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보건학석사 학위논문

Identification of
Genetic and Environmental Factors
Modulating Electrocardiographic
Intervals in Korean:
The Healthy Twin Study

한국인의 심전도 간격에 영향을 미치는
유전 및 환경 요인 분석

2015년 2월

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Abstract

Background

The electrocardiogram (EKG) is a useful and simple tool for evaluating the cardiac condition system. There are many kinds of EKG parameters indicating electrical behavior of the heart. Especially EKG intervals including PR interval, QRS complex, and QT interval are known as clinically significant parameters for assessing abnormal cardiac conditions. Recently, many researchers have noticed the availability of the EKG interval as a clinical parameter to predict a specific cardiovascular disease.

Objective

The purpose of this study is to identify genetic and environmental factors modulating PR interval, QRS complex, and QTc interval. Genetic factors including heritability and genetic loci were suggested for each EKG interval, and compared with the results from former studies. In addition, the effects of environmental factors including cigarette smoking and alcohol consumption were statistically estimated for each EKG interval.

Methods

Individuals from the Healthy Twin Study were selected as the study population. Of the 3,479 attendees at the baseline cohort, 79 individuals were excluded for PR interval, 62 individuals were excluded for QRS complex, and 96 individuals were excluded for QTc interval. Total number of study population was 3,400 for PR interval, 3,417 for QRS complex, and 3,383 for QTc interval.

Every phenotype used in this study was examined according to the standard protocol

of the Healthy Twin Study. The EKG results including heart rate and EKG intervals were measured by using standard 12-lead electrocardiography, and recorded at a paper speed of 25mm/s. A single lead (lead II) was used to measure each EKG interval. The results were automatically measured first, and then validated by a trained technician.

Two kinds of single nucleotide polymorphism (SNP) microarray chips were used for genotyping: Affymetrix Genome-wide Human SNP Array 6.0 (Affymetrix SNP microarray), and Illumina HumanCore-12 v1.0 BeadChip (Illumina SNP microarray). The genotyped markers were cleaned through quality control (QC) procedure, and the results were imputed with the Asian reference data from the 1000 Genomes Project by using SHAPEIT2 and IMPUTE2 algorithms. Total 4,174,873 markers were selected as final markers.

Family-based score test for association (FASTA) method was used to decorrelate the familial relationships among study participants. The heritability of each EKG interval and the association between specific locus and EKG intervals were evaluated by using the package GenABEL in R version 3.0.2. Environmental factors including cigarette smoking and alcohol consumption status were statistically analyzed in SAS version 9.3.

Results

Heritability for each EKG interval was evaluated as higher levels: 0.45 to 0.46 for PR interval, 0.35 to 0.37 for QRS complex, and 0.43 to 0.48 for QTc interval. In addition, several loci contributing EKG intervals were identified. For PR interval, four identified loci were significant and the related gene, *CAVI* was replicated with several previous studies. For QRS complex and QTc interval, several insignificant (with

$5.0 \times 10^{-8} < P$) SNPs were identified. Environmental factors including cigarette smoking and alcohol consumption status were significantly verified with $P < 5.0 \times 10^{-8}$.

Conclusion

The results from this study suggest that both genetic and environmental factors affect EKG intervals including PR interval, QRS complex, and QTc interval. In consideration of the potential value of EKG intervals, these findings are significant as reaffirming the result from previous genome-wide association studies in Korean population and suggesting future directions.

Keywords: *electrocardiography, electrocardiographic intervals, PR interval, QRS complex, QT interval, corrected QT interval, genome-wide association study, heritability, environmental factors, and the Healthy Twin Study*

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Contents

Abstract	i
List of Tables	vi
List of Figures	vii
Introduction	1
1. Electrocardiographic Interval	1
1.1. Definition	1
1.2. Physiological Implication	2
2. Previous Study on Electrocardiographic Interval	2
2.1. Association with Cardiovascular Disease	2
2.2. Genetic Study	4
3. Purpose of the Study	6
Methods	7
1. Study Population	7
2. Phenotype Measurement	8
2.1. Questionnaire Survey and Physical Examination	8
2.2. Electrocardiography Measurement	8
3. Genotype Measurement	9
3.1. Genotype Arrays	9
3.2. Genotype Imputation	9

4. Statistical Analysis	10
4.1. Heritability Analysis	10
4.2. Genome-wide Association Study	11
Results	12
1. Study Population	12
2. Genetic Factors	13
2.1. Heritability	13
2.2. Genome-wide Association Study	13
3. Environmental Factors	25
Discussion	29
1. Implications and Study Limitations	29
2. Conclusion	31
References	33
Abstract in Korean	40

List of Tables

Table 1. Basic Characteristics of Study Population for Each EKG Interval	-----12
Table 2. Heritability Estimates of Each EKG Interval	-----13
Table 3. Top SNPs for PR Interval	-----15
Table 4. Top SNPs for QRS Complex	-----15
Table 5. Top SNPs for QTc Interval	-----15
Table 6. Effects of Environmental Factors on PR Interval	-----26
Table 7. Effects of Environmental Factors on QRS Complex	-----27
Table 8. Effects of Environmental Factors on QTc Interval	-----28

List of Figures

Figure 1. Description of Normal Electrocardiogram	1
Figure 2. Manhattan Plot for PR Interval	16
Figure 3. Quantile-Quantile Plot for PR Interval	16
Figure 4. Regional Plot and LD Plot for PR Interval on CHR 7	17
Figure 5. Regional Plot and LD Plot for PR Interval on CHR 12	18
Figure 6. Manhattan Plot for QRS Complex	19
Figure 7. Quantile-Quantile Plot for QRS Complex	19
Figure 8. Regional Plot and LD Plot for QRS Complex on CHR 9	20
Figure 9. Regional Plot and LD Plot for QRS Complex on CHR 20	21
Figure 10. Manhattan Plot for QTc Interval	22
Figure 11. Quantile-Quantile Plot for QTc Interval	22
Figure 12. Regional Plot and LD Plot for QTc Interval on CHR 18	23
Figure 13. Regional Plot and LD Plot for QTc Interval on CHR 1	24
Figure 14. PR Interval by Cigarette Smoking and Alcohol Consumption	26
Figure 15. QRS Complex by Cigarette Smoking and Alcohol Consumption	27
Figure 16. QTc Interval by Cigarette Smoking and Alcohol Consumption	28

Introduction

1. Electrocardiographic Interval

1.1. Definition

The electrocardiogram (EKG) is a conventional instrument to evaluate the cardiac conduction system. Most electrical behavior of the heart is recorded at the EKG paper. Although the EKG simply documents electric potential changes in the heart, it could be used to figure out abnormal cardiac conditions. There are many kinds of EKG parameters which indicate electrical behavior of the heart: P wave, QRS complex, T wave and U wave. Especially the EKG intervals, including PR interval, QRS complex, and QT interval, are known as clinically significant parameters for assessing abnormal cardiac conditions. These EKG parameters are briefly described in Figure 1.

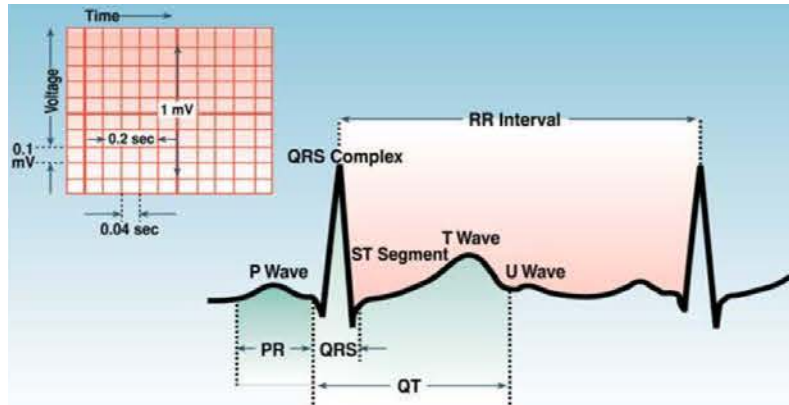


Figure 1. Description of Normal Electrocardiogram

PR interval is measured from the starting point of P wave to the starting point of QRS complex on the EKG printout. QRS complex is measured as the time duration of QRS complex, and QT interval is measured from the starting point of QRS complex to the end point of T wave. QT interval is usually modified to corrected QT interval (QTc

interval) by using heart rate. The EKG intervals are routinely reported on the EKG printout.

1.2. Physiological Implication

Each EKG interval indicates a specific function of the heart. PR interval, for example, reflects the atrial function of the cardiac conduction system. As mentioned above, the time duration between the starting point of P wave and QRS complex is considered PR interval. P wave indicates the atrial muscle depolarization and QRS complex indicates the ventricular muscle depolarization. Therefore, PR interval could be the parameter showing whole flow of electric potential changes in the atrium. On the other hand, both QRS complex and QTc interval reflect the ventricular behavior of the heart. The whole process of ventricular depolarization is reflected in QRS complex. QTc interval, moreover, indicates ventricular muscle repolarization. Consequently, whole flow of electric potential changes in the ventricle is reflected in QTc interval. From a clinical point of view, the normal range of PR interval is between 120 and 200 milliseconds. The normal range for QRS complex is shorter than 100 milliseconds. In the case of QTc interval, the range is shorter than 440 milliseconds.

