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A Common Missense Variant in the Neuregulin1 Gene is associated with Both Schizophrenia and Sudden Cardiac Death

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Abstract

Background—Both schizophrenia and epilepsy have been linked to increased risk of sudden cardiac death (SCD). We hypothesized that DNA variants within genes previously associated with schizophrenia and epilepsy may contribute to an increased risk of SCD.

Objective—To investigate the contribution to SCD susceptibility of DNA variants previously implicated in schizophrenia and epilepsy.

Methods—From the ongoing Oregon Sudden Unexpected Death Study, comparisons were performed among 340 SCD cases presenting with ventricular fibrillation and 342 controls. We tested for association between 17 SNPs mapped to 14 loci previously implicated in schizophrenia and epilepsy using logistic regression, assuming additive, dominant and recessive genetic models.

Results—The minor allele of the non-synonymous SNP rs10503929 within the Neuregulin 1 gene (*NRG1*) was associated with SCD under all three investigated models, with the strongest association for the recessive genetic model (recessive $P=4.01\times10^{-5}$, OR= 4.04; additive $P=2.84\times10^{-7}$, OR= 1.9 and dominant $P=9.01\times10^{-6}$, OR= 2.06). To validate our findings, we further explored the association of this variant in the Harvard Cohort SCD study. The SNP rs10503929 was associated with an increased risk of SCD under the recessive genetic model (P=0.0005, OR= 2.7). This missense variation causes a methionine to threonine change and functional effects are currently unknown.

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Conclusions—The observed association between a schizophrenia-related *NRG1* variant and SCD may represent the first evidence of coexisting genetic susceptibility between two conditions that have an established clinical overlap. Further investigation is warranted to explore the molecular mechanisms of this variant in the pathogenesis of SCD.

Keywords

sudden cardiac death; association study; genetics; schizophrenia; epilepsy; neuregulin-1

Introduction

Sudden cardiac death (SCD) remains a major health problem claiming 250,000-300,000 US lives annually, and the public health implications of this condition are compounded by a lack of efficient methods for prediction and prevention (1-2). While SCD is a complex trait with multiple contributing factors, several studies have established the existence of a significant hereditary component (3-5). As tools for genetic analysis have evolved, the search for genetic predictors has extended from Mendelian family-based studies to broader genome-wide analyses with identification of novel loci associated with SCD (6-8).

Another strategy to identify novel genetic predictors for SCD would be to identify potential genetic overlap with disease conditions that have established associations with SCD. Several studies have documented a three-fold increased risk of SCD in patients with schizophrenia compared to the general population (9-10). While anti-psychotic agents have also been associated with SCD risk (11), SCD risk in schizophrenia can be independent of first or second-generation antipsychotic agents used for treatment of disease (10). There is an established increased risk of SCD among subjects with epilepsy (12) as well, but mechanistic links between these conditions are poorly understood. We therefore hypothesized that genetic variants previously implicated in schizophrenia and epilepsy may be associated with SCD in patients presenting with ventricular fibrillation (VF).

Methods

Study sample

A total of 682 participants (340 cases and 342 controls) were identified from the Oregon Sudden Unexpected Study (Oregon-SUDS), an ongoing prospective study of out of hospital SCD in the Portland, Oregon metropolitan area. Detailed methods for this study have been described previously (13-14). Briefly, SCD cases were identified from the emergency medical services (EMS) system, the county medical examiner's office and 16 local hospitals. All SCD cases with DNA available identified from 2002-2009 who presented with ventricular fibrillation (VF) and aged 35-80 were included in the present study.

To minimize population stratification, we restricted analysis to white non-Hispanic cases. Clinical history prior to arrest was obtained for each subject from existing medical records at hospitals and clinics in the study region. SCD was defined as described in a recent consensus document (1) as a sudden unexpected pulseless condition without obvious extra-cardiac cause, occurring after a rapid witnessed collapse or, if unwitnessed, within one hour of symptom onset. Unwitnessed cases were also included as probable SCD, if the patient was found dead within 24 hours of having last been seen alive and in normal state of health. All identified cases were adjudicated and included as SCD or probable SCD after comprehensive review of available clinical data, including arrest circumstances documented by the EMS responders, existing medical records, and autopsy information if available. Cases with chronic terminal illnesses, known non-cardiac causes of SCD, traumatic deaths and overdose were excluded.

