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Genetic contributors to serum uric acid levels in Mexicans and their effect on premature coronary artery disease

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ABSTRACT

Background: Serum uric acid (SUA) is a heritable trait associated with cardiovascular risk factors and coronary artery disease (CAD). Genome wide association studies (GWAS) have identified several genes associated with SUA, mainly in European populations. However, to date there are few GWAS in Latino populations, and the role of SUA-associated single nucleotide polymorphisms (SNPs) in cardiovascular disease has not been studied in the Mexican population.

Methods: We performed genome-wide SUA association study in 2153 Mexican children and adults, evaluated whether genetic effects were modified by sex and obesity, and used a Mendelian randomization approach in an independent cohort to study the role of SUA modifying genetic variants in premature CAD.

Results: Only two loci were associated with SUA levels: *SLC2A9* ($\beta = -0.47$ mg/dl, $P = 1.57 \times 10^{-42}$ for lead SNP rs7678287) and *ABCG2* ($\beta = 0.23$ mg/dl, $P = 2.42 \times 10^{-10}$ for lead SNP rs2231142). No significant interaction between *SLC2A9* rs7678287 and *ABCG2* rs2231142 genotypes and obesity was observed. However, a significant

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ABCG2 rs2231142 genotype*sex interaction ($P = 0.001$) was observed in adults but not in children. Although SUA levels were associated with premature CAD, metabolic syndrome and decreased glomerular filtration rate (eGFR), only *ABCG2* rs2231142 was associated with decreased eGFR in the premature CAD group.
Conclusions: SUA elevation was independently associated with premature CAD, metabolic syndrome and decreased eGFR in the Mexican population. However, a Mendelian randomization approach using the lead SUA-associated SNPs (*SLC2A9* and *ABCG2*) did not support a causal role of elevated SUA levels for premature CAD.
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1. Introduction

Serum uric acid (SUA), the final product of purine metabolism, has been independently associated with cardiovascular risk factors including metabolic syndrome, glomerular filtration rate and intima media thickness [1–3] and was associated with subclinical atherosclerosis independently of other cardiovascular risk factors in Mexican adults from the GEA (Genetics of Atherosclerotic Disease) study [4]. Uric acid can act as an antioxidant, but can also activate prooxidant and proinflammatory pathways involved in cardiovascular, renal, and metabolic diseases [5]. Heritability of SUA levels has been estimated at 63% [6], and >28 different *loci* have been associated with this trait [7]. Overall, the combined effect of the lead associated genetic variants at *SLC2A9* and *ABCG2* explain 3% to 4% of SUA variance [8]. Interestingly, there is evidence that the effect of both variants can be modulated by gender and the presence of obesity [7,9,10]. *SLC2A9* variants have been found to be associated with SUA in Hispanic children living in the United States [11]. However, genome-wide studies seeking associations with SUA in Hispanic populations are scarce.

Because genes are transmitted randomly, polymorphisms in *loci* affecting serum SUA levels allow further investigation of the link between uric acid and cardiovascular disease eliminating the influence of confounders and avoiding reverse causality [12]. Some Mendelian randomization studies have explored this relationship with conflicting results [13,14]. However, this has not been analyzed in the Mexican or other Hispanic populations. Thus, our aims were: 1) to perform a genome-wide association study (GWAS) seeking single nucleotide polymorphisms (SNPs) that affect SUA levels in Mexican children and adults; 2) to explore the influence of gender and obesity on the effect of the associated variants; and 3) to use a Mendelian randomization approach to further explore the causal relationship between SUA and premature coronary artery disease, as well as other cardiovascular risk factors in the Mexican GEA cohort.

2. Methods

In a discovery phase, we performed genome-wide association studies with SUA levels in obese and normal-weight children and adults. SNPs with genome-wide significance were then tested for association with premature CAD, metabolic syndrome and decreased estimated glomerular filtration rate (eGFR).

