Genome-wide association study identifies locus at chromosome 2q32.1 associated with syncope and collapse

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Aims	Syncope is a common condition associated with frequent hospitalization or visits to the emergency department. Family aggregation and twin studies have shown that syncope has a heritable component. We investigated whether common genetic variants predispose to syncope and collapse.
Methods and results	We used genome-wide association data on syncope on 408 961 individuals with European ancestry from the UK Biobank study. In a replication study, we used the Integrative Psychiatric Research Consortium (iPSYCH) cohort ($n = 86\,189$), to investigate the risk of incident syncope stratified by genotype carrier status. We report on a genome-wide significant locus located on chromosome 2q32.1 [odds ratio = 1.13, 95% confidence interval (CI) 1.10–1.17, $P = 5.8 \times 10^{-15}$], with lead single nucleotide polymorphism rs12465214 in proximity to the gene zinc finger protein 804a (*ZNF804A*). This association was also shown in the iPSYCH cohort, where homozygous carriers of the C allele conferred an increased hazard ratio (1.30, 95% CI 1.15–1.46, $P = 1.68 \times 10^{-5}$) of incident syncope. Quantitative polymerase chain reaction analysis showed *ZNF804A* to be expressed most abundantly in brain tissue.
Conclusion	We identified a genome-wide significant locus (rs12465214) associated with syncope and collapse. The association was replicated in an independent cohort. This is the first genome-wide association study to associate a locus with syncope and collapse.
Keywords	Syncope • Genetic • Genome-wide association study

1. Introduction

Syncope is defined as a transient loss of consciousness due to short-term global cerebral hypoperfusion.[1] It is characterized by sudden onset, short duration, and spontaneous recovery.[1,2] Syncope is a common condition in the general population and accounts for approximately 1% of all visits to European emergency departments.[3] It occurs more frequently in women than men, with the estimated incidence rates ranging from 2.6

to 19.5 per 1000 person-years. Highest incidence rate is seen in women aged >80.[4,5] Syncope can be classified into neurally-mediated reflex syncope (neurocardiogenic), syncope due to orthostatic hypotension, and cardiac syncope. Reflex syncope (vasovagal syncope; VVS), which is a subtype of neurally-mediated reflex syncope, is the most frequent type of syncope.[4] The overall mortality in relation to syncope and collapse has been reported to be 0.28% between 2000 and 2005 in the USA, and the highest risk of mortality has been observed for cardiac syncope.[6]

The predisposing factors for syncope comprise of a broad spectrum ranging from life-threating diseases, as well as side effects to pharmacological agents, to benign causes.[2,3] Syncope occurs frequently in patients with underlying cardiac disease, in particular in genetic cardiac arrhythmias, e.g. long and short QT syndromes,[7] Brugada syndrome,[8] and catecholaminergic polymorph ventricular tachycardia.[9] In the latter, syncope may be the only presenting symptom. Improved understanding of the pathophysiological mechanisms is therefore warranted. A recent Danish study on symptoms preceding sudden death in the young, revealed that syncope had occurred 24 h preceding death in 17% of victims.[10] Despite the high use of diagnostic tests, the diagnostic yield remains low (30–48%).[11]

Family aggregation studies of VVS have predominantly suggested complex inheritance,[12] and twin studies have shown higher concordance rates for VVS in monozygotic twin pairs compared with dizygotic twin pairs.[13]

Previous studies, that have associated genetic loci to syncope,[14–16] have suffered from small sample sizes ($n \sim 50$–150) and have failed to replicate. A genome-wide copy number variations (CNV) study of VVS, showed that CNV segments were longer in affected individuals compared with unaffected individuals.[17]

The UK Biobank project has extensive phenotypic and genotypic data on more than 500 000 participants from the general population, which enables researchers to study common traits. In the present study, we used UK Biobank metadata to examine the genetic basis underlying syncope and collapse.

2. Methods

2.1 Study population, UK Biobank

UK Biobank is a large, population-based, prospective cohort study with more than 500 000 participants aged between 40 and 69 years at time of recruitment (2006–2010). The biobank holds a variety of health-related information on participants, including health records, imaging, lifestyle indicators, cognitive function, biomarkers from blood and urine, and more.[18] Imputed genome-wide genotype data are available for all participants, including information on population structure, relatedness, and genotype level quality. A full description on analyses of genotype data and details on quality control are provided in the UK Biobank release paper by Bycroft et al.[19] In brief, several tests for marker-based quality control (QC) were performed including tests for batch effects, plate effects, deviations from Hardy–Weinberg equilibrium (HWE; $P < 10^{-6}$), sex effects, array effects, and discordance across control replicates. Thereafter, sample-based QC was performed, including tests for sex mismatch and extreme heterozygosity and high missing rates (>0.05). Pre-imputation, principal component analysis (PCA) was performed in both marker and sample-based QC. In the UK Biobank pre-imputation, there were 812 428 markers before QC, and 805 426 markers left after QC. A subset of ethnically matched samples with British ancestry was identified, based on PCA.[19] In this subset, syncope was defined using the International Classification of Disease (ICD)-9 code 780.2 and the ICD-

10 code R55. Cases were not excluded due to other concurrent diseases.

2.2 Replication cohort, Integrative Psychiatric Research Consortium

Since 1981, all new-born babies in Denmark have had dried blood spot samples collected for the Danish Neonatal Screening Biobank (DNSB) at Statens Serum Institute (SSI). The Integrative Psychiatric Research Consortium (iPSYCH) is a population-based study selected from a birth cohort comprised of all singleton individuals born in between the years 1981 and 2005 ($n = 1\,472\,762$). In total, 86 189 individuals have been selected. Hereof, 30 000 individuals were randomly selected to represent the general population and 57 764 individuals were diagnosed with at least one of six major psychiatric diagnoses (attention deficit/hyperactivity disorder, anorexia nervosa, autism spectrum disorder, affective disorder, bipolar affective disorder, or schizophrenia). Psychiatric diseases were identified using their unique civil registration number, which enables linkage to the National Patient Registry and Psychiatric Central Research Registry in which diagnoses are coded according to the ICD 10th revision (ICD-10). Diagnoses prior to 1994 were coded according to the ICD 8th revision, and converted to equivalent ICD-10 codes.

