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rs17465637 Variant of *MIA3* May Be Associated with Coronary Artery Disease among Filipinos

UP-PGH Cardiovascular Genetics Study Group

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Genetics is an important component in the development of coronary artery disease (CAD); however, studies on the Filipino population are lacking. This study aimed to determine the association of polymorphisms with the development of CAD among Filipinos. This is an age- and sex-matched case-control association study involving 122 adult Filipinos with CAD and 230 control participants without CAD. DNA from blood samples were genotyped for candidate single-nucleotide polymorphisms (SNPs) using Illumina GoldenGate Genotyping (GGGT) assay. Candidate variants and clinical data were correlated with the occurrence of CAD using chi-square and logistic regression analysis. Of the candidate variants analyzed, only rs17465637 in *MIA3* (adjusted OR 2.38; $p = 0.024$) was found to have a nominal association with the development of CAD among Filipinos after adjusting for hypertension, type 2 diabetes mellitus (T2DM), and smoking status. This finding may potentially allow earlier identification of Filipino patients at risk for CAD. Validation of these findings in a larger cohort is recommended.

Keywords: coronary artery disease, Filipinos, *MIA3*, polymorphism, rs17465637

INTRODUCTION

Ischemic heart disease remains to be the leading cause of death and disability worldwide. It accounts for 45% of cardiovascular disease-related mortalities, with the Asian region comprising half of its global burden (Beltrame *et al*. 2012; Cassar *et al*. 2009; Ohira and Iso 2013). In the latest World Health Organization's (WHO) Global Health Estimates released in late-2020, deaths due to ischemic heart diseases increased from 1 million in the year 2000 to 2.3 million in 2019 in the Western Pacific region, which encompasses the Philippines (WHO 2020). Locally, the mortality rate of ischemic heart disease, which includes CAD, was at 12.7% in 2016 (Bersales 2018).

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Atherosclerosis is central to the development of CAD. It is initiated by the migration of monocytes to subendothelial cells and is promoted by the efflux of low-density lipoprotein (LDL) in large arteries. Migrated monocytes differentiate into macrophages, which in turn bind LDL, forming the fatty streak from foam cells. These – together with collagen-rich fibrous caps – form an atherosclerotic plaque, which can expand, limiting blood flow through the vessel (Sayols-Baixeras *et al*. 2014). CAD presents with plaque buildup in at least one major coronary artery, resulting in at least 50% stenosis in its diameter on coronary angiography (Cannon *et al*. 2013).

Atherosclerotic processes may be influenced by multiple genetic factors. Individuals with first-degree relatives diagnosed with CAD are 2–3 times at risk of inheriting the disease (Scheuner 2004). Genome-wide association studies (GWAS) explored how genetics may influence CAD development. One of the most important loci is 9p21, which, is involved in inflammatory signaling, lipid metabolism, and coronary atherosclerosis. It is carried by nearly 75% of the world's population and is associated with the risk of first coronary heart disease (CHD) event (Dehghan *et al.* 2016; Erdmann *et al*. 2018). Aside from the 9p21 locus, Samani and colleagues (2007) identified four additional loci in chromosomes 1, 10, and 15 to be associated with CAD in a combined analysis of the Wellcome Trust Case Control Consortium (WTCCC) and German Myocardial Infarction Family Study. Similarly, the CARDIOGRAMplus C4D Consortium identified a total of 46 susceptibility loci associated with CAD in Europeans and South Asians (Schunkert *et al*. 2011).

Present clinical risk assessment of CAD relies mainly on traditional risk factors with minimal consideration for genetic predisposition, which may result in an underestimation of risk and missed opportunities to prevent disease in at-risk individuals (Scheuner 2004). The inclusion of SNPs in risk assessment improves risk prediction over a 15-year follow-up (Bolton *et al*. 2013), supporting the need for genetic testing to identify person's susceptibility to CAD development. However, most studies associating CAD with genetic polymorphisms were performed on a predominantly European cohort of white ancestry (McPherson and Tybjaerg-Hansen 2016); no published studies including a Filipino cohort have been noted by the authors. To address this relevant knowledge gap, this study was done to identify genetic variants associated with susceptibility to developing CAD among Filipinos. After validation on a larger population, these variants may serve as genetic markers that can help identify genetically-predisposed patients who will benefit from early preventive interventions. Findings may also contribute to a better understanding of CAD pathogenesis, especially in the context of the Filipino population.

