journal OF NEGATIVE & NO POSITIVE RESULTS

ISSN-e: 2529-850X
Volumen 10 pp 687-699
Year: 2026
DOI: 10.19230/jonnpr.6210

ORIGINAL

Reading Competence in Mexican Undergraduate Students: Lack of Association with *FOXP2* and *ROBO1* Genetic Variants

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Received June 2nd, 2026; Accepted August 21th, 2026

How to cite this paper:
Limon-Fernandez HA, Sanchez-Loyo LM, Rangel-Villalobos H, Gómez-Velázquez FR, Sánchez-Enríquez S, Ramírez-De los Santos S, Becerra-Solano LE, Sanchez-Gonzalez VJ. Reading competence in Mexican undergraduate students: lack of association with *FOXP2* and *ROBO1* genetic variants. JONNPR. 2026;10: pp 687-699 doi:10.19230/jonnpr.6210.

Abstract

Introduction: Reading comprehension competence is a complex cognitive skill influenced by both genetic and environmental factors. While previous studies have identified associations between specific gene variants and reading abilities, most research has focused on European-ancestry populations, leaving a gap in understanding these relationships in diverse genetic backgrounds. **Objective:** This study investigates the potential association between two gene variants, rs2253478 (*FOXP2*) and rs1995402 (*ROBO1*), and reading comprehension competence in Mexican undergraduate students. **Materials and methods:** A total of 223 students were assessed for reading skills, and only 37 participants underwent genetic analysis. Participants were divided into average and superior reading groups based on their test scores. **Results:** Although significant differences in reading performance were observed between the groups, no association was found between the genotypes of the two variants and reading competence in odds-ratio tests. Allelic and genotypic frequencies for both variants were consistent with Hardy-Weinberg equilibrium, indicating no external influences on these frequencies. Comparisons with global populations revealed that the Mexican sample clustered closely with Spanish populations, suggesting a conservation of sequences similar to European populations. **Discussion:** These findings may suggest that the rs2253478 and rs1995402 variants do not significantly impact reading comprehension competence in this population, highlighting the complexity of genetic influences on cognitive traits. Despite the small sample size, this study contributes to the growing body of research on the genetic basis of reading by exploring these associations in a non-European population, highlighting the need for further research in diverse genetic and cultural contexts.

Keywords: *FOXP2*, *ROBO1*, reading competence, gene variants, Mexican population, cognitive genetics.

Introduction

Understanding written material is a crucial skill for academic achievement, involving various cognitive functions (1), influenced by the brain's neural networks (2). Neuroimaging and neurophysiological studies have been demonstrated that reading comprehension competence relies on well-synchronized neural activity across fronto-temporo-parietal regions, with a strong left-lateralization for language processing (3). However, despite extensive research on the neurobiology of reading, the genetic contributions to reading comprehension competence remain unclear, particularly in populations without linguistic or cognitive impairments (4,5).

Several genes have been implicated in the development and function of neural circuits associated with language and reading. One of the most studied genes is *FOXP2*, a transcription factor essential for the development of brain structures involved in speech and language (6,7). *FOXP2* is expressed in critical language-related areas such as the basal ganglia, frontal cortex, and cerebellum, playing a key role in motor coordination, vocal learning, and grammatical processing (8–11). Variants in *FOXP2* have been associated with phonological processing, word spelling, and non-word reading tasks (5,12). One specific single nucleotide polymorphism (SNP), rs2253478 (A>G), has been linked to variations in spelling and reading performance, suggesting a role in reading skills (12).

Another gene of interest is *ROBO1*, which is involved in axon guidance, neuronal migration, and the formation of interhemispheric connections, particularly the corpus callosum (4,13,14) through retiring or maintaining receptors to favor axon projections through endocytosis (15,16). *ROBO1* expression in the frontal and temporal cortices suggests a role in auditory and phonological processing, which are crucial for reading (17,18). Genetic variants in *ROBO1* have been associated with dyslexia, working memory processing, and word repetition abilities (19,20). The SNP rs1995402 (T>G) has been linked to reading and spelling performance, making it a relevant candidate for studies on genetic influences on reading skills (19).

