Title: Retrospective Analysis in Precision Genomics Clinic: Detection Rates, Diagnostic Yield, and Expansion of Genetic Etiologies of ASD

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Introduction: Autism Spectrum Disorders (ASDs) and developmental delay (DD) are among the top referral indications to pediatric genetics clinics. Studies have shown about 25% of individuals with ASD have an underlying genetic etiology (Schaefer et al., 2013). Identifying the exact genetic etiology is crucial to provide accurate genetic counseling, risk assessment, and prognosis for patients and their families. Recent studies suggest infants that have an older biological sibling with ASD have an estimated overall recurrence risk of 18.7% (Ozonoff et al. 2011). Further, detection of an exact genetic etiology enables targeted testing for siblings and other family members. This allows for diagnosis at an early age, as well as access to early intervention therapies which have been shown to improve educational and behavioral outcomes (Peters-Scheffer 2011). Due to the valuable insight and practical positive implications that come with a detecting a genetic etiology of ASD, we sought to evaluate detection rates and diagnostic yield of common genetic testing methodologies used for patients referred for ASD and DD within the UC Davis Genomic Medicine Clinics. The purpose of this study was to analyze the effectiveness of testing technologies, increase diagnostic yield, and provide families with information regarding more comprehensive genetic tests and ongoing research studies.

Method: We conducted a retrospective analysis of over 500 patients referred to the Genomic Medicine Clinics over a 16 month period. By using referral record terminology pertaining to developmental disorders, over 30% of individuals were identified with referral indications of ASD/DD. Of patients referred for ASD/DD, genetic testing was deemed appropriate by the genetics team (board certified genetic counselor and /or board certified geneticist) in 70% of cases and performed in greater than 40%. Subsequent analysis of testing methods, detection rates, and diagnostic yield were then performed.

Results: Preliminary data suggest about 25-30% of these patients have an identifiable genetic abnormality. Of those with abnormal genetic testing results, 85% were identified by use of a chromosomal microarray (CMA), an array-based comparative genomic hybridization technique. For the remainder of patients with non-diagnostic test results, further testing such as whole exome sequencing (WES) was discussed. Analysis of WES recommendations, detection rates, and diagnostic yields within this cohort are pending. Of note, several novel variants have been identified in candidate genes using this methodology.

Discussion: In the absence of a clear underlying genetic etiology, ASDs are thought to have multifactorial inheritance (Pletcher et al., 2007). Identifying the underlying genetic etiology provides appropriate care for patients, more accurate information and risk estimates for families, as well as contributes to the development of therapeutic options. We anticipate that while use of more advanced genetic testing analyses such as whole exome and whole genome sequencing can increase identifiable genetic causes of ASD/DD, the high detection rates from CMAs stress the importance of the ACMG guidelines to perform first tier genetic testing (CMA and Fragile X) before more comprehensive recommendations are pursued.

References/Citations: