G34 Comprehensive Molecular Genetic Testing for the Cardiac Channelopathy Genes in 42 Cases of Sudden Infant Death and Sudden Unexplained Death in the City of New York Revealed High Mutation Rate

Yingying Tang, MD, PhD, Erik T. Bieschke, MS, Erin Labitzke, Jennifer D'Andrea, MSFS, Stacey Sainte-Marie, MSFS, Dawei Wang, Jean Jeudy, Yoonhee A. Kim, Stephanie Pack, Lucy En, Barbara A. Sampson, and Mechthild K. Prinz, PhD, Office of Chief Medical Examiner, Department of Forensic Biology, 421 East 26th Street, New York, NY 10016*

The goal of this presentation is to investigate the mutation rate of the channelopathy genes in the SIDS/SUDS population.

This presentation will impact the forensic science community by highlighting the importance of implementing molecular genetic testing for the channelopathy genes in routine SIDS/SUDS investigations to assist medical examiners in the determination of cause and manner of death.

Sudden infant death syndrome (SIDS)* and sudden unexplained death syndrome (SUDS)* are vexing challenges in the field of Forensic Pathology. SIDS and SUDS are recognized as complex and multifactorial, requiring interaction between genetic and acquired risk factors during sensitive developmental stages or growth phases. It has been reported that 2-5% of apparent SIDS/SUDS cases are in fact due to a group of cardiac arrhythmia syndromes, collectively called channelopathies, where at least eight causative genes are known. Since the channelopathies affect the cardiac electric conduction system and cause arrhythmias, the diseases leave no structurally demonstrable autopsy findings. Currently, the only available means to allow postmortem diagnosis of channelopathies is through the use of molecular genetic testing to detect mutations in the causative genes.

In order to investigate the mutation rate of the channelopathy genes in the SIDS/SUDS population, our laboratory has validated methodologies in genetic mutation analysis. Presented in this study is a comprehensive mutational analysis of multiple channelopathy genes: a cardiac sodium channel gene, *SCN5A*; three cardiac potassium channel genes, *KCNE1*, *KCNE2, and KCNQ1*; and a cardiac ryanodine receptor gene, *RyR2*. The study population consisted of 42 cases with the cause of death certified as "SIDS" or "undetermined" by the New York City Office of Chief Medical Examiner. The methods utilized were designed to be highly sensitive, specific, reproducible, cost-effective and high throughput. This was accomplished using DNA-based PCR and cycle sequencing analysis to detect any nucleotide changes in the protein coding region. Heart, liver and spleen samples were used.

In testing the *SCN5A* gene, five cases carried a known pathogenic missense mutation, S1103Y; one case carried a known pathogenic missense mutation L619F; two cases carried an unknown, but likely pathogenic missense mutation, P656L; and one case carried an unknown, but likely pathogenic missense mutation, I1837T. In testing the *KCNE 1&2* genes, we found that two cases carried two different known mutations, D85N (in *KCNE1*) and Q9E (in *KCNE2*). These two mutations previously have been shown to be associated with acquired Long QT syndrome. In testing the *RyR2* gene, the authors found that one case carried an unknown, but likely pathogenic missense mutation, G4471R. Genetic testing for *KCNQ1* gene is still in progress. All of the mutations identified in this study are heterozygous. Collectively, the pathogenic mutation rate is about 28% (12/42). Specifically, the mutation rate is most frequent in *SCN5A* gene 21% (9/42), while the mutation rates in other genes are less common.

This study highlights the importance of implementing molecular genetic testing for the channelopathy genes in routine SIDS/SUDS investigations to assist medical examiners in the determination of cause and manner of death.

* SIDS is defined as the sudden death of an infant under one year of age, which remains unexplained after a thorough investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history.

* SUDS is the sudden death of an individual over one year of age and like SIDS, the death remains unexplained after a thorough case investigation, which includes performance of a complete autopsy, examination of the death scene, and review of the clinical history.

Molecular Genetic Testing, Channelopathy, SIDS/SUDS

 ** Presenting Author*