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**SUPPLEMENTAL METHODS**

**Definitions.** The diagnoses of LQT3, BrS-1, PCCD and SSS were made according to the ESC/AEPC guidelines and HRS/EHRA/APHRS recommendations.12,15 SIDS was defined as the sudden death of an infant under one year of age, that remained unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene and review of the clinical history.12,16 Cardiac conduction abnormality was defined as PR interval prolongation and/or QRS complex prolongation and/or axis deviation according to age. Atrioventricular and intraventricular conduction disturbances were classified according to the age at the time of diagnosis using consensually agreed definitions and practice guidelines.17,18 DCM was defined by left ventricular (LV) dilation (i.e., LV end-diastolic dimension ≥2 standard deviation [SD] above normal for body-surface area) and depressed LV systolic function (LV fractional shortening or LV ejection fraction ≥2 SD below normal for age).19 Negative ECG phenotype was defined as patients with a confirmed pathogenic *SCN5A* mutation but a completely normal electrocardiogram and transthoracic echocardiography. A proband was defined as the first patient in a family diagnosed with a sodium channelopathy, non-probands were all other relatives. A major cardiac event (MCE) was defined as the occurrence of arrhythmic syncope, SCD at any age (including SIDS), ACA, ventricular fibrillation, monomorphic ventricular tachycardia, polymorphic VT with torsades de pointes characteristics, electrical storm or heart transplantation for intractable arrhythmias.

**ECG analysis.** Baseline 12-lead ECG and the ECG recorded at time of PM/ICD implantation or at last follow-up visit in non-paced patients were analyzed. Analysis of RR interval, PR interval, QTc value, QRS axis and duration was done by four medical investigators (AEB, ML, AJ and VP) blinded to patient phenotype, cardiac events and genotype. All measurements were averaged. Atrioventricular and intraventricular conduction disturbances were classified according to the age at the time of diagnosis using accepted definitions and practice guidelines (Online Table 13).17,18 The QT interval was corrected for heart rate using the Bazett’s formula. Suggested QTc values for diagnosing QTc prolongation among our study population were QTc ≥480 ms in repeated ECGs or QTc ≥460 ms in case of a previous MCE.15

**SUPPLEMENTAL RESULTS**

**Baseline clinical characteristics.** Isolated PCCD, overlap phenotype, isolated LQT3 and isolated BrS1 were the four ‘major’ ECG phenotypes at baseline.

The initial resting ECG was already diagnostic in 276 (62%) patients. All patients had Holter monitoring, signal averaged ECG and ECG with high precordial leads. Pharmacological provocation test with sodium-channel blockers was used in 39 patients (9%; Ajmaline, N=24; Flecainide, N=7; Pilsicainide, N=5; Procainamide, N=5) at a median age of 12.3 (IQR: 5) years, leading to the diagnosis of drug-induced Brugada syndrome in 27 patients. An exercise treadmill test was performed in 127 (29%) patients at a median age of 12.8 (IQR: 5) years, unmasking LQTS in 11 patients with normal QTc at resting ECG.

Isolated PCCD patients: 113 patients [25.6%, 58.4% boys, 40.7% probands, median age at diagnosis: 6.8 (IQR: 11.6) years] had baseline PCCD; 29.2% were symptomatic at diagnosis presenting with cardiac arrest (17.7%) or syncope (11.5%). A family history for SCD/ICD implantation was present in 58.4% or PCCD/PM implantation in 25.7%. 6/18 (33%) ICD implanted, isolated PCCD patients had at least one appropriate shock.

Overlap phenotype patients: The 69 patients [15.6%, 65.2% boys, 43.5% probands, median age at diagnosis: 5.8 (IQR: 10.0) years] with overlap phenotype underwent genetic testing because of cardiac arrest (23.2%), syncope (20.3%) or because of familial screening (56.5%). Various associations were observed (Online Table 3). A family history of SCD/ICD implantation was present in 53.6% and of PCCD/PM implantation in 26.1%. 9/17 (53%) ICD implanted, overlap phenotype patients had at least one appropriate shock. In the 41 patients who had another baseline ECG phenotype, the median delay until the diagnosis of an overlap syndrome was established was 3.9 years (N= 41 patients; 2.7-10.4 years).

Isolated LQT3 patients: 47 patients [10.6%, 48.9% boys, 61.7% probands, median age at diagnosis: 10.1 (IQR: 9.4) years] displayed a baseline isolated LQT3 ECG phenotype; 42 of them (89.4%) demonstrated either late-onset, peaked and/or biphasic T-waves or asymmetrical peaked T waves, both described as typical LQT3 patterns. Although 46.8% were asymptomatic at diagnosis, 23.4% were diagnosed because of cardiac arrest and 29.8% because of syncope. A family history of either SCD/ICD implantation or PCCD/PM implantation was noted in 46.8% and 12.8% respectively. 2/11 (18%) ICD implanted, isolated LQT3 patients had at least one appropriate shock.

Isolated BrS1 patients: 8 patients [1.8%, 75.0% boys, 50.0% probands, median age at diagnosis: 8.9 (IQR: 9.2) years] had baseline BrS1, one of whom was drug-induced, the seven others being spontaneous; 37.5% were symptomatic at diagnosis presenting with cardiac arrest (12.5%) or syncope (25.0%). They presented with a family history of SCD/ICD implantation in 50.0% or PCCD/PM implantation in 50.0%. 1/3 (33%) ICD implanted, isolated BrS1 patients had at least one appropriate shock.

**Clinical outcomes.**

Overlap phenotype patients:69 patients had a baseline diagnosis of an overlap syndrome. In the 41 patients who had another baseline ECG phenotype, the median delay until the diagnosis of an overlap syndrome was established was 3.9 years (N= 41 patients; 2.7-10.4 years).

ICD implanted patients: There was no uniform cut-off for VT in ICD programming. Cut-offs for VT and VF were 195bpm (150-240) and 222bpm (188-300), respectively. Sustained VT duration was programmed for 14/77 patients.

**Genotype- phenotype correlations.**

The most common SCN5A mutations per phenotype are presented in Supplemental Table 14.

*SCN5A* mutations were de novo variants in 69/442 patients (15.6%), whilst they were inherited in 347/442 patients (78.5%) and this was unclear in 26 patients. Of the 69 patients with a definite *de novo SCN5A* mutation, 21 had an overlap phenotype, 16 an isolated PCCD phenotype, 16 a negative ECG phenotype, 15 an isolated LQT3 phenotype and 1 an isolated SSS phenotype. *De novo* *SCN5A* mutations accounted for 40.0% of the 16% of patients with inaugural syncope and 66.1%% of the 14% of patients with inaugural aborted cardiac arrest.

**SUPPLEMENTAL TABLES**

**Table 1: Clinical characteristics according to baseline ECG phenotypes (n=442)**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Negative ECG phenotype  (n=196) | Isolated LQT3  (n=47) | Isolated BrS-1  (n=8) | Isolated PCCD  (n=113) | Isolated  SSS  (n=6) | Isolated DCM  (n=3) | Overlap phenotype  (n=69) | p value |
| Male, n (%) | 102 (52.0) | 23 (48.9) | 6 (75.0) | 66 (58.4%) | 4 (66.7%) | 0 (0.0) | 45 (65.2) | 0.13 |
| Median age at diagnosis, yrs (IQR) | 8.8  (8.7) | 10.1  (9.4) | 8.9  (9.2) | 6.8  (11.6) | 13.4  (9.1) | 7.0  (3.1) | 5.8  (10.0) | 0.32 |
| Proband, n (%) | 65 (33.2) | 29 (61.7) | 4 (50.0) | 46 (40.7) | 3 (50.0) | 1 (33.3) | 30 (43.5) | **0.02** |
| Mode of presentation |  |  |  |  |  |  |  | **<0.001**\* |
| Cardiac arrest at diagnosis, n (%)  Syncope at diagnosis, n (%)  Asymptomatic at diagnosis, n (%) | 13 (6.6)  26 (13.3)  157 (80.1) | 11 (23.4)  14 (29.8)  22 (46.8) | 1 (12.5)  2 (25.0)  5 (62.5) | 20 (17.7)  13 (11.5)  80 (70.8) | 1 (16.7)  1 (16.7)  4 (66.7) | 0 (0.0)  0 (0.0)  3 (100.0) | 16 (23.2)  14 (20.3)  39 (56.5) |  |
| FH of SCD or ICD | 108 (55.1) | 22 (46.8) | 4 (50.0) | 66 (58.4) | 4 (66.7) | 2 (66.7) | 37 (53.6) | 0.88 |
| FH of PCCD or PM | 29 (14.8) | 6 (12.8) | 4 (50.0) | 29 (25.7) | 0 (0.0) | 0 (0.0) | 18 (26.1) | **0.03\*** |
| Median FU length, yrs (IQR) | 5.9  (5.1) | 5.9  (9.2) | 8.1  (8.4) | 5.7  (5.9) | 2.9  (6.3) | 6.3  (1.8) | 5.7  (7.4) | 0.69 |
| PM, n (%) | 11 (5.6) | 3 (6.4) | 1 (12.5) | 13 (11.6) | 0 (0.0) | 0 (0.0) | 10 (14.7) | 0.21 |
| ICD, n (%) | 26 (13.3) | 11 (23.4) | 3 (37.5) | 18 (15.9) | 2 (33.3) | 0 (0.0) | 17 (25.0) | 0.08 |
| SVT, n (%) | 2 (1.0) | 2 (4.3) | 0 (0.0) | 4 (3.5) | 0 (0.0) | 0 (0.0) | 7 (10.1) | **0.04** |
| First MCE, n (%) | 40 (20.4) | 25 (53.2) | 3 (37.5) | 38 (33.6) | 2 (33.3) | 0 (0.0) | 31 (44.9) | **<0.001** \*¥ |
|  |  |  |  |  |  |  |  |  |
| Death or transplantation, n (%) | 1 (0.5) | 6 (12.8) | 0 (0.0) | 3 (2.6) | 0 (0.0) | 0 (0.0) | 4 (5.8) | **0.01** \*¥ |

LQT3: long QT syndrome type 3; BrS-1: Brugada syndrome type 1; PCCD: progressive cardiac conduction defect; SSS: sick sinus syndrome; DCM: dilated cardiomyopathy; FH: family history; FU: follow-up; PM: pacemaker; ICD: implantable cardioverter defibrillator; SVT: supraventricular tachycardia; MCE: major cardiac event; Transplantation: orthotopic heart transplantation because of intractable ventricular arrhythmias; SD= sudden death.

