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SHORT COMMUNICATION

Candidate SNPs associated with anxiety and depression in children and adolescents in the USH1C gene

SNPs candidatos asociados con la ansiedad y la depresión en niños y adolescentes en el gen USH1C

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ABSTRACT

Introduction: anxiety and depression in children and adolescents are growing concerns globally, with significant rates of diagnosis across diverse populations. According to the Centers for Disease Control and Prevention (CDC), approximately 7,1 % of children aged 3 to 17 years in the United States have been diagnosed with anxiety, and 3,2 % with depression. The aim of this study is to analyze the correlation between SNPs in the USH1C gene and predisposition to anxiety and depression in children and adolescents from specific populations.
Method: genotypes from the 1000 Genomes Project were used to evaluate SNPs in Southeast Asian and European populations. Linkage disequilibrium (LD) analysis was performed using VcfTools and the biological effects of the SNPs were assessed using the Variant Effect Predictor (VEP).
Results: two SNPs, rs4757538 and rs16934376, were identified, which showed strong LD with SNP rs79878474 in South Asian populations ($r^2 > 0,7$), suggesting their possible association with anxiety and depression. Allele frequencies varied significantly between populations. Hardy-Weinberg equilibrium analysis showed significant imbalance at the global level, but not within individual populations
Conclusions: the analyzed SNPs might be related to predisposition to anxiety and depression in specific populations. These findings underline the importance of considering genetic diversity in future studies and developing personalized interventions to address these disorders in children and adolescents.

Keywords: Depression; Children; Adolescents; USH1C Gene.

RESUMEN

Introducción: la ansiedad y la depresión en niños y adolescentes son preocupaciones crecientes a nivel global, con tasas significativas de diagnóstico en diversas poblaciones. Según los Centros para el Control y la Prevención de Enfermedades (CDC), aproximadamente el 7,1 % de los niños de 3 a 17 años en los Estados Unidos han sido diagnosticados con ansiedad, y el 3,2 % con depresión. El objetivo de este estudio es analizar la correlación entre SNPs en el gen USH1C y la predisposición a la ansiedad y la depresión en niños y adolescentes de poblaciones específicas.
Método: se utilizaron genotipos del Proyecto de los 1000 Genomas para evaluar SNPs en poblaciones del sudeste asiático y europea. Se realizó un análisis de desequilibrio de ligamiento (LD) utilizando VcfTools y se evaluaron los efectos biológicos de los SNPs mediante el Variant Effect Predictor (VEP).

Resultados: se identificaron dos SNPs, rs4757538 y rs16934376, que mostraron un fuerte LD con el SNP rs79878474 en poblaciones del sur de Asia (r^2 > 0,7), sugiriendo su posible asociación con la ansiedad y la depresión. Las frecuencias alélicas variaron significativamente entre poblaciones. El análisis de equilibrio de Hardy-Weinberg mostró un desequilibrio significativo a nivel global, pero no dentro de las poblaciones individuales
Conclusiones: los SNPs analizados podrían estar relacionados con la predisposición a la ansiedad y la depresión en poblaciones específicas. Estos hallazgos subrayan la importancia de considerar la diversidad genética en futuros estudios y el desarrollo de intervenciones personalizadas para abordar estos trastornos en niños y adolescentes.

Palabras clave: Depresión; Niños; Adolescentes; Gen USH1C.

INTRODUCTION

Anxiety and depression in children and adolescents represent a growing global concern. According to the Centers for Disease Control and Prevention (CDC), approximately 7,1 % of children aged 3 to 17 years in the United States have been diagnosed with anxiety, and 3,2 % with depression.[1] In India, it is estimated that one in four adolescents suffers from depression, according to the World Health Organization.[2] Environmental factors play a critical role in the development of these disorders. A study found that early-life stress and school support are important determinants in the onset of anxiety and depression in different cohorts, and the quality of the school environment is negatively correlated with symptoms of anxiety and depression, suggesting that a better school environment can help reduce these symptoms.[3]