MATERIALS AND METHODS

Study Design

An age- and sex-matched case-control study was performed, with cases defined as participants diagnosed with CAD based on any one of the following: a) angiographic evidence of significant stenosis involving at least one large epicardial artery; b) atypical angina with an abnormal stress test or findings suggestive of ischemia; or c) history of revascularization *via* coronary angioplasty. Controls were individuals who were age- and sex-matched with cases were chest pain-free and were not diagnosed with CAD based on the criteria above. Cases and controls included participants who may or may not have other cardiovascular risk factors or comorbidities such as hypertension, dyslipidemia, or T2DM. Hypertension was defined as having systolic blood pressure of 140 mmHg or higher, or diastolic blood pressure of 90 mmHg or higher. Individuals labeled as hypertensive in their charts were also included in this group. Dyslipidemia is defined as the presence of any of the following: total cholesterol (TC) ≥ 200 mg/dL or 5.17 mmol/L, low-density lipoprotein cholesterol (LDL-C) ≥ 160 mg/dL or 4.14 mmol/L, high-density lipoprotein cholesterol (HDL-C) < 35 mg/dL or 0.90 mmol/L, or triglycerides (TG) ≥ 200 mg/dL or 2.25 mmol/L. Cut-off values for those with additional risk factors were also considered: LDL-C cut-off for those with 0–1 risk factors is 160 mg/dL; for those with two or more risk factors with a 10-yr risk ≤ 20%, the cut-off is 130 mg/dL; and for those with CHD or CHD risk equivalents (10-yr risk > 20%), the cut-off was 100 mg/dL. Lastly, those with the intake of any lipid-lowering medication and/or previous diagnosis of dyslipidemia were also included in the dyslipidemia group. T2DM is defined as having an FBS of 126 mg/dL, HbA1c of 6.5%, or a previous diagnosis of T2DM. For the lifestyle factors, alcohol drinking and smoking pertain to those whoever drank alcohol or smoked tobacco products.

Participants were included if they were at least 18 years old, of Filipino descent up to the 3rd degree of consanguinity, and able to provide informed consent. On the other hand, participants were excluded if they had any of the following conditions at the time of recruitment: decompensated heart failure, decompensated chronic lung disease, decompensated chronic liver disease, end-stage renal disease, active malignancy, secondary hypertension, secondary dyslipidemia, or pregnancy.

Study participants composed of patients, their watchers, and volunteer staff were enrolled from the Philippine General Hospital, different communities in Metro Manila, and private medical clinics from July 2013 to March 2017. Demographic data and clinical characteristics of the participants were obtained through interviews and

chart review. Blood samples were collected to measure and record the lipid profile and serum creatinine levels of participants.

DNA Extraction and Quantification

DNA from the blood of the participants were extracted using the QiaAmp DNA Minikit (QIAGEN, Victoria, Australia) following the spin protocol for blood buffy coat specified in the manufacturer's instruction manual. DNA was quantified using a spectrometer at 260nm and stored at –20 °C until use prior to genotyping. These are similar to the methods done in studies published earlier by the authors (Reganit *et al*. 2020; Sy *et al*. 2020).

Genotyping

A customized bead chip (GGGT bead chip, Illumina, Inc., San Diego, CA, USA) was designed in 2012 using candidate SNPs, which have shown evidence of association with susceptibility to CAD and other risk factors. These were selected after an extensive search was done in the following databases: PharmGKB (Pharmacogenomics Knowledgebase) database, NHGRI GWAS (National Human Genome Research Institute GWAS) catalog, PubMED, and patent databases (*e.g.* Patentscope and Espacenet), where risk and protective odds ratios (ORs) were provided. The selected SNPs were submitted to Illumina, Inc. for scoring to determine the suitability of the SNPs to discriminate genetic variants, as well as estimate their specificity.

Customized genotyping of candidate SNPs was performed using DNA microarray technology following the GGGT assay protocol specified in the manufacturer's manual. After microarray processing, the bead chip was imaged on the HiScan System, and data from these images were analyzed using GenomeStudio software. Variant selection and genotyping methods were similar to methods done in earlier studies (Reganit *et al*. 2020; Sy *et al*. 2020).

Data Analyses

Quality control. Using GenomeStudio 2.0 and PLINK version 2.05.10, genotype data from participants with call rates > 95% and with individual missingness < 0.05 (missingness test) in PLINK were included. Additional thresholds for inclusion were used for the genetic variants: minor allele frequency > 0.01 (frequency test), genotype missingness of < 0.05 (missingness test), and Hardy-Weinberg equilibrium (HWE) of $p < 0.001$ for controls (HWE test).

Statistical analysis. Chi-squared and Fisher exact tests were performed to assess for significant differences between alleles (allelic association test) and among genotypes (genotypic association tests) using PLINK version 2.05.10. Genotypic models (additive, dominant, recessive) were identified based on the distribution of the genotypes between the cases and controls. Tests for genotypic association were done setting the cut-off at Bonferroni-corrected $p < 0.05$, if applicable. Upon determination of models, the genotypes were recoded for univariate analysis using Stata 14. Univariate logistic regression analysis was done to determine the association of SNPs with CAD, with a cut-off *p*-value set at 0.05. Multiple logistic regression was performed to include possible confounding clinical factors. Quality control and statistical analyses were similar to the methods done in studies published earlier (Reganit *et al*. 2020; Sy *et al*. 2020).

Ethical Considerations

All procedures have been reviewed in compliance with ethical standards of the University of the Philippines Manila's Research Ethics Board (study protocol code UPMREB-2012-0183-01) on 04 Oct 2012.

RESULTS

Using an age- and sex-matched case-control design, a total of 352 participants (122 cases with CAD and 230 controls without the disease) were enrolled in the study. After quality control, the final set of samples for analysis included 347 participants (Figure 1A). Table 1 summarizes the clinical characteristics of the participants. Co-morbidities such as hypertension, dyslipidemia, T2DM, and smoking history were significantly more frequent among the participants with CAD.

