

Title	PR interval genome-wide association meta-analysis identifies 50 loci associated with atrial and atrioventricular electrical activity
Authors	<p>van Setten, Jessica;Brody, Jennifer A.;Jamshidi, Yalda;Swenson, Brenton R.;Butler, Anne M.;Campbell, Harry;Del Greco, Fabiola M.;Evans, Daniel S.;Gibson, Quince;Gudbjartsson, Daniel F.;Kerr, Kathleen F.;Krijthe, Bouwe P.;Lyytikainen, Leo-Pekka;Mueller, Christian;Mueller-Nurasyid, Martina;Nolte, Ilja M.;Padmanabhan, Sandosh;Ritchie, Marylyn D.;Robino, Antonietta;Smith, Albert V.;Steri, Maristella;Tanaka, Toshiko;Teumer, Alexander;Trompet, Stella;Ulivi, Sheila;Verweij, Niek;Yin, Xiaoyan;Arnar, David O.;Asselbergs, Folkert W.;Bader, Joel S.;Barnard, John;Bis, Josh;Blankenberg, Stefan;Boerwinkle, Eric;Bradford, Yuki;Buckley, Brendan M.;Chung, Mina K.;Crawford, Dana;den Hoed, Marcel;Denny, Josh C.;Dominiczak, Anna F.;Ehret, Georg B.;Eijgelsheim, Mark;Ellinor, Patrick T.;Felix, Stephan B.;Franco, Oscar H.;Franke, Lude;Harris, Tamara B.;Holm, Hilma;Iaria, Gandin;Iorio, Annamaria;Kahonen, Mika;Kolcic, Ivana;Kors, Jan A.;Lakatta, Edward G.;Launer, Lenore J.;Lin, Honghuang;Lin, Henry J.;Loos, Ruth J. F.;Lubitz, Steven A.;Macfarlane, Peter W.;Magnani, Jared W.;Leach, Irene Mateo;Meitinger, Thomas;Mitchell, Braxton D.;Munzel, Thomas;Papanicolaou, George J.;Peters, Annette;Pfeufer, Arne;Pramstaller, Peter P.;Raitakari, Olli T.;Rotter, Jerome I.;Rudan, Igor;Samani, Nilesh J.;Schlessinger, David;Aldana, Claudia T. Silva;Sinner, Moritz F.;Smith, Jonathan D.;Snieder, Harold;Soliman, Elsayed Z.;Spector, Timothy D.;Stott, David J.;Strauch, Konstantin;Tarasov, Kirill V.;Thorsteinsdottir, Unnur;Uitterlinden, Andre G.;Van Wagoner, David R.;Voelker, Uwe;Voelzke, Henry;Waldenberger, Melanie;Westra, Harm Jan;Wild, Philipp S.;Zeller, Tanja;Alonso, Alvaro;Avery, Christy L.;Bandinelli, Stefania;Benjamin, Emelia J.;Cucca, Francesco;Doerr, Marcus;Ferrucci, Luigi;Gasparini, Paolo;Gudnason, Vilmundur;Hayward, Caroline;Heckbert, Susan R.;Hicks, Andrew A.;Jukema, J. Wouter;Kaeae, Stefan;Lehtimaki, Terho;Liu, Yongmei;Munroe, Patricia B.;Parsa, Afshin;Polasek, Ozren;Psaty, Bruce M.;Roden, Dan M.;Schnabel, Renate B.;Sinagra, Gianfranco;Stefansson, Kari;Stricker, Bruno H.;van der Harst, Pim;van Duijn, Cornelia M.;Wilson, James F.;Gharib, Sina A.;de Bakker, Paul I. W.;Isaacs, Aaron;Arking, Dan E.;Sotoodehnia, Nona</p>
Publication date	2018

