Usefulness of Single Nucleotide Polymorphisms as Predictors of Sudden Cardiac Death

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The pathophysiology of sudden cardiac death (SCD) remains incompletely understood. Genetic mutations can create a favorable substrate for SCD. Our aim is to evaluate the evidence of single nucleotide polymorphisms (SNPs) as predictors of SCD. We searched the Medline database (2000 to 2017) and selected all case-control or cohort studies that reported associations between SNPs and SCD. Our search terms included "polymorphisms" and "sudden death." We collected the study design, population ethnic background, gene testing strategy, the association between the SNP and SCD, and the cardiovascular comorbidities of the population. Our search yielded 723 studies, of which we included 24 based upon our inclusion criteria. The studies had a total population of 78,165 participants, with a median age of 62.5 years (IQR 56 to 66) and 35% (IQR 13 to 32) were female. Almost all studies were conducted in white patients of European descent and the most commonly used genetic strategy was candidate gene panels. Fifteen of the studies had a case-control design that included SCD patients without known heart disease as the comparison group and the other 9 studies included patients with heart failure and coronary artery disease. The studies evaluated 53 SNPs and the most common genetic loci were SCN5A, RyR2, CASQ2, NOSA1P, and AGTR. SNPs with the 3 strongest statistically significant ORs >1 were: rs6684209 of CASQ2 (odds ratio [OR] 19), rs3814843 of CALM1 (OR 5.5), and rs35594137 of GJA5 (OR 3.6). In Conclusion, many SNPs are associated with SCD, with the strongest associations seen in SNPs of genes related to intracellular calcium handling. These findings were generated primarily using a candidate gene strategy in white patients with European descent. **(Am J Cardiol 2019;123:1900−1905)**

Sudden cardiac death (SCD) is a major public health problem.[1] Even though coronary artery disease (CAD) is the most common cause of SCD, myocardial fibrosis and hypertension mediated hypertrophy show a sharp increase in incidence.[2] In these patients, myocardial fibrosis and/or hypertrophy can serve as a substrate for arrhythmia triggers.[3] Genetic predisposition can create a vulnerable substrate leading to changes in left ventricular structure or altered repolarization, both in turn, can increase the risk of arrhythmias and SCD.[4] Moreover, family history of cardiac arrest in a first-degree relative is associated with a 2-fold increase in risk of cardiac arrest.[5] Genetic testing is a valuable tool in the management of inherited cardiovascular disease (CVD).[6] However, the use of genetic screening tool is controversial and the addition of a genetic test result to clinical variables might help in further identifying those at the highest SCD risk. Because, many single nucleotide polymorphisms (SNPs) have been associated with SCD, a first logical step is to identify all associations. The aim of our study is to evaluate the evidence supporting SNPs as a predictor of SCD in adult patients with and without structural heart disease.

Methods

We accessed MEDLINE through PubMed. Our search strategy included the following search terms: single-nucleotide Polymorphism OR Polymorphism OR "Polymorphism, Genetic"[Mesh] OR "Genetic Predisposition to Disease"[Mesh] OR Genetic Susceptibility OR Genetic Susceptibilities OR Genetic Predisposition OR Genetic Predispositions OR polymorphism OR polymorphisms)))) AND ((Sudden Cardiac Death OR Cardiac Sudden Death OR Sudden Cardiac Arrest OR "Death, Sudden, Cardiac"[Mesh])))) AND (association [Text Word] OR risk[Text Word]). To ensure a comprehensive literature search, we examined reference lists from our retrieved articles and reference literature from journals

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cited most frequently in the literature searches. We conducted our search in February 2018.

We defined SCD as death within 1 hour of symptom onset or during sleep in a stable patient.[1] We included studies that reported on the general population or on specific CVDs. We defined SCD occurring in the general population as a case-control study where there was no previously known cardiovascular status of the cases or if the study included a low prevalence of CVD.[7] We classified a study as including patients with a specific cardiovascular condition if >50% of the population had either heart failure (HF) or CAD.

Eligibility criteria for inclusion in this analysis were case-control or cohort studies, reporting original data from SCD patients, reporting on SNPs associated with SCD. As a first step in the review process, 2 members of the study team independently reviewed the abstracts identified by the search and excluded those that did not meet our eligibility criteria. Articles were considered for inclusion if their 2 investigators independently reviewed each eligible article identified by the abstract review process. We also conducted a quality evaluation of each included study using the critical appraisal skills tool and report this on the supplementary appendix.

