Journal of Geriatric Cardiology (2016) 13: 789–797

Review · **Open Access** ·

Epidemiology and genetics of ventricular fibrillation during acute myocardial infarction

Charlotte Glinge, Stefan Sattler, Reza Jabbari, Jacob Tfelt-Hansen

Department of Cardiology, Heart Centre, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

Abstract

Sudden cardiac death (SCD) from ventricular fibrillation (VF) during coronary artery disease (CAD) is a leading cause of total and cardiovascular mortality, and in more than half of SCD cases VF occurs as the first symptom of CAD. Several epidemiological studies have shown that sudden death of a family member is a risk factor for SCD and VF during acute myocardial infarction (MI), independent of traditional risk factors including family history of MI, suggesting a genetic component in the susceptibility to VF. To prevent SCD and VF due to MI, we need a better understanding of the genetic and molecular mechanisms causing VF in this apparently healthy population. Even though new insights and technologies have become available, the genetic predisposition to VF during MI remains poorly understood. Findings from a variety of different genetic studies have failed to reach reproducibility, although several genetic variants, both common and rare variants, have been associated to either VF or SCD. For this review, we searched PubMed for potentially relevant articles, using the following MeSH-terms: "sudden cardiac death", "ventricular fibrillation", "out-of-hospital cardiac arrest", "myocardial infarction, myocardial ischemia", "coronary artery disease", and "genetics". This review describes the epidemiology and evidence for genetic susceptibility to VF due to MI.

J Geriatr Cardiol 2016; 13: 789–797. doi:10.11909/j.issn.1671-5411.2016.09.006

Keywords: Family history; Genetics; Myocardial infarction; Sudden cardiac death; Ventricular fibrillation

1 Introduction

Sudden cardiac death (SCD) is a worldwide leading cause of all death (15%–20%) and more than half of all cardiovascular deaths.[1–8] Coronary artery disease (CAD) and its ultimate consequence, myocardial infarction (MI), are believed to underlie 75% of SCDs and is an even more common cause of death among the elderly.[1,9] During the acute phase of MI, studies have suggested that 3%–12% of all MI cases develop ventricular fibrillation (VF) resulting in sudden cardiac arrest (SCA), the real number is beyond doubt higher as many are found dead.[10–14] SCD is one of the main challenges to clinicians, because in more than half of the cases CAD has not previously been recognized clinically, and SCD occurs as its first symptom.[15,16] Previous studies have shown that a family history of sudden death is a risk factor for SCD and VF due to MI,[10,17–20] independent of traditional risk factors for CAD including a family history of MI,[10,19] strongly suggesting a genetic component. However, the underlying genetic factors are largely unknown and the predisposing genetic architecture is complex and most likely polygenetic.[7] The understanding of the risk factors and underlying genetic cause of VF due to MI have major clinical implications and there is an urgent need to understand the underlying pathophysiological mechanisms in order to predict and prevent development of VF and SCD. The ultimate goal is to prevent adverse cardiac events through early identification of individuals at risk. Identification of genetic susceptibility factors will provide deeper insight into the mechanisms of VF caused by MI, which might result in better targets for prevention and development of new therapies. Therefore, this review will focus on describing the epidemiology and the evidence for genetic susceptibility to VF due to MI.

2 Method

We searched PubMed for articles published the last 20 years, last search 10th January 2016. The full search strategy in PubMed included the following MeSH-terms: Death, Sudden, Cardiac AND Ventricular Fibrillation AND Myo-

Correspondence to: Charlotte Glinge, MD, Department of Cardiology, the Heart Centre, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark. E-mail: cglinge@gmail.com

Telephone: +45-3545-0639 **Fax:** +45-3545-7705

Received: March 29, 2016 **Revised:** June 21, 2016

Accepted: July 29, 2016 **Published online:** September 28, 2016

cardial Infarction OR Myocardial Ischemia OR coronary artery disease (399 hits), Out-of-Hospital Cardiac Arrest AND Ventricular Fibrillation AND Myocardial Infarction OR Myocardial Ischemia OR coronary artery disease (26 hits), Genetics AND Death, Sudden, Cardiac OR Ventricular Fibrillation (102 hits). Both abstracts and full-text papers were reviewed. In addition, references from reviewed articles were searched for other relevant articles.

3 Burden of SCD and VF caused by MI

SCD is a major public health problem affecting millions of people each year worldwide.[21–26] The incidence of SCD and SCA increases with age,[27,28] and therefore most commonly affecting older persons. Although studies indicate that incidence of SCD[29] and VF as a cause of out-of-hospital cardiac arrest[30] is declining, VF itself is the most common underlying arrhythmia in SCDs.[1,8,15,31] In the thrombolytic era, the incidence of ventricular arrhythmias in patients with acute MI ranged from 3.7%–10.2% in large randomized studies.[32–34] However, in the era of primary PCI, the incidence of ventricular arrhythmias appears to be lower.[11,35] In two separate studies among 5745 and 5373 enrolled ST-elevation myocardial infarction (STEMI) patients with primary percutaneous coronary intervention (PPCI), VF or VT occurred in 5.7% and 9.3%, respectively.[11,35] Nevertheless, the true incidence of VF is underestimated as individuals who suffer SCD out-of-hospital are not covered by these studies. Investigating the epidemiology of the phenotype is complicated by the fact that patients that develop VF during acute MI have a high mortality.

