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RESEARCH ARTICLE

The first genome-wide association study in the Argentinian and Chilean populations identifies shared genetics with Europeans in Alzheimer's disease

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Abstract

INTRODUCTION: Genome-wide association studies (GWAS) are fundamental for identifying loci associated with diseases. However, they require replication in other ethnicities.

METHODS: We performed GWAS on sporadic Alzheimer's disease (AD) including 539 patients and 854 controls from Argentina and Chile. We combined our results with those from the European Alzheimer and Dementia Biobank (EADB) in a meta-analysis and tested their genetic risk score (GRS) performance in this admixed population.

RESULTS: We detected apolipoprotein E ε4 as the single genome-wide significant signal (odds ratio = 2.93 [2.37–3.63], $P = 2.6 \times 10^{-23}$). The meta-analysis with EADB summary statistics revealed four new loci reaching GWAS significance. Functional annotations of these loci implicated endosome/lysosomal function. Finally, the

Itziar de Rojas and Maria Carolina Dalmasso contributed equally to this work.

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AD-GRS presented a similar performance in these populations, despite the score diminished when the Native American ancestry rose.

DISCUSSION: We report the first GWAS on AD in a population from South America. It shows shared genetics modulating AD risk between the European and these admixed populations.

KEYWORDS

admixture, genetic risk score, genetics, genome-wide association study, Hispanic, Latin America, Native-American ancestry, South America

Highlights

- This is the first genome-wide association study on Alzheimer's disease (AD) in a population sample from Argentina and Chile.
- Trans-ethnic meta-analysis reveals four new loci involving lysosomal function in AD.
- This is the first independent replication for *TREM2L*, *IGH-gene-cluster*, and *ADAM17* loci.
- A genetic risk score (GRS) developed in Europeans performed well in this population.
- The higher the Native American ancestry the lower the GRS values.

1 | INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder responsible for most dementia cases worldwide in the elderly population.[1] Although there are numerous studies on AD with the most diverse approaches, the causes and etiology of the disease remain poorly understood. Among them, genome-wide association studies (GWASs) and meta-analyses thereof have led to the identification of more than 80 genetic variants contributing to the susceptibility of AD.[2–4] However, the majority of these studies have been performed in European and Asian populations,[5] hindering thereby their translation to populations with different or mixed ancestries, based on possible differences in the genomic structure and/or allele frequencies. These differences might also involve different causative variants across ancestries or allelic heterogeneity, therefore implicating alternative pathogenic and potentially population-specific mechanisms.

Latin American populations are diverse, not only culturally, but also in their genetic ancestry composition.[6] South American populations present a large genetic diversity in Native American, African, and mestizo populations, between and within countries.[6,7] This diversity is likely to have an impact on the distribution of genetic determinants of AD risk across different geographic regions. Unfortunately, systematic genetic studies for translating findings from European to Latin American populations are scarce.[8–10] In fact, 1.3% of individuals in the NHGRI-EBI GWAS Catalog are Hispanic or Latin American.[5] Consequently, we report here the first GWAS on AD in a population sample from the southern cone of South America. We explored the detected suggestive loci and the known AD variants, in terms of effect size and direction, in a population from Argentina and Chile. We performed a meta-analysis of these populations with the previous results observed by the European Alzheimer and Dementia Biobank (EADB)[2] to search for additional AD risk signals. Finally, because combined effects of known variants in a genetic risk score (GRS) can identify individuals at the highest risk of future AD,[2,3] we tested the performance of the AD-GRS reported by EADB[2] in this admixed population. Exploring different populations will likely contribute to a better understanding of the pathophysiology of AD. Importantly, understanding population-shared genetic risk factors, and the allelic heterogeneity of AD, will translate into improved prevention and/or treatment for different populations via precision medicine.

1.1 | METHODS

1.1.1 | Data collection

Participants in this study were recruited from multiple sources. Further sample descriptions can be found in Table 1.

The Argentinian samples were recruited in the context of the Alzheimer's Genetics in Argentina–Alzheimer Argentina consortium (AGA-ALZAR, https://www.gaaindata.org/partner/AGA), from the following centers: Medical Research Institute A. Lanari (C1427ARO, Buenos Aires), Hospital de Clínicas José de San Martín (C1120AAF, Buenos Aires), Hospital HIGA-Eva Perón (B1650NBN, General San Martín), Hospital El Cruce (B1888AAE, Florencio Varela), and several geriatric centers across Jujuy and Mendoza provinces, organized and

coordinated by their respective Public Ministry of Health. The study (protocol CBFIL#22) was approved by the ethical committee (HHS IRB#00007572, IORG#006295, FWA00020769), and all participants and/or family members gave their informed consent.[11] Diagnosis of AD followed diagnostic criteria from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).[12,13] Peripheral blood or saliva samples were processed to obtain DNA using the QIAmp DNA mini kit (Qiagen) and genotyped using the Illumina Infinium Global Screening Array (GSA) v.1.0 combined with a GSA shared custom content.

