

Sudden Cardiac Arrest and Rare Genetic Variants in the Community

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Background—Sudden cardiac arrest (SCA) ranks among the most common causes of death worldwide. Because SCA is most often lethal, yet mostly occurs in individuals without previously known cardiac disease, the identification of patients at risk for SCA could save many lives. In unselected SCA victims from the community, common genetic variants (which are not disease-causing per se, but may increase susceptibility to ventricular fibrillation) are found to be associated with increased SCA risk. However, whether rare genetic variants contribute to SCA risk in the community is largely unexplored.

Methods and Results—We here investigated the involvement of rare genetic variants in SCA risk at the population level by studying the prevalence of 6 founder genetic variants present in the Dutch population (PLN-p.Arg14del, MYBPC3-p.Trp792fsX17, MYBPC3-p.Arg943X, MYBPC3-p.Pro955fsX95, PKP2-p.Arg79X, and the Chr7q36 idiopathic ventricular fibrillation risk haplotype) in a cohort of 1440 unselected Dutch SCA victims included in the Amsterdam Resuscitation Study (ARREST). The six studied founder mutations were found to be more prevalent (1.1%) in the ARREST SCA cohort compared with an ethnically and geographically matched set of controls (0.4%, n=1379; $P<0.05$) or a set of Dutch individuals drawn from the Genome of the Netherlands (GoNL) study (0%, n=500; $P<0.02$).

Conclusions—This finding provides proof-of-concept for the notion that rare genetic variants contribute to some extent to SCA risk in the community. (*Circ Cardiovasc Genet.* 2016;9:147-153. DOI: 10.1161/CIRCGENETICS.115.001263.)

Key Words: arrhythmia ■ cardiac arrest ■ founder mutations ■ genetics ■ population genetics

Sudden cardiac arrest (SCA) ranks among the most common causes of death worldwide.^{1,2} SCA incidence in the community varies between 0.6 and >1.4 per 1000 individuals. Because SCA is most often lethal, yet commonly occurs in individuals without previously known cardiac disease, the identification of patients at risk for SCA could save many lives.^{3,4} SCA usually results from ventricular fibrillation (VF).^{2,5} The causes of VF are highly complex and may entail genetic and acquired causes and their interactions. Acquired causes for SCA (eg, cardiovascular disease, comorbidities, medication use) are well-established.⁵ Their prevalence rises with advancing age; accordingly, SCA most commonly afflicts older people. Emerging evidence also implicates genetic factors in SCA risk. In young SCA victims, rare genetic variants with large biological effects (mutations) that cause cardiomyopathies or primary electric disease

contribute importantly to SCA risk. This insight was gained from highly selected cohorts of young SCA victims seen at specialized Cardiogenetics departments.^{6,7} In unselected SCA victims from the community, common genetic variants (which, because of their small contribution to risk, are not disease-causing per se, but may increase susceptibility to VF) have recently been found to be also associated with increased SCA risk.^{8,9} However, whether rare genetic variants contribute to SCA in the community is largely unexplored.¹⁰

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Here, we investigated the contribution of rare genetic variants to SCA risk at the population level by studying the prevalence of 6 Dutch founder mutations previously linked

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to cardiomyopathies or primary electric disease in a cohort of unselected Dutch SCA victims from the community.^{11–15} These known pathogenic variants were chosen based on their recurrence in DNA diagnostic testing of patients with inherited cardiac disorders at Cardiogenetics departments in the Netherlands.

Methods

In this case–control study, we compared the prevalences of 6 founder mutations previously identified in familial occurrences of SCA between one case cohort of unrelated Dutch SCA victims from the AmsterdAM Resuscitation STudies (ARREST) and 3 control cohorts of unrelated Dutch individuals: (1) Amsterdam area controls; (2) Genome of the Netherlands (GoNL) study¹⁶; (3) Prevention of Renal and Vascular Endstage Disease (PREVEND) study.¹⁷ This study was conducted at the Academic Medical Center, a university hospital in Amsterdam, the Netherlands, and approved by the relevant Medical Ethics Committees. Informed consent was obtained from all controls and cases who survived their SCA.

