H184 Mutations of Plakophilin-2 (PKP2) in Sudden Unexplained Death (SUD)

Junyi Lin, Shanghai, CHINA; Bi Xiao, Shanghai, CHINA; Ziqin Zhao, MS, Shanghai, CHINA; Sisi Cheng, Shanghai, CHINA; Yiwen Shen, Shanghai, CHINA; Mingchang Zhang, Department of Forensic Medicine Fudan University, Shanghai 200032, CHINA*

Learning Overview: After attending this presentation, attendees will know PKP2 mutations may occur in cases of SUD, specifically in patients without evidence of fibrofatty change, and that PKP2 protein defect in itself is arrhythmogenic.

Impact on the Forensic Science Community: This presentation will impact the forensic science community by introducing attendees to the results of DNA sequencing of PKP2 extracted from postmortem heart tissues of 25 Western patients dying from SUD and 25 Chinese Han patients dying from SUD.

SUD remains a puzzle in forensic medicine. PKP2 has been linked to Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), which may cause life-threatening ventricular arrhythmias and sudden death. Fatal arrhythmias resulting in sudden death also occur in the absence of morphologic cardiac abnormalities at autopsy and have been linked to ion channel mutations in a subset of cases, but so far not to PKP2. This study sequenced all 14 exons of PKP2 in DNA extracted from the postmortem heart tissues of 25 Western patients and 25 Chinese Han patients dying from SUD. The primers were designed using the Primer Express 3.0 software. Direct sequencing for both sense and antisense strands was performed with a BigDye Terminator DNA sequencing kit on a 3130 xl Genetic Analyzer. Mutation damage prediction was made using Mutation Taster and Polyphen. In 6 of the 25 cases of Western SUD samples, 6 PKP2 mutations (p.F339S, P665S, p.P665S, p.Y217TfsX45, p.E540, and p.S615T) were identified, 3 of which were probably pathogenic according to Mutation Taster and Polyphen. In 2 of 25 cases of Chinese Han SUD samples, 2 PKP2 mutations (p.R691Q, p.L366P) were identified, 1 of which was probably pathogenic according to Mutation Taster and Polyphen .The present study also confirms that the PKP2 mutation (p.Y217TfsX45) which was found in a patient dying of SUD could reduce the expression of PKP2 and could also promote the autophagy to decrease the expression of Cx43.

Data collected in this study suggest a link between the PKP2 mutations and SUD cases in both Western and Chinese Han population. However, PKP2 mutations are more frequent in Western SUD cases than in Chinese Han population cases and have complications in that medical examiners who perform molecular genetic screening in cases of SUD need to be aware that PKP2 mutations may also be able to cause fatal arrhythmias even in patients with a morphological normal heart.

Plakophilin-2, Desmosomal Mutation, Sudden Unexplained Death