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RESEARCH ARTICLE

Admixture mapping of cognitive function in diverse Hispanic and Latino adults: Results from the Hispanic Community Health Study/Study of Latinos

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Abstract

INTRODUCTION: We conducted admixture mapping and fine-mapping analyses to identify ancestry-of-origin loci influencing cognitive abilities.

METHODS: We estimated the association of local ancestry intervals across the genome with five neurocognitive measures in 7140 diverse Hispanic and Latino adults

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(mean age 55 years). We prioritized genetic variants in associated loci and tested them for replication in four independent cohorts.

RESULTS: We identified nine local ancestry–associated regions for the five neurocognitive measures. There was strong biological support for the observed associations to cognitive function at all loci and there was statistical evidence of independent replication at 4q12, 9p22.1, and 13q12.13.

DISCUSSION: Our study identified multiple novel loci harboring genes implicated in cognitive functioning and dementia, and uncovered ancestry-relevant genetic variants. It adds to our understanding of the genetic architecture of cognitive function in Hispanic and Latino adults and demonstrates the power of admixture mapping to discover unique haplotypes influencing cognitive function, complementing genome-wide association studies.

KEYWORDS
admixture mapping, cognitive abilities, gene mapping, genetics, Hispanic/Latino, neurocognitive function

Highlights

- We identified nine ancestry-of-origin chromosomal regions associated with five neurocognitive traits.
- In each associated region, we identified single nucleotide polymorphisms (SNPs) that explained, at least in part, the admixture signal and were tested for replication in independent samples of Black, non-Hispanic White, and Hispanic/Latino adults with the same or similar neurocognitive tests.
- Statistical evidence of independent replication of the prioritized SNPs was observed for three of the nine associations, at chr4q12, chr9p22.1, and chr13q12.13.
- At all loci, there was strong biological support for the observed associations to cognitive function and dementia, prioritizing genes such as *KIT*, implicated in autophagic clearance of neurotoxic proteins and on mast cell and microglial-mediated inflammation; *SLC24A2*, implicated in synaptic plasticity associated with learning and memory; and *MTMR6*, implicated in phosphoinositide lipids metabolism.

1 | BACKGROUND

Cognitive function, the set of mental abilities related to the acquisition, storage, manipulation, and retrieval of information, is a key component of brain health and aging. Prevention of late-life cognitive decline is a major public health priority and identifying individuals who would most benefit from early intervention is of great societal interest.[1] In the era of precision medicine, genetic information is emerging as a powerful tool for improving risk assessment and therapeutic optimization models.[2] Twin studies have estimated that the heritability of cognitive function is ≈ 50% to 80% and remains high throughout life.[3–5] Genome-wide association studies (GWAS) conducted primarily in populations of European ancestry have revealed the polygenic nature of cognitive abilities[6,7] but genetic discoveries in other populations, including Hispanics/Latino populations, are lagging. The lack of diversity in genetic studies curtails progress and raises concerns that it amplifies already considerable health disparities.[8,9]

Hispanics/Latino individuals comprise the largest ethnic or racial minority group in the United States, with an estimate of 62.1 million, representing 18.5% of the overall US population in 2020.[10] Racial and ethnic differences in the prevalence and incidence of cognitive impairment and dementia have been well documented.[11–14] In particular, compared to White adults, Hispanic/Latino adults are ≈ 1.5 times more likely to have Alzheimer's disease (AD) and related dementias (ADRD).[15] Moreover, by 2060, they will face the largest increase in the prevalence of ADRD of any racial or ethnic group in the United States.[16] US Hispanic/Latino individuals are diverse with regard to their origin, culture, history, and socioeconomic and cardiovascular risk factors. They also vary in measures of cognitive function, which cannot be fully accounted for by these factors.[17] Genetically, US

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Hispanic/Latino individuals have uniquely admixed genomes, encompassing African, Amerindian, and European ancestries.[18] Patterns of recent admixture in genomic regions (local ancestry) can be leveraged in gene mapping when frequencies of trait-associated genetic variants located within these regions differ among ancestries. Unlike GWAS, which treats heterogeneity in genetic ancestry as a confounder in genetic analyses, admixture mapping exploits it to search for ancestry-related genomic regions associated with traits.[19] Thus, it is often viewed as a complement to GWAS.

To identify genomic regions associated with cognitive function among diverse middle-aged and older Hispanics/Latino adults, we performed admixture mapping followed by fine mapping and GWAS imputed to the TOPMed reference panel in 7140 individuals from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL).

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using PubMed. While Hispanic and Latino individuals are underrepresented in genetic studies of cognitive functioning, their admixed genome provide a unique opportunity to identify novel ancestry-of-origin loci influencing cognitive abilities. Relevant papers are cited.
2. **Interpretation**: This study identified nine genome-wide significant loci associated with five neurocognitive measures. Fine mapping and functional annotation of the identified loci provided robust biological support for these associations and there was independent replication of prioritized variants at loci on chromosome 4q12, 9p22.1, and 13q12.13.
3. **Future directions**: Further investigation using a wider spectrum of genetic variation beyond common single nucleotide polymorphisms and in larger populations of diverse ancestry may allow for a more comprehensive characterization of the complex haplotypes identified by admixture mapping. Integration of additional multiomic data may help further refine the findings into clinically actionable gene sets.