2.1. Subjects

A total of 1080 children aged 6–12 years (553 normal-weight controls and 527 obesity cases) and 1073 adults aged 18–82 years (486 normal-weight controls and 587 obesity cases) were included in the study. Children were recruited from a summer camp for offspring of Mexican Health Ministry employees and the Hospital Infantil de México. Obese and normal-weight adults were recruited from several health institutions and public universities in Mexico City. Recruitment and inclusion criteria for children and adults have been described elsewhere [15,16].

The Mendelian randomization study for premature CAD included 704 non-diabetic subjects with premature CAD and 1075 healthy controls aged 21 to 79 years from the Mexican GEA cohort. The GEA study was designed to examine the genetic bases of premature CAD in the Mexican population. As previously described [17], GEA participants were unrelated and of self-reported Mexican mestizo ancestry for 3 generations. Premature CAD was defined as history of myocardial infarction, angioplasty, revascularization surgery or coronary stenosis >50% on angiography, diagnosed before age 55 in men and before age 65 in women. Controls were apparently healthy asymptomatic individuals without personal or family history of premature CAD. In addition, 1269 adults from the Consortium for the Analysis of the Diversity and Evolution of Latinoamerica [CANDELA, [18]] were used to assess the association of *SLC2A9* rs7678287 and *ABCG2* rs2231142 with eGFR.

All adult participants and parents or legal guardians of children provided informed consent, and all children assented to participate. This study was conducted according to the principles expressed in the Declaration of Helsinki and were approved by the Ethics Committees of participant institutions.

2.2. Anthropometric and biochemical parameters

Anthropometric measurements were determined following the procedures recommended by Lohman et al. [19] and included weight, height, waist circumference and hip circumference. All instruments were calibrated following the standard methods of the manufacturers. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. In adults, obesity status was determined according to World Health Organization (WHO) criteria [20]. In children, obesity was defined as BMI ≥95th percentile for age and gender based on Centers for Disease Control and Prevention (CDC) reference data [21]. Biochemical parameters including fasting glucose, insulin, total cholesterol, HDL-c, triglycerides, creatinine, insulin and uric acid serum levels were performed using standardized procedures as previously described [15]. Insulin sensitivity was estimated with the homeostasis model assessment for insulin resistance (HOMA-IR).

Hyperuricemia in adults was defined as SUA > 7.0 mg/dl in men and >5.7 mg/dl in women [22]. In children, presence of hyperuricemia was determined from sex and age specific cut-off values [23]. Metabolic syndrome was defined according to ATP III criteria [24]. Glomerular filtration rate was estimated with the CKD-EPI formula [25]. An eGFR <60 ml/min/1.73 m^2 was considered decreased.

2.3. SNP genotyping and quality control

Genomic DNA was isolated from peripheral white blood cells using standard methods. A total of 2153 children and adults included in the discovery phase were genotyped using the Multhi-Ethnic Genotyping Array (MEGA, Illumina, San Diego, CA, USA), which included >1600 k SNPs. Fifteen Nahua and Totonac trios were also genotyped with this platform to be used as Native American reference population (NAT) for the ancestry analysis.

Standard quality control (QC) measures included the removal of SNPs with call rate < 95% (61,757 SNPs), minor allele frequency < 5% (950,818 SNPs) and deviation from Hardy-Weinberg's equilibrium with a $P < 1 \times 10^{-5}$ (8372 SNPs). A total of 624,242 SNPs remained after QC measures. Haplotype phase determination and imputations were performed in Beagle [26] and imputed SNPs with a dosage $r^2 < 0.8$ were discarded. After imputation, 865,896 SNPs were included in the final analysis. All subjects with call rate <5% or with sex inconsistencies were removed from the analysis. The quantile-quantile (QQ) plot for the uric acid GWAS was well calibrated for the null hypothesis ($\lambda GC = 1.002$; Supplementary Fig. 1), indicating adequate control for confounders.

Genome-wide association with SUA was tested in 4 groups (normal-weight and obese children and normal-weight and obese adults) under an additive model using mixed linear regression adjusting for sex, age, and either BMI in adults or BMI percentile in children. Identity-by-descent (IBD) was estimated using Plink v1.07 [27]. Because IBD analysis revealed that 4.6% of children and 8.1% of adults had a first-degree relative within their respective study group, genetic relationship matrices from genome-wide data were considered for the analysis using GCTA software [28]. An inverse variance method was used to perform a meta-analysis of the 4 groups [29]. A *P*-value $<5 \times 10^{-8}$ was considered genome-wide significant. Group heterogeneity in meta-analysis was evaluated by I^2 and Cochrane's Q [30] using the R package meta.