Research has shown that genetic factors play a significant role in the development of anxiety and depression in children and adolescents. Twin studies have estimated that the heritability of depression in this population ranges from 31% to 42%.[4] Specific genetic variants, such as those related to potassium channels and insulin secretion regulation, have been associated with an increased risk of developing these disorders.[5] Additionally, recent research has identified single nucleotide polymorphisms (SNPs) in genes related to stress response and emotional regulation that are significantly associated with symptoms of anxiety and depression in youth.[6] These findings highlight the importance of considering genetic predisposition when addressing the prevention and treatment of anxiety and depression in childhood and adolescence.

According to the World Health Organization[2], one in four adolescents in India suffers from depression, highlighting the importance of these factors. Additionally, school support is negatively correlated with symptoms of anxiety and depression, suggesting that a better school environment can help mitigate these symptoms.[3] The studies by Kendler et al.[4] have also demonstrated that the heritability of depression in adolescents is significant. Cai et al.[5] found that variants in potassium channels are associated with an increased risk of developing these disorders. These findings underline the need for early interventions at both the environmental and genetic levels to address these disorders in childhood and adolescence.

The polymorphism rs79878474 has been identified as a significant genetic marker associated with anxiety and depression in children and adolescents. This SNP is located in the USH1C gene, which encodes a protein involved in the function of potassium channels in the nervous system.[3] Studies have shown that mutations in USH1C can affect emotional regulation and stress response, which is closely related to the occurrence of anxiety and depression symptoms.[5] Additionally, research suggests that the expression of USH1C in the brain, particularly in regions such as the cerebellum, can influence the development of mood disorders.[6] These findings emphasize the importance of considering specific genetic variants such as rs79878474 in the evaluation and treatment of anxiety and depression in young populations.

METHOD

Phased genotypes of the USH1C gene were downloaded from the 1000 Genomes Project, phase 3, version v5a[7] for two major populations: the Southeast Asian population (N=489, 1694 SNPs) and the European population (N=503). The selection of these populations is due to the focus on the Indian and European populations in the study by Thapaliya et al.[3] The GRCh 37,13 human genome assembly was used as the reference for the analysis.

Linkage disequilibrium (LD) analysis was carried out using the VcfTools software. The correlation statistic r^2 was calculated to evaluate the degree of LD between the SNPs. The r^2 value is a measure of the correlation between two loci, where a value of 1 indicates perfect correlation (no recombination) and a value of 0 indicates no correlation (independent segregation).[8] SNPs with an r^2 value of at least 0,7 were identified, which is considered a strong correlation in the context of LD.[9]

For the SNPs linked to rs79878474, the Variant Effect Predictor (VEP) tool from Ensembl was used to gather information on the biological effect of these variants.[10] This tool allows the evaluation of the possible functional

consequences of the identified SNPs, providing detailed information on their potential impact on protein structure and function, gene regulation, and disease susceptibility. VEP also integrates data from multiple sources, including annotations of known variants, predictions of functional impact, and gene expression data, to offer a comprehensive assessment of the possible biological role of each variant. This evaluation is necessary to understand how intronic variants, such as rs4757538 and rs16934376, might influence genetic predisposition to anxiety and depression in different populations. Additionally, VEP allows the identification of pleiotropic effects of these SNPs, which is fundamental for a holistic approach in genomic medicine. The integration of these data facilitates the prioritization of variants for subsequent functional studies and the development of specific therapeutic interventions.

RESULTS

Two SNPs were found to have strong linkage disequilibrium ($r^2 > 0,7$) with SNP rs79878474 in the South Asian population: rs4757538 ($r^2 = 0,759$) and rs16934376 ($r^2 = 0,755$) (Figure 1). Both showed an r^2 value of 0,693 in the Bengali population in Bangladesh, 0,698 in the Gujarati population in western India, 0,761 in the Indian Telugu population in the United Kingdom, 0,839 in the Punjabi population in Lahore, Pakistan, and 0,802 in the Tamil population in the United Kingdom. These SNPs showed moderate linkage in the European population ($r^2 = 0,335$). Table 1 shows information on the SNPs analyzed here.