Despite these findings, most genetic studies on reading have focused on European-ancestry populations, leaving a significant gap in understanding how these variants influence reading comprehension competence in diverse genetic backgrounds, such as Mexican populations (21). Additionally, genetic influences on reading are likely polygenic and interact with environmental factors, making it challenging to isolate the effects of individual SNPs (22).

To address these gaps, this study investigates the association between *FOXP2* (rs2253478) and

ROBO1 (rs1995402) genetic variants and reading comprehension competence in Mexican undergraduate students. Reading comprehension competence was assessed using the PROLEC-SE-R screening version (23), which evaluates lexical, syntactic, and semantic processes. Given previous findings on *FOXP2* and *ROBO1* in European samples, we hypothesized that these variants would be associated with individual differences in reading comprehension competence in our sample. The results in this study will contribute to a more comprehensive understanding of the genetic basis of reading comprehension competence by exploring these associations in a non-European population.

Materials and methods

Population sample

Undergraduate students were recruited via e-mail or text messaging. 223 undergraduate students (West, Mexico) completed the surveys and psychometric measures online. Only 37 students (27 female, 20.37 years old, SD = 1.42) participated with their blood sample, which were distributed into two groups: 1) Average Group (n = 21): participants within quartiles 1 to 3 with 146 to 190 points for screening index in reading test PROLEC-SE-R screening version; 2) Superior Group (n = 16): participants with scores higher than 191 points for the screening index in PROLEC-SE-R. In addition, a control population sample from the same region (West, Mexico) was analyzed for the studied genetic variants: rs2253478 (n=80) and rs1995402 (n=79).

All subjects gave online informed consent to participate. The observational study was approved by the Research Ethics Committee from Centro Universitario de Los Altos, Universidad de Guadalajara (Mexico, 2021; register code: CEI-01-2021-003). All surveys and psychometric measures were taken online during the SARS-COVID pandemic. An exploratory and cross-sectional design with two phases was done: the first phase for psychometric assessment of reading competence, the second phase for genetic variant analysis.

Assessment of reading comprehension competence

We applied the PROLEC-SE-R in the screening version (23), a practical and widely-used tool. This test has 6 subtests for assessing lexical (lexical selection and semantic categorization tests), syntactic (grammatical structures and grammatical judgment tests), and semantic (expositive text comprehension and narrative text comprehension) processes. Each process is evaluated using 2 tasks, with a limited time, except for the Narrative Text Comprehension subtest, with no time limit. The participants were provided with a link to the sociodemographic questionnaire and the PROLEC-SE-R test. The regulatory application times were strictly timed, with an additional minute for reading instructions.

Once the responses were collected, each subtest was evaluated on the TEAEdiciones® platform (https://www.teaediciones.net). The platform provided the net scores for each subtest. These scores were recorded in a database, and a sum of the scores from each subtest was calculated to obtain the total score. Based on the total score for the index in PROLEC-SE-R screening version, students were classified into study groups (average and superior groups).

Genotyping process

For 37 participants DNA extraction was carried out from their blood samples using the Macherey-Nagel kit® (24). DNA sample concentration was assessed using a BioDrop UV/Vis Spectrophotometer, and they were aliquoted to 20 ng/µL. Allelic discrimination for the selected SNPs was done by qPCR using TaqMan® assays with the standard conditions as recommended by the supplier in the QuantStudio 5 instrument (*ThermoFisher Scientific*). The *q*PCR assays were as carried out in a total volume of 10 µL, including 2 µL of DNA template. The PCR reaction included 3 µL of Master Mix, 0.25 µL of TaqMan probes, and 4.75 µL of RNAase free water.

