Absence of Calsequestrin 2 Causes Severe Forms of Catecholaminergic Polymorphic Ventricular Tachycardia

Alex V. Postma, Isabelle Denjoy, Theo M. Hoornanje, Jean-Marc Lupoglazoff, Antoine Da Costa, Pascale Sebillion, Marcel M.A.M. Mannens, Arthur A.M. Wilde, Pascale Guicheney

Abstract—Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare arrhythmogenic disorder characterized by syncopal events and sudden cardiac death at a young age during physical stress or emotion, in the absence of structural heart disease. We report the first nonsense mutations in the cardiac calsequestrin gene, CASQ2, in three CPVT families. The three mutations, a nonsense R33X, a splicing 532+1 G>A, and a 1-bp deletion, 62delA, are thought to induce premature stop codons. Two patients who experienced syncopes before the age of 7 years were homozygous carriers, suggesting a complete absence of calsequestrin 2. One patient was heterozygous for the stop codon and experienced syncopes from the age of 11 years. Despite the different mutations, there is little phenotypic variation of CPVT for the CASQ2 mutations. Of the 16 heterozygous carriers of these various mutations, 14 were devoid of clinical symptoms or ECG anomalies, whereas 2 of them had ventricular arrhythmias at ECG on exercise tests. In line with this, the diagnosis of the probands was difficult because of the absence of a positive family history. In conclusion, these additional three CASQ2 CPVT families suggest that CASQ2 mutations are more common than previously thought and produce a severe form of CPVT. The full text of this article is available at http://www.circresaha.org.

Key Words: calsequestrin ■ tachycardia ■ syncope ■ arrhythmia ■ genetics

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an uncommon arrhythmogenic disorder occurring in children and adolescents with a structurally normal heart. Patients suffering from CPVT are exposed, at a young age, to syncopal events and sudden cardiac death (SCD) due to stress-induced ventricular tachyarrhythmia. The resting ECG, including the QTc interval, is generally normal, but sinus bradycardia may be observed. CPVT has a highly malignant course when untreated, with estimates of mortality ranging from 30% to 50% by the age of 20 to 30 years. Furthermore, there is a clear correlation between the age of the first syncope and the severity of the disease, with a worse prognosis in the case of early occurrence. β-Blockers without sympathomimetic activity are clinically effective in reducing syncope, but sometimes an implantable defibrillator may be needed.

The genetic basis of this inherited arrhythmogenic disorder has been established by the identification of autosomal dominant mutations in the cardiac ryanodine receptor gene (RYR2). More recently, Lahat et al reported on one consanguineous CPVT family and their associated homozygous missense mutation in calsequestrin 2 (CASQ2), effectively describing a recessive form of CPVT. Both genes play a crucial role in the excitation-contraction coupling; they are involved in the release of Ca2+ from the sarcoplasmatic reticulum (SR) before contraction of the myocyte.

Genetic and clinical evaluation of our CPVT population allowed us to identify three new mutations in CASQ2. In the present study, we report on three families: two CPVT families with phenotypes fitting a recessive mode of inheritance and one family with a possible autosomal dominant mode of inheritance, with their associated nonsense mutations.

Materials and Methods

CPVT Families

The probands of the three families were referred to Paris or Amsterdam for syncope (n=2) and rescued cardiac arrest (n=1). CPVT diagnosis was established by documenting bidirectional ventricular tachycardia (VT), which was reproducibly induced by exercise stress testing and/or isoproterenol infusion in the absence of structural heart abnormalities as assessed by clinical history, blood chemistry, ECG, and echocardiography. All probands had a normal QTc interval at rest. A familial history of syncope or sudden death

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Clinical Data of CASQ2 CPVT Families

