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Over Expression of Mapk8ip3 Patient Variants in Zebrafish to Establish a Spectrum of Phenotypes in a Rare-Neurodevelopmental Disorder

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Abstract : Mapk8ip3 (Mitogen-Activated Protein Kinase 8 Interacting Protein 3) is a gene that codes for the JIP3 protein, which is a part of the JIP scaffolding protein family. This protein is involved in axonal vesicle transport, elongation and regeneration. Variants in the Mapk8ip3 gene are associated with a rare-genetic condition that results in a neurodevelopmental disorder that can cause a range of phenotypes including global developmental delay and intellectual disability. Currently, there are 18 known individuals diagnosed to have sequenced confirmed Mapk8ip3 genetic disorders. This project focuses on examining the impact of a subset of missense patient variants on the Jip3 protein function by overexpressing the mRNA of these variants in a zebrafish knockout model for Jip3. Plasmids containing cDNA with individual missense variants were reverse transcribed, purified, and injected into single-cell zebrafish embryos (Wild Type, Jip3 -/+, and Jip3 -/-). At 6-days post mRNA microinjection, morphological, behavioral, and microscopic phenotypes were examined in zebrafish larvae. Morphologically, we compared the size and shape of the zebrafish during their development over a 5-day period. Total locomotive activity was assessed using the Microtracker assay and patterns of movement over time were examined using the DanioVision assay. Lastly, we used confocal microscopy to examine sensory axons for swelling and shortened length, which are phenotypes observed in the loss-of-function knockout Jip3 zebrafish model. Using these assays during embryonic development, we determined the impact of various missense variants on Jip3 protein function, compared to knockout and wild-type zebrafish embryo models. Variants in the gene Mapk8ip3 cause rare-neurodevelopmental disorders due to an essential role in axonal vesicle transport, elongation and regeneration. A subset of missense variants was examined by overexpressing the mRNA of these variants in a Jip3 knock-out zebrafish. Morphological, behavioral, and microscopic phenotypes were examined in zebrafish larvae. Using these assays, the spectrum of disorders can be phenotypically determined and the impact of variant location can be compared to knockout and wild-type zebrafish embryo models.

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