Alzheimer's breakthrough: Genetic link to gut disorders confirmed

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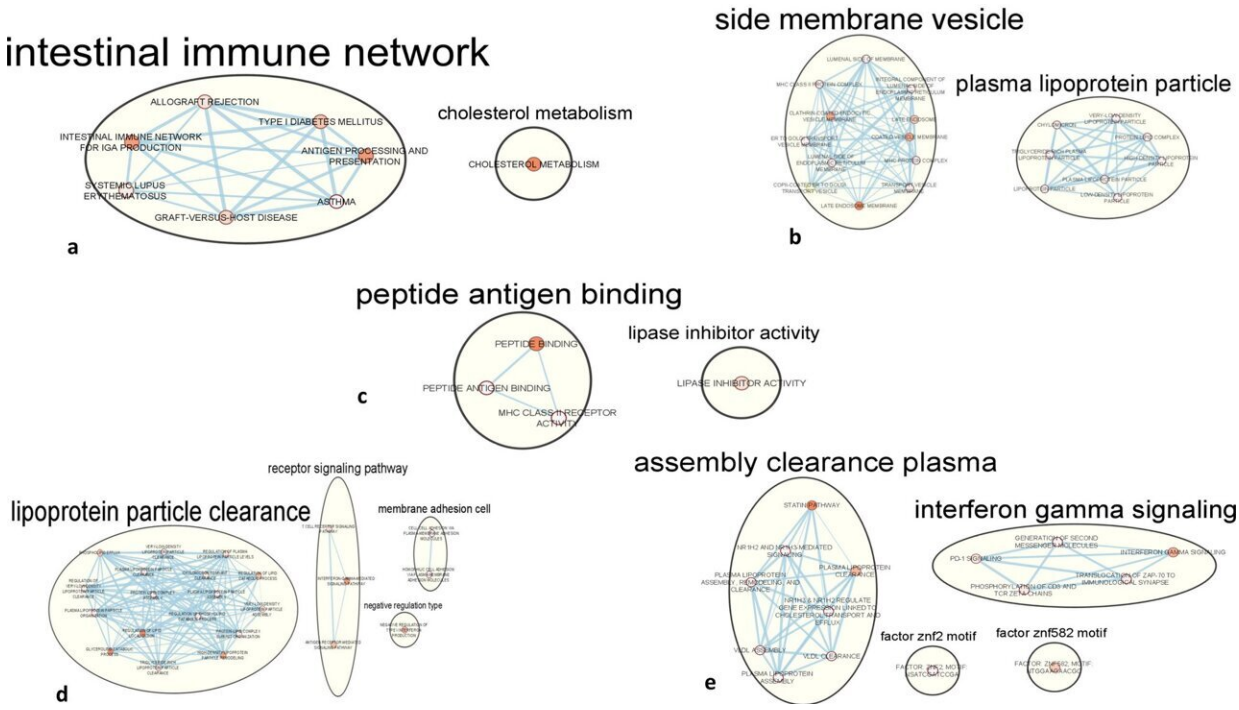

Clusters of significantly enriched biological pathways for AD and GERD. **a** KEGG: Kyoto Encyclopedia of Genes and Genomes pathways: *intestinal immune network* (allograft rejection, intestinal immune network for IGA production, type 1 diabetes mellitus, systemic lupus erythematous, antigen processing and presentation, graft-versus-host disease, asthma), and *cholesterol metabolism* (cholesterol metabolism). **b** Gene Ontology: Cellular Components: *side membrane vesicle* (lumenal side of membrane, MHC class II protein complex, integral component of lumenal side of endoplasmic reticulum [ER] membrane, clathrin-coated endocytic vesicle membrane, late endosome, ER to Golgi transport vesicle membrane, coated vesicle membrane, lumenal side of ER membrane, MHC protein complex, COPII-coated ER to Golgi transport vesicle,

