

Fifteen Genetic Loci Associated With the Electrocardiographic P Wave

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Background—The P wave on an ECG is a measure of atrial electric function, and its characteristics may serve as predictors for atrial arrhythmias. Increased mean P-wave duration and P-wave terminal force traditionally have been used as markers for left atrial enlargement, and both have been associated with increased risk of atrial fibrillation. Here, we explore the genetic basis of P-wave morphology through meta-analysis of genome-wide association study results for P-wave duration and P-wave terminal force from 12 cohort studies.

Methods and Results—We included 44456 individuals, of which 6778 (16%) were of African ancestry. Genotyping, imputation, and genome-wide association study were performed at each study site. Summary-level results were meta-analyzed centrally using inverse-variance weighting. In meta-analyses of P-wave duration, we identified 6 significant ($P < 5 \times 10^{-8}$) novel loci and replicated a prior association with *SCN10A*. We identified 3 loci at *SCN5A*, *TBX5*, and *CAV1/CAV2* that were jointly associated with the PR interval, PR segment, and P-wave duration. We identified 6 novel loci in meta-analysis of P-wave terminal force. Four of the identified genetic loci were significantly associated with gene expression in 329 left atrial samples. Finally, we observed that some of the loci associated with the P wave were linked to overall atrial conduction, whereas others identified distinct phases of atrial conduction.

Conclusions—We have identified 6 novel genetic loci associated with P-wave duration and 6 novel loci associated with P-wave terminal force. Future studies of these loci may aid in identifying new targets for drugs that may modify atrial conduction or treat atrial arrhythmias. (*Circ Cardiovasc Genet.* 2017;10:e. DOI: 10.1161/CIRCGENETICS.116.001667.)

Key Words: arrhythmia ■ atrial function ■ electrocardiography ■ genetic variation ■ genome-wide association study

The electrocardiographic P wave is a measure of electric activation of the atria and was first described by Bayliss and Starling over 120 years ago.¹ P-wave indices (PWI) describe atrial electric function and are quantified as measures

of duration and voltage from the surface ECG. The clinical utility of PWI has been demonstrated by their relation to atrial electrophysiology using invasive intracardiac studies^{2,3} and by their assessment as risk factors for atrial fibrillation (AF).⁴⁻⁷

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P-wave terminal force—derived from the product of the duration of the negative phase of the P wave in lead VI and its terminal depth (Figure 1)—has been used as an ECG marker for the presence of left atrial enlargement.⁸ In addition to terminal force, P-wave duration has been used widely because of its accessibility from the ECG. Elucidation of the associations of genetic variants related to PWI may improve our understanding of the biology underlying atrial conduction and further inform the genetic determinants of risk of arrhythmias, including AF.

See Editorial by Bezzina
See Clinical Perspective

We sought to enhance our understanding of atrial electric function by conducting large genome-wide association studies (GWAS) of PWI in individuals of European and African ancestry. Prior GWAS have distinguished genetic loci uniquely associated with P-wave duration from those associated with the PR interval and the PR segment.^{9,10} The largest study evaluating common variants associated with P-wave maximal duration, to date, included 16468 individuals of European ancestry and identified 3 significant genetic loci.¹⁰ There have been no reports on common genetic variants associated with P-wave terminal force.

In the present investigation, we examined the genome-wide associations of maximum P-wave duration and P-wave terminal force in 12 cohorts, including >44000 individuals of European and African American ancestry. We hypothesized that the PWI examined have novel genetic associations, distinct from those previously identified as associated with the PR interval.

Materials and Methods

Study Cohorts

Participants of European or African ancestry from 12 studies contributed to the present analyses (Table I in the Data Supplement): ARIC Study (Atherosclerosis Risk in Communities), CHS (Cardiovascular Health Study), ERF Study (Erasmus Rucphen Family), FHS (Framingham Heart Study), KORA (Cooperative Health Research in the Augsburg Region), GHS I (Gutenberg Health Study I), MESA (Multi-Ethnic Study of Atherosclerosis), RS I-III (Rotterdam Studies I, II, and III), SHIP (Study of Health in Pomerania), and 3 distinct studies affiliated with the Women's Health Initiative (WHI) clinical trials: GARNET (Genome-wide Association Research Network), MOPMAP (Modification of Particulate Matter-Mediated Arrhythmogenesis in Populations), and SHARe (SNP Health Association Resource Project). The study was limited to participants with available DNA and consent for genetics research. We excluded individuals in whom we could not determine PWI and individuals with a history of AF, an implanted pacemaker or ICD, WPW syndrome, and complete heart block or who received medication altering atrioventricular nodal conduction (β -blockers, dihydropyridine calcium channel blockers, type I and III antiarrhythmic medication, and digoxin). Individuals with mitral valve disease were not excluded. All participants had given their written informed consent to participation, and all studies were approved by their respective institutional review boards or equivalent ethical committees.