SCA Cases

The 1440 SCA cases in this study (mean age 64 years, 78% men) were included in ARREST in the period June 2007 until December 2011.⁹ ARREST is an ongoing prospective community-based SCA registry coordinated from the Academic Medical Center and designed to establish the genetic^{8,9} and clinical¹⁸ determinants of SCA and outcome of resuscitation attempts¹⁹ in the community. The ARREST study protocol is described in detail elsewhere.²⁰ In short, the ARREST research group collects data of all cardiopulmonary resuscitation efforts in collaboration with all Emergency Medical Services in the North Holland province of the Netherlands; this study region contains the Amsterdam area and covers 2404 km² (urban and rural communities) with a population of 2.4 million people. ARREST catches >95% of all individuals with out-of-hospital SCA in whom a resuscitation is attempted.²¹ ECG recordings from the ambulance monitor/defibrillator or automated external defibrillator are used to determine whether VF had occurred. SCA cases are defined as individuals with a cardiac arrest in an out-of-hospital setting, with VF. Individuals with an obvious noncardiac cause of VF (eg, trauma, intoxication, drowning, suicide) are excluded. Individuals in whom only asystole (but no ventricular tachycardia/VF) is recorded are also excluded because we cannot ensure that cardiac arrest stemmed from cardiac causes, as asystole is the end stage of any cardiac arrest, or may be because of noncardiac causes (eg, respiratory failure).²² Medical histories are obtained from the general practitioner, and the immediate cause of SCA is obtained from hospital records. Genomic DNA is extracted from peripheral blood samples drawn during routine patient care, according to standard procedures. Written informed consent is obtained from all surviving SCA cases.

Control Cohorts

Amsterdam Area Controls

Amsterdam area controls, collected in a region overlapping the geographic capture area of ARREST, were 1379 healthy volunteer blood donors of Dutch European descent at Sanquin Blood Supply (67% male, mean age 53 years).²³

GoNL Controls

GoNL controls were all 500 unrelated individuals from the database of the GoNL study, which comprised whole genome–sequenced individuals distributed evenly across the Netherlands (covering 11 of its 12 provinces) without selection on the basis of phenotype or disease.^{16,24}

PREVEND Controls

PREVEND controls were all 8261 individuals from the database of the PREVEND study, which comprised inhabitants of the city of Groningen in the north of the Netherlands.¹⁷

Founder Mutations: Selection and Genotyping

The following 6 founder mutations were selected for the study because of their recurrence (indicative of a founder effect) in DNA diagnostic testing of patients with inherited cardiac disorders at Cardiogenetics departments in the Netherlands.^{11–15} These mutations included 3 mutations associated with hypertrophic cardiomyopathy (mutations MYBPC3-p.Trp792fsX17, MYBPC3-p.Arg943X, MYBPC3-p.Pro955fsX95); 1 mutation associated with arrhythmogenic right ventricular cardiomyopathy (ARVC; PKP2-p.Arg79X); 1 mutation associated with an overlap phenotype of dilated cardiomyopathy (DCM) and ARVC (PLN-p.Arg14del), and a founder haplotype linked to idiopathic VF (IVF; the Chr7q36 IVF risk-haplotype), which was detected by either the chr7:154002240 c.-340C>T or the chr7:g.154056404. TA/- variant, both of which are unique to the risk haplotype.^{12,25}

Genotyping for the 6 founder mutations was conducted in the ARREST case cohort and the Amsterdam area control cohort and performed on the MassARRAY system using time-of-flight matrix-assisted laser desorption ionization (MALDI-TOF) mass spectrometry with the iPLEX Gold chemistry (Sequenom Inc, San Diego CA). Primers were designed using Assay Designer 4.0.0.2 with iPLEX Gold default parameters. The polymerase chain reaction (PCR) primers used are listed in Table I in the Data Supplement. Automated genotype calling was done with Typer Analyzer 4.0.22.67. We included DNA from a known carrier for each mutation as a positive control. Genotype clustering was visually checked by an experienced evaluator. Once carriership of a founder mutation was identified, this was subsequently validated by PCR-Sanger sequencing.

Statistical Analysis

We used Mantel-Haenszel tests stratified according to age group (age <50 and age ≥50 years) to evaluate whether the proportions of founder mutation carriers in ARREST significantly differed ($P<0.05$) from that observed in the control cohorts. We then used the Fisher exact test to test for significance within the 2 age groups. Error bars denote the standard error (SE) of the proportion (based on group size). Confidence intervals are given as $\pm 2 \times SE$.

