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# The Role of Mutations on Gene GRN, in CLN11 Syndrome

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## 1. Abstract

CLN11 disease is a disorder that primarily affects the nervous system. Individuals with this condition typically show signs and symptoms in adolescence or early adulthood. This condition is characterized by recurrent seizures (epilepsy), vision loss, problems with balance and coordination (cerebellar ataxia), and a decline in intellectual function. Seizures in CLN11 disease often involve a loss of consciousness, muscle stiffness (rigidity), and generalized convulsions (tonic-clonic seizures). Vision loss is gradual over time and is due to a condition called retinitis pigmentosa, which is caused by the breakdown of the light-sensitive layer at the back of the eye (retina). People with CLN11 disease can also develop clouding of the lenses of the eyes (cataracts) and rapid, involuntary eye movements (nystagmus). Affected individuals can also develop muscle twitches (myoclonus), walking problems and falling (gait disturbance), and impaired speech (dysarthria). Over time, people with CLN11 disease develop short-term memory loss and loss of executive function, which is the ability to plan and implement problem-solving strategies and actions. They may also become irritable and impulsive. Some affected individuals experience visual hallucinations involving people or animals. CLN11 disease is one of a group of disorders known as neuronal ceroid lipofuscinoses (NCLs). All of these disorders affect the nervous system and typically cause progressive problems with vision, movement, and thinking ability. The different NCLs are distinguished by their genetic cause. Each disease type is given the designation "CLN," meaning ceroid lipofuscinosis, neuronal, and then a number to indicate its subtype.

**2. Keywords:** CLN11 syndrome; GRN gene; Epilepsy disorder; Cerebellar ataxia; Walking disorder

## 3. Overview of CLN11 Syndrome

CLN11 syndrome is a genetic disorder that primarily affects the nervous system. People with the disease usually show symptoms in adulthood or early adulthood. This condition is characterized by recurrent seizures (epilepsy), loss of vision, balance and coordination problems (cerebellar ataxia), and decreased mental function [1].

## 4. Clinical Signs and Symptoms of CLN11 Syndrome

Seizures in CLN11 syndrome often include loss of consciousness, muscle cramps (stiffness), and generalized seizures (tonic-clonic seizures).

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Loss of vision occurs gradually and is due to a condition called retinitis pigmentosa, which is caused by the breaking of the light-sensitive layer in the back of the eye (retina). People with CLN11 can also develop cataracts (cataracts) and rapid and involuntary eye movements (nystagmus) [1,2].

