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Whole genome sequencing analysis identifies sex differences of familial risk contributing to phenotypic patterns in autism spectrum disorder

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Background: Sexual dimorphism in autism spectrum disorder (ASD) is widely recognized, with a higher prevalence in males. The female protective effect (FPE) has been proposed, which assumes that females with protective effect have a higher liability threshold for being ascertained as ASD. However, FPE for familiar risk has not been examined and comprehensibly evaluated for associations with various phenotypes, warranting further investigation. In this study, we analyzed sex differences in whole genome sequencing (WGS) and deep phenotyping data from a Korean ASD data.

Methods: We analyzed WGS of Korean ASD data (676 families; 2,266 individuals) for de novo, and common variants. We compared gene-disruptive de novo variants including protein truncating variant (PTV) across sex. We computed polygenic score (PS) for ASD (PS_{ASD}) and the concentration of IL17A (PS_{IL17A}). We compared the PS_{ASD} and assessed the associations with ASD core symptoms. To investigate FPE in ASD families, we further expanded our analysis to control siblings and parents and assessed PS_{ASD} and phenotypic scores. Additionally, we examined whether PS_{IL17A} in mother contributes to sex-biased risk to ASD.

Results: Our WGS study presents evidence supporting the FPE: higher de novo PTV in ASD females, and male-biased susceptibility of PS_{ASD} toward ASD core symptoms. Although we found a higher PS_{ASD} in ASD males compared to ASD females, we found a higher PS_{ASD} in female siblings and mothers compared to male siblings and fathers. Female siblings and mothers, however, exhibited less severe symptoms than male siblings and fathers. These results suggest that females are more protected from the polygenic risk. Maternal PS_{IL17A} was enriched in ASD males, especially in the low severity group, indicating a potential additive risk of maternal PS_{IL17A} in male ASD liability.

Conclusions: To the best of our knowledge, our study represents the first genomic investigation of FPE in individuals with East Asian ancestry. We present a new WGS and comprehensive phenotype collection, thus providing robust supporting evidence for FPE in ASD. By considering the associations between genetic factors, sex, and immune biology, our study provides valuable insights into the underlying genetic mechanisms driving sex differences.