Of the 81 variants selected for the study, 46 variants were removed after quality control with PLINK: 40 SNPs failed the Hardy-Weinberg test ($p > 0.001$) among controls, five SNPs had missing genotype data for more than 5% of the individuals, and one SNP was removed because the minor allele frequency was lower than 1% (Figure 1B). None of the variants had statistically significant associations with CAD after adjusting for multiple testing (*i.e.* Bonferroni-adjusted $\alpha < 0.001$); however, two variants are nominally associated with CAD. On simple conditional logistic regression analysis, the AA genotype of rs17465637 in *MIA3* was associated with 2.09 times higher odds of CAD compared to the AC and CC genotypes in a recessive model, while the TG and TT genotypes of rs8055236 in CDH13 double the odds of CAD compared to the GG genotype in a dominant model (Appendix Table I). Among the clinical variables, three were significantly different between the two groups: hypertension (crude OR 7.45; *p*-value < 0.001), T2DM (crude OR 2.00; *p*-value 0.004), and smoking history (crude OR 1.99; *p*-value 0.005) (Appendix Table II). Multiple conditional logistic

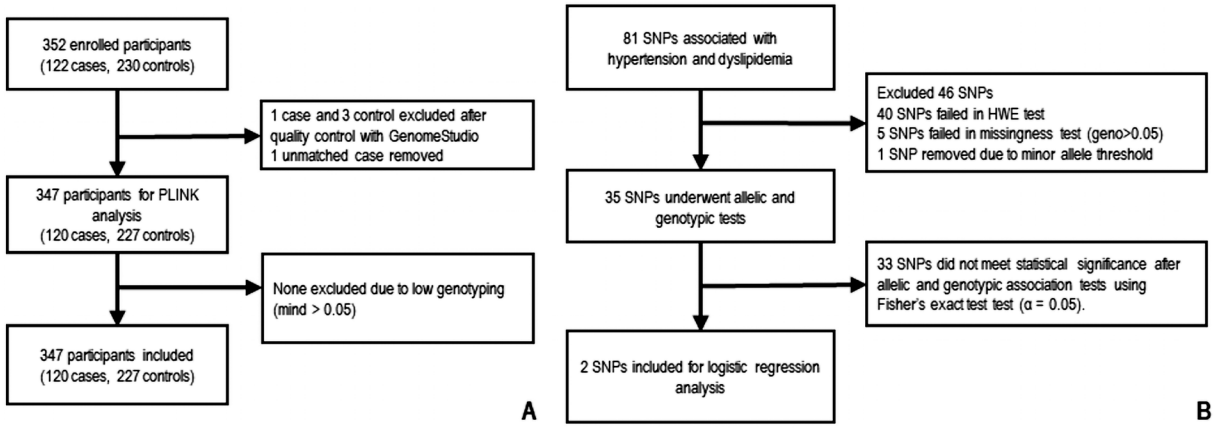

Figure 1. Overview of data processing and analysis. A total of 347 participants (A) and 81 SNPs (B) were analyzed to determine association of clinical metadata and genetic variants with CAD. Abbreviations: mind – individual missingness; SNP – single nucleotide polymorphism; HWE – Hardy-Weinberg equilibrium; geno – genotypic missingness; MAF – minor allele frequency.

Table 1. Clinical characteristics of study participants.

Characteristics	Participants with CAD n = 120	Participants without CAD n = 227	*p*-value*
Age > 60 yr old	47.50	40.53	0.254
Male sex	82.50	81.94	> 0.999
Comorbidities, %			
Elevated BMI ≥ 25 kg/m^2	47.90	52.23	0.471
Hypertension	92.50	68.72	< 0.001
Dyslipidemia	100	52.42	< 0.001
T2DM	42.50	27.31	0.004
Lifestyle factors, %			
Alcohol drinking	78.33	70.48	0.102
Smoking	60.00	44.05	0.005

Abbreviations: BMI – body mass index; CAD – coronary artery disease
*Statistical significance was set at $P < 0.05$ using conditional logistic regression; except for age, sex, and dyslipidemia (Fisher's exact test was used).

regression analysis was performed to determine if the genetic variants will retain their association with CAD after adjusting for hypertension, T2DM, and smoking (Table 2). Dyslipidemia was not included in the multiple regression analysis due to the lack of within-group variances. Of the two variants, only rs17465637 retained statistical significance (adjusted OR 2.38, $p = 0.024$).

DISCUSSION

This study investigated the association of genetic variants with susceptibility to CAD among adult Filipinos. The variant rs17465637 in *MIA3* retained its nominal significance after adjusting for important clinical factors such as hypertension, smoking, and T2DM.

In the current study, the A allele of rs17465637 was found to be nominally associated with CAD susceptibility on allelic association analysis (unadjusted OR 1.433; *p*-value 0.039). Participants with two copies of the A allele had

Table 2. Association of genetic variants on multiple logistic regression.

Genetic variants	Adjusted OR (95% CI)	*p*-value*
rs17465637 in *MIA3* (recessive model)	2.38 (1.12,5.06)	0.024
rs8055236 in *CDH13* (dominant model)	1.68 (0.94,3.01)	0.079

Abbreviations: *MIA3* – MIA SH3 domain ER export factor 3; *CDH13* – cadherin 13; OR – odds ratio; CI – confidence interval
*Significance set at $p < 0.05$ on conditional logistic regression, adjusted for hypertension, T2DM, and smoking.

increased odds of CAD on genotypic analysis, and this association was retained after adjusting for hypertension, T2DM, and smoking status (recessive model; adjusted OR 2.38, $p = 0.024$). The frequency of the A risk allele of rs17465637 among study participants is 28%; this is less than the global frequency of 50% found among participants of the 1000 Genomes Project. It is also less than the frequency in East Asians (39%), South Asians (42%), admixed Americans (49%), and Africans (81%). On the other hand, it is almost identical to the allele frequency observed in Europeans (26%) (1000 Genomes Project Consortium 2015; NCBI 2018).

