C	T	0.0001624	0.009434
rs143159728	9	ABO	C	T	0.01072	0.0566
rs587682147	9	ABO	T	C	0.01072	0.05189
rs587774481	9	ABO	G	A	0.01072	0.05189
rs587635767	9	ABO	T	G	0.01056	0.03774
rs1752339	9	ABO	C	T	0.4602	0.5425
rs148667000	9	ABO	A	G	0.0003248	0.01415
rs142141716	9	ABO	G	T	0.01072	0.05189
rs587716454	9	ABO	G	C	0.01072	0.05189
rs587682443	9	ABO	T	C	0.001949	0.01887
rs587764387	9	ABO	T	C	0.001949	0.01887
rs587637585	9	ABO	T	C	0.001949	0.01887
rs144140881	9	ABO	AG	A	0.01072	0.05189
rs1927315	9	ABO	T	C	0.4602	0.5425
rs514659	9	ABO	T	C	0.2335	0.3679
rs644234	9	ABO	A	G	0.2442	0.4292

rs140796254	9	ABO	G	A	0.01072	0.05189
rs143309559	9	ABO	C	T	0.01072	0.05189
rs643434	9	ABO	C	T	0.2442	0.4292
rs145489959	9	ABO	G	A	0.0003248	0.01415
rs587698906	9	ABO	A	G	0.0004872	0.004717
rs139081859	9	ABO	CA	C	0.0003248	0.01415
rs142956930	9	ABO	T	C	0.006983	0.03302
rs8176668	9	ABO	T	C	0.2278	0.07547
rs574311	9	ABO	A	G	0.4615	0.6415
rs587663040	9	ABO	T	C	0	0.004717
rs488775	9	ABO	C	G	0.4588	0.6415
rs7036642	9	ABO	A	G	0.2116	0.07547
rs8176661	9	ABO	G	A	0.00747	0.05189
rs596141	9	ABO	C	T	0.4682	0.3538
rs587763606	9	ABO	G	A	0.0004872	0.004717
rs587707823	9	ABO	A	C	0.1853	0.3962
rs34357864	9	ABO	T	C	0.2334	0.4245
rs2769071	9	ABO	C	G	0.2321	0.4292
rs7041458	9	ABO	T	C	0.00747	0.05189
rs677355	9	ABO	T	C	0.2321	0.4198
rs676457	9	ABO	G	A	0.2317	0.4151
rs79343853	9	ABO	A	C	0.05083	0.01415
rs527210	9	ABO	T	C	0.2314	0.4009
rs675201	9	ABO	T	G	0.4547	0.5472
rs550057	9	ABO	A	T	0.1652	0.283
rs674302	9	ABO	T	C	0.2332	0.4057
rs551100	9	ABO	T	C	0.4562	0.5519
rs663054	9	ABO	A	G	0.4454	0.5425
rs7046674	9	ABO	C	T	0.2119	0.1226
rs554833	9	ABO	C	T	0.2324	0.4057
rs8176649	9	ABO	C	T	0.209	0.1226
rs660340	9	ABO	C	T	0.2777	0.4575
rs581107	9	ABO	T	C	0.2778	0.4575
rs8176647	9	ABO	A	G	0.06138	0.009434
rs659104	9	ABO	G	A	0.2775	0.4151
rs647800	9	ABO	C	A	0.2882	0.4151
rs473533	9	ABO	A	G	0.2775	0.4151
rs147960974	9	ABO	C	A	0.0001624	0.004717
rs475419	9	ABO	T	C	0.2766	0.4104
rs476410	9	ABO	T	C	0.2775	0.4151
rs645982	9	ABO	C	A	0.2775	0.4151
rs500498	9	ABO	T	C	0.2775	0.4151
rs145218729	9	ABO	C	A	0.0001624	0.004717

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rs8176644	9	ABO	T	C	0.04953	0.01415
rs505922	9	ABO	A	T	0.2283	0.3302
rs507666	9	ABO	C	T	0.1374	0.2453
rs529565	9	ABO	C	T	0.229	0.3349
rs8176641	9	ABO	G	A	0.05992	0.009434
rs532436	9	ABO	C	A	0.1811	0.2406
rs8176639	9	ABO	A	C	0.05992	0.009434
rs8176760	9	ABO	A	G	0.0003248	0.009434
rs3749461	3	CCR2	G	A	0.02842	0.1179
rs3918362	3	CCR2	A	G	0.02842	0.1179
rs3092963	3	CCR2	T	C	0.2892	0.4198
rs3918365	3	CCR2	A	G	0.02842	0.1179
rs1799865	3	CCR2	AAT	A	0.2892	0.4198
rs3138042	3	CCR2	C	T	0.2892	0.4198
rs140253702	3	CCR2	C	A	0.0003248	0.004717
rs1860264	3	CCR9	G	A	0.2621	0.4528
rs186153536	3	CCR9	T	C	0.0003248	0.004717
rs74808020	3	CCR9	C	T	0.0354	0.08491
rs530595037	3	CCR9	A	G	0.0003248	0.004717
rs552329766	3	CCR9	T	C	0.0003248	0.004717
rs12631321	3	CCR9	T	A	0.0354	0.08491
rs150667470	3	CCR9	C	G	0.0004872	0.004717
rs6441930	3	CCR9	G	A	0.2621	0.4528
rs138421181	3	CCR9	T	C	0	0.004717
rs115004584	3	CCR9	C	T	0.0003248	0.004717
rs78414305	3	CCR9	A	G	0.0003248	0.004717
rs115826613	3	CCR9	A	G	0	0.004717
rs74739895	3	CCR9	C	T	0.0003248	0.004717
rs75018424	3	CCR9	C	G	0.03524	0.08491
rs78044818	3	CCR9	T	G	0.0003248	0.004717
rs74337052	3	CCR9	A	G	0	0.004717
rs7636844	3	CCR9	A	G	0.1406	0.08491
rs2286486	3	CCR9	C	A	0.1406	0.08019
rs116350857	3	CCR9	C	T	0	0.004717
rs6441931	3	CCR9	G	A	0.1406	0.08491
rs34338823	3	CCR9	A	T	0.04141	0.01415
rs115227401	3	CCR9	C	T	0.0003248	0.004717
rs76478208	3	CCR9	G	A	0.0003248	0.004717
rs6783694	3	CCR9	A	ATTC	0.0003248	0.004717
rs6441932	3	CCR9	G	A	0.272	0.4481
rs116264461	3	CCR9	T	C	0.0003248	0.004717
rs77676459	3	CCR9	C	A	0.0003248	0.004717
rs114406614	3	CCR9	C	T	0	0.004717

rs144180015	3	CCR9	A	G	0.0003248	0.004717
rs9862611	3	CCR9	G	T	0.2714	0.4481
rs71325091	3	CCR9	CG	C	0.04141	0.01415
rs6441933	3	CCR9	A	G	0.272	0.4481
rs141167007	3	CCR9	A	G	0	0.004717
rs57527954	3	CCR9	A	G	0.272	0.4481
rs9834860	3	CCR9	A	G	0.272	0.4481
rs116207980	3	CCR9	AT	A	0	0.004717
rs12638201	3	CCR9	AT	A	0.03037	0.07547
rs56058226	3	CCR9	C	T	0.3823	0.3113
rs75078036	3	CCR9	G	A	0.02939	0.07075
rs9855205	3	CCR9	A	G	0.05213	0.009434
rs3764864	3	CCR9	A	T	0.07373	0.03774
rs6782814	3	CCR9	G	A	0.08672	0.2264
rs9823523	3	CCR9	A	C	0.05602	0.02358
rs3774642	3	CCR9	A	G	0.02923	0.07547
rs3774641	3	CCR9	C	T	0.1172	0.05189
rs1488371	3	CCR9	G	A	0.2761	0.4434
rs147753307	3	CCR9	C	T	0.001624	0.01415
rs2236938	3	CCR9	A	G	0.1159	0.25
rs17764980	3	CCR9	C	T	0.04157	0.01415
rs79663567	3	CCR9	T	G	0	0.004717
rs73830609	3	CCR9	A	C	0.002436	0.01415
rs17714101	3	CCR9	T	A	0.04157	0.01415
rs1985356	3	CCR9	C	T	0.1567	0.3538
rs1985463	3	CCR9	C	T	0.207	0.3821
rs59817490	3	CCR9	G	A	0.003897	0.01415
rs7614342	3	CCR9	C	G	0.1565	0.3538
rs79587259	3	CCR9	T	C	0.02907	0.07075
rs61751653	3	CCR9	G	A	0.001786	0.009434
rs74718475	3	CCR9	C	A	0	0.004717
rs73830610	3	CCR9	A	T	0.003897	0.01415
rs17714228	3	CCR9	T	C	0.04157	0.01415
rs875891	3	CCR9	G	T	0.1554	0.3538
rs875890	3	CCR9	T	C	0.2069	0.3821
rs62245098	3	CCR9	T	C	0.1565	0.3585
rs28595837	3	CCR9	A	G	0.02225	0.05189
rs9881306	3	CCR9	A	G	0.05213	0.009434
rs28501674	3	CCR9	G	A	0.1552	0.3538
rs61565453	3	CCR9	A	T	0.1565	0.3585
rs71325092	3	CCR9	G	A	0.04157	0.01415
rs79179998	3	CCR9	A	C	0.05213	0.009434
rs57295094	3	CCR9	G	C	0.1549	0.3538

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rs6791859	3	CCR9	G	A	0.1609	0.3443
rs4683147	3	CCR9	A	G	0.3966	0.566
rs74945326	3	CCR9	C	T	0.04108	0.009434
rs62245101	3	CCR9	G	A	0.1146	0.2311
rs62245102	3	CCR9	A	C	0.1593	0.3396
rs7638236	3	CXCR6	T	C	0.019	0.04245
rs4535265	3	CXCR6	T	C	0.4108	0.5094
rs9869848	3	CXCR6	A	G	0.1111	0.1887
rs9875616	3	CXCR6	A	G	0.109	0.1887
rs13091979	3	CXCR6	A	G	0.4105	0.5094
rs13091821	3	CXCR6	A	G	0.4105	0.5094
rs17078449	3	CXCR6	C	T	0.1471	0.08019
rs936938	3	CXCR6	A	G	0.4074	0.5
rs2171531	3	CXCR6	T	C	0.04579	0.009434
rs17078454	3	CXCR6	C	T	0.1466	0.08019
rs57204020	3	CXCR6	T	C	0.1465	0.08019
rs7634640	3	CXCR6	G	A	0.07616	0.1651
rs55920693	3	CXCR6	T	G	0.04579	0.009434
rs3774640	3	CXCR6	G	A	0.1465	0.08019
rs3774639	3	CXCR6	A	G	0.4105	0.5094
rs3774638	3	CXCR6	A	G	0.1465	0.08019
rs7627147	3	CXCR6	T	C	0.01851	0.04245
rs2234350	3	CXCR6	T	C	0.1259	0.1887
rs2234351	3	CXCR6	T	A	0.1462	0.08019
rs191811571	3	CXCR6	C	T	0.0001624	0.004717
rs3774635	3	CXCR6	A	C	0.4074	0.5
rs936939	3	CXCR6	C	T	0.1465	0.08019
rs143980719	3	CXCR6	T	C	0.001949	0.01415
rs2234355	3	CXCR6	A	G	0.02533	0.06132
rs17078464	3	CXCR6	A	G	0.01835	0.04245
rs2054866	3	CXCR6	G	A	0.4074	0.5
rs58442576	3	CXCR6	C	T	0.01851	0.04245
rs4683156	3	CXCR6	T	C	0.4105	0.5094
rs56239523	3	CXCR6	T	C	0.01851	0.04245
rs58050797	3	CXCR6	C	A	0.01835	0.04245
rs1994488	3	CXCR6	T	C	0.4074	0.5
rs35501575	3	CXCR6	A	G	0.04596	0.009434
rs1552489	3	CXCR6	C	A	0.4074	0.5
rs8107316	19	DPP9	A	G	0.2243	0.3066
rs72977966	19	DPP9	A	G	0	0.004717
rs8105807	19	DPP9	C	G	0.3037	0.3679
rs10421782	19	DPP9	A	C	0.3027	0.3679
rs2885734	19	DPP9	A	T	0.3037	0.3679

rs114346470	19	DPP9	T	C	0.0001624	0.004717
rs34136596	19	DPP9	A	G	0.0006496	0.004717
rs113439332	19	DPP9	A	T	0.0328	0.1321
rs113094386	19	DPP9	AC	A	0.005684	0.01887
rs2277735	19	DPP9	A	G	0.2947	0.3821
rs60199752	19	DPP9	C	T	0.2241	0.3066
rs35408525	19	DPP9	G	A	0.0006496	0.004717
rs11671605	19	DPP9	C	T	0.2241	0.3066
rs4401152	19	DPP9	T	A	0.2244	0.3019
rs72977989	19	DPP9	G	T	0.2241	0.3019
rs139518006	19	DPP9	G	A	0.0001624	0.004717
rs11670257	19	DPP9	C	T	0.3514	0.5
rs2277733	19	DPP9	C	A	0.3365	0.25
rs732631	19	DPP9	T	A	0.2756	0.3396
rs2006231	19	DPP9	A	T	0.4292	0.3443
rs2109069	19	DPP9	T	A	0.2462	0.3208
rs2109070	19	DPP9	T	A	0.2446	0.3208
rs3833278	19	DPP9	A	G	0.3909	0.3208
rs1467941	19	DPP9	G	A	0.3988	0.3255
rs1467942	19	DPP9	G	A	0.404	0.3349
rs56945978	19	DPP9	C	G	0.4256	0.3443
rs758510	19	DPP9	C	G	0.3474	0.2783
rs2277732	19	DPP9	C	T	0.1504	0.2925
rs10420007	19	DPP9	G	A	0.3953	0.3208
rs10420225	19	DPP9	T	C	0.4292	0.3443
rs530191556	19	DPP9	T	C	0.3964	0.3255
rs4683148	3	FYCO1	T	C	0.4112	0.5377
rs2171530	3	FYCO1	T	C	0.2196	0.316
rs9831315	3	FYCO1	G	A	0.4055	0.5283
rs560966886	3	FYCO1	T	C	0.0001624	0.004717
rs72622922	3	FYCO1	T	C	0.0003248	0.01415
rs185588322	3	FYCO1	T	C	0.001624	0.01415
rs7129	3	FYCO1	T	C	0.4058	0.5283
rs1994492	3	FYCO1	T	G	0.04222	0.009434
rs1994493	3	FYCO1	T	G	0.04222	0.009434
rs3796373	3	FYCO1	T	G	0.2212	0.3208
rs3733103	3	FYCO1	A	G	0.4112	0.533
rs75928798	3	FYCO1	A	G	0.04206	0.009434
rs2291470	3	FYCO1	A	G	0.4057	0.5283
rs11130078	3	FYCO1	A	G	0.2204	0.3349
rs148655132	3	FYCO1	C	G	0.001624	0.01415
rs11707672	3	FYCO1	C	G	0.0112	0.04245
rs6800954	3	FYCO1	T	C	0.1502	0.09906

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rs140100519	3	FYCO1	T	C	0.001624	0.01415
rs2248228	3	FYCO1	T	G	0.4094	0.5094
rs60237998	3	FYCO1	C	T	0.1512	0.08962
rs60110056	3	FYCO1	C	G	0.01543	0.04245
rs58491168	3	FYCO1	T	A	0.019	0.04245
rs4683149	3	FYCO1	C	T	0.4052	0.5047
rs2373087	3	FYCO1	A	G	0.04417	0.009434
rs7631809	3	FYCO1	A	G	0.1504	0.08962
rs2373088	3	FYCO1	A	G	0.06414	0.1557
rs62245106	3	FYCO1	A	G	0.113	0.0566
rs12638598	3	FYCO1	G	C	0.207	0.1132
rs35831747	3	FYCO1	T	C	0.04417	0.009434
rs77709797	3	FYCO1	T	C	0.1166	0.0566
rs1532070	3	FYCO1	A	G	0.06431	0.1557
rs6778225	3	FYCO1	A	G	0.1484	0.08491
rs13099120	3	FYCO1	A	T	0.04417	0.009434
rs6778324	3	FYCO1	T	C	0.1483	0.08491
rs60779624	3	FYCO1	G	A	0.1484	0.08491
rs190039371	3	FYCO1	T	C	0.1166	0.0566
rs41289614	3	FYCO1	A	T	0.03459	0.009434
rs35477280	3	FYCO1	C	G	0.04417	0.009434
rs4683152	3	FYCO1	A	C	0.4094	0.5094
rs13066516	3	FYCO1	A	G	0.04417	0.009434
rs200582580	3	FYCO1	C	T	0.04401	0.009434
rs1072755	3	FYCO1	T	C	0.4055	0.5
rs77902290	3	FYCO1	C	T	0.04417	0.009434
rs532777636	3	FYCO1	G	A	0.04579	0.009434
rs62242787	3	FYCO1	A	G	0.1543	0.07547
rs17078471	3	FYCO1	C	T	0.002111	0.009434
rs35257780	3	FYCO1	T	C	0.04628	0.009434
rs34000569	3	FYCO1	C	T	0.04628	0.009434
rs34324101	3	FYCO1	T	C	0.04628	0.009434
rs13069079	3	FYCO1	T	C	0.04628	0.009434
rs34849862	3	FYCO1	T	C	0.04628	0.009434
rs62242788	3	FYCO1	T	C	0.1263	0.0566
rs35209528	3	FYCO1	T	C	0.04628	0.009434
rs75918913	3	FYCO1	T	C	0.03995	0.009434
rs57036895	3	FYCO1	G	A	0.01543	0.03774
rs13079869	3	FYCO1	A	G	0.04677	0.009434
rs33910087	3	FYCO1	A	G	0.04693	0.009434
rs3796376	3	FYCO1	A	G	0.1354	0.0566
rs17215008	3	FYCO1	C	T	0.04644	0.009434
rs71325098	3	FYCO1	G	A	0.04644	0.009434

rs71325100	3	FYCO1	C	T	0.04644	0.009434
rs41289622	3	FYCO1	T	C	0.04644	0.009434
rs11130081	3	FYCO1	A	G	0.002111	0.009434
rs12639598	3	FYCO1	A	G	0.405	0.5047
rs144873702	3	FYCO1	G	A	0.000812	0.01415
rs751552	3	FYCO1	A	G	0.4053	0.5142
rs751553	3	FYCO1	T	C	0.4053	0.5142
rs904634	3	FYCO1	T	C	0.08379	0.1604
rs13066062	3	FYCO1	C	T	0.04644	0.009434
rs6781668	3	FYCO1	G	A	0.1351	0.0566
rs9844821	3	FYCO1	A	G	0.07161	0.1509
rs57228214	3	FYCO1	T	C	0.02192	0.05189
rs9849771	3	FYCO1	G	A	0.09337	0.1604
rs9849818	3	FYCO1	C	T	0.08396	0.1604
rs4682801	3	FYCO1	A	G	0.1291	0.2547
rs35537559	3	FYCO1	T	C	0.1971	0.09434
rs59767267	3	FYCO1	A	G	0.1314	0.0566
rs3821883	3	FYCO1	G	A	0.1346	0.0566
rs36122610	3	FYCO1	G	A	0.04628	0.009434
rs138017682	3	FYCO1	T	C	0.0006496	0.009434
rs34442130	3	FYCO1	T	C	0.04628	0.009434
rs931704	3	FYCO1	T	C	0.4039	0.4764
rs4683159	3	FYCO1	A	G	0.203	0.316
rs13075758	3	FYCO1	T	A	0.04628	0.009434
rs11130082	3	FYCO1	T	G	0.2035	0.3208
rs6802312	3	FYCO1	T	C	0.1159	0.2547
rs56972507	3	FYCO1	T	C	0.02144	0.04717
rs3733097	3	FYCO1	A	G	0.4058	0.5189
rs17078495	3	FYCO1	T	C	0.4058	0.5189
rs13086858	3	FYCO1	C	G	0.2035	0.3208
rs139886125	3	FYCO1	G	A	0.000812	0.01415
rs737452	3	FYCO1	G	C	0.4058	0.5189
rs730983	3	FYCO1	G	A	0.4039	0.4906
rs59226168	3	FYCO1	T	C	0.1898	0.1038
rs67044455	3	FYCO1	T	C	0.4058	0.533
rs62242796	3	FYCO1	C	T	0.1898	0.1038
rs7653682	3	FYCO1	A	T	0.1159	0.2877
rs72891712	3	FYCO1	A	T	0.02257	0.07547
rs1873000	3	FYCO1	A	G	0.203	0.3538
rs7628447	3	FYCO1	G	T	0.2035	0.3538
rs12635657	3	FYCO1	T	G	0.4057	0.5283
rs2133660	3	FYCO1	G	A	0.2371	0.3774
rs146216196	3	FYCO1	T	C	0.001786	0.01887