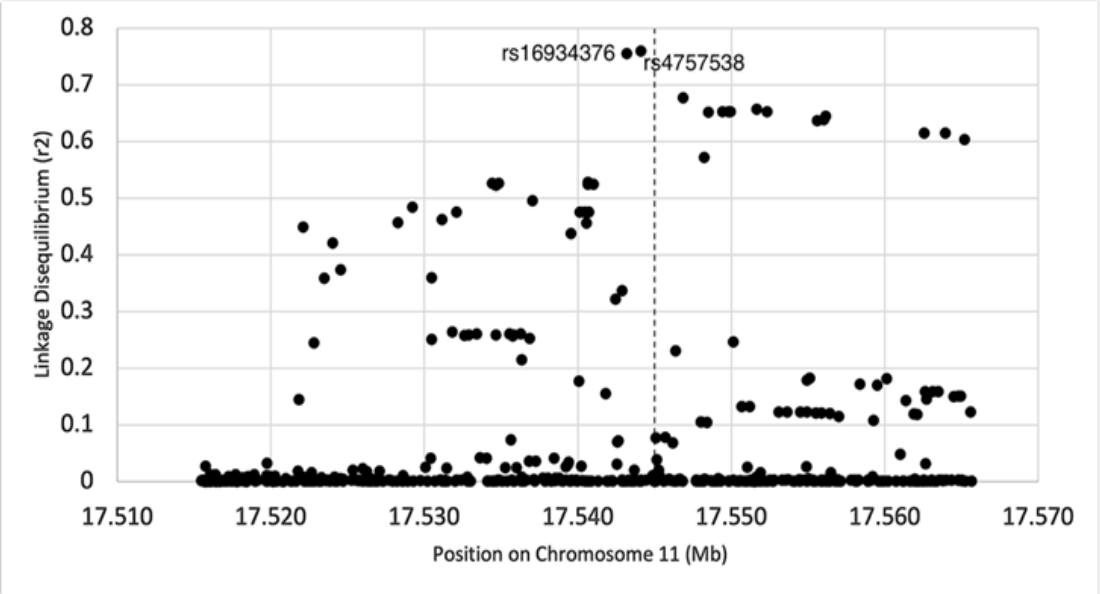

Figure 1. Linkage disequilibrium (r2) along the USH1C gene in south Asian populations

Table 1. SNPs analyzed

SNP	Comercial Chips	Citation	Phenotype
rs79878474	Illumina_HumanOmni5 Illumina_HumanOmni2.5	Thapaliya et al.[3]	Anxiety and depression in children and adolescents
rs4757538	Illumina_Human610_Quad Illumina_1M-duo Illumina_HumanOmni5	-	-
rs16934376	Affy GeneChip 500K Affy GenomeWideSNP_6.0	Lv et al., 2017[11]	Acute myeloid leukemia

Allele frequencies of SNPs rs79878474, rs4757538, and rs16934376 reveal variations among the major global populations. For SNP rs79878474 (allele T), the highest frequencies are found in American populations, with Peruvians from Lima (88,2 %), and the lowest frequencies in African populations, especially Luhya from Webuye, Kenya (58,1 %), and in South Asian populations such as Indian Telugu in the United Kingdom (69,1 %). For SNP rs4757538 (allele G), the highest frequencies are also observed in American populations (100% in Lima) and the lowest in South Asian populations, with Indian Telugu in the United Kingdom showing a frequency of 70,6 %. For SNP rs16934376 (allele G), the same pattern as for the previous SNP is observed. Figure 2 shows the allele frequencies for the three SNPs here analyzed.

