Heterozygous Deletion of Valine at Position 2321 of RYR2 in Two Siblings with Sudden Cardiac Death

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BACKGROUND

Ryanodine receptor 2 (RYR2) is one of the major components of a calcium channel that supplies calcium to cardiac muscle cells and mediates sarcoplasmic release of stored calcium ions, thereby playing a key role in triggering cardiac muscle contraction. Defects in the *RYR2* gene may cause autosomal dominant ventricular arrhythmias, including catecholaminergic polymorphic ventricular tachycardia (CPVT; OMIM#604772) and ventricular arrhythmias due to cardiac ryanodine receptor calcium release deficiency syndrome (CRDS; OMIM#115000). Although the clinical penetrance greatly varies, affected individuals may present with recurrent cardiac arrhythmias, cardiac arrest, syncope, and seizures with a mortality rate of 30-50%. Generally, gain-of-function of the RYR2 calcium channel causes CPVT by spontaneous releases of calcium ions, whereas loss of function leads to CRDS through calcium alternans. Most patients affected with CPVT or CRDS have been described to have missense variants in the *RYR2* gene. The molecular mechanism of these missense variants in CPVT and CRDS is considered dominant-negative. Here we report two siblings with cardiac arrest who carried an in-frame deletion in *RYR2*.

CASE PRESENTATION

A 16-year-old male with normal growth and development presented with sudden cardiac arrest that occurred right after rock climbing in a gym. He was able to be resuscitated at an intensive care unit and was diagnosed with CPVT. The proband's younger brother had previously passed away at the age of 10 after serial events of status epilepticus. The family history is significant for heart palpitations, syncope, or myocardial infarction in multiple members on the maternal side. Blood samples were used for trio exome sequencing and chromosomal microarray analysis (CMA).

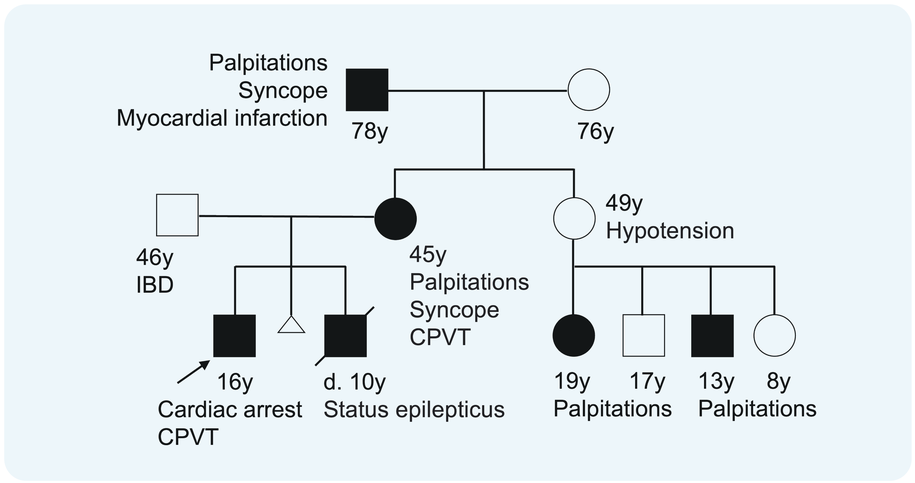

Figure 1. Pedigree and Family History. Filled circles and squares represent phenotypes potentially related to RYR2 disorders.

Trio exome sequencing identified a heterozygous variant in the *RYR2* gene of both proband and mother, c.6957_6959del (NM_001035.3) which results in an in-frame deletion of the amino acid valine at position 2321 (Figure 2). No other causative variants were identified in this trio exome analysis and concurrent CMA. This deletion has not been observed in gnomAD. Of note, a valine to methionine change of this residue has been reported in an individual with sudden cardiac death. Sanger sequencing for this *RYR2* variant in this family revealed that V2321del is carried by the mother who was also affected and the deceased younger brother. Other members of the maternal family were tested for this variant, and this appears to be de novo within the mother (Figure 3). V2321del is located in the helical domain of *RYR2* and among one (2246-2534) of the four mutation clusters associated with CPVT and CRDS (Figure 4).