Dried blood spots were obtained from the DNSB for genotyping of the selected patients ($n = 86\,189$), as described previously by Pedersen et al.[20] Genotyping was performed at the Broad Institute on the Infinium PsychChip v1.0 array. DNA processing, genotyping, including imputation, was successful on 77 639 samples.

Single nucleotide polymorphisms (SNPs; $n = 246\,369$) were phased into haplotypes using SHAPEIT3 and imputed using Impute 2 with reference haplotypes from the 1000 Genomes Project phase 3, generating a total of 8 018 013 imputed variants. As a QC measure, variants with imputation quality (INFO <0.2), deviations from HWE ($P < 1 \times 10^{-6}$), association with imputation batch ($P < 5 \times 10^{-8}$), differing imputation quality between cases and controls ($P < 1 \times 10^{-6}$), and minor allele frequencies (MAFs) <0.01 were excluded. On a sample level, controls were made for abnormal sample heterozygosity, high levels of missing genotypes (>1%), sex concordance, inconsistencies among duplicate samples and sample relatedness. PCA and KING robust algorithm was used to identify a subset of unrelated ethnically matched individuals, as described previously by Schork et al.[21] Syncope and collapse was defined by ICD-8 code 782.5 or ICD-10 code R55.

2.3 The PheWeb browser

The Michigan PheWeb browser[22] is a publicly available resource generated from phenome-wide associations using UK Biobank that features 1403 in-house defined binary traits (UK Biobank application number 24460). Only variants with MAF >0.01 and info score >0.3 were used in the PheWeb browser.[23]

2.4 Estimation of statistical power

With an estimated disease prevalence of 0.01, ~9000 cases and 100 000 controls in the study cohort, odds ratio (OR) of 2, and a significant P-value defined as less than 0.05/1403 (traits in PheWeb), a disease allele frequency above 0.01 is needed in order to obtain a power of 0.9. Based on this, variants with a MAF <0.01 were excluded.

2.5 Statistical analyses

In the UK Biobank cohort, a logistic mixed model was implemented in the framework of the Scalable and Accurate Implementation and

Generalized mixed model (SAIGE) method.[23] This allows for having related individuals in the model. SAIGE also controls for inflated Type 1 errors which otherwise can arise with imbalanced case–control ratios in logistic mixed models. SAIGE first generate relatedness estimates and a null model. Thereafter, the null model is fitted with the respective SNP, the genetic kinship matrix and adjustment for age at recruitment, sex, array batch, and principal components 1–4.

In the iPSYCH cohort subset, the underlying time scale was age. Follow-up began at age one and all individuals were followed to the event of syncope, death, emigration, or 30 April 2017, which ever occurred first. The association between genotype and risk of syncope was assessed by a Cox regression analysis adjusted for sex. Absolute risk of syncope and collapse was predicted from the Cox regression model with death as a competing risk. The absolute risk is illustrated as cumulative incidence stratified by genotype and sex. We found no violation on proportional hazard model assumptions (Supplementary Information). We also replicated significant associations using logistic regression adjusted for age, sex, and the ten first principal components.

2.6 Partitioning of the heritability

Partitioned linkage disequilibrium score regression (LDSC) was used to estimate heritability attributable to cell-type groups and H3K4Me1 cell-type annotations, as described by Finucane *et al.*[24] The major histocompatibility region (MHC-region; chr6:25-35Mb) was excluded from analysis. We used previously computed linkage disequilibrium LD scores and allele frequencies based on data from the 1000 Genomes Project with European ancestry (see *URLs*).

Cell-types were grouped into: adrenal/pancreas, cardiovascular, central nervous system, connective bone, gastrointestinal, haematopoietic, kidney, liver, skeletal muscle, and other. Annotations from H3K4Me1 imputed gapped peaks were based on Roadmap Epigenomics Mapping Consortium data,[25] as described by Demontis *et al.*[26]

The authors of LDSC (see *URLs*) state that mixed model summary statistics should not be used to estimate SNP-heritability but can be used for genetic correlation and partitioned heritability. This genome-wide association study (GWAS) is analysed with a mixed model regression. Therefore, we did not evaluate the intercept and SNP heritability.

2.7 Genetic correlations of syncope and collapse with other traits

We investigated genetic correlation (r_g) of syncope and collapse with 20 other traits, using LDSC.[27] Traits were selected based on availability of appropriate summary statistics, widespread prevalence, relevance for public health and if deemed to have a biological plausible correlation with syncope (Supplementary material online, *Data S1*). The MHC region and SNPs with MAF <0.05 were excluded from analyses and only phenotypes with a mean χ^2 >1.02 were considered. Pre-computed LD scores for HapMap3 SNPs were used in the regression (see *URLs*). We applied Bonferroni correction and a $P < 0.05/20$ was considered significant.

2.8 Gene-set enrichment

We performed gene-set enrichment analyses using two independent methods, MAGMA v1.6[28] and MAGENTA v1.2.[29] The aim was to verify enrichment in equivalent biological pathways using both methods. Only autosomal SNPs, excluding the MHC region, with a MAF >0.01 were included in the analyses. Gene-sets ranged from 10 to 1000 genes. For MAGMA, the 1000 Genomes Project Phase 3 was used as a reference panel and gene sets ($n = 10\,655$) from MsigDB v5.2,[30] with a gene window of 5 kb at each end of the gene intervals. Default settings were used for analyses using MAGENTA with a combined gene set (GO, Panther, Ingenuity, KEGG, Reactome, Biocarta; $n = 10\,992$).

