

World Journal of *Diabetes*

World J Diabetes 2019 November 15; 10(11): 517-545



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The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yan-Liang Zhang*

Proofing Production Department Director: *Xiang Li*

NAME OF JOURNAL

World Journal of Diabetes

ISSN

ISSN 1948-9358 (online)

LAUNCH DATE

June 15, 2010

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Timothy Koch

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-9358/editorialboard.htm>

EDITORIAL OFFICE

Ruo-Yu Ma, Director

PUBLICATION DATE

November 15, 2019

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Observational Study

Type 1 diabetes loci display a variety of native American and African ancestries in diseased individuals from Northwest Colombia

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Author contributions: Alfaro JM and Pineda-Trujillo N designed and coordinated the study; Gomez-Lopera N performed most of the data analyses; Pineda-Trujillo N and Leal SM wrote the manuscript.

Supported by Colciencias-Colombia grant No. 111556933366 and CODI-Universidad de Antioquia, and Scholarship from Colciencias, call No. 727 (from 2015).

Institutional review board

statement: The ethics committee of the Medical Research Institute of the Medicine Faculty at University of Antioquia considers that the project does not contain ethical tensions that violate the rights and welfare of the participants. The risk involved in the study is minimum.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: None to declare.

STROBE statement: We have read the STROBE Guidelines, and the manuscript was prepared and revised according to them.

Open-Access: This article is an open-access article that was

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Abstract

BACKGROUND

Type 1 diabetes (T1D) is a complex disease with a higher incidence in Europeans than other populations. The Colombians Living in Medellín (CLM) is admixed with ancestry contributions from Europeans, Native Americans (NAT) and Africans (AFR).

AIM

Our aim was to analyze the genetic admixture component at candidate T1D loci in Colombian individuals with the disease.

METHODS

Seventy-four ancestry informative markers (AIMs), which tagged 41 T1D candidate loci/genes, were tested by studying a cohort of 200 Northwest Colombia diseased individuals. T1D status was classified by testing for glutamic acid decarboxylase (GAD-65 kDa) and protein tyrosine-like antigen-2 auto-antibodies in serum samples. Candidate loci/genes included *HLA*, *INS*, *PTPN22*, *CTLA4*, *IL2RA*, *SUMO4*, *CLEC16A*, *IFIH1*, *EFR3B*, *IL7R*, *NRP1* and *RNASEH1*, amongst others. The 1,000 genome database was used to analyze data from 94 individuals corresponding to the reference CLM. As the data did not comply with a normal distribution, medians were compared between groups using the Mann-Whitney *U*-test.

RESULTS

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Manuscript source: Unsolicited manuscript

Received: July 18, 2019

Peer-review started: July 21, 2019

First decision: August 31, 2019

Revised: September 10, 2019

Accepted: October 7, 2019

Article in press: October 7, 2019

Published online: November 15, 2019

P-Reviewer: Dabla PK, Neri V

S-Editor: Yan JP

L-Editor: Filipodia

E-Editor: Zhang YL



Both T1D patients and individuals from CLM displayed mainly European ancestry (61.58 *vs* 62.06) followed by Native American (27.34 *vs* 27.46) and to a lesser extent the AFR ancestry (10.28 *vs* 10.65) components. However, compared to CLM, ancestry of T1D patients displayed a decrease of NAT ancestry at gene *EFR3B* (24.30 *vs* 37.10) and an increase at genes *IFIH1* (32.07 *vs* 14.99) and *IL7R* (52.18 *vs* 39.18). Also, for gene *NRP1* (36.67 *vs* 0.003), we observed a non-AFR contribution (attributed to NAT). Autoimmune patients (positive for any of two auto-antibodies) displayed lower NAT ancestry than idiopathic patients at the MHC region (20.36 *vs* 31.88). Also, late onset patients presented with greater AFR ancestry than early onset patients at gene *IL7R* (19.96 *vs* 6.17). An association analysis showed that, even after adjusting for admixture, an association exists for at least seven such AIMs, with the strongest findings on chromosomes 5 and 10 (gene *IL7R*, $P = 5.56 \times 10^{-6}$ and gene *NRP1*, $P = 8.70 \times 10^{-19}$, respectively).

CONCLUSION

Although Colombian T1D patients have globally presented with higher European admixture, specific T1D loci have displayed varying levels of Native American and AFR ancestries in diseased individuals.

Key words: Type 1 diabetes; Genetic admixture; Native American; Idiopathic; Colombia

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Core tip: We have tested the effect of genetic admixture in a set of Colombian patients with Type 1 Diabetes (T1D). We show that, although no differences between T1Ds and Colombians living in Medellín arose globally, there appear to be ancestry differences when looking at specific T1D loci/genes (*e.g.*, genes *EFR3B*, *IFIH1*, *IL7R* and *NRP1*). Also, when comparing patient ancestry according to the presence/absence of T1D-related auto-antibodies or age at onset of the disease, differences were also observed. The most striking differences in ancestry occurred outside the HLA region, which is considered the master risk locus in T1D and for autoimmune diseases overall. This in itself is a striking observation.

