Evaluation of 18,911 Individuals with Autism Reveals that Exome Analysis Provides Higher Diagnostic Rates and Reduced Time to Diagnosis than Traditional Testing Strategies

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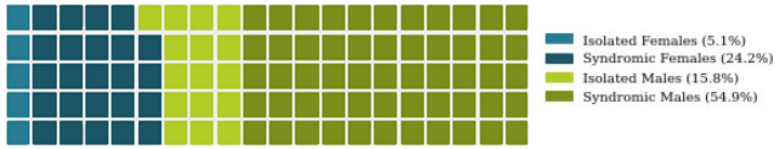
BACKGROUND

Roughly 1/59 children have been diagnosed with autism spectrum disorders (ASD); however very few large studies have evaluated the genetic basis of autism and current guidelines only recommend exome analysis after significant clinical review and focused genetic testing. This study evaluated the diagnostic outcome of exome analysis for autistic individuals, with and without comorbidities, and highlight genes not previously associated with ASD.

STUDY DESIGN

- Retrospective review of exome analysis from 18,911 individuals noted to have autism or autistic behavior, by referring physician
- Syndromic autism defined as having two or more specific comorbidities (dysmorphic features, seizures, developmental delay, muscle or skeletal abnormality)

A.



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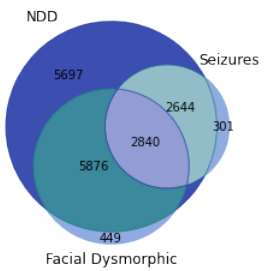

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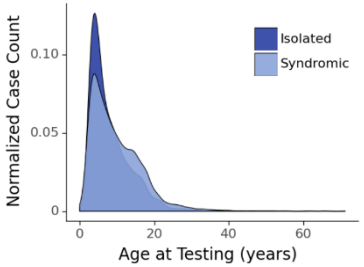


Figure 1. Distribution of Cohort
A. Approx.1:2 female to male ratio; 1:5 and 1:4 isolated to syndromic ratio, respectively. **B.** Patients with selected co-morbidities (n=17935) **C.** Ages at testing; mode 3 yrs, isolated median 6.4 yrs, syndromic median 8.4 yrs.

RESULTS

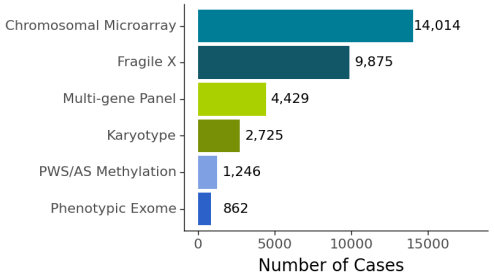
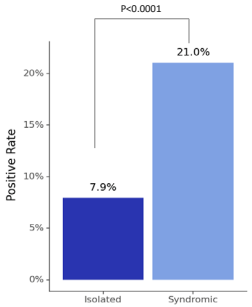


Figure 2. Prior Genetic Testing
Almost 90% of individuals had at least one prior (negative) genetic test consistent with diagnostic guidelines put forth by the American College of Medical Genetics.

A.



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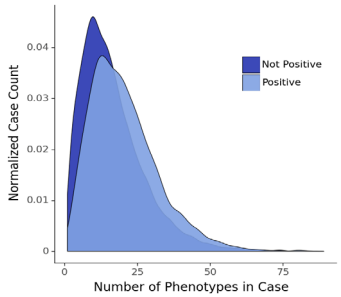
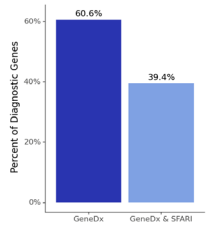


Figure 3. Diagnostic Yields
A. Individuals with syndromic ASD had a significantly higher diagnostic rate than isolated ASD cases. **B.** Patients with more HPO terms have higher diagnostic yields.

Figure 4. Diagnostic Genes
Positive findings were identified in 698 genes; 78 genes were reported in >10 cases. The most common being SHANK3.

RESULTS

A.



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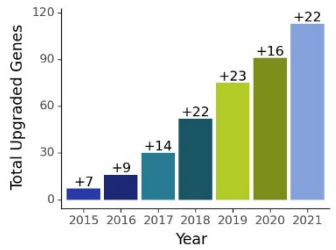

Figure 5. Emerging genes
A. Diagnostic findings were reported in 417 (60%) genes that were absent from SFARI. **B.** Initial analysis identified 1337 emerging genes that did not have an established connection to autism. Upon reanalysis, 113 of these genes were upgraded to disease-causing, starting in 2015.

CONCLUSIONS

Despite a recommendation from the AAP to screen for autism between the ages of 18-24 months, the median ages at testing were 6.4 and 8.4 years for isolated and syndromic.[2] Prior testing likely contributed to the delay in molecular diagnosis, as 89% of individuals had prior negative testing. The high positive rate of exome analysis (7.9-21.0%) suggests that it should precede FMR1 and array CGH. Individuals with multiple presenting features were more likely to have a disease associated molecular finding. Additionally, 60% of disease-causing genes in this study are not on the SFARI list and many more were considered emerging at the time of reporting, supporting the use of a broad testing approach, that is not limited to curated gene-lists, to increase diagnostic results for individuals with autism.

REFERENCES

1. Baio, J., Wiggins, L., Christensen, D. L., Maenner, M. J., Daniels, J., Warren, Z., ... & Dowling, N. F. (2018). Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2014. MMWR Surveillance Summaries, 67(6), https://gene.sfari.org/ (accessed on September 26th, 2021)
2. Hyman SL, Levy SE, Myers SM, AAP COUNCIL ON CHILDREN WITH DISABILITIES, SECTION ON DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS. Identification, Evaluation, and Management of Children With Autism Spectrum Disorder. Pediatrics. 2020;145(1):e20193447