VF was defined as a pulseless condition with characteristic features on the cardiac recording performed by EMS personnel. The initial rhythm among 65% of cases was determined using recorded rhythm strips from the arrest event; the remainder were determined from the EMS report.

Since ≥80% of adult subjects with SCD have been demonstrated to have significant CAD by autopsy (15), control subjects ascertained from the same geographic region were enrolled if they had definite CAD (defined as history of MI, PCI, CABG, or ≥50% stenosis on coronary angiogram), but no history of SCD. In order to include controls over the broad spectrum of CAD, these were identified from patients undergoing coronary angiography or visiting cardiology clinics at one of the region's major participating health systems, and patients transported by the region's EMS system with complaints suggestive of coronary ischemia. Medical records for each potential control were reviewed after obtaining consent; those with documented CAD as described above were enrolled, and a blood sample collected. For this analysis, control subjects were also restricted to white non-Hispanics aged 35-80. All aspects of this study were approved by the appropriate Institutional Review Boards.

The Harvard Cohort SCD Study

The Harvard Cohort SCD Study is a prospective nested case-control study sampled from observational cohorts and clinical trials. The studies include the Physicians' Health Study (PHS I and II), the Nurses' Health Study (NHS), the Health Professionals Follow-up Study (HPFS), the Women's Health Study (WHS), and the Women's Antioxidant Cardiovascular Study (WACS). SCD cases were confirmed by medical record review (hospital, emergency room, autopsy, and emergency medical services reports) and next-of-kin description of the circumstances surrounding death. SCD was considered definite if the cardiac arrest that precipitated death occurred within one hour of symptom onset as documented by medical records or had an autopsy consistent with SCD (i.e. acute coronary thrombosis or severe CAD without myocardial necrosis or other pathologic findings to explain death) (16). Deaths were also classified as arrhythmic or non-arrhythmic based on the definition of Hinkle and Thaler (17). An arrhythmic death was defined as an abrupt, spontaneous collapse of the circulation (pulse disappeared) without evidence of prior circulatory impairment (shock, congestive heart failure) or neurologic dysfunction (change in mental status, loss of consciousness, or seizure). Deaths preceded by circulatory or neurologic impairment were considered non-arrhythmic deaths, and these deaths were excluded from the SCD endpoint even if the death occurred within one hour of symptom onset. Deaths that fulfilled the criteria for arrhythmic death, but occurred after more than one hour of symptoms, were also included in the combined endpoint of sudden and/or arrhythmic cardiac death. Unwitnessed deaths or deaths that occurred during sleep were considered probable SCDs if the participant was documented to be symptom free when last observed within the preceding 24 hours, and circumstances suggested that the death could have been sudden. Analyses including and excluding these probable SCDs were performed, and results were not substantially different when these probable cases were excluded (data not shown).

Controls were selected using risk-set sampling with up to three controls for each case matched on study cohort, sex, age (+/−1 year), ethnicity, smoking status (current, never, past), time and date of blood sampling, fasting status, and presence or absence of cardiovascular disease (myocardial infarction, angina, CABG, or stroke) prior to death. To reduce the risk of population stratification, analyses were limited to self-described whites in these predominantly European derived cohorts.

SNP selection

For genotyping, we selected 17 SNPs previously associated with schizophrenia and idiopathic epilepsy through candidate gene and GWAS approaches (18-24). These genes were all reported to be associated with schizophrenia or idiopathic epilepsy in at least one population of European descent. Seven of the 17 investigated SNPs in the present study were nonsynonymous.

Genotyping and Quality control in the discovery and replication samples

SNPs were genotyped using the Fluidigm system (http://www.fluidigm.com). All SNPs had at least 93% genotype call rate. For quality control, we performed duplicate genotyping of 12% of the total samples for five SNPs using Taqman assays (ABI Prism 7900HT sequence detection system; Applied Biosystems, Foster City, CA). No discordant genotypes were observed in the duplicate samples. The percentage agreement between samples was 100%. All SNPs were tested for possible violation of Hardy-Weinberg equilibrium.