\* Analysis with exclusion of BrS-1, DCM and SSS

¥ Cox proportional hazards regression analysis

**Table 2: Characteristics of cardiac events in the 28 patients who received appropriate ICD shocks**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | ECG phenotype | Age at first MCE  (years) | Type of first MCE | Age at ICD implant  (years) | FU length (years) | MCEs after ICD implant (N) | TdP  (N) | VT  (N) | VF  (N) | Electrical storm  (N) | Heart transplant  (N) | Alive at last follow-up |
| Patient 1 | Isolated PCCD | 0.2 | Syncope | 14.3 | 20.4 | 9 | 0 | 8 | 0 | 1 | 0 | Alive |
| Patient 2 | Overlap | 0.2 | ACA | 7.2 | 10.4 | 8 | 1 | 1 | 6 | 0 | 0 | Alive |
| Patient 3 | Isolated BrS1 | 11.5 | Syncope | 11.5 | 5.4 | 1 | 0 | 0 | 1 | 0 | 0 | Alive |
| Patient 4 | Overlap | 1.7 | ACA | 4.5 | 12.6 | 2 | 0 | 2 | 0 | 0 | 0 | Alive |
| Patient 5 | Negative | 9.5 | ACA | 13.5 | 23.7 | 4 | 0 | 1 | 1 | 2 | 0 | Alive |
| Patient 6 | Isolated PCCD | 12.1 | ACA | 16.1 | 17.7 | 1 | 1 | 0 | 0 | 0 | 0 | Alive |
| Patient 7 | Overlap | 0.0 | ACA | 0.1 | 2.0 | 5 | 2 | 0 | 0 | 2 | 1 | Dead |
| Patient 8 | Isolated PCCD | 14.8 | Syncope | 15.4 | 19.3 | 1 | 0 | 0 | 1 | 0 | 0 | Alive |
| Patient 9 | Isolated PCCD | 6.0 | VF | 14.0 | 13.6 | 0 | 0 | 0 | 0 | 0 | 0 | Alive |
| Patient 10 | Isolated LQT3 | 1.0 | Syncope | 1.1 | 9.0 | 5 | 0 | 0 | 3 | 2 | 0 | Alive |
| Patient 11 | Isolated PCCD | 9.1 | Syncope | 14.5 | 19.7 | 4 | 0 | 0 | 4 | 0 | 0 | Alive |
| Patient 12 | Negative | 0.2 | ACA | 3.7 | 21.2 | 8 | 0 | 0 | 8 | 0 | 0 | Alive |
| Patient 13 | Negative | 0.0 | ACA | 1.2 | 5.3 | 2 | 1 | 0 | 0 | 1 | 0 | Alive |
| Patient 14 | Isolated PCCD | 0.0 | ACA | 1.2 | 5.3 | 10 | 0 | 0 | 7 | 2 | 1 | Dead |
| Patient 15 | Negative | 0.0 | ACA | 1.1 | 5.3 | 2 | 0 | 0 | 1 | 1 | 0 | Alive |
| Patient 16 | Negative | 13.6 | ACA | 14.7 | 14.8 | 3 | 1 | 0 | 1 | 1 | 0 | Alive |
| Patient 17 | Negative | 14.4 | Syncope | 14.7 | 8.5 | 0 | 0 | 0 | 0 | 0 | 0 | Alive |
| Patient 18 | Overlap | 8.9 | Syncope | 8.9 | 5.7 | 15 | 5 | 2 | 8 | 0 | 0 | Alive |
| Patient 19 | Negative | 10.8 | Syncope | 12.5 | 3.1 | 1 | 0 | 1 | 0 | 0 | 0 | Alive |
| Patient 20 | Overlap | 14.7 | Syncope | 16.3 | 3.7 | 3 | 0 | 1 | 1 | 1 | 0 | Alive |
| Patient 21 | Isolated LQT3 | 2.5 | ACA | 2.6 | 1.9 | 2 | 1 | 0 | 0 | 1 | 0 | Alive |
| Patient 22 | Overlap | 14.6 | Syncope | 15.1 | 1.6 | 0 | 0 | 0 | 0 | 0 | 0 | Alive |
| Patient 23 | Overlap | 11.7 | Syncope | 14.8 | 6.7 | 0 | 0 | 0 | 0 | 0 | 0 | Alive |
| Patient 24 | Overlap | 11.6 | Syncope | 11.7 | 4.2 | 0 | 0 | 0 | 0 | 0 | 0 | Alive |
| Patient 25 | Negative | 11.2 | ACA | 11.2 | 5.6 | 1 | 0 | 0 | 0 | 1 | 0 | Alive |
| Patient 26 | Overlap | 0.0 | VT | 3.4 | 5.1 | 0 | 0 | 0 | 0 | 0 | 0 | Alive |
| Patient 27 | Isolated SSS | 0.2 | VF | 0.8 | 1.9 | 0 | 0 | 0 | 0 | 0 | 0 | Alive |
| Patient 28 | Negative | 6.0 | Syncope | 6.0 | 11.2 | 0 | 0 | 0 | 0 | 0 | 0 | Alive |

LQT3: long QT syndrome type 3; BrS1: Brugada syndrome type 1; PCCD: progressive cardiac conduction defect; SSS: sick sinus syndrome; Negative: negative ECG phenotype; Overlap: overlap phenotype; ICD: implantable cardioverter defibrillator; MCE: major cardiac event; ACA: aborted cardiac arrest; VT: ventricular tachycardia; TdP: polymorphic VT with torsades de pointes; VF: ventricular fibrillation; FU: follow-up

**Table 3: Phenotypes and family history (n=442)**

|  |  |  |
| --- | --- | --- |
| Phenotype and family history | Baseline, n (%) | At last follow-up, n (%) |
| Phenotype |  |  |
| Negative phenotype | 196 (44.3) | 143 (32.4) |
| LQT3 | 78 (17.6) | 110 (24.9) |
| Isolated LQT3 | 47 (10.6) | 50 (11.3) |
| Overlap phenotype including LQT3 | 31 (7.0) | 60 (13.6) |
| BrS-1 | 38 (8.6) | 65 (14.7) |
| Isolated spontaneous BrS-1 | 8 (1.8) | 14 (3.2) |
| Overlap phenotype including BrS-1 | 30 (6.8) | 51 (11.5) |
| PCCD | 172 (38.9) | 220 (49.8) |
| Isolated PCCD | 113 (25.6) | 119 (26.9) |
| Overlap phenotype including PCCD | 59 (13.3) | 101 (22.8) |
| SSS | 23 (5.2) | 24 (5.4) |
| Isolated SSS | 6 (1.4) | 4 (0.9) |
| Overlap phenotype including SSS | 17 (3.8) | 20 (4.5) |
| DCM | 3 (0.7) | 7 (1.6) |
| Isolated DCM | 3 (0.7) | 2 (0.5) |
| Overlap phenotype including DCM | 0 (0.0) | 5 (1.1) |
| Overlap phenotype | 69 (15.6) | 110 (24.9) |
| LQT3 and BrS-1 | 4 (0.9) | 6 (1.4) |
| LQT3 and PCCD | 20 (4.5) | 36 (8.1) |
| LQT3 and SSS | 4 (0.9) | 2 (0.4) |
| LQT3 and DCM | 1 (0.2) | 0 (0.0) |
| BrS-1 and PCCD | 24 (5.4) | 37 (8.4) |
| PCCD and SSS | 10 (2.3) | 8 (1.8) |
| PCCD and DCM | 3 (0.7) | 4 (0.9) |
| LQT3 and BrS-1 and PCCD | 0 (0.0) | 6 (1.4) |
| LQT3 and BrS-1 and SSS | 1 (0.2) | 1 (0.2) |
| LQT3 and PCCD and SSS | 1 (0.2) | 8 (1.8) |
| LQT3 and PCCD and DCM | 0 (0.0) | 1 (0.2) |
| BrS-1 and PCCD and SSS | 1 (0.2) | 1 (0.2) |
|  |  |  |
| Family history of |  |  |
| Syncope | 156 (35.3) |  |
| Atrial fibrillation | 18 (4.1) |  |
| SSS | 63 (14.3) |  |
| PCCD | 62 (14.0) |  |
| DCM | 14 (3.2) |  |
| MEPPT | 1 (0.2) |  |
| SCD | 134 (30.3) |  |
| Including SIDS | 22 (5.0) |  |
| Aborted cardiac arrest | 72 (16.3) |  |
| PM implantation | 65 (14.7) |  |
| ICD implantation | 138 (31.2) |  |

LQT3: long QT syndrome type 3; BrS-1: Brugada syndrome type 1; PCCD: progressive cardiac conduction defect; SSS: sick sinus syndrome; DCM: dilated cardiomyopathy; MEPPT: multifocal ectopic Purkinje-related premature contractions; SCD: sudden cardiac death; SIDS: sudden infant death syndrome; PM: pacemaker; ICD: implantable cardioverter defibrillator.

