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Original Article

Preliminary genome wide screening identifies new variants associated with coronary artery disease in Indian population

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Abstract: Aim: Coronary artery disease (CAD) is a major health problem in developed and developing nations. Development of CAD involves a complex interaction between genetics and lifestyle factors. Individuals with high-risk genetic predisposition along with poor lifestyle are more inclined to the development of CAD. Advancement in genotyping technologies and increase in genome wide studies has provided a platform to identify new risk factors associated with CAD and associated complexities. Methodology: In this study we performed genome wide screening in 76 well-defined CAD cases and 77 control samples in Indian population. Interestingly, new variants are identified in three genes *viz*, VLDLR, IFITM2 and C2CD4C. Results: The odds ratios observed for variant rs1869592 (*VLDLR*), rs1059091 (*IFITMI*) and rs7247159 (*C2CD4C*) were 2.6 (1.4-4.8 95% CI), 1.9 (95% CI 1.2-3.1) and 2.1 (1.2-3.7 95% CI), respectively with significant *P* value <0.01. These variants that are associated with pathogenesis of CAD were not previously reported in literature. Moreover, we anticipate that these variants will be further validated using a larger sample size.

Keywords: GWAS, association, coronary artery disease, Indian population

Introduction

CAD (Coronary Artery Disease) is associated with atherosclerosis in coronary arteries and is usually asymptomatic [1]. Atherosclerosis is the constriction of blood vessels, leading to poor supply of oxygen to heart and an imbalance is created between supply and demand of oxygen [2]. CAD is a broad term that encloses the diagnosis of myocardial infarction, silent myocardial ischemia, and angina pectoris. The mortality rate due to CAD has decreased but it still causes one third of all the deaths in individuals above 35 years of age [3]. The risk factors include smoking, psychological factors, diabetes, obesity, alcohol, physical inactivity, hypertension, diet, and many others [4]. Genetic factors play an important role along with the other factors. Several genetic studies have characterized 9p21 as the most established locus associated with CAD [5-7]. Various variants in this locus have been observed to be causing risk of CAD in different ethnicities; in Irish population rs10757274, rs2383206 and rs1333049 were observed to be strongly associated with CAD (level of significance ranges from 10^{-6} to 10^{-7}) [8]. In Indians the rs10757278 and rs2383207 at 9p21 have been replicated and these two variants were found be strongly associated with CAD (*P* values 10^{-5}) [9]. However, the same locus has shown debatable results where the variants have shown no association with severe CAD in individuals [10, 11], indicating either that there are multiple genes playing role in pathogenicity of CAD or genetic heterogeneity due to pooling of different individuals of different ancestry [12]. Additionally, *PCSK9* gene variant E670G (rs505151) has also been evaluated in various ethnicities and is considered among the most explored variant associated with CAD with significant *P* value <0.05 [13-15]. These two genes along with other variants CAD can only explain ~50% of genetic heritability using genome wide variants

[16] whereas heritability of CAD is between 40-60% based on family and twin studies [17]. Still, this variant effect is limited when evaluated in a sporadic population and almost 8% of the population inherits genetic predisposition towards the risk of CAD [18], indicating that polygenic inheritance plays pivotal role in complex disorders like CAD [18, 19]. With advent of genome wide association studies, novel variants associated with CAD were identified and such studies also show that the small effects of common variants play crucial role in pathogenesis [5, 18, 20, 21]. Perturbingly, most of the studies took place in a European population and limited studies were carried out in South Asians [18, 22]; such studies are scanty especially in Indian ethnicity. However, the burden of CAD is speculated to be higher in Indians than other global populations [23, 24]. In addition to CAD burden, prevalence of coronary heart diseases in India increased from 1.6 to 7.4% and 1 to 13.2% in rural and urban populations respectively [25]. Increasing CAD burden and high involvement of genetic factors highlights a dire need to conduct genome wide screening in Indian population groups. Such studies may identify the population specific risk variants. Since there is a scarcity of information related to the genetic risk factors involved in CAD in an Indian population, we performed preliminary genome wide screening to identify novel putative genetic variations associated with CAD.

Materials and methods

Sample selection and collection

A total of 153 individuals (77 controls and 76 cases) were included in the study. The patients undergoing Percutaneous Coronary Intervention (PCI) at Army Research and Referral Hospital, New Delhi India were included in the study and all cases were not consecutive coronary artery disease (CAD) patients; they were selected based on Coronary Angiography (CAG). They underwent CAG to address a culprit lesion, followed by planned PCI for a complex lesion later. Patients were referred by an interventional cardiologist and informed consent was obtained.