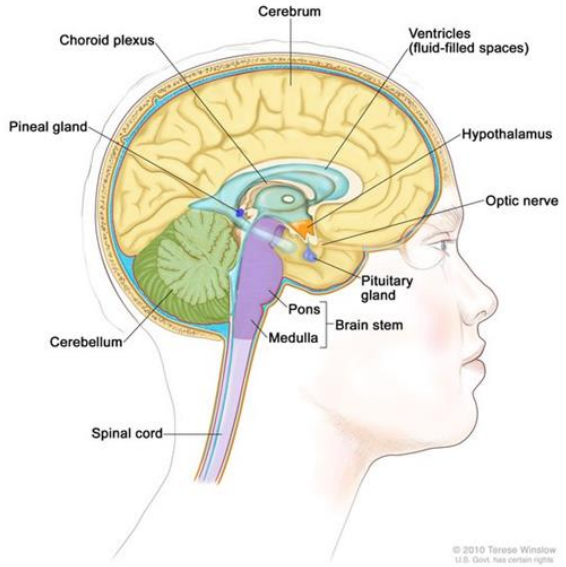


**Figure 1:** Schematic of the structure of the human brain [1].

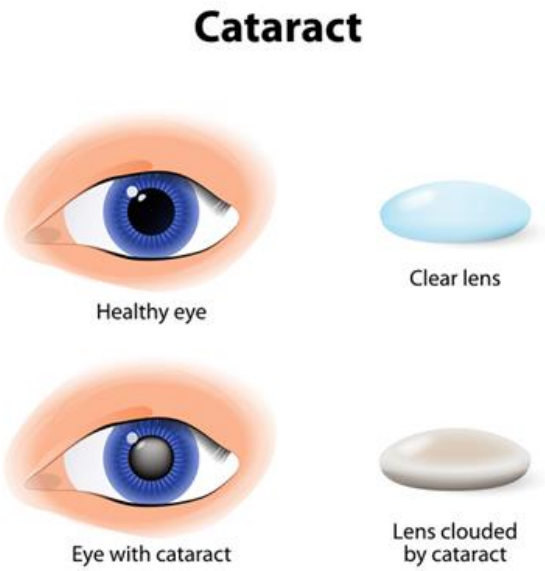


**Figure 2:** Schematic of a healthy eye lens versus a cataract lens in the eye [1].

People with the condition can also have muscle cramps (myoclonus), difficulty walking and falling (walking disorder), and speech problems (dysarthria). Over time, people with CLN11 develop short-term memory loss and executive function, which is the ability to plan and execute problem-solving strategies and actions. They may also be irritable and impulsive. Some sufferers experience visual hallucinations involving humans or animals [1,3].

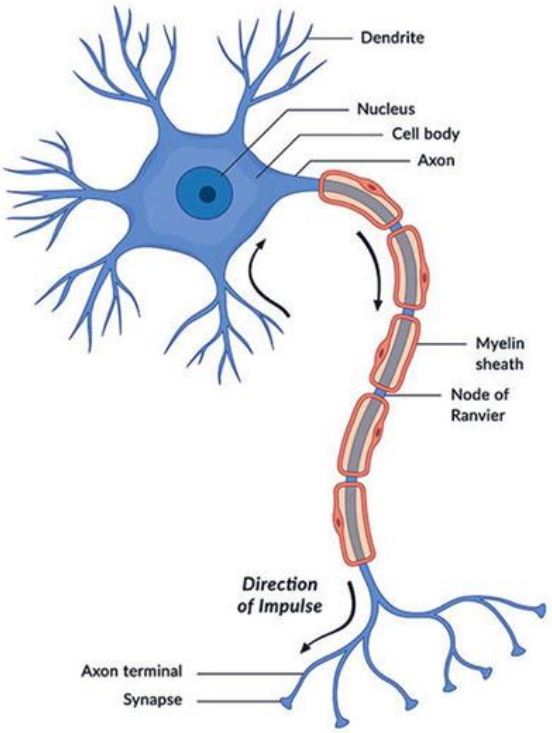


**Figure 3:** Schematic of the structure of the nerve fiber.

CLN11 syndrome is a disorder known as cerebral nerve lipofuscinosis (NCLs). All of these disorders affect the nervous system and typically cause progressive problems with vision, movement, and thinking ability. Different NCLs are distinguished by their genetic cause. Each type of disease is called a "CLN," meaning cerebral, neural lipophysinosis, followed by a number to indicate its subtype [1,4].

## 5. Etiology of CLN11 Syndrome

CLN11 syndrome is caused by a mutation in the GRN gene, which is located in the long arm of chromosome 17 at 17q21.31. This gene provides the instructions for the synthesis of a protein called progranulin. Progranulin is active in many different tissues of the body, where it helps control the growth, division and survival of cells. The function of progranulin in the brain is not well understood, although it appears to play an important role in the survival of neurons [1,5]. Mutations in the GRN gene that cause CLN11 cause complete loss of the functional protein progranulin. This lack of progranolin causes the death of nerve cells in the brain, although the exact mechanism is

unknown. Extensive loss of neurons in CLN11 disease leads to symptoms in adulthood or before adulthood [1,5].

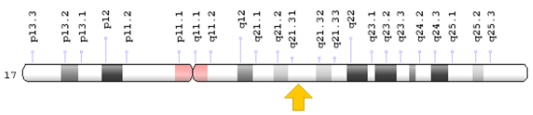

**Figure 4:** Schematic view of chromosome 17 where the GRN gene is located in the long arm of this chromosome as 17q21.31. [1].

