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IMPACT OF GEPHYRIN ALTERNATIVE SPLICING ON INHIBITORY SYNAPSES FUNCTION

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Brain function relies on a balance between excitation and inhibition of neuronal transmission. Disruption of inhibitory circuits is currently proposed as one of the common neurologic alteration responsible for several neurodevelopmental disorders. The Gephyrin (GPHN) gene is the main molecular organizer of inhibitory synapses in mammalian and misregulation of its expression, in particular, its splicing regulation, is a risk factor for schizophrenia, Autism Spectrum Disorders (ASDs), and epileptogenesis. Because GPHN expression is currently assayed only using short read sequencing, which is unappropriated to assess alternative splicing, we do not picture yet the diversity issued of its expression.

Using long read sequencing, we reveal an impressive and unexpected diversity of transcripts expressed by GPHN (more than 300), which contrast to the only two alternative transcripts annotated in the *Ensembl* database. Several new exons and new alternative splicing events are regulated during the inhibitory circuit formation in mouse Cerebellum. We are currently questioning how this diversity modulates the inhibitory synapses. Our data represent the first stone required to develop the future correcting therapeutic of GPHN splicing, like those recently released for SMA (Spinal Muscular Atrophy) and DMD (Duchenne Muscular Dystrophy) with the Spinraza and Eteplirsen respectively.

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