Age and gender matched healthy controls were selected for the study with no family history of CVD or any other disorder. Those who self-reported a history of CVD were excluded from the study. Alood sample was collected properly by a phlebotomist. The vials were stored at 4°C. The study was approved by Institute Ethics Committee Army Hospital (R&R), Hospital, Delhi (approval number-IEC Regn No.01/2022). The detailed characteristics of CAD cases and healthy controls are summarized in Supplementary Tables 1 and 2.

DNA isolation and genotyping

Upon receiving the samples, the DNA was isolated using QIAGEN DNA Investigator Kit and the quality and concentration was checked by 1% Agarose gel electrophoresis. After the isolation of DNA, the samples underwent the protocol of Illumina Infinium High-Throughput Screening (HTS) Assay for genotyping. DNA was amplified in a 96 well plate by adding the reagents along with the DNA and then the plate was incubated overnight at 37°C in the hybridization oven for 20-24 hours. After incubation, the DNA was fragmented and precipitated in the plate. After precipitation of DNA, a blue color pellet was seen which contains the DNA. The pellet was re-suspended and 14 µl of DNA was loaded onto the BeadChip and were kept in the hybridization chamber. The hybridization chamber was kept in the hybridization oven at 48°C for 16-24 hours. Bead chips were taken out and loaded onto the chamber rack for washing and staining. The chamber racks were setup in a water circulator to regulate the temperature and were washed and stained using different reagents. The BeadChips were dried in a vacuum desiccator before imaging. After these were dried, the BeadChips were scanned using the iScan control software. After the scanning, the *idat* files so obtained were uploaded in the Genome Studio 2.0 to observe the call rate. The call rates obtained was greater than 99%. The genome studio plink plug-in was used to convert the genotyping data into plink format for further analyses.

Statistical and in silico analyses

The statistical analysis was mainly performed using Plink v.1.9 with maximum 10,000 permutations. Each SNP was tested for Hardy Weinberg Equilibrium (HWE) [26]. The data filtering technique was adopted from previous studies [27, 28]. The result obtained was in the form of odds Ratio (OR) adjusted for age, gender, and BMI with 95% Confidence Interval. Additionally, Calculated OR and allele count was used to cal-

Table 1. Allele frequency distribution and variants associated with risk of CAD

Chromosome	SNPs	Gene (Functional Annotation)	Risk Allele	RAF in cases	*P* value*	OR (95% CI)
9	rs1869592	VLDLR (Intronic Variants)	A	0.2905	0.0014	2.6 (1.4-4.8)
11	rs1059091	IFITM2 (Missense Variant)	A	0.5066	0.0051	1.9 (1.2-3.1)
19	rs7247159	C2CD4C (3 prime UTR)	A	0.3071	0.0051	2.1 (1.2-3.7)

RAF-Risk Allele Frequency, OR-Odds Ratio, P is significant <0.01, *Adjusted for age, gender, and BMI, HWE in controls >0.05.

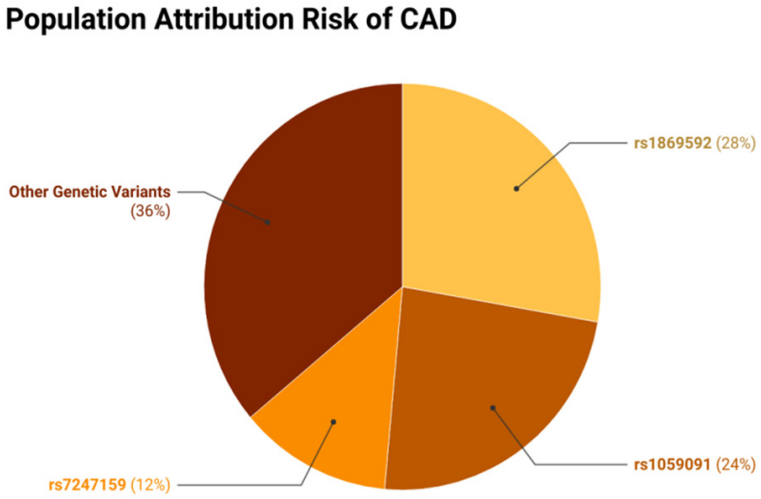

Figure 1. Population attribution risk recognized by three associated variants in study population group.

culate population attribution risk (PAR) using PAR calculator of Center for Clinical Research and Biostatistics (CCRB) (www2.ccrb.cuhk.edu.hk). Network analysis was performed using GeneMania prediction server [29]. The gene specificity towards expression quantitative trait loci (eQTL) was predicted using FUMA GWAS [30].

