SUPPLEMETAL MATERIAL

SUPPLEMENTAL TEXT

Supplementary Text: Description of Participating Studies

The Hispanic Community Health Study/ Study of Latinos (HCHS/SOL) The HCHS/SOL is a multicenter, community-based cohort study of U.S. Hispanics/Latinos (1). Goals of the study are to examine the prevalence of and risk factors for several disorders including heart, lung, blood, and kidney phenotypes. HCHS/SOL investigators sampled 16,415 males and females aged 18-74 years at baseline from four study communities: The Bronx, NY, Chicago, IL, Miami, FL, and San Diego, CA. HCHS/SOL recruitment centers were selected so that the study would include at least 2,000 participants in each of the following designations: Mexican, Puerto Rican, Dominican, Cuban, and Central and South American.

The Multiethnic Study of Atherosclerosis (MESA) MESA was initiated in 2000 to investigate subclinical cardiovascular disease and the risk factors that predict progression to clinically overt cardiovascular disease (2). The population-based cohort included 6,814 asymptomatic males and females aged 45–84 at study baseline from six field centers (Winston-Salem, NC; St. Paul, MN; Chicago, IL; Los Angeles, CA; New York, NY; Baltimore, MD). MESA investigators enrolled participants of Caucasian (38%), African American (28%), Hispanic (22%) and (12%) Chinese descent. The current study was restricted to Hispanics/Latino MESA participants who gave consent for DNA use. ECGs were measured at study baseline.

Women's Health Initiative Clinical Trial (WHI) The WHI comprises both randomized clinical trials (CT) and an observational study (OS). This study is limited to WHI CT participants, as

ECGs were not collected for WHI OS participants (3). The three WHI clinical trials were designed to allow randomized, controlled evaluation of 1) estrogen with or without progestin treatment, 2) calcium/vitamin D supplementation, and 3) dietary modification on the risk of breast and colorectal cancer, cardiovascular disease, and bone fractures. Between 1993 and 1998, the trials enrolled 68,132 postmenopausal women aged 50–79 years who were followed at 1 of 75 US examination sites (including satellites, remote sites, and their changes in location). Women were ineligible if they had medical conditions predictive of survival time less than 3 years, if they were known to have conditions inconsistent with study participation and adherence, or if they were active participants in another randomized, controlled trial. Those who remained eligible and interested were invited to follow-up examinations at 1, 3, 6, and 9 years. ECGs were measured at study baseline and analyses were restricted and Hispanics/Latino WHI participants. During replication, European descent participants were drawn from the Women's Health Initiative Memory Study (WHIMS) (4) and African American participants were drawn from the Single Nucleotide Polymorphism (SNP) Health Association Resource Project (SHARe) (5).

Supplementary Text: Methods

Exclusion Criteria: Individuals were excluded based on the following criteria: PR unavailable, poor electrocardiogram (ECG) quality, non-sinus rhythm including atrial fibrillation and atrial flutter on ECG, pacemaker implantation, second or third degree heart block, extreme PR values (PR $\leq$ 80 ms or $\geq$ 320 ms), prevalent heart failure or myocardial infarction, or Wolff-Parkinson-White syndrome on ECG.

Genotyping: Participants were genotyped on the Affymetrix Genome-Wide Human SNP Array 6.0 (MESA, WHI) or an Illumina custom array, consisting of the Illumina Omni 2.5M array (HumanOmni2.5-8v1-1) and approximately 150,000 custom SNPs selected to include ancestry informative markers, variants characteristic of Native American populations, previously identified GWAS loci, and candidate-gene polymorphisms (HCHS/SOL) (6). See below for additional details on quality control metrics in each study. Prior to imputation, study-specific exclusions of genotyped SNPs included SNPs with call rates <90% or ≤95% and a minor allele frequency (MAF) <1% (Supplemental Table 1). Genotypes were imputed using the 1000 Genomes Phase 1 reference panel (7). SNPs with poor imputation quality (oevar < 0.5) were excluded from future analyses in all studies.

HCHS/SOL Quality Control Procedures: HCHS/SOL was genotyped on an Illumina custom array. Samples were checked for sex mismatch, gross chromosomal abnormalities, unexpected duplicates, sample call rate ≥99%, contamination, and batch effects. Additionally, SNPs were filtered out if they had Mendelian errors, duplicate-sample discordance, or deviation from Hardy-Weinberg equilibrium (HWE; $P < 10^{-5}$) in a meta-analysis of nine ancestry groups within which individuals had both parents from the same country of origin). SNPs were further excluded if they had positional duplicates or were monomorphic (8).

