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Alzheimer's risk gene may begin to affect brains as early as childhood

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People who carry a high-risk gene for Alzheimer's disease show changes in their brains beginning in childhood, decades before the illness appears, new research from the Centre for Addiction and Mental Health (CAMH) suggests.

The gene, called SORL1, is one of a number of genes linked to an increased risk of late-onset Alzheimer's disease, the most common form of the illness. SORL1 carries the gene code for the sortilin-like receptor, which is involved in recycling some molecules in the brain before they develop into beta-amyloid a toxic Alzheimer protein. SORL1 is also involved in lipid metabolism, putting it at the heart of the vascular risk pathway for Alzheimer's disease as well.

"We need to understand where, when and how these Alzheimer's risk genes affect the brain, by studying the biological pathways through which they work," says Dr. Aristotle Voineskos, head of the Kimel Family Translational Imaging-Genetics Laboratory at CAMH, who led the study. "Through this knowledge, we can begin to design interventions at the right time, for the right people."

The study was recently published online in *Molecular Psychiatry* with Dr. Voineskos's graduate student, Daniel Felsky as first author, and was a collaborative effort with the Zucker Hillside Hospital/Feinstein Institute in New York and the Rush Alzheimer's Disease Center in Chicago.

To understand SORL1's effects across the lifespan, the researchers

studied individuals both with and without Alzheimer's disease. Their approach was to identify genetic differences in SORL1, and see if there was a link to Alzheimer's-related changes in the brain, using imaging as well as post-mortem tissue analysis.

In each approach, a link was confirmed.

In the first group of healthy individuals, aged eight to 86, researchers used a brain imaging technique called diffusion tensor imaging (DTI). Even among the youngest participants in the study, those with a specific copy of SORL1 showed a reduction in white matter connections in the brain important for memory performance and executive function.

The second sample included post-mortem brain tissue from 189 individuals less than a year old to 92 years, without Alzheimer's disease. Among those with that same copy of the SORL1 gene, the brain tissue showed a disruption in the process by which the gene translated its code to become the sortilin-like receptor.

Finally, the third set of post-mortem brains came from 710 individuals, aged 66 to 108, of whom the majority had mild cognitive impairment or Alzheimer's. In this case, the SORL1 risk gene was linked with the presence of amyloid-beta, a protein found in Alzheimer's disease.

Dr. Voineskos notes that risk for Alzheimer's disease results from a combination of factors – unhealthy diet, lack of exercise, smoking, high blood pressure combined with a person's genetic profile – which all contribute to the development of the illness. "The gene has a relatively small effect, but the changes are reliable, and may represent one 'hit', among a pathway of hits required to develop Alzheimer's disease later in life".

While it's too early to provide interventions that may target these

changes, "individuals can take measures in their own lifestyle to reduce the risk of late-onset Alzheimer's disease." Determining whether there is an interaction with this risk gene and lifestyle factors will be one important next step.

In order to develop genetically-based interventions to prevent Alzheimer's disease, the biological pathways of other risk genes also need to be systematically analyzed, the researchers note.

This research does, however, build on a previous CAMH imaging-genetics study on another gene related to Alzheimer's disease. That study showed that a genetic variation of brain-derived neurotrophic factor (BDNF) affected brain structures in Alzheimer's.

"The interesting connection is that BDNF may have important therapeutic value. But there is data to suggest that the effects of BDNF won't work unless SORL1 is present, so there is the possibility that if you boost the activity of one gene, the other will increase," says Dr. Voineskos, adding that BDNF therapeutics are in development. A next stage in the research, he says, is to look at the interaction of BDNF and SORL1.

Provided by Centre for Addiction and Mental Health