2.9 Biological and functional annotation

Functional mapping and annotation were made using FUMA v1.3.[31] Genome-wide significant SNPs with the lowest P and an $r^2 < 0.6$ from each other were defined as distinct significant SNPs and were used to define the border of the genomic risk locus.[31] Lead SNPs were defined by the same conditions but with $r^2 < 0.1$. Pairwise LD structure of SNPs was based on the 1000 Genomes Project Phase 3.[32] Variant annotation for each locus was made on distinct significant SNPs and SNPs in LD with these, with a maximum distance of 250 kb and $P < 0.05$, referred to as candidate SNPs. Gene mapping of annotated SNPs was based on genomic position (max distance 10 kb), expression quantitative trait loci (eQTL) and chromatin interaction studies. The eQTLs were identified from GTEx v.7 with a false discovery rate (FDR) <0.05. Annotated SNPs were assigned chromatin interaction states (FDR threshold <10^-6, 500 bp promoter region window) based on the most common of 15-state chromHMM across 127 cell types from Roadmap epigenomics data.[25]

2.10 Cross-trait association analysis

To assess pleiotropic effects of identified SNPs, we conducted a phenome-wide association study (PheWAS) on 13 different traits (syncope included) relating to arrhythmias, cardiovascular disease, mental disorders, neurological, and metabolic diseases (see Supplementary material online, *Data S2*; see *URLs*). We looked at the association between distinct significant SNPs and the abovementioned traits. Next, we investigated pleiotropy of the top ten associated lead SNPs in each of these traits. P value threshold for lead SNPs was set to $P < 1 \times 10^{-6}$. Lead SNPs were identified through LD clumping SNPs in PLINK v1.9[33] with a $r^2 > 0.1$ and a physical distance of 1500 kb. To avoid incidental identification of the same or nearby risk loci, we used a large threshold for physical distance when clumping.

2.11 Association of gene expression and risk of syncope

We used MetaXcan[34] to investigate mediating effects of gene expression levels on syncope and collapse. MetaXcan performs gene-based association analyses of predicted gene expression and phenotype risk, using summary statistics and eQTL data. We used a precomputed transcriptome prediction model based on GTEx v.7 and the 1000 Genomes Project covariance (see *URLs*) and default software settings. MetaXcan results were complemented with an eQTL colocalization analyses, using Sherlock.[35] Sherlock uses a Bayesian framework to match GWAS associations with gene eQTL signals. A significant overlap of a locus associated with a phenotype and the eQTL of a gene implies a likely functional role for that gene in the phenotype.

2.12 Quantitative polymerase chain reaction

In order to assess gene expression in tissues, we performed quantitative polymerase chain reaction (qPCR) experiments on 12- to 15-week-old male Wistar rats from Taconic (Ejby, Denmark), euthanized by cervical dislocation. Experiments were performed in accordance with the European Union legislation for the protection of animals used for

scientific purposes, and approved by the Danish National Animal Experiments Inspectorate.

RNA extraction, reverse transcription and qPCR analysis were performed as described previously.[36] In brief, RNA was isolated from cerebral arteries, brain, and heart using the RNeasy Micro Kit (Qiagen, Denmark). Reverse transcription was performed as per the manufacturer's instructions with the Nanoscript 2 kit (Primerdesign, UK). qPCR was performed with 25 ng of cDNA per well and a primer concentration of 250 nM, using Precision-iC SYBR green mastermix (Primerdesign, UK) with the CFX96 Real-Time PCR Detection System (Bio-Rad, Denmark). The most stable reference genes were determined by geNorm analysis (Biogazelle qbase+) and were found to be actin beta, topoisomerase I, and calnexin. The mean Cq values of these reference genes were used to determine the relative abundance of the zinc finger protein 804A gene (ZNF804A). Primers for ZNF804A were designed in-house and

synthesized by Tag Copenhagen A/S (Denmark) with the following sequences: sense—5′-CGCTGCCCATGTTGTATCTA-3′; anti-sense— 5′CCCACGATGATACCGACATAAC-3′. The following cycling conditions were used: initial activation at 95°C for 10 min, followed by 40 cycles of 95°C for 15 s, and 60°C for 1 min, and data were collected during each cycling phase. Melt curve analysis, to ensure each primer set amplified a single, specific product, completed the protocol.

3. Results

3.1 Genome-wide significantly associated syncope risk locus

The UK Biobank subset had 408 961 ethnically matched individuals, with 9163 cases and 399 798 controls. Using logistic mixed model regression,
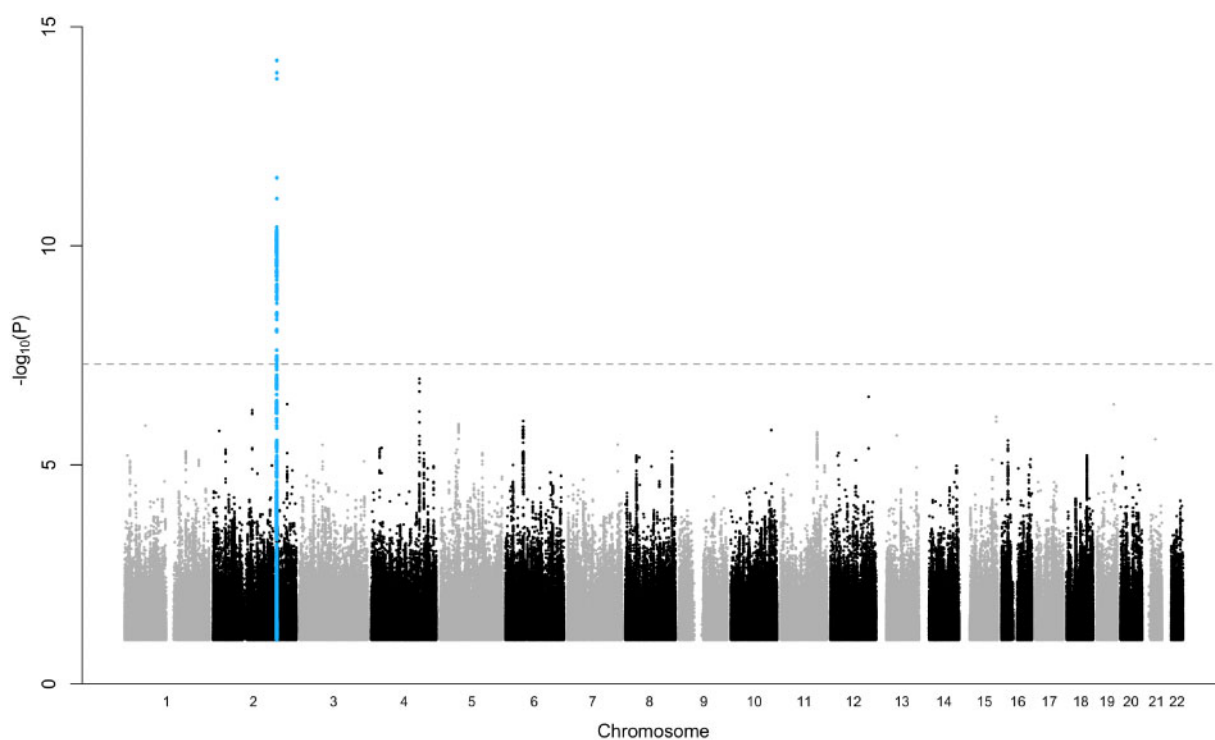

