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A systematic review of single nucleotide polymorphisms in sudden cardiac death

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Abstract

Background: 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.

Methods: 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.

Results: 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 56–66) and 34.5% (IQR 13–32) 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. Single nucleotide polymorphisms with the 3 strongest statistically significant ORs greater than 1 were: rs6684209 of CASQ2 (OR 19), rs3814843 of CALM1 (OR 5.5), and rs35594137 of GJA5 (OR 3.6).

Conclusions: 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.

Introduction

Sudden cardiac death (SCD) is a major public health problem¹. Even though cardiovascular-related deaths show a downward trend, the incidence of SCD remains steady.² Possible explanations for this trend could be the lack of effective population screening and preventive strategies.

SCD can present in patients with heart failure (HF) and coronary artery disease (CAD). However, the majority of cases occur in patients without a known history of heart disease.³ The pathogenesis of SCD in the absence of known structural heart disease remains incompletely understood. Among key pathways⁴ implicated in the development of SCD are changes in the coronary vascular and left ventricular structure, inflammation, and altered repolarization. Genetic predisposition can create a vulnerable substrate like changes in left ventricular structure or altered repolarization, both in turn, can increase the risk of arrhythmias and sudden death.

Many single nucleotide polymorphisms (SNPs) have been associated with SCD. Moreover, family history of cardiac arrest in a first-degree relative is associated with a 2-fold increase in risk of cardiac arrest.² Therefore, the aim of our study is to evaluate the evidence supporting SNPs as a predictor of sudden cardiac death in adult patients with and without structural heart disease.

Methods

Search strategy

We accessed MEDLINE through PubMed, the Internet access site provided by the National Library of Medicine. MEDLINE includes articles from 2000 to 2017. 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 cited most frequently in the literature searches. We conducted our search in February 2018.

Selection Criteria

Eligibility criteria for inclusion in this analysis included case-control or cohort studies reporting original data from patients with SCD, and an association with a SNP was studied. As a first step in the review process, two members of the study team independently reviewed the abstracts identified by the search and excluded those that did not meet our eligibility criteria. If there was no abstract or if the reviewers could not determine whether the article met the eligibility criteria from the abstract, the team obtained a full copy of the article to review. Articles were considered for inclusion if they Two investigators independently reviewed each eligible article identified by the abstract review process.

Data extraction

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 two reviewers in either quality or content abstraction were resolved by consensus. Relevant baseline characteristics were reported in evidence tables. 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.

Definition of SCD

We defined SCD as death within one hour of symptom onset or during sleep in a stable patient.¹ We included studies that reported on the general population or on specific cardiovascular diseases. 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 cardiovascular disease³. We classified a study as including patients with a specific cardiovascular condition if more than 50% of the population had either HF or CAD.

Definition of SNPs

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 mechanisms it regulates. We defined the association of the SNP with SCD as the SCD odds ratio (OR). We also collected the method of identifying the SNP, either through candidate gene or genome wide association study.

Results

Literature search

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.

Baseline characteristics

Table 1 shows the baseline characteristics of the included studies. The majority of the studies accepted for inclusion had a case-control design (n=17) and included 78,165 participants with a median age of 62.5 years (IQR 56–66); 34.5 % (IQR 13–32) were female. Thirty-seven percent of the studies were exclusively conducted in the United States.

Eighteen studies were conducted in White subjects of European descent and 4 studies were conducted in Chinese Han. No studies were conducted in Hispanics and only one study included Black subjects.

Eleven studies were conducted in general populations. The remaining 13 studies were conducted in specific populations, 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 and the most common gene loci included were SCN5A (4 studies), RyR2 (2 studies), CASQ (3 studies), NoSAP (5 studies) and AGTR (3 studies).

Association between SNPs and SCD

Table 2 shows the association between SNPs and SCD. Of the 53 SNPs, 36 had reported ORs, and the remaining reported mean allele frequencies. The five SNPs with statistically significant ORs greater than 1 were rs6684209 (OR 19), rs3814843 (OR 5.5), rs35594137 (OR 3.6), rs3814843 (3.4), and rs35594137 (OR 3.0). The SNPs associated with statistically significant ORs less than one were rs35594137 (OR 0.3), rs7521023 (OR 0.4), rs12567209 (OR 0.5), rs790896 (OR 0.6) and rs3864180 (OR 0.8).

