Conclusions: Patient-specific hiPSC-CMs are able to recapitulate single-cell phenotype features of BrS with CACNB2 mutation and may provide novel opportunities to further elucidate the cellular disease mechanism.
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10 years of follow-up in carriers of a RyR2 pathogenic mutation with uncertain penetrance. What have we learned?

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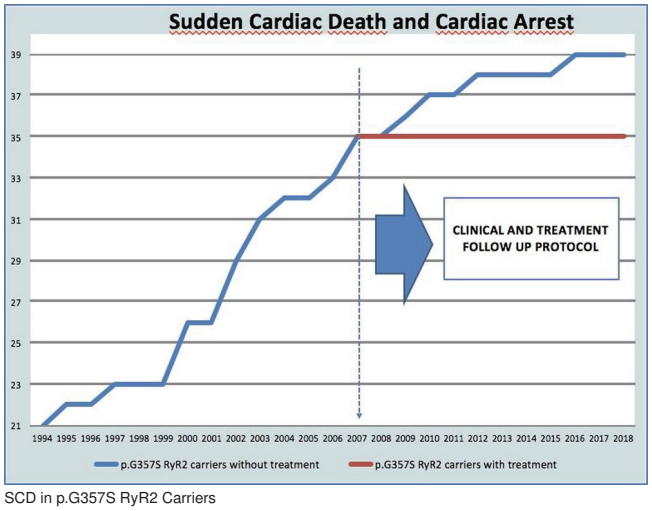
Background: Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a genetic disorder with high incidence of sudden cardiac death (SCD). It has been described that mutations in RyR2 gene are responsible for most of the clinical presentations of this disease. These mutations have an incomplete, and often uncertain penetrance in asymptomatic carriers. We discovered a family with more than 1400 members with high incidence of SCD (35 SCD, mean age 18±8 years, 24 (67%) male) in Gran Canaria (Spain). After a genetic screening, since 2007, 219 alive carriers of a RyR2 mutation (G357S) were identified.
Purpose: To describe our experience after long-term follow-up in a population of 219 carriers of (p.G357S) RyR2 gene mutation
Methods: A clinical protocol of treatment and follow-up was offered to all alive carriers members, based on repeated exercise stress tests (ET), with an objective of maximum heart rate less than theoretical 80% and the absence of ventricular arrhythmias (VA), increasing or changing betablockers (BB) to achieve it. An implantable cardioverter defibrillator (ICD) was proposed, when the symptoms persisted or the objective was not achieved. Recently flecainide has been added. We have developed a quantitative score to evaluate ventricular arrhythmias during exercise.
Results: The mean time of follow-up was 99±35 months (mean age 44,63±22,65 years, range 0–81). After more than 10 years of application of the protocol, no SCD or cardiac arrests have occurred in this group. However, 4 events (2 SCD, 2 recovered SCD) occurred between those that refused or did not know the protocol. 50 p. (22%) have left the follow-up, with a mean age of 59±21 years. 3085 reviews were performed: 2747 underwent ET, 1484 were on treatment with propranolol, 1192 with other BB, 409 without any treatment. 18 p. (10.4%) received flecainide, in combination with BB, and one of them as monotherapy due to side effects of BB. In 66,7% of these patients with flecainide, the exercise-induced VA quantitative score was reduced by more than 50% in consecutive exercise test. ICD was indicated and implanted, as a result of this protocol, to 47 subjects (21%) programmed with a ventricular fibrillation (VF) threshold of 220 bpm. 6 appropriate discharges (66% without treatment), occurred in 4 patients (8.5%) and 5 inappropriate discharges in 4 patients (4,9%, both without treatment, one because of an inappropriate VF low threshold).



SCD in p.G357S RyR2 Carriers

Conclusions: Pathogenic mutations in RyR2 require a monitoring protocol that has been shown to be useful in management of CPVT, and should be recommended to carriers of a CPVT-related mutation and, probably, to all CPVT patients. The treatment with BB, BB + flecainide and ICD has been shown to be effective in the long-term follow-up of these patients.

