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SCN5A variation is associated with electrocardiographic traits in the Jackson Heart Study

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Abstract

Background—Understanding variation in the normal electrical activity of the heart, assessed by the electrocardiogram (ECG), may provide a starting point for studies of susceptibility to serious arrhythmias, such as sudden cardiac death during myocardial infarction or drug therapy. Recent genetic association studies of one ECG trait, the QT interval, have identified common variation in European-descent populations, but little is known about the genetic determinants of ECG traits in populations of African-descent.

Methods and Results—To identify genetic risk factors, we have undertaken a candidate gene study of ECG traits in collaboration with the Jackson Heart Study (JHS), a longitudinal study of 5,301 African Americans ascertained from the Jackson, Mississippi area. Nine quantitative ECG traits were evaluated: P, PR, QRS, QT, and QTc durations, heart rate and P, QRS and T axes. We genotyped 72 variations in the predominant sodium channel gene expressed in heart, *SCN5A*, encoding the $Na_v1.5$ voltage-gated sodium channel in 4,558 subjects. Both rare and common variants in this gene have previously been associated with inherited arrhythmia syndromes and variable conduction. Adjusting for age, sex, and European ancestry, we performed tests of association in 3,054 unrelated participants and identified 14 significant associations ($p<1.0\times10^{-4}$), of which 13 are independent based upon linkage disequilibrium. These variants explain up to 2% of the variation in ECG traits in the JHS.

Conclusions—These results suggest that *SCN5A* variation contributes to ECG trait distributions in African Americans and these same variations may be risk or protective factors associated with susceptibility to arrhythmias.

Keywords

electrocardiography; arrhythmia; genetics; ion channels; cardiovascular diseases

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CONFLICT OF INTEREST DISCLOSURES

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INTRODUCTION

Many factors are known to influence electrocardiograph (ECG) measurements, including underlying heart disease such as coronary heart disease or hypertension, drug therapy, body mass index, and age. These factors, however, do not explain the majority of the trait variance observed in ECG traits, and a large portion of the variance remains unknown[1, 2]. Studies in twins and populations have reported that >35% of the variance observed for specific ECG traits is heritable[3–8]. Given the heritability of ECG traits, it is possible that common genetic variation in genes that modulate the electrical activity of the heart can explain a proportion of the unknown trait variance observed in the general population. Insights into such normal variability may in turn provide the starting point for predicting serious cardiovascular events such as drug-induced arrhythmias or Sudden Cardiac Death (SCD)[4–7]. SCD accounts for 10–20% of all deaths in adults, and risk factors include underlying heart disease and a family history of SCD[5–7].

The opening of sodium channels is responsible for initiating and propagating action potentials in cardiac and other excitable cells[8–17]. Sodium channels are encoded by nine pore-forming alpha subunit genes[8], and each channel consists of a single pore-forming α-subunit and a variable number of function-modifying β-subunits and other interacting proteins[9]. The $NA_v1.5$ sodium channel α subunit (encoded by *SCN5A*) is the predominant α-subunit expressed in cardiac muscle[11, 12]. Mutations in *SCN5A* have been identified in cardiac conduction disease, long QT syndrome, Brugada syndrome, and other life threatening arrhythmias[10, 16–18].

In addition to rare variants, other studies have implicated common variants in *SCN5A* with arrhythmia susceptibility or with variable ECG traits[13, 15, 19–21]. One non-synonymous *SCN5A* variant, rs7626962, (S1103Y, which is sometimes reported as S1102Y depending whether the reference sequence includes a common splice variant that eliminates a single residue)[22] is common in African populations and rare in others. This SNP has been implicated in susceptibility to SCD, drug-induced arrhythmias, and SIDS in African American populations[23–25]. With this exception, however, there is very little information on ion channel variation in African Americans. This lack of data cannot be underscored as epidemiologic studies have demonstrated that the risk factor burden for CVD differs across race/ethnicities, with African Americans typically having a greater burden compared with European and Mexican Americans[26]. The rural south region of the US, which has the largest African American population, has a higher rate CVD compared to other regions[27, 28].