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Age at First Syncope, y</th>
<th>Age at Diagnosis, y</th>
<th>Current Age, y</th>
<th>HR at Diagnosis, bpm</th>
<th>Median HR Age Group</th>
<th>QTC, ms</th>
<th>PVT Threshold, bpm</th>
<th>Symptoms</th>
<th>Treatment</th>
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<tr>
<td>Proband</td>
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<tr>
<td>Family I (n=1)</td>
<td>62delA</td>
<td>6.5</td>
<td>6.5</td>
<td>14</td>
<td>70</td>
<td>88</td>
<td>428</td>
<td>100</td>
<td>Exercise-induced syncope</td>
</tr>
<tr>
<td>Family II (n=1)</td>
<td>532+1 G/A</td>
<td>5</td>
<td>7</td>
<td>10</td>
<td>63</td>
<td>88</td>
<td>403</td>
<td>120</td>
<td>Syncope/cardiac arrest</td>
</tr>
<tr>
<td>Family III (n=1)</td>
<td>R33*</td>
<td>11</td>
<td>18</td>
<td>24</td>
<td>46</td>
<td>74</td>
<td>440</td>
<td>95</td>
<td>Exercise-induced syncope</td>
</tr>
</tbody>
</table>

Mean±SD 8±3 11±7 15±8 60±12 424±19 105±13

Heterozygous carriers

Family I (n=6) 62delA ... ... 26±7 79±9 422±16 ...
Family II (n=4) 532+1 G/A ... ... 25±14 73±11 413±6 ...
Family III (n=5) R33* ... ... 48±19 70±9 387±21 ...

Wild type

Family II (n=1) ... ... ... 12 82 425 ...
Family III (n=10) ... ... ... 39±22 78±7 391±26 ...

HR indicates heart rate.

was absent in families I and II. Family members were evaluated by 12-lead resting ECG, exercise test, and Holter recording. All individuals gave informed consent to the clinical and genetic study, which was approved by the internal ethics committee.

Genotyping of Candidate Genes

Mutation screening was performed on genomic DNA samples that were extracted from peripheral blood lymphocytes by standard methods. The genomic sequence of the CASQ2 gene (accession No. NM_000219), and KCNE1 (accession No. NM_002667), and 50% of RYR2 were screened. In contrast, screening of the entire coding regions of the CASQ2 gene revealed three new mutations, with each specific to a distinct family.

CASQ2 Mutations in CPVT Families

Family I

A 6.5-year-old girl (II-2, Figure 2) was initially referred after syncope occurred subsequent to a facial trauma while she was playing in school. A neurological evaluation was performed without detecting any anomaly by magnetic resonance imaging. A second syncopal event occurred 1 month later while she was running. The resting ECG was normal regarding heart rate and QTc interval (Table). During hospitalization, a Holter recording demonstrated salvos of premature VT (PVT) at a triggering rate of 100 bpm, preceded by isolated polymorphic ventricular bigeminy. An exercise test triggered ventricular bigeminy and polymorphic salvos (see Figure 1).

Nadolol was started at 80 mg daily, but a new stress-induced syncopal event occurred 6 months later, and the nadolol dosage was increased to 160 mg daily. The child remained asymptomatic for 4 years. The last Holter recording still demonstrated isolated polymorphic ventricular premature beats (VPBs). A new stress-induced syncopal event occurred recently (at 160 mg of nadolol), and an implantable cardioverter-defibrillator (ICD) was proposed to the patient. The family pedigree suggests a recessive pattern of transmission; however, the family is not aware of consanguinity. The family history was negative for sudden death or syncope, and exercise tests did not reveal any stress-induced ventricular arrhythmia in the remaining family.

