H113 Detection of Genetic Variations in Cardiac Channelopathies Using Ion Torrent™ Next Generation Sequencing in a Cohort of Autopsy-Negative Sudden Unexplained Deaths

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After attending this presentation, attendees will better understand the considerable interest in next generation sequencing technology and the manner in which it performs a thorough genetic analysis of arrythmogenic disorders in postmortem investigations.

This presentation will impact the forensic science community by demonstrating the implementation of a new strategy using the Ion Torrent™ Personal Genome Machine® (PGM™) System that allows the simultaneous study of the major arrythmogenic genes in a quick and cost-efficient manner.

Background: Genetic testing for cardiac channelopathies in Sudden Unexplained Deaths (SUDs) has developed substantially over the last years. The Next-Generation Sequencing (NGS) technology provides an unprecedented opportunity to screen genetic variation underlying the arrythmogenic genes in a short period of time at low cost. The goal of this study is to develop a strategy of systematic postmortem mutation detection on the major genes implicated in cardiac channelopathies (long QT syndrome, short QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia) in order to identify the possible cause of death and to develop prevention measures for relatives.

Materials and Methods: NGS workflow based on an AmpliSeq™ panel was designed for sequencing 23 targeted genes on the Ion Torrent™ PGM™ Sequencer. The molecular analyses focused on 16 SUD cases of young people (under 35 years of age), autopsied at the Institute of Legal Medicine of Strasbourg over a period of five years. In all cases, the cause of death could not be determined after a rigorously autopsy associated with histopathological and toxicological analyses according to the guidelines of the Association for European Cardiovascular Pathology. DNA was extracted from fresh frozen tissue (heart and liver).

Results: An average of 150 variants were identified per sample; however, after the prioritization using a novel scoring program (VaRank), the number of putative variants, secondarily confirmed by sequencing, was reduced significantly. In a case of SUD that occurred during a psychiatric hospitalization, a heterozygous substitution on the *Ank2* gene, previously described as an ankyrin-B mutation associated with cardiac dysfunction, was successfully identified. Moreover, in a case of SUD that occurred during an attraction in an amusement park, a heterozygous substitution on the *Ryr2* gene, not previously described, was successfully identified, which might be damaging according to the bioinformatics prediction. Some interpretation problems encountered due to the multiplicity of identified variants were illustrated and the necessity to correlate the genetic results to the clinical data in order to identify the possible cause of death was highlighted.

Conclusion: This study illustrates that the NGS approach based on AmpliSeq™ libraries and Ion Torrent™ PGM™ sequencing may be an efficient approach integrated to the postmortem examination.

Next Generation Sequencing, Ion Torrent™, Sudden Cardiac Death