2 | METHODS

2.1 | Study sample

HCHS/SOL is a community-based cohort study of 16,415 self-identified Hispanic/Latino adults, 18 to 74 years old, recruited from randomly selected households in four US metropolitan areas (Chicago, Illinois; Bronx, New York; Miami, Florida; and San Diego, California). Biospecimens and health information were collected at the baseline examination in 2008 through 2011, which included physical measures, behavioral and lifestyle factors, and sociodemographic assessments.[20,21] The study was approved by the institutional review board at each participating institution and all participants provided written informed consent.

2.2 | Measures of cognitive function

At the baseline examination, HCHS/SOL participants older than 45 years of age (sample size = 9652) underwent a cognitive assessment including the Six-Item Screener (SIS, global mental status), Brief Spanish English Verbal Learning Test (B-SEVLT, verbal learning and memory), Word Fluency Test (WFT, executive and verbal functioning), and Digit Symbol Substitution Test (DSST, psychomotor speed and sustained attention).[22] In addition, a measure of general cognitive function (G) defined as the value of the first unrotated principal component of the standardized scores for B-SEVLT, WFT, and DSST was derived for each participant.[6] Because the distribution of the SIS score was skewed, this measure was dichotomized for analysis, with a score of 0 to 4 indicating low mental status and 5 or 6 indicating normal mental status. A detailed description of the cognitive tests measured in HCHS/SOL is given in Table S1 in supporting information.

2.3 | Genotypes and imputation

Details of genotyping and quality control procedures were reported elsewhere.[18] Briefly, genotyping was performed on an Illumina custom array, SOL HCHS Custom 15041502 B3, consisting of the Illumina Omni 2.5 M array (HumanOmni2.5-8v1-1) and ≈ 150,000 custom single nucleotide polymorphisms (SNPs). After standard quality control procedures,[23] a total of 12,803 samples were successfully genotyped for 2,232,944 SNPs. These genotypes were then pre-phased and used for imputation with the TOPMed reference panel (freeze 5b), yielding ≈ 57 million variants.[24]

2.4 | Genetic analysis groups and local ancestry

HCHS/SOL participants self-identified as primarily belonging to one of six background groups: Central American, Cuban, Dominican, Mexican, Puerto Rican, and South American. Based on these groups, a multi-dimensional clustering method was used to construct a "genetic analysis group" variable.[18] The genetic analysis groups are similar to self-identified background groups with regard to cultural and environmental characteristics but are more genetically homogeneous. Among them, the Mainland group (Mexican, Central American, and South American) has a higher proportion of Amerindian ancestry, with the Mexican subgroup generally having the highest. The Caribbean group (Cuban, Dominican, and Puerto Rican) has a higher proportion of African ancestry, with the Dominican subgroup generally having the highest. Additional information about the distribution of admixture proportions in HCHS/SOL is described in Conomos et al.[18]

Local ancestry is defined as the genetic ancestry of an individual at a particular chromosomal location; an individual can have 0, 1, or 2

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copies of an allele derived from each ancestral population. Local ancestry inference was performed as described by Browning et al.[25] Briefly, local African, Amerindian, and European ancestries were inferred from a set of quality-controlled SNPs across the genome using RFMix[26] and used to calculate the average values of local ancestries at 14,815 non-overlapping intervals (local ancestry intervals [LAI]) on autosomal chromosomes, each spanning tens to hundreds of thousands of base pairs.

2.5 | Admixture mapping analysis

We tested the association of each cognitive measure with LAI counts (0, 1, or 2) of African, Amerindian, and European ancestries individually and, in secondary analyses, of all ancestries jointly. We used mixed models as described in Jian et al.[27] and implemented in the GENetic EStimation and Inference in Structured samples (GENESIS) R package.[28] The models adjusted for age, sex, field center, sampling weight, and the top five principal components of ancestry as fixed effects; and for kinship, household, and census block group as random effect. For continuous traits, which allow for heteroscedasticity in the error variance, genetic analysis groups are used to fit separate residual variance components. For the dichotomous trait SIS, they were included as fixed effects in the model. Based on previously reported simulation analyses in HCHS/SOL, we used a P value threshold of 5.7×10^{-5}, which controls the family-wise error rate of admixture mapping at level 0.05.[25] Because cognitive function and level of education are correlated both genetically and phenotypically, we performed analyses with and without adjustment for education level (< high school, = high school, or > high school). We did not adjust for the number of traits examined because the cognitive traits are correlated.[27]

2.6 | Fine mapping and replication analysis

We further examined regions with significant admixture signals to identify SNPs in those regions that were significantly associated with the respective cognitive function measures and could explain, at least in part, the admixture signal. Single SNP association analyses were conducted as described by Jian et al.[27] using genotyped and TOPMed-imputed SNPs with minor allele frequency (AF) > 0.01 and imputation scores > 0.4. Analyses were conducted in the overall sample and the Mainland and Caribbean subgroups. Because admixture mapping associations can be driven by either AF differences or effect size differences between ancestral groups, in each LAI, candidates SNPs were prioritized based on their strength of association (P value and effect size) with the cognitive measure of interest, their differences in strength of association between the Mainland and Caribbean subgroups as appropriate, and/or their differences in estimated AF among continental ancestry groups as implemented in AFA.[29] Candidate variants were then functionally annotated using QTLbase,[30] FUMA,[31] and Ensembl VEP,[32] and pruned for linkage disequilibrium (LD). Additional annotation of these variants was performed by PheWAS analysis in the GWASAtlas.[33] We then performed conditional admixture analysis including the candidate SNPs as covariates in the admixture mapping model described above.

