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HUMAN GENETICS

Autism — clues from brains and protein domains

> DUF1220 copy number is linearly associated with increasing severity of the three main symptoms of ASDs

Autism and autism spectrum disorders (ASDs) result in impaired social interaction and communication, as well as repetitive behaviours. Abnormalities in neural development characterize the disorders, although the genetic factors behind ASDs are complex and highly variable between individuals. Now, two new papers show that autism is most likely to develop during pregnancy and that, in individuals with ASD, DUF1220 copy number is linearly associated with increasing severity of the three main symptoms of ASDs.

Early brain overgrowth is a common feature of autism, which affects several cortical and subcortical regions, including the prefrontal and temporal cortices. Stoner *et al.* studied post-mortem cortex tissue from 22 children who died between the ages of 2 and 15, half of whom had autism. They used RNA *in situ* hybridization on these samples to measure the expression levels of 25 genes (including genes that are differentially expressed among the six layers of the cortex, genes previously associated with autism and control genes) that usually have robust and specific expression patterns. The cortical layers are built up during pregnancy; however, Stoner and colleagues report that the genetic markers that usually associate with the different cortical layers were disrupted in patchy regions across these layers in 10 of the 11 samples from children with autism, which suggests that the pathogenesis of autism is already occurring *in utero*. The frontal regions (which are associated with communication and social comprehension) and the temporal region of the cortex (which is associated with language) were the most affected by these focal patches, and the researchers suggest that this reflects the symptoms seen in these individuals.

In the second study, a team led by James Sikela hypothesized that DUF1220 — a copy-number polymorphic protein domain that shows a substantial human-specific increase in copy number and that is linked to both brain size and evolution — might be related to the timing and rate of neurogenesis. In this hypothesis, if neurons are produced too quickly, then it could result in an overabundance of poorly connected neurons. The researchers found that CON1 (a subtype of DUF1220) has a Gaussian frequency distribution ranging from 56–88 copies in the human population. "This meant that DUF1220, as a gene-coding region, would be capable of generating a broad continuum of phenotypic variation," explains Sikela. Importantly, they found that DUF1220 dosage is linearly associated with the severity of the main symptoms of autism. "As CON1 copy number increases, each of the three primary symptoms of ASDs — impaired social reciprocity, impaired communicative ability and increased repetitive behaviours — become incrementally worse," says Sikela. Although the link between CON1 copy number and autism severity is found in individuals with ASDs, the authors note that the range of copy number is similar to that seen in the general population, which means that there are likely to be other causal mechanisms for the disease to manifest itself. Moving forward, the team now plan to examine the other five subtypes of DUF1220 to see whether they are also associated with ASDs.

Taken together, these studies provide insights into the timing of ASD onset and link the severity of ASDs to copy-number variation in the genome. Interestingly, the same gene family that might have facilitated the evolutionary expansion of the human brain is now implicated with autism severity, and this might explain why autism, which is heritable and maladaptive, persists at a high frequency worldwide.

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ORIGINAL RESEARCH PAPERS Stoner, R. *et al.* Patches of disorganization in the neocortex of children with autism. *N. Engl. J. Med.* **370**, 1209–1219 (2014) | Davis, J. M. *et al.* DUF1220 dosage is linearly associated with increasing severity of the three primary symptoms of autism. *PLoS Genet.* **10**, e1004241 (2014)