

1 **Multi-ancestry GWAS of the electrocardiographic PR interval identifies 210 loci underlying**
2 **cardiac conduction**

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289

290 **Abstract**

291 The electrocardiographic PR interval reflects atrioventricular conduction, and is associated with
292 conduction abnormalities, pacemaker implantation, atrial fibrillation (AF), and cardiovascular
293 mortality^{1,2}. We performed multi-ancestry (N=293,051) and European only (N=271,570) genome-
294 wide association (GWAS) meta-analyses for the PR interval, discovering 210 loci of which 149
295 are novel. Variants at all loci nearly doubled the percentage of heritability explained, from 33.5%
296 to 62.6%. We observed enrichment for genes involved in cardiac muscle development/contraction
297 and the cytoskeleton highlighting key regulation processes for atrioventricular conduction.
298 Additionally, 19 novel loci harbour genes underlying inherited monogenic heart diseases
299 suggesting the role of these genes in cardiovascular pathology in the general population. We
300 showed that polygenic predisposition to PR interval duration is an endophenotype for
301 cardiovascular disease risk, including distal conduction disease, AF, atrioventricular pre-
302 excitation, non-ischemic cardiomyopathy, and coronary heart disease. These findings advance our
303 understanding of the polygenic basis of cardiac conduction, and the genetic relationship between
304 PR interval duration and cardiovascular disease.

305

306 **Main text**

307 The electrocardiogram is among the most common clinical tests ordered to assess cardiac
308 abnormalities. Reproducible waveforms indicating discrete electrophysiologic processes were
309 described over 100 years ago, yet the biological underpinnings of conduction and repolarization
310 remain incompletely defined. The electrocardiographic PR interval reflects conduction from the
311 atria to ventricles, across specialised conduction tissues such as the atrioventricular node and the
312 His-Purkinje system. Pathological variation in the PR interval may indicate heart block or pre-
313 excitation, both of which can lead to sudden death². The PR interval also serves as a risk factor for
314 AF and cardiovascular mortality¹⁻³. Prior genetic association studies have identified 64 PR interval
315 loci⁴⁻¹³. To enhance our understanding of the genetic and biological mechanisms of atrioventricular
316 conduction, we performed GWAS meta-analyses of autosomal and X chromosome variants
317 imputed mainly with the 1000 Genomes Project reference panel¹⁴ using an additive model and
318 increased sample size. Our primary meta-analysis included 293,051 individuals of European
319 (92.6%), African (2.7%), Hispanic (4%), and Brazilian (<1%) ancestries from 40 studies
320 (**Supplementary Tables 1-3**). We also performed ancestry-specific meta-analyses (**Fig. 1**).

321 We identified a total of 210 genome-wide significant loci ($P < 5 \times 10^{-8}$), of which 149 were not
322 previously reported (**Table 1, Fig. 2**). Of the 149 novel loci, 141 were discovered in the multi-
323 ancestry analysis, and 8 additional novel loci were identified in the European ancestry analysis
324 (**Table 1, Fig. 2, Supplementary Tables 4-5, Supplementary Fig. 1-4**). We considered only
325 variants present in >60% of the maximum sample size, a filtering criterion used to ensure
326 robustness of associated loci (**Online Methods**). There was strong support for all 64 previously
327 reported loci (61 at $P < 5 \times 10^{-8}$ and 3 at $P < 1.1 \times 10^{-4}$; **Supplementary Tables 6-7**). No additional
328 novel loci were identified in African or Hispanic/Latino ancestry meta-analyses (**Supplementary**

329 **Table 8, Supplementary Fig. 1 and 3**) or X chromosome meta-analyses (**Supplementary Fig.**
330 **5**). In secondary analyses, we examined the rank-based inverse normal transformed residuals of
331 PR interval. Results of absolute and transformed trait meta-analyses were highly correlated
332 ($\rho > 0.94$, **Supplementary Tables 5, 9-10, Supplementary Fig. 6-7**).

333 By applying joint and conditional analyses in the European meta-analysis data, we identified
334 multiple independently associated variants ($P_{\text{joint}} < 5 \times 10^{-8}$ and $r^2 < 0.1$) at 12 novel and 25 previously
335 reported loci (**Supplementary Table 11**). The overall variant-based heritability (h^2_g) for the PR
336 interval estimated in 59,097 unrelated European participants from the UK Biobank (UKB) with
337 electrocardiograms was 18.2% (**Online Methods**). In the UKB, the proportion of h^2_g explained by
338 variation at all loci discovered in our analysis was 62.6%, compared to 33.5% when considering
339 previously reported loci only.

340 The majority of the lead variants at the 149 novel loci were common (minor allele frequency,
341 $\text{MAF} > 5\%$). We observed 6 low-frequency ($\text{MAF} 1\text{-}5\%$) variants, and one rare ($\text{MAF} < 1\%$)
342 predicted damaging missense variant (rs35816944, p.Ser171Leu) in *SPSB3* encoding
343 SplA/Ryanodine Receptor Domain and SOCS Box-containing 3. *SPSB3* is involved in degradation
344 of SNAIL transcription factor, which regulates the epithelial-mesenchymal transition¹⁵, and has
345 not been previously associated with cardiovascular traits. In total, we identified missense variants
346 in genes at 12 novel and 6 previously reported loci (**Supplementary Table 12**). At *MYH6*, a
347 previously described locus for PR interval^{6,10}, sick sinus syndrome¹⁶, AF and other cardiovascular
348 traits¹⁷, we observed a novel predicted damaging missense variant in *MYH6* (rs28711516,
349 p.Gly56Arg). *MYH6* encodes the α -heavy chain subunit of cardiac myosin.

350 PR interval lead variants (or best proxy [$r^2 > 0.8$]) at 39 novel and 23 previously reported loci
351 were significant cis-eQTLs (at a 5% false discovery rate (FDR) in left ventricle (LV) and right
352 atrial appendage (RAA) tissue samples from the Genotype-Tissue Expression (GTEx) project¹⁸
353 (**Supplementary Table 13**). Variants at 21 novel loci were significant eQTLs in both tissues with
354 consistent directionality of gene expression. We also performed a transcriptome-wide analysis to
355 evaluate associations between predicted gene expression in LV and RAA with the PR interval. We
356 identified 120 genes meeting our significance threshold ($P < 4.4 \times 10^{-6}$, after Bonferroni correction);
357 26 genes were not localised at PR interval loci (≥ 500 kb from a lead variant) representing
358 potentially novel regions (**Supplementary Table 14, Supplementary Fig. 8**). Longer PR interval
359 duration was associated with decreased levels of predicted gene expression for 61 genes, and
360 increased levels for 59 genes (**Fig. 3**).

361 Most PR interval variants were annotated as non-coding. We therefore explored whether
362 associated variants or proxies were located in transcriptionally active genomic regions. We
363 observed enrichment for DNase I-hypersensitive sites in fetal heart tissue ($P < 9.36 \times 10^{-5}$,
364 **Supplementary Fig. 9**). Analysis of chromatin states indicated variants at 103 novel and 52
365 previously reported loci were located within regulatory elements that are present in heart tissues
366 (**Supplementary Table 15**), providing support for gene regulatory mechanisms in specifying the
367 PR interval. To identify distal candidate genes at PR interval loci, we assessed the same set of
368 variants for chromatin interactions in a LV tissue Hi-C dataset¹⁹. Forty-eight target genes were
369 identified (**Supplementary Table 16**). Variants at 38 novel loci were associated with other traits,
370 including AF and coronary heart disease (**Supplementary Table 17, Supplementary Fig. 10**).

371 Candidate genes indicated by bioinformatics and *in silico* functional annotations at each novel
372 locus are summarised in **Supplementary Tables 18-19**, and include 19 genes known to underlie

373 monogenic cardiovascular diseases. Enrichment analysis of genes at PR interval loci using
374 DEPICT²⁰ indicated heart development ($P=1.87\times 10^{-15}$) and actin cytoskeleton organisation
375 ($P=2.20\times 10^{-15}$) as the most significantly enriched processes (**Supplementary Table 20**). Ingenuity
376 Pathway Analysis (IPA) supported heart development, ion channel signaling and cell-
377 junction/cell-signaling amongst the most significant canonical pathways (**Supplementary Table**
378 **21**).

379 Finally, we evaluated associations between genetic predisposition to PR interval duration and
380 16 cardiac phenotypes chosen *a priori* using ~309,000 unrelated UKB European participants not
381 included in our meta-analyses²¹. We created a polygenic risk score (PRS) for PR interval using the
382 multi-ancestry meta-analysis results (**Fig. 4, Supplementary Table 22**). Genetically determined
383 PR interval prolongation was associated with higher risk of distal conduction disease
384 (atrioventricular block; odds ratio [OR] per standard deviation 1.11, $P=3.18\times 10^{-8}$) and pacemaker
385 implantation (OR 1.06, $P=0.0005$). In contrast, genetically determined PR interval prolongation
386 was associated with reduced risk of AF (OR 0.94, $P=1.30\times 10^{-11}$) and atrioventricular pre-
387 excitation (Wolff-Parkinson-White syndrome; OR 0.83, $P=8.36\times 10^{-4}$). Genetically determined PR
388 interval prolongation was marginally associated with a reduced risk of non-ischemic
389 cardiomyopathy (OR=0.95, $P=0.046$) and coronary heart disease (OR 0.99, $P=0.035$). Results were
390 similar when using a PRS derived using the European ancestry meta-analysis results
391 (**Supplementary Fig. 11, Supplementary Table 22**).