Results

Genetic association analyses

We conducted genome wide screening in 153 individuals which includes 76 cases and 77 controls. Anthropometric characteristics of the participants are summarized in Supplementary Table 1. We observed three novel variants in chromosome 9, 11, and 19 that were found to be associated with CAD in studied population groups. The OR observed for the variant rs-1869592 of very low density lipoprotein receptor (VLDLR) gene was 2.6 with 95% CI 1.4-4.8. The OR observed for the variant rs1059091 of interferon induced transmembrane protein 1 (IFITM1) gene showed OR 1.9 with 95% CI of 1.2-3.1. The third variant that increased risk of CAD was rs7247159 of C2 calcium-dependent domain containing 4C (C2CD4C) gene and OR observed was 2.1 with 95% CI 1.2-3.7. The level of significance observed for all the three variants was <0.01. Statistical analyses showed that all the three variants observed are associated with the risk of CAD in an Indian population (**Table 1**). Other variants that have shown association are summarized in Supplementary Table 3.

Population attribution risk calculation

The observed allele count was used to calculate PAR and PAR observed for the variant rs-1869592 was 28.5%, rs1059091 was 24.3% and rs7247159 was 12.8%. The summarized PAR values are presented in **Figure 1**.

Functional mapping and annotation of associated SNPs

Furthermore, to observe the specificity of these variants in specific tissues (coronary artery) out of three, two genes (*i.e. IFTM1 and VLDLR*) that were observed show expression in the coronary artery tissue (**Figure 2**). Our statistical analyses and gene expression data support our observation that the variants discovered increase risk of CAD.

Discussion

South Asians represent more than 23% of global population and are significantly exposed to a risk of CAD [31]. Genome wide polygenic risk score study of CAD in South Asians observed that the Indian cohort samples have a times higher risk of developing CAD on the basis of

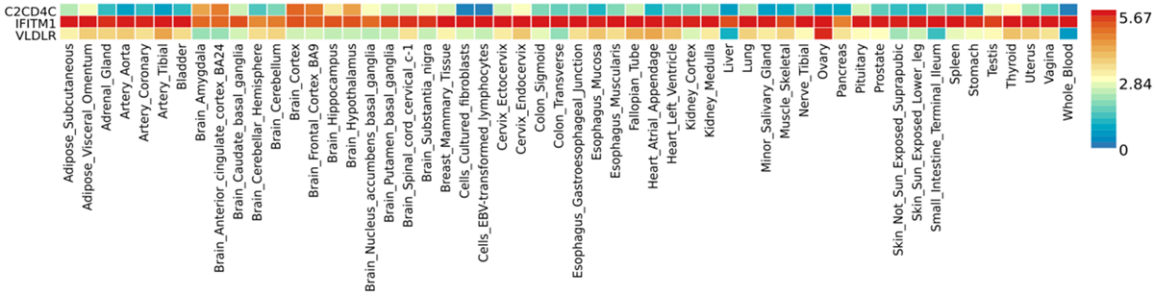

Figure 2. Heat map of gene expression of the genes that were observed associated with CAD in studied population group.

polygenic risk models [32]. It has been speculated that genome wide screening in Indian-specific endogamous groups may provide an insight of novel risk variants and would contribute in understanding the missing heritability of CAD. It is also important to replicate established CAD markers in Indian population groups. Population-based case control studies have observed that various established loci were significantly associated with risk of CAD in Indians [9, 33, 34]. Genome wide screening studies are almost absent in Indian ethnic groups. The present study was population based genome wide case-control association in Indian population where we evaluated 153 individuals (77 cases of CAD and 76 controls). As per our knowledge, this is the first study of CAD specifically focused on an Indian population.

Three variants, rs1869592, rs1059091, rs7247159 of genes VLDLR, IFITM1 and C2CD4C, respectively were found to be associated with risk of CAD in the studied population group. In this genome wide screening, ~0.7 million markers were evaluated. It observed only three markers in chromosome nine, eleven and nineteen that have show a significant association with the studied trait. Among these three significant variants, rs1869592 of *VLDLR* showed higher odds of 2.6 whereas the odds observed in other two variants were 1.9 and 2.1 for variants rs1059091 (*IFITM2*) and rs7247159 (*C2CD4C*), respectively for CAD risk. Additionally, variants rs1869592 of VLDLR genes showed a higher significance level than other two variants supported by high PAR *i.e.,* 28%. We further searched the scientific literature to explore the connection of gene observed with their speculated functional applications.

