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Genome-wide association study of perioperative myocardial infarction after coronary artery bypass surgery

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ABSTRACT

Objectives: Identification of patient subpopulations susceptible to develop myocardial infarction (MI) or, conversely, those displaying either intrinsic cardioprotective phenotypes or highly responsive to protective interventions remain high-priority knowledge gaps. We sought to identify novel common genetic variants associated with perioperative MI in patients undergoing coronary artery bypass grafting using genome-wide association methodology.

Setting: 107 secondary and tertiary cardiac surgery centres across the USA.

Participants: We conducted a stage I genome-wide association study (GWAS) in 1433 ethnically diverse patients of both genders (112 cases/1321 controls) from the Genetics of Myocardial Adverse Outcomes and Graft Failure (GeneMAGIC) study, and a stage II analysis in an expanded population of 2055 patients (225 cases/1830 controls) combined from the GeneMAGIC and Duke Perioperative Genetics and Safety Outcomes (PEGASUS) studies. Patients undergoing primary non-emergent coronary bypass grafting were included.

Primary and secondary outcome measures: The primary outcome variable was perioperative MI, defined as creatine kinase MB isoenzyme (CK-MB) values ≥10× upper limit of normal during the first postoperative day, and not attributable to preoperative MI. Secondary outcomes included postoperative CK-MB as a quantitative trait, or a dichotomised phenotype based on extreme quartiles of the CK-MB distribution.

Results: Following quality control and adjustment for clinical covariates, we identified 521 single nucleotide polymorphisms in the stage I GWAS analysis. Among these, 8 common variants in 3 genes or intergenic regions met $p<10^{-5}$ in stage II. A secondary analysis using CK-MB as a quantitative trait (minimum $p=1.26\times10^{-3}$ for rs609418), or a dichotomised phenotype based on extreme CK-MB values (minimum $p=7.72\times10^{-6}$ for rs4834703) supported these findings. Pathway analysis revealed that genes harbouring top-scoring variants cluster in pathways of biological relevance to extracellular matrix remodelling, endoplasmic reticulum-to-Golgi transport and inflammation.

Conclusions: Using a two-stage GWAS and pathway analysis, we identified and prioritised several potential susceptibility loci for perioperative MI.

Strengths and limitations of this study

- This is the first genome-wide association study of perioperative myocardial infarction, using prospective cohorts of cardiac surgical patients, standard definitions of the primary phenotype and full adjustment for non-genetic risk factors.
- We conducted comprehensive and complementary single marker and pathway-based genome-wide association analyses.
- The study is powered to detect relatively large effect sizes.
- Rare genetic variant effects not analysed.
- Predominantly Caucasian cohort, thus findings cannot be generalised to other populations.

INTRODUCTION

Despite advances in surgical techniques and pharmacological therapy, the incidence of myocardial infarction (MI) after coronary artery bypass grafting (CABG) remains as high as 19%, and is associated with increased mortality and long-term morbidity.[1] Strategies to identify subpopulations of patients at risk for developing large myocardial infarcts on the one hand, or those displaying an intrinsic cardioprotective state on the other hand, remain high-priority knowledge gaps and could inform selection of more specific protective agents.[2]

The evidence for heritability of MI is striking, supported both by family studies and, recently, by a number of well powered and replicated genome-wide association studies (GWAS), which primarily implicate common genetic variants at the 9p21 locus in multiple racial groups.[3–6] However, although family-

based methods are not practical for studying perioperative MI (PMI), its genetic basis is strongly suggested by several observations, including wide variability in incidence and severity that is poorly explained by clinical and procedural risk factors, different racial susceptibility profiles and results from preclinical animal models. Indeed, extensive genetic variability has been found in biological pathways implicated in the pathophysiology of postoperative MI, such as the complex acute inflammatory response to cardiac surgery. Mounting evidence for heritability of a proinflammatory state suggests that individual genetic history may also significantly modulate the magnitude of postoperative inflammatory response after cardiac surgery.[7] Yet only a few studies have identified allelic associations with altered susceptibility to myocardial ischaemia-reperfusion injury in cardiac surgical populations, all based on a candidate gene association approach.[8–12] Thus, the overall influence of common genetic variation on the incidence of PMI remains poorly understood.

Recently, integrated testing of genes involved in the same biological pathway has emerged as an alternative strategy for evaluating the combined effects of multiple genetic variants with small effect size on a disease phenotype.[13–15] Given the polygenic nature of disease susceptibility, this approach is increasingly being used to identify groups of gene variants with shared cellular function that are enriched for disease, while also improving the statistical power of GWAS. In this study, we adopted this strategy by first employing genome-wide association methodology to identify common genetic variants associated with PMI after CABG, followed by pathway-based analyses to uncover biological mechanisms of relevance to PMI.

METHODS

The study design and reporting of the results follow the recommendations by 'Strengthening the Reporting of Genetic Association Studies' (STREGA).[16] We performed a joint two-stage[17] GWAS combined with a pathway analysis approach.

Patient populations

The stage I cohort (discovery cohort) comprised 1493 ethnically diverse subjects who underwent an isolated CABG with cardiopulmonary bypass for the first time and were enrolled between 2002 and 2003 in the Institutional Review Board (IRB) approved Genetics of Myocardial Outcomes and Graft Failure (GeneMAGIC) ancillary substudy of the multicentre Project of Ex-vivo Vein Graft Engineering via Transfection (PREVENT-IV).[18] Of those, 1433 patients met eligibility requirements after applying quality control criteria and excluding patients with missing genotypes or phenotypic information.

In stage II, we tested the top genetic variants in an expanded data set in which an additional 622 patients of self-reported European ancestry were added to the discovery data set, leading to a total of 2055 patients. The additional patients underwent CABG with cardiopulmonary bypass between 1997 and 2006 as part of the Perioperative Genetics and Safety Outcomes Study, an IRB-approved longitudinal study at the Duke University Medical Center.[11 12]

Definition of PMI

PMI was defined according to the universal definition of MI[19] as an elevation in the plasma level of creatine kinase MB isoenzyme (CK-MB) that was >10 times the upper limit of normal, as measured by a core laboratory within 24 h after surgery, and that was not attributable to an intervening clinical event or preoperative MI (adjudicated by the PREVENT-IV Clinical Events Committee).[18]

Genotyping and quality controls

Genomic DNA was isolated from whole blood or saliva using standard procedures. Genotyping in both cohorts was performed on the Illumina Human610-Quad BeadChip at the Duke Genomic Analysis Facility. Sample and genotype quality control of data flow included assessment of call rates, gender check, cryptic relatedness, SNP missingness and the Hardy-Weinberg equilibrium, as previously described.[20] We used principal components derived from the EIGENSTRAT[21] method to control for population stratification (see online supplementary methods).

Statistical analysis

Univariate regression analysis was performed to test differences in demographic, clinical and procedural characteristics between patients with and without postoperative MI; statistically significant covariates were subsequently used to adjust genetic association tests. Genome-wide association analyses performed in the stage I cohort used multivariable logistic regression models implemented in PLINK 1.07, assuming an additive genetic model, and including significant clinical covariates and the top 10 principal components to adjust for population stratification (see online supplementary table S1). Statistical significance for stage I analyses was a priori arbitrarily defined as a two-tailed $p<0.001$, to balance between the overly conservative Bonferroni correction and type II error, given that we had an a priori defined replication data set to obviate type I error. In stage II analyses, the same clinical covariate and principal component adjustments (re-estimated for the expanded data set) were applied, with statistical significance defined as a Bonferroni adjusted p value of 0.05/number of SNPs identified in stage I, to control the overall type I error rate. Haplotype association analysis was performed in the stage II cohort for genes tagged by the significant SNPs, adjusting for the same clinical covariates and principal components. Secondary analyses were performed for the top SNPs identified in the stage II cohort, using the continuous phenotype of CK-MB values and a dichotomised extreme CK-MB

phenotype, which included participants within the first and fourth quartiles of the CK-MB distribution. For CK-MB, a linear regression model was applied with adjustment for the same set of covariates as in the primary analysis. For the extreme CK-MB subset, we reassigned trait status as '0' for participants within the first CK-MB quartile, and '1' for participants within the fourth CK-MB quartile from the stage II cohort. Logistic regression with the same set of covariates was performed. Finally, we employed pathway analysis to prioritise association results and provide biological interpretation, using functional ontology enrichment analysis tools implemented in MetaCore (GeneGO, St. Joseph, MI; see online supplementary methods).

RESULTS

PMI was observed in 112 of 1433 patients (7.8%) and in 225 of 2055 patients (10.9%) in stage I and II cohorts, respectively (see online supplementary table S2). Aortic cross-clamp time, number of coronary artery grafts, and procedures in addition to CABG were significantly associated with PMI in stage I analyses. Stage II analyses showed that extracardiac arteriopathy and year of surgery also played significant roles. All the clinical variables identified above were included in multivariable logistic regression models to adjust the genetic association tests for potential confounders (see online supplementary table S2).

After applying quality control criteria (see online supplementary methods: A.1. Quality control of data flow), 534 390 markers were analysed for association with PMI in stage I. While none of the SNPs reached genome-wide significance (figure 1), 521 SNPs met the a priori defined discovery threshold of $p<0.001$ (minimum $p=2.76\times10^{-6}$, rs2044061 on chromosome 8) and were subsequently analysed in stage II (see online supplementary table S10). A quantile-quantile (Q-Q) plot of observed versus expected p values showed that the population substructure was well adjusted for (see online supplementary figure S2).

In stage II analyses, eight of the 521 SNPs met the Bonferroni correction threshold ($p<9.6\times10^{-5}$ for 521 SNPs). The top 2 SNPs (rs10454444 and rs10913237), located in the pregnancy-associated plasma protein A2 gene (*PAPPA2*), were in high linkage disequilibrium, with p values for stage II of 2.43×10^{-6} (OR 0.46; 95% CI 0.33 to 0.63) and 2.47×10^{-6} (OR 0.46; 95% CI 0.33 to 0.63), respectively. In addition, one intronic SNP in histone deacetylase-4 (*HDAC4*), two in the SEC24 family, member D (*SEC24D,* a member of the cytoplasmic coat protein complex II, COPII), and two located in intergenic regions were associated with PMI (table 1).

When CK-MB was tested as a quantitative trait, all eight SNPs remained significantly associated with plasma levels of CK-MB. However, rs4834703 in *SEC24D* ($p=7.72\times10^{-6}$) and rs10200850 in *HDAC4* ($p=8.26\times10^{-5}$) showed the strongest association, followed by the 2 SNPs in *PAPPA2* ($p=0.0001$; table 2). When the dichotomised extreme CK-MB phenotype was studied in the stage II cohort, only the 2 SNPs located in *SEC24D* (rs4834703 and rs6822035, $p=0.002$) and rs609418 in the intergenic region between *RFXAP* and *SMAD9* ($p=0.001$) remained nominally significant (table 2). Overall, the rs4834703 SNP in *SEC24D* consistently showed strong association signals across postoperative MI, quantitative CK-MB and the extreme CK-MB traits.

The haplotype structures of genic regions surrounding the significant SNPs in *PAPPA2*, *HDAC4* and *SEC24D* are shown in online supplementary figure S3, and the results of haplotype analysis are shown in table 3 and online supplemental table S3. Haplotype analysis performed for the linkage disequilibrium blocks containing the significant markers showed that the A-A haplotype (rs6822035, rs10518325) in *SEC24D* had the most

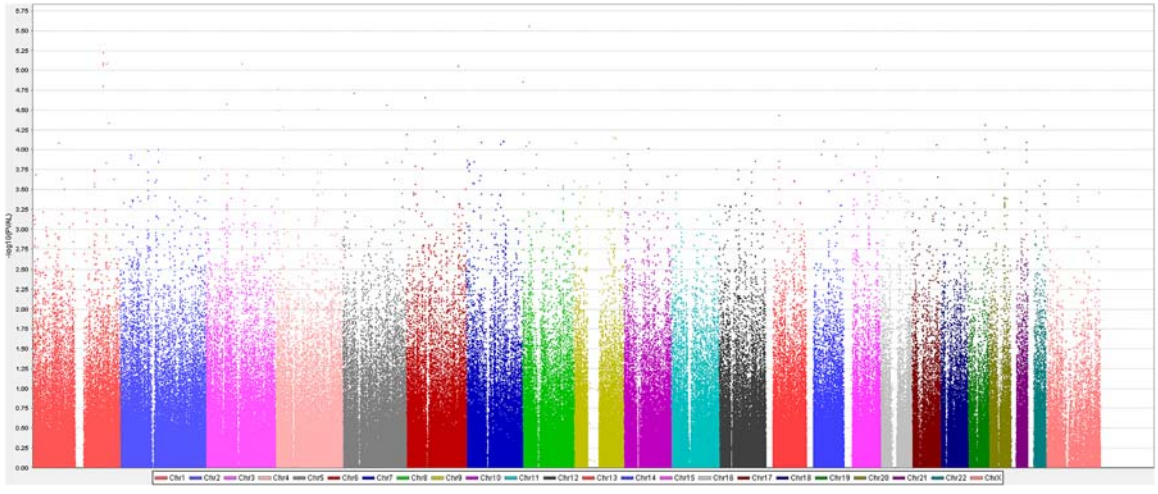

Figure 1 Manhattan plot of genome-wide association with perioperative myocardial infarction in stage I analysis. The x axis represents the genome in physical order (coloured by chromosome); the y axis showing $-\log_{10}(p)$ for all single nucleotide polymorphisms (SNPs). None of the SNPs reached genome-wide significance ($p<9.09\times10^{-8}$), but 521 SNPs met the prespecified discovery threshold $p<0.001$ for inclusion in stage II analyses (minimum $p=2.76\times10^{-6}$, rs2044061 on chromosome 8).

Table 1 Top eight SNP associated with postoperative myocardial infarction

Chr	SNP	Base pair	Gene symbol	Stage I: discovery data set*				Stage II: expanded data set*			
				MAF				MAF			
				Controls N=1321	Cases N=112	OR (95% CI)	p Value	Controls N=1830	Cases N=225	OR (95% CI)	p Value
1	rs10489478	176 566 350	*PAPPA2*	0.18	0.09	0.41 (0.25 to 0.66)	2.67×10^{-4}	0.18	0.11	0.47 (0.34 to 0.65)	4.70×10^{-6}
1	rs10913237	176 630 416	*PAPPA2*	0.18	0.09	0.39 (0.24 to 0.64)	1.85×10^{-4}	0.19	0.11	0.46 (0.33 to 0.63)	2.47×10^{-6}
1	rs10454444	176 649 181	*PAPPA2*	0.18	0.09	0.39 (0.24 to 0.64)1	1.81×10^{-4}	0.19	0.11	0.46 (0.33 to 0.63)	2.43×10^{-6}
2	rs10 200 850	240 234 901	*HDAC4*	0.06	0.13	2.22 (1.42 to 3.46)	4.34×10^{-4}	0.06	0.11	2.23 (1.57 to 3.17)	8.18×10^{-6}
4	rs4834703	119 691 624	*SEC24D*	0.09	0.18	2.27 (1.54 to 3.34)	3.13×10^{-5}	0.09	0.16	1.98 (1.47 to 2.66)	6.80×10^{-6}
4	rs6822035	119 710 421	*SEC24D*	0.29	0.40	1.73 (1.29 to 2.33)	2.59×10^{-4}	0.28	0.36	1.65 (1.32 to 2.05)	9.55×10^{-6}
12	rs2303970	74 471 340	*TRHDE*|*LOC552889*	0.48	0.35	0.58 (0.43 to 0.78)	3.51×10^{-4}	0.48	0.36	0.62 (0.50 to 0.76)	8.89×10^{-6}
13	rs609418	37 417 427	*RFXAP*|*SMAD9*	0.25	0.35	1.73 (1.28 to 2.33)	3.14×10^{-4}	0.25	0.33	1.67 (1.34 to 2.09)	5.81×10^{-6}

*Adjusted for clinical characteristics including extracardiac arteriopathy, recent myocardial infarction, procedure other than CABG only, year of surgery, number of diseased vessels and aortic cross-clamp time.
HDAC4, histone deacetylase-4; *PAPPA2*, pregnancy-associated plasma protein A2; *RFXAP*, regulatory factor X-associated protein; *SEC24D*, SEC24-related protein D; *SMAD9*, mother against decapentaplegic homolog 9; *TRHDE*, thyrotropin-releasing hormone-degrading ectoenzyme; intergenic region is expressed by two franking genes with '|' in between.
CABG, coronary artery bypass grafting; Chr, chromosome; MAF, minor allele frequency (based on the discovery data set); SNP, single nucleotide polymorphisms.

significant association with postoperative MI ($p=5.54\times10^{-7}$, OR 1.87; 95% CI 1.46 to 2.39, table 3).

In multivariate risk factor-adjusted stage I and II analyses, we found no evidence for association between genetic variation at the 9p21 locus and incident postoperative MI, including the rs10116277 SNP previously associated with MI and mortality in non-surgical[20] and cardiac surgical[8 9] cohorts (see online supplementary figure S4).

The top 10 enriched pathway maps for the stage I analysis SNPs are shown in online supplementary figure S5. The most significant were 'Cell adhesion: extracellular matrix remodelling' and 'Cytoskeleton remodelling: TGF, WNT, and cytoskeletal remodelling' (enrichment p value=1.9×10^{-8} and 7.3×10^{-6}, respectively). The most significant canonical pathway maps in stage I and II comparative analyses were 'Immune response: NFAT signalling and leucocyte interaction' and 'Cell adhesion: extracellular matrix remodelling' ($p=7.2\times10^{-4}$ and 1.1×10^{-3}, respectively; see online supplementary tables S4 and 5).

DISCUSSION

We present the first report of a two-stage GWAS involving 225 PMI cases and 1830 controls. After accounting for clinical and procedural covariates, we identified eight significant SNPs mapped to three genes (*PAPPA2*, *HDAC4*, *SEC24D*) and two intergenic regions. The most significant association with PMI was exhibited by rs10454444 in *PAPPA2* ($p=2.43\times10^{-6}$) in single-marker analyses, by *SEC24D* A-A (rs6822035, rs10518325, $p=5.54\times10^{-7}$) in haplotype analyses, and by *SEC24D* SNPs in secondary analyses when CK-MB was evaluated as a quantitative trait (rs4834703, $p=2.43\times10^{-6}$) or as an extreme CK-MB phenotype (rs4834703 and rs6822035, p=0.002).

