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CLINICAL RESEARCH
Genetics

Genetic variants associated with syncope implicate neural and autonomic processes

Hildur M. Aegisdottir [1,2], Rosa B. Thorolfsdottir [1], Gardar Sveinbjornsson [1], Olafur A. Stefansson [1], Bjarni Gunnarsson[1], Vinicius Tragante [1], Gudmar Thorleifsson [1], Lilja Stefansdottir[1], Thorgeir E. Thorgeirsson [1], Egil Ferkingstad [1], Patrick Sulem [1], Gudmundur Norddahl [1], Gudrun Rutsdottir [1], Karina Banasik [3], Alex Hoerby Christensen [4,5,6], Christina Mikkelsen [7,8], Ole Birger Pedersen [6,9], Søren Brunak [3], Mie Topholm Bruun [10], Christian Erikstrup [11,12], Rikke Louise Jacobsen [7], Kaspar Rene Nielsen [13], Erik Sørensen [7], Michael L. Frigge [1], Kristjan E. Hjorleifsson [1], Erna V. Ivarsdottir [1], Anna Helgadottir [1], Solveig Gretarsdottir [1], Valgerdur Steinthorsdottir [1], Asmundur Oddsson [1], Hannes P. Eggertsson [1], Gisli H. Halldorsson [1], David A. Jones [14], Jeffrey L. Anderson[15,16], Kirk U. Knowlton [15,17], Lincoln D. Nadauld[14,18], DBDS Genomic Consortium†, Magnus Haraldsson[2,19], Gudmundur Thorgeirsson [1,2,20], Henning Bundgaard [6,21], David O. Arnar [1,2,20], Unnur Thorsteinsdottir [1,2], Daniel F. Gudbjartsson [1,22], Sisse R. Ostrowski [6,7‡], Hilma Holm [1*‡], and Kari Stefansson [1,2*‡]

[1]deCODE genetics/Amgen, Inc., Sturlugata 8, Reykjavik 101, Iceland; [2]Faculty of Medicine, University of Iceland, Vatnsmyrarvegur 16, Reykjavik 101, Iceland; [3]Novo Nordisk Foundation Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3A, Copenhagen 2200, Denmark; [4]The Unit for Inherited Cardiac Diseases, Department of Cardiology, The Heart Centre, Copenhagen University Hospital - Rigshospitalet, Blegdamsvej 9, Copenhagen 2100, Denmark; [5]Department of Cardiology, Herlev-Gentofte Hospital, Copenhagen University Hospital, Borgmester Ib Juuls Vej 1, Herlev 2730, Denmark; [6]Department of Clinical Medicine, University of Copenhagen, Blegdamsvej 3B, Copenhagen 2200, Denmark; [7]Department of Clinical Immunology, Copenhagen University Hospital - Rigshospitalet, Blegdamsvej 9, Copenhagen 2100, Denmark; [8]Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Blegdamsvej 3A, Copenhagen 2200, Denmark; [9]Department of Clinical Immunology, Zealand University Hospital - KÃ¸ge, LykkebÃ¦kvej 1, KÃ¸ge 4600, Denmark; [10]Department of Clinical Immunology, Odense University Hospital, J. B. WinslÃ¸ws Vej 4, Odense 5000, Denmark; [11]Department of Clinical Immunology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, Aarhus 8200, Denmark; [12]Department of Clinical Medicine, Aarhus University, Nordre Ringgade 1, Aarhus 8000, Denmark; [13]Department of Clinical Immunology, Aalborg University Hospital, Urbansgade 32, Aalborg 9000, Denmark; [14]Precision Genomics, Intermountain Healthcare, 600 S. Medical Center Drive, Saint George, UT 84790, USA; [15]Intermountain Medical Center, Intermountain Heart Institute, 5171 S. Cottonwood Street Building 1, Salt Lake City, UT 84107, USA; [16]Department of Internal Medicine, University of Utah, 30 N 1900 E, Salt Lake City, UT 84132, USA; [17]School of Medicine, University of Utah, 30 N 1900 E, Salt Lake City, UT 84132, USA; [18]School of Medicine, Stanford University, 291 Campus Drive, Stanford, CA 94305, USA; [19]Department of Psychiatry, Landspitali, The National University Hospital of Iceland, Hringbraut, Reykjavik 101, Iceland; [20]Department of Medicine, Landspitali, The National University Hospital of Iceland, Hringbraut, Reykjavik 101, Iceland; [21]The Capital Regions Unit for Inherited Cardiac Diseases, Department of Cardiology, The Heart Centre, Copenhagen University Hospital - Rigshospitalet, Blegdamsvej 9, Copenhagen 2100, Denmark; and [22]School of Engineering and Natural Sciences, University of Iceland, Hjardarhagi 4, Reykjavik 107, Iceland

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* Corresponding authors: Tel: +354 570 1900, Fax: +354 570 1901, Emails: hilma.holm@decode.is; kstefans@decode.is

† DBDS Genomic consortium: Steffen Andersen[1], Kristoffer Burgdorf[2], Maria Didriksen[2], Khoa Manh Dinh[3], Thomas Folkmann Hansen[4], Henrik Hjalgrim[5], Gregor Jemec[6], Poul Jennum[7], Pär Ingemar Johansson[2], Margit Anita Hørup Larsen[2], Susan Mikkelsen[3], Mette Nyegaard[8], Hreinn Stefánsson[9], Susanne Sækmose[10], Henrik Ullum[11], Thomas Werge[12], and the following co-authors Karina Banasik, Ole Birger Pedersen, Søren Brunak, Mie Topholm Bruun, Christian Erikstrup, Kaspar Rene Nielsen, Erik Sørensen, Unnur Thorsteinsdottir, Daniel F. Gudbjartsson, Sisse R. Ostrowski and Kari Stefansson.

[1]Department of Finance, Copenhagen Business School, Copenhagen, Denmark; [2]Department of Clinical Immunology, Copenhagen University Hospital—Rigshospitalet, Copenhagen, Denmark; [3]Department of Clinical Immunology, Aarhus University Hospital, Aarhus, Denmark; [4]Danish Headache Center, Department of Neurology, Rigshospitalet—Glostrup, Copenhagen University Hospital, Copenhagen, Denmark; [5]Department of Epidemiology Research, Statens Serum Institut, Centre for Cancer Research, Danish Cancer Society, Copenhagen, Denmark; [6]Department of Dermatology, Zealand University hospital – Roskilde, Roskilde, Denmark; [7]Department of Clinical Neurophysiology, University of Copenhagen, Copenhagen, Denmark; [8]Department of Biomedicine, Aarhus University, Aarhus, Denmark; [9]deCODE genetics/Amgen, Inc., Sturlugata 8, Reykjavik 101, Iceland; [10]Department of Clinical Immunology, Zealand University Hospital – Køge, Køge, Denmark; [11]Statens Serum Institute, Copenhagen, Denmark; [12]Institute of Biological Psychiatry Mental Health Centre, Sct. Hans, Copenhagen University Hospital—Roskilde, Roskilde, Denmark.

‡ These authors share senior authorship.

