Title: **Developing a fruit fly model of a rare genetic multiorgan syndrome for insights into immunity and neurodegeneration**

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Abstract
A key aspect of P4 (predictive, preventive, personalized, participatory) medicine is the development of genome sequencing, allowing the identification of alleles that cause rare genetic diseases. Genome-wide association studies (GWAS), meanwhile, identify genes involved in chronic age-related conditions, which represent our most significant healthcare burden. These genes frequently overlap, reinforcing the importance of studying genetic diseases affecting small numbers of patients, beyond helping those patients.

Mutations in NHLRC2 are implicated in the rare genetic multiorgan syndrome FINCA (fibrosis, neurodegeneration, and cerebral angiomatosis), which was first described in Finnish patients. The syndrome involves frequent infections, suggesting an immune component. NHLRC2 has also been identified in a screen for phagocytosis regulators, and as a biomarker for Alzheimer's disease.

NHLRC2 is conserved across animals and plants. Complementing work by collaborators at the University of Oulu working with human patients and mouse models, the Experimental Immunology group at TAU is developing fly and fish models of FINCA. The fly lacking NHLRC2 develops and propagates normally, in contrast to the severe phenotypes observed in other animals. However, the mutant fly does display immune, neurological, and behavioral phenotypes, allowing study of the role of this gene in healthy animals, and specific aspects of FINCA, while taking advantage of the genetic tools, low cost, and fast generation times of the fly model. Most strikingly, flies lacking NHLRC2 have a defect in their normal climbing behavior, observed most clearly at a young age. This matches some of the neurological phenotypes observed in patients and in the mouse model.