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rs139044419	3	FYCO1	A	G	0.001786	0.01887
rs1846615	3	FYCO1	C	T	0.2371	0.3774
rs1873001	3	FYCO1	C	T	0.2371	0.3774
rs142154067	3	FYCO1	AT	A	0.001786	0.01887
rs146285477	3	FYCO1	C	T	0.04628	0.009434
rs182171107	3	FYCO1	C	G	0.0006496	0.009434
rs1500003	3	FYCO1	A	G	0.2371	0.3774
rs79067698	3	FYCO1	A	G	0.001786	0.01887
rs1392288	3	FYCO1	C	G	0.1673	0.3349
rs17330872	3	FYCO1	C	T	0.04628	0.009434
rs188114046	3	FYCO1	A	G	0.001786	0.01887
rs142571332	3	FYCO1	G	C	0.04579	0.009434
rs71327003	3	FYCO1	G	T	0.04612	0.009434
rs188401375	21	IFNAR2	T	C	0.0006496	0.004717
rs17860118	21	IFNAR2	G	A	0.01754	0.08962
rs566208153	21	IFNAR2	C	T	0.02907	0.0566
rs13052526	21	IFNAR2	G	A	0.01608	0.04717
rs574424283	21	IFNAR2	A	C	0.4208	0.3491
rs2248420	21	IFNAR2	A	G	0.4227	0.3443
rs189110596	21	IFNAR2	T	C	0.002273	0.01415
rs7509997	21	IFNAR2	A	C	0.02452	0.0566
rs17860142	21	IFNAR2	C	A	0.4229	0.3443
rs8130779	21	IFNAR2	A	G	0.02631	0.0566
rs9974669	21	IFNAR2	G	A	0.02631	0.0566
rs570824030	21	IFNAR2	C	T	0.02663	0.0566
rs3153	21	IFNAR2	A	G	0.4227	0.3443
rs1187	21	IFNAR2	T	G	0.0004872	0.004717
rs12482014	21	IFNAR2	T	C	0.4229	0.3443
rs17860160	21	IFNAR2	A	G	0.01608	0.04717
rs12482193	21	IFNAR2	G	A	0.4285	0.3491
rs17860165	21	IFNAR2	T	C	0.4229	0.3443
rs117489085	21	IFNAR2	T	C	0.0003248	0.004717
rs545411453	21	IFNAR2	G	T	0.0003248	0.004717
rs8128785	21	IFNAR2	G	C	0.03215	0.0566
rs2229207	21	IFNAR2	T	C	0.01803	0.06132
rs1051393	21	IFNAR2	G	A	0.4329	0.316
rs62226154	21	IFNAR2	C	T	0.02436	0.04717
rs62226157	21	IFNAR2	G	C	0.4112	0.3396
rs144683777	21	IFNAR2	T	C	0.000812	0.01887
rs10211925	21	IFNAR2	C	A	0.0229	0.04717
rs17860183	21	IFNAR2	A	T	0.1669	0.04245
rs2834159	21	IFNAR2	C	G	0.02079	0.04245
rs12053666	21	IFNAR2	G	A	0.4104	0.2925

rs2834160	21	IFNAR2	G	C	0.01689	0.04245
rs2834162	21	IFNAR2	T	C	0.01786	0.04245
rs17860211	21	IFNAR2	A	G	0.01786	0.04245
rs2073362	21	IFNAR2	T	C	0.01689	0.06132
rs17860220	21	IFNAR2	T	C	0.01673	0.06132
rs147496374	21	IFNAR2	A	C	0.00341	0.02358
rs4817555	21	IFNAR2	T	C	0.04027	0.1226
rs59738559	21	IFNAR2	G	C	0.04108	0.1226
rs2834166	21	IFNAR2	C	A	0.3357	0.2547
rs11911133	21	IFNAR2	G	A	0.4732	0.3774
rs181597872	21	IFNAR2	C	T	0.0003248	0.004717
rs2300371	21	IFNAR2	A	G	0.4048	0.2925
rs1058961	3	LZTFL1	C	T	0.2408	0.4481
rs35624553	3	LZTFL1	G	C	0.03638	0.009434
rs139540257	3	LZTFL1	T	C	0.007145	0.02358
rs2064061	3	LZTFL1	T	G	0.3459	0.5189
rs67959919	3	LZTFL1	A	T	0.03638	0.009434
rs148112944	3	LZTFL1	G	T	0	0.004717
rs11385942	3	LZTFL1	T	C	0.03832	0.009434
rs11130077	3	LZTFL1	A	G	0.2311	0.3019
rs6796097	3	LZTFL1	A	G	0.001299	0.009434
rs190577088	3	LZTFL1	T	C	0.0004872	0.004717
rs35508621	3	LZTFL1	A	G	0.03459	0.004717
rs758389	3	LZTFL1	T	C	0.0009743	0.009434
rs34288077	3	LZTFL1	T	C	0.03443	0.004717
rs141146648	3	LZTFL1	A	G	0.0151	0.0566
rs150719194	3	LZTFL1	C	T	0.0001624	0.004717
rs35081325	3	LZTFL1	G	A	0.03443	0.009434
rs35731912	3	LZTFL1	C	T	0.03459	0.009434
rs17078371	3	LZTFL1	C	G	0.001462	0.009434
rs112101762	3	LZTFL1	A	G	0.001137	0.009434
rs113181700	3	LZTFL1	T	C	0.001137	0.009434
rs4683146	3	LZTFL1	T	G	0.3344	0.434
rs34326463	3	LZTFL1	A	G	0.03426	0.004717
rs73064425	3	LZTFL1	T	C	0.03475	0.009434
rs138727962	3	LZTFL1	T	C	0.0001624	0.004717
rs184214751	3	LZTFL1	T	G	0.0009743	0.009434
rs71325089	3	LZTFL1	A	G	0.02907	0.004717
rs61185149	3	LZTFL1	T	C	0.008931	0.02358
rs13081482	3	LZTFL1	G	A	0.03491	0.009434
rs75826707	3	LZTFL1	G	A	0.003248	0.01415
rs9871972	3	LZTFL1	T	C	0.3407	0.5
rs140227473	3	LZTFL1	A	G	0.001624	0.009434

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rs75507082	3	LZTFL1	A	G	0.02907	0
rs79657519	3	LZTFL1	C	A	0.001624	0.009434
rs148060386	3	LZTFL1	A	G	0.0001624	0.004717
rs2191031	3	LZTFL1	G	C	0.1161	0.0566
rs28607988	3	LZTFL1	T	C	0.04498	0.01415
rs77009309	3	LZTFL1	A	G	0.02972	0.1132
rs12639224	3	LZTFL1	A	G	0.138	0.2075
rs12639252	3	LZTFL1	T	A	0.0004872	0.004717
rs2373086	3	LZTFL1	T	G	0.02842	0.1226
rs112212287	3	LZTFL1	T	C	0.01624	0.06132
rs7614687	3	LZTFL1	A	G	0.01072	0.0566
rs57319220	3	LZTFL1	G	A	0.0544	0.02358
rs34518147	3	LZTFL1	G	C	0.04125	0.01415
rs9852270	3	LZTFL1	T	C	0.2621	0.4528
rs560506883	3	LZTFL1	T	C	0.0001624	0.004717
rs77000397	3	LZTFL1	G	A	0	0.004717
rs114742054	3	LZTFL1	A	G	0	0.004717
rs12633699	3	LZTFL1	A	G	0.05505	0.01415
rs34847985	3	LZTFL1	A	G	0.2131	0.3726
rs34549672	3	LZTFL1	C	G	0.2811	0.4434
rs75442536	3	LZTFL1	A	G	0.02273	0.0566
rs59451221	3	LZTFL1	T	C	0.06041	0.1745
rs9836836	3	LZTFL1	G	A	0.1341	0.0566
rs35280891	3	LZTFL1	T	C	0.04157	0.009434
rs181980885	3	LZTFL1	A	G	0.001624	0.01415
rs186530132	3	LZTFL1	T	C	0.001624	0.01415
rs112707117	3	LZTFL1	G	A	0.001624	0.01415
rs34068335	3	LZTFL1	C	A	0.04206	0.009434
rs558702333	3	NRBF2P2	A	T	0.0006496	0.004717
rs35334665	3	NRBF2P2	T	C	0.04726	0.009434
rs115932896	3	NRBF2P2	T	A	0.001299	0.01415
rs71327009	3	NRBF2P2	A	G	0.04726	0.009434
rs189659509	3	NRBF2P2	C	T	0.001299	0.009434
rs35161099	3	NRBF2P2	A	G	0.04726	0.009434
rs12054287	3	NRBF2P2	A	G	0.1323	0.05189
rs60080146	3	NRBF2P2	T	C	0.0177	0.03774
rs59676542	3	NRBF2P2	C	T	0.01819	0.03774
rs58035200	3	NRBF2P2	C	T	0.1958	0.1085
rs7623460	3	NRBF2P2	C	T	0.2658	0.1934
rs71327010	3	NRBF2P2	T	C	0.04726	0.009434
rs7623476	3	NRBF2P2	G	A	0.1957	0.1085
rs7956880	12	OAS1	A	G	0.1728	0.08962
rs10744785	12	OAS1	TC	T	0.2512	0.1557

rs4766662	12	OAS1	C	A	0.2407	0.1415
rs2240190	12	OAS1	T	G	0.03491	0.1274
rs34137742	12	OAS1	A	G	0.07616	0.1226
rs45542343	12	OAS1	G	A	0.03215	0.1038
rs75344264	12	OAS1	T	C	0.1082	0.184
rs2057778	12	OAS1	C	T	0.1772	0.1179
rs2285934	12	OAS1	A	C	0.2459	0.1509
rs4767023	12	OAS1	T	C	0.2621	0.1604
rs45495393	12	OAS1	C	T	0.07567	0.1274
rs56006713	12	OAS1	A	T	0.0009743	0.009434
rs12423440	12	OAS1	T	C	0.0492	0.08491
rs10774671	**12**	**OAS1**	C	A	**0.2748**	**0.184**
rs1131476	12	OAS1	T	C	0.1806	0.1132
rs2660	**12**	**OAS1**	T	C	**0.1806**	**0.1085**
rs7135577	12	OAS1	T	G	0.1806	0.1226
rs4767024	12	OAS1	T	C	0.1801	0.1226
rs4767025	12	OAS1	A	G	0.1801	0.1226
rs4767026	12	OAS1	A	G	0.1807	0.1226
rs4767027	12	OAS1	A	G	0.1801	0.1226
rs4767028	12	OAS1	A	G	0.1806	0.1226
rs4767029	12	OAS1	C	G	0.1801	0.1226
rs75628555	12	OAS1	C	T	0.04758	0.08491
rs4767030	12	OAS1	T	C	0.1806	0.1226
rs10850092	12	OAS1	G	A	0.1801	0.1226
rs6489864	12	OAS1	A	G	0.1801	0.1226
rs6489865	12	OAS1	G	T	0.1801	0.1226
rs10850093	12	OAS1	C	G	0.1801	0.1226
rs10850094	12	OAS1	C	T	0.1801	0.1226
rs10850095	12	OAS1	G	A	0.1801	0.1226
rs10774672	12	OAS1	C	T	0.1807	0.1226
rs10850096	12	OAS1	G	C	0.1801	0.1226
rs10850097	12	OAS1	C	T	0.1981	0.1415
rs10774673	12	OAS1	G	A	0.1801	0.1226
rs10774674	12	OAS1	C	G	0.1801	0.1226
rs3803057	12	OAS1	A	G	0.1312	0.06132
rs1298962	12	OAS2	T	G	0.1702	0.09906
rs1298301	12	OAS2	A	G	0.1632	0.2453
rs1293774	12	OAS2	A	T	0.1702	0.09906
rs117666908	12	OAS2	A	G	0.03361	0.06604
rs1293773	12	OAS2	A	AC	0.1629	0.2406
rs1293772	12	OAS2	T	G	0.1819	0.08019
rs531734809	12	OAS2	C	G	0	0.004717
rs1293771	12	OAS2	T	C	0.1819	0.08019

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rs1293770	12	OAS2	T	C	0.163	0.2358
rs12301619	12	OAS2	C	T	0.003735	0.01415
rs1293768	12	OAS2	A	G	0.1798	0.08019
rs150169230	12	OAS2	T	A	0.0001624	0.004717
rs1293767	12	OAS2	A	G	0.1259	0.06132
rs1293766	12	OAS2	A	G	0.1575	0.2311
rs1293765	12	OAS2	C	A	0.1645	0.07547
rs1293764	12	OAS2	A	G	0.1639	0.07547
rs1293763	12	OAS2	G	A	0.1523	0.2217
rs11066464	12	OAS2	A	G	0.2085	0.2736
rs757402	12	OAS2	G	A	0.1366	0.0566
rs200629605	12	OAS2	A	T	0.02744	0.06132
rs7975318	12	OAS2	G	C	0.1682	0.2311
rs757401	12	OAS2	AAT	A	0.1366	0.0566
rs557969944	12	OAS2	C	T	0	0.004717
rs5800979	12	OAS2	A	T	0.3746	0.5047
rs34886194	12	OAS2	G	A	0.2075	0.2689
rs1293762	12	OAS2	A	C	0.1845	0.08962
rs1293760	12	OAS2	C	T	0.1846	0.08962
rs1293759	12	OAS2	T	G	0.1177	0.04245
rs1293758	12	OAS2	A	G	0.2949	0.1038
rs1298961	12	OAS2	A	T	0.3303	0.1179
rs1635142	12	OAS2	A	G	0.1189	0.04245
rs1293757	12	OAS2	T	C	0.1189	0.04245
rs1293756	12	OAS2	A	G	0.1189	0.04245
rs1293754	12	OAS2	G	A	0.1192	0.04245
rs1293753	12	OAS2	T	G	0.1184	0.04245
rs1293752	12	OAS2	A	G	0.1315	0.04717
rs1293751	12	OAS2	T	C	0.1315	0.04717
rs2525848	12	OAS2	C	A	0.1315	0.04717
rs1296061	12	OAS2	A	G	0.1315	0.04717
rs2072137	12	OAS2	C	T	0.4147	0.6038
rs1293749	12	OAS2	T	C	0.134	0.05189
rs2003480	12	OAS2	C	T	0.4367	0.283
rs1293748	12	OAS2	T	A	0.134	0.05189
rs2240185	12	OAS2	T	A	0.4834	0.6698
rs929291	12	OAS2	A	G	0.1497	0.07547
rs1293747	12	OAS2	A	G	0.2986	0.2217
rs1293746	12	OAS2	A	G	0.285	0.2075
rs16942430	12	OAS2	T	C	0.05797	0.01887
rs1293745	12	OAS2	T	C	0.2858	0.2028
rs1293744	12	OAS2	C	G	0.2858	0.2028
rs1293743	12	OAS2	A	G	0.1613	0.06604

rs15895	12	OAS2	T	C	0.1624	0.06604
rs574059077	12	OAS2	A	G	0	0.004717
rs13311	12	OAS2	T	C	0.4721	0.684
rs1058480	12	OAS2	T	C	0.1626	0.06604
rs3815178	12	OAS3	T	C	0.1884	0.1226
rs1859331	12	OAS3	C	T	0.2756	0.1462
rs1859330	12	OAS3	T	C	0.2762	0.1462
rs1859329	12	OAS3	T	C	0.1884	0.1226
rs7299132	12	OAS3	T	C	0.1884	0.1226
rs6489879	12	OAS3	G	C	0.1884	0.1226
rs4238033	12	OAS3	C	T	0.1884	0.1226
rs4767041	12	OAS3	T	C	0.1954	0.1321
rs10850102	12	OAS3	T	C	0.1177	0.2642
rs7955267	12	OAS3	T	C	0.1954	0.1321
rs7311182	12	OAS3	T	C	0.188	0.1226
rs73433165	12	OAS3	A	G	0.0001624	0.004717
rs10735079	12	OAS3	G	T	0.195	0.1274
rs6489880	12	OAS3	T	G	0.1884	0.1226
rs7980275	12	OAS3	T	C	0.1949	0.1321
rs7977345	12	OAS3	A	G	0.1954	0.1321
rs6489881	12	OAS3	A	G	0.1954	0.1321
rs6489882	12	OAS3	T	C	0.1884	0.1226
rs7131998	12	OAS3	A	G	0.1853	0.1274
rs2269899	12	OAS3	A	G	0.1924	0.1368
rs11066456	12	OAS3	C	T	0.1452	0.2075
rs12427406	12	OAS3	C	T	0.126	0.1887
rs10850104	12	OAS3	A	C	0.3358	0.4292
rs11066457	12	OAS3	T	C	0.3688	0.4528
rs34647135	12	OAS3	A	G	0.3358	0.4292
rs7965570	12	OAS3	A	C	0.1332	0.2123
rs1974518	12	OAS3	G	A	0.4003	0.4764
rs71465868	12	OAS3	C	T	0.0328	0
rs12824584	12	OAS3	C	T	0.0006496	0.004717
rs146042277	12	OAS3	T	C	0.0004872	0.004717
rs10850105	12	OAS3	G	A	0.1475	0.08962
rs7310667	12	OAS3	G	A	0.1665	0.1132
rs4767042	12	OAS3	A	G	0.4003	0.4764
rs78069989	12	OAS3	C	G	0.00341	0.01887
rs78220999	12	OAS3	T	C	0.1468	0.08962
rs4435062	12	OAS3	A	C	0.3709	0.4481
rs150390228	12	OAS3	T	C	0.1468	0.08962
rs10744789	12	OAS3	G	A	0.1468	0.08962
rs140303054	12	OAS3	G	C	0.0004872	0.004717

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rs57771566	12	OAS3	C	G	0.002923	0.01415
rs138971703	12	OAS3	G	A	0.002436	0.01415
rs4238034	12	OAS3	A	C	0.147	0.08962
rs4766677	12	OAS3	A	G	0.4021	0.4764
rs4766678	12	OAS3	G	A	0.4029	0.4858
rs58603713	12	OAS3	T	C	0.002923	0.01415
rs2158393	12	OAS3	T	C	0.3707	0.4481
rs2072136	12	OAS3	T	G	0.3704	0.4481
rs2072135	12	OAS3	T	C	0.1466	0.2028
rs60439830	12	OAS3	A	G	0.00341	0.01887
rs55688670	12	OAS3	A	G	0.03556	0.07075
rs45607836	12	OAS3	C	T	0.03556	0.07075
rs4767044	12	OAS3	A	G	0.1174	0.06132
rs2240189	12	OAS3	T	C	0.1565	0.2123
rs1557866	12	OAS3	T	C	0.1172	0.06132
rs45489899	12	OAS3	G	A	0.00341	0.01887
rs3937434	12	OAS3	T	C	0.1174	0.06132
rs2016831	12	OAS3	T	C	0.1174	0.06132
rs11837165	12	OAS3	T	C	0.0003248	0.004717
rs757405	12	OAS3	T	G	0.1179	0.0566
rs73422036	12	OAS3	A	G	0.003248	0.01887
rs45620632	12	OAS3	T	C	0.001624	0.0283
rs11837367	12	OAS3	G	T	0.003248	0.01887
rs2010604	12	OAS3	C	T	0.1387	0.08491
rs739903	12	OAS3	A	G	0.1772	0.2358
rs2072133	12	OAS3	T	C	0.195	0.2594
rs4767045	12	OAS3	C	G	0.1181	0.05189
rs45583340	12	OAS3	A	C	0.0001624	0.004717
rs75755877	12	OAS3	C	T	0.002923	0.01415
rs10744791	12	OAS3	G	A	0.1181	0.05189
rs73422042	12	OAS3	A	G	0.002923	0.01415
rs7023	12	OAS3	C	T	0.1772	0.2358
rs2251109	3	SLC6A20	T	C	0.2369	0.3538
rs116082988	3	SLC6A20	A	G	0	0.004717
rs17078308	3	SLC6A20	A	G	0.004385	0.01887
rs144151884	3	SLC6A20	C	A	0	0.004717
rs116590098	3	SLC6A20	A	G	0	0.004717
rs2531750	3	SLC6A20	A	G	0.2363	0.1509
rs7621856	3	SLC6A20	A	G	0.4756	0.3821
rs2286489	3	SLC6A20	A	G	0.448	0.6085
rs113497906	3	SLC6A20	A	T	0.0001624	0.004717
rs6770261	3	SLC6A20	A	G	0.2834	0.3585
rs7634267	3	SLC6A20	A	G	0.02079	0.08019

rs9857669	3	SLC6A20	T	C	0.1639	0.2264
rs7641997	3	SLC6A20	G	C	0.1655	0.1132
rs575208313	3	SLC6A20	T	C	0.2441	0.316
rs143341618	3	SLC6A20	A	G	0.0001624	0.004717
rs567829326	3	SLC6A20	A	G	0	0.004717
rs62242259	3	SLC6A20	C	G	0.1807	0.09434
rs9867918	3	SLC6A20	C	T	0.1622	0.217
rs186253736	3	SLC6A20	G	A	0.0001624	0.004717
rs74850924	3	SLC6A20	C	T	0.001299	0.01415
rs369845989	3	SLC6A20	T	C	0.0006496	0.004717
rs4327428	3	SLC6A20	C	G	0.1468	0.2358
rs2108917	3	SLC6A20	A	G	0.2746	0.5142
rs720626	3	SLC6A20	A	G	0.01932	0.04717
rs6768156	3	SLC6A20	G	T	0.2813	0.5047
rs189427751	3	SLC6A20	A	G	0.0001624	0.004717
rs758388	3	SLC6A20	T	G	0.01965	0.0566
rs2077017	3	SLC6A20	G	A	0.01965	0.06132
rs9818982	3	SLC6A20	A	G	0.1504	0.2075
rs17279437	3	SLC6A20	T	A	0.05196	0.1226
rs1468541	3	SLC6A20	A	G	0.02371	0.09906
rs565220072	3	SLC6A20	A	G	0.0001624	0.004717
rs13314717	3	SLC6A20	G	C	0.003735	0.0283
rs17078335	3	SLC6A20	A	G	0.000812	0.009434
rs57133084	3	SLC6A20	T	C	0.004547	0.01415
rs2742396	3	SLC6A20	G	A	0.4449	0.2123
rs2531748	3	SLC6A20	T	C	0.4591	0.2264
rs6771661	3	SLC6A20	A	G	0.001462	0.009434
rs59375543	3	SLC6A20	A	C	0.0004872	0.004717
rs2252547	3	SLC6A20	T	C	0.3509	0.5283
rs543762608	3	SLC6A20	C	G	0.0006496	0.004717
rs12493913	3	SLC6A20	C	G	0.3553	0.25
rs576940167	3	SLC6A20	C	T	0.0006496	0.004717
rs17078339	3	SLC6A20	G	A	0.3115	0.1981
rs34987516	3	SLC6A20	A	G	0.3284	0.2075
rs142086756	3	SLC6A20	G	A	0.0003248	0.004717
rs184263104	3	SLC6A20	T	C	0.0003248	0.004717
rs2531747	3	SLC6A20	T	C	0.1843	0.3349
rs9848415	3	SLC6A20	G	A	0.302	0.1887
rs57126329	3	SLC6A20	A	C	0.2267	0.09906
rs2159272	3	SLC6A20	A	G	0.2808	0.467
rs7644870	3	SLC6A20	C	A	0.3404	0.2075
rs1860263	3	SLC6A20	T	C	0.3454	0.2123
rs545193808	3	SLC6A20	C	A	0	0.004717

