The genetics of autism:

contributions of multiple genes

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Although the causes of autism are still not well understood, we do know that genetics play a large role. Indeed, research shows that if you had an identical twin who was autistic, you would have a 70 to 90% chance of also being autistic. This would indicate that genetics contribute 70 to 90% of causality in autism.

Picture your DNA as an encyclopedia made up of 46 volumes : your chromosomes. Then, within these 46 volumes, over 27,000 paragraphs : your genes. One or more of these paragraphs or genes may be partially or completely modified, and in such cases we refer to a *mutation* of the gene(s).

The simplest scenario involves a mutation of a single gene which explains a person's autism symptoms. This is the case in a mutation of the FMR1 gene on the X chromosome, which causes Fragile X Syndrome. This mutation is associated with intellectual disability and atypical facial features, and also with autistic signs in about 50% of cases. Therefore, there are some cases in which autism can be explained by a mutation in a single gene, such as FMR1, making the cause very clear. However, this is only the case for a small portion of the autistic population.

In most autistic people, we tend to find mutations of many genes at the same time. This combination of altered genes contribute to an autism diagnosis. We see this on alterations of a small portion of chromosome 16, in the 16p11.2 region, which affects 31 different genes. Almost as though a page containing 31 paragraphs was torn out or duplicated in one of our encyclopedia volumes! This mutation is associated with autism in 20% of cases, but has also been linked to intellectual disability and schizophrenia.

Studies have currently identified only about a hundred genes which can contribute to an autism diagnosis. This isn't much when you consider our total of 27,000 genes! However, as previously mentioned, modifying these genes does not always lead to autism. People with the same mutation could develop psychiatric disorders and/or autism, but not always.

It is also important to consider that, beyond this group of clearly identified genes, most other mutations are only observed in a very small number of individuals. Despite the scientific community's efforts, the precise effect of these mutations remains unknown.

A team led by Dr. Sébastien Jacquemont, physician and geneticist at Sainte-Justine Pediatric University Hospital Center (Montreal, Canada), has recently published studies interested in developing new tools to estimate the effects of these mutations. In other terms, they produced a technique allowing them to estimate the overall contribution of a mutation on autism diagnosis. They estimated that, of our 27,000 genes, around 40% can increase risk for autism when presenting with a mutation. This would support the hypothesis that a large proportion of genes are involved in autism and that a complex combination of several genetic mutations would explain the condition. From these results, an online clinical tool (https://cnvprediction.urca.ca/) was developed to assist clinicians in giving a probability estimate for autism given a certain mutation.

In conclusion, though it is clear that autism is largely explained by genetics, in the majority of cases we do not find any mutations to the hundred or so genes which have been clearly identified. Mutations to a single gene, as is the case in Fragile X, are even rarer. Autism is therefore due to a combination of mutations to several genes, but we cannot yet precisely define what effect this has. New tools are necessary to study this phenomenon.

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Main references:

1. Tick, B., Bolton, P., Happé, F., Rutter, M., & Rijsdijk, F. (2016). Heritability of autism spectrum disorders : a meta-analysis of twin studies. *Journal of Child Psychology and Psychiatry, 57(5), 585-595.*
2. D'Angelo, D., Lebon, S., Chen, Q., Martin-Brevet, S., Snyder, L. G., Hippolyte, L., ... & Pain, A. (2016). Defining the effect of the 16p11. 2 duplication on cognition, behavior, and medical comorbidities. JAMA psychiatry, 73(1), 20-30.
3. https://gene.sfari.org/database/human-gene/
4. Douard, E., Zeribi, A., Schramm, C., Tamer, P., Loum, M. A., Nowak, S., et al. (2020). Effects-sizes of deletions and duplications on autism risk across the genome. *bioRxiv*.