[BIOINFO 2023]

Oligogenic contribution of rare variants for autism spectrum disorder

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by high heritability and genetic heterogeneity. Recent large-scale genomic studies have identified de novo and common variations associated with ASD, stratifying risk under a monogenic and polygenic model. Recently, rare inherited variants have been emerging as a genetic factor explaining oligogenic inheritance where two or more genetic variations occur concurrently in ASD cases and combinatorial contribution to risk. To test this, we analyzed ~2,400 ASD cases and their family members from the Korean ASD-WGS cohort and evaluated genetic association of oligogenic rare variants in ASD. Integrating ~2,500 WGS data of general population from the National Project of Bio Big Data, we defined rare variant specific to Korean population as those having allele frequency < 1%, and prioritized disrupting rare variants, including protein-truncating variants and missense variants. From this, we identified the multiple combinations of disrupting rare variants observed only for ASD cases and risk genes affected by oligogenic inheritance. To characterize risk genes, we explored cell-type specific expression pattern in developing human brain. Taken together, we suggest oligogenic inheritance of rare variants associated with ASD and putative risk genes to understand a novel ASD neurobiology.