The Chilean samples recruited correspond to patients with AD and control subjects, from different studies. Control individuals ($n = 791$) were recruited from the Alexandros longitudinal study,[14] of community-dwelling older adults (≥60 years old) of different demographic origins and socioeconomic levels, mainly in the study of healthy life expectancy, free of disability and dementia. All participants were randomly selected from 18 primary health care centers and signed an informed consent on enrolment after they had received written and verbal information about the study. The ethical committee of the Institute of Nutrition and Food Technology (INTA), University of Chile (Acta 23, 2012), approved the study protocol (FONDECYT n°1130947). Cognitive status was determined through the Mini-Mental State Examination (MMSE)[15] with a cut-off of 21/22, previously validated in Chile.[16] AD patients ($n = 91$) were recruited at Biomedica Research Group, a clinical research center performing industry-sponsored international multicenter studies in Santiago. Subjects were comprehensively studied and diagnosed following the NINCDS-ADRDA[12,13] criteria for AD. The GWAS study was approved by the ethics committee "Servicio de Salud Metropolitano Oriente" (SSMO). Additional AD cases and control individuals (32 AD and 20 controls) from Santiago were recruited from the GERO[17] (Geroscience Center for Brain Health and Metabolism) study at the Memory and Neuropsychiatric Center of the Hospital del Salvador and Faculty of Medicine of the University of Chile. The FONDAP GERO project n°15150012 was also approved by the ethics committee of the SSMO.

A total of 934 samples ($n = 800$ DNA and $n = 134$ frozen blood) were sent to Ace Alzheimer Center Barcelona (Barcelona, Spain) for processing. DNA was extracted from peripheral blood according to standard procedures using the Chemagic system (Perkin Elmer). For the starting DNA samples, a re-extraction protocol using the Chemagic system was also followed to purify the DNA samples. Only samples reaching DNA concentrations of > 10 ng/μL and presenting high integrity were included for genotyping. Finally, AD cases ($n = 123$) and controls ($n = 252$) were randomized across sample plates to avoid batch effects. We used the Axiom 815K Spanish biobank array (Thermo Fisher) at the Spanish National Centre for Genotyping (CeGEN, Santiago de Compostela, Spain) for genotyping.

1.2 | Quality control and imputation

Details on quality control (QC) and imputation procedures are provided in previous publications,[3,18] and performed using PLINK 2.0[19] (www.cog-genomics.org/plink/2.0/). Briefly, individuals with low-quality samples, excess of heterozygosity, sex discrepancies, duplicates, and familial relations between samples (PI-HAT > 0.1875) were excluded from the analysis. Variants with a call rate below 97%, a deviation from the Hardy–Weinberg equilibrium (HWE, $P < 1 \times 10^{-6}$), or differential missingness between cases and controls were also removed from the analysis. A total number of 1018 samples from Argentina and 375 samples from Chile remained after QC. To maximize genetic coverage, we performed single-nucleotide polymorphism (SNP) imputation on genome build GRCh38 using the Trans-Omics for Precision Medicine (TOPMed) imputation server.[20–22] Statistical power was estimated using the Genetic Power Calculator tool[23] (https://zzz.bwh.harvard.edu/gpc/cc2.html), and PowerPlot.R (https://github.com/ilarsf/gwasTools).

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using standard sources like PubMed. Genome-wide association studies (GWAS) are fundamental for identifying loci associated with diseases. They have identified more than 80 variants associated with Alzheimer's disease (AD) risk. However, main studies have been performed on Caucasians, hindering thereby their translation to other populations. All relevant citations were included.
2. **Interpretation**: We report the first AD GWAS on the Argentinian and Chilean populations. Trans-ethnic meta-analysis revealed four new loci implicating lysosomal function in AD. The European-developed AD genetic risk score (GRS) performed well in these South American populations, despite the score declines with the increase in Native American ancestry.
3. **Future directions**: To improve our knowledge of AD genetics, a large initiative in Latin American populations is ongoing to increase the studied sample size. This will refine the definition of personalized AD risk profiles by a population-tailored GRS.

1.3 | Global ancestry analysis

Global ancestry was estimated as described previously.[11] Briefly, 446 ancestry informative markers (AIMs), specifically selected to estimate ancestry in Latin Americans,[24] were extracted from the Argentinian and Chilean datasets and the reference populations in 1000 Genomes (http://www.internationalgenome.org/): Caucasian (CEU, $n = 85$), Yorubas African (YRI, $n = 88$), and Native American[25] (NAM, $n = 46$). Only AIMs present in all populations and balanced distributed among reference populations and chromosomes, were used to estimate ancestry ($n = 356$). They were all merged in one PLINK v1.9 file (http://www.cog-genomics.org/plink/1.9/), and ancestry was

TABLE 1 Descriptive characteristics of the samples across datasets.