Statistical analysis

a) Analysis of reading comprehension competence:

To assess differences in the scores subtest and total score between the study groups (data with non-normal distribution), U Mann-Whitney test for independent groups was applied using SPSS v. 23. For comparisons between multiple groups, the Kruskal-Wallis test was employed. No adjustes were done for non-parametric test.

b) Analysis of Genetic Variants:

The SNP data analysis in the two studied groups (cases) and the control population sample included estimation of allele and genotype frequencies, and evaluation of the Hardy-Weinberg equilibrium (HW) agreement. The Excel complement GenAlex 6.5 was employed for all these purposes (25). The odds ratio (OR) was assessed to evaluate the SNP association by chi-square tests (26). For this purpose, we used the online platform SNPStats (https://snpstats.net/start.htm) (27) to estimate genetic differences between behavioral phenotypes based on the PROLEC-SE-R scores. Subsequent comparisons were made based on genotypes using the Kruskal-Wallis test.

We compared our results with worldwide population previously studied. For the variant rs2253478 in the *FOXP2* gene, we used Caucasian, Australian, and Spanish population data (28,29). We took German population data for rs1995402 in the *ROBO1* gene (30) (Table 1). We estimated genetic distances between populations that were graphically represented using principal component analysis (PCoA) using the GenAlex 6.5 software (25).

Table 1. Information of the Mexican and worldwide populations employed for comparison based on the variants rs2253478 and rs1995402 of the *FOXP2* and *ROBO1* genes.

Gen SNP Population	Sample Size (n)	Country	Abbreviation	References
***FOXP2* – rs2253478**				
Mexican Cases	37	West, Mexico	MxCase	This study
Mexican Controls	80	West, Mexico	MxCtrl	This study
Australian Cases	211	Australia	AusCase	McCarthy *et al.* (2014)
Australian Controls	122	Australia	AusCtrl	McCarthy *et al.* (2014)
Spanish Cases	293	Spain	SpainCase	Tolosa *et al.* (2010)
Spanish Controls	340	Spain	SpainCtrl	Tolosa *et al.* (2010)
***ROBO1* – rs1995402**				
Mexican Cases	37	West, Mexico	MxCase	This study
Mexican Controls	80	West, Mexico	MxCtrl	This study
German Cases	383	Germany	GerCase	Müller *et al.* (2016)
German Controls	357	Germany	GerCtrl	Müller *et al.* (2016)

Results

Performance of reading comprehension competence

We examined the differences between the average group (AG) and the superior group (SG) (Table 2), where differences were expected due to the distribution criteria of the participants. In lexical processes, participants in the SG demonstrated higher scores in the Semantic Categorization test (Mdn= 86.5) compared to the AG (Mdn= 59.8, U= 18.5, z= -4.587, p= 0.000, r= -0.75). Differences were also observed in the lexical index, with the SG scoring higher (Mdn= 128.5) than the AG (Mdn= 99, U= 18.5, z= -4.588, p= 0.000, r= -0.75). However, no significant differences were observed in the Lexical Selection subtest (U= 128.5, z= -1.218, p> 0.05).

Differences between groups were also observed in syntactic-grammatical processes. The SG (Mdn= 23) scored higher than the AG (Mdn= 22, U= 96.5, z= -2.271, p= 0.023, r= -0.37) in the Grammatical Structures I test. Similarly, in the Grammatical Judgments test, the AG (Mdn= 22) scored lower than the SG (Mdn= 32, U= 33, z= -4.169, p= 0.000, r= -0.685). The syntactic index also showed significant differences, favoring the SG (Mdn= 54.5) over the AG (Mdn= 45, U= 36, z= -4.08, p= 0.000, r= -0.67). In the total score, the SG showed a higher score (Mdn= 198.5) compared to the AG (Mdn= 158, U= 0.0, z= -5.156, p= 0.000, r= -0.847).

Table 2. Description of Scores Obtained by Groups in the PROLEC-SE-R Battery Tests (n = 37).

