Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare arrhythmogenic disorder characterised by adrenergic induced bidirectional and polymorphic ventricular tachycardia. It occurs in children and adolescents and causes syncope and sudden cardiac death at a young age in the absence of structural heart disease. The resting electrocardiogram (ECG), including the QTc interval, is thought to be normal. The mortality of CPVT is extremely high reaching 30–50% by the age of 30 when untreated. Furthermore, there is a clear correlation between the age of the first syncope and the severity of the disease, with a worse prognosis in case of early occurrence. β Blockers without sympathomimetic activity are clinically effective in reducing syncope, but implantation of an automatic internal defibrillator is occasionally needed in these patients.

The genetic basis of CPVT had been initially elucidated by the establishment of linkage between the disease and chromosomal region 1q42. Subsequently, two groups independently discovered autosomal dominant missense mutations in the ryanodine type 2 receptor (RYR2) associated with CPVT. The RYR2 gene, located on 1q42, encodes the cardiac ryanodine receptor, which is the major calcium release channel on the sarcoplasmic reticulum (SR) in cardiomyocytes. More recently, two studies reported consanguineous CPVT families associated with homozygous missense and nonsense mutations in calsequestrin 2 (CASQ2), a Ca²⁺ binding protein located in the SR, thus describing a recessive form of CPVT. Both RYR2 and CASQ2 play a crucial role in the excitation-contraction coupling, by their involvement in the storage and release of Ca²⁺ from the SR, which subsequently activates cardiomyocyte contraction.

We collected 24 CPVT probands and their family members with documented polymorphic ventricular arrhythmias occurring during physical or emotional stress with a normal heart. The aim of this study was to establish the genetic and phenotypic characterisation of the probands and their family members to allow assessment of the clinical features, response to therapy, and possible genotype-phenotype correlation. We identified 13 RYR2 missense mutations in 12 CPVT probands and report here the family history, genetic, and clinical characterisation of these probands and their family members, and their response to therapy.

Methods

CPVT families

Families were referred to Paris or Amsterdam, CPVT diagnosis was established in the proband by documenting the occurrence of the characteristic ECG pattern of the disease (mono/polymorphic ventricular premature beats followed by bi-directional ventricular tachycardia and salvos of polymorphic ventricular tachycardia) in the absence of structural heart abnormalities as assessed by clinical examination, blood chemistry, electrocardiography, and echocardiography. When a CPVT diagnosis was established in the proband, 12 lead resting ECG, exercise test, and Holter recording were proposed to family members. Stress induced ventricular beats and couplets were considered sufficient evidence to label additional family members as affected. Patients with a RYR2 mutation labelled as non-penetrant were indistinguishable from healthy individuals. The QTc interval was calculated with the Bazett formula; normal resting heart rates were established with reference to published criteria. 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 extracted from peripheral blood lymphocytes using standard methods. The genomic sequence of the RYR2 gene (GenBank accession no. NM_001035) was used to design intrinsic primers for 45 exons, covering areas with known function or mutations, resulting in the amplification of 53 fragments.

Abbreviations: CASQ2, calsequestrin 2; CCD, central core disease; CPVT, catecholaminergic polymorphic ventricular tachycardia; ECG, electrocardiogram; ICD, implantable cardioverter defibrillator; PVC, premature ventricular contraction; RYR2, ryanodine type 2 receptor; SA, sino-atrial; SR, sarcoplasmic reticulum
Among the 13 mutations identified, only one had previously been reported (V4771I). Interestingly, for three of the identified RYR2 mutations, a corresponding RYR1 mutation has been described. The H4762P RYR2 mutation is equivalent to the H4833Y RYR1 mutation which is associated with central core disease (CCD), a neuromuscular disorder (N Monnier, personal communication). In addition, the RYR2 mutations P4902S (family 12) and A2394G (family 3) correspond to the RYR1 mutations P4972L and A2428T, respectively, which are associated with malignant hyperthermia.21

