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Human Genetics 2016: Optimizing clinical understanding of genomic variants in autism and other disorders of development - E Robert Wassman - Lineagen Inc., USA

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Chromosomal microarray (CMA) is a standard first-tier diagnostic for autism spectrum disorders (ASD) and other neurodevelopmental conditions and is now complemented by whole exome sequencing (WES) to identify potentially pathogenic variants in over half of such cases today.

We have optimized testing for these conditions through an enhanced design CMA (FirstStepDxPLUS) based on an Affymetrix platform with 88435 probes added in genomic regions strongly associated with neurodevelopmental conditions for a total of 2.8 million probes across the whole genome.

Application of this CMA to a real-world clinical referral base of over 7300 individuals yielded the highest reported clinical yield for CMA in these disorders with 10.0% abnormal and 20.7% VUS or over 30% overall. We have further extended the utility of the increased probe density to assess smaller copy number variants (CNVs), which may be of clinical significance.

We have implemented use of a "critical exome mapper" algorithm, which identifies highly conserved, preferentially brain-expressed exons, which are disproportionately impacted by de novo mutations in ASD. Across 2600 CNVs from 2100 individuals we identified over 1400 genes predicted to have critical exons from neurodevelopment, among which ~20-25% were not identified by clinical databases (e.g., OMIM) of known disease associated genes.

This aids in the assessment of potential for pathogenicity of VUSs and identifies potentially targetable genes for therapeutic intervention in the future. This approach is applicable to WES data as well and evidence is accumulating supporting a non-traditional additive contribution of genetic variants to pathogenesis in these disorders.

This work is partly presented at World Congress on Human Genetics November on 07- 08, 2016 held at Barcelona, Spain