4 Pathophysiology of VF caused by MI

The pathophysiology of VF during MI is complex and is associated with both environmental and genetic causes.[1,7,10,19,20,36,37] VF in the setting of MI is most likely the result from the complex interaction of multiple factors, including ongoing ischemia, hemodynamic alterations, electrolyte abnormalities, macro-reentry due to different conduction velocities in ischemic and non-ischemic areas, genetic, and environmental triggers.[38–42] Acute obstruction of the coronary flow will affect the resting membrane potential and inward and outward ionic fluxes during the action potential leading to alterations in conduction, refractoriness, and automaticity in cardiac muscle cells.[43] Most common VT provoked by early after depolarization that degenerates first to VF, followed by an increase in VT frequency and QRS width, and later to asystole.[8,44] Experimental studies have found that there are different phases of in which post-MI VF occurs.[43,45] The first phase (phase 1a or "immediate ventricular arrhythmias") occurs between 2–10 min after occlusion, with the highest incidence of arrhythmias at 5–6 min, and the second phase (phase 1b or "delayed ventricular arrhythmias") occurs from 12–30 min after occlusion, with a peak at 15–20 min.[43]

5 Risk factors associated with VF caused by MI

Clinically, it is difficult to assess the risk of SCD and VF due to MI in the general population, because most episodes occur mainly in low risk subgroups without known risk factors as pointed out by Huikuri, *et al*.[15] The majority of the VF and SCD cases is thought to occur in asymptomatic individuals without a preexisting structural cardiac disease and represents the first manifestation of CAD.[15,16,31,46–48] Patients with similar risk factors for MI may suffer from VF/SCD, while others do not. Over the last decades, manifold screening strategies to lower the burden of SCD in the general population have been discussed.[49–51] The optimal way of lowering the burden of SCD is to prevent MI. One approach is finding patients at risk before the triggering MI event where angina is the classical symptom, even among the young patients experiencing SCD due to CAD.[52] Recent reviews have focused on existing and novel risk stratification tools for SCD due to ventricular arrhytmias.[53,54] They highlighted that the majority of SCDs occur in individuals without known heart disease, where risk prediction of the unpredicted is difficult. However, in most of these studies it is difficult to differentiate between risk factors for MI and risk factors for VF due to MI. In an attempt to narrow the phenotype, identify a population with a similar pathology and phenotype, two studies have investigated VF during first STEMI.[10,19] The first study to differentiate between risk factors for STEMI and risk factors for the development of VF in the acute phase of STEMI was the AGNES (Arrhythmia Genetics in the Netherlands) study.[19] In AGNES, patients with their first acute STEMI with VF (cases, n = 330) were compared to patients with their first STEMI without VF (controls, n = 372). Interestingly, hypercholesterolemia was significantly lower in patients who developed VF during their first STEMI than those who did not have such arrhythmia.[19] However, these findings were not confirmed in our Danish nationwide prospective GEVAMI (GEnetic causes of Ventricular Arrhythmia in patients with first ST-elevation Myocardial Infarction) case-control study among patients with first STEMI with VF (cases, n = 219) and without VF (controls, n = 441) before PPCI.[10] Furthermore, a similar result to our GEVAMI

study was found in the Nurses´ Health Study from the US, which reported that a history of hypercholesterolemia was not a significant predictor for SCD.[31] In addition, there is considerable evidence that traditional cardiovascular risk factors, such as hypertension, obesity, smoking, lipid abnormalities and diabetes, are not specific enough to identify patients at high risk to VF and SCD caused by MI.[10,15] However, in the GEVAMI study, we identified several patients characteristics associated with a significantly higher risk of VF before PPCI after adjusting for common cardiovascular risk factors, infarct location, and thrombolysis in myocardial infarction (TIMI) flow.[10] These independent risk factors included younger age (< 60 years), a family history of sudden death, the absence of pre-infarction angina, statin use, a history of atrial fibrillation, and alcohol intake greater than seven units/week.[10]

6 Heritability of VF, familial aggregation

Several studies have previously demonstrated a familial aggregation of SCD/SCA and sudden death, suggesting a possible influence of genetic factors on SCA and SCD risk.[10,17–20] The first of these studies was published in 1998 by Friedlander, *et al*.[17] showing that a family history of MI or primary cardiac arrest was independently associated with an increased risk of primary cardiac arrest (RR = 1.57; 95% CI: 1.27–1.95). Furthermore, the authors reanalyzed their data by differentiating between family history of MI and family history of sudden death among first-degree relatives and found that a parental history of early onset (age < 65 years) of sudden death was associated with an increased risk of primary cardiac arrest (OR = 2.69; 95% CI: 1.35–5.36), after adjustment for parental history of MI and other risk factors.[55] However, a major limitation of this case-control study is that the matched control group consisted of healthy volunteers without a history of cardiovascular disease, and not patients with CAD. The observational Paris Prospective Study I confirmed that parental sudden death is an independent risk factor for sudden death in middle-aged men (*n* = 7746).[18] A family history of sudden death on either the paternal or the maternal side of family was associated with a nearly 2-fold increased risk of sudden death, and if both parents had a history of sudden death, there was a 9-fold increased risk of dying suddenly. Furthermore, the study indicated that even though a family history of sudden death increased the risk for sudden death it did not increase the risk for acute MI, suggesting the possibility of different risk factors for sudden death and MI.[18] However, important is that these two initial studies[17,18] did not distinguish between the different phenotypes of sudden death (arrhythmic *vs*. non-arrhythmic), nor between underlying CAD (STEMI *vs*. non-STEMI).