**Table 4: Clinical characteristics of isolated LQT3 patients who experienced cardiac events (n=25)**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | *SCN5A* mutation (c.) | Age at first MCE  (years) | Type of first MCE | Age at first recurrence | Type of first recurrence | Drugs at the time of first recurrence | Other treatment | Length of FU (years) | Total number of MCEs | Alive at last FU |
| Patient 1 | c4519\_4527del | 5.3 | Syncope | n/a | n/a | n/a | ICD | 8.0 | 1 | Alive |
| Patient 2 | c5329G>A | 15.5 | ACA | n/a | n/a | n/a | ICD | 3.3 | 1 | Alive |
| Patient 3 | c5236G>A | 7.8 | Syncope | n/a | n/a | n/a | n/a | 22.9 | 1 | Alive |
| Patient 4 | c4901T>C | 6.0 | Syncope | n/a | n/a | n/a | n/a | 6.2 | 1 | Alive |
| Patient 5 | c4458C>A | 1.1 | Syncope | 7.4 | VF | mexiletine | ICD, LCSD | 9.0 | 6 | Alive |
| Patient 6 | c5350G>A | 10.9 | Syncope | n/a | n/a | n/a | n/a | 2.3 | 1 | Alive |
| Patient 7 | c5287G>A | 0.1 | ACA | 1.2 | TdP | propranolol (2 mg/kg/d) | n/a | 12.5 | 3 | Dead |
| Patient 8 | c1231G>A | 11.8 | Syncope | 21.8 | TdP | nadolol (1 mg/kg/d) | n/a | 25.7 | 2 | Alive |
| Patient 9 | c1231G>A | 7.1 | Syncope | n/a | n/a | n/a | ICD | 6.1 | 1 | Alive |
| Patient 10 | c5296A>C | 2.5 | ACA | 3.3 | VF | mexiletine + propranolol (2 mg/kg/d) | ICD | 1.9 | 3 | Alive |
| Patient 11 | c5287G>A | 0.7 | SCD | n/a | n/a | n/a | n/a | 0.0 | 1 | Dead |
| Patient 12 | c1231G>A | 5.3 | ACA | n/a | n/a | n/a | ICD | 3.6 | 1 | Alive |
| Patient 13 | c2065C>T | 10.1 | ACA | n/a | n/a | n/a | n/a | 14.9 | 1 | Alive |
| Patient 14 | c3556G>A | 15.2 | Syncope | n/a | n/a | n/a | n/a | 3.8 | 1 | Alive |
| Patient 15 | c1273G>A | 13.6 | Syncope | n/a | n/a | n/a | n/a | 5.0 | 1 | Alive |
| Patient 16 | c5350G>A | 14.3 | Syncope | n/a | n/a | n/a | PM | 5.9 | 1 | Alive |
| Patient 17 | c5287G>A | 0.1 | ACA | n/a | n/a | n/a | ICD | 0.8 | 1 | Alive |
| Patient 18 | c4442G>A | 0.6 | ACA | n/a | n/a | n/a | n/a | 12.1 | 1 | Alive |
| Patient 19 | c2821\_2822delTCinsAA | 0.1 | ACA | 0.2 | VF | mexiletine + propranolol (2 mg/kg/d) | n/a | 4.7 | 6 | Dead |
| Patient 20 | c5300A>G | 14.0 | Syncope | 26.8 | SCD | no treatment\* | n/a | 12.8 | 2 | Dead |
| Patient 21 | c1231G>A | 10.9 | Syncope | 11.9 | TdP | propranolol (2 mg/kg/d) | n/a | 10.7 | 3 | Alive |
| Patient 22 | c4519\_4527del | 16.2 | Syncope | n/a | n/a | n/a | LCSD | 26.5 | 1 | Alive |
| Patient 23 | c4519\_4527del | 16.6 | SCD | n/a | n/a | n/a | PM | 13.0 | 1 | Dead |
| Patient 24 | c5972G>A | 16.2 | Syncope | 16.3 | TdP | propranolol (2 mg/kg/d) | ICD | 2.0 | 4 | Alive |
| Patient 25 | c3989C>A | 0.0 | ACA | 0.1 | Syncope | mexiletine + propranolol (unknown dose) | n/a | 0.2 | 3 | Dead |

All but one patient (receiving propranolol 1 mg/kg/d) had no treatment at the time of first MCE

\*betablocker voluntarily interrupted by the patient who died off treatment.

LQT3: long QT syndrome type 3; PM: pacemaker; ICD: implantable cardioverter defibrillator; MCE: major cardiac event; SCD: sudden cardiac death; SIDS: sudden infant death syndrome; LCSD: left cardiac sympathetic denervation; FU: follow-up.

**Table 5: SCN5A mutations (442 patients, 445 mutations, 185 unique mutations)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| SCN5A mutation (c.) | exon | Mutant (p.) | Functional effect | n |
| Truncation mutations [n=81 mutations, 44 distinct mutations] | | | | |
| c127C>T | 2 | pArg43\* | Loss of function | 1 |
| c268del | 2 | pGln90Trpfs\*14 | Loss of function | 1 |
| c393-1C>T | 4 |  | Loss of function | 1 |
| c468G>A | 4 | pTrp156\* | Loss of function | 1 |
| c611+1G>A | 5 |  | Loss of function | 2 |
| c703+1G>A | 6 |  | Loss of function | 1 |
| c870del | 7 | pAsn291Thrfs\*52 | Loss of function | 2 |
| c934+1G>A | 7 |  | Loss of function | 2 |
| c1036G>T | 9 | pGlu346\* | Loss of function | 1 |
| c1603C>T | 12 | pArg535\* | Loss of function | 4 |
| c1890G>A | 12 | pThr631Valfs\*101 | Loss of function | 3 |
| c1936del | 13 | pGln646Argfs\*5 | Loss of function | 7 |
| c2274delG | 15 | pIle759Phefs\*6 | Loss of function | 3 |
| c2320del | 15 | pTyr774Thrfs\*28 | Loss of function | 2 |
| c2335C>T | 15 | pGln779\* | Loss of function | 2 |
| c2520del | 16 | pAsn841Thrfs\*2 | Loss of function | 1 |
| c2550del\_2551dupGT | 16 | pPhe851Cysfs\*19 | Loss of function | 1 |
| c2582\_2583del | 16 | pPhe861Trpfs\*90 | Loss of function | 6 |
| c2998C>T | 17 | pGln1000\* | Loss of function | 1 |
| c3045\_3046del | 17 | pGu1015Aspfs\*14 | Loss of function | 1 |
| c3175C>T | 17 | pGln1059\* | Loss of function | 1 |
| c3207\_3211dup | 17 | pGlu1071Glyfs\*76 | Loss of function | 1 |
| c3313G>T | 18 | pGlu1105\* | Loss of function | 1 |
| c3318dup | 18 | pGlu1107Argfs\*24 | Loss of function | 2 |
| c3319G>T | 18 | pGlu1107\* | Loss of function | 1 |
| c3352C>T | 18 | pGln1118\* | Loss of function | 2 |
| c3491dup | 19 | pGlu1165Argfs\*6 | Loss of function | 2 |
| c3572G>A | 20 | pTrp1191\* | Loss of function | 2 |
| c3666+1del | 20 | pLeu1222Leufs\*7 | Loss of function | 2 |
| c3840+1G>A | 21 |  | Loss of function | 5 |
| c3900\_3903dup | 22 | Leu1302Valfs18 | Loss of function | 1 |
| c4105G>T | 23 | pGly1369\* | Loss of function | 1 |
| c4118del | 23 | pLeu1373\* | Loss of function | 4 |
| c4245+1G>T | 23 |  | Loss of function | 1 |
| c4299+1dup | 24 | pGly1031fs\*27 | Loss of function | 1 |
| c4423del | 24 | pGln1475Asnfs\*6 | Loss of function | 1 |
| c4437+5G>A | 25 |  | Loss of function | 1 |
| c4845C>G | 28 | pTyr1615\* | Loss of function | 1 |
| c4867C>T | 28 | pArg1623\* | Loss of function | 1 |
| c5083C>T | 28 | pGln1695\* | Loss of function | 1 |
| c5321\_5324dup | 28 | pPhe1775Leufs\*15 | Loss of function | 2 |
| c5433T>G | 28 | pTyr1811\* | Loss of function | 1 |
| c5830C>T | 28 | pArg1944\* | Loss of function | 2 |
| c6017del | 28 | pPro2006Leufs\*32 | Loss of function | 1 |
|  |  |  |  |  |