This disparity of CVD in African Americans is an emergent concern to clinicians and epidemiologists. Admixed populations such as Hispanics and African Americans have different genetic backgrounds due to the mixture of distinct of ancestral populations[29, 30] and patterns of linkage disequilibrium (LD) compared with European-descent populations[31]. Thus, it is possible that genetic determinants associated with ECG traits can vary depending on the ancestral populations. Given these potential differences, we genotyped 72 common single nucleotide polymorphisms (SNPs) in the *SCN5A* gene in 4,558 African Americans from the Jackson Heart Study (JHS) to test for an association with nine ECG traits: P, PR, QT, QTc and QRS durations, heart rate, and the P, QRS and T axes. We identified 14 significant associations at $p<1.0\times10^{-4}$, 13 of which have not been described in populations of European-descent. Overall, *SCN5A* variations reported here explains up to 2% of the variation in ECG traits. This study represents an important first step in the identification and characterization of genetic variants associated with ECG traits in African-descent populations.

METHODS

Population characteristics and ECG measurements

The Jackson Heart Study (JHS) was developed to help resolve the disparity of cardiovascular disease among African Americans[32]. The JHS is a longitudinal study established in 2000 to characterize the determinants of CVD in 5,301 African Americans ascertained in Jackson, Mississippi[33]. For the purpose of genetic analysis, consenting family members age 21 or older were ascertained[32]. The participants' ages ranged from 21–85 years old at the time of ascertainment (Supplementary Figure 1), and 62% of the participants were female. Each participant received a clinical examination and interview on CVD status and other environmental factors during enrollment. ECG measurements were collected during the clinical examination using the Marquette MAC/PC digital electrocardiograph[34]. All measurements were documented and sent by phone to the Electrocardiographic Reading Center (ECGRC) in Minnesota. The Minnesota Code Modular ECG Analysis System (MC-MEANS) computer program was used by the ECGRC to generate representative averaged measurements of ECG waves simultaneously over all leads. Population demographics and summary statistics of ECG measurements are given in Table 1.

Genotyping

Blood samples were collected from consented individuals during enrollment for future genetic analysis. DNA was isolated from blood samples and genotyped for 72 single nucleotide polymorphisms (SNPs) using the Sequenom iPlex Gold assay on the MassARRAY platform (San Diego, CA). SNPs were selected based on the linkage disequilibrium patterns in African Americans[31]. The location of the genotyped SNPs, minor allele, minor allele frequencies, Hardy-Weinberg p-values, and genotyping call rates are given in Supplementary Table 1.

Statistical analysis

The JHS in this analysis is comprised of 3,071 unrelated participants and 1,487 related participants from 263 families selected for genotyping. Unrelated individuals from 263 pedigrees with two or more successfully genotyped relatives were randomly selected and analyzed. Individuals selected by this random algorithm had to have all phenotype information and have at least 95% genotyping efficiency for targeted SNPs. In two families, only one participant was genotyped; as a result, these participants were always selected. We repeated the random selection several times, and data suggest that our results are robust to the random selection process (data not shown).

To determine if ECG traits were strongly correlated (i.e., redundant), we calculated pairwise correlations for 11 ECG traits (Supplementary Table 2). Prolonged QRS duration (>120 m/sec) is an indication of congestive heart failure. Patients with abnormal QRS duration measurements (>120 m/sec) were excluded from the QRS analysis (n = 169; Supplementary Figure 2A); however, these patients were included in subsequent analysis with the other ECG traits. The exclusion of these patients in the analysis of QRS duration or other ECG traits yielded similar results compared with the inclusion of these patients (data not shown) due to the relatively small sample size of patients with prolonged QRS duration compared with the overall sample size. Of all ECG traits, T and QT durations and PR duration in leads II and VI were highly correlated (r^2=0.93 and 0.87 respectively). To minimize redundancy, we chose to analyze QT duration instead of both QT and T durations and PR in lead II instead of both PR in leads II and VI. Although modest, a correlation was also observed for P wave and PR durations, QTc and QT duration, as well as QTc and heart rate (r2 >0.40, Supplementary Table 1). All of these moderately correlated traits were retained for subsequent analyses.

For the analysis, we excluded SNPs with a minor allele frequency (MAF) <0.05, genotyping efficiency <95% or Hardy Weinberg equilibrium (HWE) p-value <0.0001. Using these criteria, seven SNPs were excluded from the analysis. We also excluded 280 DNA samples due to poor genotyping efficiency, resulting in a total study population of 3,054 participants.

