Indiana-ACC Poster Competition Abstract

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Do **NOT** alter this form by deleting parts of it (including this text) or adding new boxes.
Please structure your clinical research abstract using the following headings: * Background * Objective * Methods * Results (if relevant) * Conclusion
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Title:

High Prevalence of RyR2 and CSQ2 Variants in Patients with Drug-Induced Long QT

Abstract: (Your abstract must use Normal style and must fit into the box. You may not alter the size of this)

Abstract

Objectives: To test the hypothesis that there is a genetic pre-disposition to Drug-induced long QT (diLQTS).

Introduction: Drug-induced QT prolongation (diLQT) can result in torsades de pointes due to early afterdepolarizations and abnormal intracellular calcium (Ca) handling. Rare variants of ion channel genes have been previously demonstrated but the role of Ca handling proteins is unclear.

Hypothesis: Patients with diLQT have increased burden of variances of Ca handling protein genes including type 2 ryanodine receptor (RYR2) and calsequestrin (CASQ2).

Methods: We searched 2,306,335 records in the Indiana Network for Patient Care electronic database between 01/01/2012 to 07/31/2013 for ECGs with QTc > 500 ms in patients who had received a QT prolonging drug. A manual review was performed to ascertain a normal baseline QTc and QTc prolongation within 7 days (antibiotics) or 60 days exposure (non-antibiotics). The selected patients were cross referenced with the Indiana Biobank for availability of specimens for genetic analyses.

Results: We identified 12 patients with diLQT [ondansetron (n= 6), citalopram (n=3), fluconazole (n=2), amiodarone (n=1), levofloxacin (n=1) and azithromycin (n=1) (2 patients received 2 drugs)]. Sequencing of the coding regions and splice sites flanking sequence of 246 genes associated with cardiovascular abnormalities was performed in these 12 DNA samples using a custom Next Generation Sequencing targeted enrichment approach.

Results: All 12 patients harbored rare or common variants with known functional effect on ion channel activity or previously associated with QTc prolongation in large population studies Genetic variants were identified in *KCNE1* (p.S38G in 9 patients), *SCN5A* (p.P2006A in 1; p.H558R in 3; p.S1103Y in 4), *KCNH2* (p.K897T in 3; p.R1047L in 1), *ANK2* (p.P2835S in 1), and in the Ca handling protein genes *RYR2* (p.G1886S in 3; p.Q2958R in 3) and *CASQ2* (p.H244R in 2; p.T66A in 7). Variants were also found in *TNNT2* (p.R285C in 1), TCAP (p.R106C in 1), LAMA4 (p.S109X in 1), *NEBL* (p.Y89X in 1) and *GATA5* (p.Q3R in 1). Three patients had 1 *RYR2* variant, three had 1 *RYR2* and 1 CASQ2 variant, two patients carried 1 CASQ2 variant and two had 2 *CASQ2* variants (10/12, or 83%).

Conclusion: The majority of patients with diLQT had one or more variants in RyR2 and CSQ2. Ca handling abnormalities may play an important role in the development of diLQT.

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