**Clinical evaluation of RYR2 mutation carriers**

Of the 12 probands included in the study, nine were referred because of syncopal events and three after rescued cardiac arrest related to life threatening arrhythmias (polymorphic ventricular tachycardia or ventricular fibrillation) occurring during physical or emotional stress (three males, nine females; table 1). Altogether we identified 54 RYR2 mutation carriers including the probands (32 female, 22 male). The median age of onset of the symptoms was 9 years among the probands and 12 years amongst all the carriers (range 4–51 years; tables 1 and 2). Six of the 12 probands presented with seizures during the course of the syncopal events, while no seizure was reported among the other carriers. Previous syncopal events were reported in 26 of the 54 RYR2 mutation carriers (48%), with a median age for the first syncope of 12 years. Moreover, a history of sudden cardiac death was present in seven of 12 families (58%) with a total of 20 lethal events (10 males, 10 females), with a median age at death of 28 years (fig 1, table 2). In all the RYR2 mutation carriers most of the resting ECG parameters were normal including the QTc interval (mean 399 (SD 24); table 1), except for the mean resting heart rate, which was lower than that of age and gender matched groups (see below and table 1). As we did not type the complete RYR2 gene we can not state for certain that a patient has no RYR2 mutation. As a result, we can not make a sound comparison between the clinical characteristics of the group of patients with a mutation and the group without a mutation.

**Genotype-phenotype relation in RYR2 mutation carriers**

CPVT diagnosis was confirmed in all the probands by the use of exercise tests, which reproducibly showed the occurrence of characteristic ECG patterns with mono/polymorphic ventricular premature beats followed by bi-directional ventricular tachycardia and salvos of polymorphic ventricular tachycardia. Exercise tests performed in the 38 additional family members carrying a mutation and aged over 5 years were positive for arrhythmic events in only 27 RYR2 carriers. Eleven RYR2 mutation carriers were considered to be phenotypically unaffected (fig 1). Four were too young to perform exercise testing. Therefore, the overall penetrance was 78% (39/50). Three of the eight autosomal dominant families display complete penetrance based on stress tests (families 1, 3, 7; fig 1), while penetrance was incomplete in the other five families (2, 5, 6, 10, and 12) (fig 1, table 1). In family 12, a 24 year old man (II-6) displayed clear cut exercise induced PVT only at the third exercise test, the two first being normal.

**Treatment and follow up of RYR2 mutation carriers**

CPVT is a life threatening disease as shown by the high number of sudden deaths in the families. Therefore, 50 RYR2 mutation carriers (>5 years old) were treated with β blockers (1–2 mg/kg per day nadolol, 3–4 mg/kg per day propranolol, 50–100 mg per day metoprolol) which were individually titrated until the maximal heart rate was <110 bpm at exercise tests or Holter recordings, in order to prevent polymorphic ventricular salvos. β Blocker treatment had a favourable overall outcome in this group, as 11 of the 12 probands are symptom free with a median follow up period of 6 years (table 1). The remaining proband experienced sudden cardiac death due to non-compliance with the β blocker treatment, after a CPVT diagnosis had been established. Of the 50 treated RYR2 patients, 49 (98%) were...
symptom free with a median follow up period of 24 months, although some continued to have isolated premature ventricular contractions (PVCs) at exercise tests (table 2). In two RYR2 positive patients an implantable cardioverter defibrillator (ICD) was implanted. The first ICD was implanted in a man aged 51 (family 5, II-1) because the aetiology of the syncope in a familial context of sudden death had not been known when he was younger, and the second in a symptomatic 18 year old girl because of poor compliance (III-2, family 3). Over a follow up of 1 year, this latter patient received two appropriate shocks to terminate ventricular fibrillation; β-blocker treatment was maintained in both patients. In the four youngest RYR2 mutation carriers (<5 years old), we could not establish a definite clinical phenotype as they were too young to perform exercise testing (fig 1). However, as Holter recordings did not show any ventricular arrhythmia or PVCs, β blockers have not been started so far. These children are regularly checked with biannual Holter recordings.