The pioneering Dutch AGNES study was the first study to suggest an association between family history of sudden death and VF caused by first STEMI.[19] In this population, recruited at multiple Dutch heart centers, they demonstrated that individuals with a history of sudden death in a parent or siblings had 3.3 times the odds of VF compared with individuals with no family history of sudden death, even after adjustment for SCD risk factors, including degree of ST-segment elevation. In our own Danish GEVAMI study,[10] familial sudden death occurred significantly more frequently among cases than controls (38% *vs*. 26%, respectively) resulting in an odds ratio of 1.80 (95% CI: 1.27–2.56; $P = 0.001$). These data support a strong role for heritable factors in the risk for VF during a first MI.[10,19] Moreover, in contrast to previous studies, these two studies[10,19] only included patients who experienced their first acute coronary event, because the risk factors and mechanisms of SCD may differ significantly between those with and without a prior MI. Another study, from Finland showed that the risk of SCD appears to be high if two or more first-degree relatives have experienced SCD.[20] Subjects with a family history of SCD among first-degree relatives have an increased risk of dying suddenly during an acute coronary event. Despite the different population characteristic and methods in the studies above,[10,17–20] the results taken together demonstrated that there is a familial aggregation of VF during STEMI and SCD, suggesting that shared genetic variants may influence vulnerability to VF due to MI and SCD.

7 Genetics, susceptibility to ischemic VF

Even though the literature mentioned above indicates a genetic predisposition to VF during acute MI, little is known about the exact genetic component that increases the vulnerability to VF caused by MI in the general population. The allelic architecture of complex disorders such as VF due to MI and SCD are likely to involve both common variants with modest effect and rare variants with stronger effects.[56] Several studies have examined the association of common and rare genetic variants to either SCA and/or SCD.[37,57–80] However, only few of the variants identified in these studies have been replicated, and many do not yet have a clear functional implication, and furthermore, a minority of the studies have focused on VF and SCD in the context of CAD (Table 1).

The genetic component of VF and SCD due to MI have primarily been investigated using either candidate gene or genome-wide approaches, however, the rapid expansion and

Table 1. Selected single nucleotide polymorphisms with evidence for association with sudden cardiac death and ventricular fibrillation due to coronary artery disease.

Gene	rsID	Chromosome locus	Most severe consequence	OR (95% CI)	Reference
NOS1AP	rs10918859	1q21	Intron variant		Westaway, *et al*.[58]
	rs12084280	1q23	Intergenetic variant		
CASQ2	rs7521023	1p13	3 prime UTR Variant		Refaat, *et al*.[79] Westaway, *et al*.[58]
	rs17500488	1q13	Intron variant	2.72 (1.44–5.13)	
	rs3010396	1q13	Intron variant		
	rs7366407	1q13	Intergenic variant		
ACYP2	rs1559040	2p16	Intron variant	1.54 (1.32–1.79)	Aouizerat, *et al*.[66]
ZNF385B	rs16866933	2q31	Intron variant	1.69 (1.48–1.93)	Aouizerat, *et al*.[66]
	rs4621553	5q22	Intergenic variant	1.40 (1.24–-1.58)	
RAB3GAP1	rs6730157	2q21	Intron variant	1.60	Huertaz-Vazquez, *et al*.[74]
SCN5A	rs11720524	3p22	Intron variant	1.35 (1.05–1.74)	Albert, *et al*;[57] Marcsa, *et al*.[80]
GPD1L	rs9862154	3q22	Upstream gene variant		Westaway, *et al*.[58]
AGTR1	rs263936	3q24	Intergenic variant	1.13 (1.04–1.22)	Aouizerat, *et al*.[66]
GRIA1	rs12189362	5q33	Intron variant	1.50 (1.32–1.69)	Aouizerat, *et al*.[66]
ZNF365	rs2077316	10q21	Intron variant	2.41	Huertaz-Vazquez, *et al*.[74]
GPC5 (GLYPIAN 5)	rs3864180	13q31	Intron variant	0.85 (0.74–0.98)	Arking, *et al*.[65]
AP1G2	rs2281680	14q11	Splice region variant	1.38 (1.23–1.54)	Aouizerat, *et al*.[66]
	rs11624056	14q31	Intergeneic variant	1.43 (1.26–1.62)	
DEGS2	rs7157599	14q32	Missense variant	1.13 (1.08–1.19)	Aouizerat, *et al*. [66]
	rs17718586	17q24	Intergeneic variant	1.53 (1.32–1.78)	
	rs597503	18p11	Upstream gene variant	1.45 (1.27–1.65)	
CXADR	rs2824292	21q21	Intergeneic variant	1.78 (1.47–2.13)	Bezzina, *et al*.[37]
KCTD1	rs16942421	18q11	Intron variant	1.68 (1.43–1.98)	Aouizerat, *et al*. [66]

OR: odds ratio; UTR: untranslated region.

genetic testing options create unique opportunities and challenges in the future. The candidate gene approach represents a hypothesis-driven method, examining association of VF and SCD risk with common and rare variants in candidate genes selected from biologically important molecular pathways involved in arrhythmogenesis. The limitation of the candidate gene approach is that it does not discover novel susceptibility factors in the genes that are not examined, and therefore, is limited by the current state of knowledge or qualified hypothesis of the investigators. In addition to candidate gene studies, genome-wide association studies (GWAS) have been performed directly on VF and SCD cases to identify novel genetic variants associated with VF and SCD risk.[37,64–67] GWAS are aimed to identify common allelic variants that have a low relative risk of disease. GWAS use an unbiased approach, scanning hundreds of thousands of sequence variations throughout the genome for an association with the disease of interest.