Association between SNPs and SCD in specific populations

The SNPs most frequently associated with statistically significant ORs greater than 1 in the general population were rs3814843 (OR 5.5) and rs35594137 (OR 3.6). In women, the SNPs were rs35594137 (OR 3.6), rs35594137 (OR 3.0), and rs499818 (OR 2.4). Meanwhile, in men, the SNPs were rs10757278 (OR 1.8) and rs13376333 (OR 1.7).

The statistically significant ORs greater than 1 for SNPs in HF were rs6684209 (OR 19) and rs790896 (OR 1.6) and in CAD were rs2077316 (OR 2.4) and rs10692285 (OR 2.0).

Genetic loci association and protein expression

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

Discussion

Our study summarizes the identification of many individual SNPs related to SCD and identifies several SNPs with a modest or strong association with SCD. We also found specific SNPs with differential associations between SNPs and SCD in the general population as well as specific cardiovascular diseases.

Our study has several limitations. First, the case-control design limits the ability to evaluate prior cardiovascular disease 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 adrenoreceptors. 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. Finally, we did not include meeting abstracts or citations in languages other than English.

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 its distribution. 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 is CALM1 that codes for calmodulin, a protein that regulates many enzymes and channels through calcium binding such as the ryanodine receptor (inhibited by calmodulin-Ca²⁺ 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.⁵

The genetic association with SCD in specific cardiovascular diseases is similar. 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 heart failure.

Little is known about ethnic and gender disparities regarding SNPs that are associated with SCD. 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 one 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 (OR=3.0 on women younger than 50 years, and an OR=3.6 in women older than 50), 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. 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 variants⁶. Second, the studies reported on specific SNPs and did not report on linkage disequilibrium among genes in close proximity to SNPs associated with SCD. The phenomenon of linkage disequilibrium is well documented and could provide stronger associations⁶. Third, we lack sufficient knowledge about the biology of SCD to be able to choose candidate genes wisely and agnostically, and therefore GWAS are a better way to discover genes related to SCD⁷

In conclusion, many SNPs are associated with SCD and the mechanism could be related to intracellular calcium handling. This study is a starting point for future studies that aim to look at population strategies to attempt to screen for subjects at risk for SCD. However, there is a need to conduct GWAS in racial minorities, since there are data suggesting the presence of variants thought to be associated with SCD-associated diseases such as hypertrophic cardiomyopathy in normal African populations.³²