2. Previous Study on Electrocardiographic Interval

2.1. Association with Cardiovascular Disease

Several established researches suggest that PR interval could be used as a prognostic parameter to prevent adverse cardiac conditions. Prolonged PR interval (PR>200ms) was reported as a significant risk factor for atrial fibrillation^{3, 26, 30, 33}. The association between prolonged PR interval and the risk of atrial fibrillation was replicated in the

Health, Aging, and Body Composition Study (Health ABC) and the Copenhagen ECG study^{20, 26}. Prolonged PR interval also increases the risk of pacemaker implantation, and all-cause mortality³. In the case of all-cause mortality, however, has inconsistent association with prolonged PR interval; the association was not reported in the Third National Health and Nutrition Examination Survey (NHANES-III) and the Health ABC study^{19, 20}. Recently, Soliman et al³² suggested the other hypothesis to explain these inconsistent reports; the level of P wave duration to PR interval ratio is associated with all-cause mortality. According to the study, the contribution of P wave duration to PR interval could be used as a predictor for adverse cardiac conditions³².

QRS complex is also related with cardiac conditions. Prolonged QRS complex ($QRS \geq 120\text{ms}$) was reported as a risk factor for heart failure, sudden cardiac death in coronary disease, and all-cause mortality^{9, 16, 37, 38}. According to Wang et al³⁸, those with prolonged QRS complex have a higher risk of hospitalization for heart failure, all-cause mortality, and cardiovascular death compared those with normal QRS complex ($QRS < 120$). In the group of coronary disease patients, prolonged QRS complex was reported as an independent risk factor for sudden cardiac death³⁷. The association between prolonged QRS complex and sudden cardiac death was replicated in the general male participants; prolonged QRS complex was reported as a significant risk predictor of sudden cardiac death¹⁶. According to Desai et al⁹, Prolonged QRS complex could be a strong predictor of cardiovascular mortality; the survival rate in the group of patients with prolonged QRS complex is significantly lower than the rate in normal group⁹.

QTc interval, especially prolonged QTc interval ($QTc > 440\text{ms}$ in male, $QTc > 460\text{ms}$ in female) was reported as a significant risk factor for sudden cardiac death, coronary heart disease mortality, cardiovascular mortality, and all-cause mortality^{35, 39, 40}.

Abnormal prolongation of QTc interval was identified as an independent risk factor for sudden cardiac death in general population aged 55 years and older³⁵. Both shortened and prolonged QTc interval, according to the results from the NHANES-III, increase the all-cause mortality. Although statistical parameters are not significant, these abnormal QTc intervals are associated with the risk of mortality due to cardiovascular disease and coronary heart disease⁴⁰. On the other hand, Zhang et al³⁹ performed a meta-analysis to assess the association between QTc interval and mortality. As a result, they identified consistent associations between prolonged QTc interval and increased mortality due to all-cause and coronary heart disease. In addition, both shortened and prolonged QTc intervals were reported as a risk factor for atrial fibrillation, recently²⁵.

2.2. Genetic study

EKG intervals are known as heritable risk factors for adverse cardiac conditions. Several established researches support the significant heritability of EKG intervals^{12, 17, 21, 23, 24}. Heritability, according to Newton-Cheh et al²³, is 0.34 for PR interval and 0.39 for QT interval. The research performed in a rural Chinese population suggest the heritability is 0.34 for PR interval, 0.42 for QRS complex, and 0.40 for QTc interval¹⁷. On the other hand, the research based on European descent population suggests the heritability is 0.40 for PR interval, 0.33 for QRS complex, and 0.30 for QT interval¹². The heritability for QRS complex was reported as 0.36 in older women recruited from a twin study²¹, and the significant heritability for QT interval was 0.35 as a result from the Framingham Heart Study²⁴. These reported heritability support the existence of genetic factors contributing to EKG intervals. Genome-wide association study (GWAS) is usually conducted to identify genetic variations contributing to specific traits. Indeed, many GWAS focused on those genetic factors have been

performed.

Several research groups performed GWAS on PR interval and identified significant loci modulating the EKG interval^{1, 12, 13, 23, 27, 29, 31}. Seven population-based European studies in the CHARGE consortium performed GWAS and identified nine loci associated with PR interval: *SCN10A*, *CAVI-CAV2*, *SCN5A*, *ARHGAP24*, *TBX5-TBX3*, *SOX5*, *NKX2-5*, *MEIS1*, and *WNT11*²⁷. Four of these loci were replicated (with $P < 5.0 \times 10^{-8}$) in European descent study: *SCN10A*, *ARHGAP24*, *CAVI*, and *TBX5*¹². *SCN5A* was also identified from GWAS in African American population^{1, 31}, and several novel loci were reported from East Asian studies¹³. According to the other East Asian study²⁹, many of these loci modulating PR interval are shared by different ethnic groups including European, African, and Asian. Although statistical parameters are not significant, several loci associated with PR interval were also identified in Framingham Heart Study²³.

GWAS on QRS complex and QTc interval have also been performed and identified several significant loci contributing these EKG intervals^{12, 13, 22, 23, 28, 34}. In the case of study on QRS complex, twenty-two novel loci were identified (with $P < 5.0 \times 10^{-8}$) from large population GWAS of European descent: *SCN10A-SCN5A*, *CDKN1A*, *PLN-BRD7P3*, *NFIA*, and so on³⁴. In addition, two significant loci associated with QRS complex were reported from European descent study: *TBX5*, and *SCN10A*¹². Two novel loci were also reported (with $P < 1.0 \times 10^{-5}$) from Korean and Japanese study¹³. For QT interval, ten novel loci associated with QT interval were identified from the QTGEN consortium: *NOS1AP*, *CNOT1*, *KCNQ1*, *KCNH2*, and *SCN5A*²². The other European ancestry consortium named QTSCD also reported several loci for QT interval: *NOS1AP*, *NDRG4*, *PLN*, *KCNQ1*, *ATP1B1*, *KCNH2*, *LITAF*, and *SCN5A*²⁸. These loci were mutually replicated in the results from QTGEN and QTSCD

consortium. There are several reported loci for QRS complex and QT interval in Framingham Heart Study, although they are not significant²³.

3. Purpose of the Study

EKG intervals are simple and important parameters to figure out abnormal cardiac conditions. As verified by previous studies, EKG intervals are associated with a number of fatal heart conditions, for example atrial fibrillation, pacemaker implantation, heart failure, and sudden cardiac death. Recently, many researchers have noticed the availability of the EKG interval as a clinical parameter to predict a specific cardiovascular disease. In consideration of the potential value of EKG intervals, this study was focused on the identification of genetic and environmental factors modulating PR interval, QRS complex, and QTc interval. Genetic factors including heritability and genetic loci were suggested for each EKG interval, and compared with the results from former studies. Especially, the replication of newly found loci from this study was check to confirm the identification of the loci. In addition, the effects of environmental factors including cigarette smoking and alcohol consumption were statistically estimated for each EKG interval.

Methods

1. Study Population

To identify genetic factors contributing to EKG intervals in Korean, individuals from the Healthy Twin Study were selected as the study population. The Healthy Twin Study is a cohort study of twin pairs of the same sex, aged 30 and over, and their first-degree family members who are interested in participating in the study. It is a cohort in progress since 2005. The study design and protocols of the original cohort were described previously³⁶. The baseline cohort was independently reconstructed for analysis on PR interval, QRS complex, and QTc interval. Exclusion criteria for each EKG interval were almost same: a) individual without the EKG interval measurement b) individual with EKG technicians' records about abnormal cardiac conditions including atrial flutter/fibrillation, myocardial infarction, ventricular assist device (VAD), and ectopic pacemaker c) individual with missing covariate. In the case of QTc interval, individuals with prolonged QRS complex were excluded additionally. Exclusion criteria were consulted from previous researches on EKG intervals^{12, 22, 27, 28}.

Of the 3,479 attendees at the baseline cohort, 79 individuals were excluded for PR interval: individuals without the PR interval measurements (n=59), individuals with EKG technicians' records about abnormal cardiac conditions (n=13), and individuals without systolic blood pressure (SBP) measurements (n=7). For QRS complex, 62 individuals were excluded: individuals without the QRS complex measurements (n=30), individuals with EKG technicians' records about abnormal cardiac conditions (n=25), and individuals without systolic blood pressure (SBP) measurements (n=7). In addition, 96 individuals were excluded for QTc interval: individuals without the QTc interval measurements (n=30), individuals with EKG technicians' records about

abnormal cardiac conditions (n=25), individuals with prolonged QRS complex (n=34), and individuals without systolic blood pressure (SBP) measurements (n=7). In conclusion, total number of study population was 3,400 for PR interval, 3,417 for QRS complex, and 3,383 for QTc interval.

2. Phenotype Measurement

2.1. Questionnaire Survey and Physical Examination

Every participant in the Healthy Twin Study took a questionnaire survey and physical examination including anthropometry, clinical test, and biological specimen collection at one of the three clinical centers located in Seoul, Pusan, and Cheonan. To reduce bias resulted from measurement difference between clinical centers, the survey methods were organized into a standard protocol. All of research coordinators and assistants were trained by the protocol to provide a standardized survey for each participant. Detailed information on the questionnaire survey and physical examination was described in the previous report on the Healthy Twin Study³⁶.

2.2. Electrocardiography Measurement

All attendees for the Healthy Twin Study were provided standard 12-lead electrocardiography. The EKG results including heart rate and EKG intervals were recorded at a paper speed of 25mm/s. A single lead (lead II) was used to measure each EKG interval. Heart rate, PR interval, QRS complex, and QTc interval were automatically measured first, and then the EKG results were validated by a trained technician.

3. Genotype Measurement

3.1. Genotype Arrays

Genotyping was conducted by using two kinds of single nucleotide polymorphism (SNP) microarray chips: Affymetrix Genome-wide Human SNP Array 6.0 (Affymetrix SNP microarray), and Illumina HumanCore-12 v1.0 BeadChip (Illumina SNP microarray). Genomic DNA extracted from all participants' blood samples at their recruitment was genotyped with these SNP microarray chips. The genotyped markers were cleaned through quality control (QC) procedure in accordance with following exclusion criteria: a) minor allele frequency (MAF) < 0.01, b) Hardy-Weinberg equilibrium (HWE) < 0.001, c) genotype missing rate > 0.05, d) Mendelian error > 3 families, e) non-Mendelian error > 3 families. By conducting quality control procedure, total number of genetic markers was 541,643 for Affymetrix SNP microarray, and 275,067 for Illumina SNP microarray.