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rs13064991	3	SLC6A20	G	A	0.2272	0.1415
rs28437706	3	SLC6A20	T	C	0.06382	0.1038
rs9852457	3	SLC6A20	T	C	0.06382	0.1038
rs182605899	3	SLC6A20	A	C	0.0003248	0.004717
rs59776512	3	SLC6A20	A	G	0.06285	0.1179
rs73062389	3	SLC6A20	T	C	0.004385	0.01415
rs7615978	3	SLC6A20	C	T	0.06479	0.1179
rs543563855	3	SLC6A20	T	C	0	0.004717
rs7618553	3	SLC6A20	T	C	0.06479	0.1038
rs147310206	3	SLC6A20	A	G	0.0003248	0.004717
rs188376831	3	SLC6A20	T	C	0	0.004717
rs2271616	3	SLC6A20	A	T	0.01153	0.0283
rs11085726	19	TYK2	T	C	0.0003248	0.004717
rs2304256	19	TYK2	A	G	0.2061	0.316
rs12720270	19	TYK2	T	G	0.1916	0.283
rs34725611	19	TYK2	T	C	0.2061	0.3019
rs569826524	19	TYK2	C	G	0.4432	0.6038
rs12610298	19	TYK2	T	C	0.1892	0.25
rs62130729	19	TYK2	T	C	0.189	0.2594
rs280499	19	TYK2	T	C	0.07584	0.1179
rs280500	19	TYK2	G	A	0.03832	0.1132
rs12720218	19	TYK2	T	G	0.02793	0.08962
rs280501	19	TYK2	T	G	0.04206	0.1132
rs71327006	3	XCR1	A	G	0.04726	0.009434
rs547178387	3	XCR1	T	C	0.0004872	0.004717
rs559851604	3	XCR1	T	C	0.0004872	0.004717
rs71327007	3	XCR1	T	G	0.04726	0.009434

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SNP	Location	Allele	Consequence	IMPACT	SYMBOL	Gene	Feature_type	REF_ALLELE
rs200040076	3:46008467-46008467	A	missense_variant	MODERATE	FYCO1	ENSG00000163820	Transcript	G
rs113318190	3:45978012-45978012	A	missense_variant	MODERATE	FYCO1	ENSG00000163820	Transcript	G
rs181118021	3:46062694-46062694	A	missense_variant	MODERATE	XCR1	ENSG00000173578	Transcript	G
rs56390333	9:136131064-136131064	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs2072134	12:113409176-113409176	A	3_prime_UTR_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	G
rs35494115	9:136131389-136131389	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs16942374	12:113403751-113403751	A	missense_variant	MODERATE	OAS3	ENSG00000111331	Transcript	G
rs118149076	19:4724025-4724025	A	upstream_gene_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	G
rs371569951	9:136131590-136131590	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs72977997	19:4716147-4716147	A	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	G
rs200932155	9:136131635-136131635	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs75191837	19:4707472-4707472	C	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	T
rs8176716	9:136133065-136133065	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs184655598	3:45806282-45806282	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G
rs41289608	3:45928138-45928138	A	5_prime_UTR_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs144511372	21:34635175-34635175	T	upstream_gene_variant	MODIFIER	IL10RB	ENSG00000243646	Transcript	C
rs79006711	3:45925881-45925881	A	upstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs35018800	19:10464843-10464843	A	missense_variant	MODERATE	TYK2	ENSG00000105397	Transcript	G
rs9411372	9:136134068-136134068	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs61736301	9:136137555-136137555	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs6775854	3:45934927-45934927	A	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs7648467	3:45936322-45936322	A	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C
rs141064206	3:46021058-46021058	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs141476300	3:46021220-46021220	A	missense_variant	MODERATE	FYCO1	ENSG00000163820	Transcript	G
rs7619256	3:46029181-46029181	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs17078408	3:45939924-45939924	G	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	T
rs1053878	9:136131651-136131651	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs140002692	3:46010179-46010179	A	missense_variant	MODERATE	FYCO1	ENSG00000163820	Transcript	G
rs145828326	3:46011836-46011836	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs8176705	9:136135506-136135506	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs55882956	19:10469919-10469919	A	missense_variant	MODERATE	TYK2	ENSG00000105397	Transcript	G

rs75894880	19:4690630-4690630	T	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	A
rs543040	9:136143000-136143000	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs582094	9:136145484-136145484	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs79945697	19:4707056-4707056	A	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	G
rs8176739	9:136131523-136131523	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs613534	9:136143120-136143120	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs74840661	19:4700652-4700652	T	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	C
rs597988	9:136144284-136144284	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs597974	9:136144297-136144297	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs576123	9:136144308-136144308	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs545971	9:136143372-136143372	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs612169	9:136143442-136143442	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs8176663	9:136144427-136144427	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs544873	9:136143212-136143212	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs78788550	19:4701151-4701151	C	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	T
rs114625537	19:4709231-4709231	A	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	G
rs75192040	3:45949240-45949240	T	downstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C
rs491626	9:136144873-136144873	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs492488	9:136144960-136144960	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs493246	9:136144994-136144994	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs495203	9:136145240-136145240	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs582118	9:136145471-136145471	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs7466899	9:136131069-136131069	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs494242	9:136145118-136145118	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs564601460	3:45997814-45997814	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs141155944	3:46008820-46008820	T	missense_variant	MODERATE	FYCO1	ENSG00000163820	Transcript	C
rs150785981	3:46008841-46008841	A	missense_variant	MODERATE	FYCO1	ENSG00000163820	Transcript	G
rs181518477	3:46012975-46012975	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs140228956	3:46016969-46016969	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs189847748	3:46018207-46018207	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs61732395	12:113405328-113405328	A	missense_variant	MODERATE	OAS3	ENSG00000111331	Transcript	G

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rs73539528	19:4685259-4685259	A	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	G
rs57034092	19:4695384-4695384	A	splice_donor_region_variant,intron_variant	LOW	DPP9	ENSG00000142002	Transcript	G
rs16992502	19:4705580-4705580	C	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	T
rs146554934	3:46006955-46006955	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs114548859	3:46008108-46008108	G	synonymous_variant	LOW	FYCO1	ENSG00000163820	Transcript	A
rs77896301	3:46011634-46011634	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs75726990	3:46011654-46011654	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs113305890	19:4680128-4680128	T	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	A
rs3947589	3:46034086-46034086	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs60431156	3:45961954-45961954	C	3_prime_UTR_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs62245098	3:45945762-45945762	A	downstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs61565453	3:45946576-45946576	A	downstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C
rs57295094	3:45947101-45947101	A	downstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C
rs28501674	3:45946460-45946460	T	downstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C
rs2373086	3:45918670-45918670	T	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	C
rs875891	3:45945157-45945157	A	downstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs143174772	9:136137600-136137600	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs151155628	9:136137641-136137641	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs145090216	9:136138074-136138074	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs587707823	9:136145409-136145409	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs7614342	3:45940817-45940817	T	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	A
rs1985356	3:45940441-45940441	A	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C
rs45620632	12:113407773-113407773	A	missense_variant	MODERATE	OAS3	ENSG00000111331	Transcript	G
rs113439332	19:4696103-4696103	G	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	A
rs2108917	3:45809843-45809843	C	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	A
rs7653682	3:46029271-46029271	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	A
rs17860118	21:34602794-34602794	T	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	G
rs3749461	3:46395313-46395313	G	5_prime_UTR_variant	MODIFIER	CCR2	ENSG00000121807	Transcript	A
rs3918362	3:46395930-46395930	G	intron_variant	MODIFIER	CCR2	ENSG00000121807	Transcript	A
rs3918365	3:46398364-46398364	G	intron_variant	MODIFIER	CCR2	ENSG00000121807	Transcript	A
rs10901251	9:136126129-136126129	C	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A

rs8176692	9:136137937-136137937	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs138313692	9:136140283-136140283	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs148667000	9:136141177-136141177	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs145489959	9:136142447-136142447	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs139081859	9:136143192-136143192	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs72622922	3:45957055-45957055	A	downstream_gene_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs6768156	3:45810604-45810604	T	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	A
rs6791859	3:45948216-45948216	G	downstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	A
rs62245102	3:45948930-45948930	T	downstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C
rs6782814	3:45936945-45936945	C	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs2240190	12:113346127-113346127	A	intron_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	C
rs34085694	9:136127605-136127605	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs144683777	21:34615486-34615486	G	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	C
rs1058961	3:45865006-45865006	A	3_prime_UTR_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	T
rs8176661	9:136144640-136144640	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs7041458	9:136145988-136145988	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs1468541	3:45814303-45814303	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	T
rs77009309	3:45913521-45913521	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	C
rs2742396	3:45819701-45819701	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	C
rs2531748	3:45819837-45819837	G	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	A
rs59451221	3:45951550-45951550	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	G
rs2769071	9:136145974-136145974	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs1298961	12:113434156-113434156	C	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	A
rs10850102	12:113378835-113378835	T	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	A
rs1392288	3:46034791-46034791	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs677355	9:136146046-136146046	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs676457	9:136146227-136146227	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs1860264	3:45923085-45923085	C	upstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	A
rs6441930	3:45924953-45924953	C	upstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	T
rs9852270	3:45921043-45921043	C	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	T
rs875890	3:45945287-45945287	A	downstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	T

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rs1985463	3:45940636-45940636	C	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	A
rs8176676	9:136140577-136140577	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs644234	9:136142217-136142217	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs643434	9:136142355-136142355	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs6802312	3:46025941-46025941	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs13311	12:113448652-113448652	A	3_prime_UTR_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	C
rs1293758	12:113433587-113433587	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	T
rs139568229	9:136139383-136139383	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs149756392	9:136139395-136139395	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs145595975	9:136139460-136139460	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs148824570	9:136139589-136139589	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs146458069	9:136139672-136139672	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs141515001	9:136139833-136139833	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs149567216	9:136140469-136140469	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs143159728	9:136140613-136140613	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs7614687	3:45919904-45919904	T	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	C
rs2236938	3:45938939-45938939	A	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs2159272	3:45829995-45829995	G	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	A
rs8176684	9:136138874-136138874	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs554833	9:136147160-136147160	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs4817555	21:34626124-34626124	A	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	G
rs147279040	9:136138978-136138978	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs674302	9:136146664-136146664	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs73660468	9:136127907-136127907	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs660340	9:136147553-136147553	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs527210	9:136146431-136146431	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs581107	9:136147702-136147702	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs59738559	21:34626338-34626338	T	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	-
rs7634267	3:45806056-45806056	C	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	T
rs9862611	3:45931982-45931982	A	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C
rs6441932	3:45930222-45930222	G	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	A

rs6441933	3:45932847-45932847	G	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	A
rs57527954	3:45933344-45933344	G	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C
rs9834860	3:45933647-45933647	C	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	A
rs2277732	19:4723670-4723670	A	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	C
rs45542343	12:113349099-113349099	A	intron_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	G
rs34847985	3:45949753-45949753	G	downstream_gene_variant	MODIFIER	Y_RNA	ENSG00000201635	Transcript	A
rs2531747	3:45828586-45828586	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	T
rs13291798	9:136127481-136127481	G	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs2072137	12:113440921-113440921	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	T
rs280500	19:10490402-10490402	G	upstream_gene_variant	MODIFIER	TYK2	ENSG00000105397	Transcript	A
rs587736740	9:136140169-136140169	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs587682147	9:136141110-136141110	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs587774481	9:136141113-136141113	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs142141716	9:136141226-136141226	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs587716454	9:136141304-136141304	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs144140881	9:136141877-136141877	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs140796254	9:136142304-136142304	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs143309559	9:136142339-136142339	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs144873702	3:46016687-46016687	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs139886125	3:46027293-46027293	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	A
rs569981396	9:136125870-136125870	C	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs557530257	9:136131779-136131779	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs181170522	9:136139715-136139715	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs587663040	9:136144145-136144145	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs138421181	3:45925170-45925170	T	upstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C
rs115826613	3:45926390-45926390	A	upstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs74337052	3:45927163-45927163	G	upstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	T
rs116350857	3:45928008-45928008	A	upstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs114406614	3:45930947-45930947	T	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs141167007	3:45933141-45933141	G	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C
rs116207980	3:45933969-45933969	T	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C

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rs79663567	3:45939088-45939088	A	5_prime_UTR_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs74718475	3:45943737-45943737	A	downstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs72977966	19:4681093-4681093	G	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	C
rs148112944	3:45872918-45872918	T	intron_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	C
rs77000397	3:45921511-45921511	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	T
rs114742054	3:45921627-45921627	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	G
rs531734809	12:113421261-113421261	T	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	C
rs557969944	12:113429808-113429808	C	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	T
rs574059077	12:113448578-113448578	A	3_prime_UTR_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	G
rs116082988	3:45797352-45797352	C	3_prime_UTR_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	T
rs144151884	3:45799142-45799142	G	3_prime_UTR_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	A
rs116590098	3:45799278-45799278	G	3_prime_UTR_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	A
rs567829326	3:45807402-45807402	G	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	C
rs545193808	3:45834349-45834349	G	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	A
rs543563855	3:45835585-45835585	G	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	T
rs188376831	3:45837089-45837089	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G
rs2240185	12:113444117-113444117	G	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	C
rs1488371	3:45938089-45938089	C	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	T
rs1873000	3:46029458-46029458	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs2252547	3:45821624-45821624	C	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	T
rs7628447	3:46030003-46030003	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs4682801	3:46021218-46021218	T	synonymous_variant	LOW	FYCO1	ENSG00000163820	Transcript	G
rs488775	9:136144534-136144534	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs8176668	9:136144059-136144059	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs2373088	3:45968404-45968404	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs13314717	3:45817328-45817328	T	synonymous_variant	LOW	SLC6A20	ENSG00000163817	Transcript	C
rs1532070	3:45970842-45970842	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs8176760	9:136150379-136150379	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs2064061	3:45871203-45871203	C	intron_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	A
rs12720218	19:10490888-10490888	A	upstream_gene_variant	MODIFIER	TYK2	ENSG00000105397	Transcript	G
rs574311	9:136144110-136144110	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G

rs62245101	3:45948875-45948875	A	downstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs34549672	3:45949954-45949954	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	C
rs146216196	3:46032144-46032144	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs139044419	3:46032210-46032210	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs142154067	3:46033101-46033101	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs79067698	3:46034560-46034560	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	A
rs188114046	3:46035925-46035925	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs9411475	9:136127268-136127268	C	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs4683147	3:45948264-45948264	A	downstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs280501	19:10491322-10491322	T	upstream_gene_variant	MODIFIER	TYK2	ENSG00000105397	Transcript	C
rs72891712	3:46029398-46029398	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs112212287	3:45919528-45919528	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	G
rs587682443	9:136141355-136141355	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs587764387	9:136141356-136141356	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs587637585	9:136141358-136141358	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs17860183	21:34616549-34616549	T	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	A
rs7036642	9:136144626-136144626	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs9871972	3:45909090-45909090	T	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	C
rs17860220	21:34623919-34623919	G	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	A
rs2073362	21:34620801-34620801	G	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	A
rs7634640	3:45982119-45982119	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs2133660	3:46031957-46031957	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs1846615	3:46032388-46032388	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs1873001	3:46032847-46032847	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs1500003	3:46033819-46033819	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	A
rs34266669	9:136126495-136126495	T	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs199969472	9:136126498-136126498	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs141146648	3:45889587-45889587	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	G
rs7849280	9:136126636-136126636	G	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs2286489	3:45804069-45804069	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	C
rs147496374	21:34625037-34625037	G	missense_variant	MODERATE	IFNAR2	ENSG00000159110	Transcript	C

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rs514659	9:136142203-136142203	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs550057	9:136146597-136146597	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs2229207	21:34614250-34614250	A	missense_variant	MODERATE	IFNAR2	ENSG00000159110	Transcript	T
rs17279437	3:45814094-45814094	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G
rs11670257	19:4713430-4713430	A	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	G
rs2003480	12:113443225-113443225	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	T
rs507666	9:136149399-136149399	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs12554336	9:136128663-136128663	G	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs10901253	9:136128772-136128772	C	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs11244053	9:136129360-136129360	G	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs4962114	9:136129611-136129611	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs4962115	9:136129642-136129642	G	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs4962116	9:136129716-136129716	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs115932896	3:46062389-46062389	G	3_prime_UTR_variant	MODIFIER	XCR1	ENSG00000173578	Transcript	A
rs74850924	3:45808345-45808345	C	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	T
rs58081338	9:136128329-136128329	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs62574567	9:136128421-136128421	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs57126329	3:45829562-45829562	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G
rs659104	9:136147823-136147823	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs473533	9:136148035-136148035	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs476410	9:136148368-136148368	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs645982	9:136148409-136148409	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs500498	9:136148647-136148647	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs7870156	9:136128080-136128080	C	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs9844821	3:46019722-46019722	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs475419	9:136148231-136148231	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs142956930	9:136143330-136143330	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs1859330	12:113376388-113376388	A	missense_variant	MODERATE	OAS3	ENSG00000111331	Transcript	G
rs1859331	12:113376331-113376331	A	5_prime_UTR_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	C
rs10751502	9:136129079-136129079	C	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs2077017	3:45812473-45812473	G	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	A

rs7469795	9:136130893-136130893	C	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs11130082	3:46025518-46025518	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs13086858	3:46026699-46026699	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs60484807	9:136128467-136128467	G	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs3092963	3:46396938-46396938	G	intron_variant	MODIFIER	CCR2	ENSG00000121807	Transcript	A
rs1799865	3:46399798-46399798	C	synonymous_variant	LOW	CCR2	ENSG00000121807	Transcript	T
rs3138042	3:46401032-46401032	G	intron_variant	MODIFIER	CCR2	ENSG00000121807	Transcript	A
rs138017682	3:46024528-46024528	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs182171107	3:46033769-46033769	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs11707672	3:45964389-45964389	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs7644870	3:45830886-45830886	C	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	A
rs1860263	3:45832052-45832052	G	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	A
rs8176757	9:136130012-136130012	C	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs4683159	3:46025013-46025013	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	A
rs647800	9:136148000-136148000	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs12554580	9:136128603-136128603	C	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs147753307	3:45938484-45938484	A	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs185588322	3:45959697-45959697	T	3_prime_UTR_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs148655132	3:45964352-45964352	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	A
rs140100519	3:45965077-45965077	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs181980885	3:45953578-45953578	T	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	C
rs186530132	3:45953925-45953925	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	G
rs112707117	3:45954246-45954246	T	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	C
rs657152	9:136139265-136139265	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs11130078	3:45964168-45964168	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs2251109	3:45796951-45796951	T	3_prime_UTR_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	C
rs904634	3:46017304-46017304	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	A
rs9849818	3:46020594-46020594	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs2304256	19:10475652-10475652	A	missense_variant	MODERATE	TYK2	ENSG00000105397	Transcript	C
rs5800979	12:113429904-113429904	C	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	-
rs3774642	3:45937782-45937782	G	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C

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rs1293772	12:113420604-113420604	C	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	A
rs1293771	12:113421295-113421295	G	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	A
rs1058480	12:113449116-113449116	A	3_prime_UTR_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	G
rs75018424	3:45926947-45926947	G	upstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	T
rs15895	12:113448288-113448288	C	stop_lost	HIGH	OAS2	ENSG00000111335	Transcript	A
rs74808020	3:45924167-45924167	C	upstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs12631321	3:45924897-45924897	T	upstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C
rs1293768	12:113424501-113424501	C	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	T
rs1293743	12:113447572-113447572	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	C
rs17078335	3:45818419-45818419	G	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	A
rs35537559	3:46021452-46021452	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs67044455	3:46028791-46028791	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs758388	3:45812104-45812104	G	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	A
rs150326069	9:136137847-136137847	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs147960974	9:136148224-136148224	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs145218729	9:136148697-136148697	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs191811571	3:45984372-45984372	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs114346470	19:4691102-4691102	G	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	C
rs139518006	19:4713387-4713387	A	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	C
rs560966886	3:45956874-45956874	T	downstream_gene_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs150719194	3:45889656-45889656	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	C
rs138727962	3:45901597-45901597	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	G
rs148060386	3:45910289-45910289	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	G
rs560506883	3:45921382-45921382	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	C
rs150169230	12:113424858-113424858	G	missense_variant	MODERATE	OAS2	ENSG00000111335	Transcript	C
rs73433165	12:113379823-113379823	T	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	C
rs45583340	12:113409691-113409691	T	3_prime_UTR_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	C
rs113497906	3:45804597-45804597	T	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	C
rs143341618	3:45806320-45806320	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G
rs186253736	3:45807903-45807903	C	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G
rs189427751	3:45811313-45811313	G	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	A

rs565220072	3:45816798-45816798	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G
rs4683148	3:45956060-45956060	T	downstream_gene_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs12638201	3:45934279-45934279	A	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs587635767	9:136141122-136141122	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs73422036	12:113407260-113407260	T	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	G
rs11837367	12:113407993-113407993	G	3_prime_UTR_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	A
rs9875616	3:45979877-45979877	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs1293752	12:113437814-113437814	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	C
rs1293751	12:113438413-113438413	C	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	T
rs2525848	12:113439622-113439622	C	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	A
rs1296061	12:113439881-113439881	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	G
rs143980719	3:45986795-45986795	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs529565	9:136149500-136149500	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs9831315	3:45956362-45956362	C	downstream_gene_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs4327428	3:45809329-45809329	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	C
rs2291470	3:45962942-45962942	A	3_prime_UTR_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs12635657	3:46031029-46031029	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs7129	3:45959759-45959759	A	3_prime_UTR_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs111207633	9:136130214-136130214	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs7466519	9:136131002-136131002	G	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs9848415	3:45828841-45828841	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G
rs3733103	3:45962595-45962595	G	3_prime_UTR_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs78069989	12:113393875-113393875	C	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	T
rs60439830	12:113399653-113399653	G	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	T
rs45489899	12:113405472-113405472	G	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	C
rs1293760	12:113431578-113431578	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	G
rs1293762	12:113430836-113430836	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	T
rs17078339	3:45822437-45822437	G	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	A
rs9869848	3:45978806-45978806	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs1293749	12:113442257-113442257	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	C
rs1293748	12:113444024-113444024	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	T