Heart rate in RYR2 mutation carriers is significantly lower
Available resting ECGs in the absence of treatment were reviewed in 67 genotyped individuals (40 RYR2 mutation carriers and 27 family members without RYR2 mutation). The resting heart rate of the 12 RYR2 CPVT probands was on average 20 bpm lower than that of age and gender matched controls’ (table 1). Likewise, RYR2 carriers had in general a lower heart rate than their family members without a mutation, irrespective of mutation or family, as they deviated significantly more from age and gender matched control heart rates (212 bpm vs 2 bpm, p = 0.002; fig 3). A further analysis of the genotyped population according to gender revealed that male RYR2 carriers tended to deviate more from control heart rates than female RYR2 carriers (−19 bpm vs −7 bpm, p = 0.067; fig 3). Interestingly, the heart rate of phenotypically affected RYR2 carriers was also significantly lower than that of their clinically unaffected family members (including seven silent RYR2 mutation carriers) (−12 bpm vs −2 bpm, p = 0.012).
DISCUSSION
Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare arrhythmogenic disorder characterised by syncopal events and sudden cardiac death occurring in young subjects during physical stress or emotion in the absence of structural heart disease. Mutations in calcium handling proteins located in the SR, such as RYR2 and CASQ2, have been associated with CPVT. We report here on the genetic and clinical evaluation of 12 CPVT families with RYR2 mutations.

The phenotypes of the CPVT probands share many similarities: syncopal episodes were usually triggered by exercise or emotion. During exercise testing there was a threshold in the heart rate before the appearance of ventricular arrhythmias, which was individually highly reproducible. The initial resting ECG demonstrated a normal QTc interval in all probands, however, most of them had, compared to control values, sinus bradycardia as previously reported in non-genotyped populations. The age of onset of CPVT symptoms in our RYR2 probands (9 years) and the overall age of onset among all our RYR2 patients (12 years) are comparable to previously reported (RYR2) probands. However, some CPVT probands may present a much later age of onset, as one of our RYR2 patients was asymptomatic until 51 years of age. In such cases, which could be misleading, it is crucial to document a positive family history of sudden death. In 50% of our RYR2 probands exercise induced syncopal episodes were accompanied by seizures, which were probably convulsive movements owing to pan-cerebral hypoperfusion. Based on these seizures, the patients were initially referred to a neurologist who recommended anti-epileptic treatment. However, this did not lead to syncope resolution, and in most cases the diagnosis of CPVT was established only after an exercise ECG or a subsequent syncopal event. Treatment with β blockers had a favourable overall outcome in our group, as 11 of the 12 probands are symptom free with a median follow up period of 6 years. The remaining proband unfortunately experienced sudden cardiac death due to non-compliance after appropriate diagnosis and treatment. In total, 98% of the 50 treated patients of the 12 families are symptom free with a median follow up period of 24 months, although isolated premature ventricular beats were seen at follow up exercise tests. The β blocker doses required to keep the patients symptom free are higher than those used in the long-QT syndrome. Consequently, poor compliance in these patients with spontaneous resting bradycardia could potentially result in serious consequences; however, we were not faced with this in our population. Additionally, we do not rule out the possibility of ICD implantation especially when follow up stress tests or Holter recordings show polymorphic ventricular salvos. In contrast to our group of patients, a recent publication with a comparable follow up time shows that seven of 19 genotyped RYR2 probands had episodes of ventricular tachycardia/ventricular fibrillation while on β blockers. The discrepancy in efficacy of β blocker treatment between the two studies could reflect a difference in β blocker dosage, a difference in underlying RYR2 mutations, or more mildly affected subjects in our CPVT families compared to the latter study. Obviously, larger groups of genotyped CPVT probands are needed to address the issue of β blocker efficacy in CPVT with longer follow up.
Table 1 Clinical data of CPVT probands

