Spontaneous mutations and the genetic mysteries of autism

A new study has refined estimates about the total contribution of a particular kind of genetic mutation called de novo mutation to autism spectrum disorder (ASD).

These mutations arise “spontaneously” in a child and do not occur in either parent. At least 30% of all ASD is caused by de novo mutations, according to Cold Spring Harbor Laboratory Assistant Professor Ivan Iossifov, a quantitative biologist and first author of the paper n Nature. The team analyzed the genomes of over 2,500 “simplex” families – those in which a single child but neither parent nor siblings, if any, have ASD,

The authors say 30% is a conservative estimate and consists of three subtypes of de novo mutations. Among these are three major contributors. One kind are called “missense” mutations. Another are called “likely gene-disrupting” mutations (abbreviated as LGD). Both subtypes are small in size – “misspellings” involving 20 DNA letters or less. Missense mutations (which lead to errors in proteins that affect their function), are more common but individually less harmful; LGD mutations are rarer, but are often devastating. The third type are large-scale copy number variations, which the team described in earlier work.

All the mutations hit the coding part of genes, but there are other types of mutations that the teams cannot yet detect using current technology, which is why the 30% is a conservative estimate.

One of the team’s findings is that missense de novo mutations cause a total of 12% of all autism, while LGD de novo mutations cause 9%. Together, then, they account for some 21% of autism. However, not every mutation carries the same weight: about 13% of missense de novo mutations, or 1 in 7, were thought to cause ASD in the group under study. In contrast, 43% of the less frequent LGD mutations were deemed causal.

A second finding of the new study is that the pool of spontaneously mutated genes contributing to ASD across the population totals about 400. Humans have roughly 21,000 genes. The key question, of course, is which genes confer the highest risk of ASD when mutated.

The new study was able to demonstrate something not shown previously: that ASD caused by de novo mutations generally divides into two different risk classes. In one class are comparatively high-IQ males (who are also the highest-functioning). The other class includes males with low IQ and all nearly all affected females, who tend to have low IQ.

Importantly, the team found recurrent de novo gene-disrupting mutations in 27 genes, which make them highly likely to be causal factors in the most severe cases – i.e., in low-IQ males with ASD and in females with ASD. Such disruptive mutations are so rare that finding them more than once in a sample of several thousand people is powerful proof of their importance in ASD.

Why girls get autism less

Girls are thought to have a protective factor, still unidentified, against the impact of potentially causal mutations. But the new data reinforces the view that when females do get ASD, it is often because genes that are highly active in early development incur devastating, disrupting mutations. No such temporal pattern is seen in boys. But the same mutations, in boys, are hypothesized to be responsible for the more severe male ASD cases, including boys with low IQ.

The research in the new paper is based on whole exome sequencing – sequencing only the 2% of the full human genome that encodes proteins. Prior exome studies of intellectual disability and schizophrenia, the authors note, have turned up sets of genes significantly overlapping those identified in the new ASD study. The largest overlap is seen in genes that express messages to which proteins called FMRP bind. FMRP is the protein encoded by the gene FMR1, whose dysfunction causes Fragile-X syndrome and is a major risk factor in intellectual disability.

“Our findings lend new weight to the hypothesis that there are specific functional categories of genes – likely conserved by evolution in development of the human neurological system and brain – that strongly contribute to autism’s causation, such as genes expressed during embryonic development and genes that encode proteins that remodel chromatin, the bundles in which our DNA is stored,” says co-author and Assistant Professor Michael Ronemus.