An Immunologic Basis for the Pathogenesis of Autism Spectrum Disorder: Toll-like Receptor Mechanisms and Downstream Processes

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Autism Spectrum Disorder (ASD) is a common neurodevelopmental disorder characterized by behavioral irregularities. Causal variation has been implicated in only 30-40% of ASD diagnoses; it is unclear if a strong genetic component underlies the remaining cases. To address this gap, an Autism Research Initiative organized the biological specimen collection and exome sequencing of (i) an ASD cohort without apparent causal variation; and (ii) unaffected parents and siblings (when available). I was provided access to the raw dataset, which I used to (i) identify unique de-novo variants and map them to their respective genes, (ii) compare gene candidates with those identified in previous studies, and (iii) determine if gene-sets and pathways were enriched that could account for ASD phenotypes. I identified 2,751 genes that were significantly and uniquely mutated in the population. There were 93 genes (21%) that had been previously implicated in ASD. Pathway analysis indicated that a significant percentage of the ASD cohort had perturbations in Vitamin D receptor pathways (19.7%-37.8% of cases), Cell Cycle pathways (12.8%-30.1% of cases), and T-Cell related pathways (20.9%-36.4% of cases). These pathways implicated Toll-like Receptor mechanisms and its downstream processes: NF-κB activation, T-Cell and cytokine activation, and Vitamin D receptor production. An immunologic basis for the pathogenesis of some forms of ASD has been hypothesized in clinical studies, but has not been validated at the molecular level. This study is the first to propose underlying genetic mechanisms for this hypothesis as well as potential therapeutic and diagnostic targets for ASD.