<table>
<thead>
<tr>
<th>RYR2 mutation</th>
<th>Gender</th>
<th>Age of onset, years</th>
<th>Penetrance, %</th>
<th>Resting ECG pre med, bpm (age, of group)*</th>
<th>Median HR age group</th>
<th>QTc, ms</th>
<th>Symptoms</th>
<th>Exercise test VT threshold, bpm</th>
<th>Exercise test ECG characteristics</th>
<th>Follow up, years</th>
<th>Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family 4</td>
<td>M</td>
<td>4</td>
<td>NA</td>
<td>70 (4)</td>
<td>98</td>
<td>28</td>
<td>410</td>
<td>X syncope, seizure</td>
<td>BG, PC, PMVT</td>
<td>Sudden death at 20</td>
<td>French</td>
</tr>
<tr>
<td>Family 8</td>
<td>F</td>
<td>4</td>
<td>De novo</td>
<td>50 (14)</td>
<td>73</td>
<td>23</td>
<td>374</td>
<td>X syncope, seizure, CA</td>
<td>BG, PC, PMVT</td>
<td>90</td>
<td>Dutch</td>
</tr>
<tr>
<td>Family 9</td>
<td>F</td>
<td>6.5</td>
<td>De novo</td>
<td>70 (7)</td>
<td>89</td>
<td>19</td>
<td>400</td>
<td>X syncope</td>
<td>MPVB, PMVT</td>
<td>140</td>
<td>French</td>
</tr>
<tr>
<td>Family 7</td>
<td>M</td>
<td>7</td>
<td>100</td>
<td>60 (8)</td>
<td>88</td>
<td>28</td>
<td>400</td>
<td>X syncope, seizure</td>
<td>PPVB, SPVT</td>
<td>130</td>
<td>French</td>
</tr>
<tr>
<td>Family 2</td>
<td>F</td>
<td>8</td>
<td>100</td>
<td>66 (5)</td>
<td>84</td>
<td>18</td>
<td>410</td>
<td>CA, exercise VT</td>
<td>BG, PC</td>
<td>135</td>
<td>Dutch</td>
</tr>
<tr>
<td>Family 1</td>
<td>F</td>
<td>9</td>
<td>100</td>
<td>43 (12)</td>
<td>78</td>
<td>35</td>
<td>380</td>
<td>X syncope</td>
<td>BG, PMVT</td>
<td>110</td>
<td>Dutch</td>
</tr>
<tr>
<td>Family 3</td>
<td>F</td>
<td>9</td>
<td>100</td>
<td>60 (10)</td>
<td>78</td>
<td>18</td>
<td>440</td>
<td>X syncope, seizure, CA</td>
<td>MPVB, PMVT</td>
<td>140</td>
<td>French</td>
</tr>
<tr>
<td>Family 6</td>
<td>F</td>
<td>10</td>
<td>66</td>
<td>58 (14)</td>
<td>76</td>
<td>18</td>
<td>405</td>
<td>X syncope</td>
<td>BG, PMVT</td>
<td>110</td>
<td>French</td>
</tr>
<tr>
<td>Family 11</td>
<td>F</td>
<td>12</td>
<td>NA</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>X syncope</td>
<td>PPVB, PMVT</td>
<td>130</td>
<td>Dutch</td>
</tr>
<tr>
<td>Family 12</td>
<td>F</td>
<td>13</td>
<td>65</td>
<td>60 (13)</td>
<td>76</td>
<td>16</td>
<td>414</td>
<td>X syncope, seizure</td>
<td>PPVB, PMVT</td>
<td>120</td>
<td>French</td>
</tr>
<tr>
<td>Family 10</td>
<td>F</td>
<td>13</td>
<td>Compound</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>X syncope</td>
<td>BG, PMVT</td>
<td>60 W</td>
<td>French</td>
</tr>
<tr>
<td>Family 5</td>
<td>M</td>
<td>51</td>
<td>64</td>
<td>73 (17)</td>
<td>70</td>
<td>–3</td>
<td>351</td>
<td>X syncope, seizure</td>
<td>MPVB, PC, PMVT</td>
<td>110</td>
<td>French</td>
</tr>
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<tr>
<td></td>
<td></td>
<td>9 (4–51)*</td>
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</tbody>
</table>

*Median (range); †mean (SD).
BG, monomorphic bigeminy; CA, cardiac arrest; MPVB, monomorphic premature ventricular beat; NA, not available; PC, polymorphic couplets; PMVT, polymorphic ventricular tachycardia; PPVB, polymorphic premature ventricular beat; SPVT, sustained polymorphic ventricular tachycardia; VT, ventricular tachycardia; X syncope, exercise induced syncope.

