Elucidating the Behavioral, Pathogenetic, and Therapeutic Implications of Selectively Inhibited Monogenic Variants in Fragile X Syndrome Associated Genetic Epilepsy in Drosophila melanogaster

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Fragile X Syndrome (FXS) is the most common “single-gene” cause of intellectual disability (ID) and autism spectrum disorder (ASD) worldwide, often manifesting understudied seizure comorbidities in early childhood development. Herein, the Drosophila orthologs of five previously unstudied candidate genes (GK5, RGPD4, CHD2, KCNA1, and TTLL4) were functionally characterized in vivo to i) interpret the pathogenetic consequences of the loss-of-function (LOF) of target genes, ii) elucidate sex differences in seizure risk modification, and iii) assess the interaction of genetic risk loci and existing FXS treatment compounds for novel targeted therapeutic development. Utilizing fly strains containing RNAi-mediated KD of rigorously-identified Drosophila orthologs of target genes, genetic mating schemes using the elav GAL4-UAS system were implemented for all 10 crosses to enable pan-neuronal expression of target knockdown constructs to faithfully recapitulate FXS pathophysiology. Over 2,500 adult flies underwent a 10-second vortex to stimulate mechanical shock and induced seizure conditions; immediate response to external stimulus was assessed. In females, KCNA1 LOF was shown to significantly exacerbate seizure risk ($p < 0.05$). Conversely, in males, GK5 LOF was shown to significantly attenuate seizure risk ($p < 0.05$). Additionally, RGPD4 LOF was shown to elicit significantly different seizure frequencies in male and female flies ($p < 0.05$). Utilizing in silico molecular docking, 3 robust alternative treatment modalities that target the elucidated seizure suppressor/enhancer genes were identified to replace current clinical management techniques aimed merely at symptomatic alleviation and patient presentation, serving as a prominent basis for pharmacological intervention.

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