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References

- Goldberger JJ, Basu A, Boineau R, Buxton AE, Cain ME, Canty JM Jr, Chen PS, Chugh SS, Costantini O, Exner DV, Kadish AH, Lee B, Lloyd-Jones D, Moss AJ, Myerburg RJ, Olgin JE, Passman R, Stevenson WG, Tomaselli GF, Zareba W, Zipes DP, Zoloth L. Risk stratification for sudden cardiac death: a plan for the future. *Circulation*. 2014; 129: 516–526. [PubMed: 24470473]
- Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jimenez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation*. 2017; 135: e146–e603. [PubMed: 28122885]
- Myerburg RJ, Goldberger JJ. Sudden Cardiac Arrest Risk Assessment: Population Science and the Individual Risk Mandate. *JAMA Cardiol*. 2017; 2: 689–694. [PubMed: 28329250]
- Deo R, Albert CM. Epidemiology and genetics of sudden cardiac death. *Circulation*. 2012; 125: 620–637. [PubMed: 22294707]
- Billman GE, McIlroy B, Johnson JD. Elevated myocardial calcium and its role in sudden cardiac death. *FASEB J*. 1991; 5: 2586–2592. [PubMed: 1714409]
- Altshuler D, Daly MJ, Lander ES: Genetic mapping in human disease. *Science* 2008; 322:881–888 [PubMed: 18988837]
- Farrell MS, Werge T, Sklar P, Owen MJ, Ophoff RA, O'Donovan MC, Corvin A, Cichon S, Sullivan PF: Evaluating historical candidate genes for schizophrenia. *Mol Psychiatry* 2015; 20:555–562 [PubMed: 25754081]
- Yin Z, Guo Y, Zhang J, Zhang Q, Li L, Wang S, Wang C, He Y, Zhu S, Li C, Zhang S, Zha L, Cai J, Luo B, Gao Y. Association between an indel polymorphism in the 3'UTR of COL1A2 and the risk of sudden cardiac death in Chinese populations. *Leg Med (Tokyo)*. 2017; 28: 22–26. [PubMed: 28738217]
- Ivanova AA, Maksimov VN, Ivanoshchuk DE, Orlov PS, Novoselov VP, Savchenko SV, Voevoda MI. Association of Polymorphism in SCN5A, GJA5, and KCNN3 Gene with Sudden Cardiac Death. *Bull Exp Biol Med*. 2017; 163: 73–77. [PubMed: 28577096]
- Ivanova AA, Maksimov VN, Orlov PS, Ivanoshchuk DE, Savchenko SV, Voevoda MI. Association of the genetic markers for myocardial infarction with sudden cardiac death. *Indian Heart J*. 2017; 69 Suppl 1: S8–S11. [PubMed: 28400043]
- Wang S, Zhang Z, Yang Y, Wang C, Tao R, Hu S, Yin Z, Zhang Q, Li L, He Y, Zhu S, Li C, Zhang S, Zhang J, Sheng L, Wu F, Luo B, Gao Y. An insertion/deletion polymorphism within 3'UTR of RYR2 modulates sudden unexplained death risk in Chinese populations. *Forensic Sci Int*. 2017; 270: 165–172. [PubMed: 27987400]