Cohort		AD cases	Controls	*P-value*
Argentina (*N* = 1018)	*N*	416	602	
	Female (%)	66.1	71.2	*0.05*
	Age* (years)	76.3 ± 6.6	72.5 ± 7.5	*2.2e-16*
	APOE ε4† (%)	42.8	19.1	*2.9e-16*
	NAM ancestry† (%)	18.8 ± 21.6	24.8 ± 25.4	*6.2e-05*
Chile (*N* = 375)	*N*	123	252	
	Female (%)	53.7	69.4	*0.004*
	Age* (years)	79.6 ± 10.9	81.7 ± 7.4	*0.39*
	APOE ε4† (%)	50.4	18.7	*1.5e-9*
	NAM ancestry‡ (%)	37.0 ± 11.7	38.7 ± 10.5	*0.16*

Abbreviations: AD, Alzheimer's disease; *APOE*, apolipoprotein E; *N*, number of samples; NAM, Native American.
*Mean ± standard deviation.
†Percent frequency of *APOE ε4* allele.
‡Mean ± standard deviation of NAM ancestry proportion.

predicted using ADMIXTURE v1.3.0.[26] Plots and analysis were performed with R (www.R-project.org/).

1.4 | Association analysis

Several logistic regression models, adjusted for different combinations of age, sex, and the first six principal components (PCs), were evaluated using PLINK 2.0[19] in the Argentinian and Chilean populations. Models fitting were evaluated by Quantile-plots (QQ-plots) and genomic inflation factors, obtained using the R package qqman,[27] and distribution of cases and controls across different PCs on principal component analysis plots. The best model in both populations was using the first four PCs as covariates. Low imputation quality variants ($R^2 < 0.3$) or rare variants (minor allele frequency [MAF] < 1%) were excluded. After study-specific variant filtering and QC procedures, a fixed effects inverse-variance weighted meta-analysis[28] with the Argentinian and Chilean summary statistics was performed for AD association. Plots and analysis were performed with R (www.R-project.org/). Regional plots were generated with LocusZoom[29] and loci were annotated as the closest genomic feature.

In addition, these Latin populations were combined with EADB stage I summary statistics[2] in a fixed effects inverse-variance weighted meta-analysis.[28] Random effects meta-analysis was also performed with METASOFT,[30] observing similar results.

1.5 | Genetic risk score

A weighted individual GRS was calculated based on the AD genetic variants and effect size from the recent meta-GWAS published[2] by the EADB consortium. Eighty of the selected variants presented high quality in the Argentinian and Chilean cohorts. The GRSs were generated by multiplying the genotype dosage of each risk allele for each variant by its respective weight and then summing across all variants. GRS association with AD cases was tested by a logistic regression model adjusted by 4 PCs in each cohort. The influence of NAM ancestry over GRS was estimated by a linear regression model adjusted by sex, age, and phenotype (control = 0, case = 1) in pooled Argentinian and Chilean samples. The linear model was plotted separately for cases and controls to test the interaction between NAM ancestry and disease. In addition, pooled samples were split in quintiles using NAM ancestry proportion. Differences in GRS values among quintiles were assessed by analysis of variance followed by Tukey post hoc test, and GRS association in each quintile was tested using the same logistic regression model described above. Differences in frequency between the most European (quintiles 1 and 2) and the most NAM individuals (quintiles 4 and 5) were estimated by a logistic regression model of ancestry (mostEUR = 0, mostNAM = 1) versus the 80 SNPs, adjusted by phenotype, sex, and age; *P*-values were Bonferroni corrected. All analyses were performed with R (www.R-project.org/).

2 | RESULTS

2.1 | Population admixture in Argentinian and Chilean samples

Genome-wide genotyped data was generated in two samples from the southern cone of Latin America (Table 1), Argentina (n = 1018) and Chile (n = 375). We first explored the ancestry admixture of both populations, observing an admixture between EUR and NAM, without a significant contribution of African ancestry (Figure 1A). While the admixture of Chilean participants is more homogenous, with 75% of the samples showing 30% to 50% NAM ancestry, the Argentinian samples showed more diverse admixture along the NAM and EUR axis, with 32% of individuals having > 30% NAM ancestry (Figure 1A and B). Besides differences in recruitment between the Chilean (only one city,