PWI Measurement

Participants in all cohorts underwent a standardized, digital 12-lead ECG at rest in the supine position as a component of the cohort examination. All PWI were quantified using contemporary software algorithms from digitized tracings. Electrocardiograms from the ARIC, CHS, and MESA and data from the 3 WHI clinical trials substudies were

automatically processed at the Epidemiological Cardiology Research Center of Wake Forest University School of Medicine (Winston Salem, NC) using General Electric (GE) 12-SL software (GE, Milwaukee, WI) running under GE MUSE and Magellan Research Work Station. ECGs in FHS were read independently at FHS and analyzed using GE 12-SL software. PWI calculated using GE 12-SL software have previously been reported as having a repeatability of 100%.⁴ In GHS I, ECGs were recorded using the Welch Allyn CardioPerfect electrocardiograph (Skaneateles Falls, NY), and PWI were calculated using the GE Healthcare software CASE, CardioSoft, version 6 (Palatine, IL). In ERF and RSI-III, electrocardiograms were recorded using the ACTA Gnosis IV ECG recorder (Esaote Biomedica, Florence, Italy), and in SHIP, electrocardiograms were recorded using the Personal 120LD (Esaote, Genova, Italy). In ERF, RSI-III, and SHIP, electrocardiograms were analyzed with the Modular ECG Analysis System.¹¹ KORA used the AMEDTEC ECGpro system (AMEDTEC Medizintechnik Aue GmbH, Aue, Germany) and analyzed tracings using the Hannover ECG system (Corscience GmbH&Co. KG, Erlangen, Germany).

PWI were selected for their availability across cohorts. P-wave duration in each lead was calculated by summing the durations of the positive and negative phase of the P wave in each lead. The maximum P-wave duration was selected as the highest value among the 12 leads. P-wave terminal force, specific to right precordial lead VI, was calculated as the product of the duration and voltage of the negative deflection of the P wave in lead VI. Distributions of the PWI by cohort are presented in Table II in the Data Supplement. P-wave terminal force was not available in KORA and GHS.

Genotyping

Details on genotyping methods, quality control, imputation, and software are provided in detail in Table III in the Data Supplement. All cohorts used genome-wide arrays for genotyping. Genotyping was performed independently in each cohort using the following arrays: Affymetrix 6.0 genome-wide array (ARIC, KORA, GHS, MESA, SHIP, and WHI SHARe), Illumina 370 (CHS), Affymetrix 500K+50K (FHS), Illumina Infinium (RSI-III), Illumina Quad (WHI GARNET), and Affymetrix Titan (MOPMAP). Samples with call rates <95% (ARIC, GHS, MESA, WHI MOPMAP, and WHI SHARe), <97% (CHS, FHS), or <98% (KORA, Rotterdam, ERF, and GARNET) at genotyped markers were excluded.

Expression Quantitative Trait Loci Analyses

A complete description is enclosed in Methods in the Data Supplement. In brief, expression Quantitative Trait Loci (eQTL) analyses were performed from human left atrial tissue samples and from the Genotype-Tissue Expression (GTEx) database.

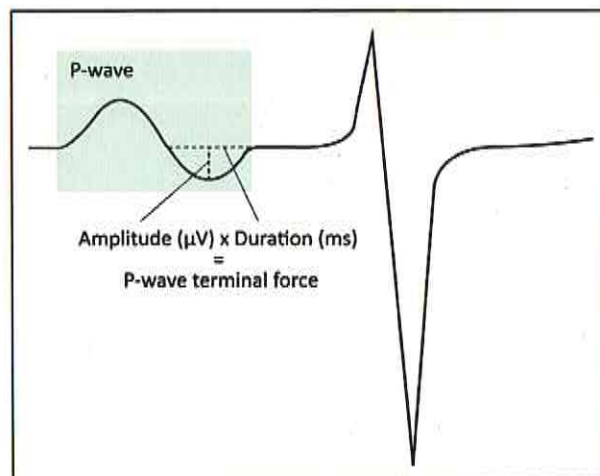


Figure 1. Calculation of P wave terminal force. ECG with the P wave highlighted in green and calculation of P wave terminal force depicted in lead VI.

Estimation of the Variance Explained by the Significant Genetic Variants

Results from the meta-analyses were used to estimate the percentage of the variance that can be explained by the most significant single nucleotide polymorphism (SNP) at each genetic locus as described by Hibar et al.¹² We calculated estimated variance explained for SNPs identified in both separate and combined ancestry analyses and adjusted for age, sex, RR interval, and the maximum number of principal components adjusted for in any of the ancestry-matched GWAS.

Evaluation of the Genetic Associations Between P-Wave Duration and P-Wave Terminal Force

We performed a summary-level analysis to test the association between the genetic variants associated with P-wave duration and the measured P-wave terminal force and vice versa in the European ancestry group. To define independent signals, we performed linkage disequilibrium (LD) clumping by selecting SNPs with $P < 1 \times 10^{-5}$ and assigning all SNPs within 250 kb in each direction in moderate LD ($r^2 > 0.5$) and $P < 0.05$ to the same clump. LD clumping was iterated until all SNPs with $P < 1 \times 10^{-5}$ had been clumped, using PLINK v.1.9.¹³ To assess whether the selected LD threshold was sufficient to identify independent variants, we also performed LD clumping using lower thresholds ($r^2 > 0.1$ and $r^2 > 0.05$). LD information was obtained from the Framingham Heart Study. Genetic risk scores (GRS) were then created for both ECG traits, including only SNPs significantly associated with the trait and that were not in LD with any other significant SNPs. The scores were used to evaluate the association between the genetically determined P-wave duration and measured P-wave terminal force and between the genetically determined P-wave terminal force and measured P-wave duration, using the R-package gtx.¹⁴ The association results were then used to estimate the fraction of the total variance of each trait that could be explained by the GRS of the other trait.