Citation: Gomez-Lopera N, Alfaro JM, Leal SM, Pineda-Trujillo N. Type 1 diabetes loci display a variety of native American and African ancestries in diseased individuals from Northwest Colombia. *World J Diabetes* 2019; 10(11): 534-545

URL: <https://www.wjgnet.com/1948-9358/full/v10/i11/534.htm>

DOI: <https://dx.doi.org/10.4239/wjd.v10.i11.534>

INTRODUCTION

Type 1 diabetes (T1D) is a heterogeneous disease with pathogenic processes and phenotypic characteristics that show marked variation. It is accepted that genetic effects are an important factor for this heterogeneity. *HLA* confers the major genetic susceptibility to T1D, contributing up to 50%; it is located on chromosome 6p21^[1]. In addition, over 50 non-*HLA* genes (so far) increase susceptibility to T1D^[2,3]. Recently, we have identified that *RNASEH1* gene variants associate with T1D in Northwest Colombia^[4]. This gene, which is located on chromosomal region 2p25, has not thus far been associated elsewhere with the disease. A wide geographical variation in the incidence of T1D both among and within countries has been reported^[5]. Incidence of T1D is higher in Europeans^[6-8] than in Latin American countries^[7,8]. Genetic admixture is a factor that influences allelic frequencies in a population; this, in part, may contribute to explaining the differences observed in T1D epidemiology.

Three studies in Latin America have tested the admixture effect on T1D. Two of these were carried out in Brazil^[9,10] and the third in Cuba^[11]. These three studies found that T1D patients are mostly of European descendant and not necessarily different than controls. Thus, one Brazilian study and the one from Cuba reported that patients carried a greater European component than their controls; this observation was established as a risk factor^[9,11].

In Colombia, the admixture process was produced differently in each region of the country. Populations in southern Colombia show higher values of Native American

ancestry (NAT, average 60%), whilst African (AFR) ancestry is more observed in the region of Chocó (average 68%) and the Caribbean coast (average 30%)^[12-14]. On the other hand, northwest Colombia, inhabited by the “paisa” population, exhibits the highest percentage of European ancestry, which ranges in studies from 47-79%^[15-19]. In Colombia, the admixture effect has been examined for some complex diseases such as type 2 diabetes^[20], asthma^[21], cancer^[22,23], dengue patients^[24], Alzheimer’s disease^[17], as well as for cardio-metabolic parameters^[25].

Although much of the work on the admixture effect on several phenotypes has been done in Latin America and Colombia, none has tested this effect on T1D in Colombian patients. Our purpose was to analyze the genetic admixture composition of a set of Colombian T1D patients, by testing previously reported admixture informative markers (AIMs) in the vicinity of previously reported T1D candidate genes/loci. Besides, two chromosomal regions of high relevance to T1D in our population were tested more thoroughly. These loci were *6p21* (*HLA*), which is globally accepted as the T1D master risk locus, and *2p25* (*RNASEH1*), which has been reported solely in Colombia, so far. We inferred individual patient proportions of European, AFR and NAT ancestry components. Although the European component was higher than the two other parental contributions in a global analysis, some loci are clearly non-Europeans in cases *vs* the reference population, or between T1D categories. This study shed light on the genetics of T1D in a Colombian population, and reinforces the importance of including different approaches when looking for T1D genetic architecture. This is suggested by finding no admixture differences in strongly associated T1D loci, such as *HLA* (*IDDM1*) or *IDDM2*. In contrast, a strong genetic admixture effect was observed for other loci not described as high determinants for developing T1D. For instance, this was the case for chromosomal regions *5p13.2* and *10p11.22*.

MATERIALS AND METHODS

Study population

The study group consisted of 200 Colombian individuals with T1D. Their age at onset was < 15 years. Diagnostic criteria were according to the American Diabetes Association^[26]. Patients were considered as “Paisas” according to a self-reported questionnaire asking for their geographical origin back until their great-grandparents. Other questions included gender, age at onset, and other family members with autoimmune diseases.

Patients were identified in the main pediatric endocrinology institutes from Antioquia: Program of Pediatric Endocrinology (Universidad de Antioquia and Hospital San Vicente Fundación), IPS Universitaria, Universidad Pontificia Bolivariana, Instituto Antioqueño de Diabetes and Clínica Integral de Diabetes. This study was approved by the ethics committee of the Faculty of Medicine at Universidad de Antioquia. Informed consent was obtained from patients and their parents before drawing blood samples.

Auto-antibodies testing

Two diabetes-related autoantibodies (AABs) were tested in sera samples from the 200 patients. These AABs were glutamic acid decarboxylase (GAD-65 kDa) and protein tyrosine-like antigen-2 (IA-2), as reported previously^[4]. They were measured using a commercial ELISA-based kit (AESKULISA and LifeSpan BioSciences, Inc) according to the manufacturer's instructions. If a patient presented with at least one of these AABs, he/she was classified as autoimmune (T1AD), or was otherwise classified as idiopathic (T1BD).

Genotyping and admixture estimation

Genomic DNA was isolated from peripheral blood samples using either the phenol-chloroform or salting out protocols. A set of 75 AIMs was tested in 200 T1D patient samples using the Competitive genotyping Allele-Specific PCR technology (KASPTM), which was undertaken by the Company LGC Genomics Ltd. Details of this method can be obtained from <https://www.lgcgroup.com/genotyping/>.