MESA Quality Control Procedures: MESA participants were genotyped on the Affymetrix Genome-Wide Human SNP Array 6.0. Samples were then checked for genotype concordance between SNPs genotyped on the Affymetrix Genome-Wide Human SNP Array 6.0 and SNPs previously genotyped using Sequenom iPLEX. SNPS with a call rate < 90%, monomorphic SNPs, and SNPs that mapped to multiple locations were removed. Samples with a call rate <

95% were also removed. Samples were then checked for excess heterozygoxity (to identify poor DNA or contamination), sample duplication (using IBD estimates), cryptic relatedness, and sample outliers. HWE was performed and SNPs with $P < 10^{-6}$ were excluded (9).

WHI Quality Control Procedures: WHI participants were genotyped on the Affymetrix Genome-Wide Human SNP Array 6.0. Samples were then excluded if their call rate was <95%, if they were related to another individual (with preference for the retained individual in a related pair going to parent over offspring). SNPs were excluded if they failed HWE ($P \leq 10^{-6}$), had a low call rate (<95%), did not map to a chromosomal location (10).

Statistical Analysis: Genome-wide analyses were performed by each cohort independently across approximately 25 – 39 million SNPs assuming an additive genetic model, using linear regression (MESA, WHI) or linear mixed models (HCHS/SOL) (6). All analyses were adjusted for age, sex, study center or region, height, body mass index, systolic blood pressure, heart rate, beta blocker use, and study principal components of ancestry to maintain consistency with prior PR GWAS (11-17). Furthermore, analyses in HCHS/SOL incorporated estimates of relatedness and sample weights into all analyses and allowed for heterogeneous variance estimates by genetic background group (6). Study specific results were corrected for genomic inflation (λ, Supplemental Figure 1), after which they were combined with inverse-variance weighted meta-analysis conducted in METAL (18). We used a genome-wide significance threshold of $P<5x10^{-8}$. This value reflects a Bonferroni correction whereby 0.05 is divided by 1 million. Due to linkage disequilibrium (LD) across the genome, many SNPs are inherited together and therefore in high correlation with each other. We estimate that after accounting for LD, we have conducted 1 million independent tests, which is therefore used as the denominator in our

Bonferroni correction. For all significant index SNPs, we performed conditional analyses by adjusting for the index SNPs and any subsequently significant SNPs until no remaining genome-wide significant SNPs were identified. Heterogeneity between contributing studies was assessed using Cochran's Q statistic and I^2.

Generalization of Previously Reported PR SNPs: For SNPs previously associated with PR in published GWAS reports (11, 16), we examined evidence for generalization using the approach described by Sofer *et al.* (19). The method assigns an r-value to every index SNP. The r-values quantify the evidence for replication, controlling for false discovery rate, and are based on the r-values developed by Heller *et al.* (20). Sofer *et al.* extended the r-values to also account for the direction of the observed association. The generalization null hypothesis testing generalization of the PR index SNPs to Hispanics/Latinos was rejected when the r-value was less than 0.05, controlling the false discovery rate of the generalization null hypothesis.

Replication of Novel Associations: For novel associations, we attempted to replicate our results in populations of East Asian, European, and African descent using exclusion criteria and analytic procedures that overlapped with previously described approaches. The European and African descent replication populations were provided by the WHI study (see above for cohort and genotyping information). For the East Asian replication populations, we identified published summary statistics of the association between 2.1 million SNPs (352,228 genotyped SNPs [Affymetrix Genomewide Human SNP Array 5.0] and 1.8 million imputed SNPs [HapMap Phase 2 CHB+JPT reference panel]) and PR provided by Hong *et al.* (14). If an index SNP was not available, we queried the SNAP database for proxy SNPs (21) using an appropriate HapMap2 ethnic population (CEU, AFR, CHB+JPT), an r^2 limit at 0.8, and a distance of 500

kilobases from the index SNP. Here, r^2 represents the correlation between two SNPs in linkage disequilibrium, calculated as follows:

$$r^2 = \frac{D_{AB}^2}{p_A(1-p_A)p_B(1-p_B)}$$

where D_{AB}^2 represents the squared disequilibrium coefficient between SNPs A and B (difference between observed and expected allele frequencies), p_A represents the allele frequency at SNP A, and p_B represents the allele frequency at SNP B. We used a Bonferroni correction of 0.05/number of statistical tests to determine significance.