Results

Prevalence of Founder Mutations in ARREST and Controls

All founder mutations were successfully genotyped in the ARREST cases and Amsterdam area controls with an average call rate of 98%. All positive controls for the founder mutations were properly called.

None of the 1440 SCA cases in ARREST carried the MYBPC3-p.Pro955fsX95 mutation or the Chr7q36 IVF risk haplotype. Sixteen cases (mean age 57 years, 75% men) were heterozygous carriers of one of the 4 remaining founder mutations: 8 carried the PLN-p.Arg14del mutation, 6 carried MYBPC3-p.Trp792fsX17, and 1 each carried MYBPC3-p.Arg943X or PKP2-p.Arg79X (Figure 1 and Table 1). Their place of residence is shown in Figure 2. When considered in aggregate, the proportion of carriers in ARREST was 1.1% (16 of 1440 cases). Among young cases (age <50 years, range 22–46), this proportion was higher (6/202, 3%) than among older (age ≥50 years, range 57–86) cases (10/1238, 0.8%).

Among the 1379 Amsterdam area controls, 6 (0.4%) carried the founder mutations PLN-p.Arg14del ($n=3$), MYBPC3-p.Trp792fsX17 ($n=2$), or MYBPC3-p.Arg943X ($n=1$). None carried the MYBPC3-p.Pro955fsX95 mutation or the Chr7q36 IVF risk haplotype. The proportion of carriers was similar among young and older controls at 0.42% (2/474) and 0.45% (4/895), respectively.