We also tested the identified variants for replication in independent samples of Black and non-Hispanic White individuals from the Atherosclerosis Risk in Communities (ARIC) study, in two samples of Hispanic/Latino individuals from the Genetics of Brain Structure (GOBS) and the Texas Alzheimer's Research and Care Consortium (TARCC), and in published GWAS studies of general cognitive function[6] and DSST[34] from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium. A description of the data available in these cohorts is provided in the supporting information (see Table S2). Genetic association analyses were conducted within race adjusting for age, sex, principal components of ancestry, and field center (ARIC only).

3 | RESULTS

3.1 | Sample characteristics

The final sample used for analyses comprised 7140 individuals with both cognitive and genotyping data. Table 1 describes the characteristics of the sample overall and stratified by Mainland and Caribbean subgroups. The mean age was 55 years, and 60.5% were women. The average proportions of African, Amerindian, and European ancestry were 15%, 28%, and 57%, respectively.

3.2 | Admixture mapping

We identified significant local ancestry-associated regions with each of the five cognitive tests. Table 2 shows the most significant LAI in each of the nine associated regions. Although effect sizes are not biologically meaningful, the sign of the beta coefficient indicates an increase or decrease in the respective cognitive test with each additional copy of the corresponding ancestry at the locus. Adjusting for education did not significantly impact these results. Counts of African ancestry in four regions on chromosome 13q12.11, 4q12, 10p12.2, and 9p22.1 were associated with DSST, G, SIS, and WFT, respectively. Counts of Amerindian ancestry in a region on 1q25.2 were associated with DSST; and in two regions on 12q14.2 and 12q15 with SIS. Counts of European ancestry in a region on 8p22 were associated with B-SEVLT; and in a region on 13q12.13 with both DSST and G. Three loci showed significant associations in the joint test: chr13q12.11 was associated with DSST and 10p12.2 and 12q15 were associated with SIS.

3.3 | Fine mapping of associated LAIs and gene prioritization

We next performed fine mapping of each associated LAI via SNP association testing. Table 3 shows the prioritized candidate variants in

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TABLE 1 Descriptive characteristics of HCHS/SOL participants in the total sample and in the Mainland and Caribbean subgroups.

Trait	Total sample ($n = 7140$)	Mainland ($n = 3635$)	Caribbean ($n = 3505$)
Age (years), mean (SD)	55.4 (7.5)	54.7 (7.3)	56.0 (7.7)
Women, *n* (%)	4319 (60.5%)	2289 (63.0%)	2030 (57.9%)
Education ≥ high school, *n* (%)	4133 (58.0%)	1961 (54.1%)	2172 (62.1%)
SIS (dichotomized)[a]	6058 (84.9%)	3196 (88.0%)	2862 (81.7%)
B-SEVLT, mean (SD)	8.2 (2.9)	8.8 (2.8)	7.6 (2.9)
WFT, mean (SD)	18.2 (7.2)	19.1 (7.5)	17.3 (6.8)
DSST, mean (SD)	33.9 (13.5)	34.6 (13.6)	33.1 (13.3)
G, mean (SD)	0.0 (1.3)	0.2 (1.3)	−0.2 (1.3)
Genetic analysis groups, *n* (%)			
Central American	734 (10.3)	734 (20)	–
Cuban	1462 (20.6)	–	1462 (42)
Dominican	680 (9.6)	–	680 (20)
Mexican	2369 (33.3)	2369 (65)	–
Puerto Rican	1334 (18.8)	–	1334 (38)
South American	532 (7.5)	532 (15)	–
Global ancestry proportion[b], mean (SD)			
African	0.15 (0.17)	0.06 (0.05)	0.24 (0.20)
Amerindian	0.28 (0.23)	0.46 (0.17)	0.09 (0.06)
European	0.57 (0.21)	0.48 (0.17)	0.67 (0.20)

Abbreviations: B-SEVLT, Brief Spanish English Verbal Learning Test; DSST, Digit Symbol Substitution Test; G, general cognitive function; HCHS/SOL, Hispanic Community Health Study/Study of Latinos; *n*, sample size; SD, standard deviation; SIS, Six Item Screen; WFT, Word Fluency Test.

[a]Proportion of participants with a score ≥ 5.

[b]Estimated by averaging the local ancestry calls across all chromosomes.

TABLE 2 Admixture association results for the cognitive traits.