Linkage Disequilibrium Analysis: LD was calculated with the r^2 correlation statistic, using the 1000 Genomes meta-populations as reference (AMR, EUR, AFR, and ASN) and visualized using the LocusZoom program. CAFs across global populations were similarly calculated using the four 1000 Genomes reference meta-populations. Additionally, we used RFMix to estimate local ancestry for HCHS/SOL (22). Based on the local ancestry calls, ancestry-specific allele frequencies were estimated for top SNPs using the R/Bioconductor package ASAFE (23).

Bioinformatic Annotation of Associated Variants: For loci associated with PR at a genome-wide significance level in our Hispanic/Latino population, we used epigenetic data from the ENCODE (24) and RoadMap (25) projects to examine evidence of functional annotation using HaploReg v4.1 (26). SNPs correlated with the Hispanic/Latino index SNP at an $r^2 > 0.8$ were identified using the AMR population and results were restricted to annotation found in available heart tissue (fetal heart, right atrium, and right or left ventricle).

Additionally, for novel variants associated with PR, we queried publically available data from genetic association studies of clinical phenotypes associated with PR (atrial fibrillation, stroke, heart failure) to identify possible associations our novel Hispanic/Latino index SNPs. To identify publically available datasets, the GWAS catalog (27) was queried for published GWAS of atrial fibrillation, stroke, and heart failure. Each published study was examined to identify any with publically posted summary results. Furthermore, dbGap was searched for analyses with atrial fibrillation, stroke, or heart failure in the file name or description. From here, all analysis results from studies with atrial fibrillation, stroke, or heart failure phenotypic outcomes were examined for possible associations with our Hispanic/Latino index signals. Furthermore, because many studies were from older imputation panels (e.g. HapMap imputation panels) and therefore did not contain our index signal for all loci, we identified SNPs in LD with the Hispanic/Latino index SNP using the AMR HapMap2, an r^2 limit at 0.8, and a distance of 500 kilobases from the index SNP using HaploReg v4.1 (26). All SNPs identified were also examined for associations with atrial fibrillation, stroke, and heart failure. We used a Bonferroni correction of 0.05/# of phenotypes examined (3) to determine signicance.

SUPPLEMENTAL FIGURES AND TABLES

Supplementary Tables

Supplemental Table 1. ECG and genotype measurement methods for Hispanic Community Health Study/Study of Latinos (HCHS/SOL), Multiethnic Study of Atherosclerosis (MESA), and Women's Health Initiative Clinical Trial (WHI)

Study	HCHS /SOL	MESA	WHI
	ECG Measurements		
ECG Machine	GE MAC 1200	GE MAC 1200	Marquette MAC PC
ECG Measurement System	GE Marquette 12-SL	GE Marquette 12-SL software (2001 version)	Marquette 12SL
	Genotype		
Array	Illumina HumanOmni2.5-8v1-1 + custom content	Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA)	Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA)
Genotype calling software	GenomeStudio v2011.1	Birdseed v1.33	Birdseed
SNP call rate genotyping exclusion	<98%	<95%	≤95%
SNP MAF genotyping exclusion	NA	<1%	<1%
SNP MAC genotyping exclusion	NA	NA	NA
P HWE genotyping exclusion	<1e-5	<1e-6	<1e-6
MAF imputation exclusion	MAC >=2 in any of the 4 reference panels (AFR, AMR, ASN, EUR)	0.01	NA
Imputation quality exclusion	NA*	0.4	NA*
Imputation software	IMPUTE2	IMPUTE2	MaCH v1.0.16
Build used for Imputation	1000 Genomes Phase I release 3 (NCBI build 37 / hg19)	1,000 Genomes Phase I integrated variant set (NCBI build 37 / hg19)	1,000 Genomes Phase I (NCBI Build 37/ hg19)
GWAS statistical analysis software	R/Bioconductor GENESIS package	SNPTEST2	ProbAbel
Related Individuals?	Yes	No	No
Familial Adjustment method	Kinship coefficients in Mixed model	NA	NA
# SNPs measured	2,232,944	881666	934,930
# SNPSs imputed	25,568,744	39×10^6	38×10^6
# SNPs passing QC	17,322,742	8,637,954	8,217,098

No imputation quality filter was applied prior to analysis for HCHS/SOL or WHI. Instead, study-specific results were filtered for effective N which was calculated as follows: 2(Number of Participants)*(Minor Allele Frequency for SNP of interest)*(1-Minor Allele Frequency)*(Imputation Quality). Only SNPs with effective N > 30 were brought forward for meta-analysis.