392 To summarise, in meta-analyses of nearly 300,000 individuals we identified 210 loci, of which
393 149 were novel, underlying cardiac conduction as manifested by the electrocardiographic PR
394 interval. Apart from confirming well-established associations in loci harbouring ion-channel
395 genes, our findings further underscore the central importance of heart development and

396 cytoskeletal components in atrioventricular conduction^{10,12,13}. We also highlight the role of
397 common variation at loci harboring genes underlying monogenic forms of heart disease in cardiac
398 conduction.

399 We report signals in/near 13 candidate genes at novel loci with functional roles in cytoskeletal
400 assembly (*DSP*, *DES*, *OBSL1*, *MYH11*, *PDLIM5*, *LDB3*, *FHL2*, *CEFIP*, *SSPN*, *TLN*, *PTK2*, *GJA5*
401 and *CDH2*; **Fig. 5**). *DSP* and *DES* encode components of the cardiac desmosome, a complex
402 involved in ionic communication between cardiomyocytes and maintenance of cellular integrity.
403 Mutations in the desmosome are implicated in arrhythmogenic cardiomyopathy (ACM) and dilated
404 cardiomyopathy (DCM)²²⁻²⁶. Conduction slowing is a major component of the pathophysiology of
405 arrhythmia in ACM and other cardiomyopathies^{27,28}. *OBSL1* encodes obscurin-like 1, which
406 together with obscurin (OBSCN) is involved in sarcomerogenesis by bridging titin (TTN) and
407 myomesin at the M-band²⁹. *PDLIM5* encodes a scaffold protein that tethers protein kinases to the
408 Z-disk, and has been associated with DCM in homozygous murine cardiac knockouts³⁰. *FHL2*
409 encodes calcineurin-binding protein four and a half LIM domains 2, which is involved in cardiac
410 development by negatively regulating calcineurin/NFAT signaling in cardiomyocytes³¹. Missense
411 mutations in *FHL2* have been associated with hypertrophic cardiomyopathy³². *CEFIP* encodes the
412 cardiac-enriched FHL2-interacting protein located at the Z-disc, which interacts with *FHL2*. It is
413 also involved in calcineurin–NFAT signaling, but its overexpression leads to cardiomyocyte
414 hypertrophy³³.

415 Common variants in/near genes associated with inherited arrhythmia syndromes were also
416 observed, suggesting these genes also affect atrioventricular conduction and cardiovascular
417 pathology in the general population. Apart from *DSP*, *DES*, *MYH11* and *GJA5* listed above, our
418 analyses indicate 15 additional candidate genes (*ADRB1*, *ALPK3*, *BMPRI1*, *BMPRI2*, *CRYAB*,

419 *DERL3, DNAH11, DTNA, ETV1, HCN4, MYOZ2, PDE3A, RYR2, SPEG, LDB3*) at novel loci
420 causing Mendelian or other inherited forms of cardiovascular disease. Two genes we highlight are
421 *HCN4* and *RYR2*. *HCN4* encodes a component of the hyperpolarization-activated cyclic
422 nucleotide-gated potassium channel which specifies the sinoatrial pacemaker “funny” current, and
423 is implicated in sinus node dysfunction, AF, and left ventricular noncompaction³⁴⁻³⁶. *RYR2* encodes
424 a calcium channel component in the cardiac sarcoplasmic reticulum and is implicated in
425 catecholaminergic polymorphic ventricular tachycardia³⁷.

426 Genes with roles in autonomic signaling in the heart (*CHRM2, ADCY5*) were indicated from
427 expression analyses. *CHRM2* encodes the M2 muscarinic cholinergic receptors that bind
428 acetylcholine and are expressed in the heart³⁸. Their stimulation results in inhibition of adenylate
429 cyclase encoded by *ADCY5*, which in turn inhibits ion channel function. Ultimately, the signaling
430 cascade can result in reduced levels of the pacemaker “funny” current in the sinoatrial and
431 atrioventricular nodes, reduced L-type calcium current in all myocyte populations, and increased
432 inwardly rectifying $I_{K,Ach}$ potassium current in the conduction tissues and atria causing
433 cardiomyocyte hyperpolarization³⁹. Stimulation has also been reported to shorten atrial action
434 potential duration and thereby facilitate re-entry, which may lead to AF⁴⁰⁻⁴².

435 By constructing PRSs, we also observed that genetically determined PR interval duration is an
436 endophenotype for several adult-onset complex cardiovascular diseases, the most significant of
437 which are arrhythmias and conduction disorders. For example, our findings are consistent with
438 previous epidemiologic data supporting a U-shaped relationship between PR interval duration and
439 AF risk¹. Although aggregate genetic predisposition to PR interval prolongation is associated with
440 reduced AF risk, top PR interval prolonging alleles are associated with decreased AF risk (e.g.,
441 localized to the *SCN5A/SCN10A* locus) whereas others are associated with increased AF risk (e.g.,

442 localized to the *TTN* locus), consistent with prior reports⁸. These findings suggest that genetic
443 determinants of the PR interval may identify distinct pathophysiologic mechanisms leading to AF,
444 perhaps via specifying differences in tissue excitability, conduction velocity, or refractoriness.
445 Future efforts are warranted to better understand the relations between genetically determined PR
446 interval and specific arrhythmia mechanisms.

447 In conclusion, our study more than triples the reported number of PR interval loci, which
448 collectively explain ~62% of trait-related heritability. Our findings highlight important biological
449 processes underlying atrioventricular conduction which include both ion channel function, and
450 specification of cytoskeletal components. Our study also indicates that common variation in
451 Mendelian cardiovascular disease genes contributes to population-based variation in the PR
452 interval. Lastly, we observed that genetic determinants of the PR interval provide novel insights
453 into the etiology of several complex cardiac diseases, including AF. Collectively, our results
454 represent a major advance in understanding the polygenic nature of cardiac conduction, and the
455 genetic relationship between PR interval duration and arrhythmias.

456

457 **Online Methods**

458 **Contributing studies**

459 A total of 40 studies (**Supplementary Note**) comprising 293,051 individuals of European
460 (N=271,570), African (N=8,173), Hispanic (N=11,686), and Brazilian (N=485) ancestries
461 contributed GWAS summary statistics for PR interval. All participating institutions and co-
462 ordinating centres approved this project, and informed consent was obtained from all study
463 participants. Study-specific design, sample quality control and descriptive statistics are provided
464 in **Supplementary Tables 1-3**. For the majority of the studies imputation was performed for
465 autosomal chromosomes and X chromosome using the 1000 Genomes (1000G) project¹⁴ reference
466 panel or a most recently released haplotype version (**Supplementary Table 2**).

467

468 **PR interval phenotype and exclusions**

469 The PR interval was measured in milliseconds from standard 12-lead electrocardiograms (ECGs),
470 except in the UK-Biobank in which it was obtained from 4-lead ECGs (CAM-USB 6.5, Cardiosoft
471 v6.51) recorded during a 15 second rest period prior to an exercise test (**Supplementary Note**).
472 We excluded individuals with extreme PR interval values (<80ms or >320ms), second/third degree
473 heart block, AF on the ECG, or a history of myocardial infarction or heart failure, Wolff-
474 Parkinson-White syndrome, pacemakers, receiving class I and class III antiarrhythmic
475 medications, digoxin, and pregnancy.

476

477 ***Study-level association analyses***

478 We regressed the absolute PR interval on each genotype dosage using multiple linear regression
479 with an additive genetic effect and adjusted for age, sex, height, body mass index, heart rate and
480 any other study specific covariates. To account for relatedness, linear mixed effects models were
481 used for family studies. To account for population structure, analyses were also adjusted for
482 principal components of ancestry derived from genotyped variants after excluding related
483 individuals. Analyses of autosomal variants were conducted separately for each ancestry group. X
484 chromosome analyses were performed separately for males and females. Analyses using rank-
485 based inverse normal transformed residuals of PR interval corrected for the aforementioned
486 covariates were also conducted. Residuals were calculated separately by ancestral group for
487 autosomal variants, and separately for males and females for X chromosome variants.

488

489 ***Centralized quality control***

490 We performed quality control centrally for each result file using EasyQC version 11.4⁴³. We
491 removed variants that were monomorphic, had a minor allele count (MAC) <6, imputation quality
492 metric <0.3 (imputed by MACH) or 0.4 (imputed by IMPUTE2), had invalid or mismatched
493 alleles, were duplicated, or if they were allele frequency outliers (difference >0.2 from the allele
494 frequency in 1000G project). We inspected PZ plots, effect allele frequency plots, effect size
495 distributions, QQ plots, and compared effect sizes in each study to effect sizes from prior reports
496 for established PR interval loci to identify genotype and study level anomalies. Variants with
497 effective MAC ($=2 \times N \times \text{MAF} \times \text{imputation quality metric}$) <10 were omitted from each study prior
498 to meta-analysis.

499

500 *Meta-analyses*

501 We aggregated summary level associations between genotypes and absolute PR interval from all
502 individuals (N=293,051), and only from Europeans (N=271,570), African Americans (N=8,173),
503 and Hispanic/Latinos (N=12,823) using a fixed-effects meta-analysis approach implemented in
504 METAL (release on 2011/03/25)⁴⁴. For the X chromosome, meta-analyses were conducted in a
505 sex-stratified fashion. Genomic control was applied (if inflation factor $\lambda_{GC}>1$) at the study level.
506 Quantile–quantile (QQ) plots of observed versus expected $-\log_{10}(P)$ did not show substantive
507 inflation (**Supplementary Figs. 1-2**).

