Improvement of the genetic decoding of neurodevelopmental disorders

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A result that will help in the future diagnosis of children with neurodevelopmental disorders, such as intellectual disability, autism or schizophrenia. A video illustrates this scientific analysis with medical applications.

A key question in biology is understanding how brain works. Neurons transmit information in the form of electrical impulses and chemical signals. Alterations in the function of the neurons can lead to neurological and psychiatric disorders. Neurodevelopmental disorders (NDDs) are a group of frequent and often severe pediatric conditions that can manifest as intellectual disability, autism or early-onset psychiatric symptoms. The recent development of higher resolution genetic diagnostic tools has revealed the prevalence of genetic anomalies, such as copy number variations (for example, loss of a gene) in children with NDDs.

Two HUDERF patients with neurodevelopmental disorders exhibiting cognitive and behavioral symptoms showed partial loss of the DLG2 gene, which plays an important role in the development, plasticity and stability of synapses.

A research team led by Dr. Guillaume Smits, Nicolas Deconinck and Catheline Vilain of HUDERF and Professor Gianluca Bontempi of ULB worked at integrating large genomic, epigenomic, transcriptomic and clinical datasets. The computational experiments pinpointed two novel DLG2 promoters and coding exons conserved in humans and mice and

present in the fetal brain. The deletion of these new regions were found to be statistically associated with developmental delay and intellectual disability in two independent patient cohorts, supporting the pathogenic role of these new elements into the neurodevelopmental symptoms of both HUDERF patients. The results of this work have been published in the international journal *Genome Medicine*.

From a medical perspective, the findings will help physicians in improving diagnoses of children with NDDs, intellectual disability, autism and schizophrenia. From a scientific point of view, this work shows how the in silico integration of multiple large datasets can improve genome studies. It also sheds light on the molecular causes of neurodevelopmental disorders and improves fundamental knowledge about the DLG2 gene.

More information: Claudio Reggiani et al, Novel promoters and coding first exons in DLG2 linked to developmental disorders and intellectual disability, *Genome Medicine* (2017). DOI: 10.1186/s13073-017-0452-y

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