



FAME4-associating YEATS2 knockdown impairs dopaminergic synaptic integrity and leads to seizure-like behaviours in *Drosophila melanogaster*

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ABSTRACT

Familial adult myoclonus epilepsy (FAME) is a neurological disorder caused by a *TTTA/TTCA* intronic repeat expansion. FAME4 is one of the six types of FAME that results from the repeat expansion in the first intron of the gene *YEATS2*. Although the RNA toxicity is believed to be the primary mechanism underlying FAME, the role of genes where repeat expansions reside is still unclear, particularly in the case of *YEATS2* in neurons. This study used *Drosophila* to explore the effects of reducing *YEATS2* expression. Two pan-neuronally driven *dsDNA* were used for knockdown of *Drosophila YEATS2* (*dYEATS2*), and the resulting molecular and behavioural outcomes were evaluated. *Drosophila* with reduced *dYEATS2* expression exhibited decreased tolerance to acute stress, disturbed locomotion, abnormal social behaviour, and decreased motivated activity. Additionally, reducing *dYEATS2* expression negatively affected tyrosine hydroxylase (*TH*) gene expression, resulting in decreased dopamine biosynthesis. Remarkably, seizure-like behaviours induced by knocking down *dYEATS2* were rescued by the administration of L-DOPA. This study reveals a novel role of *YEATS2* in neurons in regulating acute stress responses, locomotion, and complex behaviours, and suggests that haploinsufficiency of *YEATS2* may play a role in FAME4.

1. Introduction

Familial adult myoclonic epilepsy (FAME) is a group of rare diseases with an autosomal dominant inheritance, which are characterized by cortical myoclonus and infrequent seizures (Guerrini et al., 2001; Kuwano et al., 1996). Cortical hyperexcitability as well as dysfunction and degeneration of both the cortex and cerebellum seem to be the

prominent features of FAME subjects (Lagorio et al., 2019; Latorre et al., 2020; van den Ende et al., 2018).

Although the disease entity of FAME was established early in the 90's based on clinical, electrophysiological, and neuropathological observations, the underlying pathogenic genetic variants have been only recently identified (Depienne et al., 2023). In fact, the same pentanucleotide repeat expansion composed of two different motifs, namely a

Abbreviations: Alu, short stretch of DNA originally characterized by the action of the *Arthrobacter luteus* (Alu) restriction endonuclease; CNS, central nervous system; DA, dopamine; FAME4, familial adult myoclonic epilepsy type 4; L-DOPA, Levodopa, 3,4-dihydroxyphenylalanine; MN, motor neurons; NMJ, neuromuscular junctions; nSyb, n-synaptobrevin; SAMD12, Sterile Alpha Motif Domain-Containing Protein 12; SLB, seizure-like behaviour; TH, tyrosine hydroxylase; YEATS, Yaf9, ENL, AF9, Taf14, and Sas5.

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