	Average Group (n = 21)			**Superior Grup (n = 16)**				
PROLEC-SE-R Index/Test	*Mean*	*SD*	*Median*	*Mean*	*SD*	*Median*	*U-value*	*p-value*
Lexical Selection (LS)	41.04	4.51	42	42.9	2.91	42.5	128.5	.229
Semantic Categorization (SC)	59.8	13.29	57	84.8	5.57	86.5	18.5	p < 0.001 **
Grammatical Structures (GS)	21.9	1.81	22	23.1	0.72	23	96.5	0.027*
Grammatical Judgement (GJ)	23.8	5.22	22	31.3	2.09	32	33	p < 0.001 **
Expositive Comprehension (EC)	8.3	1.19	8	8.6	1.58	9	133.5	0.294
Narrative Comprehension (NC)	6.7	1.41	7	7.3	1.66	7.5	128	0.229
Lexical Index (LEX)	100.9	12.76	99	127.7	4.82	128.5	18.5	p < 0.001 **
Sintactical Index (SINTAX)	45.7	6.22	45	54.5	2.34	54.5	36	p < 0.001 **
Semantical Index (SEM)	15.04	1.85	15	15.9	2.79	16.5	120	0.147
Total Score (TOTAL)	161.7	11.52	158	198.1	4.55	198.5	0.00	p < 0.001 **

For U de Mann-Whitney:*p< 0.05 (one-tailed & two-tailed). **p< 0.01 (one-tailed & two-tailed).

Allele and Genotype frequencies for SNPs

For Mexican cases and control groups the allele and genotype frequencies were estimated for the studied SNPs in *FOXP2* and *ROBO1* genes (Table 3). The genotype distribution agreed with Hardy-Weinberg expectations in both case and control groups. Similarly we compared these frequencies between AG and SG of the Mexican cases, adjusted by the total score values, lexical index, syntactic index, or semantic index (see complementary material, Table A-1). However, no significant differences were observed and odds ratios were not significant. Estimated φ-values for these comparisons were under 0.1, indicating low statistical power explained by the small sample sizes.

Additional OR comparisons in a co-dominant model, adjusted for the PROLEC-SE-R subtests, also yielded non significant p-values.

Table 3. Allele and genotype frequencies for rs2253478 and rs1995402 gene variants, plus Hardy-Weinberg equlibrium test (p-value) in Mexican Cases and Controls, plus comparison into de Case group clustered by PROLEC-SE-R performance.

Population/Variant *rs2253478*	**Alleles**		**Genotypes**			**HWE**
	A	**G**	**AA**	**AG**	**GG**	***p-value***
Mexican Cases n= 37	0.405	0.595	0.162	0.486	0.351	0.956[s]
Mexican Controls n= 80	0.431	0.569	0.188	0.488	0.325	0.956
Superior Group n= 16	0.375	0.625	0.125	0.500	0.375	OR= no significant
Average Group n= 21	0.429	0.571	0.191	0.476	0.333	
rs1995402	**T**	**G**	**GG**	**GT**	**TT**	***p-value***
Mexican Cases n= 37	0.473	0.527	0.270	0.514	0.216	0.855
Mexican Controls n= 79	0.487	0.513	0.253	0.519	0.228	0.731
Superior Group n= 16	0.469	0.531	0.313	0.438	0.251	OR= no significant
Average Group n= 21	0.476	0.524	0.238	0.571	0.190	

Worldwide comparison of the rs2253478 and rs1995402 variants.

A higher frequency of AG homozygotes and GG heterozygotes compared to AA heterozygotes is observed in all populations (see Figures 1 and 2). The dendrogram below (Figure 3) describes the relationship of the studied populations; the same information can be corroborated in Nei's genetic distance model (Table 4). It should be noted that the Mexican cases (Figure 3, a) look more related to the Spanish cases and controls in the study by Tolosa *et al*. (2010), while the Mexican controls are more related to the Australian controls and more distant from the Australian cases (McCarthy-Jones *et al*., 2014). Meanwhile, for the rs1995402 variant it was observed that in the Mexican and German populations analyzed, the allele frequency tends towards the greater presence of the reference allele G (Figure 2, left). As can be seen in the dendrogram in Figure 3 (b) and the values of Nei's genetic distances (Table 4), the Mexican and German population groups tended to be related among their neighbors and there was no genetic closeness between populations.