Among these eight SNPs, rs4834703 in *SEC24D* showed the most consistently strong association with all three phenotypes evaluated in this study. The transport protein *SEC24D* is an integral component of cytoplasmic COPII transport machinery, a key player in vesicle trafficking of secretory proteins from the endoplasmic reticulum (ER) to the Golgi apparatus for delivery to downstream compartments. COPII is responsible for cargo sorting and vesicle morphogenesis, with roles in modulating ER exit, cell surface transport, lipid secretion and cholesterol biosynthesis, and function of G protein-coupled receptors. Conditions of ischaemia, oxidative injury or acute phase-response result in ER stress through accumulation of misfolded proteins, which leads to activation of the unfolded protein response (UPR) signalling pathway. If the protective mechanisms activated by the UPR are insufficient, cells die by apoptosis and autophagy. However, altered expression or function of SEC24 proteins could also explain ER trapping of misfolded proteins under conditions of ER stress,[22 23] with SEC24D being the only isoform implicated in extracellular matrix secretion.[24] Animal

Table 2 Association of the top eight SNP with CK-MB as a quantitative trait and as an extreme phenotype in the joint analysis data set

Chr	SNP	Base pair	Gene symbol	MAF (Overall)	CK-MB as a quantitative trait*		CK-MB as an extreme phenotype*	
					β-Coefficient	p Value	OR (95% CI)	p Value
1	rs10489478	176 566 350	*PAPPA2*	0.17	–5.40	2.27×10^{-4}	0.77 (0.574 to 1.047)	0.1
1	rs10913237	176 630 416	*PAPPA2*	0.18	–5.58	1.30×10^{-4}	0.78 (0.578 to 1.052)	0.1
1	rs10454444	176 649 181	*PAPPA2*	0.18	–5.59	1.21×10^{-4}	0.77 (0.575 to 1.043)	0.09
2	rs10200850	240 234 901	*HDAC4*	0.07	9.26	8.26×10^{-5}	1.49 (0.950 to 2.326)	0.08
4	rs4834703	119 691 624	*SEC24D*	0.10	8.54	7.72×10^{-6}	1.82 (1.242 to 2.654)	0.002
4	rs6822035	119 710 421	*SEC24D*	0.30	4.42	4.81×10^{-4}	1.48 (1.152 to 1.903)	0.002
12	rs2303970	74 471 340	*TRHDE|LOC552889*	0.47	–2.93	0.01	0.84 (0.669 to 1.047)	0.12
13	rs609418	37 417 427	*RFXAP|SMAD9*	0.26	4.80	2.26×10^{-4}	1.56 (1.189 to 2.034)	0.001

*Adjusted for clinical characteristics including extracardiac arteriopathy, recent myocardial infarction, procedure other than CABG only, year of surgery, number of diseased vessels, and aortic cross-clamp time using either linear regression (B-coefficient) or logistic regression (OR, 95% CI) analyses.
HDAC4, histone deacetylase-4; *PAPPA2*, pregnancy-associated plasma protein A2; *RFXAP*, regulatory factor X-associated protein; *SEC24D*, SEC24-related protein D; *SMAD9*, mother against decapentaplegic homolog 9; *TRHDE*, thyrotropin-releasing hormone-degrading ectoenzyme.
CABG, coronary artery bypass grafting; Chr, chromosome; CK-MB, creatine kinase MB isoenzyme; MAF, minor allele frequency (based on the expanded data set); SNP, single nucleotide polymorphisms.

models of defects in *SEC24D* involve characteristic skeletal malformations, whereas its complete disruption results in early-embryonic lethality.[25] However, there are no reports of human diseases associated with genetic variation in *SEC24D*.

PAPPA2 is a metalloproteinase that regulates local insulin-like growth factor (IGF) bioavailability by specifically cleaving IGF-binding protein 5 (IGFBP-5). In experimental models of myocardial ischaemia, IGFBP-5 inhibits both myocardial IGF-1, with implications for inflammation-linked angiogenesis and repair processes,[26] and IGF-2, limiting its cardioprotective effects following ischaemia reperfusion.[27 28] The related protein PAPPA1 cleaves IGFBP-4 and is activated and released from vulnerable atherosclerotic plaques. PAPPA1 has been extensively studied as a cardiovascular risk biomarker for the diagnosis and prognosis of acute coronary syndrome;[29 30] however, the role of PAPPA2 in cardiovascular biology has not been previously reported. Consistent with our single-marker analysis findings, the GWAS pathway analysis identified significant contributions of variants in other IGF system component genes, namely IGF-2 and the IGF-1 receptor (see online supplementary figure S6 and table S5).

HDAC4, a member of the HDAC family, mediates changes in the chromatin structure by removing acetyl groups from the core histones, resulting in transcriptional repression. HDAC4 is highly expressed in the myocardium, where it plays an important role in the regulation of gene expression and is involved in myocardial cell cycle progression, differentiation and apoptosis.[31] Experimental HDAC inhibition is associated with a profound reduction in ischaemia-induced myocardial cell death,[31] by triggering preconditioning effects and

Table 3 Estimated haplotype frequencies in the *SEC24D* gene and results of association tests with incidence of PMI in the stage II analysis cohort (n=2055)

SNP1	SNP2	Haplotype	Haplotype frequency		OR (95% CI)	p Value
			Patients with PMI (n=225)	Patients without PMI (n=1830)		
rs6828577	rs6822035	A-A	0.3956	0.2874	1.65 (1.33 to 2.06)	8.84×10^{-6}
rs6828577	rs6822035	G-C	0.6044	0.7126	Reference	
rs6822035	rs10518325	A-G	0.03516	0.0528	0.86 (0.43 to 1.70)	0.657
rs6822035	rs10518325	C-G	0.009083	0.02636	1.39 (0.67 to 2.90)	0.378
rs6822035	rs10518325	A-A	0.3631	0.2358	1.87 (1.46 to 2.39)	5.54×10^{-7}
rs6822035	rs10518325	C-A	0.5927	0.685	Reference	
rs10518325	rs11098451	A-A	0.03097	0.06231	0.76 (0.48 to 1.19)	0.225
rs10518325	rs11098451	G-G	0.04425	0.07845	0.87 (0.58 to 1.31)	0.509
rs10518325	rs11098451	A-G	0.9248	0.8592	Reference	

Adjusted for clinical characteristics including extracardiac arteriopathy, recent myocardial infarction, procedure other than CABG only, year of surgery, number of diseased vessels, aortic cross-clamp time.
CABG, coronary artery bypass grafting; PMI, perioperative myocardial infarction; SNP, single nucleotide polymorphism.

promoting myocardial repair. Genetic variants in HDACs are important determinants of susceptibility to cardiovascular diseases,[32] suggesting functional roles for HDAC4 in modulating perioperative myonecrosis, and their potential use in predicting individual patient responsiveness to HDAC inhibition.

One of the intergenic SNPs associated with PMI (rs609418) is located near the mother against the decapentaplegic homologue 9 (*SMAD9*) gene, part of the transforming growth factor β (TGF-β) signalling pathway, which is markedly activated in the infarcted myocardium. Members of the TGF-β superfamily transduce their signal from the membrane to the nucleus via a distinct combination of transmembrane receptors and downstream effectors—the SMAD proteins.[33] TGF-β plays important and complex roles in regulating postinfarction inflammatory responses. In animal models, signalling through the SMAD transcription factors is associated with resolution of inflammation, repression of cytokine and chemokine gene synthesis, and protection against myocardial ischaemia-reperfusion injury.[34] Consistent with this single-locus gene association result, the bone morphogenetic protein pathway, which also transduces its signals via a SMAD9-dependent cascade, was identified as one of the top-scoring pathways in our GWAS pathway analysis ($p=5.2\times10^{-3}$, see online supplementary table S7). Although no direct functional roles are currently attributed to this intergenic region, a query of the Regulome and Haploreg databases reports that rs609418 is located within active regulatory elements (GATA2 transcription factor binding site by ENCODE ChIP-seq and altering regulatory motifs in Gfi1 and Mef2 by the Position-Weight Matrix, see online supplementary figure S7).

Surprisingly, we have been unable to replicate previously reported associations between common genetic variants at the 9p21 locus and risk for PMI or mortality after CABG.[8 9] Many different reasons may account for this, including inadequate sample size, variation in study design, differences in allele frequencies or variability in the definition of PMI phenotype.[35] Indeed, our observation is consistent with other studies showing that, although genetic variants at the 9p21 locus are associated with incident coronary artery disease (CAD), they may not be associated with the actual risk of MI.[36] This discrepancy between convincing associations of 9p21 with a greater burden of CAD but not with MI in the presence of underlying CAD has been further confirmed by nested case–control studies[37] as well as meta-analyses.[5 38 39] Taken together, in subjects with established CAD, such as those included in our study, any lack of association of the 9p21 locus with subsequent MI could have resulted from the presence of CAD in carriers and non-carriers of the risk variants at the 9p21 locus, which seems to primarily mediate an atherosclerotic phenotype.

The strengths of our study are (1) a relatively large population of cardiac surgery patients, (2) a prospective cohort design and (3) a combination of complementary single-marker and pathway-based genome-wide association analyses. This approach allowed us to identify genetic variants that carry only a small disease risk individually, but that jointly can contribute relatively large effects on PMI susceptibility. Furthermore, an application of results from pathway-based analysis may add structure to interpreting genomic data and allow exploration of cellular processes that functionally underpin the observed associations. Finally, by using this approach, replication of association findings at the gene and pathway level is much easier compared to replication at the individual SNP level.[13] Of note, most of the genes identified through pathway enrichment analysis in this study encode targets for therapeutic drugs that have already been developed. Thus, by improving risk assessment and identifying allele-specific therapeutic responses, further investigation of loci and pathways prioritised in this study could yield actionable results for enhancing perioperative cardioprotection.

Several limitations are worth mentioning. Power calculations (see online supplementary results B.6.) show that, based on the current sample size and incidence of PMI, our study can detect a genotypic relative risk approximately 2 with 80% power (assuming a variant with a 10% minor allele frequency and a realistic linkage disequilibrium between the tested marker and the causal locus $D'=0.8$). Thus, although our study is the largest genetic association study of PMI conducted to date, it is powered to detect only common variants with relatively large effect sizes. Most published genetic association studies of PMI have reported larger effect sizes compared with ambulatory populations (OR range 1.79–3.97).[8 10 11] The possibility of rare genetic variants that drive a pronounced clinical phenotype was not explored in this study, because only variants with minor allele frequencies >0.05 were assessed. Also, functional studies to further elucidate the potential biological effects of the SNPs identified were not feasible due to lack of plasma or tissue availability in the GeneMAGIC study. Finally, patients enrolled in our cohorts were predominantly Caucasian, and therefore our findings cannot be generalised to other ethnic groups.

In conclusion, we report the first GWAS in a cohort of patients at risk for MI after CABG surgery. On the basis of our integrated approach utilising primary (PMI) and secondary phenotypes (quantitative CK-MB, extreme CK-MB), single-marker analysis and pathway analysis, we identified several polymorphisms in the insulin growth factor system implicated in the regulation of extracellular matrix remodelling, as well as the ER-to-Golgi secretory pathway potentially involved in adaptive responses to ER stress. As other GWAS of PMI cohorts publish their results, we intend to collaborate on conducting a meta-analysis for this particular phenotype. While our GWAS results are intriguing, follow-up studies are needed to translate these initial findings into biological insights that could lead to predictive and therapeutic advances in perioperative care. For instance, in the

regions of confirmed associations, causal variants will only occasionally be among those directly genotyped. Moreover, GWAS detect almost exclusively the effects of common SNPs, offering limited power to capture any rare and structural variants, such as insertions, deletions, inversions and translocations. Detailed sequencing may be necessary to further characterise the genetic variations in the PMI-associated regions to enhance the identification of causal variants. Furthermore, as in most cases, the functions of identified genes and their variants, as well as the mechanisms by which they may contribute to PMI pathophysiology, are largely unknown. Currently, very few existing groups can bridge from genetics to molecular biology or cell physiology and to disease or novel therapy; we propose to examine the mechanisms by which variation in the observed genes is involved in myocardial ischaemia-reperfusion injury by examining their functional effects in the human myocardium from patients undergoing cardiac surgery, as well in our previously described preclinical rodent and swine models of cardioplegic arrest and cardiopulmonary bypass.[40] The use of such animal models would allow pharmacological studies targeting the identified pathways to explore the mechanism by which novel cardioprotective drugs would attenuate myocardial ischaemia-reperfusion injury, with the ultimate goal of developing personalised cardioprotective strategies.

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Contributors MDK contributed to the analysis and interpretation of data, as well as the drafting of the manuscript. Y-JL contributed to the analysis and interpretation of data and a critical revision of the manuscript. Y-JL and Y-WL contributed to the quality control and analysis of the data. JA, MFN, PKS, DJ and JPM contributed to the acquisition of data and a critical review of the manuscript. MVP contributed to the conception and design, analysis and interpretation of data, critical manuscript review and approved the final version of the submitted manuscript.

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Competing interests None.

Patient consent Obtained.

Ethics approval The Duke University School of Medicine Institutional Review Board.

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SUPPLEMENTAL MATERIAL

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Perioperative Genetics and Safety Outcomes Study (PEGASUS) Investigative Team Members

Allen AS, Davis RD, Funk B, Gaca JG, Ginsburg GS, Glower DD, Goldstein DB, Grichnik KP, Hall RL, Hauser E, Jones R, Kertai MD, Laskowitz DT, Li YJ, Lodge AJ, Mathew JP, Milano CA, Moretti EW, Newman MF, Phillips-Bute B, Podgoreanu MV, Smith MP, Smith PK, Stafford-Smith M, Swaminathan M, Welsby IJ, White WD, Willard HF

A. SUPPLEMENTAL METHODS

A.1. Quality control of data flow

The following quality control steps were taken to make sure that genotypes were correctly called.

- Infinium BeadStudio raw data analysis: Any sample that had a very low intensity or a very low call rate using the standard Illumina cluster (< 95%) was deleted. All SNPs that had a call frequency below 100% were then reclustered. Any sample that was below a 98% call rate after reclustering was deleted. Next, all SNPs that had a call frequency below 99% were deleted. Any SNPs for which >1% of samples were not called or were ambiguously called were deleted. A total of 35 samples (13 in GeneMagic and 22 in PEGASUS cohort) were deleted during this procedure.
- Minor allele frequency (MAF) check for data handling accuracy: This step performs a basic check of the data accuracy on the data flow pipeline from the output of the Illumina genotyping facility to the analytical process. We checked the MAF report from PLINK software against the original locus report generated by the genotyping facility, and ensured that the 2 matched exactly.
- Gender specification: This step compares the observed genotypes on chromosomes X and Y to the gender specification obtained from the phenotype database. Samples with X-chromosomal heterozygosity that was inconsistent with reported gender were individually inspected against the original data source. A total of 11 samples could not be reconciled and were excluded at this step (8 in GeneMagic and 3 in PEGASUS cohort)
- Cryptic relatedness: We estimated the sharing of genetic information between cohort participants by calculating identity by descent (IBD) using PLINK software. All pairs with DNA samples showing ≥ 0.125 estimated proportion of alleles IBD were inspected, and one sample from each pair was excluded from further analyses. A total of 9 samples (all in PEGASUS cohort) were excluded at this step.
- Genotype missing: This step assesses whether the genotype missing is skewed toward cases or controls, which could give rise to spurious association p-values. We used PLINK software to perform this check on the top SNPs discussed in the paper.

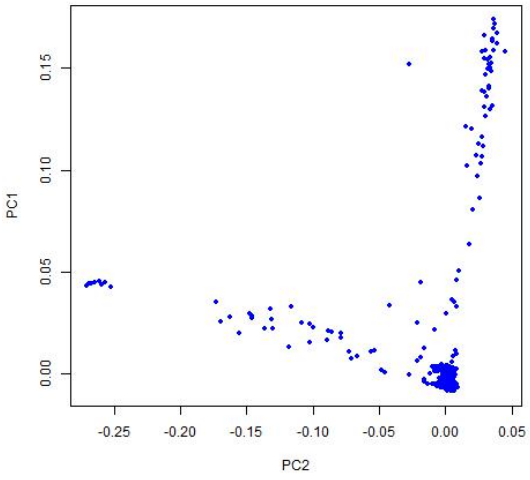
- Low MAF: We removed all SNPs with MAF < 0.01 in order to control for error in the estimation of asymptotic p-values, as alleles with such a low MAF would have no chance of approaching significance based on our sample size and perioperative MI incidence.
- Hardy-Weinberg Equilibrium (HWE): We used PLINK software to identify any observed genotypes that deviated from HWE. All markers that significantly deviated from HWE ($p < 10^{-6}$) were excluded.

Analyses were performed using PLINK 1.07, SAS/Genetics version 9.2, and R version 2.15.1.

A.2. Controlling for population stratification

We used a modified EIGENSTRAT method to control for population stratification.[1] This method derives the principal components of the correlations among the gene variants, and corrects for those correlations in the association tests. Population structure was investigated using the EigenSoft program. All 15 principal components (PCs) were computed for both datasets. Plots between pairwise PCs, particularly PC1 vs PC2, were generated to determine whether any obvious outliers deviated from the main cluster, and hence, had to be excluded from subsequent analyses (**Supplemental Figure S1**).

Supplemental Figure S1. Comparison of PC1 vs PC2 reveals potential population stratification in the discovery (Gene-Magic) dataset.



In addition, we performed multivariate regression analyses using a strategy to keep all PCs up to the last PC with $p < 0.05$ in each step, to determine the number of PCs to be used for correction in the final analysis. For instance, starting with 15 PCs in the model, if PC(i) is the last PC with $p < 0.05$, we included PC(1) to PC(i) in the next multivariate model, and then repeated the process until the last PC remained nominally significant. Using this iterative multivariate analysis, we found that the top 10 PCs were a reasonable set for the Gene-Magic dataset ($p = 0.032$), and were subsequently re-estimated and used for stage II analysis (**Supplemental Table S1**). This final set of 10 PCs was then used as covariates to adjust for ancestry, along with clinical variables, in multivariate logistic regression analysis of perioperative MI.