3.2. Genotype Imputation

For application of the whole genetic data from different SNP microarray chips to GWAS, genotyped markers from each platform were imputed with the Asian reference data from the 1000 Genomes Project⁵. The Asian reference includes 286 samples from Chinese Dai in Xishuangbanna (CDX), Han Chinese in Beijing (CHB), Japanese in Tokyo (JPT), Kinh in Ho Chi Minh City (KHV), and Southern Han Chinese (CHS)⁴. Genotype imputation was conducted by two-step process: pre-phasing and imputation¹⁴. Segmented haplotype estimation and imputation tool 2 (SHAPEIT2), the hidden Markov model (HMM)-based phasing approach, was used to phase haplotypes for each platform in this study, because it is known as the most precise method for phasing sets of known genotypes⁶⁻⁸. Each haplotype phased by

SHAPEIT2 could be imputed separately with given reference panel¹⁴. IMPUTE version 2 (IMPUTE2) is one of the most accurate and flexible imputation method for the reference panels from 1000 Genomes Project¹⁵.

After genotype imputation by two-step process, total number of genetic markers is 27,449,999 for Affymetrix SNP microarray, and 27,472,228 for Illumina SNP microarray. Among these, only the genetic markers which have quality score (info-score) exceeding 0.9 were selected: 5,980,612 markers for Affymetrix SNP microarray, and 5,693,690 markers for Illumina SNP microarray. By comparing the results from each platform, the overlapped 4,174,873 markers were selected as final markers.

4. Statistical Analysis

4.1. Heritability Analysis

Heritability analysis was conducted to estimate genetic determinants for EKG intervals. In this study, narrow sense of heritability (h^2) was used as an index for assessing genetic determinants. In general, specific phenotypic traits with heritability over 0.3 are considered to be heritable, and over 0.5 are considered to be highly heritable. To estimate heritability for EKG intervals, statistical models were suggested in two ways; EKG intervals were initially adjusted for age and sex (model 1), then additionally adjusted for height, body mass index (BMI), systolic blood pressure (SBP), and heart rate (model 2). These covariates were consulted from previous GWAS for EKG intervals conducted by consortia^{12, 22, 27, 28, 31}. In the case of statistical models for QTc interval, heart rate was not included as a covariate, because it was already used to correct QT interval. Heritability was evaluated from these models for

each EKG interval, by using the package GenABEL in R version 3.0.2.

4.2. Genome-wide Association Study

To identify specific loci associated with EKG intervals, GWAS was conducted for each EKG interval: PR interval, QRS complex, and QTc interval. Statistical model 1 and 2, the same model used to estimate heritability for EKG intervals, were used as polygenic models for GWAS. As the Healthy Twin Study was based on familial relationships³⁶, the study population need to be decorrelated by using their pedigree data. Family-based score test for association (FASTA) method was used to decorrelate the familial relationships among study participants². After decorrelation process, specific loci contributing to EKG intervals, usually detected as SNPs, were identified through GWAS. The observed test statistics of each SNP were divided by inflation factor lambda to correct the inflations of test statistics, and the corrected test statistics were used to calculate statistical significances of each specific loci. The whole process of GWAS was conducted by using the package GenABEL in R version 3.0.2. The results from GWAS for each EKG interval were visualized as Manhattan plots to screen significant (with $P < 5.0 \times 10^{-8}$) genetic polymorphisms efficiently. In addition, top signals for each EKG interval were reported with related genes by focusing on their physiological functions.

Results

1. Study Population

Basic characteristics of study population for each EKG interval are shown in Table 1. The number of participants is 3,400 for PR interval, 3,417 for QRS complex, and 3,383 for QTc interval. As participants for each EKG interval were selected from the Healthy Twin Study, basic characteristics of study population were generally normal. Especially the main objects of this study including PR interval, QRS complex, and QTc interval were located in normal ranges: between 120 and 200 milliseconds for PR interval, shorter than 100 milliseconds for QRS complex, and shorter than 440 milliseconds for QTc interval.

Table 1. Basic Characteristics of Study Population for Each EKG Interval

	PR Interval	QRS Complex	QTc Interval
Participants, N	3,400	3,417	3,383
Age, years, mean±s.d.	44.1±13.6	44.1±13.6	44.0±13.5
Sex, male, n(%)	1,382 (40.6)	1,386 (40.6)	1,366 (40.4)
Cigarette Smoking, n(%)			
Never	2,227 (65.6)	2,237 (65.5)	2,221 (65.7)
Past	572 (16.8)	575 (16.8)	565 (16.7)
Current	598 (17.6)	602 (17.6)	594 (17.6)
Alcohol Consumption, n(%)			
Never	946 (27.8)	949 (27.8)	939 (27.8)
Past	316 (9.3)	318 (9.3)	315 (9.3)
Current	2,137 (62.9)	2,149 (62.9)	2,128 (62.9)
Height, cm, mean±s.d.	162.2±8.7	162.2±8.7	162.2±8.7
Body Mass Index, kg/m ² , mean±s.d.	23.7±3.3	23.7±3.3	23.7±3.3
Total Cholesterol, mg/dL, mean±s.d.	189.1±35.7	189.1±35.7	189.0±35.7
HDL Cholesterol, mg/dL, mean±s.d.	50.2±12.6	50.3±12.6	50.2±12.6
LDL Cholesterol, mg/dL, mean±s.d.	110.6±31.2	110.5±31.2	110.5±31.2
Diabetes, n(%)	119 (3.5)	122 (3.6)	121 (3.6)
Hypertension, n(%)	447 (13.1)	448 (13.1)	438 (12.9)
Systolic Blood Pressure, mmHg, mean±s.d.	116.3±16.7	116.3±16.6	116.2±16.6
Heart Rate, beats/min, mean±s.d.	66.3±9.3	66.3±9.3	66.3±9.3
PR Interval, ms, mean±s.d.	160.3±20.7	160.3±20.7	160.2±20.7
QRS Complex, ms, mean±s.d.	88.4±10.2	88.4±10.2	88.0±9.2
QT Interval, ms, mean±s.d.	389.3±31.8	389.4±31.9	389.1±31.7
Corrected QT Interval, ms, mean±s.d.	406.4±26.3	406.4±26.3	406.2±26.1

2. Genetic Factors

2.1. Heritability

For each EKG interval, the heritability was measured based on two kinds of statistical models: a model adjusted for age and sex (model 1), and a model additionally adjusted for height, body mass index (BMI), systolic blood pressure (SBP), and heart rate (model 2). As a result, the heritability of PR interval is 0.45 for model 1, and 0.46 for model 2. These values were measured from study population of PR interval including 3,400 individuals, after decorrelation process by using FASTA method. Similarly, the heritability of QRS complex is 0.37 for model 1, and 0.35 for model 2. The values were measured from study population of QRS complex including 3,417 individuals. In the case of QTc interval, the heritability is 0.43 for model 1, and 0.48 for model 2. These values were measured from 3,383 individuals, after decorrelation. The heritability from each statistical model for EKG intervals is shown in Table 2.

Table 2. Heritability Estimates of Each EKG Interval

	Model 1		Model 2	
	Covariates	Heritability (h^2)	Covariates	Heritability (h^2)
PR Interval	Age, Sex	0.45	Age, Sex Height, BMI, SBP Heart Rate	0.46
QRS Complex	Age, Sex	0.37	Age, Sex Height, BMI, SBP Heart Rate	0.35
QTc Interval	Age, Sex	0.43	Age, Sex Height, BMI, SBP	0.48

2.2. Genome-wide Association Study

Specific loci associated with each EKG interval are identified through GWAS. The number of final markers used for analysis was 4,174,873, and the statistical models used to estimate heritability of EKG intervals were used as polygenic models for

GWAS. As a result of the association study on PR interval, four significant (with $P < 5.0 \times 10^{-8}$) SNPs were identified in model 1 and 2: rs1997571, rs1997572, rs11773845, and rs3807989. All of these four SNPs are related with *CAVI* gene, which is known as a member of the caveolin family; a family of integral membrane protein¹¹. *CAVI* gene has been already reported in several previous researches^{1, 12, 13, 27}. The other identified SNPs and related genes reported in dbSNP (<http://www.ncbi.nlm.nih.gov/projects/SNP>) are shown in Table 3. Manhattan plot and quantile-quantile plot of PR interval are shown in Figure 2 and 3. In addition, linkage disequilibrium plot and regional plot around top SNPs are described in Figure 4 and 5.

In the case of QRS complex and QTc interval, there were no significant SNPs. For QRS complex, the identified SNPs and related genes reported in dbSNP are shown in Table 4. Manhattan plot, quantile-quantile plot, linkage disequilibrium plot and regional plot of QRS complex are shown in the following figures: Figure 6, 7, 8 and 9. For QTc interval, the identified SNPs and reported genes are shown in Table 5. Manhattan plot, quantile-quantile plot, linkage disequilibrium plot and regional plot of QTc interval are shown in the following figures: Figure 10, 11, 12 and 13. All of these figures are based on model 2 for each EKG interval.

