Complex genetic architectures: Some common symptoms of trisomy 21

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Down syndrome, more commonly known as "trisomy 21" is very often accompanied by pathologies found in the general population: Alzheimer's disease, leukemia, or cardiac deficiency. In a study conducted by Professor Stylianos Antonarakis' group from the Faculty of Medicine of the University of Geneva (UNIGE), researchers have identified the genomic variations associated with trisomy 21, determining the risk of congenital heart disease in people with Down syndrome.

The targeted and specific study of chromosome 21 revealed two genomic variations, which, in combination, are the hallmark of hereditary cardiac deficiency. These results are being published in the journal *Genome Research* and add to other research conducted by the same team about chronic myeloid leukemia, a severe form of leukemia that often affects people with Down syndrome. The journal *Blood* is publishing these advances in the understanding of a disease which, like hereditary cardiac deficiencies or early Alzheimer's, affects the general population.

Heart disease is a common disorder of Down syndrome. While the presence of a third gene in the n°21 pair (which characterizes the disease) increases the risk of heart disease, it is not the sole cause: genetic variations—or polymorphisms—as well as certain environmental factors also contribute to it. Genetic variations create the diversity of human beings, their predispositions, and the differences in the expression of similar genes.

Variations increase the risk of hereditary cardiac deficiency…

As part of a study carried out on the risk of congenital heart disease in people with Down syndrome, the geneticists led by Stylianos Antonarakis who conducts the research at UNIGE's Department of Genetic and Developmental Medicine observed the dominating role of two types of polymorphisms: the nucleotide (SNP, which stands for single-nucleotide polymorphism) and the variability in the number of copies of a gene (CNV, which stands for copy number variation).

To verify these observations, the scientists created a tailor-made chromosome 21; their analyses revealed two areas of variability in the number of copies of a gene (or CNV), and one area identified by a nucleotide polymorphism (or SNP), which can be associated with the risk of heart deficiency. Therefore, this study highlights the role of two CNVs and one SNP in the cardiac pathogenesis of people with Down syndrome for the first time, revealing the genetic complexity of a common symptom of trisomy 21.

For the geneticist-authors of this study, the genetic architecture of the risk of congenital heart disease in individuals with Down syndrome must henceforth be understood as a complex combination, revealing the 21st chromosome, nucleotide polymorphism, and variability in the number of copies of a gene all at once; three factors to which we must add to the rest of the genome a still unidentified genetic variation, which Professor Antonarakis' group is already tracking.

…and also the risk of chronic myeloid leukemia

In parallel, this same group has made progress in understanding another relatively common symptom of Down syndrome, by tracking the genetic

variations that identify chronic myeloid leukemia in the body's cells.

This research is itself the subject of a publication in the latest issue of the online journal *Blood*; like the former, it contributes to the diagnostic and therapeutic improvement of major and misunderstood disorders, pathologies that are more successfully studied in people with trisomy 21, pathologies that can affect everyone.

Provided by University of Geneva