**Table 5 (suite)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| SCN5A mutations | Exon | Aminoacid changes | Effect | n |
| Missense pathogenic mutations [n=285 mutations, 95 distinct mutations] | | | | |
| c278T>C | 3 | pPhe93Ser | Loss of function | 3 |
| c362G>A | 3 | pArg121Gln | Loss of function | 1 |
| c481G>A | 4 | pGlu161Lys | Loss of function | 2 |
| c635T>C | 6 | pLeu212Pro | Gain of function | 2 |
| c665G>A | 6 | pArg222Gln | Gain of function | 1 |
| c673C>T | 6 | pArg225Trp | Gain and loss | 4 |
| c718G>A | 7 | pVal240Met |  | 1 |
| c827T>C | 7 | pLeu276Pro |  | 2 |
| c844C>T | 7 | pArg282Cys | Loss of function | 1 |
| c1007C>T | 9 | pPro336Leu | Loss of function | 1 |
| c1018C>T | 9 | pArg340Trp | Gain of function | 1 |
| c1066G>A | 9 | pAsp356Asn | Loss of function | 3 |
| c1099C>T | 9 | pArg367Cys | Loss of function | 1 |
| c1100G>A | 9 | pArg367His | Loss of function | 1 |
| c1106T>A | 9 | pMet369Lys | Loss of function | 3 |
| c1109C>T | 9 | pThr370Met | Gain of function | 4 |
| c1120T>G | 9 | pTrp374Gly | Loss of function | 2 |
| c1126C>T | 9 | pArg376Cys | Loss of function | 3 |
| c1218C>A | 10 | pAsn406Lys | Gain of function | 2 |
| c1231G>A | 10 | pVal411Met | Gain of function | 10 |
| c1540G>T | 12 | pGly514Cys | Loss of function | 2 |
| c2047T>C | 14 | pCys683Arg | Gain of function | 6 |
| c2150C>T | 14 | pPro717Leu |  | 2 |
| c2204C>T | 14 | pAla735Val | Loss of function | 1 |
| c2441G>A | 16 | pArg814Gln |  | 3 |
| c2516T>C | 16 | pLeu839Pro | Loss of function | 1 |
| c2632C>T | 16 | pArg878Cys | Loss of function | 1 |
| c2674T>A | 16 | pPhe892Ile | Loss of function | 1 |
| c2677C>T | 16 | pArg893Cys | Loss of function | 1 |
| c2690G>A | 16 | pGly897Glu | Loss of function | 1 |
| c2701G>A | 16 | pGlu901Lys | Loss of function | 7 |
| c2780A>G | 16 | pAsn927Ser | Loss of function | 1 |
| c2821T>A and c2822C>A | 17 | pSer941Asn | Gain of function | 1 |
| c2822C>T | 17 | pSer941Phe | Gain of function | 1 |
| c2893C>T | 17 | pArg965Cys | Loss of function | 2 |
| c3157G>A | 17 | pGlu1053Lys | Loss of function | 1 |
| c3556G>A | 20 | pAla1186Thr | Gain of function | 2 |
| c3662C>T | 20 | pAla1221Val |  | 2 |
| c3673G>A | 21 | pGlu1225Lys | Loss of function | 3 |
| c3694C>T | 21 | pArg1232Trp | Loss of function | 1 |
| c3718G>C | 21 | pGlu1240Gln |  | 1 |
| c3784G>A | 21 | pGly1262Ser | Loss of function | 1 |
| c3823G>A | 21 | pAsp1275Asn | Loss of function | 4 |
| c3911C>T | 22 | pThr1304Met | Gain of function | 2 |
| c3956G>T | 22 | pGly1319Val | Loss of function | 8 |
| c3974A>G | 23 | pAsn1325Ser | Gain of function | 4 |
| c3988G>A | 23 | pAla1330Thr | Gain of function | 1 |
| c3989C>A | 23 | pAla1330Asp | Gain of function | 1 |
| c3995C>A | 23 | pPro1332Gln |  | 1 |

**Table 5 (suite)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| SCN5A mutations | Exon | Aminoacid changes | Effect | n |
| Missense pathogenic mutations (suite) | | | | |
| c3995C>T | 23 | pPro1332Leu | Gain of function | 1 |
| c4000A>G | 23 | pIle1334Val | Gain of function | 3 |
| c4035G>T | 23 | pTrp1345Cys | Loss of function | 2 |
| c4037T>C | 23 | pLeu1346Pro | Loss of function | 1 |
| c4140C>G | 23 | pAsn1380Lys |  | 2 |
| c4216G>C | 23 | pGly1406Arg | Loss of function | 2 |
| c4222G>A | 23 | pGly1408Arg | Loss of function | 2 |
| c4282G>T | 24 | pAla1428Ser | Loss of function | 1 |
| c4346A>G | 25 | pTyr1449Cys | Loss of function | 2 |
| c4441G>A | 26 | pGly1481Arg |  | 1 |
| c4442G>A | 26 | pGly1481Glu |  | 1 |
| c4442G>T | 26 | pGly1481Val |  | 1 |
| c4458C>A | 26 | pPhe1486Leu | Gain of function | 1 |
| c4459A>C | 26 | pMet1487Leu | Gain of function | 1 |
| c4493T>C | 26 | pMet1498Thr |  | 2 |
| c4501C>G | 26 | pLeu1501Val |  | 4 |
| c4562T>A | 27 | pIle1521Lys | Loss of function | 2 |
| c4748G>A | 27 | pArg1583His | Loss of function | 1 |
| c4783G>A | 27 | pAsp1595Asn | Loss of function | 1 |
| c4868G>A | 28 | pArg1623Gln | Gain of function | 6 |
| c4876C>T | 28 | pArg1626Cys |  | 1 |
| c4892G>A | 28 | pGly1631Asp | Gain of function | 1 |
| c4895G>T | 28 | pArg1632Leu |  | 1 |
| c4931G>A | 28 | pArg1644His | Gain of function | 2 |
| c4978A>G | 28 | pIle1660Val | Loss of function | 2 |
| c5015C>A | 28 | pSer1672Tyr | Loss of function | 1 |
| c5129C>T | 28 | pSer1710Leu | Loss of function | 4 |
| c5164A>G | 28 | pAsn1722Asp | Loss of function | 2 |
| c5227G>A | 28 | pGly1743Arg | Loss of function | 3 |
| c5228G>A | 28 | pGly1743Glu | Loss of function | 8 |
| c5287G>A | 28 | pVal1763Met | Gain of function | 6 |
| c5287G>T | 28 | pVal1763Leu |  | 1 |
| c5296A>C | 28 | pMet1766Leu | Gain and loss | 1 |
| c5300A>G | 28 | pTyr1767Cys | Gain of function | 2 |
| c5302A>G | 28 | pIle1768Val | Gain of function | 9 |
| c5320A>C | 28 | pAsn1774His |  | 1 |
| c5320A>G | 28 | pAsn1774Asp |  | 1 |
| c5329G>A | 28 | pVal1777Met | Gain of function | 8 |
| c5329G>T | 28 | pVal1777Leu |  | 1 |
| c5350G>A | 28 | pGlu1784Lys | Gain and loss | 69 |
| c5357T>G | 28 | pLeu1786Arg |  | 1 |
| c5368G>A | 28 | pAsp1790Asn |  | 1 |
| c5369A>G | 28 | pAsp1790Gly | Gain of function | 7 |
| c5383T>A | 28 | pTyr1795Asn |  | 1 |
| c5384A>G | 28 | pTyr1795Cys | Gain of function | 2 |
| c5546A>G | 28 | pHis1849Arg | Gain of function | 1 |

**Table 5 (suite)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| SCN5A mutations | Exon | Aminoacid changes | Effect | n |
| In-frame mutations [n=32 mutations, 11 distinct mutations] | | | | |
| c2184\_2186del | 14 | pLeu729del | Loss of function | 1 |
| c4015\_4017del | 23 | pLeu1339del |  | 1 |
| c4140\_4142del | 23 | pAsn1380del | Loss of function | 3 |
| c4456\_4458del | 26 | pPhe1486del | Gain and loss | 1 |
| c4519-4527del | 26 | pGln1507\_Pro1509del |  | 9 |
| c4708\_4710dup | 27 | pIle1570dup | Loss of function | 1 |
| c4850\_4852del | 28 | pPhe1617del | Gain and loss | 4 |
| c5242\_5244del | 28 | pGly1748del |  | 1 |
| c5272\_5274del | 28 | pIle1758del |  | 3 |
| c5385\_5387dup | 28 | pTyr1795\_Glu1796insAsp | Gain and loss | 7 |
| c5972G>A | 28 | pArg1991Gln |  | 1 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| SCN5A mutations | Exon | Aminoacid changes | Effect | n |
| Unknwon functional effect [n=47 mutations, 35 distinct mutations] | | | | |
| c10T>G | 2 | pPhe4Val |  | 1 |
| c670C>T | 6 | pLeu224Phe |  | 1 |
| c680T>C | 6 | pLeu227Pro |  | 1 |
| c725C>A | 7 | pAla242Asp |  | 1 |
| c787G>A | 7 | pVal263Ile |  | 1 |
| c994G>A | 8 | pAla332Thr |  | 1 |
| c1022G>A | 9 | pCys341Tyr |  | 2 |
| c1063T>A | 9 | pPhe355Ile |  | 2 |
| c1201T>C | 10 | pSer401Pro |  | 1 |
| c1237G>A | 10 | pAla413Thr |  | 2 |
| c1273G>A | 10 | pAla425Thr |  | 1 |
| c1889C>T | 12 | pThr630Met |  | 2 |
| c2065C>T | 14 | pArg689Cys |  | 1 |
| c2207T>C | 14 | pLeu736Pro |  | 1 |
| c2335C>A | 15 | pGln779Lys |  | 2 |
| c3067C>T | 17 | pArg1023Cys |  | 2 |
| c3220A>G | 17 | pSer1074Gly |  | 1 |
| c3236C>A | 18 | pSer1079Tyr |  | 2 |
| c3236C>T | 18 | pSer1079Phe |  | 2 |
| c3598C>T | 20 | pHis1200Tyr |  | 2 |
| c3626C>G | 20 | pThr1209Arg |  | 1 |
| c3629T>C | 20 | pPhe1210Ser |  | 1 |
| c3665T>G | 20 | pLeu1222Arg |  | 1 |
| c4380C>A | 25 | pPhe1460Leu |  | 1 |
| c4424A>T | 25 | pGln1475Leu |  | 1 |
| c4473G>T | 26 | pGln1491His |  | 1 |
| c4510A>G | 26 | pLys1504Glu |  | 1 |
| c4571T>C | 27 | pIle1524Thr |  | 2 |
| c4901T>C | 28 | pLeu1634Pro |  | 1 |
| c5236G>A | 28 | pAla1746Thr |  | 2 |
| c5239G>A | 28 | pVal1747Met |  | 1 |
| c5246T>A | 28 | pIle1749Asn |  | 1 |
| c5378T>A | 28 | pMet1793Lys |  | 1 |
| c5431T>A | 28 | pTyr1811Asn |  | 1 |
| c5689C>T | 28 | pArg1897Trp |  | 2 |