Table 3. Top SNPs for PR Interval

Locus	SNP	Chromosome	Position	Allele	Effect	MAF	<i>p</i> -value
<i>CAVI</i>	rs1997571	7	116,198,621	G	3.52	0.340	1.15E-08
<i>CAVI</i>	rs1997572	7	116,198,828	A	3.52	0.340	1.15E-08
<i>CAVI</i>	rs11773845	7	116,191,301	C	3.45	0.341	2.14E-08
<i>CAVI</i>	rs3807989	7	116,186,241	A	3.41	0.342	3.42E-08
-	rs4963780	12	24,801,081	T	-4.28	0.121	5.47E-07
-	rs4963776	12	24,779,491	T	-4.22	0.123	5.54E-07
-	rs7972733	12	24,866,079	G	-2.75	0.419	6.78E-07
-	rs10743514	12	24,856,527	C	-2.90	0.326	6.88E-07
-	rs4963778	12	24,800,607	G	-4.23	0.122	7.20E-07
-	rs4963779	12	24,800,775	G	-4.23	0.122	7.20E-07

Table 4. Top SNPs for QRS Complex

Locus	SNP	Chromosome	Position	Allele	Effect	MAF	<i>p</i> -value
-	rs12555695	9	11,389,224	A	1.39	0.390	1.38E-06
-	rs12551931	9	11,389,536	C	1.39	0.390	1.38E-06
-	rs16927453	9	11,372,645	C	1.38	0.389	1.64E-06
-	rs61449875	9	11,392,259	A	1.38	0.390	1.80E-06
-	rs58031408	9	11,392,318	T	1.38	0.390	1.80E-06
-	rs16927461	9	11,376,524	G	1.37	0.389	1.93E-06
-	rs72698145	9	11,391,925	A	1.37	0.389	1.95E-06
-	rs1335480	9	11,377,178	A	1.37	0.389	1.97E-06
-	rs16927452	9	11,372,258	A	1.37	0.388	2.08E-06
-	rs16927457	9	11,374,073	T	1.37	0.389	2.14E-06

Table 5. Top SNPs for Corrected QT Interval

Locus	SNP	Chromosome	Position	Allele	Effect	MAF	<i>p</i> -value
-	rs36060753	18	74,369,374	T	-4.79	0.158	1.77E-07
-	rs78736356	18	74,362,834	A	-4.19	0.204	4.05E-07
-	rs76343510	18	74,362,835	T	-4.19	0.204	4.05E-07
-	rs80330229	18	74,373,360	T	-4.48	0.157	9.13E-07
-	rs4313886	18	74,370,742	C	-4.45	0.164	1.02E-06
<i>DIEXF</i>	rs6689839	1	210,027,026	G	-3.85	0.217	3.24E-06
-	rs6665588	1	188,047,430	T	-8.29	0.035	5.77E-06
-	rs6690051	1	188,047,729	G	-8.29	0.035	5.77E-06
-	rs72723236	1	188,047,960	T	-8.29	0.035	5.77E-06
-	rs12743461	1	188,055,971	T	-8.29	0.035	5.77E-06

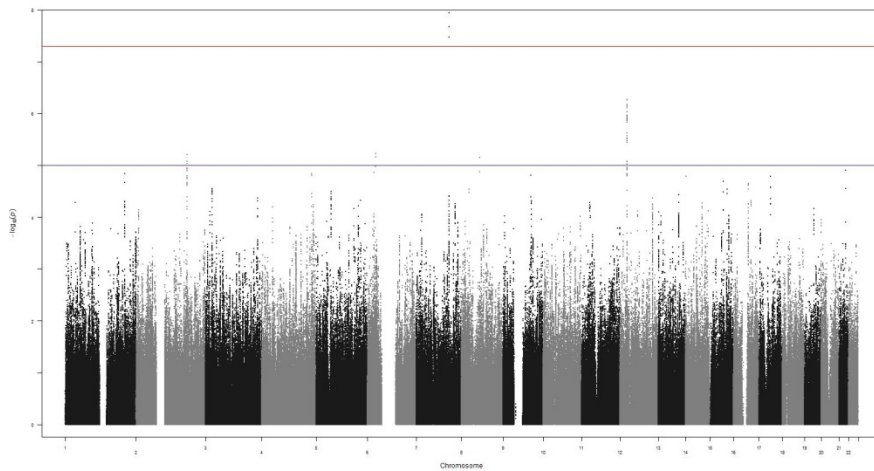


Figure 2. Manhattan Plot for PR Interval

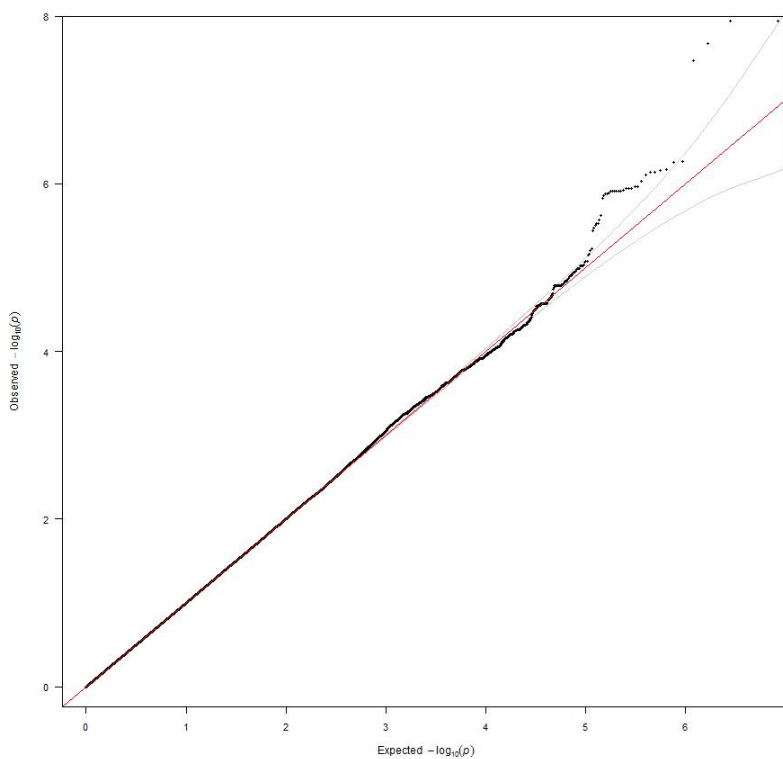


Figure 3. Quantile-Quantile Plot for PR Interval

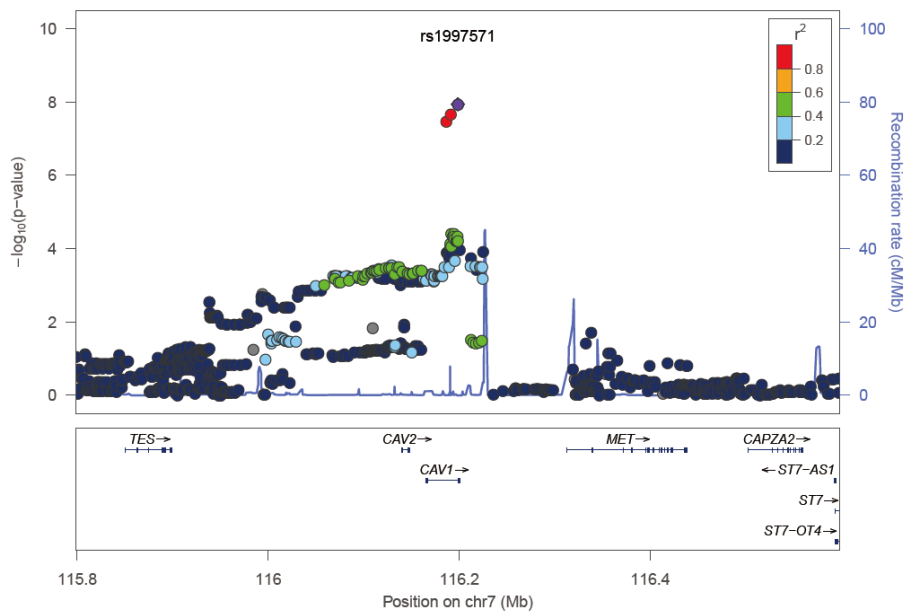


Figure 4. Regional plot and linkage disequilibrium plot for PR interval on chromosome 7. In the case of regional plot, the range of base-pair position is from 115.8Mb to 116.6Mb. The base-pair range for linkage disequilibrium plot is from 116.1Mb to 116.3Mb. Linkage disequilibrium plot has more detailed description.

