Rare coding variants in the phospholipase D3 gene confer risk for Alzheimer's disease.

Nature. 2014; 505(7484):550-4.

PLAIN LANGUAGE SUMMARY

AUDIENCE

This plain language summary is intended for adults who have been recruited for genetic testing and have limited to no understanding of basic biology.

This sample is for illustration purposes and does not constitute medical advice.

ABOUT US

Takmos LLC is a nonclinical toxicology consulting firm based in Ventura, California serving a range of industries.

We specialize in providing plain language summaries of technical materials.

CONTACT

Takmos LLC

web: www.takmos.com

email: info@takmos.com

telephone: 805-328-3290

Genetic testing of families with a history of Alzheimer's identifies a cause for the disease

Alzheimer's disease affects the brain and causes memory loss. Why do some people get Alzheimer's disease? That is not entirely understood, but the disease is often observed in multiple members of the same family.

A study of families with a history of Alzheimer's disease found a possible genetic cause.

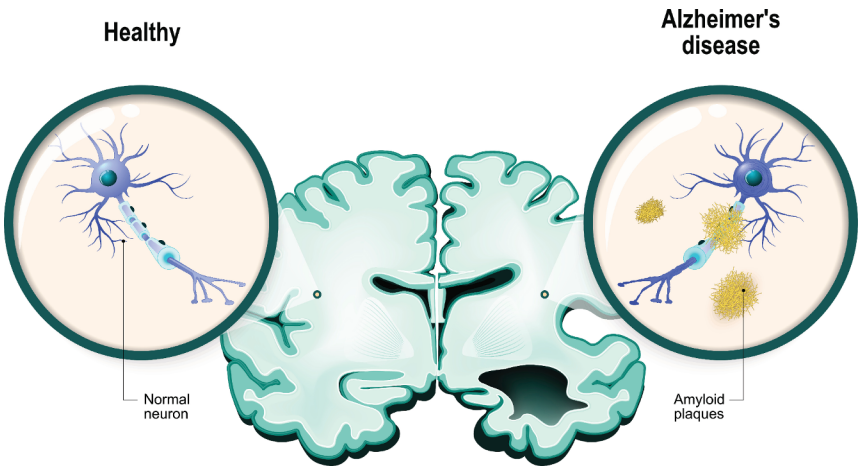
What are genes? What causes Alzheimer's disease?

Our genes or DNA are like the blueprints for a house. From these blueprints building blocks called proteins are made.

More beta amyloid protein in the brain means higher risk of Alzheimer's disease.

The body makes many different proteins. There is one particular protein called beta amyloid that causes the damage in the brain of the Alzheimer's disease patient.

How does beta amyloid cause this damage? The beta amyloid proteins stick to and damage the nerve cells in the brain forming beta amyloid plaques. These plaques cause memory loss and the other symptoms of Alzheimer's disease.



Takmos

PLAIN LANGUAGE SUMMARY CONTINUED

What is Phospholipase D3?

Phospholipase is a protein that breaks down fat in the brain and prevents beta amyloid plaques from forming.

Researchers conducted genetic testing on families with a history of Alzheimer's disease to determine if these people had a different gene for the phospholipase D3 gene. This gene is abbreviated PLD3.

How was this study performed?

More than 11,000 members of families who have a history of Alzheimer's disease were tested. Some of the people in the study had Alzheimer's disease, but many did not. By studying the genetics of this group of 14 families, researchers have identified a part of the reason for Alzheimer's disease.

What was discovered?

People who have a different "blueprint" for the PLD3 gene (this is called a "gene variant") had higher levels of beta amyloid proteins. Since beta amyloid protein is what sticks to and damages the nerve cell, people with the PLD3 gene variant have a higher risk for Alzheimer's disease.

People with the gene variant for phospholipase D3 protein had higher levels of beta amyloid protein.

What does this mean?

The study identified a particular gene variant (or slightly different blueprint) for a particular protein found in the brain. People with this variant are more likely to develop Alzheimer's disease but it is important to understand that just because someone has the genetic variant does not mean they will develop Alzheimer's disease.

Volunteering for a simple genetic test may lead to new treatments for Alzheimer's disease.

PHYSICIAN SUMMARY

Increased Alzheimer's risk is associated with coding variants in a phospholipase gene (PLD3) whose expression is inversely related to the expression of plaque forming amyloid beta peptide.

Elevated expression of PLD3 is associated with decreased expression of amyloid beta, a well-established precursor in the pathogenesis of Alzheimer's disease. PLD3 is highly expressed in the hippocampus and cortex and expression of this protein is lower in Alzheimer's neurons relative to control.

The coding variants identified in a multi-center study of >11,000 cases and controls of European descent were associated with lower expression of PLD3 and corresponding increased expression of amyloid beta. Sequencing of the PLD3 gene in a smaller African American population (cases + controls = 302) identified two variants (Val232 Met and Ala 442 Ala) in cases but not controls.

PLD3 appears to influence the processing of the amyloid precursor protein (APP); over expression of PLD3 in mouse neuroblastoma (N2A) cells *in vitro* resulted in a significant decrease in APP and amyloid beta. Conversely, knockdown of PLD3 resulted in a significant increase in amyloid beta peptides.

The PLD3 gene variants identified are not of diagnostic value due to the relative rarity, but do highlight the value of genetic testing in densely affected families to identify rare variants for risk of disease.