Proband-only Diagnostic Exome Sequencing: Trends in Diagnostic Yield at One Commercial Company

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Background

Use of family trios, typically comprised of the proband and parents, for diagnostic exome sequencing (DES) has been shown to increase diagnostic yield compared to proband-only DES (Lee, 2014; Farwell, 2015). Trio analysis can optimize variant annotation by determining phase of variants within the same gene or identifying *de novo* alterations. However, family members may not be available for testing, especially in the cases of adoption or adult patients whose parents may be deceased.

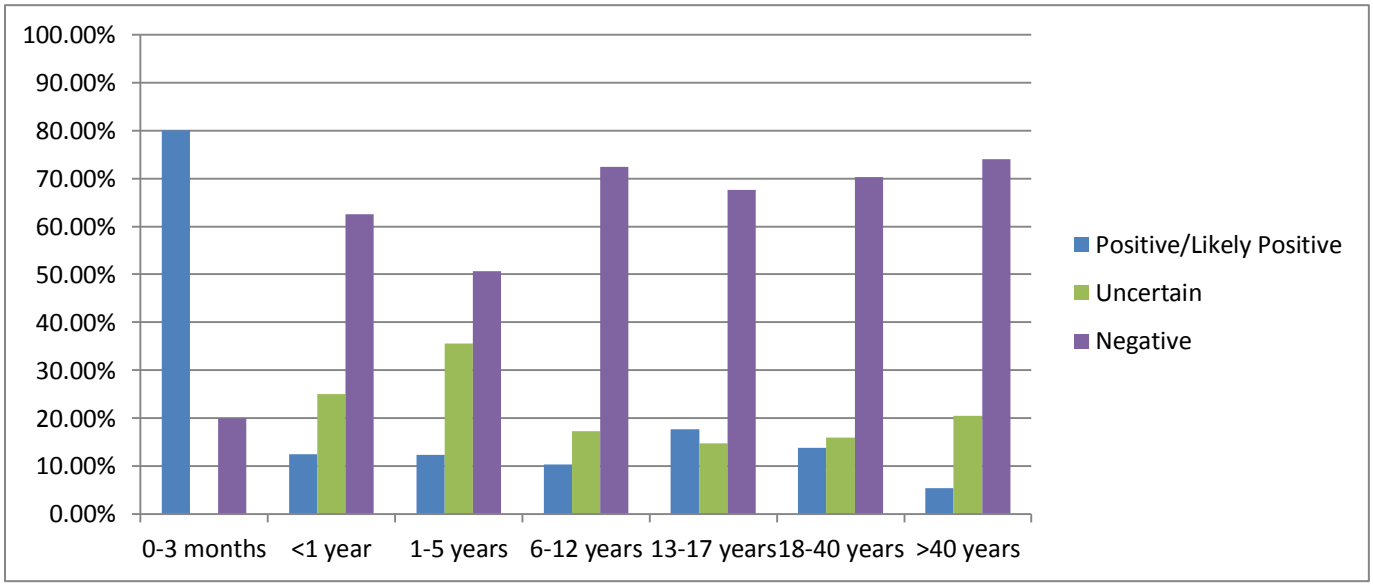
Methods

Proband-only DES ordered through a commercial lab was assessed for trends in diagnostic yield based on age at testing, age of disease onset, and clinical features. Diagnostic yield was defined as resulting in a positive or likely positive report. Trends involving uncertain reports due to unclear clinical overlap, inconsistent zygosity, and/or an identified variant of unknown significance (VUS) were also included in analysis.

Results

In total, 374 proband-only DES cases (with no other family members available for co-segregation analysis) were tested at Ambry Genetics over a 2 year period. A positive or likely positive result was identified in 12.6% of proband-only cases, which is nearly half the diagnostic rate of parent-proband trio DES tested (23.7%). Uncertain results were issued in 20.9% of cases (78/374), higher than the 10.9% reported in parent-proband trios. The neonate age group (0-3 months) had the highest diagnostic yield of 80.0% (4/5), and the diagnostic yield was lowest among individuals over 40 (5.48%; 4/73). The rate of uncertain results was fairly consistent across age groups (Figure 1). Adults with childhood-onset disease had a two-fold higher diagnostic yield compared to those with an adult-onset component of their disorder (14.9% vs. 7.0%). Adults over the age of 40 with adult-onset features had decreased diagnostic yields compared to younger adults with adult-onset features, or adults of any age with childhood onset of disease. Despite lower diagnostic yield, there was a greater level of confidence for clinical overlap in adults compared to pediatric cases. For both groups, an uncertain report was more likely due to a VUS than an unclear phenotypic overlap. Approximately half of adults who received an uncertain report had unclear clinical overlap (52.9%), while a greater percentage of pediatric cases (72.6%) had an uncertain phenotypic overlap. Individuals with progressive phenotypes had the same rate of positive, uncertain and negative reports issued, regardless of age. Half of all patients reported developmental delay or intellectual disability (52.7%; 197/374). Seizures (30.7% 115/374), abnormal brain MRI (28.6%; 107/374), and dysmorphic features (22.2%; 183/374) were other common disease categories, which are also the most common clinical indications for samples received for DES testing as a whole (Farwell, 2015). For both adults and pediatric cases, neurological, musculoskeletal and ophthalmological systems involvements were the most common in both groups. Cases with multiple congenital anomalies had the highest diagnostic rate (26.9%), while individuals with psychiatric disorders had the lowest (4.2%).

Figure 1: Report type by age



Discussion

Neonates had higher diagnostic yield compared to other age groups, suggesting that severe phenotypes presenting early in life are more likely to be diagnosable by DES, even in the absence of familial samples. However, in older adults, the diagnostic rate is much lower compared to other proband-only cases suggesting that these later-onset disorders may be multifactorial or due to a genetic alteration(s) not detectable by DES. Given that clinical overlap is a major factor in determining the significance of a variant and that certain phenotypes may present or progress as an individual ages, the clinical overlap of a disorder in an adult patient may be easier to identify. Overall, proband-only DES has lower diagnostic yield compared to DES performed on trios; however in the absence of available family members, proband-only DES is a useful diagnostic tool.

References

Farwell KD, et al. (2015) Genet Med 17(7):578-86. PMID:25356970
Lee H, et al. (2014) JAMA 312(18):1880-7. PMID:25326637

3 Talking points

The diagnostic yield of proband-only diagnostic exome sequencing (DES) is nearly half that of DES performed on trios; however in the absence of available family members, proband-only DES is a useful diagnostic tool.

Pediatric cases submitted for proband-only DES had a higher overall diagnostic rate, but adult cases tended to have a higher level of certainty for clinical overlap.

Neonates had the highest diagnostic yield (80.0%; 4/5), and adults over the age of 40 had the lowest (5.48%; 4/73).