The AIMs used have a high discriminatory power ($\delta > 45\%$) among ancestral populations (Supplementary Table S1), which increases the statistical power for estimating individual ancestry. We selected these markers from Latino populations panels reported by Mao *et al*^[27], Galanter *et al*^[28] and Ruiz-Linares *et al*^[29]. The AIMs were distributed throughout the genome, tagging previously reported T1D candidate loci. However, we chose a higher density of markers for chromosome 2 (23 AIMs) where the *RNASEH1* gene is; and for chromosome 6 (18 AIMs) where the *HLA* region

is.

The 1,000 genome database was used to extract genetic information from 94 Colombians living in Medellin (CLM) for the 74 AIMs successfully typed (<ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/release/20130502/>). These population individuals are from the same geographical region as the patients. We calculated allele and genotypic frequencies, and Hardy-Weinberg equilibrium (HWE) using PLINK v. 1.07^[30]. In addition, we considered markers that were not in linkage disequilibrium with each other. We used markers with a genotyping rate higher than 95%, without significant deviations from HWE after a Bonferroni correction.

We estimated individual European, NAT and AFR ancestry proportions using ADMIXTURE software^[31]. The proportions of each component were estimated using a supervised-learning strategy, providing the genotypes of 74 AIMs from reference populations AFR, European and NAT ($k = 3$). We used 74/75 AIMs since one failed the PCR optimization.

To find the parental population allele frequencies, genotypes from 165 Europeans (Utah residents with ancestry from northern Europe and the West, named as CEU), and 165 AFR (Yoruba people in Ibadan, Nigeria, named as YRI) genotyped in the HapMap project were selected, which are deposited in the 1,000 genome database. Since we did not have access to NAT DNA samples or publicly available NAT genotype data on all 74 AIMs, we generated the genotypes of the 74 AIMs for 150 simulated individuals, according to the allele frequencies of NAT previously reported in the panels.

Statistical analysis

Comparison between groups for continuous variables that did not comply with normal distribution was performed using the Mann-Whitney *U*-test. Thus, comparisons of ancestry medians between T1D subtypes (T1AD and T1BD) according to AABs, and individuals with early/late age at onset (*i.e.* ≤ 5 years or > 5 years, respectively) were performed. In addition, these comparisons were also done to the CLM population. We performed these analyses for AIMs distributed across the set of candidate loci and independently for loci at different chromosomes. We ran all statistical analyses and graphs in the R package V3.3.3^[32]. We also tested allelic association of these AIMs between T1D and CLM using PLINK 1.07^[30].

RESULTS

T1D versus CLM, our reference population

One out of 75 AIMs did fail the PCR optimization. Therefore, we tested a total of 74 AIMs in 200 T1D patients from Antioquia, Colombia. AIMs characteristics are shown in [Supplementary Table S1](#). Overall, the rate of genotyping was $> 96\%$ for every AIM, and there was no deviation from the HWE, after Bonferroni correction for multiple testing ($P = 6.75 \times 10^{-4}$). Also, as expected, none of the AIMs was in linkage disequilibrium with each other (data not shown).

The overall ancestral genetic makeup of the 200 T1D children showed a predominant proportion of European ancestry (EUR, Median = 61.58) followed by NAT ancestry (Median = 27.34), and AFR ancestry was found at a lower proportion (Median = 10.28, [Table 1](#) and [Figure 1](#)). [Figure 1](#) presents the ancestry distribution for the 200 T1D children studied here. It can be noticed that the European component is the prominent one. European ancestry ranged from 22% to 93%; the NAT ancestry ranged from 0 to 65%, and the AFR ancestry ranged from 0 to 40%.

Looking at the overall set of AIMs, and also at their distribution in specific loci, it was observed that diseased individuals of EUR ancestry had a median from 61.58-11.56. The lowest value was found for chromosome 5 AIMs ([Table 1](#)). NAT ancestry ranged from 52.18-24.30 in the diseased subjects. The highest value was found for gene *IL7R* AIMs (chromosome 5), and the lowest value was found for gene *EFR3B* AIMs (chromosome 2). The AFR component (AFR) ranged from 20.58 to 0.01. the lowest AFR ancestry was found for gene *IFIH1* AIMs (chromosome 2, [Table 1](#)). The wide ancestry variation across chromosomal regions is noticeable.

Overall, the CLM reference population displayed a very similar ancestry distribution compared to T1D cases. Nonetheless, specific T1D loci presented marked differences between the two groups; one such difference was observed for the gene *EFR3B*, which presented with higher NAT in the CLM population ($P = 0.02$), suggesting a protective role for developing T1D ([Table 1](#)). Also, at gene *IFIH1*, T1D patients presented with lower European ancestry ($P = 0.05$), at the expense of a higher NAT component than in CLM ([Table 1](#)). Other differences between T1D and CLM were observed for the *IL7R* and *NRP1* genes (Chromosomes 5 and 10, respectively) as

Table 1 Genetic ancestry of type 1 diabetes patients compared to Colombians living in Medellin control population