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rs79587259	3:45941187-45941187	A	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs1293765	12:113425493-113425493	C	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	T
rs75344264	12:113350105-113350105	G	intron_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	A
rs505922	9:136149229-136149229	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs1293764	12:113425679-113425679	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	T
rs12053666	21:34618439-34618439	A	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	G
rs13052526	21:34604737-34604737	C	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	T
rs17860160	21:34611320-34611320	T	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	G
rs75078036	3:45935443-45935443	C	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	T
rs12054287	3:46067586-46067586	A	intron_variant	MODIFIER	XCR1	ENSG00000173578	Transcript	G
rs1293754	12:113436597-113436597	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	T
rs758389	3:45886399-45886399	C	upstream_gene_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	T
rs184214751	3:45904011-45904011	G	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	A
rs56006713	12:113354384-113354384	A	missense_variant	MODERATE	OAS1	ENSG00000089127	Transcript	G
rs3796373	3:45960851-45960851	G	3_prime_UTR_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs1635142	12:113434518-113434518	G	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	A
rs1293757	12:113435109-113435109	G	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	A
rs1293756	12:113435293-113435293	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	C
rs1293753	12:113437706-113437706	G	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	C
rs1051393	21:34614255-34614255	A	missense_variant	MODERATE	IFNAR2	ENSG00000159110	Transcript	T
rs1293759	12:113431643-113431643	G	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	A
rs34725611	19:10477067-10477067	G	intron_variant	MODIFIER	TYK2	ENSG00000105397	Transcript	A
rs757402	12:113429102-113429102	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	G
rs757401	12:113429468-113429468	G	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	A
rs4766662	12:113345699-113345699	C	intron_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	A
rs12638598	3:45969992-45969992	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs3796376	3:46009491-46009491	T	synonymous_variant	LOW	FYCO1	ENSG00000163820	Transcript	C
rs4767023	12:113352159-113352159	A	intron_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	T
rs2171530	3:45956110-45956110	A	downstream_gene_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs6781668	3:46019283-46019283	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs7965570	12:113386624-113386624	T	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	C

rs12720270	19:10475760-10475760	A	intron_variant	MODIFIER	TYK2	ENSG00000105397	Transcript	G
rs3821883	3:46022704-46022704	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs189110596	21:34606840-34606840	C	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	A
rs3733097	3:46026259-46026259	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs17078495	3:46026641-46026641	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs737452	3:46027410-46027410	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs596141	9:136144689-136144689	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs9836836	3:45951602-45951602	C	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	G
rs8176748	9:136131289-136131289	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs2300371	21:34632241-34632241	A	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	C
rs8176745	9:136131347-136131347	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs9849771	3:46020509-46020509	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs62242259	3:45807626-45807626	G	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	A
rs2234355	3:45987980-45987980	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs59776512	3:45835415-45835415	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	-
rs59767267	3:46021559-46021559	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs75442536	3:45950911-45950911	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	G
rs751552	3:46016851-46016851	G	splice_polypyrimidine_tract_variant,intron_variant	LOW	FYCO1	ENSG00000163820	Transcript	A
rs751553	3:46016944-46016944	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs58035200	3:46068681-46068681	A	intron_variant	MODIFIER	XCR1	ENSG00000173578	Transcript	C
rs7956880	12:113345167-113345167	C	intron_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	A
rs2285934	12:113351520-113351520	A	intron_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	T
rs10744785	12:113345256-113345256	A	intron_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	C
rs7623476	3:46068843-46068843	G	intron_variant	MODIFIER	XCR1	ENSG00000173578	Transcript	A
rs112101762	3:45892596-45892596	G	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	C
rs113181700	3:45893133-45893133	C	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	A
rs73830609	3:45939238-45939238	G	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C
rs59226168	3:46028320-46028320	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs62242796	3:46029193-46029193	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs138971703	12:113397082-113397082	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	G
rs1298301	12:113418899-113418899	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	G

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rs12493913	3:45822072-45822072	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	T
rs12554339	9:136128737-136128737	C	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs11244052	9:136129125-136129125	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs62242787	3:45995908-45995908	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs7046674	9:136147012-136147012	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs8176647	9:136147755-136147755	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs8176641	9:136149802-136149802	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs8176639	9:136150317-136150317	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs8176710	9:136134537-136134537	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs8176649	9:136147295-136147295	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs60110056	3:45966671-45966671	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs7615978	3:45835570-45835570	C	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	A
rs62242788	3:46001649-46001649	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs8176682	9:136139297-136139297	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs4683146	3:45898221-45898221	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	G
rs929291	12:113444418-113444418	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	T
rs1293773	12:113420551-113420551	C	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	T
rs3803057	12:113368734-113368734	A	intron_variant,NMD_transcript_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	G
rs8176687	9:136138658-136138658	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs8176679	9:136139955-136139955	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs17078308	3:45797991-45797991	C	3_prime_UTR_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	T
rs4767045	12:113409413-113409413	A	3_prime_UTR_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	C
rs10744791	12:113410316-113410316	A	3_prime_UTR_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	G
rs6796097	3:45878988-45878988	G	intron_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	A
rs189659509	3:46065278-46065278	G	intron_variant	MODIFIER	XCR1	ENSG00000173578	Transcript	A
rs13064991	3:45834811-45834811	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G
rs3774641	3:45937833-45937833	T	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs10774671	12:113357193-113357193	A	splice_acceptor_variant	HIGH	OAS1	ENSG00000089127	Transcript	G
rs200629605	12:113429326-113429326	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	T
rs2248228	3:45965386-45965386	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs4683152	3:45974886-45974886	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C

rs7509997	21:34607358-34607358	A	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	G
rs12639598	3:46016464-46016464	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs4683149	3:45967869-45967869	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs530909128	9:136130463-136130463	G	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs140253702	3:46401606-46401606	G	3_prime_UTR_variant	MODIFIER	CCR2	ENSG00000121807	Transcript	A
rs186153536	3:45923622-45923622	G	upstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	A
rs530595037	3:45924287-45924287	C	upstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	T
rs552329766	3:45924288-45924288	G	upstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	A
rs115004584	3:45925363-45925363	G	upstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	A
rs78414305	3:45925618-45925618	G	upstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	A
rs74739895	3:45926749-45926749	G	upstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	A
rs78044818	3:45926972-45926972	A	upstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	T
rs115227401	3:45929086-45929086	T	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C
rs76478208	3:45929426-45929426	A	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	T
rs6783694	3:45929800-45929800	A	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C
rs116264461	3:45930581-45930581	A	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs77676459	3:45930814-45930814	C	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs144180015	3:45931297-45931297	G	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	A
rs576036480	21:34607449-34607449	A	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	G
rs117489085	21:34611986-34611986	G	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	C
rs545411453	21:34612133-34612133	T	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	G
rs181597872	21:34629420-34629420	A	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	G
rs11837165	12:113406699-113406699	C	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	T
rs142086756	3:45823690-45823690	A	synonymous_variant	LOW	SLC6A20	ENSG00000163817	Transcript	G
rs184263104	3:45827195-45827195	T	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	A
rs182605899	3:45835228-45835228	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G
rs147310206	3:45836492-45836492	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G
rs11085726	19:10465609-10465609	A	intron_variant	MODIFIER	TYK2	ENSG00000105397	Transcript	G
rs2531750	3:45799599-45799599	A	3_prime_UTR_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G
rs13091979	3:45980110-45980110	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs13091821	3:45980115-45980115	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	A

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rs3774639	3:45983654-45983654	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs4683156	3:45991087-45991087	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs1293766	12:113425282-113425282	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	T
rs57228214	3:46019939-46019939	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs4535265	3:45977866-45977866	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs12639224	3:45916222-45916222	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	C
rs111310794	9:136132986-136132986	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs8176694	9:136137646-136137646	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs720626	3:45810138-45810138	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	C
rs10850104	12:113385375-113385375	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	T
rs34647135	12:113386616-113386616	C	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	T
rs60199752	19:4705004-4705004	C	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	T
rs11671605	19:4705508-4705508	G	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	A
rs28595837	3:45946025-45946025	A	downstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs8107316	19:4680805-4680805	C	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	T
rs1293767	12:113425154-113425154	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	C
rs1293770	12:113421869-113421869	C	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	A
rs57771566	12:113396978-113396978	T	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	C
rs58603713	12:113398147-113398147	T	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	C
rs75755877	12:113409965-113409965	G	3_prime_UTR_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	A
rs73422042	12:113410421-113410421	T	3_prime_UTR_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	C
rs62574565	9:136128259-136128259	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs663054	9:136146920-136146920	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs9855205	3:45935698-45935698	G	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C
rs9881306	3:45946147-45946147	A	downstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs79179998	3:45947066-45947066	A	downstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs2834160	21:34620113-34620113	C	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	T
rs45495393	12:113352708-113352708	A	intron_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	C
rs11244054	9:136130225-136130225	C	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs1072755	3:45975983-45975983	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	A
rs551100	9:136146740-136146740	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T

rs11911133	21:34629175-34629175	G	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	A
rs17078371	3:45892477-45892477	G	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	A
rs6771661	3:45820507-45820507	G	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	C
rs1293763	12:113426632-113426632	C	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	T
rs757405	12:113406945-113406945	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	T
rs2277735	19:4700187-4700187	G	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	A
rs1298962	12:113418850-113418850	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	G
rs1293774	12:113419177-113419177	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	C
rs17078449	3:45980673-45980673	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs17078454	3:45981215-45981215	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs57204020	3:45981877-45981877	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	A
rs3774640	3:45983479-45983479	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs3774638	3:45983887-45983887	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs936939	3:45986623-45986623	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs2660	12:113357442-113357442	A	3_prime_UTR_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	G
rs77709797	3:45970409-45970409	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	A
rs190039371	3:45972170-45972170	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs8176702	9:136136146-136136146	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs936938	3:45980769-45980769	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs3774635	3:45986219-45986219	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	A
rs2054866	3:45990217-45990217	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	A
rs1994488	3:45992977-45992977	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs1552489	3:45993973-45993973	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs139540257	3:45869678-45869678	A	intron_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	C
rs2234350	3:45984300-45984300	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs2234351	3:45984323-45984323	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs12427406	12:113383802-113383802	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	T
rs7621856	3:45802134-45802134	C	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	T
rs71465868	12:113390363-113390363	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	G
rs2191031	3:45910870-45910870	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	G
rs55688670	12:113400746-113400746	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	C

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rs45607836	12:113401212-113401212	A	missense_variant	MODERATE	OAS3	ENSG00000111331	Transcript	G
rs8130779	21:34608625-34608625	A	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	T
rs9974669	21:34608954-34608954	C	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	G
rs72977989	19:4708568-4708568	G	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	C
rs675201	9:136146466-136146466	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs9869542	3:45934588-45934588	C	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	T
rs4401152	19:4708102-4708102	A	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	C
rs1293745	12:113446198-113446198	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	G
rs1293744	12:113446727-113446727	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	G
rs2277733	19:4714044-4714044	C	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	T
rs570824030	21:34609388-34609388	A	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	G
rs75826707	3:45908859-45908859	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	G
rs2834162	21:34620409-34620409	C	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	A
rs17860211	21:34620668-34620668	C	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	A
rs12633699	3:45922735-45922735	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	G
rs35334665	3:46061218-46061218	A	3_prime_UTR_variant	MODIFIER	XCR1	ENSG00000173578	Transcript	T
rs71327009	3:46064626-46064626	G	intron_variant	MODIFIER	XCR1	ENSG00000173578	Transcript	C
rs35161099	3:46067507-46067507	G	intron_variant	MODIFIER	XCR1	ENSG00000173578	Transcript	T
rs71327010	3:46068835-46068835	A	intron_variant	MODIFIER	XCR1	ENSG00000173578	Transcript	G
rs71327006	3:46058908-46058908	A	3_prime_UTR_variant	MODIFIER	XCR1	ENSG00000173578	Transcript	G
rs71327007	3:46059249-46059249	T	3_prime_UTR_variant	MODIFIER	XCR1	ENSG00000173578	Transcript	C
rs140227473	3:45909287-45909287	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	G
rs79657519	3:45910031-45910031	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	G
rs6778225	3:45970940-45970940	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs60779624	3:45971263-45971263	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs33910087	3:46009487-46009487	A	missense_variant	MODERATE	FYCO1	ENSG00000163820	Transcript	G
rs62245106	3:45968668-45968668	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs6778324	3:45971022-45971022	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs13079869	3:46008087-46008087	A	synonymous_variant	LOW	FYCO1	ENSG00000163820	Transcript	G
rs62130729	19:10486936-10486936	A	intron_variant	MODIFIER	TYK2	ENSG00000105397	Transcript	G
rs17215008	3:46012279-46012279	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T

rs71325098	3:46012391-46012391	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	A
rs71325100	3:46013832-46013832	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs41289622	3:46014545-46014545	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs13066062	3:46018344-46018344	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs34000569	3:45999209-45999209	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	A
rs34324101	3:46000728-46000728	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs13069079	3:46000870-46000870	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs34849862	3:46001367-46001367	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs35209528	3:46003496-46003496	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs36122610	3:46022833-46022833	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs34442130	3:46024529-46024529	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs13075758	3:46025048-46025048	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs17330872	3:46035097-46035097	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	A
rs71327003	3:46036521-46036521	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs117666908	12:113420087-113420087	G	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	A
rs57036895	3:46007419-46007419	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	A
rs35501575	3:45993645-45993645	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs2109070	19:4719485-4719485	C	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	G
rs730983	3:46028056-46028056	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs8176691	9:136138229-136138229	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs2171531	3:45981171-45981171	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs55920693	3:45983476-45983476	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs11066456	12:113383431-113383431	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	G
rs17078464	3:45990117-45990117	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	A
rs58050797	3:45992445-45992445	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs75507082	3:45909496-45909496	G	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	C
rs1131476	12:113357209-113357209	A	missense_variant	MODERATE	OAS1	ENSG00000089127	Transcript	G
rs4767044	12:113402899-113402899	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	C
rs3937434	12:113406196-113406196	C	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	A
rs2016831	12:113406460-113406460	C	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	G
rs1557866	12:113405181-113405181	C	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	A

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rs2286486	3:45927741-45927741	C	upstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	T
rs4962113	9:136127641-136127641	C	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs56972507	3:46025992-46025992	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	A
rs7627147	3:45984097-45984097	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs58442576	3:45990277-45990277	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs56239523	3:45991123-45991123	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs11066457	12:113386245-113386245	C	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	T
rs34137742	12:113348661-113348661	T	intron_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	C
rs75628555	12:113359445-113359445	T	downstream_gene_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	C
rs60237998	3:45965954-45965954	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs2109069	19:4719443-4719443	A	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	G
rs1293746	12:113445768-113445768	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	G
rs2834166	21:34626654-34626654	A	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	C
rs2006231	19:4719123-4719123	T	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	C
rs10420225	19:4724157-4724157	A	upstream_gene_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	G
rs10735079	12:113380008-113380008	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	G
rs2373087	3:45968043-45968043	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs35831747	3:45970391-45970391	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs13099120	3:45970944-45970944	G	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs35477280	3:45974092-45974092	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs13066516	3:45975443-45975443	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs77902290	3:45976662-45976662	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs7631809	3:45968325-45968325	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs61751653	3:45942971-45942971	A	missense_variant	MODERATE	CCR9	ENSG00000173585	Transcript	G
rs113094386	19:4699126-4699126	G	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	A
rs16942430	12:113446009-113446009	C	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	T
rs201439325	9:136131407-136131407	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs587698906	9:136142533-136142533	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs587763606	9:136145172-136145172	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs79343853	9:136146310-136146310	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs150667470	3:45924901-45924901	A	upstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G

rs1187	21:34610893-34610893	G	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	T
rs190577088	3:45880233-45880233	G	intron_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	A
rs12639252	3:45916386-45916386	T	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	C
rs3815178	12:113376320-113376320	A	5_prime_UTR_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	C
rs1859329	12:113376452-113376452	A	synonymous_variant	LOW	OAS3	ENSG00000111331	Transcript	C
rs7299132	12:113376913-113376913	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	T
rs6489879	12:113377822-113377822	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	G
rs4238033	12:113378081-113378081	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	T
rs6489880	12:113380271-113380271	G	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	C
rs6489882	12:113381376-113381376	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	G
rs146042277	12:113391245-113391245	G	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	A
rs140303054	12:113396695-113396695	C	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	A
rs4766678	12:113397691-113397691	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	G
rs59375543	3:45820990-45820990	C	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	T
rs547178387	3:46059120-46059120	A	3_prime_UTR_variant	MODIFIER	XCR1	ENSG00000173578	Transcript	-
rs559851604	3:46059121-46059121	A	3_prime_UTR_variant	MODIFIER	XCR1	ENSG00000173578	Transcript	C
rs1293747	12:113444845-113444845	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	G
rs7638236	3:45977641-45977641	C	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs58491168	3:45966939-45966939	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs7311182	12:113379123-113379123	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	T
rs9857669	3:45806066-45806066	T	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	C
rs7855255	9:136131895-136131895	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs8176733	9:136132168-136132168	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs2073823	9:136132516-136132516	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs8176730	9:136132525-136132525	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs11130077	3:45877712-45877712	A	intron_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	G
rs7975318	12:113429329-113429329	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	G
rs575208313	3:45806200-45806200	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	C
rs6770261	3:45804734-45804734	T	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	C
rs35508621	3:45880481-45880481	C	intron_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	T
rs687289	9:136137106-136137106	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G

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rs34288077	3:45888690-45888690	G	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	A
rs1994492	3:45960646-45960646	C	3_prime_UTR_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs1994493	3:45960700-45960700	T	3_prime_UTR_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs1752339	9:136141135-136141135	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs1927315	9:136142000-136142000	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs8176644	9:136149150-136149150	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs8176725	9:136132617-136132617	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs34326463	3:45899651-45899651	G	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	A
rs56945978	19:4721927-4721927	C	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	G
rs75928798	3:45962603-45962603	C	3_prime_UTR_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	A
rs34068335	3:45954339-45954339	T	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	C
rs7623460	3:46068764-46068764	C	intron_variant	MODIFIER	XCR1	ENSG00000173578	Transcript	A
rs10850105	12:113391363-113391363	C	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	A
rs12301619	12:113423203-113423203	C	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	A
rs12423440	12:113356309-113356309	T	intron_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	C
rs35280891	3:45951647-45951647	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	G
rs4238034	12:113397143-113397143	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	T
rs78220999	12:113395457-113395457	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	C
rs150390228	12:113395704-113395704	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	G
rs10744789	12:113396010-113396010	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	T
rs687621	9:136137065-136137065	G	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs2072133	12:113409260-113409260	A	3_prime_UTR_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	T
rs28437706	3:45834878-45834878	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G
rs9852457	3:45835076-45835076	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G
rs74945326	3:45948464-45948464	T	downstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C
rs7636844	3:45927211-45927211	T	upstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C
rs6441931	3:45928730-45928730	G	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	A
rs111590440	9:136127783-136127783	G	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs12482193	21:34611545-34611545	A	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	T
rs2072136	12:113398919-113398919	A	synonymous_variant	LOW	OAS3	ENSG00000111331	Transcript	G
rs4767041	12:113378677-113378677	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	G

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rs7955267	12:113379039-113379039	T	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	C
rs7977345	12:113380708-113380708	C	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	A
rs6489881	12:113381217-113381217	C	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	A
rs2158393	12:113398422-113398422	C	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	A
rs11066464	12:113428717-113428717	A	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	G
rs4435062	12:113395660-113395660	C	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	T
rs10211925	21:34615732-34615732	A	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	G
rs7980275	12:113380529-113380529	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	T
rs9818982	3:45812514-45812514	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G
rs17860142	21:34607870-34607870	G	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	C
rs12482014	21:34611318-34611318	T	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	C
rs17860165	21:34611730-34611730	A	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	C
rs8176735	9:136132008-136132008	T	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs8176729	9:136132528-136132528	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs2248420	21:34605778-34605778	A	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	C
rs3153	21:34609505-34609505	A	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	G
rs2072135	12:113399179-113399179	T	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	C
rs59817490	3:45940809-45940809	G	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	A
rs73830610	3:45943819-45943819	T	downstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C
rs75918913	3:46006917-46006917	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs280499	19:10489606-10489606	G	upstream_gene_variant	MODIFIER	TYK2	ENSG00000105397	Transcript	A
rs7618553	3:45835828-45835828	C	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	T
rs2010604	12:113408208-113408208	C	3_prime_UTR_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	G
rs2057778	12:113350796-113350796	C	intron_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	G
rs1974518	12:113389603-113389603	C	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	A
rs4767042	12:113393284-113393284	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	T
rs138164693	9:136134118-136134118	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs183228393	9:136134835-136134835	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs12610298	19:10485242-10485242	A	intron_variant	MODIFIER	TYK2	ENSG00000105397	Transcript	C
rs532436	9:136149830-136149830	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	G
rs2271616	3:45838013-45838013	A	upstream_gene_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G