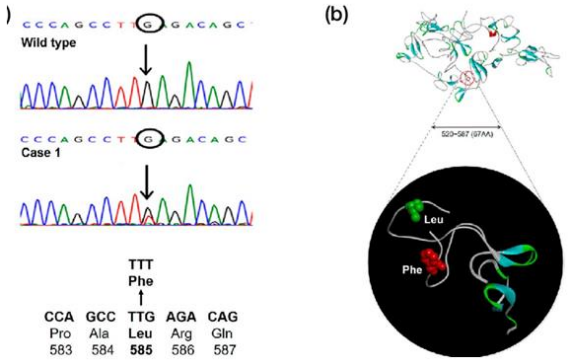


**Figure 5:** Schematic of the mutation in the GRN gene versus the nucleotide sequence of the GRN version gene [1].

CLN11 disease follows an autosomal recessive inherited pattern. Therefore, two copies of the mutated GRN gene (one from the father and the other from the mother) are required to cause the disease, and the chance of having a child with the autosomal recessive disease for each possible pregnancy is 25%. Mutations in both copies of the GRN gene destroy the production of any functional progranulin protein [1,5].

The parents of people with CLN11 each have a copy of the mutated GRN gene in each cell and generally produce about half the normal amount of progranulin protein. People with a mutated GRN gene usually do not show the signs and symptoms of CLN11, but may develop another condition called GRN-related frontotemporal degeneration, in which cognitive decline begins between the 1940s and 1960s. Becomes. Some people with two mutated GRN genes that allow the production of some functional progranulin proteins develop GRN-related frontotemporal lobes [1,6].

## 6. Frequency of CLN11 Syndrome

The prevalence of CLN11 syndrome is unknown. So far, at least 11 cases of this disease have been reported in the medical literature [1,6].