One investigator was responsible for completing the content abstraction forms (JB), and the second confirmed the accuracy of the data abstracted (LT). Differences between the 2 reviewers on content abstraction were resolved by consensus. We recorded the study design, sample size, demographic characteristics, relevant comorbidities, the SNPs associated with SCD and corresponding effect measure, and the gene loci associated with the SNP.

As part of the inclusion criteria, the studies had to report the reference cluster ID (rs or ss number of the SNP). We used the SNP to identify the genetic loci as well as the protein coded by the gene. We defined the association of the SNP with SCD as the SCD odds ratio (OR) and mean allele frequency (MAF). We also collected the method of identifying the SNP, either through candidate gene or genome wide association study (GWAS).

Because of the heterogeneity of the studies we did not pool the ORs and conducted a systematic review instead. We report medians of the means reported on each study and its corresponding interquartile range (IQR).

Results

Our search yielded 723 abstracts and the review of references yielded no additional studies. Figure 1 shows the flowchart of included and excluded studies. We excluded 686 studies at the abstract level and selected 37 for full-text review. Of the 37 selected for full-text review, we excluded 13. We therefore, included 24 studies in our systematic review.

Table 1 shows the baseline characteristics of the included studies. The studies included 78,165 participants with a median age of 62.5 years (IQR 56 to 66) and 35% (IQR 13 to 32) were female. The majority of the included studies had a case-control design (n = 17), and 37% of the studies were exclusively conducted in the United States.

Eighteen studies (75%) were conducted in white subjects of European descent and 4 studies were conducted in Chinese Han. No studies were conducted in Hispanics and only 1 study included black subjects.

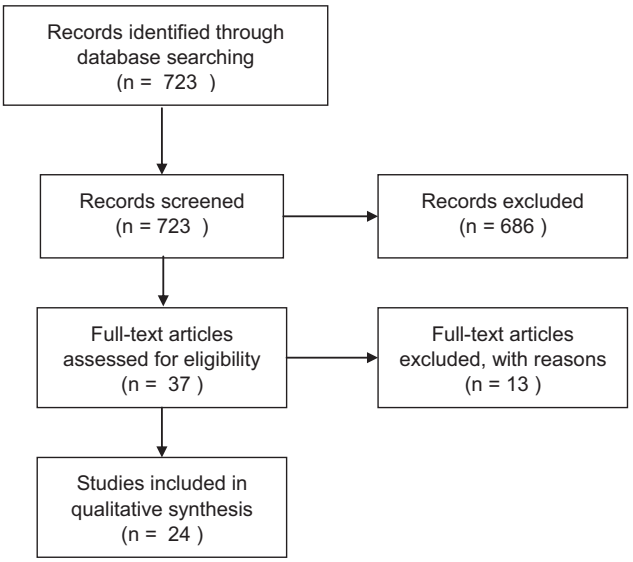

Figure 1. Flow chart of included studies.

Eleven studies (46%) were conducted in the general population. The remaining 13 studies were conducted in specific populations with known CVDs, of which 5 included patients with HF, and 4 with CAD, and the remaining 4 included both diseases.

The 24 studies included in this analysis evaluated 53 SNPs, using primarily a candidate gene strategy (63%) and the most common gene loci included were SCN5A, RyR2, CASQ, NoSAP, and AGTR. The most common single nucleotide variation was the replacement of A/G (38%) while deletions were uncommon.

Table 2 shows the association between SNPs and SCD. Of the 53 SNPs, 36 had reported ORs, and the remaining reported MAF. The 5 SNPs and the proteins coded with statistically significant ORs >1 were rs6684209-calsequestrin, rs3814843-calmodulin, rs35594137-gap junction proteins, rs3814843-calmodulin, and rs35594137-gap junction proteins. The SNPs associated with statistically significant ORs <1 were rs35594137-gap junction protein, rs7521023-calsequestrin, rs12567209, rs790896-nitric oxide, and rs3864180. Twelve studies reported MAFs for SNPs and the MAF range was 0.08 to 0.68. The highest MAF were associated with the DGES 2 gene, ESR 1, and the angiotensin receptor gene.

The SNPs most frequently associated with statistically significant ORs >1 in the general population were rs3814843 and rs35594137. In women, the SNPs were rs35594137, rs35594137, and rs499818. Meanwhile, in men, the SNPs were rs10757278 and rs13376333.

