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Experience Using A Combination Of Variant Prioritization Tools In A Large Rare Disease Cohort

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Background

The biggest challenge in genomic studies lies in data interpretation. With this in mind, GA4K is employing an advanced set of genomic tools to uncover a greater number of candidate variants in rare disease patients. These tools include novel sequencing technologies to test beyond the exome as well as machine-learning analysis methods as presented here.

About GA4K

The Genomic Answers for Kids study is led by Dr. Tomi Pastinen and funded by the Children's Mercy Research Institute. Our study aims to find diagnoses for children who have undergone a lengthy diagnostic odyssey with non-diagnostic clinical testing, as well as to better understand genetic disease as a whole. We are a multidisciplinary team of geneticists, bioinformaticians, genetic counselors, laboratory technicians, molecular biologists, and research coordinators. For more information you can contact us at **GA4K@cmh.edu**

Methods & Results

We combined two publicly available tools to aid with variant prioritization: **Exomiser** and **AMELIE**. Both tools (E/A) rely on structured phenotyping (with HPO terms) but apply algorithms that explore different features of the variants/genes. Therefore, we hypothesized that combining them would improve speed and accuracy of our analysis of genomic data.

Manual review of the combined top 50 ranked E/A candidate variants for each proband was carried out for the first 1000 cases.

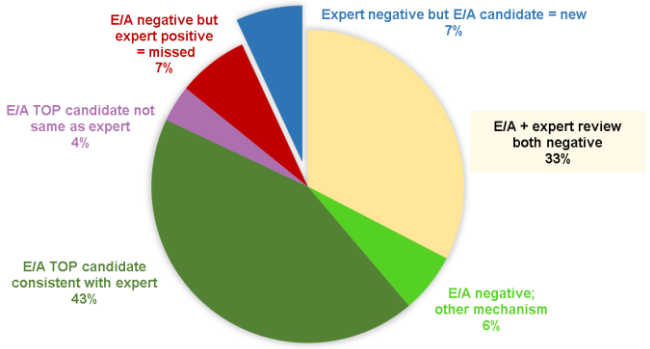

Figure 1 – Consistency between candidate variants ranked by E/A and full expert analysis of the first 1000 GA4K rare disease cases.
Only 7% of conclusive candidates found by expert analysis were not ranked by E/A. In 6% of cases, the mechanism of disease could not have been ranked (including: exonic deletions, copy number changes, variants that are too frequent and filtered out). New candidates were prioritized in 7% cases and are being further investigated; these include both known and novel genes. "E/A + expert review both negative" samples are prioritized for further testing with long-read sequencing, whole genome bisulphite sequencing and single cell analysis.

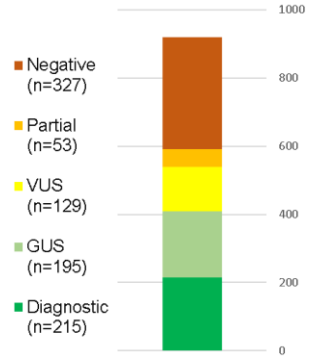

Figure 2 – Diagnostic rates from combined E/A and expert review.
To date, 919 of 1000 cases have been reviewed in depth with a diagnostic rate of 23.4% (n=215). An additional 35.3% have a compelling variant of uncertain significance in either an established or novel gene. Further, 5.8% of cases have a single variant in a known autosomal recessive disease gene.

Conclusion

The systematic use of combined E/A ranking has proven consistent with expert analysis in >80% of cases and can be implemented as a 'first pass' tool to expedite review of new data as it is generated. In addition, E/A ranking helps prioritize novel genes for further studies. We foresee that these tools will vastly speed up the analysis of our next 1000 cases.

References

Exomiser: Smedley et al. 2015; PMID: 26562621

AMELIE: Birgmeier et al. 2020; PMID: 32434849

Novel candidates genes are submitted to GeneMatcher to look for other patients with overlapping features and variants in the same gene(s): Sobreira et al. 2015; PMID: 26220891

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https://www.childrensmercy.org/genomicanswers/