Located in the long arm of Chromosome 1, rs17465637 is an intronic variant found in the *MIA SH3 domain ER export factor 3* (*MIA3*) gene (He *et al*. 2017). *MIA3* codes for a 14kDa protein of largely unknown function. It is widely expressed *in vivo* (Xie *et al*. 2011) and is also referred to as *ARNT* (Aryl Hydrocarbon Receptor Nuclear Translocator) or *TANGO1* (Transport and Golgi Organization Protein 1). *MIA3* is a tumor suppressor gene for malignant melanoma and is also important for cell growth and collagen VII (COL7A1) export to the Golgi complex from the endoplasmic reticulum (Li *et al*. 2013; Wang *et al*. 2011). The gene is involved in the adhesion of monocytes to fibrinogen and endothelial cells by modulating CD11c/CD18 activity in monocytes (Koch *et al*. 2011; Xie *et al*. 2011). *MIA3* has been implicated in the development, progression, and stability of atherosclerotic plaque, an important mechanism for the pathogenesis of CAD. A few mechanisms have been proposed to define the exact role of *MIA3* on CAD pathogenesis, but no consensus has been met.

Most GWAS point to the C allele of this variant as the risk allele, contrary to what was found from this study. There was a trend of association between rs17465637-A and accelerated development of carotid plaques and increased risk of cardiovascular events among rheumatoid arthritis patients with dyslipidemia, although logistic regression analysis turned to be non-significant (García-Bermúdez *et al*. 2012). On the other hand, a meta-analysis of the WTCC and the German MI Family Study showed that rs17465637-C conferred 20% higher odds (Cochran-Armitage trend analysis: OR 1.20; 95% CI 1.12, 1.30) of CAD in a cohort of Europeans (Samani *et al.* 2007); other meta-analysis showed similar results (Kathiresan *et al*. 2009; Schunkert *et al*. 2011; van der Harst and Verweij 2018). The association was also noted among Han Chinese, with an OR of 1.11 (95% CI 1.02, 1.21) (Li *et al*. 2013). In addition, rs17465637-C was also associated with myocardial infarction among Japanese (OR 1.45, $p = 0.006$) and white Americans (P-adjusted = 0.0034) (Hiura *et al*. 2008; Wang *et al*. 2011). A meta-analysis of 11 studies from Europe, China, United States, and New Zealand determining the association of 1q41 polymorphisms and CAD showed that the C allele was the risk allele for CAD instead of the A allele (He *et al*. 2017), while the study of Wang and colleagues showed that allele A confers a protective effect against CAD (Wang *et al*. 2011).

The upregulation of *MIA3* may explain the occurence of CAD. Studies from mapping expression quantitative trait loci (eQTLs) in the GTEx Portal database show that individuals with the AA genotype have marginally higher expression of *MIA3* in subcutaneous and omental adipose tissue and the aorta, as well as a more marked increase in expression of its antisense RNA, RP11-378J18.8 (Carithers *et al*. 2015; GTEx 2015). In a study by Arndt *et al.* (2007), it was found that *MIA3* expression reduced the attachment of monocytes to endothelial cells. Reduced attachment consequently promotes migration through endothelial cells and the monocytes, in turn, differentiate into macrophages and foam cells, forming the fatty streak and plaque in the arterial intima (He *et al*. 2017). It is possible that the SNP exerts its action on *MIA3* by causing an upregulation of the gene.

On the other hand, *MIA3* downregulation has also been proposed to explain the gene's involvement with CAD. The variant rs17465637-C is associated with the downregulation of *MIA3* expression in adipose, aortic, and tibial artery tissues (Carithers *et al*. 2015); it is also possible that the upregulated expression of the *MIA3* antisense RNA RP11-378J18.8 may also lead to reduced expression of *MIA3*. Luo *et al*. (2017) proposed that *MIA3* acts to prevent monocyte migration, such that *MIA3* knockout favors the migration of monocytes through endothelial cells. Migration through endothelial cells causes monocytes to differentiate into macrophages, hence the formation of foam cells and atherosclerotic plaque. Aside from this, the gene is also involved in collagen VII export, where defective collagen VII secretion was observed in *MIA3*/*TANGO1* knockout mice (Wilson *et al*. 2011). Reduced levels of functional collagen contribute to the degradation of the extracellular matrix composition, which consequently affects atherogenesis and arterial remodeling (Li *et al*. 2013). As a result of the imbalance between collagen synthesis and macrophage degradation, there is fibrous cap thinning, collagen degradation, and ultimately plaque instability (García-Bermúdez *et al*. 2012).

This study was age- and sex-matched in order to control the effect of age and sex on the outcomes. However, this means that the interaction of these variables with the variant cannot be measured. Similarly, because of the lack of within-group variances for dyslipidemia, its effect on the CAD-variant association could not be assessed.