Chromosomal region	Ancestry	T1D, median (IQR)	CLM, median (IQR)	P value ¹
Overall AIMs	EUR	61.58 (52.84-69.85)	62.06 (49.67-73.74)	0.675
	NAT	27.34 (21.36-34.05)	25.46 (16.12- 32.90)	0.106
	AFR	10.28 (4.0-16.83)	10.65 (6.05-16.75)	0.575
Chr2_EFR3B	EUR	60.27 (34.05-80.79)	47.88 (34.04-76.43)	0.189
	NAT	24.30 (0.01-51.24)	37.10 (1.61-62.49)	0.02
	AFR	7.17 (0.01-25.05)	0.01 (0.01-15.67)	0.06
Chr2_CTLA4	EUR	46.24 (16.82-69.52)	58.26 (30.82-82.79)	0.167
	NAT	27.96 (0.04-41.31)	25.01 (0.01-45.16)	0.829
	AFR	20.54 (0.01-41.72)	11.78 (0.01-36.59)	0.183
Chr2_RNASEH1	EUR	56.91 (31.33-73.91)	58.80 (32.75-78.43)	0.482
	NAT	27.41 (11.69-46.36)	24.81 (0.01-48.84)	0.241
	AFR	8.37 (0.01-28.24)	13.04 (0.01-23.87)	0.430
Chr2_IFIH1	EUR	42.42 (0.01-77.63)	52.01 (16.33-82.16)	0.05
	NAT	32.07 (0.01-56.74)	14.99 (0.01-41.35)	0.246
	AFR	14.99 (0.01-32.31)	17.83 (0.01-42.31)	0.181
Chr5_IL7R	EUR	11.56 (1.04-41.14)	24.75 (7.20-46.98)	7.0×10^{-3}
	NAT	52.18 (3.74-98.06)	39.18 (0.04-52.80)	1.0×10^{-4}
	AFR	15.21 (3.0-35.75)	33.89 (11.23-59.94)	1.56×10^{-5}
Chr6_MHC	EUR	51.35 (32.92-70.32)	55.86 (32.61-71.21)	0.76
	NAT	23.28 (8.92-40.0)	21.61 (5.83-43.13)	0.835
	AFR	18.87 (1.63-36.08)	19.53 (0.3-34.11)	0.660
Chr10_NRP1	EUR	63.32 (23.70-63.32)	0.03 (0.001-20.34)	2.2×10^{-16}
	NAT	36.67 (7.93-36.67)	0.003 (0.001-7.93)	2.2×10^{-16}
	AFR	0.03 (0.001-30.91)	94.23 (53.94-99.99)	2.2×10^{-16}

¹Data from Mann-Whitney *U* test. AIMs: Ancestry informative markers; IQR: Interquartile range; CLM: Colombians living in Medellin from 1,000 genomes database; Chr: Chromosome; EUR: European; NAT: Native American; AFR: African; T1D: Type 1 diabetes.

follows.

Chromosome 5 AIMs (gene *IL7R*) showed less European ($P = 7.0 \times 10^{-3}$) and less AFR ancestries (1.56×10^{-5}) in diseased subjects than the CLM population; consequently, T1D patients had more NAT ancestry than CLM subjects at this chromosomal region ($P = 1.0 \times 10^{-4}$, Table 1). Regarding chromosome 10 AIMs (gene *NRP1*), it was observed that T1D patients presented a high European component compared to CLM (63.32 *vs* 0.03, Table 1). Conversely, patients presented an almost zero AFR component for this chromosomal region compared to CLM (0.03 *vs* 94.23, Table 1). Consequently, T1D patients displayed a predominance of NAT ancestry at this locus compared to CLM (36.67 *vs* 0.003, Table 1).

An exploratory association analysis showed that, after adjusting for admixture, seven markers were associated with T1D (Supplementary Table S2 and Table 2). The most significant findings were located on chromosomes 5 and 10 ($P = 5.56 \times 10^{-6}$ and 8.70×10^{-19} , respectively). It is interesting that only one MHC marker (*rs2395656*) presented an association with the disease, and this happened with less strength in its association ($P = 0.04$) than markers at chromosomes 5 and 10 (Table 2).

Ancestral components considering T1D subtypes (according to autoimmunity and age at onset)

We stratified the T1D sample according to the presence (T1AD, autoimmune) or absence (T1BD, idiopathic) of diabetes-related AABs; we also stratified the patient group according to their age at onset, *e.g.*, early (≤ 5 years) or late (> 5 years). We found that 78% ($n = 156$) of the patients had at least one T1D specific autoantibody (GAD-65 and IA-2), while the 22% remaining ($n = 44$) were negative for these two antibodies. T1AD average age at onset was 8.25 years, whilst for T1BD it was 7.22. We did not find significant differences between men and women within these two groups (data not shown).

Over thirty percent ($n = 61$, 30.5%) of T1D individuals developed the disease before