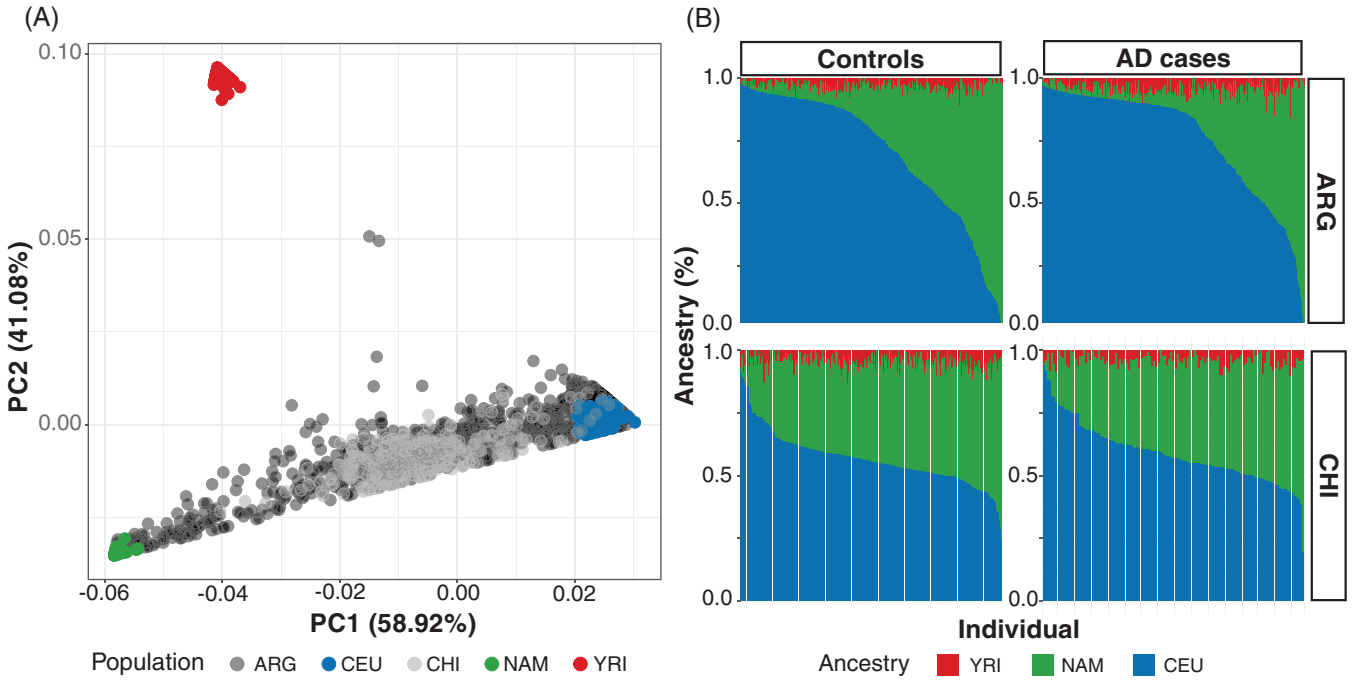


FIGURE 1 Ancestry analysis of the Argentinian and Chilean populations. A, Principal component analysis (PCA) of ancestry results for the Argentinian sample (ARG, black) and the Chilean sample (CHI, gray). Ancestral populations are Caucasians (CEU, blue), Yoruba (YRI, red), and Native Americans (NAM, green). B, Bar-plots of each sample (x-axis) versus their respective percent of Caucasian (CEU, blue), African (YRI, red), and Native American (NAM, green) ancestry (y-axis).

Santiago) and the Argentinian samples (different cities across the country), dissimilar migratory flows and policies between countries may explain these differences in ancestry proportions. Importantly, this admixture distribution is similar in cases and controls in both cohorts (Figure 1B).

2.2 | Argentinian and Chilean GWAS meta-analysis

GWAS was performed on each cohort separately and meta-analyzed as described in Materials and Methods (Figure S1A in supporting information). The combined sample size was 539 patients with AD dementia and 854 controls. Four PCs corrected inflation ($\lambda = 1.01$, Figure S1B in supporting information). As expected for a sample size with limited statistical power (Figure S2 in supporting information), only the apolipoprotein E (*APOE*) locus showed an association with the risk of AD reaching genome-wide significance (*APOE* ε4-rs429358 odds ratio [OR] = 2.93 [2.37–3.63], $P = 2.6 \times 10^{-23}$; *APOE* ε2-rs7412 OR = 0.53 [0.34–0.84], $P = 6.3 \times 10^{-3}$, Figure S1A). Fifteen loci reached a suggestive *P*-value, that is, $5 \times 10^{-8} < P < 1 \times 10^{-5}$ (Table 2). However, neither of these loci was previously reported in association with AD risk in case-control GWASs nor showed nominal significance ($P < 0.05$) in the EADB stage I[2–4] (Figure S1A and Table S1 in supporting information). Among these suggestive signals, those at *MRPL50P1* and *GPX4* deserve further mention (Table 2). At the *MRPL50P1* locus, a suggestive association (rs13002275) was previously reported in a GWAS of hippocampal volume in AD.[31] This variant is in linkage disequilibrium (LD) with our top signal rs36039096 at the same locus, with a D' = 0.91 and low $r^2 = 0.14$ due to the difference in allele frequency ($MAF_{rs13002275} = 0.39$ vs. $MAF_{rs36039096} = 0.21$ in Ad Mixed American (AMR, https://www.ncbi.nlm.nih.gov/snp/ and https://ldlink.nci.nih.gov/). On the other hand, the suggestive signal in *GPX4* is located close (52.6 Kb) to the known AD locus *ABCA7*. However, the top SNP signal in our study (rs8103283) does not show LD with the top signal described for *ABCA7* in European ancestry (D' = 0.19, $r^2 = 0.02$ in AMR, https://ldlink.nci.nih.gov/). In addition, expression quantitative trait loci analysis (https://gtexportal.org/) showed that rs8103283 is modulating the expression of *GPX4*, *POLR2E*, and *SBNO2* expression but not of *ABCA7*. Hence, *GPX4* might represent an independent signal, which needs further confirmation in larger samples.