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rs739903	12:113408874-113408874	G	3_prime_UTR_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	A
rs7023	12:113410975-113410975	A	3_prime_UTR_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	C
rs2240189	12:113403497-113403497	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	G
rs8176698	9:136136593-136136593	A	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	T
rs8176696	9:136136773-136136773	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs10420007	19:4724069-4724069	A	upstream_gene_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	G
rs11385942	3:45876461-45876461	A	intron_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	-
rs61185149	3:45907384-45907384	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	G
rs4767026	12:113359132-113359132	C	downstream_gene_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	A
rs10774672	12:113360737-113360737	A	downstream_gene_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	G
rs4766677	12:113397630-113397630	G	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	C
rs7135577	12:113358106-113358106	G	downstream_gene_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	A
rs4767028	12:113359188-113359188	G	downstream_gene_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	A
rs4767030	12:113359577-113359577	A	downstream_gene_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	C
rs17078471	3:45996583-45996583	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs11130081	3:46015182-46015182	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	G
rs34886194	12:113430203-113430203	G	intron_variant	MODIFIER	OAS2	ENSG00000111335	Transcript	A
rs28607988	3:45913338-45913338	C	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	A
rs4767024	12:113358791-113358791	A	downstream_gene_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	T
rs4767025	12:113358794-113358794	G	downstream_gene_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	C
rs4767027	12:113359157-113359157	A	downstream_gene_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	T
rs4767029	12:113359318-113359318	A	downstream_gene_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	G
rs10850092	12:113359703-113359703	A	downstream_gene_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	C
rs6489864	12:113360025-113360025	G	downstream_gene_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	A
rs6489865	12:113360302-113360302	G	downstream_gene_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	A
rs10850093	12:113360468-113360468	T	downstream_gene_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	C
rs10850094	12:113360563-113360563	C	downstream_gene_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	T
rs10850095	12:113360575-113360575	A	downstream_gene_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	T
rs10850096	12:113360786-113360786	A	downstream_gene_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	T
rs10774673	12:113361158-113361158	G	downstream_gene_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	C
rs10774674	12:113361174-113361174	A	downstream_gene_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	T

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rs1467941	19:4720523-4720523	C	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	T
rs7131998	12:113381695-113381695	C	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	A
rs2834159	21:34618089-34618089	T	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	C
rs60080146	3:46067618-46067618	G	intron_variant	MODIFIER	XCR1	ENSG00000173578	Transcript	A
rs9867918	3:45807699-45807699	C	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G
rs931704	3:46024671-46024671	A	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	T
rs71325089	3:45904548-45904548	G	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	C
rs56058226	3:45935018-45935018	T	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	C
rs45610939	9:136133396-136133396	C	intron_variant,non_coding_transcript_variant	MODIFIER	ABO	ENSG00000175164	Transcript	A
rs62226154	21:34614901-34614901	T	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	G
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rs67959919	3:45871908-45871908	A	intron_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	G
rs62226157	21:34615088-34615088	A	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	G
rs56116432	9:136131429-136131429	A	non_coding_transcript_exon_variant	MODIFIER	ABO	ENSG00000175164	Transcript	C
rs34136596	19:4693903-4693903	G	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	A
rs35408525	19:4705215-4705215	C	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	T
rs758510	19:4721991-4721991	G	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	C
rs188401375	21:34602242-34602242	A	upstream_gene_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	C
rs558702333	3:46060618-46060618	G	3_prime_UTR_variant	MODIFIER	XCR1	ENSG00000173578	Transcript	C
rs12824584	12:113390957-113390957	A	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	G
rs369845989	3:45808361-45808361	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G
rs543762608	3:45821742-45821742	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G
rs576940167	3:45822241-45822241	C	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	T
rs6800954	3:45964959-45964959	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs59676542	3:46068160-46068160	T	intron_variant	MODIFIER	XCR1	ENSG00000173578	Transcript	C
rs4962040	9:136133531-136133531	G	splice_polypyrimidine_tract_variant,intron_variant	LOW	ABO	ENSG00000175164	Transcript	A
rs7310667	12:113392182-113392182	C	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	A
rs732631	19:4719025-4719025	G	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	C
rs73062389	3:45835417-45835417	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G
rs10850097	12:113361117-113361117	G	downstream_gene_variant	MODIFIER	OAS1	ENSG00000089127	Transcript	C
rs9823523	3:45937117-45937117	G	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	A

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rs10421782	19:4685276-4685276	C	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	A
rs2269899	12:113381956-113381956	T	intron_variant	MODIFIER	OAS3	ENSG00000111331	Transcript	C
rs7641997	3:45806173-45806173	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G
rs1467942	19:4720532-4720532	A	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	G
rs13081482	3:45908116-45908116	C	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	A
rs73064425	3:45901089-45901089	T	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	C
rs8105807	19:4684642-4684642	G	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	A
rs2885734	19:4690259-4690259	C	intron_variant	MODIFIER	DPP9	ENSG00000142002	Transcript	T
rs41289614	3:45972492-45972492	T	intron_variant	MODIFIER	FYCO1	ENSG00000163820	Transcript	C
rs35731912	3:45889949-45889949	T	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	C
rs17764980	3:45939016-45939016	A	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs17714101	3:45939802-45939802	A	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs17714228	3:45945132-45945132	C	downstream_gene_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	A
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rs3764864	3:45936237-45936237	A	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
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rs71325091	3:45932407-45932407	A	intron_variant	MODIFIER	CCR9	ENSG00000173585	Transcript	G
rs57133084	3:45819197-45819197	A	intron_variant	MODIFIER	SLC6A20	ENSG00000163817	Transcript	G
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rs57319220	3:45919992-45919992	A	intron_variant,NMD_transcript_variant	MODIFIER	LZTFL1	ENSG00000163818	Transcript	G
rs8128785	21:34613967-34613967	A	intron_variant	MODIFIER	IFNAR2	ENSG00000159110	Transcript	C

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Original research

Acceptability and side effects of omega 3 in pregnant women with deficient intake

Indalecio Gustavo Martinez Velasco[ab1]*, Roman Jimenez Lopez[c2], Maria Fernanda Gallego Mora[b3], Oliver Arciniega Mancilla[c4], Diana Isabel Castro Luna[bd5], Deny Guadalupe Gonzalez Guzmán[b6], Esmeralda Galarza de la Cruz[b7]

[a] Hospital Comunitario de Tecomatlán, Servicios de Salud del Estado de Puebla. Puebla, México.
[b] Centro de Investigación en Nutrición y Educación Perinatal, Departamento de Nutrición Perinatal. Chapulco, Puebla, México.
[c] Renacimiento General Hospital, IMSS-Bienestar Hospital, Guerrero, México.
[d] Universidad Anáhuac-Campus Puebla, Facultad de Ciencias de la Salud, Cholula, Puebla, México.

ID ORCID:

[1]https://orcid.org/0000-0003-4443-2190, [2]https://orcid.org/0000-0003-4911-1003, [3]https://orcid.org/0009-0009-5056-6372, [4]https://orcid.org/0009-0007-5843-1566, [5]https://orcid.org/0009-0006-9299-5376, [6]https://orcid.org/0009-0003-5103-354X, [7]https://orcid.org/0009-0003-5422-4886

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ABSTRACT

Introduction: Omega-3 polyunsaturated fatty acids, such as EPA and DHA, are essential during pregnancy because of their benefits for maternal health and fetal development. In pregnant women with omega-3 deficiency, assessment of tolerability, acceptability and potential side effects is crucial to optimize treatment adherence. **Objective:** To determine the tolerability and main side effects in a group of pregnant women with inadequate fish intake in a rural community. **Materials and methods:** A dietary survey was carried out in a group of pregnant women attending their antenatal check-ups at a private Gyneco -obstetric facility, to investigate the need for omega-3 supplementation in a population of pregnant women using a simplified questionnaire. Two capsules containing 760 mg of EPA and 520 mg of DHA were prescribed from the 20th week of pregnancy. The presence of side effects and adherence to the prescription were documented. **Results:** Tolerance was 100.0%. Side effects included nausea 19.2%, belching 4.6%, fishy breath 2.3%, vomiting 1.5% and no cases of allergic reaction. No patient discontinued supplementation. **Conclusions:** The side effects of omega-3 PUFAs in this study were very low, resulting in excellent compliance.

Key words: preterm birth; omega-3; pregnancy; food frequency questionnaire; fish; docosahexaenoic acid.

* *Corresponding author*: Indalecio Gustavo Martinez Velasco. Hospital Comunitario de Tecomatlán, Servicios de Salud del Estado de Puebla, Mexico. Email: Indaleciomvgine@outlook.com

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RESUMEN

Introducción: Los ácidos grasos poliinsaturados n-3, como el EPA y el DHA, son esenciales durante el embarazo por sus beneficios para la salud materna y el desarrollo fetal. En mujeres embarazadas con deficiencia de omega-3, es crucial evaluar la tolerabilidad, aceptabilidad y posibles efectos secundarios para optimizar la adherencia al tratamiento. **Objetivo:** Determinar la tolerabilidad y los principales efectos colaterales en un grupo de embarazadas con ingesta deficiente de pescado en una comunidad rural. **Material y métodos:** Se realizó una encuesta nutricional en un grupo de embarazadas que asistían a su control prenatal a una institución privada de Ginecoobstetricia para investigar la necesidad de suplementación con omega-3 mediante un cuestionario simplificado en una población de embarazadas. Se prescribieron 2 cápsulas conteniendo EPA 760 mg y DHA 520 mg a partir de las 20 semanas. Se documentó la presencia de efectos colaterales y la adherencia a la prescripción. **Resultados:** Se encontró un porcentaje de tolerabilidad del 100.0%. Los efectos colaterales fueron náusea 19.2 %, eructos 4.6 %, aliento a pescado 2.3 %, vómito 1.5 % y ningún caso de reacción alérgica. Ninguna paciente abandonó la suplementación. **Conclusiones:** Los efectos colaterales de los AGPI n-3 en el presente estudio fueron muy bajos, resultando en una excelente adherencia al tratamiento.

Palabras clave: parto pretérmino; omega-3; pregnancy; food frequency questionaire; fish; docosahexanoic acid.

INTRODUCTION

Long-chain omega-3 polyunsaturated fatty acids (n-3 PUFAs), specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) promote fetal neural and brain development when there is adequate intake of these nutrients during pregnancy.[1-4] Fish and other seafood, as well as plant-based foods such as chia seeds, are the primary sources of EPA and DHA in the diet during gestation in the Mexican population.[5-6]

Due to different studies showing that DHA requirements are insufficient in pregnant women in Latin America, including Mexico,[7-8] it is extremely important to supplement this population for two reasons: the first is that the placenta has a low conversion capacity (from 2% to 10%), which is insufficient to produce the necessary amount for fetal brain development, and the second is the low accessibility and cost in rural communities.[9-10]

The use of supplements is widely marketed in other countries;[11] however, few published articles on this topic worldwide make it essential to explore this area at the national level and even more so in communities with low accessibility and poverty.

Different side effects have been reported in the literature, including dizziness, diarrhea, nausea, belching, difficulty swallowing the capsule, fishy breath, and fatigue.[12]

This study aims to investigate the acceptability and side effects of omega-3 in a population with low fish intake in a rural Mexican community.

MATERIAL AND METHODS

Pregnant patients who attended their first prenatal visit at the Center for Nutrition Research and Perinatal Education from January 2022 to December 2023 were included. Each patient was invited to participate in the study and provided written information through a brochure and a video about the importance of consuming fish and/or supplements with n-3 PUFA to prevent preterm birth. Patients who agreed to participate in the study were asked to sign a consent form and complete a questionnaire during the first consultation, which included demographic, gynecological-obstetric, and fish intake frequency data (Annex 1).

Patients with low fish intake (never or only once a month) were given a supplement containing 760 mg of EPA and 520 mg of DHA per capsule (Herbalifeline, Herbalife Nutrition USA), prescribed twice daily, starting in week 20 of gestation. After one month, the patient was scheduled for a follow-up appointment to collect acceptability and side effects data. Inclusion criteria were age 18 to 35 years, gestational age of 14 to 19 weeks, and low fish consumption according to a simplified questionnaire. Exclusion criteria: Patient with a fish, shrimp, or other seafood allergy and intake of any vitamin containing any n-3. Elimination criteria: Patients with hyperemesis gravidarum and patients who discontinued treatment for another reason.

This project was carried out following the ethical principles established in the Declaration of Helsinki and with the approval of the local research committee (CLIS003) and the ethics of the institution's research committee.

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RESULTS

During the period, 138 were included, corresponding to the group with deficient fish intake, meaning those who never consumed it or only once a month. Eight patients were excluded from the group with deficient intake: 6 due to a history of fish allergy and two due to hyperemesis gravidarum, resulting in 130 patients who entered the group that received the supplement (Figure 1).

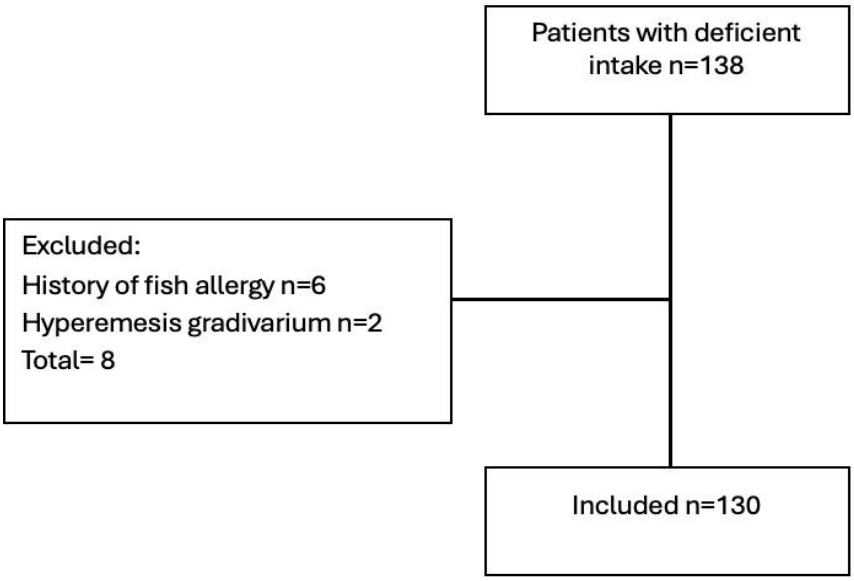

Figure 1. Flow diagram

The supplement's tolerability was 100.0%. 27.6% of the group reported side effects, the most common of which were nausea, belching, fishy breath, and vomiting (Table 1). There were no reported cases of allergy. No side effect prompted the discontinuation of the supplement.

Table 1. Side effects

TYPE OF EFFECT	No.	%
Nausea	25	19.2
Burping	6	4.6
Fishy breath	3	2.3
Vomit	2	1.5
Skin rash	0	0
TOTAL	36	27.6

Some patients experienced two side effects simultaneously.

DISCUSSION

After more than three decades of study, the benefits of omega-3 PUFA intake during pregnancy have been more clearly defined, primarily regarding DHA and EPA. Derived from the latest Cochrane review on the action of omega-3 during pregnancy published in 2018, which included over 70 controlled studies conducted by Middleton et al.,[13] strong evidence was found in qualitative studies. Pregnant women assigned to the group with fish, fish oil, DHA, or EPA intake or who were recommended to consume foods with omega-3 had an 11% reduction in the risk of preterm birth before 37 weeks and a 42% reduction in the risk of early preterm birth before 34 weeks.

Current guidelines recommend a regular consumption of 224-336 g, or 2 to 3 servings of fish per week during pregnancy, to consume an average of 200 mg/day of DHA.[14] Recent data shows that nearly a quarter of pregnant women in the United States do not consume fish, and only 16% take supplements.[15]

It has been shown that the requirements for omega-3 during pregnancy are insufficient in our country. Al-Hinai, in a cohort of pregnant women where the consumption of n-3 PUFAs was quantified using a standard food questionnaire during the different trimesters of pregnancy, demonstrated that in the first and second trimester, the 50th percentile of consumption was reported at 20 mg/day of EPA and 40 mg/day for DHA, and in the third trimester, the 50th percentile of consumption was reported at 10 mg/day of EPA and 40 mg/day for DHA, demonstrating the low consumption of PUFAs and consequently a higher risk of preterm birth.[16]

There are biochemical studies to determine the amount of omega-3 fatty acids through blood; however, they are not yet available in our country, making it very important to know the requirements through daily food frequency records (DFR). The DFR is a simple and inexpensive method, with its main drawback being the complexity involved in carrying it out and the time required by both the interviewer and the interviewee.[17] An important aspect to consider is knowing its degree of correlation. A correlation is considered low when it is < 0.30, moderate or acceptable between 0.30-0.49, and high if it is > 0.50.[18-19] Several studies have been published on the correlation between food frequency questionnaires and omega-3 levels in pregnant women. In Mexico, Parra et al. reported a good correlation between α-linolenic acid, DHA and EPA in erythrocyte membranes in a population of pregnant women, which was 0.32, 0.35 and 0.36, acceptable correlation.[20]

Reports from different countries in Europe (Norway and Switzerland) and Asia (China and Japan) have shown a good correlation between the level of n-3 AGPI and the food frequency consumption questionnaire.[21-24]

To skip lengthy questionnaires, Crawford at the Kansas Medical Center validated a simplified 7-question questionnaire called DHA-FFQ, also using graphical support in 1,355 pregnant patients, achieving an acceptable result when comparing the extensive questionnaire of the National Cancer Institute Diet Questionnaire II (DHQ II) with a shortened questionnaire, reporting a correlation level of 0.52 with the level of DHA in red blood cells versus 0.35 from the DHQ II.25 More recently, a study by Christifano et al. was published in which the DHA-FFQ was modified to create an electronic format of consecutive responses that can be completed by the respondent without the need for a trained interviewer, aiming to make it more practical for health personnel.[26]

Within the safety and tolerability aspect of current marine oil preparation prescription, a low frequency of adverse events has been found. According to the British National Formulary (BNF), side effects are classified as follows: common (burping, constipation, diarrhea, gastrointestinal discomfort, gastrointestinal disorders, nausea, vomiting), uncommon (dizziness, gout, bleeding, headache, hyperglycemia, hypotension, skin reactions, altered taste) and rare (liver disorders).[27] In a recent article on the clinical use and efficacy of EPA-DHA, Elgar describes that most studies involving omega-3 use in humans, have documented mild side effects, however, she mentions evidence of more serious effects, such as an increased risk of bleeding, possibly due to the inhibitory effect of marine oils on platelet aggregation in healthy patients, despite this, no cases of postoperative bleeding in patients undergoing surgery were found in 20 reviewed studies,[28] which is a relevant consideration given the potential need for cesarean section in a percentage of pregnant patients.

Adverse effects have been reported in the non-pregnant population, with a relative risk of dysgeusia 4.2, fatigue 3.6, constipation 3.2 and vomiting 2.2.[29] In the pregnant population, literature describing adverse effects is limited. According to Freeman, in a case series of 59 patients, 13 (22%) reported uncommon side effects, including dizziness, diarrhea, nausea, burping, reflux, difficulty swallowing capsules, bad breath and fatigue. The most common effect were difficulty breathing, bad taste and reflux; however, no patient discontinued the medication due to intolerance.[12] Given the increasing use of omega-3 supplements among pregnant women, both with and without a prescription, it is

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important to remain aware of the potential adverse effects associated with their use.

The main weakness of our study is that it was based on only one question about supplementation; however, we believe that it is practical and feasible for general practitioners or specialists to implement, because of the lack of availability of a nutrition specialist in their care center and, above all, because of the workload and extensive information provided during obstetric consultations, which makes it difficult to adequately assess this issue in prenatal consultations.[30]

One of the strengths of our study is that it was conducted in a rural area where fish is not available. The study found that the surveyed pregnant women have a deficient consumption rate of 53%, which is higher than that of the United States, where a percentage of 24.6% is reported, and in Australia, at 19.3%.[31-32]

CONCLUSIONS

Our data suggest that omega-3 supplementation during the perinatal period is well tolerated, with very low side effects, consequently improving the health of both the mother and the newborn.

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CONFLICT OF INTEREST

The authors of the article declare that they have no conflict of interest.

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ANNEX 1. QUESTIONNAIRE

1. What is your age?
2. What is your highest educational level?
   a) Primary
   b) Secondary
   c) Junior High School
   d) Professional
3. What is your obstetric history?
   a) First pregnancy
   b) Second pregnancy
   c) Multiple pregnancies
4. What is your marital status?
   a) Single
   b) Free union
   c) Married
5. How often do you consume fish?
   a) Never or less than once per month
   b) Less than once per week
   c) 1 or 2 times per week
   d) More than 3 times per week
6. Have you experienced any of the following side effects?
   a) Nausea
   b) Burping
   c) Fishy breath
   d) Vomiting
   e) Skin rash

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Review Article

Effectiveness of physiotherapy techniques for treating diastasis abdominis: A narrative systematic review

Natalie Fastag Weber[a1*], Begoña Maciel Cámara[a2], Vivian Dichi Michan[b3], Moisés Jonathan Magos Chong[a4], Artemio Efraim Cruz Vélez[a5], Irlanda Olvera Gómez[ac6]

[a]Universidad Anáhuac México, Facultad de Ciencias de la Salud, Estado de México.
[b]Universidad del Valle de México, Facultad de Ciencias de la Salud, Estado de México.
[c]División de Investigación. Hospital Juárez de México, Ciudad de México.