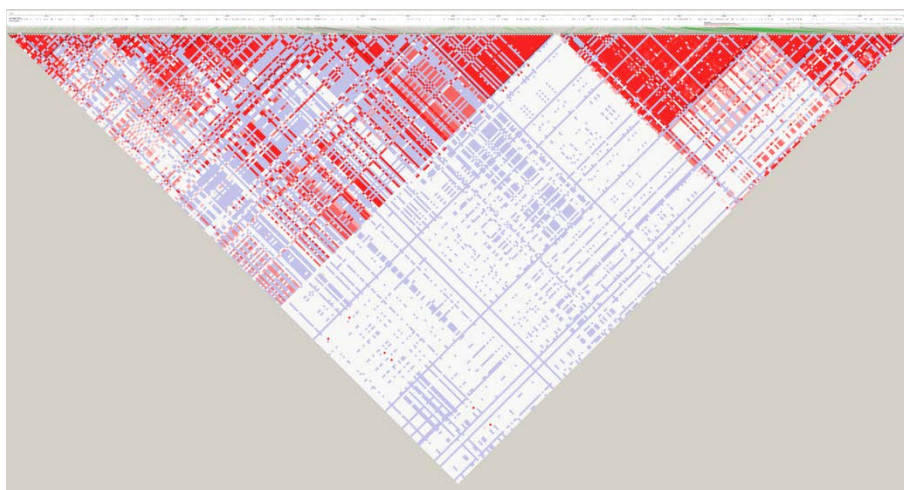
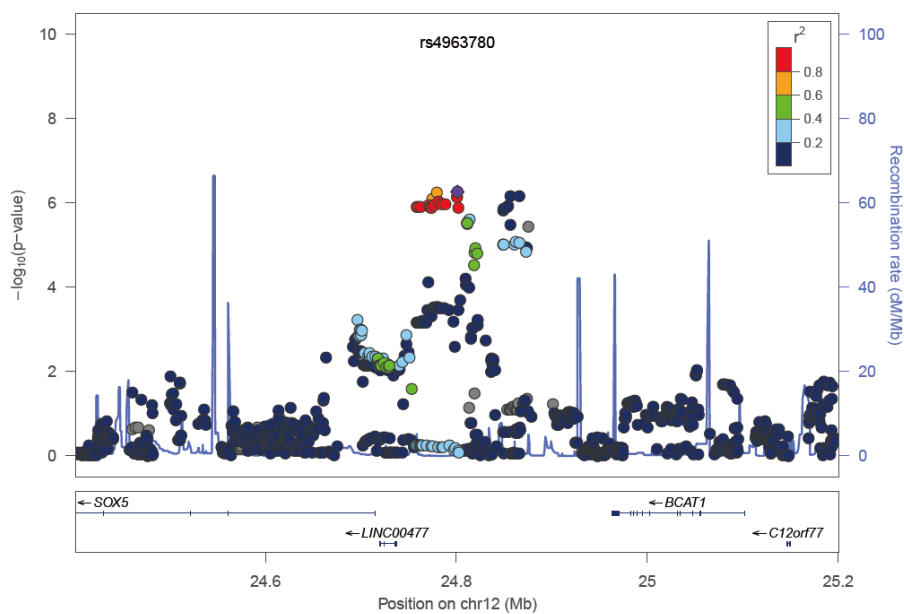


Figure 5. Regional plot and linkage disequilibrium plot for PR interval on chromosome 12. In the case of regional plot, the range of base-pair position is from 24.4Mb to 25.2Mb. The base-pair range for linkage disequilibrium plot is from 24.7Mb to 24.9Mb. Linkage disequilibrium plot has more detailed description.

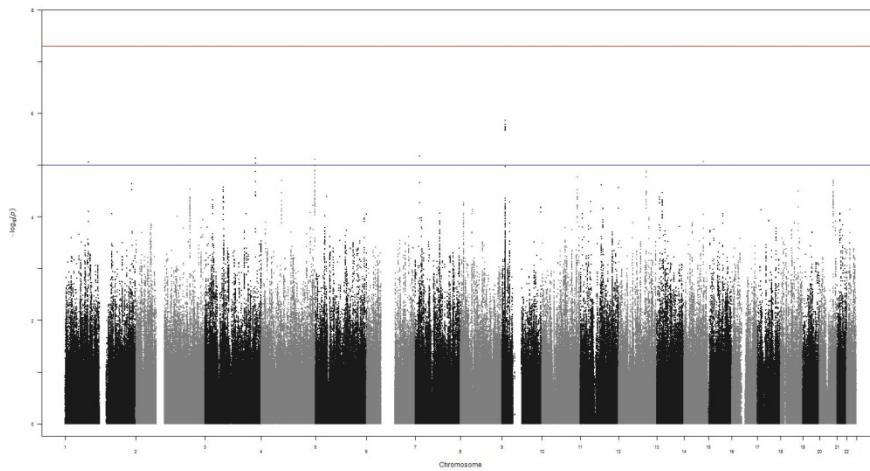


Figure 6. Manhattan Plot for QRS Complex

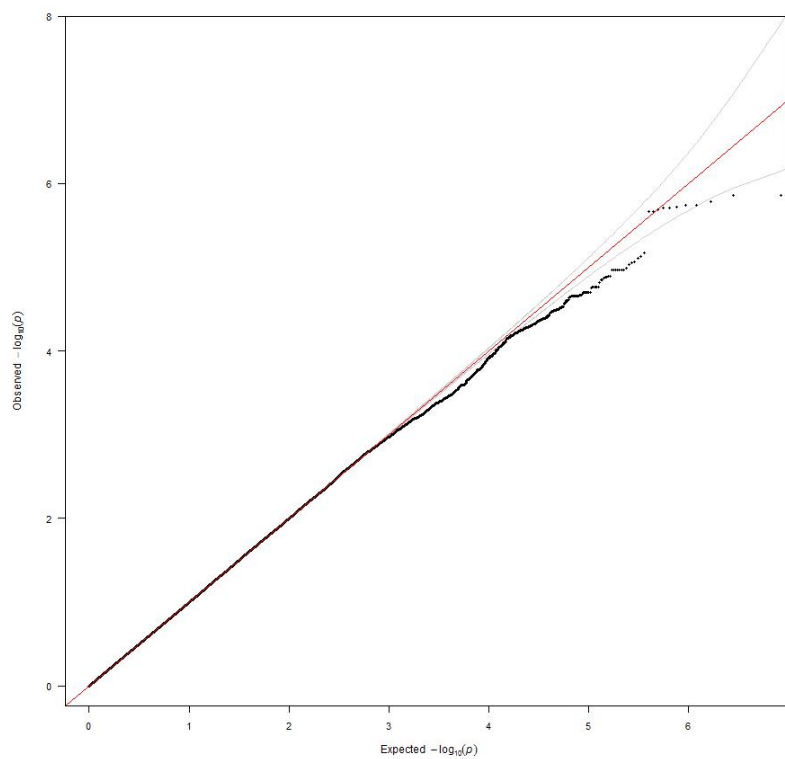


Figure 7. Quantile-Quantile Plot for QRS Complex

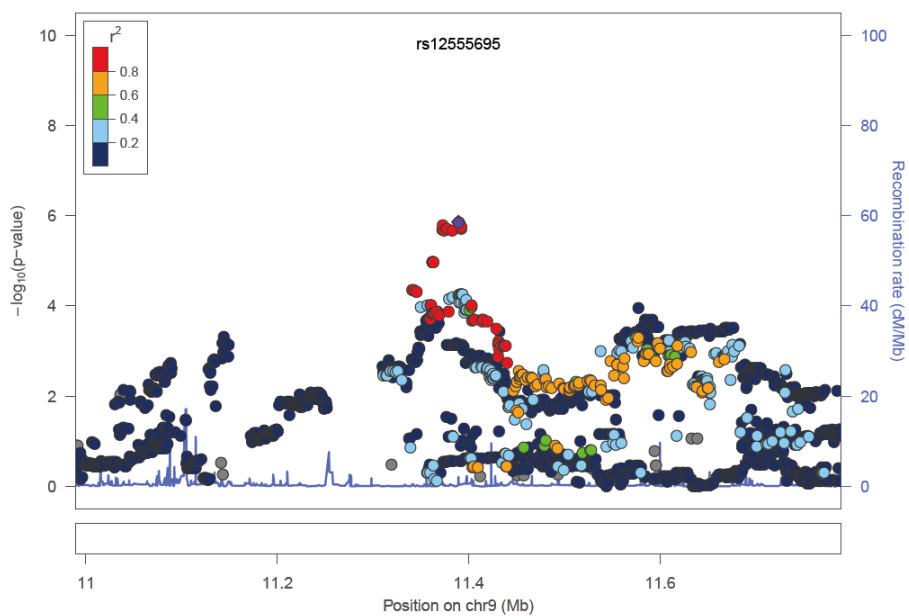


Figure 8. Regional plot and linkage disequilibrium plot for QRS complex on chromosome 9. In the case of regional plot, the range of base-pair position is from 11.0Mb to 11.8Mb. The base-pair range for linkage disequilibrium plot is from 11.3Mb to 11.5Mb. Linkage disequilibrium plot has more detailed description.

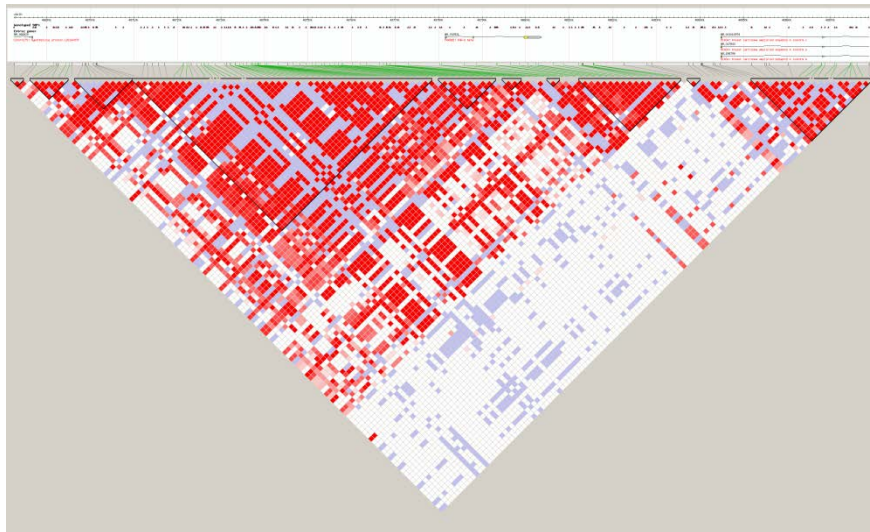
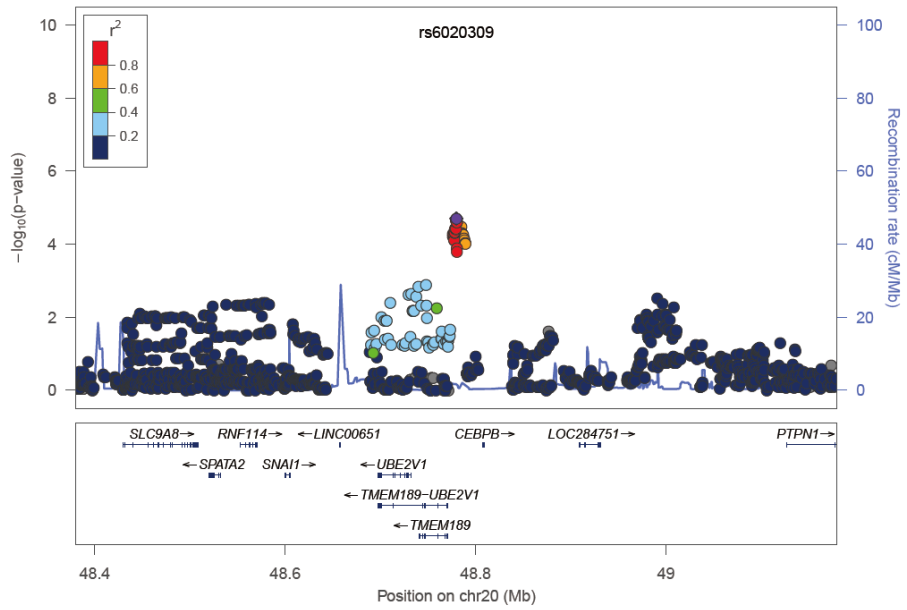