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Novel SCN5A mutation associated with multifocal ectopic purkinje-related premature contractions

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Background/Introduction: Mutations in the SCN5A gene that encodes the cardiac sodium (Na+) channel alpha-subunit, Nav1.5, can cause a variety of arrhythmic disorders. Recently a new cardiac phenotype characterized by multifocal ectopic Purkinje-related premature contractions (MEPPC) was described, caused by a gain-of-function mutation (p.R222Q) in SCN5A which results in hyperexcitability of the fascicular-Purkinje system. So far, only 3 SCN5A mutations have been associated with this MEPPC-like syndrome.
Purpose: We present a family with an identical clinical phenotype due to a novel SCN5A mutation.
Methods: A Dutch family with a MEPPC-like syndrome consisting of sinus, atrial and junctional beats competing with multifocal premature ventricular contractions (PVCs) and sudden death underwent cardiac and genetic evaluation.
Results: Genetic testing of several genes associated with arrhythmias revealed a heterozygous variant c.629T>G in the SCN5A gene. This results in substitution of a valine for a glycine at position 210 (p.V210G). This substitution is located in the S3 segment of domain I of Nav1.5. The affected amino acid is highly conserved across species. The variant was absent form the Genome Aggregation Database. In total, 6 of 17 family members demonstrated the same phenotype (Figure 1). Of these 6 patients, all had junctional rhythms, normal left ventricular function and QTc intervals and 5 patients experienced frequent multifocal PVCs, nonsustained ventricular tachycardias and atrial arrhythmias. One patient underwent ajmaline testing which did not demonstrate a type 1 Brugada pattern but was associated with a reduction of ventricular ectopy. The PVC burden in the affected patients varied from 0.3% to 9%. Sudden death was reported in 1 male (65 years old) and 2 females (55 and 73 years old) (Figure 1). Sanger sequencing showed complete co-segregation of the SCN5A mutation with the phenotype in this family.

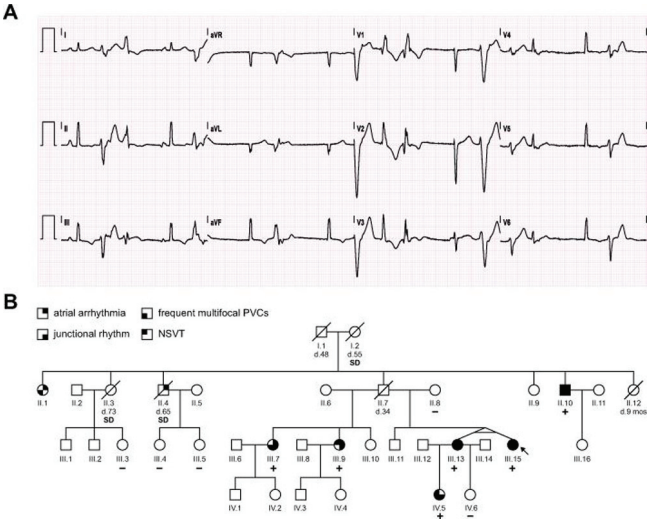

Figure 1

Conclusion: We present a family with a clinical phenotype similar to MEPPC caused by a novel SCN5A mutation.

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The importance of variant re-evaluation in massive parallel sequencing: results from hypertrophic cardiomyopathy genetic testing as an example

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Background: Although massively parallel sequencing (MPS) has allowed us to increase the number of disease-related genes we could analyse in a single genetic diagnostic test, it also conveys an increase of genetic variants of unknown significance (VUS), which are difficult to interpret. Since genetic tests are usually performed once in a lifetime of a patient, it is crucial to assure high quality tests and clinically meaningful results.
Purpose: Evaluate the impact of variant re-interpretation.
Methods: We have incorporated the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) recommendations for variant interpretation and re-evaluated 86 genetic variants variants after 1–2 years since their initial interpretation. Genetic variants were previously