Clinical presentation of IDDMSSD syndrome likely associated with molecular location of mutation in PAK1 gene

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A recent study from Texas Children's Hospital and Baylor College of Medicine has expanded the clinical spectrum of a new epileptic disorder called Intellectual Developmental Disorder with Macrocephaly, Seizures, and Speech Delay (IDDMSSD) with the identification of the first

recurrently affected residue identified in the protein kinase domain of PAK1 protein.

The study, published in the *American Journal of Medical Genetics: Part A*, found potential correlations between how and which organ systems are affected in individuals with this rare disorder and the protein domains where the mutations are present.

The study was led by Texas Children's child neurologist, Dr. Hsiao-Tuan Chao, who is also an assistant professor at Baylor College and an investigator at the McNair Medical Institute with the Robert and Janice McNair Foundation, Cain Pediatric Neurology Research Foundation Laboratories, and the Jan and Dan Duncan Neurological Research Institute (Duncan NRI) at Texas Children's Hospital. The study was conducted through the Undiagnosed Genetic Epilepsies Initiative launched in the above-mentioned institutions.

"We are grateful to the families and clinicians for their support of our Undiagnosed Genetic Epilepsies Initiative. I am proud of my dedicated team and collaborators who made it possible to identify the rare genetic alteration in the gene p21-activated kinase 1 (PAK1) and expand our understanding of PAK1-related IDDMSSD. To the best of our knowledge, our study has now raised the number of individuals identified with IDDMSSD to eight worldwide.," said Chao.

PAK1 belongs to the PAK family of kinases which encode evolutionarily conserved serine/threonine kinases that regulate key signal transduction pathways required for multiple developmental processes. Genetic variations in different PAK family members have been implicated in different neuronal disorders. In mice, *Pak1* is highly expressed in the brain, where it regulates fundamental processes such as cell proliferation and neuronal migration.

The initial disease-causing variants in PAK1 were found to be present in the auto-regulatory domain of the encoded protein, which inhibits the protein kinase domain. Thus, it was believed that this disorder is a result of constitutive activation due to the malfunction of the 'off' switch. This study expands on prior knowledge in the field by identifying the third disease-causing mutation in the protein kinase domain, and the first recurrent mutation affecting the same residue.

To evaluate if there was any correlation between the protein domain location of the eight known disease-causing PAK1 variants and the spectrum of symptoms, the researchers compared the symptoms of individuals with PAK1 variants in either the auto-regulatory or the protein kinase domains. They found that the three PAK1 variants affecting the kinase domain were more often associated with severe epilepsy that was refractory and not responsive to medication. In addition, the protein kinase domain variants were more often associated with non-neurological symptoms. PAK1 variants in the autoregulatory domain of PAK1 were more often associated with relatively more controllable seizures that were responsive to medication but posed an increased risk of autism spectrum disorder. Thus, this study expands our knowledge of the phenotypic spectrum of IDDMSSD.

"PAK1 is expressed widely in various tissues in the body. Somatic mutations in this gene that result in increased expression of this gene lead to different cancers, suggesting that potential strategies developed in the cancer field to inhibit the protein kinase activity may also be helpful in treating this neurological condition for individuals who have PAK1 variants leading to constitutive activation of the kinase," Dr. Chao said.

More information: Melina L. Corriveau et al, PAK1 c. 1409 T > a (p. Leu470Gln) de novo variant affects the protein kinase domain, leading to epilepsy, macrocephaly, spastic quadriplegia, and hydrocephalus: Case report and review of the literature, *American Journal of Medical Genetics*

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