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Research Category

Basic Science

Abstract Title

Disease modelling and functional assessment of DHX15 variants in *Drosophila melanogaster*

Authors

Name	Role	Profession
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Background

DHX15 encodes a highly conserved ATP-dependent RNA helicase involved in mRNA spliceosome disassembly, antiviral immunity, and ribosome biogenesis. DHX15 has not previously been established as a cause of human disease. Our clinical collaborators have identified a cohort of 26 individuals with de novo DHX15 variants, identified through genome sequencing. Proband exhibit developmental delay, intellectual disability, epilepsy, and structural brain abnormalities. Affected individuals require ongoing multidisciplinary care and no disease-specific treatments are available as management remains limited to symptomatic treatment.

Objective

We will use *Drosophila* to functionally assess de novo DHX15 variants identified in this cohort and determine the role of fly Dhx15 in the nervous system. Given the DHX15 gene constraint, we hypothesize that missense DHX15 variants act as loss-of-function.

Methods

We are generating transgenic *Drosophila* that conditionally express human DHX15 as an in vivo model of DHX15 function. We generated plasmids containing human reference DHX15, 16 de novo patient-derived missense variants, a benign missense control, and a helicase-dead control. Transgenic flies will be assessed using overexpression assays. To establish neuronal functions, pan-neuronal Dhx15 knockdown was performed using nSyb-GAL4 and two independent RNAi lines, with luciferase RNAi as a control. Motor

function and heat- and mechanically induced seizures were assessed in 10-day old flies.

Results

Preliminary data indicates that reference DHX15 ubiquitous overexpression is viable and does not cause toxicity in flies. Pan-neuronal Dhx15 knockdown results in significant motor deficits and heat-induced seizures in both male and female flies compared with controls. These phenotypes were reproduced using two independent RNAi lines.

Conclusion

Our preliminary findings demonstrate that Dhx15 is required for normal neurological function and is important for motor and seizure susceptibility in *Drosophila*. Using rescue-based strategies, the generated transgenic flies will enable direct comparison of human reference and patient-derived DHX15 variants to determine the functional assessment of missense DHX15 variants.