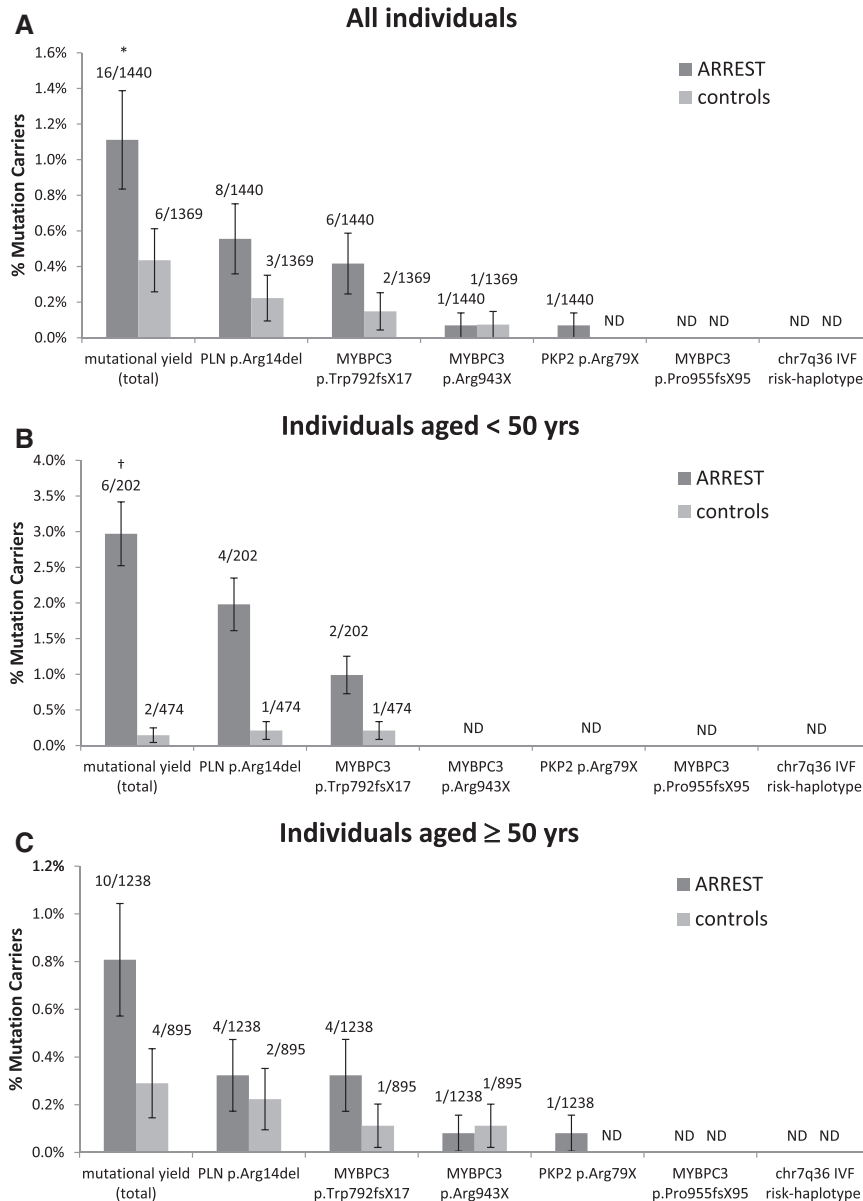


Figure 1. Prevalence of the 6 founder mutations in the genotyped sudden cardiac arrest (SCA) cases ($n=1426$) and in the Amsterdam area controls ($n=1379$) in all cases and controls (**A**) and according to age group (**B** and **C**); ND: not detected. * denotes statistical significance ($P<0.05$) using Mantel-Haenszel test stratified for age group; † denotes statistically significant difference between SCA cases and controls ($P<0.05$) using Fisher exact test. ARREST indicates AmsteRdam REsuscitation STudies.

When the founder mutations were considered in aggregate, we found an enrichment of carriership among ARREST cases compared with Amsterdam area controls (1.1% versus 0.4%, Mantel-Haenszel test; $P=0.028$). The difference in prevalence was strongest among young individuals (3.0% versus 0.4%, Fisher's exact; $P=0.01$) and not statistically significant among older individuals (0.8% versus 0.5%, Fisher's exact; $P=0.42$). When considered separately, there was no statistically significant difference in the abundance of the PLN-p.Arg14del, MYBPC3-p.Trp792fsX17 or MYBPC3-p.Arg943X mutations between both cohorts ($P>0.05$). We additionally looked up the prevalence of the 6 founder mutations in the GoNL database of 500 unrelated Dutch subjects. No control from GoNL carried any of the founder mutations. We

further focused on the most commonly encountered founder mutation in ARREST, the PLN-p.Arg14del mutation. We looked up the prevalence of this mutation in the database of the PREVENT study, which consisted of 8267 individuals recruited from the region where PLN-p.Arg14del is thought to have originated and where it is, therefore, expected to be most prevalent in the general population.^{17,26} We found that PLN-R14del occurred significantly more often in ARREST than in PREVENT (0.56% versus 0.07%, Fisher's exact; $P<0.0003$, Table 2).

Clinical Characteristics of Cases

Although mutation carriership was not known before the SCA episode in any of the cases, all young cases, but no older case,

Table 1. Clinical Characteristics of SCA Cases

	<i>PLN</i> -p. <i>R14Del</i> (N=8)	<i>MYBPC3</i> -p. <i>Trp792fsX17</i> (N=6)	<i>MYBPC3</i> -p. <i>Arg943X</i> (N=1)	<i>PKP2</i> -p. <i>Arg79X</i> (N=1)
Demographic data				
Mean age, y	53.8±22.0	60.7±21.3	65	57
Age <50 y	4	2	0	0
Male sex	5	5	1	1
Family history of SCA	4	2	1	0
Putative cause of SCA in young cases (<50 y), N=6				
DCM	4	0	0	0
ARVC	0	1	0	0
IVF	0	1	0	0
Putative cause of SCA in older cases (≥50 y), N=10				
Acute myocardial infarction	3	1	1	0
ARVC	0	0	0	1
HCM	0	1	0	0
IVF	1	1	0	0
Died before diagnosis	0	1	0	0

Data are mean±SD or number. ARVC indicates arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; IVF, idiopathic ventricular fibrillation; and SCA, sudden cardiac arrest.

were referred to a Cardiogenetics department for DNA analysis after the SCA episode.

Young Cases

Four young cases were already treated for DCM before their SCA episode, including 3 with heart failure. DNA analysis at the Cardiogenetics department, initiated after their SCA episode, revealed that they all carried the *PLN*-p.Arg14del mutation. In the 2 remaining young cases, we found the *MYBPC3*-p.Trp792fsX17 mutation. In both, carriership was unknown before the present study. In one of them, the diagnosis after the clinical workup after SCA was ARVC; accordingly, ARVC-related genes were screened at the Cardiogenetics department (*PLN*, *PKP2*, *DSP*, *DSG2*, *DSC2*, *JUP*, *TMEM43*), but no pathogenic mutation was found. In the other case, no putative cause for SCA was found at the post-SCA clinical workup, yielding the diagnosis IVF; no subsequent DNA analysis was conducted.