Figure 9. Regional plot and linkage disequilibrium plot for QRS complex on chromosome 20. In the case of regional plot, the range of base-pair position is from 48.4Mb to 49.2Mb. The base-pair range for linkage disequilibrium plot is from 48.7Mb to 48.9Mb. Linkage disequilibrium plot has more detailed description.

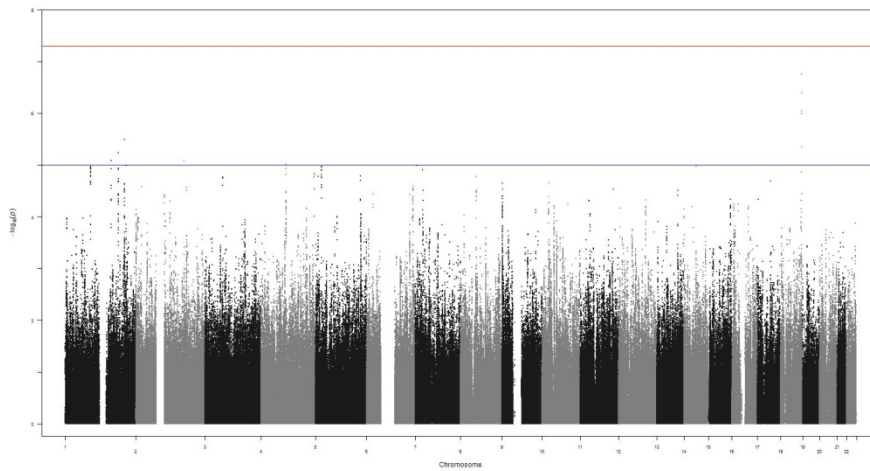


Figure 10. Manhattan Plot for Corrected QT Interval

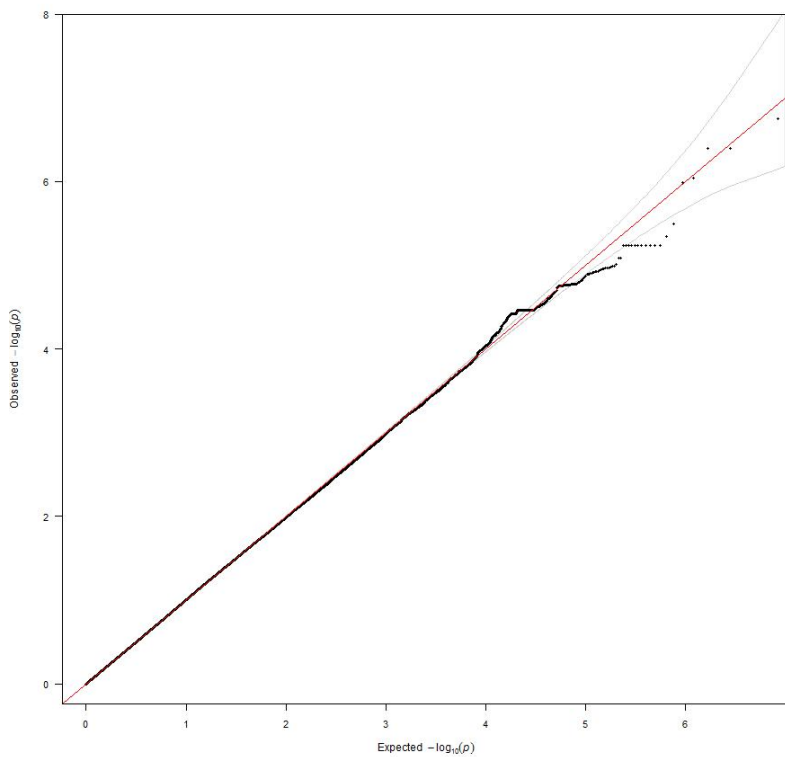


Figure 11. Quantile-Quantile Plot for Corrected QT Interval

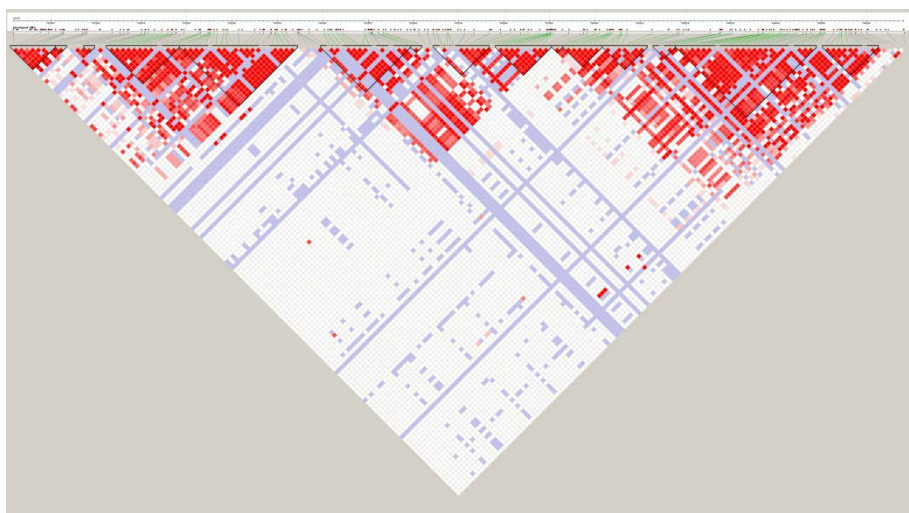
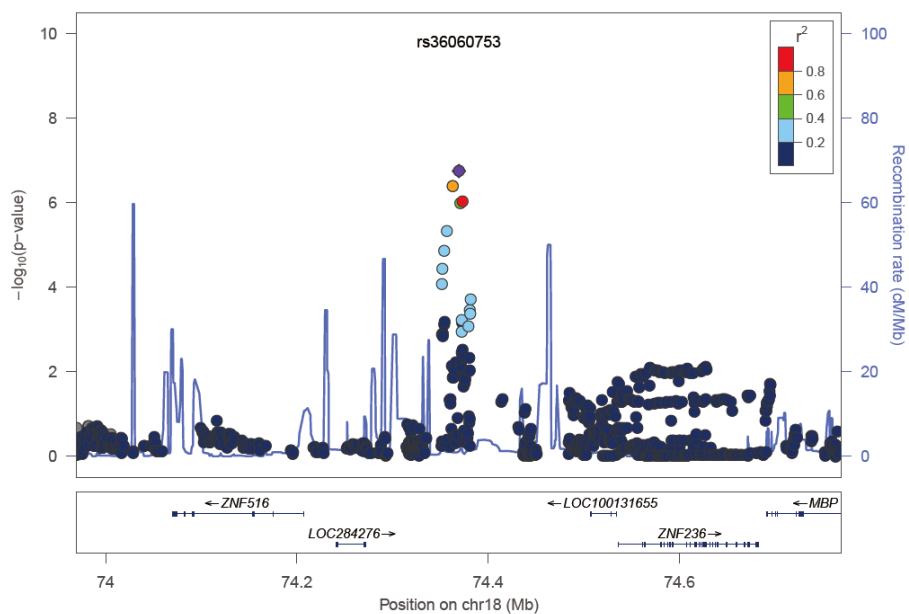


Figure 12. Regional plot and linkage disequilibrium plot for corrected QT interval on chromosome 18. In the case of regional plot, the range of base-pair position is from 74.0Mb to 74.8Mb. The base-pair range for linkage disequilibrium plot is from 74.3Mb to 74.5Mb. Linkage disequilibrium plot has more detailed description.