**Table 6: Comparison between VUS and other mutations (n=442)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Gain of function, loss of function or both gain and loss of function  (n=350) | Variants of unknown significance  (n=92) | p value |
| Diagnosis |  |  |  |
| Male, n (%) | 161(46) | 35(38) | 0.19 |
| Proband, n (%) | 128(37) | 50(54) | **0.003** |
| Age at diagnosis, yrs (IQR) | 8.0(9.2) | 8.6(10.1) | 0.64 |
| Diagnosis ≤1year, n (%) | 58(17) | 17(18) | 0.64 |
| Mode of presentation, n (%)  Cardiac arrest at diagnosis, n (%)  Syncope at diagnosis, n (%)  Asymptomatic at diagnosis, n (%) | 50(14)  52(15)  24871) | 12(13)  18(20)  62(67) | 0.55 |
|  |  |  |  |
| Phenotype |  |  |  |
| Isolated LQT3 at baseline, n (%) | 33(9) | 14(15) | 0.13 |
| Isolated BrS-1 at baseline, n (%) | 7(2) | 1(1) | 0.48 |
| Isolated PCCD at baseline, n (%) | 91(26) | 22(24) | 0.40 |
| Isolated DCM at baseline, n (%) | 3(1) | 0(0) | 0.50 |
| Isolated SSS at baseline, n (%) | 5(1) | 1(1) | 0.64 |
| Overlap phenotype at baseline, n (%) | 53(15) | 16(17) | 0.35 |
| Negative phenotype at baseline, n (%) | 158(45) | 38(41) | 0.29 |
|  |  |  |  |
| ECG parameters |  |  |  |
| Median age at ECG, yrs (IQR) | 8.0(9.4) | 8.(10.3) | 0.37 |
| Median heart rate, bpm (IQR) | 78.9(34.8) | 78.9(34.8) | 0.72 |
| Median PR interval, ms (IQR) | 160(48) | 160(60) | 0.83 |
| Median QRS complex, ms (IQR) | 80(30) | 80(32) | 0.92 |
| Median QT interval, ms (IQR) | 360(100) | 385(120) | 0.07 |

QTc: corrected QT interval; AV block: atrioventricular block; RBBB: right bundle branch block; LBBB: left bundle branch block; SVT: supraventricular tachycardia; BrS1: Brugada syndrome type 1; LQT3: long QT syndrome type 3.

**Table 7: Clinical characteristics according to *SCN5A* mutation location (domains) (N=442)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | N-terminus  (n=7) | DI-DIV (n=325) | C-terminus  (n=110) | p value | Analysis | HR (95%IC) |
| Diagnosis |  |  |  |  |  |  |
| Male, n (%) | 5 (71.4) | 183 (56.3) | 58 (52.7) | 0.77 |  |  |
| Proband, n (%) | 3 (42.9) | 141 (43.4) | 34 (30.9) | 0.06 |  |  |
| FH of CCD-PM, n (%) | 0 (0.0) | 58 (17.8) | 28 (25.4) | 0.11 |  |  |
| FH of SCD-ICD, n (%) | 3 (42.9) | 170 (52.3) | 70 (63.6) | 0.13 |  |  |
| Median age at diagnosis, yrs (IQR) | 7.4 (10.6) | 7.1 (9.9) | 10.1 (6.7) | **0.01** |  |  |
| Diagnosis ≤1year, n (%) | 2 (28.6) | 62 (19.1) | 11 (10.0) | 0.08 |  |  |
| Mode of presentation, n (%)  Cardiac arrest at diagnosis, n (%)  Syncope at diagnosis, n (%)  Asymptomatic at diagnosis, n (%) | 2 (28.6)  1 (14.3)  4 (57.1) | 56 (17.2)  54 (16.6)  215 (66.1) | 4 (3.6)  15 (13.6)  91 (82.7) | **0.001** |  |  |
|  |  |  |  |  |  |  |
| Phenotype |  |  |  |  |  |  |
| Isolated LQT3 at baseline, n (%) | 0 (0.0) | 31(9.5) | 16 (14.5) | 0.29 |  |  |
| Isolated BrS-1 at baseline, n (%) | 0 (0.0) | 7 (2.2) | 1 (0.9) | 0.72 |  |  |
| Isolated PCCD at baseline, n (%) | 1 (14.3) | 87 (26.8) | 25 (22.7) | 0.64 |  |  |
| Isolated DCM at baseline, n (%) | 0 (0.0) | 3 (0.9) | 0 (0.0) | 0.59 |  |  |
| Isolated SSS at baseline, n (%) | 0 (0.0) | 5 (1.5) | 1 (0.9) | 0.56 |  |  |
| Overlap phenotype at baseline, n (%) | 2 (28.6) | 51 (15.7) | 16 (14.5) | 0.55 |  |  |
| Negative ECG phenotype at baseline, n (%) | 4 (57.1) | 141 (43.4) | 51 (46.4) | 0.67 |  |  |
|  |  |  |  |  |  |  |
| Outcomes |  |  |  |  |  |  |
| Median FU length, yrs (median, IQR) | 4.7 (5.9) | 5.7 (5.8) | 7.2 (6.3) | 0.06 |  |  |
| MCE, n (%) | 3 (42.9) | 115 (35.4) | 21 (19.1) | **0.0002\*** (cox) | DI-DIV vs C-term  N-term vs C-term | 2.9 (1.7-4.9)  4.5 (1.1-18.6) |
| ICD implantation, n (%) | 3 (42.9) | 52 (16.0) | 22 (20.0) | 0.1 |  |  |
| At least one appropriate shocks, n (%) | 0 (0.0) | 24 (46.2) | 4 (18.2) | **0.03** |  |  |
| Death or transplantation, n (%) | 0 (0.0) | 14 (4.3) | 0 (0.0) | n/a |  | n/a |

FH: family history; PCCD: progressive cardiac conduction disorder; PM: pacemaker; SCD: sudden cardiac death; ICD: implantable cardioverter defibrillator; LQT3: long QT syndrome type 3; BrS-1: Brugada syndrome type 1; SSS: sick sinus syndrome; DCM: dilated cardiomyopathy; FU: follow-up; MCE: major cardiac event; Transplantation: orthotopic heart transplantation because of intractable ventricular arrhythmias; n/a = not applicable. **\*** Cox proportional hazards regression analysis

**Table 8: Phenotype and outcomes according to *SCN5A* mutation location (segments) (n=241)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | S1-S4  (n=80) | S5-S6  (n=161) | p-value |
| Diagnosis |  |  |  |
| Male, n (%) | 38 (47.5) | 91 (56.5) | 0.12 |
| Proband, n (%) | 34 (42.5) | 69 (42.9) | 0.53 |
| FH of CCD-PM, n (%) | 11 (13.7) | 25 (15.5) | 0.85 |
| FH of ICD-SCD, n (%) | 35 (43.7) | 88 (54.7) | 0.13 |
| Median age at diagnosis, yrs (IQR) | 8.4  (9.2) | 6.9  (10.1) | 0.08 |
| Diagnosis ≤1year, n (%) | 12 (15.0) | 34 (21.1) | 0.3 |
| Symptomatic, n (%) | 33 (41.2) | 56 (34.8) | 0.39 |
| Mode of presentation, n (%)  Cardiac arrest at diagnosis, n (%)  Syncope at diagnosis, n (%)  Asymptomatic at diagnosis, n (%) | 12 (15.0)  17 (21.2)  51 (63.7) | 27 (16.8)  25 (15.5)  109 (67.7) | 0.55 |
|  |  |  |  |
| Phenotype |  |  |  |
| Isolated LQT3 at baseline, n (%) | 2 (2.5) | 16 (9.9) | 0.04 |
| Isolated BrS-1 at baseline, n (%) | 3 (3.8) | 3 (1.9) | 0.4 |
| Isolated PCCD at baseline, n (%) | 20 (25.0) | 43 (26.7) | 0.88 |
| Isolated DCM at baseline, n (%) | 0 (0.0) | 0 (0.0) | - |
| Isolated SSS at baseline, n (%) | 1 (1.3) | 1 (0.6) | 0.56 |
| Overlap phenotype at baseline, n (%) | 13 (16.3) | 28 (17.4) | 0.49 |
| Negative phenotype at baseline, n (%) | 41 (51.3) | 70 (43.5) | 0.27 |
|  |  |  |  |
| Outcomes |  |  |  |
| Median FU length, yrs (IQR) | 5.7  (5.1) | 5.8  (6.3) | 0.76 |
| MCE, n (%) | 29 (36.3) | 57 (35.4) | 0.52\* |
|  |  |  |  |
| ICD implantation, n (%) | 13 (16.2) | 32 (19.9) | 0.6 |
| At least one appropriate shocks, n (%) | 10 (76.9) | 12 (37.5) | **0.02** |
| Death or transplantation, n (%) | 1 (1.3) | 6 (3.7) | 0.36\* |

LQT3: long QT syndrome type 3; BrS-1: Brugada syndrome type 1; PCCD: progressive cardiac conduction disorder; CA: cardiac arrest (includes aborted cardiac arrest and sudden cardiac death); MCE: major cardiac event; ICD: implantable cardioverter defibrillator.