Genotyping and QC in the Harvard Cohorts—Genomic DNA was extracted from the buffy coat fraction of centrifuged blood using Qiagen Autopure kits (Valencia, CA) in NHS, HPFS, and WACS and from whole blood in PHS I. In WHS and PHS I, DNA was extracted using the MagNA Pure LC instrument with the MagNA Pure LC DNA isolation kit (Roche Applied Science, Penzberg, Germany). rs10503929 was genotyped on the Sequenom platform (San Diego, CA) which resolves allele-specific single-base extension products using mass spectrometry (MALDI-TOF). Genotyping was conducted without knowledge of case status, and samples were labeled by study code only. Matched case-control pairs were handled identically, shipped in the same batch, and assayed in the same analytical run to avoid batch effects. Genotypes passed our quality control thresholds (call rate > 90%, Hardy-Weinberg equilibrium $p>0.01$ in controls). Blinded replicate quality control samples were included and genotyped with 100% concordance.

Statistical Analysis

Clinical characteristics of SCD cases and CAD controls from the Oregon-SUDS were compared using t-tests for continuous variables and Pearson chi-square or Fisher exact tests for categorical variables (Table 1). Hardy-Weinberg Equilibrium was examined using the χ^2 test. To test the association between each SNP and SCD, logistic regression analyses for the additive (allele T vs. allele C), recessive (TC, TT vs. CC) and dominant (CC,TC vs. TT) genetic models with adjustment for age and gender covariates was performed. The statistical analysis was performed using PLINK (version 1.07, http://pngu.mgh.harvard.edu/~purcell/PLINK/) (25).

In the Harvard Cohorts, conditional logistic regression was utilized to determine the association between rs10503929 and the risk of sudden and/or arrhythmic cardiac death. The age-adjusted conditional odds ratios were estimated for each cohort separately under an additive, dominant, and recessive model of inheritance. Fixed effect meta-analyses using inverse variance weights were conducted based on the summary conditional logistic regression results for each cohort (26), and PROC MIXED in SAS was used for estimation of the summary effects. Tests for heterogeneity of the genetic effect across sites were conducted using the Q-statistic.

Results

The clinical characteristics of SCD cases presenting with VF and CAD controls from the Oregon-SUDS are summarized in table 1. The genotype distributions of all SNPs were in Hardy-Weinberg equilibrium in controls with the exception of rs9272219 (near *HLA*-

DQA1) and rs821616 (*DISC1*) which were excluded from further analyses. The association analysis for the additive genetic model for each SNP is shown in table 2. Strong evidence for association was observed for the nonsynonymous SNP rs10503929 within the *NRG1* gene, the minor allele C was associated with an increased risk of SCD under the additive (OR= 1.9; CI 95%, 1.5-2.5; $P=2.84\times10^{-7}$), dominant (OR= 2.06; CI 95%, 1.5-2.7; $P=9.01\times10^{-6}$) and recessive (OR= 4.04; CI 95%, 2.0-7.5; $P=4.01\times10^{-5}$) genetic models.

No other statistically significant association was observed between the remaining SNPs and SCD. The results remained significant after adjusting for 15 investigated SNPs and three genetic models (45 statistical tests, corrected p-value= 0.000012 for additive result).

Replication Harvard Cohorts—To validate the association between the SNP rs10503929 and SCD in a separate population, we genotyped the SNP rs10503929 in 1,853 individuals from the Harvard Cohort SCD Study. The mean age of subjects was 63.98 and 36.2% (n=670) were women. Table 3 shows the cohort-specific associations for rs10503929 and SCD. Meta-analysis of the six Harvard cohort studies showed significant evidence for association with SCD only under the recessive genetic model (P=0.0005, OR= 2.7; corrected P= 0.0016 [after adjustment for the three genetic models of inheritance]). We observed that the SNP rs10503929 was significantly associated with an increased risk of SCD in the recessive model in the Physician's Health Study I and Physician's Health Study II. These cohorts are composed only of males. No significant association was observed for the additive and dominant genetic models.

