Diagnostic exome sequencing is successful in providing diagnoses among patients with intellectual disability and developmental delay: strong family history correlates with an increased novel genetic etiology detection rate

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OBJECTIVE:

To summarize DES (diagnostic exome sequencing) findings in individuals with intellectual disability and/or developmental delay (ID/DD).

BACKGROUND:

As part of a comprehensive evaluation for individuals with ID, the AAN, ACMG, and AAP recommend genetic testing. Due to genetic heterogeneity in ID, first-tier genetic tests are often uninformative. Since 2011, DES has become an effective diagnostic tool in cases with unknown etiologies.

DESIGN/METHODS:

Retrospective analysis was performed on the first unselected 1200 samples submitted for DES at our laboratory. Analysis scheme and results categories were previously described (Farwell, 2014).

RESULTS:

67% of patients (806/1200) had syndromic ID/DD. Diagnostic yield in individuals with ID/DD was 30% in characterized genes (243/806) and 7% in novel genes (52/806), compared to 23% (91/394) and 4% (14/394), respectively, in individuals without ID/DD (chi square p-value = 6e-4). Uncertain findings in characterized genes and negative results were reported in 79 (10%) and 432 (54%) individuals with ID/DD, respectively, compared to 36 (9%) and 253 (64.2%) individuals without ID/DD. Among individuals with ID/DD, positive/likely positive findings were identified in 24.5% (13/53), 28.5% (40/141), and 31% (189/601) of individuals with strong (≥1 relative with similar phenotype), mild (≥1 relative with ID/DD), and no family history, respectively. Novel genetic etiology detection in individuals with ID/DD and strong family histories (7/53, 13%) was more than double that in those with mild family history (3%) (p-value =1.0e-2) and absent/unknown family history (7%) (p-value=9e-2)]. The de novo rate among individuals with positive findings and strong family histories was 2%, as the majority (52/53) were inherited in an autosomal recessive or X-linked fashion.

CONCLUSIONS:

These data highlight the utility of DES in providing a molecular diagnosis given the heterogeneity of ID/DD and demonstrate that strong family history of ID/DD is a positive predictor of informative DES results and increased novel genetic etiology detection.