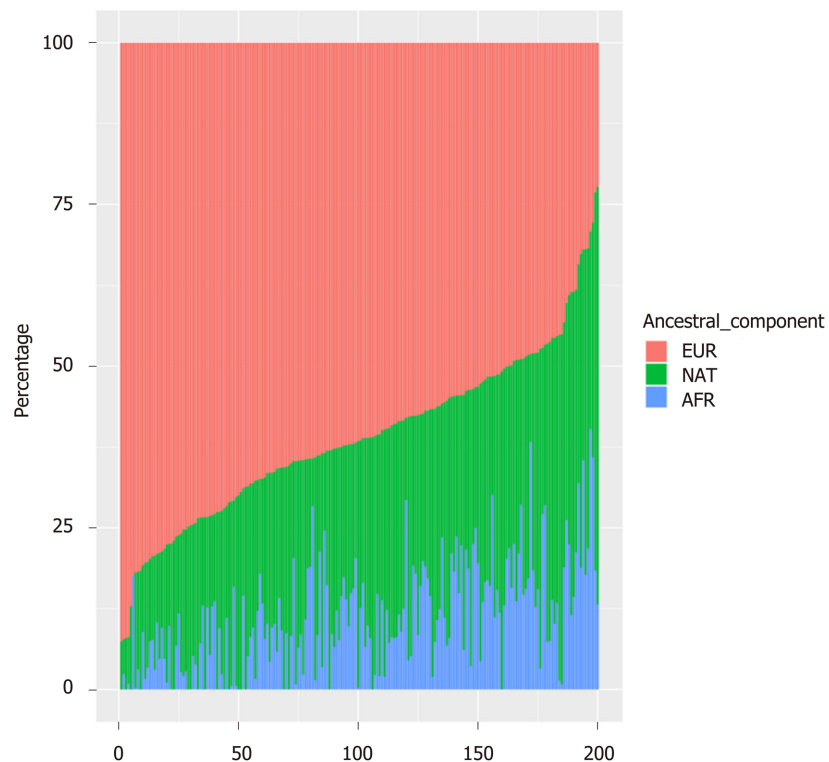


Figure 1 Ancestry proportions of 200 type 1 diabetes patients from Colombia. EUR: European; NAT: Native American; AFR: African.

the age of 5 years, with an average age at onset of 2.66 years. The remaining sample (69.5%, $n = 139$) presented with an age at onset after 5 years, with a mean for this category of 10.28 years. As in the stratification by AABs, we did not find significant differences between men and women within the age at onset categories (data not shown). Regarding the autoimmune category, comparisons among ancestral genetic composition led to the identification of no differences for the 74 AIMs taken together (Table 3). However, looking at individual loci, it was observed that *MHC* AIMs present with lower NAT ancestry in the autoimmune subgroup ($P = 0.019$, Table 3).

In addition, when comparing diseased individuals in the autoimmune categories to CLM population, it was observed that gene *EF3B* AIMs present differences in their ancestral components (Supplementary Table S3). Thus, autoimmune patients presented with less NAT ancestry ($P = 0.032$), whilst T1D idiopathic category presented with higher AFR ancestry ($P = 0.016$). Regarding the age at onset categories, it was observed that the AFR ancestry is significantly higher in the late onset subgroup at gene *IL7R* AIMs ($P = 0.023$, Table 4). Comparing these two categories to the CLM population showed no significant differences for either the overall set of AIMs nor specific loci (Supplementary Table S3).

DISCUSSION

T1D incidence differences among countries, mainly related to European *versus* non-Europeans, led us to assess whether our T1D patients had a predominantly European ancestral component or other. Our analyses were based on 74 AIMs located on previously reported T1D loci/genes. AIM deltas (δ s) between the NAT, European and AFR populations indicated that they were appropriate discriminators. We found that T1D patients from northwest Colombia are predominantly of European ancestry, followed by NAT and AFR components. Proportion estimates of the three parental populations for this sample were consistent with those reported in previous studies for Colombians, but using different sets of markers^[13,16,19,20,29].

We also compared T1D children to CLM. Analyzing the overall set of AIMs found no statistically significant differences in the ancestral genetic component between the two groups. Comparable results were obtained by Gomes *et al*^[10] in Sao Paulo-Brazil; they noted that the European component predominated in both T1D patients and controls, followed by AFR and NAT ancestry; however, no significant differences

Table 2 Significant findings in an exploratory association analysis

CHR	SNP	A1	MAF		OR ^a	95%CI	P value ¹	EMP1
			T1D	CLM				
2	rs798364	A	0.18	0.27	0.62	0.40-0.96	0.034	0.035
2	rs1606237	T	0.33	0.26	1.55	1.04-2.30	0.031	0.031
5	rs700164	T	0.56	0.35	2.38	1.62-3.48	5.56 × 10 ⁻⁶	3.0 × 10 ⁻⁶
6	rs9378428	C	0.38	0.48	0.61	0.42-0.89	0.010	0.018
6	rs2523747	G	0.42	0.30	1.68	1.13-2.51	0.010	0.012
6	rs2395656	G	0.23	0.28	0.63	0.41-0.98	0.040	0.041
10	rs3123687	G	0.15	0.86	0.04	0.02-0.08	8.70 × 10 ⁻¹⁹	1.0 × 10 ⁻⁶

¹Odds ratio and *P* value adjusted for genetic admixture. This table extracts the significant findings shown in [Supplementary Table S2](#). CHR: Chromosome; A1: Minor allele; MAF: Minor allele frequency; CI: Confidence interval; EMP1: Empirical *P* value obtained by permutation tests; OR: Odds ratio; SNP: Single nucleotide polymorphism; T1D: Type 1 diabetes; CLM: Colombians living in Medellin.

between cases and controls were observed. For the contrary, a study conducted in ten Brazilian cities showed that T1D patients presented a higher percentage of European component than the healthy population^[9]. Similarly, a study by Diaz-Horta *et al*^[11] found a higher proportion of European component in cases than in controls. Even more, they found a risk association with the European ancestry.