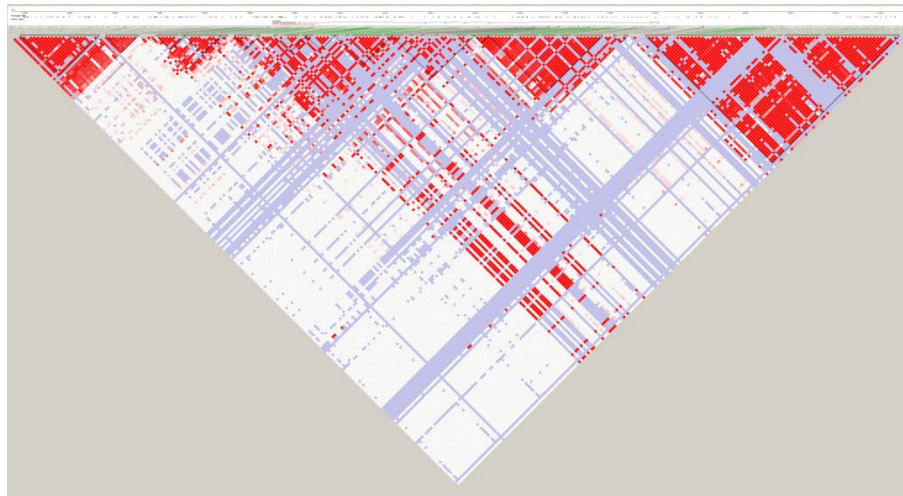
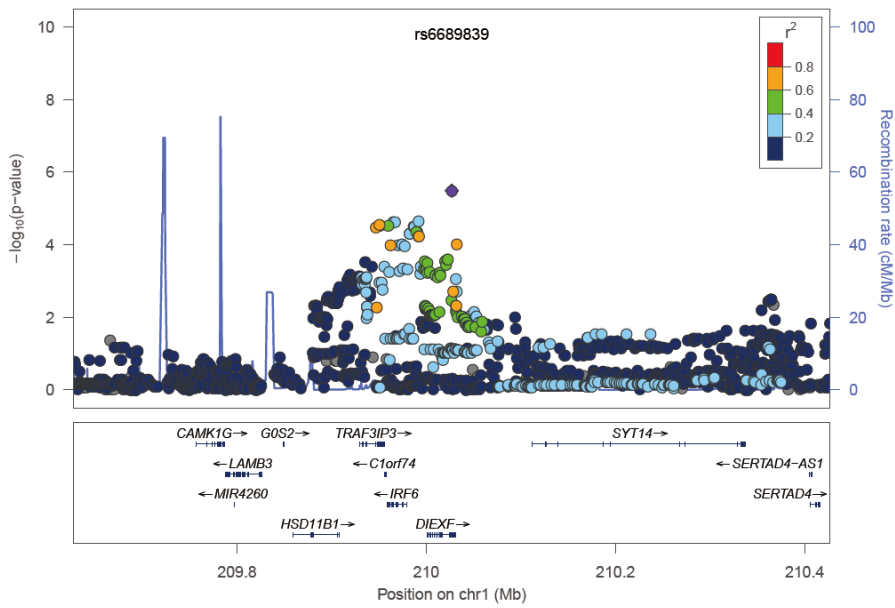


Figure 13. Regional plot and linkage disequilibrium plot for corrected QT interval on chromosome 1. In the case of regional plot, the range of base-pair position is from 209.6Mb to 210.4Mb. The range for linkage disequilibrium plot is from 209.9Mb to 210.1Mb. Linkage disequilibrium plot has more detailed description.

3. Environmental Factors

Environmental factors including cigarette smoking and alcohol consumption are statistically examined to evaluate the effects of these factors for each EKG interval. Each environmental factor was classified into three groups: never, former and current behavior group. In the case of PR interval, each group of cigarette smoking had significantly different level of PR interval. For alcohol consumption, never drinker group was shown as significantly different with former and current drinker group. The results are shown in Table 6 and Figure 14. In the case of QRS complex, all of cigarette smoking group had significantly different level of QRS complex. However, only the difference between never and current drinker group is statistically significant for alcohol consumption status. The results are shown in Table 7 and Figure 15. In the case of QTc interval, all of cigarette smoking group had shown as significantly different from each other group. For alcohol consumption, current drinker group had significantly different level of QTc interval. The results are shown in Table 8 and Figure 16.

Table 6. Effects of Environmental Factors on PR Interval

	Difference	Estimate	Standard Error	<i>p</i> -value
Cigarette Smoking	Never - Former	-6.42	0.96	< 0.0001
	Never - Current	-3.04	0.95	0.0014
	Former - Current	3.38	1.20	0.0050
Alcohol Consumption	Never - Former	3.21	1.34	0.0171
	Never - Current	1.78	0.81	0.0276
	Former - Current	-1.43	1.25	0.2530

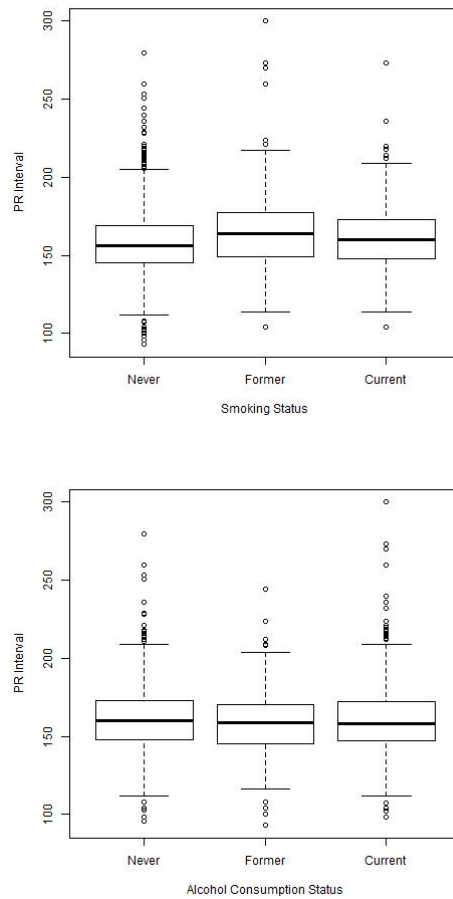


Figure 14. PR interval by cigarette smoking and alcohol consumption. In the figure for cigarette smoking, each number represents the following status: 1) never smoker 2) former smoker 3) current smoker. Similarly, in the description for alcohol consumption, each number represents the following status: 1) never drinker 2) former drinker 3) current drinker.

Table 7. Effects of Environmental Factors on QRS Complex

	Difference	Estimate	Standard Error	<i>p</i> -value
Cigarette Smoking	Never - Former	-4.89	0.47	< 0.0001
	Never - Current	-3.75	0.46	< 0.0001
	Former - Current	1.15	0.58	0.0491
Alcohol Consumption	Never - Former	-1.02	0.66	0.1197
	Never - Current	-1.73	0.40	< 0.0001
	Former - Current	-0.71	0.61	0.2461

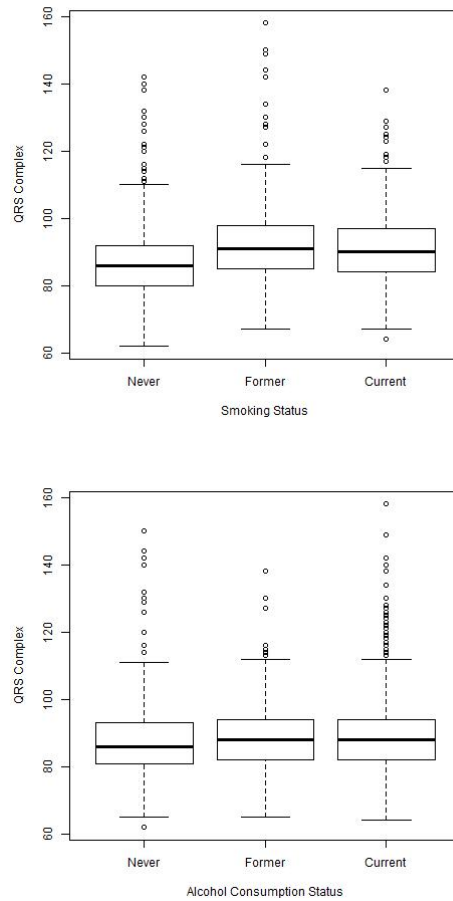


Figure 15. QRS complex by cigarette smoking and alcohol consumption. In the figure for cigarette smoking, each number represents the following status: 1) never smoker 2) former smoker 3) current smoker. Similarly, in the description for alcohol consumption, each number represents the following status: 1) never drinker 2) former drinker 3) current drinker.

Table 8. Effects of Environmental Factors on Corrected QT Interval

	Difference	Estimate	Standard Error	<i>p</i> -value
Cigarette Smoking	Never - Former	8.57	1.20	< 0.0001
	Never - Current	14.08	1.18	< 0.0001
	Former - Current	5.51	1.50	0.0002
Alcohol Consumption	Never - Former	2.31	1.68	0.1690
	Never - Current	8.84	1.01	< 0.0001
	Former - Current	6.53	1.56	< 0.0001

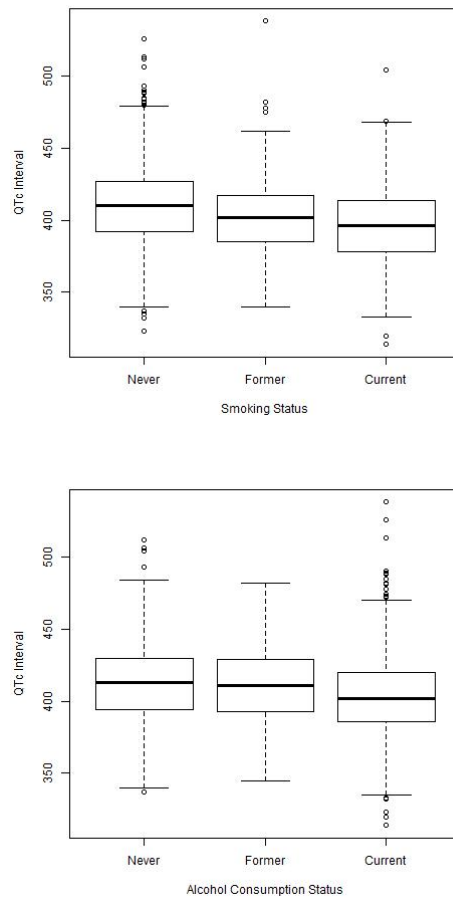


Figure 16. Corrected QT interval by cigarette smoking and alcohol consumption. In the figure for cigarette smoking, each number represents the following status: 1) never smoker 2) former smoker 3) current smoker. Similarly, in the description for alcohol consumption, each number represents the following status: 1) never drinker 2) former drinker 3) current drinker.