The statistically significant ORs >1 for SNPs in HF were rs6684209 and rs790896 and in CAD were rs2077316 and rs10692285.

The gene loci most frequently associated were CASQ2 which codes for calsequestrin 2, CALM1 which codes for calmodulin, and GJAS which codes for gap junction proteins. For studies evaluating SCN5A loci, the ORs range

Table 1
Baseline characteristics of the 24 included studies

Author/reference	Year	Country	Study design and number	Genetic testing	Mean age	Female (%)	Genetic loci	SNPs	Mutation
Yin	2017	China	Case (79) control (328)	CG	49.8	9	COL1A2 gene	rs3917	7bp indel
Ivanova	2017	Russia	Case (379) control (377)	CG	53	29	GJA5 gene	rs35594137	SNV G/A
							SCN5A gene	rs1805124	SNV A/G
							KCNN3 gene	rs13376333	SNV C/T
Ivanova	2017	Russia	Case (285) control (421)	CG	53.2	30	9p21 locus	rs1333049	SNV C/G
							9p21 locus	rs10757278	SNV A/G
							6p 24 locus	rs499818	SNV A/G
Wang	2017	China	Case (51) control (442)	CG	50.0	11	RYR2 gene	rs10692285	4bp Indel
Wieneke	2016	USA	Cohort (1145)	GWAS	61.6	16	GNAS gene	rs12481583	SNV C/T
Liu	2015	China	Cohort (1429)	CG	63.7	21	CALM1 gene	rs3814843	SNV A/C/T
							CD38 gene	rs1800051	SNV A/C
							TRDN	rs361508	SNV A/G
Marcsa	2015	Hungary	Case (360) control (300)	CG	68.0	33	SCN5A gene	rs11720524	SNV C/G
Refaat	2014		Case (114) control (311)	CG	63.1	12	CASQ2 gene	rs7521023	SNV A/G
							CASQ2 gene	rs6684209	SNV C/T
Liu	2014	China	Cohort (1908)	CG	62.2	21	NOS1AP gene	rs12567209	SNV G/A
Huertas	2013	USA	Case (948) control (3050)	GWAS	60.8	28	RAB3GAP1 gene	rs6730157	SNV A/G
							ZNF365 gene	rs2077316	SNV A/G/T
Huertas	2013	USA	Case (340) control (342)	CG	63.4	21	NRG1 gene	rs10503929	SNV C/T
Lahtinen	2012	Finland	Cohort (27,629)	CG	51.9	54	SCN5A gene	rs41312391	SNV A/G
							4q25 locus	rs2200733	SNV C/T
Westaway	2011	USA	Case (134) control (147)	GWAS	66	29	CASQ2 gene	rs17500488	SNV T/C
							CASQ2 gene	rs3010396	SNV A/G
							CASQ2 gene	rs7366407	SNV A/T
							NOS1AP gene	rs12084280	SNV C/G
							NOS1AP gene	rs10918859	SNV A/G
							GPD1L gene	rs9862154	SNV C/G
Aouizerat	2011	USA	Case (89) control (520)	GWAS	72.8	8	AGTR1 gene	rs263936	SNV C/T
							AGTR1 gene	rs903051	N/A
							NOS1AP gene	rs4292933	SNV A/G
							CSMD2 gene	rs1325258	SNV A/G
							CAC1AC gene	Rs7132154	SNV A/G
							ESR1 gene	rs3003922	SNV G/C
							DEGS2 gene	rs2895845	N/A
							GRIA1 gene	rs7714428	N/A
							KCTD1 gene	rs10853666	N/A
							ZNF385B gene	rs16866933	SNV A/G
							ZNF385B gene	rs9973399	N/A
Arking	2011	USA	Cohort (14,265)	GWAS			BAZ2B locus	rs174230	SNV A/C/G/T
							BAZ2B locus	rs4665058	SNV A/G
Ran	2010	China	Case (1244) control (1032)	CG	56.6	18	RYR2 gene	rs3766871	SNV A/G/T
Albert	2010	USA	Case (516) control (1522)	CG	64.2	36	KCNQ1 gene	rs2283222	SNV C/T
							SCN5A gene	rs11720524	SNV C/G
Arking	2010	USA	Case (424) control (226)	GWAS	59.4	27	GPC5 gene	rs3864180	SNV A/G/T
Buysschaert	2010	Belgium, Britain	Case (205) control (2737)	CG	65		9p21 locus	rs1333049	SNV C/G