Further analysis disaggregating the candidate loci tested led us to find a different ancestry composition for MHC AIMS. Lower NAT ancestry was observed in T1AD compared to T1BD patients (Table 3). Ancestry variation at the HLA region has been reported for Latin American populations. However, such variation has shown an excess of the AFR component in these populations, including CLM^[16,33,34]. It has been suggested that the excess of the AFR component in the HLA region in Latin America is due to a positive selection orchestrated by the presence of infectious agents during the process of the conquest. The European conquerors brought to America, African and European diseases such as smallpox, measles, and influenza, which caused massive epidemics and were responsible for the extinction of many native populations^[34]. Given this historical background, these AFR fragments could obtain a selective advantage, since the AFR populations have the most diverse repertoire in HLA^[35,36]. However, the ancestry variation observed here shows that the European component is higher in autoimmune (T1AD) than T1BD, in combination with lower NAT in T1AD than T1BD (Table 3).

Another gene with remarkable findings is *IFIH1*. This observation is of particular interest to our population, since we had found in the past that SNP *rs10930046*, which is located at *IFIH1*, associates with T1D in our population^[37]. This SNP has been reported as a rare variant in European populations (MAF = 0.02) related to Psoriasis^[38]. Interestingly, we found in our previous study that this variant MAF = 0.3^[37]. Therefore, such an allele frequency difference could have been speculatively explained by random genetic drift, involving over-representation of European chromosomes with such variants at the time of conquering Colombia. However, in the present study, evidence suggests that this allele frequency difference between populations might be a NAT contribution.

It is worth mentioning that *IFIH1* AIMS presented wide values for the AFR component comparing autoimmune to idiopathic patients (14.99 *vs* 0.01, Table 3), without reaching statistical significance. This was the case since the interquartile range overlapped between these two autoimmune categories. Neither gene *CTLA4* nor *RNASEH1* AIMS revealed significant contributions to T1D, either looking to the overall set of AIMS or in any of the loci/genes analyzed. Regarding *CTLA4*, this observation makes sense when related to our previous finding of no association of this gene variant with T1D^[37]. However, a different situation holds for the *RNASEH1* gene.

RNASEH1 gene variants have thus far been associated with T1D only in the northwest Colombia population and not elsewhere in the world^[4]. It has not even been reported in GWA studies using large sample sizes, albeit mostly of European origin^[3]. Analyzing a larger sample size of T1D patients from this region in Colombia will allow us to conclude whether there really is an ancestry effect related to *RNASEH1* gene variants in T1D.

Unexpectedly, we found that ancestry for chromosomes 5 and 10 were sharply different between T1D patients and the CLM population (Tables 1 and 3). The former

Table 3 Genetic ancestry for type 1 diabetes patients stratified according to autoimmunity

Chromosomal region	Ancestry	T1AD, median (IQR)	T1BD, median (IQR)	P value ¹
Overall AIMs	EUR	61.92 (53.57-70.89)	59.79 (49.70-68.03)	0.333
	NAT	27.07 (20.82-33.48)	29.16 (21.57-37.06)	0.312
	AFR	10.19 (2.88-16.01)	11.54 (5.55-17.80)	0.344
Chr2_EFR3B	EUR	60.28 (36.24-83.66)	59.79 (32.34-80.01)	0.551
	NAT	25.16 (0.01-51.24)	21.92 (0.01-45.95)	0.979
	AFR	4.53 (0.01-23.32)	14.41 (0.01-27.36)	0.119
Chr2_CTLA4	EUR	53.34 (16.82-70.53)	41.16 (16.62-60.86)	0.231
	NAT	26.28 (4.55-41.31)	32.69 (9.35-50.25)	0.343
	AFR	20.54 (0.01-41.73)	19.47 (0.01-42.52)	0.764
Chr2_RNASEH1	EUR	58.96 (37.72-73.87)	47.50 (26.38-78.10)	0.506
	NAT	26.92 (14.19-45.66)	31.59 (0.01-51.98)	0.885
	AFR	6.85 (0.01-28.24)	11.71 (0.01-27.86)	0.657
Chr2_IFIH1	EUR	41.90 (0.01-76.72)	42.42 (0.01-67.93)	0.708
	NAT	32.56 (0.01-55.56)	27.39 (2.01-56.89)	0.985
	AFR	14.99 (0.01-42.31)	0.01 (0.01-36.48)	0.654
Chr5_IL7R	EUR	13.27 (1.02-43.73)	9.19 (1.77-33.67)	0.555
	NAT	50.94 (38.08-98.60)	53.12 (31.82-95.13)	0.984
	AFR	14.68 (3.17-33.94)	17.98 (2.75-41.01)	0.634
Chr6_MHC	EUR	52.31 (37.26-72.43)	45.73 (19.25-67.03)	0.087
	NAT	20.32 (7.12-37.06)	31.88 (17.65-44.62)	0.019
	AFR	18.50 (3.21-36.04)	21.13 (0.53-36.56)	0.905
Chr10_NRP1	EUR	63.32 (28.61-69.09)	63.31 (6.89-63.32)	0.092
	NAT	36.67 (7.93-36.67)	36.67 (7.93-59.79)	0.282
	AFR	0.25 (1e-05-26.0)	0.52 (1e-05-37.80)	0.848

¹Mann-Whitney *U* test. AIMs: Ancestry informative markers; IQR: Interquartile range; Chr: Chromosome; EUR: European; NAT: Native American; AFR: African; T1AD: Autoimmune type 1 diabetes; T1BD: Idiopathic type 1 diabetes.

involves chromosomal region 5p13.2 (*IL7R*)^[39]. This region was assessed with only one AIM, which clearly discriminates between NAT and non-NAT (Supplementary Table S1). As shown in Table 1, the T1D ancestry observed for this locus is confidently greater for NAT, at the expense of the two other ancestries. It is also apparent that AFR ancestry at this locus contributes to late onset of the disease (Table 4). Such results, in turn, should be taken with caution since this AIM does not clearly discriminate between EUR and AFR (Supplementary Table S1). Therefore, we cannot rule out the possibility that this effect is of European origin.

