Autism From Mars?: Decoding the Genetic Underpinning of Sex Bias in Autism Through Big Data Analysis

Lee, Junu (School: Lexington High School)

Autism spectrum disorder (ASD) has a well-documented sex bias, in which males are diagnosed approximately four times more frequently than females. Although recent human studies have identified a genetic etiology of ASD, the sex bias in ASD still remains largely unexplained because the frequencies of autosomal ASD-associated genetic variations are equal between males and females. However, if expression levels of ASD-causing genes are different between males and females, such differences may contribute to the sex bias in ASD. Therefore, I specifically determined whether spatial and temporal gene expression patterns of ASD-causing genes are different between males and females, aiming to decode the genetic underpinning of the sex bias in ASD. Focusing on the 102 ASD-associated genes, analyses of the GTEx RNAseq data revealed modest differences between males and females for 17 genes in ASD-relevant brain regions. Importantly, these candidate genes showed stronger collective sex-dependent expression in the gene set enrichment analysis (GSEA), which was subsequently validated in independent PsychENCODE data. Furthermore, linear regression analysis and GSEA of PsychENCODE data showed that gene expression patterns of candidates are age-dependent. In addition, gene ontology analysis revealed the functional relevance of the 17 candidate genes in chromatin remodeling and synaptic regulation. Taken together, the candidate genes discovered through big data analysis suggest that sex and age-dependent ASD-associated genes contribute to the sex bias in ASD. These novel insights into the sex bias are highly significant as they inform underlying disease mechanisms of ASD, forming the genetic basis for new therapeutic strategies for ASD.

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