

MORE FOCUS ON ADOA

ADOA at a glance

ADOA stands for Autosomal Dominant Optic Atrophy, a rare hereditary disorder of the optic nerve that affects approximately 1 in 30,000 people.

Symptoms vary between individuals, even within the same family. Some experience only minor visual impairment, while others may become nearly blind. Between 10% and 20% of patients have ADOA-plus, which includes extra-ocular symptoms.

Visual loss usually starts in early childhood, though onset can also occur during adolescence or early adulthood. The average age of onset is around 10 years. Due to limited awareness and the variable clinical presentation, diagnosis is sometimes delayed until adulthood.

Increased awareness of ADOA-related visual complaints can reduce this diagnostic delay. Greater focus on ADOA is essential.

Features

ADOA is characterized by slowly progressive, bilateral visual loss. Common symptoms include reduced visual acuity, blurry vision, decreased contrast sensitivity, and color vision abnormalities.

In ADOA-plus, optic nerve degeneration may be accompanied by hearing loss, balance issues, muscle weakness, impaired coordination, or reduced sensation. The visual decline in ADOA-plus may progress more rapidly than in classic ADOA.

Diagnostics

Optic atrophy (OA) is often first detected during an ophthalmological exam. Genetic testing can confirm a diagnosis of ADOA and help rule out other conditions. However, a genetic cause is not always identified.

Differential diagnoses for ADOA include glaucoma, Leber's hereditary optic neuropathy, optic neuritis, and other optic neuropathies (e.g., due to vitamin B12 deficiency, toxins such as alcohol or tobacco, ischemia, or trauma).

Cause

ADOA is a mitochondrial disease inherited in an autosomal dominant pattern. Several genes are associated with ADOA, most commonly OPA1 (40–70%).

OPA1 encodes a protein essential for various mitochondrial functions. This protein supports membrane stability and regulates mitochondrial fusion, thereby enhancing energy production under high demand.

Pathogenic OPA1 variants result in reduced levels of functional protein, impairing mitochondrial response to energy needs and leading to tissue damage.

Retinal ganglion cells, which have high energy requirements, are among the first to be affected. The papillomacular bundle (the temporal part of the optic nerve) is especially vulnerable, explaining characteristic findings on eye exams.