The proband’s coding regions of KCNQ1, KCNE1, KCNH2, KCNK1, and SCN5A did not reveal any abnormal conformers by PCR–single-strand conformation polymorphism screening. In contrast, screening of CASQ2 revealed a homozygous 1-bp deletion in the proband at nucleotide 62 of exon 1 (62delA, Figure 2). This deletion generates a frameshift in the reading frame, which leads to a stop codon 14 amino acids downstream from the deletion. Both parents and four of the proband’s brothers are silent heterozygous carriers without any symptoms or ECG abnormalities at exercise testing (Table). One brother inherited two wild-type alleles, and his phenotype is indistinguishable from that of his parents or brothers (Table). Because the proband is homozygous for this deletion inducing the stop codon, we assume that there is a total absence of functional CASQ2 protein in the proband.
Family II

The proband of family II (III-1, Figure 2) is a 10-year-old male patient initially referred to the pediatric neurologist at the age of 3 years for breath-holding spells. The spells increased in both frequency and severity over time, with symptoms including paleness, cyanosis, and tachypnea. An epileptic disorder was suggested, and carbamazepine therapy was initiated. The patient was resuscitated at 7 years of age after he experienced syncope during exercise. The ECG obtained immediately after the resuscitation efforts showed sinus bradycardia (heart rate 65 bpm) and a prolonged QTc interval (550 ms). Propranolol therapy was initiated at 2 mg/kg, and the QTc interval had normalized on subsequent ECGs. Despite this, the patient developed PVTs at heart rates >125 bpm, which led to an increase in propranolol dosage to 4 mg/kg. Since then, the patient has remained free of tachycardia and symptoms with a follow-up of 3 years (Table). The proband is the oldest child of consanguineous parents (first cousins) and has two younger siblings (aged 8 and 6 years) who are asymptomatic. The remaining family

Figure 1. ECG recording in lead II of the proband of family I showing a normal QTc interval (428 ms) and a slow heart rate (70 bpm) at admission (A). Examples of polymorphic VPBs at the beginning of the stress test (B), followed by self-terminating polymorphic salvos as the heart rate increases >100 bpm (C). Recorded at 25 mm/s and 10 mm/mV.

Figure 2. Pedigrees of the three CPVT CASQ2 families and their associated mutations. Solid symbols indicate affected individuals with a bidirectional VT, syncope, and a CPVT diagnosis; half-filled symbols, individuals with VPB and bigeminy on the ECG during exercise tests; open symbols, asymptomatic individuals after exercise testing; and —, presence of the mutation. Mutations are displayed according to their amino acid number or nucleotide number, where applicable. Sequences given are of individual I-1 in family I, individual III-1 in family II, and individual III-3 in family III.
members are also asymptomatic, and no sudden death has been reported. Subsequent exercise tests and Holter recordings of the family revealed that the proband’s brother (III-3) had doublets and runs of PVTs, for which he was treated by β-blockers at the age of 5 years. Exercise tests were normal for the rest of the family members.

After exclusion of the above-mentioned candidate genes, we screened CASQ2 and found a homozygous intronic base-pair change (from G to A) 1 bp downstream from exon 4 (532+1 G/A, Figure 2). The intronic G/A base-pair change in family II occurs at the fully conserved 532+1 position in the 5′ splice site.8 The effect of the mutation would either be (1) the abolishment of the authentic donor splice site and the subsequent utilization of a completely conserved cryptic donor splice site 55 bp downstream or (2) exon skipping, producing a CASQ2 transcript lacking exon 4. Unfortunately, we cannot determine in vitro the exact splicing effect, because there is no patient heart tissue available, and attempts to amplify CASQ2 mRNA from the proband’s naïve lymphocytes failed. However, regardless of the mechanism, a frameshift occurs in the reading frame, and a premature stop codon for CASQ2 is introduced by this +1 G/A mutation. Genotyping of the family revealed that the youngest brother (III-3) of the proband, with a CPVT phenotype, also carries the homozygous splicing defect. The parents, their other son (II-2), and two other family members are heterozygous for the splicing defect, fitting with the recessive mode of transmission (Figure 2). Because the proband is homozygous for the 532+1 G/A splicing mutation, we assume that there is a total absence of functional CASQ2 protein in this patient, as observed in family I.

