

Exploring the genetic origins of autism

25 February 2015, by Dominique Nancy

The geneticist Sébastien Jacquemont is the new holder of the Canada Research Chair in Genetics of Neurodevelopmental Disorders and Associated Dysregulation in Energy Balance at the University of Montreal. He moved to the city in September to join the Faculty of Medicine and work with members of the Sainte-Justine University Hospital Research Center.

"I wagered that here we would succeed in creating selected cohorts based on [genetic mutations](#), a key factor in making new scientific breakthroughs in the field. Montreal enjoys an enviable reputation in the neuroscience sector. I hope to be able to enrich and expand my expertise."

An internationally recognized specialist in neuropsychiatric and neurodevelopmental disorders such as autism and fragile X syndrome, Dr. Jacquemont has published a number of scientific articles in the journal *Nature* on the [chromosomal abnormalities](#) associated with these diseases. "Individuals usually receive two copies of chromosomes from their parents," states the geneticist. "Sometimes, the process is accompanied with structural errors. For example, DNA segments can be lost, which is called 'deletion.' It is a bit as if a whole chapter of a book is missing. In the case of 'duplication,' duplicate segments are passed down from one of the parents, resulting in the presence of three copies."

In 2010, Sébastien Jacquemont and his French colleagues discovered a link between [body mass index](#) and the number of copies of a region of chromosome 16. More specifically, they demonstrated that obesity, autism and the deletion of DNA fragments were associated. In 2011, his team revealed that a loss in locus 16p11.2 was linked to a 70% risk of obesity, developmental delay and increased cerebral growth, whereas a duplication of this fragment of the chromosome was associated with low weight, schizophrenia and brain volume deficiency.

The impairments noted on chromosome 16 only

explain a small number of autism cases (about 1%). However, through the work done by Sébastien Jacquemont's team, we now know that the gene dosage of this region modulates cerebral growth.

Genetic under-dosage and over-dosage

Since autism syndrome was described in 1943 by the psychiatrist Léo Kanner, there has been a debate as to its causes: is one born autistic or does one become so?

Today, the genetic dimension of autism, long dismissed by a portion of the psychiatric community, can no longer be ignored. "The risk of an autistic child having a sibling with the syndrome is 10 times higher than that in the general population," points out Dr. Jacquemont. Autism is a genetic component in approximately 60% to 90% of the cases. This link has been demonstrated in studies conducted on monozygotic (identical) and dizygotic (non-identical) twins.

However, we have not yet been able to explain the fact that boys are four times as likely as girls to be affected by autism. A recent study conducted on two large populations with genetic variations published in the *American Journal of Human Genetics* in 2014 unravels some of the mystery surrounding this fact. The findings reveal many more hereditary DNA defects in girls than in boys. "This shows that for the same number of genetic defects, girls fare better than boys. Their brain seems to be better armed to deal with certain mutations and compensate for them," stresses Dr. Jacquemont, lead author of the study.

Another hypothesis is that the more adaptable behavior of girls, who are naturally more apt to communicate and socialize, could counterbalance the genetic mutations that handicap boys. "Nothing is sure," admits the geneticist, "but it could in part explain why we see fewer young girls."

This neurological disorder, which varies in degree of severity, is also called Autism Spectrum Disorder

(ASD). It is characterized by social interaction problems, verbal communication difficulties and repetitive and stereotyped behaviors. In only a small proportion of people does ASD result from a single gene anomaly. Most cases depend on variable combinations of mutations.

Thanks to the Canada Research Chair in Genetics of Neurodevelopmental Disorders and Associated Dysregulation in Energy Balance, Dr. Sébastien Jacquemont is able to consolidate the work he is carrying out on chromosomal abnormalities associated with [neurodevelopmental disorders](#). One of the promising research axes of his studies focuses on the effects of gene dosage on cognitive and psychiatric symptoms. Using clinical, genetic, neuroimaging and biomarker data, he hopes to elucidate the mechanisms by which certain genes lead to deficiencies and clinical symptoms.

The investigator wonders: "Can we show that other clinical traits like behavior and cognition are also correlated with gene dosage? Are there changes in the brain of individuals who present genetic mutations? The overall mechanism of under-dosage and over-dosage could enable us to understand why we find the same genes but not the same mutations in autism and schizophrenia."

For the time being, while the harmful effect of mutations on development has been proven, investigators ignore how the structural variations can have such diverse clinical manifestations. Their characterization could lead to the development of diagnostic tools and open therapeutic avenues.

Region involved in the reward system

Since his medical residency at the University of Nantes, France, in 1996, Sébastien Jacquemont has seen genetics take off. For example, he cites as an example: "It was the stone age at that time. Progress made in the field has now made it possible to analyze the differences in the number of copies on DNA segments on the whole human genome."

As a witness and agent of the advances made in this science, Dr. Jacquemont has been among the first to apply clinical knowledge to research as a

method of investigation. The 42-year-old comes to Montreal with the energy of a young man. The father of two young daughters and a teenage girl loves fresh air. While his workload is heavy, you can still probably see him walking on Mount Royal or skiing in the Laurentians.

In any case, he did not wait until his new office was set up to pursue his research. He has also just finished a study that is attracting a great deal of attention. About fifty people with a genetic mutation on chromosome 16 agreed to "take a little trip" to an MRI scanner in order to record the anatomy of their brain. The results published in the journal *Molecular Psychiatry* show that the chromosome 16 region controls the structure of the neural circuit involved in the reward system.

Provided by University of Montreal

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