The low density lipoprotein receptor (LDLR) gene is comprised of cell surface proteins that have role in receptor based lipid endocytosis [35]. It also plays important roles in VLDL-triglyceride metabolism and the reelin signaling pathway [36]. Significant relation between VLDL cholesterol levels and atrial cholesterol concentration was observed in atrial biopsies obtained during coronary artery surgery [37]. Additionally, VLDLR was observed to be an independent risk factor in atherosclerosis as VLDLR mRNA was found to be highly induced in atherosclerotic lesions [38]. The variant rs1869592 of VLDLR showed a lower risk of CAD in our studied population, indicating the variant may influence the metabolism of lipoprotein and may have a role in CAD.

Another variant that was found to be associated with risk of CAD is rs1059091 of IFITM1 gene. Interferon Induced Trans membrane Protein 1 plays key role in body defense against viruses and parasites, exhibits anti-proliferative and differentiating activities, and immune-modulating responses [39]. Interferons play a protective role in cardiomyocytes by fighting against viral infection. There is growing *in vitro* evidence that interferons play a critical role in cardiomyocyte apoptosis [40]. The interferon upregulation increased susceptibility towards vascular diseases in systemic lupus erythromatosus patients [41]. An *In vivo* study reveals that interferons (IFITM1 and IFITM3) are possibly involved in differentiation and cell proliferation during heart development [39]. The study highlights that IFITM1 may have a role in impairment associated with CAD and the missense variant that is found is associated with development of CAD.

A third variant that was observed to be associated with the risk of CAD in the studied population group was rs7247159 of C2CD4C gene. It is C2 Calcium Dependent Domain Containing 4C Protein Coding gene [42]. Some SNPs in