Older Cases

In 5 of 10 older cases (50%), workup after SCA revealed that they had acute myocardial infarction at the time of SCA; we found that they carried *PLN*-p.Arg14del (n=3), *MYBPC3*-p.Trp792fsX17 (n=1), or *MYBPC3*-p.Arg943X (n=1). Investigation into the cause of SCA in the 5 remaining cases yielded the diagnoses hypertrophic cardiomyopathy (*MYBPC3*-p.Trp792fsX17 [n=1]); IVF in 2 cases (*PLN*-p.Arg14del [n=1] and *MYBPC3*-p.Trp792fsX17 [n=1]); one case was already

known to have ARVC (*PKP2*-p.Arg79X), whereas the last case died before a diagnosis was made (*MYBPC3*-p.Trp792fsX17).

Discussion

We provide proof-of-concept for the notion that rare genetic variants contribute to SCA risk in the community by demonstrating that 6 founder mutations associated with SCA in the setting of familial cardiomyopathy or primary electric disease are more prevalent in an unselected cohort of SCA victims from the community compared with 3 control cohorts.

The mutations studied here were selected because they are among the most prevalent SCA-associated founder mutations in the Netherlands.^{11–15} For instance, the *PLN*-p.Arg14del mutation, identified in 10% to 15% of Dutch patients with DCM or ARVC, is the most prevalent cardiomyopathy-associated mutation in the Netherlands.¹⁷ Similarly, the *MYBPC3*-p.Trp792fsX17 mutation is found in 17% of hypertrophic cardiomyopathy index patients in the Netherlands.²⁷ Of note, besides their recurrence in patients with similar phenotypes, the pathogenicity of some of the mutations has also been demonstrated in functional studies. *PLN* (phospholamban) is involved in regulating the activity of the cardiac isoform of the sarcoplasmic reticulum Ca²⁺ ATPase, and the *PLN*-p.Arg14del mutation has been shown to impair Ca²⁺ handling in cardiomyocytes.²⁸ Studies in cardiomyocytes from patients with the *MYBPC3*-p.Trp792fsX17 (c.2373dupG) or the *MYBPC3*-p.Pro955fsX95 (c.2864_2865delCT) mutation uncovered haploinsufficiency of the sarcomeric protein *MYBPC3*, alongside deranged phosphorylation of contractile proteins, increased Ca²⁺-sensitivity, and reduced maximal force-generating capacity.²⁹ Although no functional studies have been conducted on the fourth founder mutation that we detected in ARREST, that is the *PKP2*-p.Arg79X mutation, it is likely that this mutation leads to haploinsufficiency; functional studies in mice that are haploinsufficient for *PKP2* uncovered desmosomal abnormalities at the intercalated disc, as well as deficits in sodium channel function.³⁰

Not all 6 mutations were found in the SCA cohort. This may be related to the size of the SCA cohort. Also, the geographic origin of the respective mutation in relation to the capture region of ARREST (Figure 2), combined with the age of the founder mutation and migration patterns, may play a role. The consideration of such factors necessitates that studies investigating the role of such mutations in the community use geographically matched controls because gradients may exist in the population frequency of such founder mutations,¹⁵ even in a small country, such as the Netherlands. Accordingly, when we studied the GoNL database of individuals recruited evenly across the Netherlands, we found no carriers of any founder mutation. In contrast, we did find such carriers in the Amsterdam area control cohort, which was recruited in the same geographic region as the ARREST case set and, therefore, likely represents the best-matched control cohort. Similarly, when we focused on the *PLN*-p.Arg14del mutation, we additionally compared with the PREVENT control cohort because this mutation is believed to have originated in the region where this cohort was recruited. Accordingly, we found carriers of the *PLN*-p.Arg14del mutation in this region. Still, even when the ARREST case cohort was compared with both geographically matched control cohorts, the prevalence of the respective founder mutations was higher in the ARREST case cohort. This

