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A Meta-Analysis of Genome-Wide Association Studies of the Electrocardiographic Early Repolarization Pattern

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Abstract

Background—The early repolarization pattern (ERP) is common and associated with risk of sudden cardiac death. ERP is heritable and mutations have been described in syndromic cases.

Objective—To conduct a meta-analysis of genome-wide association studies (GWAS) to identify common genetic variants influencing ERP.

Methods—We ascertained ERP based on electrocardiograms in three large community-based cohorts from Europe and the US: the Framingham Heart Study, the Health 2000 Study, and the KORA F4 Study. We analyzed GWAS in participants with and without ERP by logistic regression assuming an additive genetic model and meta-analyzed individual cohort results. We then sought to strengthen support for findings that reached $p < 1 \times 10^{-5}$ in independent individuals by direct genotyping or in-silico analysis of genome-wide data. We meta-analyzed the results from both stages.

Results—Of 7482 individuals in the discovery stage, 452 showed ERP (ERP positive: mean age 46.9±8.9 years, 30.3% women; ERP negative: 47.5±9.4 years, 54.2% women). After meta-analysis, eight single nucleotide polymorphisms reached $p < 1 \times 10^{-5}$: The most significant finding was intergenic rs11653989 (odds ratio 0.47; 95% confidence interval 0.36–0.61; $p=6.9 \times 10^{-9}$). The most biologically relevant finding was intronic to *KCND3*: rs17029069 (odds ratio 1.46; 95% confidence interval 1.25–1.69; $p=8.5 \times 10^{-7}$). In the replication step (7151 individuals), none of the eight variants replicated, and combined meta-analysis results failed to reach genome-wide significance.

Conclusions—In a GWAS, we were not able to reliably identify genetic variants predisposing to ERP, presumably due to insufficient statistical power and phenotype heterogeneity. The reported heritability of ERP warrants continued investigation in larger well-phenotyped populations.

Keywords

Early repolarization; Sudden cardiac death; Arrhythmia; GWAS; Meta-analysis; Electrocardiogram

Introduction

The electrocardiographic early repolarization pattern (ERP) has long been considered a benign normal ECG variant.^{1,2} Recent case-control studies, however, have demonstrated an association of inferior and lateral ERP to idiopathic ventricular fibrillation,^{3,4} and subsequent large-scale community-based studies have suggested an increased risk of all-cause and cardiac mortality, and sudden death.^{5,6} Most recently, a subtype of ERP, defined by horizontal or descending ST-segment morphology, was shown to confer the highest risk for an arrhythmic death, whereas an ascending ST-segment morphology, common in young male athletes, was associated with benign prognosis.⁷ The population prevalence of ERP across recent studies ranged between 3 and 13%.^{5,6,8,9}

Mutations in *KCNJ8*^{10,11}, *CACNA1C*, *CACN2B*, and *CACNA2D1*¹² have been reported in individuals with ERP and sudden cardiac death, but the genetic determinants of ERP at the population level remain undefined. ERP appears to be heritable. An investigation in families from the UK reported a heritability estimate of 0.49⁸ and an odds ratio (OR) of 2.5 for ERP in the offspring of at least one affected parent.⁸ Findings from the Framingham Heart Study (FHS) reported a sibling recurrence risk of 1.89 for ERP.⁹

Here we sought to identify common genetic determinants of ERP by performing a meta-analysis of genome-wide association studies (GWAS) in individuals of European descent followed by independent replication, comprising a total of 940 subjects with ERP and 13,693 controls drawn from population- and community-based study samples.

Methods

Description of Study Cohorts

All study procedures were approved by the local institutional review boards of each center. Study participants provided written informed consent, including consent to use DNA for genetic analyses of cardiovascular disease. Individuals were considered eligible for the GWAS stage if they had both genome-wide genotyping data and electrocardiograms (ECGs) available. We excluded participants of non-European ancestry, with a QRS-duration >120ms, <18 years of age (and <80 years of age in the Health 2000 Study (H2K)), presenting with non-sinus rhythm or with a heart rate >100/min. A summary of excluded

subjects is presented in Supplemental Table 1. Detailed descriptions of cohorts can be found in the Supplemental Methods.

The **Framingham Heart Study (FHS)** is a prospective community-based study started in 1948 to evaluate potential risk factors for coronary heart disease. In 2002, a third generation of participants was recruited (Generation 3, n=4,095), and here, 3,726 participants with both GWAS and ECG data were studied.