While the group is not discounting the fact that some of

the variants excluded due to failure in the HWE test may have true associations with CAD, the *pre-hoc* qualifiers were put into place to make sure that the SNPs included after quality control do not deviate from HWE. The large number of variants that failed the Hardy-Weinberg test may be due to the small sample size of this pilot study, so it is recommended that future studies should use a larger sample size to identify other variants that might have been missed.

Available polygenic risk scores for coronary heart disease (PRS_{CHD}) have been developed to complement clinical risk scores and conventional risk stratification. A PRS_{CHD} developed among a large cohort of individuals of mostly European ancestry was shown to be associated with a modest, statistically significant improvement in predictive accuracy for CAD (Elliott *et al*. 2020). However, due to differences in genetic parameters like allele frequency and effect sizes, this may not be applicable to other populations. While data from this current study may not be sufficient to derive a PRS_{CHD} specific to Filipinos, this knowledge may be essential to the development of a validated and customized PRS_{CHD}, as was done among Koreans (Bhak *et al*. 2021). Whole-genome sequencing may also be done to identify variants that may be significant in the Filipino population.

The definitive action of *MIA3* on monocyte migration has yet to be established. Studies show that both the upregulation and downregulation of the gene may affect the pathogenesis of CAD. This may suggest that the variant may be exerting heterogeneous effects that may be influenced by differences in ethnic background and the environment. It is also highly likely that linkage disequilibrium among different ethnic groups may manifest as inconsistent association patterns (Lin *et al*. 2007). Moreover, the precise action of the SNP on *MIA3* is also unclear. However, the study highlights the importance of this locus in CAD pathogenesis, warranting further investigations.

Future studies may explore how rs17465637 specifically interacts with *MIA3* as data regarding this is currently limited. In relation, the specific action of *MIA3* on monocyte migration should also be looked upon. Additionally, further studies on the differences in risk alleles observed in the Filipino population could provide insight into the management of Filipino CAD patients.

CONCLUSION

The candidate variant rs17465637 in *MIA3* (adjusted OR 2.38; $p = 0.024$) was found to have a nominal association with the presence of CAD among adult Filipinos after adjusting for selected risk factors such as hypertension, T2DM, and smoking status.

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STATEMENT ON CONFLICT OF INTEREST

The authors declare no conflicts of interest.

NOTES ON APPENDICES

The complete appendices section of the study is accessible at http://philjournsci.dost.gov.ph

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APPENDICES

Table I. Association of genetic variants on simple logistic regression.

SNP	Chr	Nearest gene	Genotype	Model	Allele frequency	Crude OR (95% CI)	*p*-value*
rs17465637	1	*MIA3*	AA vs AC/CC	Recessive	0.28	2.09 (1.07,4.09)	0.032
rs8055236	16	*CDH13*	TG/TT vs GG	Dominant	0.11	2.0 (1.17,3.41)	0.011

Abbreviations: SNP – single nucleotide polymorphism; Chr – chromosome; OR – odds ratio; *MIA3* – MIA SH3 domain ER export factor 3; *CDH13* – cadherin 13; CI – confidence interval
*Significance set at $p < 0.05$ using conditional logistic regression

Table II. Association of clinical characteristics on simple logistic regression.

Variables	Crude OR (95% CI)	*p*-value*
Hypertension	7.45 (3.13, 17.76)	< 0.001
T2DM	2.00 (1.24, 3.22)	0.004
Smoking	1.99 (1.23, 3.23)	0.005
Alcohol drinking	1.65 (0.90, 3.03)	0.102
Abnormal eGFR (< 60 mL/min)	2.11 (0.99, 4.53)	0.054
Abnormal BMI ≥ 25 kg/m^2	0.84 (0.54, 1.33)	0.471

Abbreviations: EGFR – estimated glomerular filtration rate; BMI – body mass index; OR – odds ratio; CI – confidence interval
*Significance set at $p < 0.05$ using conditional logistic regression

Table III. List of 81 SNPs included in the study.