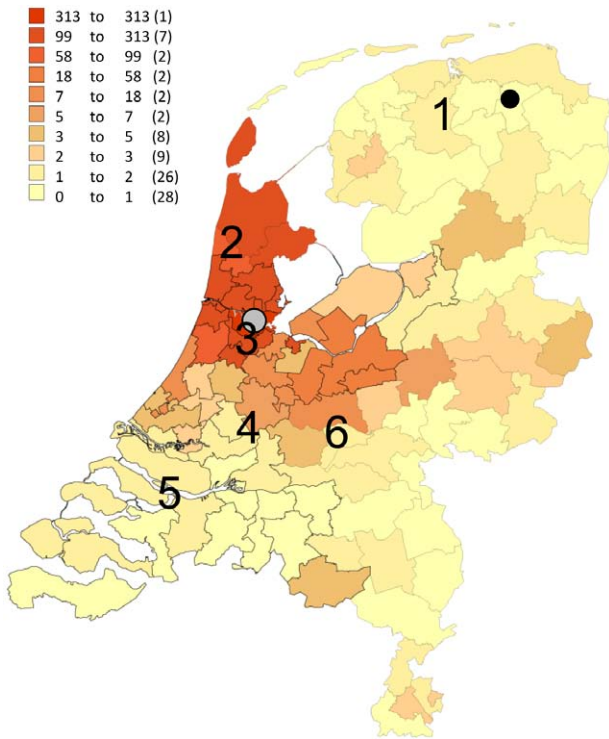


Figure 2. Distribution of the genotyped sudden cardiac arrest (SCA) cases (ARREST) according to their place of residence. The number of SCA cases per region is indicated by the shade of red (in parenthesis: the number of postal code regions, 90 in total). Each region contains 180 000 inhabitants on average. Bold numbers refer to the location of the presumed origin of the respective founder mutations: (1) PLN-p.Arg14del; (2) MYBPC3-p.Trp792fsX17; (3) PKP2-p.Arg79X; (4) Chr7q36 IVF risk-haplotype; (5) MYBPC3-p.Arg943X; (6) MYBPC3-p.Pro955fsX95. The city of Amsterdam (grey dot) is located in the heart of the ARREST and Amsterdam area regions; Groningen (black dot) is the city where the PREVENT cohort was recruited. ARREST indicates AmsteRdam REsuscitation STudies; and PREVENT, Prevention of Renal and Vascular Endstage Disease.

finding supports the notion that founder mutations are relevant for SCA occurrence in the community at large.

This notion is consistent with previous insights that these mutations are pathogenic and contribute importantly to SCA

in young individuals without acquired causes for SCA. Such individuals, who suffer SCA despite seemingly full health, are typically referred to a Cardiogenetics department. Indeed, the 4 young PLN-R14del patients had a phenotype typical for PLN-R14del (DCM with reduced QRS voltages on the ECG) and were all referred to a Cardiogenetics department, where this mutation was subsequently identified. It is likely that the PLN-R14del mutation contributed importantly to the occurrence of VF in these patients, given that this mutation is known to be associated with a high incidence of malignant cardiac arrhythmias and sudden death.³¹ Multiple mechanisms may cause arrhythmia in PLN-R14del mutation carriers. Primary disruptions in electric properties, specific to this mutation, may contribute (delayed afterdepolarizations caused by disrupted cellular Ca²⁺ homeostasis). Moreover, reentrant arrhythmias may arise from the structural changes associated with the development of DCM; sudden cardiac death is a frequent occurrence in all DCM cases irrespective of the underlying genetic defect (30% of all deaths associated with DCM).³² Distinguishing the contribution of both possibilities was impossible in our cohort because all SCA cases with this mutation also had DCM. Such distinction may come from future studies. For instance, SCA risk could be compared between PLN-R14del mutation carriers without DCM and carriers of other DCM-related mutations without DCM. Similarly, direct comparison of SCA risk between a cohort of DCM patients with the PLN-R14del mutation and DCM patients without this mutation may be considered.