**Family III**

The proband of family III (III-3, Figure 2) has presented with syncopal events since the age of 11 years. Her syncopal episodes were of short duration and occurred at the end of exercise. The initial diagnosis was vagal syncope, and CPVT was not diagnosed until the 18th year. At that time, a Holter recording demonstrated numerous polymorphic VPBs with couplets during sinus tachycardia. Resting ECG showed sinus bradycardia and a borderline QTc interval (Table). A subsequent stress test confirmed CPVT by showing polymorphic ventricular salvos >135 bpm. Nadolol (80 mg/d) was started, leading to the disappearance of syncopal events. She has been completely asymptomatic under nadolol with a 6-year follow-up. The family history was negative for syncope or sudden death; nonetheless, exercise tests of the family demonstrated episodes of bigemini and VPBs in the maternal grandfather (I-3) and uncle (II-8).

The coding regions of KCNQ1, KCNE1, KCNH2, KCNK1, and SCN5A did not reveal any abnormal conformers by PCR–single-strand conformation polymorphism screening. Subsequent sequencing of CASQ2 revealed a heterozygous mutation in the first exon of CASQ2, which changes an arginine into a stop codon at position 33 (R33*). Segregation analysis of the family suggests that this nonsense mutation was inherited from the mother’s family, with five additional carriers (Figure 2). The proband’s mother, her sister, and a nephew carry the heterozygous R33X nonsense mutation but are phenotypically normal, and they had no ECG abnormalities during exercise tests. The grandfather and uncle do have mild CPVT symptoms detectable during exercise tests as described above, but they have never experienced syncope.

**Discussion**

CPVT is a rare arrhythmogenic disorder characterized by syncopal events and SCD at young age during physical stress or emotion, in the absence of structural heart disease. Diagnosis of CPVT is difficult because rest ECGs are usually normal. Holter recordings and especially exercise tests are useful in uncovering CPVT. Mutations in Ca2+−handling proteins located in the SR, such as RYR2 and CASQ2, are associated with CPVT. RYR2 CPVT mutations have an autosomal dominant mode of transmission, whereas the one published CASQ2 CPVT mutation has an autosomal recessive transmission. In the present study, we report the first nonsense mutations in the cardiac calsequestrin gene, CASQ2, in three additional CPVT families.

In contrast to the array of different mutations leading to CASQ2 CPVT (see below), the phenotypes of the three probands share many similarities: the probands reported syncopes were always preceded by exercise or emotion, and exercise testing in the probands showed an average threshold of 110 bpm before the appearance of PVT, which was reproducibly induced in the same proband. Their QTc intervals are within normal parameters; however, the probands have a relative resting bradycardia (60 bpm), which differs from that of healthy children in their age groups (88 and 74 bpm) (Table).9 Interestingly, all probands had runs of PVT and doublets on their Holter recordings, without any reported symptoms; thus, Holter recordings might be useful in detecting (CASQ2) CPVT. Treatment with β-blockers has had a favorable overall outcome: two of the three probands are symptom free with a mean follow-up period of 4 years: for the other proband, an ICD is being considered. The above-mentioned phenotype (exercise-induced syncope, PVT thresholds, normal QTc intervals, and bradycardia) is in concordance with the homozygous carriers of the consanguineous family described by Lahat et al4 with an average heart rate of 64 bpm, a PVT threshold of 110 bpm, and a QTc interval of 420 ms. Thus, regardless of the precise nature of the mutation or its effect (see below), it appears that CASQ2 mutations generate a homogeneous phenotype. Nevertheless, the homozygous carriers of the family described by Lahat et al and our reported CASQ2 probands may represent a specific early age of onset subgroup among CASQ2 CPVT probands that does not exclude the possibility of CASQ2 CPVT probands with a different phenotype, including a later age of onset. The age of onset of CPVT symptoms appears to differ somewhat between our three CASQ2 CPVT families. The two homozygous CASQ2 probands, of families I and II, have an earlier age of onset than the heterozygous proband of family III (6 versus 10.5 years, respectively). This might be explained by the autosomal recessive transmission; because there is no compensation from wild-type protein, homozygous mutations produce a more severe phenotype and thus surface earlier. Comparison between CASQ2 CPVT probands and published RYR2 CPVT probands shows a similarity in
CPVT symptoms, threshold of PVT, and QTc interval. The effectiveness of the therapy also seems similar between those groups. A recent publication, with a comparable follow-up time, shows that in 7 of 19 genotyped RYR2 probands, episodes of VT/ventricular fibrillation occurred while the patients were on β-blockers of equivalent dosage. In line with those RYR2 probands, the CASQ2 proband of family I experienced a stress-related syncpe while she was taking β-blockers; the other two CASQ2 probands remain symptom free. Regarding the relative bradycardia, it is difficult to compare between CASQ2 and RYR2 probands, because RYR2 probands’ heart rates are either pooled within a single family or are not reported. In an overview of nongenotyped CPVT patients, which did not include our CASQ2 probands, Leenhardt et al describe bradycardia similar to that of our CASQ2 probands. However, because that patient group most likely contained both CASQ2 and RYR2 mutation carriers, no conclusion can be drawn from this study. Interestingly, sinoatrial (SA) node cells, which serve as the primary pacemaker of the heart, have RYR channels and functional SR. Moreover, substances that interfere with SR function have a negative chronotropic effect on the SA node. Thus, the bradycardia seen in the CASQ2 probands could be a direct effect of the impaired Ca2⁺ handling of their SA nodal cells. Overall, it seems that there is a large phenotypic overlap among CASQ2 probands and a smaller overlap between CASQ2 probands and published RYR2 probands.