ID ORCID:

[1]https://orcid.org/0009-0006-6826-2850, [2]https://orcid.org/0009-0003-8980-5509, [3]https://orcid.org/0009-0000-1034-0584, [4]https://orcid.org/0009-0005-7154-6144, [5]https://orcid.org/0009-0003-3549-3116, [6]https://orcid.org/0000-0003-1698-6559

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ABSTRACT

Introduction: The body undergoes anatomical and physiological changes during pregnancy to support fetal development. One significant musculoskeletal change is abdominal diastasis (AD), which involves the separation of the rectus abdominis muscles, causing lumbopelvic stability issues. A proper evaluation and classification of AD are essential for its treatment. Some of the issues are instability, potentially leading to abdominal hernias, lower back pain, poor posture, deficiencies in the pelvic area, and loss of strength. The surgical reconstruction of the *linea alba* is the prevailing standard of medical treatment for AD, however, alternative therapeutic interventions, including various forms of physiotherapy, have been shown to be efficacious in the management of associated symptoms. **Objectives:** The objective of this study is to identify and assess the effectiveness of physiotherapy techniques for the treatment of AD in postpartum women, with a particular focus on determining which treatment approach results in the most effective reduction of the inter-recti distance. **Materials and methods:** A narrative systematic review was conducted. A comprehensive search was conducted in various databases, including PEDro, PubMed, ELSEVIER, and EBSCO, yielding a total of 62 articles. After the removal of duplicates, 33 articles were selected for further analysis, with publications spanning from 2017 to 2024, and written in both Spanish and English languages. The final selection comprised studies that met the predetermined inclusion criteria, encompassing the utilization of exercises and/or deep core stability, muscle strengthening, deep core stability, kinesiotape, neuromuscular electrical stimulation, and hypopressive techniques. **Results:** The results of the study indicated that the most efficacious treatments for AD are abdominal exercises, muscle strengthening, and deep core stability. **Conclusions:** The most effective physiotherapy treatment for AD is exercise and/or core stability, which may serve as an effective adjunct treatment to conventional care.

Key words: techniques; treatment; abdominal diastasis; non-surgical treatment; physiotherapy.

* *Corresponding author*: Natalie Fastag Weber. Universidad Anáhuac México, Facultad de Ciencias de la Salud. Huixquilucan, Estado de México, México. Address: Av. Universidad Anáhuac núm. 46, Lomas Anáhuac, 52786. Huixquilucan, Estado de México, México. Email: natalie.fastagwe@anahuac.mx

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RESUMEN

Introducción: Durante el embarazo, el cuerpo experimenta cambios anatómicos y fisiológicos significativos, entre ellos la diástasis abdominal (AD), que implica la separación de los músculos rectos del abdomen. Este cambio puede causar inestabilidad lumbopélvica, dolor lumbar, mala postura, deficiencias pélvicas y pérdida de fuerza, además de aumentar el riesgo de hernias abdominales. La reconstrucción quirúrgica de la línea alba es el tratamiento estándar para la AD, pero las intervenciones de fisioterapia podrían ser una alternativa efectiva para controlar los síntomas y mejorar los resultados. **Objetivo:** Evaluar la efectividad de técnicas fisioterapéuticas para tratar la AD en mujeres posparto y determinar qué tratamiento reduce mejor la distancia entre los rectos abdominales. **Material y métodos:** Se realizó una revisión narrativa sistemática de 33 artículos seleccionados tras buscar en bases como PEDro, PubMed y ELSEVIER. Los estudios analizados incluían técnicas como ejercicios abdominales, fortalecimiento muscular, estabilidad profunda del core, kinesiotape, estimulación eléctrica neuromuscular y técnicas hipopresivas. **Resultados:** Los ejercicios abdominales, el fortalecimiento muscular y la estabilidad del core fueron las intervenciones más efectivas para tratar la AD. **Conclusión**: El ejercicio y la estabilidad del core son tratamientos fisioterapéuticos eficaces para la AD y pueden complementar los cuidados médicos habituales, mejorando los resultados y la calidad de vida de las mujeres en el posparto.

Palabras clave: técnicas; tratamiento; diástasis abdominal; fisioterapia; diastasis postparto; tratamiento no quirúrgico.

INTRODUCTION

During pregnancy, the mother's body undergoes changes in terms of anatomy, biomechanics and physiology. A significant proportion of these alterations commence shortly after fertilization and persist throughout the entire duration of pregnancy, with the maternal body returning to its pre-pregnancy state following the postpartum and location period, as defined by the World Health Organization (WHO) and characterized by a duration ranging from six months to two years.[1,2] Diastasis abdominis (AD) is one of the more common postpartum conditions. AD is defined as the separation of the rectus abdominis muscles along the *linea alba.*[3] Approximately 30% to 70% of women experience AD during pregnancy, and 60% of them continue to have AD for the rest of their lives.[4] During the third trimester of pregnancy, the incidence of AD exceeds 60%, while in the immediate postpartum period the incidence is about 53% and in the late postpartum period the incidence declines to 36%.[5] The prevalence of AD is 33% at 21 weeks of gestation, increasing to 60% at 6 weeks postpartum and decreasing to 45% to 32% between 6 and 12 months postpartum, respectively.[6]

The primary consequences of AD are reduced mobility and limited physical exertion, resulting from the laxity of the abdominal wall muscles.[7,8] An understanding of the anatomy of the abdominal wall muscles is fundamental to the comprehension of AD. These muscles play a crucial role in maintaining pelvic and lumbar stability, which can be compromised in individuals affected by AD. The *linea alba* represents the fusion of the aponeurosis of the transversus abdominis, the external oblique, the internal oblique and the rectus abdominis muscles.[9]

The internal and external oblique muscles contribute to trunk support and rotation. When there is AD coordinated contraction of these muscles become less effective, impacting the stability and biomechanics of the pelvis and abdomen.[9] The transversus abdominis, the deepest layer, works as a natural corset helping the core stability. AD interferes with this muscle's ability to maintain tension along the *linea alba* and control intra-abdominal pressure, leading to an increased lumbar curvature.[9] The rectus abdominis muscle separation weakens the *linea alba*, impacting on the postural balance and trunk functionality.[9]

POSTPARTUM DIASTASIS ABDOMINIS

One of the more common pathologies in the postpartum period is diastasis abdominis (AD), this refers to the separation of the rectus abdominis muscles, in which these are separated along the *linea alba.*[10] To achieve good lumbopelvic stability it is essential to have proper functioning of the articular, fascial, muscular and nervous components of the abdomen.[10] An alteration in any of these structures can compromise stability, potentially leading to abdominal hernias, lower back pain, poor posture, deficiencies in the pelvic area, loss of strength.[8] In some cases, it may cause more complicated issues such as respiratory defects, limited trunk movements, primarily rotation, bending and

flexion, support of the abdominal viscera, aesthetic defects and persistent lumbopelvic pain.[11] Some risk factors include maternal age, multiparity, previous cesarean sections, obesity, multiple pregnancies, ethnicity and fetal macrosomia.[12]

DIASTASIS ABDOMINIS EXPLORATION FOR DIAGNOSIS

In the physical examination for diagnosing AD, an abdominal bulge is usually observed, which worsens with the contraction of the rectus abdominis muscles or a Valsalva maneuver.[13] The diagnosis should be confirmed through imaging studies such as ultrasound, computed tomography or magnetic resonance imaging of the rectus abdominis, measuring the separation between the muscles in three segments; at the level of the xiphoid process, 3 cm above the umbilicus, and 2 cm below the umbilicus.[14]

DIASTASIS ABDOMINIS CLASSIFICATION

The anatomy and classification of AD are fundamental aspects for the comprehension of the abdominal wall conditions, that is why different ways of classification of AD are described in this review.[15] Nahabedian establishes that anatomical structures include the *linea alba*, rectus abdominis, internal and external obliques and their fascias.[15] The *linea alba* is composed of organized collagen fibers and has a distance of 11 to 21 mm between the xiphoid process and the umbilicus, a distance of 2 to 11 mm between the umbilicus and the pubic symphysis.[15]

The German Hernia Society and the International Endohernia Society propose that the rectus abdominis muscles have a separation of no more than 1 to 2 cm and a separation greater than 2 cm is considered AD.[16] The European Hernia Society classifies diastasis recti based on three criteria: type, distance between the rectus abdominis muscles, and the presence of a concomitant umbilical and/or epigastric hernia.[17] The classification has four grades: I, II, III and IV; each grade is subdivided depending on whether the woman is postpartum or has adiposity and whether a hernia is present.[17] The distance is divided into three categories: D1 >2-3 cm, D2 >3-5 cm and D3 >5 cm.[17]

According to Keramidas *et al.* in 2022, AD can be classified into four types: type A, with a separation of 2-3 cm, indicating mild AD; Type B, with a separation of 3-5 cm, indicating a moderate AD; Type C, with a separation of 5-7 cm, indicating severe AD and Type D, with a separation of 7-9 cm, indicating very severe AD. They say diastasis must be measured subxiphoid, epigastric, umbilical, infraumbilical and suprapubic.[18] Beer *et al.* mention that abdominal diastasis is considered based on the following distances: 15 mm at the level of the xiphoid process, 22 at the supraumbilical level, and 16 mm at the infraumbilical level.[14] This study aims to evaluate physiotherapy treatment options for AD, providing a comprehensive perspective that can guide evidence-based clinical practice and future research. With the main objective to identify and assess the effectiveness of physiotherapy techniques for treating AD in postpartum women, determining which treatment best reduces the inter-recti distance.

MATERIALS AND METHODS

Study design

This study is a narrative systematic review conducted following the PRISMA methodology. This review aims to synthesize the available evidence of the most effective physiotherapy techniques for treating abdominal diastasis in postpartum AD.

Search strategy

A comprehensive search of articles published between 2017 and October 2024 was conducted in the databases PEDro, PubMed, ELSEVIER, and EBSCO. The search included studies written in both English and Spanish, using terms such as “techniques”, “treatment”, “abdominal diastasis”, “non-surgical treatment”, and “physiotherapy”, with their respective translations.

Methodological quality and risk of bias

The measurement of the risk of bias and the quality of bias of the articles included was evaluated independently by two evaluators; through the risk of bias assessment tool PEDro scale. This was used to analyze the methodological quality of all the selected articles, given that its use is recommended for the analysis of evidence in clinical trials.

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Eligibility criteria

The selection of studies was based on the PICO criteria **(Table 1).** The evaluated indicators included the reduction of the inter recti distance measured at three different points: subxiphoid, umbilical and infraumbilical; increased strength of the abdominal muscles, improvement in deep core stability and reduction in lumbopelvic pain. These outcomes were analyzed to assess the effectiveness of physiotherapy techniques in treating AD in postpartum women.

Table 1: Description of the PICO acronym and MeSH (Medical Subject Headings) terms for the search of studies

Acronym	Definition	Term
P	Participants/articles	Postpartum women with diagnosis of diastasis abdominis.
I	Intervention	Physiotherapy techniques and treatments.
C	Comparison	Different techniques and treatments used or no intervention.
O	Results	Effects of used techniques.

Inclusion criteria included: studies with variables determined before and after the intervention; participants treated solely through physiotherapy interventions; articles in English and Spanish; publications from 2017 to October 2024, any other sources published before 2017 or written in a language besides English or Spanish were excluded. Exclusion criteria include studies that involve the administration of medications for pain or inflammation; studies where the treatment is surgical; and theses. The articles included experimental studies, observational studies and original and review research. A total of 62 scientific articles were evaluated, matching our search criteria. Initially selected through a review of their titles and abstracts. Subsequently, a full-text review was performed to make the final selection of studies based on the established inclusion and exclusion criteria **(Figure 1).**

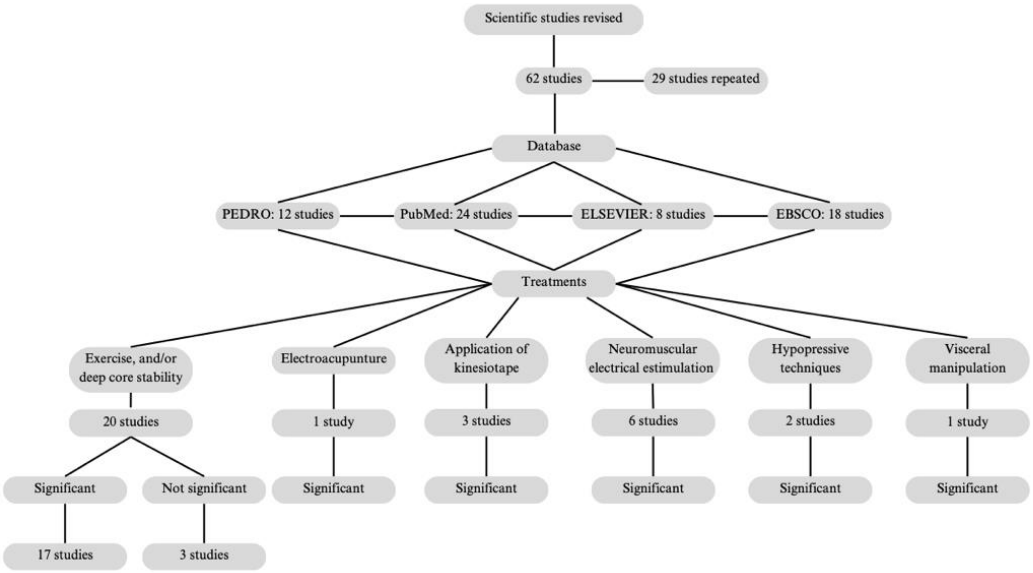

Figure 1: PRISMA flow chart for analyzing results.

Data extraction and management

Data were collected through a review of the full texts and evaluated. Additionally, the PEDro scale was used to assess the methodological quality and risk of bias of the selected studies.

Data analysis

The results of the selected studies were synthesized, and the effectiveness of different physiotherapy techniques in reducing abdominal diastasis in postpartum women was evaluated. The results were summarized in a flowchart using the PRISMA methodology **(See Figure 1).**

RESULTS

Study selection

A thorough review of 62 scientific articles, obtained from bases such as PEDro, wich contributed with 7 studies, PubMed 18 studies, ELSEVIER contributed with 8 studies and EBSCO with 18 studies. Among the final 33 studies, there were 23 experimental studies, 8 observational studies and 2 original and review research studies. Sample sizes varied significantly: 8 studies involved over 90 participants, 3 included 50-89 participants, 19 reported 10-49 participants and 3 had fewer than 10 participants, 3 of the reviewed studies did not disclose participant numbers. The studies primarily focused on interventions such as exercise and deep core stability (20 studies), neuromuscular electrical stimulation (6 studies), kinesiotape (3 studies), hypopressive techniques (2 studies), visceral manipulation (1 study) and electroacupunture (1 study). Of these, 90.0% demonstrated significant reductions in AD severity, employing longer and more frequent sessions of treatment. These protocols used treatment sessions that were 2 to 5 times per week and between 30 to 50 minutes per session. This variation in session duration and frequency highlights the different approaches used, which could influence the congruity of results among different intervention types **(Table 2).**

Table 2. Details of the included studies

Study	Participants	Intervention	Duration	Frequency	Outcomes	Authors
Experimental Study	198 participants	Neuro-Muscular Electrical Stimulation (NMES)	12 weeks	3 times a week x 30 minutes	Significant results	35
Experimental Study	40 participants	Neuro-Muscular Electrical Stimulation (NMES)	4 weeks	3 times a week x 30 minutes	Significant results	36
Experimental Study	175 participants	Exercises and/or deep core stability	16 weeks	1 time a week x 45 minutes	Not significant results	19
Experimental Study	35 participants	Exercises and/or deep core stability	4 weeks	5 times per week x 50 minutes	Significant results	20
Experimental Study	98 participants	Hypopressive techniques	1 session	Once	Significant results	42
Observational Study	30 participants	Exercises and/or deep core stability	Immediate	Once	Significant results	21
Experimental Study	42 participants	Neuro-Muscular Electrical Stimulation (NMES)	8 weeks	3 times a week x 30 minutes	Significant results	37
Observational Study	93 participants	Exercises and/or deep core stability	6 weeks.	Six 20-minute sessions	Significant results	22

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Original and Review	8 participants	Exercises and/or deep core stability	12 weeks	3 times a week	Significant results	23
Experimental Study	8 participants	Exercises and/or deep core stability	12 weeks	3 times a week	Significant results	23
Experimental Study	175 participants	Exercises and/or deep core stability	16 weeks	1 time a week x 45 minutes	Not significant results	24
Observational Study	504 participants	Exercises and/or deep core stability	3 to 12 months post-partum	>2 x week 2-5 x week <5 x week 1-2 x week	Significant results	25
Observational Study	38 participants	Exercises and/or deep core stability	Immediate	Once	Significant results	26
Experimental Study	60 participants	Neuro-Muscular Electrical Stimulation (NMES)	8 weeks	3 times a week x 30 minutes	Significant results	12
Experimental Study	66 participants	Neuro-Muscular Electrical Stimulation (NMES)	6 weeks	3 times a week x 20 minutes	Significant results	38
Experimental Study	24 participants	Kinesiotape	6 weeks	3 times a week x 30-45 minutes	Significant results	39
Experimental Study	37 participants	Exercises and/or deep core stability	6 weeks	2 times a week x 40 minutes	Significant results	4
Observational Study	3 participants	Visceral manipulation (VM)	18 to 36 weeks	Every 3 to 4 weeks	Significant results	45
Experimental Study	110 participants	Electro-acupuncture	2 weeks	5 times a week x 30 minutes	Significant results	44
Experimental Study	24 participants	Kinesiotape	48 hours	Once	Significant results	40
Experimental Study	35 participants	Exercises and/or deep core stability	4 weeks	5 times a week x 50 minutes	Significant results	20
Experimental Study	32 participants	Neuro-Muscular Electrical Stimulation (NMES)	6 weeks	7 times a week x 20 minutes	Significant results	44
Observational Study	46 participants	Hypopressive techniques	8 weeks	2 times a week x 45 minutes	Significant results	43
Experimental Study	41 participants	Exercises and/or deep core stability	8 weeks postpartum.	3 times a week x 10 minutes	Significant results	27
Original and Review	24 participants	Kinesiotape	Not specified	Not specified	Significant results	41
Experimental Study	38 participants	Exercises and/or deep core stability	Not specified	Not specified	Significant results	28
Observational Study	38 participants	Exercises and/or deep core stability	Not specified	Not specified	Significant results	31
Observational Study	19 participants	Exercises and/or deep core stability	Not specified	2 times a week	Significant results	30
Experimental Study	96 participants	Exercises and/or deep core stability	Not specified	2 times a week x 30 minutes	Non significant results	29

Experimental Study	40 participants	Exercises and/or deep core stability	8 weeks	3 times a week x 30 min	Significant results	11
Experimental Study	45 participants	Exercises and/or deep core stability	8 weeks	3 times a week	Significant results	32
Experimental Study	32 participants	Exercises and/or deep core stability	12 weeks	Weekly sessions	Significant results	33
Experimental Study	70 participants	Exercises and/or deep core stability	12 weeks	5 times a week x 10 minutes	Significant results	26

Exercise and/or core stability effects on AD

The effects of different exercises and core stability techniques on AD were evaluated. Specific types of exercises included isometric contractions, Pilates, and deep abdominal muscle strengthening. Muscular endurance was defined as the ability to sustain contractions over a specific period or test. For core stability-based techniques, improvements in reducing the inter recti distance were specifically assessed trough ultrasound imaging, along with their impact on lumbopelvic stability. Protocols ranged from 4 to 16 weeks, including supervised and self-guided exercises, performed 2 to 5 times per week for 30 to 50 minutes each session. Significant improvements were showed in 90.0% of the protocols noted in endurance, inter-recti distance, and functionality. However, a few studies showed no significant differences when comparing intervention groups to control groups.[4,11,19-34]

The effect of neuromuscular electrical stimulation

Neuromuscular electrical stimulation was used as a technique across several studies. Protocols combined NMES with exercise and/or core stabilization. Protocols were applied from 2 to 5 weeks, with a frequency of 2 to 5 times a week in sessions of 20-30 minutes.

Results showed significant improvements in abdominal wall muscle strength, inter-recti distance, and waist-hip ratio. A greater effectiveness was observed when NMES were combined with exercise.[12, 35-38]

Kinesiotape use for treating AD

Kinesiotape was used as a complementary therapy for AD. Studies evaluated both immediate and short-term effects, using applications averaging 48 hours. The results in these studies showed improvements in lumbopelvic stability and inter-recti distance, especially when combined with exercise.[39-41]

Hypopressive techniques

Hypopressive techniques were used as an alternate core strengthening protocol, reducing AD. These were implemented in structured, short-duration sessions. Results indicated that hypopressives might enhance the tensile response of the *linea alba*, having a direct impact on AD.[42,43]

Electroacupuncture

Electroacupuncture combined with physical exercises, was evaluated as an intervention for postpartum women with AD. The protocol was applied 5 days a week, for 2 weeks and 30 minutes per session. Significant reductions were found between the inter-recti distance, the lack of advanced and more extensive research could be beneficial for the use of electroacupuncture as treatment of AD.[44]

Visceral manipulation

Visceral manipulation was used as a therapeutic approach focusing on the mobility of abdominal structures, targeting the jejunoileal area in women with AD. This intervention involved sessions spaced from 18 to 36 weeks with treatment every 4 weeks. Results showed decreased pain levels, improved functional activity and a better bowel function as well as enhanced bladder function.[45]

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Adverse events

Adverse events were not reported in any of the included studies.