In addition, we looked for the 83 sentinel signals reported by Bellenguez et al.[2] Nine of these variants were replicated in this population presenting a similar effect size and a *P*-value < 0.05 (Table S2 in supporting information).

2.3 | Comparison of Argentinian and Chilean GWAS to previous results in Caucasians

We looked for shared genetics between these South American populations with Caucasians, by meta-analyzing EADB stage I with the

TABLE 2 Suggestive SNPs in Argentina–Chile meta-analysis.

Chr	Position*	Marker	Effect allele	Freq.	OR [95% CI]†	*P*-value	*Loci* ‡
1	163485057	rs2820864	C	0.65	0.68 [0.58–0.81]	8.33e-06	*RNA5SP62*
2	35789890	rs36039096	A	0.83	0.60 [0.48–0.74]	2.93e-06	*MRPL50P1*
2	40071018	rs35392935	T	0.02	3.49 [2.04–5.96]	4.63e-06	*SLC8A1-AS1*
2	67888895	rs7595509	A	0.31	0.63 [0.52–0.76]	3.35e-06	*LINC01812*
2	235676849	rs12465126	A	0.69	1.60 [1.32–1.93]	1.68e-06	*AGAP1*
5	6573819	rs553467	A	0.70	1.60 [1.33–1.92]	4.99e-07	*LINC01018*
5	31656661	rs29745	A	0.89	0.52 [0.39–0.69]	8.38e-06	*PDZD2*
8	77958623	rs7016182	C	0.83	1.71 [1.36–2.14]	4.31e-06	*AC084706.1*
9	92567110	rs74457370	A	0.90	0.52 [0.40–0.68]	1.21e-06	*CENPP*
9	97591519	rs2805792	T	0.18	0.61 [0.49–0.76]	9.70e-06	*TMOD1*
9	134858932	rs57464688	A	0.05	2.44 [1.65–3.59]	6.59e-06	*MIR3689F*
13	85053369	rs9566005	C	0.87	0.58 [0.46–0.74]	8.60e-06	*AL356313.1*
14	20490566	rs949937	A	0.85	0.59 [0.47–0.74]	5.65e-06	*PNP*
19	1103523	rs8103283	A	0.21	0.61 [0.49–0.76]	8.18e-06	*GPX4*
21	34364698	rs34532322	A	0.27	1.59 [1.31–1.91]	1.41e-06	*KCNE2*

Abbreviations: Chr, chromosome; CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism.
*Position in bp; Freq., effect allele frequency.
†Odds ratio [95% confidence interval].
‡Name of *loci* is the closest feature.

TABLE 3 Significant SNPs in EADB-Argentina–Chile meta-analysis.

Chr	Position*	Marker	Effect allele	Freq	OR [95%CI]†	*P*-value	Annotation‡	Direction§	Locus
2	9409624	rs10169262	T	0.202	0.95 [0.94-0.96]	4.70E-08	ITGB1BP1	—	ADAM17
4	59984152	rs376291994	A	0.997	0.65 [0.60–0.71]	3.79E-08	AC097655.1	–?	new
6	28259100	rs1531681	A	0.579	0.96 [0.95–0.96]	4.11E-08	NKAPL	—	new
8	125446584	rs115038899	T	0.185	1.08 [1.06–1.09]	3.27E-08	TRIB1	+++	new
14	106669877	rs11849532	A	0.131	0.93 [0.92—0.95]	4.59E-08	IGHVII-65-1	—	IGH gene
18	32075509	rs61392417	T	0.632	0.95 [0.95–0.96]	3.89E-08	AC011825.3	—	new

Abbreviations: Chr, chromosome; CI, confidence interval; EADB, European Alzheimer and Dementia Biobank; OR, odds ratio; SNP, single nucleotide polymorphism.
*Position in bp; Freq, effect allele frequency.
†Odds ratio [95% confidence interval].
‡Closest feature in the genome.
§Direction of the effect in EADB stage I, Argentina and Chile summary statistics, respectively; plus sign (+), OR > 1; minus sign (–), OR < 1; question mark (?), missing SNP.

