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Investigating the Genetic Architecture of the PR Interval using Clinical Phenotypes

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Abstract

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Background—One potential use for the PR interval is as a biomarker of disease risk. We hypothesized that quantifying the shared genetic architectures of the PR interval and a set of clinical phenotypes would identify genetic mechanisms contributing to PR variability and identify diseases associated with a genetic predictor of PR variability.

Methods and Results—We used ECG measurements from the Atherosclerosis Risk in Communities (ARIC) study (n=6,731 subjects) and 63 genetically-modulated diseases from the Electronic Medical Records and Genomics (eMERGE) network (n=12,978). We measured pairwise genetic correlations (rG) between PR phenotypes (PR interval, PR segment, P wave duration) and each of the 63 phenotypes. The PR segment was genetically correlated with atrial fibrillation (AF) [rG=-0.88, p=0.0009]. An analysis of metabolic phenotypes in ARIC also showed that the P wave was genetically correlated with waist circumference [rG=0.47, p=0.02]. A genetically predicted PR interval phenotype based on 645,714 SNPs was associated with AF [OR=0.89 per standard deviation change, 95% CI (0.83–0.95), p=0.0006]. The differing pattern of associations among the PR phenotypes is consistent with analyses that show that the genetic correlation between the P wave and PR segment was not significantly different than 0 (rG=-0.03 [0.16]).

Conclusions—The genetic architecture of the PR interval comprises modulators of AF risk and obesity.

Keywords

ECG; genetic association; genetic epidemiology; atrial fibrillation

Journal Subject Terms

Electrophysiology; Genetic; Association Studies; Catheter Ablation and Implantable Cardioverter-Defibrillator

Introduction

The PR interval is an electrophysiological parameter derived from a cardiac electrocardiogram and measures the duration of conduction through the atrium and atrioventricular (AV) node. The PR interval comprises two components: the P wave, which primarily measures atrial conduction, and the PR segment, which primarily reflects AV nodal conduction. One potential use for the PR interval is as a biomarker for future disease risk. For instance, a prolonged PR interval is associated with an increased risk for atrial fibrillation (AF).^{1,2} If such associations are driven by heritable variation affecting both phenotypes, then a risk classifier based on genetic factors modulating the PR interval could be used to identify individuals at high risk for AF. Since heritable genetic risk is determined at birth, genetic classifiers can be evaluated at early time points, thereby enhancing early prevention and risk stratification strategies.

To date, a relatively small number of single nucleotide polymorphisms (SNPs) associated with the PR interval have been identified by genome wide association studies (GWAS)^{3–5}, and they only account of a small portion of the underlying genetic variability. Hence,

building and evaluating a robust genetic classifier for the PR interval based on known SNPs is not feasible. Newer genetic approaches, such as those based on generalized linear mixed models (GLMM) that measure the contribution of very large numbers of SNPs to a phenotype, can circumvent this limitation.^{6–8} Furthermore, these methods can also identify genetically related phenotypes across data sets by measuring genetic correlations based on additive genetics between pairs of phenotypes.^{8–10} A phenotype that is genetically correlated (i.e. has a non-zero genetic correlation) with the PR interval likely shares common physiological mechanisms and, potentially, can be predicted by a PR interval-based genetic classifier.

We used mixed modelling approaches to probe the additive genetic architecture of the PR interval based on the extent to which its architecture was shared by a set of clinically-recognized diseases. This approach identifies both clinical diagnoses genetically related to the PR interval and genetically-mediated disease mechanisms underlying PR variability. Specifically, we employed a discovery-oriented approach whereby we measured genetic correlations between PR interval phenotypes and a collection of clinical phenotypes. To ensure that associations are attributable to shared genetic risk factors and not environmental factors, we tested associations across populations: PR interval phenotypes were from the prospectively studied Atherosclerosis Risk in Communities (ARIC) cohort¹¹ and clinical phenotypes were from the Electronic Medical Records and Genomics (eMERGE) network, a consortium of medical centers with observational electronic health records (EHR)-linked DNA biobanks data sets.¹² We show distinct patterns of genetic disease associations among the PR phenotypes and that PR interval variability is driven by genetic factors associated with electrophysiological and metabolic phenotypes.

Materials and Methods

An overview of the analyses is presented in Figure 1.

Study populations

Analysis data sets—*ARIC*: The ARIC population was derived from 13,113 genotyped adult subjects and comprised 6,732 unrelated European ancestry (EA) subjects with normal ECGs.¹¹ Genetic and phenotypic data were downloaded from dbGaP (phs000280.v3.p1). ***eMERGE*:** The eMERGE population comprised 12,978 unrelated EA adult subjects collected by the eMERGE Phase I Network [Vanderbilt University (VUMC), Marshfield Clinic, Northwestern University, Mayo Clinic and Group Health Research Institute], a consortium of medical centers using electronic health records as a tool for genomic research.¹³ Genetic data for the eMERGE network is available through dbGaP (phs000360.v2.p1).

