

## Maternal Copy Number Variants (CNV) transmission to their Autism Spectrum Disorder (ASD) sons correlates with phenotypic traits

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Autism Spectrum Disorder (ASD) is characterized by impairments in social communication and repetitive behaviors, a clinical presentation spectrum and a high male:female ratio. Behavioral traits in the ASD spectrum are prevalent in unaffected family members, highlighting a trait heritability likely mediated by genetic factors that impact ASD risk. Here we tested the hypothesis that CNV-transmitting parents of ASD children exhibit higher scores of quantitative ASD traits tests as compared to CNV non-transmitting parents. Parental scores for the Social Responsiveness Scale (SRS) (N=456) and the Broader Autism Phenotype Questionnaire (BAPQ) (N=341) and CNV inheritance patterns to affected children were obtained from the Autism Genome Project database. We applied the Mann–Whitney  $U$  test to compare ASD traits in CNV transmitting and non-transmitting parents.

There were no significant differences between the SRS and BAPQ scores from CNV-transmitting and non-transmitting parents. However, when dissected by relative pairs, a significant difference between CNV transmitting and non-transmitting mothers to their sons was identified for SRS ( $P=0.040$ ), BAPQ global ( $P=0.008$ ) and BAPQ domains scores *aloofness* ( $P = 0.015$ ) and *pragmatic language deficits* ( $P = 0.019$ ). A trend for BAPQ global ( $P=0.048$ ) in mother–all children pairs was also identified. Our findings indicate that unaffected mothers who transmit CNVs of putative clinical significance to their affected sons tend to have more ASD traits than the CNV-non-transmitting mothers. The results reinforce previous reports of significant maternal transmission bias to sons, further correlating this increased risk with phenotypic presentation in mothers. The results further support the prevalent hypothesis of a higher genetic risk tolerance in females due to putative protective factors, explaining the maternal bias in CNV and ASD transmission to sons compared to daughters.