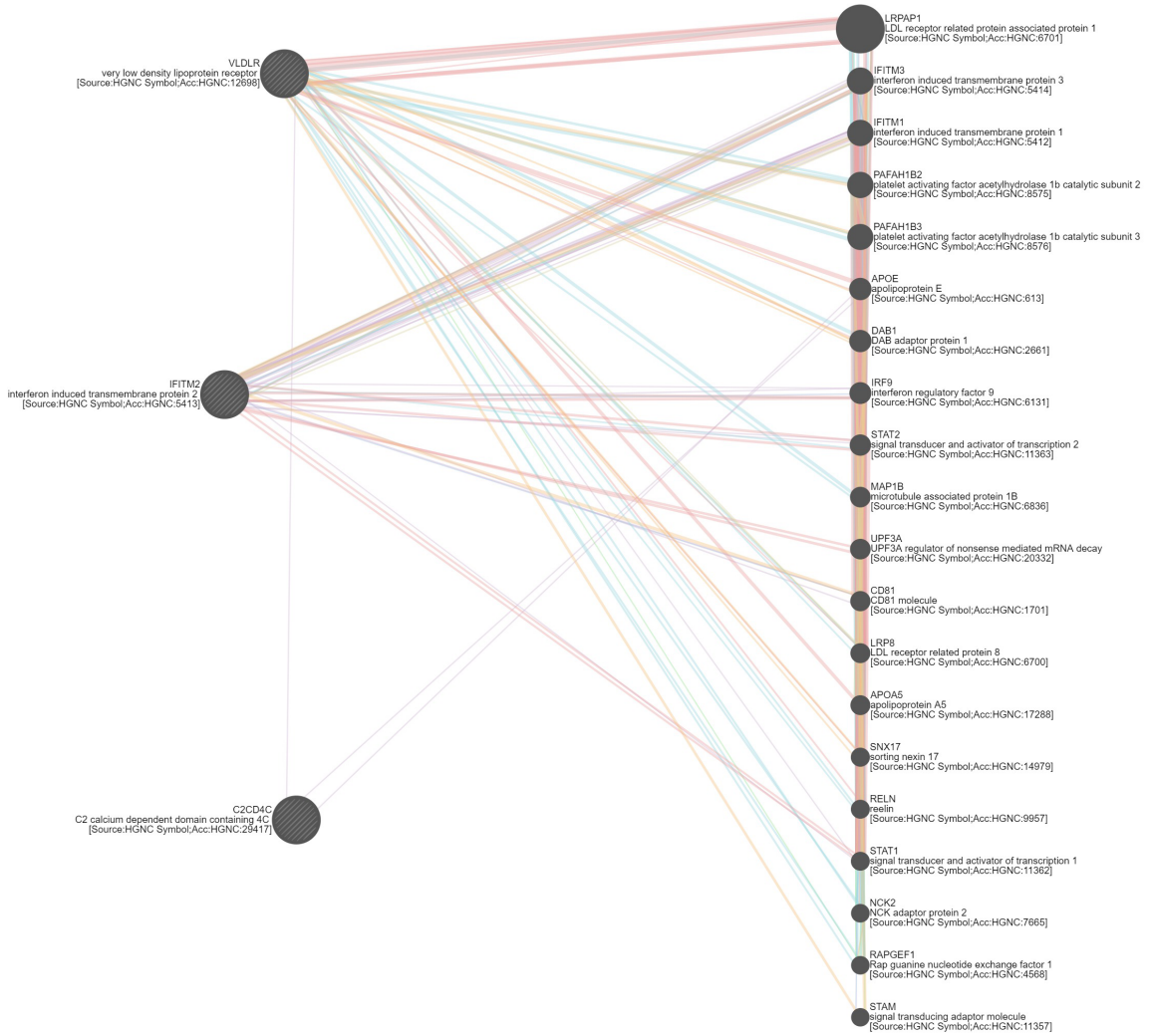

Figure 3. Network analyses represent genetic interaction among identified genes associated with CAD.

C2CD4C region were previously associated with clinical cardiovascular events [43]. There were previously reported SNPs in the C2CD4C gene, and our results agree, highlighting a role of the identified variant in CAD. We performed network analysis among the identified genes using GeneMania. All three genes are 70% functionally interconnected and 30% in co-expression as well as in pathways (**Figure 3**).

In conclusion, our study suggests SNPs in *VLDLR, IFITM1 and C2CD4C* are commonly associated with CAD in Indian population groups. To the best of our knowledge the variants so observed in present study have never been reported in other populations. Additionally, PAR calculation shows that all three associated variants contribute >10% of attributed risk towards CAD, highlighting more genetic variants is needed to be explored to have precise evidence about the genetic susceptibility towards CAD in Indians. Moreover, network analyses have shown an increased effect in associations suggesting the importance of gene-gene and pathway based interaction between multiple functionally important genes (**Figure 2**). Our study was not able to attain the GWAS threshold (*i.e.* $p>5*10^{-8}$), is the only limitation and the plausible reason could be small sample size (N = 153). Moreover, the putative functional annotations of these variants indicate that these might have strong regulatory role in CAD which further warrants functional validation studies of these variants. These variants should be added in polygenic risk modeling, as there is scarcity of GWAS of such disor-

ders specifically for Indian population groups, where the incidence rate of CAD is soaring. We anticipate further such genome wide screening of Indian populations with larger sample size would contribute in understanding the missing heritability of CAD.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Distribution of risk factors among CAD cases and healthy controls

Data	Cases (N = 76)*	Controls (N = 77)**
Age (in years)	59.7 (±17.9)	57.47 (±19.03)
Gender (in percentage)	Male = 88.16%	Males = 71.43
	Females = 11.84%	Females = 28.57%
BMI (in Kg/m^2)	23.9 (±3.7)	24.1 (±4.0)
Smoking (in percentage)	Yes = 17.1%	--
	No = 82.9%	
Alcohol Consumption (in percentage)	Yes = 21.05%	--
	No = 78.95%	
Hypertension (in percentage)	Yes = 21.05	--
	No = 78.95	
Diabetes (in percentage)	Yes = 28.95	--
	No = 71.05	
Thyroid (in percentage)	Yes = 3.95	--
	No = 96.05	

*All cases are confirmed by Coronary Angiography (CAG), **All controls are healthy with no indications of CAD with any family history of CAD or disorders associated with CAD.

Supplementary Table 2. Clinical profile of CAD cases

Data	Total CAD patients (n = 76)
Stable CAD	41 (53.9%)
Acute Coronary Syndrome	35 (46.1%)
Unstable Agina	7 (9.1%)
NSTEMI (Non-ST-elevation myocardial infarction)	5 (9.2%)
STEMI (ST-elevation myocardial infarction)	23 (30.3%)
LV Dysfunction	17 (22.4%)
Severe	5 (6.6%)
Moderate	2 (2.6%)
Mild	10 (13.15%)
Culprit Lesion (The angiographic distribution of CAD in patients)	
Triple Vessel Disease	17 (22.4%)
Double Vessel Disease	14 (18.4%)
LAD (Left anterior descending artery)	50 (64.9%)
RCA (Right coronary artery)	28 (36.8%)
LCX (Left circumflex artery)	17 (22.4%)