Replication data sets—*BioVU AF registry*: The Vanderbilt Lone AF registry data set comprised 1,690 European ancestry patients between 18 and 65 years of age enrolled through Vanderbilt's inpatient and outpatient services, as previously described, and had 1,022 AF cases and 668 control subjects.¹⁴ Of the cases, 220 have lone AF, 444 have paroxysmal AF and 259 have persistent AF. ***BioVU VESPA data set*:** The BioVU VESPA

study population comprised 1,206 AF adult cases and 2,405 controls from VUMC's collection of genotyped patients.^{15,16}

All data sets were predominantly composed of self-reported whites so only EA subjects were evaluated, defined using STRUCTURE¹⁷ in conjunction with ancestry informative markers, with European ancestry defined as or >80% (eMERGE subjects) >90% (all other data sets) probability of being in the HapMap CEU cluster.

Genetic Data

ARIC: Genotype data were acquired on the Affymetrix 6.0 SNP array. Quality control steps for the ARIC data set followed the guidelines accompanying the dbGaP release and included removing SNPs with pre-identified chromosomal anomalies and with >5 discordant calls in replicate samples, and used a subset of unrelated subjects identified by the ARIC study.

eMERGE: SNP genotype data were acquired on the Illumina Human660W-Quadv1_A.

BioVU AF data set: Subjects were genotyped on the Illumina 610-quad Beadchip.¹⁴ *BioVU*

VESPA: Subjects were genotyped on the Illumina HumanOmni1-Quad and HumanOmni5-Quad platforms. Quality control steps for the eMERGE and BioVU data sets used established protocols¹⁸ including filtering for a sample missingness rate<2.0%, a SNP missingness rate<2.0% and a SNP deviation from Hardy-Weinberg<0.001

All data sets were imputed to the October 2014 release of the 1000 Genomes cosmopolitan reference haplotypes. SNPs were pre-phased using SHAPEIT¹⁹ and imputed using IMPUTE2.²⁰ The genetic correlation analyses used an intersection of the unimputed ARIC and imputed eMERGE data set and contained 503,404 SNPs with MAF>1.0%. The BSLMM analyses used an LD-reduced (r-square=0.9) set of SNPs with MAF>1.0% present on all platforms (n= 645,714 SNPs).

Phenotype data

The clinical phenotypes for the eMERGE and BioVU data sets were based on PheWAS Phecodes which are collections of related International Classification of Disease, Ninth revision, Clinical Modification (ICD9) diagnosis codes.²¹⁻²⁴ There are over 1,600 defined Phecodes, described at <http://PheWAScatalog.org>. For each Phecode, cases are subjects with two or more instances of the phenotype appearing their medical record on two separate dates.²³ Controls with no instances of the phenotype were randomly selected. There were 315 phenotypes with more than 500 cases in the eMERGE data set. Atrial fibrillation cases and controls were based on PheWAS code 427.21 ("Atrial Fibrillation") which has been previously used in other genetic studies.^{22,23,25}

ARIC phenotypes came from the GENEVA substudy (pht000114.v2.p1) and from ECG measurements taken at visit 1 (pht004071.v1.p1). Subjects with a baseline ECG diagnosis of atrial fibrillation, AV block other than first degree, Wolff-Parkinson-White, a non-sinus rhythm or a pacemaker were excluded. Subjects on AV nodal blocking drugs were also excluded. The PR interval was extracted from the ECG. The P wave duration was based on lead aVR and the PR segment duration was calculated as the difference between the PR segment and P wave duration. Subjects with a PR interval 80 or 320 ms were excluded, as were subjects with a P wave duration 50 or 140 ms. Phenotypes definitions for metabolic

phenotypes were based on previously described thresholds for the ARIC data set²⁶: elevated waist circumference (≥ 102 cm [men] or ≥ 88 cm [women]); insulin resistance (fasting glucose ≥ 100 mg/dl or history of diabetes); hypertension (systolic blood pressure ≥ 130 mm Hg, diastolic blood pressure ≥ 85 mm Hg or use of antihypertensive medications); elevated triglycerides (≥ 150 mg/dl or use of medications for elevated lipids); low HDL cholesterol (<40 mg/dl [men] or <50 mg/dl [women] or use of medications for elevated lipids); and metabolic syndrome (3 or more abnormal metabolic components). Subjects who were not fasting for >8 hours at their first visit were excluded from the analysis of metabolic phenotypes (n=150).

Analyses

Linear mixed models (LMM) and generalized LMM (GLMM) estimate the additive-genetic variance or liability, respectively, attributable to a collection of common SNPs among unrelated individuals by modelling the genetic similarity between pairs of individuals as random effects.^{6,7,27} The linear mixed model is expressed as:

$$y = X\beta + g_G + \varepsilon \quad \text{and} \quad \text{var}(g_G) = A_G \sigma_G^2$$

where y is phenotype vector, X is a vector of fixed effects (covariates and principal components) and ε is a vector of errors. The term g_G is a vector of random polygenic effects, and A_G is often referred to as the Genetic Relationship Matrix (GRM), with each element in the matrix defined by the equation $(1/N) \sum_{i=1}^N (x_{ij} - 2p_i)(x_{ik} - 2p_i) / 2p_i(1-p_i)$ where N is the number of SNPs analyzed, x is the genotype at that SNP (coded 0, 1 or 2) for individuals j and k , and p is the allele frequency. The variance components are estimated by a restricted maximum likelihood (REML) algorithm. These analyses used LMMs and GLMMs as implemented in the Genome-wide Complex Trait Analysis (GCTA) program.^{6,7,9,27,28} To ensure only unrelated subjects are analyzed, subjects with a genetic relatedness score >0.05 were excluded. Genetic liability estimates, adjusting for birth decade, sex and 20 principal components (PCs), were computed for each eMERGE PheWAS phenotype²⁹ with >500 cases, and phenotypes with a genetic liability estimate $p < 0.05$ (n=63) were used for the exploratory genetic correlation analyses (Supplementary Table 1).

