CNV CHARACTERIZATION, INHERITANCE AND PHENOTYPIC CORRELATIONS IN FAMILIES WITH AUTISM

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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 (CNVs), 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 disorder[2]. However, to adequately assess pathogenicity, a detailed characterization of patients CNVs and phenotype is required. The goal of this study was to establish the clinical and etiological relevance for ASD of potentially pathogenic CNVs identified in a Portuguese population sample by whole genome CNV analysis, through the detailed characterization of CNVs and correlation with clinical phenotypes. Analysis of the AGP genome-wide CNV results using 1M SNP microarray[2] identified a total of 14218 CNVs in 342 Portuguese probands. We selected 291 CNVs, present in 191 individuals (19 females and 172 males), using the following criteria: 1) CNVs that contained implicated/candidate genes for ASD; 2) CNVs in genomic regions known to be implicated/candidate for ASD; 3) CNVs in regions associated with syndromes with ASD symptoms; and 4) high confidence CNVs that did not overlap more than 20% with controls in available databases. We explored recurrence rates, genic content, regulatory elements, inheritance patterns and phenotypic correlations.

CNV characterization and distribution

The identified 282 CNVs ranged from about 5 Kb to 3.7 Mb, with **66%** being **deletions**. Large CNVs (>500 Kb) were more frequently duplications than deletions. There were 180 (**64%**) **genic CNVs**, ranging from one gene (73% of all genic CNVs) to 25 genes in a single CNV. Although most CNVs (61%) were present in a single individual, 24 common CNVs (8.8%), defined as CNVs with a frequency of 1% or higher in the sample population, distributed in 6 genomic regions, were identified in 26 individuals. Each of these common CNVs were present in 3 to 6 individuals, and encompassed implicated regions/genes for autism[1,2], such as 16p13.11 (N=3), *DPYD* (N=5), *PARK2* (N=6), and *VPS13B* (N=3). Using the 314 genes present in the genic CNVs, a network was built using String software[3], which included 85 of these genes (Fig.1). This network is enriched in the following Biological Processes: **CNS development** (14 genes; p-value=0.03) and **regulation of cellular catabolic processes** (11 genes; p-value=0.035), and **includes several genes associated with autism**.

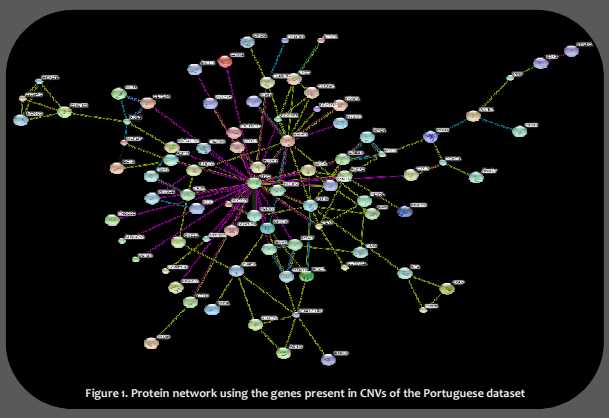

Figure 1. Protein network using the genes present in CNVs of the Portuguese dataset

CNVs and phenotypic correlation

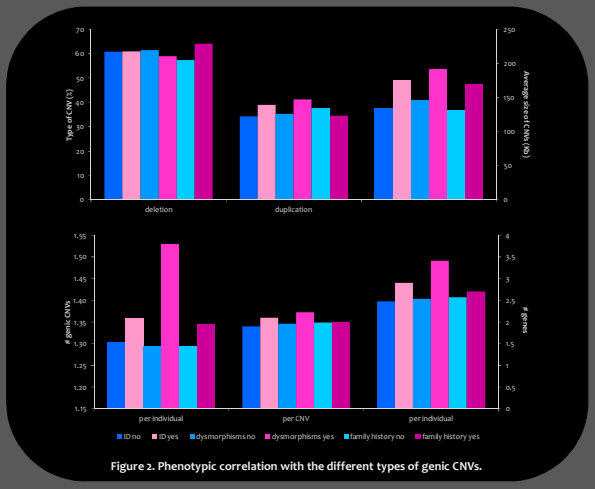

Figure 2. Phenotypic correlation with the different types of genic CNVs.

Our sample consisted of individuals with no severe intellectual disability and no gross chromosomal aberrations or obvious dysmorphisms. However, minor features of the phenotype, including minor dysmorphisms and macrocephaly, were observed in our sample. **We analyzed 180 genic CNVs in 139 individuals.** We looked for differences in the type, size and number of the genic CNVs and in the number of genes implicated, in different phenotypic categories (Fig. 2): 1) intellectual disability (ID): no (N=79) and yes (IQ=35-69; N=59); 2) minor dysmorphisms: no (N=122) and yes (N=17); and 3) family history of neuropsychiatric disorders: no (N=61) and yes (N=78). As observed previously, there were more deletions than duplications, regardless of the phenotype. **Individuals with ID, dysmorphisms and/or family history, had a higher burden of genic CNVs and number of genes affected *per* individual. Also, the average size of the CNVs was larger.**

CNV inheritance and parental personality traits

We further correlated data for autistic traits in the parents, using the Broad Autism Phenotype Questionnaire (BAPQ) and Social Responsiveness Scale (SRS), with the type of inheritance of the CNV (inherited *vs* de novo; Fig. 3). **A significant excess of autistic traits was observed in the fathers that transmitted a CNV, mainly in the "aloof" personality, which is defined as lacking interest in social interaction.** However, the paternal inheritance does not seem to explain all changes, indicating a putative maternal contribution. Also, we calculated familial correlation for all pair types, using the SRS questionnaire results from parents and probands (data not shown). **A significant correlation between the SRS results from both parents supports the idea of assortative mating in ASD.**

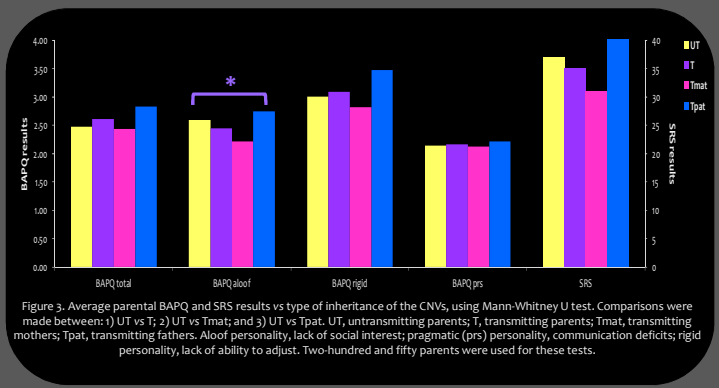

Figure 3. Average parental BAPQ and SRS results *vs* type of inheritance of the CNVs, using Mann-Whitney U test. Comparisons were made between: 1) UT *vs* T; 2) UT *vs* Tmat; and 3) UT *vs* Tpat. UT, untransmitting parents; T, transmitting parents; Tmat, transmitting mothers; Tpat, transmitting fathers. Aloof personality, lack of social interest; pragmatic (prs) personality, communication deficits; rigid personality, lack of ability to adjust. Two-hundred and fifty parents were used for these tests.

BIBLIOGRAPHY: 1. Betancur C. (2010) *Brain Res* **1380**:42-77; 2. Pinto D. *et al.* (2010) *Nature* **466**:368-72; 3. Franceschini A. *et al.* (2013) *Nucleic Acids Res.* 41:D808-15.

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