MAPK8IP3-Related Neurodevelopmental Disorder

Wendy Chung, MD, PhD, Clinical and Molecular Geneticist, Kennedy Family Professor of Pediatrics and Medicine, Columbia University Medical Center and Alexa Geltzeiler, ScM, CGC, Department of Pediatrics, Columbia University Medical Center, and the Wolverine Foundation

Introduction

- Defective transport of cargo along the axons of neurons underlies a variety of rare genetic neurodevelopmental disorders
- MAPK8IP3 (Mitogen-Activated Protein Kinase 8 Interacting Protein 3) is highly expressed in neurons
- MAPK8IP3 encodes for JIP (JNK-interacting Protein 3) which functions as a scaffold/adapter protein linking cargos to the dynein and kinesin motors
- JIP3 is important for multiple cellular process in the developing brain, including axon guidance and the development of the thalamus, hippocampus, and cortical plate
- Heterozygous pathogenic variants in this gene that lead to neurodevelopmental disease have been identified in at least 20 individuals
- There is a spectrum of severity ranging from mild developmental delays to more severe cognitive and physical impairments
- Treatment of affected individuals is typically symptom-driven and supportive, focusing on speech, physical, and social development

Signs and Symptoms

- Individuals with MAPK8IP3-related disorder have a spectrum of neurodevelopmental disabilities
- All affected individuals experience some level of global developmental delay including problems with muscle tone (bone hypertonia and hypotonia have been reported) and walking, impaired intellectual development, and poor or absent speech
- Some individuals have brain abnormalities visible on MRI including thin corpus callosum, cerebral atrophy, perisylvian polymicrogyria, and delayed myelination
- EEG abnormalities, including slow waves with spikes, have been reported
- Other reported features include:
  - Precocious puberty
  - Short stature
  - Facial dysmorphism (round face, thin upper lip, and/or prominent nasal bridge)
  - Scoliosis
  - Cortical visual impairment

Causes

- MAPK8IP3-related neurodevelopmental disorder is caused by pathogenic variants in the MAPK8IP3 gene
- To date, all known occurrences of MAPK8IP3-related disorder have been de novo, with rare cases of gonadal mosaicism
- Both missense and truncating variants in MAPK8IP3 have been reported
- No clear phenotype-genotype correlation has been identified

Affected Populations

- The number of individuals with MAPK8IP3-related disorder is unknown, due to the newly described nature of this condition and variable access to genetic testing
- To date, there are 18 affected individuals in the published literature

Related Diagnosis

- KIF1A-Related Disorder is another rare neurodegenerative disorder that affects motor proteins involved in the transport of vesicles and organelles
- Pathogenic variants in KIF1A cause neurological disorders and disabilities ranging from mild to life threatening
- Symptoms include intellectual disability, developmental delays, and diminished muscle tone (hypotonia)
- The treatment for KIF1A-Related Disorder is directed at the specific symptoms that each patient develops

Standard Therapies

- Occupational, physical, speech, and feeding therapies may be utilized to address specific developmental delays
- Genetic counseling is reccomended for affected individuals and their families

Investigational Therapies

- Research into the natural history, cellular mechanisms, and potential treatment of MAPK8IP3-related disorder is ongoing
- Please visit www.wolvfdn.com if you are interested in participating in research or if you are a provider looking to refer a patient to the current MAPK8IP3 natural history study
- If you are a family interested in connecting with other families with this mutation, please visit https://curemapk8ip3.com

Supporting Organizations

- The Wolverine Foundation: www.wolvfdn.com
  - The Wolverine Foundation serves to advance research and discover novel therapeutic approaches to treat the neurodevelopmental disease caused by pathogenic variants in MAPK8IP3
  - The Foundation aims to accomplish these goals by supporting a team of researchers to:
    1. Investigate disease mechanisms and novel therapeutic approaches associated with MAPK8IP3-Related neurodevelopmental disorder
    2. Manage a diverse portfolio of research projects that encourages scientific collaboration to more directly connect academic research, drug discovery, and clinical development. Our activities extend from exploratory biology to the identification and validation of therapeutic targets, and from drug discovery and development to clinical studies and trials

References

Iwasawa S, Yanagi K, Kikuchi A, et al. Recurrent de novo MAPK8IP3 variants cause neurological phenotypes. Ann. Neurol. 2019;85: 927-933

Platzer K, Sticht H, Edwards SL, et al. De novo variants in MAPK8IP3 cause intellectual disability with variable brain anomalies. Am. J. Hum. Genet. 2019;104: 203-212

Kelkar N, Gupta S, Dickens M, Davis RJ. Interaction of a mitogen-activated protein kinase signaling module with the neuronal protein JIP3. Molec. Cell. Biol. 2000;20: 1030-1043

Ito M, Yoshioka K, Akechi M, et al. SAP1, a novel Jun N-terminal protein kinase (JNK)-binding protein that functions as a scaffold factor in the JNK signaling pathway. Molec. Cell. Biol. 1999;19: 7539-7548