Global admixture estimates were calculated[35] to determine the amount European ancestry using ANCESTRYMAP Version 2.0[36] and expressed as "mean percent European ancestry" based on a probabilistic term representing the genome-wide mean percentage of European ancestry as determined from markers on the autosomes. European ancestry was associated with durations (P, QTc, and QRS) and T axes ($p<0.05$).

We calculated skewness and kurtosis and performed formal tests of normality for all ECG traits. For QRS duration, the skewness (0.34) and kurtosis (2.4) suggested that this ECG trait is normally distributed. However, QRS duration failed a formal test of normality while all other ECG traits followed a normal distribution. Based on these results, we performed tests of association for QRS duration untransformed and log transformed (data not shown). Because the results did not differ between the untransformed and transformed analyses, we chose to present the untransformed results for ease of interpretation.

Using linear regression, we performed single SNP tests of association assuming an additive genetic model for 65 SNPs that passed QC in the unrelated sample with nine ECG traits using PLINK[37]. Analyses were performed unadjusted and adjusted for age, sex, and European ancestry, and results were plotted using Synthesis-View [38]. To account for multiple testing, we employed a significance threshold of $p<1.0 \times 10^{-4}$. We also performed unadjusted family-based tests of association for all ECG traits using the QFAM procedure from PLINK[37]. This method uses traditional linear regression but uses permutation to correct for family structure. We employed this method with all genotyped samples that passed quality control [5 families (n=19) were removed due to Mendelian errors] and tested for an association with each SNP for all ECG traits. The results from this analysis are consistent with results from the unrelated samples (data not shown). To determine the amount of the variance in ECG traits explained by each SNP, R^2 was computed using STATA version 10. Linkage disequilibrium (r^2) was calculated using Haploview [39].

RESULTS

ECG interval durations

The P, PR, QRS, QT and QTc durations were tested for an association with 65 SNPs in *SCN5A* that passed quality control measures. Overall there were 14 significant associations ($p<1.0 \times 10^{-4}$) amongst 65 SNPs for P, PR, QRS and QT durations. PR duration had the most significant SNP associations, with eight SNPs significantly associated with decreased PR duration: nonsynonymous rs7626962 (S1103Y) and seven intronic SNPs (Table 2). Three intronic SNPs were associated with increased PR duration but not with any other ECG trait. Four SNPs were associated with decreased P wave duration, one with decreased QRS duration. A single intronic SNP was associated with increased QRS duration, but no other ECG trait. Unique to QT duration, rs9311195 was associated with decreased QT duration (Table 2). There were no significant associations observed with QTc duration at $p<1.0\times10^{-4}$ (Supplementary Table 3).

Heart Rate

Of the *SCN5A* SNPs tested for an association with heart rate, none of the associations survived the significance threshold of $p<1.0 \times 10^{-4}$. Two SNPs that were also associated with decreased P and PR duration trended towards significance with increased heart rate: SNPs rs7629265 ($\beta= 0.97$, $p= 0.04$) and rs7626962 ($\beta= 0.91$, $p= 0.05$) (Supplementary Table

3). These two SNPs are in high linkage disequilibrium (LD) with one another (r^2=0.87); thus, these associations are not independent.

ECG axes

In addition to ECG durations, the P, QRS and T axes were also tested for an association with the same 65 SNPs. There were no significant associations with our SNPs and ECG axes measurements using a significance threshold of $p<1.0\times10^{-4}$ (Supplementary Table 3). One SNP that was associated with decreased PR duration trended towards significance with P axis (β= 1.95, p= 0.05).

SNPs associated with multiple ECG traits

Intronic SNP rs3922844 was associated with increased P, PR, and QRS. SNPs rs7374138, rs7626962, rs76229265, rs7637849, rs7627552, and rs6763048 consistently trended towards decreased PR, QRS and P wave durations (Figure 1). Although most SNPs did not survive our significance threshold for QRS duration, SNPs that were associated with PR and P wave duration trended towards significance with QRS duration compared with other ECG traits.

