B·DEBATE International Center for Scientific Debate BARCELONA

Sant Joan de Déu HOSPITAL MATERNOINFANTIL - UNIVERSITAT DE BARCELONA

Sant Joan de Déu Research Foundation

GABRIELLA HORVATH

CV

PARTICIPANT AT:

CONNECTING THE GROWING BRAIN

UNDERSTANDING NEUROPAEDIATRIC DISEASES THROUGH SYNAPTIC COMMUNICATION

November, 26th-27th, 2015, Barcelona

Gabriella Horvath, Biochemical Geneticist, BC Children's Hospital and Vancouver General Hospital, Vancouver, Canada

Gabriella Horvath, Biochemical Geneticist, BC Children's Hospital and Vancouver General Hospital, Vancouver, BC, Canada, since 2006. Main research interest is in primary and secondary neurotransmitter disorders and movement disorders in inborn errors of metabolism. Currently working on the research project: biogenic amine release from synaptic vesicle in presence of deficient intraneuronal calcium in sodium channel mutations. Another research area of interest is looking at phosphorylation status of biogenic amine synthetic enzymes in CSF in patients with secondary neurotransmitter deficiencies.

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ABSTRACT

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Unraveling Secondary Neurotransmitter Deficiencies in Genetic Disorders

Despite numerous reports of secondary CSF neurotransmitter deficiencies in genetic disorders, pathophysiology is still not fully understood. We reviwed 377 patients for whom CSF neurotransmitter analysis was performed between 2009-2013 in our centre. 70 had abnormal NT values; 2 identified with congenital NT disorders. The majority had primary epilepsy syndromes. 15 patients with secondary NT deficiencies and good. clinical response to L-dopa/carbidopa and 5-hydroxytryptophan in terms of improvement in seizures, psychiatric and/or movement disturbances were enrolled for whole exome Sequencing (Omics2TreatID study, Vancouver). Proteomic, metabolomic, protein phosphorylation studies, intracellular calcium content, full transcriptome analyses were conducted to validate genotypes and reveal mechanism of secondary NT deficiencies. Pathogenic mutations in genes encoding signal transductions pathways, chanellopathies, lysosomal protein, or splicing coactivator were identified. In 10 of 15 patients. In vitro experiments showed secondary NT deficiencies due to biogenic amine synthetic enzyme deficiency (inactive form of enzyme due to lack of phosphorylation), intracellular calcium signaling abnormalities, or up- and/or down-regulated genes in pathways related to biogenic amine metabolism. Using a systems biology approach, the complex pathophysiology of secondary neurotransmitter deficiencies was further elucidated. Therapy with dopamine and serotonin precursors is helpful in many cases.

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