(*continued*)

Table 1 (***Continued***)

Author/reference	Year	Country	Study design and number	Genetic testing	Mean age	Female (%)	Genetic loci	SNPs	Mutation
Tseng	2009	USA	Case (89) control (520)	GWAS	73.0	9	TGFBR2 gene	rs9838682	SNV A/G
Newton	2009	USA	Case (516) control (1540)	CG	64.2	36	*CDKN2B genes*	rs10757274	SNV A/G
Sotoodehnia	2009	USA	Case (211) control (730)	CG	59	20	AGTR1 gene	rs1492099	SNV A/G
							KNG1 gene	rs710448	SNV C/T
Eijgelsheim	2009	Netherlands	Cohort (5974)	GWAS		59	NOS1AP gene	rs12567209	SNV A/G
							NOS1AP gene	rs16847549	N/A
Kao	2009	USA	Cohort (19295)	GWAS			NOS1AP gene	rs12567209	SNV A/G
							NOS1AP gene	rs16847548	SNV C/T

CAD = coronary artery disease; CG = candidate gene; CVD = cardiovascular diseases; GWAS = genome wide association study; HF = heart failure.

from 1.2 to 1.3. Moreover, for studies evaluating RyR2 receptor loci, the ORs range from 1.9 to 2.0. For studies evaluating CASQ, the OR was 2.0, for NOSAP the OR ranges from 1.0 to 1.2, and for AGTR the OR ranged from 1.1 to 1.3.

Nine studies evaluated the association between genes and SCD using GWAS. All studies reported on white populations and 4 of them were conducted in the general population. Seven studies reported on ORs, the median OR was 1.3(IQR 1.1 to 1.6). The most commonly evaluated SNPs were related to nitric oxide.

Discussion

Our study summarizes the body of evidence of many individual SNPs related to SCD. We also identify several SNPs with a modest or strong association with SCD and point to specific SNPs with differential associations with SCD according to the population where it was evaluated. The SNPs with the strongest associations with SCD are related to calcium handling and cytoskeleton proteins.

Our study has several limitations. First, the case-control design of many included studies limits the ability to evaluate prior CVD prevalence since most of the included studies are based on cases of SCD that occurred out of the hospital. Second, we excluded 14 studies that did not meet our strict definition of SNPs and some of those excluded studies reported mutations in adrenergic receptors. Third, we could not capture the variability regarding the genetic model used (recessive, dominant, or additive) or how those variables were accounted for because it was not readily available in the studies.

We found that the SNPs with the strongest associations with SCD were located on genes coding for proteins related to calcium release from the sarcoplasmic reticulum and the movement of calcium during the myocardial excitation-contraction coupling. The first is the CASQ2 gene that codes for calsequestrin, a protein that stores calcium inside the sarcoplasmic reticulum until the ryanodine receptors open for calcium release to the cytoplasm. The second, CALM1 that codes for calmodulin, a protein that regulates many enzymes and channels through calcium binding such as the ryanodine receptor (inhibited by calmodulin-Ca^{2+} complex). The third strongest association is with the GJA5 gene that codes for the connexin protein of gap junctions that allow a synchronized contraction of the myocytes, due to an even distribution of calcium after its release from the sarcoplasmic reticulum. The relationship between calcium and SCD has been documented in animals during the exercise-plus-ischemia tests in which elevated intracellular calcium facilitates the development of malignant arrhythmias.[8]

In studies that included patients with HF, SNPs of CASQ2 gene showed an even stronger association with SCD. This may have been due to the asynchrony of contraction more evident on a hypertrophied myocardium. The RYR2 gene coding for ryanodine receptor was also associated with SCD in patients with HF.

Unfortunately, almost all studies were conducted in white patients with European descent or very homogenous Chinese populations. No studies have reported associations between SNPs and SCD in Hispanics and only 1 study recruited black patients and accounted for it in the multivariate analysis. The same situation was seen with gender since only a few studies reported results in women. Women with SCD, in contrast to men, were mainly associated with SNPs of GJA5, but also rs499818, a SNP reported by GWAS, was related to SCD in women.

Our results were generated from studies that primarily used a candidate gene strategy, indicating an a priori hypothesis about the biological function of those genes/pathways studied, which is a limitation of the SCD gene field. This could explain the association between the calcium handling pathway as the most frequently studied. However, we found that the genes associated with the pathway had at least a modest association and several of those findings started with a GWAS approach.