					Education adjusted			Education unadjusted		
Trait	Tested ancestry	Cytoband	Lead LAI position (GRCh38)	Ancestry frequency	Effect	SE	*P* value	Effect	SE	*P* value
DSST	AFR	13q12.11	(21116728,21229882)[a]	0.146	−1.332	0.297	**7.29E−06**	−1.384	0.334	**3.41E-05**
DSST	EUR	13q12.13	(25214448,25394838)	0.564	0.876	0.212	**3.67E-05**	0.929	0.241	1.19E-04
DSST	AMR	1q25.2	(178964455,178987418)	0.273	−0.981	0.249	7.95E-05	−1.220	0.283	**1.62E-05**
G	EUR	13q12.13	(25214448,25394838)	0.565	0.090	0.022	**3.22E-05**	0.097	0.025	7.92E-05
G	AFR	4q12	(54573726,54700100)	0.138	0.126	0.031	5.19E-05	0.145	0.035	**4.38E-05**
B-SEVLT	EUR	8p22	(17426461,17506432)	0.569	0.216	0.053	3.99E-05	0.228	0.054	**2.01E-05**
SIS	AFR	10p12.2	(24029836,24137764)[a]	0.146	−0.311	0.073	2.09E-05	−0.328	0.072	**5.53E-06**
SIS	AMR	12q14.2	(62918508,63107546)	0.273	−0.273	0.065	**2.97E-05**	−0.259	0.064	5.74E-05
SIS	AMR	12q15	(67887626,68071929)[a]	0.273	−0.287	0.065	**1.03E-05**	−0.271	0.064	2.61E-05
WFT	AFR	9p22.1	(19523986,19604080)	0.141	−0.68	0.19	3.63E-04	−0.864	0.207	**2.96E-05**

Note: The most significant LAI in the associated region is shown. Ancestry frequency represents the proportion of intervals inferred as inherited from the tested ancestry in the total sample.

Abbreviations: AFR, African; AMR, Amerindian; B-SEVLT, Brief Spanish English Verbal Learning Test; DSST, Digit Symbol Substitution Test; EUR, European; G, General cognitive function; LAI, local ancestry interval; *n*, sample size; SD, standard deviation; SE, standard error; SIS, Six Item Screen; WFT, Word Fluency Test.

[a]Also significant in the joint test.

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TABLE 3 Selected variants in top admixture peaks and their association with the respective cognitive trait.

				Estimated AF[a]			Overall				Caribbean				Mainland			
Trait/ locus	Associated ancestry	SNP	NEA/ EA	AFR	EUR	AMR	AF	Beta	SE	*P*	AF	Beta	SE	*P*	AF	Beta	SE	*P*
DSST/ 13q12.11[b]	AFR	rs74036988	A/G	0.21	0.01	0.01	0.03	−2.14	0.51	2.7E-05	0.05	−2.29	0.57	7.0E-05	0.01	−1.36	1.07	0.21
		rs507334	C/T	0.36	0.01	0.01	0.06	−1.54	0.39	7.6E-05	0.09	−1.58	0.44	3.6E-04	0.02	−1.13	0.81	0.16
		rs115317486	A/G	0.11	0.01	0.01	0.02	−2.63	0.67	8.3E-05	0.03	−3.22	0.79	4.7E-05	0.01	−1.52	1.23	0.21
DSST/ 13q12.13[b]	EUR	rs9551193	A/G	0.17	0.90	0.29	0.62	0.84	0.20	1.9E-05	0.65	0.89	0.29	2.6E-03	0.57	0.81	0.26	1.7E-03
G/ 13q12.13[b]								0.08	0.02	1.7E-04		0.09	0.03	3.1E-03		0.07	0.03	1.0E-02
DSST/ 1q25.2	AMR	rs2773080	T/C	0.48	0.61	0.92	0.67	−0.68	0.22	1.6E-03	0.60	−0.55	0.3	6.0E-02	0.73	−0.84	0.31	7.6E-03
		rs10798638	C/T	0.15	0.07	0.01	0.06	1.22	0.41	3.0E-03	0.08	0.46	0.53	0.38	0.04	2.37	0.64	2.1E-04
		rs10798723	A/G	0.91	0.55	0.10	0.48	0.77	0.21	3.1E-04	0.59	0.54	0.3	0.07	0.37	0.93	0.29	1.4E-03
		rs7518566	C/T	0.29	0.16	0.03	0.14	1.10	0.28	1.1E-04	0.18	0.86	0.37	2.0E-02	0.11	1.46	0.43	6.7E-04
G/ 4q12	AFR	rs2855775	G/C	0.13	0.01	0.01	0.02	0.24	0.08	1.4E-03	0.03	0.14	0.09	0.11	0.01	0.43	0.14	1.8E-03
		rs73816436	G/C	0.04	0.00	0.00	0.007	0.34	0.12	5.6E-03	0.01	0.42	0.13	1.0E-03	0.002	−0.02	0.36	0.95
		rs78537672	G/A	0.01	0.05	0.01	0.03	−0.24	0.06	5.4E-05	0.04	−0.22	0.08	5.2E-03	0.02	−0.27	0.09	3.2E-03
B-SEVLT/ 8p22	EUR	rs11203840	A/G	0.04	0.13	0.06	0.09	0.30	0.08	1.1E-04	0.09	0.14	0.11	0.22	0.09	0.44	0.11	3.0E-05
		rs7820095	G/A	0.21	0.01	0.01	0.03	−0.54	0.14	1.0E-04	0.05	−0.55	0.16	5.6E-04	0.01	−0.48	0.28	0.08
		rs6996711	C/T	0.61	0.41	0.17	0.62	−0.18	0.05	1.1E-04	0.55	−0.11	0.07	0.11	0.68	−0.27	0.07	5.9E-05
SIS/ 12q14.2[b]	AMR	rs139117576	C/T	0.01	0.01	0.11	0.03	−0.54	0.15	2.0E-04	0.007	−0.43	0.12	5.2E-04	0.06	−0.13	0.09	0.14
		rs139722987	G/A	0.001	0.02	0.01	0.02	0.61	0.18	7.3E-04	0.03	0.61	0.22	4.8E-03	0.01	0.62	0.32	5.4E-02
SIS/ 12q15[b]	AMR	rs56716396	G/A	0.01	0.05	0.63	0.21	−0.29	0.07	1.0E-05	0.09	−0.33	0.11	2.6E-03	0.31	−0.27	0.08	1.3E-03
		rs7956612	C/T	0.17	0.23	0.78	0.37	−0.23	0.05	1.4E-05	0.003	−0.22	0.07	3.4E-03	0.47	−0.25	0.08	1.5E-03
SIS/ 10p12.2	AFR	rs74360794	T/C	0.09	0.01	0.01	0.01	−0.75	0.19	6.1E-05	0.02	−0.64	0.20	1.5E-03	0.005	−1.49	0.50	2.9E-03
		rs111338558	G/C	0.28	0.00	0.05	0.06	−0.35	0.10	4.5E-04	0.07	−0.36	0.12	3.2E-03	0.04	−0.36	0.18	5.0E-02
		rs7909638	A/G	0.83	0.31	0.15	0.34	−0.19	0.05	4.2E-04	0.41	−0.28	0.07	4.2E-05	0.27	−0.05	0.09	0.59
WFT/ 9p22.1	AFR	rs78934697	A/C	0.19	0.01	0.01	0.03	−1.49	0.36	3.8E-05	0.04	−1.68	0.41	4.1E-05	0.01	−0.82	0.76	0.28
		rs3003713	C/T	0.62	0.63	0.29	0.53	−0.47	0.12	1.1E-04	0.59	−0.72	0.17	2.0E-05	0.48	−0.25	0.17	0.14