**\***Cox proportional hazards regression analysis

**Table 9: Clinical characteristics according to *SCN5A* mutation function (N=442)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Phenotype | Gain of function  (n=87) | Loss of function  (n=178) | Gain and loss of function  (n=85) | Unknown functional effect  (n=92) | p value | HR (95% IC) |
| Diagnosis |  |  |  |  |  |  |
| Male, n (%) | 43(49.4) | 79(44.4) | 39(45.9) | 35(38.0) | 0.48 |  |
| Proband, n (%) | 43(49.4) | 58(32.6) | 27(31.8) | 50(54.3) | 0.001 |  |
| FH of PCCD or PM, n (%) | 7(8.0) | 44(24.7) | 20(23.5) | 15(16.3) | 0.005 |  |
| FH of SCD or ICD, n (%) | 44(50.6) | 109(61.2) | 52(61.2) | 38(41.3) | 0.008 |  |
| Median age at diagnosis, yrs (IQR) | 7.0(11.8) | 7.0(8.9) | 9.8(6.7) | 8.6(10.2) | 0.19 |  |
| Diagnosis ≤1year, n (%) | 23(26.4) | 25(14.0) | 10(11.8) | 17(18.5) | 0.05 |  |
| Mode of presentation, n (%)  Cardiac arrest at diagnosis, n (%)  Syncope at diagnosis, n (%)  Asymptomatic at diagnosis, n (%) | 26(29.9)  14(16.1)  47(54.0) | 22(12.4)  27(15.2)  129(72.5) | 2(2.4)  11(12.9)  72(84.7) | 12(13.0)  18(19.6)  62(67.4) | <0.001 |  |
|  |  |  |  |  |  |  |
| Phenotypes |  |  |  |  |  |  |
| Isolated LQT3 at baseline, n (%) | 23(26.4) | 1(0.6) | 10(11.8) | 16(17.4) | <0.001 |  |
| Isolated BrS-1 at baseline, n (%) | 1(1.1) | 8(4.5) | 4(4.7) | 1(1.1) | 0.28 |  |
| Isolated PCCD at baseline, n (%) | 10(11.5) | 68(38.2) | 19(22.4) | 22(23.9) | <0.001 |  |
| Isolated DCM at baseline, n (%) | 1(1.1) | 1(0.6) | 0(0.0) | 0(0.0) | 0.67 |  |
| Isolated SSS at baseline, n (%) | 3(3.4) | 0(0.0) | 0(0.0) | 1(1.1) | 0.03 |  |
| Overlap syndrome at baseline, n (%) | 7(8.0) | 34(19.1) | 12(14.1) | 16(17.4) | 0.11 |  |
| Negative ECG phenotype at baseline, n (%) | 39(44.8) | 48(27.0) | 30(35.3) | 26(28.3) | 0.02 |  |
|  |  |  |  |  |  |  |
| Outcomes |  |  |  |  |  |  |
| Median FU length, yrs (IQR) | 5.8(5.9) | 4.7(5.8) | 7.0(5.6) | 6.3(7.3) | 0.02 |  |
| MCE, n (%) | 41(47.1) | 52(29.2) | 14(16.5) | 32(34.8) | <0.001(cox) | Gain vs loss 2.3(1.4-3.9)  Gain and loss vs loss 0.4(0.2-0.8)  Unknown vs loss 1.2(0.7-2.1) |
| ICD implantation, n (%) | 30(34.5) | 23(13.1) | 12(14.1) | 12(13.0) | <0.001 |  |
| At least one appropriate shock, n (%) | 14(46.7) | 9(39.1) | 3(25.0) | 2(16.7) | 0.25 |  |
| Death or transplantation, n (%) | 6(6.9) | 3(1.7) | 1(1.2) | 4(4.3) | 0.18  (cox) |  |

FH: family history; PCCD: progressive cardiac conduction defect; PM: pacemaker; SCD: sudden cardiac death; ICD: implantable cardioverter defibrillator; Group 1: cardiac arrest as first symptom; Group 2: syncope as first symptom; Group 3: asymptomatic at diagnosis; LQT3: long QT syndrome type 3; BrS-1: Brugada syndrome type 1; SSS: sick sinus syndrome; DCM: dilated cardiomyopathy; FU: follow-up; MCE: major cardiac event; Transplantation: orthotopic heart transplantation because of intractable ventricular arrhythmias.

**Table 10: Clinical characteristics according to *SCN5A* mutation type (N=442)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Phenotype | Non missense pathogenic mutation  (n=113) | Missense pathogenic mutation  (n=283) | Unknown  (n=46) | p-value |
| Diagnosis |  |  |  |  |
| Male, n (%) | 61 (54.0) | 158 (55.8) | 27 (58.7) | 0.85 |
| Proband, n (%) | 36 (31.9) | 119 (42.0) | 23 (50.0) | 0.06 |
| FH of PCCD or PM, n (%) | 36 (31.9) | 42 (14.8) | 8 (17.4) | **0.001** |
| FH of SCD or ICD, n (%) | 70 (61.9) | 155 (54.8) | 18 (39.1) | **0.03** |
| Median age at diagnosis, yrs (IQR) | 5.8 (9.7) | 8.6 (9.4) | 10.3 (8.7) | **0.02** |
| Diagnosis ≤1year, n (%) | 24 (21.2) | 49 (17.3) | 2 (4.3) | **0.02** |
| Mode of presentation, n (%)  Cardiac arrest at diagnosis, n (%)  Syncope at diagnosis, n (%)  Asymptomatic at diagnosis, n (%) | 19 (16.8)  17 (15.0)  77 (68.1) | 37 (13.1)  42 (14.8)  204 (72.1) | 6 (13.0)  11 (23.9)  29 (63.0) | 0.47 |
|  |  |  |  |  |
| Phenotypes |  |  |  |  |
| Isolated LQT3 at baseline, n (%) | 7 (6.2) | 34 (12.0) | 6 (13.0) | 0.17 |
| Isolated BrS-1 at baseline, n (%) | 2 (1.8) | 5 (1.8) | 1 (2.2) | 0.87 |
| Isolated PCCD at baseline, n (%) | 42 (37.2) | 61 (21.6) | 10 (21.7) | **0.006** |
| Isolated DCM at baseline, n (%) | 2 (1.8) | 1 (0.4) | 0 (0.0) | 0.30 |
| Isolated SSS at baseline, n (%) | 1 (0.9) | 5 (1.8) | 0 (0.0) | 0.83 |
| Overlap syndrome at baseline, n (%) | 23 (20.4) | 39 (13.8) | 7 (15.2) | 0.27 |
| Negative ECG phenotype at baseline, n (%) | 36 (31.9) | 138 (48.8) | 22 (47.8) | **0.007** |
|  |  |  |  |  |
| Outcomes |  |  |  |  |
| Median FU length, yrs (IQR) | 6.3 (6.0) | 5.9 (5.6) | 4.7 (5.6) | 0.14 |
| MCE, n (%) | 39 (34.5) | 83 (29.3) | 17 (37.0) | 0.51\* |
|  |  |  |  |  |
| ICD implantation, n (%) | 18 (16.1) | 54 (19.1) | 5 (10.9) | 0.38 |
| At least one appropriate shock, n (%) | 6 (33.3) | 21 (38.9) | 1 (20.0) | 0.78 |
| Death or transplantation, n (%) | 3 (2.7) | 10 (3.5) | 1 (2.2) | 0.84\* |

FH: family history; PCCD: progressive cardiac conduction defect; PM: pacemaker; SCD: sudden cardiac death; ICD: implantable cardioverter defibrillator; Group 1: cardiac arrest as first symptom; Group 2: syncope as first symptom; Group 3: asymptomatic at diagnosis; LQT3: long QT syndrome type 3; BrS-1: Brugada syndrome type 1; SSS: sick sinus syndrome; DCM: dilated cardiomyopathy; FU: follow-up; MCE: major cardiac event; Transplantation: orthotopic heart transplantation because of intractable ventricular arrhythmias.

**\*** Cox proportional hazards regression analysis

**Table 11: Clinical characteristics according to specific mutations**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ***SCN5A* mutation** | **absence** | **presence** | **P value** | **Analysis** | **HR (95%CI)** |
| **pGlu1784Lys** |  |  |  |  |  |
| Proband, n(%) | 159 (89.3) | 19 (10.7) | 0.02 |  |  |
| Median age at diagnosis, yrs (IQR) | 7.4 (9.9) | 10.5 (5.9) | 0.002 |  |  |
| Mode of presentation |  |  |  |  |  |
| cardiac arrest, n (%) | 62 (100.0) | 0 (0.0) | <0.001 |  |  |
| syncope, n (%) | 61 (87.1) | 9 (12.9) |  |  |  |
| asymptomatic, n (%) | 250 (80.6) | 60 (19.4) |  |  |  |
| MCE, n(%) | 129 (92.8) | 10 (7.2) | 0.0002\* | absence vs presence | 3.7 (1.8-7.6) |
|  |  |  |  |  |  |
| **pGly1319Val** |  |  |  |  |  |
| Proband, n(%) | 171 (96.1) | 7 (3.9) | 0.008 |  |  |
|  |  |  |  |  |  |
| **pVal1763Met** |  |  |  |  |  |
| Proband, n(%) | 173 (97.2) | 5 (2.8) | 0.04 |  |  |
| Median age at diagnosis, yrs (IQR) | 8.1 (9.2) | 0.5 (1.6) | <0.001 |  |  |
| Mode of presentation |  |  | <0.001 |  |  |
| cardiac arrest, n (%) | 56 (90.3) | 6 (9.7) |  |  |  |
| syncope, n (%) | 70 (100.0) | 0 (0.0) |  |  |  |
| asymptomatic, n (%) | 310 (100.0) | 0 (0.0) |  |  |  |
| MCE, n(%) | 133 (95.7) | 6 (4.3) | <0.0001\* | Presence vs absence | 15.4 (5.4-43.4) |
|  |  |  |  |  |  |
| **pVal411Met** |  |  |  |  |  |
| Proband, n(%) | 168 (94.4) | 10 (5.6) | <0.001 |  |  |
| Mode of presentation |  |  | <0.001 |  |  |
| cardiac arrest, n (%) | 58 (93.5) | 4 (6.5) |  |  |  |
| syncope, n (%) | 65 (92.9) | 5 (7.1) |  |  |  |
| asymptomatic, n (%) | 309 (99.7) | 1 (0.3) |  |  |  |
| MCE, n(%) | 130 (93.5) | 9 (6.5) | <0.0001\* | Presence vs absence | 5.1 (2.3-11.4) |
|  |  |  |  |  |  |
| **pTyr1795\_Glu1796insAsp** |  |  |  |  |  |
| Median age at diagnosis, yrs (IQR) | 8.2 (9.5) | 0.7 (7.1) | 0.02 |  |  |

Age at diagnosis is expressed in years; SD: standard deviation; CE: cardiac event; Med.: median; MCE: major cardiac event.