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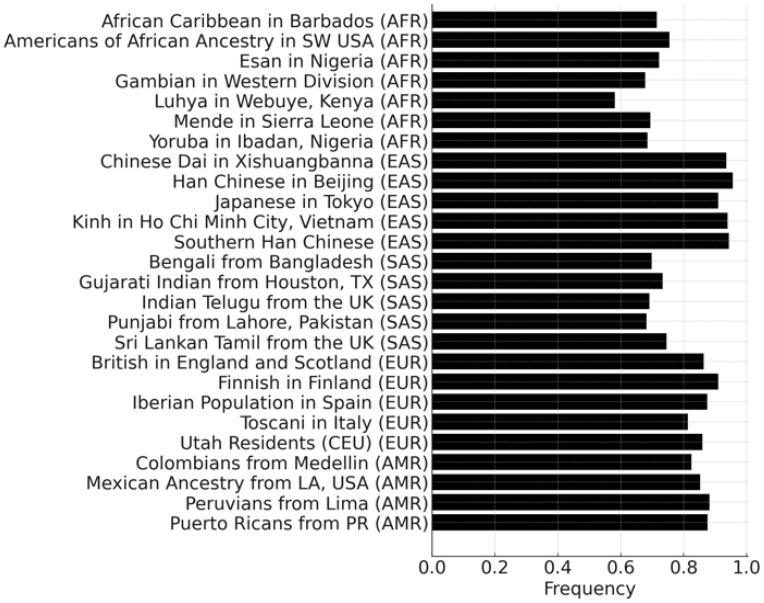
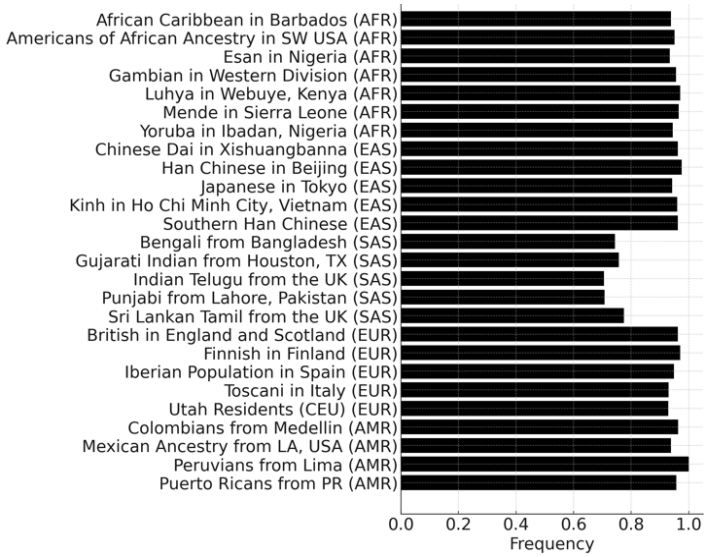
rs79878474



rs4757538



rs16934376

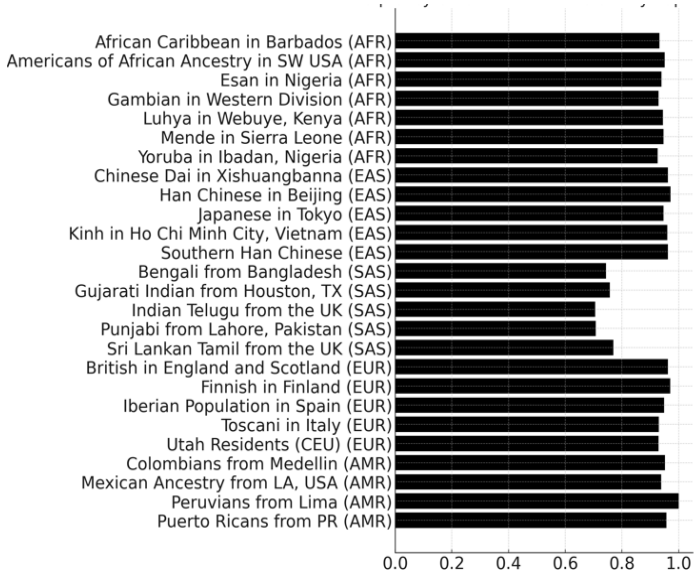


Figure 2. Allele frequencies for the three SNPs

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Hardy-Weinberg equilibrium analysis was performed globally and in the five major populations. Globally, a significant disequilibrium was found (p= 5x10-5). However, in the African, East Asian, South Asian, European, and American populations, the p-values were 0,606, 0,084, 0,672, 0,634, and 0,921, respectively. These values suggest that there is not enough evidence to reject the hypothesis of Hardy-Weinberg equilibrium in these major populations.