The role of founder mutations in older SCA victims seems more complex. Four of 8 SCA patients who carried the PLN-p.Arg14del mutation were of older age. In 3 of them, acute myocardial infarction was most likely the immediate cause of SCA, and they were not found to have DCM. Although there was no clear evidence to suggest that carriership of PLN-p.Arg14del contributed to SCA in these patients, it is conceivable that the pathophysiological changes imposed by the mutation conspired with the pathophysiological changes during acute myocardial infarction, thereby increasing the susceptibility to VF. Phospholamban (the protein product of *PLN*) is crucially involved in maintaining cellular calcium homeostasis, and calcium overload, caused by acute myocardial infarction, may be

Table 2. Prevalence of Founder Mutations in SCA Cases and Controls

Founder Mutation	ARREST Cases	Amsterdam Area Controls	GoNL Controls	PREVENT Controls
PLN-p.Arg14del	8/1426 (0.56%)	3/1348 (0.22%)	0/500 (0%)	6/8261 (0.07%)*
MYBPC3-p.Trp792fsX17	6/1420 (0.42%)	2/1354 (0.15%)	0/500 (0%)	n.a.
MYBPC3-p.Arg943X	1/1417 (0.07%)	1/1354 (0.07%)	0/500 (0%)	n.a.
PKP2-p.Arg79X	1/1419 (0.07%)	0/1331 (0%)	0/500 (0%)	n.a.
MYBPC3 p.Pro955fsX95	0/1440 (0%)	0/1350 (0%)	0/500 (0%)	n.a.
Chr7q36 IVF risk-haplotype	0/1440 (0%)	0/1379 (0%)	0/500 (0%)	n.a.
Total yield	16/1440 (1.1%)	6/1379 (0.44%)	0/500 (0%)	n.a.
<i>P</i> value		<i>P</i> <0.05	<i>P</i> <0.02	

ARREST indicates AmsteRdam REsuscitation STudies; GoNL, genome of the Netherlands; PREVENT, Prevention of Renal and Vascular Endstage Disease; IVF, idiopathic ventricular fibrillation; n.a., not applicable; and SCA, sudden cardiac arrest. The *P* value reflects the likelihood that the observed difference in prevalence between the SCA cases and the respective controls is based on chance (Fisher's exact test).

**P*=0.00029 for PLN-p.Arg14del PREVENT vs ARREST.

sufficiently exacerbated by PLN-p.Arg14del to result in VF.^{17,33} To provide further evidence that carriership of PLN-p.Arg14del contributed to SCA during acute myocardial infarction, it would be desirable to compare SCA incidence during acute myocardial infarction between a cohort of carriers of this mutation and a cohort of noncarriers. A similar comparison could be made between carriers and noncarriers of other rare variants.

The older carriers were not referred to a Cardiogenetics department for DNA testing, probably because SCA is not an unexpected occurrence at their age. Even in both young MYBPC3-p.Trp792fsX17 carriers who were referred to the Cardiogenetics department after SCA, this mutation was not found, as *MYBPC3* was not screened, given the lack of an identifiable cardiac phenotype (IVF) in one carrier and a non-*MYBPC3*-associated phenotype (ARVC) in the other. This highlights the difficulties of targeted (phenotype-based) DNA screening, which result from incomplete penetrance and a diverse clinical spectrum.

Our findings may provide a basis to design or modify guidelines for DNA testing in SCA victims in the community. With the current protocols, DNA testing is largely limited to SCA patients with a high likelihood for carriership (eg, because of young age, family history, or clinical suspicion of a particular disease) and to genes implicated in a particular phenotype. As a result, mutations with a clear disease-causing potential but reduced penetrance or variable expression will be missed (eg, the 4 older PLN-p.Arg14del carriers and the young MYBPC3-Trp792fsX17 carriers in our study). Thus, mutation-carrying relatives of these patients will not be identified, depriving them of the opportunity for early detection and treatment of subclinical cardiac disease with the associated risk of SCA. Conversely, broad genetic testing in all SCA patients regardless of likelihood of carriership (ie, not only in the case of Sudden Arrhythmogenic Death Syndrome as currently recommended in the guidelines³⁴ and independent of the underlying phenotype, ie, including MI, DCM, and hypertrophic cardiomyopathy cases) would raise medical, ethical, and logistical concerns. This is particularly true if comprehensive testing of large gene panels is conducted, such as currently used in molecular autopsy,³⁵ as unavoidably many genetic variants with unclear clinical significance will be discovered in this scenario. A possible compromise could be to systematically test only for the presence of a set of founder mutations with proven pathogenicity in all SCA victims. For instance, the PLN-p.Arg14del mutation is clearly pathogenic²⁶ and not unique to the Netherlands because it belongs to the European-shared founder mutation category³⁶ and was also found in Germany and in the United States, suggesting a possible common ancestor from the Netherlands between these populations.¹⁷ In hot spots for this mutation in these countries, specific screening for this mutation and other locally identified founder mutations may be considered in SCA patients.