Figure 1 Manhattan plot. Manhattan plot showing the association of single nucleotide polymorphisms (SNPs) with syncope and collapse in a genome-wide association study of 9163 cases and 399 798 controls. The grey dashed horizontal line marks the threshold for genome-wide significance ($P = 5 \times 10^{-8}$). Statistical significance of SNPs is shown on the y-axis as -log10(P) as a function of chromosomal position (x-axis). P-values are calibrated from score test with saddlepoint approximation.

Table 1 SNPs in identified risk locus

rsID	Chr	Position	Ref	Alt	Gnomad MAF (EUR)	P-value	nCand. SNPs
rs12465214	2	185198135	C	A	0.45	5.78E-15	160
rs2219224	2	185211739	G	A	0.52	1.03E-09	41
rs17582219	2	184983620	A	G	0.34	3.70E-09	40
rs7593266	2	184965195	T	G	0.45	2.40E-08	149
rs12621296	2	185099836	A	G	0.62	3.27E-08	131

Chr, chromosome; EUR, European (non-Finnish); MAF, minor allele frequency; nCand. SNPs, the number of unique candidate SNPs in the genomic locus.

related individuals kinship coeffcients, principal components, sex and age at recruitment were included as covariates (genomic inflation factor $\lambda = 1.07$; *Figure 1*, Supplementary material online, *Figure S1*). We identified one novel genome-wide significant locus at chromosome 2q32.1 [lead SNP rs12465214, OR = 1.13 for the risk allele C, 95% confidence interval (CI) 1.10–1.17, $P = 5.8 \times 10^{-15}$]. In total, we identified five distinct significant SNPs residing in the same locus (rs12465214, rs7593266, rs17582219, rs12621296, rs2219224; *Table 1*, Supplementary material online, *Figure S2*).

3.2 Replication of GWAS locus

In the iPSYCH subset, we analysed 54 656 individuals. In total, 2352 syncope events occurred during a median follow-up of 24.86 years (interquartile range 19.62–29.97). The median age at syncope onset was 18.2 years. There were 51 929 controls. Sample overview can be found in *Table 2*. For rs12465214, we found an increased hazard ratio (HR) of syncope and collapse for the reference group (CC) compared with homozygous carriers (AA, HR = 1.30, 95% CI 1.15–1.46, $P < 0.001$), and compared with heterozygous carriers (CA, HR = 1.15, 95% CI 1.03–1.28, $P = 0.02$) (*Figure 2*).

Table 2 Baseline characteristics

	Syncope event	No syncope event
Female	1564	24 006
Male	788	27 923
Median age (IQR)	27.8 (8.1)	24.7 (10.4)

Baseline characteristics of the iPSYCH cohort at the end of follow-up, without the individuals who died during follow-up.
iPSYCH, the Integrative Psychiatric Research Consortium; IQR, interquartile range; SD, standard deviation.

Women had an almost doubled hazard rate for syncope compared with men (HR = 1.93, 95% CI = 1.77–2.10, $P < 0.001$) (*Figure 2*).

With logistic regression, the effect size of the lead SNP was comparable to the main finding in UK Biobank (risk allele C, OR = 1.13, 95% CI 1.07–1.18, $P = 8.82 \times 10^{-6}$).

3.3 Genetic correlation with other traits

We found significant genetic correlation (r_g) with nine of 20 phenotypes, and an additional five reached nominal significance (*Figure 3*, Supplementary material online, *Data S3*). Overall health rating (higher rating indicates poorer health) was the most correlated phenotype ($r_g = 0.43$, $P = 9.63 \times 10^{-16}$). This was supported by a negative correlation with hand grip strength ($r_g = -0.18$, $P = 8.75 \times 10^{-4}$), a proxy for overall health status.[37] The genetic overlap with coronary artery disease ($r_g = 0.41$, $P = 6.99 \times 10^{-15}$) was substantiated by the significant correlation with related traits such as angina, hypertension, body mass index, and atrial fibrillation (*Figure 3*). Anxiety was highly correlated with syncope, but with a broad mean standard error (SE) and the correlation did not reach the Bonferroni threshold ($r_g = 0.67$, $P = 2.53 \times 10^{-3}$). Anxiety had a mean χ^2 of 1.0298, which indicates a low polygenetic signal. The r_g to anxiety is therefore rather unreliable. Two other psychiatric phenotypes, attention deficit hyperactivity disorder ($r_g = 0.20$, $P = 2.16 \times 10^{-3}$) and depression ($r_g = 0.15$, $P = 2.32 \times 10^{-3}$), demonstrated a significant genetic overlap with syncope. Height demonstrated a small negative correlation with syncope ($r_g = -0.10$, $P = 8.03 \times 10^{-3}$). However, this association was not significant after Bonferroni adjustment.