Table 2 Clinical data of all RYR2 mutation carriers

<table>
<thead>
<tr>
<th></th>
<th>RYR2 CPVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of probands</td>
<td>12</td>
</tr>
<tr>
<td>Total no. of mutation carriers</td>
<td>54</td>
</tr>
<tr>
<td>Families with juvenile sudden death</td>
<td>7/12 (58%)</td>
</tr>
<tr>
<td>Age of onset all carriers, years</td>
<td>12 (4–51)*</td>
</tr>
<tr>
<td>Clinically affected</td>
<td>39</td>
</tr>
<tr>
<td>Phenotype undetermined</td>
<td>4</td>
</tr>
<tr>
<td>Silent gene carrier</td>
<td>11</td>
</tr>
<tr>
<td>Gender</td>
<td>32F/22M</td>
</tr>
<tr>
<td>Exercise related syncope</td>
<td>26/54 (48%)</td>
</tr>
<tr>
<td>Patients on β blockers</td>
<td>50/54</td>
</tr>
<tr>
<td>Follow up, years</td>
<td>2 (2–37)*</td>
</tr>
<tr>
<td>VT/VF on β blockers</td>
<td>1/50</td>
</tr>
</tbody>
</table>

*Median (range);
VT/VF, ventricular tachycardia/ventricular fibrillation.

Analogous to other inherited arrhythmogenic diseases, RYR2 CPVT has variable expressivity. Eleven out of the 50 RYR2 mutation carriers tested (22%) presented no ventricular arrhythmia during repeated exercise tests. Eight belong to two families (10 and 12) suggesting that three RYR2 mutations, G4662S, H4762P, and P4902S, may represent mutations with partial penetrance. Nevertheless, sudden deaths occurred in both families and seven of these silent gene carriers are female, hinting at a possible gender bias, which is in line with a recent study that suggests that male gender is a risk factor for syncope in genotyped RYR2 patients.

A low heart rate in CPVT patients has been reported in the initial description of the disease before genetic defects were recognised. In this study we observed that RYR2 mutation carriers have a significantly lower heart rate than their genetically unaffected family members on resting ECGs, irrespective of mutation position or family. Moreover, there is also a noteworthy difference between genders in the deviation in heart rates; male carriers have a lower heart rate than female carriers. This is in concordance with the fact that females have on average a slightly higher heart rate. The fact that CPVT patients with a RYR2 mutation have significant bradycardia could direct molecular diagnosis in (young) patients without structural heart disease presenting with syncope and a slow heart rate but with normal QTc at resting ECG. These findings cannot be compared to previous (RYR2) CPVT studies, as the heart rates in these studies were either pooled within a single family or not reported.

A more recent study of 29 non-genotyped Japanese CPVT patients, with a similar age of onset, also demonstrated sinus bradycardia. A possible link between ryanodine receptors and heart rate is the presence of RYR2 channels and functional SR in sino-atrial (SA) node cells, which serve as the primary pacemaker of the heart. Moreover, substances that interfere with SR function, such as ryanodine and cyclopiazonic acid, have a negative chronotropic effect. Thus, the bradycardia seen in the RYR2 mutation carriers could be a direct effect of the impaired Ca²⁺ handling of their SA nodal cells. Alternatively, it could represent a feedback mechanism by the vagal system; a low average heart rate reduces the likelihood of reaching the deleterious threshold at which CPVT is induced.

We identified 13 RYR2 missense mutations, of which 12 are novel. These mutations cluster within three functionally important regions of RYR2: the binding site for the FKBP12.6 protein that stabilises the RYR2 channel, the calcium binding site, and the channel forming transmembrane domains as
previously observed\textsuperscript{14} (fig 4). Moreover, diseases such as malignant hyperthermia and CCD, which are associated with mutations in the ryanodine receptor specific for skeletal muscle, RYR1, also show mutational clustering in the same areas.\textsuperscript{16} Interestingly, three of our mutations even occur on positions corresponding to known RYR1 mutations in MD and CCD, suggesting that these areas are of major importance to the function of ryanodine receptors. Unfortunately, there is no clear correlation among RYR2 probands between the region of mutation and the phenotype of the proband, in contrast to what was reported for RYR1 probands.\textsuperscript{16}

We identified RYR2 mutations in 50% of the screened CPVT probands. Mutations in RYR2 cluster into the three protein areas described above, but also within discrete mutational

![Figure 3](https://www.jmedgenet.com/)

**Figure 3** Corrected heart rates, calculated as observed resting heart rate (before medication) minus the heart rate according to age and gender-dependent trends,\textsuperscript{9} of 67 genotyped individuals (40 family members with a RYR2 mutation, 27 family members without a RYR2 mutation). Zero means an observed heart rate according to those trends. (A) Wildtype family members v RYR2 mutation carriers, (B) the effect of gender and genotype on the resting heart rate in wildtype family members and RYR2 mutation carriers, and (C) clinically unaffected individuals (27 wildtype family members and seven silent RYR2 mutation carriers) v phenotypically affected CPVT patients (33 mutation carriers).