Chr	rs ID	Implicated gene	Alleles	Minor allele	MAF	AF based on 1000 Genomes Project*						Fate
						Global	AFR	AMR	EAS	EUR	SAS	
9	rs10306114	PTGS1	A/G	G	0.217579	0.0541	0.1293	0.0288	0	0.0696	0.0102	Excluded after QC (HWE test $p > 0.001$)
14	rs10498345	(Intergenic)	A/T	A	0.121037	0.1098	0.1513	0.1383	0.1845	0.0089	0.0603	No statistical significance
5	rs1062535	ITGA2	A/G	A	0.387608	(No data available)						No statistical significance
3	rs1065776	P2RY1	T/C	T	0.009009	0.1104	0.2239	0.0706	0.0347	0.0497	0.1258	Excluded after QC (GENO > 0.05)
9	rs10757274	CDKN2B-AS1	A/G	G	0.466912	0.404	0.1755	0.4179	0.5288	0.492	0.4836	Excluded after QC (GENO > 0.05)
9	rs10757278	CDKN2B-AS1	A/G	G	0.476945	0.4081	0.1589	0.4553	0.5437	0.4742	0.5041	No statistical significance
12	rs10861032	(Intergenic)	T/C	T	0.371758	0.638	0.5628	0.7997	0.5079	0.8698	0.5204	No statistical significance
12	rs11066015	ACAD10	A/G	A	0.341499	0.0357	0	0.0029	0.1756	0	0	Excluded after QC (HWE test $p > 0.001$)
5	rs1126643	ITGA2	T/C	T	0.204611	0.3377	0.2806	0.4424	0.2827	0.4026	0.3303	No statistical significance
12	rs1165668	TTC41P	A/G	G	0.210375	0.3351	0.3011	0.3847	0.3611	0.2843	0.3712	No statistical significance
5	rs11748327	(Intergenic)	T/C	T	0.383285	0.1817	0.0711	0.1585	0.1548	0.3072	0.2464	Excluded after QC (HWE test $p > 0.001$)
6	rs11752643	MTCO3P1	T/C	T	0.132047	0.0132	0.003	0.0101	0.0198	0.0258	0.0092	No statistical significance
3	rs11924705	(Intergenic)	T/C	C	0.131657	0.2556	0.2133	0.3055	0.0774	0.4324	0.2791	No statistical significance
1	rs12041331	PEAR1	A/G	G	0.282421	0.6655	0.5348	0.7968	0.5417	0.9076	0.6278	Excluded after QC (HWE test $p > 0.001$)
1	rs12091564	HJV	T/C	C	0.462536	0.1973	0.3782	0.1844	0.1756	0.0447	0.1411	Excluded after QC (HWE test $p > 0.001$)
10	rs12248560	CYP2C19	T/C	T	0.168588	0.1532	0.2352	0.1196	0.0149	0.2237	0.136	Excluded after QC (HWE test $p > 0.001$)
1	rs12566888	PEAR1	T/G	T	0.416427	0.3932	0.646	0.219	0.4921	0.0924	0.3824	No statistical significance
3	rs13078881	BTD	C/G	C	0.188761	0.0186	0.0023	0.0187	0	0.0427	0.0348	Excluded after QC (HWE test $p > 0.001$)
4	rs1320267	(Intergenic)	G/C	G	0.275758	0.5765	0.643	0.4625	0.6012	0.5686	0.5501	Excluded after QC (HWE test $p > 0.001$)
7	rs13232179	CRYGN	A/T	T	0.416427	0.7618	0.9002	0.8833	0.506	0.8907	0.6196	No statistical significance