Supplemental Table S1: Principal component analysis of the study populations

	ANALYSIS OF MAXIMUM LIKELIHOOD ESTIMATES									
	DISCOVERY DATSET					REPLICATION DATASET				
Parameter	**DF**	**Estimate**	**Standard error**	**Wald chi-square test**	**P-value**	**DF**	**Estimate**	**Standard error**	**Wald chi-square test**	**P-value**
Intercept	1	-2.635	0.127	434.325	<0.0001	1	-2.153	0.076	798.277	<0.0001
Principal component 1	1	-31.474	14.214	4.903	0.027	1	18.429	8.413	4.798	0.029
Principal component 2	1	-5.486	3.826	2.056	0.152	1	-4.009	3.338	1.443	0.230
Principal component 3	1	-7.575	3.497	4.691	0.03	1	-3.239	3.230	1.006	0.316
Principal component 4	1	-0.431	3.479	0.015	0.901	1	-1.266	3.119	0.165	0.685
Principal component 5	1	18.941	9.623	3.874	0.049	1	-1.642	4.828	0.116	0.734
Principal component 6	1	0.519	7.944	0.004	0.948	1	-15.494	7.678	4.073	0.044
Principal component 7	1	-2.231	10.001	0.049	0.824	1	12.985	6.873	3.569	0.059
Principal component 8	1	-10.793	9.043	1.424	0.233	1	2.244	4.825	0.216	0.642
Principal component 9	1	29.876	11.661	6.564	0.01	1	-8.120	5.366	2.289	0.130
Principal component 10	1	-22.775	10.593	4.623	0.032	1	7.487	4.650	2.592	0.107

DF, degrees of freedom

A.3. Haplotype analysis

For the final candidate genes prioritized based on the significance of SNP association tests, we first identified the linkage disequilibrium (LD) blocks harboring the significant SNPs. Within each LD block, we performed haplotype association analysis using sliding windows of 3 markers across the region. This was conducted for the expanded dataset, by constructing multivariable logistic regression models adjusting for the same clinical covariates and PCs used for single marker analyses.

A.4. GWAS pathway analysis

SNPs with a covariate-adjusted association p-value < 0.01 in stage I GWAS were subjected to functional ontology enrichment analyses using tools implemented in the MetaCore software suite (GeneGO, St. Joseph, MI). Enrichment analysis begins by assigning SNPs to genes, and matching these geneIDs with geneIDs in functional ontologies in highly curated canonical pathway maps in MetaCore. The aggregation of GWAS associations for the genes in tested pathways, ie, the significance of enrichment, is computed as the p-value of a hypergeometric model.[2] Canonical pathways enriched in stage I and stage II analyses were further compared; and the probability of a random intersection between the set of genes in common in the 2 cohorts, and functional ontology entities was estimated as p-value of a hypergeometric distribution in MetaCore.

B. SUPPLEMENTAL RESULTS

B.1. Patient characteristics

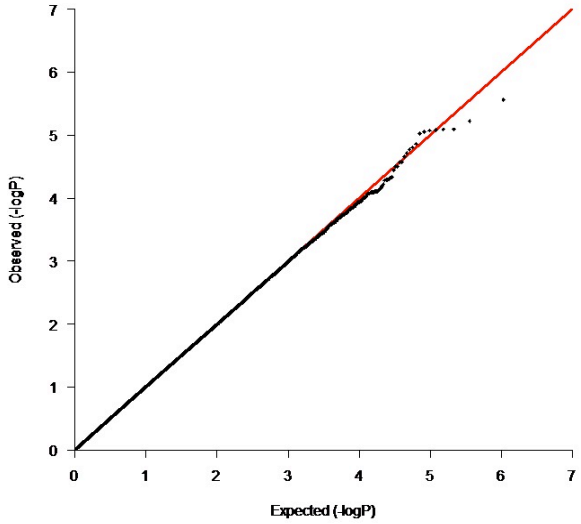
Supplemental Table S2. Clinical characteristics of the study populations

	STAGE I ANALYSIS (N=1433)				STAGE II ANALYSIS (N=2055)			
Characteristics	**No PMI, (n=1321)**	**PMI (n=112)**	**OR (95%CI)**	**P-value***	**No PMI (n=1830)**	**PMI (n=225)**	**OR (95%CI)**	**P-value***
Extracardiac arteriopathy	251 (19.0)	20 (17.9)	0.93 (0.56-1.53)	0.77	754 (41.2)	128 (56.9)	1.88 (1.42-2.49)	<0.0001
Recent myocardial infarction	256 (19.4)	23 (20.5)	1.08 (0.67-1.74)	0.77	393 (21.5)	39 (17.3)	0.77 (0.53-1.10)	0.15
Procedure other than CABG only	126 (9.5)	23 (20.5)	2.45 (1.50-4.02)	0.0004	153 (8.4)	51 (22.7)	3.21 (2.26-4.58)	<0.0001
Year of surgery by year								
1997					26 (1.4)	3 (1.3)	1.0	
1998					70 (3.8)	8 (3.6)	0.99 (0.24-4.02)	0.98
1999					87 (4.8)	3 (1.3)	0.30 (0.06-1.57)	0.15
2000					77 (4.2)	14 (6.2)	1.58 (0.42-5.92)	0.50
2001					49 (2.7)	12 (5.3)	2.12 (0.55-8.20)	0.28
2002	146 (11.1)	9 (8.0)	1.0		188 (10.3)	20 (8.9)	0.92 (0.26-3.32)	0.90
2003	1175 (88.9)	103 (92.0)	1.42 (0.70-2.87)	0.33	1189 (65.0)	109 (48.4)	0.80 (0.24-2.67)	0.71
2004					32 (1.8)	8 (3.6)	2.17 (0.52-9.0)	0.29
2005					80 (4.4)	36 (16.0)	3.90 (1.11-13.72)	0.03
2006					32 (1.8)	12 (5.3)	3.25 (0.83-12.75)	0.09
Number of diseased vessels								
0	67 (5.1)	6 (5.3)	1.0		69 (3.8)	6 (2.7)	1.0	
1	259 (19.6)	29 (25.9)	1.25 (0.50-3.14)	0.63	276 (15.0)	32 (14.2)	1.33 (0.54-3.32)	0.54
2	519 (39.3)	43 (38.4)	0.93 (0.38-2.26)	0.86	595 (32.5)	52 (23.1)	1.01 (0.42-2.43)	0.99
3	476 (36.0)	34 (30.4)	0.80 (0.32-1.97)	0.62	885 (48.4)	130 (57.8)	1.69 (0.72-3.97)	0.22
4					5 (0.3)	5 (2.2)	11.5 (2.58-51.24)	0.0014
Aortic cross clamp time, min	51.2±36.8	71.9±32.4	1.015 (1.01-1.02)	<0.0001	55.0±35.2	80.5±36.7	1.019 (1.015-1.023)	<0.0001

Descriptive statistics of clinical variables are presented as count (percent frequency) for categorical variables and mean ± SD for continuous variables. PMI, postoperative myocardial infarction; CABG, coronary artery bypass surgery; extracardiac arteriopathy, defined as any one or more of the following: claudication, carotid occlusion or > 50% stenosis, and/or previous or planned intervention on the abdominal aorta, limb arteries or carotids; OR (95%CI), univariate odds ratio (95% confidence interval). *Comparisons made using the *t*-test or Wald chi-square test, as appropriate. Clinical variables were included in the final multivariate logistic regression analysis if significant ($p < 0.05$) in univariate analyses.

B.2. Single-locus GWAS analysis - population structure adjustment

Supplemental Figure S2. Quantile - Quantile (Q-Q) plot representation of the GWAS association results in the discovery dataset

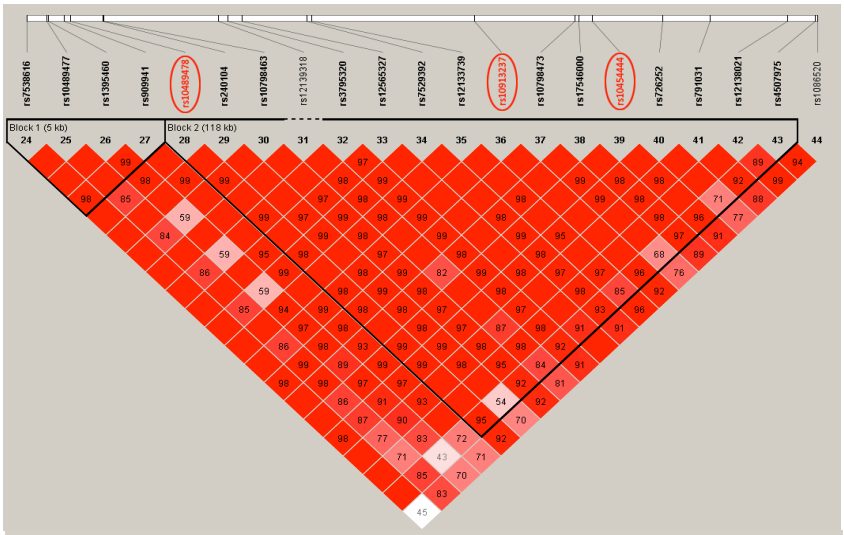


Distribution of expected (under the null hypothesis) vs observed p-values for single nucleotide polymorphisms that are associated with perioperative myocardial infarction, based on a whole genome-wide analysis. The red diagonal line represents the line obtained if the observed distribution did not deviate from the expected distribution. All p-values were corrected for the inflation factor ($\lambda = 1.0073$).

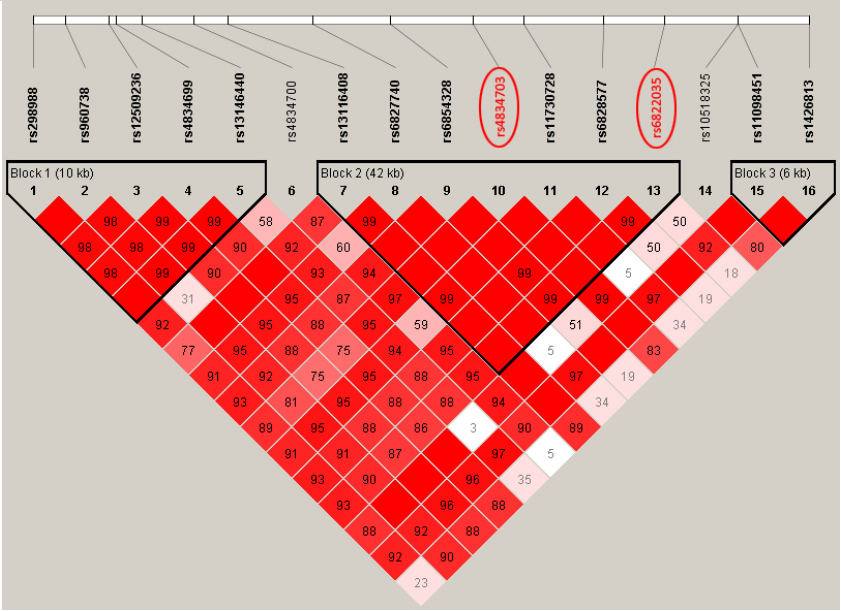
B.3. Haplotype analysis of genes harboring top scoring SNPs

Supplemental Figure S3. Linkage disequilibrium (LD) structures of **[A]** *PAPPA2* (1q23-q25 chromosome region), **[B]** *SEC24D* (4q26 chromosome region), and **[C]** *HDAC4* (2q37.3 chromosome region), and displayed as pairwise correlation plots using HapMap database (CEU European ancestry) (Haploview). Regions of LD are shaded in bright red (strong LD) and lighter for moderate or weak LD. The physical location of the individual SNPs associated with perioperative myocardial infarction in 2-stage analyses is circled in red. True haplotype blocks in the population are marked with black lines in the correlation plot.

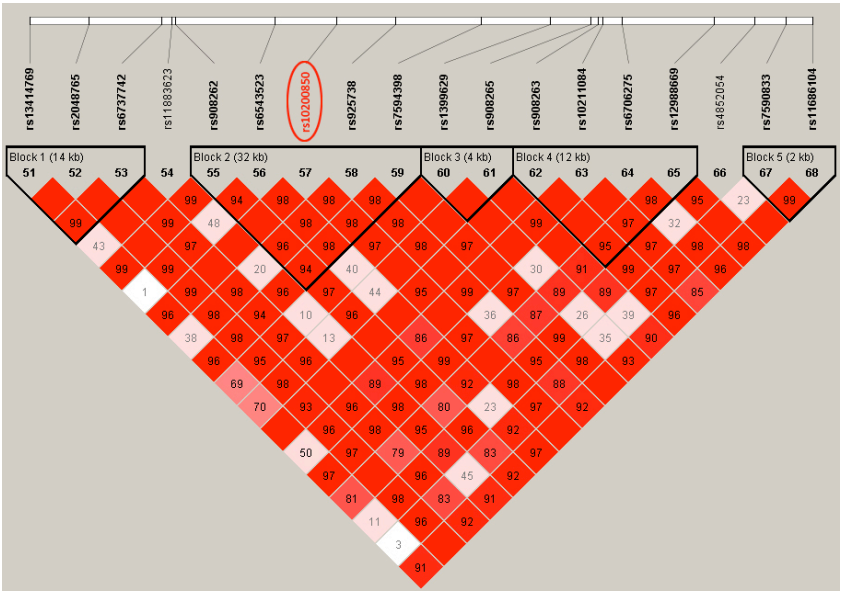
A. *PAPPA2* gene



B. *SEC24D* gene



C. *HDAC4* gene



Supplemental Table S3. Results of the haplotype analyses for *PAPPA2 and HDAC4*

CHR	GENESYMBOL	BP1	BP2	SNP1	SNP2	HAPLOTYPE	F	OR	STAT	P
1	PAPPA2	176562608	176562796	RS10489477	RS1395460	AA	0.166	0.464	19.5	1.01E-05
1	PAPPA2	176562608	176562796	RS10489477	RS1395460	GG	0.655	1.43	9.56	0.00199
1	PAPPA2	176562608	176562796	RS10489477	RS1395460	GA	0.179	1.08	0.292	0.589
1	PAPPA2	176562796	176565307	RS1395460	RS909941	AG	0.344	0.698	9.56	0.00198
1	PAPPA2	176562796	176565307	RS1395460	RS909941	GA	0.576	1.29	5.58	0.0182
1	PAPPA2	176562796	176565307	RS1395460	RS909941	GG	0.0786	1.22	1.16	0.282
1	PAPPA2	176565307	176566350	RS909941	RS10489478	GA	0.175	0.474	20.8	4.98E-06
1	PAPPA2	176565307	176566350	RS909941	RS10489478	AG	0.578	1.29	5.55	0.0184
1	PAPPA2	176565307	176566350	RS909941	RS10489478	GG	0.248	1.19	2.17	0.141
1	PAPPA2	176566350	176571431	RS10489478	RS240104	AG	0.175	0.474	20.8	4.98E-06
1	PAPPA2	176566350	176571431	RS10489478	RS240104	GG	0.589	1.25	4.47	0.0345
1	PAPPA2	176566350	176571431	RS10489478	RS240104	GA	0.237	1.23	3.16	0.0754
1	PAPPA2	176571431	176571578	RS240104	RS10798463	GG	0.241	0.631	12.2	0.000477
1	PAPPA2	176571431	176571578	RS240104	RS10798463	AA	0.237	1.23	3.16	0.0754
1	PAPPA2	176571431	176571578	RS240104	RS10798463	GA	0.522	1.17	2.38	0.123
1	PAPPA2	176571578	176589732	RS10798463	RS12139318	GC	0.193	0.515	18.8	1.45E-05
1	PAPPA2	176571578	176589732	RS10798463	RS12139318	AC	0.759	1.58	12.2	0.000477
1	PAPPA2	176571578	176589732	RS10798463	RS12139318	GA	0.0485	1.28	1.24	0.266
1	PAPPA2	176589732	176591291	RS12139318	RS3795320	CC	0.197	0.5	20.3	6.47E-06
1	PAPPA2	176589732	176591291	RS12139318	RS3795320	CA	0.755	1.62	13.4	0.000248
1	PAPPA2	176589732	176591291	RS12139318	RS3795320	AC	0.0485	1.28	1.24	0.266
1	PAPPA2	176591291	176593524	RS3795320	RS12565327	CG	0.245	0.616	13.4	0.000256
1	PAPPA2	176591291	176593524	RS3795320	RS12565327	AG	0.675	1.49	11.4	0.00075
1	PAPPA2	176591291	176593524	RS3795320	RS12565327	AA	0.0795	1.02	0.0109	0.917
1	PAPPA2	176593524	176603840	RS12565327	RS7529392	GA	0.244	0.618	13.2	0.000274
1	PAPPA2	176593524	176603840	RS12565327	RS7529392	GG	0.676	1.49	11.3	0.000796
1	PAPPA2	176593524	176603840	RS12565327	RS7529392	AG	0.0801	1.02	0.00645	0.936