Discussion

A number of SNPs within ion channels have been implicated in schizophrenia (23), epilepsy (18,22) and cardiac arrhythmias (27). Previously, a pathogenic link between long QT syndrome and epilepsy was reported in a subset of well characterized long QT patients (28), suggesting underlying electrical processes common to cardiac and neurologic functions. We examined whether SNPs previously associated with schizophrenia and epilepsy have a role in SCD susceptibility; and observed a strong genetic association between the minor allele of the missense variant rs10503929 and SCD risk under all three investigated models of inheritance (additive, recessive and dominant). We therefore examined the contribution of this variant in an independent population from the Harvard Cohorts SCD study and found that rs10503929 was associated with an increased risk of SCD under the recessive genetic model. It is worth noting that the association with the highest effect size was observed for the recessive model both in the discovery and replication populations ($P=4.01\times10^{-5}$, OR= 4.04; P=0.0005, OR= 2.7 respectively). *NRG1* is a signaling protein that mediates cell-cell interactions and is involved in important biological processes of schizophrenia (20), epilepsy (29) and heart development and function (30-31). NRG-1 acts by activating the tyrosine kinase of ErbB receptors. It has been shown that NRG1-ErbB signaling activates intracellular pathways implicated in the regulation of cardiac muscle differentiation and axon guidance in the central nervous system (30). Similarly, a previous study showed that NRG1 mutant mice died during embryogenesis presenting with heart malformations and abnormalities in the development of Schwann cell precursors (31). These studies suggest that NRG1 signaling play an important role in the development of neurological and cardiac disorders.

The SNP rs10503929 is located in exon 11 of *NRG1* and results in a change of the non-polar methionine to a polar threonine. The amino acid substitution is located in a residue of the trans-membrane domain that is highly evolutionarily conserved across species. *NRG1* isoforms that contain this region remain attached to the membrane playing a role in proteolytic cleavage and release of the bioactive fragment of the protein (32). *NRG1* was

previously identified as a candidate gene for schizophrenia in a linkage analysis of Icelandic families (33). Subsequent studies reported the minor allele of rs10503929, which was associated with SCD in our study, was protective against schizophrenia (24). In contrast, Yokley et al. recently showed that the minor allele of rs10503929 is associated with a decrease in cognitive performance in schizophrenic families (34). Further investigation of how this variant might be mechanistically related to ventricular arrhythmogenesis may provide insights into the pathogenesis of SCD as well as the clinically identified overlap between schizophrenia and SCD.

There are certain limitations of this analysis that should be acknowledged. In the Harvard cohorts, the association of rs10503929 was observed only under the recessive genetic model and driven exclusively by males. However, these findings could be related to the relatively small sample of the investigated Harvard cohorts. There were few SCD affected women enrolled in the WACS and WHS cohorts, and we cannot rule out the possibility of false negative findings caused by small sample sizes. However, we were able to replicate our findings for the recessive genetic model in an independent population. It is worth noting that a nominal P-value of 0.05 was observed for the additive genetic model in the PHSII Study from the Harvard Cohorts. We observed substantially higher genetic risk ratios for the recessive model than for the additive or dominant models in the discovery and replication populations, in which the ORs were 4.04 and 2.66 respectively. Our findings were consistent, suggesting that the CC genotype could have increased risk of SCD more than the TT or CT genotypes. However, we recognize that the small sample size in our study limited the ability to draw more solid conclusions.

To reduce heterogeneity, all participants included in the present study were white and of European descent. The scope of this study does not permit a detailed functional evaluation of the associated SNP. However, by using bioinformatics tools, we found that rs10503929 is predicted to be involved in alternative splicing (unpublished information) (35), suggesting an important role of this missense variant in gene regulation.

In conclusion, our findings suggest that *NRG1*, previously associated with the pathogenesis of schizophrenia and epilepsy, may be implicated in the susceptibility of SCD. Functional analyses are warranted to investigate the specific role of this variant in the pathogenesis of SCD.

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Abbreviations

CABG	coronary artery bypass graft
CAD	coronary artery disease
EMS	emergency medical system
HPFS	Health Professionals Follow-up Study
NRG1	Neuregulin-1

MI	myocardial infarction
NHS	Nurses' Health Study
Oregon-SUDS	Oregon-Sudden Unexpected Death Study
PCI	percutaneous coronary intervention
PHS I and II	Physicians' Health Study I and II
SCD	sudden cardiac death
VF	ventricular fibrillation
WACS	Women's Antioxidant Cardiovascular Study
WHS	Women's Health Study

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Table 1

Clinical characteristics of SCD cases and CAD controls from the Oregon SUDS

	SCD cases with VF	CAD controls	*P-value
N, Participants with genotype data	340	342	
Sex, women†	20.9	30.4	0.004
Age, years‡	63.4±12.5	64.3±10.0	0.27
BMI‡	29.5±6.6	30.1±6.8	0.23
Subjects with Schizophrenia	3	2	0.68
Subjects with epilepsy	7	11	0.47

VF, Ventricular fibrillation; BMI, body mass index

*P value from t-test for continuous variables and Pearson chi-square test of Fisher exact test for categorical variables.