A bivariate extension of the GLMM was used to undertake the exploratory genetic correlation analyses (Supplementary Table 1). Here, y is now comprised of pairs of phenotype vectors. For each pair of traits (t_1 and t_2), the bivariate GLMM estimates the genetic variance (σ_G^2) for the phenotypes and the genetic covariance between the phenotypes $\text{cov}_g(G_{t1}, G_{t2})$.^{9,10} The genetic covariance is a measure of how much pairs of traits change together based on the additive genetic effects from common SNPs. This model is most commonly applied to data from two different non-overlapping samples, where the trait (y) values are simply set to missing when not observed (e.g., for subjects in the study of trait t_1 , their t_2 values are set to missing).^{9,10} The genetic correlation between pairs of traits is then defined as: $r_G = \text{cov}_g(G_{t1}, G_{t2}) / \sqrt{(\sigma_{Gt1}^2)(\sigma_{Gt2}^2)}$. This genetic correlation is a measure of the extent to which the additive genetic effects estimated from common SNPs are shared between a pair of traits. r_G is computationally analogous to a Pearson's correlation coefficient, and has a value of -1 to $+1$. Genetic correlations were computed between the

ARIC PR phenotypes (PR interval, the P wave and PR segment) and each eMERGE PheWAS phenotype (n=63), adjusting for age, sex and 20 PCs. P-values for genetic correlations were determined using a likelihood ratio test comparing the bivariate GLMM to a model where the genetic correlation was fixed at 0. While standard errors are given for rG point estimates, the 95% confidence intervals surrounding these estimates under the assumption of asymptotic normality may fall outside the range of plausible values for rG. False discovery rate (FDR)-adjusted p-values (q-values) were determined using a Benjamini-Hochberg (B-H) adjustment. While not all pheWAS phenotype pairs are independent, the test statistics meet B-H criteria by the positive regression dependent criterion.³⁰

Bayesian Sparse linear mixed modelling (BSLMM) was used to compute genetically predicted levels of PR phenotypes in the eMERGE and BioVU data sets. BSLMM employs a hybrid of GLMM and sparse regression models.³¹ In general, this method estimates the proportion of variance explained by a set of SNPs and the distribution of effect sizes for the SNPs and then jointly models the contribution of all SNPs to the phenotypic variance. The posterior SNP weights generated by this approach can be used in conjunction with SNP genotypes to compute a genetically predicted value for a phenotype. Each PR phenotype in the ARIC data set was first adjusted for age, gender and 3 PCs using linear regression. BSLMM was then used to generate SNP effect sizes (α and β) for the PR phenotype residuals. These effect sizes were then used to compute the genetically predicted value for a PR phenotype for an individual in the eMERGE and BioVU data sets using the equation:

$$\text{Predicted phenotype} = \sum (\alpha_i + \beta_i \gamma_i * (\text{number of reference alleles for SNP}_i))$$

where α is the small SNP effect, $\beta\gamma$ is the large SNP effect.

Multivariable logistic regression adjusting for 3 PCs, age and sex was used to test the association between the predicted phenotype levels and the EMR PheWAS and AF phenotypes. The predicted phenotypes were set to have a standard deviation of 1, so ORs reflect risk per standard deviation increase in the predicted phenotype. A FDR-adjusted q-value < 0.1 was considered significant.

Genetic risk scores based on either odds ratios (OR) or Beta coefficients for previously reported SNPs reaching genome-wide significance ($p < 5 \times 10^{-8}$) were computed for the PR interval (n=9 SNPs), BMI (n=98) and atrial fibrillation (n=10 SNPs).^{5,14,32} The SNPs used to compute the GRS in each data set are shown in Supplementary Tables 2 and 3. A GRS was computed using previously the published association statistics for each individual using the formulas:³³

$$\begin{aligned} \text{PR interval and BMI: Score} &= \sum \beta_i * (\text{number of reference alleles for SNP}_i) \\ \text{AF: Score} &= \sum \log(\text{OR}_i) * (\text{number of reference alleles for SNP}_i) \end{aligned}$$

Only 8 of 9 SNPs for the PR GRS passed QC protocols and were used in the calculations. To ascertain whether the genetic risk scores are differentially associated with the PR

phenotypes, partial correlation coefficients between each PR phenotype and each GRS were computed using PROC CORR (SAS) and adjusted for age and sex.

All quality control analyses and SNP association analyses were performed using PLINK v1.07.³⁴ Genetic liability and correlation estimates were computed using the GCTA v1.24.²⁷ BSLMM is part of the GEMMA v0.94.1 program package.³¹ All other analyses were performed using SAS v9.3 (SAS Institute, Cary, NC).

