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Subtopic: Cardiovascular Diseases

Novel phenotype-genotype correlations in an Emirati family with heterogeneous phenotypes of Brugada syndrome, long-QT syndrome and sudden cardiac death.

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Introduction

Brugada syndrome (BrS) is a rare inherited cardiac arrhythmia disorder, predisposing patients to sudden cardiac death (SCD), which is due to polymorphic ventricular tachyarrhythmia or ventricular fibrillation. Congenital long QT syndrome (LQTS) is another life-threatening cardiac arrhythmia characterised by prolongation of the QT interval on the ECG and resulting in an increased risk for *torsades de pointes* (TdP) which can trigger syncope, seizures and SCD. BrS and LQTS are typically inherited in an autosomal dominant manner.

Herein, we report the first case of a consanguineous family with heterogeneous phenotypic expression of LQTS, BrS and SCD, harbouring two rare missense mutations in the *KCNH2* gene.

Methods & Results

Genetic analysis by targeted next generation sequencing of a 24 year old female proband presenting with BrS in the setting of a rare manifestation of rapid atrial fibrillation and ventricular arrhythmia identified a missense rare heterozygous variant R791W in the *KCNH2* gene. Family history revealed SCD in a young sibling. Cascade screening of family members showed the father has compound heterozygous mutations R791W/H1153Y in the *KCNH2* gene, with 1 young male sibling having LQTS and carrying the R791W variant and 3 siblings being carriers of the H1153Y variant.

Conclusion

Current work identifies novel clinically-important genotype-phenotype correlations of two independent mutations in *KCNH2* associated with varied phenotypes of BrS and LQTS in the same family. This is the first example of a *KCNH2* mutation showing pleiotropic behaviour. The putative LQTS-causing R791W variant has not been described before to be associated with BrS.

The silent carriers of the H1153Y variant demonstrate normal resting QT interval but could be at risk for TdP and SCD and as QTc penetrance is variable in this family, regular follow-up is crucial. In LQTS, disease severity and response to therapy vary according to the specific genotype and position and type of the mutation in the protein. In the case of the youngest male sibling we observed a QTc shortening with Nadolol treatment, confirming the efficacy of β-blockers as a first line of therapy in patients with LQT2.

The clinical goal of identifying the genetic basis of these cardiac channelopathies is to personalise and optimize treatment approaches. This study highlights the clinical importance of early and comprehensive cascade testing in family members at a young age.
There are currently no clear clinical risk stratification techniques to guide therapy in asymptomatic family members, such that specific high-risk genotypes will inform invasive (ICD) and/or medical therapies to prevent sudden death.