**ANALYSIS OF A SARDINIAN MULTIPLEX FAMILY WITH AUTISM SPECTRUM DISORDER POINTS TO POST-SYNAPTIC DENSITY GENE VARIANTS AND IDENTIFIES CAPG REGION AS FUNCTIONALLY RELEVANT FOR THE DISEASE**

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Autism spectrum disorders (ASDs) are a group of neurodevelopmental disorders with high heritability. The possible role of CNVs on ASD susceptibility and their effects on gene expression are well established. However, even in presence of relevant CNVs, combining CNV analysis with sequencing data is warranted to elucidate the complex ASD genetic architecture. We performed a genetic characterization of two ASD siblings from Sardinia by genome-wide CNV analysis and whole exome sequencing (WES), to identify novel genetic alterations associated with ASD.

SNPs array data revealed a rare heterozygous microdeletion involving CAPG, ELMOD3 and SH2D6 genes, in both ASD siblings. CAPG encodes for a postsynaptic density (PSD) protein regulating spine morphogenesis and synaptic formation. The reduced CAPG mRNA and protein expression levels in ASD patients highlighted the functional relevance of CAPG as a candidate gene for ASD. WES analysis revealed a rare frameshift mutation in VDAC3 and 4 missense damaging variants in other genes encoding for PSD proteins. Moreover, very high expression levels of a transcript produced by the fusion of the interrupted ELMOD3 and SH2D6 genes have been detected in the deletion carriers, suggesting that this transcript does not undergo mechanisms of nonsense-mediated decay and might encode for a chimeric protein. Interestingly, since similar heterozygous and homozygous deletions of the same region have been described in ASD patients from different population, low CAPG levels and this fusion transcript may be very likely present in these patients, suggesting their involvement, together with other genetic variants, in ASD phenotype.

This study identified CAPG and VDAC3 as candidate genes and provided additional support for genes encoding PSD proteins in ASD susceptibility. Finally, it highlighted the possible involvement of a gene fusion in ASD phenotype. Future studies will investigate the possible production of a chimeric protein and its function.