2.4. Global and local ancestry estimation

European (CEU) and Yoruba (YRI) individuals from the 1000 genomes project and the aforementioned NAT individuals were used as reference populations. Multidimensional scaling components were calculated in Plink v1.07 [27]. Ancestral proportions were determined with Admixture [31]. Local ancestry was determined to identify the origin of chromosomal segments found to be associated with SUA using RFMix [32]. Genetic associations with SUA loci were tested separately in subjects whose local ancestry at both chromosomes was either NAT or CEU, using linear regression models adjusting for sex, age, BMI or BMI percentile and the first two multidimensional scaling components.

2.5. Gene-obesity and Gene-gender interactions affecting SUA levels

A linear mixed model was used to evaluate possible interactions between the gene variation and obesity or gender affecting SUA levels with the R package coxme. The model included the genetic relationship matrix as a random effect, and sex, age, BMI or BMI percentile, obesity and genotype*sex or genotype*obesity interaction terms as fixed effects.

2.6. Mendelian randomization study of premature CAD, metabolic syndrome and decreased eGFR in the GEA cohort

Two genome-wide SUA-associated SNPs were genotyped in the GEA cohort with the KASP assays (LGC, U.S. http://www.lgcgroup.com). Call rate exceeded 95% for all SNPs tested, with no discordant genotypes in 10% of duplicate samples. No SNPs deviated from Hardy–Weinberg equilibrium in any group ($P > 0.05$). Genetic associations with premature CAD, metabolic syndrome, and decreased eGFR were tested using logistic regression under an additive model adjusting for age, sex, BMI, systolic and diastolic blood pressure, HDL-c, triglycerides and HOMA-IR, as appropriate. Genetic associations with eGFR levels in GEA controls, GWAS adults and CANDELA participants were tested using linear regression under an additive model adjusting for age, sex and BMI. Association results were meta-analyzed by inverse variance in a random model [29].

3. Results

The anthropometric and biochemical characteristics of the study groups (children and adults) stratified by the presence of obesity are described in Supplementary Table 1. Supplementary Fig. 2 compares SUA levels in these groups. Hyperuricemia was more frequent in obese individuals (34.7% in children and 33.2% in adults) than in lean individuals (8.3% in children and 12.8% in adults).

3.1. Genome-wide scan

Genome-wide genotypes were available from 2153 Mexican-mestizo subjects including 1080 children and 1073 adults. In children and adults, *SLC2A9* reached genome wide significance ($P = 6.73 \times 10^{-26}$ and $P = 8.86 \times 10^{-19}$, respectively), while *ABCG2* was borderline significant ($P = 4.21 \times 10^{-6}$ and $P = 7.47 \times 10^{-6}$, respectively) (Table 1). The association of both loci with SUA levels was confirmed in the joint analysis (*SLC2A9* lead SNP rs7678287, $P = 1.57 \times 10^{-42}$, and *ABCG2* rs2231142, $P = 2.42 \times 10^{-10}$) (Fig. 1). Overall, a total of 128 SNPs in the *SLC2A9* region showed genome-wide significance for association with SUA. After conditioning the analysis for the lead *SLC2A9* signal (rs7678287), another lead SNP in low linkage disequilibrium (rs7675964, $r^2 = 0.23$) was significantly associated with SUA ($P_{conditioned} = 5.41 \times 10^{-17}$), suggesting the effect of both SNPs is independent.