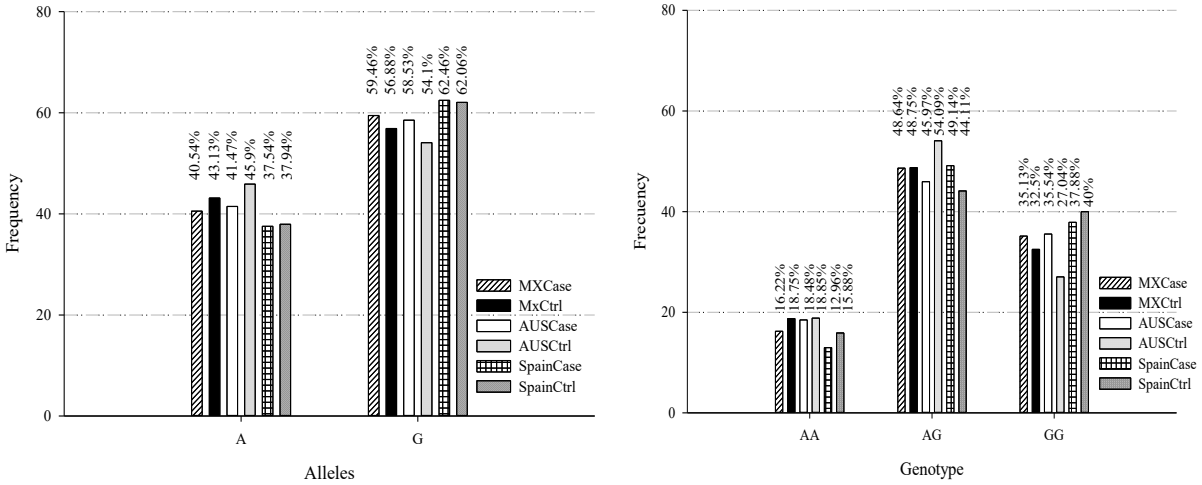


Figure 1. Allele (left) and Genotype frequencies (right) in Mexican and European-descended populations for the variant rs2253478 in the *FOXP2* gene.