About the Cure ADOA Foundation

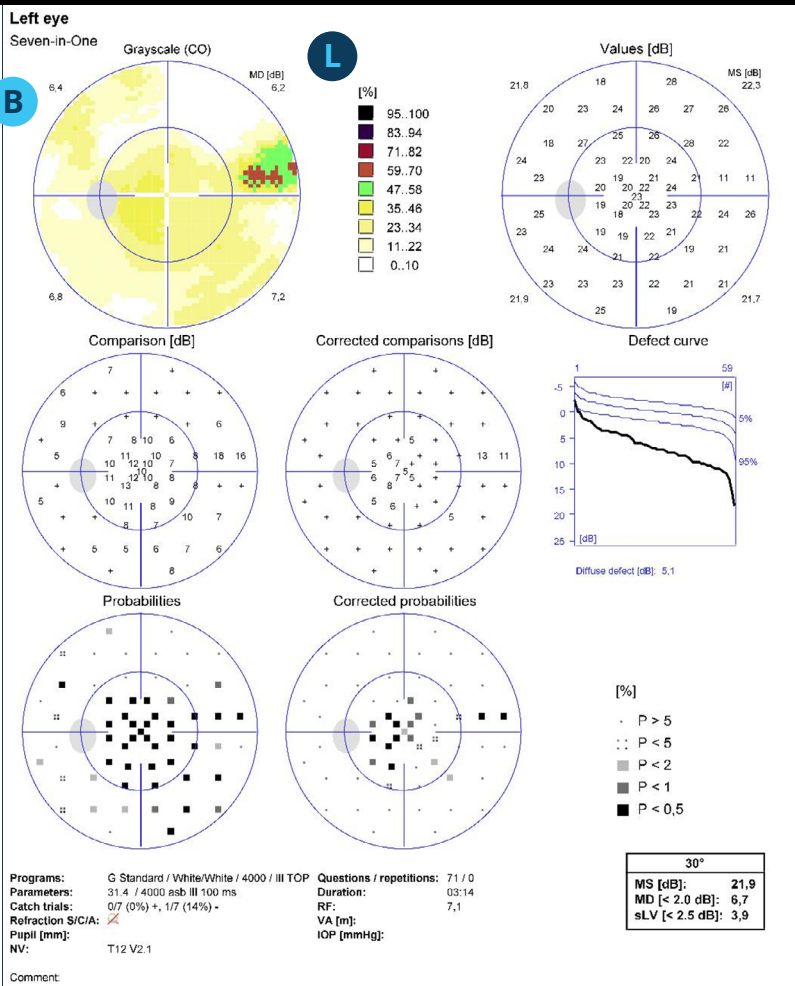
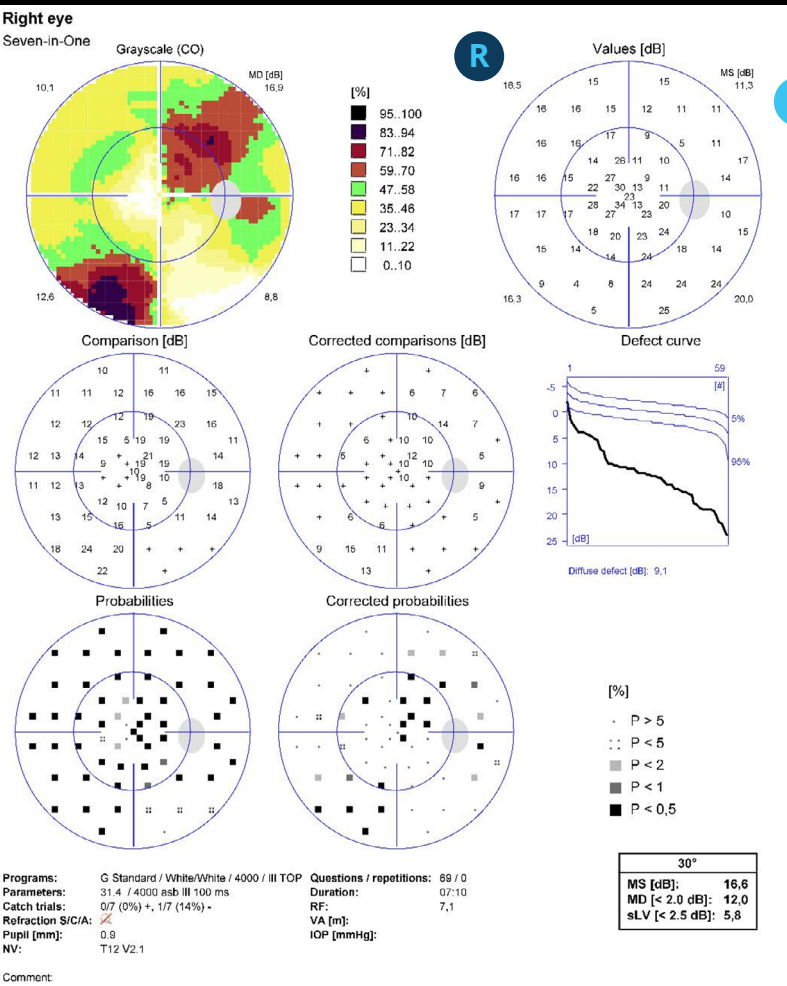
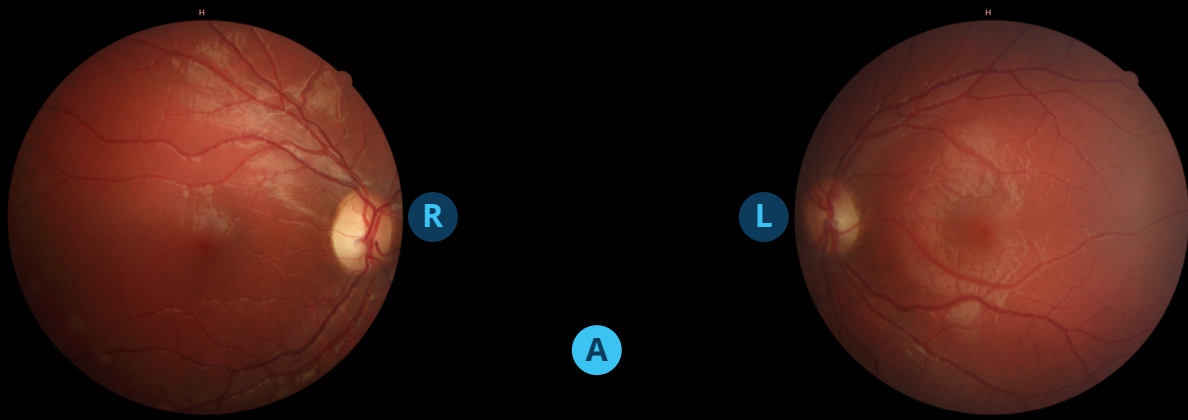
Since November 2018, the Cure ADOA Foundation has supported individuals with ADOA(-plus), focusing on four key areas: scientific research, advocacy, raising awareness, and peer support. The ultimate goal is to prevent and cure ADOA(-plus).

