Calcium signaling and molecular adhesion processes may hold the key to genetic risk for Autism. A molecular pathway analysis on two independent samples

Antonio Drago(1), Marco Calabro’(2), Concetta Crisafulli(2), Uffe Birk Jensen(3)

1. Department of Clinical Medicine, Aarhus University - Psykiatrisk Forskningsenhed Vest, Herning, Denmark.
2. Department of Biomedical Science and Morphological and Functional Images, University of Messina, Via Consolare Valeria, 98125 Messina, Italy.
3. Department for Clinical Genetics, Aarhus University Hospital, Aarhus, Denmark

Background

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that appears early in life and is characterized by limited interest and lacking ability in social interactions, repetitive behavior and dysfunction in social communication. Motor and intellectual deficits, together with mood and sleep disorder and sensory and gastrointestinal abnormalities are also common in ASD [1]. ASD affects up to 1% of the general population [2] and has a genetic counterpart, resulting in an estimated concordance rate as high as 60-70% in identical twins and 5 – 30% in siblings [3,4]. The definition of the genetic basis of ASD is still to be achieved, de novo mutations may explain a part of the missing heritability, as it was consistently shown that they may play a role in ASD [15–18]. Nevertheless, the impact of de novo mutations is not as relevant as the one brought by inheritance: it was estimated that 49% of the genetic architecture of ASD is related to common inherited variants, 3% by de novo mutations and 3% by rare inherited variants [19]. Combined international GWAS databases provide an unprecedented opportunity to describe the common inherited variants that are associated with ASD.

Hypothesis under analysis

Enrichment in common genetic variations clusters in specific molecular pathways and such clustering can be replicated in independent ASD samples.

Methods

Genetic data were available from the NIMH. The Autism Dataset 4 sample was chosen for the investigation sample. The Autism Dataset 3 served as a replication sample. Plink [28] served for the TDI GWAS analysis and genetic annotations. R [29] and dedicated packages served for the permutations analysis and QQ-plot creation. Haploview [30] served for the identification of the known available SNPs for each gene. The Gene Ontology Consortium was interrogated to detect enriched GO annotations.

Investigation sample. TDI associations were run and results annotated. Quality of results was checked. Variations associated with Autism at P<10E-4 were selected and genes identified (genelist1). Enriched GO terms were searched in genelist1 and genes within the enriched GO terms were selected (genelist2). SNPs belonging to genelist2 were annotated. A simulation test was run in R to avoid false positive finding. Replication sample. SNPs were derived from genelist2 and the incidence of observed vs expected significant associations was checked.

Results

The central nervous system development pathway (GO:0007417) was enriched in both samples (table 1). The SNPs belonging to the index pathway in the investigation sample (n=1124) were identified in the replication sample. 519 SNPs were detected, that were belonging to the index pathway from the investigation sample, were represented in the replication sample and had the same direction of association with Autism as in the investigation sample. The prevalence of SNPs associated with Autism in the replication sample was 5.4% at a p level of 0.05 and 1.9% at a p level of 0.01 (Figure 1). After the permutation analysis, the prevalence of SNPs associated with Autism was confirmed at a p level of <0.01, and not confirmed at a p level of <0.05.

Conclusion

Genes belonging to the GO:0007417 may hold the genetic variations that drive the risk to ASD. In particular, genes that code for proteins related to the adhesion processes may be associated with ASD. Further analyses are necessary to confirm those results.