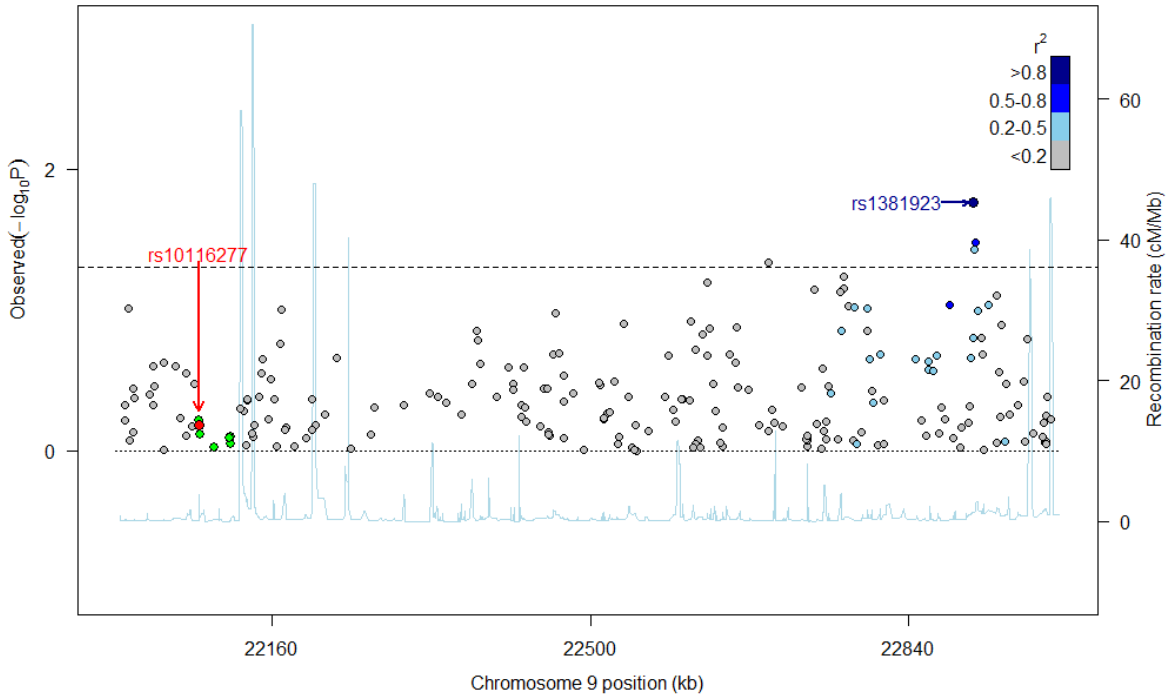
1	PAPPA2	176603840	176604564	RS7529392	RS12133739	AA	0.177	0.46	22.2	2.52E-06
1	PAPPA2	176603840	176604564	RS7529392	RS12133739	GA	0.756	1.62	13.3	0.000264
1	PAPPA2	176603840	176604564	RS7529392	RS12133739	AG	0.0675	1.23	1.13	0.288
1	**PAPPA2**	**176604564**	**176630416**	**RS12133739**	**RS10913237**	**AA**	**0.176**	**0.46**	**22.1**	**2.56E-06**
1	PAPPA2	176604564	176630416	RS12133739	RS10913237	AG	0.756	1.62	13.3	0.000269
1	PAPPA2	176604564	176630416	RS12133739	RS10913237	GG	0.0674	1.23	1.13	0.288
1	**PAPPA2**	**176630416**	**176646383**	**RS10913237**	**RS10798473**	**AG**	**0.176**	**0.461**	**22.1**	**2.65E-06**
1	PAPPA2	176630416	176646383	RS10913237	RS10798473	GA	0.489	1.29	5.98	0.0145
1	PAPPA2	176630416	176646383	RS10913237	RS10798473	GG	0.336	1.16	1.85	0.174
1	PAPPA2	176646383	176647000	RS10798473	RS17546000	GA	0.351	0.665	12.2	0.000484
1	PAPPA2	176646383	176647000	RS10798473	RS17546000	AA	0.489	1.29	5.98	0.0145
1	PAPPA2	176646383	176647000	RS10798473	RS17546000	GG	0.161	1.17	1.39	0.239
1	**PAPPA2**	**176647000**	**176649181**	**RS17546000**	**RS10454444**	**AG**	**0.176**	**0.461**	**22.1**	**2.60E-06**
1	PAPPA2	176647000	176649181	RS17546000	RS10454444	AA	0.663	1.42	9.13	0.00252
1	PAPPA2	176647000	176649181	RS17546000	RS10454444	GA	0.161	1.17	1.39	0.239
1	**PAPPA2**	**176649181**	**176660247**	**RS10454444**	**RS726252**	**GG**	**0.176**	**0.461**	**22.1**	**2.59E-06**
1	PAPPA2	176649181	176660247	RS10454444	RS726252	AA	0.591	1.28	5.11	0.0238
1	PAPPA2	176649181	176660247	RS10454444	RS726252	AG	0.232	1.23	3.09	0.0787
1	PAPPA2	176660247	176667810	RS726252	RS791031	GA	0.245	0.625	12.7	0.000371
1	PAPPA2	176660247	176667810	RS726252	RS791031	AA	0.591	1.28	5.11	0.0238
1	PAPPA2	176660247	176667810	RS726252	RS791031	GC	0.164	1.18	1.44	0.231
1	PAPPA2	176667810	176680137	RS791031	RS12138021	AA	0.769	0.832	2.43	0.119
1	PAPPA2	176667810	176680137	RS791031	RS12138021	CA	0.164	1.18	1.42	0.234
1	PAPPA2	176667810	176680137	RS791031	RS12138021	AG	0.0665	1.2	0.831	0.362
1	PAPPA2	176680137	176684432	RS12138021	RS4507975	AG	0.227	0.721	5.97	0.0146
1	PAPPA2	176680137	176684432	RS12138021	RS4507975	AA	0.706	1.23	3.05	0.0806
1	PAPPA2	176680137	176684432	RS12138021	RS4507975	GG	0.0615	1.17	0.537	0.464
2	HDAC4	240201797	240208154	RS13414769	RS2048765	GG	0.061	2.18	18.4	1.79E-05
2	HDAC4	240201797	240208154	RS13414769	RS2048765	AA	0.663	0.804	3.83	0.0503
2	HDAC4	240201797	240208154	RS13414769	RS2048765	GA	0.276	0.962	0.102	0.749
2	HDAC4	240208154	240216021	RS2048765	RS6737742	GG	0.061	2.19	18.6	1.58E-05

2	HDAC4	240208154	240216021	RS2048765	RS6737742	AG	0.718	0.773	5.06	0.0244
2	HDAC4	240208154	240216021	RS2048765	RS6737742	AA	0.221	0.986	0.012	0.913
2	HDAC4	240216021	240217116	RS6737742	RS11883623	AG	0.221	0.986	0.0128	0.91
2	HDAC4	240216021	240217116	RS6737742	RS11883623	GG	0.185	1.01	0.00304	0.956
2	HDAC4	240216021	240217116	RS6737742	RS11883623	GA	0.594	1.01	0.00252	0.96
2	HDAC4	240217116	240217522	RS11883623	RS908262	GC	0.182	1.01	0.00393	0.95
2	HDAC4	240217116	240217522	RS11883623	RS908262	AC	0.594	0.995	0.0024	0.961
2	HDAC4	240217116	240217522	RS11883623	RS908262	GA	0.224	1	0.00029	0.986
2	HDAC4	240217522	240228263	RS908262	RS6543523	CG	0.266	1.32	5.92	0.015
2	HDAC4	240217522	240228263	RS908262	RS6543523	CA	0.51	0.8	4.6	0.032
2	HDAC4	240217522	240228263	RS908262	RS6543523	AA	0.221	0.978	0.0301	0.862
2	**HDAC4**	**240228263**	**240234901**	**RS6543523**	**RS10200850**	**GA**	**0.0614**	**2.21**	**19.6**	**9.58E-06**
2	HDAC4	240228263	240234901	RS6543523	RS10200850	AG	0.73	0.75	6.47	0.011
2	HDAC4	240228263	240234901	RS6543523	RS10200850	GG	0.208	1.02	0.0282	0.867
2	HDAC4	240234901	240241255	RS10200850	RS925738	AG	0.0615	2.14	17.7	0.000026
2	HDAC4	240234901	240241255	RS10200850	RS925738	GA	0.414	0.812	3.61	0.0575
2	HDAC4	240234901	240241255	RS10200850	RS925738	GG	0.524	0.968	0.0946	0.758
2	HDAC4	240241255	240250456	RS925738	RS7594398	GA	0.0645	2.13	17.9	2.32E-05
2	HDAC4	240241255	240250456	RS925738	RS7594398	AG	0.415	0.819	3.31	0.0689
2	HDAC4	240241255	240250456	RS925738	RS7594398	GG	0.52	0.965	0.112	0.737
2	HDAC4	240250456	240257958	RS7594398	RS1399629	AA	0.0649	2.12	17.8	2.43E-05
2	HDAC4	240250456	240257958	RS7594398	RS1399629	GA	0.423	0.84	2.58	0.108
2	HDAC4	240250456	240257958	RS7594398	RS1399629	GG	0.512	0.945	0.286	0.593
2	HDAC4	240257958	240262287	RS1399629	RS908265	GG	0.13	0.905	0.388	0.533
2	HDAC4	240257958	240262287	RS1399629	RS908265	AG	0.488	1.06	0.301	0.583
2	HDAC4	240257958	240262287	RS1399629	RS908265	GA	0.382	0.986	0.0174	0.895
2	HDAC4	240262287	240263103	RS908265	RS908263	GA	0.0721	0.827	0.819	0.365
2	HDAC4	240262287	240263103	RS908265	RS908263	GG	0.546	1.07	0.387	0.534
2	HDAC4	240262287	240263103	RS908265	RS908263	AG	0.382	0.986	0.0174	0.895
2	HDAC4	240263103	240263584	RS908263	RS10211084	AG	0.0721	0.827	0.823	0.364
2	HDAC4	240263103	240263584	RS908263	RS10211084	GG	0.723	1.09	0.482	0.487

2	HDAC4	240263103	240263584	RS908263	RS10211084	GA	0.205	0.978	0.0302	0.862
2	HDAC4	240263584	240265617	RS10211084	RS6706275	GA	0.31	0.747	6.34	0.0118
2	HDAC4	240263584	240265617	RS10211084	RS6706275	GG	0.485	1.29	6.18	0.0129
2	HDAC4	240263584	240265617	RS10211084	RS6706275	AG	0.205	0.978	0.0302	0.862
2	HDAC4	240265617	240275570	RS6706275	RS12988669	AA	0.309	0.748	6.28	0.0122
2	HDAC4	240265617	240275570	RS6706275	RS12988669	GA	0.52	1.27	5.11	0.0238
2	HDAC4	240265617	240275570	RS6706275	RS12988669	GG	0.17	1.02	0.0248	0.875

B.4. Chromosome 9p21 locus and perioperative MI

Supplemental Figure S4. Single nucleotide polymorphisms at 9p21 locus previously associated with incident myocardial infarction[3] and mortality[4] after CABG.

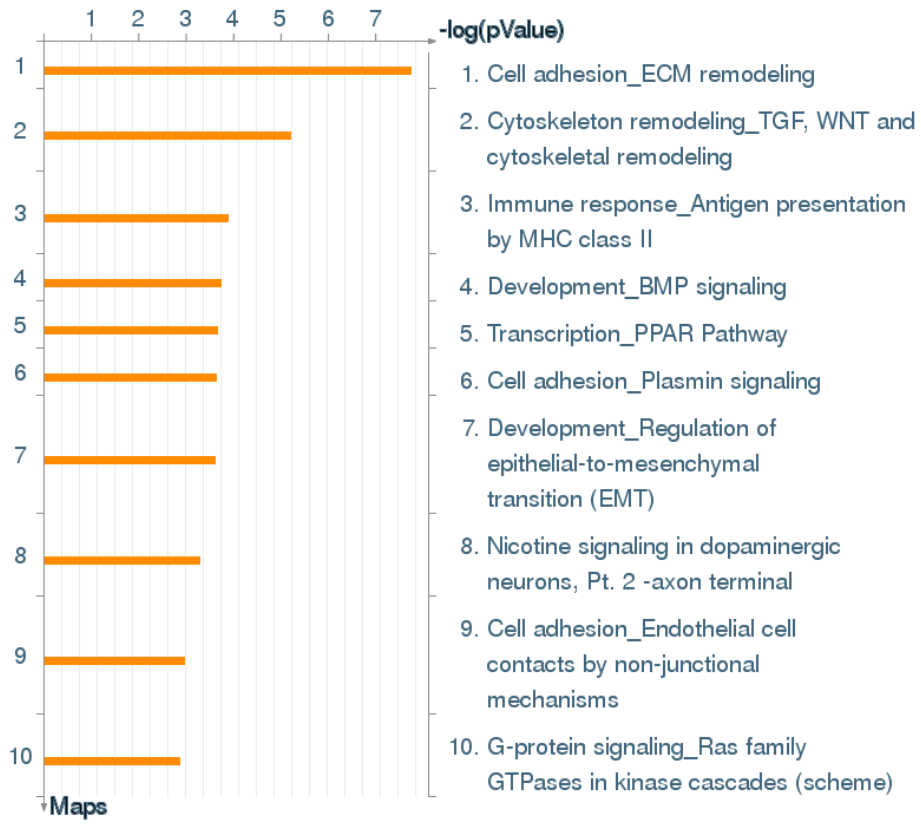


The dashed horizontal line indicates the nominal significance threshold, p = 0.05. The green dots represent single nucleotide polymorphisms (base pair) at the 9p21 locus previously identified as predictors of perioperative MI: rs1547705 (22082375, intron); rs1333040 (22083404, intron); rs4977574 (22098574, intron); rs944797 (22115286, intron); rs2383207 (22115959, intron); rs1537375 (22116071, intron). The red dot represents rs10116277 (22081397) variant, which was previously associated with myocardial infarction in both non-surgical and cardiac surgical cohorts. The dark blue point rs1381923 (22909438, unknown function) is the most significant variant in this plotted region. All p-values are the results of multivariate risk factor-adjusted analyses.

B.5. GWAS pathway analysis results

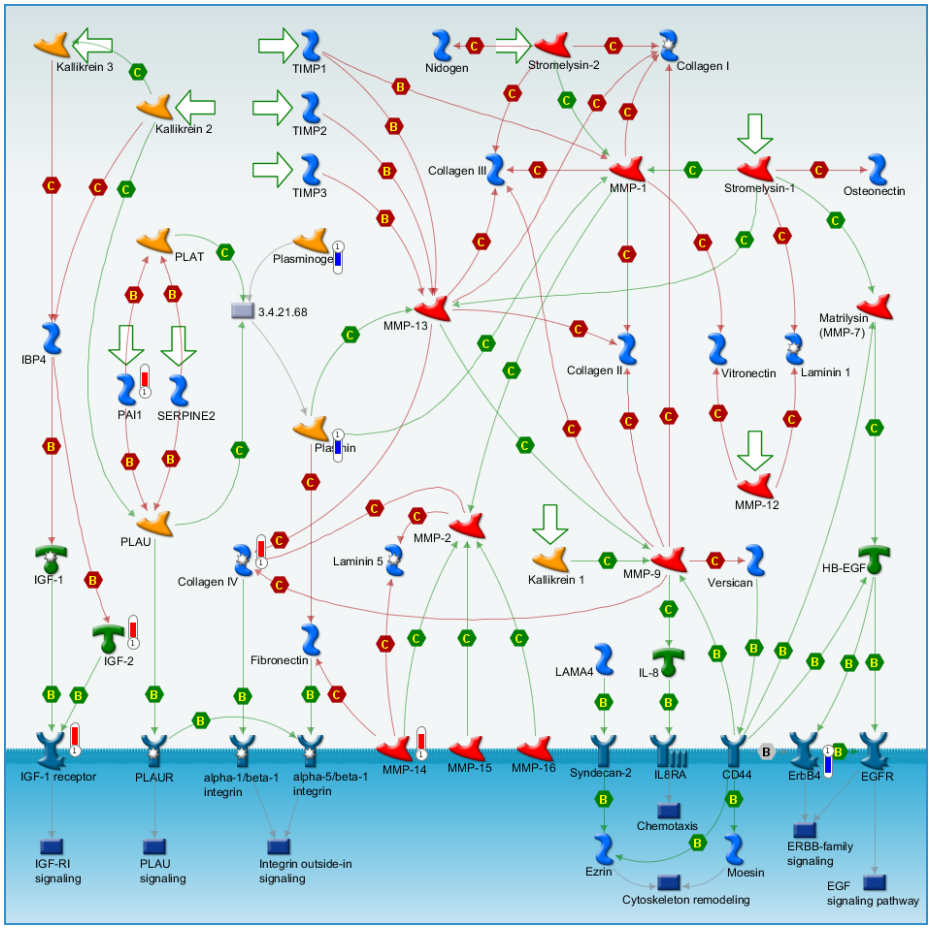
Of the 534,350 SNPs included in analysis, 250,740 were recognized, and 66,893 were mapped to 19,163 genes within MetaCore. Stage I cohort analysis in MetaCore identified several canonical pathways after functional enrichment analysis with SNPs that passed the p-value and odds-ratio filters ($p < 0.01$, $0.9 < OR > 1.1$).

Supplemental Figure S5. GenGo Canonical Pathway Maps histograms after enrichment analysis with SNPs that passed the threshold and p-value filter in GWAS stage I analyses.



The top 10 canonical maps for enriched SNPs are shown as histogram plots. Results are tabulated/sorted in the histogram based on calculated –log(p-values) of hypergeometric distribution statistics.

Supplemental Figure S6. The top scoring pathway map based on the enrichment distribution in GWAS stage I analysis – *Cell adhesion: extracellular matrix remodeling.*



Top-scoring SNPs based on GWAS stage I results are linked to genes and visualized on the maps as thermometer-like symbols. Up-ward thermometers are red and indicate an odds ratio >1 for association with perioperative MI, and down-ward (blue) ones indicate an odds ratio for association < 1. Letters "B", and "C" indicate physical interactions, B, binding; and C, cleavage. Arrows with hexagons indicate positive (green), negative (red), and unspecified (gray) effects. Arrows without hexagons indicate technical link (gray). For further information on pathway elements please see: http://pathwaymaps.com/pdf/MC_legend.pdf

Top-scoring pathways in stage I analyses were compared with enriched pathways in the stage II cohort. The probability of a random intersection between a set of genes common to both cohorts with functional ontology entities was estimated as p-value of hypergeometric distribution using the Compare Experiments Workflow in MetaCore. The top 4 scored canonical pathway maps (lowest p-values), based on the enrichment distribution, are presented below.

1. *Immune response_NFAT signaling and leukocyte interaction* ($p = 7.2*10^{-4}$). Nuclear factors of activated T-cells (NFATs) is a family of calcium-dependent transcription factors with pivotal roles in regulating immune responses, which include interactions between antigen-presenting cells and other leukocytes, and expression of a variety of cytokines by coupling changes in intracellular calcium concentration to gene expression. Variants in CD247, calcium channels, MHC class II, and NFAT that map to this pathway, and their association with perioperative MI is presented below in **Supplemental Table S4**.

SNPid	Gene Symbol	Gene Name	OR	p-value
rs2982480;rs2984800;rs2995054	CD247	CD247 molecule	2.16	0.00311
rs42051;rs7804449;rs1544462;rs1156325; rs2237526;rs2018982	CACNA2D1	calcium channel, voltage-dependent, alpha 2/delta subunit 1	0.71	0.00368
rs1779244;rs2068357	CACNB2	calcium channel, voltage-dependent, beta 2 subunit	0.50	0.00162
rs3117016;rs9380342	HLA-DPB2	major histocompatibility complex, class II, DP beta 2 (pseudogene)	2.45	0.00795
rs3129882	HLA-DRA	major histocompatibility complex, class II, DR alpha	1.49	0.00580
rs1562724;rs1017860;rs8090864	NFATC1	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 1	1.45	0.00362

2. *Cell adhesion and extracellular matrix (ECM) remodeling* ($p = 1.1*10^{-3}$). An important pathway involved in responses to myocardial injury, is comprised of matrix metalloproteinases (MMPs), their endogenous tissue inhibitors (TIMPs), and various collagens. Furthermore, the plasminogen-plasmin system and its regulators (PAI-1) are implicated in proteolytic degradation of ECM. Finally, 2 categories of growth factors are part of this canonical pathway – insulin-like growth factors 1 and 2 (IGF-1 and IGF-2), and heparin-binding EGF-like growth factor (HB-EGF) – and all are involved in regulating cell growth, proliferation, and survival. IGF-1 and IGF-2 function by activating the IGF-1 receptor, but their

bioavailability is regulated by a family of insulin-like growth factor binding proteins (IGFBP4)., HB-EGF activates the epidermal growth factor receptor (EGFR) and v-erb-a erythroblastic leukemia viral oncogene homolog 4 (ErbB4), leading to cell proliferation, cell survival, and tissue remodeling (**Supplemental Table S5**).

