

# Deafness-dystonia-optic Neuronopathy Syndrome

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Deafness-dystonia-optic neuronopathy (DDON) syndrome, also known as Mohr-Tranebjærg syndrome, is characterized by hearing loss that begins early in life, problems with movement, impaired vision, and behavior problems. This condition occurs almost exclusively in males.

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## 1. Introduction

The first symptom of DDON syndrome is hearing loss caused by nerve damage in the inner ear (sensorineural hearing loss), which begins in early childhood. The hearing impairment worsens over time, and most affected individuals have profound hearing loss by age 10.

People with DDON syndrome typically begin to develop problems with movement during their teens, although the onset of these symptoms varies among affected individuals. Some people experience involuntary tensing of the muscles (dystonia), while others have difficulty coordinating movements (ataxia). The problems with movement usually worsen over time.

Individuals with DDON syndrome have normal vision during childhood, but they may develop vision problems due to breakdown of the nerves that carry information from the eyes to the brain (optic atrophy). Affected individuals can develop an increased sensitivity to light (photophobia) or other vision problems beginning in adolescence. Their sharpness of vision (visual acuity) slowly worsens, often leading to legal blindness in mid-adulthood.

People with this condition may also have behavior problems, including changes in personality and aggressive or paranoid behaviors. They also usually develop a gradual decline in thinking and reasoning abilities (dementia) in their forties. The lifespan of individuals with DDON syndrome depends on the severity of the disorder. People with severe cases have survived into their teenage years, while those with milder cases have lived into their sixties.

## 2. Frequency

DDON syndrome is a rare disorder; it has been reported in fewer than 70 people worldwide.

## 3. Causes

Mutations in the *TIMM8A* gene cause DDON syndrome. The protein produced from this gene is found inside the energy-producing centers of cells (mitochondria). The TIMM8A protein forms a complex (a group of proteins that work together) with a very similar protein called TIMM13. This complex functions by transporting other proteins within the mitochondria.

Most mutations in the *TIMM8A* gene result in the absence of functional TIMM8A protein inside the mitochondria, which prevents the formation of the TIMM8A/TIMM13 complex. Researchers believe that the lack of this complex leads to abnormal protein transport, although it is unclear how abnormal protein transport affects the function of the mitochondria and causes the signs and symptoms of DDON syndrome.

### 3.1. The Gene Associated with Deafness-dystonia-optic Neuronopathy Syndrome

- TIMM8A

## 4. Inheritance

DDON syndrome is inherited in an X-linked recessive pattern. The gene associated with this condition is located on the X chromosome, which is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause DDON syndrome. Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females. Females who carry one altered copy of the *TIMM8A* gene are typically unaffected; however, they may develop mild hearing loss and dystonia. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

## 5. Other Names for This Condition

- deafness syndrome, progressive, with blindness, dystonia, fractures, and mental deficiency
- deafness-dystonia-optic atrophy syndrome
- Jensen syndrome
- Mohr-Tranebjærg syndrome
- opticoacoustic nerve atrophy with dementia

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