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Molecular Network Points to Possible Treatment Targets for Alzheimer's Disease

by a *Genomeweb* staff reporter

NEW YORK (*GenomeWeb News*) – Late-onset Alzheimer's disease is linked to potentially targetable changes to specific pathways and processes in the brain, according to a new molecular network-based analysis of the condition.

An international team led by investigators in the US and Iceland did array-based gene expression profiling on more than 1,600 post-mortem brain samples from 549 individuals with or without late-onset Alzheimer's disease.

Together with DNA genotyping information for the same individuals, the researchers used this expression data to put together molecular networks for cases and controls that provided a peek at processes at play during late-onset Alzheimer's disease development and progression.

Their findings, published online today in *Cell*, indicate that inflammation and immune-related pathways have a central role in the disease, as do a related type of brain cell called microglia.

"Defining the precise steps of the inflammatory response crucial to causing Alzheimer's disease has been elusive," the study's co-lead author Bin Zhang, a researcher affiliated with the Icahn School of Medicine at Mount Sinai and Sage Bionetworks, said in a statement. "We are pleased to discover these novel insights into that process."

In particular, he and his colleagues found that the Alzheimer's disease network tended to show a jump in representation by an apparent regulatory gene called TYROBP. And in mouse models of disease, dialing up representation of the gene led to gene expression changes reminiscent of those found in brain samples from people with Alzheimer's disease.

"Our network-based integrative analysis not only highlighted the immune-microglia module as the molecular system most strongly associated with the pathophysiology of [late-onset Alzheimer's disease] but also identified key network regulators, including TYROBP," the researchers wrote.

Though past studies have untangled some of the genetic and brain features of Alzheimer's disease, Zhang and his co-authors noted, the precise molecular pathways and processes that go awry as the condition develops and progresses have been tricky to determine, leading to treatments meant to alleviate some symptoms of the disease rather than addressing its causes.

"Despite decades of intensive research, the causal chain of mechanisms behind [late-onset Alzheimer's disease] remains elusive," they noted, adding that "there are no effective disease-modifying therapies, and the only available treatment remains symptomatic."

In the hopes of getting at a more concrete molecular explanation for the disease, researchers brought together genotyping and brain gene expression data for 376 individuals with late-onset Alzheimer's disease and 173 control individuals who hadn't exhibited signs of dementia.

Along with Illumina and Perlegen array-based DNA genotyping profiles for each person, the group had access to 1,647 post-mortem brain samples. Gene expression patterns in the samples — which represented dorsolateral prefrontal cortex, visual cortex, and cerebellum regions of the brain — were ascertained using Agilent arrays.

Indeed, molecular networks developed using the case and control data pointed to widespread rearrangements in brain samples from those with Alzheimer's disease, study

continued on next page

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authors noted.

They found that expression changes were particularly pronounced in the prefrontal cortex region of the brain, for instance, with expression changes turning up more often in genes from certain functional groups and/or genes known for their expression in certain brain cell types.

When they dug into these results in more detail — using an integrative network strategy to tally up apparent links between network modules and features of Alzheimer's disease — the investigators found a few processes that jumped to the forefront.

In particular, that analysis pointed to Alzheimer's disease-related dysfunction in a pathway linked to both immune function and the activity of a set of immune- and defense-related support cells in the brain known as microglia.

At the heart of that set of interacting factors, researchers found a regulatory gene called TYROBP, which interacts with a gene called TREM2 that's been implicated in Alzheimer's disease through studies looking at possible low-frequency risk variants.

Together with mouse model data linking higher-than-usual TYROBP expression to features of Alzheimer's disease, the network data hints that it might be possible to target the TYROBP-TREM2 pathway to treat or prevent late-onset Alzheimer's disease.

"This discovery enables us to design more specific compounds that target these key steps precisely," noted Mount Sinai's Zhang in a statement, "in contrast to existing anti-inflammatory drugs that may be less ideal for hitting this target."

An independent study published online today in Neuron, meanwhile, found a different sort of evidence suggesting microglia-related mishaps may contribute to Alzheimer's disease.

The Massachusetts General Hospital and Harvard Medical School-based authors of that study delved into the function of an innate immune system-related gene called CD33, based on prior research into late-onset Alzheimer's disease that pointed to a protective variant in the gene.

That team's findings indicated that CD33 expression by microglia cells is more pronounced in those with Alzheimer's disease than those without, apparently influencing microglia-mediated clearance of amyloid beta plaque-related proteins in the brain.