Supplementary Table 3. Variants shown association with CAD

CHR	SNPs	BP	A1	A2	*p* value	OR
2	rs4643574	315215	A	G	0.04695	0.5547
2	rs59365208	322579	A	G	0.04912	1.9
2	rs1511326	478095	A	C	0.01323	1.794
2	rs59053869	730616	A	C	0.04491	1.624
2	rs55681810	733101	G	A	0.003864	1.973
2	rs13428401	733534	C	A	0.02477	2.902
2	rs4854364	741003	G	A	0.008459	1.889
6	rs11242709	209159	A	G	0.000506	2.813
6	rs908026	455419	G	A	0.03233	0.5873
6	rs12202284	471136	A	C	0.03555	0.3639

6	rs17236435	474260	A	G	0.02988	4.783
6	rs11242905	474405	G	A	0.01684	1.797
6	rs9392573	480628	A	G	0.0128	1.872
6	rs62388784	527329	A	G	0.01151	0.1733
6	rs2493037	533866	A	G	0.04998	2.182
6	rs6904638	541668	A	G	0.00511	0.3969
6	rs9405932	702434	A	G	0.04858	2.787
6	rs9405947	714311	A	G	0.03374	2.135
9	rs13293251	275216	A	G	0.03233	0.5873
9	rs1556022	326767	A	G	0.01646	1.737
9	rs7854418	335545	A	G	0.03846	0.6209
9	rs7855377	349518	A	C	0.005909	0.4698
9	rs1887528	354680	A	G	0.03481	0.6036
9	rs10972267	359381	G	A	0.01936	0.5302
9	rs12335885	359395	A	G	0.03636	0.5645
9	rs10974325	417477	G	A	0.01291	1.827
9	rs10815054	476518	G	A	0.0175	2.438
9	rs10974726	476996	G	A	0.03362	2.312
9	rs2021846	537031	A	G	0.03873	2.2
9	rs10975061	543631	A	G	0.01897	1.82
9	rs2296055	676954	G	A	0.01041	2.068
9	rs4742226	678088	C	A	0.01824	1.835
9	rs73639400	683423	G	A	0.001658	2.526
9	rs13296848	701529	A	G	0.03984	1.606
9	rs7860464	710966	A	G	0.04858	2.787
9	rs34680571	712066	C	A	0.0151	3.754
9	rs11789987	712599	A	G	0.005826	0.5287
9	rs7043585	720179	A	G	0.03033	1.776
9	rs10815530	724217	G	A	0.01168	0.5592
9	rs4740943	853004	G	A	0.02946	1.658
9	rs10739166	857511	A	C	0.004358	0.5073
9	rs10815892	859401	A	G	0.0491	1.718
9	rs7859005	1128641	G	A	0.0379	1.627
9	rs10960072	1174357	A	G	0.02222	0.5786
9	rs12341911	1183069	A	G	0.01987	0.1225
9	rs10961113	1362503	A	G	0.02915	0.3947
9	rs10961278	1393733	A	G	0.004354	4.003
9	rs56309544	1401847	A	G	0.03338	0.2148
9	rs6474799	1404008	A	C	0.03785	1.936
9	rs9406478	1447107	G	A	0.03709	2.276
9	rs1537229	1461491	A	G	0.01995	0.5819
9	rs77936933	1702480	A	G	0.0331	0.1391
9	rs59340403	1817040	A	C	0.04999	0.2899
9	rs1556412	1823898	A	G	0.04999	0.2899
9	rs16935641	1925055	A	G	0.008693	0.2741
9	rs7040790	2013962	C	A	0.01232	0.5514
9	rs2376311	2116715	A	G	0.009738	3.313
9	rs62528854	2243407	G	A	0.0426	0.3198
9	rs986567	2593528	A	G	0.04371	2.11
9	rs117558446	2611095	A	G	0.0331	0.1391

