GRN-Related Frontotemporal Lobar Degeneration

Subjects: Genetics
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Definition

GRN-related frontotemporal lobar degeneration is a progressive brain disorder that can affect behavior, language, and movement.

1. Introduction

The symptoms of this disorder usually become noticeable in a person's fifties or sixties, and affected people typically survive 7 to 13 years after the appearance of symptoms. However, symptoms can begin as early as a person's thirties or as late as a person's eighties. The features of this condition vary significantly, even among affected members of the same family.

Behavioral changes are the most common early signs of *GRN*-related frontotemporal lobar degeneration. These include marked changes in personality, judgment, and insight. It may become difficult for affected individuals to interact with others in a socially appropriate manner. Affected people may also become easily distracted and unable to complete tasks. They increasingly require help with personal care and other activities of daily living.

Many people with *GRN*-related frontotemporal lobar degeneration develop progressive problems with speech and language (aphasia). Affected individuals may have trouble speaking, remembering words and names (dysnomia), and understanding speech. Over time, they may completely lose the ability to communicate (mutism). People with this condition also experience a decline in intellectual function (dementia).

Some people with *GRN*-related frontotemporal lobar degeneration also develop movement disorders, such as parkinsonism and corticobasal syndrome. The signs and symptoms of these disorders include tremors, muscle stiffness (rigidity), unusually slow movement (bradykinesia), walking problems (gait disturbance), involuntary muscle spasms (myoclonus), uncontrolled muscle tensing (dystonia), and an inability to carry out purposeful movements (apraxia).

2. Frequency

The prevalence of *GRN*-related frontotemporal lobar degeneration varies worldwide. It affects an estimated 3 to 15 per 100,000 people aged 45 to 64.

3. Causes

GRN-related frontotemporal lobar degeneration results from mutations (pathogenic variants) in the *GRN* gene. This gene provides instructions for making a protein called progranulin. Progranulin is active in many different tissues in the body, where it helps control the growth, division, and survival of cells. Progranulin's function in the brain is not well understood, although it appears to play an important role in the survival of nerve cells (neurons).

Most mutations in the *GRN* gene prevent any progranulin from being produced from one copy of the gene in each cell. As a result, cells make only half the usual amount of progranulin. It is unclear how a shortage of this protein leads to the features of *GRN*-related frontotemporal lobar degeneration. However, studies have shown that the disorder is characterized by the buildup of a protein called TAR DNA-binding protein 43 (TDP-43) in certain brain cells. The TDP-43 protein forms clumps (aggregates) that may interfere with

cell functions and ultimately lead to cell death. Researchers are working to determine how mutations in the *GRN* gene, and the resulting loss of progranulin, are related to a buildup of TDP-43 in the brain.

The features of *GRN*-related frontotemporal lobar degeneration result from the gradual loss of neurons in regions near the front of the brain called the frontal and temporal lobes. The frontal lobes are involved in reasoning, planning, judgment, and problem-solving, while the temporal lobes help process hearing, speech, memory, and emotion. The death of neurons in these areas causes problems with many critical brain functions. However, it is unclear why the loss of neurons occurs in the frontal and temporal lobes more often than other brain regions in people with *GRN*-related frontotemporal lobar degeneration.

3.1. The gene associated with GRN-related frontotemporal lobar degeneration

- GRN

4. Inheritance

GRN-related frontotemporal lobar degeneration has a pattern of inheritance known as incomplete autosomal dominance. This means having one copy of the altered gene generally results in milder signs and symptoms than having both copies of the altered gene. People with a mutation in one copy of the *GRN* gene in each cell (heterozygotes) have some functional progranulin protein and develop *GRN*-related frontotemporal lobar degeneration. Usually, people with a mutation in both copies of the *GRN* gene in each cell (homozygotes) do not produce any functional progranulin protein. These individuals have the signs and symptoms of another condition called CLN11 disease, in which movement and neurological problems begin in adolescence or early adulthood. However, some people with two *GRN* gene mutations that allow the production of some functional progranulin protein have *GRN*-related frontotemporal lobar degeneration.

In most cases of *GRN*-related frontotemporal lobar degeneration, an affected person has a parent and other family members with the condition.

5. Other Names for This Condition

- frontotemporal lobar degeneration
- FTD-GRN
- FTD-PGRN
- FTDP-17 GRN
- FTDU-17
- FTLD
- FTLD with TDP-43 pathology
- FTLD-TDP
- GRN-related frontotemporal dementia
- HDDD1
- HDDD2
- hereditary dysphasic disinhibition dementia

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Keywords

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