The second striking finding involves chromosomal region 10p11.22 (gene *NRP1*)^[40]. Although the opposite ancestry contributions between T1D and CLM are evident (Table 1), it is worth keeping in mind that the only AIM (*rs3123687*) used for this locus is highly informative for AFR and non-AFR ancestries (*i.e.*, either EUR or NAT). Given this information, we are aware that the conclusion regarding greater NAT contribution in our study could eventually go towards greater EUR ancestry. Therefore we can only tell that the difference observed is non-AFR, but are not able to define whether it is European or NAT.

The actual SNPs reported as associated with disease in these two genes (*IL7R* and *NRP1*) have not yet been tested in the sample presented here. However, a test of association using the AIMs analyzed here, after adjusting for the admixture effect, revealed that AIM *rs700164* associates with affected status (5.56×10^{-6} , Supplementary Table S2 and Table 2) and that similarly *rs3123687* strongly associates with the disease ($P = 8.07 \times 10^{-19}$, Supplementary Table S2 and Table 2) for *IL7R* and *NRP1* genes, respectively. A verification of this finding should be performed using the transmission disequilibrium test (TDT). The TDT is not susceptible to population structure issues, such as admixture. This analysis is to be done for the actual SNPs, as the parents for the patients presented here are available. Such association analyses should include choosing gene variants from the genetic variability in this set of patients, and should also consider the LD blocks observed in this population.

No ancestry differences were found overall when comparing T1AD to idiopathic (T1BD) (Table 3). T1AD, whose etiology and pathology are better characterized, has a

Table 4 Genetic ancestry for type 1 diabetes patients stratified according to age at onset

Chromosomal region	Ancestry	Early age at onset, ≤ 5 yr	Late age at onset, > 5 yr	P value ¹
Overall AIMs	EUR	62.06 (54.50-71.38)	61.12 (51.66-68.68)	0.420
	NAT	25.40 (18.14-33.55)	27.75 (21.86-34.35)	0.345
	AFR	11.09 (3.90-17.25)	10.19 (3.88-16.91)	0.927
Chr2_EFR3B	EUR	57.65 (34.05-82.17)	62.45 (42.04-80.67)	0.419
	NAT	25.16 (1.27-52.11)	24.30 (0.01-51.73)	0.607
	AFR	5.02 (0.01-27.29)	7.37 (0.01-23.32)	0.941
Chr2_CTLA4	EUR	58.49 (24.63-78.80)	46.09 (12.90-66.30)	0.180
	NAT	26.28 (3.98-39.82)	30.19 (4.55-42.10)	0.362
	AFR	18.05 (0.01-37.80)	20.68 (0.01-41.72)	0.701
Chr2_RNASEH1	EUR	56.84 (44.50-72.18)	56.91 (28.02-74.15)	0.672
	NAT	27.22 (0.01-31.22)	28.03 (8.15-48.58)	0.472
	AFR	3.38 (0.01-31.22)	8.62 (0.01-27.20)	0.917
Chr2_IFIH1	EUR	41.35 (0.01-66.94)	42.42 (4.44-76.73)	0.126
	NAT	33.05 (0.67-57.49)	29.05 (0.01-53.09)	0.339
	AFR	14.57 (0.01-42.31)	1.01 (0.01-42.31)	0.796
Chr5_IL7R	EUR	9.38 (0.33-41.70)	12.86 (1.73-43.11)	0.338
	NAT	53.83 (39.76-99.60)	50.94 (30.21-88.75)	0.197
	AFR	6.17 (1.01-29.03)	19.96 (9.6-37.36)	0.023
Chr6_MHC	EUR	51.67 (32.23-63.29)	52.07 (34.26-71.84)	0.596
	NAT	30.57 (13.47-43.21)	26.71 (7.69-37.39)	0.480
	AFR	15.03 (4.46-36.05)	20.52 (1.08-36.73)	0.118
Chr10_NRP1	EUR	63.32 (23.70-63)	63.32(43.07-69.08)	0.357
	NAT	36.68 (7.93-36.67)	36.67 (7.93-36.68)	0.797
	AFR	0.16 (0.001-39.1)	0.38 (0.001-63.3)	0.498

¹Mann-Whitney *U* test. AIMs: Ancestry informative markers; IQR: Interquartile Range; Chr2: Chromosome 2; Chr6: Chromosome 6; EUR: European; NAT: Native American; AFR: African.

higher incidence in Europe^[6]; on the contrary, T1BD is reported mainly in AFR and Asian countries^[26]. Our results are different from those by Piñero-Piloña *et al*^[41], who reported a high incidence of T1BD in Mexican patients, whose predominant ancestral component was NAT. Our cohort presents a majority of autoimmune cases (78%) and, as described here, their predominant ancestry is of European contribution.