Structured Graphical Abstract

Key Question

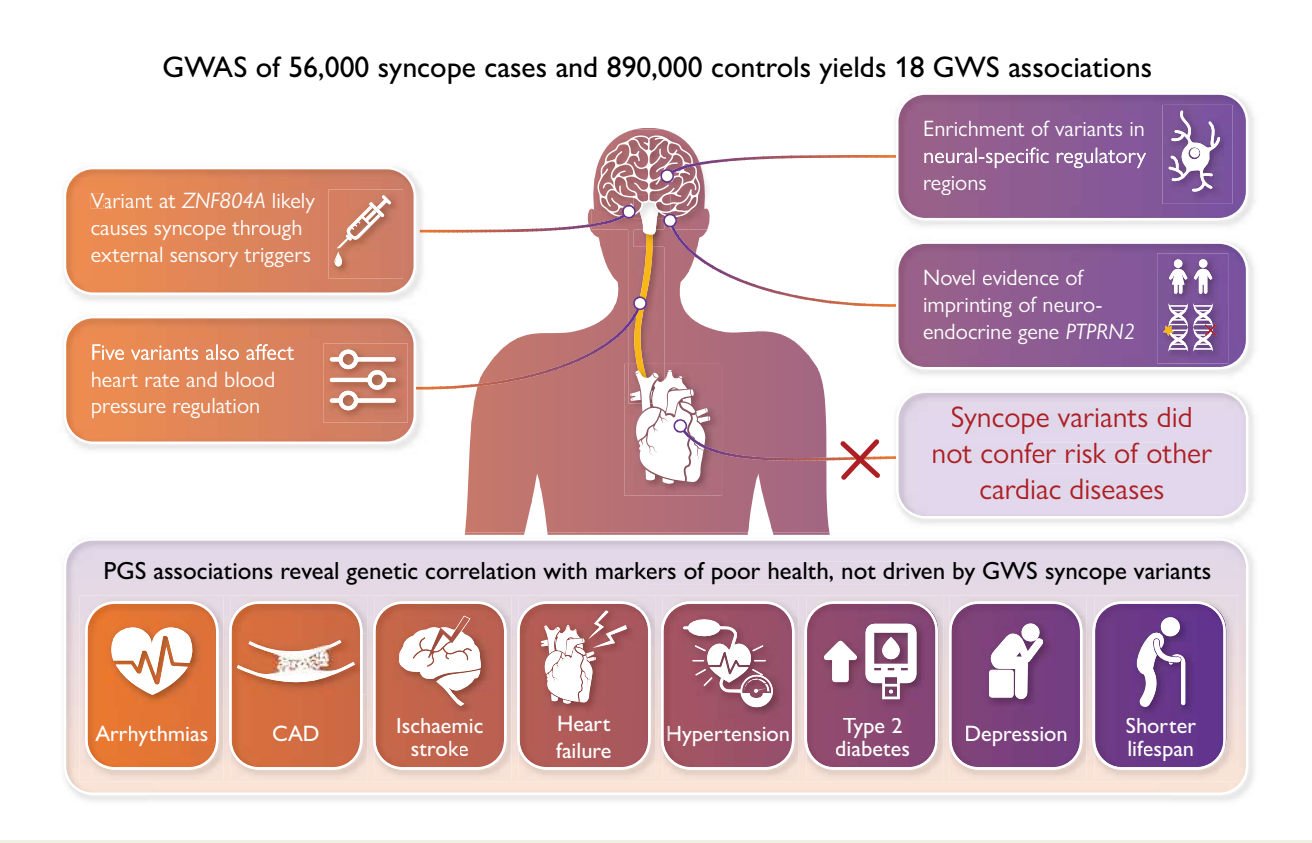
What is the genetic background of syncope? Can we further assess the aetiology of genetic associations with syncope through subphenotypes and other traits? Is there genetic correlation with other traits?

Key Finding

Eighteen genome-wide significant associations with syncope were found, which were preferentially located in neural-specific regulatory regions. Syncope variants did not confer risk of other disorders. Polygenic score analysis demonstrated genetic correlation with other disorders.

Take Home Message

The identified genetic associations with syncope point to neural regulatory processes and implicate the vasovagal reaction and autonomic heart rate and blood pressure regulation but not cardiovascular diseases.



The genetic architecture of syncope was investigated using large-scale GWAS data from several populations of European descent. A total of 18 sequence variants associated with syncope, which were significantly enriched in regulatory elements specific to neural tissue. There was no evidence that the syncope associations were mediated through cardiovascular or other diseases, but genetic correlation with poor cardiovascular and mental health was observed.

Keywords Syncope • GWAS • Meta-analysis • Vasovagal reaction • *PTPRN2* • Imprinting

Abstract

Aims Syncope is a common and clinically challenging condition. In this study, the genetics of syncope were investigated to seek knowledge about its pathophysiology and prognostic implications.

Methods and results This genome-wide association meta-analysis included 56 071 syncope cases and 890 790 controls from deCODE genetics (Iceland), UK Biobank (United Kingdom), and Copenhagen Hospital Biobank Cardiovascular Study/Danish Blood Donor Study (Denmark), with a follow-up assessment of variants in 22 412 cases and 286 003 controls from Intermountain (Utah, USA) and FinnGen (Finland). The study yielded 18 independent syncope variants, 17 of which were novel. One of the variants, p.Ser140Thr in *PTPRN2*, affected syncope only when maternally inherited. Another variant associated with a vasovagal reaction during blood donation and five others with heart rate and/or blood pressure regulation, with variable directions of effects. None of the 18 associations could be attributed to cardiovascular or other disorders. Annotation with regard to regulatory elements indicated that the syncope variants were preferentially located in neural-specific regulatory regions. Mendelian randomization analysis supported a causal effect of coronary artery disease on syncope. A polygenic score (PGS) for syncope captured genetic correlation with cardiovascular disorders, diabetes, depression, and shortened lifespan. However, a score based solely on the 18 syncope variants performed similarly to the PGS in detecting syncope risk but did not associate with other disorders.

Conclusion The results demonstrate that syncope has a distinct genetic architecture that implicates neural regulatory processes and a complex relationship with heart rate and blood pressure regulation. A shared genetic background with poor cardiovascular health was observed, supporting the importance of a thorough assessment of individuals presenting with syncope.

Introduction

Syncope, defined as a transient loss of consciousness resulting from cerebral hypoperfusion, is a common condition estimated to affect 20%–40% of the general population during their lifetime.[1–3] Both the evaluation and the management of syncope pose a substantial challenge to clinicians. It is often difficult to establish the underlying cause, and up to half of cases are of undetermined aetiology after diagnostic work-up.[4] Furthermore, the prognosis is variable and challenging to predict.[1–3,5] Thus, an improved understanding of the pathophysiology of syncope is called for, to which genetic research could provide important contributions.

Most syncopal episodes are deemed neurocardiogenic, also known as vasovagal syncope (VVS).[3] VVS is mediated through a primary vasovagal reaction (VVR) to various triggers, causing cardioinhibition and/or vasodilation, accompanied by a drop in blood pressure.[2,3,6] Although VVS is benign in most cases, some individuals suffer from recurrent episodes with a concurrent risk of injury and reduced quality of life.[7] Syncope is also commonly caused by arrhythmias or structural heart disease (cardiac syncope) or autonomic insufficiency (including orthostatic syncope).[3,6,8,9] Cardiac syncope is associated with the highest risk of morbidity and mortality.[2,3] The distribution of age at first syncopal episode is bimodal, peaking in teenage years and again around 70 years of age.[10,11] The proportion of syncope attributed to non-VVS rises substantially with age, but age-related physiologic changes in autonomic adaptability and the added burden of comorbidity and polypharmacy increase susceptibility to all types of syncope.[3,9,11,12]

Family and twin studies have indicated a complex pattern of inheritance in VVS.[13–15] Some common variants in candidate gene studies have been linked to tilt table test outcomes or VVS in small samples, but replication is lacking.[16] A candidate gene study of VVS in 160 subjects found sex-specific associations with common variants in genes involved in serotonergic pathways.[17] The only published genome-wide association study (GWAS) of syncope with ~9000 cases reported an association at 2q32.[18] It is proposed to confer the risk of syncope through the nearby gene *ZNF804A*, which is involved in brain development.[19]

In this study, we performed a GWAS meta-analysis of 56 071 cases and 890 790 controls of European descent derived from three countries and tested the identified variants in data from two additional populations. We tested the syncope variants for association with VVR during blood donation and other relevant phenotypes and investigated their functional genomic annotations to gain insight into the underlying biology. Finally, we used genetic scores and Mendelian randomization (MR) to explore relationships between syncope and other traits.

