Analysis of Differences in Detection Rates Between Parent-Proband Trios and Non-Parent Trios in Diagnostic Exome Sequencing

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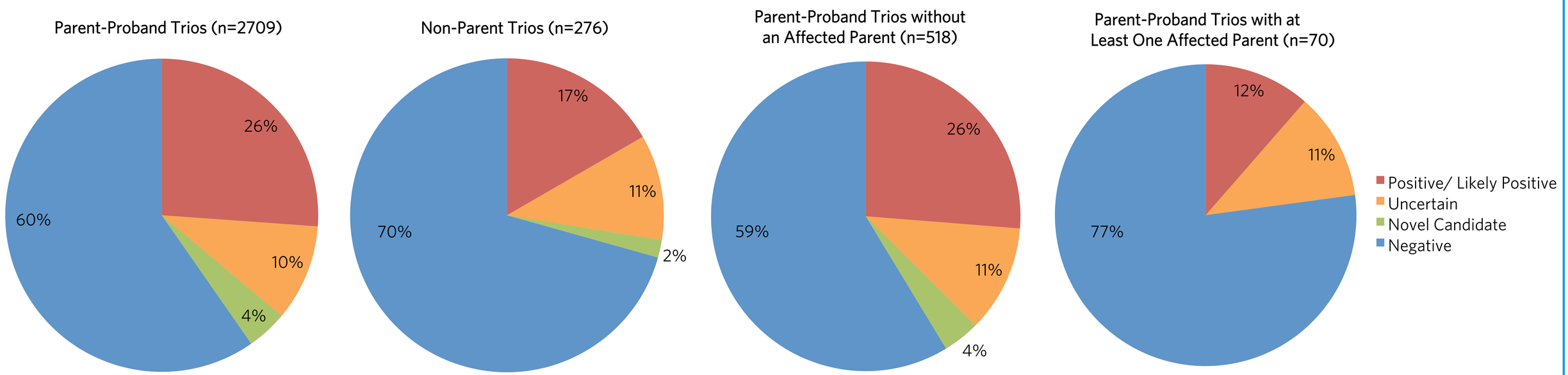
BACKGROUND

- Diagnostic Exome Sequencing (DES) is a powerful diagnostic tool for patients with undiagnosed genetic disease
- Previous study has shown that the sequencing of two additional family members to create a trio leads to an increased detection rate in patients (Farwell, 2014).
- Sequencing the exomes of the parents and the proband in parallel provides a useful tool by showing the parental origin of inherited alterations and prioritizing *de novo* alterations.

METHODS

- Retrospective analysis of the first 2985 consecutive DES cases with at least three people sequenced . Cases were split into two categories: non-parent trios (cases with three or more individuals sequenced, but which did not include both parents) and parent-proband trios.
  - Sequencing and analysis were performed as previously described (Farwell, 2014).
- For each case the overall category of the report was noted. Results could fall into a number of categories.
  - Positive or Likely positive which indicate a likely cause was identified which is associated with a previously characterized genetic etiology.
  - Uncertain which indicates a possible cause has been identified which is associated with a previously characterized genetic etiology.
  - Candidate or Suspected candidate which indicate a possible cause was identified with an uncharacterized genetic etiology.
  - Negative which indicated that no possible causes were identified in our analysis.
- Fisher exact tests were used to see if there was a significant difference in the likelihood to receive different results between non-parent-trios and parent-proband. trios.
- Additional data on parental affected status was available for a subset (n=588) of parent-proband trio cases which allowed for Fisher exact tests comparing cases with at least one parent affected with those without an affected parent.

EXOME RESULTS BY TEST CATAGORIES FOR DIFFERENT TYPES OF TRIOS



RESULTS

- Parent-proband trio cases (708/2709; 26.1%) were significantly more likely than non-parent trio cases (46/276; 16.7%) to have a positive/likely positive result (p = .0005).
- Among cases that received analysis for uncharacterized genetic etiologies, parent-proband trio cases (114/1839; 6.2%) were significantly more likely than non-parent trio cases (5/197; 2.55%) to receive a novel candidate (p = .037).
- Additionally among the parent-proband trio cases, cases without an affected parent (136/518; 26.3%) were significantly more likely than those with at least one affected parent (8/70;11.4%) to receive a positive/likely positive result (p = .007).
- A small number of cases (n=28) had four or more people sequenced of this group there were 2 likely positives, 1 uncertain, and 25 negatives.
- Overall, use of a parent-proband trio is more likely to find a reportable result for both characterized and uncharacterized genetic etiologies.

TAKE-HOME POINTS

- The increased utility of the parent-proband trio for variant evaluation gives a higher chance of yielding a reportable finding than other trios
- While it is generally helpful to send in as many relevant family members as possible, when providing counseling to families where obtaining a parent-proband trio may be difficult, the potential benefits of the parent-proband trio should be carefully considered before choosing to proceed with an alternative trio.

REFERENCES

1. Farwell KD, Shahmirzadi L, El-Khechen D, *et al.* Enhanced utility of family-centered diagnostic exome sequencing with inheritance model-based analysis, results from 500 unselected families with undiagnosed genetic condtions. *Genetics in medicine: offical journal of the American College of Medical Genetics*. Jul 2015;17(7): 578-586.

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