Evaluation of hERG-linked Short QT Syndrome (human ether-a-go-go related gene) functions of hERG, particularly their impact on cardiac arrhythmia.

Support from SADS UK is helping scientists and clinicians understand and combat a rare condition called short QT syndrome that is associated with an increased risk of sudden cardiac death. For the heart to pump blood round the body, electrical activity must spread through the heart's chambers in an orderly sequence. This depends on the coordinated opening and closing of proteins called 'ion channels' in heart muscle cells. Mutations to genes encoding ion channels have been found in individuals and families diagnosed with the short QT syndrome. A number of these mutations affect ion channels that carry potassium ions, causing them to pass too much potassium out of heart cells and consequently altering electrical excitability in ways that increase vulnerability to cardiac arrhythmias.

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Short QT syndrome has been proposed as an eligible disorder for the 100,000 genomes initiative. The aim in doing this is to enable the identification of novel genetic causes of the syndrome and thereby better understand causation and help treatments. If new gene associations with the syndrome can be found, this is likely both to increase understanding of mechanisms that regulate cardiac electrical activity and to feed into rational treatment strategies for this rare, but important heart condition.

Graham Stuart, lead cardiologist for the inherited cardiac conditions service in Bristol and Jules Hancox, Professor of Cardiac Electrophysiology at the University of Bristol have worked together to understand how particular gene mutations (called "I560T" and "S631A") lead to altered potassium channel activity in the heart in the short QT syndrome. Through laboratory studies of cells engineered to express these mutant ion channels, their research team has characterized the changes in function that lead to excessive potassium ion movement in these forms of short QT syndrome.

Patients who are identified to have short QT syndrome are often fitted with implantable defibrillators, which protect against potentially lethal cardiac events. Some patients may not be suitable for such electrical devices and the administration of appropriate antiarrhythmic drugs can help reduce the likelihood of patients who have devices needing defibrillation shocks. The Bristol team has demonstrated that for both of these mutations, an antiarrhythmic drug called quinidine reduces the excessive potassium ion movement that they produce. This indicates that quinidine may be an effective antiarrhythmic treatment in these forms of the short QT syndrome.

“We are immensely grateful for the support SADS UK has given us in conducting this work”, they said. “The hard work of SADS UK fund-raisers has helped us work towards identifying a potential therapeutic strategy for these particular forms of the short QT syndrome.”

The outcomes of these studies have now been published and are available with open access:

Butler A, Zhang Y, Stuart AG, Dempsey CE, Hancox JC (2018) Action potential clamp characterization of the S631A hERG mutation associated with short QT syndrome. Physiological Reports, 6(17) e13845. doi: 10.14814/phy2.13845.

https://physoc.onlinelibrary.wiley.com/doi/full/10.14814/phy2.13845

Butler A, Zhang Y, Stuart AG, Dempsey CE, Hancox JC (2018) Functional and pharmacological characterization of an S5 domain hERG mutation associated with short QT syndrome.

Heliyon, 5(4):e01429. doi: 10.1016/j.heliyon.2019.e01429.
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