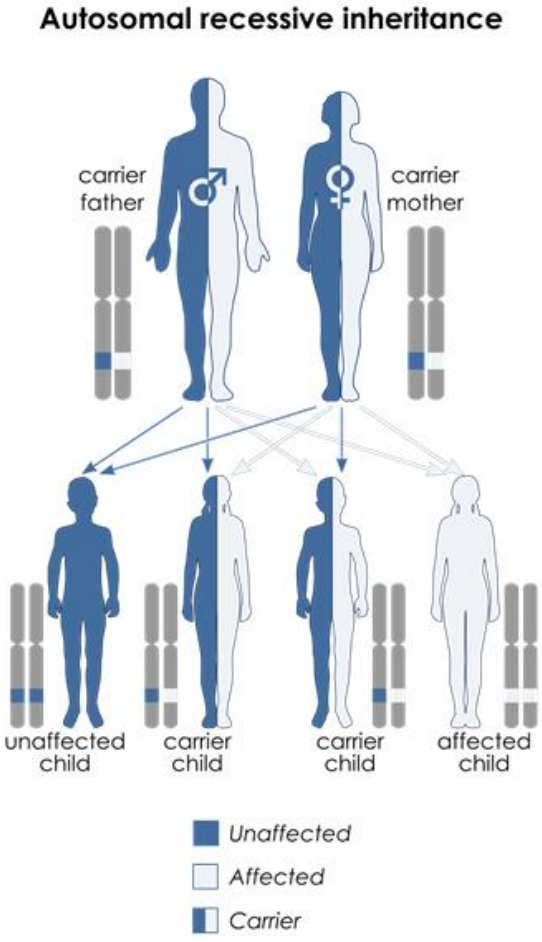


**Figure 6:** Schematic of the autosomal recessive inherited pattern that CLN11 syndrome follows [1].

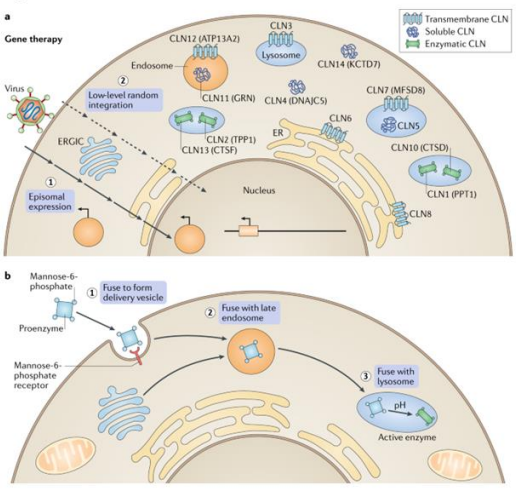


**Figure 7:** Schematic of how CLNs function in cells [1].

## 7. Diagnosis of CLN11 Syndrome

CLN11 syndrome can be diagnosed based on the clinical findings of some patients and some pathological tests. The most accurate way to diagnose

this syndrome is to test molecular genetics for the GRN gene to check for possible mutations [1,7].

## 8. Treatment Routes for CLN11 Syndrome

The treatment and management strategy for CLN11 syndrome is symptomatic and supportive. Treatment may be performed with the efforts and coordination of a team of specialists including a neurologist, physiotherapist, ophthalmologist, psychiatrist, and other health care professionals. There is no effective treatment for this disease and all clinical measures are to reduce the suffering of patients. Genetic counseling is also essential for all parents who want a healthy baby [1,7].

## 9. Discussion and Conclusion

CLN11 disease is a disorder that primarily affects the nervous system. Individuals with this condition typically show signs and symptoms in adolescence or early adulthood. This condition is characterized by recurrent seizures (epilepsy), vision loss, problems with balance and coordination (cerebellar ataxia), and a decline in intellectual function. CLN11 syndrome is caused by a mutation in the GRN gene, which is located in the long arm of chromosome 17 at 17q21.31. This gene provides the instructions for the synthesis of a protein called progranulin. Progranulin is active in many different tissues of the body, where it helps control the growth, division and survival of cells.

There is no effective treatment for this disease and all clinical measures are to reduce the suffering of patients. Genetic counseling is also essential for all parents who want a healthy baby [1,7].

## References


1. Asadi S. Human Cryptogenics Diseases Book. Amidi Publications. Iran; 2021.
2. Almeida MR, Macário MC, Ramos L, Baldeiras I, Ribeiro MH, Santana I. Portuguese family with the co-occurrence of frontotemporal lobar degeneration and neuronal ceroid lipofuscinosis phenotypes due to progranulin gene mutation. Neurobiol Aging. 2016; 41: 200.e1-200.e5.
3. Canafoglia L, Morbin M, Scaioli V, Pareyson D, D'Incerti L, Fugnanesi V, et al. Recurrent generalized seizures, visual loss, and palinopsia as phenotypic features of neuronal ceroid lipofuscinosis due to progranulin gene mutation. Epilepsia. 2014; 55: e56-59.
4. Faber I, Prota JR, Martinez AR, Lopes-Cendes I, França MC Júnior. A new phenotype associated with homozygous GRN mutations: complicated spastic paraplegia. Eur J Neurol. 2017; 24: e3-e4.
5. Huin V, Barbier M, Bottani A, Lobrinus JA, Clot F, Lamari F, et al. Homozygous GRN mutations: new phenotypes and new insights into pathological and molecular mechanisms. Brain. 2020; 143: 303-319.
6. Kamate M, Detroja M, Hattiholi V. Neuronal ceroid lipofuscinosis type-11 in an adolescent. Brain Dev. 2019; 41: 542-545.
7. Smith KR, Damiano J, Franceschetti S, Carpenter S, Canafoglia L, Morbin M, et al. Strikingly different clinicopathological phenotypes determined by progranulin-mutation dosage. Am J Hum Genet. 2012; 90: 1102-1107.



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