DISCUSSION

The findings of this study corroborate previous research on the effectiveness of physiotherapy techniques for treating diastasis recti (DR). Recent studies have highlighted that deep core strengthening exercises, such as hypopressives and isometric exercises, are effective in reducing inter-recti distance and improving lumbopelvic stability[5,34] (See Table 2).

Additionally, literature indicates that combining techniques like kinesiotape application and specific exercises can significantly enhance abdominal strength and alleviate DR-associated pain.[11,40]

Despite the observed benefits, some studies have reported variability in outcomes depending on the postpartum timing of the interventions. For instance, Gluppe *et al*. found that interventions initiated within the first 6 weeks postpartum achieve greater reductions in inter-recti distance compared to those started later.[24] These findings underscore the importance of timing in treatment initiation and the need to personalize interventions based on individual patient characteristics.[9]

However, one challenge identified in this review is the lack of consistency in evaluation methods, as seen in studies using varied techniques to measure functionality and inter-recti distance.[15,18] Therefore, it is recommended to standardize methodologies to facilitate result comparison and improve the quality of available evidence.

AD is one of the most common conditions after postpartum and some women live with this condition all their lives. However, one of the limitations found was the lack of scientific articles and studies in literature, making it extremely difficult to find the most effective treatment for this condition.

AD is relevant because 30-70% of women have it after giving birth, and 60% of them continue to have AD in their postpartum period. This affects their everyday activities and prevents them from having a good quality of life. This condition may cause abdominal hernias, lumbopelvic pain, bad posture, pelvic deficiencies, and decreased strength. However, different physiotherapy treatments are used to treat AD, helping patients to have a fully functional abdominal wall without having to get a surgical repair of their *linea alba*.

The results of this study suggest that exercise and/or core stability have a significant impact on the reduction of AD. Previous investigations stand out because of the effectiveness of the strengthening of the abdominal wall muscles. Additional data shows that neuromuscular electrical stimulation (NMES) can also be effective, according to the studies found that were all significant.

In comparison with other techniques like the use of Kinesio tape and hypopressive techniques, the results were all significant but showed less effectiveness due to the limited number of studies. The articles on visceral manipulation and electroacupuncture present both interventions as notable but lack further evidence to confirm their effectiveness, primarily due to insufficient high-quality research on these approaches.

Some studies had well-designed methods, while others had flaws, like a small number of participants, very few sessions, or short clinical trial periods. The strengths of this review are that the studies included were from multiple countries and four different databases which provided a global perspective. However, a weakness is that only studies written in English and Spanish were included, which might limit the findings. The diversity of treatment approaches provides a broad and updated vision of the different physiotherapy options for the treatment of AD.

CONCLUSION

In conclusion, following a comprehensive analysis of the various techniques employed in the treatment of AD, it was determined that abdominal exercises, muscle strengthening, and deep core stability represent the most efficacious techniques for the comprehensive treatment of AD in postpartum women. These techniques may serve as an effective adjunct treatment in conjunction with standard care.

CONFLICT OF INTEREST

The authors declared that they had no conflicts of interest.

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Review Article

Pediatric physiotherapeutic intervention in Classical Ehlers-Danlos

Mónica Planas Rego[a1], Paulette Laniado Abud[a2], Miguel Ángel Martínez Camacho[a3], Natalie Fastag Weber[a4], Paloma Gómez Llano[a5], Irlanda Olvera Gómez[ab6]

[a]Universidad Anáhuac México, Facultad de Ciencias de la Salud, Estado de México, México.
[b]Hospital Juárez de México, División de Investigación, Ciudad de México, México.

ID ORCID:

[1]https://orcid.org/0009-0005-7768-1240, [2]https://orcid.org/0009-0002-3312-765X, [3]https://orcid.org/0000-0001-5088-4666, [4]https://orcid.org/0009-0006-6826-2850, [5]https://orcid.org/0009-0001-5847-8686, [6]https://orcid.org/0000-0003-1698-6559

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ABSTRACT

Ehlers-Danlos Syndrome (EDS) is a group of genetic connective tissue disorders characterized by mutations in the genes encoding collagen, collagen-modifying enzymes and other extracellular matrix proteins. These alterations result in clinical manifestations such as joint hypermobility, skin fragility and musculoskeletal complications, which have a significant impact on patients' quality of life. Although scientific evidence on the physiotherapeutic management of EDS is limited, it has been observed that specific interventions can improve joint stability, muscle strength and functionality, especially in pediatric patients. The aim of this article is to provide an updated review of EDS in the pediatric population and to propose a comprehensive and multidisciplinary physiotherapeutic approach focusing on the prevention of complications, management of symptoms and promotion of active participation in activities of daily living.

Key words: ehlers-danlos syndrome (eds); classical ehlers-danlos syndrome (ceds); pediatrics; physical therapy; treatment; collagen.

* *Corresponding author*: Mónica Planas Rego. Universidad Anáhuac México, Facultad de Ciencias de la Salud. Address: Av. Universidad Anáhuac núm. 46, Lomas Anáhuac, 52786. Huixquilucan, Estado de México, México. Estado de México, México. Email: Tel.: +52 55 5627 0210. Email: monica.planasre@anahuac.mx

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RESUMEN

El Síndrome de Ehlers-Danlos (SED) es un grupo de trastornos genéticos del tejido conjuntivo caracterizados por mutaciones en los genes que codifican el colágeno, las enzimas modificadoras de colágeno y otras proteínas de la matriz extracelular. Estas alteraciones generan manifestaciones clínicas como hiperlaxitud articular, fragilidad cutánea y complicaciones musculoesqueléticas, que impactan significativamente en la calidad de vida de los pacientes. Aunque la evidencia científica sobre el manejo fisioterapéutico del SED es limitada, se ha observado que intervenciones especializadas pueden mejorar la estabilidad articular, la fuerza muscular y la funcionalidad, especialmente en pacientes pediátricos. Este artículo tiene como objetivo proporcionar una revisión actualizada sobre el SED en población pediátrica y proponer un abordaje fisioterapéutico integral y multidisciplinario, centrado en la prevención de complicaciones, el manejo de síntomas y la promoción de la participación activa en las actividades de la vida diaria.

Palabras clave: síndrome de ehlers-danlos (sed); síndrome de ehlers danlos clásico (cSED); pediatría; fisioterapia; tratamiento; colágeno.

INTRODUCTION

Ehlers-Danlos Syndrome (EDS) is a group of inherited connective tissue disorders characterized by defects in collagen synthesis leading to widespread structural weakness of the skin, joints, blood vessels and other tissues. The term was first introduced in 1934 by Pommeau Delille and Soussie, referring to the Danish dermatologist Edvard Laurits Ehlers, who described dermal hyperelasticity and joint hypermobility in 1901, and the French physician Henri-Alexandre Danlos, who identified molluscoid pseudotumours in 1908.[1]

The 2017 International Classification of EDS defines 13 different types, including classical (cEDS), vascular (vEDS) and hypermobile (hEDS), each with unique genetic and clinical characteristics. These conditions often result in musculoskeletal instability, chronic pain, frequent dislocations, proprioceptive deficits and fatigue, which significantly impair daily function and quality of life. Given these challenges, physiotherapy plays a key role in optimizing joint stability, preventing injury and promoting functional independence.[2]

An essential component of physiotherapeutic management in cEDS is progressive strength training, which targets muscle groups to compensate for joint laxity and improve dynamic stability. Strengthening exercises, particularly those focusing on core stability and postural control, help reduce the incidence of joint subluxations and improve biomechanical efficiency. Additionally, neuromuscular re-education and proprioceptive training enhance joint awareness, reducing the risk of falls and injuries.

The Physiotherapeutic Intervention Model (PIM) provides a structured framework for patient care, encompassing examination, evaluation, diagnosis, prognosis, intervention, and re-evaluation. By integrating the International Classification of Functioning, Disability, and Health (ICF), physiotherapists can tailor interventions to address both physical impairments and activity limitations, ensuring a holistic and patient-centered approach.

Ultimately, a well-designed physiotherapy program that includes strength training, joint stabilization exercises, proprioceptive retraining and pain management strategies can significantly improve the functional outcomes and quality of life of people with EDS. Through a combination of targeted interventions and patient education, physiotherapists empower individuals to manage their condition effectively, promoting long-term musculoskeletal health and improved daily function.[3]

MATERIALS AND METHODS

A comprehensive literature search was conducted in the PubMed database using Medical Subject Headings (MeSH) terms, guided by the PICO (population, intervention, comparison, outcome) framework to ensure a focused research question. The PICO question was formulated as follows: In pediatric patients with Classical Ehlers-Danlos Syndrome (cEDS), does the use of physiotherapy interventions (such as strengthening exercises, hydrotherapy and early mobilization) improve joint stability, reduce pain, increase muscle strength and improve quality of life compared with standard care without specialized physiotherapy? The search strategy included the following MeSH terms: ("Ehlers-Danlos Syndrome"[Mesh]) AND "Physical Therapy Modalities"[Mesh]) OR "Exercise"[Mesh]) OR "Hydrotherapy"[Majr]) AND "Muscle Strength"[Mesh]) OR "Quality of Life"[Majr]) OR "Joint Instability"[Majr].

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The selection of articles was carried out in three stages. First, duplicates were removed using reference management software. Second, titles and abstracts were screened to identify studies that met the inclusion criteria, which required explicit mention of Ehlers-Danlos syndrome and a focus on physiotherapy interventions in pediatric populations. Finally, full-text articles were reviewed to confirm their relevance. Initially, 754 articles were retrieved. After applying the inclusion criteria, the selection was narrowed down to 28 articles that specifically addressed physiotherapy management in pediatric patients with CEDS.

The search was limited to articles published between 2013 and 2023 and available in English and Spanish. Only studies conducted on human subjects, specifically paediatric patients diagnosed with CEDS, were included. Only open access articles were included to ensure accessibility and reproducibility of results. Systematic reviews with meta-analyses and clinical trials were prioritised due to their high level of evidence; however, observational studies and case reports were also included to provide a broader understanding of the topic.

Data extraction included study design, sample characteristics, intervention details, outcomes measured and key findings. This methodology ensured a structured and transparent approach to identifying, appraising and synthesising the available evidence on physiotherapy interventions for paediatric patients with classic Ehlers-Danlos syndrome.

Classical Ehlers-Danlos

Ehlers-Danlos syndrome is an autosomal dominant connective tissue disorder characterised by atrophic scarring, hypertensive skin and joint hypermobility. Patients with classical Ehlers-Danlos syndrome also have frequent rapid bruising, fragile skin that feels "velvety" to the touch, and frequent wounds that leave atrophic scars. Patients with classic Ehlers-Danlos often have scoliosis and mitral valve prolapse[4,5.]

Molecular and genetic mechanisms

Collagen and protein defects are found in all types of Ehlers-Danlos, with an abnormal nucleation of collagen fibrils so there is an alteration in the organization of cell fibrils. Due to the mutation in the COL5A1 and COL5A2 genes in patients with Classical Ehlers-Danlos, it synthesizes approximately half of the type V collagen compared to people without the mutation or structural involvement.[6-8]

The collagen fibers in Classical EDS have a variable fiber diameter with an irregular border.[6]

Epidemiology

According to the Ehlers Danlos Society, the prevalence of Ehlers-Danlos syndrome varies depending on the type. Specifically speaking of Classical Ehlers-Danlos, the prevalence is 1 in 20,000-40,000 people worldwide, however, information on the epidemiology in Mexico is limited.[9]

Natural history of the disease

Classical Ehlers-Danlos syndrome involves several clinical features and changes over time. The progression of the manifestations of EDS depends on different factors.

The first clinical manifestation that patients encounter is easy bruising in early childhood when they are learning to crawl and appear with the slightest trauma.[10] Likewise, skin hyperextensibility and joint hypermobility can lead to an increased propensity for joint dislocation become visible in early stages.[11] Other visible signs are "cigarette paper" scars and slow tissue repair as patients are easily injured and must be sutured.[4] Patients may experience pain throughout their lives; however, it is not disabling.

Voermans mentions that patients may have minimal, moderate or severe muscle weakness, delaying developmental milestones.[12] It is common for patients with a proper diagnosis to be monitored with cardiac workup.

A study in the American Journal of Medical Genetics states that 33% of patients with cEDS have osteopenia.[10] In the ocular aspect, patients may have thin, transparent and steep corneas.[13] Another characteristic is gastrointestinal problems with nausea being the main symptom.[4]

Patients have a normal life expectancy compared to someone without the disease,[11] however they may have cardiovascular problems such as aneurysms, ruptured arteries, and ruptured mitral and tricuspid valves.[10]

Diagnosis

To make a proper diagnosis it is important to first identify that the patient does have the disease and then specify the type.

For the screening of Ehlers-Danlos, the Beighton test (1998) must be performed.[15] The specifications of this test can be found in (Table 1). It is also necessary to complement family history to find where the inheritance comes from, and which are the signs that the relative presented. To determine the type, it is necessary to consult the criteria shown in the International Classification of Ehlers-Danlos Syndrome (2017).[16]

Table 1. Specific tests

Test	Description
Observation and palpation	Observation can provide an overview of the patient's development.[19] To complement the evaluation, palpation of the tissues is necessary to perceive joint motion, muscle weakness or tension, edema/fibrosis, and areas of reflex activity.[20]
Beighton (1998)	It requires 4 points or more out of a total of 9. The subjects are evaluated on a 9-point scale, considering 1 point for each hypermobile site, performed on both hemispheres and measuring the following:[15] – Hyperextension of the elbows (more than 10º), with the subject seated on a stool and with the arm explored by the examiner in extension. – Passive touching of the forearm with the thumb, with the wrist in flexion, with the subject in the same position as before. – Passive extension of the index finger to more than 90°, with the subject seated and with the palm of the hand fully resting on the examination table. – Hyperextension of the knees (10° or more), with the subject in the supine position. The examiner explores the joint, determining its degree of extension.
Canadian Occupational Performance Measure (COPM)	It is a tool used to measure patients' improvement in daily activities.[21]
Faces Pain Scale-Revised (FPS-R)	The Faces Pain Scale-Revised (FPS-R), is used to assess pain in pediatric patients by means of 6 faces, ranging from 0 to 10 in multiples of 2 (0, 2, 4, 6, 8, 10).[22]
Functional tests	The pediatric balance scale and the Functional Strength Measurement to assess balance and strength actively with different movements.[23]
Maximum repetition	To measure the force, it is recommended to evaluate the patient's Maximum Repetition,[23] "defined as the capacity of a defined muscle or muscle group to exert force against a resistance in a single maximal effort".[24]
Maximum heart rate	Patients with Ehlers-Danlos may present cardiovascular manifestations such as mitral valve prolapse; tricuspid valve prolapse or aortic dilation.[7]
Gait examination	A gait examination can prevent, and correct sequelae caused by different pathologies.[25]
Neurological evaluation	Patients with Ehlers Danlos may have alterations in the nervous system; therefore, it is recommended to test for myotomes, dermatomes and osteotendinous reflexes.[26]

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If the diagnosis is unclear, it can be confirmed by genetic testing to determine which gene or enzyme is affected.[16]

Multidisciplinary approach

It is crucial to note that EDS involves several factors, and a comprehensive approach is essential for this intervention, which will require transdisciplinary collaboration.

Since there is no cure for the disease, the treatment should be focused on preventing the progression and complications of the disease by a multidisciplinary team where the health-care specialists can assess the affections that patients have in their respective fields.[11] This team commonly includes a geneticist, physical therapist, rheumatologist, orthopedist, cardiologist or vascular surgeon, pain specialist, neurologist, nutritionist, psychologist, and psychiatrist to manage all the symptoms that these patients may have throughout their lives.[17,18] Also the patient's family members can be referred to a psychologist for support if required.[8]

Physiotherapeutic assessment

In order to provide personalized treatment and meet the needs of pediatric patients, it is necessary to carry out a series of specific tests on an ongoing basis. (Table 1) These help to get to know the patient better and to define short- and long-term goals more precisely, in a measurable and observable way.

Physiotherapeutic intervention

The physiotherapeutic intervention approach for Ehlers-Danlos syndrome in pediatric patients must be adapted to a preventive model. Since the diagnosis is part of the prevention and risk reduction associated with the syndrome, the intervention will be directed towards the creation of new physical practices with the purpose of maintaining the patient's well-being (Table 2).

Table 2. Example of a Pediatric Physiotherapeutic Intervention in Classical Ehlers Danlos

Type	Description
Workout games	It has been shown that workout games are an effective way to include daily activities as part of the treatment. They make the rehabilitation plan and physical therapy activities more entertaining and interactive.[29]
Strength	A circuit combining stability and strength exercises will be performed in which different muscle groups will be worked by strengthening the closed kinetic chain (CKC) and open kinetic chain (OKC) in the most didactic way and integrating their daily life activities.[30] Exercise will be used to prevent pain, to improve proprioception, balance and strength.[31] To carry out the strengthening plan, it is recommended for it to be done through games that involve weight load in several muscle groups using 40% of the maximum repetitions (MR) for each of the muscle to begin with, and each week it should be increased by 5% until they reach 60% of the MR.[24,32]
Hydrotherapy	It is recommended to assist swimming lessons in a 28-32°C pool, since exercise without load is useful to promote muscle development and coordination. For sessions of 30 minutes to tolerance. When working in an aquatic environment, the goal is to provide a setting where the patient feels safe and faces a reduced risk of injury. Heart rate must be monitored and kept between 40-60% of their maxHR.[30,33]
Protection for injury prevention	Patients should be encouraged to wear joint protection during physical activity, free play or walks to school. Bandages, knee, elbow and shin pads can be used to prevent dermal injuries due to skin fragility.[34]
Home plan	Develop personalized work plans by giving families the necessary guidance to continue therapy at home. This approach aims to actively involve the family in the rehabilitation process while integrating therapeutic exercises into their daily routines.[35]

Family education	Education is essential to positively influence the relationship between patients and family members in matters related to their health. When there is no information and education about pathologies, there are different problems such as the wrong use of medications, ineffective treatments and lack of treatment attachment.[36] The exercises that are performed in the therapy so that the family members can learn and support the treatment for better results.
Notes for the therapist - While performing the exercises, take care of the patient's posture and the correct performance of the exercises. - If the patient experiences pain or discomfort, reduce the time or end the exercise. - If the patient cannot do the exercise, it must be modified.	
CKC = *Closed Kinetic Chain*, OKC = *Open Kinetic Chain* MR = *Maximum Repetitions*, maxHR = *Maximum Heart Rate*	

The approach will be "Top-Down"; these interventions are also called "activity interventions." because it "focuses on the functional goals of the client, rather than those client factors or skill deficits that impede function".[27] Since EDS has no known cure, the approach seeks to manage symptoms and promote quality of life from a global perspective (Table 2). According to the WHO, meaningful participation can also improve quality of life by increasing acceptance and support from family members, caregivers, peers and the community.[28]

DISCUSSION

An in-depth review was conducted to analyze the population, interventions, comparisons and outcomes of pediatric physiotherapy interventions in Classical Ehlers-Danlos Syndrome (cEDS). Despite efforts to gather relevant information, a significant gap in scientific evidence regarding the physiotherapeutic management of cEDS has been identified. This lack of research and awareness often results in inadequate treatment for patients.

For this reason, it is of utmost importance to make an informative and formative program to educate the general population, as well as health professionals, so that patients with Ehlers-Danlos are treated in the best way in all the health fields they require, depending on the signs and symptoms they present. Despite the limitation in the lack of information about the disease, in physiotherapy, we work on the different body functions and structures through exercises, mobilizations and different techniques that provide patients with stability and strength, among other things. It is of utmost importance that in a patient with pediatric EDS there are interventions based on the patient's participation and activities of daily living to improve the affected structures. This syndrome is a heterogeneous disease, therefore, the goals and treatment of patients should be specialized and individualized for each one of them, always focusing on improving their quality of life and achieving their personal goals. Understanding the disease is essential, both by the patient and family members, so that patients can have a follow-up treatment and a home plan and can work with the prevention of complications and sequels.

CONCLUSION

Although there is still no cure, treatment should focus on preserving function and preventing complications of the disease to give these patients a better quality of life.

Exercise games are a great tool for rehabilitation plans and the implementation of physical activity, as they make the experience more didactic and entertaining for children. For an optimal outcome, the family should be educated about the disease and the importance of physiotherapy intervention. It is also important to involve other health professionals to cover the areas outside the scope of physiotherapy.

As a suggestion for future studies, it is recommended to test the proposed intervention in a child who has Classical Ehlers Danlos, adapting it to the child's needs and characteristics, to obtain the results and improvements of the proposed intervention.

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CONFLICTS OF INTEREST

The authors declared that they had no conflicts of interest.