However, looking at chromosomal regions along the analysis stratified by age at onset of T1D, we found that patients with a late onset of the disease have a greater AFR component, which was more marked on chromosome 5 (Table 4). This suggests that AFR ancestry could be a risk factor for developing the disease at a late age in our population (over 2/3 of the sample had age at onset > 5 years), which can modify the metabolic phenotype of patients, and influence the risk of late complications of diabetes^[42].

Our study has an important limitation regarding the number and location of the AIMs. Thus, chromosomes 5 and 10 were tested with just a few such markers. It will be worth testing more AIMs nearby these two loci to further examine the differences revealed. Also, the reference population we used (CLM from the 1,000 genome database), although supposedly unaffected and older than our patients, were typed by a different method from the one we used to type our T1D cases. Nonetheless, both groups share comparable genetic ancestries.

Our study's strength is its population choice. As described, the northwest Colombia population is the one with a greater European component in the country^[15-19]. Thus, our results make much more sense regarding the overall European contribution, together with the apparent unexplored NAT input to T1D, in addition to certain contributions of the AFR ancestry for late age at onset.

In conclusion, this study describes the ancestral genetic composition of 200 T1D patients from an admixed population from northwest Colombia. Consistently, we found a predominant proportion of European followed by NAT ancestry. No statistical difference was observed in the distribution of the proportions of ancestral genetic components between T1D patients and the CLM reference population. A variation in chromosomal segments derived from the parental populations was

observed when comparing individuals with T1AD *versus* T1BD, and those who had an early (≤ 5 years) or late (> 5 years) age at onset of the disease. These results demonstrate that the study of the genetic admixture provides new perspectives in the delineation of the genetic architecture underlying autoimmune diseases. Finally, performing a novel study in this sample, including unbiased distribution of AIMs through the whole genome, could help find undetected loci in previous studies, which would contribute to complete the T1D genetic architecture for our population. This will also contribute to making approaches, such as the polygenic risk score, become more accurate for these types of populations.

ARTICLE HIGHLIGHTS

Research background

Type 1 diabetes (T1D) is described as a disease predominantly in white populations. Subtypes of the disease are also more frequent in different ethnicities. Thus, the autoimmune form of the disease is observed more frequently in Caucasian countries, whilst the idiopathic form is more frequently observed in African and Asian countries. The patients included in this study are from Northwest Colombia. This is an admixed population originated by a three ethnic contribution. This population has been described as the most European in the country, followed by the Native American ancestry, and with its least significant component being African contribution.

Research motivation

In this study, we looked at the genetic ancestry of a set of 200 diseased subjects from Northwest Colombia. We were interested in describing whether their global ancestry, as well as some specific genomic regions, were of which particular ancestry. Only a few of these types of studies have been reported in Latin American populations, and none have occurred in Colombia.

Research objectives

We aimed at describing the ancestry composition of a cohort of Colombian patients with T1D. This description included both global analysis as well as specific tests on loci/genes previously related to the disease.

Research methods

We studied 200 diseased subjects from Northwest Colombia. We tested 75 admixture informative markers (AIMs) distributed through a set of previously reported genes (or chromosomal regions) associated with T1D. The disease was classified as either autoimmune or idiopathic in the study subjects. This was done by testing two disease-related auto-antibodies (AABs). If at least one such AAB was present, then the disease was classified as autoimmune. We also classified the age at onset of the disease as early (≤ 5 years) or late (> 5 years). The reference population of Colombians living in Medellin (CLM) was compared to the set of patients presented here. We applied appropriate statistical tests given the non-normality of the data obtained.

Research results

Seventy eight percent of the patients presented at least one AAB. Over two thirds (69.5%) of the subjects developed the disease after 5-years-old. There were no significant differences between genders among the affected individuals. Seventy four AIMs were successfully tested (one failed the PCR optimization). It was observed that both the diseased and CLM groups were predominantly of European ancestry (61.58 *vs* 62.06), followed by Native American (24.30 *vs* 37.10) and African ancestries (10.28 *vs* 10.65). In addition, specific genes such as *EFR3B*, *IFIH1*, *IL7R* and *NRP1* displayed differential Native American or African rather than European contributions. In addition, we found that autoimmune patients displayed lower Native American ancestry than idiopathic cases.

Research conclusions

Our study shows that diseased individuals from Northwest Colombia are predominantly of European ancestry, followed by native American and African ancestries. Also, other European contributions were found for specific genes in our study.

Research perspectives

MHC is expected to play the strongest role in T1D susceptibility. However, this was not the observation in our study. Our results suggest that different loci effect sizes might be at play in our admix population. This is inferred from the observation of the significance strength observed for MHC ancestry compared to other loci. Therefore, it would be worth testing AIMs in this sample (expanded with extra individuals from the same region in Colombia) throughout the whole genome. This way, it would be feasible to reveal differences in local ancestry either for known or unknown loci associated with T1D in our population. This would help complete the genetic architecture of the disease, particularly for our population. In turn, this would contribute to the knowledge of the disease biology, and would also make this sample population appropriate for applying approaches such as the polygenic risk score.

ACKNOWLEDGEMENTS

We are very grateful to the patients that participated in this study. We are also very grateful to Doctors Martin Toro, Maria Victoria Lopera, Jorge García and Alejandra Velez for contributing patients to this study.

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