508 Given the large sample size we undertook a one-stage discovery study design. To ensure the
509 robustness of this approach we considered for further investigation only variants reaching genome-
510 wide significance ($P<5\times 10^{-8}$) present in at least 60% of the maximum sample size (N_{max}). We
511 declared as novel any variants mapping outside the 64 loci previously reported (**Supplementary**
512 **Note, Supplementary Table 6**). We grouped genome-wide significant variants into independent
513 loci based on both distance ($\pm 500\text{kb}$) and linkage disequilibrium (LD, $r^2<0.1$) (**Supplementary**
514 **Note**). We assessed heterogeneity in allelic effect sizes among studies contributing to the meta-
515 analysis and among ancestral groups by the I^2 inconsistency index⁴⁵ for the lead variant in each
516 novel locus. LocusZoom⁴⁶ was used to create region plots of identified loci.

517 Meta-analyses (multi-ancestry [N=282,128], European only [N=271,570], and African
518 [N=8,173]) of rank-based inverse normal transformed residuals of PR interval were also
519 performed. Because not all studies contributed summary level association statistics of the
520 transformed PR interval, we considered as primary the meta-analysis of absolute PR interval for

521 which we achieved the maximum sample size. Any loci that met our significance criteria in the
522 meta-analyses of transformed PR interval were not taken forward for downstream analyses.

523

524 *Conditional and heritability analysis*

525 Conditional and joint GWAS analyses were implemented in GCTA v1.91.3⁴⁷ using summary level
526 variant statistics from the European ancestry meta-analysis to identify independent association
527 signals within PR interval loci. We used 59,097 unrelated (kinship coefficient >0.0884) UK
528 Biobank participants of European ancestry as the reference sample to model patterns of LD
529 between variants. We declared as conditionally independent any genome-wide significant variants
530 in conditional analysis ($P_{\text{joint}} < 5 \times 10^{-8}$) not in LD ($r^2 < 0.1$) with the lead variant in the locus.

531 Using the same set of individuals from UK Biobank, we estimated the aggregate genetic
532 contributions to PR interval with restricted maximum likelihood as implemented in BOLT-
533 REML⁴⁸. We calculated the additive overall variant-heritability (h^2_g) based on 333,167 LD-pruned
534 genotyped variants, as well as the h^2_g of variants at PR interval associated loci only. Loci windows
535 were based on both distance ($\pm 500\text{kb}$) and LD ($r^2 > 0.1$) around novel and previously reported
536 variants (**Supplementary Note**). We then calculated the proportion of total h^2_g explained at PR
537 interval loci by dividing the h^2_g estimate of PR interval loci by the total h^2_g .

538

539 ***Bioinformatics and in silico functional analyses***

540 We use Variant Effect Predictor (VEP)⁴⁹ to obtain functional characterization of variants including
541 consequence, information on nearest genes and, where applicable, amino acid substitution and
542 functional impact, based on SIFT⁵⁰ and PolyPhen-2⁵¹ prediction tools. For non-coding variants,
543 we assessed overlap with DNase I-hypersensitive sites (DHS) and chromatin states as determined
544 by Roadmap Epigenomics Project⁵² across all tissues and in cardiac tissues (E083, fetal heart;
545 E095, LV; E104, right atrium; E105, right ventricle) using HaploReg v4⁵³.

546 We assessed whether any PR interval variants were related to cardiac gene expression using
547 GTEx¹⁸ version 7 cis-eQTL LV (N=272) and RAA (N=264) data. If the variant at a locus was not
548 available in GTEx, we used proxy variants ($r^2 > 0.8$). We report results only for associations at a
549 false discovery rate (FDR) of 5%. We then evaluated the effects of predicted gene expression
550 levels on PR interval duration using S-PrediXcan⁵⁴. GTEx¹⁸ genotypes (variants with MAF > 0.01)
551 and normalized expression data in LV and RAA provided by the software developers were used
552 as the training datasets for the prediction models. The prediction models between each gene-tissue
553 pair were performed by Elastic-Net, and only significant (FDR 5%) models for prediction were
554 included in our analysis. We used the European meta-analysis summary-level results (variants with
555 at least 60% of maximum sample size) as the study dataset and then performed the S-PrediXcan
556 calculator to estimate the expression-PR interval associations. In total, we tested 5,366 and 5,977
557 associations in LV and RAA, respectively. Significance threshold was set at $P = 4.4 \times 10^{-6}$
558 ($= 0.05 / (5,977 + 5,366)$) to account for multiple testing corrections.

559 We applied GARFIELD (GWAS analysis of regulatory or functional information enrichment
560 with LD correction)⁵⁵ to analyse the enrichment patterns for functional annotations of the European

561 meta-analysis summary statistics, using regulatory maps from the Encyclopedia of DNA Elements
562 (ENCODE)⁵⁶ and Roadmap Epigenomics⁵² projects. This method calculates odds ratios and
563 enrichment P-values at different GWAS P-value thresholds (denoted T) for each annotation by
564 using a logistic regression model accounting for LD, matched genotyping variants and local gene
565 density with the application of logistic regression to derive statistical significance. Threshold for
566 significant enrichment was set to $P=9.36 \times 10^{-5}$ (after multiple-testing correction for the number of
567 effective annotations).

568 We identified potential target genes of regulatory variants using long-range chromatin
569 interaction (Hi-C) data from the LV¹⁹. Hi-C data was corrected for genomic biases and distance
570 using the Hi-C Pro and Fit-Hi-C pipelines according to Schmitt *et al.* (40kb resolution – correction
571 applied to interactions with 50kb-5Mb span). We identified the promoter interactions for all
572 potential regulatory variants in LD ($r^2 > 0.8$) with our lead and conditionally independent PR
573 interval variants and report the interactors with the variants with the highest regulatory potential
574 (RegulomeDB ≥ 2) to annotate the loci.

575 We performed a literature review, and queried the Online Mendelian Inheritance in Man
576 (OMIM) and the International Mouse Phenotyping Consortium databases for all genes in regions
577 defined by $r^2 > 0.5$ from the lead variant at each novel locus. We further expanded the gene listing
578 with any genes that were indicated by gene expression or chromatin interaction analyses. We
579 performed look-ups for each lead variant or their proxies ($r^2 > 0.8$) for associations ($P < 5 \times 10^{-8}$) for
580 common traits using both GWAS catalog⁵⁷ and PhenoScanner v2⁵⁸ databases. For AF, we
581 supplemented the variant listing with a manually curated list of all overlapping variants ($r^2 > 0.7$)
582 with PR interval from two recently published GWASs^{59,60}.

583

584 *Gene set enrichment and pathway analyses*

585 We used DEPICT (Data-driven Expression-Prioritized Integration for Complex Traits)²⁰ to
586 identify enriched pathways and tissues/cell types where genes from associated loci are highly
587 expressed using all genome-wide significant ($P < 5 \times 10^{-8}$) variants in our multi-ancestry meta-
588 analysis present in at least 60% of N_{\max} ($N=20,076$). To identify uncorrelated variants for PR
589 interval, DEPICT performed LD-clumping ($r^2=0.1$, window size=250kb) using LD estimates
590 between variants from the 1000G reference data on individuals from all ancestries after excluding
591 the major histocompatibility complex region on chromosome 6. Gene-set enrichment analysis was
592 conducted based on 14,461 predefined reconstituted gene sets from various databases and data
593 types, including Gene ontology, Kyoto encyclopedia of genes and genomes (KEGG),
594 REACTOME, phenotypic gene sets derived from the Mouse genetics initiative, and protein
595 molecular pathways derived from protein-protein interaction. Finally, tissue and cell type
596 enrichment analysis was performed based on expression information in any of the 209 Medical
597 Subject Heading (MeSH) annotations for the 37,427 human Affymetrix HGU133a2.0 platform
598 microarray probes.

599 Ingenuity Pathway Analysis (IPA) was conducted using an extended list comprising 593 genes
600 located in regions defined by $r^2 > 0.5$ with the lead or conditionally independent variants for all PR
601 interval loci, or the nearest gene. We further expanded this list by adding genes indicated by gene
602 expression analyses. Only molecules and/or relationships for human or mouse or rat and
603 experimentally verified results were considered. The significance P-value associated with
604 enrichment of functional processes is calculated using the right-tailed Fisher's exact test by

605 considering the number of query molecules that participate in that function and the total number
606 of molecules that are known to be associated with that function in the IPA.

607

608 *Associations between genetically determined PR interval and cardiovascular conditions*

609 We examined associations between genetic determinants of atrioventricular conduction and
610 candidate cardiovascular diseases in unrelated individuals of European ancestry from UK Biobank
611 (N~309,000 not included in our GWAS meta-analyses) by creating PRSs for PR interval based on
612 our GWAS results. We derived two PRSs. One was derived from the multi-ancestry meta-analysis
613 results, and the other from the European meta-analysis results. We used the LD-clumping feature
614 in PLINK v1.90⁶¹ ($r^2=0.1$, window size=250kb, $P=5\times 10^{-8}$) to select variants for each PRS. Referent
615 LD structure was based on 1000G all ancestry, and European only data. In total, we selected 743
616 and 582 variants from multi-ancestry and European only meta-analysis results, respectively. We
617 calculated the PRSs for PR interval by summing the dosage of PR interval prolonging alleles
618 weighted by the corresponding effect size from the meta-analysis results. A total of 743 variants
619 for the PRS derived from multi-ancestry results and 581 variants for the PRS derived from
620 European results (among the variants with imputation quality >0.6) were included in our PRS
621 calculations.

622 We selected candidate cardiovascular conditions *a priori*, which included various cardiac
623 conduction and structural traits such as bradyarrhythmia, AF, atrioventricular pre-excitation, heart
624 failure, cardiomyopathy, and congenital heart disease. We ascertained disease status based on data
625 from baseline interviews, hospital diagnosis codes (ICD-9 and ICD-10), cause of death codes

626 (ICD-10), and operation codes. Details of individual selections and disease definitions are
627 described in **Supplementary Table 23**.