Statistical Analysis

Each cohort conducted an independent association analysis relating genotype to P-wave duration and P-wave terminal force. Cohorts with participants of African ancestry performed separate analyses by race. Adjustment for principal components was performed in individual studies if appropriate. Cohorts used linear regression models that adjusted for participant age, sex, RR interval, and cohort or site in a primary analysis and further adjusted for hypertension (defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or treatment with an antihypertensive) and body mass index (weight [kg]/height [m]²) in a secondary analysis.

Genetic variants were given a marker identifier (ID) consisting of chromosome number and chromosomal position before meta-analysis to avoid inconsistencies in reference SNP ID numbers (rsIDs) from the Single Nucleotide Polymorphism database (dbSNP) across different builds. Cohort-specific summary statistics were pooled for inverse-variance weighted fixed-effect meta-analyses, which were performed separately for maximum P-wave duration and P-wave terminal force. Both ancestry-specific and combined ancestry analyses were performed for both traits. Variants that were not present in at least 2 studies were excluded. Associations with 2-sided $P < 5 \times 10^{-8}$ were considered genome-wide significant.

Results

The study sample for maximum P-wave duration included 37 678 individuals of European ancestry and 6 778 of African ancestry. Because KORA and GHS did not contribute to analyses of the P-wave terminal force, the total number of individuals of European ancestry for that meta-analysis was 33 955. Descriptive characteristics of the study participants are provided in Table II in the Data Supplement. The 3 WHI clinical trial cohorts included only women, while the remaining cohorts included both sexes. Mean age within study ranged from 46 ± 16 to 72 ± 5 years. Mean P-wave duration was highly

consistent across cohorts. In contrast, P-wave terminal force had a wider range with proportionately larger standard deviation. Details regarding study design, genotyping, GWAS, and imputation are listed in Table III in the Data Supplement.

P-Wave Duration

In the primary analyses, we identified 9 loci associated with P-wave duration, 5 of which have not been associated with P-wave duration previously. The most significant variant from each locus is listed in Tables IV and Table V in the Data Supplement. Table VI in the Data Supplement displays a comparison of the genome-wide significant loci across P-wave duration and P-wave terminal force analyses. Figure 2 depicts the Manhattan plots for the P-wave duration analysis, stratified by ancestry. Figure IA in the Data Supplement shows the Manhattan plot for pooled ancestries, and Figure II in the Data Supplement shows the regional plots for all genetic loci associated with P-wave duration in this study. Table VII in the Data Supplement summarizes the relationship between significant genetic loci in the present GWAS of P-wave duration and previous PWI GWAS.

Genetic Loci Unique to P-Wave Duration

We identified an association between P-wave duration and a variant on chromosome 5 (rs4276421) that resides ≈ 100 kb upstream of *HCN1*. On chromosome 7, we identified a locus comprising *CAVI* and *CAV2*, with the most significant variant located intronic to *CAVI*. More than 40 variants at this locus had significant or near significant eQTLs for *CAVI/CAV2* in European American left atrial samples (Table VIII in the Data Supplement). The most significant variant in the combined ancestry analysis (rs3801995) was in moderate LD (Utah residents with Northern and Western European ancestry from the Centre d'Etude du Polymorphisme Humain collection [CEU] $r^2 = 0.56$), with the most significant variants in previous GWAS of PR interval,^{10,15-17} which are in perfect LD (rs3807989 and rs11773845; CEU $r^2 = 1$) with each other. The most significant variant in Europeans (rs13242816) was not in LD (CEU $r^2 = 0.11$) with previously identified variants at this locus. A third locus was identified on chromosome 2, and the top hit (rs11689011) was intronic to the gene *EPAS1*. On chromosome 1, we identified a locus (most significant SNP rs562408) surrounding the gene *SSBP3*. The lead SNP and 5 other variants were significant eQTLs for *SSBP3* in European American left atrial samples (Table VIII in the Data Supplement), and the lead SNP in Europeans was the strongest cis eQTL for this gene; similar results were found in the GTEx database (Table IX in the Data Supplement). Another locus was located on chromosome 4 with rs2285703 intronic to the gene *CAMK2D*.

Last, in the meta-analysis of European and African-American ancestries combined, we identified an additional genetic locus associated with P-wave duration on chromosome 3. The top variant, rs1467026, was located upstream of *CAND2* and was in moderate LD (CEU $r^2 = 0.67$) with a variant associated with AF by Sinner et al¹⁸ in 2014. Rs1467026 has been shown to be a significant eQTL for *CAND2* ($P = 7.5 \times 10^{-27}$) in skeletal muscle in the GTEx database (Table IX in the Data Supplement), though this was not found to be a significant eQTL in left atrial tissues.

