CHRD 2024: Abstract Submission Form

Presenter Name
Zoe Goldstone-Joubert

Presenter Status
Masters Student

Role in the project
Design
Perform Experiments
Analyze Data
Write Abstract

Research Category
Basic Science

Title
Using Drosophila melanogaster as a Model Organism to Determine the Phenotypic Spectrum of Pathogenic KAT6A and KAT6B Variants

Background
There are over 500 reported cases of KAT6 syndromes worldwide. Pathogenic variants in the KAT6A gene cause Arboleda-Tham syndrome and pathogenic variants in the KAT6B gene cause genitopatellar syndrome or Say-Barber-Biesecker-Young-Simpson syndrome. Individuals present with a range of features including intellectual disability, speech delay, feeding difficulties and congenital anomalies. In addition, individuals with KAT6B syndromes have genital and skeletal features. Most KAT6A and KAT6B (KAT6A/B) variants are de novo and are present in a heterozygous state. Truncating variants likely lead to loss-of-function and haploinsufficiency. However, the impact of missense variants is difficult to predict.

Objective
Functional studies will allow for assessment of both truncating and missense variants.

Methods
Ubiquitous and tissue-specific overexpression studies were conducted using the UAS-GAL4 system in Drosophila melanogaster. KAT6A/B reference genes and 19 KAT6A/B variants were assessed. Experiments were conducted at 29 and 25 degrees celsius. Both sexes were examined with a minimum of n=20. Progeny was visually genotyped and Mendelian ratios were used to assess variant function. Statistical analysis included ANOVA followed by Tukeys post hoc and graphs were constructed using Prism GraphPad version 10.

Results
Our preliminary results show that ubiquitous overexpression of KAT6A/B truncating variants display a range of function including non-disruptive, partial, and complete loss-of-function. These initial results correlate with our hypothesis and serve as a calibration for missense variant testing. Additionally, ubiquitous overexpression of KAT6A missense variants does not display loss-of-function, whereas ubiquitous overexpression of KAT6B missense variants shows a range of partial to complete loss-of-function. Finally, wing-specific overexpression of reference KAT6A shows an abnormal morphological phenotype at 29 degrees celsius, however, overexpression of reference KAT6B does not show an abnormal phenotype.

Conclusion
Our ubiquitous overexpression data shows a range of function across truncating and missense variants as well as gene-specific differences. Wing-specific overexpression will help clarify this range of function and allow us to identify a clearer genotype-phenotype correlation.

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No

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