Novel gene variants that modify the risk of late-onset Alzheimer's disease discovered
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Late-onset Alzheimer's disease (LOAD) is the most common form of dementia in the elderly, affecting almost 44 million people worldwide. Despite decades of research, genetic factors that predispose individuals to LOAD are not clearly understood. With a growing elderly population in the U.S. and many other developed countries, there is an urgent need for precise prognostic biomarkers and viable treatment options. Apart from advanced age, variants in the apolipoprotein E (APOE) gene are a strong predictor of disease risk. Those who carry the ?4 variant have a higher risk of developing Alzheimer's, while those who carry a different variant, ?2, are typically protected. Surprisingly, many individuals do not conform to these rules—a puzzle that has confounded researchers. Some people with APOE?4 remain disease-free while some APOE?2 carriers develop the disease.

Using a novel methodology, researchers at Baylor College of Medicine and Texas Children's Hospital examined the genomes of these "rule-breaker" individuals, which led to the identification of 216 new gene variants, many previously not suspected to play a role in this disease. This is an exciting first step toward understanding this paradox. The newly-identified biomarkers could potentially be used in the future to refine risk assessment and patient prognosis in APOE?2 and APOE?4 carrier populations and act as therapeutic targets for this untreatable condition.

The study, led by Drs. Olivier Lichtarge and Juan Botas, professors of molecular and human genetics at Baylor College of Medicine and investigators at the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital, was published in Alzheimer's and Dementia.

"We wanted to test if people who show paradoxical outcomes might have other genetic variants that blunted the risky or protective effects of the APOE genotype they carry," Lichtarge said. "To search for those variants, Young Won Kim, a graduate student in my lab, designed new algorithms to compare and contrast the genetic variants present in each patient. We were then fortunate to be able to test these with a unique high-throughput fruit fly screen developed by Juan and his team at the Duncan NRI. This is a good example of the power of comparative studies across species and only feasible through multidisciplinary collaborations."

A novel computational approach finds 216 genes with differential variants in paradoxical populations

The wide spectrum of clinical presentations and complex inheritance patterns of LOAD, and its co-occurrence with other neuropathologies, heart-related disorders and age-associated cognitive impairments are some of the reasons why scientists have found the puzzle of paradoxical APOE ?2 and ?4 patients particularly challenging.

In this study, researchers tapped into the largest whole exome dataset available for this condition, called the Alzheimer's Disease Sequencing Project (ADSP).
"To screen for potential candidate variants, I focused on the coding regions of the human genome and estimated the functional impact of genetic variants by factoring in all the past evolutionary changes at the same gene positions. Through a series of regression analyses, we found 216 genes with significant differences in mutational load between the two paradoxical patient groups. Many of these genes showed involvement in known Alzheimer's disease pathways such as synaptic biology, dendritic spine pruning, and inflammatory responses in the brain. Also, we were able to use machine learning algorithms to predict which APOE?4 carriers would remain healthy and which APOE?2 carriers would develop Alzheimer's based on the variants they carry in the 216 genes," lead author, Young Won Kim, said.

High-throughput robotic screen of fruit flies validates candidate genes

The researchers' next step was to experimentally test the biological relevance of these 216 gene variants in modifying Alzheimer's disease pathogenesis.

"Testing so many genes for their impact on neuronal dysfunction in vivo is a daunting task. So, we leveraged fruit flies engineered in our lab to develop Alzheimer's pathology and used a high-throughput behavioral screen based on custom-made robots unique to the Duncan NRI to test the ability of each variant-associated gene to modify the disease pathology. This allowed us to validate many candidate genes and experimentally demonstrate their ability to modify disease pathology," Botas said.

"The robotic assays provided us with a quantitative assessment of the actual neuronal impairment. We used movement-specific behavioral assays as the main readout of nervous system function. Additionally, we obtained precise information of how variants in each gene modified its physiological function, meaning whether the impact on neuronal function was a result of the gene's under-performance (loss-of-function) or over-performance (gain-of-function). This information is critical for the future development of these biomarkers for therapeutic interventions, either by inhibiting or activating these genes in the future," Dr. Ismael Al-Ramahi, co-lead author and assistant professor at Baylor, added.

"To summarize, by focusing on paradoxical patient populations, we can now study the genetic modifiers that give them their special power to live a disease course different than expected. Here, in Alzheimer's disease, this may improve risk evaluation and point to gene targets for drugs that blunt the disease pathogenesis. Also, the massive use of evolutionary information seems to have made up for a relatively small number of patients (just 480) in this study, which is much less than a typical genome-wide association study. We think this makes our study design an attractive alternative way to study other health conditions with 'rule-breaking' patients. To conclude, this is the first proof-of-concept study to demonstrate the feasibility of integrating evolutionary biology and machine learning with high-throughput Drosophila genetics and neurobiology assays, to examine why some patients 'break free' of the genetic rules of disease," Lichtarge concluded.


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