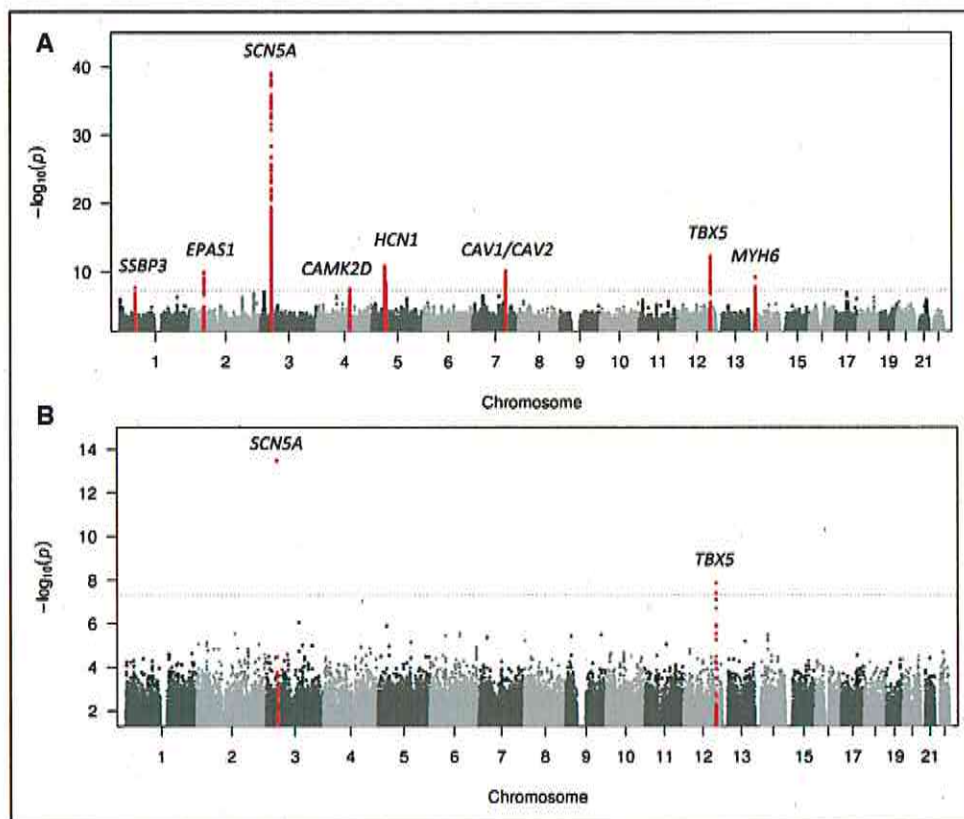


Figure 2. Manhattan plot of meta-analysis results for genome-wide association of maximum P wave duration for European and African American ancestry. **A**, European ancestry meta-analysis results. **B**, African American ancestry meta-analysis results. The dashed horizontal lines represent the genome-wide significance threshold. Genetic loci that reached genome-wide significance are highlighted in red.

Genetic Loci Previously Associated With Electrocardiographic Traits

We identified an association between P-wave duration and the *SCN5A* region in both Europeans and African Americans. The most significant European variant (rs41312411) at the *SCN5A* locus was in strong LD with the most significant variant (rs11708996; CEU $r^2=0.94$) from the first PR interval GWAS by Pfeufer et al¹⁵ and in moderate LD with a variant associated with both PR segment¹⁰ and PR interval¹⁹ (rs6599222; CEU $r^2=0.55$). In African Americans, we replicated the association between SNP rs3922844 and the PR interval observed in 2 previous GWAS in African Americans^{19,20}; this variant also has been associated with the PR segment in Europeans.¹⁰

In individuals of European ancestry, we identified an additional association signal in the adjacent *SCN10A* gene. The most significant variant at the *SCN10A* locus (rs6790396) was in strong LD with the following previously identified variants: (1) rs6800541 (CEU $r^2=1$), which was previously associated with PR interval¹⁵; (2) rs6795970 (CEU $r^2=0.97$), which was associated with both PR interval and P-wave duration in an Indian Asian population²¹ and PR interval in Europeans¹⁶; and (3) rs6801957 (CEU $r^2=0.97$), which was associated with PR interval,^{20,22} PR segment,¹⁰ and P-wave duration.¹⁰ There also was strong (CEU $r^2=0.87$) and moderate (Yoruba in Ibadan, Nigeria [YRI] $r^2=0.51$) LD between our lead *SCN10A* variant and a variant associated with PR interval in African Americans (rs6798015).

In both Europeans and African Americans, we identified a locus with the most significant variant located intronic to the gene *TBX5*. The lead variants in all ancestry analyses were significant eQTLs for *TBX5* in both European American and African American left atrial samples (Table VIII in the Data Supplement). The most significant SNP in the African American ancestry group (rs1895582) was also an eQTL for *TBX5* in left ventricular tissue in GTEx (Table IX in the Data Supplement). The same SNP, rs1895582, was in strong LD (YRI $r^2=0.81$) with a variant previously associated with PR interval in African Americans. The most significant variant (rs148020424) in Europeans was surrounded by an ≈ 300 kb LD block, bordered by 2 recombination hot spots. There were no LD data available between rs148020424 and previously associated SNPs at this locus. However, the most significant variant in our combined ancestry analysis (rs7312625) was previously associated with PR interval in African Americans. Rs7312625 was in strong LD (YRI $r^2=0.81$) with the most significant variant in African Americans in our study and in moderate LD with rs1895585 (YRI $r^2=0.78$), the most significant variant in the *TBX5* region from a previous GWAS on PR interval in African Americans.²⁰ SNP rs7312625 was also in moderate LD with rs3825214 (CEU $r^2=0.76$), an intronic variant in *TBX5* previously associated with heart rate in Europeans.¹⁶