7.1 Common genetic variants

The first GWAS to identify common genetic variants, single nucleotide polymorphisms (SNP), associated with VF during acute MI was in the Dutch AGNES study.[37] This GWAS was conducted in a set of 972 individuals, 515 cases (STEMI patients with VF) and 457 controls (STEMI patients without VF). The most significant association with VF was found at 21q21 (rs2824292, OR = 1.78, 95% CI: 1.47–2.13; $P = 3.3 \times 10^{-10}$) and was replicated in an independent case-control set consisting of 146 cases of out-of-hospital cardiac arrest, individuals with MI complicated by VF from the ARREST study and 391 individuals who survived an acute MI (OR = 1.49, 95% CI: 1.14–1.95; $P = 0.004$). Interestingly, the closest gene to this SNP is *CXADR*, which encodes a coxsackievirus and adenovirus receptor previously implicated in myocarditis and dilated cardiomyopathy and which has been identified as a modulator of cardiac conduction. However, this locus has not been implicated in arrhythmia susceptibility.[81–83] Even though this SNP reached GWAS significance, the SNP was not replicated in a smaller German case-control study (cases = 90; controls = 167).[84] In a large scale meta-analysis of several GWAS two SNPs (rs6730157 in the *RAB3GAP1* gene

on chromosome 2q21 and rs2077316 in the *ZNF365* gene on chromosome 10q21) were associated with SCD due to CAD.[74] Furthermore, in a combined meta-analysis among 1283 SCD cases from five separate studies and 20,000 control individuals, all of European ancestry a locus at chromosome 2q24.2 (rs4665058) was found to be associated with SCD with a relatively strong effect size (OR:1.92, 95% CI: 1.57–2.34).[67] However, this SNP was not found in the AGNES study. Another GWAS reported 11 gene associations for SCA due to VF in patients with CAD, including validation of 4 previous published gene associations for SCA.[66] A novel genetic locus, *GPC5*, for SCA due to CAD was identified in the ongoing Oregon Sudden Unexpected Death Study (Oregon-SUDS), and further validated in 2 other cohorts.[65] The minor allele of *GPC5* (GLYPICAN 5, rs3864180) was associated with a lower risk of SCA (OR = 0.85).

Previous candidate studies have reported that common variants in genes encoding ion-channel subunits contribute to SCD risk.[57–62] A systematic candidate-gene study reported that common variants in or near *CASQ2*, *GPD1L* and *NOS1AP* were associated with increased risk of SCD in patients with CAD.[58] They observed and validated significant associations between SCD risk and SNPs in genes previously associated with relatively rare inherited forms of arrhythmias. Furthermore, in a combined analysis of six prospective cohort studies, two common intronic variants in *KCNQ1* and *SCN5A* were associated with SCD in individuals of European ancestry.[57] The SNPs rs2283222 in *KCNQ1* and rs11720524 in *SCN5A* were significantly associated with SCD (OR = 1.30 and 1.36, respectively).[57] However Marcsa, *et al*.[80] were unable to reach a significant signal for rs11720524 in a heterogeneous SCD cohort. In this case-control study they included both established and probable ischemic cardiac death cases (n = 360) and age-matched controls (n = 300).[80]

It should be noted that these studies mentioned above identified a variety of variants without detecting variants from the other studies. There is no obvious explanation for this disparity. Several reasons exist for a failure to replicate SNPs. First, it could be insufficient power to detect the modest effect size. Second, it could be because of differences in the clinical phenotypes. Third, the effect of the risk allele may differ between populations because of gene-gene or gene-environment interactions.[85] This lack of replication highlights the difficulties, which is commonly seen in genetic studies related to SCD and VF, and probably relates to the heterogeneity, both within and between studies. Larger sample sizes and homogenous enriched subgroups will be needed to identify and replicate additional genetic variants associated with VF during acute MI. More studies need to be done to uncover a causal relationship. Using well-defined phenotype subset of individuals with a certain disease can facilitate gene discovery from complex traits, such as VF during STEMI.

7.2 Rare genetic variants

As mentioned above it is possible that VF due to MI is caused by rare variants with variable penetrance. To date, few studies have examined rare variants in genes encoding ion-channels,[59,62,63,86,87] such as variants in the *SCN5A* gene, which encodes the α-subunit of the cardiac sodium channel responsible for cardiac action potential and conduction and are known to be risk factors for arrhythmia.[86,87] The rare genetic variants that contribute to SCD and VF caused by MI are largely unknown and unexplored. Stecker, *et al*.[59] found no unique or rare allelic variants of *SCN5A* among the 77 cases of SCA with associated CAD and 91 control individuals. In contrast, Albert, *et al*.[62] identified five unique or rare missense variants in three exons of *SCN5A* in 60 women with SCD. This study aimed to find mutations in cardiac ion channel genes, so the entire coding sequence and splice junctions of five ion channel genes associated with *SCN5A*, *KCNE1*, *KCNE2*, *KCNQ1* and *KCNH2*, were directly sequenced. A recent study that aimed to investigate the role of *SCN5A* mutations and polymorphisms in the development of VF during acute MI reported that only two of 49 MI/VF patients (4.1%) demonstrated *SCN5A* variants that may be the cause of VF.[86] A small case-control study of VF survivors with CAD (n = 45) found significantly higher frequency of selected, rare coding variants in five long QT genes.[88] Another small study of 19 patients with VF during acute MI found one missense mutation (G400A) in *SCN5A*.[89,90] However, the potential association of *SCN5A* mutations with VF during acute MI remains unclear, and requires further investigation. These data suggest that mutations or rare variants may contribute to SCD and VF due to MI, but also emphasizes the need for further investigation. Such rare variants are best detected by direct sequencing. Because of the rapid development of next generation sequencing (NGS) technologies, large-scale sequencing projects are becoming possible allowing the examination of rare genetic variants. NGS facilitates rapid sequencing of the entire genome and/or exome in a highly efficient and cost effective manner. However, whole genome and exome methods are still too expensive to use at a large scale for most research groups.