The **Health 2000 Study (H2K)** is an epidemiological survey conducted in Finland in 2000–2001 and represents the Finnish adult population aged ≥ 30 years. Of the total H2K population (n=8028), 2082 subjects with both GWAS data and ECGs were investigated here.

The **Cooperative Health Research in the Augsburg Region (KORA) F4 Study (KORA F4)** was conducted in 2006–2008 in men and women aged 32–81 years. After exclusions, of 3080 participants, we studied 1674 with available GWAS and ECG data.

Replication cohorts

Participants of **H2K** not contributing to the GWAS analysis were included in the replication analyses. After exclusions, the replication sample consisted of 2996 individuals.

Participants of **KORA F4** not included in the GWAS analysis, but with DNA samples available (n=1226) were recruited for replication (n=1140).

Further individuals for replication were available from the **MONitoring Cardiovascular Disease (MONICA) / KORA S1 and S2 Study Subcohort (MONICA/KORA S1/S2)**. Here, 1351 participants (644 from S1 and 707 from S2) were eligible for study.

Individuals were also included from the **Young Finns Study (YFS)**, a population-based, ongoing prospective multicentre study between five Finnish university hospitals. After exclusions, the replication sample from YFS consisted of 466 subjects.

From the South Italian village of **Carlantino**, 1668 individuals had been recruited from 1998–2005, and 285 individuals were available for analysis. A second Italian cohort was derived from the project **Genetic Park of Friuli Venezia Giulia (FVG)**, where 913 individuals remained in the dataset for analysis.

Ascertainment of ERP

ERP was determined on 12-lead ECGs by specifically trained physicians experienced in cardiac electrophysiology. The identical coding protocol was applied at each participating site. Measurements were performed for each lead separately. From among the leads, the one with the earliest offset of the QRS complex was defined as the reference point for J-point elevations. Criteria for the diagnosis of ERP required a J-point elevation of ≥ 0.1 mV compared to the baseline (defined as the T-P segment) in ≥ 2 leads within at least one regional territory. ERP was considered in inferior (leads II, III, aVF) or lateral (leads I, aVL, V4, V5, V6) regional territories, and was categorized as showing either slurring, notching, discrete, or mixed morphology. We assessed the morphology and amplitude of the ST segment at 100 ms after the J-point. ST-segments with an amplitude >0.1 mV were considered ascending; for amplitudes ≤ 0.1 mV, we distinguished between horizontal and descending morphologies.

Genotyping and replication SNP selection

GWAS Genotyping platforms included: Affymetrix 5.0 and a 50,000 SNP custom Illumina chip (FHS), Illumina Human610-Quad (H2K), and Affymetrix 6.0 (KORA F4). Cohort-based information on the genotyping process and quality control criteria are provided in Supplemental Table 2. Replication genotyping was performed using iPLEX single base primer extension with matrix-assisted laser desorption / ionization time-of-flight (MALDI-TOF) mass spectrometry (Sequenom Inc, San Diego, California, USA) for H2K, KORA F4, and MONICA/KORA S1/S2. All sites used identical genotyping assays. All genotyping was performed according to the manufacturer's instructions. For replication in Carlantino, FVG and YFS, we used in-silico results available from previous genome-wide genotyping.