It is striking that (induced) nonsense CASQ2 carriers in the three families are asymptomatic or mildly affected, despite the fact that they probably have half of the normal amount of CASQ2 protein. However, it has been shown that the predominant consequence of nonsense mutations is not the synthesis of truncated proteins. Rather, the majority of nonsense transcripts are recognized and efficiently degraded by the cell via a pathway known as nonsense-mediated mRNA decay (NMD). Moreover, in diseases such as β-thalassemia and Marfan’s syndrome, NMD is a potent modulator of the phenotype; nonsense mutations in the first part of a gene usually result in very mild or asymptomatic phenotypes. In contrast, nonsense mutations in later exons are not degraded and result in truncated protein, possible interaction with the wild-type protein, and a severe phenotype. Because our reported nonsense mutations occur early in the gene, we believe that NMD might explain why nonsense CASQ2 carriers are asymptomatic or mildly affected. Nonetheless, although our nonsense heterozygous CASQ2 mutation carriers are not inducible by exercise testing, they most likely have compromised Ca2⁺-binding ability in the SR. Alarming, phenotypically normal RYR2 mutation carriers with normal exercise tests do experience syncpe and SCD, implying that an asymptomatic phenotype does not guarantee protection from CPVT. In this respect, a long-term follow-up study in asymptomatic heterozygous CASQ2 mutation carriers might reveal if they are (also) at risk for developing CPVT.

Conversely, nonsense homozygotes, arguably putative null alleles, as seen in families I and II, are severely affected. In accordance with NMD, homozygosity for these nonsense mutations would result in the complete absence of functional CASQ2 protein. As described earlier, RYR2 homozygote knockout mice die during embryonic life; thus, it seems that properly regulated Ca2⁺ release is crucial. Similarly, a SR lacking buffered Ca²⁺, because of the absence of CASQ2, would seem incompatible with life, inasmuch as regulated Ca²⁺ release would be compromised. Because both homozygous probands survived the first years, a mechanism must exist that provides Ca²⁺ buffering in the SR in the absence of functional CASQ2 protein. One possibility is the upregulation of other Ca²⁺-binding proteins, such as HRC or sarcalumenin, which have both been identified in the SR of cardiac muscle and have been shown to bind Ca²⁺ reminiscent of calsequestrin. Alternatively, an increase or upregulation of phospholamban and SERCA activity could produce an adequate level of Ca²⁺ in the absence of the buffering power of CASQ2. Unfortunately, we are unable to verify this because there is no heart tissue available. Attempts to amplify or detect CASQ2 in native lymphocytes failed, probably because of its heart specificity. Regardless of the mechanism, it is clear that homozygosity for nonsense mutations in CASQ2 cosegregates with the CPVT and produces a severe phenotype. In this respect, it is important to analyze pedigrees of CPVT probands carefully because consanguinity might infer CASQ2 involvement. Moreover, sporadic CPVT cases without familial involvement may be explained by recessive transmission of CASQ2 mutations.