12. Wieneke H, Svendsen JH, Lande J, Spencker S, Martinez JG, Strohmer B, Toivonen L, Le Marec H, Garcia-Fernandez FJ, Corrado D, Huertas-Vazquez A, Uy-Evanado A, Rusinaru C, Reinier K, Foldesi C, Hulak W, Chugh SS, Siffert W. Polymorphisms in the GNAS Gene as Predictors of Ventricular Tachyarrhythmias and Sudden Cardiac Death: Results From the DISCOVERY Trial and Oregon Sudden Unexpected Death Study. *J Am Heart Assoc.* 2016; 5: 10.1161/JAHA.116.003905.
13. Liu Z, Liu X, Yu H, Pei J, Zhang Y, Gong J, Pu J. Common Variants in TRDN and CALM1 Are Associated with Risk of Sudden Cardiac Death in Chronic Heart Failure Patients in Chinese Han Population. *PLoS One.* 2015; 10: e0132459. [PubMed: 26196381]
14. Marcsa B, Denes R, Voros K, Racz G, Sasvari-Szekely M, Ronai Z, Toro K, Keszler G. A Common Polymorphism of the Human Cardiac Sodium Channel Alpha Subunit (SCN5A) Gene Is Associated with Sudden Cardiac Death in Chronic Ischemic Heart Disease. *PLoS One.* 2015; 10: e0132137. [PubMed: 26146998]
15. Refaat MM, Aouizerat BE, Pullinger CR, Malloy M, Kane J, Tseng ZH. Association of CASQ2 polymorphisms with sudden cardiac arrest and heart failure in patients with coronary artery disease. *Heart Rhythm.* 2014; 11: 646–652. [PubMed: 2444446]
16. Liu X, Pei J, Hou C, Liu N, Chu J, Pu J, Zhang S. A common NOS1AP genetic polymorphism, rs12567209 G>A, is associated with sudden cardiac death in patients with chronic heart failure in the Chinese Han population. *J Card Fail.* 2014; 20: 244–251. [PubMed: 24418727]
17. Huertas-Vazquez A, Nelson CP, Guo X, Reinier K, Uy-Evanado A, Teodorescu C, Ayala J, Jerger K, Chugh H, WTCCC+, Braund PS, Deloukas P, Hall AS, Balmforth AJ, Jones M, Taylor KD, Pulit SL, Newton-Cheh C, Gunson K, Jui J, Rotter JJ, Albert CM, Samani NJ, Chugh SS. Novel loci associated with increased risk of sudden cardiac death in the context of coronary artery disease. *PLoS One.* 2013; 8: e59905. [PubMed: 23593153]
18. Huertas-Vazquez A, Teodorescu C, Reinier K, Uy-Evanado A, Chugh H, Jerger K, Ayala J, Gunson K, Jui J, Newton-Cheh C, Albert CM, Chugh SS. A common missense variant in the neuregulin 1 gene is associated with both schizophrenia and sudden cardiac death. *Heart Rhythm.* 2013; 10: 994–998. [PubMed: 23524320]
19. Lahtinen AM, Noseworthy PA, Havulinna AS, Jula A, Karhunen PJ, Kettunen J, Perola M, Kontula K, Newton-Cheh C, Salomaa V. Common genetic variants associated with sudden cardiac death: the FinSCDgen study. *PLoS One.* 2012; 7: e41675. [PubMed: 22844511]
20. Westaway SK, Reinier K, Huertas-Vazquez A, Evanado A, Teodorescu C, Navarro J, Sinner MF, Gunson K, Jui J, Spooner P, Kaab S, Chugh SS. Common variants in CASQ2, GPD1L, and NOS1AP are significantly associated with risk of sudden death in patients with coronary artery disease. *Circ Cardiovasc Genet.* 2011; 4: 397–402. [PubMed: 21685173]
21. Aouizerat BE, Vittinghoff E, Musone SL, Pawlikowska L, Kwok PY, Olgin JE, Tseng ZH. GWAS for discovery and replication of genetic loci associated with sudden cardiac arrest in patients with coronary artery disease. *BMC Cardiovasc Disord.* 2011; 11: 29–2261–11–29. [PubMed: 21658281]
22. Arking DE, Junttila MJ, Goyette P, Huertas-Vazquez A, Eijgelsheim M, Blom MT, Newton-Cheh C, Reinier K, Teodorescu C, Uy-Evanado A, Carter-Monroe N, Kaikkonen KS, Kortelainen ML, Boucher G, Lagace C, Moes A, Zhao X, Kolodgie F, Rivadeneira F, Hofman A, Witteman JC, Uitterlinden AG, Marsman RF, Pazoki R, Bardai A, Koster RW, Dehghan A, Hwang SJ, Bhatnagar P, Post W, Hilton G, Prineas RJ, Li M, Kottgen A, Ehret G, Boerwinkle E, Coresh J, Kao WH, Psaty BM, Tomaselli GF, Sotoodehnia N, Siscovick DS, Burke GL, Marban E, Spooner PM, Cupples LA, Jui J, Gunson K, Kesaniemi YA, Wilde AA, Tardif JC, O'Donnell CJ, Bezzina CR, Virmani R, Stricker BH, Tan HL, Albert CM, Chakravarti A, Rioux JD, Huikuri HV, Chugh SS. Identification of a sudden cardiac death susceptibility locus at 2q24.2 through genome-wide association in European ancestry individuals. *PLoS Genet.* 2011; 7: e1002158. [PubMed: 21738491]
23. Ran Y, Chen J, Li N, Zhang W, Feng L, Wang R, Hui R, Zhang S, Pu J. Common RyR2 variants associate with ventricular arrhythmias and sudden cardiac death in chronic heart failure. *Clin Sci (Lond).* 2010; 119: 215–223. [PubMed: 20408814]