Statistical Analysis

For GWAS, imputation of >2.5 million HapMap SNPs based on the CEU population was performed using Mach v1.0.1x¹³ in all three cohorts (Supplemental Table 2). In each study, we adjusted for population structure applying the principal components method,¹⁴ or stratified by identity-by-descent cluster groups as implemented in PLINK.¹⁵ The primary analysis was conducted separately at each site using logistic regression assuming an additive genetic model. Models were adjusted for age at ECG, sex, and RR interval. Prior to meta-analysis, we used genomic control methods to account for remaining population stratification: site-specific results with a genomic inflation factor $\gamma > 1.0$ were corrected by multiplying the standard error of the SNP regression parameter with the square root of the study-specific γ (Supplemental Figure 1). We used the ratio of the observed to expected variance of the imputed SNP genotype counts as a quality control metric for imputed SNPs. For each SNP, we included all studies with variance ratios > 0.3 . Only SNPs with a minor allele frequency > 0.01 (H2K, KORA F4) or > 0.05 (FHS) were considered. After these quality control procedures, we analyzed 2,523,555 SNPs. The meta-analysis of site-specific association results was performed simultaneously in H2K and MONICA/KORA using the meta-analysis tool METAL.¹⁶ We performed fixed-effects meta-analysis using inverse variance weights. Results from both centers were compared and inconsistencies were eliminated. Finally, one single version was used for all subsequent analyses. To account for multiple comparisons, we applied a pre-specified Bonferroni adjustment for 1 million independent tests ($p < 5 \times 10^{-8}$). We attempted to replicate SNPs that did not reach genome-wide significance: We included all SNPs with a p-value $< 1 \times 10^{-5}$, if they had a minor allele frequency > 0.05 and showed homogeneity across individual studies as assessed by an $I^2 < 0.5$ and a non-significant p-value for heterogeneity. All SNPs were clustered into loci according to their genomic position, and the top SNP of each locus was selected for replication. Replication results were calculated separately by replication site. Site-specific replication results were then meta-analyzed and this final result was used to assess positive replication. For an overall effect estimate, results of the GWAS and replication stage were finally combined. All reported p-values are 2-sided.

Results

The GWAS stage combined 7482 individuals. Their mean age across cohorts was 46.9 ± 8.9 years in participants with ERP, and 47.5 ± 9.4 years in participants without ERP. Women accounted for 30.3% of ERP positive subjects and 54.2% of ERP negative subjects. Further clinical characteristics by cohort are shown in Table 1. Details with respect to ERP and ST-segment morphology in ERP-positive individuals are presented in Table 2. Overall, 452 (6.0%) individuals demonstrated ERP, of whom 57 (12.6%) showed ERP in > 1 regional territory. A horizontal or descending ST-segment morphology was noted in 70.9% of all ERP-positive regional territories.

Following genotyping and quality control measures (Supplemental Table 1; Supplemental Figure 1), 2,523,555 SNPs were analyzed for association with ERP at the GWAS stage. The association results of the GWAS stage are presented in Figure 1, and the eight most significant SNPs, reaching p-values of $<1 \times 10^{-5}$ are shown in Table 3. We subsequently attempted replication of our results in 7151 independent samples, in which the prevalence of ERP was 6.8% (488 ERP-positive). None of the eight SNPs tested in the replication cohorts reached significance when all replication cohorts were meta-analyzed (Table 4). In the final meta-analysis, combining the results of the GWAS and the replication stages, none of the SNPs reached genome-wide significance (Table 4, Figure 2).

Of the eight SNPs we initially identified, five are located in introns of genes (Table 3). The initially most significant intronic SNP (rs17029069) is on chromosome 1p13.2, and maps to intron 2 of *KCND3*. *KCND3* encodes the voltage-gated potassium channel Kv4.3. Other intronic SNPs are rs17012480 (intron 3 of *LTBP1*), rs1541064 (intron 6 of *UBE2U*), rs6988260 (intron 3 of *FAM110B*), and rs1382629 (intron 2 of *KIAA1211*).

Discussion

In our GWAS, we included almost 15,000 individuals from community-based cohorts of European ancestry. Close to 1000 participants were identified to be ERP-positive applying the identical, standardized diagnostic criteria by investigators at all contributing sites. While the initial results of our GWAS stage suggested promising association signals, none of the signals could be replicated.

Several independent investigations have suggested that ERP is a heritable ECG phenotype. In 1877 individuals from 505 UK families, the prevalence of ERP was 5.9%, and thus in keeping with the ERP prevalence in our current analysis.⁸ The authors reported a heritability estimate of $h^2=0.49$ and an OR of 2.5 for offspring to demonstrate ERP, if 1 parent presented with ERP.⁸ Another investigation in FHS and H2K found an ERP prevalence of 6.1%.⁹ Heritability estimates for ERP fall within a similar range as other heritable ECG parameters such as the PR interval,¹⁷ the QT interval,¹⁷ or diseases identifiable by ECG, such as atrial fibrillation.¹⁸ GWAS have been successful in identifying chromosomal loci associated with each of these heritable phenotypes.^{19–22} Our inability to replicate even our pathophysiologically promising initial findings warrants some exploration.

