

THE BRAIN AND THE SKELETON: WHY THEIR DEVELOPMENT NEEDS A SUGAR

UNIL-CHUV researchers uncover a new genetic disease

The observation of patients with the unusual combination of severe intellectual disability and poor skeletal growth led Dr. Andrea Superti-Furga, professor in the Faculty of Biology and Medicine at the University of Lausanne (UNIL) and at the Centre Hospitalier Universitaire Vaudois (CHUV), to question whether there was a single underlying cause. The investigations have uncovered a new genetic disease that is yet to be named. Given the importance of these discoveries, they will be published in the prestigious journal [Nature Genetics](#); available on-line May 23rd.

In the study, nine affected individuals were ascertained, coming from Italy, Canada, the United-Kingdom, France and Japan. The youngest patient was 3 years old and the oldest was 46; some patients were siblings. The studies were done in collaboration with physicians from Italy, Canada, the United Kingdom, France and Japan; and with the participation of researchers from the British Columbia Children's Hospital and the University of British Columbia (Vancouver, Canada), the St. Michael's Hospital and the University of Toronto (Canada), the Radboud University Medical Center (Nijmegen, Netherlands), the Department of Computational Biology of the Lausanne University, as well as other researchers in Zurich, Pavia and Vienna.

International Collaboration as the key to success

"Over the last five years, Professor Luisa Bonafé, myself and our team had diagnosed this combination of clinical signs in eight patients and found the genetic mutations responsible. But it was in 2015, when we were contacted by our colleagues in Vancouver and in Nijmegen about a patient they had been studying, that things advanced rapidly." explained Professor Superti-Furga. "They had observed metabolic abnormalities in plasma, urine and cerebro-spinal fluid in that patient. We shared samples and data and this gave us much stronger evidence that all nine patients, who shared the intellectual disability with lack of speech combined with poorly growing bones, actually had the same disorder. Then, scientists from other centers helped us in figuring out many of the biochemical and molecular facets of this new disease. Collaboration really made the difference!"

Sialic acid, a marker of brain growth

The study showed that the basis for this disease is an impairment in the synthesis of sialic acid. From the Greek "*sialon*", meaning saliva (because that is where it was first found 60 years ago), sialic acid is a sugar derivative composed of eleven carbon atoms that helps cells to communicate with each other. "Sialic acid is everywhere in our body, but the brain contains much more sialic acid than any other organ. The sialic acid-rich brain also distinguishes man from our relatives, the great apes", says Superti-Furga. Sialic acid has

been credited with beneficial effects on the development of babies. Notably, human breast milk contains significantly more sialic acid than cow milk or infant formulas.

The *NANS* gene (for N-acetyl neuraminic acid synthase) codes for the enzyme that is responsible for the formation of new sialic acid in the body. Eight different genetic variations (mutations) were identified in the affected individuals in the study; these mutations are recessive, meaning that carriers are clinically unaffected; a double dose is needed to develop the disease. In individuals with two mutations, the formation of sialic acid in their cells is reduced. To confirm that the disease is caused by a deficiency of sialic acid, the genetic defect was studied in a zebrafish model: *NANS*-mutated fish had very poor skeletal growth but when sialic acid was added to their water, the defect was successfully corrected.

Towards an oral substitution therapy

To alleviate the disease, the Swiss and Canadian physicians are exploring the possibility of sialic acid substitution, given that orally administered sialic acid is safe and well tolerated. The parents of affected individuals are thrilled by such a possibility. Prof. Superti-Furga is cautious : « We do not know whether the requirements of sialic acid in prenatal development are met entirely by endogenous synthesis, and whether sialic acid can be supplied by the mother through the placenta. Then, more studies will be necessary to ascertain whether dietary supplementation with sialic acid can be of benefit for the patients. «

Implications for human nutrition ?

The incidence of *NANS* deficiency is not known but now that a biochemical and molecular test is available for the disease, it is likely that many more affected individuals will be diagnosed. However, the significance of these findings goes beyond the disorder itself and may have an impact on human nutrition science. « The observation that sialic acid is central to the development of brain functions may support existing suggestions to use sialic acid for the fortification of infant formula, to foster an optimal brain development, as well as that of nutritional supplements for elderly people to maintain their cognitive power », concludes Professor Superti-Furga.