Global ancestry analysis revealed that median NAT, CEU and YRI proportions were 67.5, 29.6 and 2.5% respectively. Supplementary Fig. 3 shows multidimensional scaling (MDS) plots generated with these 3 ancestral groups where, as expected, the study population spread between the NAT and EUR groups. Interestingly, local ancestry analysis of the region containing the *SLC2A9* locus showed different linkage disequilibrium patterns according to the European or Native American origin of the segment. The EUR-origin segment has a single LD block containing the lead SNP rs7678287, which is in LD with rs7675964 ($r^2 = 0.59$). In contrast, in the NAT-origin segments both these SNPs lie on two distinct LD blocks ($r^2 = 0.13$).

In the *ABCG2* locus, a total of 68 SNPs were associated with SUA levels with genome-wide significance. After conditioning the analysis for rs2231142, no other SNPs were associated with SUA with a significance level < 0.001. Local ancestry analysis of the *ABCG2* region identified the same SNP (rs2231142) as the lead signal both in the NAT and EUR segments. Supplementary Table 2 compares *SLC2A9* rs7678287 and *ABCG2* rs2231142 minor allele frequencies observed in the present study, with those reported in Mexican-American (MXL), CEU and YRI from the 1000 genomes project.

3.2. Interaction of SUA level-associated SNPs with gender and obesity

No interactions between SUA-associated SNPs (*SLC2A9* rs7678287 or *ABCG2* rs2231142) and obesity were observed in children, adults or in the combined sample. However, a significant interaction between *ABCG2* (rs2231142) and gender was observed in adults, but not in children. The estimated effect of rs2231142 on SUA was higher in men ($\beta = 0.43$ mg/dl) than in women ($\beta = 0.15$ mg/dl; $P_{genotype*sex} = 0.0013$; Supplementary Fig. 4).

Table 1
Lead SNPs associated with serum uric acid levels in the meta-analysis including Mexican children and adults.

SNP	CHR	Locus	MA	Normal-weight children		Obese children		All children		[a]P-Het	Normal-weight adults		Obese adults		All adults		[a]P-Het	Meta-analysis (all children and adults)		[b]P-Het
				Effect size	P	Effect size	P	Effect size	P		Effect size	P	Effect size	P	Effect size	P		Effect size	P	
rs7678287	4	*SLC2A9*	A	−0.47	2.55×10^{-13}	−0.54	3.72×10^{-14}	−0.50	6.73×10^{-26}	0.4333	−0.41	1.08×10^{-8}	−0.46	1.41×10^{-11}	−0.44	8.86×10^{-19}	0.5976	−0.47	1.57×10^{-42}	0.6435
rs2231142	4	*ABCG2*	T	0.23	8.22×10^{-5}	0.22	0.0107	0.23	4.21×10^{-6}	0.9036	0.19	0.0127	0.24	0.0003	0.22	7.47×10^{-6}	0.6392	0.23	2.42×10^{-10}	0.9695

Effect size was calculated for the minor alleles. *P*-values for additive models were adjusted for sex, age, and either BMI or BMI percentile in children. CHR: Chromosome; MA: minor allele.
[a] *P*-Het: *P*-value for heterogeneity in effect sizes between normal-weight and obese subjects.
[b] *P*-Het: *P*-value for heterogeneity in effect sizes considering all groups.

