M11. DE NOVO GENIC MUTATIONS AMONG A CHINESE AUTISM SPECTRUM DISORDER COHORT

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Background Autism spectrum disorders (ASD) are characterized by impairments in social communication and restricted or repetitive behaviors or interests. ASD has a strong but complex genetic component and the prevalence worldwide has been estimated as closer to 1%. Recurrent de novo (DN) and likely gene-disruptive (LGD) mutations are important risk factors for autism spectrum disorders (ASD) but have been primarily investigated in cohorts of European ancestry. However, no study has explored on a large scale the spectrum of DN mutations in these ASD risk genes in the Chinese population. Here we sequenced 189 risk genes in 1,543 ASD probands (1,045 from trios) with Chinese ancestry.

Methods We selected autism risk genes for targeted sequencing mainly based on the frequency and severity of DN mutations from previously published exome sequencing studies under the hypothesis that DN mutations in genes contributing to autism pathology will not differ significantly between global populations. In total, we designed 11,394 single-molecule molecular inversion probes (smMIPs) to rapidly and cost-effectively sequence the coding regions for 213 candidate genes, of which 10,493 smMIPs for 189 genes passed QC measures, across a large cohort of 1,543 autism probands (1,045 from trios) from the Autism Clinical and Genetic Resources in China (ACGC). We selected LGD (nonsense, frameshift and splice site) mutations and missense mutations with a combined annotation dependent depletion (CADD) score of greater than 30 (MIS30) for sanger validation.

Results We discovered 4,226 rare variants predicted to alter the amino acid sequence or gene splicing, and selected 120 LGD mutations and 216 MIS30 mutations for sanger validation. We report an 11-fold increase in the odds of DN LGD mutations compared to expectation under an exome-wide mutational rate model based on chimpanzee–human divergence. In aggregate, ~4% of ASD patients carry a DN mutation in one of just 29 autism risk genes. The most prevalent gene for recurrent DN mutations was SCN2A (1.1% of patients) followed by CHD8, DSCAM, MECP2, POGZ, WDFY3 and ASH1L. We identify novel DN LGD recurrences (GIGYF2, MYT1L, CUL3, DOCK8 and ZNF292) and DN mutations in genes previously implicated in ASD (ARHGAP32, NCOR1, PHIP, STXBP1, CDKL5 and SHANK1).

Discussion We have performed an investigation of DN mutations among ASD candidate risk genes in a Chinese ASD patient cohort. Among the 1,045 trios tested, we discovered 43 DN mutations in 29 of the 189 candidate genes queried by our MIP-based approach. DN mutations in SCN2A accounted for ~1.1 % of ASD patients in our Chinese cohort. This rate was higher than exome- and MIP-sequenced ASD cohorts of European descent. Patient follow-up confirms phenotypic features associated with the genetic subtypes and highlights how large global cohorts might be leveraged to identify individually rare mutations in genes that together prove pathogenic significance. Our study helps identify global risk genes providing evidence and motivation for further functional and translational studies of specific ASD risk genes, which may guide future personalized treatments.

Disclosure: Nothing to Disclose.