Three other aspects regarding the methodology of associating SNPs with SCD are worthy of comment since they could affect our results. First, the sample size of most studies was small thus limiting the power to detect common variants with frequencies below 5% or rare variants.[9] Second, the studies reported on specific SNPs and did not report on linkage disequilibrium among genes in close proximity to SNPs associated with SCD.[9] Third, we lack sufficient knowledge about the biology of SCD to be able to choose candidate genes wisely and agnostically, and

Table 2
Association between SNPs and SCD

SNP	Study	Year	Gene location	Gene loci	Protein coding by gene	Risk allele	Effect measure (95% CI) p value
rs3917	Yin	2017	7q21.3	COL1A2	Collagen type I alpha 2 chain		OR 1.8; p = 0.01
rs35594137	Ivanova	2017	1q21.1	GJA5	Protein component of gap junctions	GG	OR 3.6 (1.2-10.4); p = 0.02
						AA	OR 3.0 (2.3−3.9); p = 0.041
						GA	OR 0.3 (0.1−0.8); p = 0.036
rs1805124			3p21	SCN5A	Na channel voltage gated		
rs13376333			1q21.3	KCNN3	Voltage-independent calcium-activated K channel		
rs1333049	Ivanova	2017	9p21			CC	OR 1.7 (1.1−2.8); p = 0.01
	Buysschaert	2010		DAB2IP	DAB2 interacting protein	GC	OR 1.5 (1.0−2.3); p = 0.01
						CC	OR 1.3 (0.8−2.0); p = 0.18
rs10757278	Ivanova	2017				GG	OR 1.8 (1.2−2.8); p = 0.01
rs499818						AG	OR 2.4 (1.3−4.6); p <0.01
rs10692285	Wang	2017	1q43	RYR2	Calcium induced calcium release channel		OR 2.03 (1.0−3.7); p = 0.01
rs12481583	Wieneke	2016	20q13.32	GNAS	G protein subunit	C > T	OR 1.2 (1.0−1.5); p = 0.03
rs3814843	Liu	2015	14q32.11	CALM1	Calmodulin	CC	HR 5.5 (2.0−14.9); p <0.01
						CC	HR 3.484 (1.6−7.3); p = 0.001
rs1800051	Liu	2015		CD38		C	HR1.3 (1.0−1.7); p = 0.01
						C	
rs361508	Liu	2015	6q22.31	TRDN	Tradin (sarcoplasmic reticulum anchoring protein)	G	HR 1.247 (1.021−1.524); p = 0.03
rs11720524	Marcsa	2015	3p22.2	SCN5A	Na channel voltage gated	CC	OR 1.4; p = 0.01
	Albert	2010			Na channel voltage gated	C	OR 1.3 (1.1−1.5); p <0.01
rs7521023	Reefat	2014	1p13.3	CASQ2	Calsequestrin 2	A > G	OR 2.7 (1.4−5.11); p <0.01
						A > G	OR 0.4 (0.2−0.7); p <0.01
rs6684209						C > T	OR 19.8 (3.6−108.2); p <0.01
rs12567209	Liu	2014	1q23.3	NOS1AP	Nitric oxide synthase 1 adaptor protein	A	HR 1.6 (1.1−2.2); p <0.01
	Kao	2009				A	HR 0.5 (0.3−0.8); p< 0.01
	Eigelsheim	2009					HR 0.60; p <0.01
rs6730157	Huertas	2013	2q21	RAB3GAP1	Catalytic subunit of RabGTPase activating protein	G	OR 1.6
rs2077316			10q21	ZNF365		C	OR 2.4
rs10503929	Huertas	2013	8p12	NRG1	Neuregulin 1	-	OR 1.9; p = 2.89×10^{-7}
rs41312391	Lahtinen	2012	3p22.2	SCN5A	Na channel voltage gated	Minor T	RR 1.27 (1.1−1.4)
rs2200733				4q25		Minor T	RR 1.28 (1.1−1.41)
rs2383207			9p21	CDKN2A and CDKN2B		G	RR 1.1 (1.0−1.2); p = 0.03
rs17500488	Westaway	2011	1p13.3	CASQ2	Calsequestrin 2		MAF = 0.095; p <0.01
rs3010396				CASQ2			MAF = 0.454; p = 0.02
rs7366407				CASQ2			MAF = 0.286; p <0.01
rs12084280			1q23.3	NOS1AP	Nitric oxide synthase 1 adaptor protein		MAF = 0.11; p <0.001
rs9862154			3p22.3	GPD1L	Glycerol-3-phosphate dehydrogenase 1 like		MAF = 0.222; p <0.01
rs263936	Aouizerat			AGTR1	Angiotensin receptor type 1		OR 1.1 (1.0−1.2); p <0.01
rs903051						AA	MAF = 0.616; p <0.01
rs4292933			1q23.3	NOS1AP	Nitric Oxide synthase 1 adaptor protein		OR 1.1 (1.0−1.3); p = 0.045
rs1325258			1p35.1	CSMD2	CUB and sushi multiple domains 2		OR 2.2 (1.6−2.8); p <0.01
Rs7132154			12p13.33	CACNA1C	Calcium voltage-gated channel subunit alpha1 C		OR 1.1 (1.0−1.2); p <0.01
rs3003922			6q25.1−q25.2	ESR1	Estrogen receptor 1	GTGTAGG	MAF = 0.638; p <0.01
rs2895845				DGES2		GC	MAF = 0.688; p <0.01
rs7714428			5q33.2	GRIA1	Glutamate Ionotropic receptor AMPA type subunit 1	ACT	MAF= 0.338; p= 0.04

