Genome Biology

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Candidate genes and biological processes in *de novo* CNVs from autistic individuals

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Background

There is growing evidence that common diseases might not result from a few common variants, but rather from many rare variants across many genes/loci. This is likely to be particularly true for disorders such as autism where the fecundity of affected individuals is exceptionally low (~5%) and thus disease-predisposing alleles are unlikely to be transmitted. Since these different disease-contributing genes give rise to a shared disease phenotype, it is likely that their protein products contribute to shared biological processes, such as particular protein pathways or cellular networks. Identifying the common network(s) among these genes would allow the screening of a small subset of genes for early diagnosis and these networks could present multiple points for early intervention.

Methods

We examined two independent sets of *de novo* copy number variants (CNVs) identified in individuals with autism spectrum disorders (ASDs): (i) a large discovery set of 73 CNVs identified in 54 patients (median size 118Kb) from the Autism Genome Project (AGP) consortium [1]; and (ii) a small validation/replication set of 28 CNVs identified in 24 patients (median size 3Mb) [2]. To identify unexpected shared features among genes overlapped by these CNVs, we exploited phenotype data arising from the disruption of ~6000 human orthologues in mouse. We infer that genes are likely to act in the same biological process if, when disrupted in mouse, they exhibit comparable phenotypes. Thus, we aim to identify significantly over-represented *mouse* phenotypes among sets of *human* genes of interest (e.g. genes overlapped by autism-associated CNVs) [3].

Results

Among genes overlapped by the AGP CNVs, significant enrichments of specific mouse phenotypes were discovered (FDR<5%), most of which were either replicated (FDR<5%) or validated (p<0.05) in the Marshall set, including: (i) A significant enrichment of genes associated with four abnormal synaptic transmission phenotypes; (ii) A significant enrichment of genes associated with >10 behavioural phenotypes and five hearing phenotypes that are only found within duplicated CNVs. Many of these duplication-specific phenotypic associations are readily comparable to ASD symptoms, such as *abnormal motor learning* (60-80% of individuals with ASD exhibit impaired coordination), *non-convulsive seizures* (~1/3 of individuals with ASD suffer seizures, commonly non-convulsive) and *sensorineural hearing impairment* (25-40% individuals with ASD have hearing impairments). These enrichments identify >100 largely novel candidate genes and provide causal hypothesis for between 19-83% of patients in each cohort.

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