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HotSpots

The implications of *de novo* coding mutations in simplex autism families

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Autism spectrum disorders (ASD) are heterogeneous group of neurodevelopmental disorders that are clinically defined by impairments in social interactions and restricted and repetitive behaviours. ASD have a strong genetic component, based on high concordance rate in twin studies and the more recent demonstration of *de novo* mutations that occur spontaneously in the parental germline. Despite being highly prevalent in the population, ASD are genetically complex and display a remarkable degree of clinical variability between affected individuals. Advances in next-generation sequencing have led to the discovery of rare and *de novo* mutations associated with ASD, including copy number variations (CNVs) and non-synonymous mutations. These studies reported disruptions in hundreds of genes that are associated to ASD (1, 2).

Recent study by Iossifov and colleagues further strengthens the role of *de novo* coding mutations in ASD(3). The authors extended their prior Whole Exome Sequencing (WES) study in the Simons Simplex Collection (SSC) of families, in which each family has one ASD-affected child and one unaffected child, by including a larger number of samples. The current study comprised 2,500 probands, and 1,911 unaffected siblings and their parents, representing one of the largest WES study in Simplex families to date. The authors observed that the rate of 'likely gene disrupting' (LGD) mutations, representing frameshift, non-sense or splice-site mutations was significantly higher (~43%, $p = 2 \times 10^{-5}$) in ASD-affected child compared to those in the unaffected siblings. The rate of missense mutations was also accountable to ASD diagnoses, although at a lower estimate of approximately 13%. From all LGD-gene alleles examined, no additional variants were found on the opposite alleles, thereby excluding the possibility of homozygous loss of function or compound heterozygosity of the affected genes. Increased paternal age have been previously suggested as a risk factor of ASD (4), and the current study also observed a similar trend of an increased autism rate in the older Simplex family parents.

Next, the authors further classify the genes that are affected by LGD mutations into six functional gene

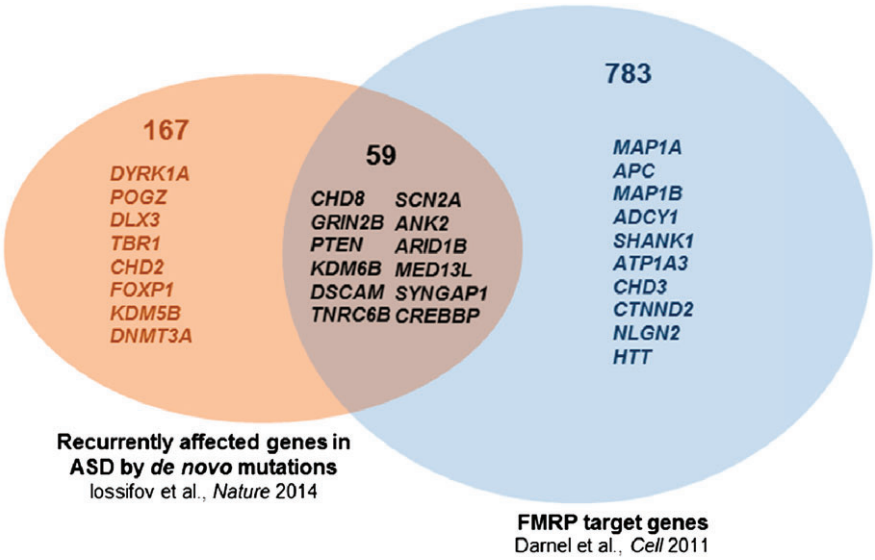

Fig. 1. Venn diagrams showing the overlapping genes between recurrent LGD/missense targets in the current study (shown in orange) and the previously published FMRP target genes (shown in blue). Approximately 25% of the genes (59 of 226 genes) affected by *de novo* mutations in ASD are FMRP targets. Representative lists of genes in each category are depicted.

classes with known involvement in ASD: (i) FMRP target genes, given that Fragile X syndrome is the most common form of inherited autism, (ii) chromatin modifiers, (iii) embryonically expressed genes, (iv) post-synaptic density proteins, (v) essential genes and (vi) Mendelian disease genes. Interestingly, *de novo* LGD targets in affected subjects were significantly enriched for FMRP target genes ($p = 4 \times 10^{-4}$) and chromatin modifiers genes ($p = 3 \times 10^{-4}$). No significant enrichment for these gene sets is seen in unaffected siblings, indicating that preferential LGD mutations reside uniquely in ASD-affected individuals. Missense mutations in affected subjects were also enriched in FMRP targets ($p = 0.03$), suggesting this functional gene class as a key pathway that is prone to ASD-related mutations.

Quantitative traits, such as IQ score, are highly variable in ASD and have a strong male bias in SSC families (2). To probe for an association between *de novo* mutation and IQ, the authors divided the affected male population into higher and lower IQ groups. They observed that the frequency of *de novo* LGD mutations could significantly affect the IQ score, and those with LGD mutations in FMRP targets have an average of 14-point drop ($p = 0.001$). Interestingly, LGD targets in lower IQ affected males are significantly enriched for FMRP associated and chromatin modifier gene classes whereas in higher IQ males there are no significant differences among gene classes, supporting the involvement of convergent pathways that are deregulated in ASD.

Moreover, significant overlaps of affected genes were only seen in affected females and affected males of lower IQ, ($p = 7 \times 10^{-7}$), indicating a plausible shared genetic mechanism between the two groups. Lastly, they observed 22 of 254 LGD events and 60 of 944 missense mutations to be recurrent within the joint class of affected females and males of lower IQ. The authors provided an estimate of approximately 400 genes that are susceptible to ASD (Fig. 1). Although the penetrance cannot be determined, some of the mutations within the genes reported in this study such as *CHD8*, *GRIN2B* and *DYRK1A* have been identified previously in ASD or other neurodevelopmental disorders.

In conclusion, this study expands on previous findings and further strengthens the notion of convergent molecular pathways shared in ASD, as shown by vulnerability of FMRP-associated genes and chromatin modifiers that are recurrently affected in ASD individuals. This raises the possibility that therapies developed for genetically defined forms of ASD, such as Fragile X syndrome, may be of wide benefit to patients with ASD in general.

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