Ethics Statement

The eMERGE study has been approved by the Institutional Review Board (IRB) at each site.^{12,15} Vanderbilt's BioVU resource operates as nonhuman subjects research according to the provisions of 45 *Code of Federal Regulations*, part 46, with oversight by Vanderbilt's Institutional Review Board (IRB), as previously described.¹⁵ IRB approval for the current study was obtained through Vanderbilt's IRB.

Results

The ARIC population comprised 6,731 unrelated EA subjects with a normal ECG. Their median age was 54 years and 45% of subjects were males (Supplementary Table 4). Almost a quarter of subjects had three or more metabolic syndrome phenotypes. The eMERGE data set comprised 12,978 subjects, of which 48% were male, with an average of 44 clinical diagnoses per subject (Supplementary table 1).

Clinical phenotypes genetically correlated with PR phenotypes

The estimated heritability explained by the SNPs for the PR interval in the ARIC data set was 0.23 (standard error 0.05) (Table 1). We measured the genetic correlation (r_G) between the PR interval and 63 eMERGE phenotypes (listed in Supplementary Table 1). The strongest genetic correlations were with "atrial fibrillation/atrial flutter" [$r_G = -0.59$, $p = 0.02$] and AF [$r_G = -0.57$, $p = 0.02$], but were not significant (FDR $q > 0.1$) after adjusting for multiple testing (Figure 2A and Table 2). (Characteristics of the AF cases and controls are shown in Supplementary Table 5).

We next examined the P wave and the PR segment durations (Table 1), which comprise the PR interval. The point estimate of the genetic correlation between the PR segment and the PR interval [$r_G = 0.89$ (0.04)] was larger than that for the P wave and the PR interval [$r_G = 0.49$ (0.16)]. The genetic correlation between the P wave and the PR segment was not significantly different from zero ($r_G = -0.03$ [0.16]). The PR segment showed a similar pattern of genetic correlations with the eMERGE phenotypes as the PR interval, with the exception that the genetic correlation with AF was significant after multiple testing correction [$r_G = -0.88$ (95% CI: -1.6 to -0.19), $p = 0.0009$, FDR $q = 0.047$] (Table 2 and Figure 2B). For both the PR interval and PR segment, the AF correlation was negative indicating that genetic factors associated with a longer interval are associated with a decreased risk of AF. There were no significant genetic correlations with the P wave (Figure 2C). The most strongly genetically correlated phenotype was type 2 diabetes [$r_G = 0.49$, $p = 0.008$, FDR $q = 0.26$].

We examined the impact of adjusting for PR phenotypes on the genetic correlation between the PR interval duration and AF. Adjusting for the P wave duration minimally impacted the genetic correlation between the PR interval and AF [$r_G = -0.84$, $p = 0.001$] (Table 2). In contrast, adjusting for the PR segment further attenuated the P-wave-AF correlation [$r_G = 0.33$, $p = 0.22$] (Table 2). Thus, the genetic signal in the PR interval that is associated with AF is most strongly captured by the PR segment.

Associations with a genetically predicted PR interval

The mixed models analyses indicate that a highly polygenic SNP-based genetic classifier could capture up to ~23% of the variability of the PR interval. We used BSLMM³¹ to construct a highly polygenic SNP classifier for the PR interval in the ARIC data set, and this was used to impute a genetically predicted PR interval for each subject in the eMERGE population. We then tested for an association between the predicted PR interval and 261 clinical phenotypes (with >250 cases and a genetic liability $p < 0.2$).³⁵ Significant associations were seen with arrhythmia phenotypes including AF [OR=0.89, 95% CI (0.83–0.95), $p = 0.0006$, FDR $q = 0.04$] (Table 3 and Figure 2D). Thus, a genetically predicted prolonged PR interval is associated with decreased AF risk. The magnitude of this association was modestly attenuated when adjusting for genetic risk scores based on significant GWAS SNP associations for the PR interval and AF or when adjusting for these SNPs ($n = 17$) as covariates, though the p -value was no longer significant in the latter model (Table 3). While no associations with an opposite direction of effect were significant, the strongest associations were with first degree AV block, a diagnosis of a prolonged PR interval, and morbid obesity (Figure 2D). Analyses using a genetically predicted PR segment or P wave duration did not identify any significant associations, though the top associations for the PR segment were the same as those seen for the genetically predicted PR interval (Supplemental Figure 1).

Validating the atrial fibrillation association

To confirm the genetic correlation between the PR interval and AF, we tested the association between the genetically predicted PR interval and AF in two independent data sets. A second EHR-derived data set (1,206 AF cases and 2,405 controls) that used the same AF phenotype definition as the discovery set had a significant association [OR=0.90 (0.85–0.98), $p = 0.01$] (Table 3). A comparable result was seen using subjects (1022 cases, 668 controls) from Vanderbilt's AF registry [OR=0.90 (0.81–0.99), $p = 0.03$] (Table 3). There was a similar magnitude and direction of effect when the results were stratified by AF subtypes (lone, paroxysmal and persistent AF) (Table 3).

PR components and metabolic syndrome phenotypes

Other than AF, the strongest genetic correlations for the PR phenotypes were with metabolic phenotypes (diabetes, obesity). Epidemiological studies have also shown that P wave duration is positively associated with metabolic syndrome phenotypes.²⁶ We measured the genetic correlations between each PR interval component and metabolic phenotypes in the ARIC subjects. The PR interval and PR segment were not genetically correlated with any metabolic phenotype (Table 4). The P wave was positively genetically correlated with waist circumference [$r_G = 0.47$, $p = 0.03$].