Argentinian and Chilean summary statistics. First, we explored the 83 previously reported SNPs.[2] Fifty-one of them were significant ($P < 5 \times 10^{-8}$) after meta-analysis, while 50 were significant in EADB stage I (Table S2). The variant reaching significance was rs60755019 in *TREM2L*, meaning this signal is replicated in the Argentinian and Chilean populations (Table S2). In addition, we compared *P*-values before and after meta-analysis, despite significance. We observed that 48 out of the 83 SNPs[2] improved their *P*-values after meta-analysis, suggesting these variants are shared among Europeans and the populations studied here (Table S2). Then, we looked for significant signals besides the 83 known ones. Interestingly, we detected six significant SNPs, which were not significant in EADB stage I (Table 3). Two of these SNPs are in high LD with the sentinel variants previously reported[2] in the loci *ADAM17* and *IGH-gene-cluster* (Table 3, Table S2). These two signals reached GWAS-significance in EADB stage I+II[2]; then, we provide the first independent replication confirming both loci. The other four SNPs are novel associations with AD risk (Table 3). Next, we did functional annotation for these novel loci. rs376291994 is a rare variant in chromosome (chr) 4, not close to any known coding gene. rs1531681 in chr6 seems to modulate brain expression of most zinc finger proteins in the locus (https://gtexportal.org/). These types of proteins have been linked to brain disorders[32] and in particular, ZKSCAN3

with AD in a mouse model.[33] rs115038899 in chr8 is closed to the gene *TRIB1* and is in LD (D' = 0.85, r^2 = 0.70) with rs17405319, which has been associated with several lipid-related traits (https://www.ebi.ac.uk/gwas/variants/rs17405319). Finally, rs61392417 in chr18 seems to modulate the expression of *RNF138* in whole blood (https://gtexportal.org/), which is an E3 ubiquitin-protein ligase, phosphorylated upon DNA damage, mediating homologous recombination, involved in the innate immune system pathways.

2.4 | EADB genetic risk score performance in the Argentinian and Chilean populations

Finally, we sought to explore whether the GRS reported by the EADB[2] consortium can classify cases and controls accurately in the studied populations. To compute the GRS in our sample, we included the 80 SNPs that passed quality controls in both the Argentinian and Chilean datasets, with the effect sizes reported in European ancestry (Table S3 in supporting information). GRS values were normally distributed and logistic regression analysis revealed an association with AD in both Argentinian (GRS_{mean} = 50.4, GRS_{range}[40.1–61.8], OR = 1.06, $P = 7.4 \times 10^{-4}$) and Chilean (GRS_{mean} = 49.5, GRS_{range}[39.3–60.9], OR = 1.16, $P = 1.6 \times 10^{-6}$) populations.

Because the South American populations analyzed here are genetic admixtures, we investigated whether the NAM ancestry was affecting the GRS values and/or association with the disease. A linear regression model showed that the proportion of NAM ancestry is indeed modulating the GRS values (effect size (β) = −4.84, $P < 2 \times 10^{-16}$), without interacting with the disease (Figure S3 in supporting information). To explore this observation in detail, we split the studied South American sample in quintiles depending on NAM ancestry proportion (Figure 2). Quintiles 1 to 3, containing a larger proportion of Caucasian ancestry individuals, showed GRS values not significantly different among them. Conversely, quintiles 4 and 5, containing a higher proportion of NAM samples, showed GRS values significantly different between them, and smaller than those observed in quintiles 1 through 3 ($P < 0.001$). While the GRS mean value decreases as the NAM ancestry proportion increases, the GRS association with AD remains similar in each quintile. The effect size for the GRS association is the same in quintile 1 as in quintile 5 (Figure 2).

Differences in GRS values depend on the frequency of risk alleles in the population analyzed. Consequently, the differences observed in the GRS values in samples with a higher proportion of NAM ancestry may be explained by differences in the risk allele frequency between European and NAM ancestries. To test this hypothesis, we combined quintiles 1 and 2 in one group (mostEUR) and quintiles 4 and 5 in the mostNAM group, and compared risk allele frequencies for each of the 80 SNPs included in the GRS between groups. This comparison showed that allele frequency between both groups was significantly different ($P_{Bonferroni} < 0.05$) in 38 SNPs, of which 24 showed a lower frequency and 14 had a higher frequency in the mostNAM group (Tables S4 and S5 in supporting information).

