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Diagnostic exome sequencing for patients with a family history of consanguinity: over 40% of positive results do not follow an autosomal recessive pattern

Zöe Powis[1], Kelly Gonzalez[1], Cameron Mroske[1], Layla Shahmirzadi[1], Dima El-Khechen[1], Christina Alamillo, Ruth Baxter[1], Bridgette Tippin[1], Elizabeth C. Chao[1,2], Sha Tang[1]

1. Ambry Genetics, Aliso Viejo, CA, 92656
2. Department of Pediatrics, University of California, Irvine, Irvine, CA 92697

Diagnostic exome sequencing (DES) is an effective tool for diagnosis in intractable cases where the underlying cause is thought be genetic. Recent journals have numerous case reports of individuals with consanguineous family histories identified in whom with rare genetic conditions by DES. It is commonly assumed that patients with a family history of consanguinity will have increased detection rates for rare autosomal recessive disorders through DES. Herein, we report the results from the patients referred to Ambry Genetics (Aliso Viejo CA) for DES with a reported consanguineous family history.

Of the first 500 unselected cases referred for DES, 41 (8.2%) had a known consanguineous family history. The degree of consanguinity varied from uncle and niece (F=1/8), first cousins (F=1/16), multiple loops of consanguinity, to "distant consanguinity." The degree of consanguinity in these families did not increase the likelihood of a positive exome result.

Amongst patients with known consanguinity, 14 (34.2%) had a positive result in a characterized gene, 5 (12.2%) had an uncertain result, 3 (7.3%) had a novel result and 19 (46.3%) had a negative result. These results are not statistically significantly different from the overall breakdown of all patients for DES analysis. Of the positive results, 8 had homozygous mutations (*ACAT1, ALS2, NEB, PDE6B, SPAST, TCIRG1, TMEM231, UBE3B*) and 6 (43%) had a molecular etiology unrelated to consanguinity. Four had alterations in autosomal dominant genes (*VPS35, MPZ, CHD7, TRPS1*) and two in X-linked genes (*ARHGEF9* and *SHROOM*). Four of the mutations (*CHD7, MPZ, ARHGEF9, TRPS1*) arose *de novo*. All the alterations found in novel genes are inherited in an autosomal recessive fashion (*DGK2, ZNF302, SV2A*). Although it was believed that individuals with known consanguinity would be more likely to have a positive result within an autosomal recessive gene, this did not prove to be the case. In summary, these results highlight that all inheritance patterns should be considered when testing patients with a known family history of consanguinity.