Postmortem Genetic Testing: Contributions to Revealing Cause of Death and Familial Cascade Testing

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Postmortem genetic testing, often called the "molecular autopsy" can identify cause of death in individuals who die suddenly and unexpectedly. Genetic testing can also lead to cascade testing of family members, which can determine who in a family needs preventative screening and/or management, and ultimately save lives. We have analyzed DNA samples from 64 postmortem cases between August 2012 and October 2016 with multigene panel testing using Next Generation Sequencing and targeted chromosomal microarray at our diagnostic laboratory. Clinical history was taken from test order forms, pedigrees, and clinic notes. Other than sudden cardiac arrest, which was present in 95% of cases (36/38 cases in which this was indicated on the test order form), a personal clinical history of cardiomyopathy, arrhythmia, or both cardiomyopathy and arrhythmia was the most common indication for testing; approximately 30% of probands had cardiomyopathy, 15% had arrhythmia, and 33% had both cardiomyopathy and arrhythmia. Of the 64 postmortem samples that were tested, 23% had a positive result, which includes likely pathogenic variants and pathogenic mutations, 44% had a variant of uncertain significance (VUS) result, and 33% were found to be negative. Forty-five family members from 11 families pursued cascade testing for likely pathogenic or pathogenic mutation(s) found in the proband. Single-site analyses were performed, and in 32% of family members tested, at least one likely pathogenic or pathogenic mutation was detected. In 68% of family members tested, the familial variant(s) was not detected; risk for these individuals to develop cardiac disease is no different than that of the general population, and therefore they do not need to undergo additional cardiac screening. Limitations to this retrospective study include lack of clinical history provided on the test order form, pedigree or clinic note, as well as limited information regarding which families may have pursued single-site testing at an outside laboratory. Our data show that postmortem genetic testing can be helpful in determining a genetic cause of sudden cardiac death, as well as provide valuable information to family members regarding screening and risk management.