Methods

Meta-analysis study populations

The main elements of the study design are presented in Supplementary material online, *Figure S1*. First, we searched for syncope associations by performing a meta-analysis of GWAS data on 56 071 cases and 890 790 controls from three European countries; deCODE genetics in Iceland, UK Biobank[20] and a combined Danish sample from the Copenhagen Hospital Biobank Cardiovascular Study (CHB-CVS)[21] and the Danish Blood Donor Study (DBDS).[22] These studies have been approved by the Icelandic Data Protection Authority and the National Bioethics Committee of Iceland (VSNb2015030022 and VSNb2015120006), the National Committee on Health Research Ethics in Denmark (NVK-1708829 and NVK-1900988), and the Danish Data Protection Agency (P-2019-93 and P-2019-99). The UK Biobank data were accessed under application number 56 270. Syncope cases were defined by the International Classification of Diseases (ICD) code for syncope and collapse (ICD-10: R55, ICD-9: 780.2, ICD-8: 7825), in addition to 698 self-reported cases from the deCODE health study.[23] The association of the syncope variants with recurrent syncope was tested using a subset of syncope cases with repeated recordings of syncope diagnoses (recurrent syncope).

We used extensive phenotype data to assess whether the syncope associations were attributable to other disorders, such as cardiovascular disease, and to determine whether the variants affected specific syncope subgroups based on age at first documented syncopal episode, comorbid heart disease, use of blood pressure and/or heart rate (BP/HR)-lowering medication, and source of diagnosis. We also tested variants for

association with VVR occurring at a 450 mL blood donation session (961 cases from the DBDS).[22]

Genome-wide association study analysis

Treating phenotype status as the response and allele count as a covariate, we applied logistic regression to test for association between sequence variants and syncope in each group and then performed a meta-analysis. To determine thresholds for genome-wide significance, we grouped variants according to functional annotations from Ensembl Variant Effect Predictor[24] when correcting for multiple testing, yielding thresholds ranging from 3.9×10^{-10} for lowest-impact variants to 1.3×10^{-7} for highest-impact variants.[25]

Additional populations

We assessed the syncope variants in a separate meta-analysis of 22 412 syncope cases and 286 003 controls, combining publicly available GWAS summary statistics from the biobank FinnGen in Finland (see URL https://r7.finngen.fi/) and our GWAS of syncopecases and controls from Intermountain Healthcare in Utah, USA, genotyped and analysed at deCODE genetics.

Functional analyses

We assessed the potential consequences of coding syncope variants on protein function, using predictive models by AlphaFold.[26] The functional role of the syncope variants was further examined using ENCODE's encyclopaedia of DNA regulatory elements,[27,28] with regard to tissue-specific mechanisms, and in-house and publicly available data on gene expression (*cis*-eQTL) and proteomics (pQTLs). For the pQTL analysis, we tested associations of syncope variants with protein levels in plasma samples from deCODE and UK Biobank, obtained using high-throughput protein assays, SomaScan[29] (deCODE) and Olink[30] (UK Biobank), detecting 4907 and 1459 proteins, respectively.

Furthermore, the GWAS summary statistics were analysed with regard to gene and tissue set enrichment using Data-Driven Expression-Prioritized Integration for Complex Traits (DEPICT).[31] We also utilized the Icelandic syncope GWAS to estimate narrow-sense SNP heritability (h2g) enrichment of variants in 16 tissue-specific functional elements, using stratified LD score regression (S-LDSC).[32] Fifteen other categories (based on chromatin state, conservation, and predicted impact) were included in the regression.

Genetic correlation analyses

We calculated a polygenic score (PGS) for syncope ($PGS_{syncope}$) using LDpred[33] and a genetic score based only on the effects of the 18 genome-wide significant syncope variants (GS_{18}) and examined their correlation with syncope and other traits. Finally, we applied PGSs for potentially causal or genetically correlated phenotypes to assess their role in syncope risk, with subsequent MR analysis to evaluate causality.

For further details, see *Supplementary Methods*.

Results

Meta-analysis yields 18 genome-wide significant associations

We conducted a meta-analysis of three syncope GWASs, from deCODE genetics (Iceland), the UK Biobank, and the CHB-CVS/DBDS (Denmark), including 56 071 cases and 890 790 controls. Case characteristics and comorbidities are outlined in Supplementary material online, *Table S1*. In concurrence with epidemiological studies,[11,34] we observed a bimodal distribution of age at first documented syncopal episode with one peak around 18–25 years of age and another after 50 years of age, with the earlier peak being more prominent among women than among men (*Figure 1*). There were differences in the distribution of age at first syncope between the populations that are most likely a consequence of the different recruitment strategies (see Supplementary material online, *Figure S2*).

The meta-analysis yielded 18 syncope variants under the additive model (*Table 1*, Supplementary material online, *Tables S2 and S3*, *Figure S3*). All variants are common (minor allele frequency (MAF) > 5%), and all associations are novel, except rs12465214 at chr2q32 (upstream of *ZNF804A*).[18] All variants associated with syncope in all three sample sets with concordant effects and $P < 0.05$, except for the *PKHD1* variant, which had $P > 0.05$ in the Danish GWAS (see Supplementary material online, *Table S2*).

We tested the variants in a combined GWAS dataset including 22 412 syncope cases and 286 003 controls from FinnGen and Intermountain (see Supplementary material online, *Table S4*). Fourteen variants, including the *PKHD1* variant, associated with syncope with $P < 0.05$ with the same effect direction as in the main meta-analysis but consistently with smaller effects. We conducted a power analysis,[35] taking into account scaled-down effects and the effective sample size in FinnGen and Intermountain (see *Supplementary Methods*), which yielded 13.2 expected variants with $P < 0.05$, which was in accordance with the 14 variants.

We calculated the narrow-sense SNP-heritability of syncope using the meta-analysis summary statistics and LD score regression. The fraction of heritability explained on an observed scale was 1.4% (SE = 0.1%), whereas on a liability scale, assuming a syncope prevalence of 30%, the fraction was 9.0% (SE = 0.7%).

The most significant syncope association was with rs12465214 near *ZNF804A* (OR = 1.10, $P = 3.6 \times 10^{-49}$). The variant associated with earlier age at first syncope ($\beta = -0.022$ SD, $P = 7.0 \times 10^{-4}$, *Table 1* and Supplementary material online, *Table S5*), but its effect size did not differ between age subgroups (first syncope before or after 40 years of age, Supplementary material online, *Table S6*). This variant also associated with a VVR during blood donation (OR = 1.22, $P = 2.2 \times 10^{-5}$, *Table 1*, Supplementary material online, *Table S7*), with a larger effect than for syncope overall ($P_{het} = 0.029$).

Leveraging long-range phasing of haplotypes, where the parent of origin is assigned to each haplotype in the deCODE samples,[36] we found that p.Ser140Thr (rs3800855) in *PTPRN2* (MAF = 14%) associated with syncope only when maternally inherited ($OR_{mat} = 1.12$, $P_{mat} = 5.3 \times 10^{-5}$, $OR_{pat} = 0.97$, $P_{pat} = 0.36$, $P_{het} = 5.1 \times 10^{-4}$). No parent-of-origin-specific effects were observed for the other variants, nor was there any significant heterogeneity of effects between male and female cases for any variant (see Supplementary material online, *Table S8*).

In the syncope subgroup analysis, the variant at *MC4R* had a higher effect among those with first syncope after 40 years of age and variants in *MAML3* and *AGBL1* had higher effects in those without comorbid heart disease after correcting for multiple testing (four tests were performed for 18 variants, resulting in the threshold $P_{het} < 5.6 \times 10^{-4}$). Several other variants exhibited heterogeneity between subgroups using a nominal threshold ($P_{het} < 0.05$, *Table 1*, Supplementary material online, *Table S6*).

No variants had higher effects in comorbid heart disease or BP/HR lowering medication subgroups (see Supplementary material online, *Table S6*). None of the variants had significantly different effects in the recurrent syncope subset compared with syncope in the main meta-analysis (see Supplementary material online, *Table S9*).

