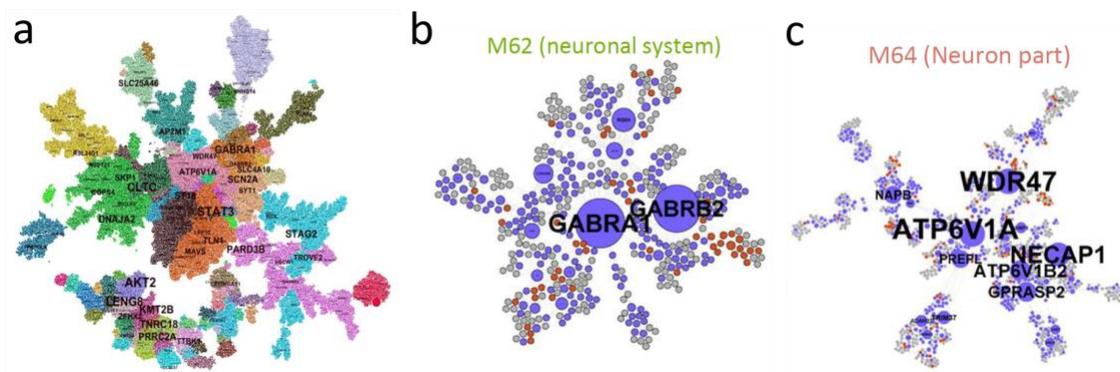


## Potential New Therapies for Alzheimer’s Disease are Revealed through Network Modeling of Its Complex Molecular Interactions

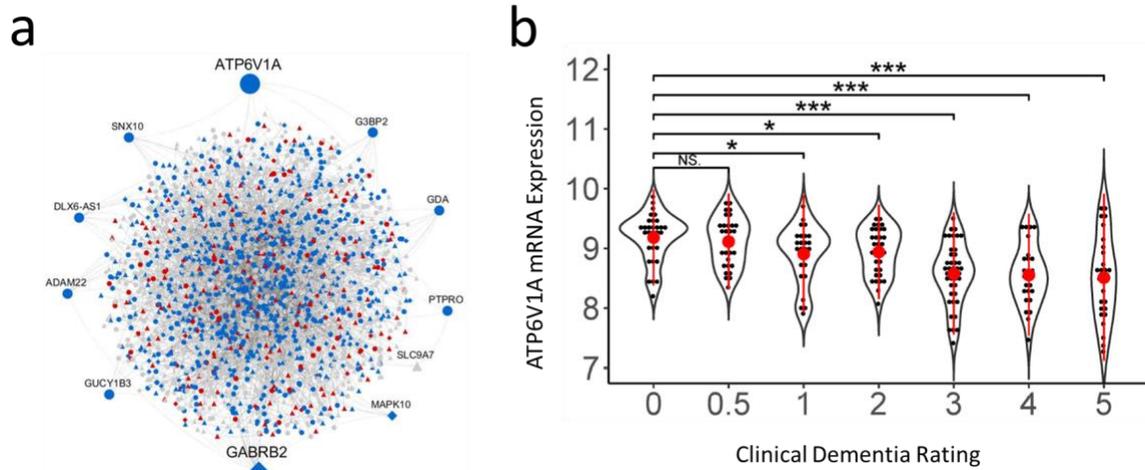
(New York, NYH – November 24, 2020) -- Researchers from Mount Sinai and the National Center for Geriatrics and Gerontology in Japan have identified new molecular mechanisms driving late-onset Alzheimer’s Disease (LOAD), as well as a promising therapeutic candidate for treatment, according to a study in the journal *Neuron*. LOAD is the most prevalent form of dementia among people over age 65, a progressive and irreversible brain disorder affecting more than 5.5 million people in the U.S., and the sixth leading cause of death.

“Our study advances the understanding of LOAD pathogenesis by revealing not only its global structures, but detailed circuits of complex molecular interactions and regulations in key brain regions affected by LOAD,” said the lead author Bin Zhang, PhD, Professor of Genetics and Genomic Sciences at the Icahn School of Medicine at Mount Sinai and Director of the Center for Transformative Disease Modeling. “The network models we created serve as a blueprint for identifying novel therapeutic targets that respond directly to the urgent need for new ways to prevent, treat, and delay the onset of LOAD.”



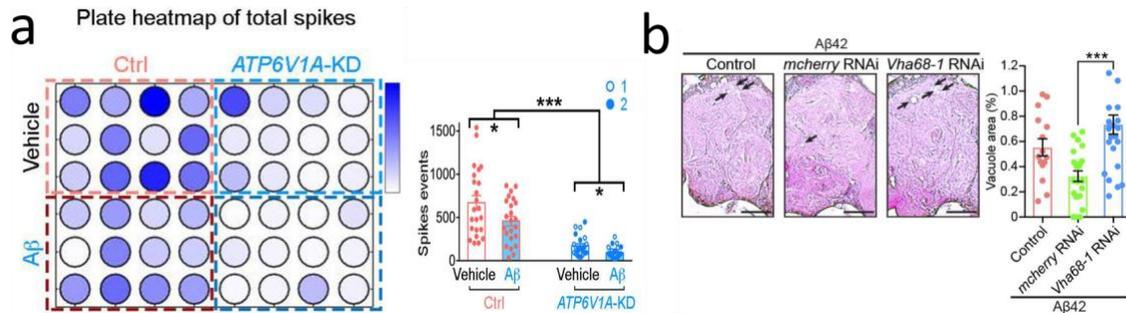
A global gene coexpression network in LOAD (a) and the top two subnetworks most associated with LOAD.