628 We tested the PRSs for association with cardiovascular conditions using logistic regression.
629 We adjusted for enrolled age, sex, genotyping array, and phenotype-related principal components
630 of ancestry. Given correlation between traits, we did not establish a pre-specified significance
631 threshold for the analysis and report nominal associations ($P < 0.05$).

632

633 **Tables**

634 **Table 1** Novel genome-wide significant loci associated with PR interval (N = 149).

Locus ID	Nearest gene(s)	rsID	Chr	Position	EA/OA	EAF	N	Beta	SE	P
Multi-ancestry meta-analysis										
1	<i>HSPG2</i>	rs7529220	1	22282619	C/T	0.84	293050	0.58	0.09	2.1×10^{-10}
2	<i>AIM1L</i>	rs12031946	1	26679041	C/T	0.13	293051	0.59	0.10	2.4×10^{-9}
3	<i>MAP7D1</i>	rs1475267	1	36620801	G/C	0.16	293050	0.50	0.09	2.1×10^{-8}
4	<i>EDN2</i>	rs12751675	1	41955714	G/A	0.75	293050	0.56	0.08	1.8×10^{-13}
5	<i>SSBP3</i>	rs603901	1	54741767	T/C	0.58	293051	0.43	0.06	3.3×10^{-11}
6	<i>NFIA</i>	rs6587924	1	61895257	A/C	0.49	293051	0.35	0.06	2.7×10^{-8}
7	<i>CDC7</i>	rs13447455	1	91966445	A/G	0.64	293051	0.38	0.07	1.7×10^{-8}
8	<i>GJA5</i>	rs1692144	1	147281349	C/T	0.79	293051	0.65	0.08	1.7×10^{-16}
9	<i>DPT</i>	rs531706	1	168692137	C/G	0.28	293051	0.39	0.07	3.4×10^{-8}
10	<i>PRRX1</i>	rs61824886	1	170615660	C/G	0.85	293051	0.67	0.09	6.2×10^{-13}
11	<i>C1orf98</i>	rs819636	1	200271408	C/T	0.33	293051	0.38	0.07	1.7×10^{-8}
12	<i>HLX</i>	rs6678632	1	221138612	T/C	0.44	293051	0.47	0.06	4.9×10^{-13}
13	<i>ADCK3</i>	rs3768419	1	227173477	C/G	0.48	291546	0.49	0.06	1.6×10^{-14}
14	<i>SIPA1L2</i>	rs1285678	1	232712145	A/G	0.47	287628	0.52	0.07	2.6×10^{-15}
15	<i>RYR2</i>	rs10802580	1	237194922	G/A	0.76	286413	0.45	0.08	6.9×10^{-9}
16	<i>SMYD3</i>	rs28468565	1	246157144	A/G	0.66	287628	0.49	0.07	8.9×10^{-13}
17	<i>LINC01249</i>	rs12616546	2	4824622	A/G	0.68	293051	0.53	0.07	9.2×10^{-15}
18	<i>STRN</i>	rs17496249	2	37102249	A/G	0.55	293051	0.64	0.06	1.4×10^{-23}
19	<i>EML4</i>	rs6728830	2	42537995	C/A	0.96	291132	1.02	0.18	1.9×10^{-8}
20	<i>EPAS1</i>	rs11894252	2	46533376	T/C	0.42	293047	0.45	0.06	2.3×10^{-12}
21	<i>FBXO11</i>	rs7588761	2	48150587	T/C	0.07	288153	0.75	0.13	5.3×10^{-9}
22	<i>SPTBN1</i>	rs4519566	2	54824815	G/A	0.79	293051	0.54	0.08	4.7×10^{-12}
23	<i>LINC01812/C1D</i>	rs7584373	2	68079211	A/G	0.35	293051	0.38	0.07	1.5×10^{-8}
24	<i>FHL2/LOC285000</i>	rs13006682	2	106104856	C/T	0.34	293051	0.51	0.07	6.7×10^{-14}
25	<i>NCKAP5</i>	rs17816356	2	134326085	A/C	0.05	289723	0.96	0.16	7.9×10^{-10}
26	<i>TEX41</i>	rs76909456	2	145453968	G/A	0.24	293051	0.48	0.08	1.8×10^{-10}
27	<i>LINC01473/ZC3H15</i>	rs138711926	2	187033804	G/A	0.04	280792	0.98	0.18	4.7×10^{-8}
28	<i>SDPR</i>	rs58577564	2	192723128	A/T	0.10	291546	0.78	0.11	7.5×10^{-13}

Locus ID	Nearest gene(s)	rsID	Chr	Position	EA/OA	EAF	N	Beta	SE	P
Multi-ancestry meta-analysis										
31	<i>TMEM198</i>	rs13023533*	2	220414019	T/C	0.55	293051	0.41	0.06	1.1×10^{-10}
32	<i>LSM3</i>	rs6442433	3	14275759	C/G	0.79	291836	0.71	0.08	1.9×10^{-19}
33	<i>THRB</i>	rs60325252	3	24465080	C/T	0.71	293051	0.75	0.07	9.1×10^{-27}
34	<i>TRAK1</i>	rs11921457	3	42103045	T/G	0.81	292301	0.69	0.09	8.0×10^{-16}
35	<i>LAMB2</i>	rs9865051*	3	49166069	T/C	0.78	293051	0.49	0.08	3.7×10^{-10}
36	<i>ADCY5</i>	rs1000368	3	123117165	T/C	0.26	293051	0.43	0.07	2.5×10^{-9}
37	<i>TSC22D2</i>	rs201481721	3	150176904	D/I	0.03	223845	1.32	0.22	1.8×10^{-9}
38	<i>RAP2B</i>	rs4680046	3	153000092	T/C	0.49	293051	0.47	0.06	1.2×10^{-13}
40	<i>FNDC3B</i>	rs4894803	3	171800256	G/A	0.39	293046	0.49	0.07	1.8×10^{-13}
41	<i>FGF12</i>	rs4687352	3	192373761	A/C	0.41	293051	0.53	0.06	1.3×10^{-16}
42	<i>DLG1</i>	rs143879787	3	196799232	I/D	0.73	226107	0.51	0.08	1.4×10^{-9}
43	<i>SRD5A3</i>	rs77422711	4	56123105	A/G	0.02	273824	1.85	0.30	6.4×10^{-10}
44	<i>LPHN3</i>	rs28540500	4	62409801	C/G	0.38	293051	0.42	0.07	2.4×10^{-10}
45	<i>FGF5</i>	rs36034102	4	81202048	T/G	0.27	292217	0.43	0.07	3.5×10^{-9}
46	<i>PDLIM5</i>	rs2172448	4	95506214	A/G	0.55	288153	0.37	0.06	9.4×10^{-9}
48	<i>SLC12A7</i>	rs4975572	5	1054197	T/C	0.46	293051	0.62	0.07	5.5×10^{-21}
49	<i>SUB1</i>	rs17441816	5	32629419	G/A	0.29	293051	0.51	0.07	4.7×10^{-13}
50	<i>HCN1</i>	rs10039283	5	45864843	A/G	0.41	293051	0.64	0.06	3.2×10^{-23}
51	<i>NR2F1</i>	rs4869412	5	92455655	G/A	0.49	293051	0.40	0.06	2.3×10^{-10}
53	<i>STARD4</i>	rs67968533	5	111046342	C/T	0.09	293051	0.66	0.11	4.8×10^{-9}
54	<i>LOC101927421/ ZNF608</i>	rs12654442	5	124343851	T/C	0.27	293051	0.46	0.07	2.8×10^{-10}
55	<i>SLC27A6</i>	rs2577531	5	128299279	C/T	0.59	293051	0.38	0.06	3.8×10^{-9}
56	<i>FGF18</i>	rs78810186	5	170868622	T/C	0.11	290821	0.74	0.10	1.4×10^{-12}
57	<i>LINC01411</i>	rs4868384	5	173779209	T/A	0.47	290336	0.47	0.06	2.5×10^{-13}
58	<i>DSP</i>	rs72825038	6	7527269	A/G	0.09	293051	0.94	0.11	2.7×10^{-16}
59	<i>DEK</i>	rs214502	6	18227546	A/C	0.58	291546	0.42	0.07	9.9×10^{-11}
60	<i>HDGFL1</i>	rs6922960	6	22570189	C/T	0.28	291546	0.61	0.07	5.6×10^{-18}
61	<i>LRRC16A</i>	rs139915396	6	25351477	I/D	0.10	226107	0.69	0.13	4.2×10^{-8}
62	<i>CDKN1A</i>	rs730506	6	36645968	C/G	0.20	293051	0.62	0.08	6.5×10^{-15}
63	<i>TFEB</i>	rs1015149	6	41658889	T/C	0.47	293051	0.45	0.06	1.6×10^{-12}
64	<i>RCAN2</i>	rs871728	6	46452619	C/T	0.42	293051	0.52	0.07	1.3×10^{-15}