Associations between PR components and genetic risk scores

Finally, we examined whether there was a differential association between genetic risk scores based on known genetic modulators of the PR interval, atrial fibrillation and weight (measured by body mass index [BMI]), and the PR phenotypes. The PR GRS was significantly linearly correlated with each PR phenotype, and had the largest linear correlations with PR interval and PR segment (Table 5). The AF GRS was weakly correlated with the P wave duration (partial $r=0.024$, $p=0.049$), while the BMI GRS was correlated with both the PR interval (partial $r=0.035$, $p=0.004$) and P wave (partial $r=0.048$, $p<0.001$) (Table 5).

Discussion

We employed a discovery-oriented approach to identify clinical phenotypes modulated by genetic factors that also modulate the PR interval. We found that AF risk was genetically correlated with the PR interval, and this association was also observed using a highly polygenic risk score derived from the PR interval. We also observed genetic correlations with metabolic phenotypes including measures of adiposity. Thus, the genetic architecture underlying PR interval variability is driven, in part, by SNP variation that predisposes to AF risk and SNP variation which modulates body mass. Our analyses also found that the constitutive components of the PR interval (the PR segment and the P wave) were associated with different phenotypes and further characterizing their individual genetic architectures may enable the development of better genetic risk prediction tools.

While the PR interval is a genetically modulated measure of cardiac conduction, relatively few SNPs associated with this phenotype have been identified.³⁻⁵ This paucity is not unexpected, as the genetic variability underlying many complex phenotypes is driven by numerous SNPs with small effect sizes that are difficult to detect by GWAS. We used modelling approaches which analyze the contributions of large number of SNPs to broadly characterize the genetic architecture of the PR interval. We found that common SNP variation accounted for at least 23% of phenotypic variability in the PR interval, indicating that much of the additive heritability of PR interval is currently hidden. When we examined the individual constituents of the PR interval, we found that the genetic correlation between PR segment and P wave durations was not significantly different for zero, suggesting that they differing genetic architectures. This observation is consistent with GWAS studies which have found that these intervals are associated with different SNPs.³⁶ To further characterize the genetic architectures of the PR phenotypes, we examined their genetic correlations with a large number of clinical phenotypes.

The individual PR phenotypes were not uniformly genetically correlated with the same clinical phenotypes. The most significant association was between the PR interval and PR segment and AF. The genetic correlation was negative, indicating that a genetically prolonged PR interval is associated with decreased risk of AF. This finding was not anticipated, as epidemiological studies have frequently observed that a prolonged PR interval is associated with an increased risk of AF.^{1,2} This epidemiological association is attributed, in part, to prolongation in the PR interval due to acquired structural changes to the atrium that manifest as slowed atrial conduction and lead to increased atrial

arrhythmogenicity.³⁷ Indeed, the PR interval duration increases with age, cardiac diseases³⁸ and metabolic phenotypes such as obesity and hypertension.^{39–41} These increases are most pronounced for the P wave.²⁶ These epidemiological associations are consistent with the trends in the genetic correlations that we observed when analyzing P wave duration. The P wave was most strongly genetically correlated with metabolic phenotypes including waist circumference and type 2 diabetes and a genetically predicted P wave duration was most strongly associated with a diagnosis of obesity. While not significant, the genetic correlation between the P wave and AF was positive, suggesting that a prolonged P wave duration is associated with an increased risk of AF. In turn, these results indicate that there are genetic factors, such as those that modify BMI, which prolong the PR interval by affecting the P wave and which increase the risk of AF.

The epidemiological association between PR interval and AF is U-shaped, as a short PR interval is also associated with increased AF risk.^{42–45} Hence, our observation that a genetically shorter PR interval and PR segment is associated with an increased AF risk suggest the inverse association is genetically mediated, and that a short PR interval represents an accumulation of PR-shortening genetic variants, some of which also predispose to AF risk. Our results also suggest that the genetic mechanisms modulating the PR interval duration modulate AF risk in different directions. Thus, the genetic risk relationships between AF and each PR phenotype should be evaluated individually to better define this association. Another approach to examining the U-shaped relationship between the PR interval and AF is to employ non-linear statistical models. However, we believe that ascribing the non-linear association to the individual effects of the PR phenotypes is biologically more plausible than non-linear additive genetic effects underlying the PR interval. Our findings also indicate there is opportunity for more discovery. For instance, we found that a genetic risk score comprised known AF SNPs more strongly reflected the genetic risk associated with the P wave, as compared to the PR segment. Thus, identifying and evaluating additional SNP variants associated with the PR segment may reveal additional genetic mechanisms contributing to AF risk.

A significant genetic correlation between a pair of phenotypes suggests that they are modulated by a common set of genetic factors. Hence, a genetic predictor derived from one phenotype should associate with the other phenotype, provided that that predictor is able to capture a sufficient portion of the underlying genetic architecture of the first phenotype. We used BSLMM, which models phenotypes based on large numbers of SNP, to compute genetically predicted PR intervals in three data sets. This genetically predicted PR interval was associated with AF risk in each data set, and the direction was consistent with that observed with the genetic correlations analyses. As larger sample sizes become available and new polygenic modelling techniques are developed, it may be possible to develop a PR interval-derived genetic classifier which can robustly predict AF risk and can offer sufficient lead time to maximize the benefit of intervention strategies.