**\***Cox proportional hazards regression analysis

**Table 12: Multivariable analysis on first CE (n=424)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | HR | 95% CI | p  value |
| Genotype |  |  | 0.03 |
| Single *SCN5A* mutation | 1 |  |  |
| Double *SCN5A* mutation | 2.1 | 0.3-13.9 | 0.45 |
| Compound genotype | 3.7 | 1.2-12.0 | 0.03 |
| *SCN5A* mutation functional effect |  |  | 0.001 |
| Loss-of-function | 1 |  |  |
| Gain-of-function | 1.8 | 0.9-3.31 | 0.07 |
| Both gain- and loss-of-function | 0.5 | 0.2-0.9 | 0.04 |
| Variants of unknwon significance | 0.8 | 0.4-1.4 | 0.4 |
| Interaction Age ≤1 year at diagnosis and Proband status |  |  | 0.0002 |
| Age ≤1 year at diagnosis in proband patients | 35.4 | 16.2-77.6 | <0.0001 |
| Age ≤1 year at diagnosis in relative patients | 3.2 | 1.1-9.1 | 0.03 |

Multivariable analysis was stratified on baseline phenotype.

**Table 13: Considered cut-off values for definition of cardiac conduction abnormalities according to age**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | Infants and  young children  <4 yrs | Children and teenagers  ≥4 yrs and <16 yrs | Adults  ≥ 16 yrs |
| 1st-degree AV block | PR interval, ms | ≥ 160 | ≥ 180 | ≥ 200 |
| Left axis deviation | QRS axis, ° | -30° and beyond | -30° and beyond | -30° and beyond |
| Right axis deviation | QRS axis, ° | +180° and beyond | +140° and beyond | +90° and beyond |
| Incomplete RBBB | QRS complex, ms | 80 ≤ QRS < 90 \* | 90 ≤ QRS < 100 \* | 110 ≤ QRS < 120 \* |
| Complete RBBB | QRS complex, ms | QRS ≥ 90 \*\* | QRS ≥ 100 \*\* | QRS ≥ 120 \*\* |
| Incomplete LBBB | QRS complex, ms | 80 ≤ QRS < 90 # | 90 ≤ QRS < 100 # | 110 ≤ QRS < 120 # |
| Complete LBBB | QRS complex, ms | QRS ≥ 90 ## | QRS ≥ 100 ## | QRS ≥ 120 ## |
| Non-specific IVCA | QRS complex, ms | QRS ≥ 80 † | QRS ≥ 90 † | QRS ≥ 110 † |
| Left anterior FB | QRS complex, ms | < 120 ‡ | < 120 ‡ | < 120 ‡ |
| Left posterior FB | QRS complex, ms | < 120 ‡‡ | < 120 ‡‡ | < 120 ‡‡ |

BBB: bundle branch block; IVCA: intraventricular conduction abnormality; FB: fascicular block.

\* and rsr’, rsR’ or rSR’ in leads V1 or V2.

\*\* and rsr’, rsR’ or rSR’ in leads V1 or V2.

# and absent q wave in leads I, V5 and V6; and R peak time > 60 ms in leads V5 and V6 but normal in leads V1, V2 and V3.

## and broad notched or slurred R wave in leads I, aVL, V5 and V6, eventually associated with a RS pattern in V5 and V6; and absent q wave in leads I, V5 and V6; and R peak time > 60 ms in leads V5 and V6 but normal in leads V1, V2 and V3.

† and no criteria for RBBB or LBBB.

‡ and frontal plane axis between -45° and -90°; and qR pattern in lead aVL; and R peak time ≥ 45 ms in aVL.

‡‡ and Frontal plane axis between 100° and 180°; and rS pattern in leads I and aVL; and qR pattern in leads III and aVF

Adapted from [Priori *et al*, 2015; Surawicz *et al*, 2009; Schwartz *et al*, 2002; Rijnbeek *et al*, 2001]

**Table 13bis: Baseline ECG characteristics according to main ECG phenotypes and age groups (n=442)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ECG characteristics | Negative ECG phenotype | Isolated LQT3 | Isolated BrS-1 | Isolated PCCD | Overlap phenotype |
| Infants and young children <4 yrs | n=53 | n=10 | n=2 | n=39 | n=27 |
| Heart rate, bpm | 108.4 ± 28.0 | 123.2 ± 19.3 | 116.5 ± 16.3 | 102.3 ± 27.2 | 107.2 ± 28.1 |
| ECG intervals, ms |  |  |  |  |  |
| PR | 127.9 ± 18.9 | 112.8 ± 27.4 | 135.0 ± 21.2 | 167.7 ± 22.5 | 173.7 ± 32.3 |
| Conducted QRS | 73.1 ± 13.6 | 65.8 ± 15.8 | 70.0 ± 14.1 | 85.5 ± 24.7 | 98.0 ± 34.6 |
| Corrected QT | 426.2 ± 35.7 | 545.6 ± 37.9 | 392.6 ± 3.4 | 426.6 ± 27.8 | 486.9 ± 84.71 |
|  |  |  |  |  |  |
| Children and teenagers ≥4 yrs and <16 yrs | n=143 | n=37 | n=6 | n=74 | n=42 |
| Heart rate, bpm | 78.0 ± 21.6 | 73.6 ± 22.7 | 71.7 ± 12.6 | 72.8 ± 16.2 | 82.8 ± 51.2 |
| ECG intervals, ms |  |  |  |  |  |
| PR | 142.6 ± 21.5 | 142.3 ± 20.7 | 150.0 ± 24.5 | 196.5 ± 40.6 | 176.5 ± 30.4 |
| Conducted QRS | 79.5 ± 15.0 | 78.2 ± 13.7 | 73.3 ± 10.3 | 111.8 ± 20.8 | 103.0 ± 30.5 |
| Corrected QT | 426.3 ± 29.7 | 535.4 ± 45.6 | 403.5 ± 42.6 | 436.5 ± 24.5 | 462.6 ± 65.5 |

LQT3: long QT syndrome type 3; BrS-1: Brugada syndrome type 1; PCCD: progressive cardiac conduction defect; SSS: sick sinus syndrome; DCM: dilated cardiomyopathy; N/A: not applicable.

**Table 14: Most common *SCN5A* mutations per phenotype (n=442)**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Negative ECG phenotype  (n=196) | Isolated LQT3  (n=47) | Isolated BrS-1  (n=8) | Isolated PCCD  (n=113) | Isolated  SSS  (n=6) | Isolated DCM  (n=3) | Overlap phenotype  (n=69) | p value |
| pGlu1784Lys | 29 (15) | 13 (28) | 0 (0) | 17 (15) | 0 (0) | 0 (0) | 10 (14) | 0.33 |
| pIle1768Val | 6 (3) | 1 (2) | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 1 (1) | 0.78 |
| pGly1743Glu | 6 (3) | 0 (0) | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 1 (1) | 0.69 |
| pVal411Met | 2 (1) | 5 (11) | 0 (0) | 2 (2) | 0 (0) | 0 (0) | 1 (1) | 0.04 |
| pGln1507\_Pro1509del pGly1319Val  pTyr1795\_Glu1796insAsp | 4 (2)  6 (3)  4 (2) | 5 (11)  0 (0)  0 (0) | 0 (0)  0 (0)  1 (13) | 0 (0)  2 (2)  1 (1) | 0 (0)  0 (0)  0 (0) | 0 (0)  0 (0)  0 (0) | 0 (0)  0 (0)  1 (1) | **0.01**  0.61  0.34 |
| pAsp1790Gly | 5 (3) | 0 (0) | 0 (0) | 1 (1) | 1 (17) | 0 (0) | 0 (0) | 0.18 |
| pAsp356Asn | 1 (1) | 0 (0) | 0 (0) | 2 (2) | 0 (0) | 0 (0) | 0 (0) | 0.65 |
| pGln646Argfs5 | 0 (0) | 0 (0) | 0 (0) | 5 (4) | 0 (0) | 0 (0) | 2 (3) | **0.05** |
| pGlu901Lys | 3 (2) | 0 (0) | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 3 (4) | 0.47 |
| pVal1763Met | 2 (1) | 3 (6) | 0 (0) | 0 (0) | 1 (17) | 0 (0) | 0 (0) | **0.01** |

LQT3: long QT syndrome type 3; BrS-1: Brugada syndrome type 1; PCCD: progressive cardiac conduction defect; SSS: sick sinus syndrome; DCM: dilated cardiomyopathy.

**SUPPLEMENTAL FIGURES**

**Figure 1: Mode of presentation at diagnosis of cardiac sodium channelopathy**

The diagnosis of cardiac sodium channelopathy was most often made because of a family history and an abnormal electrocardiogram obtained as a screening tool (red area, 67.9%). In green are the patients diagnosed after presentation for syncope (15.8%). Sudden cardiac death or resuscitated cardiac arrest was the cause of diagnosis in 14.0% of patients.