8 Perspectives

VF and SCD caused by MI remains a major public health

problem. Despite tremendous research on risk stratification for predicting VF and SCD, it is still an enormous challenge for physicians to predict risk, especially in the general population.[53,54,91,92] To understand this complex phenotype, we need a solid and complete understanding of clinical, genetic and epigenetic risk factors for VF in the setting of acute MI (Figure 1). Identification of genetic factors that predispose to VF during ischemia is important for further genetic testing which may contributes to a better risk stratification. Identification of genetic susceptibility factors will provide deeper insight into the mechanisms and perhaps identify better targets for prevention and development of new therapies. A recent comprehensive study highlighted that genetic risk scoring can be used to predict the risk of SCD.[93] This study showed that a score formed of the most significant common genetic risk variants for CAD is associated significantly with the occurrence of CAD-related out-of-hospital SCD.[93] Furthermore, in the past years, interest has been focused on epigenetics and the importance of epigenetics alterations which are heritable changes in gene expression or phenotype that do not involve a change in DNA sequence.[94–96] There is a growing evidence that epigenetic factors may modify the genetic variations. Future research needs to incorporate epigenetics for a better understanding of this complex phenotype, and to build a bridge between genes and risk factors. Progress in both the genetic and epigenetic field will have an important impact on our understanding of this unique phenotype.

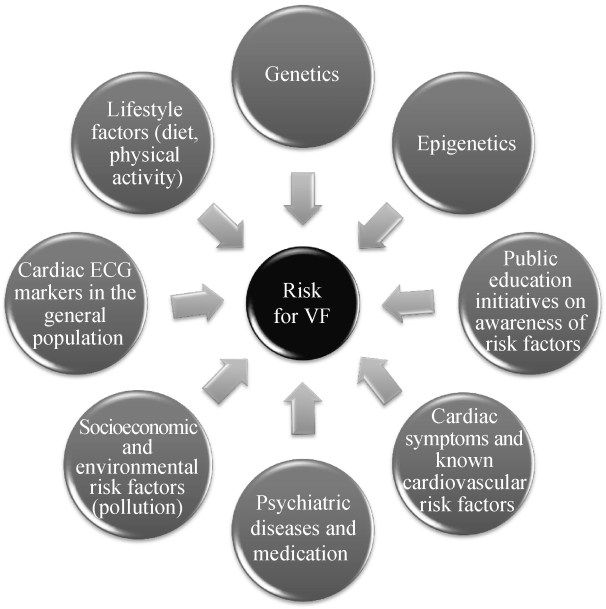

Figure 1. Possible ways for future research to assess risk factors for VF caused by MI.[97] Modified figure from Jabbari.[97] MI: myocardial infarction; VF: ventricular fibrillation.

9 Conclusions

Several studies have shown that a family history of sudden death increases the risk of experiencing a cardiac arrest during acute MI, which suggests a genetic background. Generally, the manifestation of VF during acute MI should be considered as the interaction of several genetic and non-genetic factors. Developing an understanding of genetic contributions to VF during acute MI may support the current management, including risk stratification in the general population, thereby improving our ability to predict and prevent. Ideally, we would have a prediction model including genetic and epigenetic risk factors that allows clinicians to identify patients at risk for VF. This systematic review confirmed that after decades of research, the genetics of VF during acute ischemia and SCD due to MI largely remain to be explained.

Acknowledgments

Jacob Tfelt-Hansen has received funding from the Novo Nordic Foundation. Charlotte Glinge has received funding from the Research Fund of Rigshospitalet, University Hospital of Copenhagen, Denmark. The authors wish to thank Noah Zach Laird who assisted in the proof-reading of the manuscript.

References

1 Deo R, Albert CM. Epidemiology and genetics of sudden cardiac death. *Circulation* 2012; 125: 620–637.
2 Adabag AS, Luepker RV, Roger VL, *et al*. Sudden cardiac death: epidemiology and risk factors. *Nat Rev Cardiol* 2010; 7: 216–225.
3 Turakhia M, Tseng ZH. Sudden cardiac death: epidemiology, mechanisms, and therapy. *Curr Probl Cardiol* 2007; 32: 501–546.
4 Gillum RF. Geographic variation in sudden coronary death. *Am Heart J* 1990; 119: 380–389.
5 Sara JD, Eleid MF, Gulati R, *et al*. Sudden cardiac death from the perspective of coronary artery disease. *Mayo Clin Proc* 2014; 89: 1685–1698.
6 Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: epidemiology, transient risk, and intervention assessment. *Ann Intern Med* 1993; 119: 1187–1197.
7 Marsman RF, Tan HL, Bezzina CR. Genetics of sudden cardiac death caused by ventricular arrhythmias. *Nat Rev Cardiol* 2014; 11: 96–111.
8 Zipes DP, Wellens HJ. Sudden cardiac death. *Circulation* 1998; 98: 2334–2351.
9 de Vreede-Swagemakers JJ, Gorgels AP, Dubois-Arbouw WI, *et al*. Out-of-hospital cardiac arrest in the 1990's: a population-based study in the Maastricht area on incidence, charac-

