EXTREMELY RARE VARIANTS IN EIF4A2 ARE ASSOCIATED WITH A NEURODEVELOPMENTAL DISORDER CHARACTERIZED BY HYPOTONIA, INTELLECTUAL DISABILITY AND EPILEPSY

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Keywords: Neurodevelopment; Initiation factors; Protein translation; Disease gene discovery; Fruit flies

Background: Eukaryotic Initiation Factor-4A2 encodes EIF4A2, an ATP-dependent RNA helicase subunit of the eIF4F complex, which recognizes the 5'cap structure of mRNAs and is required for mRNA binding to the ribosome. The fruit fly homolog eIF4A mediates the negative regulation of Decapentaplegic (Dpp) signaling. In the fly, Dpp-signaling regulates embryo patterning, eye and wing morphogenesis, and stem cell identity determination. The vertebrate homolog of Dpp, TGF-β/BMP, is a key regulator of neuronal development, and function and is associated with various neurological disorders. Prior fly studies revealed that both gain and loss of function (GOF and LOF) eIF4A alleles modulate the rough eye and wing serration phenotypes associated with Dpp GOF and LOF, respectively. Despite the role of EIF4A2 homologs in key developmental processes, human disease-causing variants have not previously been identified. Here, we report eleven individuals with extremely rare variants in EIF4A2 who all present with global developmental delay or intellectual disabilities, significant hypotonia, and epilepsy in most cases.

Materials/Methods: To determine the pathogenicity of EIF4A2 variants in vivo, we generated transgenic fruit flies overexpressing human EIF4A2 wild-type (WT) and variant cDNAs using GAL4-UAS targeted gene expression. Expression of human EIF4A2 WT and variants were confirmed by immunostaining.

EIF4A2 variants were expressed in neurons (elav-GAL4), wings (nubbin-GAL4), and eyes (GMR-GAL4) to check the phenotype manifestations in the respective tissues.

Results: Neuronal overexpression of EIF4A2 p.L344F, p.G364E, and p.T243I resulted in motor defects. Wing specific expression of EIF4A2 p.T216I caused wing serration, which is consistent with loss of Dpp signaling and suggests this is a GOF variant. The eye specific overexpression of EIF4A2 p.L344F, p.G364E, and p.T243I exacerbates the rough eye phenotypes associated with Dpp GOF, suggesting these are LOF variants. Finally, GMR-GAL4 mediated knockdown of fly eIF4a using two different RNAi lines results in pupal lethality that is fully rescued by human EIF4A2 WT. However, the EIF4A2 p.T243I and p.T216I variants fail to rescue the pupal lethality.

Conclusions: Together, these findings reveal that these de novo EIF4A2 variants are pathogenic and alter fruit fly development in a dominant manner through either GOF or LOF mechanisms. Our work establishes a role for EIF4A2 dysfunction in human neurodevelopmental disorders characterized by epilepsy and intellectual disability.

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