Locus ID	Nearest gene(s)	rsID	Chr	Position	EA/OA	EAF	N	Beta	SE	P
Multi-ancestry meta-analysis										
65	<i>LOC101927686</i>	rs111739590	6	113978255	C/T	0.81	293051	0.50	0.08	1.5×10^{-9}
66	<i>TCF21</i>	rs12190287	6	134214525	G/C	0.37	290979	0.43	0.07	2.9×10^{-10}
67	<i>RP1-155D22.1</i>	rs206708	6	164532059	A/T	0.70	293051	0.47	0.07	1.9×10^{-11}
68	<i>GET4</i>	rs10226357	7	925949	G/A	0.59	293050	0.39	0.07	3.1×10^{-9}
69	<i>DGKB</i>	rs56352403	7	14453835	G/A	0.64	291623	0.56	0.07	1.4×10^{-16}
70	<i>PRPS1L1</i>	rs6961768	7	18040476	A/C	0.43	293051	0.38	0.06	3.0×10^{-9}
71	<i>DNAH11</i>	rs62441680*	7	21622494	C/T	0.17	293051	0.62	0.08	2.3×10^{-13}
72	<i>ELMO1</i>	rs4720244	7	37398113	C/G	0.64	293051	0.42	0.07	3.6×10^{-10}
73	<i>SEMA3A</i>	rs62472627	7	83998676	C/T	0.14	293051	0.61	0.09	6.7×10^{-11}
74	<i>CHRM2</i>	rs1424569	7	136569416	C/T	0.53	293051	0.36	0.07	4.6×10^{-8}
75	<i>DLC1</i>	rs1188285	8	13130478	C/T	0.56	293050	0.45	0.06	2.4×10^{-12}
76	<i>MTUS1</i>	rs4921804	8	17550623	G/A	0.63	289672	0.39	0.07	4.4×10^{-9}
77	<i>XPO7</i>	rs56317071	8	21775838	C/G	0.12	293050	0.57	0.10	1.2×10^{-8}
78	<i>RBPM5</i>	rs4545054	8	30302465	C/T	0.49	293050	0.36	0.06	2.0×10^{-8}
80	<i>RP11-1082L8.3</i>	rs35006907	8	125859817	A/C	0.31	293050	0.48	0.07	1.6×10^{-12}
81	<i>PTK2</i>	rs10106406	8	142006198	C/G	0.45	282729	0.40	0.07	1.4×10^{-9}
82	<i>TRPM3</i>	rs6560168	9	73482647	T/A	0.45	292407	0.45	0.06	2.2×10^{-12}
83	<i>SPATA31D5P/ RASEF</i>	rs7043482	9	85135915	A/C	0.65	293050	0.42	0.07	8.3×10^{-10}
84	<i>ASTN2</i>	rs1407243	9	119314851	C/T	0.60	293051	0.37	0.06	9.1×10^{-9}
85	<i>PLPP7</i>	rs4584185	9	134203545	C/T	0.45	278484	0.48	0.07	6.1×10^{-13}
86	<i>BEND7</i>	rs7916672	10	13534234	T/C	0.58	293051	0.35	0.06	3.8×10^{-8}
87	<i>CCDC7</i>	rs2947080	10	32847962	G/C	0.64	293051	0.41	0.07	4.6×10^{-10}
88	<i>CEFIP</i>	rs10776558*	10	50510406	C/T	0.53	293050	0.42	0.06	2.8×10^{-11}
89	<i>TMEM26</i>	rs74813029	10	63194576	A/G	0.17	293051	0.54	0.09	3.3×10^{-10}
90	<i>COL13A1</i>	rs2642608	10	71559723	T/C	0.27	293051	0.42	0.07	3.8×10^{-9}
91	<i>ZMIZ1</i>	rs1769758	10	80898969	T/G	0.50	267464	0.50	0.07	1.0×10^{-11}
92	<i>U3</i>	rs117443987	10	88509088	T/A	0.92	288153	1.00	0.12	6.1×10^{-17}
93	<i>ADRB1</i>	rs67234920	10	115782061	G/A	0.89	293051	0.67	0.11	2.3×10^{-10}
94	<i>FGFR2</i>	rs2912774	10	123348662	T/G	0.42	288153	0.48	0.07	1.3×10^{-13}
95	<i>MPPED2</i>	rs553951	11	30432176	C/T	0.73	293051	0.39	0.07	3.8×10^{-8}
96	<i>WT1</i>	rs11031737	11	32372772	G/A	0.52	293051	0.35	0.06	4.5×10^{-8}

Locus ID	Nearest gene(s)	rsID	Chr	Position	EA/OA	EAF	N	Beta	SE	P
Multi-ancestry meta-analysis										
97	<i>PCNXL3</i>	rs12801636	11	65391317	A/G	0.24	293051	0.41	0.07	4.1×10^{-8}
98	<i>CRYAB</i>	rs12808601	11	111776066	G/A	0.70	293050	0.51	0.07	3.1×10^{-13}
99	<i>USP28</i>	rs144789148	11	113666335	G/A	0.05	290495	0.96	0.17	6.4×10^{-9}
100	<i>PDE3A</i>	rs10770646	12	20544361	T/C	0.79	288153	0.53	0.08	6.4×10^{-11}
101	<i>SSPN</i>	rs78518764	12	26306484	T/C	0.86	293051	0.61	0.10	2.1×10^{-10}
102	<i>ARID2</i>	rs76611452	12	46209520	T/C	0.04	286416	1.19	0.19	1.5×10^{-10}
103	<i>SRGAP1</i>	rs17099893	12	64283014	A/G	0.06	291836	0.95	0.14	9.9×10^{-12}
104	<i>MIR6074</i>	rs4026608	12	66394664	T/C	0.62	293051	0.38	0.07	6.5×10^{-9}
105	<i>SLC6A15</i>	rs10862858	12	84806298	A/G	0.43	293051	0.46	0.06	1.1×10^{-12}
106	<i>HCFC2</i>	rs2629745	12	104503806	A/G	0.88	293051	0.69	0.10	1.7×10^{-12}
107	<i>RIC8B</i>	rs3759310	12	107166122	G/C	0.36	293051	0.56	0.07	4.5×10^{-17}
108	<i>UBE3B</i>	rs2004359*	12	109976893	G/T	0.47	291836	0.42	0.06	5.0×10^{-11}
109	<i>TESC</i>	rs7972416	12	117491824	A/G	0.66	293051	0.45	0.07	1.8×10^{-11}
110	<i>FREM2</i>	rs9634754*	13	39261151	G/T	0.69	293051	0.41	0.07	4.4×10^{-9}
111	<i>FGF14</i>	rs9513995	13	102878269	T/C	0.74	287628	0.50	0.07	2.1×10^{-11}
112	<i>ARHGEF40</i>	rs12885183	14	21545230	G/A	0.22	283907	0.49	0.08	8.5×10^{-10}
113	<i>RP11-562L8.1</i>	rs7146955	14	29750244	G/A	0.59	293051	0.44	0.06	6.7×10^{-12}
114	<i>AKAP6</i>	rs3784192	14	32923336	A/G	0.20	293051	0.55	0.08	3.0×10^{-11}
115	<i>NFKBIA</i>	rs8904	14	35871217	G/A	0.63	287252	0.40	0.07	1.6×10^{-9}
116	<i>SYNE2</i>	rs1255908	14	64457638	T/G	0.69	291546	0.52	0.07	6.0×10^{-14}
117	<i>FLRT2</i>	rs17712080	14	86041160	G/A	0.75	293050	0.47	0.07	2.0×10^{-10}
118	<i>RP11-1070N10.3</i>	rs179145	14	95983975	A/G	0.38	287627	0.41	0.07	5.2×10^{-10}
119	<i>MARK3</i>	rs3759579	14	103851272	A/G	0.41	287627	0.42	0.07	1.2×10^{-10}
120	<i>RBPM2</i>	rs3935716*	15	65035979	A/G	0.15	293051	0.61	0.10	1.2×10^{-10}
121	<i>CORO2B</i>	rs11330601	15	69021265	I/D	0.55	222818	0.43	0.08	1.4×10^{-8}
122	<i>HCN4</i>	rs8039168	15	73664723	A/T	0.83	293051	0.60	0.09	2.0×10^{-12}
123	<i>ALPK3</i>	rs6496452	15	85372645	A/T	0.55	287628	0.55	0.06	1.3×10^{-17}
124	<i>LINC00924/NR2F2</i>	rs62008078	15	96460899	C/T	0.44	285649	0.48	0.07	4.4×10^{-13}
125	<i>SPSB3</i>	rs35816944*	16	1828030	G/A	0.99	247100	2.70	0.44	1.3×10^{-9}
126	<i>SRL</i>	rs79321945	16	4282284	C/A	0.78	293051	0.50	0.08	2.1×10^{-10}
128	<i>LOC101927480/ LINC02140</i>	rs1186818	16	54598337	G/A	0.24	293051	0.43	0.07	9.0×10^{-9}