There are several limitations to this study. We used phenotypes derived from EHR data sets, which often lack rigid phenotype definitions and can have incomplete ascertainment. Incomplete ascertainment and phenotype misclassification can attenuate associations. In support of the validity of our EHR AF phenotype, we note that it has been used for several

genetic studies and has been shown to replicate known SNP associations.^{22,23,25} It is possible that the genetic correlations we observed are spurious and are caused by SNPs simultaneously tagging disparate causative genetic variants that impact the phenotypes through distinct mechanisms.⁴⁶ However, all of our genetic correlations are supported by epidemiological observations, so this is unlikely for the phenotypes we identified. Our AF cases also had more comorbidities as compared to our controls, which could inflate genetic correlation estimates for risk factors related to the metabolic syndrome. We also did not have sufficient individuals of other ancestries to evaluate and validate our findings in these other racial groups.

In conclusion, we used mixed models to characterize the genetic architecture of the PR interval. We found that SNP variants which predispose to AF and elevated body mass, modulate the PR interval and that these variants differentially influence the P wave and PR segment durations. Future GWAS studies should examine the constitutive PR phenotypes separately in order to more fully define the genetic modulators of the PR interval. Furthermore, focusing on genetic variation underlying the PR segment may identify novel AF genetic risk factors and mechanisms, which may lead to better AF risk prediction models.⁴⁷ Finally, a portion of the genetic predisposition towards AF is driven by genetic factors for metabolic risk factors including obesity, highlighting the continued need for aggressive risk modification and treatment for these predisposing conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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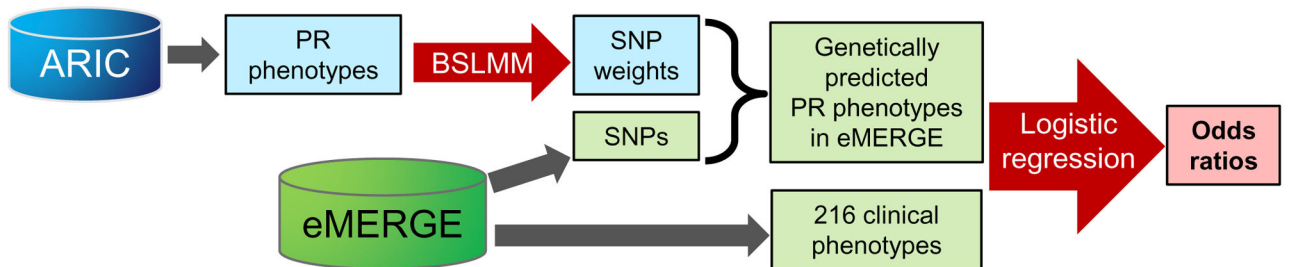
Clinical Perspective

Biomarkers which predict disease risk enable risk stratification and disease prevention. Since many biomarkers and diseases are modulated by underlying genetic risk, it is possible to associate them based on this shared genetic risk. Importantly, these genetic associations can be assessed across different datasets, as long as all subjects have genotypic data, and the approach can be used to study relationships between potential biomarkers and disease. Here, we measured genetic correlations, a measure of genetic association, between a potential biomarker, the PR interval (and its individual components, the P wave and the PR segment), and 63 electronic health record (EHR) disease phenotypes. The ECG phenotypes were analyzed in the Atherosclerosis Risk in Communities (ARIC) cohort, and the EHR phenotypes in the Electronic Medical Records and Genomics (eMERGE) network. We found that a genetically predicted PR interval was associated with atrial fibrillation (AF) risk, consistent with previous epidemiological studies, but with an opposite direction of association. The individual components had different genetic architectures, were not correlated with each other, and AF risk was predominantly associated with genetically-determined PR segment. This study establishes that the shared genetic architectures of clinical phenotypes like AF and putative biomarkers like the PR and its components can identify epidemiological associations, validate the biomarkers, and point to disease mechanisms.

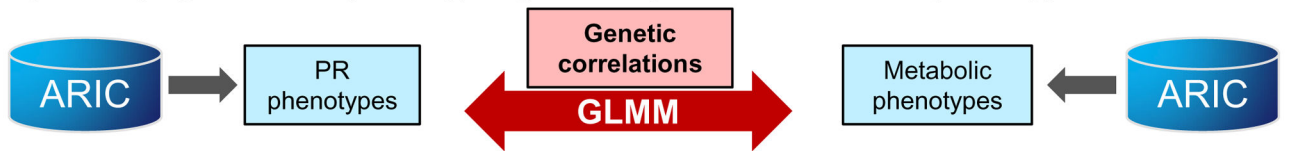
A) Identifying clinical phenotypes types genetically correlated with PR phenotypes.



B) Identifying clinical phenotypes associated with genetically predicted PR phenotypes.



C) Identifying metabolic phenotypes genetically correlated with PR phenotypes.



D) Identifying genetic risk scores (GRS) associated with PR phenotypes.