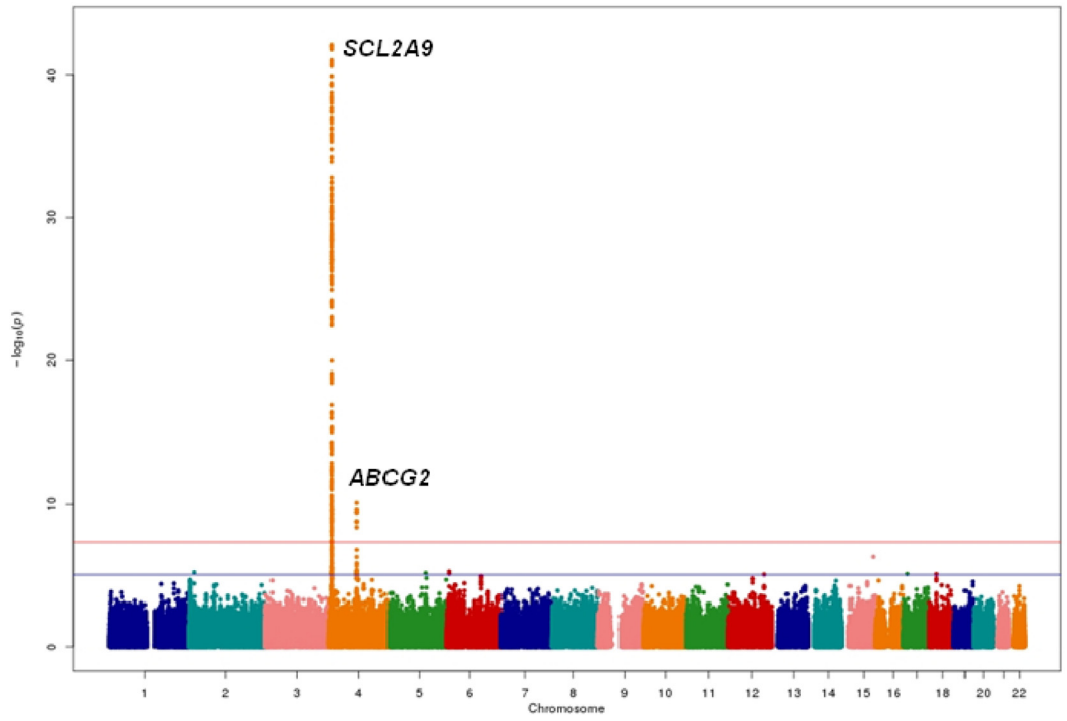

Fig. 1. GWAS for SUA levels in the Mexican population. Manhattan plot for serum uric acid meta-analysis showing the -log10 transformed *P*-value of SNPs for 2153 Mexican children and adults. The red line indicates the genome-wide significance level ($P = 5 \times 10^{-8}$). Genes closest to the SNP with the lowest *P*-value at each locus are indicated.

3.3. Role of SUA and associated SNPs in premature CAD, metabolic syndrome and glomerular filtration rate in the GEA cohort

SUA levels were associated with a higher risk of premature CAD (OR = 1.21, $P = 9.43 \times 10^{-5}$ after adjusting for age, sex, BMI, HOMA-IR, systolic and diastolic blood pressures, total cholesterol, HDL-c and triglyceride levels). In both controls and premature CAD patients, SUA was associated with an increased risk for metabolic syndrome (OR = 1.40, $P = 8.3 \times 10^{-10}$ in controls after adjusting for age and sex) and with decreased eGFR (OR = 1.43, $P = 0.012$ in controls after adjusting for BMI, HOMA-IR, HDL-C, triglycerides, systolic and diastolic blood pressures) (Table 2). Both *SLC2A9* rs7678287 and *ABCG2* rs2231142 were significantly associated with SUA in cases and controls ($\beta = -0.31$ mg/dl, $P = 2.94 \times 10^{-9}$ for rs7678287; and $\beta = 0.28$ mg/dl, $P = 4.79 \times 10^{-8}$ for rs2231142). The Mendelian randomization approach showed that *SLC2A9* rs7678287 and *ABCG2* rs2231142 were not associated with premature CAD or metabolic syndrome in the GEA cohort when analyzed individually or in combination (Table 2). However, *ABCG2* rs2231142 was significantly associated with decreased eGFR in the total GEA population ($P = 0.013$). This SNP was significantly associated with decreased eGFR in premature CAD patients ($P = 0.011$), but not in GEA controls ($P = 0.239$). We extended this analysis to the previously genotyped adult population (GWAS, n = 1073 adults), and an independent group of 1269 adults from the CANDELA-Mexico study. SNP rs2231142 was not associated with eGFR levels, or with decreased eGFR in any group (Supplementary Table 3).

4. Discussion

The association between obesity and hyperuricemia is known [33]. Consistently, the prevalence of hyperuricemia in the present study was significantly higher in obese than in lean individuals in both children and adults from Mexico City. The overall prevalence of hyperuricemia in children (21%) was similar to that previously reported in Mexican-American children (25%) [11]. In the present genome-wide association study, *SLC2A9* and *ABCG2* were the only loci associated with SUA levels in the combined analysis including Mexican children and adults. *SLC2A9* and *ABCG2* polymorphisms have been previously associated with SUA levels in other populations [7].