Note: Selected SNPs are those most strongly associated with the respective cognitive trait and with differentiated allele frequency among African, Amerindian, and European ancestries.
Abbreviations: AF, allele frequency; AFR, African; AMR, Amerindian; NEA, non-effect allele; EA, effect allele; EUR, European; SE, standard error; SNP, single nucleotide polymorphism.
[a] Implemented in AFA.[29]
[b] Cognitive trait is adjusted for education.

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each admixture peak, their association with the respective cognitive trait, their observed allele frequencies in HCHS/SOL, and estimated allele frequencies in the three continental ancestries. Their functional annotation is shown in Table S3 in supporting information.

3.3.1 | Fine mapping of LAI on 13q12.11 associated with DSST

Two independent SNPs, rs74036988 and rs507334, were most strongly associated with DSST in the overall sample. Both were common in populations of African ancestry (AF = 0.21 and 0.36, respectively) but rare in populations of European or Amerindian ancestry (AF = 0.01). Both were functionally annotated as an expression quantitative trait locus (eQTL) for a long non-coding RNA *LINC00539* in brain and immune cells. In the Caribbean subgroup, the strongest association with DSST in the region was for rs115317486, annotated to an enhancer active in neurons and predicted as an eQTL of *FGF9* in multiple brain tissues. This SNP was common in populations of African ancestry (AF = 0.11) but rare in populations of European or Amerindian ancestry (AF = 0.01).

3.3.2 | Fine mapping of LAI on 13q12.13 associated with DSST and G

rs9551193 had the strongest association with both DSST and G in the overall sample and exhibited a large AF difference between European ancestry (AF = 0.90) and African or Amerindian ancestry (AF = 0.17 and 0.29, respectively). rs9551193 is located in an intron of *NUP58* and is functionally annotated as an eQTL of *NUP58* in blood cells and as an eQTL and a protein QTL (pQTL) of *MTMR6* in multiple tissues including the brain.

3.3.3 | Fine mapping of LAI on 1q25 associated with DSST

We prioritized several SNPs within two regions located ≈ 800 kb apart. rs2773080 exhibited large AF differences between ancestries, was most common in Amerindian ancestry (AF = 0.92), and was more strongly associated with DSST in the Mainland subgroup than in the other groups. The strongest association in the Mainland subgroup was for rs10798638, which was weakly correlated with rs2773080 (r^2 = 0.13) and showed no association in the Caribbean subgroup even though it was twice as common. It is located in an intron of *RALGPS2*. In the region distal from the admixture peak, several SNPs showed even stronger associations with DSST. Among them, rs7518566 and rs10798723, in weak LD (r^2 = 0.23), showed the strongest associations with DSST in the overall sample; strong differences in association strength between the Mainland and Caribbean subgroups; and strong differences in estimated allele frequencies among the three continental ancestries. rs7518566 is located downstream of *FAM163A* and was identified as an eQTL of *TOR1AIP1* in the brain. rs10798723 is located in the 5′ untranslated region of *FAM163A* and was identified as an eQTL of that gene in the brain.

3.3.4 | Fine mapping of LAI on 4q12 associated with G

The strongest association with G in the overall sample in the 4q12 region was observed with rs78537672, which was similarly strongly associated in the Mainland and Caribbean subgroups. Within the admixture peak boundaries, rs2855775 showed the strongest association with G in the overall sample. This SNP is common in African ancestry (AF = 0.13) but rare in the other ancestries (AF = 0.01). It is located in an intron of *KIT*. rs73816436 showed the strongest association with G in the Caribbean subgroup and showed differentiated allele frequencies among continental ancestries, being polymorphic in African ancestry (AF = 0.04) but extremely rare or absent in other ancestries. None of these SNPs were in LD with each other.