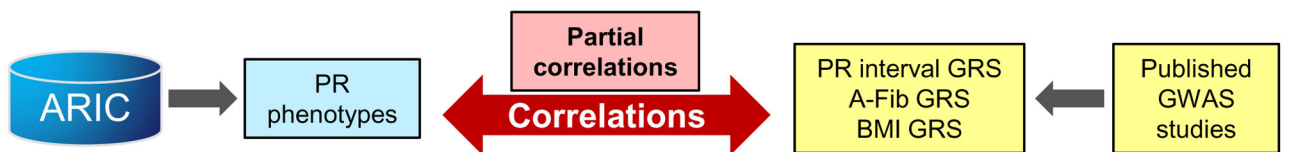


Figure 1.

Overview of approach. A) GLMMs were used to measure the pair-wise genetic correlations (r_G) between each ARIC PR phenotype (PR interval, PR segment and P wave duration) and each genetic eMERGE phenotype. B) BSLMMs were used to compute SNP weights for each PR phenotype. These weights were used to compute genetically predicted PR phenotype values in eMERGE subjects. Logistic regression was used to test the association between the predicted PR phenotypes and eMERGE clinical phenotypes. C) GLMMs were used to compute r_G between ARIC PR phenotypes and metabolic phenotypes. D) Partial correlation coefficients were calculated between ARIC PR phenotypes and genetic risk scores based on SNPs identified by prior GWAS studies.

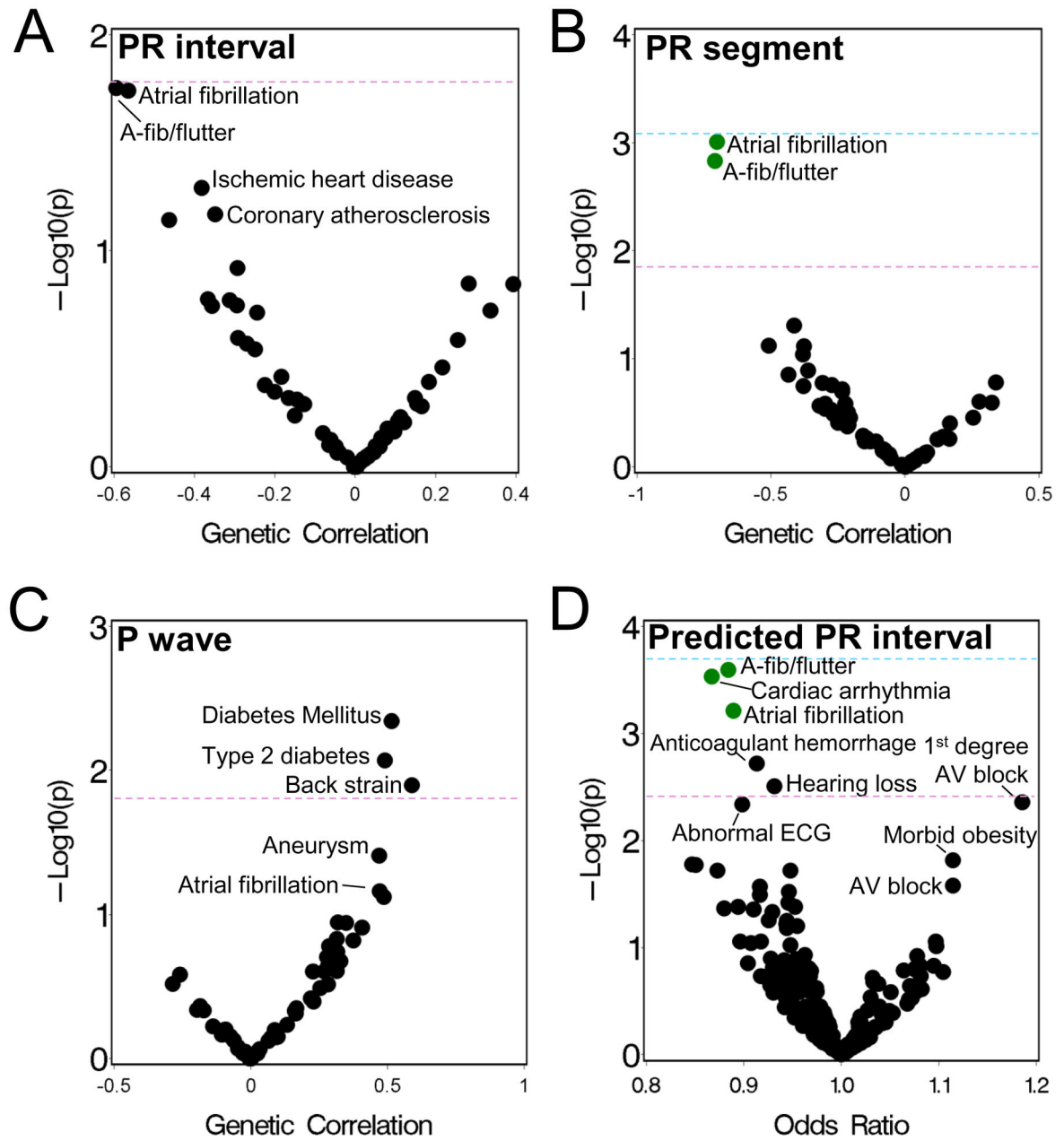


Figure 2.