Website: www.adoa.eu/en/

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Example (8-year-old with 0.3 visual acuity) (Images published with patient's consent)

- A** Fundus: Bilateral temporal pallor of the optic discs.
- B** Visual field: Generalized sensitivity loss with relative central scotomas
- C** OCT RNFL: Temporal thinning of retinal nerve fiber layer bilaterally.
- D** OCT GCL: Central thinning of the ganglion cell layer.

Ophthalmological findings

Typical findings in ADOA include:

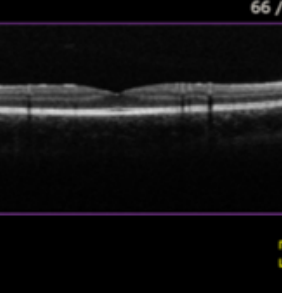
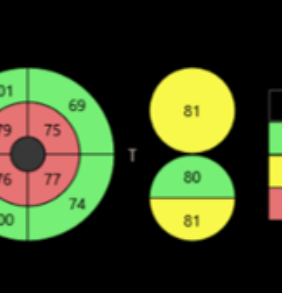
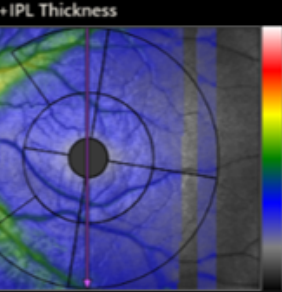
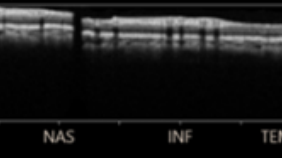
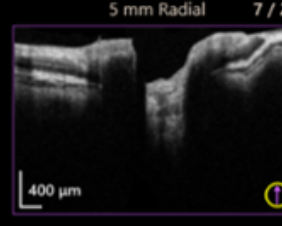
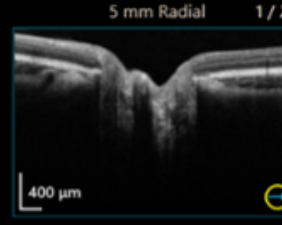
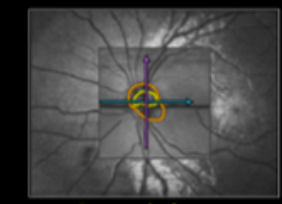
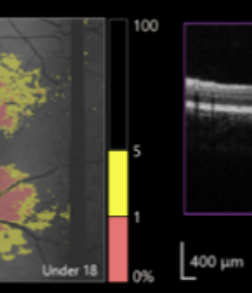
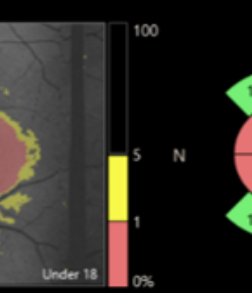
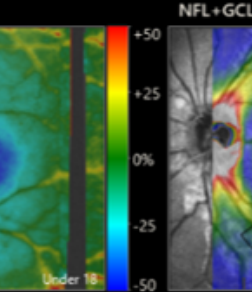
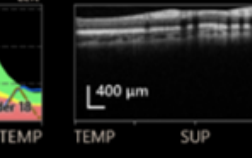
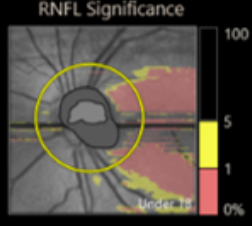
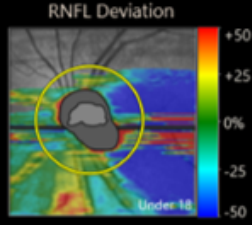
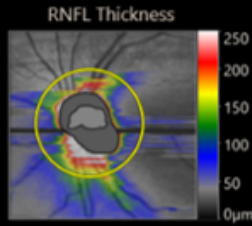
