Increased frequency of the autism broader phenotype in mothers transmitting etiological CNVs to sons affected by Autism Spectrum Disorder (ASD)

Asif M, Conceição IC, Kwiatkowska K, Rasga C, Café Cátiá, Sousa L, Oliveira G, Couto F, Vicente AM

1Instituto Nacional de Saúde Doutor Ricardo Jorge, Lisboa; 2Biosystems and Integrative Sciences Institute, Lisboa; 3University of Lisbon, Faculty of Sciences, DEIO and CEAUL, Portugal 4Unidade de Neurodesenvolvimento e Autismo do Serviço do Centro de Desenvolvimento da Criança and Centro de Investigação e Formação Clínica, Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra, 3000-602 Coimbra, Portugal; 5University Clinic of Pediatrics and Institute for Biomedical Imaging and Life Science, Faculty of Medicine, University of Coimbra, 3000-354 Coimbra, Portugal; 6Department of Informatics, Faculty of Sciences, University of Lisbon; 7Instituto Gulbenkian de Ciência, Oeiras

Autism Spectrum Disorder is a frequent neurodevelopmental disorder with a high male to female ratio. An increased prevalence of autism-like personality traits is found in unaffected relatives of ASD children, suggesting a genetic liability of a broader autism phenotype. We therefore hypothesized that the parents of ASD children who transmit etiological CNVs might exhibit ASD traits more frequently than non-transmitting parents. To test this hypothesis, we analysed CNV inheritance and parental behavioral traits in families from the Autism Genome Project, assessed using the Broad Autism Phenotype Questionnaire (BAPQ) (N=341) and the Social Responsiveness Scale (SRS) (N=456). We selected CNVs spanning well-established candidate genes for ASD, and compared transmitting and non-transmitting parental test scores using a t-test corrected for multiple testing by the Group Benjamini-Hochberg Procedure.

Overall, CNV-transmitting parents did not differ significantly in BAPQ and SRS scores from non-transmitting parents. However, independent analyses of relative pairs revealed a significant difference in BAPQ global ($t=-2.18$; adjusted $P=0.032$), BAPQ aloofness domain ($t=-2.61$; adjusted $P=0.032$) and SRS scores ($t=-2.03$; adjusted $P=0.047$) between mothers transmitting and mothers not transmitting etiological CNVs to their affected sons. Our findings indicate that mothers presenting personality traits in the broader autism phenotype are frequently carriers of pathogenic CNVs that they transmit to their ASD sons. The results from the analyses of maternal phenotype and CNV transmission patterns to sons support previous reports of maternal transmission bias to male offspring, and the prevalent hypothesis of a higher genetic risk tolerance in females due to putative protective factors. (FCT PD/BD/52485/2014)