Phenotypes genetically associated with PR phenotypes. (A–C) Genetic correlations between the (A) PR interval, (B) PR segment and (C) P wave duration, measured in ARIC subjects, and 63 phenotypes measured in eMERGE subjects, adjusted for age, gender and PCs. P-values are based on a likelihood ratio test comparing a full model to a model where the genetic correlation was fixed at 0. (D) Plot of p-value versus odds-ratio (OR) from logistic regression analyses of the association between a genetically predicted PR interval and 261 eMERGE phenotypes, adjusted for sex, gender and PCs. ORs represent the risk per standard deviation change in the predicted PR interval. For all graphs, each point represents a

phenotype and green colored points have an FDR $q < 0.1$. The purple dotted line denotes the expected false positive rate, and the blue line corresponds to a Bonferroni correction.

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Table 1

Heritability/liability estimates for the ARIC cohort.

Characteristic	Heritability/liability (s.e.) [*]
EKG parameters [mean (s.d.)]	
PR interval duration (ms)	0.23 (0.05)
P wave duration (ms)	0.19 (0.05)
PR segment duration (ms)	0.18 (0.05)
Metabolic traits [n (%)][†]	
Waist circumference	0.14 (0.04)
Insulin Resistance	0.05 (0.04)
Hypertension	0.18 (0.04)
Triglycerides	0.15 (0.04)
HDL cholesterol	0.14 (0.04)
Metabolic syndrome	0.21 (0.04)

^{*} Heritability or liability estimates or metabolic traits and ECG phenotypes are based on genetic linear mixed models adjusting for age, sex and 20 principal components.

[†] See Methods for metabolic trait definitions.

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Table 2

Genetic correlations (rG)^{*} between PR components and atrial fibrillation.

Adjustment	PR interval		P wave		PR segment	
	rG (s.e.)	P-value	rG (s.e.)	P-value	rG (s.e.)	P-value
None	-0.57 (0.27)	0.02	0.48 (0.29)	0.07	-0.88 (0.35)	0.0009
P wave adjusted [†]	-0.84 (0.34)	0.001	--	--	-0.84 (0.34)	0.001
PR segment adjusted [‡]	0.33 (0.28)	0.22	0.32 (0.28)	0.22	--	--

^{*} Genetic correlations between the PR component measured in ARIC subjects and AF measured in eMERGE. Genetic correlations were adjusted for age, sex and 20 PCs.

[†] Additional covariates for ARIC subjects added to the model.

Table 3

Association between a genetically predicted PR interval and atrial fibrillation.

Data set	Subjects	Cases/Controls	OR (95% CI) *	P-value
eMERGE	All AF cases	1,547 / 3,128	0.89 (0.83–0.95)	0.0006
	All AF cases, GRS adjusted [†]	1,547 / 3,128	0.90 (0.83–0.98)	0.02
	All AF cases, SNP adjusted [‡]	1,547 / 3,128	0.90 (0.81–1.01)	0.06
BioVU EHR set	All AF	1,206 / 2,405	0.90 (0.85–0.98)	0.01
	All AF	1,022 / 668	0.90 (0.81–0.99)	0.03
BioVU AF registry	Lone AF	220 / 668	0.87 (0.74–1.03)	0.1
	Paroxysmal	444 / 668	0.90 (0.80–1.02)	0.09
	Persistent	259 / 668	0.93 (0.80–1.08)	0.34

* The odds-ratio is per standard deviation increase in the genetically predicted PR interval. All association models are adjusted for age, gender and 3 PCs.

[†] Adjusted for genetic risk scores for atrial fibrillation and the PR interval.

[‡] Adjusted for SNPs (n=17) previously associated with AF or the PR interval by GWAS.

Table 4

Genetic correlations (rG)* between PR components and metabolic syndrome phenotypes in ARIC.

	PR interval		P wave		PR segment	
	rG (s.e.)	P-value	rG (s.e.)	P-value	rG (s.e.)	P-value
Metabolic phenotype						
Waist circumference	0.16 (0.19)	0.42	0.47 (0.21)	0.03	-0.06 (0.22)	0.80
Insulin resistance	-0.21 (0.30)	0.47	-0.14 (0.32)	0.66	-0.21 (0.33)	0.52
Hypertension	-0.10 (0.17)	0.56	0.23 (0.19)	0.22	-0.23 (0.19)	0.22
Triglycerides	-0.17 (0.18)	0.34	-0.14 (0.20)	0.46	-0.11 (0.20)	0.57
HDL cholesterol	-0.15 (0.19)	0.44	-0.15 (0.21)	0.62	-0.11 (0.22)	0.31
Metabolic syndrome	-0.05 (0.16)	0.76	-0.06 (0.17)	0.72	-0.03 (0.17)	0.66

* Analyses are adjusted for age, sex and 20 PCs.

Table 5

Partial correlation coefficients (r) * between PR interval, AF and BMI genetic risk scores and PR phenotypes.

Phenotype	PR GRS		AF GRS		BMI GRS	
	Partial r	p-value	Partial r	p-value	Partial r	p-value
PR interval	0.17	<.0001	0.014	0.25	0.04	0.004
P wave duration	0.07	<.0001	0.024	0.049	0.05	<0.001
PR segment	0.14	<.0001	0.002	0.87	0.01	0.36

* Correlations are adjusted for age and sex.