24. Albert CM, MacRae CA, Chasman DI, VanDenburgh M, Buring JE, Manson JE, Cook NR, Newton-Cheh C. Common variants in cardiac ion channel genes are associated with sudden cardiac death. *Circ Arrhythm Electrophysiol*. 2010; 3: 222–229. [PubMed: 20400777]
25. Arking DE, Reinier K, Post W, Jui J, Hilton G, O'Connor A, Prineas RJ, Boerwinkle E, Psaty BM, Tomaselli GF, Rea T, Sotoodehnia N, Siscovick DS, Burke GL, Marban E, Spooner PM, Chakravarti A, Chugh SS. Genome-wide association study identifies GPC5 as a novel genetic locus protective against sudden cardiac arrest. *PLoS One*. 2010; 5: e9879. [PubMed: 20360844]
26. Buysschaert I, Carruthers KF, Dunbar DR, Peuteman G, Rietzschel E, Belmans A, Hedley A, De Meyer T, Budaj A, Van de Werf F, Lambrechts D, Fox KA. A variant at chromosome 9p21 is associated with recurrent myocardial infarction and cardiac death after acute coronary syndrome: the GRACE Genetics Study. *Eur Heart J*. 2010; 31: 1132–1141. [PubMed: 20231156]
27. Tseng ZH, Vittinghoff E, Musone SL, Lin F, Whiteman D, Pawlikowska L, Kwok PY, Olgin JE, Aouizerat BE. Association of TGFBR2 polymorphism with risk of sudden cardiac arrest in patients with coronary artery disease. *Heart Rhythm*. 2009; 6: 1745–1750. [PubMed: 19959123]
28. Newton-Cheh C, Cook NR, VanDenburgh M, Rimm EB, Ridker PM, Albert CM. A common variant at 9p21 is associated with sudden and arrhythmic cardiac death. *Circulation*. 2009; 120: 2062–2068. [PubMed: 19901189]
29. Sotoodehnia N, Li G, Johnson CO, Lemaitre RN, Rice KM, Rea TD, Siscovick DS. Genetic variation in angiotensin-converting enzyme-related pathways associated with sudden cardiac arrest risk. *Heart Rhythm*. 2009; 6: 1306–1314. [PubMed: 19716087]
30. Eijgelsheim M, Newton-Cheh C, Aarnoudse AL, van Noord C, Witteman JC, Hofman A, Uitterlinden AG, Stricker BH. Genetic variation in NOS1AP is associated with sudden cardiac death: evidence from the Rotterdam Study. *Hum Mol Genet*. 2009; 18: 4213–4218. [PubMed: 19643915]
31. Kao WH, Arking DE, Post W, Rea TD, Sotoodehnia N, Prineas RJ, Bishe B, Doan BQ, Boerwinkle E, Psaty BM, Tomaselli GF, Coresh J, Siscovick DS, Marban E, Spooner PM, Burke GL, Chakravarti A. Genetic variations in nitric oxide synthase 1 adaptor protein are associated with sudden cardiac death in US white community-based populations. *Circulation*. 2009; 119: 940–951. [PubMed: 19204306]
32. Manrai AK, Funke BH, Rehm HL, Olesen MS, Maron BA, Szolovits P, Margulies DM, Loscalzo J, Kohane IS. Genetic misdiagnoses and the potential for health disparities. *N Engl J Med*. 2016; 18;375:655–65.

Figure 1:
Flow chart of included studies

Table 1:

Baseline characteristics of the 24 included studies

Author/reference	Year	Country	Study Design	Number	Mean Age	Female, %	Population	Genetic testing	SNPs
Yin	2017	China	case control	79	49.8	9	General		rs3917
Ivanova	2017	Russia	case control	379	53	29	General		rs35594137
									rs1805124
									rs13376333
Ivanova	2017	Russia	case control	285	53.2	30	General		rs133304
									rs10757278
									rs499818
Wang	2017	China	case control	51	50.0	11	General		rs10692285
Wieneke	2016	USA	cohort	297	61.6	16	HF		rs12481583
Liu	2015	China	cohort	185	63.7	21	HF		rs3814843
									rs1800051
									rs361508
Marcsa	2015	Hungary	case control	360	68.0	33	CAD		rs11720524
Refaat	2014		case control	114	63.1	12	CAD HF		rs7521023
									rs6684209
Liu	2014	China	cohort	169	62.2	21	CAD HF		rs12567209
Huertas	2013	USA	case control	948	60.8	28	CAD		rs6730157
									rs2077316
Huertas	2013	USA	case control	340	63.4	21	CAD		rs10503929
Lahtinen	2012	Finland	cohort		51.9	54	General		rs41312391
									rs2200733
Westaway	2011	USA	case control	134	66	29	CAD		rs17500488
									rs3010396
									rs7366407
									rs12084280
									rs9862154

