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Research Category
Basic Science

Abstract Title
Genetic Screen of Conserved 22q11.2 Genes in Neurons and Glia Using Drosophila melanogaster

Background
22q11.2 deletion syndrome (DS) is a highly heterogeneous genetic condition which affects 1 in 1000-6000 births. 22q11.2 DS causes a wide range of symptoms including, but not limited to ASD, ADHD, schizophrenia, and seizures. 22q11.2 DS is typically caused by de novo non-homologous meiotic recombination events and little is known about which 22q11.2 genes are important in the pathogenesis of 22q11.2 DS. We hypothesize that 22q11.2 DS phenotypes are largely caused by haploinsufficiency of a fraction of 22q11.2 genes.

Objective
Determine which 22q11.2 genes are critical in the pathogenesis of 22q11.2 DS via knockdown of conserved gene orthologues in either neurons or glia of Drosophila melanogaster.

Methods
RNAi-mediated knockdown of 22q11.2 DS gene orthologues is performed in neurons or glia using the UAS-GAL4 system in Drosophila melanogaster. First, when flies eclosed, mendelian ratios were calculated to assess lethality from RNAi-induced knockdown of target genes. Second, lifespan of the flies is recorded up to day 20. At day 20, flies were assessed on their ability to climb in a straight line and on their susceptibility to mechanically induced seizures.

Results
In neuronal knockdown, to date, we have identified seven lethal genes, four genes causing reduction in lifespan, six genes causing locomotion defects, and four genes which increase the flies' susceptibility to mechanically induced seizures. In glial knockdown, we have identified ten lethal genes, one gene causing reduction in lifespan, seven genes causing locomotion defects, and two genes which increase the flies' susceptibility to mechanically induced seizures.

Conclusion
Our results support our hypothesis that only a subset of the conserved genes knocked down in the brain cause a phenotype. Identifying genes that cause a strong phenotype when knocked down in Drosophila may justify studying their orthologues in a mammalian system to determine their relevance in the mammalian central nervous system and as potential therapeutic targets.

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