Chr	rs ID	Implicated gene	Alleles	Minor allele	MAF	AF based on 1000 Genomes Project*						Fate
						Global	AFR	AMR	EAS	EUR	SAS	
9	rs1333042	CDKN2B-AS1	A/G	A	0.324207	0.3213	0.034	0.5029	0.3046	0.502	0.4121	No statistical significance
9	rs1333048	CDKN2B-AS1	A/C	A	0.254335	0.5579	0.7368	0.5331	0.4613	0.5089	0.4836	No statistical significance
9	rs1333049	CDKN2B-AS1	G/C	G	0.319885	0.5819	0.7867	0.5447	0.4633	0.5278	0.5092	No statistical significance
11	rs1350445	(Intergenic)	T/C	T	0.463977	0.7754	0.8071	0.8372	0.625	0.7704	0.8487	Excluded after QC (HWE test $p > 0.001$)
1	rs1400544	(Intergenic)	A/T	A	0.181556	0.7049	0.5234	0.7997	0.8452	0.7594	0.682	No statistical significance
5	rs1502050	DNAH5	A/G	A	0.461095	0.6831	0.612	0.7219	0.8948	0.6988	0.5174	Excluded after QC (HWE test $p > 0.001$)
3	rs1523127	NR1I2	T/G	G	0.485591	0.488	0.8759	0.4467	0.2163	0.3668	0.3978	Excluded after QC (HWE test $p > 0.001$)
19	rs1613662	GP6	A/G	G	0.412104	–	0.2526	0.0908	0.0337	0.1451	0.2157	Excluded after QC (HWE test $p > 0.001$)
19	rs1671152	GP6	T/G	T	0.373199	–	0.3328	0.0836	0.0327	0.1412	0.2178	Excluded after QC (HWE test $p > 0.001$)
12	rs17034045	(Intergenic)	T/C	C	0.378963	0.1685	0.1407	0.0677	0.2629	0.0596	0.2924	No statistical significance
1	rs17114046	PLPP3	A/G	G	0.443804	0.1038	0.1997	0.0821	0.0208	0.1183	0.0603	Excluded after QC (HWE test $p > 0.001$)
15	rs17228212	SMAD3	T/C	C	0.195965	0.1266	0.0976	0.1326	0.001	0.2903	0.1227	Excluded after QC (HWE test $p > 0.001$)
2	rs17458018	FN1	T/C	C	0.170029	0.0453	0.0106	0.0403	0	0.0586	0.1288	No statistical significance
1	rs17465637	MIA3	A/C	A	0.311239	–	0.8132	0.4856	0.3948	0.2624	0.4202	With nominal association
5	rs17577085	SPRY4-AS1	T/G	G	0.380403	0.0541	0.0045	0.0259	0.0565	0.0885	0.1033	Excluded after QC (HWE test $p > 0.001$)
1	rs17672135	FMN2	T/C	C	0.479827	0.1222	0.1044	0.0893	0.1488	0.1093	0.1554	Excluded after QC (HWE test $p > 0.001$)
10	rs17878459	CYP2C19	A/G	A	0.384726	0.991	0.9962	0.9942	1	0.9642	1	Excluded after QC (HWE test $p > 0.001$)
15	rs1994016	ADAMTS7	T/C	T	0.461095	0.2179	0.0961	0.2839	0.0913	0.3996	0.2791	Excluded after QC (HWE test $p > 0.001$)
6	rs2048327	SLC22A3	A/G	A	0.488473	0.7087	0.9697	0.5476	0.5357	0.6481	0.7106	No statistical significance
1	rs2229238	IL6R	T/C	C	0.455331	–	0.7731	0.8631	0.8065	0.7803	0.7894	Excluded after QC (HWE test $p > 0.001$)
10	rs28399504	CYP2C19	A/G	G	0.178674	0.0008	0	0.0029	0.001	0.001	0	Excluded after QC (HWE test $p > 0.001$)
14	rs28756981	ACYP1	A/C	C	0.317919	0.0044	0	0.0058	0	0.0169	0.001	Excluded after QC (HWE test $p > 0.001$)
5	rs2896103	DNAH5	T/C	T	0.260807	0.3081	0.3654	0.2709	0.1052	0.3012	0.4734	No statistical significance
6	rs3127599	LPAL2	A/G	A	0.239067	0.2322	0.3139	0.1484	0.1081	0.3201	0.2188	No statistical significance
19	rs3211371	CYP2B6	T/C	C	0.237681	0.9465	0.9887	0.928	0.997	0.8877	0.911	Excluded after QC (HWE test $p > 0.001$)
9	rs35305327	WDR31	A/C	C	0.273775	0.0024	0	0.0029	0	0.006	0.0041	Excluded after QC (HWE test $p > 0.001$)
10	rs3739998	JCAD	C/G	C	0.240634	0.7482	0.9402	0.5476	0.8175	0.5785	0.7342	No statistical significance
16	rs3785161	CES1P1	A/C	C	0.173913	0.1605	0.0439	0.1801	0.253	0.2087	0.1595	No statistical significance
6	rs3798220	LPA	T/C	C	0.059078	0.0513	0.0045	0.2161	0.0883	0.0099	0.002	No statistical significance
10	rs3849150	WDFY4	T/C	T	0.317003	0.1206	0.174	0.0937	0.002	0.1431	0.1667	Excluded after QC (HWE test $p > 0.001$)
10	rs41291556	CYP2C19	T/C	C	0.211816	0.001	0.0008	0	0	0.003	0.001	Excluded after QC (HWE test $p > 0.001$)
10	rs4244285	CYP2C19	A/G	G	0.489914	0.7786	0.8298	0.8948	0.6875	0.8549	0.6421	No statistical significance
17	rs4290	ACE	T/C	C	0.496951	0.9183	0.764	0.9712	1	0.997	0.9243	Excluded after QC (GENO > 0.05)
2	rs4971516	LDAH	T/C	T	0.482709	0.9129	0.9047	0.9481	0.88	0.9553	0.8896	Excluded after QC (HWE test $p > 0.001$)
9	rs4977574	CDKN2B-AS1	A/G	A	0.252161	0.605	0.8593	0.5836	0.4692	0.508	0.5164	No statistical significance
10	rs4986893	CYP2C19	A/G	A	0.455331	0.0142	0.0023	0	0.0556	0	0.0123	Excluded after QC (HWE test $p > 0.001$)
10	rs501120	(Intergenic)	A/G	G	0.177233	0.3327	0.5023	0.2233	0.3423	0.1461	0.363	No statistical significance
13	rs510335	F7	T/G	T	0.060519	0.2041	0.3608	0.1311	0.0397	0.1252	0.2945	No statistical significance
9	rs514659	ABO	A/C	C	0.373288	(no data available)						Excluded after QC (GENO > 0.05)
12	rs5443	GNB3	T/C	T	0.39049	0.4922	–	–	–	–	–	Excluded after QC (HWE test $p > 0.001$)
10	rs56337013	CYP2C19	T/C	T	0.194524	(No data available)						Excluded after QC