3.4 Cell-type specific analyses

Annotations for ten cell types and H3K4Me1 cell-type annotations from Roadmap were used to estimate partitioned heritability of syncope and collapse into functional categories, as described by Finucane *et al.*[24] We found a significant enrichment of SNPs located in adrenal and pancreas
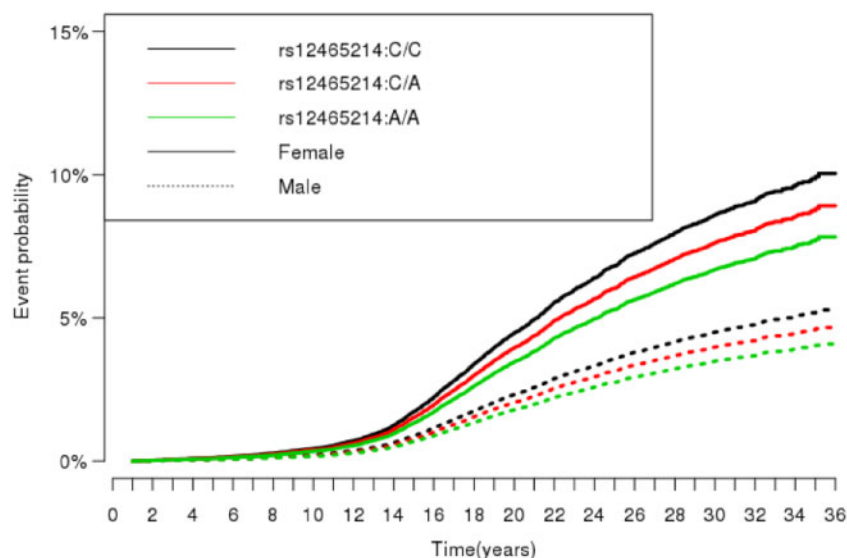

Figure 2 Cox regression model. Cumulative incidence of syncope and collapse, stratified by genotype and gender. In total, 2352 syncope and collapse events occurred in 54 656 individuals. Estimates were based on a Cox regression model taking the competing risk of death into account.
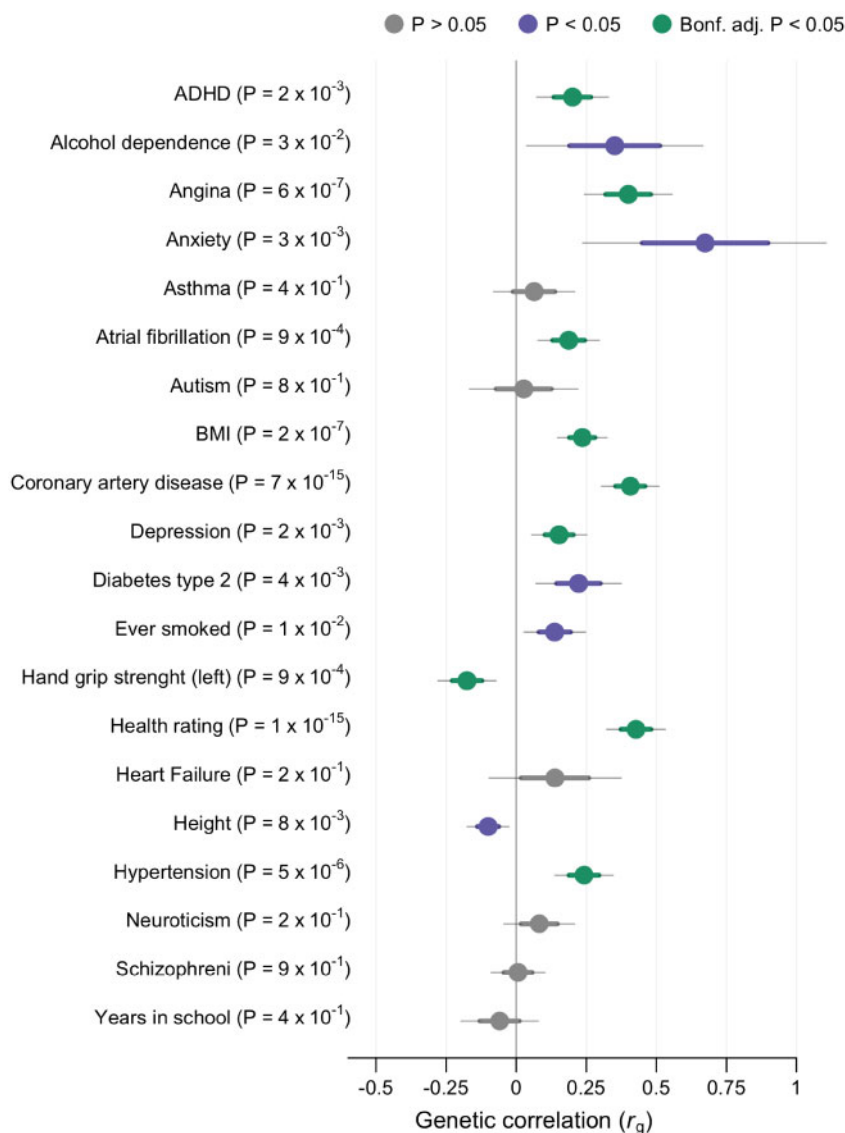
Figure 3 Genetic correlation. LD score regression revealing genetic correlation with syncope and collapse (9163 cases and 399 798 controls) and other phenotypes. Sample sizes of external genome-wide association studies are shown in Supplementary material online, *Data S1*. Phenotypes with negative log10(P) are displayed on the *y*-axis. *X*-axis show genetic correlation (r_g). Dots are estimated values with thick lines indicating mean standard error (SE) and thin lines 1.96 × SE. Significant association after Bonferroni corrections is denoted with green colour. Nominal significance is denoted with violet colour and non-significant correlations with grey. Standard errors and *P*-values were derived from using block jackknife resampling.

regulatory elements (enrichment = 7.03, SE = 2.12, $P = 1 \times 10^{-3}$; Supplementary material online, *Figure S4*, *Data S4*). Whereas partitioned heritability analyses based on imputed gapped peaks from H3K4Me1 did not reveal any significant H3K4Me1 cell-type annotations (Supplementary material online, *Figure S5*, *Data S5*).