SLC2A9/GLUT9 is a high-capacity urate transporter with a role in renal urate reabsorption [34], previously associated with SUA in Mexican-American children and adults [11,35]. In the present study, the associations and effect sizes of rs7678287 (*SLC2A9*) were stronger in children, which is consistent with previous observations in Mexican-American children [11]. Interestingly, the conditional analysis based on the lead *SLC2A9* SNP (rs7678287) identified an independent SNP (rs7675964) associated with SUA levels ($r^2 = 0.23$), supporting a previous hypothesis of multiple independent variants residing in the region [36]. Although the GWAS in Mexican-American children did not report whether SUA-associated signals within this region were independent [11], LD between their lead SNP (rs11723388) and rs7675964 (one of the lead SNPs in the present study) was low ($r^2 = 0.11$), suggesting the presence of two different LD blocks in this region in Mexican Americans. Thus, both studies are consistent with the hypothesis of an independent association of both signals with SUA levels, although the functional variants responsible for these associations remain to be identified.

The *ABCG2* gene encodes a protein known to mediate renal and intestinal urate excretion as a urate efflux transporter [37]. The rs2231142 missense variant (Glu141Lys) has been found to be a loss of function variant in two independent studies [38,39]. The association of this SNP with SUA levels in adults is consistent with previous findings in other populations including Mexican Americans [35], however to our knowledge the association with SUA levels in children is novel. In contrast with findings in the *SLC9A2* region, after the conditioned analysis based on the lead *ABCG2* SNP, no other SNPs within the region showed significant association with SUA levels. This is consistent with the functional character of *ABCG2*/Glu141Lys.

No significant interaction between *SLC2A9* rs7678287 and *ABCG2* rs2231142 genotypes and obesity was observed. However, in agreement with previous studies [40], a significant *ABCG2* genotype*sex interaction ($P = 0.001$) was observed in adults but not in children, where the effect

Table 2
Association of SUA levels, and Mendelian randomization of SUA-associated SNPs for premature CAD, metabolic syndrome and decreased eGFR.

	Serum uric acid						SLC2A9 rs7678287						ABCG2 rs2231142					
	CAD cases		Controls		Whole sample		CAD cases		Controls		Whole sample		CAD Cases		Controls		Whole sample	
	[a]OR (95% CI)	*P*	[a]OR (95% CI)	*P*	[a]OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Premature CAD	–		–		1.21 (1.09–1.32)	9.43×10^{-5}	–		–		0.99 (0.82–1.21)	0.996	–		–		0.97 (0.80–1.17)	0.760
Metabolic syndrome	1.37 (1.21–1.55)	8.31×10^{-7}	1.40 (1.26–1.56)	8.3×10^{-10}	1.38 (1.28–1.50)	6.4×10^{-15}	0.83 (0.62–1.10)	0.204	1.19 (0.90–1.38)	0.304	1.00 (0.84–1.19)	0.979	0.82 (0.61–1.11)	0.201	1.02 (0.82–1.26)	0.869	0.94 (0.79–1.11)	0.463
Decreased eGFR	1.88 (1.41–2.57)	3.32×10^{-5}	1.43 (1.07–1.89)	0.012	1.65 (1.36–1.99)	2.2×10^{-7}	1.06 (0.49–2.12)	0.864	0.75 (0.35–1.46)	0.435	0.94 (0.56–1.50)	0.798	2.63 (1.25–5.60)	0.011	1.43 (0.77–2.58)	0.239	1.77 (1.12–2.75)	0.013