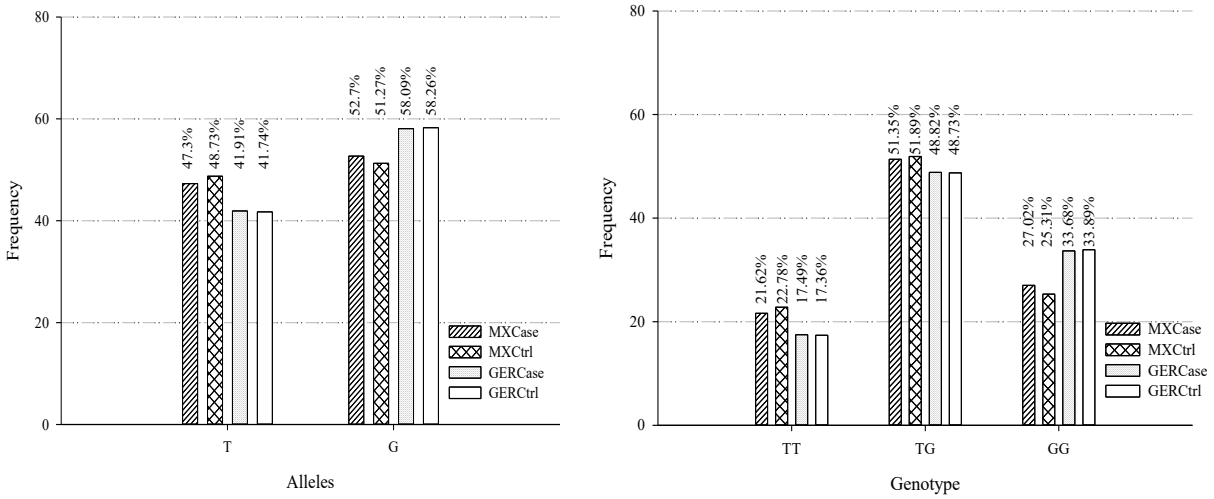
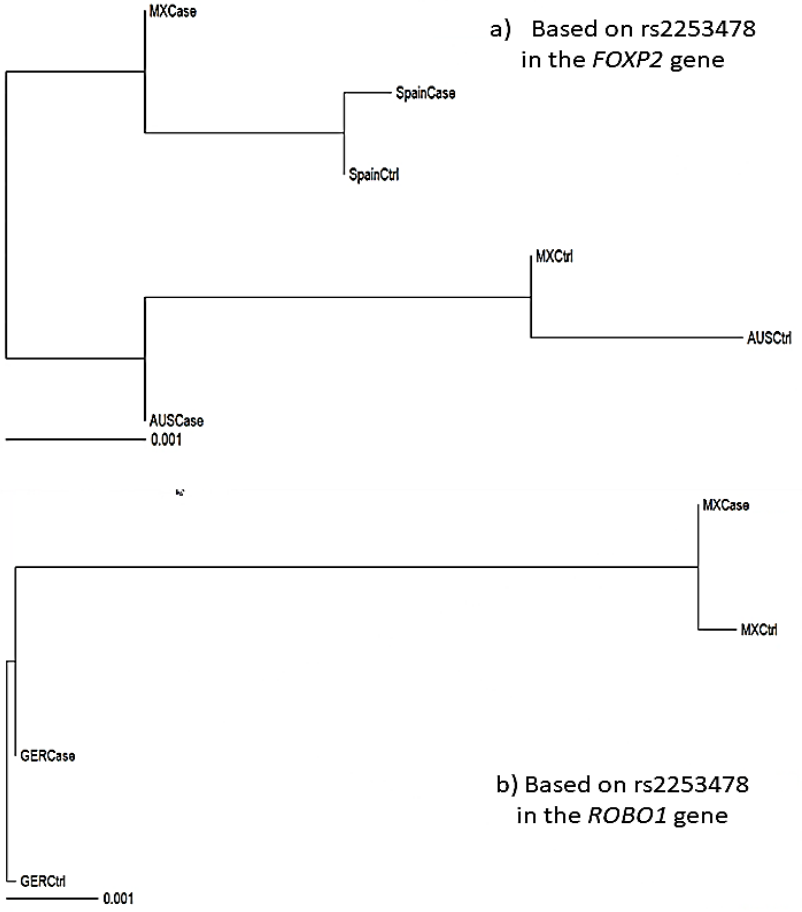


Figure 2. Allele (left) and Genotype frequencies (right) observed in Mexican and European-descended populations for the variant rs1995402 in the *ROBO1* gene.

Table 4. Genetic distances between the studied Mexican populations and populations of European origin for rs2253478 in the *FOXP2* gene (below diagonal) and rs1995402.of the *ROBO1* gene (above diagonal).

	MxCase	MxCtrl	AusCase	AusCtrl	SpainCase	SpainCtrl	GerCase	GerCtrl
MxCase	*	0.000	-	-	-	-	0.006	0.006
MxCtrl	0.001	*	-	-	-	-	0.009	0.010
AusCase	0.000	0.001	*	-	-	-	-	-
AusCtrl	0.006	0.002	0.004	*	-	-	-	-
SpainCase	0.002	0.006	0.003	0.013	*	-	-	-
SpainCtrl	0.001	0.005	0.002	0.012	0.000	*	-	-
GerCtrl	-	-	-	-	-	-	*	p < 0.001

Figure 3. Dendrogram representing genetic distances between the Mexican populations and populations of European origin the studied SNPs.