A first explanation may be false-positive initial findings, which failed to replicate. In our study, <10% of the 15,000 participants were ERP-positive. A post-hoc power analysis revealed that we had 80% power to detect an OR of 1.68. We anticipate that with an increased sample size and thus increased statistical power, susceptibility loci for ERP will eventually be identified. While increased sample size can help to identify true loci associated with disease, it was still worth pursuing the current analysis as loci for other traits have been identified with similar sample sizes. Specifically, the first GWAS for the QT interval consisted of an initial stage of only 200 individuals, yet it successfully identified the locus most significantly associated with the QT interval.²³ Similarly, for atrial fibrillation a cohort of only 636 cases and 804 controls identified the 4q25 locus for the arrhythmia.²⁴

A second explanation for the non-replication of genetic loci might be that ERP is a more heterogeneous phenotype than initially anticipated. The prevalence of ERP appears variable. Despite a very homogeneous definition across participating cohorts, our prevalence ranged from 3%–13%. In a Japanese study, the prevalence reached almost 24%.²⁵ ERP can be subclassified based on the affected regional territory, ST segment morphology, amplitude, and J point morphology, a process that results in fragmentation of the phenotype into distinct and individually rare patterns. Also, there may be interactions with other clinical factors such as

sex and race. Community-based investigations in Europe and Japan indicated that ERP in inferior or lateral territories is associated with the highest risk of mortality.^{5, 6, 25} A Finnish study found that only a horizontal or descending ST-segment was associated with adverse outcomes.²⁶ Subsequently, in patients with idiopathic ventricular fibrillation a combination of ERP and a horizontal ST segment was associated with a markedly increased odds of arrhythmias compared to the presence of ERP alone.²⁷ Higher ERP amplitudes also conferred an increased risk of death.⁵ The importance of sex has been controversial; one study suggested that the ERP-effect on mortality is more pronounced in males,⁶ whereas others have shown that women are particularly at risk.²⁸ An increased SCD risk has been demonstrated in white, but not in black individuals.²⁸ ERP might be subjected to temporal changes as well.²⁹ In conclusion, the non-replication of our GWAS findings could be due to a too un-specific definition of ERP. Future investigations will need to focus on the subtypes with the strongest heritability and the strongest evidence for clinical implications. Presently, we lacked sufficient statistical power to adequately examine subtypes.

Although not genome-wide significant, one particularly interesting locus was on chromosome 1 intronic to *KCND3*. The gene encodes the voltage-gated potassium channel $K_{v4.3}$, a key channel underlying the cardiac transient outward current I_{to} .³⁰ The current is of great importance for the early phase of repolarization,³¹ and reported to be the predominant contributor to phase I of the cardiac action potential.³² Its transmural dispersion leads to different shapes of the cardiac action potential in endo- vs. epicardial layers, and results in the ERP notch or slur on the surface ECG.³² Genetic variants in *KCND3* possibly lead to altered channel properties that could underlie an increased arrhythmogenic potential. A mutation in *KCND3* has been described to cause the Brugada syndrome, in which the early phase of cardiac repolarization is critically involved as well.³³ In contrast, *KCND3* mutations were described to be rare in patients with long QT syndrome, where late phases of cardiac repolarization are important.³⁴ However, since the association of common variants at this locus to ERP was not significant considering the burden of testing, these potential functional links remain purely speculative.

Strengths and limitations

Strengths of our study are the highly standardized assessment of ERP status and a large collaborative effort to provide maximally achievable statistical power. However, sample size considerations limited our ability to explore the heterogeneity of ERP in subgroup analyses. Also, successful replication of variants predisposing to ERP might have been prevented by residual confounding. It will require further studies to refine ERP phenotype in more detail. Despite our intention to increase statistical power, our study still did not yield enough participants to reliably identify common genetic variants associated with ERP. All investigated ECGs stem from a single time point. As ERP showed temporal variability in prior studies, we cannot exclude that we have missed ERP positive individuals. All participants were of European descent. We therefore cannot comment on genetic predisposition to ERP in different ethnicities. Carlantino and FVG are isolated populations that could have influenced our genetic analyses if genetic substructure exists. However, the heterogeneity of the results of these two cohorts appeared to be similar to other cohorts in our study.