SNPid	Gene Symbol	Gene Name	OR	P-value
rs953386;rs2391823	COL4A1	collagen, type IV, alpha 1	1.76	0.00162
rs884904;rs845552	EGFR	epidermal growth factor receptor	1.67	0.00238
rs9288433;rs3817429;rs2371276;rs1473636;rs7425448;rs10932384;rs6740117;rs12053361;rs17803152;rs7594456;rs4672615;rs1851169;rs6747637	ERBB4	v-erb-a erythroblastic leukemia viral oncogene homolog 4 (avian)	0.53	0.00613
rs2033178	IGF1	insulin-like growth factor 1 (somatomedin C)	0.50	0.00901
rs8038056;rs8028620;rs2139924;rs3784604	IGF1R	insulin-like growth factor 1 receptor	1.90	0.00383
rs734351	IGF2	insulin-like growth factor 2 (somatomedin A)	1.57	0.00159
rs12454479;rs8086477;rs12454564	LAMA3	laminin, alpha 3	2.01	0.00165
rs762052	MMP14	matrix metallopeptidase 14 (membrane-inserted)	1.60	0.00863
rs1050813	SERPINE1	serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1	1.38	0.00874
rs783147	PLG	plasminogen	0.68	0.00979

3. *Regulation of lipid metabolism_RXR-dependent regulation of lipid metabolism via PPAR, RAR, and VDR* ($p = 5.1*10^{-3}$; **Supplemental Table S6**).

SNPid	Gene Symbol	Gene Name	OR	P-value
rs12364396	CPT1A	carnitine palmitoyltransferase 1A	1.779	0.006433
rs1286767;rs2164360;rs2033447	RARB	retinoic acid receptor, beta	1.647	0.005116

4. *BMP (bone morphogenic protein) signaling pathway* ($p = 5.2*10^{-3}$). BMPs are members of the TGF-β superfamily, with important roles in embryonic development including cardiomyogenesis and apoptosis. BMPs transduce their signals via 2 pathways: SMAD-dependent (including SMAD9[8]), and SMAD-

independent cascade. BMP activity can be regulated by intracellular inhibitory SMADs (like SMAD6) or extracellularly by secreted antagonists (like gremlin). Variants in SMAD9 and SMAD6 were associated with an increased incidence of perioperative MI (**Supplemental Table S7**).

SNPid	Gene Symbol	Gene Name	OR	p-value
rs11858577	SMAD6	SMAD, mothers against DPP homolog 6	2.30	0.0002506
rs7998663	SMAD9	Mothers against decapentaplegic, drosophila, homolog of, 9	2.47	0.000167
rs884940	SKI	ski oncoprotein	0.61	0.0006749

In summary, functional analysis of genome-wide association data using biological ontologies allowed us to supplement our single marker analysis results by identifying a number of additional candidates for further investigation as biomarkers for perioperative MI. It also highlighted the potential mechanistic importance of several signaling pathways that have not previously been implicated in the complex and multifactorial pathogenesis of perioperative ischemia-reperfusion injury.

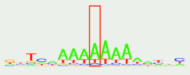
Supplemental Figure S7 summarizes RegulomeDB (regulome.stanford.edu) and HaploReg v2 (http://www.broadinstitute.org/mammals/haploreg/haploreg.php) database results for rs609408 (intergenic variant, located 1.5kb 3' of SMAD9).

A. RegulomeDB supporting data for rs609418

Protein Binding Filter:

Method	Location	Bound Protein	? Cell Type	Additional Info	Reference
ChIP-seq	chr13:37417308..37417652	GATA2	SH-SY5Y		ENCODE

Motifs Filter:

Method	Location	Motif	? Cell Type	PWM	Reference
PWM	chr13:37417418..37417435	Elf3			19443739

B. HaploReg v2 summary for rs609418 and variants with $r^2 \geq 0.8$

Query SNP: rs609418 and variants with $r^2 >= 0.8$

chr	pos (hg19)	LD (r^2)	LD (D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq	SiPhy cons	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	eQTL tissues	Motifs changed	GENCODE genes	dbSNP func annot
13	37396093	0.98	-0.99	rs1980881	G	A	0.34	0.74	0.55	0.74		GM12878	Huvec				5 altered motifs	RFXAP	intronic
13	37396218	0.98	-0.99	rs1980880	A	G	0.34	0.74	0.55	0.74			Huvec, GM12878				6 altered motifs	RFXAP	intronic
13	37400621	0.9	-0.99	rs7983276	T	A	0.33	0.76	0.55	0.76							Mef2,TATA	RFXAP	intronic
13	37401286	0.9	-0.99	rs7984398	T	C	0.33	0.76	0.55	0.76							Foxp1,Pou2f2,TATA	RFXAP	intronic
13	37407492	0.89	1	rs1571320	C	G	0.45	0.23	0.33	0.24				Ishikawa,HRCEpiC,RPTEC			AP-1	4.3kb 3' of RFXAP	
13	37407870	0.9	1	rs4943419	C	T	0.45	0.23	0.33	0.24							TEF	4.6kb 3' of RFXAP	
13	37408545	0.9	1	rs6563501	A	G	0.45	0.23	0.33	0.24				FibroP,HMVEC-LBl,NH-A			HDAC2,Tgif1	5.3kb 3' of RFXAP	
13	37408734	1	-1	rs9315450	T	C	0.35	0.74	0.55	0.74				4 cell types			Smad	5.5kb 3' of RFXAP	
13	37409508	0.9	1	rs9566166	G	A	0.45	0.23	0.33	0.24				Th2			Mef2,SIX5	6.3kb 3' of RFXAP	
13	37410696	1	-1	rs9315451	A	C	0.35	0.74	0.55	0.74							HDAC2	7.5kb 3' of RFXAP	
13	37410794	0.9	1	rs4943421	C	G	0.46	0.23	0.34	0.24							Zic	7.6kb 3' of RFXAP	
13	37411589	0.9	1	rs11838533	A	G	0.40	0.23	0.33	0.24				Th1			Pax-4	7.4kb 3' of SMAD9	
13	37412644	0.9	1	rs4943423	C	T	0.51	0.24	0.33	0.24							GATA	6.3kb 3' of SMAD9	
13	37413544	0.9	1	rs7982338	A	C	0.47	0.23	0.33	0.24				BE2_C,HIPEpiC	SRF		CTCF,NF-I,p53	5.4kb 3' of SMAD9	
13	37413557	0.9	1	rs7981675	C	T	0.47	0.23	0.33	0.24				BE2_C,HIPEpiC	SRF		4 altered motifs	5.4kb 3' of SMAD9	
13	37414795	0.9	1	rs4943426	T	C	0.46	0.23	0.34	0.24			H1					4.2kb 3' of SMAD9	
13	37416234	0.88	1	rs9635072	G	A	0.39	0.23	0.34	0.23							7 altered motifs	2.7kb 3' of SMAD9	
13	37417048	1	-1	rs7325187	G	T	0.34	0.74	0.54	0.74								1.9kb 3' of SMAD9	
13	37417206	0.9	1	rs9576121	T	C	0.46	0.23	0.34	0.24							6 altered motifs	1.8kb 3' of SMAD9	
13	37417427	1	1	rs609418	A	C	0.67	0.26	0.46	0.26					GATA2		Gfi1,Mef2	1.5kb 3' of SMAD9	
13	37417894	0.89	1	rs9634749	C	A	0.46	0.23	0.34	0.24							ATF3,ATF6	1.1kb 3' of SMAD9	
13	37418491	0.99	1	rs35652793	TA	T	0.67	0.26	0.46	0.26							8 altered motifs	476bp 3' of SMAD9	
13	37419042	0.83	0.98	rs60270973	AGTT	A	0.46	0.22	0.34	0.23							HEY1,Sox	SMAD9	
13	37420348	0.98	1	rs642866	A	G	0.66	0.26	0.46	0.25							12 altered motifs	SMAD9	3'-UTR
13	37423032	0.87	1	rs4943431	G	A	0.42	0.23	0.34	0.23			Huvec		CTCF,RAD21		4 altered motifs	SMAD9	intronic
13	37431353	0.97	1	rs10629368	A	ACT	0.80	0.28	0.51	0.25							14 altered motifs	SMAD9	intronic
13	37434744	0.95	0.99	rs636514	G	A	0.78	0.28	0.51	0.25							CACD,NRSF	SMAD9	intronic

and detailed view for rs609418

Sequence facts

chr	pos (hg19)	Reference	Alternate	1000 Genomes Phase 1 Frequencies				Sequence constraint		dbSNP functional annotation
				AFR	AMR	ASN	EUR	by GERP	by SiPhy	
chr13	37417427	A	C	0.67	0.26	0.46	0.26	No	No	none

Closest annotated gene

Source	Distance	Direction	ID/Link	Common name	Description
GENCODE	3'	1540	ENSG00000120693.9	SMAD9	SMAD family member 9 [Source:HGNC Symbol;Acc:6774]
RefSeq	3'	1539	NM_001127217	SMAD9	SMAD family member 9 [Source:HGNC Symbol;Acc:6774]

Proteins bound by ChIP (ENCODE)

Cell ID	Protein
SH-SY5Y	GATA2

Regulatory motifs altered

PWM	Strand	Ref	Alt	Match on:
				Ref: TGCTATGCAGCTGGATAACTATTTCCAAAATAAATCACAAGCACGCTTTTCTGATCCCT Alt: TGCTATGCAGCTGGATAACTATTTCCAAACTAAATCACAAGCACGCTTTTCTGATCCCT
Gfi1_2	+	10.5	11.2	HNWAATCHBDKSH
Mef2_disc1	+	12.1	7.3	DDKYTATTTTTRDMH

B.6. Power calculation

We used Genetic Power Calculator (http://pngu.mgh.harvard.edu/~purcell/gpc/) to estimate the effect size that our study sample size can detect with 80% power. As an example, we used rs4834703 in the *SEC24D* gene, which has 0.1 MAF and odds ratio (OR) of 1.98 from the stage II analysis. In this power calculation, we assumed 11% disease prevalence, 0.1 MAF for the marker, and the same study sample sizes (225 cases and 1830 controls). We varied the minor allele frequency of the disease locus (0.05, 0.1, 0.15) to assess the genotypic relative risk (GRR) that our study sample size can detect with 80% power. We used the same significant threshold described in the paper, 9×10^{-5}, for the stage II analysis. We assumed an additive model to define GRR of Aa and AA genotypes, that is, *GRR_Aa = x and GRR_Aa = 2x*, where *x* is equivalent to the OR for the minor allele. If the marker tested was in complete linkage disequilibrium (D' = 1) with the disease locus, we found that our sample size has approximately 80% power to detect a GRR = 2.6 for a rare disease locus (MAF = 0.05) and GRR = 1.8 for a more common disease locus (MAF = 0.1 and 0.15). The effect sizes become slightly higher when D' is assumed at 0.8 between disease locus and marker (**Supplemental Table S8**). The OR for rs4834703 in the *SEC24D* gene in our study was 1.97, which is consistent with the estimate here. Although somewhat controversial, current evidence supports joint 2-stage analysis designs over replication analyses in GWAS, based on increased statistical power of joint analyses,[5, 6] which formed the rationale for our study design.

Supplemental Table S8. GRR estimates that our dataset can detect a given disease locus MAF at approximately 80% power when marker MAF = 0.1, sample size = 225 cases and 1830 controls, and disease prevalence = 11%.

D'	Disease locus MAF	Odds Ratio	Power
1	0.05	2.6	0.8
	0.1	1.8	0.84
	0.15	1.75	0.81
0.8	0.05	3.1	0.8
	0.1	2.15	0.84
	0.15	2	0.82

B.7. Supplemental Table S9. Details of the top 521 SNPs identified in discovery dataset