In family III, we found a heterozygous nonsense mutation that is present not only in the proband but also in five additional family members. However, as opposed to the heterozygous nonsense carriers in families I and II, it seems that some nonsense carriers in family III have at least a mild phenotype on exercise. The R33X nonsense mutation produces episodes of bigeminy and VPB on exercise testing in two of the five carriers besides the proband, although they have no reported syncpe. The remaining three nonsense carriers of family III do not exhibit any symptoms of CPVT. The mild phenotype in the two carriers may represent a phenocopy caused by underlying ischemic heart disease or another common cardiac disease. Alternatively, a reason for the mild or absent phenotypes in the heterozygous carriers and the strongly affected proband of family III could be reduced penetrance, analogous to a recent study on CPVT reporting that 17% of RYR2 mutation carriers have no phenotype. This would make the R33X mutation the first autosomal dominant mutation for CASQ2. Alternatively, on the basis of the unaffected parents and the similarity in phenotype between the homozygous CASQ2 probands and the heterozygous CASQ2 proband, a second mutation in the Ca²⁺-handling pathway, besides a CASQ2 mutation, might be present in the heterozygous CASQ2 proband, leading to CPVT. In this way, the clearly affected proband and the mildly affected family members are explained by a multifactorial form of CPVT. With regard to this, we excluded several Ca²⁺-handling and ion channel genes by sequencing, although we cannot eliminate the possibility of mutations in other genes acting as a second disease allele in the heterozygous proband of family III. However, a second gene or the influence of a second gene altering Ca²⁺ handling will be difficult to find in the asymptomatic parents, because it is not
producing a phenotype in spite of exercise testing. In conclusion, the heterozygous nonsense mutation in family III shows a different phenotype from nonsense mutations in families I and II; either the family’s distinct phenotype is altered by incomplete penetrance, or the Ca\textsuperscript{2+} handling in the proband is further compromised by an additional mutation, suggesting a multifactorial form of CPVT.

In summary, we report the first nonsense mutations in the cardiac calsequestrin gene, CASQ2, in three CPVT families. Sequencing of CASQ2 revealed three different nonsense (inducing) mutations. However, despite the different mutations, there is little interphenotypic variation of CPVT for the CASQ2 mutations besides the age of onset in the homozygous probands. Family pedigrees suggest that two CASQ2 mutations are homozygous (consanguineous) and that the other mutation is either autosomal dominant with reduced penetrance or a component of a multifactorial form of CPVT. The unforeseeable risk of juvenile sudden death (50%) and the proven efficacy of \(\beta\)-blocker/ICD therapy for CPVT emphasize the role of genetic screening for early diagnosis and preventive strategies. In addition, the evidence that mutations in the \(R Y R 2\) and CASQ2 genes are involved in CPVT could lead to a more specific and effective pharmacological treatment. Finally, it is noteworthy that complete absence of CASQ2 in our two homozygous probands, as predicted from the mutations, is compatible with life.

Limitations of the Study

We identified two frameshift mutations in the probands of families I and II, and we argue that these frameshifts lead to null alleles. Because we did not have myocytes of the probands and because we are not able to get them (for obvious reasons), we cannot show in vitro that there is an absence of CASQ2 protein in the probands and prove the null allele hypothesis.

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References

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