Phenotypic categorization of putative pathogenic CNVs in a population of Autism Spectrum Disorder patients

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Phenotypic categorization and distribution

The 149 genic CNVs selected were identified in 127 individuals (12 females and 115 males), ranging from 5 Kb to 3 Mb, 58% were deletions, and included from one gene (67% of all genic CNVs) to 25 genes in a single CNV. Large CNVs (>500 Kb) were more frequently duplications. Although most CNVs (82%) were present in a single individual, 26 CNVs (17%), distributed across 14 genomic regions, were present in more than one individual, and some encompassed regions/genes implicated in autism1, such as 16p13.11 (N=3), PARK2 (N=5), and YPS13B (N=3), as well as putative novel genes for ASD (eg UBC, SLC25A44, TERT). Network analysis of the 309 genes mapping to genic CNVs, using the String software1, yielded a network including 67 genes (Fig. 1). This network is enriched in the following Biological Processes: regulation of apoptotic processes (14 genes; p-value=0.05), and PPAR and ErbB signaling pathways (5 genes; p-value=0.02 in both cases). This data adds novel genes for autism to the list of potential candidates, and identifies biological pathways not previously associated with ASD.

Phenotypic correlations

This patient sample consisted of individuals with no severe intellectual disability (IQ>35) and no gross chromosomal aberrations or obvious dysmorphisms, but included some subjects with minor dysmorphisms or macrocephaly. We explored differences in the type, size and number of the genic CNVs and in the number of genes implicated, in relation to 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=77); and 3) family history of neuropsychiatric disorders: no (N=61) and yes (N=78). As observed in previous studies, there were more deletions than duplications, regardless of the phenotype. In general, individuals with ID, dysmorphisms and/or family history, had a higher burden of genic CNVs, higher number of genes affected (both per CNV and per individual) and a larger average CNV size. At least 7 individuals presented CNVs disrupting genes frequently identified in ASD patients, which constitute an etiological diagnosis. Most CNVs contained only one gene, and were present in a single individual, regardless of phenotypic category, thus reinforcing the role of rare variants in this disease and the large heterogeneity in ASD etiology.

CNV inheritance and parental personality traits

We further evaluated correlations between data for autistic traits in the parents and CNV inheritance, using the Broad Autism Phenotype Questionnaire (BAPQ) and the Social Responsiveness Scale (SRS). 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. Paternal inheritance does not explain all changes, indicating a putative maternal contribution. Using SRS questionnaire results from parents and probands, we also calculated familial correlations for de novo or inherited CNVs and all parent-offspring and parental pair types (data not shown). While there were no SRS correlations between any parent-offspring types for de novo or inherited CNVs, a significant correlation between the SRS results from both parents supports the idea of assortative mating in ASD.


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