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Case Report

Slow desensitization to fluconazole in woman with maculopapular exanthema

Pilar Alza[a1]*, Milagros Moreno[a2], Marcela Soria[a]

[a] HIGA Gral. San Martín, Servicio de Alergia, La Plata, Argentina

ID ORCID:

[1]https://orcid.org/0009-0001-8695-9022, [2]https://orcid.org/0000-0001-8647-2591

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ABSTRACT

Introduction: Desensitisation is a procedure that modifies the immune response to a pharmaceutical agent, thereby creating a transient tolerance to the drug in question. This allows the patient with an allergic reaction to continue receiving the requisite treatment without interruption. Once the desensitization process is terminated, the patient's hypersensitivity to the drug resumes. This case study presents the case of a 53-year-old woman with a personal history of kidney transplant who presents to the hospital with a lesion on the hallux of the left foot at the starting point of onychocryptosis, with a positive culture for cryptococci. The presumptive diagnosis is disseminated disease due to compatible lesions in the lungs, as indicated by computed tomography. Therefore, long-term treatment with fluconazole is recommended. During the administration of the antifungal agent, the patient developed a maculopapular rash with pruritus, which was diagnosed as a hypersensitivity reaction to the drug. Consequently, a slow desensitization procedure was performed to ensure the patient's safety and efficacy of treatment. **Objectives:** Describe a slow desensitization protocol in a patient with a non-IgE-mediated maculopapular reaction. Additionally, the medical history and clinical history of the patient, as well as the time of onset of symptoms after administration of the drug, were analyzed. Furthermore, a literature review on similar allergic reactions was conducted, and the medical and pharmacological interventions used were specified. **Material and methods:** We observed desensitization protocols in patients with a history of allergy and their subsequent monitoring. A desensitization protocol comprising 15 consecutive steps was implemented, adapted from a protocol for oral TMS in patients with HIV infection and a history of allergy to the antibiotic in question, as described by Absar et al. [11]. **Results:** The procedure was straightforward and efficacious, and thus the patient proceeded with the recommended dosage for the infectious condition. **Conclusion:** It was determined that the desensitization procedure is safe when conducted by trained medical professionals in a controlled setting.

Key words: *Cryptococcus neoformans;* transplant; hypersensitivity; disseminated infection; desensitization; fluconazole.

* *Corresponding author*: Pilar Alza. HIGA General San Martin. Address: Calle 1 y 70 La Plata, Buenos Aires, Argentina. Tel.: 2216231156. Email: pilaralza27@gmail.com

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RESUMEN

Introducción: La desensibilización es un procedimiento que modifica la respuesta inmune a un agente farmacológico, creando así una tolerancia transitoria al medicamento en cuestión. Esto permite que el paciente con una reacción alérgica continúe recibiendo el tratamiento necesario sin interrupción. Una vez finalizado el proceso de desensibilización, la hipersensibilidad del paciente al medicamento se reanuda. Este reporte de caso presenta el caso de una mujer de 53 años con antecedentes personales de trasplante renal que se presenta en el hospital con una lesión en el hallux del pie izquierdo en el punto inicial de onicocriptosis, con un cultivo positivo para criptococos. El diagnóstico presuntivo es una enfermedad diseminada debido a lesiones compatibles en los pulmones, como lo indica la tomografía computarizada. Por lo tanto, se recomienda un tratamiento a largo plazo con fluconazol. Durante la administración del agente antifúngico, la paciente desarrolló un exantema maculopapular con prurito, que fue diagnosticado como una reacción de hipersensibilidad al medicamento. En consecuencia, se llevó a cabo un procedimiento de desensibilización lenta para garantizar la seguridad del paciente y la eficacia del tratamiento. **Objetivos:** Describir un protocolo de desensibilización lenta en una paciente con una reacción maculopapular no mediada por IgE. Además, se analizaron los antecedentes médicos y la historia clínica de la paciente, así como el tiempo de aparición de los síntomas tras la administración del medicamento. Asimismo, se realizó una revisión de la literatura sobre reacciones alérgicas similares y se especificaron las intervenciones médicas y farmacológicas empleadas. **Material y métodos:** Observamos protocolos de desensibilización en pacientes con antecedentes de alergia y su posterior monitoreo. Se implementó un protocolo de desensibilización compuesto por 15 pasos consecutivos, adaptado de un protocolo para TMS oral en pacientes con infección por VIH y antecedentes de alergia al antibiótico en cuestión. **Resultados:** El procedimiento fue sencillo y eficaz, permitiendo así que la paciente continuara con la dosificación recomendada para la condición infecciosa. **Conclusión:** Se determinó que el procedimiento de desensibilización es seguro cuando es realizado por profesionales médicos capacitados en un entorno controlado.

Palabras clave: *Cryptococcus neoformans*; trasplante; hipersensibilidad; infección diseminada; desensibilización; fluconazol.

INTRODUCTION

Cryptococcosis represents the third most common infection among transplant patients, following candidiasis and aspergillosis. The fungus of the Cryptococcus genus has a worldwide distribution. It is predominantly found in soils contaminated by bird feces, and its transmission occurs through inhalation of soil contaminated with capsulated yeasts, which are between 2 to 6 µm in diameter. It is an opportunistic disease that primarily affects individuals infected with the human immunodeficiency virus (HIV), transplant recipients, and those undergoing immunosuppressive therapy. Nevertheless, this infection also occurs in patients without HIV, with a reported incidence of 10% to 30% of cases by Silviane Bezerra Pinheiro et al. in 2021.[1] In this study, it was found that the mortality rate in these patients was high, exceeding 57.2% in 2020. The most common clinical presentation in these patients is cryptococcal meningitis. A study by Deus et al. (2022) describes that, although the main site of infection is at the pulmonary level, extrapulmonary disease is common, especially infection of the central nervous system (CNS).[2]

The treatment for disseminated cryptococcosis comprises the administration of intravenous amphotericin B in conjunction with fluorocytosine. The efficacy of fluconazole, a first-generation azole, was evaluated at 200 to 400 mg/day as an alternative treatment option, given its low toxicity profile. It is indicated for low-risk patients, such as those without neurological alterations or with a leukocyte count of less than 20 cells/ml in cerebrospinal fluid (CSF).[2] Fluconazole is a safe and well-tolerated drug; however, it can cause adverse reactions, including gastrointestinal symptoms, and, in rare cases, hypersensitivity reactions such as fixed skin rash and maculopapular exanthema. In the event of a reaction of this nature, it is imperative to discontinue the offending medication and pursue an alternative therapeutic avenue. In the event that the offending drug is irreplaceable and the type of hypersensitivity reaction allows for it, a desensitization protocol should be attempted.

Patients with chronic degenerative diseases, including but not limited to diabetes, cancer and inflammatory bowel disease, etc. Repeated exposure may result in hypersensitivity to first-line drugs. In the context of precision medicine, a more individualized approach offers the potential for the development of new tools for the management of these types of reactions. In accordance with the traditional classification system proposed by Gell and Coombs in 1963,[3] four distinct types of RHD have been identified. The first, Type I

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or immediate hypersensitivity reaction, is characterized by a rapid onset, occurring within minutes to a few hours following the interaction between the antigen (Ag) and the preformed immunoglobulin E (IgE) antibody (Ac) in individuals who have been previously sensitized. The antigen combines with two IgE antibodies bound to its membrane receptors (Fcε RI) on pre-sensitized mast cells and basophils, which results in the degranulation of vasoactive and inflammatory mediators, including histamine, tryptase, platelet-activating factor (PAF), leukotrienes, chemotactic factors, growth factors, and others.

This results in increased capillary permeability, vasodilation, glandular hypersecretion of mucus, smooth muscle spasm, and tissue infiltration of eosinophils. These reactions are accompanied by a late phase reaction, which occurs between two and four hours after contact with the antigen and is characterized by the infiltration of inflammatory cells. The symptoms of anaphylaxis include urticaria, allergic rhinitis, allergic asthma, angioedema and anaphylactic shock. An illustrative example of this type of reaction is that observed in response to beta-lactams. Type II hypersensitivity reactions are associated with a humoral cytotoxicity mechanism, which is mediated by IgG and IgM. This mechanism has the capacity to opsonize, recruit leukocytes and activate complement, thereby triggering inflammatory responses or inducing functional changes at the level of receptors. This has been observed in cases involving cell phones.[4] Cases of anemia and thrombocytopenia due to linezolid have been reported to result from this mechanism.[5,6] The case of erythema nodosum caused by oral contraceptives provides an example of a type III hypersensitivity reaction. Immune complexes are formed by the union of antigen present in the circulation with antibodies. The subsequent tissue damage will be contingent upon the sites where these immune complexes are deposited, rather than being a consequence of the origin of the triggering antigen. The formation of immune complexes activates the complement system, initiating a cascade of reactions that facilitate the migration of PMN cells and the release of lysosomal proteolytic enzymes and permeability factors from the tissues, thereby contributing to the inflammatory process.

Other drugs that are also capable of generating adverse reactions through this mechanism have been observed to manifest as serum sickness or hypersensitivity vasculitis. These include cefaclor, cephalexin, trimethoprim-sulfamethoxazole, amoxicillin, non-steroidal anti-inflammatory drugs, diuretics and some biologicals. The type IV hypersensitivity reaction is a delayed cellular response, mediated by sensitized T lymphocytes that have been induced to produce cytokines that mediate inflammation. The sensitization phase commences upon the initial entry of the allergen into the body, whereupon it is processed by antigen-presenting cells and presented to T lymphocytes that recognize the allergen in conjunction with the molecules of the major histocompatibility complex class II. This process is facilitated by MHC II, which induces T cell differentiation towards Th1 cells, resulting in cytokine release and subsequent inflammation.

At present, type IV reactions are classified according to the effector cell involved and the corresponding cytokines into the following categories: a) Type IVa reactions are characterized by the activation of the Th1 profile, with macrophages and INF-γ, TNF-α serving as the effector cells. b) Type IVb reactions, on the other hand, are typified by the activation of the Th2 profile, with eosinophil effector cells and the release of cytokines such as interleukins IL-5, IL-4 and IL-13. c) Type IVc reactions in this instance, the effector cells are cytotoxic T lymphocytes, which result in the release of granzymes B and perforins.

Finally, type IVd is characterized by the involvement of neutrophils as effector cells, accompanied by the release of the chemokine CXCL8 and the granulocyte-macrophage colony-stimulating factor (GM-CSF).[7,8] Severe reactions to immunological medications are included in the category of delayed hypersensitivity mechanisms. This group encompasses a range of drug-induced cutaneous reactions, including skin rashes, erythema morbilliformis, fixed eruptions associated with drugs such as sulfonamides, beta-lactams, anticonvulsants, and more severe forms of dermatitis, such as drug sensitivity reaction with eosinophilia and systemic symptoms (DRESS) and necrolysis. Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP) and other conditions such as drug-induced vasculitis/pemphigoid.

New methodologies for a more comprehensive understanding of drug hypersensitivity entail the characterization of reactions according to phenotype, endotype, and biomarkers.[4] A novel approach to this classification was proposed by Mariana C. Castells et al. in 2017.[9]

Immediate reactions, defined as those occurring within one to six hours of drug administration, represent a distinct category of drug-induced responses. This phenotype typically encompasses the IgE-mediated endotype of mast cell activation, driven by epitope-specific IgE with mast cells serving as the primary effectors. Other endotypes include direct complement activation, drug-hypersensitivity reactions (DHR) mediated by cyclooxygenase-1 inhibition, which are referred to as aspirin-exacerbated respiratory disease (AERD), and aspirin-exacerbated skin disease. Additionally,

reactions may occur due to certain components of medications, such as tetrahydroisoquinoline (THIQ). The signals are transmitted via the G protein-coupled receptor (Mrgp X2), which has the capacity to induce the release of histamine through the activation of mast cells. It has been documented that symptoms such as fever, chills, and abdominal discomfort have manifested during DHRs in response to the administration of monoclonal medications, oxaliplatin, and taxanes. Such reactions, designated as "cytokine storm reactions," are mediated by the release of proinflammatory cytokines that activate macrophages and other immune cells with FcγR receptors. Regarding type IV or late reactions, they manifest in a more heterogeneous manner and occur several days or weeks following administration of the drug in question. The symptoms are mediated by T cells, manifesting as maculopapular rash or late urticaria, and may also affect other organs, including the liver, lungs, and kidneys. Additionally, hematological alterations may occur. Severe cutaneous drug reactions (SCAR) encompass AGEP, DRESS, Sweet's syndrome (SSJ), and neutrophilic eruption with telangiectasias (NET). These have a distinct clinical presentation and can potentially be life-threatening if appropriate treatment is not promptly initiated.

Desensitization is a procedure that induces a temporary state of hyporesponsiveness/tolerance by gradually increasing suboptimal doses of the offending drug. It is performed under close medical surveillance and its immunological basis consists of achieving temporary tolerance by reducing the reactivity of the effector cells of the immune system such as mast cells and basophils and increasing regulatory cells (Treg cells) avoiding the presentation of immediate reactions. Desensitization protocols have been developed that are used in patients with allergic reactions to antibiotics such as penicillin, chemotherapeutic and biological agents, insulins, sulfonamides, and many other drugs.[10] In cases where the offending medication is essential and no satisfactory alternative exists or is available, the possibility of desensitization should always be considered. Desensitization treatment may be indicated in cases where there is a compelling need for a particular medication or prophylaxis, where the medication is irreplaceable, is more effective than alternative treatments, has a unique mechanism of action, or where the potential benefit outweighs the risks. Absolute contraindications include a serious or life-threatening reaction, such as a severe cutaneous adverse reaction (SCAR), or a severe general symptom, such as fever, chills, nausea, pain, a severe headache, dyspnea, hypertension or hypotension with or without end-organ involvement. Additionally, contraindications include a drug-induced autoimmune disorder. Relative contraindications include anaphylaxis, age, pre-existing liver or kidney involvement, autoimmune disorders, patients with unstable heart disease, any simultaneous treatment that could interfere in the event of anaphylaxis, and uncontrolled asthma. The case of a female patient presenting with a rash is presented. The patient was diagnosed with late-onset maculopapular disease, for which a slow desensitization procedure was indicated.

CLINICAL CASE

A 53-year-old female patient with a personal medical history of end-stage renal failure (ESRD) secondary to bilateral polycystic kidney disease, diagnosed at 17 years of age, denies a history of allergy. Received an unrelated unilateral kidney transplant in 2021 without other surgical complications. It did not present any complications, until in the year 2023, suffered active kidney rejection In July 2023, the patient was admitted to the hospital due to an area of phlogosis and local erythema on the left leg with an entrance due to onychocryptosis in the hallux. This was classified as a severe skin and soft tissue infection (STI), and treatment was initiated with intravenous antibiotics. Skin and soft tissue cultures show positive results for capsulated yeasts compatible with cryptococcosis, so in order to rule out disseminated infection in the context of an immunocompromised patient, lumbar puncture (LP) is performed to detect polysaccharide capsular antigen (CrAg) in CSF, and microscopy with Indian ink, which is negative. The antibiotic was discontinued and intravenous induction treatment with liposomal amphotericin B was started. A computed axial tomography (CT) scan of the thorax was conducted, which revealed the presence of isolated nodular images with ground glass in the region of the right lower lobe of the lung. This was interpreted as indicative of an infectious etiology. A decision was made to administer liposomal amphotericin B for a period of 15 days, followed by a 14-day course of oral fluconazole. Two days after treatment with fungicides, the patient developed a rash comprising reddish maculopapular lesions distributed asymmetrically, with a predilection for the trunk and abdomen. This was primarily related to liposomal Amphotericin B, so treatment was suspended and continued only with intravenous fluconazole. The administration of hydrocortisone in conjunction with diphenhydramine was indicated for the purpose of alleviating the symptoms, with an adequate clinical response. Following a two-day course of fluconazole, the patient once again exhibited a pruritic maculopapular rash (MPE) on the trunk, without evidence of mucosal or systemic involvement. It was decided that the intravenous fluconazole should be switched to an oral route, due to the suspicion that the reaction was related

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to the method of administration and excipients. The eruption persists with the EMP, which worsens with each oral administration of fluconazole. Consequently, a consultation is held with the dermatology service of the hospital, which determines the definitive diagnosis to be simple pharmacoderma secondary to fluconazole. The treatment is then suspended. Subsequently, a consultation was requested from the allergy service for evaluation. In light of the patient's development of a maculopapular rash without systemic involvement, coupled with the unfeasibility of conducting skin tests given the patient's concurrent antihistamine and steroid treatment, and the absence of superior therapeutic alternatives for the underlying infection, a decision was made to pursue a slow desensitization protocol to oral fluconazole. The procedure was conducted in 15 consecutive steps, with the dose gradually increased until the desired level was reached. The treatment was well tolerated, and the patient did not experience any adverse reactions (Table 1).

Table 1. Slow desensitization protocol table to oral fluconazole adapted from protocol for TMS[11]

DAY	STEPS	SOLUTION	CONCENTRATION	DOSE	TOTAL (mg)
1	1	TO	1mg	0.2ml	0.2
2	2	TO	1mg	0.4ml	0.4
3	3	TO	1mg	0.8ml	0.8
4	4	TO	1mg	1.6ml	1.6
5	5	TO	1mg	3.2ml	3.2
6	6	TO	1mg	6.4ml	6.4
7	7	b	10mg	1.0ml	10
8	8	b	10mg	2.0ml	twenty
9	9	b	10mg	4.0ml	40
10	10	c	50 mg (comp or syrup)	1	fifty
11	11	c	50 mg (comp or syrup)	2	100
12	12	c	50 mg (comp or syrup)	3	150
13	13	c	200 mg (comp)	1	200
14	14	c	100 mg (comp)	3	300
15	15	c	200 mg (comp)	2	400

DISCUSSION

There are few case reports or desensitization protocols described for adverse reactions to fluconazole. In 1996, Craig et al described a fluconazole desensitization protocol in an HIV-positive patient with cryptococcal meningitis who developed a pruritic rash in the armpits in addition to hypereosinophilia. Subsequently, dyspnoea and tachycardia were also observed. In this case, a protocol for trimethoprim/sulfamethoxazole (TMS) described by Absar et al. was employed, with the patient tolerating the entire procedure without clinical complications.[11,12] In a further case report published in 2008, Randolph and colleagues describe the rapid desensitization of a patient with a bone and soft tissue infection caused by cryptococcus. This was achieved in just eight hours, following the administration of the second dose of fluconazole, which had resulted in the development of a pruritic erythematous maculopapular rash. The procedure was completed without any clinical complications, and the patient was subsequently discharged without any adverse effects or complications.[13] The third case reported was that of a 76-year-old patient with a history of class IV IgA nephropathy with hematogenous and CSF dissemination of cryptococcus (cryptococcal meningitis) who, 15 days

after commencing treatment with fluconazole, presented with a generalized pruritic rash that originated in the abdomen and subsequently disseminated throughout the body. Following the hypothesis of a delayed hypersensitivity reaction to fluconazole, the drug was suspended, resulting in an improvement in the skin lesions. In light of the crucial role the drug played in the treatment plan, a rapid intravenous desensitisation procedure was conducted prior to the administration of antihistamines.[14] It is crucial for the planning of the study and treatment of hypersensitivity reactions to provide an accurate description of the morphology of the lesions and the chronology of the administration of the drug and the onset of symptoms. This should be done by considering the route of administration, the role of drug metabolites, and other additional factors that may affect the speed or progression of the reaction.[15] In the case of the patient, a comprehensive review of the complete medical history of all the administered medications and their chronological relationship with the onset of symptoms, as well as the route of administration and the duration of treatment, should have been conducted. A comprehensive assessment of the presenting signs and symptoms, the characteristics of the lesions, their topography and the manner of their progression was conducted. The mucous membranes of the mouth, eyes and genitals were examined, as well as the search for signs of severity, including laboratory parameters. The patient exhibited a maculopapular rash, without evidence of mucosal involvement, and laboratory studies demonstrated normal parameters for her underlying pathology. The patient began to present symptoms seven days after the commencement of antifungal therapy, which comprised amphotericin B and fluconazole. Initially, amphotericin B was suspected as the causative agent, and the drug was therefore discontinued. However, when the reaction persisted and the itching and rash worsened with each intake of fluconazole, the diagnostic suspicion was directed towards fluconazole. Despite the existence of a substantial corpus of literature and desensitisation protocols in the context of immediate reactions, this is not the case for non-immediate reactions. In this latter category, there is no common consensus on the indication and implementation of desensitisation protocols. In cases of immediate IgE-dependent reactions, it is established that glucocorticoids are ineffective in preventing the activation of mast cells and that antihistamines are only capable of masking the early signs of an allergic reaction. Furthermore, they are unable to prevent the onset of severe reactions during the course of treatment. In contrast, this phenomenon does not occur in immediate reactions whose pathophysiology is not IgE-dependent. This is exemplified by monoclonal drugs, which can benefit from the use of premedication. In the case of the patient, it was decided that performing skin tests would be contraindicated due to the administration of antihistamines and immunosuppressive treatment, which can result in false negative results. Consider desensitization since the offending medication was essential for the treatment of disseminated cryptococcosis and there were no other appropriate alternatives in a transplant patient. Desensitization is indicated when the treatment with the offending drug is more effective than other pharmacological alternatives, when the reaction is not serious and is well documented clinically, when the benefits of the drug outweigh the risk and when no alternative drug is available that does not present cross-reactivity. It has been demonstrated that in cases of non-IgE-mediated reactions, such as the maculopapular reaction presented by the patient, the desensitization procedure can be performed without contraindications. This is not the case in severe DHR. In the EAACI guidelines from 2014 and 2018, experts confirm that desensitization in delayed DHR is only indicated for fixed eruptions or uncomplicated exanthems, as was the case for the patient.[15,4]

CONCLUSION

Desensitization is a key procedure for the secure reintroduction of allergenic medications to the patient, thereby enabling the continuation of primary treatment for the underlying disease. The procedure is safe when conducted in a controlled setting by highly trained healthcare professionals in collaboration with other specialties, thereby ensuring a multidisciplinary approach. The patient's risk profile, comorbidities and established treatments must be considered and an appropriate protocol followed. At present, further experience is required to define the specific steps to be followed. It is also evident that future research processes must be conducted to establish standardized protocols for non-severe late-type allergic reactions.

CONFLICT OF INTEREST

There are no conflicts of interest.

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