Considering the proband's clinical features, family history, and the expected pathogenicity of this variant, the molecular result suggests that the loss of V2321 in RYR2 is explanatory for this patient's presentation.

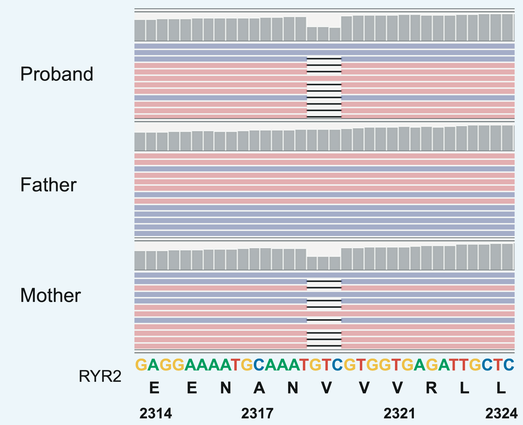

Figure 2. *RYR2*:c.6957_6959del (p.V2321del) in trio exome sequencing. The V2321del in RYR2 appeared in the proband and the mother.

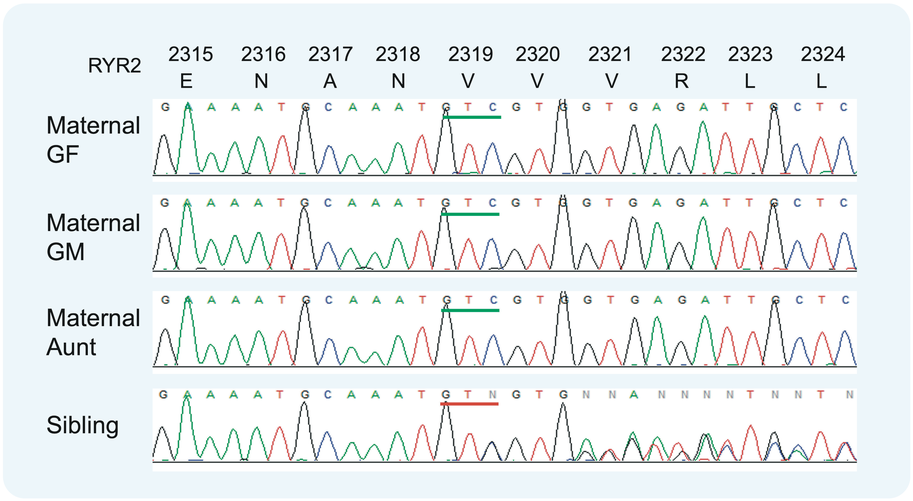

Figure 3. Known familial mutation (KFM) studies by Sanger sequencing. The deceased brother carried the V2321del mutation but not in the maternal grandfather, grandmother, and aunt, indicating that V2321del in the mother was de novo.

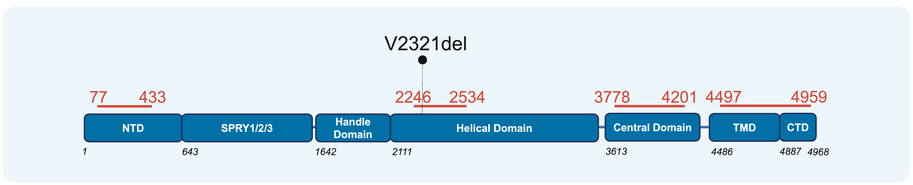

Figure 4. Four mutational hotspots of CPVT and CRDS in RYR2. V2321del is located in the hotspot of the helical domain.

CONCLUSIONS

This case report describes the events of sudden cardiac death in two siblings of a family, most likely due to an in-frame deletion resulting in a loss of an amino acid at position 2321. The pathogenicity of V2321del was able to be confirmed through family studies and review of functional domains in the RYR2 protein. A functional study may further define the underlying molecular mechanism.

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