TITLE: Diagnostic Yield of Exome Sequencing in Adults with Rare Disease: An Eight-Year Retrospective Study

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INTRODUCTION

The high diagnostic yield and positive medical management impact of exome sequencing (ES) has been well-characterized in pediatric individuals with rare disease. From this data, recommendations on when to pursue ES as a first-tier test have been developed and influence the accessibility of ES. However, the clinical utility of ES in an adult population with rare disease remains poorly defined. Prior studies of ES in adults have shown a wide range of diagnostic rates, but these findings have limited generalizability due to small study populations, narrow phenotypic scope, and/or specialized inclusion criteria or analysis methods. Characterization of the phenotypes of adults undergoing ES, reported results, and factors impacting diagnostic yield are crucial for identifying adult populations most likely to benefit from ES and informing testing recommendations.

METHODS

We performed a retrospective review of adults (age ≥18y) who underwent clinical ES over an eight-year period at one commercial laboratory. Demographics including age, reported sex at birth, reported race/ancestry, and indication for testing were described and the outcomes of ES were assessed. We also grouped ES by familial configuration status (parental trio, non-parental trio, duo, or proband-only). A logistic regression was used to assess the impact of demographic factors and familial configuration on the likelihood of receiving a diagnosis.

RESULTS

In total, 2,098 adult probands were included in the analysis. The average age of probands was 35y (range of 18-88y). Proband-only exome was most common (44%), followed by parental trio (40%), duo (9%), and non-parental trio (7%).

The overall diagnostic yield was 15.7%. Uncertain results, including suspicious variants in candidate genes, were returned to an additional 16.0%. Of the 97.4% who elected secondary finding analysis, 2.6% received a positive result. Of diagnostic results with known inheritance, a majority were de novo (33%; 110/329).

Diagnostic yield varied greatly by indication for testing (range 6.1-42.9%). The most common indications were neurodevelopmental (13.3%), neuromuscular (11.5%), connective tissue (11.9%), metabolic (5.6%), and seizures (4.7%). Diagnostic yield was highest for the following indications: undergrowth/failure to thrive (42.9%; 6/8), intellectual disability (32.9%; 25/76), neurodevelopmental (31.2%; 87/279), overgrowth (28.6%; 2/7), and multiple congenital anomalies (25.6%; 20/78). Many indications for testing were significantly less likely to receive a diagnosis

compared to an indication of intellectual disability including: immune, connective tissue, neuromuscular, cardiovascular, structural brain anomaly, neuropathy, endocrine, and non-ataxic movement disorder.

Having parental trio analysis significantly increased the diagnostic yield to 21.8% (182/834;$p<0.05$). Neither age, sex, nor race was significant for predicting the likelihood of a diagnostic result.

CONCLUSIONS

This study provides insight into which factors impact diagnostic yield of ES in an adult rare disease cohort. The value of parental samples for trio analysis is significant; however, parental trios made up only 44% of adult ES cases compared to 74% of pediatric ES cases tested at the same lab during the same time period. Additionally, we found that two of the most frequent indications for testing (neuromuscular and connective tissue) were significantly less likely to receive a diagnosis. The combination of reduced parental availability in an adult cohort and proportion of testing for low-yield indications likely contribute to the overall diagnostic yield of 15.7%. Given the wide range of diagnostic yield by indication, a focus on indication-based guidelines for exome as a first tier-test should be explored to increase access to ES in adults who can benefit from testing.