†Data are presented as %

‡Data are presented as means ± SD

Table 2

Association results for the 15 SNPs investigated in this study with SCD

Chr	SNP	Gene	BP	A1	MAF	OR	95% CI	*P
1	rs6675281	*DISC1*	230020724	T	0.15	0.97	(0.72-1.31)	0.8618
1	rs1130183	*KCNJ10*	158278136	A	0.07	1.12	(0.73-1.73)	0.5907
2	rs1344706	*ZNF804A*	185486673	C	0.39	1.00	(0.80-1.25)	0.9936
2	rs4673628	*ERBB4*	213387139	A	0.47	0.87	(0.71-1.06)	0.17
2	rs1026882	*ERBB4*	213387139	C	0.45	0.90	(0.72-1.13)	0.38
6	rs13194053	*Near to HIST1H2A*	27251862	C	0.15	0.81	(0.60-1.10)	0.1944
6	rs3131296	*NOTCH4*	32280971	T	0.11	0.80	(0.57-1.12)	0.2023
8	rs10503929	*NRG1*	32733525	C	0.22	1.94	(1.50-2.50)	**2.84E-07**
8	rs3924999	*NRG1*	32453108	A	0.39	1.02	(0.80-1.29)	0.85
9	rs7045881	*PLAA*	26925996	T	0.10	1.42	(0.99-2.06)	0.05797
10	rs10761482	*ANK3*	61755343	T	0.22	0.86	(0.66-1.12)	0.2673
11	rs6265	*BDNF*	27636492	T	0.19	1.29	(0.99-1.70)	0.05848
11	rs12807809	*Near to NRGN*	124111495	C	0.15	0.93	(0.69-1.25)	0.6364
12	rs1006737	*CACNA1C*	2215556	A	0.33	1.11	(0.88-1.40)	0.3697
20	rs1801545	*KCNQ2*	61516722	C	0.085	1.10	(0.74-1.64)	0.6192

Chr, chromosome; BP, base pairs; A1, minor allele, MAF, minor allele frequency; OR, odds ratio; CI, confidence interval; *P, p-value for the additive genetic model of inheritance.

Table 3

Age-adjusted association between rs10503929 and Sudden Cardiac Death in the Harvard Cohorts

Cohort	Cases/controls	MAF cases	OR	95%CI	Additive P	OR	95% CI	Dominant P	OR	95% CI	Recessive P
PHSI	127/376	0.20	1.29	0.91-1.82	0.16	1.07	0.70-1.64	0.76	4.33	1.73-10.84	**0.0018**
PHSII	71/208	0.25	1.56	1.01-2.43	0.05	1.46	0.82-2.58	0.20	3.68	1.27-10.66	**0.016**
HPFS	104/297	0.17	0.99	0.65-1.51	0.96	0.87	0.55-1.38	0.56	4.36	0.96-19.75	0.056
WHS	35/93	0.17	1.07	0.54-2.14	0.84	1.18	0.52-2.69	0.69	0.65	0.07-6.04	0.70
WACS	37/109	0.19	0.72	0.36-1.46	0.37	0.90	0.40-2.04	0.80	-	-	-
NHS	102/294	0.18	0.83	0.55-1.26	0.38	0.82	0.51-1.33	0.43	0.68	0.18-2.50	0.56
Meta-analysis	476/1,377	0.19	1.10	0.91-1.32	0.32	1.00	0.81-1.25	0.96	2.66	1.53-4.61	**0.0005**

PHSI, Physician's Health Study I; PHSII, Physician's Health Study II; HPFS, Health Professionals Study; WHS, Women Health Study; WACS, Women's Antioxidant Cardiovascular Study; NHS, Nurse Health Study; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval.