

# 18<sup>th</sup> Annual Cardiologists Conference

June 19-21, 2017 Paris, France

## Genetic ventricular arrhythmia: Clinical presentation and disease modeling using iPSC-derived cardiomyocytes

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**Background & Aim:** Genetic cardiac arrhythmias are often severe, but due to their rare nature, no specific treatment exists. Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a severe arrhythmia caused by mutations in the *RyR2* gene. This gene is important in regulating Ca<sup>2+</sup> release from sarcoplasmic reticulum. The purpose of this study was to create induced pluripotent stem cells (iPSCs) from individuals having CPVT and to study the functional properties of the cardiomyocytes.

**Methodology:** iPSC lines were derived from six individuals carrying different *RyR2* gene mutations. Arrhythmias of cardiomyocytes were analyzed using Ca<sup>2+</sup> imaging.

**Findings:** Patients' heart rates were increased by stress exercise test and this induced in all of them polymorphic ventricular extra beats. When their cardiomyocytes were treated with adrenaline, similar irregular beating was observed. If the patients were treated with dantrolene, in some individuals all arrhythmias were abolished, but in some, it did not have any effect. As their cardiomyocytes were treated with the same drug, adrenaline-induced arrhythmias were abolished, but only from those cardiomyocytes derived from individuals who also clinically responded to the treatment. However, arrhythmias were not abolished from cardiomyocytes derived from the patients having no response to the medication.

**Conclusion & Significance:** With this drug, we could demonstrate that all individuals did not respond to this medication the same way even though their clinical phenotype was the same and they had mutations in the same gene. Importantly, iPSC-derived cardiomyocytes demonstrated the very same phenomenon: If the patient responded, also his cardiomyocytes responded, but if the drug did not remove arrhythmias from the patient, they were not abolished from his cardiomyocytes either. This study demonstrate that iPSC-derived cells reproduce the effect observed in the patients and they could be used to tailor medication especially in patients having severe, potentially lethal arrhythmias.

### Biography

Katriina Aalto-Setälä is the Professor of Physiology at School of Medicine, University of Tampere and a Cardiologist at Heart Hospital, Tampere University Hospital, Finland. She works as an invasive Cardiologist and is In-charge of the genetic cardiac outpatient clinic at Heart Hospital. Her research at University of Tampere focuses on Human Genetic Cardiac Diseases such as genetic arrhythmias and atherosclerosis with the help of induced pluripotent stem cell (iPSC) technology. The main aim of the research group is to learn more about the basic pathology of the genetic diseases as well as to test current and new pharmaceutical agents to correct the abnormalities. Her research group in collaboration with researches at Tampere Technical University has also invented new methods to monitor and analyze the maturity and functionality cardiomyocytes.

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