teristics and survival. *J Am Coll Cardiol* 1997; 30: 1500–1505.
10 Jabbari R, Engstrøm T, Glinge C, *et al*. Incidence and risk factors of ventricular fibrillation before primary angioplasty in patients with first ST-elevation myocardial infarction: a nationwide study in Denmark. *J Am Heart Assoc* 2015; 4: e001399.
11 Mehta RH, Starr AZ, Lopes RD, *et al*. Incidence of and outcomes associated with ventricular tachycardia or fibrillation in patients undergoing primary percutaneous coronary intervention. *JAMA* 2009; 301: 1779–1789.
12 Mehta RH, Harjai KJ, Grines L, *et al*. Sustained ventricular tachycardia or fibrillation in the cardiac catheterization laboratory among patients receiving primary percutaneous coronary intervention: incidence, predictors, and outcomes. *J Am Coll Cardiol* 2004; 43: 1765–1772.
13 Henriques JPS, Gheeraert PJ, Ottervanger JP, *et al*. Ventricular fibrillation in acute myocardial infarction before and during primary PCI. *Int J Cardiol* 2005; 105: 262–266.
14 Bougouin W, Marijon E, Puymirat E, *et al*. Incidence of sudden cardiac death after ventricular fibrillation complicating acute myocardial infarction: a 5-year cause-of-death analysis of the FAST-MI 2005 registry. *Eur Heart J* 2014; 35: 116–122.
15 Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med* 2001; 345: 1473–1482.
16 Deedwania P. Global risk assessment in the presymptomatic patient. *Am J Cardiol* 2001; 88: 17J – 22J.
17 Friedlander Y. Family history as a risk factor for primary cardiac arrest. *Circulation* 1998; 97: 155–160.
18 Jouven X, Desnos M, Guerot C, *et al*. Predicting sudden death in the population: the Paris Prospective Study I. *Circulation* 1999; 99: 1978–1983.
19 Dekker LR. Familial sudden death is an important risk factor for primary ventricular fibrillation: a case-control study in acute myocardial infarction patients. *Circulation* 2006; 114: 1140–1145.
20 Kaikkonen KS, Kortelainen M-L, Linna E, *et al*. Family history and the risk of sudden cardiac death as a manifestation of an acute coronary event. *Circulation* 2006; 114: 1462–1477.
21 Chugh SS, Jui J, Gunson K, *et al*. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. *J Am Coll Cardiol* 2004; 44: 1268–1275.
22 Zheng ZJ, Croft JB, Giles WH, *et al*. Sudden cardiac death in the United States, 1989 to 1998. *Circulation* 2001; 104: 2158–2163.
23 Straus SMJM, Bleumink GS, Dieleman JP, *et al*. The incidence of sudden cardiac death in the general population. *J Clin Epidemiol* 2004; 57: 98–102.
24 Winkel BG, Holst AG, Theilade J, *et al*. Nationwide study of sudden cardiac death in persons aged 1-35 years. *Eur Heart J* 2011; 32: 983–990.
25 Hayashi M, Shimizu W, Albert CM. The spectrum of epidemiology underlying sudden cardiac death. *Circ Res* 2015; 116: 1887–1906.
26 Risgaard B, Winkel BG, Jabbari R, *et al*. Burden of sudden cardiac death in persons aged 1 to 49 years: nationwide study in Denmark. *Circ Arrhythm Electrophysiol* 2014; 7: 205–211.
27 Holmberg M, Holmberg S, Herlitz J. Incidence, duration and survival of ventricular fibrillation in out-of-hospital cardiac arrest patients in Sweden. *Resuscitation* 2000; 44: 7–17.
28 Kannel WB, Wilson PW, D'Agostino RB, *et al*. Sudden coronary death in women. *Am Heart J* 1998; 136: 205–212.
29 Niemeijer MN, van den Berg ME, Leening MJG, *et al*. Declining incidence of sudden cardiac death from 1990-2010 in a general middle-aged and elderly population: the Rotterdam Study. *Heart Rhythm* 2015; 12: 123–129.
30 Hulleman M, Berdowski J, de Groot JR, *et al*. Implantable cardioverter-defibrillators have reduced the incidence of resuscitation for out-of-hospital cardiac arrest caused by lethal arrhythmias. *Circulation* 2012; 126: 815–821.
31 Albert CM, Chae CU, Grodstein F, *et al*. Prospective study of sudden cardiac death among women in the United States. *Circulation* 2003; 107: 2096–2101.
32 Volpi A, Cavalli A, Santoro L, *et al*. Incidence and prognosis of early primary ventricular fibrillation in acute myocardial infarction—results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) database. *Am J Cardiol* 1998; 82: 265–271.
33 Newby KH, Thompson T, Stebbins A, *et al*. Sustained ventricular arrhythmias in patients receiving thrombolytic therapy: incidence and outcomes. *Circulation* 1998; 98: 2567–2573.
34 Henkel DM, Witt BJ, Gersh BJ, *et al*. Ventricular arrhythmias after acute myocardial infarction: a 20-year community study. *Am Heart J* 2006; 151: 806–812.
35 Jabbari R, Risgaard B, Fosbøl EL, *et al*. Factors associated with and outcomes after ventricular fibrillation before and during primary angioplasty in patients with ST-segment elevation myocardial infarction. *Am J Cardiol* 2015; 116: 678–685.
36 Spooner PM, Albert C, Benjamin EJ, *et al*. Sudden cardiac death, genes, and arrhythmogenesis: consideration of new population and mechanistic approaches from a national heart, lung, and blood institute workshop, part I. *Circulation* 2001; 103: 2361–2364.
37 Bezzina CR, Pazoki R, Bardai A, *et al*. Genome-wide association study identifies a susceptibility locus at 21q21 for ventricular fibrillation in acute myocardial infarction. *Nat Genet* 2010; 42: 688–691.
38 Brezins M, Elyassov S, Elimelech I, *et al*. Comparison of patients with acute myocardial infarction with and without ventricular fibrillation. *Am J Cardiol* 1996; 78: 948–950.
39 Gheeraert PJ, Henriques JP, De Buyzere ML, *et al*. Out-of-hospital ventricular fibrillation in patients with acute myocardial infarction: coronary angiographic determinants. *J Am Coll Cardiol* 2000; 35: 144–150.
40 Volpi A, Maggioni A, Franzosi MG, *et al*. In-hospital prognosis of patients with acute myocardial infarction complicated by primary ventricular fibrillation. *N Engl J Med* 1987; 317: 257–261.

