

Research

The Genetics of Early-Onset Alzheimer's *Clues to Alzheimer Pathology*

<p>MOST CASES OF EARLY-ONSET Alzheimer's disease are known as the familial form of the disease. This means that a causal factor can be passed from one generation to the next. Because certain families have had long histories of early-onset Alzheimer's, researchers had a logical place to begin searching for genes associated with the disease. Since the 1980s, when this effort began, scientists have identified three gene mutations that play a causal role in the early-onset familial Alzheimer's disease.</p> <p>Identifying these genes is in itself an important step in Alzheimer research, but determining what proteins the genes encode and how those proteins function in healthy and diseased brains will help researchers reveal the molecular processes that are fundamental to Alzheimer's disease. A brief look at ongoing research focusing on two of these genes reveals progress as well as hurdles in the path of explaining the complexities of Alzheimer's.</p>	<p>Investigating suspect genes In 1995, researchers identified two genes known as the presenilin genes after conducting genetic screening tests on families with histories of early-onset Alzheimer's.</p> <p>These genes provide instructions for the production of proteins called presenilin-1 and presenilin-2. Mutations of the presenilin-1 gene, located on chromosome 14, may be responsible for 70 to 80 percent of all cases of early-onset familial Alzheimer's. Mutations of the presenilin-2 gene, located on chromosome 1, may account for up to 20 percent of familial cases.</p> <p>Researchers suspected that presenilin proteins play an important role in Alzheimer pathology because mutations of the presenilin genes are associated with increased production of beta-amyloid protein fragments ($A\beta$). $A\beta$ is the primary component of amyloid plaques, abnormal structures that accumulate in brains affected by Alzheimer's disease.</p>	<p>Although the role of plaques in Alzheimer's is unknown, evidence suggests that they may contribute to the degeneration of brain cells.</p> <p>The link between presenilin gene mutations and increased production of $A\beta$ is being diligently researched. Scientists have learned that $A\beta$ is clipped from a parent molecule by enzymes in a two-step process. While the activities of the enzymes were known, their identities and the genes that encoded them remained a mystery. Researchers referred to the mystery enzyme activity as beta-secretase (β-secretase) and gamma-secretase (γ-secretase).</p> <p>In 1999, scientists reported on the identity of a likely candidate for β-secretase, a protein most often identified by the acronym BACE. And in 2000, researchers offered compelling evidence that the presenilin proteins were, in fact, responsible for γ-secretase activity. This evidence was a milestone in defining Alzheimer pathology, but many</p>
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<p>Since the 1980s, when this effort began, scientists have identified three gene mutations that play a causal role in early-onset familial Alzheimer’s disease.</p> <hr/> <p>questions remained. Are other proteins involved in the production of Aβ? What do presenilin proteins do in a healthy brain and how do mutations affect protein activity? Can scientists develop pharmaceutical treatments that target these proteins without disrupting other essential processes in the brain?</p> <p>Researchers are investigating these questions on many fronts, and the Alzheimer’s Association is providing research grants to support these endeavors. Two research grant recipients who are contributing to this growing body of knowledge about presenilins are highlighted in the following paragraphs. Their work is helping the research community to construct a more complete picture of the role these proteins play in early-onset Alzheimer’s and to understand molecular processes that may contribute to all forms of the disease.</p>	<p style="text-align: center;">SPOTLIGHT ON RESEARCH</p> <p>John Hardy, PhD In 1999, the Alzheimer’s Association granted a two-year, \$200,000 Zenith Fellows Award to John Hardy, PhD, of the Mayo Clinic in Jacksonville, Florida. Hardy’s research group is investigating whether the mutation of a presenilin gene results in a gain or loss of a protein’s function. In other words, although the mutated genes are associated with increased levels of Aβ, it is not clear whether the mutations result in “overactive” or “underactive” proteins. This question is further complicated because researchers have observed at least 40 different mutated versions of the presenilin genes, and every mutation may not affect protein activity similarly.</p> <p>In investigations with certain mutated versions of presenilin-1 genes, Hardy’s group found evidence that mutations result in a loss of protein function. The researchers also observed that the loss of function caused an increase in a form of Aβ that is more likely to form plaques. Through ongoing work on the</p>	<p>outcomes of mutated presenilin genes, they hope to discover how to target presenilin-1 for therapeutic interventions.</p> <p style="text-align: center;">SPOTLIGHT ON RESEARCH</p> <p>Jie Shen, PhD Jie Shen, PhD, of Brigham and Women’s Hospital in Boston, Massachusetts, received a three-year, \$180,000 research grant in 1999 to fund her group’s investigation of both the normal and altered function of presenilin-1. Shen and her colleagues have studied mice that were genetically altered not to produce presenilin-1. The researchers observed that these mice did not develop normal brain cells. The evidence suggested that the protein is important in early stages of brain development when cells are becoming more specialized to carry out a particular brain function.</p> <p>The researchers also studied mice that had a version of the presenilin-1 gene programmed to operate during development but to shut down in certain regions of the brain later in life. Shen’s group observed that when the altered presenilin-1 genes shut down, the level</p>
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A β declined. They also noted that other important cellular functions – in which presenilins seemed to play a role during brain development – were not altered by the absence of presenilin proteins later in life. This detail is an important clue for researchers in determining whether it is “safe” to target presenilins for Alzheimer therapy.

As researchers reveal more about how presenilins contribute to A β production, we will have a clearer understanding of the molecular processes of Alzheimer’s. One of the next steps will test compounds that may inhibit presenilin protein activity. These investigations may lead to new drugs that can be tested in the laboratory, in animal studies, and in clinical trials. If this work brings about successful pharmaceutical treatments, we may, in years to come, be able to alter or slow the progression of Alzheimer’s disease.

R_x Corner

<p>FDA Approves Fourth Alzheimer Drug On February 28, 2001, the United States Food and Drug Administration (FDA) approved galantamine hydrobromide (Reminyl®), the fourth drug marketed specifically to treat symptoms of mild to moderate Alzheimer’s. In clinical trials comparing galantamine to placebo (inactive treatment) participants receiving galantamine showed better results in measures of thinking and reasoning, daily</p>	<p>functioning and behavior. Like other approved Alzheimer drugs, galantamine is a cholinesterase inhibitor. This class of drugs temporarily increases the brain’s supply of acetylcholine, a nerve messenger chemical that becomes deficient in the Alzheimer brain as cell death progresses. For a fact sheet about galantamine or cholinesterase inhibitors in general, please call the Association’s Contact Center at (800)272-3900.</p>
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