Locus ID	Nearest gene(s)	rsID	Chr	Position	EA/OA	EAF	N	Beta	SE	P
Multi-ancestry meta-analysis										
129	<i>CNOT1</i>	rs7199856*	16	58584772	G/T	0.26	292217	0.56	0.07	8.6×10 ⁻¹⁵
130	<i>LINC01082/IRF8</i>	rs904199	16	86184639	G/A	0.08	287629	0.73	0.12	7.9×10 ⁻¹⁰
131	<i>ZFPM1</i>	rs28634651	16	88553198	T/C	0.61	261197	0.51	0.07	2.1×10 ⁻¹²
132	<i>MINK1</i>	rs7774	17	4801163	A/C	0.33	293051	0.43	0.07	8.6×10 ⁻¹⁰
133	<i>EFCAB5</i>	rs55866125*	17	28312993	T/C	0.52	293051	0.42	0.06	3.2×10 ⁻¹¹
134	<i>CACNA1G</i>	rs757416	17	48666064	T/C	0.63	293051	0.69	0.07	2.5×10 ⁻²⁵
135	<i>CSHL1</i>	rs2006122	17	61987405	T/A	0.27	293051	0.42	0.07	5.8×10 ⁻⁹
136	<i>PRKCA</i>	rs9909004	17	64306133	C/T	0.42	291623	0.38	0.06	2.9×10 ⁻⁹
138	<i>AC100791.2</i>	rs745570*	17	77781725	G/A	0.53	293051	0.35	0.06	3.4×10 ⁻⁸
139	<i>CDH2</i>	rs11083300	18	26339589	G/C	0.46	293050	0.35	0.06	3.8×10 ⁻⁸
140	<i>GAREM</i>	rs982521	18	30029141	C/T	0.18	293050	0.75	0.09	1.7×10 ⁻¹⁸
141	<i>DTNA</i>	rs1786595	18	32399259	C/T	0.74	293050	0.47	0.07	6.9×10 ⁻¹¹
142	<i>CCBE1</i>	rs12961264	18	57138957	C/T	0.23	293050	0.51	0.08	1.1×10 ⁻¹¹
143	<i>STK11</i>	rs3795063	19	1217560	C/G	0.65	268324	0.49	0.08	7.3×10 ⁻¹¹
144	<i>ZNF358</i>	rs113394178	19	7581244	A/C	0.60	212667	0.46	0.08	2.1×10 ⁻⁸
145	<i>TMEM59L</i>	rs111551996	19	18733355	G/T	0.95	290902	0.95	0.16	8.0×10 ⁻¹⁰
146	<i>RNF24/SMOX</i>	rs16989138	20	4031653	G/A	0.43	291546	0.53	0.07	7.1×10 ⁻¹⁶
147	<i>KIAA1755</i>	rs6023939	20	36832526	C/A	0.54	293051	0.44	0.06	6.7 ×10 ⁻¹²
148	<i>DERL3</i>	rs2070464	22	24183875	G/A	0.38	291836	0.54	0.07	6.2 ×10 ⁻¹⁶
149	<i>PHF5A</i>	rs9607805	22	41854446	T/C	0.70	287628	0.42	0.07	5.6 ×10 ⁻⁹
European meta-analysis										
29	<i>BMPR2</i>	rs2103208	2	203373030	G/A	0.49	271570	0.36	0.07	4.8×10 ⁻⁸
30	<i>AC007563.5</i>	rs6435953	2	217628087	C/T	0.16	271570	0.51	0.09	2.1×10 ⁻⁸
39	<i>MLF1</i>	rs6799180*	3	158333891	A/G	0.47	271570	0.37	0.07	2.2×10 ⁻⁸
47	<i>MYOZ2</i>	rs78277783	4	120070079	A/T	0.27	266672	0.42	0.08	2.1×10 ⁻⁸
52	<i>FER</i>	rs6889995	5	108210304	G/A	0.22	266672	0.44	0.08	4.3×10 ⁻⁸
79	<i>AZIN1</i>	rs565720	8	103914366	A/C	0.77	271570	0.44	0.08	3.1×10 ⁻⁸
127	<i>MYH11</i>	rs72772025	16	15834729	T/C	0.27	269591	0.41	0.08	3.5×10 ⁻⁸
137	<i>CASKIN2</i>	rs7501873	17	73505172	G/A	0.22	271570	0.45	0.08	4.9×10 ⁻⁸

636 There was no evidence of heterogeneity for any of the newly identified loci across individual
637 studies ($P_{\text{heterogeneity}} \geq 0.001$) or across ancestry groups ($P_{\text{heterogeneity}} > 0.01$).

638 Locus ID: unique locus identifier; Nearest gene(s): Nearest annotated gene(s) to the lead
639 variant; rsID, variant accession number; Chr, chromosome; Position, physical position in build
640 37; EA, effect allele; OA, other allele; EAF, effect allele frequency; N, total sample size
641 analyzed; beta, effect estimate in milliseconds; SE, standard error; P, P-value.

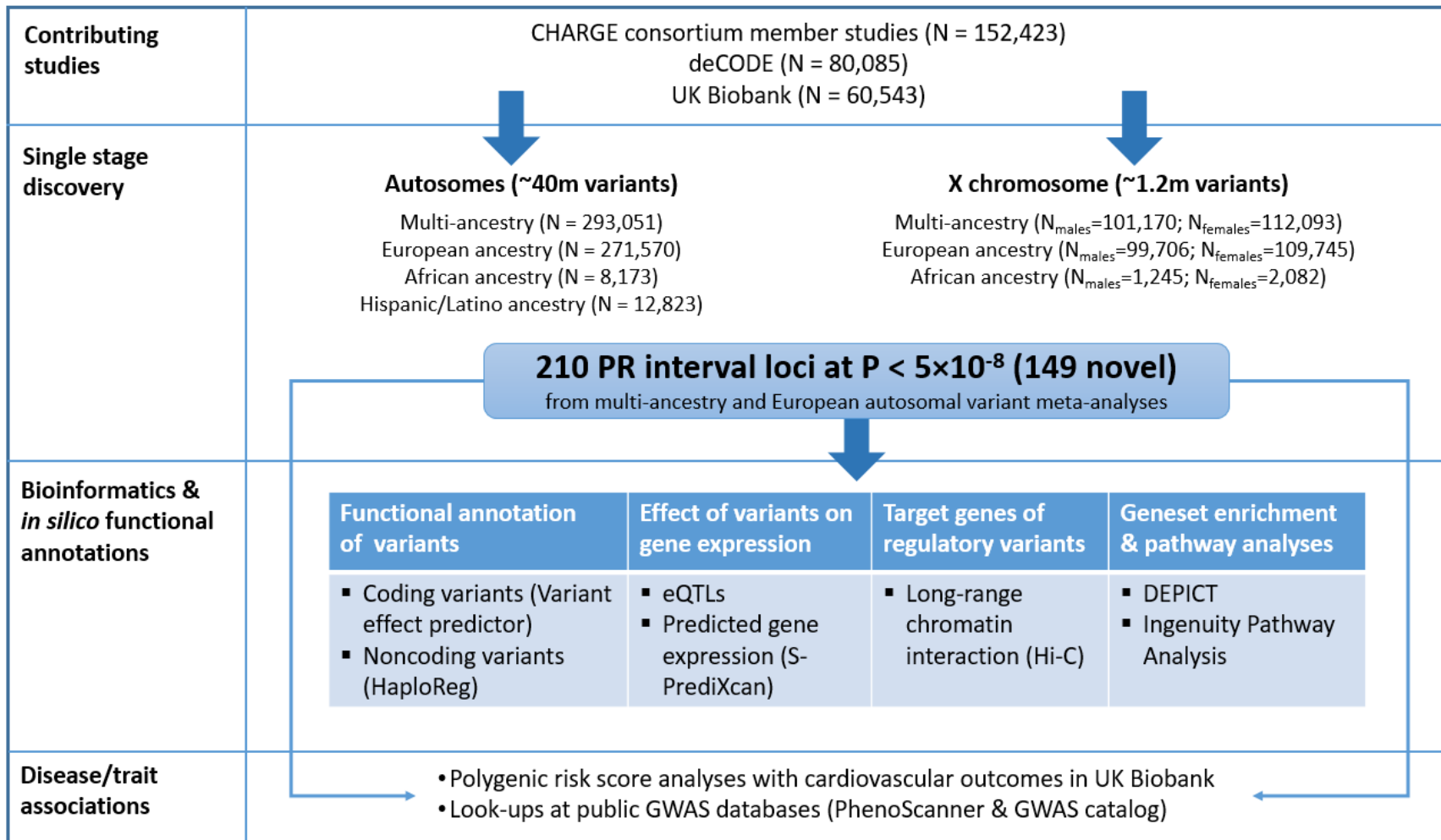
642 * Missense variant or variant in high LD ($r^2 > 0.8$) with missense or splice site variant(s).

643

644 **Figures**

645 **Figure 1** Overview of the study design.

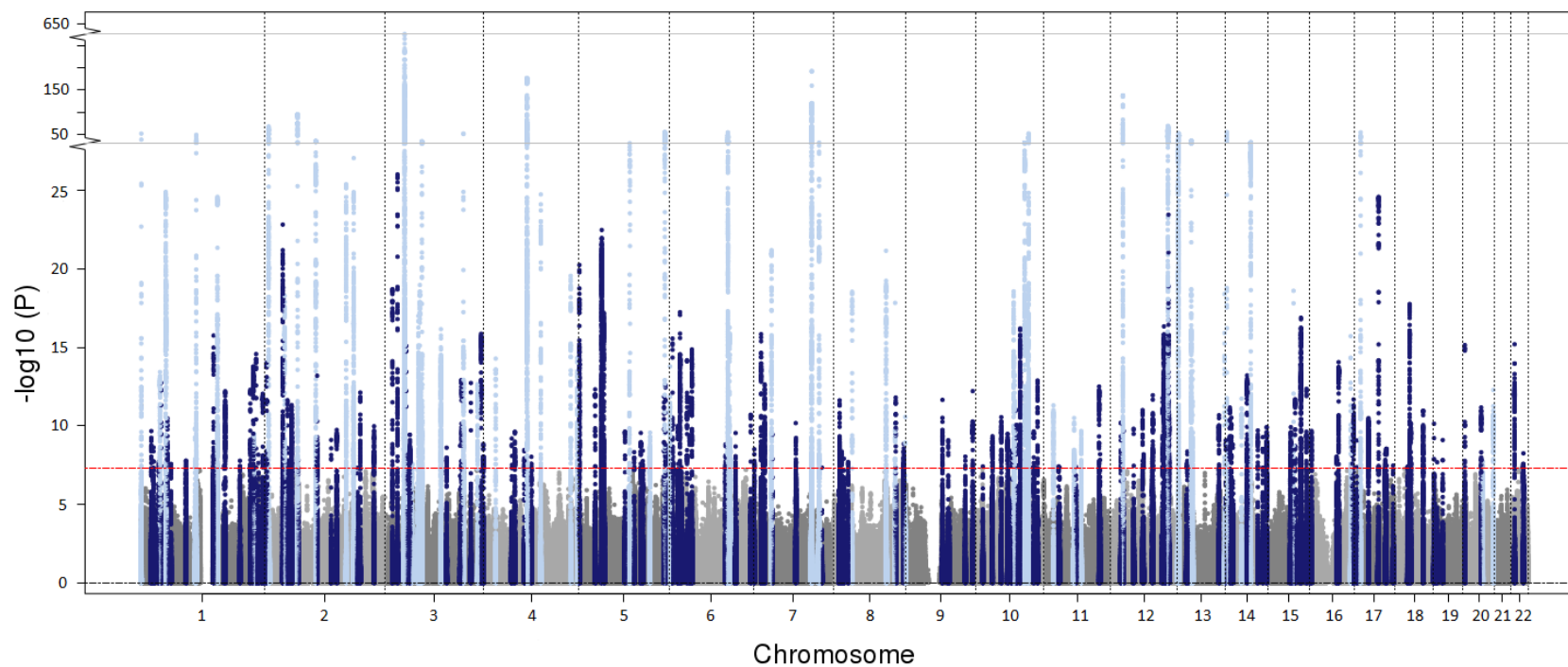
646 Figure includes overview of contributing studies, single-stage discovery approach, and downstream bioinformatics and *in silico*
647 annotations we performed to link variants to genes, and polygenic risk score analysis to link variants to cardiovascular disease risk.



