

CACNA1C Exon 16 Variant in Patients with Polymorphic Ventricular Tachycardia

Amanda M Marshall, MD¹, John D Kugler, MD, LuAnn Mill, RN, Kris Houston, RN Lois Starr, MD, Christopher C Erickson, MD

¹*Children's Hospital and Medical Center, Omaha, NE*

Introduction:

Timothy Syndrome (TS) has been described in two forms, TS 1 and 2. Both are the result of a variant in the CACNA1C gene (exon 8/8A) and affected patients demonstrate prolongation of the QTc. Only TS1 is associated with extra-cardiac manifestations.

We describe two unrelated patients with normal extra-cardiac phenotypes, history of polymorphic ventricular tachycardia and the same exon 17 CACNA1C variant .

Methods:

Review of our internal patient database from our Genetic Arrhythmia Clinic identified two patients with the exact same variant on CACNA1C (c2314_2316delGAG). One patient (Patient 1) presented with sudden cardiac arrest but with normal QTc and the other (Patient 2) with syncope and QTc prolongation. Both patients had an ICD implanted and both have received appropriate shocks for polymorphic ventricular tachycardia.

Results:

Patient 1. Review of ECGs and exercise testing for Patient 1 showed normal QTc on resting ECG and no QT prolongation with exercise or during recovery. Family history of patient 1 is notable for a grandchild of the paternal grandfather's sister who had sudden death at age eleven and a son of Patient 1 who is genotypically positive but phenotypically negative with normal ECG.

Patent 2. Review of ECGs and exercise testing for Patient 2 demonstrated resting QTc of 492ms and prolongation of QTc to 504ms during recovery phase of exercise testing. In addition to her QTc prolongation, Patient 2 is also known to have very mild aortic stenosis secondary to a bicuspid aortic valve. Family history includes two biological sisters, one with baseline QTc of 490ms and abnormal T waves and one with baseline QTc of 502ms and abnormal T waves. Both sisters have declined commercial testing at this time and parents have refused any ECG or genetic testing.

Conclusion:

We describe two unrelated patients with documented sustained polymorphic ventricular tachycardia requiring ICD shock with the exact same variant on CACNA1C. In spite of the affected portion of the protein predicted to be in a domain without specific function and the variant resulting only in a deletion in one out of five glutamic acids, the presence of cardiac arrest in these two patients raises concern of the functional importance of this variant. Similarly we cannot explain why one patient has manifest QTc

prolongation and the other is completely normal. Based on these findings, functional testing of this variant is warranted.