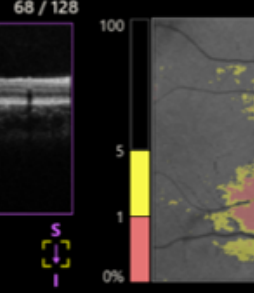
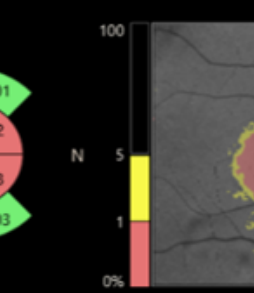
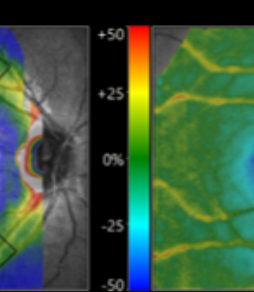
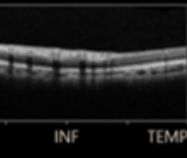
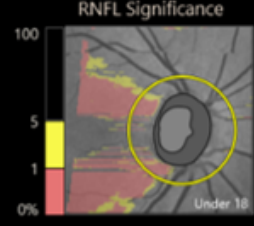
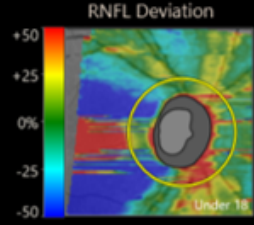
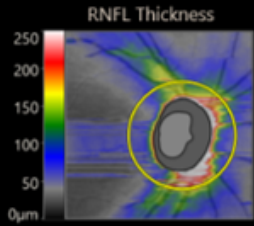
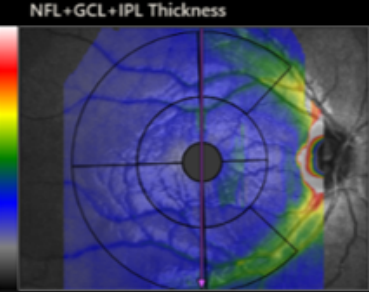
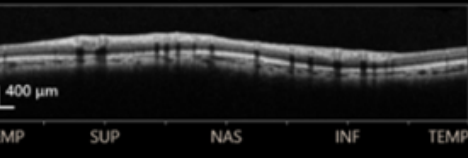
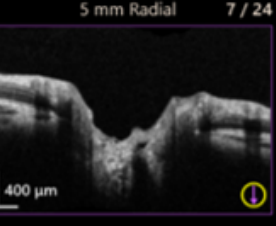
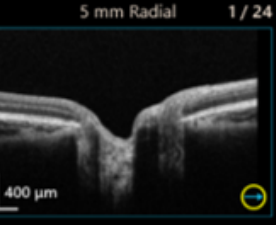
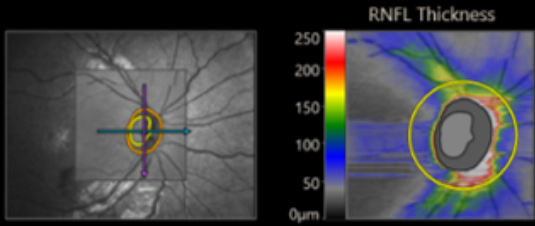
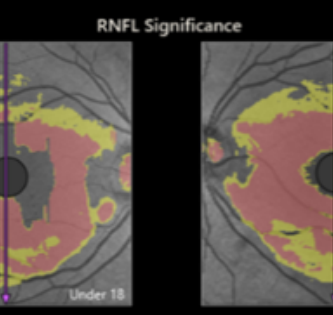
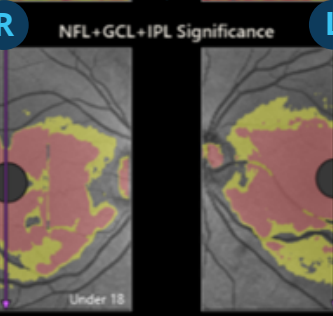
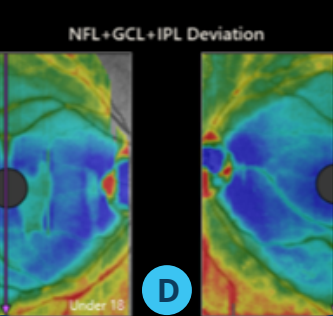
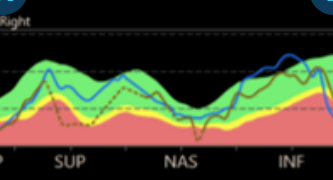
- Fundus examination: Pale optic discs, especially temporally.
- OCT (Optical Coherence Tomography): Thinning of the ganglion cell and retinal nerve fiber layers.
- VEPs (Visual Evoked Potentials): Initially small responses, later delayed or absent.
- Visual field testing: Central scotomas may be present.
- Color vision: Early tritan defects (blue-yellow), followed by red-green deficits.