9	rs11790563	2616042	A	G	0.0332	1.676
9	rs1869592	2632250	A	C	0.001464	2.639
9	rs12001327	2801706	G	A	0.01885	0.1209
9	rs6476233	3085371	G	A	0.03121	0.5833
9	rs10969874	3091208	G	A	0.007914	3.182
9	rs10970967	3250025	C	A	0.01115	0.5323
9	rs12236365	3733568	G	A	0.01965	0.192
9	rs60069291	3763952	A	G	0.03109	1.843
9	rs10758497	3851138	G	A	0.02161	0.5758
9	rs624290	3928115	G	A	0.004191	0.4
9	rs514716	3929424	G	A	0.02928	0.5152
9	rs13299873	4145545	G	A	0.03583	0.5819
9	rs10814891	4226630	A	G	0.04435	0.6078
9	rs4097544	4303264	G	A	0.03066	3.023
9	rs12350802	4314701	A	G	0.02684	3.927
9	rs59865522	4421123	A	G	0.01689	2.038
9	rs10815017	4546594	A	G	0.01696	0.5159
9	rs12553697	4591655	G	A	0.002597	2.67
9	rs295258	4845242	G	A	0.02404	0.5713
9	rs7864244	4909719	A	G	0.01731	1.788
9	rs71490248	4911899	G	A	0.005887	0.5197
9	rs7025867	4937872	G	A	0.0318	1.692
9	rs10975043	5299385	A	C	0.007983	0.528
9	rs1478938	5931216	G	A	0.04348	2.302
9	rs7044750	5983655	G	A	0.03882	2.701
9	rs10435816	6225535	G	A	0.01586	1.819
9	rs41306063	6415643	G	A	0.0331	0.1391
9	rs41281769	6551009	C	A	0.01735	5.352
9	rs16924682	6552278	C	A	0.04417	0.5205
9	rs10975829	6786677	C	A	0.02649	3.414
9	rs10975914	6935864	C	A	0.009844	9.5
9	rs77387324	6938672	G	A	0.01735	5.352
9	rs702279	6969634	A	C	0.04459	0.624
9	rs10975955	6996653	A	G	0.004097	0.3511
9	rs818882	7015330	A	C	0.04365	0.5542
9	rs10815545	7198770	A	C	0.02477	2.902
9	rs10115790	7345304	A	G	0.01188	0.4567
9	rs10976267	7376457	G	A	0.004784	0.5143
9	rs4360345	7378095	A	G	0.04701	1.737
9	rs7871958	7379168	A	G	0.006069	1.883
9	rs7875214	7379214	G	A	0.0071	0.5319
9	rs10758869	7513262	G	A	0.004469	0.4729
9	rs10976342	7515401	G	A	0.006045	0.2331
9	rs74563685	7592809	C	A	0.04164	0.4826
9	rs186629	7725346	G	A	0.02312	1.814
9	rs1332900	7726450	G	A	0.03747	1.67
9	rs10976570	7780025	G	A	0.03486	0.4217
9	rs10976571	7780039	A	G	0.04386	0.4198
9	rs1407467	7968906	C	A	0.02661	0.5821
9	rs4615627	8010033	A	C	0.02136	2.099

9	rs12001886	8253224	G	A	0.04462	3.545
9	rs7861890	8255046	G	A	0.02976	0.5598
9	rs7039677	8256711	G	A	0.02419	0.5547
9	rs10815810	8262808	A	G	0.03066	3.023
9	rs3847287	8339227	A	G	0.03013	7.386
9	rs116782075	8418715	G	A	0.04602	0.23
9	rs7028474	8428381	A	G	0.03079	2.644
9	rs12352744	8436084	C	A	0.01965	0.192
9	rs1323588	8453781	A	G	0.03933	1.612
9	rs55855913	8655496	G	A	0.0262	2.318
9	rs2137346	8678922	C	A	0.03944	2.143
9	rs4742531	8706540	C	A	0.02997	1.65
9	rs7021929	8745095	A	C	0.02658	4.921
9	rs17576912	8781848	G	A	0.02528	0.4423
9	rs7846894	8880355	A	G	0.02958	0.5965
9	rs7867067	8890946	G	A	0.01017	0.4625
9	rs7853293	8894013	G	A	0.02055	0.5846
9	rs72706235	8925192	G	A	0.0374	3.214
9	rs1433548	8937116	G	A	0.03446	0.6097
9	rs7852703	8955010	C	A	0.01025	1.843
9	rs78840328	9001759	A	G	0.03013	7.386
9	rs66514248	9166788	G	A	0.02747	0.4907
9	rs7034934	9216473	G	A	0.01389	0.5141
9	rs12336488	9228107	G	A	0.049	0.5829
9	rs7018892	9230415	A	G	0.0487	2.034
9	rs4742571	9235372	A	C	0.002027	2.395
9	rs10977620	9258114	G	A	0.03047	0.5425
9	rs4740975	9321113	A	G	0.03971	1.604
9	rs17606608	9374664	A	G	0.03785	1.936
9	rs10977713	9389169	G	A	0.002519	0.4347
9	rs1333108	9459099	G	A	0.005938	2.041
9	rs7871358	9463789	G	A	0.03873	2.2
9	rs16929560	9474970	A	C	0.008163	1.923
9	rs4551426	9495226	G	A	0.008869	0.5222
9	rs117589065	9498171	A	G	0.02988	4.783
9	rs1408122	9756868	A	G	0.03188	2.034
9	rs768225	9770741	G	A	0.003864	1.973
9	rs12238410	9772434	A	G	0.02098	2.654
9	rs72692717	9867163	C	A	0.03013	7.386
9	rs10759119	9981323	G	A	0.02112	1.85
9	rs210035	10051451	C	A	0.03987	1.604
9	rs16925550	10227095	A	G	0.0175	2.438
9	rs58950125	10382986	A	G	0.03368	1.895
9	rs114854298	10393771	G	A	0.01689	2.038
9	rs16926616	10904815	A	G	0.001815	0.4099
9	rs11999352	10913676	G	A	0.002719	0.4231
9	rs7021524	10928314	G	A	0.004055	0.5019
9	rs10738194	10931959	A	C	0.001657	0.4514
9	rs10809261	10957549	A	G	0.01809	0.5328
9	rs7858983	10962971	A	G	0.03646	0.5952