Chr	rs ID	Implicated gene	Alleles	Minor allele	MAF	AF based on 1000 Genomes Project*						Fate
						Global	AFR	AMR	EAS	EUR	SAS	
17	rs5918	ITGB3	T/C	C	0.170118	0.0889	0.0915	0.1023	0.0089	0.1322	0.1135	Excluded after QC (HWE test $p > 0.001$)
1	rs599839	CELSR2	A/G	G	0.273775	–	0.8215	0.2522	0.0655	0.2217	0.2618	Excluded after QC (HWE test $p > 0.001$)
7	rs662	PON1	A/G	A	0.337176	–	0.2474	0.5014	0.3343	0.7097	0.5757	No statistical significance
1	rs6668968	AQP10	A/G	A	0.497118	0.2732	0.2685	0.2349	0.2093	0.3181	0.3262	Excluded after QC (HWE test $p > 0.001$)
1	rs6685323	AQP10	T/C	T	0.48415	0.2933	0.3434	0.2363	0.2103	0.3181	0.3262	Excluded after QC (HWE test $p > 0.001$)
2	rs6711736	LINC01320	A/G	A	0.233429	0.3752	0.2057	0.3285	0.6042	0.3946	0.3814	No statistical significance
3	rs6785930	MED12L	A/G	A	0.408696	0.2418	0.1672	0.2781	0.2113	0.3151	0.273	Excluded after QC (HWE test $p > 0.001$)
3	rs6787801	MED12L	A/G	G	0.237752	0.4728	0.4985	0.4424	0.4077	0.498	0.501	Excluded after QC (HWE test $p > 0.001$)
3	rs6798347	MED12L	A/G	A	0.432886	0.2891	0.3351	0.2205	0.2788	0.2018	0.3763	Excluded after QC (GENO > 0.05)
22	rs688034	SEZ6L	T/C	T	0.00731	0.1196	0.0688	0.17	0.002	0.3082	0.0798	Excluded after QC (MAF < 0.01)
6	rs6905288	VEGFA	A/G	G	0.174352	–	0.4992	0.4006	0.2589	0.4036	0.1759	No statistical significance
16	rs71647871	CES1	A/G	A	0.138329	(No data available)						Excluded after QC (HWE test $p > 0.001$)
4	rs7697839	STK32B	A/G	G	0.322767	0.0641	0.1135	0.0303	0.0516	0.0368	0.0624	Excluded after QC (HWE test $p > 0.001$)
5	rs7715811	DNAH5	T/C	T	0.273775	0.3157	0.3858	0.2738	0.1062	0.3012	0.4816	No statistical significance
16	rs8055236	CDH13	T/G	T	0.123919	0.262	0.5772	0.1239	0.131	0.1819	0.1513	With nominal association
10	rs869244	(Intergenic)	A/G	A	0.298551	0.3814	0.3215	0.4135	0.4137	0.3519	0.4366	Excluded after QC (HWE test $p > 0.001$)
6	rs9349379	PHACTR1	A/G	G	0.319885	0.3774	0.0303	0.3761	0.6855	0.4006	0.5061	Excluded after QC (HWE test $p > 0.001$)
9	rs944797	CDKN2B-AS1	T/C	T	0.474063	0.513	0.587	0.4986	0.4782	0.493	0.4796	No statistical significance
13	rs9546711	(Intergenic)	A/G	A	0.463977	0.2208	0.062	0.1614	0.4236	0.2008	0.2894	No statistical significance
3	rs9818870	MRAS	T/C	T	0.010086	0.0879	0.1006	0.0692	0.0258	0.1431	0.091	No statistical significance

Abbreviations: Chr – chromosome number; rs ID – reference sequence ID; MAF – minor allele frequency – AFR – African; AMR – admixed American; EAS – East Asian; EUR – European, SAS – South Asian; *PTGS1* – prostaglandin-endoperoxide synthase 1; *ITGA2* – integrin subunit alpha 2; *P2RY1* – purinergic receptor P2Y1; *CDKN2B-AS1* – cyclin dependent kinase inhibitor 2B antisense RNA1; *ACAD10* – acyl-CoA dehydrogenase family member 10; *TTC41P* – tetratricopeptide repeat domain 41 pseudogene; *MTCO3P1* – MT-CO3 pseudogene 1; *PEAR1* – platelet endothelial aggregation receptor 1; *HJV* – hemojuvelin BMP co-receptor; *CYP2C19* – cytochrome p450 family 2 subfamily C member 19; *BTD* – biotinidase; *CRYGN* – crystalline gamma N; *DNAH5* – dynein axonemal heavy chain 5; *NR1I2* – nuclear receptor subfamily 1 group I member 2; *GP6* – glycoprotein VI platelet; *PLPP3* – phospholipid phosphatase 3; *SMAD3* – SMAD family member 3; *FN1* – fibronectin 1; *MIA3* – MIA SH3 domain ER export factor 3; *SPRY4-AS1* – sprout RTK signaling antagonist 4 antisense RNA 1; *FMN2* – formin 2; *ADAM* – metallopeptidase with thrombospondin type 1 motif 7; SLC22A3 – solute carrier family 22 member 3; IL6R – interleukin 6 receptor; ACYP1 – acylphosphatase 1; LPAL2 – lipoprotein(a) like 2, pseudogene; *CYP2B6* – cytochrome P450 family 2 subfamily B member 6; WDR31 – WD repeat domain 31; JCAD – junctional cadherin 5 associated; CES1P1 – carboxylesterase 1 pseudogene 1; *LPA* – lipoprotein(a); *WDFY4* – WDFY family member 4; *ACE* – angiotensin I converting enzyme; *LDAH* – lipid droplet associated hydrolase; F7 – coagulation factor VII; *ABO, ABO* – alpha 1-3-N-acetylgalactosaminyltransferase and alpha 1-3-galactosyltransferase; *GNB3* – *G* protein subunit beta 3; *ITGB3* – integrin subunit beta 3; *CELSR2* – cadherinEGF LAG seven-pass G-type receptor 2; *PON1* – paraoxonase 1; *AQP10* – aquaporin 10; *LINC01320* – long intergenic non-protein coding RNA 1320; *MED12L* – mediator complex subunit 12L; *SEZ6L* – seizure related 6 homolog like; *VEGFA* – vascular endothelial growth factor A; *CES1* – carboxylesterase 1; *STK32B* – serine/threonine kinase 32B; *CDH13* – cadherin 13; *PHACTR1* – phosphatase and actine regulator 1; *MRAS* – muscle RAS oncogene homolog.

Data for the 1000 Genomes Project data was obtained from The Ensembl Variant Effect Predictor (McLaren *et al.* 2016). The MAFs for the variants were computed from the consolidated study population (*i.e.* cases and controls).