H132 Molecular Testing in Sudden Death Associated With Epilepsy in a Forensic Office: Genotype-Phenotype

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Learning Overview: The goal of this presentation is for attendees to understand the role of molecular testing in epilepsy death investigations.

Impact on the Forensic Science Community: This presentation will impact the forensic science community by increasing the understanding of the value of molecular testing in determining cause and manner of death.

Epilepsy increases the risk of sudden death and presents significant challenges for the certifying medical examiners. Molecular genetic methods in conjunction with standard Neuropathologic (NP) evaluation in a cohort of 65 non-traumatic, non-alcohol-related seizure cases were undertaken. These were selected over a four-year period from among those with "Epilepsy" or "Seizure" on the death certificate, and/or submitted for NP evaluation; subjects were aged 2 weeks to 47 years (median, 22.6 years), and there were 37 males, 27 females, and 1 transgender female. Molecular analysis of a panel of 132 genes, associated with dominant epilepsy syndromes or neurodevelopmental disorders with epilepsy, was performed. NP features under analysis comprised End-Folium Sclerosis ([EFS]; neuronal loss and gliosis, CA4), Mesial Temporal Sclerosis ([MTS]; neuronal loss and gliosis, CA4 and CA1/CA3), hippocampal dysgenesis (macroscopic asymmetry and Dentate Gyrus [DG] abnormalities), and cerebral dysgenesis (e.g., abnormal cortical gyration, callosal agenesis, heterotopia, hamartia).

Pathogenic or likely pathogenic variants were found in three (4.6%): (1) a frameshift variant in CACNA1H, with MTS; (2) a nonsense variant in SCN1A (Dravet Syndrome), with EFS and subarachnoid heterotopia; and (3) a splice-site missense variant in SCN2A, with EFS. Twenty-two (33.8%) had Variants of Uncertain Significance (VUS): two had cerebral dysgenesis (GRIN2B; GLI2, GLRA1, KMt2D in a decedent with trisomy 21); and ten had EFS, with or without other NP (CDKL5, CHD2, SCN9A, GFAP, LGI1, GLI2, FLNA, HCN1, SPTAN1, NSD1, FLNA, HCN1, CRYAB P AR variant carrier, DSC2). One carrier of a TBCD loss-of-function variant had EFS, focal cortical dysplasia IIIA, and cerebellar polymicrogyria. Four with VUSs had no NP findings. The remaining 40 subjects (61.5%) tested negative, among them three with hippocampal dysgenesis, one with Doose syndrome and DG bilamination, and one with Lennox-Gastaut syndrome and cerebral dysgenesis.

In summary, this preliminary cohort of non-traumatic epilepsy deaths with molecular testing identifies mutations that contribute etiologically specific information impacting both death certification as well as potential care of surviving family members.

Epilepsy, Sudden Death, Molecular Testing

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