Conclusion

In conclusion, we have performed a multicenter meta-analysis of GWAS attempting to identify SNPs associated with ERP. Limited statistical power and potentially unrecognized phenotypic heterogeneity are potential explanations for our non-replication results. Future investigations will require many collaborating centers and high phenotype resolution based on unified diagnostic criteria to adequately identify common variant associations to ERP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

CI	confidence interval
ECG	electrocardiogram
ERP	early repolarization pattern
FHS	Framingham Heart Study
FVG	Genetic Park of Friuli Venezia Giulia
GWAS	genome-wide association study
H2K	Health 2000 Study
KORA F4	Cooperative Health Research in the Augsburg Region (KORA) F4 Study
MONICA / KORA S1/ S2	MONItoring Cardiovascular Disease (MONICA) / KORA S1 and S2 Study Subcohort
MALDI-TOF	Matrix-assisted laser desorption / ionization time of flight
OR	odds ratio
SCD	sudden cardiac death
SNP	single nucleotide polymorphism
YFS	Young Finns Study

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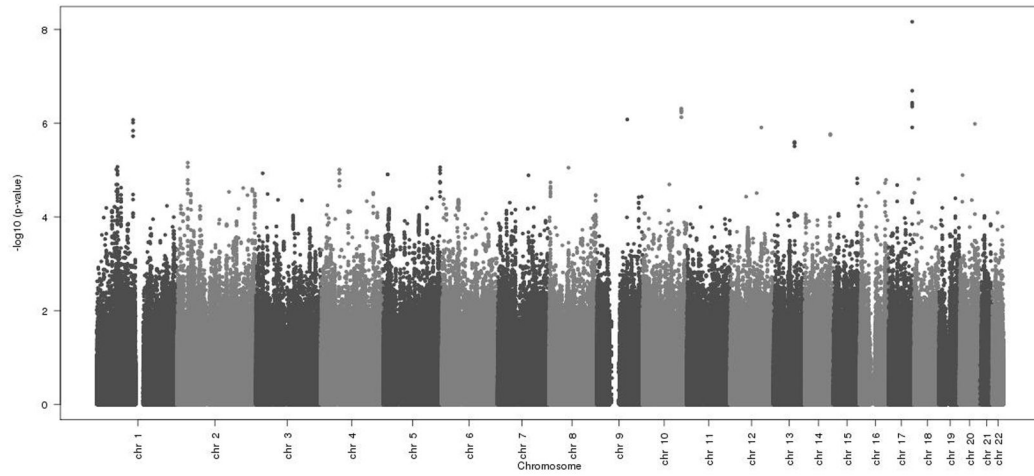


Figure 1. Genome-wide association results from GWAS meta-analysis for association with ERP
The physical chromosomal position of each SNP is plotted on the x-axis; the $-\log_{10}(p \text{ value})$ of the SNP-ERP association is plotted on the y-axis. chr – chromosome.