Functional analysis of syncope variants points to involvement of neural-specific regulatory regions

We prioritized causal genes by evaluating the effect of the syncope variants, and highly correlated variants ($R^2 > 0.8$), on amino acid sequence, mRNA expression in in-house and external transcriptomics

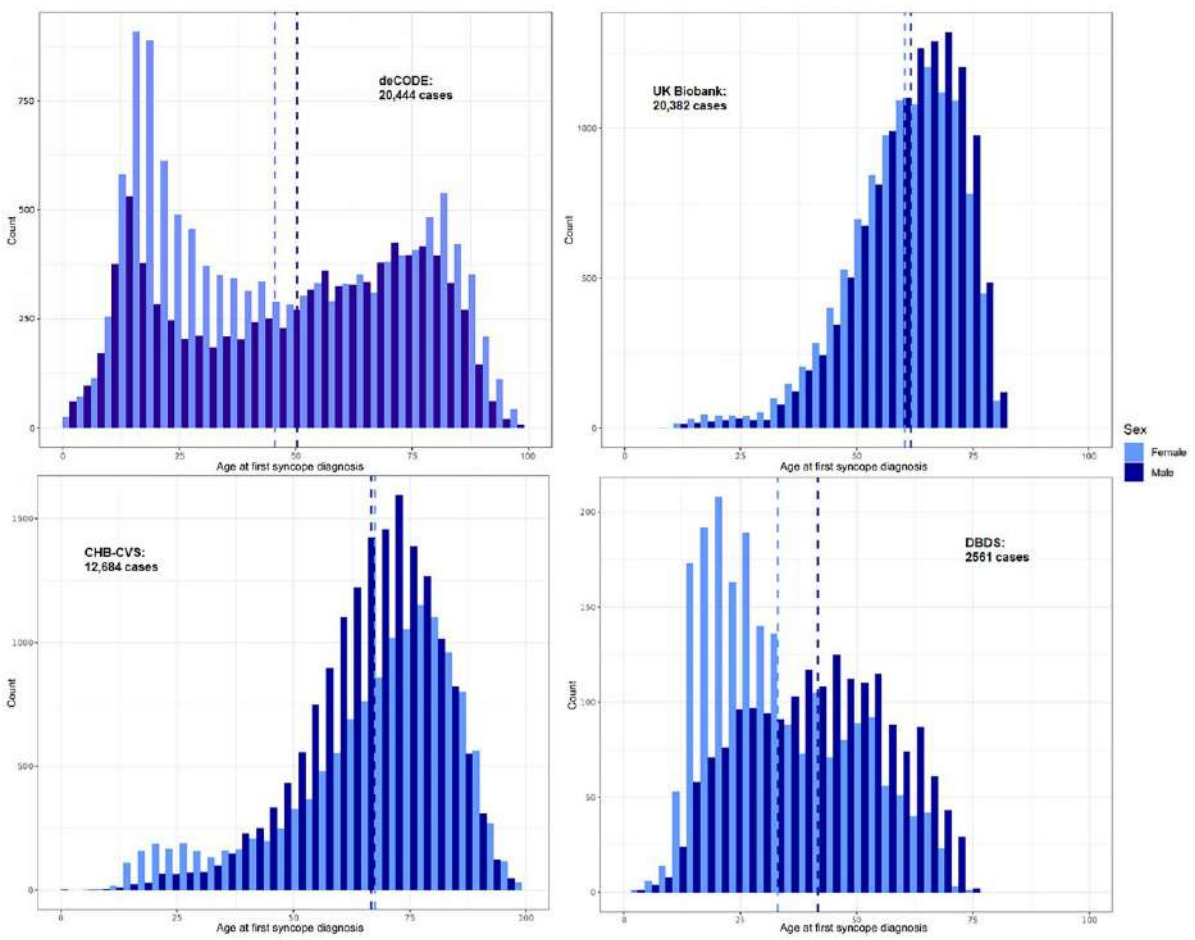


Figure 1 Histograms showing the distribution of estimated age at first syncope episode, based on first documented diagnosis among the different syncope cohorts. Men are represented with dark blue and women with light blue. The vertical dotted lines represent mean values for each sex. CHB-CVS and DBDS were combined as one dataset in the meta-analysis but are shown separately to depict the difference in age distribution. Sex proportions among syncope cases are as follows: 57.6% women and 42.4% men in deCODE, 48.9% women and 51.1% men in UK Biobank, 43.8% women and 56.2% men in CHB-CVS, and 53.3% women and 46.7% men in DBDS.

datasets (*cis*-eQTLs), protein plasma levels in deCODE and UK Biobank proteomics datasets (pQTLs), and proximity to genes (see *Supplementary Methods*). Two syncope variants were missense (p.Pro279His in *TTC30A* and p.Ser140Thr in *PTPRN2*). No syncope variants were found to affect gene expression or protein levels. Therefore, one candidate gene per locus was prioritized by effect on amino acid sequence (in *TTC30A* and *PTPRN2*) or proximity (non-coding variants) (*Table 1*).

The potential effects of the missense variants on protein function were assessed through predictive structural models.[26] The model for neurosecretory vesicle protein phogrin, encoded by *PTPRN2*,[37] is low confidence in the position of p.Ser140Thr but predicts that the variant is situated in an alpha helix in the extracellular domain of this transmembrane protein. Serine and threonine are highly similar amino acids, and this substitution is not deemed likely to have deleterious effects.[38] On the other hand, p.Pro279His in *TTC30A*, caused by the minor allele that protects against syncope, is predicted to be damaging.[38] According to a high-confidence structural model,[26] proline at position 279 forms a hydrogen bond with valine at position 239. Disruption of this bond by substitution with histidine might impact the structural stability of the protein. The function of TTC30A is not well known, but it is thought to play a role in intraflagellar transport.[39]

Seven of the 18 prioritized genes (*ZNF804A*, *ANKFN1*, *PCDH20*, *MC4R*, *RNF220*, *CSMD3*, and *PTPRN2*) are expressed more in the brain than in other tissues as reported by Human Protein Atlas.[40] However, the meta-analysis summary results did not yield a significant enrichment of gene, tissue, or cell-type sets in DEPICT,[31] with an estimated false discovery rate (FDR) > 0.2 for all sets (see Supplementary material online, *Tables S10* and *S11*).

To shed further light on the functional role of the syncope associations, we annotated the 18 syncope variants (including correlated variants with $R^2 > 0.8$) according to ENCODE's encyclopaedia of DNA regulatory elements and tissue-specific open chromatin regions[27,28] (see Supplementary material online, *Table S12*). Out of 16 possible tissue-specific annotation categories, syncope variants (or correlated variants) were most frequently found within neural-specific regulatory regions (12 out of 18 loci, $P = 2.0 \times 10^{-3}$, see *Supplementary Methods*).

Two of the neural-specific annotations refer to the syncope variants themselves, rs9714119 in *SATB1* and rs12906962 at *MCTP2*. The latter is not in LD ($R^2 > 0.8$) with any other variants and therefore is most likely to have a role in the syncope association. Two other neural-specific annotations refer to variants correlated with the missense syncope variants in *TTC30A* and *PTPRN2*. The associations are more likely to exert their effects through alterations in encoded proteins rather than the non-coding regulatory functions of correlated variants, although we cannot exclude the possibility of more than one causal variant on the same haplotype.

We applied S-LDSC to the deCODE GWAS summary statistics[32] to estimate narrow sense SNP heritability (h2g) enrichment for annotated sets of sequence variants (see *Supplementary Methods*). In addition to the 16 tissue-specific annotations, this analysis also included 15 other annotations based on impact on transcription, histone modification, and conservation. The analysis did not show tissue-specific enrichment (see Supplementary material online, *Table S13*) but revealed a significant enrichment of variants in DNA elements that are highly conserved in humans and other mammalian species, i.e. sites with less variation than would be expected under neutral evolution ($P = 1.2 \times 10^{-4}$), and a significant depletion in transcribed regions ($P = 4.3 \times 10^{-6}$).