**Figure 2: Location of *SCN5A* variants to the protein topology**

Cardiac sodium channel is constituted by four domains (DI to DIV), each of them consisting of six transmembrane segments (S1 to S6), which are interconnected by extracellulat and cytoplasmic loops. Of the 241 cases whose *SCN5A* mutations were localized to one of the 4 transmembrane-spanning regions, 80 (33.2%) localized to either DI S1-S4, DII S1-S4, DIII S1-S4, or DIV S1-S4 and 161 (66.8%) localized to the S5, P-loop, and S6 regions containing the pore and selectivity filter of the sodium channel (DI S5-S6, DII S5-S6, DIII S5-S6, or DIV S5-S6)

Adapted from van Hoeijen DA et al. Expert Opin Pharmacother. 2014;15:1875-87.

**Figure 3: Freedom from major cardiac event according to *SCN5A* mutation functional effect**

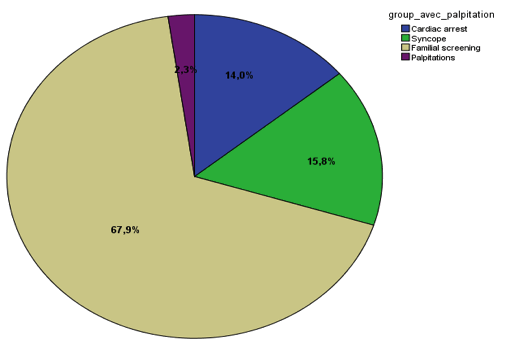
Occurrence of MCE also differed according to *SCN5A* mutation functional effect (p<0.0001)

**Figure 4: Freedom from major cardiac event according to *SCN5A* mutation type**

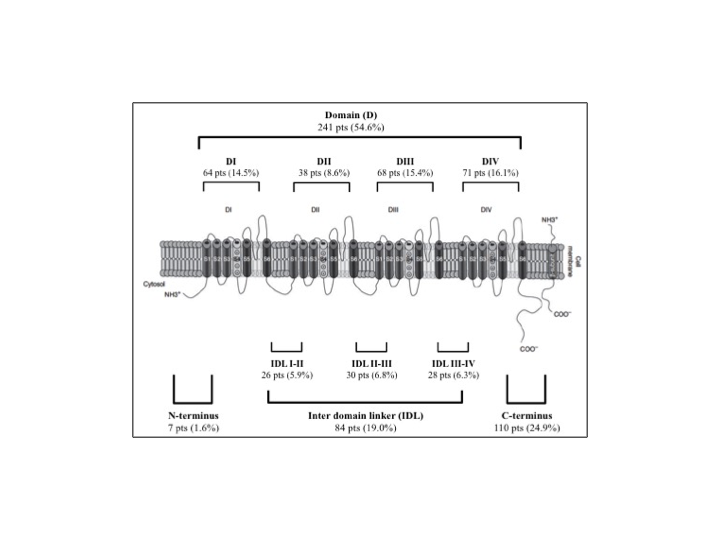
Mutation type did not associate with outcomes (p=0.52).

**Figure 5: ECG samples of *SCN5A* mutation-positive children**

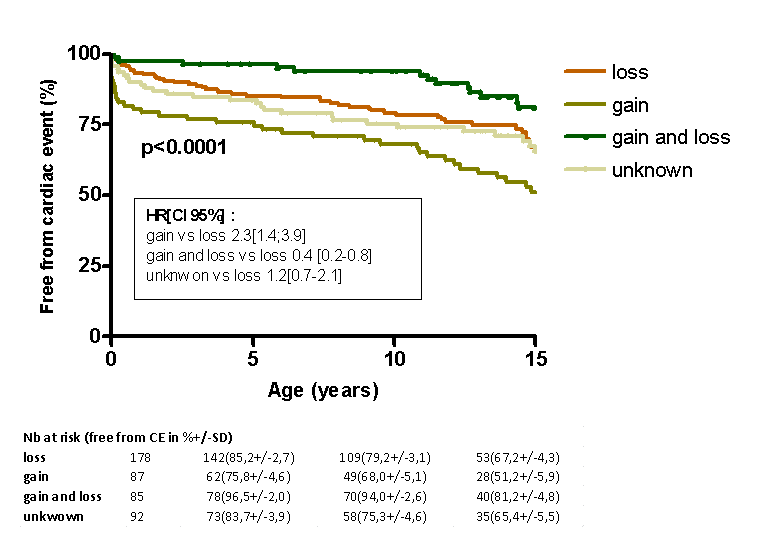
**Panel A:** (SCN5Aped#234, France). Aborted cardiac arrest in a newborn at day 14 of life. 12-lead ECG showed a severe bradycardia at 58 bpm due to a functional 2/1 AV block and a typical long QT syndrome type 3 pattern with a prolonged QTc at 765ms and late-onset peaked/biphasic T wave. A gain-of-function SCN5A-c.5287G>A mutation was identified. **Panel B:** (SCN5Aped#399, Japan). Appropriate ICD shock delivered to treat a ventricular fibrillation in a 12 year-old girl with isolated long QT syndrome type 3 due to a gain-of-function SCN5A-c.1231G>A mutation. **Panel C:** (SCN5Aped#93, Denmark). Exercise-induced syncope in an 11 year-old boy whose 12-lead ECG demonstrated a spontaneous, typical Brugada syndrome type 1 pattern with a coved-type ST segment elevation. A gain-and-loss of function SCN5A-c.673C>T variant was identified. **Panel D:** (SCN5Aped#393, Japan). Permanent, complete AV block with a narrow QRS complex escape rhythm in a 14 year-old boy diagnosed with a low heart rate on a routine exam. QTc was 481ms. A gain-of-function SCN5A-c.5384 mutation was identified. **Panel E:** (SCN5Aped#331, France). 12-lead ECG in a newborn who had syncope at day 1 of life, showing a first-degree AV block (PR interval: 210ms) and intra-ventricular conduction disturbances (QRS 160ms). QTc was 481ms and later normalized to 404ms. A loss-of-function SCN5A-c.1126C>T was identified.

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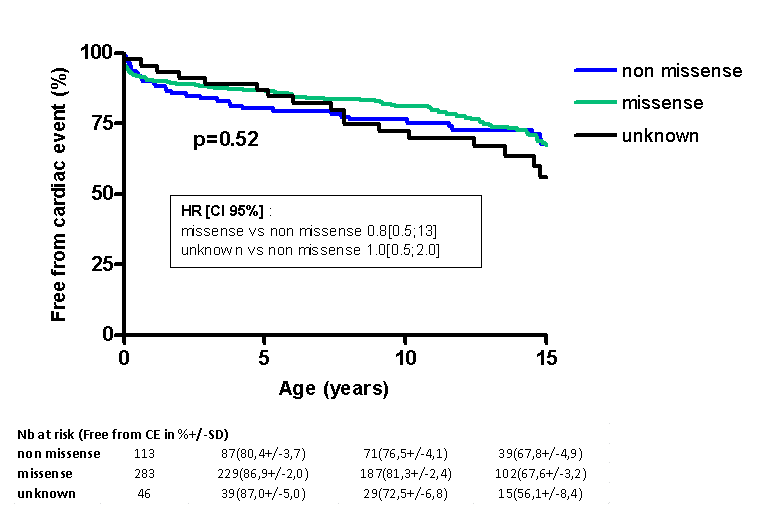
**Figure 1**

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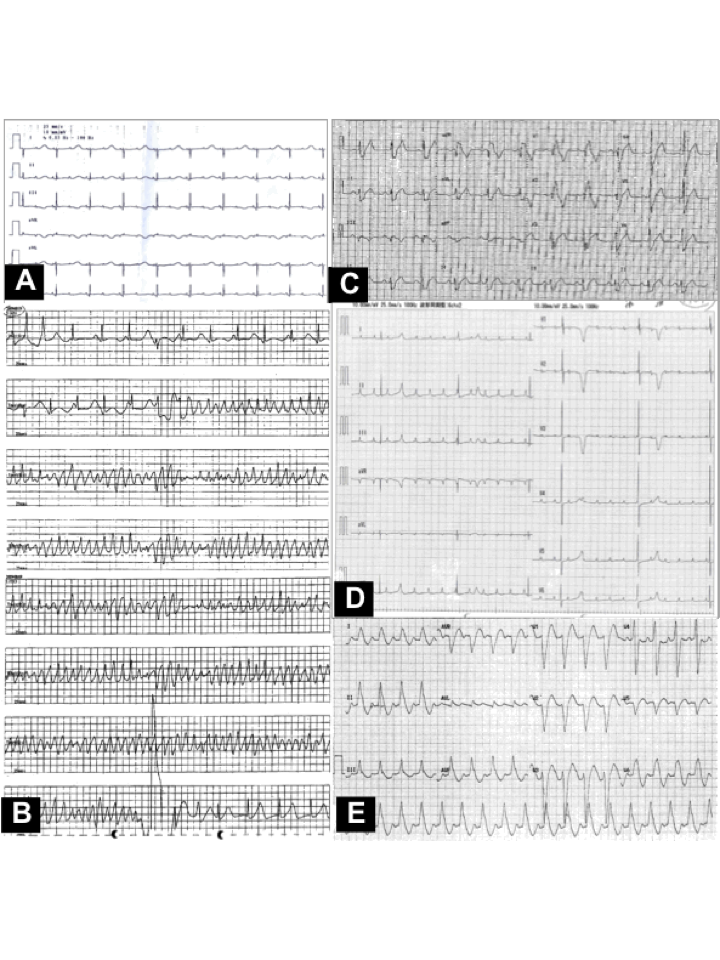
**Figure 2**

****

**Figure 3**

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**Figure 4**



**Figure 5**

**LIMITATIONS**

The 25 years of data collected for this study represents a limitation, since clinical practice has evolved and considerable progress has been made in medical management of probands, screening of relatives and early cardiac pacing and/or ICD implantation. In addition, since patients were included from 25 tertiary, high-volume hospitals, young and/or symptomatic children were more likely to be included in the database, constituting a bias in inclusion. Data on genotype-positive adult relatives were not available.

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