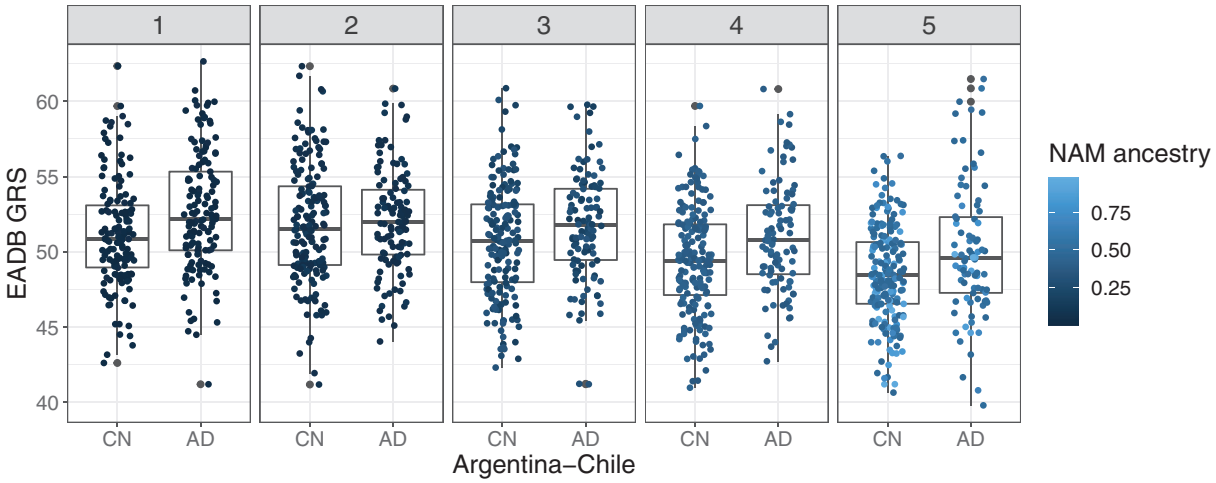
3 | DISCUSSION

Understanding the genetics of AD is one of the best ways to improve our knowledge about the underlying pathophysiological processes. In this regard, GWAS have been pivotal for the identification of genomic regions associated with the disease. Unfortunately, large international initiatives have focused their research on European ancestry, limiting the generalizability of genetic findings across populations with different ancestries.[5,34] Herein, admixture populations living in Latin America still represent a major gap for genetic research.[10] To begin filling this gap, we present here the kickoff study to elucidate AD genetics in the understudied South American population. We carried out the first AD GWAS using 1393 samples from Argentina and Chile, generating the first GWAS summary statistics accessible for these southernmost populations.

While our study lacks statistical power for claiming new population-specific signals, it is suitable for replication and translation of previously validated loci. Consequently, we provide here an extensive analysis of the main associations reported in European AD GWAS.[2–4] We confirmed our previous observation for the *APOE* locus, and provided independent validation for several of the 83 SNPs tested, evidencing that they can be translated from Europeans to the Argentinian and Chilean populations. Among these translated signals, we provide the first independent replication for *TREM2L*, *IGH-gene-cluster*, and *ADAM17* signals. Therefore, we confirm that these loci contribute to AD susceptibility in populations other than the Europeans. Additionally, we validate a common variant in the *PLCG2* locus, which together with our previous observation[11] reinforces the contribution of this locus to the susceptibility of AD in Argentinians. In addition, we identified four new risk loci, involved in lipid metabolism, immune response, and autophagy, all mechanisms previously linked to AD. As our knowledge of the genetic architecture of AD increases, novel pathways are connected to the pathophysiology of AD including the endosome/lysosome trafficking/function. In our study, the novel genetic loci provide further support for the involvement of this pathway in the pathogenic mechanism operating in AD. Furthermore, we contribute additional evidence for the hypothesis that biological pathways involving lysosomal function might be a shared pathological mechanism across neurodegenerative diseases.

Several studies have shown that GRS generated from European ancestry GWAS works more accurately in Europeans than in non-Europeans.[34,35] In our hands, the AD-GRS developed in Europeans[2] presented a similar performance in the Argentinian and Chilean populations (OR = 1.09, $P = 3.14 \times 10^{-8}$) as in the European/Spanish population (GR@ACE[3], OR = 1.095, $P = 9.63 \times 10^{-88}$), independently of the degree in NAM ancestry present in the target. This means that this GRS could be generalized also to Hispanics/Latinos, as it was observed for other phenotypes.[36,37] This can be explained because the admixture found in Argentinians and Chileans includes different proportions of European ancestry. On the other hand, GRS trans-ethnic performance also seems to depend on the sample size of the

(A)



(B)

Quintile	NAM range (%)	CN	AD	OR [95%CI]	P	GRS mean [range]	
1	0 - 3.9	142	137	1.12 [1.08-1.15]	1,50E-03	51.9 [51.4-52.3]	ns
2	3.9 - 14.2	163	115	1.03 [0.99-1.06]	4,78E-01	51.9 [51.5-52.4]	
3	14.4 - 34.5	171	107	1.07 [1.04-1.11]	4,54E-02	51.1 [50.7-51.6]	***
4	34.5 - 44.9	183	95	1.14 [1.10-1.19]	5,00E-04	50.0 [49.5-50.4]	*
5	44.9 - 97.5	192	86	1.11 [1.07-1.15]	4,70E-03	49.0 [48.6-49.5]	