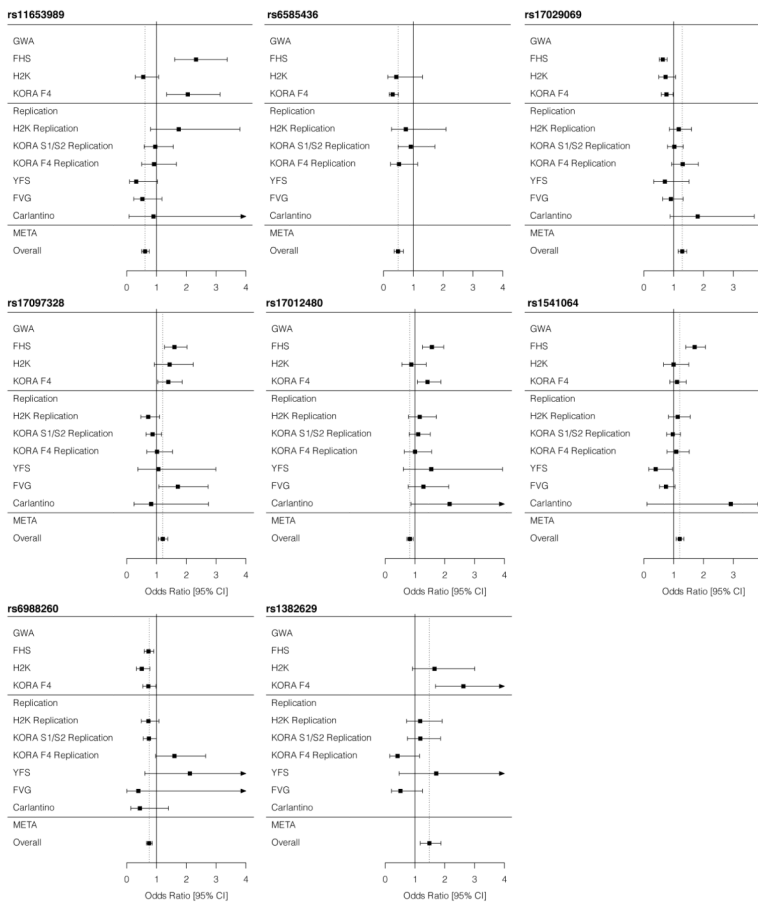


Figure 2. Association results by cohort for SNPs selected for replication

For each SNP we attempted to replicate, ORs and 95% CIs are plotted by cohort and for the meta-analyzed results. For each SNP panel, the upper section represents cohorts included in the GWAS stage, the middle section those included in the replication stage, and the lower section depicts meta-analysis results. CI – confidence interval; META – meta-analysis; OR – odds ratio.

Table 1

Baseline characteristics of the GWAS study sample FHS H2K KORA F4

Study	FHS		H2K		KORA F4	
	ERP +	ERP -	ERP +	ERP -	ERP +	ERP -
Number, total	3726		2082		1674	
Females, n (%)	52 (23%)	1946 (56%)	16 (26%)	1054 (52%)	69 (42%)	809 (54%)
Age, years (mean \pm SD)	37 \pm 9.0	40 \pm 8.8	46 \pm 10.2	50 \pm 10.9	60 \pm 8.4	61 \pm 8.8
Age, range	19 to 63	19 to 72	31 to 72	30 to 75	44 to 78	31 to 81
RR interval, ms (mean \pm SD)	1060 \pm 184.5	985 \pm 158.2	1045 \pm 180.3	977 \pm 157.1	964 \pm 159.9	944 \pm 143.3

GWAS – genome wide association study; ERP – early repolarization pattern; FHS – Framingham Heart Study; H2K – Health 2000 Study; n – number; SD – standard deviation.

Table 2

Early repolarization pattern by GWAS cohorts

	FHS	H2K	KORA F4
ERP positive ECGs, n (%)	227 (6.1%)	61 (2.9%)	164 (9.8%)
ERP positive regional territories, n	243	66	200
Regional territories			
Inferior, n (%)	81 (33.3%)	19 (28.8%)	109 (54.5%)
Lateral, n (%)	162 (66.7%)	47 (71.2%)	91 (45.5%)
ERP morphology across regional territories			
Notching, n (%)	85 (35.0%)	23 (34.8%)	33 (16.5%)
Slurring, n (%)	73 (30.0%)	18 (27.3%)	70 (35.0%)
Discrete, n (%)	24 (9.9%)	3 (4.5%)	0 (0%)
Mixed, n (%)	61 (25.1%)	22 (33.3%)	97 (48.5%)
ST-segment analysis across regional territories			
Ascending, n (%)	87 (35.8%)	38 (57.6%)	23 (11.5%)
Horizontal, n (%)	156 (64.2%)	28 (42.4%)	146 (73.0%)
Descending, n (%)	0 (0%)	0 (0.0%)	31 (15.5%)

In an ERP-positive ECG, ERP can occur in more than one regional territory (inferior or lateral). A mixed ERP morphology indicates different morphologies across leads. ERP morphologies and ST-segment information is provided across regional territories. GWAS – genome wide association study; ERP – early repolarization pattern; FHS – Framingham Heart Study; H2K – Health 2000 Study; n – number.

