GENETICS

Flies give wings to human disease studies

Chemically induced mutations on the fruit fly X chromosome reveal the genetic basis of certain human neurologic disorders.

Fruit flies are evolutionarily distant from humans, and yet numerous human disease genes have counterparts in the fruit fly genome. Thus, tinkering with the genes in fruit flies and analyzing the outcomes have advanced our understanding of the cause and mechanisms of human diseases.

In a recent collaborative study, a team led by Hugo Bellen and Michael Wangler from Baylor College of Medicine reported a collection of X chromosome–linked recessive mutations in the fruit fly, generated by chemical mutagenesis. The selected mutations are lethal in homozygous form, underlying the importance of affected genes in a fly's development and growth. However, because the fatal outcome prevents the functional studies of mutated genes, the researchers induced the same mutations in only some cells in fly tissues such as the wings, thorax or eyes and selected for mutants that presented with morphological changes known to be associated with neuronal pathways. The phenotypic and genetic mutant screens identified multiple mutations in 165 genes that are linked to various aspects of the development, function and maintenance of the *Drosophila* nervous system.

The researchers also probed data collected from human families with hereditary neurologic diseases of undetermined cause, checking for rare allelic variants in the genes homologous to those identified in the *Drosophila* screen. They mapped mutations in three genes (*DNM2*, *CRX* and *ANKLE2*) in six families suffering from three different neurologic disorders. Mutated *DNM2* and *CRX* genes cause Charcot-Marie-Tooth disease and childhood blindness, respectively. However, the mutation in *CRX* pinpointed by researchers seems to contribute to a distinct and unexpected eye disease: Bull's eye maculopathy. Finally, the researchers found that two siblings with severe microcephaly shared a rare variant of the *ANKLE2* gene, and the corresponding mutation introduced in the homologous *Drosophila* gene caused a similar brain developmental defect. These results newly identify *ANKLE2* as a neurodevelopmental gene.

Because genes tend to work in evolutionarily conserved pathways, the researchers predict that the phenotypic information of fly mutants in their collection may provide important guidance in future efforts to understand the functional role of human homologs in health and disease.

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RESEARCH PAPERS

Yamamoto, S. *et al.* A *Drosophila* genetic resource of mutants to study mechanisms underlying human genetic diseases. *Cell* **159**, 200–214 (2014).