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Cross-species strategy might be a powerful tool for studying human disease

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A new study takes advantage of genetic similarities between mammals and fruit flies by coupling a complex genetic screening technique in humans with functional validation of the results in flies. The new strategy, published by Cell Press on February 3rd in The *American Journal of Human Genetics*, has the potential to be an effective approach for unraveling genetically complex human disorders and providing valuable insights into human disease.

Genome-wide association studies (GWASs) involve sifting through the complete set of DNA from many individuals to identify genetic variations associated with a particular disease. Although this technique has proven to be a powerful tool for developing a better understanding of diseases, such as Alzheimer's disease (AD), that involve multiple genetic variations, there are substantial limitations. Perhaps most significantly, follow-up studies aimed at validating disease-associated genetic variations in humans require large sample sizes and a great deal of effort. The current study validates GWAS results by using an inventive alternative approach.

"Simple genetic models of human disease, such as in the fruit fly, have been important experimental tools for many years, particularly for large-scale functional testing of genes," explains a senior study author, Mel B. Feany, MD, PhD, from Brigham and Women's Hospital.. "We therefore hypothesized that the fly disease model might fulfill the growing need for efficient strategies for validation of association signals identified by GWAS."

Dr. Joshua M. Shulman and colleagues implemented a two-stage strategy to enhance a GWAS of AD neuropathology by integrating the results of gene discovery in humans with functional screening in a fly model system relevant to AD biology. Specifically, the researchers evaluated 19 genes from 15 distinct genomic regions identified in a human GWAS designed to identify genes that influence AD pathology. In six out of these 15 genomic regions, a causal gene was subsequently identified in the fly disease model on the basis of interactions with the neurotoxicity of Tau protein, a well-known constituent of AD pathology.

The authors also discuss the potential for application of their technique to studies examining other human diseases. "Evidence is emerging in support of a polygenic model of inheritance for complex genetic disorders, particularly neuropsychiatric diseases, in which hundreds or even thousands of common gene variants collectively contribute to disease risk," says co-author Philip L. De Jager, MD, PhD, also of Brigham and Women's Hospital. "Our strategy of coupling human GWAS with functional genetic screening in a model organism will likely be a powerful strategy for follow-up of such signals in the future in order to prioritize genes and pathways for further investigation."

Provided by Cell Press