Author/reference	Year	Country	Study Design	Number	Mean Age	Female, %	Population	Genetic testing	SNPs
Aouizerat	2011	USA	case control	89	72.8	8	HF		rs263936
									rs903051
									rs4292933
									rs1325258
									Rs7132154
									rs3003922
									rs2895845
									rs7714428
									rs10853666
									rs16866933
									rs9973399
									rs174230
									rs4665058
									rs3766871
									rs2283222
									rs11720524
Arking (1)	2011	USA	cohort	3119			General		
Ran	2010	china	case control	1244	56.6	18	HF		
Albert	2010	USA	case control	516	64.2	36	CVD		
Arking (2)	2010	USA	case control	424	59.4	27	General		
Bussyschaert	2010	Belgium, Britain	case control	205	65		CAD		
Tseng	2009	USA	case control	89	73.0	9	HF		
Newton	2009	USA	case control	516	64.2	36	General		
Sotoodentia	2009	USA	case control	211	59	20	General		
Eijgelsheim	2009	Netherlands	cohort	208		59	General		rs710448
									rs12567209
									rs16847549
Kao	2009	USA	cohort				General		rs12567209
									rs16847548
									rs10918859

HF: heart failure, CAD: coronary artery disease, CVD: cardiovascular diseases

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 (1)	2017	1q21.1	GJA5	protein component of gap junctions	GG	OR 3.6(1.2–10.4)p=0.02
rs1805124			3p21	SCN5A	Na channel voltage gated	AA	OR 3.0; 95%CI=2.3–3.9; p=0.041
rs13376333			1q21.3	KCNJ3	voltage-independent calcium-activated K channel	GA	OR 0.3; 95%CI=0.1–0.8; p=0.036
rs1333049	Ivanova (2)	2017	9p21			CC	OR 1.7(1.1–2.8)p = 0.01
	Busyhaert	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 (2)	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, 95% CI 1.651–7.350, P = .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, 95% CI 1.021–1.524; P = 0.03
rs11720524	Marcusa	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

SNP	Study	Year	Gene location	Gene loci	Protein coding by gene	Risk allele	Effect measure (95% CI) p-value
rs2077316			10q21	ZNF365		C	OR 2.4
rs10503929	Huertas	2013	8p12	NRG1	Neuregulin 1		
rs41312391	Lahtinen	2012	3p22.2	SCN5A	Na channel voltage gated		RR 1.27(1.1–1.4)
rs2200733							RR 1.28 (1.1–1.41)
rs2382207			9p21	CDKN2A and CDKN2B			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	GPDL	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 Alpha 1 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
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		HR 1.9 (1.2–2.9) p<0.01
rs790896							HR 1.5(1.1–2.1) p=0.01
rs2283222	Albert	2011	11p15.5-p15.4	KCNQ1	Potassium Voltage-Gated Channel Subfamily Q Member 1	T	OR 1.6 (1.2–2.2) p<0.01
rs174230	Arking (1)	2011	2q24.2	BAZ2B	Bromodomain Adjacent To Zinc Finger Domain 2B	T/C	HR 0.6 (0.4–0.9) p<0.01
							OR 1.3 (1.1–1.6) p<0.01
							OR 1.3 (0.9–1.9) p= 0.03

SNP	Study	Year	Gene location	Gene loci	Protein coding by gene	Risk allele	Effect measure (95% CI) p-value
rs4665058						A/C	OR 1.6 (1.2–2.1) p=
rs3864180	Arking (2)	2011	13q31.3	GPC5	Glypican 5		HR 0.8 (0.7 to 0.9) p<0.01
rs1333049	Busychaert	2010	9p21	Proximity with CDKN2A and CDKN2B			HR 1.4 (1.0–1.9) p=0.02
rs9838682	Tseng	2009	3p24.1	TGFBR2	Transforming Growth Factor Beta Receptor 2		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	Sotoodentia	2009	3q24	AGTR1	Angiotensin II Receptor Type 1		OR 0.6(0.4–0.9)
Haplotype 2?			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					HR 1.2 p <0.01
rs10918859	kao	2009	1q23.3	NOS1AP	Nitric Oxide Synthase 1 Adaptor Protein		HR = 0.5(0.3–0.8) p< 0.01

OR= Odds ratio, HR: Hazard ratio, RR: Relative risk, MAF: Mean allele frequency.