3.5 Functional annotation

Based on the lead SNP and distinct significant SNPs in the risk locus, 244 candidate SNPs were identified and annotated (Supplementary material online, *Data S6*). Five SNPs (rs7349369, rs716544, rs12473165, rs12478223, rs12468883), in LD with the distinct significant SNP rs2219224 were naively mapped by position (genomic distance <10 kb) to *MIR548AE1*. In GTEx v.7, 134 candidate SNPs were associated with

gene expression (eQTL; FDR >10^{-3}; *Figure 4*, Supplementary material online, *Figure S2*, *Data S7*). The eQTLs were predominantly mapped in thyroid tissue to the nearby gene *ZNF804A*, with the strongest association for rs67219359 ($P = 4 \times 10^{-8}$, r^2 with rs12465214 = 0.77). The risk locus had several significant chromatin interactions observed through Hi-C data ($n = 1588$; FDR <10^{-6}), with 210 chromatin interactions mapping to regional genes (*Figure 4*, Supplementary material online, *Data S8*). In total, 26 genes mapped to the risk locus through position, eQTL and chromatin interactions (Supplementary material online, *Data S9*). Ten genes were protein coding, with the gene *ZNF804A* demonstrating strongest evidence for interaction with the risk locus.

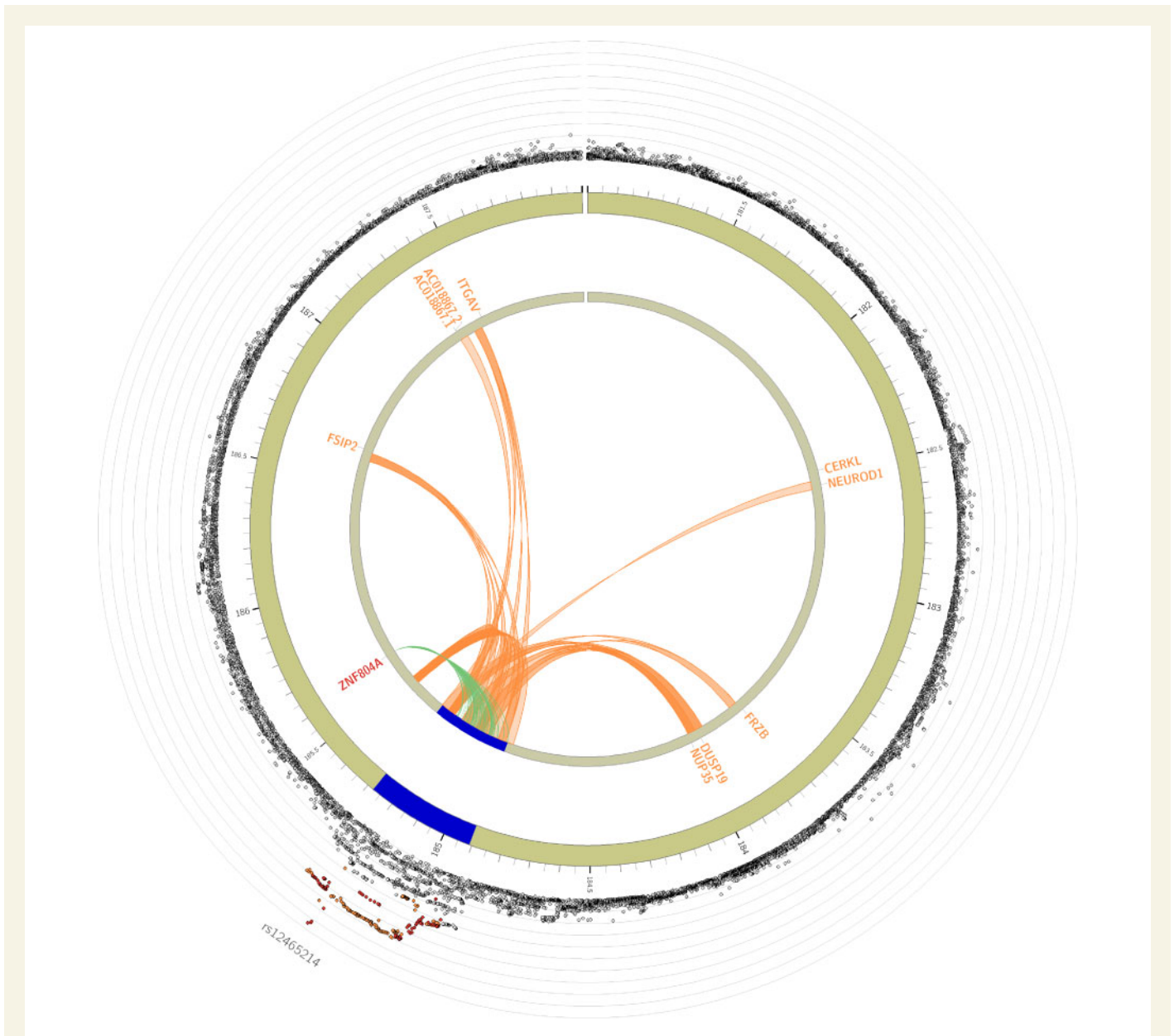Gene set enrichment analysis, with MAGMA and MAGENTA, did not reveal any significant gene sets.