CHR	SNP	BP	GENE SYMBOL	Minor allele	Minor allele frequency	Odds ratio	95% CI Lower Limit	95% CI Upper Limit	P-value
8	RS2044061	19723503	INTS10 | LPL	G	0.3117	2.004	1.499	2.68	2.76E-06
1	RS6660197	200703541	DDX59 | CAMSAP1L1	A	0.1266	2.368	1.63	3.438	5.99E-06
1	RS12756886	200840467	CAMSAP1L1 | GPR25	G	0.1215	2.342	1.612	3.404	8.12E-06
3	RS6788848	103028245	LOC100287880 | ALCAM	G	0.237	1.995	1.473	2.702	8.15E-06
1	RS12060387	210819848	HHAT	A	0.05196	3.218	1.925	5.379	8.27E-06
1	RS12742404	200811765	CAMSAP1L1	G	0.1204	2.338	1.609	3.397	8.44E-06
6	RS3861449	148300251	SAMD5 | SASH1	A	0.2655	1.985	1.467	2.686	8.77E-06
15	RS894157	90168108	C15orf42	G	0.1012	2.333	1.604	3.394	9.42E-06
8	RS2235118	2027154	MYOM2	C	0.1319	2.184	1.536	3.107	1.38E-05
1	RS2292096	200826769	CAMSAP1L1	G	0.1279	2.282	1.569	3.318	1.57E-05
4	RS4689485	6578487	MAN2B2	A	0.1606	2.054	1.479	2.851	1.71E-05
5	RS7721080	31973116	PDZD2	G	0.04521	3.173	1.868	5.391	1.94E-05
6	RS9382274	53877181	LRRC1 | C6orf142	A	0.07399	2.601	1.673	4.044	2.20E-05
3	RS1038517	59949140	FHIT	A	0.0898	2.477	1.622	3.782	2.68E-05
5	RS331706	124890054	ZNF608 | GRAMD3	A	0.1478	2.128	1.495	3.027	2.71E-05
4	RS4834703	119691624	SEC24D	A	0.09379	2.271	1.544	3.342	3.13E-05
4	RS4302525	6552201	PPP2R2C | MAN2B2	A	0.1457	2.039	1.458	2.853	3.18E-05
13	RS9547679	37402440	RFXAP	A	0.07962	2.63	1.662	4.162	3.63E-05
1	RS12723891	217143384	ESRRG	G	0.1103	2.126	1.479	3.056	4.62E-05
19	RS3745752	48339300	CRX	G	0.4011	1.844	1.373	2.476	4.84E-05
22	RS138195	46151880	ATXN10	G	0.371	1.819	1.362	2.429	5.04E-05
6	RS2876669	148216298	SAMD5 | SASH1	A	0.2328	1.891	1.389	2.573	5.12E-05
4	RS4631029	21796070	KCNIP4 | NCRNA00099	G	0.09885	2.214	1.507	3.253	5.14E-05
20	RS6067635	49698104	MULTIPLE_GENES:3755,100128598	A	0.2601	1.903	1.393	2.6	5.24E-05
16	RS12920403	19756059	IQCK	G	0.1235	2.109	1.464	3.036	6.06E-05
6	RS9405142	1632299	GMDS	G	0.01484	5.575	2.4	12.95	6.46E-05
9	RS12115781	112672877	MULTIPLE_GENES:445815,114299	C	0.08401	2.359	1.545	3.601	6.97E-05
9	RS7042036	119766969	ASTN2	G	0.3168	1.81	1.351	2.425	7.13E-05
19	RS11668505	48348363	CRX | SULT2A1	G	0.3984	1.803	1.347	2.414	7.43E-05
7	RS10270298	104210910	LHFPL3	A	0.04825	3.011	1.743	5.2	7.76E-05
14	RS10140464	49210639	MDGA2 | RPS29	G	0.198	1.894	1.38	2.6	7.82E-05
6	RS9352851	81392952	BCKDHB | FAM46A	A	0.3728	1.787	1.34	2.384	7.82E-05
7	RS10953524	106618074	PIK3CG | PRKAR2B	G	0.499	0.5472	0.4056	0.7381	7.86E-05
21	RS928873	43293371	PRDM15	A	0.278	0.4756	0.3287	0.6881	8.05E-05
7	RS2299146	42033195	GLI3	A	0.302	1.763	1.33	2.337	8.10E-05
8	RS6586870	19709775	INTS10 | LPL	A	0.3934	1.8	1.344	2.412	8.11E-05
1	RS12122147	74838630	TNNI3K	G	0.1004	2.181	1.48	3.214	8.14E-05
9	RS457417	4855514	RCL1	C	0.1306	2.027	1.426	2.883	8.27E-05
15	RS11638941	39481950	LOC100289563 | C15orf54	G	0.1424	2.008	1.418	2.843	8.47E-05
7	RS2058894	97296791	ACN9 | TAC1	A	0.0368	3.17	1.783	5.636	8.52E-05
17	RS11077582	69911104	LOC124685 | SOX9	A	0.06309	2.456	1.568	3.845	8.62E-05
8	RS13254568	11514144	BLK | GATA4	A	0.1732	1.978	1.406	2.783	8.91E-05
20	RS2425810	44890910	CDH22 | SLC35C2	A	0.3924	1.787	1.335	2.391	9.38E-05
10	RS3847355	71725020	COL13A1 | H2AFY2	A	0.442	1.789	1.336	2.396	9.57E-05
5	RS10078649	179877533	GFPT2 | CNOT6	A	0.09818	2.174	1.471	3.212	9.80E-05
21	RS4276100	43275896	LOC100288232 | PRDM15	G	0.2652	1.823	1.348	2.467	9.91E-05
2	RS11686987	107128885	RGPD3 | LOC644604	A	0.03038	3.33	1.817	6.105	9.97E-05
16	RS8055711	7040933	A2BP1	A	0.2881	1.825	1.348	2.47	1.00E-04
2	RS4853374	78442014	SNAR-H | REG3G	A	0.1353	2.076	1.436	3.002	0.0001033
19	RS7260368	57135195	ZNF71	G	0.4855	1.756	1.321	2.335	0.0001076
6	RS9361640	81392005	BCKDHB | FAM46A	C	0.3013	1.793	1.333	2.412	0.0001118
10	RS2895524	12595147	CAMK1D	A	0.3465	0.5135	0.3662	0.7201	0.000112
14	RS17112396	42397496	LRFN5 | FSCB	A	0.01316	6.11	2.436	15.32	0.0001143
8	RS7839240	39746386	ADAM2 | IDO1	G	0.3998	1.763	1.322	2.353	0.0001152
4	RS2880099	156432368	LOC100287564 | GUCY1A3	A	0.1191	2.059	1.426	2.974	0.0001162
2	RS4951964	31300544	GALNT14	A	0.02767	3.535	1.86	6.719	0.0001165
14	RS1242558	83235421	SEL1L | FLRT2	A	0.2912	1.785	1.329	2.398	0.0001186
15	RS12913680	90098150	LOC283761 | C15orf42	A	0.1093	2.144	1.452	3.164	0.0001236
2	RS2894595	227237862	KIAA1486 | IRS1	C	0.2895	1.77	1.322	2.37	0.0001245
4	RS1398835	21849857	NCRNA00099	A	0.09987	2.12	1.444	3.113	0.0001262
9	RS7035935	112706482	PALM2	C	0.06748	2.47	1.555	3.923	0.0001278
2	RS11686479	31309930	GALNT14	A	0.028	3.505	1.845	6.66	0.0001284
7	RS8461168	2170759	MAD1L1	G	0.2756	1.766	1.318	2.365	0.0001368
13	RS6563501	37408545	RFXAP | SMAD9	G	0.2257	1.827	1.34	2.491	0.0001385
12	RS11111722	104104227	STAB2	A	0.05162	2.752	1.634	4.633	0.0001398
2	RS11685519	107122121	RGPD3 | LOC644604	A	0.03138	3.156	1.746	5.702	0.0001408
7	RS4346898	21951033	CDCA7L	A	0.391	1.715	1.299	2.264	0.0001422
21	RS870531	43276783	LOC100288232 | PRDM15	A	0.3292	0.5185	0.3697	0.7273	0.0001424
5	RS716866	168645723	SLIT3	G	0.4356	1.741	1.308	2.317	0.0001427
5	RS6595621	124989579	ZNF608 | GRAMD3	A	0.2375	1.858	1.35	2.556	0.0001429
1	RS1183044	209255814	PLXNA2 | LOC642587	A	0.4922	1.744	1.309	2.323	0.000146
7	RS4140805	7727101	RPA3	C	0.4214	1.747	1.309	2.33	0.0001501
5	RS10447192	8896731	LOC100128382 | SEMA5A	A	0.4069	0.5487	0.4022	0.7486	0.0001528
2	RS858940	50945699	NRXN1	A	0.3836	1.743	1.307	2.324	0.0001535
7	RS10263415	7724805	LOC729652 | RPA3	A	0.4244	1.755	1.312	2.349	0.000154
10	RS17452064	11242471	CUGBP2	C	0.1088	2.059	1.416	2.995	0.0001571
15	RS8041127	90135196	C15orf42	A	0.1043	2.118	1.435	3.128	0.0001596
6	RS6456676	25350468	LRRC16A	C	0.01181	6.973	2.543	19.12	0.0001614
7	RS3778973	2151178	MAD1L1	A	0.208	1.809	1.329	2.462	0.0001653
13	RS7998663	37435150	SMAD9	G	0.07456	2.47	1.542	3.954	0.000167
8	RS10086641	39754780	ADAM2 | IDO1	A	0.4035	1.738	1.303	2.318	0.0001693
4	RS1878943	9766888	LOC100128096 | DRD5	A	0.1926	1.848	1.342	2.546	0.0001704
6	RS220702	46867717	GPR116	G	0.09885	2.161	1.446	3.231	0.0001718
11	RS554341	128685761	FLI1 | KCNJ1	G	0.1334	1.946	1.374	2.754	0.0001746
20	RS7508996	40396739	CHD6 | PTPRT	G	0.08603	2.294	1.487	3.539	0.000175
10	RS2184035	19778072	C10orf112	A	0.04453	2.7	1.606	4.538	0.0001773
7	RS7802845	111723488	DOCK4	G	0.07794	2.318	1.493	3.598	0.0001797
12	RS1316899	55966101	OR6C4 | OR10P1	A	0.1619	1.844	1.339	2.541	0.0001813
1	RS10454444	176649181	PAPPA2	G	0.1754	0.3867	0.2352	0.6359	0.0001814
7	RS17482047	7755484	RPA3	G	0.08835	2.177	1.448	3.272	0.0001832
1	RS10913237	176630416	PAPPA2	A	0.1748	0.3866	0.2349	0.6362	0.0001846
15	RS4774964	57854873	CGNL1 | GCOM1	G	0.1859	0.4038	0.2508	0.65	0.0001892
12	RS3871519	93915922	MRPL42 | SOCS2	A	0.3526	0.5349	0.3851	0.7429	0.0001894
2	RS1595422	78434830	SNAR-H | REG3G	A	0.1326	2.03	1.4	2.943	0.0001897
4	RS298988	119648399	SEC24D	A	0.226	1.793	1.32	2.437	0.0001899
4	RS1491152	130547852	C4orf33 | LOC100132483	G	0.3347	1.74	1.3	2.329	0.0001949
20	RS6022863	52556423	SUMO1P1 | BCAS1	A	0.4028	0.5521	0.4038	0.7548	0.0001965
8	RS4875192	3187176	CSMD1	A	0.03914	2.825	1.634	4.883	0.0001996
15	RS17738087	26905021	GABRB3	G	0.0975	2.117	1.425	3.145	0.0002022
3	RS17061897	60020954	FHIT	A	0.0587	2.476	1.534	3.994	0.0002039
1	RS6577559	9238095	GPR157 | LOC727721	A	0.1231	1.985	1.382	2.85	0.000205
4	RS6839725	21870314	LOC100131836 | KCNIP4	A	0.09312	2.101	1.42	3.11	0.0002053
11	RS1816775	13783230	FAR1 | SPON1	A	0.3728	1.71	1.288	2.269	0.0002075
4	RS10516398	21746541	KCNIP4	A	0.09791	2.085	1.414	3.074	0.0002086
15	RS4288951	27751567	GABRG3	A	0.08947	2.283	1.476	3.532	0.0002089
3	RS9883142	7017919	GRM7	A	0.3052	1.717	1.29	2.285	0.0002102
3	RS12631018	116501764	LOC285194 | IGSF11	G	0.1684	1.913	1.358	2.696	0.0002105
7	RS17171847	41370672	C7orf10 | INHBA	G	0.09312	2.121	1.425	3.157	0.0002106
15	RS6494826	70049111	LOC145837 | C15orf50	A	0.4318	1.738	1.297	2.33	0.0002164
10	RS984668	124120559	BTBD16 | PLEKHA1	A	0.3542	1.736	1.296	2.325	0.0002167
17	RS10512598	73038132	ATP5H	A	0.05634	2.532	1.547	4.144	0.0002202
2	RS7594398	240250456	HDAC4	A	0.0695	2.28	1.47	3.536	0.000232
1	RS12032817	83177365	LPHN2 | TTLL7	G	0.3934	1.703	1.283	2.261	0.0002321
5	RS17105323	146114766	PPP2R2B	G	0.03205	3.205	1.723	5.96	0.0002336
12	RS11171580	55975171	OR6C4 | OR10P1	C	0.2335	1.772	1.306	2.404	0.0002349
1	RS821717	232059805	DISC1	C	0.2107	0.4419	0.2859	0.683	0.0002365
13	RS17424088	23087983	FGF9 | LOC646201	A	0.1055	2.068	1.404	3.046	0.0002365
2	RS17027173	103057043	IL18RAP	A	0.2156	1.814	1.32	2.493	0.0002383
16	RS16956168	56249774	DKFZP434H168 | GNAO1	A	0.1738	1.887	1.345	2.649	0.0002397
13	RS7332913	79933284	RBM26	G	0.4909	0.5783	0.4317	0.7748	0.0002424
13	RS2763810	79979679	RBM26	A	0.4906	0.5783	0.4317	0.7748	0.0002424
7	RS2700976	37400570	ELMO1	A	0.2302	1.756	1.3	2.373	0.0002431
14	RS8009218	100057672	CCDC85C	G	0.4541	1.733	1.292	2.325	0.0002438
2	RS17015041	78416572	SNAR-H | REG3G	G	0.1397	1.975	1.373	2.841	0.0002458
22	RS6007696	47968450	LOC100289420 | FAM19A5	G	0.1765	1.878	1.341	2.631	0.0002459
9	RS10809097	1057797	DMRT2 | SMARCA2	G	0.1373	1.999	1.38	2.895	0.0002483
15	RS11858577	67066563	SMAD6	A	0.07422	2.3	1.473	3.591	0.0002506
13	RS2147568	79991226	RBM26 | NDFIP2	G	0.4906	0.5797	0.4329	0.7762	0.0002516
10	RS7910400	6310176	PFKFB3 | LOC399715	G	0.4224	0.5523	0.4018	0.7591	0.000254
2	RS3828312	100184719	AFF3	A	0.2045	1.82	1.32	2.508	0.0002564
12	RS10859508	93919441	MRPL42 | SOCS2	A	0.3552	0.5428	0.3911	0.7533	0.0002576
4	RS6822035	119710421	SEC24D	A	0.2955	1.734	1.29	2.329	0.0002593
9	RS7855908	71517082	PIP5K1B	G	0.05466	2.712	1.588	4.631	0.0002598
7	RS2723520	17813677	AHR | SNX13	G	0.4521	1.719	1.285	2.299	0.0002609
3	RS967331	61447737	FHIT | PTPRG	A	0.1559	1.902	1.347	2.686	0.0002631
7	RS11763025	21920165	DNAH11	A	0.3502	1.692	1.275	2.244	0.0002649
20	RS2425847	44907927	CDH22 | SLC35C2	G	0.3856	1.706	1.28	2.274	0.0002664
1	RS10489478	176566350	PAPPA2	A	0.1734	0.4052	0.2493	0.6586	0.0002668
10	RS1915613	66483216	LOC100287799 | ANXA2P3	A	0.248	0.4801	0.3235	0.7124	0.0002689
23	RS7051093	90319063	LOC100288789 | PABPC5	A	0.1842	0.2732	0.1359	0.5491	0.0002701
6	RS6456672	25347733	LRRC16A	C	0.01417	6.505	2.374	17.82	0.0002709
23	RS5940927	90309551	LOC100288789 | PABPC5	A	0.1831	0.2738	0.1362	0.5504	0.000277
23	RS10522055	90307072	LOC100288789 | PABPC5	G	0.1831	0.2738	0.1362	0.5504	0.000277
20	RS2425807	44881545	CDH22 | SLC35C2	G	0.4136	1.714	1.281	2.291	0.0002808
8	RS4510897	72277458	EYA1 | MSC	G	0.1552	1.898	1.343	2.682	0.0002813
8	RS10808467	1153208 34	CSMD3 | TRPS1	A	0.4899	0.5774	0.4291	0.7768	0.0002854
22	RS5754826	34476759	LARGE | ISX	A	0.2893	0.5043	0.3483	0.73	0.0002861
9	RS752357	36744752	MELK | PAX5	G	0.3478	0.5406	0.3877	0.7538	0.0002875
1	RS10489477	176562608	PAPPA2	A	0.169	0.3777	0.2231	0.6396	0.0002909
9	RS11792612	17442000	CNTLN	A	0.1798	1.812	1.314	2.5	0.0002932
10	RS12780002	6308484	PFKFB3 | LOC399715	A	0.3342	0.5359	0.3821	0.7514	0.0002986
8	RS6997580	115321807	CSMD3 | TRPS1	C	0.4882	0.5787	0.4301	0.7787	0.000305
3	RS1284745	102324326	ZPLD1 | LOC100287880	G	0.3313	1.714	1.279	2.297	0.0003073
1	RS10801786	90595332	ZNF326 | BARHL2	C	0.1781	1.816	1.313	2.511	0.0003103
13	RS609418	37417427	RFXAP | SMAD9	C	0.2551	1.731	1.284	2.333	0.0003138
6	RS4708617	168389858	HGC6.3 | KIF25	A	0.1134	0.2382	0.1091	0.5198	0.0003142
4	RS3108140	107334044	LOC100288276	A	0.3107	1.7	1.273	2.269	0.0003187
2	RS1370631	78410008	SNAR-H | REG3G	G	0.141	1.949	1.355	2.803	0.0003233
2	RS2901929	78428973	SNAR-H | REG3G	G	0.141	1.949	1.355	2.803	0.0003233
2	RS2164850	78423757	SNAR-H | REG3G	A	0.141	1.949	1.355	2.803	0.0003233
16	RS4786590	5125365	ALG1	G	0.0135	6.207	2.291	16.81	0.0003296
14	RS4902165	63115447	FLJ43390 | KCNH5	G	0.1387	1.921	1.345	2.744	0.0003297
6	RS7753022	86176625	NT5E	A	0.1397	1.975	1.362	2.864	0.0003344
21	RS2839401	43302079	PRDM15 | C2CD2	A	0.2402	0.4871	0.3288	0.7217	0.0003358
9	RS11144511	78218231	OSTF1 | PCSK5	A	0.4501	1.71	1.275	2.293	0.0003408
11	RS12799462	13977738	FAR1 | SPON1	C	0.2034	0.4419	0.2825	0.6911	0.0003456
6	RS12192975	20431741	E2F3	A	0.05634	2.357	1.474	3.769	0.0003457
23	RS180484	150318158	HMGB3 | LOC100128688	G	0.3481	1.961	1.356	2.837	0.0003485
10	RS161016	110039615	LOC100128304 | LOC645318	G	0.3381	0.5504	0.3967	0.7635	0.0003497
16	RS7188523	55313079	LOC100132339 | IRX6	A	0.04757	2.643	1.551	4.504	0.0003502
12	RS2303970	74471340	TRHDE | LOC552889	A	0.4673	0.5823	0.4328	0.7833	0.0003512
5	RS297853	168628678	SLIT3	A	0.3367	1.683	1.265	2.239	0.0003513
4	RS1908125	134392080	PCDH10 | PABPC4L	G	0.2068	1.757	1.29	2.394	0.0003531
7	RS2237429	42031224	GLI3	A	0.1883	1.791	1.301	2.466	0.0003571
8	RS6989246	2015119	MYOM2	A	0.09514	2.071	1.389	3.088	0.0003573
8	RS7820007	142731821	FLJ43860 | NCRNA00051	A	0.3921	1.695	1.269	2.264	0.0003578
6	RS6932311	25346376	LRRC16A	A	0.01383	6.219	2.279	16.97	0.0003597
22	RS138204	46161875	ATXN10	A	0.3647	1.686	1.266	2.247	0.0003607
12	RS2365432	74439038	TRHDE | LOC552889	A	0.4136	0.5733	0.4223	0.7783	0.0003619
15	RS4777184	70007323	LOC145837 | C15orf50	A	0.365	1.704	1.271	2.284	0.0003629
7	RS10233681	71941439	CALN1 | TYW1B	A	0.2554	0.4969	0.3382	0.73	0.000366
4	RS6828577	119704501	SEC24D	A	0.2939	1.713	1.274	2.302	0.0003672
7	RS17410662	96231614	FLJ42280 | SHFM1	A	0.1427	1.877	1.327	2.655	0.0003686
6	RS744143	20418718	E2F3	A	0.07596	2.156	1.412	3.29	0.0003701
20	RS6033188	11585276	JAG1 | LOC728573	G	0.1353	0.3323	0.1812	0.6095	0.0003707
5	RS4298224	8894289	LOC100128382 | SEMA5A	A	0.3698	0.5636	0.411	0.7729	0.0003729
2	RS10179116	100174645	AFF3	A	0.3522	1.714	1.273	2.306	0.0003763
12	RS10431428	93898858	MRPL42 | SOCS2	G	0.2831	1.769	1.292	2.422	0.0003775
15	RS2289486	90161355	C15orf42	G	0.09177	2.068	1.385	3.086	0.0003776
7	RS1404508	96228434	FLJ42280 | SHFM1	A	0.1518	1.855	1.32	2.608	0.0003779
4	RS6854328	119683492	SEC24D	A	0.2939	1.711	1.272	2.3	0.0003788
2	RS13030183	79909989	CTNNA2	A	0.4467	1.681	1.262	2.239	0.0003823
9	RS10969620	30323457	LOC100289571 | LOC100288436	A	0.0948	1.983	1.358	2.894	0.0003898
6	RS6568370	105845531	PREP	C	0.1087	2.048	1.378	3.045	0.0003918
2	RS12469727	227301483	KIAA1486 | IRS1	A	0.1653	1.819	1.307	2.532	0.0003923
2	RS13422448	49743324	FSHR | NRXN1	C	0.3188	0.5325	0.3758	0.7545	0.0003934
23	RS5941802	90288180	LOC100288789 | PABPC5	C	0.179	0.2835	0.1412	0.5693	0.000394
16	RS899236	56352905	GNAO1	A	0.2095	1.789	1.297	2.469	0.0003944
17	RS767234	69886832	LOC124685 | SOX9	A	0.2186	1.766	1.289	2.42	0.0003964
20	RS3091869	45425918	LOC100127904 | EYA2	A	0.4325	1.665	1.256	2.207	0.0003971
16	RS17720036	27139728	C16orf82 |	G	0.1309	1.929	1.341	2.775	0.0003997
10	RS6593445	45359483	LOC100289168 | TMEM72	G	0.1501	1.854	1.317	2.609	0.0004009

Supplemental Table S9. Details of the top 521 SNPs identified in discovery dataset (***cont***)