Diverse associations of syncope variants with heart rate and blood pressure

To further characterize the syncope variants, we tested them for associations with related phenotypes in combined deCODE, UK Biobank, and CHB-CVS/DBDS datasets (*Table 1*, Supplementary material online, *Tables S14–S32*). These included cardiovascular, neuropsychiatric, and endocrine disorders, as well as blood pressure, heart rate, electrocardiogram measurements, various laboratory blood measurements, anthropometric traits, lifespan, and grip strength as a predictor of overall health[41] (see Supplementary material online, *Table S14*). After verification through colocalization analysis (see Supplementary material online, *Tables S33 and S34*), seven syncope variants associated with one or more phenotypes ($P < 0.05/816$ tests $= 6.1 \times 10^{-5}$). Syncope risk alleles at *MAML3* and *SATB1* associated with less depression risk (OR = 0.98, $P = 4.6 \times 10^{-6}$) and lower blood HbA1c levels ($\beta = -0.010$, $P = 1.0 \times 10^{-6}$), respectively. Other associations were with heart rate and blood pressure traits and are shown in *Figure 2*. We observed previously reported associations at *RNF220, BCL11A*, and *MCTP2* with resting heart rate (RHR), heart rate increase in response to exercise (HRinc), and heart rate recovery after exercise (HRR10-50, numbers represent seconds after exercise cessation), as well as blood pressure in the case of the *MCTP2* variant.[42–44] Additionally, the variant at *CSMD3* associated with HRR10 and the *PKHD1* variant associated with RHR. Although the *PKHD1* variant is in high LD with a variant for diastolic blood pressure ($R^2 = 0.88$), colocalization analysis did not support a joint association with syncope (see Supplementary material online, *Tables S24 and S33*). The effects associated with heart rate and blood pressure traits were directionally inconsistent with syncope risk (*Figure 2*).

Correlation of $PGS_{syncope}$ with syncope and other traits

A PGS for syncope ($PGS_{syncope}$) based on the UK Biobank GWAS associated with syncope in the deCODE data (OR = 1.17, $P = 2.7 \times 10^{-60}$ for each SD increase in $PGS_{syncope}$), and the effect was consistent in all syncope subgroups (see Supplementary material online, *Table S35*). There was a linear increase in syncope prevalence with rising $PGS_{syncope}$, and this was more prominent among women (see Supplementary material online, *Figure S4*).

We tested the association of $PGS_{syncope}$ with the same phenotypes used to test for association with the individual syncope variants, except for HRinc and HRR10-50 (individual data not available) (see Supplementary material online, *Table S35*). After accounting for multiple testing, a higher $PGS_{syncope}$ associated with an increased risk of hypertension, hypotension, ischaemic stroke, atrial fibrillation, sick sinus syndrome, atrioventricular block, heart failure, type 2 diabetes, use of BP/HR-lowering medications and depression, increased systolic blood pressure, and shortened lifespan (*Figure 3*, Supplementary material online, *Table S36*).

GS_{18} performs similarly to $PGS_{syncope}$ in assessing syncope susceptibility

We also generated a genetic score of the 18 syncope variants (GS_{18}) using weights from the UK Biobank data (see *Supplementary Methods*). GS_{18} associated with syncope with a similar effect to the $PGS_{syncope}$ (OR = 1.18, $P = 3.6 \times 10^{-70}$ for each SD increase in GS_{18}, $P_{het} = 0.52$, Supplementary material online, *Figure S4*). The effect of GS_{18} was consistent in all syncope subgroups (see Supplementary material online, *Table S35*), but the score did not associate with any other phenotypes after accounting for multiple testing (*Figure 3*, Supplementary material online, *Table S37*). It associated with nominal significance with orthostatic hypotension (OR = 1.05, $P = 8.4 \times 10^{-3}$), atrial fibrillation (OR = 1.02, $P = 0.018$), and depression (OR = 1.02, $P = 0.040$).

Polygenic score for coronary artery disease and major depressive disorder associate with syncope

We used PGSs to examine the relationship of exposure phenotypes with syncope. PGSs for 27 phenotypes, including cardiovascular and neuropsychiatric disorders, heart rate and blood pressure traits, body mass index, and height were constructed based on the largest published meta-analyses (not including deCODE data) or UK Biobank data if no larger studies were available. The PGSs were then tested for association with syncope in the deCODE data (see Supplementary material online, *Table S38*).

PGSs for coronary artery disease (PGS_{CAD}) and major depressive disorder[45] (PGS_{MDD}) associated with syncope (OR = 1.04, $P = 9.2 \times 10^{-5}$ and OR = 1.03, $P = 3.8 \times 10^{-4}$, respectively, for each SD increase in PGSs). We subsequently tested the heterogeneity of their effect on syncope risk between different syncope subgroups ($P_{het} < 0.05/8$ tests $= 6.3 \times 10^{-3}$, Supplementary material online, *Table S35*) and found that PGS_{CAD} had a higher effect for syncope cases with heart disease, those on BP/HR-lowering medication, and those diagnosed in hospital, when compared with opposing subgroups (*Figure 4*). PGS_{MDD} had a higher effect for those not on BP/HR-lowering medication.

To assess whether CAD and MDD contribute directly to syncope, we performed MR analysis applying reported genome-wide significant CAD[46] and depression[47] variants, using an inverse variance weighted (IVW) method to test for correlation, followed by sensitivity analyses for pleiotropy (weighted median MR[48] and MR-Egger[49]) (see Supplementary material online, *Table S39*).

For CAD, the IVW results showed a weak but positive correlation ($\beta = 0.054$, $P = 7.2 \times 10^{-4}$), with a similar slope in weighted median regression ($\beta = 0.057$, $P = 0.016$), and the MR-Egger intercept test was not significant ($P = 0.295$). For depression, the IVW regression was

Table 1 Association results for lead variants of the 18 genome-wide significant syncope associations in a meta-analysis of 56 071 cases and 890 790 controls

Rs-Name Position (Hg38)	Annotation Candidate gene	EA/OA	EAF	OR (95% CI)	*P*	Higher effect in syncope subgroups[a]	Associations with other phenotypes and direction of effects[b]
rs12465214 chr2:184333408	Intergenic *ZNF804A*	C/A	49%	1.10 (1.09, 1.11)	3.6×10^{-49}	(No comorbid heart disease, no BP/ HR-lowering medication)	↓Age at first syncope ↑VVR at blood donation
rs1431318 chr17:56115162	Intron *ANKFN1*	A/G	37%	1.07 (1.06, 1.08)	5.9×10^{-26}		
rs9598328 chr13:61607185	Intergenic *PCDH20*	A/C	24%	1.08 (1.06, 1.10)	1.4×10^{-24}	(Age at first syncope ≤40)	
rs4522506 chr18:60684457	Intergenic (DHS) *MC4R*	C/T	51%	1.07 (1.06, 1.08)	7.4×10^{-22}	Age at first syncope >40	
rs138695974 chr2:188171717	Intergenic *GULP1*	G/A	18%	1.07 (1.05, 1.09)	2.5×10^{-16}		
rs7130801 chr11:106897435	Intron *GUCY1A2*	C/T	84%	1.07 (1.05, 1.09)	1.6×10^{-15}		
rs10027044 chr4:139932418	Intron *MAML3*	A/G	61%	1.06 (1.04, 1.08)	3.5×10^{-15}	No heart disease	↓Depression
rs2175484 chr8:113995166	Intergenic *CSMD3*	T/C	24%	1.05 (1.04, 1.06)	1.1×10^{-12}		↓HRR10
rs272564 chr1:44546601	Intron (DHS) *RNF220*	C/A	27%	1.05 (1.04, 1.06)	4.0×10^{-12}	(No HR/BP-lowering medication)	↑RHR ↓HRinc, HRR20-50 and PP
rs1326587 chr6:51808886	Intron *PKHD1*	T/C	76%	1.05 (1.04, 1.06)	4.1×10^{-12}		↑RHR
rs1442874 chr2:59799833	Intergenic *BCL11A*	A/T	37%	1.05 (1.04, 1.06)	1.0×10^{-11}		↑RHR ↓HRinc, HRR10-50
rs1000400 chr11:115539903	Intergenic *CADM1*	A/G	33%	1.05 (1.04, 1.07)	1.6×10^{-11}		
rs9714119 chr3:18370866	Intron *SATB1*	T/C	40%	1.04 (1.03, 1.05)	1.5×10^{-10}	(Age at first syncope ≤40)	↓HbA1c
rs11195808 chr10:112063924	Intergenic *GPAM*	A/G	89%	1.08 (1.05, 1.11)	3.0×10^{-10}		
rs76812931 chr15:86399684	Intron *AGBL1*	G/A	5%	1.10 (1.07, 1.13)	3.3×10^{-10}	No heart disease	
rs61742858 chr2:177617866	p.His279Pro *TTC30A*	G/T	80%	1.05 (1.03, 1.07)	3.3×10^{-10}	(Age at first syncope >40)	
rs12906962 chr15:94768842	Intergenic (DHS) *MCTP2*	T/C	71%	1.05 (1.03, 1.07)	4.1×10^{-10}	(Age at first syncope >40)	↓RHR, HTN, SBP and DBP ↑HRinc, HRR20-50
rs3800855 chr7:158192457	p.Ser140Thr *PTPRN2*	G/C	14%	1.06 (1.04, 1.08)	1.0×10^{-9}		