Discussion

This study aimed to examine the association between two genetic variants, rs2253478 (*FOXP2*) and rs1995402 (*ROBO1*), and reading comprehension competence in a sample of Mexican undergraduate students. Despite prior evidence suggesting that these gene variants contribute to language-related cognitive functions (4,12,19), our results (Table 2) did not support a significant relationship between the studied variants and individual differences in reading comprehension competence as seen in Table 3.

The absence of a significant association contrasts with previous findings on *FOXP2* and *ROBO1*, like in studies on dyslexia and phonological processing (5,20) or studies with lexical evaluations

(5,12,19,30,31) should be noted. One possible explanation is that our sample consisted of undergraduate students, most of whom demonstrated Reading comprehension competences above a threshold level. In contrast, prior studies identified genetic influences on broader populations, including individuals with clinically diagnosed reading difficulties (31). This suggests that the genetic effects of *FOXP2* and *ROBO1* may be more pronounced in populations with significant reading impairments rather than in populations with typical or superior reading abilities, or its impact on a cognitive phenotype are small (32). Another possible explanation is that given a small sample size, our associations were not detected or is not present.

In other studies, significant differences or associations have been observed between certain variants and reading comprehension competence, even when their phenotypic frequencies do not deviate from the HW. Tolosa *et al.* (29) found a difference in speaking ability between patients with schizophrenia and controls of Spanish Caucasian descent. However, this finding was not replicated in an Australian population of European Caucasian ancestry (28), highlighting the complexity of linguistic phenotype development.

The results of the *odds ratio* test (Table 3) and the association of haplotypes with grouping by the total screening index (Table 6 and 7 on Supplementary Material) demonstrates that No evidence of a significant association between the studied variants and behavioral performance was observed in this sample. Additionally, no close relationship allows these genotypic combinations to be inherited together. Finally, the haplotype frequencies are observed for Mexican cases and Mexican controls (Table 5 on Supplementary Material), same order of frequencies. Therefore, it can be expected that in the Mexican population studied, these are the most common combinations of the genotypes studied for each variant.

Another potential explanation of our global results is the polygenic nature of the reading ability. Genome-wide association studies (GWAS) have demonstrated that reading competence is influenced by a combination of multiple genetic variants, each exerting small effects (21). Isolated SNPs, such as rs2253478 and rs1995402, may not exert a strong enough influence on reading comprehension performance when considered independently. Future studies incorporating polygenic risk scores could provide a more comprehensive view of genetic influences on reading comprehension competence.

Genetic, Developmental and Environmental Interactions in Reading Development

While *FOXP2* and *ROBO1* have been linked to reading and language skills, their effects are not purely deterministic. Studies suggest that gene-environment interactions play a crucial role in shaping cognitive abilities, including reading (33). Our study did not account for environmental influences such as socioeconomic status, bilingualism, or literacy exposure, which may modulate the genetic expression and reading comprehension competence.

For instance, some research has shown that literacy-rich environments can enhance phonological awareness and reading skills, potentially compensating for genetic predispositions (34–36). Similarly, brain imaging studies indicate that the effects of *FOXP2* on linguistic processing are modulated by neural plasticity and environmental factors (37,38). Future studies should consider integrating neuroimaging (fMRI, MEG or EEG) and cognitive assessments to better understand the mechanisms underlying reading performance in relation to genetic variability.

Also, it has been considered that gene expression on brain differs among developmental stages (39–41), and also differs among different brain regions (42,43). This could imply that genes play different roles along human life.

Another environmental interaction to be considered is ambient contamination, but is highly speculative. Mexico has high agricultural production, it is reported that diminishes on testosterone due to pesticides, may play a role in *FOXP2* expression (44); so it could be measured gene expression among population. It is theoretically stated that language is a crucial regulator of cognitive processes (45), so if language related structures and function are not well stablished, cognition tends to fail.