We identified an association between P-wave duration and variant rs452036 on chromosome 14 in a region

encompassing *MYH6* and *MYH7*, and the same variant was also significantly associated with P-wave terminal force in our study. Rs452036 was the most significant variant in a GWAS for heart rate by Eijgelsheim et al²³ in 2010 and was in strong LD with rs365990 (CEU $r^2=0.96$, YRI $r^2=1$), which has been associated with heart rate in studies of both European and African American ancestry.^{16,23–25} Rs452036 was not in LD (CEU $r^2=0.16$) with the heart rate–associated SNP rs223116, which is intronic to *MYH7* and, thus, most likely represents an independent locus for heart rate.²³

P-Wave Terminal Force

In the primary analysis, we identified 6 loci associated with P-wave terminal force. The most significantly associated variants are listed in Tables X and XI in the Data Supplement; Figure 3 depicts the Manhattan plots, stratified by ancestry. The Manhattan plot for the pooled analysis of Europeans and African Americans is shown in Figure IB in the Data Supplement, and regional plots for all genetic loci significantly associated with P-wave terminal force are shown in Figure III in the Data Supplement. Table XII in the Data Supplement summarizes the shared associations of genetic loci between the present P-wave terminal force analysis and previous GWAS of PWI.

Genetic Loci Unique to the P Wave Terminal Force

In the European study populations, the locus with the strongest association was identified on chromosome 1 (rs12090194), intronic to *KCND3*. Rs12090194 was in weak LD (CEU $r^2=0.2$) with rs2798334, which has been associated with P-wave duration by Verweij et al¹⁰; thus, this locus seems to be specific to P-wave terminal force. A second locus was identified on chromosome 19, with the most significant variant (rs4435363) intronic to the gene *PPP5D1* and downstream of the gene *CALM3*. On chromosome 15q25, the most significant variant was an indel (rs201517563), intronic to *ALPK3*. This variant was not present in the 1000 Genomes database reference, and so there were no available LD data. However, LD data were available for the second most significant variant at this locus (rs11073730), which was located between *ALPK3* and *ZNF592*. The 15q25 locus spanned several other genes, including *NMB*, for which there were multiple significant eQTLs in European American left atrial samples (Table XIII in the Data Supplement), and rs11073730 was also a significant eQTL for several genes in various tissues in GTEx, including *ALPK3* (Table IX in the Data Supplement). In addition, 2 perfect proxies were associated with increased expression of *CSPG4P11* in tissue from the tibial nerve ($P=1.4\times 10^{-6}$ and 2.2×10^{-6}) and rs11073730, along with 14 proxies in strong LD ($r^2=0.8–1$) was associated with increased expression of *WDR73* in the muscular layer of the esophagus ($P=3.3\times 10^{-7}$ to 1.4×10^{-9}). We identified another locus in an intergenic region on chromosome 4, with the most significant variant (rs11099412) ≈ 700 kb downstream of the closest gene *PCDH18*. Finally, a locus was identified on chromosome 6, ≈ 150 kb downstream of the gene *C6orf195*. A strong proxy ($r^2=0.9$) for the most significant variant was previously associated with orthostatic hypotension.²⁶

In the African American population, one locus was identified on chromosome 11. The most significant variant (rs10832139) was located 44 kb upstream of the closest gene, *SPON1*.

Genetic Loci Associated With Heart Rate, P-Wave Duration, and P-Wave Terminal Force

On chromosome 14, we identified a locus with the most significant variant located intronic to *MYH6*. Rs445754 was in moderate LD with the most significant variant from the P-wave duration analysis in the present study (rs452036; CEU $r^2=0.7$) and the most significant variant from the first GWAS on heart rate (rs365990; CEU $r^2=0.6$).¹⁶ The variant rs365990 has been replicated in 3 subsequent GWAS of heart rate.^{16,24,25}

Variance Explained by the Genetic Loci Associated With P-Wave Duration and P-Wave Terminal Force

The most significant SNPs associated with P-wave duration explained 0.08% to 0.83% of the total variance (Tables IV and V in the Data Supplement), while the variants associated with P-wave terminal force explained 0.09% to 0.47% of the total variance (Tables X and XI in the Data Supplement).