Supplemental Table 2. Association Results Between Hispanic/Latino PR Interval Index SNPs at *ID2* and Previously Published Genetic Associations with Atrial Fibrillation*

	P-values of Association with Phenotype	
SNPs**	Low, *et al.* (28)	Christophersen, *et al.* (29)
rs6730558	0.77	0.15
rs10929547	0.77	0.34
rs13384855	0.79	0.26
rs12993630	0.64	0.13
rs3896594	0.58	0.15

*****Previously published GWAS of stroke and heart failure were also examined. However, no GWAS with publicly available data included rs6730558 or any of the four SNPs in LD with rs6730558. The rs6730558 locus was not present on HapMap imputation panels and there are not yet 1000 Genomes GWAS studies available for stroke or heart failure. Similarly, the above two studies were the only two studies of atrial fibrillation with the r6730558 locus available.
******Hispanic/Latino lead SNP indicated in bold. All other SNPs in locus are in LD ($r^2 > 0.8$) with Hispanic/Latino lead SNP in HapMap2 AMR population

Supplemental Table 3. Pairwise Linkage Disequilibrium in International HapMap Populations Between Hispanic Lead SNPs and Previously Published Index SNPs in European (13, 16), African American (11, 17), and Asian Descent (12, 14, 30) Populations at the *SCN5A*/*SCN10A* Locus Calculated Using Broad Institutes SNP Annotation and Proxy Search (SNAP) (21)

Hispanic Lead SNP	Previously Published Index SNP	r^2		
		CEU	YRI	CHB+JPT
rs3922844	rs7638909 (30)	0.05	0.01	0
	rs11708996 (16)	0.07	NA	0.003
	rs6599222 (17)	0.001	0.24	0.001
	rs6763048 (11)	0.003	0.02	NA
	rs6795970 (12, 13)	0.001	0.02	0.004
	rs6800541 (12, 14, 16)	0.01	NA	0.007
	rs6798015 (17)	0.02	0.001	0.001
	rs6599257 (12)	0.04	0.01	0.01
rs7374004	rs7638909	0.02	NA	0.01
	rs11708996	0.18	NA	0.01
	rs6599222	0.15	NA	0.006
	rs6763048	0.006	NA	NA
	rs6795970	0.01	NA	0.01
	rs6800541	0.02	NA	0.006
	rs6798015	0.02	NA	0
	rs6599257	0.09	NA	0.01
rs45567533	rs7638909	0.02	NA	0.01
	rs11708996	0	NA	0.004
	rs6599222	0.01	NA	0.04
	rs6763048	0.01	NA	NA
	rs6795970	0.04	NA	0.004
	rs6800541	0.04	NA	0.01
	rs6798015	0.08	NA	0
	rs6599257	0.11	NA	0.004
rs6801957	rs7638909	0.12	0.01	0

	rs11708996	0.07	NA	0
	rs6599222	0.05	0.05	0.02
	rs6763048	0.05	0.02	NA
	rs6795970	0.93	0.07	0.64
	rs6800541	0.97	NA	0.65
	rs6798015	0.83	0.51	0.87
	rs6599257	0.67	0.14	0.54

Abbreviations: CEU, HapMap population of Utah residents with Northern and Western European ancestry; CHB, HapMap population of Han Chinese in Beijing, China; JPT, HapMap population of Japanese in Tokyo, Japan; NA, Not applicable; r^2, measure of linkage disequilibrium (0: not correlated, 1: SNPs inherited together, complete correlation); SNP, Single nucleotide polymorphism; YRI, HapMap population of Yoruba in Ibadan, Nigeria

Supplemental Table 4. Generalization of ten loci (15 index SNPs) associated with PR interval in European descent and African American populations, controlling for False Discovery Rate

SNP	Locus	CA/NCA	Previously Published Beta (SE)	Previously Published *P*-value	R-value*
African Americans (11)					
rs3891585	*MEIS1*	A/G	2.13 (0.31)	1.42E-11	3.71E-05
rs267567	*ITGA9*	A/G	2.73 (0.41)	4.14E-11	2.78E-03
rs3922844	*SCN5A*	T/C	-4.54 (0.33)	5.26E-43	2.99E-37
rs11732231	*ARHGAP24*	C/G	2.28 (0.39)	2.96E-09	3.37E-04
rs11773845	*CAV1-CAV2*	A/C	-2.29 (0.33)	4.45E-12	1.27E-06
rs1895585	*TBX5/TBX3*	A/G	3.19 (0.35)	1.36E-19	1.81E-04
European Descent (16)					
rs11897119	*MEIS1*	C/T	1.36 (0.21)	4.62E-11	5.15E-05
rs11708996	*SCN5A*	C/G	3.04 (0.29)	6.00E-26	1.50E-20
rs6800541	*SCN10A*	C/T	3.77 (0.21)	2.10E-74	2.31E-42
rs7692808	*ARHGAP24*	A/G	-2.01 (0.22)	5.99E-20	1.52E-09
rs251253	*NKX2-5*	C/T	-1.49 (0.21)	9.45E-13	5.50E-05
rs3807989	*CAV1-CAV2*	A/G	2.30 (0.21)	3.66E-28	7.48E-18
rs4944092	*WNT11*	G/A	-1.19 (0.29)	3.22E-08	3.49E-01
rs11047543	*SOX5*	A/G	-2.09 (0.29)	3.34E-13	3.34E-08
rs1896312	*TBX5/TBX3*	C/T	1.95 (0.23)	3.13E-17	1.03E-02

