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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Background and aims

Brugada syndrome (BrS) is a rare inherited cardiac disorder, which predisposes patients to ventricular tachyarrhythmias (VT) and sudden cardiac death (SCD). Long QT syndrome (LQTS) is another life-threatening cardiac arrhythmogenic syndrome predisposing patients to *torsades de pointes* (TdP) VT, syncope, and SCD. Both BrS and LQTS are predominantly inherited in an autosomal dominant manner. BrS and LQTS are caused by different mutations in the *SCN5A, KCQN1* and *KCNH2* genes and it is highly unusual for both LQTS and BrS phenotypes to coexist within one family. Herein, we report the first case of a consanguineous family with heterogeneous phenotypic expression of LQTS, BrS and SCD caused by the same *KCNH2* mutation.

Methods & Results

A 24 year old female proband presented with rapid atrial fibrillation and ventricular arrhythmia and was clinically diagnosed with BrS. Targeted next generation sequencing identified a missense rare heterozygous variant R791W in the *KCNH2* gene. A family history of SCD in a young sibling was reported. Cascade screening identified compound heterozygous variants R791W and H1153Y in the *KCNH2* gene in the father who has LQTS,

with one young male sibling having LQTS and carrying the R791W variant and three asymptomatic siblings being carriers of the H1153Y variant.

Conclusions

We identified novel clinically-important genotype-phenotype correlations of two rare *KCNH2* variants associated with varied phenotypes of BrS and LQTS. This is the first reported example of a *KCNH2* mutation showing pleiotropic behaviour. The putative LQTS-causing R791W variant has not previously been described in association with BrS.

The carriers of the H1153Y variant demonstrate normal resting QT intervals but could be at risk for TdP and SCD. Since the corrected QT 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.

This study highlights the importance of early genetic screening in families with inherited arrhythmias where SCD is the first manifestation. Genetic diagnosis may enable earlier identification and better-individualised preventive treatment in these cases than would be possible using traditional clinical screening.