Original Citation	<p>van Setten, J. and Brody, J. A. and Jamshidi, Y. and Swenson, B. R. and Butler, A. M. and Campbell, H. and Del Greco, F. M. and Evans, D. S. and Gibson, Q. and Gudbjartsson, D. F. and Kerr, K. F. and Krijthe, B. P. and Lytikäinen, L.-P. and Müller, C. and Müller-Nurasyid, M. and Nolte, I. M. and Padmanabhan, S. and Ritchie, M. D. and Robino, A. and Smith, A. V. and Steri, M. and Tanaka, T. and Teumer, A. and Trompet, S. and Ulivi, S. and Verweij, N. and Yin, X. and Arnar, D. O. and Asselbergs, F. W. and Bader, J. S. and Barnard, J. and Bis, J. and Blankenberg, S. and Boerwinkle, E. and Bradford, Y. and Buckley, B. M. and Chung, M. K. and Crawford, D. and den Hoed, M. and Denny, J. C. and Dominiczak, A. F. and Ehret, G. B. and Eijgelsheim, M. and Ellinor, P. T. and Felix, S. B. and Franco, O. H. and Franke, L. and Harris, T. B. and Holm, H. and Ilaria, G. and Iorio, A. and Kähönen, M. and Kolcic, I. and Kors, J. A. and Lakatta, E. G. and Launer, L. J. and Lin, H. and Lin, H. J. and Loos, R. J. F. and Lubitz, S. A. and Macfarlane, P. W. and Magnani, J. W. and Leach, I. M. and Meitinger, T. and Mitchell, B. D. and Munzel, T. and Papanicolaou, G. J. and Peters, A. and Pfeufer, A. and Pramstaller, P. P. and Raitakari, O. T. and Rotter, J. I. and Rudan, I. and Samani, N. J. and Schlessinger, D. and Silva Aldana, C. T. and Sinner, M. F. and Smith, J. D. and Snieder, H. and Soliman, E. Z. and Spector, T. D. and Stott, D. J. and Strauch, K. and Tarasov, K. V. and Thorsteinsdottir, U. and Uitterlinden, A. G. and Van Wagoner, D. R. and Völker, U. and Völzke, H. and Waldenberger, M. and Jan Westra, H. and Wild, P. S. and Zeller, T. and Alonso, A. and Avery, C. L. and Bandinelli, S. and Benjamin, E. J. and Cucca, F. and Dörr, M. and Ferrucci, L. and Gasparini, P. and Gudnason, V. and Hayward, C. and Heckbert, S. R. and Hicks, A. A. and Jukema, J. W. and Kääb, S. and Lehtimäki, T. and Liu, Y. and Munroe, P. B. and Parsa, A. and Polasek, O. and Psaty, B. M. and Roden, D. M. and Schnabel, R. B. and Sinagra, G. and Stefansson, K. and Stricker, B. H. and van der Harst, P. and van Duijn, C. M. and Wilson, J. F. and Gharib, S. A. and de Bakker, P. I. W. and Isaacs, A. and Arking, D. E. and Sotoodehnia, N. (2018) 'PR interval genome-wide association meta-analysis identifies 50 loci associated with atrial and atrioventricular electrical activity', Nature Communications, 9(1), 2904 (11pp). doi: 10.1038/s41467-018-04766-9</p>
Type of publication	Article (peer-reviewed)
Link to publisher's version	https://www.nature.com/articles/s41467-018-04766-9 - 10.1038/s41467-018-04766-9
Rights	© 2018, the Author(s). Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit

	<p>to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/. - http://creativecommons.org/licenses/by/4.0/</p>
Download date	2024-09-10 18:56:58
Item downloaded from	https://hdl.handle.net/10468/6661



Description of Additional Supplementary Files

File Name: Supplementary Data 1

Description: Cohort information: cohort characteristics

File Name: Supplementary Data 2

Description: Cohort information: genotyping information

File Name: Supplementary Data 3

Description: Gene Ontology analysis. Gene Ontology analysis. List of significantly overrepresented Gene Ontology (GO) categories based on enrichment analysis of PR GWAS using parametric and non-parametric analyses. Categories were deemed significant if they reached an FDR < 0.01 in both methods. Total: total number of gene members for the GO category. Observed: the actual number of PR genes mapping to the given GO category. Expected: the expected number of PR genes mapping the GO category. P-value (parametric): probability of observing the actual number of PR genes within the given GO category based on the hypergeometric distribution. FDR (parametric): false discovery rate adjustment of the enrichment P-value. FDR (permutation): false discovery rate based on random permutation analysis (non-parametric).

File Name: Supplementary Data 4

Description: Non-synonymous SNPs. The predicted effect on protein function of nonsynonymous SNPs associated with PR interval. For each locus we annotated all SNPs with $r^2 > 0.8$ with the index or non-redundant SNPs.

File Name: Supplementary Data 5

Description: Cardiac and Blood eQTL analysis. European ancestry PR index SNPs associated with gene expression from RNA-seq in left atrial appendage (n=230) or GTEx whole blood (n=369). Given the few associations identified in whole blood, we expanded to include whole blood eQTL from Illumina gene expression array (n=5311). * indicates SNP-transcript associations found in LAA that do not replicate in RAA. ** indicates SNP-transcript associations where evidence for colocalization is less strong as detailed in Table 4B below.

File Name: Supplementary Data 6

Description: Co-localization of GWAS and eQTL associations. Our aim for identifying colocalizing genetic variants that jointly affect both molecular expression and the PR phenotype is to provide intuition regarding the candidate gene that may play a role in atrial conduction. In any given locus, we now identify a candidate gene from eQTL data (shaded in gray) if it meets the following three criteria: (1) the SNP-transcript association in LAA is significant at a genome-wide q-value 0.90) OR there

File Name: Supplementary Data 7

Description: Enrichment of PR interval genes in human diseases. List of significantly over-represented human disorders based on enrichment analysis of PR GWAS, using parametric and non-parametric methods. Categories were deemed significant if they reached an FDR < 0.01 in both approaches. Total: total number of gene members for the given disease. Observed: the actual

number of PR genes mapping to the given disease. Expected: the expected number of PR genes mapping the given disease. P-value (parametric): probability of observing the actual number of PR genes within the given GO category based on the hypergeometric distribution. FDR (parametric): false discovery rate adjustment of the enrichment P-value. FDR (permutation): false discovery rate based on random permutation analysis (non-parametric).

File Name: Supplementary Data 8

Description: Examination of PR SNPs in African-ancestry PR, as well as Europeanancestry QRS, RR, and AF.

File Name: Supplementary Data 9

Description: Examination in PR of index SNPs from AF, QRS, RR/HR Europeanancestry GWAS.