Abbreviations: CA, Coded Allele; NCA, Non-Coded Allele; SE, Standard Error; SNP, Single Nucleotide Polymorphism

* The approach described by Sofer and colleagues assigns an r-value to every index SNP. (19) The generalization null hypothesis testing generalization of the PR index SNPs to Hispanics/Latinos was rejected when the r-value was less than 0.05, controlling the false discovery rate of the generalization null hypothesis.

Supplemental Table 5. Bioinformatic characterization of seven index signals associated with PR interval in Hispanics/Latino Population

		Chromatin State[a]								
Locus	**Lead Hispanics/Latino SNP**	**Fetal Heart**	**Right Atrium**	**Left Ventricle**	**Right Ventricle**	**H3K4me1[b]**	**H3K4me3[c]**	**H3K27ac[d]**	**H3K9ac[e]**	**DNase**
ID2	rs6730558	PromP	EnhW2			FH, RA, LV, RV	FH	RA, RV	FH	Y
SLC8A1	rs17026148									N
SCN5A	rs3922844	EnhA2		EnhAc	EnhAc	FH, RA, LV, RV	FH	RA, LV, RV	FH	N
SCN10A	rs6801957	EnhA1	EnhAc	EnhW2	EnhAc	FH, RA, LV, RV	FH	RA, LV, RV	FH	Y
ARHGAP24	rs13105921	EnhW1	PromP		PromP	FH, RV	RA, RV	LV	FH	N
CAV1-CAV2	rs3807989	TxEnh5	EnhAF	TxEnh5	TxEnh5	FH, RA, LV, RV	FH	RA, LV, RV	FH	Y
SOX5	rs146974314									N

Abbreviations: FH, Fetal Heart; LV, Left Ventricle; N, No DNase Hypersensitivity; RA, Right Atrium; RV, Right Ventricle; SNP, Single Nucleotide Polymorphism; Y, DNase Hypersensitivity Present

[a]Chromatin states based on 25-state model. The following chromatin states were found for the investigated loci: PromP, Poised Promoter; EnhA2, Active Enhancer 2; EnhA1, Active Enhancer 1; TxEnh5, Transcribed 5' Preferential and Enhancer; EnhW2, Weak Enhancer 2; EnhAc, Primary H3K27ac Possible Enhancer; and EnhAF, Active Enhancer Flank.

[b]H3K4me1 is a mark of regulatory elements associated with enhancers and other distal elements but also enriched downstream of transcription starts. Evidence of epigenetic modification was examined in Fetal Heart tissue (FH), Right Atrium tissue (RA), Left Ventricle tissue (LV), and Right Ventricle tissue (RV).