CHR	SNP	BP	GENE SYMBOL	Minor allele	Minor allele frequency	Odds ratio	95% CI Lower Limit	95% CI Upper Limit	P-value
2	RS1356799	140567666	LOC647012 | LRP1B	C	0.1977	0.439	0.2783	0.6926	0.0004021
3	RS6770667	71873579	PROK2 | RYBP	A	0.2903	1.686	1.262	2.251	0.0004067
2	RS6708183	78384746	SNAR-H | REG3G	A	0.3252	1.706	1.269	2.295	0.0004101
4	RS11730104	4682267	STX18 | LOC100289434	C	0.4136	1.665	1.255	2.209	0.0004125
8	RS1497194	115351857	CSMD3 | TRPS1	G	0.4899	0.5859	0.4355	0.7883	0.0004131
20	RS8032661	44733811	NCOA5 | CD40	G	0.2208	0.4692	0.3083	0.7142	0.0004147
20	RS6064024	52546889	SUMO1P1 | BCAS1	G	0.4265	1.682	1.26	2.244	0.0004162
11	RS7926320	13782568	FAR1 | SPON1	A	0.388	1.664	1.254	2.207	0.0004164
15	RS8043317	27751786	GABRG3	A	0.05466	2.493	1.501	4.141	0.000418
17	RS1126642	42989063	GFAP	A	0.03552	2.741	1.565	4.8	0.0004211
10	RS317499	109995284	LOC100128304 | LOC645318	A	0.3357	0.5558	0.4009	0.7706	0.0004257
15	RS4777990	93018587	C15orf32	G	0.2817	1.715	1.27	2.316	0.0004304
2	RS10495786	33559429	LTBP1	G	0.1073	1.974	1.352	2.884	0.0004312
2	RS10200850	240234901	HDAC4	A	0.0652	2.22	1.424	3.462	0.0004344
2	RS8663354	108840227	MORC1 | LOC100288721	G	0.02901	3.265	1.689	6.313	0.0004352
2	RS1922351	35300334	MYADML | LOC100288911	G	0.3924	1.681	1.259	2.246	0.0004369
16	RS2356417	71356135	FTSJD1 | CALB2	G	0.1265	1.927	1.337	2.777	0.0004381
15	RS2028465	71659358	THSD4	C	0.2156	1.771	1.288	2.437	0.0004441
2	RS888281	56507299	CCDC85A	G	0.3252	1.662	1.252	2.208	0.0004457
23	RS12559251	90342188	LOC100288789 | PABPC5	C	0.175	0.2844	0.1409	0.5738	0.0004462
16	RS1424106	79216793	WWOX	A	0.4686	0.5839	0.4324	0.7884	0.0004463
2	RS17553946	155347161	GALNT13 | KCNJ3	A	0.2236	0.4806	0.3192	0.7236	0.000449
10	RS12220134	97129606	SORBS1	A	0.06174	2.421	1.477	3.966	0.0004499
2	RS16859880	220267737	DNPEP | LOC100288941	A	0.02126	4.044	1.853	8.828	0.0004507
2	RS1922353	35302429	MYADML | LOC100288911	C	0.418	1.689	1.26	2.264	0.0004518
21	RS2830247	27848998	CYYR1	G	0.07625	2.105	1.388	3.193	0.0004582
9	RS7036825	16125443	C9orf93 | BNC2	C	0.02193	3.692	1.778	7.666	0.0004596
20	RS2868714	44886189	CDH22 | SLC35C2	G	0.4879	1.676	1.255	2.237	0.0004617
13	RS9516888	97931709	MBNL2	A	0.4308	1.645	1.245	2.174	0.0004621
10	RS3932533	3925728	LOC100130652 | LOC727894	A	0.277	0.5138	0.3538	0.7461	0.0004668
9	RS2503351	19182893	ADFP | LOC100288002	G	0.1694	1.826	1.303	2.558	0.0004689
19	RS10469470	17187518	MYO9B	C	0.1276	0.3353	0.1817	0.6185	0.0004691
13	RS12869943	38356247	TRPC4	G	0.2549	0.5119	0.3517	0.745	0.0004698
2	RS328632	9247782	MBOAT2 | ASAP2	A	0.1694	0.3992	0.2386	0.6679	0.0004703
7	RS2158499	88558769	C7orf62 | ZNF804B	A	0.4163	0.5763	0.4231	0.7849	0.000472
10	RS12766986	3335061	PITRM1 | LOC100287172	G	0.1842	1.764	1.283	2.424	0.0004726
13	RS6491347	97930890	MBNL2	A	0.4372	1.641	1.243	2.167	0.0004732
6	RS6910470	149552517	UST | MAP3K7IP2	A	0.05815	2.367	1.46	3.836	0.0004738
7	RS2160138	7755797	RPA3	G	0.4565	1.676	1.255	2.239	0.0004741
12	RS1357241	74509618	TRHDE | LOC552889	C	0.4821	0.5933	0.4426	0.7952	0.0004769
22	RS929020	47971041	LOC100289420 | FAM19A5	A	0.17	1.836	1.306	2.583	0.0004774
20	RS2425835	44901836	CDH22 | SLC35C2	G	0.4337	1.673	1.253	2.234	0.0004801
9	RS11143833	71433741	PIP5K1B	A	0.01757	3.784	1.793	7.987	0.0004811
22	RS7284093	51121521	SHANK3	A	0.1492	1.876	1.318	2.671	0.000482
18	RS2564500	57230260	CCBE1	G	0.3822	1.668	1.252	2.224	0.0004825
3	RS212020	59988905	FHIT	A	0.09615	2.096	1.383	3.176	0.0004827
6	RS3869129	31410649	MICA | HCP5	A	0.2142	1.757	1.28	2.411	0.000485
15	RS1520015	37429504	MEIS2 | TMCO5A	A	0.2085	0.4596	0.2969	0.7114	0.0004863
6	RS17800315	150765510	IYD | PLEKHG1	A	0.2419	1.709	1.265	2.309	0.0004875
6	RS3899823	31410597	MICA | HCP5	A	0.2146	1.757	1.28	2.412	0.0004887
6	RS11757075	150766316	IYD | PLEKHG1	A	0.2421	1.708	1.264	2.309	0.0004914
12	RS2607916	716509	NINJ2 | LOC100049716	G	0.2301	1.738	1.274	2.372	0.0004928
15	RS8030720	90143567	C15orf42	A	0.1005	2.016	1.359	2.99	0.0004954
12	RS4489787	48811100	ZNF641 | ANP32D	G	0.1162	0.3285	0.1756	0.6147	0.0004976
14	RS2369319	96355334	TCL1A | C14orf132	A	0.1775	1.788	1.289	2.48	0.0004985
20	RS1883838	44761896	CD40 | CDH22	A	0.4126	0.5742	0.4201	0.7848	0.0005009
14	RS12897979	100056208	CCDC85C	A	0.368	1.676	1.253	2.243	0.0005036
15	RS6576617	27035375	GABRB3 | GABRA5	G	0.1053	2.004	1.354	2.965	0.0005056
18	RS4797173	466351	COLEC12	A	0.2517	1.707	1.263	2.308	0.0005061
12	RS1032725	32641200	BICD1 | FGD4	G	0.3109	1.676	1.253	2.242	0.0005065
3	RS2194938	139731000	CLSTN2	A	0.1955	1.764	1.281	2.43	0.0005077
12	RS1694747	17617111	LOC390298 | RERGL	A	0.08632	2.06	1.37	3.095	0.0005083
3	RS12497400	59986922	FHIT	G	0.1193	0.3111	0.161	0.6012	0.0005136
18	RS4797604	1213560	LOC100130247 | C18orf2	G	0.1215	2.024	1.359	3.012	0.0005148
3	RS575653	187596668	BCL6 | LOC339929	A	0.2831	1.69	1.257	2.272	0.0005167
17	RS7502216	36612948	SOCS7 | ARHGAP23	A	0.3826	0.5652	0.4095	0.7801	0.0005191
2	RS11888120	29322384	C2orf71 | CLIP4	A	0.2456	1.707	1.262	2.309	0.0005198
2	RS2390165	166059919	SCN3A	A	0.448	1.673	1.251	2.238	0.0005199
5	RS10041897	169893751	KCNMB1 | KCNIP1	A	0.225	0.4793	0.3164	0.7261	0.0005201
20	RS3092167	44922717	CDH22 | SLC35C2	A	0.4578	1.646	1.242	2.182	0.0005235
18	RS3748415	10471732	LOC100288932 / APCDD1	A	0.1144	0.2917	0.1453	0.5853	0.0005263
5	RS6891322	169897753	KCNMB1 | KCNIP1	A	0.1781	0.4204	0.2575	0.6862	0.0005278
7	RS17170988	37361023	ELMO1	C	0.2196	0.4803	0.3173	0.7272	0.0005287
6	RS2223451	150767547	IYD | PLEKHG1	A	0.2422	1.701	1.259	2.296	0.0005304
20	RS2425856	44911954	CDH22 | SLC35C2	A	0.4416	1.641	1.24	2.171	0.0005317
4	RS1438217	118039852	TRAM1L1 | LOC100288955	A	0.4335	1.652	1.243	2.194	0.0005318
12	RS10771958	32638162	BICD1 | FGD4	C	0.3107	1.667	1.248	2.226	0.0005321
7	RS2058893	97283118	ACN9 | TAC1	A	0.113	1.882	1.316	2.691	0.0005331
3	RS7626013	59961159	FHIT	G	0.1076	2.046	1.364	3.069	0.0005428
9	RS1972384	110210248	RAD23B | KLF4	A	0.1113	1.977	1.343	2.91	0.0005493
15	RS28408948	81998391	TMC3 | MEX3B	G	0.0105	7.914	2.448	25.58	0.0005494
6	RS476235	160622637	LOC100289162 | SLC22A2	A	0.3428	1.65	1.242	2.193	0.0005521
6	RS1885487	7668923	SNRNP48 | BMP6	G	0.3222	1.71	1.261	2.318	0.0005527
1	RS12061205	176554721	PAPPA2	A	0.1515	0.3932	0.2315	0.6681	0.0005568
1	RS10494201	118252257	FAM46C | LOC100131261	A	0.3151	1.658	1.244	2.209	0.0005574
12	RS1992136	109777361	FOXN4 | MYO1H	G	0.1103	0.3186	0.1664	0.6102	0.0005604
7	RS10486908	82860532	PCLO | SEMA3E	A	0.05803	2.398	1.459	3.942	0.0005634
2	RS6744657	155012888	GALNT13	A	0.237	0.4909	0.3276	0.7357	0.0005662
12	RS10861433	105877556	C12orf75 | NUAK1	A	0.226	0.4811	0.3173	0.7294	0.000568
3	RS9860107	60040105	FHIT	G	0.07996	2.157	1.393	3.34	0.0005682
9	RS11103417	137494787	RXRA | COL5A1	G	0.2436	0.5026	0.3398	0.7432	0.0005683
4	RS2196716	118055429	TRAM1L1 | LOC100288955	C	0.4764	0.5955	0.4434	0.7997	0.0005697
15	RS1435835	26412976	LOC100128714 | GABRB3	G	0.1292	1.931	1.328	2.808	0.0005763
21	RS4919983	43301781	PRDM15 | C2CD2	A	0.3155	0.5512	0.3926	0.7737	0.0005765
1	RS12067235	205281255	NUAK2	A	0.2213	0.4798	0.3158	0.7291	0.0005813
8	RS6985983	115289224	CSMD3 | TRPS1	A	0.4265	1.649	1.24	2.193	0.0005824
8	RS1552237	87045760	REXO1L2P | PSKH2	A	0.2854	1.672	1.247	2.241	0.0005854
9	RS10739231	98453680	PTCH1 | LOC100287056	A	0.4281	0.5842	0.43	0.7936	0.0005855
12	RS4767252	115187724	TBX3 | MED13L	A	0.33	1.67	1.247	2.237	0.0005858
12	RS995603	29235933	CCDC91 | FAR2	C	0.1993	1.785	1.283	2.484	0.0005862
7	RS206196	20361873	MACC1 | ITGB8	A	0.4213	0.5846	0.4305	0.7939	0.0005865

CHR	SNP	BP	GENE SYMBOL	Minor allele	Minor allele frequency	Odds ratio	95% CI Lower Limit	95% CI Upper Limit	P-value
2	RS893745	189088249	LOC729141	G	0.4933	0.5933	0.4406	0.799	0.0005872
6	RS6914476	26612363	ABT1 | ZNF322A	A	0.02328	4.264	1.864	9.752	0.0005914
4	RS6858670	137258380	LOC100289626 | LOC646316	G	0.4656	0.598	0.4459	0.8019	0.0005918
4	RS7688325	137260052	LOC100289626 | LOC646316	A	0.4656	0.598	0.4459	0.8019	0.0005918
8	RS290623	115395451	CSMD3 | TRPS1	A	0.473	0.5957	0.4433	0.8006	0.0005939
16	RS9889027	81341363	BCMO1 | GAN	G	0.2362	1.703	1.257	2.308	0.0005983
16	RS8055894	21190092	TMEM159	A	0.1414	1.894	1.315	2.728	0.0006004
7	RS1859107	21859436	DNAH11	C	0.1333	0.367	0.207	0.6506	0.0006012
9	RS2417753	109405667	LOC644620	G	0.1549	1.845	1.3	2.618	0.0006025
19	RS296366	48374538	SULT2A1	A	0.238	1.728	1.264	2.361	0.0006055
4	RS10516407	21883570	LOC100131836 | KCNIP4	A	0.1891	1.791	1.284	2.499	0.0006057
10	RS3818540	97165811	SORBS1	A	0.1043	2.08	1.369	3.162	0.0006058
10	RS10733970	58773025	ZWINT | IPMK	A	0.02161	5.501	2.075	14.58	0.0006088
1	RS6673391	30731688	LOC100288450 | MATN1	G	0.108	2.04	1.357	3.068	0.0006099
5	RS17192980	6977768	POLS | LOC442132	G	0.09959	1.951	1.331	2.859	0.0006113
10	RS4750200	6308646	PFKFB3 | LOC399715	A	0.3404	0.556	0.3974	0.7779	0.0006118
8	RS987341	18009367	ASAH1 | NAT1	A	0.05908	2.282	1.423	3.658	0.000613
16	RS7203768	73301302	LOC100288121 | LOC401859	G	0.3962	0.5831	0.4282	0.7939	0.0006145
18	RS9953631	39047265	LOC647946 | KC6	G	0.3239	0.5518	0.3926	0.7755	0.0006176
12	RS10770407	19087150	CAPZA3 | PLEKHA5	G	0.1381	1.939	1.327	2.833	0.0006179
8	RS7819086	115272300	CSMD3 | TRPS1	A	0.427	1.645	1.237	2.188	0.0006201
1	RS381115	153099345	SPRR2F | SPRR2C	A	0.1171	1.965	1.335	2.892	0.0006205
3	RS4927870	195820576	TFRC | FLJ25996	A	0.1191	1.975	1.338	2.917	0.0006207
12	RS4761520	93910308	MRPL42 | SOCS2	G	0.3067	0.5467	0.3869	0.7726	0.0006213
19	RS3786656	14506664	CD97	A	0.3364	1.645	1.237	2.188	0.0006225
10	RS2171302	3815292	LOC100287172	A	0.1721	1.826	1.293	2.578	0.000624
10	RS624964	11231831	CUGBP2	G	0.3161	1.687	1.25	2.276	0.0006241
2	RS7594456	212403434	ERBB4	A	0.3185	1.659	1.241	2.218	0.0006277
8	RS3808606	39769375	ADAM2 | IDO1	A	0.4727	1.659	1.241	2.217	0.0006282
17	RS7215344	2430126	METT10D | PAFAH1B1	G	0.2505	0.5055	0.3418	0.7476	0.0006328
17	RS7222013	66267691	SLC16A6	T	0.2498	1.737	1.265	2.384	0.0006334
10	RS317490	110051491	LOC100128304 | LOC645318	G	0.3357	0.5664	0.4088	0.7848	0.0006345
6	RS9463046	44802718	SUPT3H	G	0.03981	2.735	1.536	4.872	0.0006349
8	RS290592	115370512	CSMD3 | TRPS1	G	0.4835	0.5978	0.445	0.8031	0.0006351
11	RS1528663	13967222	FAR1 | SPON1	G	0.1916	0.4625	0.2971	0.7199	0.0006367
11	RS1507526	13940539	FAR1 | SPON1	A	0.363	1.658	1.24	2.216	0.0006371
8	RS4876325	115239083	CSMD3 | TRPS1	G	0.448	1.641	1.235	2.18	0.0006374
6	RS1333224	137801943	IFNGR1 | OLIG3	A	0.1134	1.968	1.334	2.902	0.0006387
15	RS8030303	61772892	RORA | VPS13C	A	0.02328	3.421	1.689	6.93	0.0006395
15	RS4906904	27034085	GABRB3 | GABRA5	A	0.07119	2.198	1.399	3.455	0.0006402
1	RS563189	83284533	LPHN2 | TTLL7	A	0.4204	1.634	1.233	2.167	0.0006456
3	RS6437813	108734088	MORC1	A	0.03036	3.124	1.623	6.011	0.0006474
10	RS12570530	12547825	CAMK1D	G	0.2901	0.5473	0.3871	0.7739	0.0006483
10	RS11591904	45346953	LOC100289168 | TMEM72	G	0.2783	1.678	1.246	2.26	0.0006578
20	RS6127015	52540606	SUMO1P1 | BCAS1	A	0.4585	0.5941	0.4403	0.8017	0.0006598
19	RS182420	48372195	CRX | SULT2A1	G	0.2407	1.722	1.259	2.354	0.0006606
10	RS6585876	86450858	LOC100131699 | GRID1	A	0.335	1.649	1.236	2.199	0.0006643
12	RS1800159	57593894	LRP1	A	0.3188	1.646	1.235	2.193	0.0006646
6	RS3101826	160584853	LOC100289162 | SLC22A2	A	0.3333	1.634	1.232	2.168	0.0006649
20	RS3092379	45432808	LOC100127904 | EYA2	G	0.4342	0.5947	0.4408	0.8023	0.0006705
11	RS161138	110892082	LOC120364 | C11orf53	A	0.3991	0.5867	0.4314	0.7978	0.0006739
1	RS884940	2223866	SKI	A	0.4298	1.628	1.229	2.155	0.0006749
2	RS13392442	221100327	SLC4A3 | EPHA4	A	0.03374	2.84	1.556	5.183	0.0006756
7	RS10254402	104192398	LHFPL3	G	0.06849	2.295	1.422	3.706	0.0006758
8	RS3802328	19297051	CSGALNACT1	G	0.3313	0.5617	0.4028	0.7833	0.0006762
5	RS256314	34617222	LOC729915 | LOC401180	A	0.03306	3.221	1.64	6.323	0.0006787
22	RS5754818	34464710	LARGE | ISX	A	0.4217	0.5851	0.4295	0.7971	0.000679
2	RS3771166	102986222	IL18R1	A	0.3782	1.654	1.237	2.211	0.0006793
9	RS10816456	98451928	PTCH1 | LOC100287056	A	0.225	0.5024	0.3378	0.7473	0.0006798
17	RS1858990	59735821	NACA2 | BRIP1	A	0.1707	1.783	1.277	2.488	0.0006802
7	RS10272276	41411165	C7orf10 | INHBA	G	0.198	1.75	1.267	2.417	0.000681
14	RS8017842	100055722	CCDC85C	G	0.4049	1.657	1.238	2.219	0.0006851
17	RS9910870	1471611	PITPNA | LOC100288617	A	0.2534	0.5119	0.3478	0.7535	0.0006854
9	RS7873155	16118758	C9orf93 | BNC2	C	0.02868	3.443	1.686	7.033	0.0006913
6	RS16895923	42633368	UBR2	G	0.1616	1.794	1.28	2.515	0.000692
4	RS716051	113964288	ANK2	G	0.1614	1.851	1.297	2.642	0.0006941
18	RS1019868	66753605	CCDC102B | DOK6	C	0.01284	19.66	3.516	109.9	0.0006952
2	RS10204137	102968212	IL1RL1	G	0.3802	1.652	1.236	2.209	0.0006956
2	RS10192157	102968356	IL1RL1	A	0.3802	1.652	1.236	2.209	0.0006956
2	RS10206753	102968362	IL1RL1	G	0.3802	1.652	1.236	2.209	0.0006956
9	RS10901213	133247453	HMCN2	C	0.113	1.931	1.32	2.825	0.0006968
16	RS9924119	71343397	FTSJD1 | CALB2	G	0.1184	1.915	1.315	2.788	0.0006983
15	RS4632084	70049424	LOC145837 | C15orf50	A	0.281	0.535	0.3726	0.7681	0.0006989
6	RS9497912	148296513	SAMD5 | SASH1	A	0.1269	1.901	1.311	2.756	0.0007016
2	RS831010	170139346	LRP2	G	0.165	1.792	1.279	2.511	0.0007023
12	RS7314861	29238335	CCDC91 | FAR2	A	0.1987	1.777	1.274	2.479	0.0007045
16	RS4287581	7032053	A2BP1	G	0.2594	1.703	1.252	2.318	0.0007073
10	RS17571397	12572613	CAMK1D	A	0.2601	0.5233	0.3595	0.7616	0.0007182
10	RS4021187	126756083	CTBP2	A	0.4825	0.6061	0.4535	0.8102	0.0007191
2	RS2048765	240208154	HDAC4	G	0.0641	2.183	1.388	3.433	0.0007214
2	RS4676312	107658016	LOC649489 | LOC729121	C	0.05162	2.39	1.442	3.961	0.0007214
8	RS925760	115227867	CSMD3 | TRPS1	A	0.4443	1.629	1.227	2.161	0.0007231
15	RS6494825	70046984	LOC145837 | C15orf50	A	0.4238	0.5973	0.443	0.8053	0.0007234
17	RS1971043	20043515	CYTSB	G	0.1838	0.4333	0.2668	0.7037	0.0007244
7	RS11971322	41386423	C7orf10 | INHBA	A	0.1866	1.76	1.268	2.442	0.0007256
12	RS7305820	74550782	TRHDE | LOC552889	G	0.4953	1.635	1.229	2.175	0.0007274
10	RS11188295	97125874	SORBS1	A	0.08907	2.149	1.379	3.35	0.0007291
3	RS3772460	59943532	FHIT	G	0.1086	2.005	1.339	3.003	0.0007339
9	RS295263	4840063	RCL1	G	0.1208	1.869	1.3	2.686	0.0007348
18	RS11080417	10423834	VAPA | APCDD1	A	0.2679	1.698	1.249	2.309	0.000736
17	RS7220740	59740793	NACA2 | BRIP1	A	0.3133	1.641	1.231	2.188	0.0007379
2	RS6431565	238836683	RAMP1 | UBE2F	A	0.3316	1.67	1.24	2.249	0.0007438
12	RS12823898	93860565	UBE2N | MRPL42	A	0.114	1.978	1.331	2.939	0.0007443
4	RS1395114	113953581	ANK2	A	0.191	1.797	1.278	2.526	0.0007508
11	RS627354	74028944	P4HA3 | PGM2L1	A	0.4325	1.621	1.224	2.146	0.0007512
1	RS10462021	7897133	PER3	G	0.1842	1.744	1.262	2.411	0.0007523
1	RS12125785	209254017	PLXNA2 | LOC642587	A	0.4015	0.595	0.4398	0.8049	0.0007573
13	RS9531028	80767832	LOC729479 | SPRY2	A	0.1899	0.4483	0.2811	0.7151	0.0007574
19	RS11083726	29388987	LOC148189 | LOC148145	A	0.4565	1.645	1.231	2.198	0.0007601
7	RS4730427	78285960	MAGI2	A	0.1309	0.3623	0.2006	0.6542	0.0007604
1	RS7527871	2281726	MORN1 | LOC100129534	C	0.1715	1.769	1.269	2.465	0.0007626