Discussion

1. Implications and Study Limitations

In this study, several genetic and environmental factors were examined to identify significant factors modulating EKG intervals in Korean population. For genetic factors, heritability for each EKG interval was evaluated and specific locus contributing to PR interval, QRS complex, and QTc interval were identified through GWAS. For environmental factors, typical risk factors including cigarette smoking and alcohol consumption status were examined to evaluate the effects on each EKG interval. As a result, the heritability for EKG intervals were verified on higher levels and several significant (with $P < 5.0 \times 10^{-8}$) SNPs for PR interval, which were reported from a number of previous studies^{1, 12, 13, 27}, were identified. In addition, environmental factors including cigarette smoking and alcohol consumption were verified as risk factors for modulating EKG intervals. Especially in the case of cigarette smoking status, all of EKG intervals showed significantly different levels among three groups: never smoker, former smoker and current smoker.

This study was subject to a number of latent limitations. Unexpected familial correlations, for instance, originated from shared common environmental effects could exist. In this study, the decorrelation process was conducted by using FASTA method which is known as one of the most efficient method to take familial correlations away. However, the fundamental property of study data needs to be considered, even though the decorrelation process was conducted successfully. In the case of heritability measurements, the levels for PR interval and QTc interval were higher than reported heritability. From this study, the heritability for PR interval is 0.45 for model 1, and 0.46 for model 2. These results are much higher than the

heritability from previous studies^{12, 17, 23}, considering the reported heritability for PR interval was located between the ranges of 0.34 to 0.40. In the case of QTc interval, the heritability is 0.43 for model 1 and 0.48 for model 2 while the reported values were located between 0.30 to 0.40^{12, 17, 23, 24}. Relatively higher level of heritability for EKG intervals could be induced by unexpected familial correlations.

Identified SNPs modulating each EKG interval from this study also need to be verified by comparing with other populations. For PR interval, several significant loci were identified and verified by comparing with results from previous studies. However, the other insignificant (with $5.0 \times 10^{-8} < P$) SNPs for PR interval identified from this study need to be compared with the result from other study populations. As imputed with the Asian reference data from the 1000 Genomes Project, the signals from only Korean population could be incorrect information. The replication of these locus with other studies need to be preceded before verifying the locus as PR interval modulating SNPs. Especially, the insignificant SNPs for QRS complex and QTc interval also need to be checked with results from other GWAS. In this study, there are no significant SNPs modulating QRS complex and QTc interval. To confirm these SNPs as EKG interval modulating locus, replications with other GWAS need to be checked. The association between these SNPs and EKG intervals would be verified by GWAS based on the other Korean populations.

In the case of environmental factors, the results from this study need to be validated by comparing with other researches. In this study, the level of PR interval and QRS complex for current smokers is significantly (with $P < 0.05$) higher than the levels for never smokers. In the case of QTc interval, the level for current smokers is significantly lower than the level of QTc interval for never smokers. The trends in QRS complex and QTc interval are consistent with the results from another previous

research¹⁰. In the case of alcohol consumption status, the level of PR interval and QTc interval for current drinkers is significantly lower than the levels for never drinkers. The level of QRS complex for current drinkers is significantly higher than the level of QRS complex for never drinkers. The change of QRS complex is matched with the result from former study on EKG changes after binge drinking¹⁸. PR interval and QTc interval, according to the study, were also significantly increased after binge drinking which means ingestion of 40 and 60 grams of alcohol. It is inconsistent with the results from this study. These discrepancies in the level of EKG intervals for each alcohol consumption status could be derived from the differences of study design and measurement methods.

2. Conclusion

In summary, the results from this study suggest that there are several genetic and environmental factors contributing to EKG intervals in Korean. Considering the association between EKG intervals and a number of fatal heart conditions, both genetic and environmental factors modulating PR interval, QRS complex, and QTc interval could be used as a clinical parameter to predict a specific cardiovascular disease. In the case of genetic factors, a number of SNPs associated with each EKG interval were identified as a result of this study. Especially for PR interval, *CAVI*, the reported locus from previous researches^{1, 12, 13, 27}, was reaffirmed at a significant (with $P < 5.0 \times 10^{-8}$) level. In addition, several SNPs contributing to QRS complex and QTc interval were also identified from this study, even though the results are not statistically significant. In the case of environmental factors, it was confirmed that cigarette smoking and alcohol consumption could change the duration of each EKG

intervals. In spite of latent study limitations, these factors contributing to EKG intervals could be meaningful parameters to intervene adverse cardiac conditions. Further researches are needed to confirm the specific locus associated with each EKG intervals by comparing with the results from GWAS in other populations. Moreover, additional studies focusing on the effects of cigarette smoking and alcohol consumption on each EKG intervals are needed to confirm the environmental effects identified in this study.

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국문초록

심전도 검사는 심장의 이상 징후를 비침습적인 방식으로 진단할 수 있다는 점에서 임상적으로 유용하게 이용되고 있다. 심전도 검사의 결과로 얻을 수 있는 지표들 중에서도 PR 간격과 QRS 간격, QTc 간격의 경우에는 심방과 심실의 탈분극과 재분극 등을 나타내는 지표이다. PR 간격의 경우 심방 세동 및 심방 조동과 연관되어 있고, QRS 간격의 경우에는 심부전 및 심장 돌연사와, 그리고 QT 간격의 경우 관동맥성 심장 질환 및 심장 돌연사와 연관되어 있다는 것이 선행 연구를 통하여 밝혀져 있다. 이와 같은 질환들의 경우에는 발생으로부터 사망에 이르기까지의 시간이 짧기 때문에 질환을 예방하는 것이 그만큼 중요하다고 할 수 있다. 심전도 간격은 이러한 질환들을 예방하기 위한 지표로 사용될 수 있다는 점에서 의미를 가지며, 실제로 국내외적으로 많은 연구가 이루어지고 있다.

본 연구는 한국인의 심전도 간격에 영향을 미치는 유전 및 환경 요인을 분석하여 향후 심장 질환을 예방하기 위한 지표로 활용될 수 있도록 하는데 그 목적이 있다. 이를 위하여 국내 쌍둥이 코호트(the Healthy Twin Study)에 참여한 사람들 중에서 심전도 검사 자료가 확보된 사람들을 대상으로 전장 유전체 분석과 흡연 및 음주 행태에 대한 통계적 분석을 진행하였다. 유전 요인의 경우에는 각 심전도 간격의 유전율을 계산하고, 전장 유전체 분석을 통하여 심전도 간격에 영향을 미치는 유전자 위치를 찾아내는 것을 목표로 하였다. 환경

요인의 경우, 역학적으로 전형적인 위험 요인으로 간주되는 흡연 및 음주 행태에 따라 심전도 간격이 어느 정도 차이를 보이는지를 확인하는 것을 목표로 하였다.

전장 유전체 분석을 위해 Affymetrix와 Illumina에서 생산된 단일 염기 다형성 분석 칩(SNP Chip)을 사용하였고, 각각의 칩으로부터 나온 결과를 1000 Genome Project의 아시아인 레퍼런스를 참조하여 통합하였다. 결과적으로 본 연구에서는 총 4,174,873개의 통합된 마커를 사용하여 전장 유전체 분석을 진행하였다. 연구 집단이 가족 단위로 구성된 집단이기 때문에 연구 집단 내에 존재하는 가족 관계를 FASTA 방식으로 제거하고, R(ver 3.0.2.)의 GenABEL 패키지를 사용하여 전장 유전체 분석을 진행하였다. 또한 통계 프로그램인 SAS(ver 9.3.)를 사용하여 흡연 및 음주 행태가 심전도 간격에 영향을 주는지의 여부를 통계적으로 분석하였다.

전장 유전체 분석의 결과, 각각의 심전도 간격이 높은 유전율을 가지는 것과 심전도 간격에 영향을 미치는 유전자 자리들이 확인되었다. 특히 PR 간격의 경우, 본 연구를 통하여 발견된 유전자 자리에 위치한 유전자(*CAVI*)가 선행 연구들로부터 보고된 유전자와 일치하는 것을 확인하였다. QRS 간격과 QTc 간격의 경우에는 통계적으로 유의한 유전자 자리가 발견되지는 않았다. 이러한 유전자 자리를 각각의 심전도 간격과 연관시키기 위해서는 다른 인구 집단으로부터 연구된 전장 유전체 분석 결과와 비교할 필요가 있다. 환경 요인에 대

한 분석의 경우, 흡연 및 음주 행태와 심전도 간격 사이에 통계적으로 유의한 관계가 있음을 확인하였다. 특히 흡연 행태의 경우 PR 간격과 QRS 간격, QTc 간격 모두에서 유의한 결과를 보이는 것을 알 수 있다.

본 연구의 결과 한국인의 심전도 간격에 영향을 미치는 유전 및 환경 요인이 존재하는 것이 확인되었으며, 이는 심전도 간격이 심장 질환을 예방하기 위한 지표로써 활용될 수 있다는 점을 고려할 때 의미 있는 결과라고 할 수 있다. 향후 본 연구의 결과를 기반으로 심전도 간격에 영향을 미치는 유전 및 환경 요인에 대한 추가적인 연구가 이루어지기를 기대한다.

주요어: 심전도 검사, 심전도 간격, PR 간격, QRS 간격, QT 간격, 전장 유전체 분석, 유전율, 환경 요인, *the Healthy Twin Study*

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