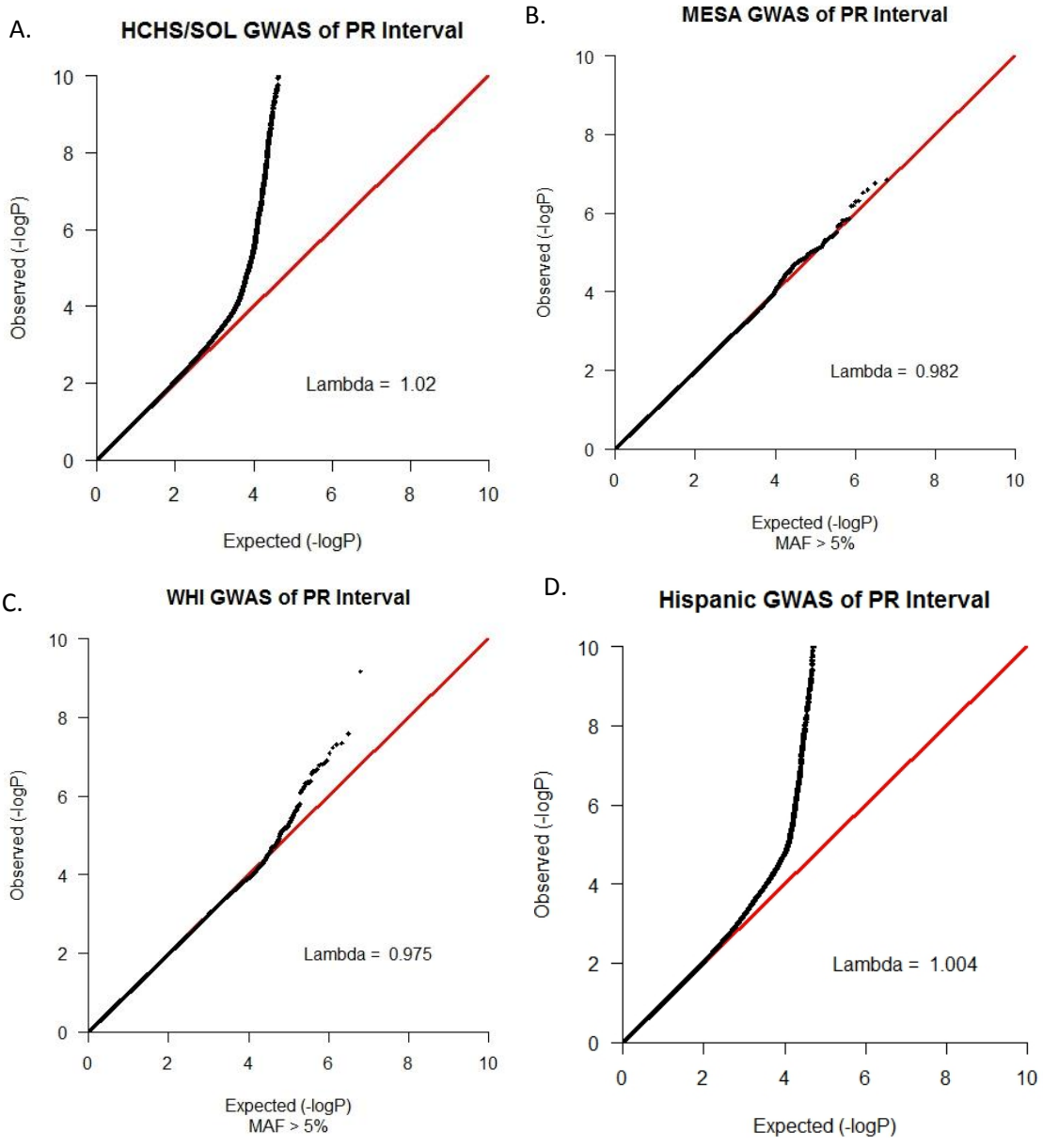
[c]H3K4me3 is a mark of regulatory elements primarily associated with promoters/transcription starts. Evidence of epigenetic modification was examined in Fetal Heart tissue (FH), Right Atrium tissue (RA), Left Ventricle tissue (LV), and Right Ventricle tissue (RV).

[d]H3K27ac is a mark of active regulatory elements and may distinguish active enhancers and promoters from inactive counterparts. Evidence of epigenetic modification was examined in Fetal Heart tissue (FH), Right Atrium tissue (RA), Left Ventricle tissue (LV), and Right Ventricle tissue (RV).