648

649

650 **Figure 2** Manhattan plot of the multi-ancestry meta-analysis for PR interval. P values are plotted on the $-\log_{10}$ scale for all variants
651 present in at least 60% of the maximum sample size. Associations of genome-wide significant ($P < 5 \times 10^{-8}$) variants at novel ($N = 141$)
652 and previously reported loci ($N = 61$) are plotted in dark and light blue colours respectively.

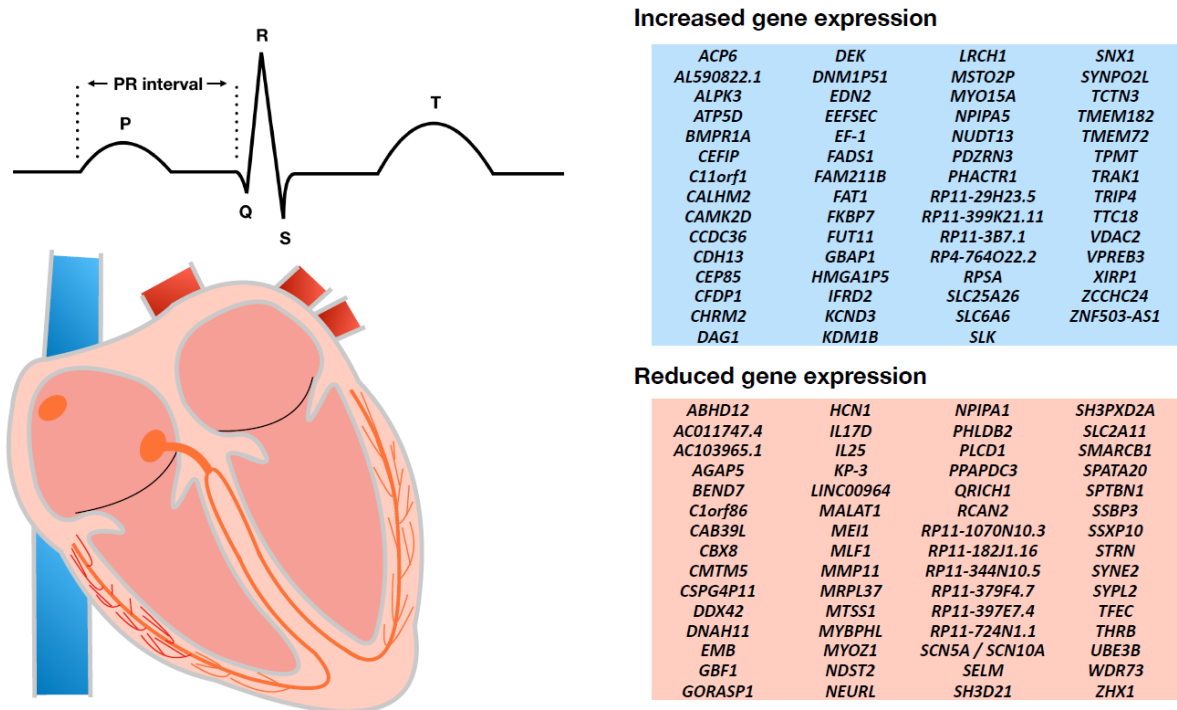


653

654

655 **Figure 3 Plausible candidate genes of PR interval from S-PrediXcan**

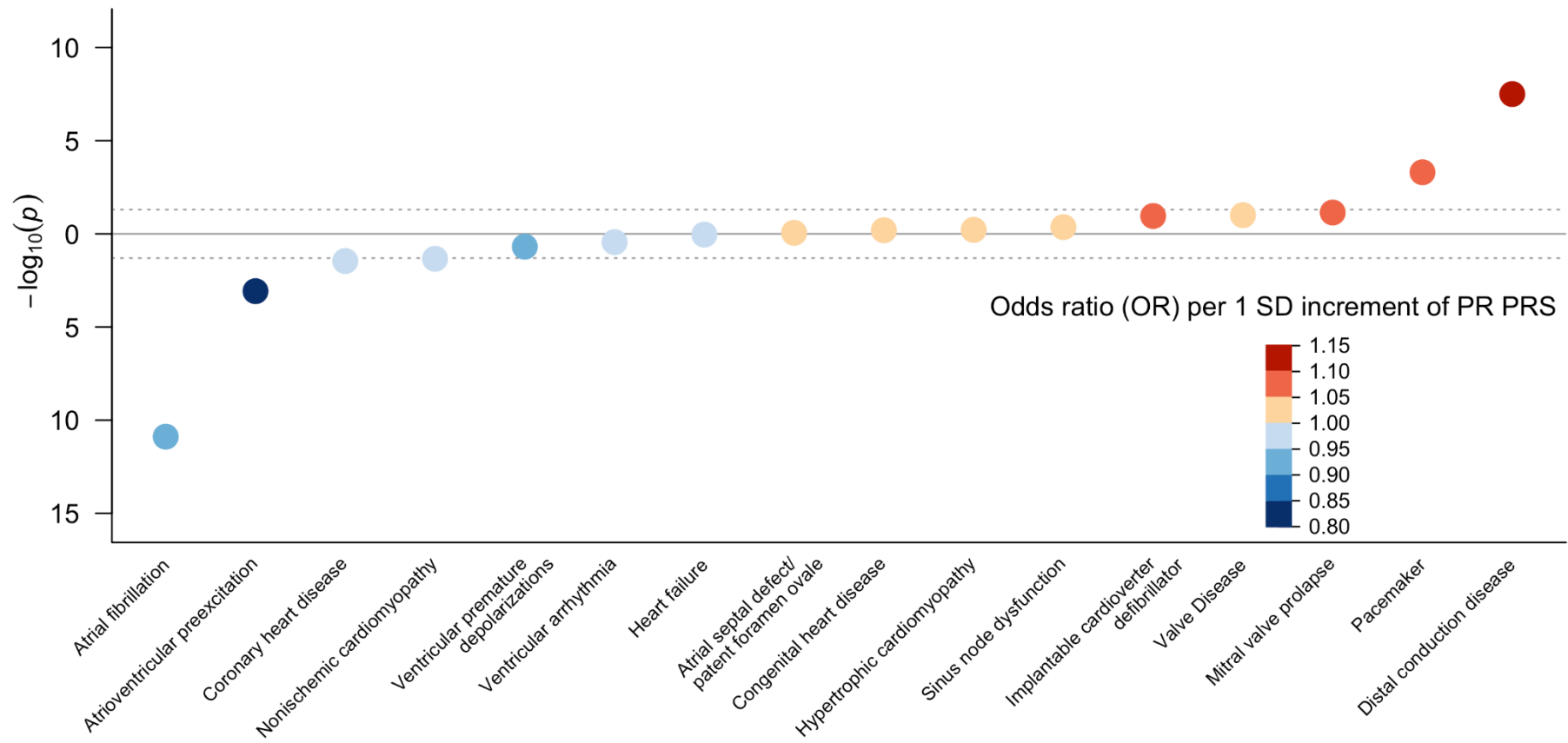
656 Diagram of standard electrocardiographic intervals and the heart. The electrocardiographic
 657 features are illustratively aligned with the corresponding cardiac conduction system structures
 658 (orange) reflected on the tracing. The PR interval (labeled) indicates conduction through the atria,
 659 atrioventricular node, His bundle, and Purkinje fibers. Right: The tables show 120 genes whose
 660 expression in the left ventricle (N=272) or right atrial appendage (N=264) was associated with PR
 661 interval duration in a transcriptome-wide analysis using S-PrediXcan and GTEX v7. Displayed
 662 genes include those with significant associations after Bonferroni correction for all tested genes at
 663 the two tissues with a $P < 4.4 \times 10^{-6}$ ($=0.05/(5,977+5,366)$). Longer PR intervals were associated
 664 with increased predicted expression of 59 genes (blue) and reduced expression of 61 genes
 665 (orange).



666

667 **Figure 4** Bubble plot of phenome-wide association analysis of multi-ancestry PR interval polygenic risk score.

668 Polygenic risk score was derived from the multi-ancestry meta-analysis results. Orange circles indicate that higher polygenic risk score of
669 prolonged PR interval is associated with an increased risk of the condition, whereas blue circles indicate that higher score is associated with lower
670 risks. The darkness of the colour reflects the effect size (odds ratio, OR) changes per 1 standard deviation increment of the polygenic risk score.
671 Given correlation between traits, we did not establish a pre-specified significance threshold for the analysis and report nominal associations ($P <$
672 0.05).



