Model Organisms Screening In Undiagnosed Diseases

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Author Block: **M. Wangler**; Baylor Coll. of Med., Houston, TX

Invertebrate model organisms such as Drosophila melanogaster have increasingly been integrated into the diagnosis of rare and undiagnosed diseases. In 2015 we established the Model Organisms Screening Center for the Undiagnosed Diseases Network. This center interfaced with clinicians and human geneticists across 12 UDN clinical sites and has led to the discovery of 33 new human disease-causing genes as well as 9 other genes with a phenotypic expansion in humans informed by model organism studies. Facilitating diagnostic focused model organisms' studies in worms, flies and zebrafish required direct communication with physicians evaluating the patient, a knowledge of human genetics evidence and versatile model organism tools for characterization of phenotypes and modeling specific human variants. One key approach has relied on "humanization" in which specialized Trojan-cassette alleles in Drosophila are phenotyped and then crossed to human cDNA transgenics to determine if the human protein can rescue a fly mutant. Over time there has been success of this method when applied to uncharacterized human variants from exome or genome sequencing. We have also employed the overall workflow of the UDN and the model organism core, specifically in Drosophila to underserved populations in Texas, an effort known as the Community Texome project. The Texome project has demonstrated success in diagnosis, including for adults with no health resources and specific cases have led to specific therapies based on the molecular and functional data. Drosophila models will continue to play a role in facilitating diagnosis and probing disease mechanisms.