Table 3

GWAS association results for the most significant SNPs

SNP	Chr	Minor/major allele	MAF	Location	Closest gene(s)	Cohort specific						Meta-analysis		
						FHS OR (95% CI)	H2K OR (95% CI)	KORA F4 OR (95% CI)	OR	95% CI	p-value			
rs11653989	17	A/T	8.3%	Intergenic	<i>MGA75B, SEC14L</i>	0.43 (0.30–0.62)	0.56 (0.29–1.07)	0.49 (0.32–0.75)	0.47	0.36–0.61	6.87×10 ⁻⁰⁹			
rs6585436	10	T/C	1.7%	Intergenic	<i>PDDZ8, EMX2</i>	-	0.43 (0.14–1.31)	0.30 (0.19–0.49)	0.32	0.21–0.50	4.88×10 ⁻⁰⁷			
rs17029069	1	T/C	35.6%	Intronic	<i>KCNJ23</i>	1.58 (1.28–1.94)	1.37 (0.94–2.02)	1.32 (1.02–1.71)	1.46	1.25–1.69	8.50×10 ⁻⁰⁷			
rs17097328	14	T/C	19.0%	Intergenic	<i>C14orf177</i>	1.60 (1.27–2.02)	1.44 (0.93–2.24)	1.40 (1.04–1.86)	1.51	1.27–1.78	1.71×10 ⁻⁰⁶			
rs17012480	2	A/G	13.6%	Intronic	<i>LTBP1</i>	0.64 (0.51–0.80)	0.88 (0.56–1.37)	0.70 (0.54–0.93)	0.69	0.58–0.81	6.97×10 ⁻⁰⁶			
rs1541064	1	A/G	38.1%	Intronic	<i>UBE2U</i>	1.70 (1.40–2.07)	1.00 (0.66–1.51)	1.11 (0.87–1.42)	1.38	1.20–1.59	8.54×10 ⁻⁰⁶			
rs6988260	8	A/G	21.0%	Intronic	<i>FAM110B</i>	0.73 (0.59–0.91)	0.51 (0.33–0.78)	0.73 (0.54–0.98)	0.69	0.59–0.81	8.92×10 ⁻⁰⁶			
rs1382629	4	A/G	2.7%	Intronic	<i>KIAA1211</i>	-	1.66 (0.91–3.01)	2.62 (1.69–4.09)	2.23	1.56–3.18	9.82×10 ⁻⁰⁶			

Results sorted by ascending p-value. All results adjusted for age, sex, and RR-interval. Chr – chromosome; CI – confidence interval; GWAS – genome wide association study; ERP – early repolarization pattern; FHS – Framingham Heart Study; H2K – Health 2000 Study; MAF – minor allele frequency; OR – odds ratio per minor allele; SNP – single nucleotide polymorphism.

Table 4

Replication and combined analysis

SNP	Chr	Closest gene(s)	GWAS Meta-analysis			Replication Meta-analysis			Overall		
			OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	
rs11653989	17	<i>MGAT5B, SEC14L</i>	0.47 (0.36-0.61)	6.87×10^{-09}	0.97 (0.70-1.34)	0.84	0.62 (0.50-0.76)	2.80×10^{-06}			
rs6585436	10	<i>PDZD8, EMX2</i>	0.32 (0.21-0.50)	4.88×10^{-07}	0.74 (0.47-1.15)	0.18	0.48 (0.35-0.66)	6.11×10^{-06}			
rs17029069	1	<i>KCND3</i>	1.46 (1.25-1.69)	8.50×10^{-07}	1.11 (0.94-1.31)	0.23	1.29 (1.15-1.44)	8.28×10^{-06}			
rs17097328	14	<i>C14orf177</i>	1.51 (1.27-1.78)	1.71×10^{-06}	0.87 (0.71-1.07)	0.19	1.21 (1.06-1.38)	4.03×10^{-03}			
rs17012480	2	<i>LTBP1</i>	0.69 (0.58-0.81)	6.97×10^{-06}	1.11 (0.90-1.37)	0.31	0.83 (0.73-0.94)	3.45×10^{-03}			
rs1541064	1	<i>UBE2U</i>	1.38 (1.20-1.59)	8.54×10^{-06}	1.01 (0.86-1.18)	0.93	1.20 (1.08-1.34)	6.80×10^{-04}			
rs6988260	8	<i>FAM110B</i>	0.69 (0.59-0.81)	8.92×10^{-06}	0.87 (0.71-1.08)	0.20	0.75 (0.66-0.86)	1.72×10^{-05}			
rs1382629	4	<i>KIF1A1211</i>	2.23 (1.56-3.18)	9.82×10^{-06}	1.09 (0.80-1.49)	0.58	1.48 (1.17-1.87)	9.12×10^{-04}			

All results adjusted for age, sex, and RR-interval. CHR – chromosome; CI – confidence interval; GWAS – genome wide association study; OR – odds ratio per minor allele; SNP – single nucleotide polymorphism.