All effects are shown for the syncope risk increasing allele. EAF is given for the deCODE cohort. Adjusted GWS thresholds (*P*) according to variant annotation: Non-DHS intergenic or intron variants: 3.9×10^{-10}, DHS site intergenic or intron variants: 1.2×10^{-9}, Missense in-frame variants: 2.6×10^{-8}.

EA, effect allele; OA, other allele; EAF, effect allele frequency; OR, odds ratio; CI, confidence interval; DHS, DNAse hypersensitivity site; HR, heart rate; BP, blood pressure; VVR, vasovagal reaction; RHR, resting heart rate; HRR, heart rate response to recovery; HRinc, heart rate response to exercise; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

[a]Subgroups where a variant's effect was higher under a Bonferroni-adjusted threshold ($P_{het} < 5.6 \times 10^{-4}$) are shown without parentheses, and subgroups where a variant's effect was higher with nominal significance ($P_{het} < 0.05$) are shown in parentheses. Numerical results are given in Supplementary material online, *Table S3*.

[b]Under a Bonferroni-adjusted threshold ($P < 6.1 \times 10^{-5}$) and after colocalization analysis. The upward-facing arrows indicate a positive effect and the downward-facing arrows indicate a negative effect of the EA. Numerical results are given in Supplementary material online, *Tables S15–S32*.

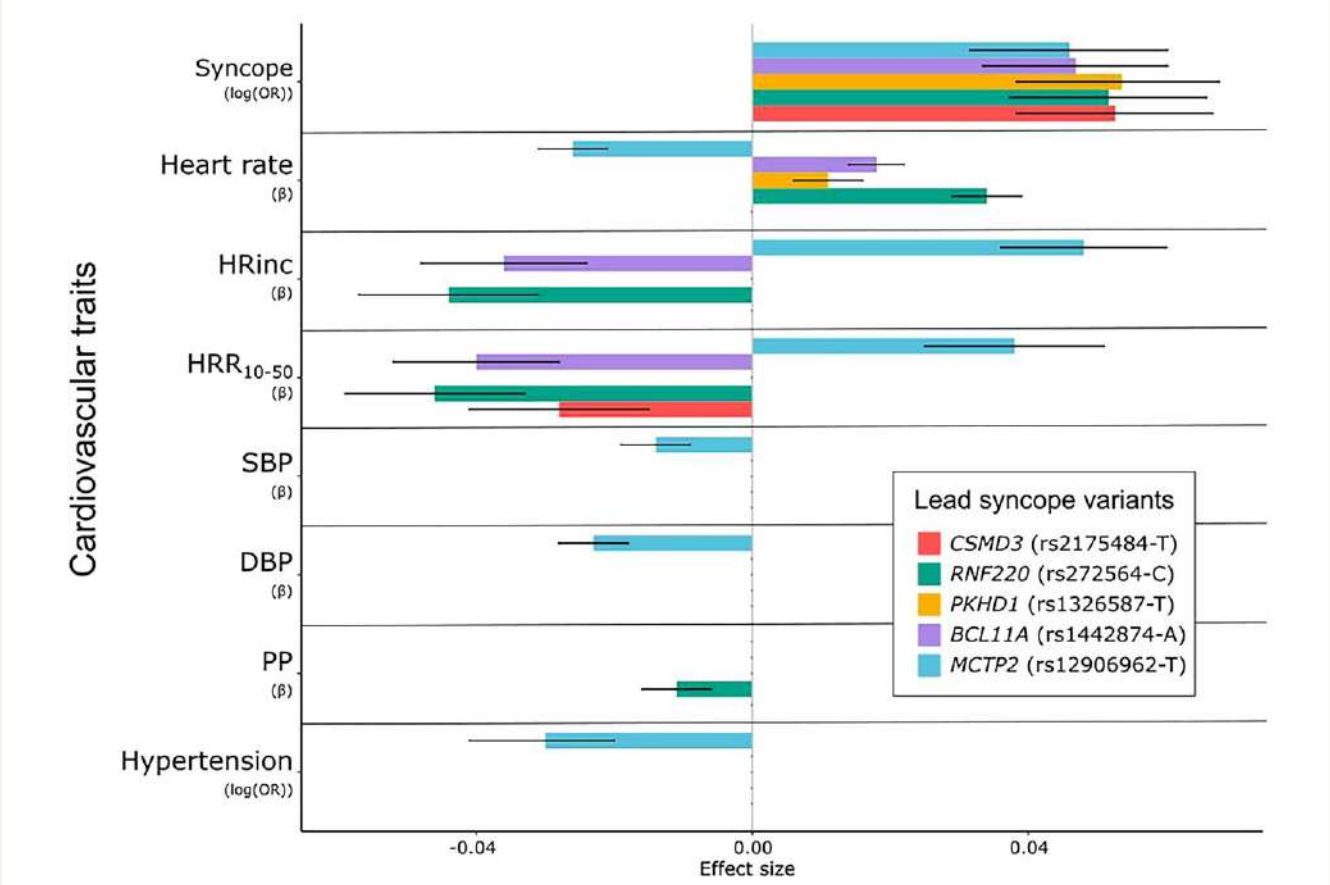


Figure 2 Significant associations of five syncope variants with cardiovascular phenotypes. Each variant is assigned a specific colour. β-values for quantitative traits are given in standard deviations (SD). The most significant association for a HRR10-50 trait is shown for each variant. If no bar is shown for a given variant, there is no independent association present with the phenotype, after verification through colocalization analysis. RHR, resting heart rate; HRinc, heart rate response to exercise, HRR10-50, heart rate response to recovery (numbers represent seconds after exercise cessation); SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

not significant after accounting for two tests ($P > 0.025$). These results, supported by the exposure-outcome effect plots (see Supplementary material online, *Figure S5*), support a causal role for CAD in synope but not for depression.

Enrichment of syncope associations among reported heart rate response variants

PGSs for heart rate response traits did not associate with syncope risk. Given the previously directionally inconsistent effects for these traits, we tested whether extremes in PGSs in either direction affected syncope risk but did not find higher syncope prevalence in either top or bottom percentiles (see Supplementary material online, *Figure S6*). We further tested associations with syncope among reported variants for heart rate response to exercise and recovery.[43] A total of 12 out of 22 variants (55%) were at least nominally significant for syncope ($P < 0.05$). However, directions and proportions of effects on syncope compared with heart rate response did not support a general causal relationship (see Supplementary material online, *Figure S7*). Enrichment of nominally significant syncope associations was less pronounced among reported variants for RHR[50] (12%) and blood pressure[51] (14%).

Discussion

We identified 18 syncope variants, 17 novel, in our study of 56 071 cases and 890 790 controls, with functional analysis highlighting neural regulatory processes. Several diseases are known to cause syncope, many of which are linked to adverse outcomes, and thus understanding whether the syncope variants are tagging serious causes or endpoints is of major importance. No variants associated with syncope with greater effects in subgroups with cardiovascular comorbidity and no syncope risk alleles associated with an increased risk of known cardiogenic causes of syncope or phenotypes indicating potentially malignant processes such as sudden cardiac death or reduced lifespan (*Structured Graphical Abstract*).