9	rs1931401	11091254	A	G	0.04656	0.576
9	rs1387292	11254070	A	G	0.02036	0.5698
9	rs12552533	11345138	A	C	0.03933	1.612
9	rs1339272	12197936	G	A	0.04487	1.758
9	rs10809725	12206054	C	A	0.01354	2.084
9	rs10960686	12509604	G	A	0.0342	0.5351
9	rs10960688	12517689	A	G	0.02562	0.4043
9	rs116720470	12539719	A	G	0.01644	1.739
9	rs4428755	12593124	A	C	0.002821	0.5009
9	rs10756383	12596588	A	C	0.02682	1.829
9	rs10960740	12652038	A	C	0.01573	0.5717
9	rs16929332	12671693	A	G	0.003592	0.3864
11	rs4029235	199673	A	G	0.01529	0.343
11	rs12363841	296682	G	A	0.04083	1.895
11	rs1059091	309127	A	G	0.005168	1.949
11	rs1128982	400040	G	A	0.03952	1.738
11	rs112888889	627517	A	G	0.0374	3.214
11	rs60218802	1059587	A	C	0.01981	2.821
18	rs74585125	308782	A	G	0.03758	2.063
18	rs76025751	369236	A	G	0.01356	2.279
18	rs75663680	373036	G	A	0.02897	2.441
18	rs9945820	373670	A	G	0.01404	0.2934
18	rs16944827	458505	A	G	0.04462	3.545
18	rs66567167	515876	C	A	0.02043	0.554
18	rs498087	614449	G	A	0.03486	0.4217
18	rs75210858	634534	G	A	0.03048	0.2617
18	rs6506474	721198	G	A	0.02237	1.692
18	rs35235427	2157996	A	G	0.0365	0.5661
18	rs1834536	2160387	A	G	0.02246	0.5369
18	rs439890	3720081	A	G	0.01476	2.572
18	rs3910707	3873447	A	C	0.03901	0.6221
18	rs7239044	3965251	G	A	0.01635	0.2703
18	rs79747906	3967852	G	A	0.009749	0.3234
18	rs7505745	4099242	A	G	0.02947	1.72
18	rs4798168	4105490	G	A	0.02506	1.756
18	rs567511	4224615	G	A	0.02168	0.5885
18	rs115942723	4232091	A	C	0.01845	0.1893
18	rs8095163	4232552	G	A	0.01965	0.192
18	rs12456121	4381357	A	G	0.03137	1.931
19	rs10410591	288771	C	A	0.02297	3.507
19	rs10422863	367089	A	G	0.04999	0.2899
19	rs59169062	405164	A	G	0.01792	1.797
19	rs7247159	406724	A	G	0.005194	2.182
19	rs117685610	406783	A	G	0.008693	0.2741
19	rs12978500	406934	C	A	0.002027	2.395
19	rs149026358	517315	A	G	0.004921	3.366
19	JHU_19.582252	582253	A	G	0.01949	0.4161
19	rs34397648	610273	A	G	0.03043	0.2614
19	rs74812357	729850	A	C	0.04161	4.406
19	rs71335276	859368	A	C	0.00355	0.3455