P-Wave Duration and P-Wave Terminal Force Are Genetically Associated

After LD clumping ($r^2>0.5$), 199 significant SNPs remained from the P-wave duration analysis and 85 significant SNPs remained from the P-wave terminal force analysis, which were included in the respective GRS. The P-wave terminal force GRS was associated with measured P-wave duration ($\beta=0.00095$; SE=0.00014; $P=2.5\times 10^{-11}$), and the P-wave duration GRS was associated with measured P-wave terminal force ($\beta=8.33$; SE=1.64; $P=3.6\times 10^{-7}$). Using lower r^2 thresholds for the LD clumping produced similar results, with even lower P values (Results in the Data Supplement). One unit increase in the genetically determined P-wave terminal force was associated with a 0.00095 ms increase in P-wave duration, whereas 1 U increase in the genetically determined P-wave duration was associated with an 8.33 $\mu\text{V} \times \text{ms}$ increase in P-wave terminal force. The estimated percentage of total variance of the measured P-wave terminal force explained by the P-wave duration GRS is 0.07%, and conversely, the estimated fraction of the total variance of the measured P-wave duration explained by the P-wave terminal force GRS is 0.1%.

Discussion

In the current work, we sought to characterize the genetic basis of the P wave and to integrate our findings with prior association studies of electrocardiographic traits quantifying atrial conduction. Our results reveal both unique and overlapping genetic loci for the different phases of atrial conduction (Figure 4). As expected, the phenotypic variance explained by the causal SNP from each genetic locus associated with P-wave duration and P-wave terminal force was small (0.08%–0.83%). Similar estimates have been reported for common variants associated with other continuous traits, such as human height and BMI, and reflect the often highly polygenic nature of common traits, which are, thus, explained by a large number of variants with

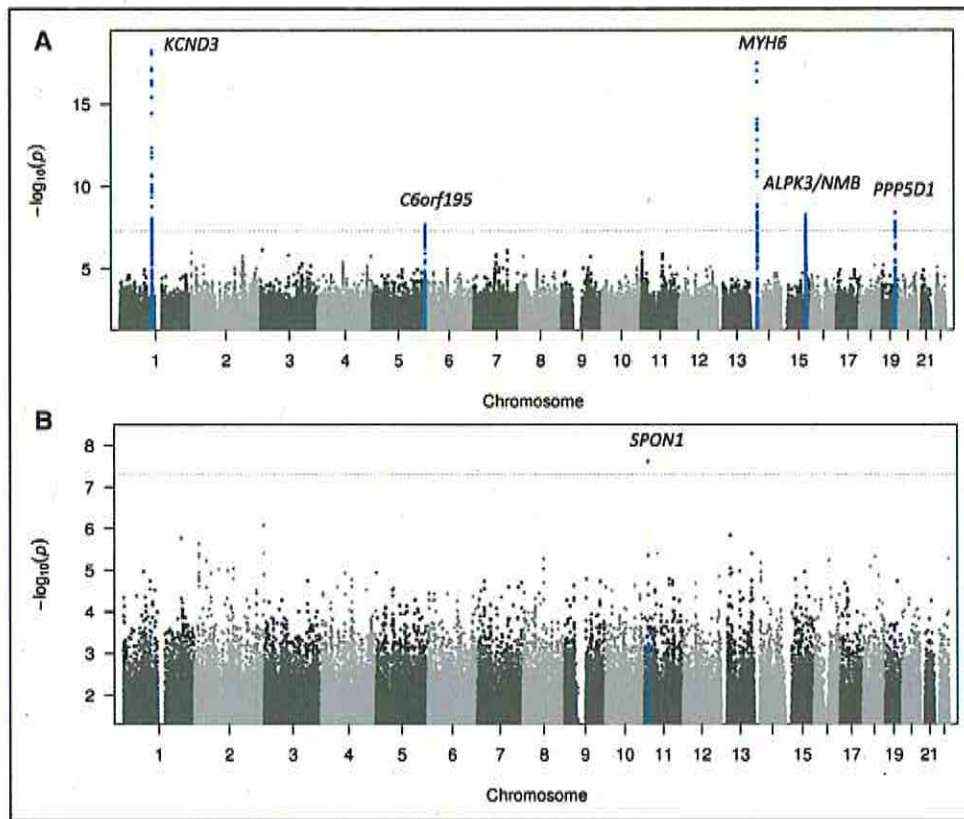


Figure 3. Manhattan plot of meta-analysis results for genome-wide association of P wave terminal force for European and African American ancestry. **A**, European ancestry meta-analysis results. **B**, African American ancestry meta-analysis results. The dashed horizontal lines represent the genome-wide significance threshold. Genetic loci that reached genome-wide significance are highlighted in blue.

small effect sizes. The larger percentage of variance explained by the variants identified in the African American ancestry group is caused by the large effect sizes of these SNPs.

In Discussion in the Data Supplement, we have provided a detailed description of the loci that are unique to either P-wave duration or P-wave terminal force, and we have discussed the broad contribution of the sodium channels, caveolin, and *TBX5* to atrial conduction.