3.3.5 | Fine mapping of LAI on 8q22 associated with B-SEVLT

SNPs located within the admixture signal boundaries were only weakly associated with B-SEVLT. Among nearby SNPs with stronger associations, three SNPs, not in LD with one another, showed similar associations in the overall sample: rs7820095, rs6996711, and rs11203840. rs11203840 had differentiated allele frequencies among the three continental ancestries, with the highest frequency in European ancestry (AF = 0.13), and had differentiated associations between the Mainland and Caribbean subgroups. It is in complete LD with an SNP (rs73210275) that had the strongest association with B-SEVLT in the Mainland subgroup. rs11203840 maps to an intron of *MTMR7* and has been identified as an eQTL of *CNOT7* in the brain and immune cells and *VPS37A* in the brain. rs7820095 showed the strongest association overall and in the Caribbean subgroup. It is in an intron of *MTMR7*.

3.3.6 | Fine mapping of LAI on 12q14.2 associated with SIS

Within the admixture peak, the strongest association with SIS in the overall sample was with the low-frequency variant rs139722987, which showed similar effect sizes across all groups. It is an intergenic SNP with no ascribed function. Located ≈ 500 kb away, rs139117576 was most strongly associated with SIS in the overall sample and was common in Amerindian ancestry but rare in the other two ancestries. It is located in an intron of *XPOT*. There were no strong associations of common SNPs with SIS in the Mainland subgroup.

3.3.7 | Fine mapping of LAI on 12q15 associated with SIS

Two SNPs in moderate LD in HCHS/SOL (r^2 = 0.5), rs56716396 and rs7956612, were most strongly associated with SIS in the overall

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sample. Both exhibited large differences in ancestry-specific allele frequencies, and both were common in Amerindian ancestry but much less so in African and European ancestry. Both SNPs are located within *IFNG-AS1* and have been associated with the expression of that gene in blood cells. rs56716396 has also been associated with circulating interleukin-2 receptor antagonist levels.[35]

3.3.8 | Fine mapping of LAI on 10p12.2 associated with SIS

Three independent SNPs were prioritized: rs74360794 showed the strongest association in the overall sample and was more common in African ancestry than in the other two ancestries (AF = 0.09 vs. 0.01). rs111338558, located directly under the admixture peak, is common in African ancestry (AF = 0.28) but rarer in Amerindian ancestry (AF = 0.05) and extremely rare in European ancestry (AF < 0.001). rs74360794 maps to an intron of *KIAA1217* and rs111338558 to the 5′ untranslated region of *KIAA1217*, for which it has been identified as an eQTL in the kidney. In the Caribbean subgroup, the strongest association was for rs7909638, which was most common in African ancestry (AF = 0.83) and showed no association in the Mainland subgroup.

3.3.9 | Fine mapping of LAI on 9p22.1 associated with WFT

rs78934697 was most strongly associated with WFT in the overall sample and was common in African ancestry but rare in the other two ancestries. rs78934697 maps to an intron of *SLC24A2* and has been identified as an eQTL of *RPS6* in the kidney. In the brain, it was also weakly associated with expression of that gene. rs3003713 was most strongly associated with WFT in the Caribbean subgroup and showed no association in the Mainland subgroup despite a similar AF in the two groups. It is located in an intergenic region near *PLIN2* and has been identified as an eQTL of *DENND4C* in immune cells.

3.3.10 | Additional biological support

We next screened the GWAS catalog to identify SNP–trait associations mapping to each LAI. As shown in Table S4 in supporting information, several SNPs in the identified LAIs are associated with traits relevant to cognitive function and cognitive aging, including imaging measures of brain morphology, AD, educational attainment, and tau protein levels. Some of these were in LD with the prioritized SNPs. We also performed a look-up of proteins encoded by genes located within associated LAIs in our recently reported proteomic analysis of cognitive function.[36] We identified two proteins with significant associations with G: FGF9 ($P = 1.9 \times 10^{-8}$) and KIT ($P = 4.2 \times 10^{-4}$); and three proteins with significant associations with DSST: FGF9 ($P = 1.7 \times 10^{-6}$), KIT ($P = 0.02$), and ANGPTL1 ($P = 2.8 \times 10^{-3}$).[36]

3.4 | Conditional analysis

Conditional admixture mapping results with the prioritized SNPs in each LAI are shown in Table 4 and Figures S1–S10 in supporting information. Except for rs9551193 on chr13q12.13 and rs56716396 on chr12q15, no single SNPs fully explained the admixture peak (joint conditional $P < 0.05$). Conditional analyses with multiple selected SNPs, jointly, significantly dampened or eliminated the respective admixture signals.

3.5 | Replication analysis

We attempted replication of associations for the prioritized variants in independent cohorts of Black, White, and Hispanic/Latino participants with cognitive data, and in two large GWAS from the CHARGE consortium (Table S5 in supporting information). Several variants showed evidence of replicated association ($P < 0.05$; i.e., same cognitive test, same direction of association, and same ancestral background as the original association in HCHS/SOL), including rs78537672 (G), rs78934697 (WFT), and rs9551193 (DSST). Notably, in a PheWAS analysis in the UK Biobank using GWASAtlas, the strongest trait association for rs9551193 was with a cognitive trait (prospective memory test, $P = 6 \times 10^{-4}$). Additionally, rs78537672 showed consistent associations with other cognitive traits besides G in ARIC Black participants. Several variants showed evidence of association in the same direction but with different cognitive traits or in another ancestral background as the original association in HCHS/SOL, including variants on chr1q25, 10p12.2, 12q14.2, 12q15, and 13q12.11. Finally, a few variants showed association with cognitive traits in at least one replication cohort but in the opposite direction as in HCHS/SOL.