Hardy-Weinberg equilibrium was analyzed for all combinations of the major populations. The results showed that the combinations Africa – East Asia, Africa - Europe, and East Asia – South Asia, present Hardy-Weinberg disequilibrium (p= 1. 2x 10-5, 0,022118, and 8,4 x 10-5, respectively). All individual populations are in Hardy-Weinberg equilibrium.

DISCUSSION

The results of this study reveal two candidate SNPs, rs4757538 and rs16934376, that exhibit strong linkage disequilibrium with SNP rs79878474 in the South Asian population. These SNPs showed r^2 values greater than 0,7, indicating a strong correlation and suggesting that they might be associated with the phenotype of anxiety and depression in children and adolescents. However, it is important to note that neither rs79878474 nor the SNPs linked to it show evidence of playing a role in the regulation of gene expression, as they are intronic variants according to the analysis with the Ensembl Variant Effect Predictor (VEP).[10]

The heterogeneity in allele frequencies among major populations significantly contributes to the Hardy-Weinberg equilibrium (H-W) results. A significant disequilibrium was found globally, but analyzing the major populations individually (African, East Asian, South Asian, European, and American) did not provide enough evidence to reject the hypothesis of Hardy-Weinberg equilibrium in any of them. However, combining certain major populations (African and East Asian, African and European, East Asian and South Asian) showed significant disequilibrium. This suggests that the mixture of populations with different allele frequencies can influence the distribution of genotypes and, therefore, the Hardy-Weinberg equilibrium.[12]

It is important to consider genetic variability among populations for future genetic association studies using the SNPs analyzed here. Genetic variability can influence the strength of the association between an SNP and a particular phenotype in different populations, as allele frequencies and linkage disequilibrium (LD) structures can vary considerably among them.[13] Additionally, genetic variability can also influence disease susceptibility and treatment response, underscoring the importance of considering ancestry in genetic association studies.[14]

Furthermore, population variability can significantly impact the genetic determination of mental health-related phenotypes.[15] Genetic variants that are common in one population may be rare in another, which can influence the susceptibility to developing anxiety and depression in different populations. Considering these differences, as described in this study, is relevant for developing more effective and personalized interventions and treatments that take genetic diversity into account.

CONCLUSIONS

The SNPs, rs79878474 rs4757538 and rs16934376 in the USH1C gene might be related to the predisposition to anxiety and depression in specific populations, especially in the context of the Southeast Asian population. Although no direct effect on the regulation of gene expression was observed, genetic variability and differences in allele frequency between populations highlight the importance of considering these factors in future studies. Furthermore, Hardy-Weinberg equilibrium analysis suggests that the admixture of different populations may influence the distribution of genotypes and, therefore, the susceptibility to these disorders. These findings underline the need to develop more personalized intervention strategies that consider genetic diversity and population structures.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Formal analysis: Sergio V. Flores, Angel Roco-Videla.
Research: Sergio V. Flores, Angel Roco, Román Montaña.
Methodology: Sergio V. Flores, Angel Roco-Videla.
Software: Sergio V. Flores.
Supervision: Sergio V. Flores.
Validation: Angel Roco-Videla, Raúl Aguilera-Eguía.
Display: Román Montaña, Raúl Aguilera-Eguía.
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Writing - proofreading and editing: Sergio V. Flores, Angel Roco, Román Montaña, Raúl Aguilera-Eguía.