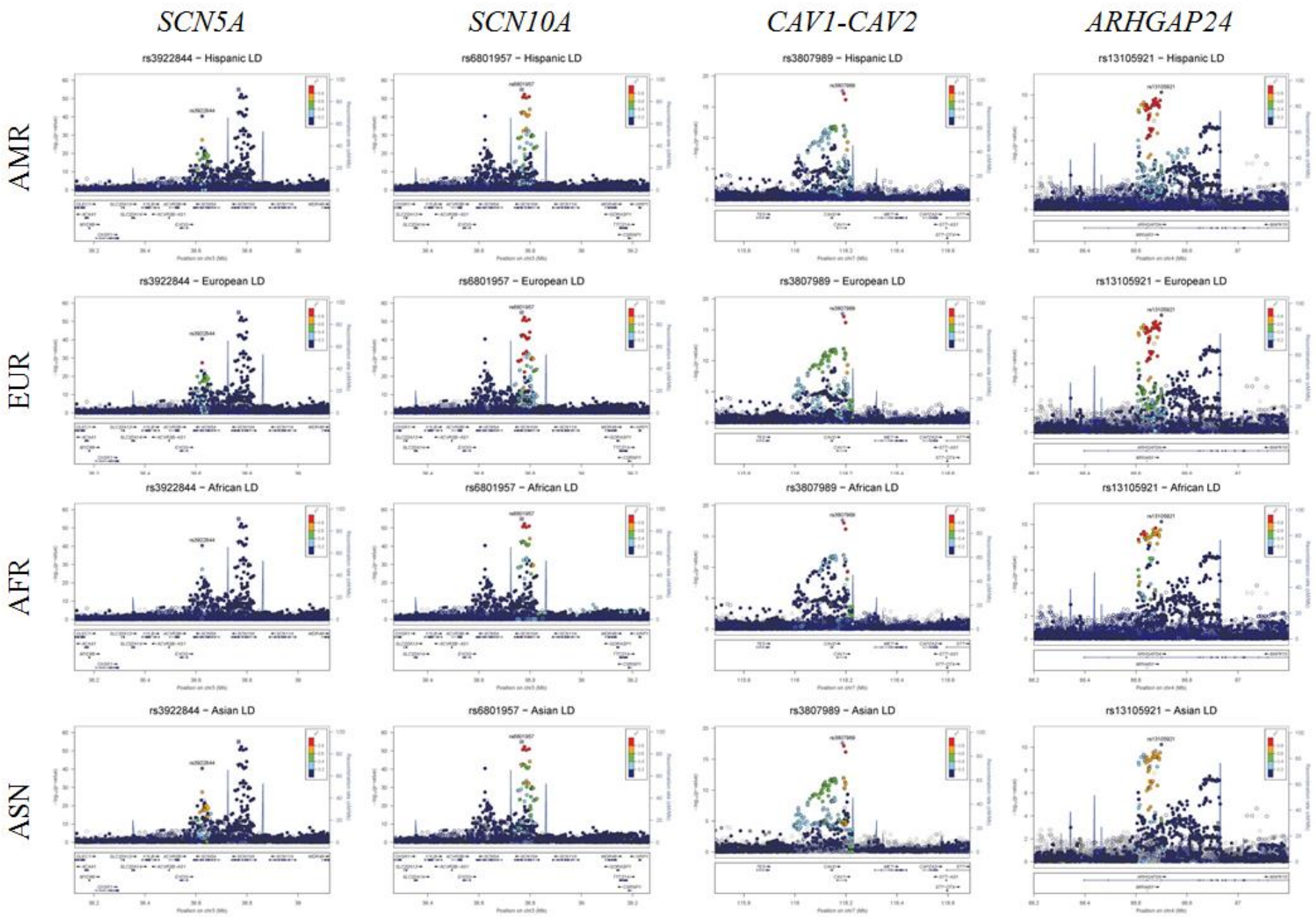
[e]H3K9ac is a mark of active regulatory elements with preference for promoters. Evidence of epigenetic modification was examined in Fetal Heart tissue (FH), Right Atrium tissue (RA), Left Ventricle tissue (LV), and Right Ventricle tissue (RV)

Supplementary Figures

Supplementary Figure 1. Study-specific (Panels A-C) and meta-analysis (Panel D) quantile-quantile plots of P-values for estimates of association between single nucleotide polymorphisms and PR interval. Hispanic Community Health Study/Study of Latinos (HCHS/SOL); Multiethnic Study of Atherosclerosis (MESA); Women's Health Initiative Clinical Trial (WHI CT)