Our findings are supported by a genetic score based on the 18 syncope variants that associates only with syncope when accounting for multiple testing. The score associates nominally with less effect on orthostatic hypotension, which may be a consequence of a true contributing factor of autonomic dysfunction to some syncope associations. We note that while no syncope variant associates significantly with orthostatic hypotension or had a greater effect on orthostatic hypotension than on syncope, our orthostatic hypotension sample set was small, and more cases would provide a better effect estimate.

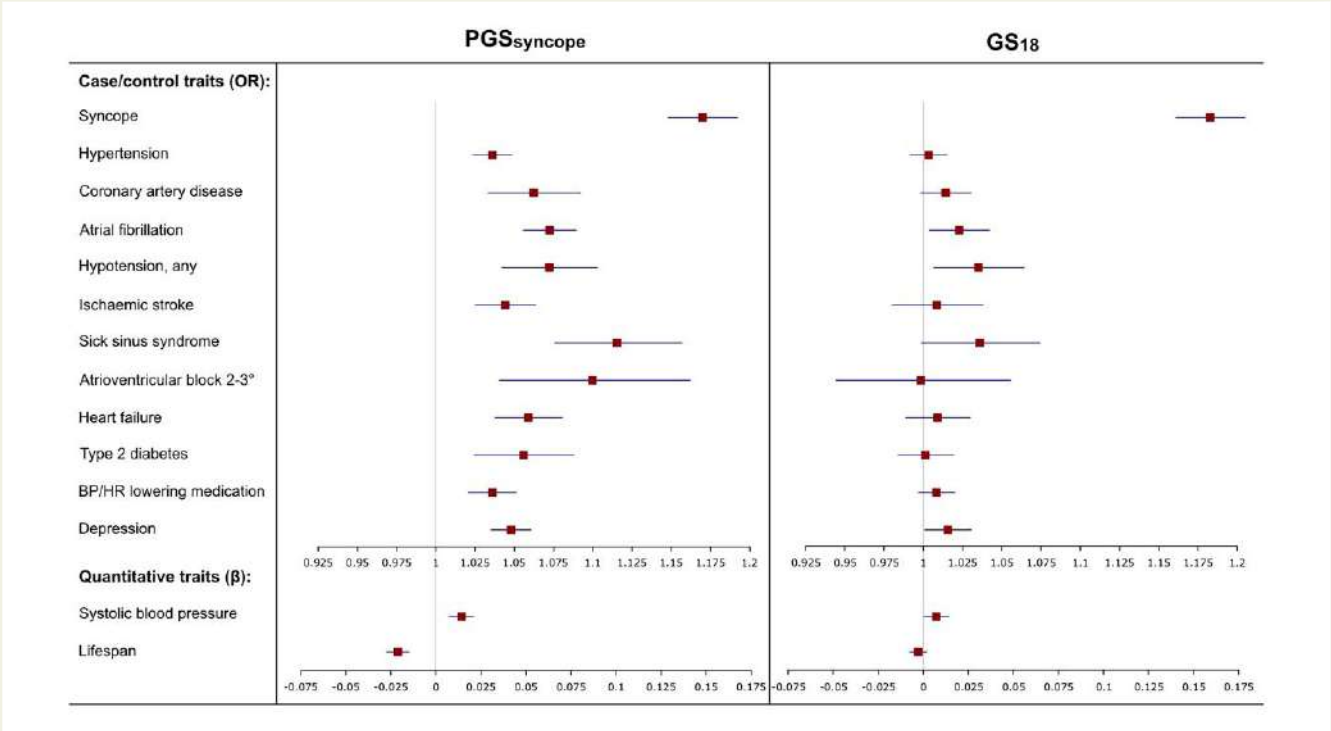


Figure 3 Association results of a polygenic score for syncope ($PGS_{syncope}$) and a genetic score based on the effects of the 18 genome-wide significant variants on syncope (GS_{18}), with individual risk of other phenotypes in deCODE data. Only the 14 phenotypes that associated with $PGS_{syncope}$ under a threshold corrected for multiple testing ($P < 1.3 \times 10^{-3}$) are shown. The forest plot shows effect estimates on the horizontal axis with a 95% confidence interval. Effects for case/control phenotypes are shown in odds ratio (OR) and effects for quantitative phenotypes (systolic blood pressure and lifespan) are given in standard deviations (SD). Effect estimates for these phenotypes reflect one SD increase in the scores.

Hence, the strongest genetic associations with syncope, identified in this study, do not implicate specific underlying diseases according to the available data, but rather suggest the involvement of neurally mediated reflexes and potentially impaired autonomic response.

Most cases in our study were identified based on an outpatient or hospital discharge diagnosis ICD-code for syncope and collapse. The code was reported to satisfy the definition of syncope in 95% of cases, in a hospital chart review study with a median age of 68.5.[4] Its reliability among younger individuals in an outpatient setting has not been assessed to our knowledge. The ICD-code should not include orthostatic hypotension, carotid sinus syncope, psychogenic syncope, or collapse without impaired consciousness but does not otherwise specify the likely cause.

The most significant syncope variant (at *ZNF804A*) associated with a VVR during a blood donation with a greater effect than for syncope. This suggests that it may mediate a VVR triggered by an external sensory stimulus, such as exposure to blood and needles or the anticipation of pain and blood loss.[52–54] *ZNF804A* is specifically expressed in the brain[40,55] and encodes a transcription factor involved in synaptic contact and neurodevelopment.[19] Several other variants associated nominally with VVR during blood donation, but the sample size may not provide enough power to conclusively capture other syncope variants that affect response to these triggers.

The missense variant p.Ser140Thr in *PTPRN2* affects syncope risk only when maternally inherited. *PTPRN2* is primarily expressed in brain and endocrine tissue and plays a role in neurotransmission through vesicle-mediated neuroendocrine signalling.[37,55,56] Although not experimentally confirmed, it is predicted to be imprinted by computational methods.[57–59] Parent-of-origin-specific phenotypic effects for p.Ser140Thr add strong evidence for the role of imprinting in *PTPRN2* expression.

Our analysis of syncope subgroups revealed that some variants associated differently with syncope depending on age. Effects of variants at *PCDH20* and *SATB1* suggest a greater involvement with earlier age at first syncope, a group more likely to report a prodrome and typical precipitating factors to VVS.[60,61] Both genes have reported roles in neuronal development and synaptic connectivity.[62–67]

Variants near *MC4R* and *MCTP2* had greater effects in later age at first syncope. Older VVS patients are more likely to report sudden unexplained falls, have more comorbidities, and experience age-related changes in autonomic regulation.[11,61] A study of late-onset syncope patients undergoing head-up tilt testing due to unexplained syncope showed that orthostatic hypotension and VVS are common precipitating factors and often coalesce.[34] *MC4R* is known to affect blood pressure regulation through preganglionic sympathetic and parasympathetic neurons.[68] The lead syncope variant near *MC4R* did, however, not associate with blood pressure.

The syncope risk allele near *MCTP2* associated with a lower RHR and blood pressure and a higher heart rate response, whereas four other variants (at *RNF220*, *BCL11A*, *CSMD3*, and *PKHD1*) associated with these traits with effects in the opposite direction. Although a decreased heart rate response is a plausible cause of syncope, our analyses do not suggest a direct causal effect of heart rate response variants, but rather that diverse biological pathways affect both phenotypes with disproportional effects.

We applied well-powered PGS analysis to explore the genetic correlation between syncope and other traits. $PGS_{syncope}$ associated

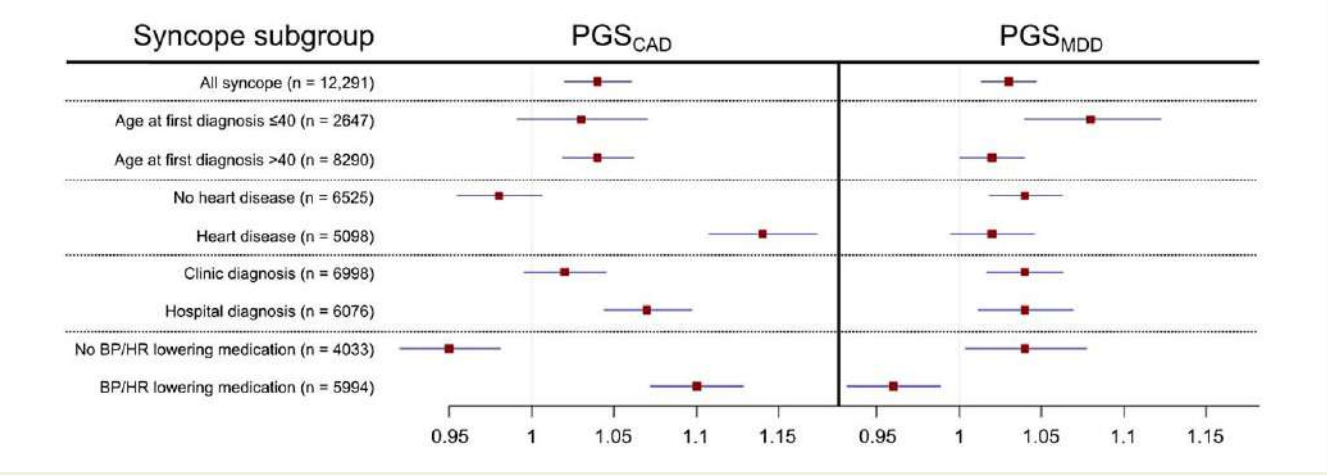


Figure 4 Association results of polygenic scores for coronary artery disease (PGS$_{CAD}$) and major depressive disorder (PGS$_{MDD}$) with syncope and different syncope subgroups in the deCODE sample. The forest plots show effect estimates given in odds ratios (OR) on the horizontal axis with a 95% confidence interval. ORs reflect one standard deviation increase in the PGSs. Heart disease includes ICD-10 based coronary artery disease (I20-25), arrhythmias/atrioventricular block (I44.1, I44.2, I45.6, I46.1, I47.1, I47.2, I47.9, I48, I49.0, I49.5), heart failure (I50), cardiomyopathy (I42), valvular disorders (I34-I37), pulmonary embolism (I26), or corresponding ICD-9/ICD-8 codes. Blood pressure/heart rate (BP/HR)-lowering medications include Anatomical Therapeutic Chemical codes C02, C03, C07, C08, and C09.

with syncope with a similar effect to that of GS$_{18}$, which was based only on genome-wide significant variants, but also associated with various cardiovascular diseases, type 2 diabetes, depression, and shortened lifespan. Therefore, PGS$_{syncope}$, which includes variants with a less stringent significance threshold, may capture effects mediated through comorbidities and polypharmacy. This contrast is also present in our analysis of regulatory elements, as we observed an enrichment of neural-specific elements among the 18 syncope variants, which was not the case when applying the summary data. When assessing individual risk, genetic scores based on summary data do not always offer additional power to that of using only established genome-wide significant variants.[69] In this case, a high PGS$_{syncope}$ that correlates with numerous markers of poor health would have an unclear meaning in individual risk assessment, whereas a high GS$_{18}$ in the absence of relevant medical history would likely support a favourable prognosis.

When we searched for risk factors that contribute directly to the development of syncope, we found that PGS$_{CAD}$ and PGS$_{MDD}$ associated with syncope, but the MR analysis provided support for causality of CAD only. The effect of PGS$_{CAD}$ on syncope is greater in subgroups with increased cardiovascular comorbidity. Thus, the effect may partly be explained by cases of cardiac and orthostatic syncope. Conversely, the effect of PGS$_{MDD}$ was similar in all subgroups except those on BP/HR-lowering medication. Epidemiological studies have shown correlation between the number of VVS episodes and prevalence of affective and anxiety disorders.[70,71] Several neural pathways are known to be involved in both autonomic regulation through the vagus nerve and depression, but the interplay with syncope remains poorly understood.[72–74] One potential factor is serotonin neurotransmission, as prior studies have shown a heightened vasovagal response to head-up tilt table testing after administering serotonin-elevating substance clomipramine,[75] and serotonin reuptake inhibitors have proved successful as treatment in some cases.[76] However, a crucial role for serotonin in VVS is debated.[77]

The absence of syncope association of PGSs based on large datasets for hypertension, heart failure, atrial fibrillation, aortic valve stenosis, heart rate, blood pressure, body mass index, height, and haemoglobin provides strong evidence against a substantial role for these traits in syncope.[78]

Strengths and limitations

The use of extensive phenotype and genotype data from large cohorts to find and interrogate sequence variants involved in syncope risk is a major strength of this study. This is reflected by the number of associations found and the implicated pathophysiology.

However, these methods also have limitations. The ICD-code for syncope does not distinguish between the different types or causes of syncope. As the three syncope populations in the meta-analysis include older individuals with heart disease, the GWAS may capture effects mediated through heart disease or other disorders. We found no evidence of this for the genome-wide significant variants when leveraging data on age, comorbidities, and medications. We cannot exclude a contributing factor of traits where data were small or unavailable. Rare diseases can likewise not be excluded as underlying causes, although this is highly unlikely, as all the variants were common. The heterogeneous background of syncope needs to be considered as a confounding factor when applying the GWAS summary statistics in further analyses, as seen in the association of PGS$_{syncope}$ with multiple disorders. Persons diagnosed with syncope frequently report a history of earlier fainting,[11] which increases our estimates of age at first syncope. Furthermore, many, especially younger individuals, do not seek assistance in the healthcare system following syncope,[79] and thus, the control groups are likely to include undiagnosed cases. This should, however, not cause false-positive associations, but this may cause a dilution of the effects of sequence variants. This limitation may subsequently cause an underestimation of explained heritability, which was found to be low in this study.

Conclusion

We describe 18 associations with syncope discovered in a large GWAS meta-analysis. There was no evidence that these associations were

mediated through known diseases. One variant associated with VVR during blood donation and five with heart rate and blood pressure traits with directionally inconsistent effects with regard to syncope risk. A functional assessment of the 18 variants implicates neural regulatory processes. A genetic score based on the 18 variants associates with syncope but not cardiovascular or other diseases. Such a score could potentially aid in individual risk assessment. PGS analysis based on GWAS summary statistics captures genetic correlation of syncope with poor cardiovascular health, depression, and shortened lifespan, reflecting a complex genetic background.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Data availability

The data underlying this article are available in the article, its *online supplementary material* and upon reasonable request to the corresponding author. The GWAS summary statistics from the syncope meta-analysis including deCODE, UK Biobank and CHB-CVS/DBDS are available at https://www.decode.com/summarydata. The UK Biobank data were accessed under application no. 56 270. FinnGen data are publicly available and were downloaded from https://finngen.fi.

Conflicts of interest

The following authors are employees of deCODE genetics/Amgen, Inc.: Hildur M Aegisdottir, Rosa B Thorolfsdottir, Gardar Sveinbjornsson, Olafur A Stefansson, Bjarni Gunnarsson, Vinicius Tragante, Lilja Stefansdottir, Thorgeir E Thorgeirsson, Egil Ferkingstad, Gudmar Thorleifsson, Michael L Frigge, Kristjan E Hjorleifsson, Erna V Ivarsdottir, Anna Helgadottir, Solveig Gretarsdottir, Valgerdur Steinthorsdottir, Asmundur Oddsson, Hannes P Eggertsson, Gisli H Halldorsson, Patrick Sulem, Gudmundur Norddahl, Gudrun Rutsdottir, Gudmundur Thorgeirsson, David O Arnar, Unnur Thorsteinsdottir, Daniel F Gudbjartsson, Hilma Holm, and Kari Stefansson.

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