![Figure 4](https://www.jmedgenet.com/)

**Figure 4** Schematic representation of the RYR2 protein, with an overview of predicted function and topology (segments I–III\textsuperscript{19}) and the location in amino acids of all the current RYR2 mutations. Indicated in bold are RYR2 mutations identified in this study with novel mutations marked with an asterisk (*); the other mutations have been previously reported.\textsuperscript{3–5 19–22}
hotspots. We found three mutations in close proximity to each other, two at amino acid position 4108 (H4108N, H4108Q) and one at position 4104 (N4104I). Moreover, a recent study also reported a CPVT mutation at position 4104 (N4104K). Interestingly, both the 4108 mutations and the reported N4104K occurred de novo. Another potential hotspot for RYR2 mutations is amino acid 4076, where we identified the same mutation (E4076K) in two unrelated families (6 and 7), leading to a similar penetrance (70%). Consequently, it appears that clustering and hotspots of RYR2 mutations are relatively common in CPVT. In vitro expression studies of these mutations could provide insight into the exact function of these specific regions.

We report one proband who inherited two independent RYR2 mutations. Analogous to our findings, a recent study described a malignant hyperthermia family in which patients received two unique RYR1 mutations, however, the RYR1 mutations were independently associated with a clinical phenotype. In contrast, family members in our study carrying only one of the RYR2 mutations were symptom free without any arrhythmia triggered by exercise testing, thus raising the possibility of a recessive form of CPVT. Alternatively, the phenotype of this family could be explained by a mutation presenting with reduced penetrance and the presence of a very rare polymorphism. Given the amount of controls screened, the negative exercise tests, and the absence of a clinical history in the single mutation carriers we believe, however, that this could be the first case of a RYR2 recessive form of CPVT.

In summary, genetic and phenotypic characterisation of our CPVT population allowed us to assess clinical features, response to therapy, and genotype-phenotype correlation. We identified 13 mutations in evolutionarily highly conserved residues in the cardiac ryanodine receptor in 12 CPVT families. In addition, we found that RYR2 mutation carriers and phenotypically affected CPVT patients have a significant resting sinus bradycardia. Consequently, CPVT should be considered a possible cause of resting bradycardia in young individuals, especially in the presence of a history of syncpe or familial sudden death. Finally, given the risk of juvenile sudden death (50%) and the efficacy of β-blocker/ICD therapy for CPVT, the identification of large numbers of RYR2 mutations calls for genetic screening, early diagnosis, and subsequent preventive strategies.

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Authors’ affiliations
A V Postma, A M Wilde, Experimental and Molecular Cardiology Group, Academic Medical Center, Amsterdam, The Netherlands
A V Postma, I Denjoy, J-M Lupoglazoff, P Guicheney, INSERM US82, Institut de Myologie, IFR 14, Groupe Hospitalier Pitié-Salpêtrière, Paris, France
I Denjoy, Service de Cardiologie, Hôpital Lariboisière, Paris, France
J Kamblow, Centre de Cardiologie du Taona, Tahiti, French Polynesia
M Alders, M M A Mannens, Department of Clinical Genetics, Academic Medical Center, Amsterdam, The Netherlands
G Vaksman, Service de Cardiologie Pédiastrique, Hospital Cardiologique, Lille, France
L Dubois-Bilot, INSERM U621, IFR 14, Groupe Hospitalier Pitié-Salpêtrière, Paris, France
P Sebillon, Laboratoire de génétique et insuffisance cardiaque, Association Claude Bernard, IFR 14, Groupe Hospitalier Pitié-Salpêtrière, Paris, France

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Ethics approval: All individuals gave informed consent to the clinical and genetic study, which was approved by the internal ethics committee.

Correspondence to: Alex V Postma, Department of Clinical and Experimental Cardiology, Academic Medical Center, Meibergdreef 9, PO Box 22700 1100 DE, Amsterdam, The Netherlands; a.v.postma@amc.uva.nl

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