41 Mehta D, Curwin J, Gomes JA, *et al*. Sudden death in coronary artery disease: acute ischemia versus myocardial substrate. *Circulation* 1997; 96: 3215–3223.
42 Tang L, Deng C, Long M, *et al*. Thrombin receptor and ventricular arrhythmias after acute myocardial infarction. *Mol Med Camb Mass* 2008; 14: 131–140.
43 Janse MJ, Wit AL. Electrophysiological mechanisms of ventricular arrhythmias resulting from myocardial ischemia and infarction. *Physiol Rev* 1989; 69: 1049–1169.
44 Bayés de Luna A, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. *Am Heart J* 1989; 117: 151–159.
45 Clements-Jewery H, Hearse DJ, Curtis MJ. Phase 2 ventricular arrhythmias in acute myocardial infarction: a neglected target for therapeutic antiarrhythmic drug development and for safety pharmacology evaluation. *Br J Pharmacol* 2005; 145: 551–564.
46 Davies MJ. Anatomic features in victims of sudden coronary death. Coronary artery pathology. *Circulation* 1992; 85: I19–I24.
47 Cupples LA, Gagnon DR, Kannel WB. Long- and short-term risk of sudden coronary death. *Circulation* 1992; 85: I11–I8.
48 Huikuri HV, Mäkikallio TH, Raatikainen MJP, *et al*. Prediction of sudden cardiac death: appraisal of the studies and methods assessing the risk of sudden arrhythmic death. *Circulation* 2003; 108: 110–115.
49 Kaltman JR, Thompson PD, Lantos J, *et al*. Screening for sudden cardiac death in the young: report from a national heart, lung, and blood institute working group. *Circulation* 2011; 123: 1911–1918.
50 Fishman GI, Chugh SS, Dimarco JP, *et al*. Sudden cardiac death prediction and prevention: report from a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop. *Circulation* 2010; 122: 2335–2348.
51 Perk J, De Backer G, Gohlke H, *et al*. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012; 33: 1635–1701.
52 Jabbari R, Risgaard B, Holst AG, *et al*. Cardiac symptoms before sudden cardiac death caused by coronary artery disease: a nationwide study among young Danish people. *Heart Br Card Soc* 2013; 99: 938–943.
53 Deyell MW, Krahn AD, Goldberger JJ. Sudden cardiac death risk stratification. *Circ Res* 2015; 116: 1907–1918.
54 Wellens HJJ, Schwartz PJ, Lindemans FW, *et al*. Risk stratification for sudden cardiac death: current status and challenges for the future. *Eur Heart J* 2014; 35: 1642–1651.
55 Friedlander Y, Siscovick DS, Arbogast P, *et al*. Sudden death and myocardial infarction in first degree relatives as predictors of primary cardiac arrest. *Atherosclerosis* 2002; 162: 211–216.
56 Bodmer W, Bonilla C. Common and rare variants in multifactorial susceptibility to common diseases. *Nat Genet* 2008; 40: 695–701.
57 Albert CM, MacRae CA, Chasman DI, *et al*. Common variants in cardiac ion channel genes are associated with sudden cardiac death. *Circ Arrhythm Electrophysiol* 2010; 3: 222–229.
58 Westaway SK, Reinier K, Huertas-Vazquez A, *et al*. 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.
59 Stecker EC, Sono M, Wallace E, *et al*. Allelic variants of SCN5A and risk of sudden cardiac arrest in patients with coronary artery disease. *Heart Rhythm* 2006; 3: 697–700.
60 Burke A, Creighton W, Mont E, *et al*. Role of SCN5A Y1102 polymorphism in sudden cardiac death in blacks. *Circulation* 2005; 112: 798–802.
61 Splawski I, Timothy KW, Tateyama M, *et al*. Variant of SCN5A sodium channel implicated in risk of cardiac arrhythmia. *Science* 2002; 297: 1333–1336.
62 Albert CM, Nam EG, Rimm EB, *et al*. Cardiac sodium channel gene variants and sudden cardiac death in women. *Circulation* 2008; 117: 16–23.
63 Crotti L, Hu D, Barajas-Martinez H, *et al*. Torsades de pointes following acute myocardial infarction: evidence for a deadly link with a common genetic variant. *Heart Rhythm* 2012; 9: 1104–1112.
64 Arking DE. A common genetic variant in the NOS1 regulator NOS1AP modulates cardiac repolarization. *Nat Genet* 2006; 38: 644–651.
65 Arking DE, Reinier K, Post W, *et al*. Genome-wide association study identifies GPC5 as a novel genetic locus protective against sudden cardiac arrest. *PloS One* 2010; 5: e9879.
66 Aouizerat BE, Vittinghoff E, Musone SL, *et al*. 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.
67 Arking DE, Junttila MJ, Goyette P, *et al*. Identification of a sudden cardiac death susceptibility locus at 2q24.2 through genome-wide association in European ancestry individuals. *PLoS Genet* 2011; 7: e1002158.
68 Eijgelsheim M. Genetic variation in NOS1AP is associated with sudden cardiac death: evidence from the Rotterdam Study. *Hum Mol Genet* 2009; 18: 4213–4218.
69 Kao WH. 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.
70 Lahtinen AM, Noseworthy PA, Havulinna AS, *et al*. Common genetic variants associated with sudden cardiac death: the FinSCDgen study. *PloS One* 2012; 7: e41675.
71 Newton-Cheh C, Cook NR, VanDenburgh M, *et al*. A common variant at 9p21 is associated with sudden and arrhythmic cardiac death. *Circulation* 2009; 120: 2062–2068.
72 Chen J, Xie X, Zhu J, *et al*. Single-nucleotide polymorphisms