Supplemental Table S9. Details of the top 521 SNPs identified in discovery dataset (***cont***)

CHR	SNP	BP	GENE SYMBOL	Minor allele	Minor allele frequency	Odds ratio	95% CI Lower Limit	95% CI Upper Limit	P-value
12	RS11046362	22460338	ST8SIA1	A	0.1046	2.003	1.336	3.001	0.000764
7	RS2204779	118438184	ANKRD7 | LOC100287273	G	0.01619	4.926	1.946	12.47	0.0007653
8	RS1606891	115206234	CSMD3 | TRPS1	A	0.4483	1.627	1.225	2.16	0.0007696
12	RS12368128	125648067	AACS | TMEM132B	A	0.2449	0.5034	0.3375	0.751	0.0007698
4	RS7656244	65170415	SRD5A2L2	A	0.1859	0.4634	0.2959	0.7255	0.0007708
2	RS6547192	78434082	SNAR-H | REG3G	A	0.1373	1.89	1.304	2.739	0.0007725
2	RS6432964	149986664	LYPD6B	G	0.3654	0.5723	0.4133	0.7924	0.0007749
8	RS167069	115423582	CSMD3 | TRPS1	G	0.4848	0.6037	0.4497	0.8102	0.0007753
8	RS10283337	1319724	LOC401442 | DLGAP2	G	0.4052	1.625	1.224	2.157	0.0007815
4	RS7676913	118043203	TRAM1L1 | LOC100288955	C	0.4706	0.6035	0.4495	0.8104	0.0007854
1	RS493631	153143048	SPRR2G | LELP1	A	0.1195	1.968	1.325	2.921	0.0007874
14	RS878554	94606179	IFI27L2 | PPP4R4	A	0.2057	1.746	1.261	2.418	0.0007884
11	RS10894162	129781016	PRDM10	A	0.02092	3.344	1.652	6.767	0.000792
5	RS1154758	162716850	GABRG2 | CCNG1	G	0.4443	0.5973	0.4421	0.8071	0.0007932
10	RS7914288	71739556	COL13A1 | H2AFY2	G	0.389	1.629	1.225	2.167	0.0007965
17	RS7219555	59740122	NACA2 | BRIP1	C	0.3151	1.636	1.227	2.181	0.0007979
12	RS10783915	59001589	XRCC6BP1 | LRIG3	G	0.332	0.5723	0.413	0.793	0.000796
5	RS951087	13328289	CTNND2 | DNAH5	A	0.1107	1.971	1.325	2.931	0.0008055
13	RS9510573	23680990	LOC646201 | SGCG	A	0.1889	1.746	1.26	2.419	0.0008068
14	RS885845	96729728	BDKRB1	A	0.37	1.639	1.228	2.189	0.0008088
1	RS6676869	209249614	PLXNA2 | LOC642587	G	0.3036	0.5568	0.3952	0.7844	0.0008115
6	RS9283918	53926867	C6orf142	A	0.05904	2.267	1.404	3.661	0.0008121
6	RS9296737	53926716	C6orf142	G	0.05904	2.267	1.404	3.661	0.0008121
3	RS9841113	116455714	LOC285194 | IGSF11	A	0.4339	1.62	1.222	2.149	0.0008144
5	RS1023617	172740329	NKX2-5 | STC2	A	0.3128	1.66	1.234	2.235	0.0008162
3	RS4076927	46730749	ALS2CL	G	0.3171	0.55	0.3875	0.7807	0.0008215
8	RS10091115	62684067	LOC100287835 | NKAIN3	C	0.3381	0.5715	0.4117	0.7934	0.0008288
12	RS2364227	93893510	MRPL42	G	0.303	0.5558	0.3939	0.7844	0.0008315
21	RS2832279	30613466	C21orf109	A	0.3323	0.5744	0.415	0.7951	0.0008317
4	RS12508492	112696927	LOC729065 | C4orf32	G	0.05331	2.324	1.417	3.81	0.0008328
6	RS6940801	169655667	THBS2 | LOC100289536	G	0.1498	1.779	1.269	2.493	0.0008332
3	RS17485052	138638081	PIK3CB | FOXL2	A	0.1991	1.75	1.26	2.43	0.0008398
12	RS10746042	106111254	C12orf75 | NUAK1	G	0.2399	1.695	1.244	2.311	0.0008398
22	RS138154	46107105	ATXN10	G	0.2319	1.673	1.237	2.263	0.0008421
1	RS12120640	74821837	TNNI3K	G	0.1205	1.86	1.292	2.678	0.0008424
20	RS2425817	44895286	CDH22 | SLC35C2	A	0.4329	1.633	1.225	2.179	0.0008438
7	RS4730197	106446900	FLJ36031 | PIK3CG	C	0.1323	0.3697	0.2061	0.6631	0.0008448
6	RS2817457	156943434	NOX3 | ARID1B	A	0.4774	1.648	1.229	2.21	0.0008462
1	RS3006993	114570444	OLFML3 | SYT6	A	0.2696	1.671	1.236	2.258	0.0008466
11	RS7128466	120491438	ARHGEF12 | GRIK4	A	0.1437	0.4015	0.2349	0.6863	0.000849
11	RS11025673	20663967	SLC6A5	G	0.3812	1.6	1.214	2.109	0.000851
3	RS1523759	77604242	ROBO2	G	0.1711	0.4267	0.2586	0.7039	0.0008541
12	RS10746041	106108279	C12orf75 | NUAK1	G	0.2264	1.711	1.248	2.347	0.0008554
6	RS4895999	134147153	MGC34034	G	0.3805	1.614	1.218	2.139	0.0008575
3	RS10804937	103308760	LOC100287880 | ALCAM	A	0.3184	1.624	1.221	2.16	0.0008578
13	RS9557607	101950392	NALCN	G	0.03036	2.92	1.555	5.484	0.0008589
10	RS10826503	29010588	BAMBI | LOC729601	A	0.3866	1.636	1.225	2.185	0.0008601
10	RS619030	11206281	CUGBP2	A	0.2328	1.712	1.248	2.349	0.0008633
18	RS151472	3447871	TGIF1	A	0.2908	1.652	1.229	2.219	0.0008653
1	RS476093	181787259	CACNA1E | ZNF648	C	0.2446	1.683	1.239	2.285	0.0008663
1	RS12130076	240918105	GREM2 | LOC645939	G	0.1238	0.3612	0.1983	0.6577	0.0008678
1	RS2169089	5088617	AJAP1 | LOC100287877	A	0.2328	0.5191	0.3529	0.7635	0.0008679
20	RS8032678	44777295	CD40 | CDH22	A	0.4514	1.631	1.223	2.176	0.000871
12	RS4766019	3089354	TEAD4	A	0.123	0.3318	0.1733	0.6353	0.0008719
2	RS16985278	18734072	KCNS3 | RDH14	A	0.2635	1.684	1.239	2.288	0.0008739
3	RS1163368	108946466	C3orf66 | DPPA2	A	0.3219	1.621	1.22	2.155	0.0008751
7	RS11971933	111717031	DOCK4	G	0.09615	2.053	1.344	3.135	0.0008756
18	RS7506330	9177894	ANKRD12	G	0.4774	0.6034	0.4481	0.8125	0.0008765
6	RS9442693	72386001	C6orf155 | RIMS1	A	0.05027	2.582	1.476	4.514	0.0008798

CHR	SNP	BP	GENE SYMBOL	Minor allele	Minor allele frequency	Odds ratio	95% CI Lower Limit	95% CI Upper Limit	P-value
5	RS31036	146615260	STK32A	C	0.3286	1.644	1.227	2.203	0.0008802
7	RS974060	97271508	ACN9 | TAC1	G	0.2939	1.643	1.226	2.201	0.0008811
2	RS10183733	135071570	MGAT5	A	0.1772	1.773	1.265	2.484	0.0008825
18	RS4306606	55334295	ATP8B1	A	0.2713	0.5341	0.3691	0.773	0.0008836
18	RS2345	75279459	GALR1 | LOC100132713	G	0.06883	2.148	1.368	3.372	0.0008951
3	RS4974500	134109630	AMOTL2 | ANAPC13	G	0.4943	0.6023	0.4466	0.8124	0.0008961
3	RS1879784	183203034	MCF2L2 | KLHL6	A	0.4757	1.643	1.226	2.202	0.000898
4	RS12511494	113770535	ANK2	A	0.141	1.859	1.289	2.682	0.0009018
6	RS2474880	63460047	KHDRBS2 | LOC100128610	A	0.4325	1.638	1.224	2.192	0.0009037
15	RS11636337	70044354	LOC145837 | C15orf50	G	0.251	0.5284	0.3625	0.7704	0.0009116
11	RS1852755	13996686	SPON1	G	0.2611	0.529	0.3631	0.7707	0.000912
9	RS16933086	36215581	GNE	A	0.2016	1.685	1.238	2.293	0.0009121
8	RS12547514	55806439	LOC100287651 | XKR4	C	0.4172	1.638	1.224	2.194	0.0009135
7	RS13237260	7779091	RPA3 | LOC729852	A	0.2415	1.665	1.232	2.252	0.000918
13	RS9532283	39394277	FREM2	A	0.4673	1.626	1.22	2.168	0.0009189
2	RS12619691	35306866	MYADML | LOC100288911	A	0.3937	1.628	1.22	2.172	0.0009197
3	RS6766938	67150565	KBTBD8 | SUCLG2	A	0.2142	1.721	1.248	2.373	0.0009197
11	RS1852757	13987892	SPON1	G	0.1866	0.4711	0.3018	0.7353	0.0009207
9	RS7846713	8079286	C9orf123 | PTPRD	A	0.2375	1.7	1.242	2.327	0.0009219
5	RS457638	80359968	RASGRF2	G	0.1867	0.468	0.2986	0.7333	0.0009227
19	RS9917042	14494473	CD97	G	0.3212	1.623	1.219	2.162	0.0009241
8	RS12677088	19309945	CSGALNACT1	A	0.3126	0.5637	0.4015	0.7913	0.0009254
6	RS6570859	148829305	SASH1	G	0.3333	0.5748	0.4141	0.7977	0.0009283
15	RS7183427	39503508	LOC100289563 | C15orf54	C	0.1835	1.766	1.261	2.472	0.0009291
10	RS11003908	55645842	PCDH15	A	0.02092	4.64	1.87	11.51	0.0009301
14	RS1197382	81146776	C14orf145	G	0.08974	0.2693	0.1238	0.5856	0.0009328
7	RS3800895	2125942	MAD1L1	A	0.2743	1.636	1.222	2.19	0.0009334
10	RS7905027	124114432	BTBD16 | PLEKHA1	G	0.3932	0.5897	0.4313	0.8063	0.0009347
2	RS6748959	175424127	GPR155 | WIPF1	G	0.4906	0.6052	0.4495	0.8148	0.0009351
9	RS10814369	36292975	GNE | LOC646993	A	0.192	1.714	1.246	2.359	0.0009351
11	RS12793784	26700112	SLC5A12	A	0.1208	1.926	1.306	2.84	0.0009361
16	RS6564372	73324074	LOC100288121 | LOC401859	A	0.4986	0.6197	0.4668	0.8228	0.0009375
2	RS7559847	222068646	SLC4A3 | EPHA4	A	0.385	1.639	1.223	2.197	0.0009419
3	RS9790156	139814577	CLSTN2	A	0.1002	1.978	1.32	2.964	0.0009425
1	RS1925421	39250964	LOC400750 | RRAGC	A	0.2567	1.645	1.225	2.21	0.0009447
23	RS10521479	55583383	LOC644893 | FOXR2	A	0.1163	2.228	1.386	3.582	0.0009464
5	RS7446493	6974432	POLS | LOC442132	G	0.1029	1.905	1.3	2.791	0.0009471
1	RS3907135	106526262	LOC642337 | LOC126987	G	0.4926	1.628	1.219	2.173	0.0009488
2	RS4588165	35326722	MYADML | LOC100288911	A	0.414	1.631	1.22	2.18	0.0009507
5	RS2401793	13332878	CTNND2 | DNAH5	C	0.1123	1.952	1.313	2.904	0.0009537
3	RS11709505	53749498	CACNA1D	G	0.2328	1.684	1.236	2.294	0.0009593
2	RS9288433	212407077	ERBB4	A	0.3101	1.634	1.221	2.187	0.000961
10	RS4751800	122636730	BRWD2	G	0.1559	0.4236	0.2543	0.7054	0.0009626
23	RS6639393	4052872	LOC729162 | NLGN4X	G	0.2684	1.885	1.294	2.747	0.0009636
20	RS6109068	11588817	JAG1 | LOC728573	G	0.1211	0.3592	0.1955	0.6599	0.0009683
7	RS7788775	141817070	LOC93432	A	0.2318	0.5088	0.3406	0.7601	0.0009702
15	RS1426079	70044495	LOC145837 | C15orf50	A	0.4123	1.63	1.219	2.178	0.0009716
7	RS2613585	111186693	IMMP2L	G	0.1164	0.317	0.1601	0.6274	0.0009726
9	RS1889321	113300835	SVEP1	G	0.2682	1.65	1.225	2.221	0.0009738
10	RS7094645	72796318	PCBD1 | UNC5B	A	0.2481	0.5231	0.3559	0.7689	0.0009773
3	RS7633016	46728659	ALS2CL	A	0.3192	0.5552	0.3913	0.7877	0.0009774
18	RS6506772	75918499	GALR1 | LOC100132713	G	0.254	0.5182	0.3505	0.7662	0.000983
3	RS13084580	39188182	CSRNP1	A	0.1111	1.906	1.299	2.798	0.000987
7	RS10276017	140979971	LOC100129514 | LOC100130169	A	0.04082	2.507	1.451	4.333	0.0009892
13	RS7323413	55363417	LOC100287887 | PRR20	C	0.03745	3.145	1.59	6.221	0.0009912
9	RS6415721	14964952	FREM1 | LOC389705	G	0.319	0.571	0.409	0.797	0.0009913
20	RS11086320	49687647	MULTIPLE_GENES:3755,100128598	G	0.3013	1.662	1.228	2.249	0.0009953
4	RS1995917	24207765	PPARGC1A | LOC729175	G	0.06545	2.127	1.357	3.333	0.0009991

C. SUPPLEMENTAL REFERENCES

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