Characterization and expression analysis of a CNV at chromosome 10q22 encompassing 14 genes in an autistic patient

Inês C. Conceição1,2, Catarina Correlo1,2,2, Joana I. Coelho1,2, Tâbaria Oliveira1,2,3, Frederico Duque1, Susana Mougou1 Guimarães Oliveira1,2, Astild M. Vicente1,2
1 Instituto Nacional de Saúde Dr. Ricardo Jorge, 1600 Lisboa, Portugal;
2 Center for Biodiversity, Functional & Integrative Genomics, Lisboa, Portugal;
3 Instituto Gulbenkian de Ciência, Oeiras, Portugal;
4 Faculdade de Ciências, Universidade de Lisboa, Portugal;
5 Centro de Desenvolvimento da Criança, Hospital Pediátrico de Coimbra, Coimbra, Portugal

Genetics of Autism Spectrum Disorders

Autism Spectrum Disorders (ASD) have a strong genetic component, with an estimated heritability of over 90%1. Recent studies carried out by the Autism Genome Project (AGP) consortium suggest that rare Copy Number Variants (CNV), characterized by submicroscopic chromosomal deletions and duplications, are more frequent in ASD compared to controls, and may play an important role in susceptibility to this disorder2-7. However, to adequately assess pathogenicity, a detailed characterization of patients CNVs is required.

A de novo deletion encompassing 14 genes

We have been characterizing potentially pathogenic rare CNVs identified by the AGP whole genome CNV analysis of 1,275 ASD individuals. CNV validation in patients and parents and characterization were performed by qPCR and Long-range PCR. One autistic patient showed a rare deletion absent in 4964 controls of European ancestry with no psychiatric disease history. This deletion was located at 10q22, and encompassed 14 genes, including ANXA7, ZMYND17, PPP3CB and CAMK2G (Figure 1). We validated this CNV as de novo, and accurate breakpoint determination showed that it is smaller than predicted by CNV identification algorithms, including only part of CAMK2G. We found that a 39-nucleotide addition occurred with the deletion, a mutational mechanism previously observed in other CNVs (Figure 2). Expression analysis of ANXA7, ZMYND17 and PPP3CB in this patient, in comparison with controls, is ongoing.

Common pathways between autism and schizophrenia?

A recent study8 identified a genetic association of the ANXA7, PPP3CB and ZMYND17 region with schizophrenia, and significant expression alterations in schizophrenic patients. ANXA7 encodes Annexin7, involved in membrane fusion. PPP3CB plays an important role in synaptic plasticity, learning and memory. ZMYND17 has no known function. Our results suggest that alterations in these genes may be risk factors co-observed in autism and schizophrenia. Additional genetic and functional studies may lead to a better understanding of the common pathways between these neuropsychiatric disorders.

The role of Annexins in ASD

Interestingly, we have identified CNVs in other Annexin genes, namely an inherited duplication in the Annexin1 gene (ANXA1) present in 12 patients and 10 parents and no control. ANXA1 plays a central role in anti-inflammatory response and neuroprotection, contributing to brain homeostasis9. The same breakpoint in all individuals was observed (Figure 3) and three new polymorphisms were identified in the 5’UTR in three patients, one of them in a putative miRNA binding site (Figure 4).