CAD: coronary artery disease; eGFR: estimated glomerular filtration rate OR: Odds ratio; CI: confidence interval. *P*-values were calculated by logistic regression. Associations with premature CAD were adjusted for age, sex, BMI, systolic and diastolic blood pressures, HOMA-IR index, total cholesterol, HDL-cholesterol and triglycerides. Associations with metabolic syndrome were adjusted for age and sex. Associations with decreased eGFR were adjusted for BMI, systolic and diastolic blood pressures, HOMA index, total cholesterol, HDL cholesterol and triglycerides. Decreased eGFR was defined as <60 ml/min/1.73 m^2. [a]OR: Odds ratio per 1-unit increase serum acid uric. This study included 704 CAD cases and 1075 controls from GEA cohort. Associations with metabolic syndrome (MS) and decreased eGFR were tested separately in CAD cases, GEA controls and in a conjoint analysis (whole sample). The GEA CAD group included 177 individuals with MS/525 without MS, and 30 with decreased eGFR/645 without decreased eGFR. The GEA control group included 313 individuals with MS/759 without MS, and 26 with decreased eGFR/1032 without decreased eGFR.

of the T allele is stronger in men than in women. These findings are consistent with observations in the male rat kidney, where testosterone was found to increase ABCG2 expression [41], and with the previously reported positive correlation between testosterone and SUA levels [42,43].

4.1. Mendelian randomization study of SUA levels for premature CAD, metabolic syndrome and eGFR in the GEA cohort

Although increased SUA levels have been associated with several coronary risk factors in various populations [44], whether increased SUA levels is an independent cardiovascular risk factor is still a matter of intense debate [45,46]. In the present study, SUA levels were associated with cardiovascular risk factors such as metabolic syndrome and eGFR, and with premature CAD even after adjustment for classic CAD risk factors. However, Mendelian randomization showed that *SLC2A9* and *ABCG2* lead polymorphisms were not associated with premature CAD or metabolic syndrome. This is consistent with a large meta-analysis including 58 studies suggesting SUA levels have no causal effect on CAD [47]. To our knowledge this is the first Mendelian randomization analysis suggesting there is no causal effect of elevated SUA levels on premature CAD in the Mexican population.

The relationship between SUA and renal function seems to be complex and is not fully understood [12]. This relationship most likely involves distinct pathways affected by different genes. In this regard, while *SLC9A2* rs7678287 showed the strongest and most significant association with SUA levels, it did not affect eGFR as a measure of renal function in premature CAD patients or in any of the control groups. In contrast, *ABCG2* rs2231142 was significantly associated with decreased eGFR in non-diabetic premature CAD patients from the GEA cohort. The association of only *ABCG2* rs2231142 and not *SLC9A2* rs7678287 with eGFR suggests that the relationship between SUA modifying alleles and renal function is not necessarily mediated directly by urate, as previously proposed [12]. Interestingly, a stronger effect of *ABCG2* rs2231142 on SUA in certain pathological conditions such as chronic kidney disease has been previously reported [48]. This is probably related to the significant contribution of ABCG2 to extra-renal clearance of urate through the gut, conditioning urate renal overload [49]. The association of rs2231142 with decreased eGFR only in premature CAD patients may be related to the higher frequency of decreased eGFR observed in these patients as compared to GEA controls (OR = 1.84, 95% CI = 1.13–3.01, $P = 0.0134$), perhaps affecting both renal and extra-renal urate clearance mechanisms. However, the association of ABCG2 with renal function in CAD needs to be confirmed in an independent sample.

Certain limitations of the study must be pointed out. Firstly, only SNPs in two loci (*SLC2A9* and *ABCG2*) were found to have a genome-wide association with SUA levels, which explained 3% of the variation in the study population. Further studies are required to identify the missing heritability of SUA levels in this population. Moreover, while Mendelian randomization suggested there is no causal effect of elevated SUA levels on premature CAD, whether intracellular uric acid plays a causal role in CAD or other metabolic diseases remains to be determined. Finally, because the sample size was relatively small, the association of rs2231142 *ABCG2* with decreased eGFR in the CAD group requires replication in other data sets before drawing conclusions.

5. Conclusion

According to the present genome-wide association study, *SLC2A9* and *ABCG2* are the main contributing loci to SUA variation in both children and adults from Mexico. SUA elevation was independently associated with premature CAD, metabolic syndrome and decreased eGFR in the Mexican population. However, a Mendelian randomization approach did not support a causal role of elevated SUA levels for premature CAD.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.107.

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