Previous genetic and genome-wide association studies have identified some genetic mutations associated with LOAD, but the causal variants of the disease have remained uncharacterized. To explore the molecular mechanisms driving the pathogenesis of LOAD, the Mount Sinai-led team performed an integrative network biology analysis of a whole genome and RNA sequencing dataset from multiple cortical brain regions of hundreds of donors, both healthy and with LOAD. This work revealed thousands of molecular changes and uncovered numerous neuron-specific gene subnetworks dysregulated in LOAD.



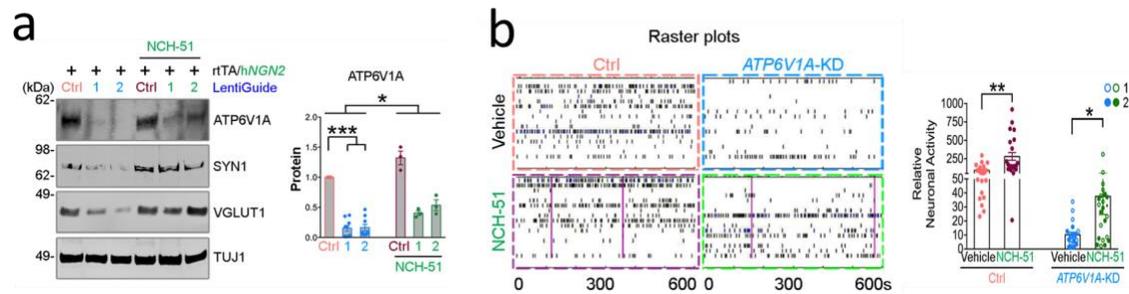
Gene causal network (a) reveals *ATP6V1A* as one key regulator down-regulated in LOAD (b).

From that investigation researchers predicted that *ATP6V1A*, a protein-coding gene, played a major role in a critical signaling pathway in the brain, and that its deficit could be traced to LOAD.



Down-regulation of *ATP6V1A* in human iPSC derived neurons (a) and *Drosophila* (b) worsened LOAD-related neurodegeneration.

That linkage was evaluated using two methods: a CRISPR-based technique to manipulate *ATP6V1A* levels in donor-matched brain cells *in vitro*, and in RNAi-based knockdown in transgenic *Drosophila* models, meaning that genetic material is artificially introduced into fly models and specific genes are effectively silenced to study the effects. Indeed, the knockdown of *ATP6V1A* worsened LOAD-related neurodegeneration in both models.



The predicted drug NCH-51 increased the protein expression of ATP6V1A and improved neuronal activity in human iPSC derived neurons.

Just as significantly, researchers predicted that a drug compound, NCH-51, could normalize the dysregulated genes in LOAD, including *ATP6V1A*, and demonstrated that NCH-51 dramatically improved the neuronal and neurodegenerative effects of the *ATP6V1A* deficit in both model systems. Specifically, the CRISPR-based experiment using human induced pluripotent stem cells (hiPSC) demonstrated that repression of *ATP6V1A*, particularly in combination with  $\beta$ -amyloid -- a key neuropathological hallmark of AD -- dramatically impacted neuronal function. “The human-based system we created proved to be a promising way to model the mechanisms underlying risk and progression in diseases like LOAD where living tissues are not available,” observed Kristen Brennand, PhD, Associate Professor, Genetics and Genomic Sciences, Mount Sinai, and co-author of the study.

The *Drosophila* experiments were also revealing, demonstrating that *ATP6V1A* deficit exacerbated both  $\beta$ -amyloid -mediated toxicity and tau-mediated axon degeneration. “This finding suggested that *ATP6V1A* may have broad neuroprotective effects and be a potential therapeutic target for other tau-related neurodegenerative diseases,” says Dr. Koichi M. Iijima, Head of the Department of Alzheimer’s Disease Research at the National Center for Geriatrics and Gerontology in Japan, and senior author of the study.

As Dr. Zhang points out, the groundbreaking research by Mount Sinai and its Japanese partner could have significance beyond just LOAD. “We’ve created a framework for advanced modeling of complex human diseases in general,” he explains, “and that could well lead to the discovery of molecular mechanisms and the identification of novel targets that are able to deliver transformative new therapeutics.”

The LOAD study is supported by the NIH National Institute on Aging (NIA) and is part of the NIA-led [Accelerating Medicines Partnership - Alzheimer's Disease](#) (AMP-AD) Target Discovery and Preclinical Validation program. This public private partnership aims to shorten the time between the discovery of potential drug targets and the development of new drugs for Alzheimer’s disease treatment and prevention.

**About the Mount Sinai Health System**

The Mount Sinai Health System is New York City's largest academic medical system, encompassing eight hospitals, a leading medical school, and a vast network of ambulatory practices throughout the greater New York region. Mount Sinai is a national and international source of unrivaled education, translational research and discovery, and collaborative clinical leadership ensuring that we deliver the highest quality care—from prevention to treatment of the most serious and complex human diseases. The Health System includes more than 7,200 physicians and features a robust and continually expanding network of multispecialty services, including more than 400 ambulatory practice locations throughout the five boroughs of New York City, Westchester, and Long Island. The Mount Sinai Hospital is ranked No. 14 on *U.S. News & World Report's* "Honor Roll" of the Top 20 Best Hospitals in the country and the Icahn School of Medicine as one of the Top 20 Best Medical Schools in country. Mount Sinai Health System hospitals are consistently ranked regionally by specialty and our physicians in the top 1% of all physicians nationally by *U.S. News & World Report*.

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