4 | DISCUSSION

Our admixture mapping analyses identified multiple novel loci associated with measures of cognitive function that had not been detected in our previous GWAS.[27] This demonstrates the effectiveness of admixture mapping in complementing GWAS by exploiting admixture patterns within large genomic intervals that harbor causal variants with a wider AF spectrum than captured by GWAS. Moreover, as large GWAS of cognitive function have mostly focused on populations of European ancestry, this complementary approach provides an opportunity to identify genetic loci with differential effects on cognitive function by ancestry and may be particularly relevant for gene discovery in underrepresented populations.

Statistical evidence of independent replication of the prioritized SNPs underlying our admixture signals was generally weak, with only three formally replicated associations at chr4q12, chr9p22.1, and chr13q12.13. The region on chr4q12 associated with G spanned 125 kb and encompassed the gene encoding the receptor tyrosine kinase proto-oncogene c-KIT. In our recent proteomic profiling of

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TABLE 4 Cognitive traits admixture mapping results conditioning on the selected variants.

Trait/locus	SNP	Position (GRCh38)	Original P	Conditional P[a]	Joint conditional P[b]
DSST/13q12.11+	rs74036988	13:21329402	7.3E-06	1.3E-03	1.6E-01
	rs507334	13:20953939		2.5E-03	
	rs115317486	13:21718521		2.4E-04	
DSST/13q12.13+	rs9551193	13:25330766	3.7E-05	5.0E-02	
G/13q12.13+			3.2E-05	2.0E-02	
DSST/1q25.2	rs2773080	1:178727615	1.6E-05	2.6E-04	1.0E-2
	rs10798638	1:178909901		7.6E-05	
	rs10798723	1:179790752		1.2E-03	
	rs7518566	1:179818031		1.2E-04	
G/4q12	rs2855775	4:54686434	4.4E-05	8.2E-04	9.6E-3
	rs73816436	4:54773151		2.5E-04	
	rs78537672	4:54783763		1.4E-04	
B-SEVLT/8p22	rs11203840	8:17319696	2.01E-05	9.1E-05	1.6E-03
	rs7820095	8:17316724		2.9E-04	
	rs6996711	8:17385540		5.3E-05	
SIS/12q14.2+	rs139117576	12:64442962	5.5E-06	4.7E-04	1.1E-03
	rs139722987	12:63042198		8.6E-05	
SIS/12q15+	rs56716396	12:68055008	1.0E-05	5.0E-02	8.5E-02
	rs7956612	12:68063967		1.0E-02	
SIS/10p12.2	rs74360794	10:23716525	2.1E-05	2.4E-04	9.3E-02
	rs111338558	10:24117052		5.4E-04	
	rs7909638	10:23556488		8.9E-04	
WFT/9p22.1	rs78934697	9:19532209	3.0E-05	3.0E-03	5.7E-03
	rs3003713	9:19170823		7.4E-05	

Note: All models are adjusted for age, sex, recruitment center, genetic analysis groups, sampling weights, and five principal components of ancestry as fixed effects, and for kinship, household, and block unit as random effects; + model is additionally adjusted for education as a fixed effect.
Abbreviations: DSST, Digit Symbol Substitution Test; G, general cognitive function; LAI, local ancestry interval; SIS, Six Item Screen; SNP, single nucleotide polymorphism; WFT, Word Fluency Test.
[a]Conditional *P* value: *P* value of association of lead LAI with cognitive trait conditioning on the selected SNP.
[b]Joint conditional *P* value: *P* value of association of lead LAI with cognitive trait conditioning jointly on all selected SNPs for the locus.

cognitive function, plasma levels of c-KIT were strongly associated with G.[36] c-KIT inhibition has been suggested as a potential target for the treatment of AD through its effects on autophagic clearance of neurotoxic proteins and mast cell and microglial-mediated inflammation.[37] Interest in the repurposing of anti-cancer drugs targeting c-KIT for the treatment of AD is growing, with an initial phase 3 clinical trial showing benefit for people with mild-to-moderate AD.[38]

The locus on 9p22.1 associated with WFT overlaps with a known AD locus identified in GWAS and linkage studies.[39–41] The replicating prioritized SNP at this locus, rs78934697, was located in the *SLC24A2* gene, encoding K+-dependent Na+/Ca2+ exchanger 2 (NCKX2), which is widely expressed in the brain. Mice lacking NCKX2 have a significantly reduced calcium flow in cortical neurons and exhibit deficits in motor learning and spatial working memory.[42] It is also annotated as an eQTL of *RPS6*, encoding a ribosomal protein that is a component of the 40S subunit of ribosomes and undergoes phosphorylation to exert its physiological functions.[43] Previous reports have shown that RPS6 interacts with pathological, oligomeric tau in the human AD brain[44] and that tau accumulation coincides with less RPS6 phosphorylation.[45] Intriguingly, in our previous transcriptome-wide association analysis of WFT with genetically predicted gene expression in the same cohort, the strongest association was observed for *RPS6KB2* in the frontal cortex, which specifically phosphorylates RPS6.[27] Importantly, rs78934697 was in LD with a SNP identified in a GWAS of mathematical ability and cognitive performance in the UK Biobank.[46] It is worth noting that, given the low AF of this variant in populations of European ancestry, Biobank-size samples are necessary to detect an association by GWAS in these populations. Our admixture mapping approach detected this locus with a much more modest sample size.