FIGURE 2 GRS performance and its association with NAM ancestry. GRSs of the samples from Argentina and Chile were split into five groups (quintiles) depending on their proportion of NAM ancestry. A, Boxplot of GRSs in cases (AD) and cognitively normal individuals (CN) present in each quintile (1 to 5). The dot color represents the degree of NAM ancestry of the sample, the lighter the higher the proportion of NAM ancestry. B, Quantitative information of the quintiles. NAM range (%), proportion of NAM ancestry range; CN, number of control samples; AD, number of cases samples; OR [95% CI], GRS effect expressed as odds ratio and 95% confidence interval; P, OR associated *P*-value; GRS mean [range], mean value of GRSs and its respective range. At the right of the table, differences among GRS values estimated by two-way analysis of variance (Tukey's multiple comparisons test) are represented; ns, not significant; *, $P < 0.05$; ***, $P < 0.001$. AD, Alzheimer's disease; CI, confidence interval; EADB, European Alzheimer and Dementia Biobank; GRS, genetic risk score; NAM, Native American; OR, odds ratio

discovery GWAS. Thus, it is also possible that this GRS performed well in our South American sample because the EADB GWAS[2] was large enough (> 500K individuals) to accurately calculate the effect sizes to be used as SNP weights.

Interestingly, GRS values decrease as the NAM ancestry proportion increases. While this observation could be a real difference between the risk of AD in the European, Argentinian, and Chilean populations, these reduced GRS values seem more likely caused by incorrect variant selection and/or genetic effects used in the GRS for the target population. In other words, the genetic variants included in the GRS explain apparently less of the genetics driving AD in this ethnic admixture. Supporting this hypothesis, we observed that several SNPs included in the GRS showed significantly different risk allele frequencies between NAM and European ancestry (Tables S4 and S5). This may complicate the direct practical use of the GRS score, and/or set up a pathological predictive threshold. Further studies are needed to understand how to overcome this difficulty.

Our work has some limitations. It does not have the statistical power for a discovery GWAS and/or validation of low-frequency allelic associations, so we might have missed some genuine signals linked to the NAM ancestry, as well as true associations. In addition, this work might not be representative enough of the allelic variability present in Argentina and Chile, because of their vast territories and the limited number of recruitment centers included in the study. Still, our strength is to start generating genetic information on AD in the southern cone of South America and start identifying trans-ethnic signals, which contributes to diversity studies.

4 | CONCLUSIONS

In conclusion, we provide here the first of a series of AD GWAS to come involving populations originating from countries from Latin America. Our analysis clearly showed shared genetics among the European, Argentinian, and Chilean populations modulating the risk of AD. However, several of these loci probably carry different genetic risk variants that should be added when constructing a GRS in Native American ancestry. Furthermore, a larger initiative is now

starting to increase the sample size studied in Latin America, which will lead to a definition of population-specific estimators for the risk conferred by each variant included in the GRS. Finally, genetic research in the Latin American populations will help improve the definition of personalized risk profiles informing on the individual risk for progressing to dementia. This will likely improve our possibilities for early personalized intervention to prevent or postpone dementia.

AUTHOR CONTRIBUTIONS

Alfredo Ramírez: Laura Morelli: and Agustín Ruiz designed: conceptualized: and supervised the study; interpreted the data; and revised the manuscript. Maria Carolina Dalmasso and Itziar de Rojas contributed to data acquisition; the analysis and interpretation of the data; and co-wrote the manuscript. Data generation and sample contribution—**Argentina**: Maria Carolina Dalmasso: Natividad Olivar: Carolina Muchnik: Pablo Galeano: Lorenzo Campanelli: MEC: CL: CF: MS: MF: GJ: Mariana Soledad Sanchez Abalos: Luis Eduardo Martinez: Nancy Medel: Julieta Lisso: Zulma Sevillano: MIB: FDG: Eduardo Miguel Castaño: Claudia Kairiyama: JSA: HS: FJ: Carlos Alberto Mangone: Patricia Solis: Daniel Gustavo Politis: Silvia Kochen: Luis Ignacio Brusco: Laura Montrreal: Alfredo Ramírez; **Chile**: Sergio Gloger: Bárbara Angel: M. Victoria Chacón: Paulina Orellana: Patricio Fuentes: Agustín Ruiz: and Itziar de Rojas. All authors critically revised the manuscript for important intellectual content and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or potential conflict of interest. Author disclosures are available in the supporting information

DATA AVAILABILITY STATEMENT

The summary statistics of the meta-analysis are available to the corresponding author upon request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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