Figure 4 Circo plot displaying eQTL and chromatin interaction for the risk locus. The most outer layer shows a regional plot, displaying rsID of lead SNPs. The height of the *y*-axis indicates significance in negative log10 scale. Only SNPs with *P* < 0.05 are displayed. SNPs in genomic risk loci are colour-coded as a function of their maximum r^2 to one of the distinct significant SNPs in the locus, as follows: red (r^2 > 0.8), orange (r^2 > 0.6), green (r^2 > 0.4), and blue (r^2 > 0.2). SNPs that are not in LD with any of the independent significant SNPs (with $r^2 \leq 0.2$) are grey. The second layer shows chromosome with genomic risk loci highlighted in blue. Only mapped genes by either chromatin interaction and/or eQTLs are displayed. If the gene and links are mapped only by chromatin interactions or only by eQTLs, it is coloured orange or green, respectively. When the gene is mapped by both it is coloured red.

3.6 Transcriptome-wide analyses

Since all but one out of the 134 candidate SNPs associated with eQTL had been identified in thyroid tissue, we used the GTEx v.7 thyroid tissue transcriptome model (*n* = 344; see *URLs*) for the MetaXcan analyses. The analyses revealed a significant association between the predicted gene expression of *ZNF804A* and syncope and collapse (effect size = -0.63, variance of gene expression = 0.012, *P* = 1.04 × 10^{-10}; *Figure 5*, Supplementary material online, *Data S10*). The eQTL analysis with Sherlock revealed significant colocalization with the risk locus and *ZNF804A* (*P* = 1.92 × 10^{-5}; Supplementary material online, *Data S11*).

3.7 Cross-trait associations

The PheWAS revealed a significant association between the lead SNP rs12465214 and hypertension (*P* = 2.12 × 10^{-3}; Supplementary material online, *Figure S6* and *Data S12*).

Top lead SNPs extracted from the other phenotypes did not reveal any cross-trait associations with syncope and collapse. However, with hierarchical clustering, syncope did cluster most closely to epilepsy, recurrent seizures and convulsions (Supplementary material online, *Figure S7*).

The gene *ZNF804A* has previously been associated with schizophrenia through GWAS. Therefore, we manually looked up the
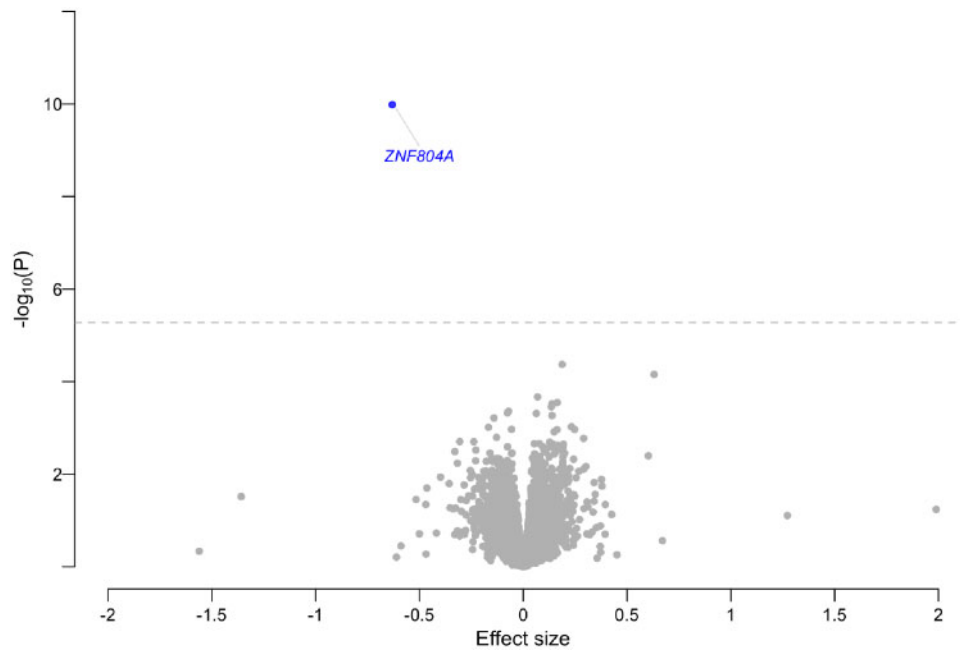
Figure 5 Volcano plot of transcriptome analysis. Plot showing results from MetaXcan transcriptome analyses based on GTEx v.7 thyroid tissue ($n = 323$) and syncope and collapse summary statistics (9163 cases and 399 798 controls). The effect size associated with increased or decreased expression with syncope risk is shown on the x-axis. The y-axis show -log10(P) for each tested gene. The dashed line indicates the Bonferroni threshold ($P = 0.05/9504$). Genes with a negative effect and significant association are demarked as blue dots. Non-significant genes are demarked as grey dots. Significance was assessed (P-values) with Wald tests.

associations of rs12465214, rs7593266, rs17582219, rs12621296, and rs2219224 in a schizophrenia GWAS by Ripke et al.[38] None of these SNPs had a nominal significant association (Supplementary material online, Data S13).

3.8 qPCR analysis

qPCR analysis revealed that *ZNF804A* was expressed most abundantly in brain tissue. Expression was also detected in the cerebral arteries, albeit at a lower level. The expression of *ZNF804A* was negligible in the heart (Figure 6).

4. Discussion

We report on the first discovery of a genome-wide significant risk locus for syncope and collapse. The lead SNP, rs12465214, residing at chromosome 2q31.1, is an intergenic variant approximately 250 kb downstream of the *ZNF804A* gene (Supplementary material online, Figure S2). Candidate SNPs in this locus map to 25 genes (ten protein coding) through either positional mapping, eQTLs, or chromatin interactions (Figure 4). This suggests a significant regulatory role of the risk locus on nearby genes. Transcriptome-wide analyses of eQTL suggest that the risk locus affects *ZNF804A* gene expression (Figure 5). *ZNF804A* is predominantly expressed in the brain, cerebral arteries, and endocrine tissue.[39] We found no evidence of expression in heart tissue. *ZNF804A* gene expression in the human brain increases from embryonic to the early foetal stage and reaches a peak around the early mid-foetal stage. Eventually, the level of *ZNF804A* gene expression decreases and stays constant in adulthood.[40] It is conceivable that abnormal blood pressure
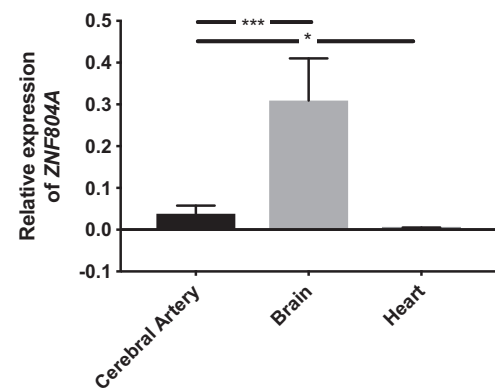