Interrelationship Between P-Wave Duration and P-Wave Terminal Force

P-wave duration and P-wave terminal force are both endophenotypes for AF; however, they represent different aspects of atrial conduction. P-wave duration reflects the depolarization of both right and left atrium, while P-wave terminal force, which is calculated from the last half portion of the P-wave, more specifically represents left atrial activation. Soliman et al⁴ have shown that the mutual PWI correlations are weak to moderate in a study of more than 15 000 individuals. In particular, P-wave duration and P-wave terminal force displayed the weakest correlation (Pearson's $R=0.08-0.29$). In this study, we found that the genetically determined P-wave duration is highly associated with the measured P-wave terminal force and vice versa but that the percentage of explained variance between the 2 PWI was small. Thus, we had expected to identify genetic loci uniquely associated with either right or left atrial activation, in addition to some overlap of genetic variants associated with both phenotypes in the present study. We did discover one genetic locus

associated with both P-wave duration and P-wave terminal force, encompassing the gene *MYH6*. The 14q11 locus includes *MYH6*, the gene encoding myosin heavy chain 6 protein, which is important in actin and calmodulin binding in the sarcomere of striated muscles. The most significant variant at this locus, rs452036, and its proxy rs365990 (CEU $r^2=0.96$) have been associated with heart rate in multiple GWAS^{16,23,24} and most likely represent the same locus. *MYH6* has been implicated in congenital heart defects,²⁷ dilated and hypertrophic cardiomyopathy,^{28,29} AF,³⁰ atrial septal defects,^{31,32} and sick sinus syndrome.³³ All of these conditions may affect inter- or intra-atrial conduction and modify P-wave duration.

According to reports that P-wave terminal force is a predictor of left atrial enlargement,⁸ one might have expected to see a predominance of structurally related genes associated with P-wave terminal force and a preponderance of genes involved in electric properties of the atrium associated with P-wave duration. Indeed, some of the genes identified in the analyses of P-wave duration are more likely to produce electric disturbances (*SCN5A*, *SCN10A*, *HCN1*, *CAV1/CAV2*, *EPAS1*, *CAND2*, and *CAMK2D*), while a selection of the genes identified in the analyses of P-wave terminal force are more likely to cause structural changes (*TBX5*, *ALPK3/NMB*, *MYH6*, and *SPON1*). However, recent studies have reported that P-wave terminal force was not associated with left atrial enlargement on echocardiography³⁴ or computed tomography volume measurement.³⁵ In a sample of 275 middle-aged Americans referred to cardiovascular magnetic resonance imaging between 2001 and 2004, electrocardiographic