in SCN5A gene in Chinese Han population and their correlation with cardiac arrhythmias. *Genet Med* 2004; 6: 159.
73 Son MK, Ki C-S, Park S-J, *et al*. Genetic mutation in Korean patients of sudden cardiac arrest as a surrogating marker of idiopathic ventricular arrhythmia. *J Korean Med Sci* 2013; 28: 1021–1026.
74 Huertas-Vazquez A, Nelson CP, Guo X, *et al*. Novel loci associated with increased risk of sudden cardiac death in the context of coronary artery disease. *PloS One* 2013; 8: e59905.
75 Gavin MC, Newton-Cheh C, Gaziano JM, *et al*. A common variant in the β2-adrenergic receptor and risk of sudden cardiac death. *Heart Rhythm* 2011; 8: 704–710.
76 Sotoodehnia N, Siscovick DS, Vatta M, *et al*. Beta2-adrenergic receptor genetic variants and risk of sudden cardiac death. *Circulation* 2006; 113: 1842–1848.
77 Tseng ZH. Genetic association studies of sudden cardiac death/arrest: the importance of context. *Heart Rhythm* 2009; 6: 1315–1317.
78 Tseng ZH, Aouizerat BE, Pawlikowska L, *et al*. Common beta-adrenergic receptor polymorphisms are not associated with risk of sudden cardiac death in patients with coronary artery disease. *Heart Rhythm* 2008; 5: 814–821.
79 Refaat MM, Aouizerat BE, Pullinger CR, *et al*. Association of CASQ2 polymorphisms with sudden cardiac arrest and heart failure in patients with coronary artery disease. *Heart Rhythm* 2014; 11: 646–652.
80 Marcsa B, Dénes R, Vörös K, *et al*. 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.
81 Marsman RFJ, Bezzina CR, Freiberg F, *et al*. Coxsackie and adenovirus receptor is a modifier of cardiac conduction and arrhythmia vulnerability in the setting of myocardial ischemia. *J Am Coll Cardiol* 2014; 63: 549–559.
82 Lim BK. Coxsackievirus and adenovirus receptor (CAR) mediates atrioventricular-node function and connexin 45 localization in the murine heart. *J Clin Invest* 2008; 118: 2758–2770.
83 Lisewski U. The tight junction protein CAR regulates cardiac conduction and cell-cell communication. *J Exp Med* 2008; 205: 2369–2379.
84 Bugert P, Elmas E, Stach K, *et al*. No evidence for an association between the rs2824292 variant at chromosome 21q21 and ventricular fibrillation during acute myocardial infarction in a German population. *Clin Chem Lab Med* 2011; 49: 1237–1239.
85 Manolio TA, Collins FS, Cox NJ, *et al*. Finding the missing heritability of complex diseases. *Nature* 2009; 461: 747–753.
86 Boehringer T, Bugert P, Borggrefe M, *et al*. SCN5A mutations and polymorphisms in patients with ventricular fibrillation during acute myocardial infarction. *Mol Med Rep* 2014; 10: 2039–2044.
87 Elmas E, Bugert P, Popp T, *et al*. The P-selectin gene polymorphism Val168Met: a novel risk marker for the occurrence of primary ventricular fibrillation during acute myocardial infarction. *J Cardiovasc Electrophysiol* 2010; 21: 1260–1265.
88 Novotny T, Kadlecova J, Raudenska M, *et al*. Mutation analysis ion channel genes ventricular fibrillation survivors with coronary artery disease. *Pacing Clin Electrophysiol* 2011; 34: 742–749.
89 Oliva A, Hu D, Viskin S, *et al*. SCN5A mutation associated with acute myocardial infarction. *Leg Med Tokyo Jpn* 2009; 11 (Suppl 1): S206–S209.
90 Hu D, Viskin S, Oliva A, *et al*. Novel mutation in the SCN5A gene associated with arrhythmic storm development during acute myocardial infarction. *Heart Rhythm* 2007; 4: 1072–1080.
91 Goldberger JJ, Basu A, Boineau R, *et al*. Risk stratification for sudden cardiac death: a plan for the future. *Circulation* 2014; 129: 516–526.
92 Myerburg RJ, Junttila MJ. Sudden cardiac death caused by coronary heart disease. *Circulation* 2012; 125: 1043–1052.
93 Hernesniemi JA, Lyytikäinen L-P, Oksala N, *et al*. Predicting sudden cardiac death using common genetic risk variants for coronary artery disease. *Eur Heart J* 2015; 36: 1669–1675.
94 Goldberg AD, Allis CD, Bernstein E. Epigenetics: a landscape takes shape. *Cell* 2007; 128: 635–638.
95 Bird A. Perceptions of epigenetics. *Nature* 2007; 447: 396–398.
96 Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. *Nat Genet* 2003; 33 Suppl: 245–254.
97 Jabbari R. Ventricular fibrillation and sudden cardiac death during myocardial infarction. *Dan Med J* 2016 2016; 63: pii: B5246.