

## **POLR3A gene**

RNA polymerase III subunit A

### **Normal Function**

The *POLR3A* gene provides instructions for making the largest piece (subunit) of an enzyme called RNA polymerase III. This enzyme is involved in the production (synthesis) of ribonucleic acid (RNA), a chemical cousin of DNA. The RNA polymerase III enzyme attaches (binds) to DNA and synthesizes RNA molecules in accordance with the instructions carried by the DNA, a process called transcription. RNA polymerase III helps synthesize several forms of RNA, including ribosomal RNA (rRNA) and transfer RNA (tRNA). Molecules of rRNA and tRNA assemble protein building blocks (amino acids) into working proteins; this process is essential for the normal functioning and survival of cells.

### **Health Conditions Related to Genetic Changes**

#### Pol III-related leukodystrophy

At least 70 *POLR3A* gene mutations have been associated with Pol III-related leukodystrophy. Leukodystrophies are conditions that involve abnormalities of the nervous system's white matter. White matter consists of nerve fibers covered by a fatty substance called myelin, which insulates nerve fibers and promotes the rapid transmission of nerve impulses. A reduced ability to form myelin (hypomyelination) leads to the signs and symptoms of Pol III-related leukodystrophy, which include intellectual disability and difficulty with coordinating movements (ataxia). Development of the teeth (dentition) is also abnormal in this disorder.

In Pol III-related leukodystrophy, *POLR3A* gene mutations may impair the ability of the subunits of the RNA polymerase III enzyme to assemble properly or result in an RNA polymerase III with impaired ability to bind to DNA. Reduced function of the RNA polymerase III molecule likely affects development and function of many parts of the body, but the relationship between *POLR3A* gene mutations and the specific signs and symptoms of this disorder is unknown.

People with Pol III-related leukodystrophy may have different combinations of its signs and symptoms. These varied combinations of clinical features were originally described as separate disorders. Affected individuals may be diagnosed with ataxia, delayed dentition, and hypomyelination (ADDH); hypomyelination, hypodontia,

hypogonadotropic hypogonadism (4H syndrome); tremor-ataxia with central hypomyelination (TACH), leukodystrophy with oligodontia (LO); or hypomyelination with cerebellar atrophy and hypoplasia of the corpus callosum (HCAHC). Because these disorders were later found to have the same genetic cause, researchers now group them as variations of the single condition Pol III-related leukodystrophy.

### Wiedemann-Rautenstrauch syndrome

Mutations in the *POLR3A* gene cause Wiedemann-Rautenstrauch syndrome, which is a condition characterized by the dramatic, rapid appearance of aging beginning early in life. Affected individuals grow slowly before and after birth. They have a characteristic facial appearance, a lack of fatty tissue under the skin (lipodystrophy), sparse hair on their head, and abnormal tooth development. Some of the mutations that cause this condition alter the blueprint for making proteins. Other mutations lead to an abnormally short blueprint. Both types of mutations result in production of abnormal subunit proteins that are thought to impair the function of RNA polymerase III. The resulting shortage of RNA synthesis likely impairs protein production in cells, affecting development and function of many parts of the body. However, it is not known exactly how changes in the *POLR3A* gene lead to the features of Wiedemann-Rautenstrauch syndrome.

Researchers suspect that mutations that cause Wiedemann-Rautenstrauch syndrome reduce RNA polymerase III function more drastically than mutations that cause Pol III-related leukodystrophy (described above), which may explain why development is affected even before birth in individuals with Wiedemann-Rautenstrauch syndrome. Because of its distinct signs and symptoms, Wiedemann-Rautenstrauch syndrome is not thought to be part of the Pol III-related leukodystrophy spectrum.

### Shingles

MedlinePlus Genetics provides information about Shingles

### Other disorders

Mutations in the *POLR3A* gene have been found in individuals with ataxia and dental abnormalities. Unlike in Pol III-related leukodystrophy (described above), these individuals do not have reduced myelination in the nervous system. When associated with *POLR3A* gene mutations, ataxia typically begins in adolescence. Affected individuals may also develop rhythmic shaking (tremor) in the arms or legs and have a reduced ability to sense vibrations, particularly in the feet. It is unclear why mutations in the same gene lead to several disorders of varying severity. Researchers are unsure if this condition is part of the spectrum of Pol III-related leukodystrophies.

### **Other Names for This Gene**

- ADDH
- DNA-directed RNA polymerase III largest subunit
- DNA-directed RNA polymerase III subunit A

- DNA-directed RNA polymerase III subunit RPC1
- HLD7
- HRPC155
- polymerase (RNA) III (DNA directed) polypeptide A, 155kDa
- polymerase (RNA) III subunit A
- RNA polymerase III 155 kDa subunit
- RNA polymerase III subunit C1
- RNA polymerase III subunit C160
- RNA polymerase III subunit RPC155-D
- RPC1
- RPC155
- RPC1\_HUMAN

## **Additional Information & Resources**

### Tests Listed in the Genetic Testing Registry

- Tests of POLR3A ([https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=11128\[geneid\]](https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=11128[geneid]))

### Scientific Articles on PubMed

- PubMed (<https://pubmed.ncbi.nlm.nih.gov/?term=%28POLR3A%5BTIAB%5D%29+OR+%28%28ADDH%5BTIAB%5D%29+OR+%28HLD7%5BTIAB%5D%29+OR+%28RPC1%5BTIAB%5D%29+OR+%28RPC155%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D%29>)

### Catalog of Genes and Diseases from OMIM

- POLYMERASE III, RNA, SUBUNIT A; POLR3A (<https://omim.org/entry/614258>)

### Gene and Variant Databases

- NCBI Gene (<https://www.ncbi.nlm.nih.gov/gene/11128>)
- ClinVar ([https://www.ncbi.nlm.nih.gov/clinvar?term=POLR3A\[gene\]](https://www.ncbi.nlm.nih.gov/clinvar?term=POLR3A[gene]))

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## Genomic Location

The *POLR3A* gene is found on chromosome 10 (<https://medlineplus.gov/genetics/chromosome/10/>).

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