ONH Measurement

ONH Parameters	Right	Left
Disc Area (mm ²)	3,29	2,61
Rim Area (mm ²)	2,03	1,88
Cup Volume (mm ³)	0,23	-
Rim Volume (mm ³)	0,29	0,30
C/D Area	0,38	0,28
C/D Vertical	0,64	0,39
C/D Horizontal	0,59	0,68
R/D Minimum	0,05	0,09
Rim Absence (°)	-	-
DDLS	4	5

RNFL Measurement

TSNIT Parameters	Right	Left
TSNIT Average (μm)	99	85
Standard Deviation	46,5	43,6
Symmetry	0,90	



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Genetic Testing

Inheritance is autosomal dominant, with a 50% chance of passing on the variant. Some cases are due to de novo mutations. Autosomal recessive optic atrophy is rare.

Testing options include:

- Targeted testing if a known family variant exists.
- A gene panel for optic atrophy.

Presymptomatic testing, prenatal diagnostics, and preimplantation genetic testing (PGT) in families with known pathogenic variants.

There is high variability in symptoms and severity, even within the same family (variable expressivity). Some carriers remain asymptomatic (incomplete penetrance).

Genetic counseling helps individuals and families make informed decisions.

Disease Progression

ADOA typically progresses slowly. Natural history studies suggest an average visual decline of 0.05 Snellen (0.03 LogMAR) per year, although rates vary greatly, even among relatives.

Some individuals remain asymptomatic. Certain OPA1 mutations, especially those in exons 8–24 (GTPase/dynamin domain), are linked to worse visual prognosis and a higher risk of developing ADOA(-plus).