Figure 6 Gene expression analysis. Relative expression of *ZNF804A* assessed by qPCR analysis in tissue from cerebral arteries ($n = 5$), brain ($n = 3$), and heart ($n = 3$) from rats. Data represent the mean ± standard error of the mean (SEM). *$P < 0.05$, ***$P < 0.001$ according to unpaired t-tests.

regulation or reduced cerebral perfusion are regulated at this locus, which could have an effect on the risk of syncope. However, further studies are warranted to assess such a relationship. Zinc finger protein (ZNF) genes have been associated with VVS previously. *ZNF28*, *ZNF845*, and *ZNF146* genes were all significantly overexpressed in a group of children with VVS compared with a control group of healthy age-matched children.[41]

Partitioned heritability analyses revealed a significant enrichment of SNPs in regulatory elements of adrenal and pancreas tissue (Supplementary material online, *Figure S4*). This enrichment may be partly driven by the discovered risk locus, suggesting an involvement of the endocrine system in syncope pathogenesis.

The cross-trait analysis revealed an association between the lead SNP rs12465214 and hypertension (Supplementary material online, *Figure S6*). This suggests a potential functional link between rs12465214 and regulation of the circulatory system, which could affect the risk for syncope.

The association of rs12465214 was replicated in an independent cohort, where the SNP was significantly associated with incident syncope. We also found that women had an almost doubled HR for syncope compared with men, emphasizing the gender difference in syncope risk (*Figure 2*). Whether this difference is attributed to actual differences in genetic risk for syncope, or reflects sex-specific differences in healthcare-seeking behaviour is not known.

We observed a strong genetic overlap between syncope and self-reported overall health rating, and a negative correlation with hand grip strength, a proxy for health status.[37] This supports the notion that syncope may be a precursor or a symptom of more severe disease. The genetic overlap with several cardiovascular diseases (CVD) reinforces this notion. Furthermore, the shared genetic component predisposing for these traits suggests similar cellular pathways to be involved in VVS and CVD.

Previously, rs1344706, in proximity to *ZNF804A*, has been associated with schizophrenia and bipolar disorder.[42] The risk locus, rs1344706, is, however, not in LD with rs12465214 ($r^2 < 0.1$). None of the five distinct significant SNPs that were listed in this study had a nominally significant association ($P < 0.05$) with schizophrenia in the GWAS by Ripke *et al.*[38] We found no genetic correlation between syncope risk and schizophrenia (*Figure 3*). Alterations in the *ZNF804A* gene have been associated with altered functional connectivity in neurons. A knockdown of the gene in human neural stem cells or developing neurons leads to altered expression of genes related to cell adhesion, neurite outgrowth, synapse formation, synapse developing, and cytokine signalling.[43] All of the mentioned functionalities have been implicated in schizophrenia.[44] Also, *ZNF804A* has been shown to interact with the gene *AXTN1*[45] encoding the ataxin 1 protein, which has been associated with spinocerebellar ataxia characterized by Purkinje cell degeneration and loss of balance and co-ordination.[46]

Previous studies in relation to VVS have identified polymorphisms in the α_{1a}-adrenergic receptor gene (*ADRA1A*),[47] the β_1-adrenergic receptor gene (*ADRB1*),[14] the gene encoding the alpha subunit of the Gs protein (*GNAS1*),[48] the adenosine A2a receptor gene (*ADORA2A*),[15] and the endothelin 1 gene (*EDN1*).[16] However, these studies were limited by small sample sizes and their results have not been replicated consistently. None of these genes were associated with syncope and collapse in the present study.

There are limitations to the present study that needs to be addressed. Firstly, phenotype definition was based on the ICD-10 code for 'syncope and collapse' which does not distinguish between subtypes of syncope. The use of the ICD-10 code R55 for syncope and collapse has previously been validated, with a positive predictive value of 95%.[49]

Secondly, drug induced prolongation of the electrocardiographic QT interval has previously been associated with increased risk of syncope and sudden unexplained death.[50] Therefore, side effects of pharmaceutical agents contributing to the tendency to syncope cannot be excluded.

The *ZNF804A* gene and the associated pathways should be examined, both in deeply phenotyped syncope cases, arrhythmia cases, and cases with symptomatic drug interactions involving either syncope or arrhythmia.

5. Conclusions

We identified a genome-wide significant locus, rs12465214, associated with syncope and collapse ($P = 5.8 \times 10^{-15}$). This finding was replicated in an independent cohort. eQTL analysis pointed at the *ZNF804A* gene, which was found to be expressed in the brain and cerebral arteries of rats. Further genetic and functional studies are required to understand the molecular mechanism of the association between the SNP and syncope and collapse.

Supplementary material

Supplementary material is available at *Cardiovascular Research* online.

URLs: Pheweb browser, http://pheweb.sph.umich.edu:5003/; Precomputed LD scores etc., https://data.broadinstitute.org/alkesgroup/LDSCORE/; LDSC, https://github.com/bulik/ldsc; MetaXcan transcriptome models, http://predictdb.org/; Phecodes, https://phewascatalog.org/phecodes.

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Translational perspective

Our study adds new knowledge to the understanding of the pathophysiological mechanisms by which genetic variants associate with the risk of syncope and collapse. It serves to generate new hypotheses for future studies which potentially can lead to an improvement of risk stratification.