Diagnostic yield for chromosome microarray analysis in patients with autistic features.

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Autism Spectrum Disorders (ASDs) are clinically heterogeneous, highly heritable neurodevelopmental disorders seen in 1-2% of children. Chromosomal microarray (CMA) is a first-tier test in the evaluation of individuals with ASDs with the diagnostic yield varying based on population examined, ranging from 5-25% in recent literature. Subjects in the majority of published studies are formally evaluated for ASD prior to inclusion; however, in the clinical setting formal autism evaluations may not occur prior to genetic testing. Herein we calculate the diagnostic rates for copy number variations (CNV) by CMA in a cohort of patients with ASD, pervasive developmental disorder not otherwise specified (PDD-NOS), or autistic features (AF) with or without formal evaluation submitted for clinical testing.

The most recent 614 unselected cases referred for postnatal microarray to Ambry Genetics (Aliso Viejo, CA) with indication for testing provided were reviewed. Patients with clinical indications including ASD, PDD-NOS and AF were included in the cohort. Of the 614 cases, 128 (21%) were reported to have ASD/PDD-NOS/AF with or without additional features excluding two patients with prior abnormal diagnostic lab results. For cases with more than one CNV identified, the CNV of highest pathogenicity determined the overall case classification. Of the 128 ASD/PDD-NOS/AF cases, 7 (5.5%) were pathogenic, 2 (1.6%) variant likely pathogenic (VLP), 37 (28.9%) variant of uncertain significance (VUS), 10 (7.8%) variant likely benign (VLB), and 72 (56.3%) normal. Overall, 9/128 (7.0%) patients had a pathogenic or VLP CNV; 6/9 (66.7%) with microdeletions, 1/9 (11.1%) with a microduplication, and 2/9 (22.2%) with sex chromosome aneuploidy. Recurrent CNVs demonstrating reduced penetrance and variable expressivity were frequent amongst the pathogenic and VLP cases including single patients with 15q11.2 BP1-BP2 microdeletion, 16p11.2 microdeletion, 15q13.3 microdeletion, distal 1q21.1q21.2 microduplication, and intragenic *NRXN1* deletion. Among VUS CNVs, two autism candidate genes were noted, *CHRNA7* and *CNTN6*.

The majority of the pathogenic/VLP results (67%) were identified in patients with additional physical findings suggesting a higher detection rate for the more complex cases. The rate of pathogenic and likely pathogenic findings is comparable to the conservative published estimates of diagnostic yield for CMA in patients with ASD.

Keywords: autism, autism spectrum disorders, pervasive developmental disorders, chromosome microarray, copy number variation