DISCUSSION

Using a candidate gene approach, we sought to identify genetic variations within *SCN5A* associated with ECG measurements in African Americans from the Jackson Heart Study. We were able to detect both previously known as well as novel genetic associations with four ECG measurements (Table 2). Notably, to our knowledge, we are the first to report an association with the genetic variant S1103Y and atrial ECG traits, PR and P wave durations. We were also able to detect novel associations between intronic rs3922844 and QRS, P wave, and PR durations. SNP rs3922844 explains approximately 2% of the variability in these traits. Consistent with previous studies, no other SNP explained greater than 2% of variance for any ECG trait[40].

To minimize redundancy in our results, we calculated linkage disequilibrium (LD) among SNPs in the unrelated participants (Supplemental Figure 3). Of the 14 significant associations, 13 SNPs represent independent associations. Correlated SNPs rs7626962/ rs7627552 are in high LD with each other (r^2= 0.87), and each likely represents the same effect. SNP pairs rs6793245/rs3935472 and rs9833086/rs4130467 are also in LD; however, they were not significantly associated with any ECG trait.

Several genome-wide association studies (GWAS) have been published for the ECG traits in populations of non-African descent. For example, two studies report associations within *SCN5A* and the QT interval [41–44]. A recent GWAS in the isolated Kosrae population from the Federated States of Micronesia identified an association between rs7638909, a SNP located in intron 27 of *SCN5A*, and the PR interval, P wave duration and PR segment[40]. Other GWAS studies on ECG traits report an association with rs7638909 (or correlated SNPs rs12053903, rs1805126 and rs1805124) with the QT interval, PR interval, and QRS duration in Icelandic and European populations[42, 45]. We tested for these associations and all ECG traits in the JHS but failed to replicate these findings. The lack of replication across studies is perhaps not surprising given the different linkage disequilibrium patterns and allele frequencies in these populations. The SNPs we choose for genotyping for this study are common in African Americans such as rs7626962 and rs7629265 but are monomorphic or rare in other populations. GWAS for ECG traits in African-descent populations has yet to be reported in the literature.

Unlike previous studies, we were unable to detect an association between S1103Y and ventricular related traits QRS, T, and QT durations at our significance threshold. Given

previous studies, we had expected to detect a strong association with S1103Y (rs7626962) and our ECG traits. The effect of 1103Y and QTc duration is consistent with previous studies ($\beta = 1.53$, $p = 0.20$; Supplementary Table 2), but given the minor allele frequency of this SNP (0.08), our study was underpowered to detect this association (20%). In our study population, there were only 20 homozygotes for the 1103Y allele; thus, it is not surprising that mean QTc is not associated with S1103Y genotype (data not shown). S1103Y was associated with P wave and PR durations ($p<1.0\times10^{-5}$), but there was no other association at $p<1.0\times10^{-4}$ with other ECG traits. A significant effect was also observed with rs7629265, with is in LD with S1103Y ($r^2= 0.87$). Intronic rs7629265 ranked higher than S1103Y in four ECG traits: PR duration, QRS duration, QT duration, and heart rate (Table 2, Supplementary Table 3). Because of the strong LD, the association with intronic rs7629265 could be a capturing the effect of S1103Y.

As opposed to mutations, the effects of common variation are less clear. Our most significant finding, rs7627552, is in LD with rs7626962 (S1103Y), a nonsynonymous missense mutation that changes the amino acid serine to tyrosine. Studies of this variant in heterologous expression systems have reported differences between variant and wild-type channels especially under stress conditions such as low pH[23, 24]. The other significant *SCN5A* SNPs from the present study are all located in the 3′ region of the gene. While none of them have obvious function, it is noteworthy that this gene region is highly conserved with mouse. Also, it may be that these associated SNPs are in linkage disequilibrium with the “causal” or functional SNPs not genotyped in this study. However, examination of the Yoruba International HapMap data in this region (100kb upstream and downstream of rs7627552) revealed only one SNP with minor allele frequency >1% in LD at $r^2>0.20$ in this region (rs7629265).

CONCLUSIONS

Genetic variation in the normal electrical activity of the heart, assessed by the ECG, may provide a starting point for studies of genetic susceptibility to serious arrhythmias, such as SCD during myocardial infarction or drug therapy. We identified several novel associations between *SCN5A* common genetic variants and the ECG traits in African Americans, and we report here the direction and magnitude of effect for all tests of association. Of the 14 significant associations, rs7627552, which is in LD with a common missense mutation (S1103Y) observed in African Americans previously associated with arrhythmia susceptibility, was the SNP most strongly associated with ECG traits P wave and PR durations. We were also able to identify 13 novel associations, one of which (rs3922844) explains as much as 2% of the variance in P wave, QRS and PR durations. Collectively, these data suggest that multiple SNPs rather than one (S1103Y) in *SCN5A* have an effect on ECG traits. The results of this study may offer insight relevant to future genetic studies of cardiac diseases in African-descent populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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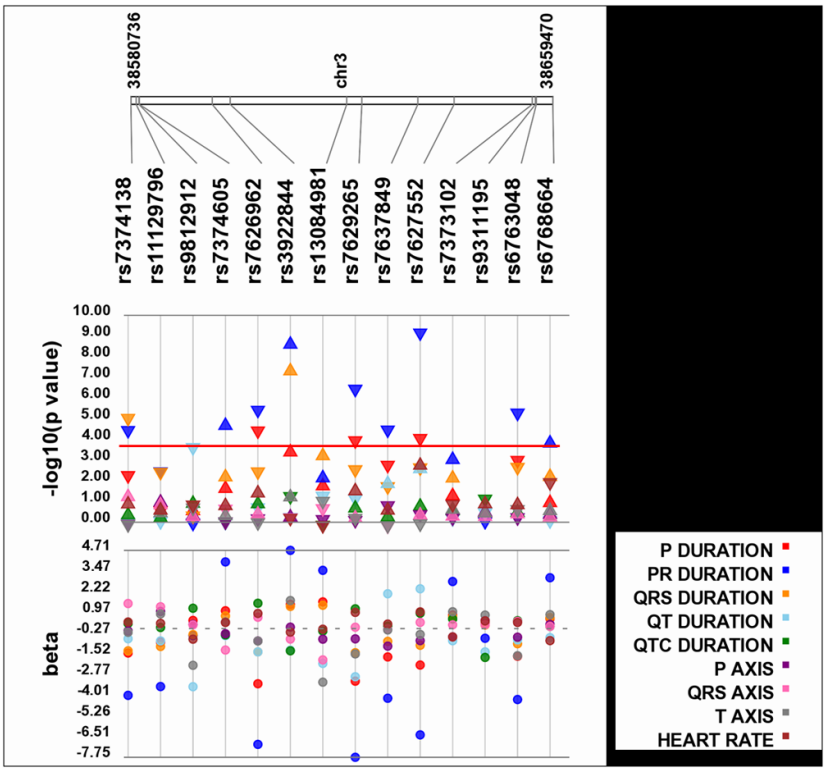

Figure 1. Significant associations across ECG traits

Each SNP was tested for an association with each ECG trait assuming an additive genetic model adjusted for age, sex, and European ancestry. P-values are $\log_{10}$ transformed along the y-axis and corresponding location for each SNP is located on the x-axis. Each point represents a p-value for each trait indicated by color (see legend). The direction of the arrows corresponds to the direction of the beta coefficient. The exact beta coefficients are reported on the bottom panel. The significance threshold is indicated by the red bar at p= 1.0×10^{-4}.

Table 1

Study population demographics and ECG trait descriptive statistics for the unrelated (n= 3,054) JHS participants.

Study Population Characteristics (n=3,054)		
Variable	**Mean or %**	**Standard Deviation (minimum, maximum)**
Age (yrs)	56.5	±11.73 (21, 85)
% Female	62	-
% Cardiovascular disease	11	-
P duration (msec)	118.5	±13.08 (80, 170)
PR duration (msec)	171.6	±33.02 (0,338)
QRS duration (msec)	92.3	±10.12 (64, 120)
QT duration (msec)	414.7	±27.64 (290, 580)
QTc duration (msec)	426.4	±27.64 (334, 594)
P axis (degrees)	48	±21.06 (−136, 151)
QRS axis (degrees)	16.9	±31.18 (−137, 157)
T axis (degrees)	30.6	±40.03 (−179, 179)
Heart rate (beats/min)	64.6	±10.72 (30, 118)

Table 2

Beta coefficients and p-values for significant SNPs associated with at least one ECG trait in unrelated JHS participants. Linear regression adjusting for age, sex, and European ancestry was performed for 65 SNPs assuming an additive model for nine quantitative ECG traits (for QRS duration only patients with <120 msec were included, n= 2,878). Fifteen significant SNPs that met our significance threshold were associated with at least one ECG trait and are listed above. In bold are significant associations at $p < 1.0\times10^{-4}$.