transport vesicle membrane, late endosome membrane), and *plasma lipoprotein particle* (chylomicron, very low-density lipoprotein [VLDL] particle, triglyceride-rich plasma lipoprotein particle, plasma lipoprotein particle, lipoprotein particle, LDL lipoprotein particle). **c** Gene Ontology: Molecular Function: peptide antigen binding (peptide binding, peptide antigen binding, MHC class II receptor activity) and *lipase inhibitor activity* (lipase inhibitor activity). **d** Gene Ontology: Biological Pathway: *lipoprotein particle clearance* (phospholipid efflux, VLDL particle clearance, regulation of plasma lipoprotein particle levels, plasma lipoprotein particle clearance, chylomicron remnant clearance, regulation of lipid catabolic process, regulation of VLDL particle clearance, protein-lipid complex assembly, plasma lipoprotein particle organization, regulation of phospholipid catabolic process, VLDL particle assembly, regulation of lipid localisation, glycolipid catabolic process, triglyceride-rich lipoprotein particle clearance, high density lipoprotein particle remodeling), *receptor signaling pathway* (T cell receptor signaling pathway, interferon-gamma-mediated signaling pathway, antigen receptor-mediated signaling pathway), *membrane adhesion cell* (cell-cell adhesion via plasma membrane adhesion molecules, homophilic cell adhesion via plasma membrane adhesion molecules), and *negative regulation type* (negative regulation of type I interferon production). **e** Reactome, Wiki pathway and Transcription Factor Binding site: *assembly clearance plasma* (statin pathway, NR1H2 and NR1H3-mediated signaling, plasma lipoprotein assembly, remodeling, and clearance, plasma lipoprotein clearance, NR1H3 and NR1H2 regulated gene expression linked to cholesterol transport and efflux, VLDL assembly, VLDL clearance, plasma lipoprotein assembly), *interferon-gamma signaling* (PD-1 signaling, generation of second messenger molecules, interferon-gamma signaling phosphorylation of CD3 and TCR ZETA chains, translocation of ZAP-70 to Immunological synapse), *Factor*: ZNF2 motif, and ZNF582 motif. AD Alzheimer's disease, GERD gastroesophageal reflux disease. Credit: *Communications Biology* (2022). DOI: 10.1038/s42003-022-03607-2

People with gut disorders may be at greater risk of developing Alzheimer's Disease (AD). A world-first Edith Cowan University (ECU) study has confirmed the link between the two, which could lead to earlier detection and new potential treatments.

AD destroys memory and thinking ability and is the most prevalent form of dementia. It has no known curative treatments and is expected to affect more than 82 million people and cost US$2 trillion by 2030.

Previous observational studies have suggested a relationship between AD and gastrointestinal tract disorders, but what underpins these relationships had been unclear—until now.

ECU's Center for Precision Health has now provided new insights into these relationships by confirming a genetic link between AD and multiple gut disorders. The study analyzed large sets of genetic data from AD and several gut-disorder studies—each of about 400,000 people.

Research lead Dr. Emmanuel Adewuyi said it was the first comprehensive assessment of the genetic relationship between AD and multiple gut disorders. The team discovered people with AD and gut disorders have genes in common—which is important for many reasons.

"The study provides a novel insight into the genetics behind the observed co-occurrence of AD and gut disorders," Dr. Adewuyi said.

"This improves our understanding of the causes of these conditions and identifies new targets to investigate to potentially detect the disease earlier and develop new treatments for both types of conditions."

Center for Precision Health director and study supervisor Professor Simon Laws said whilst the study didn't conclude gut disorders cause AD or vice versa, the results are immensely valuable.

"These findings provide further evidence to support the concept of the 'gut-brain' axis, a two-way link between the brain's cognitive and emotional centers, and the functioning of the intestines," Professor Laws said.

Is cholesterol a key?

When researchers conducted further analysis into the shared genetics, they found other important links between AD and gut disorders—such as the role cholesterol may play.

Dr. Adewuyi said abnormal levels of cholesterol were shown to be a risk for both AD and gut disorders.

"Looking at the genetic and biological characteristics common to AD and these gut disorders suggests a strong role for lipids metabolism, the immune system, and cholesterol-lowering medications," he said.

"Whilst further study is needed into the shared mechanisms between the conditions, there is evidence high cholesterol can transfer into the central nervous system, resulting in abnormal cholesterol metabolism in the brain."

"There is also evidence suggesting abnormal blood lipids may be caused or made worse by gut bacteria (H.pylori), all of which support the potential roles of abnormal lipids in AD and gut disorders."

"For example, elevated cholesterol in the brain has been linked to brain degeneration and subsequent cognitive impairment."

Hope for the future

The cholesterol link could prove vital in treating AD in the future.

While there are currently no known curative treatments, the study's findings suggest cholesterol lowering medications (statins) could be therapeutically beneficial in treating both AD and gut disorders.

"Evidence indicates statins have properties which help reduce inflammation, modulate immunity and protect the gut," Dr. Adewuyi said.

However, he said there was a need for more studies and patients needed to be assessed individually to judge whether they would benefit from statin use.

The research also indicated diet could play a part in treating and preventing AD and gut disorders. It was published in *Communications Biology*.

More information: Emmanuel O. Adewuyi et al, A large-scale genome-wide cross-trait analysis reveals shared genetic architecture between Alzheimer's disease and gastrointestinal tract disorders, *Communications Biology* (2022). DOI: 10.1038/s42003-022-03607-2

Provided by Edith Cowan University