The region on chr13q12.13, associated with DSST, spanned 200 kb and encompassed *NUP58*, encoding a nucleoporin with recently recognized amyloidogenic properties[47] and *MTMR6*, encoding

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myotubularin-related protein 6. The replicated SNP within that region, rs9551193, was an eQTL of *MTMR6* in multiple tissues and a pQTL of myotubularin-related protein 6 in brain prefrontal cortex. MTMR6 is a member of a large family of phosphatidylinositol 3-phosphate phosphatases that play a pivotal role in phosphoinositide lipids metabolism. Dysregulation of phosphoinositide metabolism has been implicated in several neurological disorders, including AD and Parkinson's disease.[48]

Even without statistical evidence of formal replication, the other loci harbor several candidate genes with strong support in the literature for a biological relationship to cognitive function. In the chr1q25.2 region associated with DSST, several SNPs in LD with the prioritized SNPs have been associated with relevant measures of brain morphology, including cortical thickness and cortical surface area.[49] Functional annotation of these SNPs points to possible roles for *ANGPTL1* and *RALGPS2*. Angiopoietin-like protein 1 is a potent regulator of angiogenesis. Its overexpression in the brain of a transgenic mouse model has been associated with a decreased cortical microvascular density and with preserved vascular integrity after cerebral ischemia.[50] Plasma levels of ANGPLT1 were associated with DSST in proteomic analysis.[36] *RALGPS2* encodes a Ras-independent guanine exchange factor (GEF) for the RalA GTPase that may be involved in cytoskeleton organization.[51] Importantly, this region of chr1q25.2 has been previously linked to AD and multiple measures of cognitive function in a genetically isolated Dutch population.[52] The admixture region on chr8p22 associated with B-SEVLT has been previously identified in a GWAS of cognitive resilience among amyloid positron emission tomography–positive older adults of European ancestry.[53] Our prioritized variant rs11203840 was in strong LD with the top variant reported in that GWAS ($r^2 = 0.83$). It has also been associated with educational attainment in the UK Biobank.[33] Functional annotation suggests that it is an eQTL for *CNOT7*, encoding a subunit of a conserved mRNA deadenylase that regulates synaptic plasticity and is essential for hippocampal-dependent learning and memory in a mouse model.[54] Moreover, two of the prioritized SNPs are intronic to *MTMR7*, belonging to the same sub-family of phosphatidylinositol 3-phosphate phosphatases as *MTMR6* described above.

Other genes of interest identified by our admixture and fine-mapping analyses include *KIAA1217*, at 10p12, a gene that is highly expressed in the brain. Genetic variation associated with the expression of its intronic miRNA, miR-603, has been implicated in AD risk.[55] *INFG* at 12q15 encodes interferon-gamma (INF-γ), a pro-inflammatory cytokine. Blood levels of inflammatory proteins, including IFN-γ, have been reported to be elevated in AD patients compared to neurologically normal individuals.[56] Higher plasma levels of INF-γ have also been associated with slower cognitive decline in cognitively normal elderly.[57] *FGF9* at 13q12.11 encodes the fibroblast growth factor 9 (FGF9) and is widely expressed in the central nervous system. There is increasing evidence for the role of fibroblast growth factors in cognitive disorders and dementia.[58] Plasma levels of FGF9 showed strong associations with G and DSST in our proteomic analysis.[36]

Our study has several limitations: The genetic diversity of this sample of Hispanic and Latino adults, and their complex admixture history, complicate identifying suitable replication cohorts. Our replication cohorts may have lacked power due to their limited sample size. They may also not adequately represent the genetic effects on cognitive function detected in HCHS/SOL due to differences in allele frequencies and effect sizes. Moreover, the admixture signals detected in this study likely represent complex haplotypes that may not be well tagged by any single SNP, as suggested by our conditional analyses. Our replication strategy, focusing on single SNP associations, may therefore not have been optimal. Additionally, because of power constraints, our fine-mapping analysis did not consider rare variants. It is possible that the admixture signals detected here may be explained in part by rare variants not tagged by the GWAS SNPs examined here. Finally, due to uncertainty in estimating local ancestry, the boundaries of the associated LAIs are imprecise and there is a possibility that the causal variants may lie outside of the genomic segments evaluated here. Additional larger studies in diverse populations representative of the rich haplotypic diversity observed in HCHS/SOL are warranted.

In summary, we identified nine novel loci for cognitive function using admixture mapping in a diverse cohort of Hispanic/Latino adults. The novel associations described here revealed candidate genes in pathways consistent with a role in cognitive functioning and dementia, and uncovered ancestry-relevant genetic variants not detected by traditional GWAS. Our study adds to our understanding of the genetic architecture of cognitive function in Hispanic and Latino adults and demonstrates the power of admixture mapping to identify unique haplotypes influencing cognitive function, complementing single-SNP GWAS association.

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CONFLICT OF INTEREST STATEMENT

The authors do not have any relevant conflicts of interest. Author disclosures are available in the supporting information.

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CONSENT STATEMENT

All human subjects provided written informed consent.

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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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