SNP	Location	P duration		QRS duration		PR lead II		QT duration	
		β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
rs11129796	Intron	−0.81 (−1.6, 0.7)	1.8E-1	−1.1 (−1.6, −0.3)	2.5E-3	−3.5 (−5.0, −0.2)	**2.4E-4**	−1.4 (−4.1, 0.3)	2.3E-1
rs13084981	Intron	1.6 (−0.0, 2.9)	2.7E-2	1.4 (0.4, 2.2)	**9.4E-4**	3.5 (0.8, 6.5)	**1.1E-2**	−0.61 (−3.1, 2.1)	6.5E-1
rs3922844	Intron	1.5 (0.4, 2.0)	**6.3E-4**	1.3 (0.8, 1.8)	**7.5E-8**	4.7 (3.1, 6.4)	**3.9E-9**	−0.68 (−2.3, 0.8)	3.9E-1
rs6763048	Intron	−1.7 (−2.5, 0.6)	**6.6E-4**	−0.91 (−1.3, −0.2)	1.4E-3	−4.3 (−6.1, −2.3)	**3.5E-6**	−0.54 (−2.8, 1.4)	5.5E-1
rs6768664	Intron	0.60 (−0.2, 1.5)	1.8E-1	0.67 (0.2, 1.2)	9.5E-3	3.0 (1.5, 4.9)	**2.3E-4**	2.4 (0.46, 3.7)	4.0E-3
rs7373102	Intron	0.81 (−0.2, 1.6)	8.1E-2	0.71 (0.13, 1.2)	1.1E-2	2.8 (1.5, 5.1)	**1.4E-4**	2.1 (−0.1, 3.3)	2.1E-2
rs7374138	Intron	−1.5 (−2.3, −0.4)	3.6E-3	−1.3 (−1.8, −0.6)	**6.2E-6**	−4.0 (−6.0, −2.1)	**2.4E-5**	−0.73 (−3.5, 0.1)	4.4E-1
rs7374605	Intron	1.1 (−0.4,1.6)	3.6E-2	0.76 (0.2, 1.4)	9.9E-3	4.0 (2.0, 6.0)	**3.3E-5**	−1.4 (−3.0, 0.7)	1.3E-1
rs7626962	Ser->Tyr	−3.3 (−4.9, −1.8)	**2.5E-5**	−1.4 (−2.2, −0.4)	2.3E-3	−6.9 (−9.9, −4.0)	**2.5E-6**	−0.74 (−3.1, 2.6)	6.1E-1
rs7627552	Intron	−2.2 (−2.9, −0.8)	**5.8E-5**	−1.0 (−1.7, −0.5)	1.5E-3	−6.4 (−3.7, −5.5)	**4.6E-10**	−2.1 (3.5, 0.5)	3.6E-2
rs7629265	Intron	−3.2 (−4.6, −1.6)	**7.5E-5**	−1.5 (−2.4, −0.6)	1.8E-3	−7.8 (−10, −4.4)	**2.4E-7**	−1.3 (−3.2, 2.5)	3.8E-1
rs7637849	Intron	−1.7 (−2.9, −0.9)	1.1E-3	−0.76 (−1.2, 0.0)	1.2E-2	−4.2 (−6.1, −2.1)	**2.3E-5**	−0.43 (−1.9, 1.9)	6.6E-1
rs9311195	Intron	0.29 (−0.5, 1.7)	6.2E-1	0.21 (−0.6, 0.7)	5.3E-1	−0.58 (−2.5, 2.0)	6.0E-1	−3.5 (−5.0, −0.7)	**1.6E-4**
rs9832586	Intron	−1.3 (−2.6,0.59)	1.1E-1	−0.58 (−1.5, 0.3)	2.1E-1	−5.2 (−7.8, −1.4)	**7.3E-4**	−2.9 (−7.4, −1.5)	4.8E-2