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Search for Gender Based Differences In Alzheimer's Disease

Round II: 21CBT INNOVATION AWARD FINALIST

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SCARB1 AS A MEDIATOR OF GENDER SPECIFIC DIFFERENCES IN ALZHEIMER'S DISEASE

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To pursue mechanisms by which gender may modify Alzheimer's Disease (AD) risk, we queried whether gender could impact human brain physiology in a manner that would be consistent with the disease. We analyzed whole-transcriptome cerebral cortex gene expression data in unaffected individuals in function of their gender as well as in AD patients and observed significant similarities between the gene expression signature observed in elderly women (vs men) and AD patients (vs unaffected controls), suggesting that AD-related molecular alterations can be observed on average in elderly unaffected women. To identify potential causal factors underlying the observed change, we then applied an innovative genomics approach to this data: differential co-expression correlation network analysis of the gender and AD transcriptomic changes identified SCARB1 – a cell surface receptor involved in cholesterol management and already known to have gender-specific functions – as a core regulatory mediator of the joint effect of gender and LOAD. Confirming this unbiased genome-wide first stage, genetic analyses revealed that a common polymorphism within SCARB1 impact LOAD age-of-onset in a gender-specific fashion in several patients cohort. These data point at SCARB1 as a gene mediating the increased LOAD risk observed in women. It makes it a therapeutic target of choice and more globally, suggest an involvement of cholesterol in the increased AD incidence observed in women and potential interest in cholesterol-lowering drugs such as statins to reduce AD risks in women. A systematic unbiased approach identified a gene involved in cholesterol and cardiovascular functions that make a very strong candidate in light of our current knowledge of both AD risk factors and gender-dependent diseases.

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