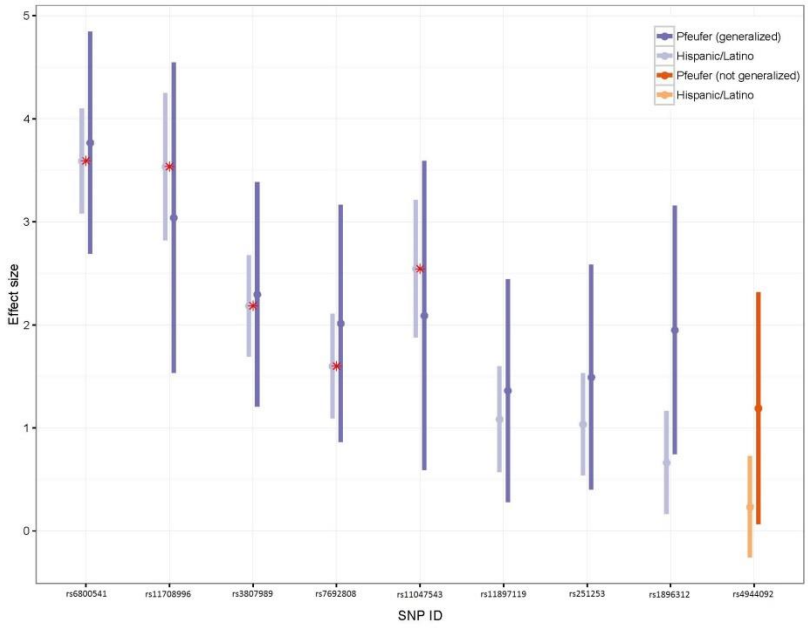


Supplemental Figure 2. LocusZoom plots of common (coded allele frequency > 0.05) single nucleotide polymorphisms at four regions (*SCN5A, SCN10A, CAV1-CAV2, ARHGAP24*) associated with PR interval in Hispanics/Latino populations. Results from the genome-wide association study meta-analysis in Hispanics/Latinos is plotted on linkage disequilibrium patterns calculated using 1000 Genomes meta-populations representing admixed American (AMR), European (EUR), African (AFR), and East Asian (ASN) populations

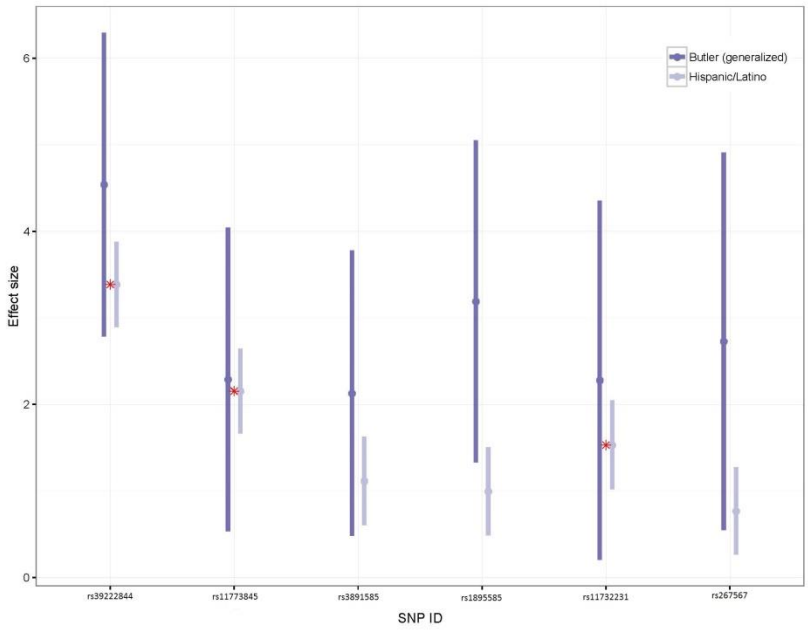

SCN5A
SCN10A
CAV1-CAV2
ARHGAP24
AMR
EUR
AFR
ASN
rs3922844 – Hispanic LD
rs6801957 – Hispanic LD
rs3807989 – Hispanic LD
rs13105921 – Hispanic LD
rs3922844 – European LD
rs6801957 – European LD
rs3807989 – European LD
rs13105921 – European LD
rs3922844 – African LD
rs6801957 – African LD
rs3807989 – African LD
rs13105921 – African LD
rs3922844 – Asian LD
rs6801957 – Asian LD
rs3807989 – Asian LD
rs13105921 – Asian LD

Supplemental Figure 3. Generalization of Ten Loci Associated with PR in European Descent or African American Populations to Hispanics/Latinos, Controlling for False Discovery Rate. Dark blue bars represent the confidence intervals for the beta estimates of the PR associated loci in European descent populations according to Pfeufer *et al.* (Panel A) (16) or Butler *et al.* (Panel B) (11) that generalized to Hispanics/Latinos (light blue bars). The red stars correspond to those lead SNPs in Hispanics/Latinos that reached genome-wide significance ($P < 5x10^{-8}$). Red bars represent the confidence interval for the beta estimates of those loci associated with European descent or African American populations (dark red) that did not generalize to Hispanics/Latinos (orange red).

A.


Pfeufer (generalized)
Hispanic/Latino
Pfeufer (not generalized)
Hispanic/Latino
Effect size
0
1
2
3
4
5
rs6800541
rs11708996
rs3807989
rs7692808
rs11047543
rs11897119
rs251253
rs1896312
rs4944092
SNP ID

B.


Butler (generalized)
Hispanic/Latino
Effect size
0
2
4
6
rs39222844
rs11773845
rs3891585
rs1895585
rs11732231
rs267567
SNP ID

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