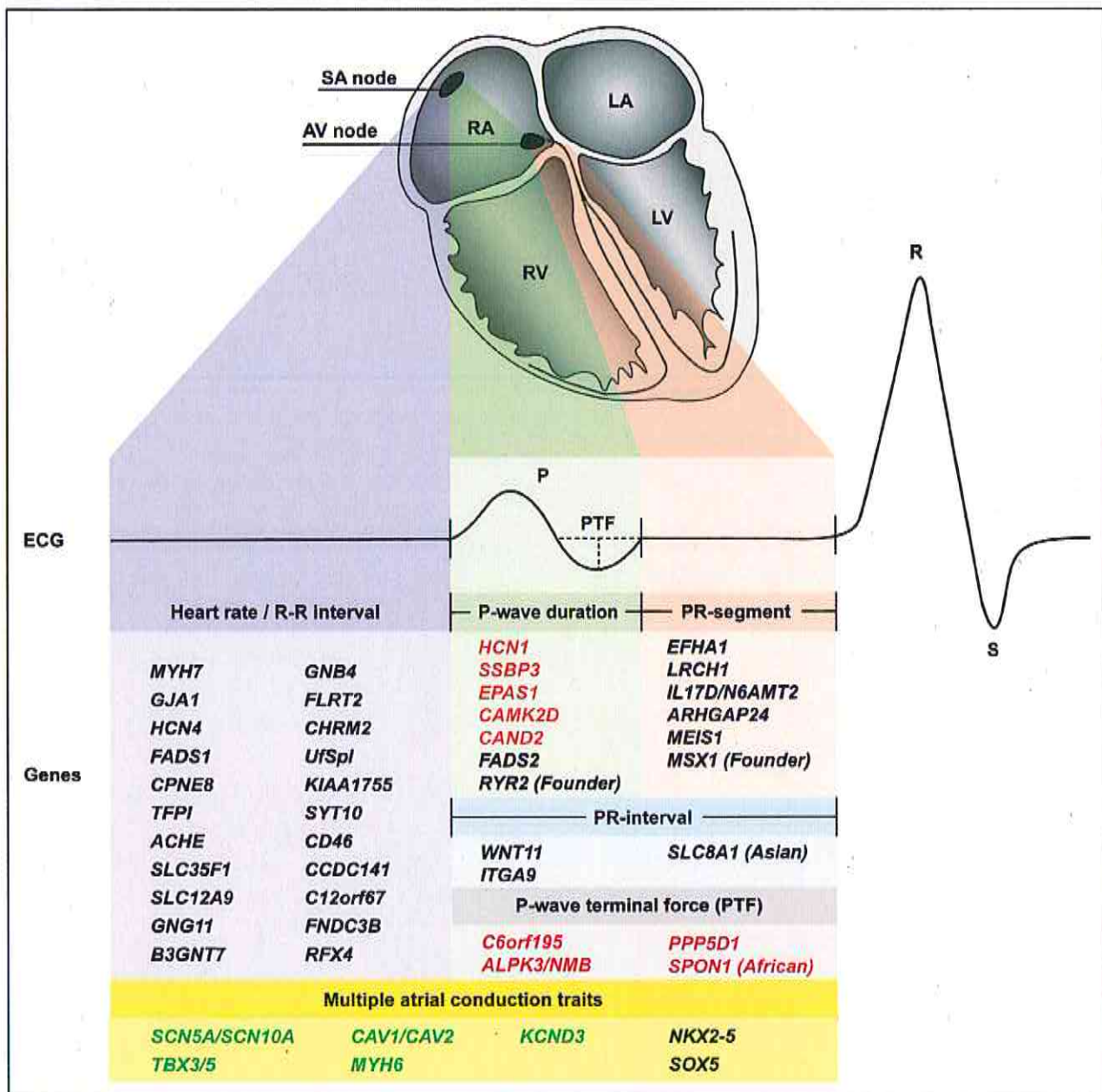


Figure 4. Integrated view of the anatomic, electric, and genetic architecture of atrial conduction. **Top**, Heart, anterior 4-chamber view, with the different phases of atrial conduction color-coded. Purple, sinoatrial node activity (heart rate); green, P wave duration; red, PR segment; blue, PR interval; gray, P wave terminal force; and yellow, overall atrial conduction. **Middle**, ECG corresponding to the different phases of atrial conduction. **Bottom**, All identified risk genes for heart rate (R-R), PR interval, and P wave indices. For each trait, only genes uniquely associated with that trait are listed. Genes associated with multiple electrocardiographic traits are listed under multiple atrial conduction traits. Red font, novel loci in the present study; green font, loci identified in both the present study and previous literature; black font, loci only identified in previous studies. AV indicates atrioventricular; LA, left atrium; LV, left ventricle; PTF, P-wave terminal force; RA, right atrium; RV, right ventricle; and SA, sinoatrial.

P-wave terminal force (negative P terminal force in V1 > 0.04 s x mm) had high specificity (88%) but low sensitivity (37%) and positive predictive value (47%) for left atrial enlargement, compared with volumetric assessment of left atrial size.³⁶

Strengths and Limitations

Strengths of our study include the substantial power obtained by including >44,000 individuals from established studies with carefully phenotyped participants. Further, the PWI

measurements were all measured digitally and calculated automatically. Last, because AF is thought to originate predominantly from the left atrium and pulmonary veins, evaluation of eQTLs in a large sample of left atrial samples provides a suitable model for functional interrogation of the genetic variants associated with AF in our study.

Our study was also subject to several limitations. First, both P-wave duration and P-wave terminal force measurements are less reproducible over time than PR interval, P-wave axis, and P-wave

area.³⁷ Second, one could consider adjusting the *P* value for significant results for the 2 traits considered ($5 \times 10^{-8}/2 = 2.5 \times 10^{-8}$); however, the P-wave duration and P-wave terminal force are only weakly correlated, and so we used a conventional threshold for genome-wide significance of 5×10^{-8} . Third, associations with *P* values in the range of 1×10^{-8} to 10^{-10} will require replication in independent cohorts. Fourth, although we included individuals of both European and African ancestry, our findings may not be generalizable to other ancestries. Fifth, the analyses in African Americans were underpowered compared with our analyses in European-ancestry individuals and require replication as other studies become available in the future. Finally, it is important to remember that we have identified markers of genetic regions involved in the P-wave indices. The genes outlined above are the genes closest to the most significant variant in each genetic region, yet it remains unclear whether they truly are the effector genes. Other genes in the same region or even more distantly located genes might actually be the causal genes. Future studies including targeted mapping of these loci and functional analyses of the implicated genes may shed light on the underlying biology.

Conclusion

We report 15 genetic loci associated with P-wave duration and P-wave terminal force, 4 of which harbor significant eQTLs in left atrial tissue. In the context of the existing knowledge of genetic factors for atrial conduction, a genetic architecture is emerging, in which specific genetic regions influence different phases of atrial conduction. Functional characterization of the novel loci may clarify the underlying pathophysiology and aid the discovery of targets for new drugs, which may modulate atrial conduction and, thus, potentially treat a range of arrhythmia disorders.

Web Resources

The Genotype-Tissue Expression (GTEx) browser, <http://www.gtexportal.org>

SNAP proxy search, <http://www.broadinstitute.org/mpg/snap/>

Locus zoom, <https://statgen.sph.umich.edu/locuszoom/>

Disclosures

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Appendix

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CLINICAL PERSPECTIVE

The electrocardiographic P wave is a measure of electric activation of the atria that can be quantified by assessing the P-wave duration or P-wave terminal force. Because measures of atrial activation have been associated with left atrial enlargement and atrial fibrillation, we sought to determine the genetic basis of P-wave duration and P-wave terminal force. We identified 6 new genetic loci that contribute to the maximum P-wave duration and 6 genetic loci that contribute to the P-wave terminal force. When integrating our results with prior work, we have identified a genetic architecture of the P wave in which some genetic loci are uniquely associated with distinct electrocardiographic parameters and others are more broadly associated with atrial conduction. Further studies evaluating the function of the genetic loci linked to atrial conduction may help elucidate the biology underlying atrial conduction, as well as provide new targets for antiarrhythmic drugs.



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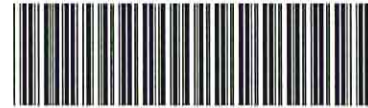
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