H142 Genetic Investigation of Sudden Cardiac Death: The State of the Art in Italy

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After attending this presentation, attendees will understand of the protocols used in forensic practice (genetics and pathology fields).

This presentation will impact the forensic science community by providing a full panoramic view of the state-of-the-art in the forensic investigation of Sudden Cardiac Death (SCD) in order to reach the best practice when being presented with these cases in routine workflow, especially regarding genetic analysis. This presentation will also impact the forensic science community by defining the key role played by the forensic pathologist, especially regarding the available options (i.e., genetics, proteomics) in the research and diagnostic procedures of sudden death cases

Background: Forensic medicine defines unexplained sudden death as a death with a non-conclusive diagnosis after autopsy. Molecular diagnosis is progressively being incorporated in forensics, mainly due to improvements in genetics. New genetic technologies may help to identify the genetic cause of death, even though the clinical interpretation of genetic data remains the current challenge. The identification of an inheritable defect responsible for arrhythmogenic syndromes could help to adopt preventive measures in family members, many of them asymptomatic but at risk of sudden death. This multidisciplinary translational research requires a specialized team. In this presentation, the state-of-the-art of the forensic approach to sudden death will be addressed. Two families with a recurrence of sudden death events investigated by molecular analysis will be presented to discuss current possibilities and limitations.

Material and Methods: Direct sequencing of the major contributing candidate genes in two families, originally diagnosed with Brugada syndrome after the probands experienced cardiac arrest and clinical and genetic analysis in their members, was performed. Pathogenicity of the variants was analyzed using family segregation, allele frequency from public databases, and conservation analysis. Phenotype-genotype correlations were analyzed statistically. Direct sequencing identified two different mutations in the SCN5A gene respectively designated E1784K — missense mutation causing the substitution of Glu by Lys — and an insertion of nucleotides TG in domain II (TGins851).

Conclusions: These results support the use of genetic testing as part of the diagnosis of SCD syndromes and to help in identifying relatives at risk of SCD; however, the identification of genetic variations in the clinical and forensic investigation of single patients using bioinformatic tools can produce erroneous conclusions regarding pathogenicity. In fact, distinguishing pathogenic mutations from rare variants is of critical importance in the interpretation of genetic testing. Therefore, segregation studies are the key to determining causality. Mutation type, mutation location, and ethnic-specificity should be viewed as variants of uncertain significance and prompt further investigation to clarify the likelihood of disease causation; however, mutations in regions such as the transmembrane, linker, and pore areas may be defined confidently as high-probability disease-causing mutations. These findings may have crucial implications for other genetic disorders involving mutational analysis, especially in postmortem setting.

Sudden Cardiac Death, Autopsy, Genetics