(*continued on next page*)

Table 2 (*Continued*)

SNP	Study	Year	Gene location	Gene loci	Protein coding by gene	Risk allele	Effect measure (95% CI) p value
rs10853666			18q11.2	KCTD1	Potassium channel tetramerization domain containing 1	CG	MAF = 0.582; p = 0.07
rs16866933			2q31.3	ZNF385B	Zinc finger protein 385B	A	MAF = 0.085; p <0.01
rs9973399						CCT	MAF= 0.516; p <0.01
rs3766871	Ran	2011	1q43	RyR2	Ryanodine receptor 2	G1886S	HR 1.9 (1.2–2.9); p <0.01
							HR 1.5 (1.1–2.1); p = 0.01
							OR 1.6 (1.2–2.2]; p <0.01
rs790896						G>A	HR 0.6 (0.4–0.9); p <0.01
rs2283222	Albert	2011	11p15.5–p15.4	KCNQ1	Potassium voltage-gated channel subfamily Q member 1	T	OR 1.3 (1.1–1.6); p <0.01
rs174230	Arking	2011	2q24.2	BAZ2B	Bromodomain adjacent to zinc finger domain 2B	T/C	OR 1.3 (0.9–1.9); p = 0.03
rs4665058						A/C	OR 1.6 (1.2–2.1)
rs3864180	Arking	2011	13q31.3	GPC5	Glypican 5	Minor	HR 0.8 (0.7– 0.9); p <0.01
rs1333049	Buysschaert	2010	9p21	Proximity with CDKN2A and CDKN2B		C	HR 1.4 (1.0–1.9); p = 0.02
rs9838682	Tseng	2009	3p24.1	TGFBR2	Transforming growth factor beta receptor 2	G/A	OR 1.6 (1.0–2.5); p = 0.02
rs10757274	Newton	2009	9p21	CDKN2A CDKN2B		G	OR 1.2 (1.0–1.4); p = 0.01
rs1492099	Sotoodehnia	2009	3q24	AGTR1	Angiotensin II receptor type 1		OR 0.6 (0.4–0.9)
			Xq23	AGTR2	Angiotensin II receptor type 2		OR 1.2 (1.1–1.5)
rs710448			3q27.3	KNG1	Kininogen 1		OR 0.44 (0.3–0.8)
rs16847548	Kao	2009	1q23.3	NOS1AP	Nitric oxide synthase 1 adaptor protein	C	HR 1.3 (1.1–1.5); p <0.01
rs16847549	Eigelsheim	2009	1q23.3	NOS1AP	Nitric oxide synthase 1 adaptor protein		HR 1.2; p <0.01

HR = hazard ratio; MAF = mean allele frequency; OR = odds ratio; RR = relative risk.

therefore GWAS are a better way to discover genes related to SCD.[10]

In conclusion, many SNPs are associated with SCD and the mechanism could be related to intracellular calcium handling. This study is a starting point to look at population strategies to screen for subjects at risk for SCD. There is a need to conduct GWAS in racial minorities, since there are data suggesting the presence of variants believed to be associated with SCD-associated diseases such as hypertrophic cardiomyopathy in normal black populations.[11]

Disclosures

No conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.02.058.

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