Comparative Genetic Analysis and Population-Specific Findings

A secondary aim of this study was to examine the allelic and genotypic frequencies of rs2253478 and rs1995402 in the Mexican population and compare them to previous reports in European populations (28–30). Our findings indicate that the genetic architecture of reading/language-related SNPs in our

Mexican sample closely resembles that of Spanish populations. This aligns with prior studies highlighting genetic continuity between Mexican and European populations due to historical migrations (46).

However, the functional implications of these genetic similarities remain unclear. While our population exhibited similar allelic distributions to those reported in European datasets, no significant genotype-phenotype correlations emerged, suggesting that genetic influences on reading may be context-dependent. These results emphasize the need for broader cross-cultural genetic studies to determine whether population differences in genetic associations stem from divergent environmental exposures, educational systems, or linguistic structures.

It is important to verify if the reported frequencies could be typical of European-descendent populations or if they remain that way in multiple human groups regardless its geographical and historical origin. Some studies propose *FOXP2* (47,48) and *ROBO1* (48) are population and evolutionary markers, particularly, *FOXP2* is highly related to be conserved transcription factor in human populations.

Limitations and Future Directions

Several limitations must be acknowledged. First, the small sample size (n = 37) reduces the reliability of the genetic findings. Given the low effect sizes typically observed for genetic variants associated with complex cognitive traits, it means multiple genetic *loci* acting in combination for this phenotype (49), a larger sample would be necessary to detect subtle associations. The lack of statistical power in our study may explain why we failed to identify significant genotype-phenotype correlations. This limitation is consistent with previous studies that have emphasized the need for larger and more diverse samples to confirm genetic associations with reading skills (21). Then, this is only an exploratory study from genetics of language on Mexican samples.

Furthermore, the sample was not fully representative of the general population from Western Mexico, as participants were undergraduate students. Given that genetic backgrounds, as also environmental (e.g., literacy exposure, educational access) (33,50) and individual factors (e.g., personality, gender) (51,52) can shape reading ability, future research should consider cross-population comparisons to assess whether the lack of association is population-specific.

Our study focused on two specific SNPs, but reading comprehension competence is likely influenced by multiple genetic *loci* acting in combination (49). Expanding the study to include a larger set of candidate genes involved in neural connectivity, phonological processing, and memory (e.g., *DYX1C1*, *KIAA0319*, *and CNTNAP2*) may provide a more complete understanding of the genetic basis of reading.

Also another limitation is not having evaluated IQ, although previous studies indicate a robust association between linguistic performance and IQ, like McArdle *et al.* (53) and Gurven *et al.* (54).

Additionally, future research should incorporate longitudinal designs to examine how genetic influences on reading development over time. Given that reading comprehension competence skills stabilize between ages 25 and 30 (53–55), investigating genetic associations across different developmental stages could clarify whether certain variants exert stronger effects during childhood *versus* adulthood.

Lastly, gene-environment interactions should be explicitly analyzed. Including educational background, bilingualism, and early language exposure as covariates could reveal how genetic predispositions interact with brain structure and literacy experiences to shape reading outcomes (31).

Supplementary material

Complementary Material for “Reading Competence in Mexican Undergraduate Students: No Asocciation with *FOXP2* and *ROBO1* Variants: Tables 5-9

Scientific contributions from this study

The present study contributes to the knowledge of behavioral genetics, and its relationship with complex genetic traits as reading competence. On this exploratory study, we found no clear associations with Single Nucleotide Variants and psychometric measures from reading processes; but founded allelic and genotypic frequencies similar to European populations on this Mexican sample. The study points the necessity to explore multiple genetic variants (e.g. through haplotypes or GWAS) and greater human samples across countries and cultures, for better conclusions about genetics of reading comprehension.

Funding

Secretaría de Ciencia, Humanidades, Tecnología e Innovación [Secretary of Science, Humanities Technology and Innovation] (SECIHTI), Mexico granted to HALF to obtain PhD (Grant number: 727484).
University of Guadalajara,, Mexico, financed and provided materials and permissions for completing this study.

Declaration of Interest Statement

The authors report that there are no competing interests to declare.

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