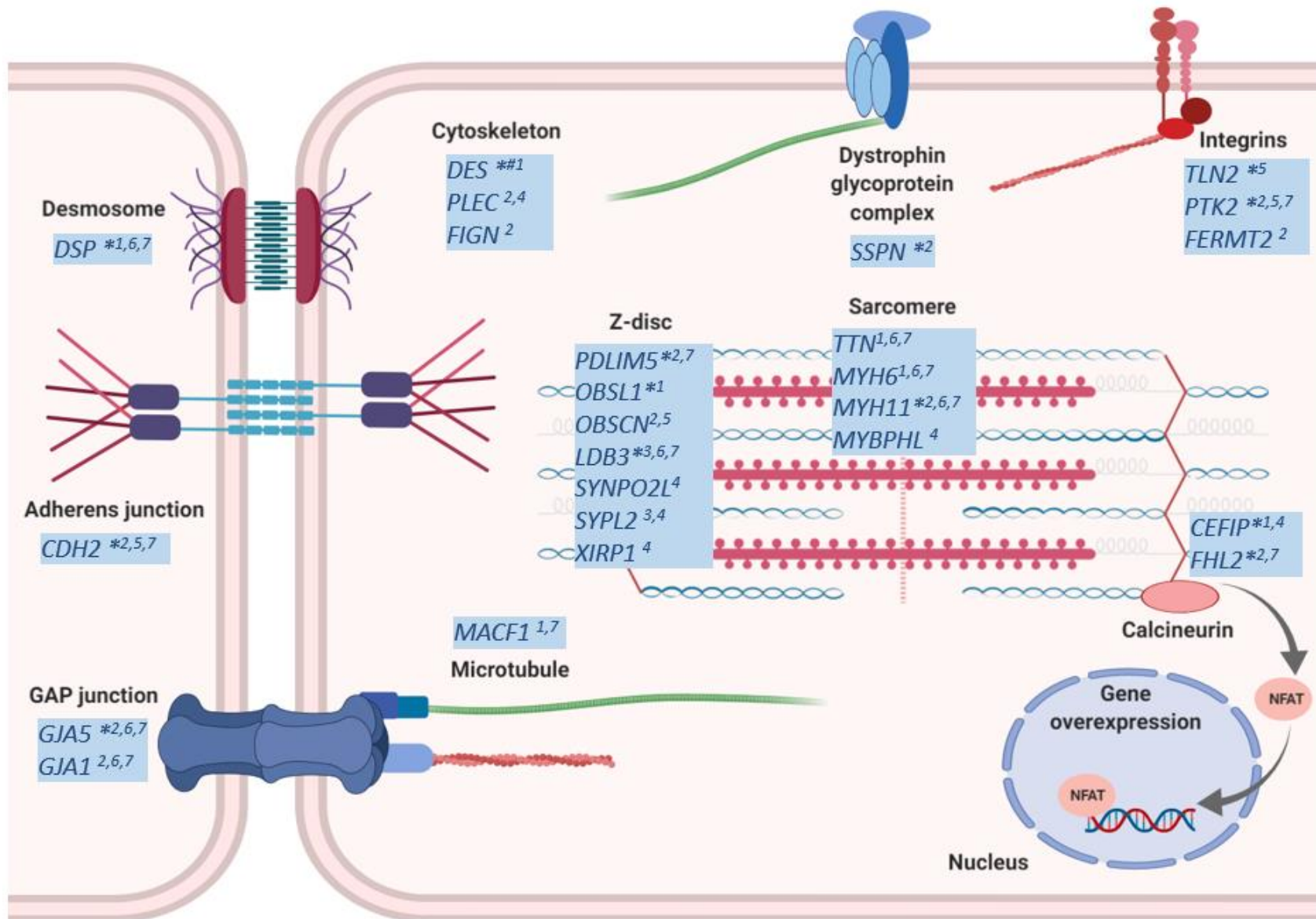
673

674

675 **Figure 5** Candidate genes in PR interval loci encoding proteins involved in cardiac muscle cytoskeleton. Candidate genes or encoded proteins are
676 indicated by a star symbol in the figure and listed in the table. More information about the genes is provided in Supplementary Tables 18-19.

677 *Novel locus, # genome-wide significant locus in transformed trait meta-analysis.

678 ¹ Missense variant; ² Nearest gene to the lead variant; ³ Gene within the region ($r^2 > 0.5$); ⁴ Variant(s) in the locus are associated with gene expression
679 in left ventricle and/or right atrial appendage; ⁵ Left ventricle best HiC locus interactor (RegulomeDB score ≤ 2); ⁶ Animal model; ⁷ Monogenic
680 cardiovascular disease.



682 **URLs**

683 1000 Genome Project: <http://www.internationalgenome.org>

684 BOLT-LMM: <https://data.broadinstitute.org/alkesgroup/BOLT-LMM/>

685 DEPICT: <https://data.broadinstitute.org/mpg/depict/>

686 DGIdb: <http://www.dgldb.org>

687 EasyQC: <https://www.uni-regensburg.de/medizin/epidemiologie->

688 [praeventivmedizin/genetische-epidemiologie/software/#](https://www.uni-regensburg.de/medizin/epidemiologie-software/#)

689 FORGE: <https://github.com/iandunham/Forge>

690 GCTA: <https://cnsgenomics.com/software/gcta/#Overview>

691 GTEx: <https://gtexportal.org/home/>

692 HRC: <http://www.haplotype-reference-consortium.org>

693 IMPUTE2: http://mathgen.stats.ox.ac.uk/impute/impute_v2.html

694 Ingenuity Pathway Analysis software:

695 <https://www.qiagenbioinformatics.com/products/ingenuity-pathway-analysis/>

696 International Mouse Phenotyping Consortium: <https://www.mousephenotype.org/>

697 IPA: <https://www.qiagenbioinformatics.com/products/ingenuity-pathway-analysis>

698 LocusZoom: <http://locuszoom.org/>

699 MACH: <http://csg.sph.umich.edu/abecasis/mach/tour/imputation.html>

700 METAL: <http://csg.sph.umich.edu/abecasis/metal/>

701 OMIM: <https://www.omim.org/>

702 RegulomeDB: <http://www.regulomedb.org>

703 S-PrediXcan: <https://github.com/hakyimlab/MetaXcan>

704 UK Biobank: <https://www.ukbiobank.ac.uk>

705

706 **Author contributions**

707 Interpreted results, writing and editing the manuscript: I.N., L.-C.W., S.A.L., and P.B.M.
708 Conceptualisation and supervision of project: S.A.L. and P.B.M. Contributed
709 to GWAS analysis plan: I.N., L.-C.W., H.R.W., Y.J., S.A.L., and P.B.M. Performed meta-
710 analyses: I.N. and L.-C.W. Performed GCTA, heritability, geneset enrichment and pathway
711 analyses, variant annotations: I.N. Performed polygenic risk score and gene expression
712 analyses: S.H.C., M.D.C., and L.-C.W. Performed HiC analyses: I.N., M.R.B., B.M., and
713 P.B.M. Performed gene literature review: I.N., L.-C.W., A.W.Hall, N.R.T., M.D.C., J.H.C.,
714 J.J.C., A.T., Y.J., S.A.L., and P.B.M. Contributed to study specific GWAS by providing
715 phenotype, genotype and performing data analyses: J.M., I.R., C.H., P.G., M.Concas, T.B.,
716 O.P., I.K., E.T., N.M.A., R.P.S., M.F.L., A.L.P.R., A.M., V.Giedraitis, E.I., A.P.M., F.D.M.,
717 L.F., M.G., A.A.Hicks, J.P.C., L.Lind, C.M.L., J.Sundström, N.J.S., C.P.N., M.B.R., S.U.,
718 G.S., P.P.M., M.K., N.M., K.N., I.N., M.Caulfield, A.Dominiczak, S.P., M.E.M., J.R.O.,
719 A.R.S., K.Ryan, D.C., L.R., S.Aeschbacher, S.Thériault, T.L., O.T.R., N.H., L.Lyytikäinen,
720 J.F.W., P.K.J., C.L.K.B., H.C., C.M.v., J.A.K., A.I., P.L.H., L.-C.W., S.A.L., P.T.E., T.B.H.,
721 L.J.L., A.V.S., V.Gudnason, E.P.B., R.J.F.L., G.N.N., M.H.P., A.C., H.M., J.W., M.Müller-
722 Nurasyid, A.P., T.M., M.W., T.D.S., Y.J., M.Mangino, M.R., Y.J.V., P.H., N.V., K.Schramm,
723 S.K., K.Strauch, M.F.S., B.L., C.R., D.F., M.J.C., M.Olesen, D.M.R., M.B.S., J.Smith, J.A.B.,
724 M.L.B., J.C.B., B.M.P., N.S., K.Rice, C.P., P.P.P., A.De Grandi, C.F., J.W.J., I.F., P.W.M.,
725 S.Trompet, S.W., M.D., S.B.F., U.V., A.S.Havulinna, A.J., K.Sääksjärvi, V.S., S.R.H., J.I.R.,
726 X.G., H.J.L., J.Y., K.D.T., R.N., R.d., D.O.M., A.C.M., F.C., J.D., E.G.L., Y.Q., K.V.T.,
727 E.J.B., D.L., H.L., C.H.N., K.L.L., A.D.M., D.J.P., B.H.Smith, B.H.Stricker, M.E.v, A.U.,
728 J.H., R.D.J., U.P., A.P.R., E.A.W., C.K., E.B., D.E.A., G.B.E., A.A., E.Z.S., C.L.A., S.M.G.,
729 K.F.K., C.C.L., A.A.S., A.S., S.Assa, M.A.S., M.Y.v., P.D.L., A.T., M.Orini, J.R., S.V.D.,

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732

733 **Competing Interests**

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743 K.Stefansson, H.H., P.S., G.S., G.T., R.B.T., U.T., D.O.A., D.F.G. are employed by deCODE
744 genetics/Amgen Inc.

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