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

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BACKGROUND

- Postmortem genetic testing can help identify cause of death in individuals who die suddenly and unexpectedly[1].
- Genetic testing can lead to cascade testing of family members, which can determine who in a family needs preventative clinical screening and/or management, and ultimately save lives.

RESULTS

- Figure 1. Distribution of cardiomyopathy and arrhythmia reported in postmortem probands.
- Figure 2. Of the 64 postmortem samples that were tested, 23% had a positive result (includes VLPs and pathogenic mutations), 44% had a variant of uncertain significance (VUS) result, and 33% had a negative result.
- Mutations or VLPs were discovered in 12 different genes with *KCNH2, TTN,* and *PKP2* being the most prevalent.
- Age of death of probands with a positive result was 17-70 years, and the average age of death was 33 years.
- Figure 3. Familial cascade genetic testing results. Relatives of 11 out of 15 positive postmortem probands pursued SSA testing.

REFERENCES

1. Lahrouchi, N., Raju, H., Lodder, E.M. et al. Utility of Post-Mortem Genetic Testing in Cases of Sudden Arrhythmic Death Syndrome. *JACC.* 2017; 69(17): 2134-2155.
2. Wijeyeratne, Y.D. and Behr, E.R. Sudden death and cardiac arrest without phenotype: the utility of genetic testing. *Trends in Card Med.* 2017; 27:207-213.

DISCLOSURE

All authors are employed by Ambry Genetics Corporation.

Figure 1. Reported Clinical History for Probands

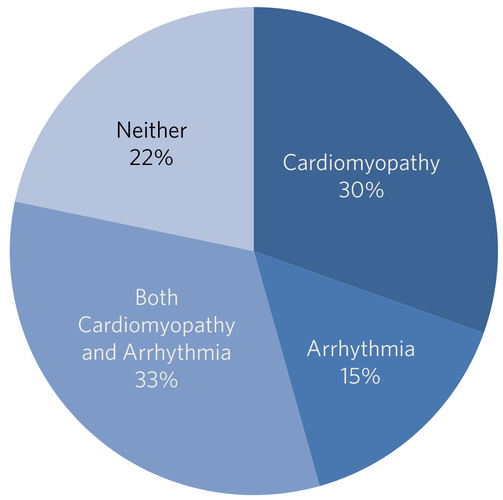


Figure 2. Genetic Test Results for Probands

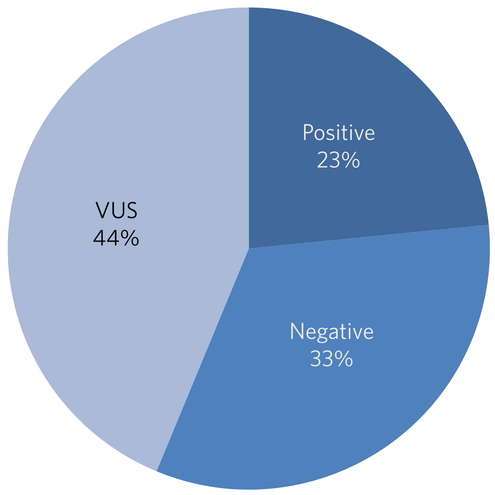
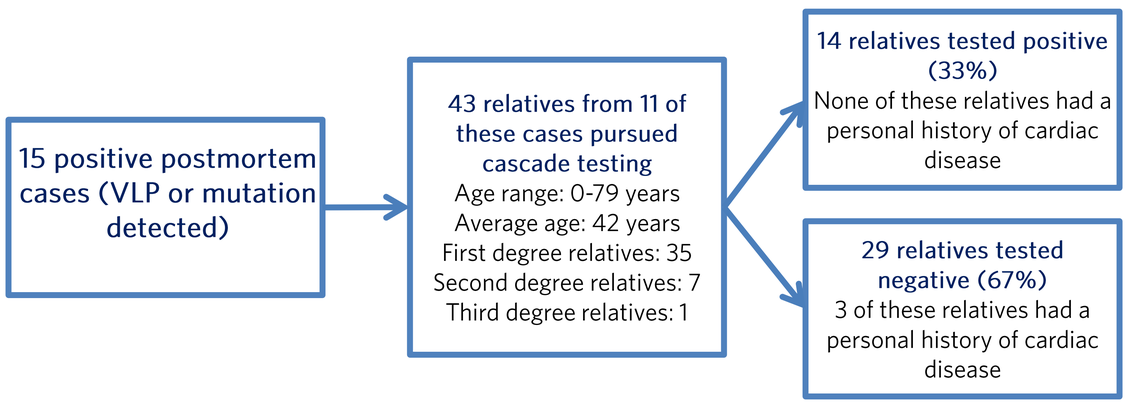


Figure 3. Cascade Testing Outcomes



METHODS

- We analyzed DNA samples from 64 postmortem cases between August 2012 and October 2016 with multigene panel testing using Next Generation Sequencing (NGS) and targeted chromosomal microarray (CMA) at our diagnostic laboratory.
- Clinical history was taken from test order forms, pedigrees, and submitted clinic notes.
- We assessed the distribution of phenotypes among these postmortem cases and correlation with positive results.
- 43 family members pursued cascade testing via single-site analysis (SSA) testing at our laboratory.
- We assessed the uptake of familial cascade testing and patterns of which family members pursued testing.

TAKE-HOME POINTS

- Postmortem genetic testing can be helpful in determining a genetic cause of sudden cardiac death. Our data shows a slightly higher yield than previous studies which report a 13-20% positive rate.[1,2]
- Mutations were most prevalent in the genes *KCNH2, TTN,* and *PKP2.*
- First degree relatives are more likely to undergo cascade testing (81%) than second degree or third degree relatives.
- Multiple asymptomatic relatives were identified who may be at risk for sudden cardiac death due to their genetic mutation status, illustrating the potential life-saving benefits of genetic testing in this population.

LIMITATIONS

- A comprehensive clinical history and clinical testing results were not provided for all patients studied.
- This study did not account for any familial cascade genetic testing that may have been done at other laboratories.