Prognosis based on genotype alone is challenging due to wide clinical variability, the diversity of mutations, and limited genotype-phenotype correlation.

Treatment, follow-up and counselling

Currently, there is no cure for ADOA(-plus). Recommended care includes regular monitoring of visual acuity, fields, and color vision.

Support from low-vision services can help with functional adaptations.

Patient Advice

Refer patients to the Cure ADOA Foundation for information and peer support. The website offers brochures, podcasts, and research updates. www.adoa.eu/en/

Encourage patients to consider:

- Healthy lifestyle choices: A balanced diet, avoiding smoking, and abstaining from alcohol and addictive substances.
- Fatigue management: Common in ADOA(-plus) due to cognitive load, depression, light sensitivity, and visual strain.
- Occupational therapists can teach energy-conservation techniques.
- Light-filtering lenses: May provide relief for some patients.

Drugs with Mitochondrial Toxicity

Certain drugs should be avoided in mitochondrial diseases like ADOA. An international expert panel published a list of safe and potentially unsafe medications in the Journal of Inherited Metabolic Disease (July 2020).

- Safe Medication safety lists are available at: <https://www.adoa.eu/en/downloads>
- Safe Medications: <https://adoa.eu/wp-content/uploads/2021/02/Medicatielijst-1-2020.pdf>
- Potentially unsafe medications: <https://adoa.eu/wp-content/uploads/2021/02/Medicatielijst-2-2020.pdf>

Genetic Counseling

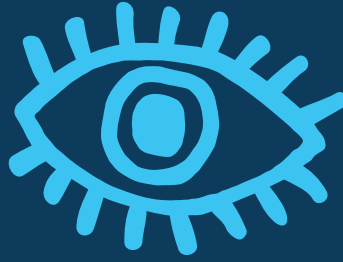
Clinical geneticists can provide inheritance guidance and family information letters. Relatives can be referred for consultations. Genetic testing is a personal decision. Genetic counselors support patients through the decision-making process. Preconception counseling is recommended for couples considering pregnancy. A clinical geneticist or social worker can assist in discussing reproductive options during pregnancy.

Scientific Developments

Several universities and pharmaceutical companies are researching potential treatments for ADOA(-plus), though most are still in the early stages.

Investigational therapies include CRISPR/Cas9 and RNA-based gene therapies.

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References

1. Yu-Wai-Man P, Griffiths PG, Burke A, Sellar PW, Clarke MP, Gnanaraj L, et al. The Prevalence and Natural History of Dominant Optic Atrophy Due to OPA1 Mutations. *Ophthalmology*. 2010;117(8):1538-46.
2. Cohn AC, Toomes C, Hewitt AW, Kearns LS, Inglehearn CF, Craig JE, Mackey DA. The natural history of OPA1-related autosomal dominant optic atrophy. *Br J Ophthalmol*. 2008;92(10):1333-6.
3. Borrelli E, Bandello F, Boon CJF, Carelli V, Lenaers G, Reibaldi M, et al. Mitochondrial retinopathies and optic neuropathies: The impact of retinal imaging on modern understanding of pathogenesis, diagnosis, and management. *Prog Retin Eye Res*. 2024;101:101264.
4. Rocatcher A, Desquiret-Dumas V, Charif M, Ferré M, Gohier P, Mirebeau-Prunier D, et al. The top 10 most frequently involved genes in hereditary optic neuropathies in 2186 probands. *Brain*. 2023;146(2):455-60.
5. Yu-Wai-Man P, Griffiths PG, Gorman GS, Lourenco CM, Wright AF, Auer-Grumbach M, et al. Multi-system neurological disease is common in patients with OPA1 mutations. *Brain : a journal of neurology*. 2010;133(Pt 3):771-86.
6. De Vries MC, Brown DA, Allen ME, et al. Safety of drug use in patients with a primary mitochondrial disease: An international Delphi-based consensus. *J Inherit Metab Dis*. 2020;43:800-818. <https://onlinelibrary.wiley.com/doi/10.1002/jimd.12196>