Clearly, we have only begun to understand the role of rare genetic variants in susceptibility to SCA in the community. Much more work is needed to identify the role of these variants in the light of possible interactions with other concomitant genetic or acquired factors that increase SCA risk. Our study is limited because of the selected number of known mutations that we studied. Future studies with larger SCA cohorts and a more unbiased approach will help to obtain a more comprehensive insight into the role of rare variants in SCA risk in the community. Still, our

study provides proof-of-concept for the notion that rare genetic variants contribute to SCA risk in the community.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Sudden cardiac arrest (SCA) ranks among the most common causes of death worldwide. Because SCA is most often lethal, yet mostly occurs in individuals without previously known cardiac disease, the identification of patients at risk for SCA could save many lives. In unselected SCA victims from the community, common genetic variants (which are not disease-causing per se, but may increase susceptibility to ventricular fibrillation) are found to be associated with increased SCA risk. However, whether rare genetic variants contribute to SCA risk in the community is still largely unexplored. The present study shows that 6 selected Dutch founder mutations (in PLN, MYBPC3, PKP2, and on Chr7q36) are more prevalent in a cohort of 1440 unselected Dutch SCA victims from the community than in an ethnically and geographically matched set of controls. This finding provides proof-of-concept for the notion that rare genetic variants contribute to SCA risk in the community and a basis to (re)design guidelines for DNA testing in SCA victims in the community. With the current protocols, DNA testing is largely limited to SCA patients with a high likelihood for carriership (eg, because of young age, family history, or clinical suspicion of a particular disease). As a result, mutations with clear disease-causing potential but reduced penetrance or variable expression will be missed. Thus, mutation-carrying relatives of these patients will not be identified, depriving them of the opportunity for early detection and treatment. Our study provides the first evidence for the usefulness of testing known founder mutations with proven pathogenicity in all SCA victims.

Sudden Cardiac Arrest and Rare Genetic Variants in the Community

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SUPPLEMENTAL MATERIAL

Supplementary Table 1 Sequence of PCR and extension primers; in brackets is the alternative allele

Gene	Chr	Mutation	Genomic position (hg19)	c.DNA	Probe sequence
<i>Chr7q36</i> <i>IVF risk-haplotype</i>	7	c.1-340C>T	154002240	c.1-340C>T	gcgccgtgggcgccggggcgggagcgggagggaggcagcgc g[c/t]atcactcgggtccccttctgcaccagcc
		TA/-	154056404	n.a.	ttagttagtatttcagatttccaacctgttggtgtgggataagg gt[ta/]gagatacagagaagcaccctgccccggaggatcactg cctggtgag
<i>PLN</i>	6	p. Arg14del (p.R14del)	118880124	c.40_42delAGA	aagtccaatacctcactcgtcagctataaga[aga]gcctcaaccatt gaaatgcctcaacaagcagctcaaaagct
<i>MYBPC3</i>	11	p.Trp792fsX17 (p.W792Vfs*41)	47359280	c.2373_2374insG (insGfsQ791, insG791)	tgcagacgcacctgcggcccccaagatcagcaactgggagagg actcctgcacagtacag[g]tgggagcccgctcctacatggcggg cagccccatcctgg
<i>MYBPC3</i>	11	p.Arg943X	47356671	c.2827C>T	gtgaaggacctgccacggggcccgctctttc[c/t]gagtgcg ggcacacaatatggc
<i>MYBPC3</i>	11	p.Pro955fsX95	47356634	c.2864_2865delCT	gcacacaatatggcaggcctggagccc[ct]gttaccaccacggag ccggtgacagtgcaggagatcctg
<i>PKP2</i>	12	p.Arg79X	33031955	c.235C>T	tattgcttgattgcaggaaatcttcac[c/t]gaaccagcagtgctcctg agtatgtctacaacctta