Commentary Article

# The function of mitochondria in autosomal-recessive optic atrophy

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**ABSTRACT**

A kind of optic neuropathy known as otic atrophy with autosomal inheritance is characterised by a progressive and permanent loss of vision. This is sometimes accompanied by other extra-ocular symptoms that are often neurological. The specific degeneration of the retinal ganglion cells, which make up the optic nerve, is what causes the loss of vision. Despite the genetic heterogeneity of autosomal OA, all of the causal genes that have been discovered so far seem to be involved in mitochondrial structure and function. RGCs are particularly susceptible to mitochondrial aberration, but the reason for this is unknown. There are presently no approved treatments for this condition, despite the fact that it is rather common. There is still a definite need for more research to determine the underlying mechanisms and create treatments for this disorder because we still don't know how abnormal mitochondrial function results in RGC mortality. The genes known to induce autosomal OA and themitochondrial dysfunction brought on by pathogenic mutations are summarised in this article. We also talk about the applicability of existing in vivo models for autosomal OA in terms of both developing treatments and deepening our understanding of the pathogenesis of autosomal OA.

**Key Words:** *Heterogeneity; Mitochondrial; Ganglion Cells; Autosomal ; Dysfunction*

## INTRODUCTION

Optic Atrophy (OA) is a diverse neurological illness that is inherited autosomally and is largely defined by the bilateral degeneration of optic nerve fibres, which results in a progressive and permanent loss of eyesight. OA is primarily referred to as dominant optic atrophy in the literature, but both dominant and recessive variants of the illness are frequent, as we will explore further below. It is regarded to be the most widespread form of hereditary optic neuropathy, with an estimated prevalence of 1 in 25,000 to 1 in 12,000 in some locations. The first or second decade of life is when the condition typically manifests, and diagnosis typically takes place in childhood. The symptoms of autosomal OA are complicated, and the degree of eyesight loss varies greatly. While some people have mild visual impairments, including colour vision problems, others have more serious visual impairments that lead to blindness. Also known as syndromic- OA, approximately 25% of patients also have extra-ocular symptoms such as ataxia, peripheral neuropathy, deafness, and myopathy. It is still unclear why some people experience syndromic OA whereas others, perhaps with the same underlying genetic variants, experience non-syndromic OA (involving visual symptoms only) Despite a small-scale, off-label trial using the coenzyme- Q10 analogue idebenone, there is currently no commercially viable treatment for autosomal OA, representing a significant unmet need for those affected. As a result, there is a clear need to improve our understanding of the molecular processes that cause this problem in order to develop new treatment plans for autosomal OA that are also applicable to other neurodegenerative disorders. The convergent evidence for mitochondrial failure underlying axonopathy in autosomal OA is discussed in this review. We also look at existing and proposed model systems for autosomal OA research, many of which would be very adaptable to other types

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of hereditary retinal and neurological diseases. The degradation of Retinal Ganglion Cells (RGCs), which carry visual information from the photoreceptors to the brain, is linked to the loss of sight in autosomal OA. The optic nerve is made up of the RGCs' axons. RGCs have a high energy need, similar to that of the majority of neurons, to maintain the constant active transport of ions against their concentration and electrical gradients necessary for membrane repolarization, maintenance of calcium reserves, and mobilisation of synaptic vesicles. This energy is largely produced by Oxidative Phosphorylation (OXPHOS), which produces ATP in conjunction with electron transport within the cristae folds of the Inner Mitochondrial Membrane (IMM). RGCs have intricate dendritic arbours and lengthy axons in terms of morphology. Additionally, and perhaps exclusively to RGCs, the retina's most distal axons are unmyelinated. RGC axons' unmyelinated section has a larger mitochondrial burden. In contrast to myelinated axons, this is typically thought to indicate a higher energy need for axon propagation. However, recent research has shown that mitochondrial accumulation occurs before RGC axon myelination, casting doubt on this presumption. Furthermore, patients with syndromic-OA show that autosomal OA-causing mutations can cause the degeneration of neurons other than RGCs, despite the fact that RGCs appear to be particularly prone to mitochondrial abnormalities. There have also been numerous accounts of autosomal OA occurring simultaneously with other neurological diseases, including hereditary Spastic Paraplegia (HSP) and Charcot-Marie-Tooth type 2 (CMT2). All of these facts show convincingly that highly elongated neurons, including RGCs, motor neurons, sensory neurons, and cerebellar purkinje cells, are especially vulnerable to the mutations causing these neurodegenerative illnesses. This underlines the significance of comparable in vivo models for a better understanding of molecular events specifically in long axons. Monogenic, genetically diverse autosomal OA is predominantly brought on by mutations in nuclear genes that code for mitochondrial proteins. Autosomal OA is most frequently caused by mutations in the OPA1 gene. However, autosomal OA is also linked to mutations in at least 10 more genes, which are covered in more detail below. Numerous chromosomal rearrangements, such as copy number variations and inversions, as well as nonsense, missense, frameshift, and splice mutations, have been discovered as disease-causing mutations. Haplo insufficiency is suggested as the main mechanism of pathogenesis in dominant variants of autosomal OA since the bulk of disease-causing mutations are likely to impede the function of the encoded protein. There are, however, some reports of semi-dominant inheritance, when people with several OA-causing mutations manifest their illness significantly more severely than heterozygous parents or siblings. The mutations in TMEM126A/OPA7, SCL25A46, MCAT, and RTN4IP1/OPA10 are connected to several forms of recessively inherited OA, and the mutations in WFS1, ACO2/OPA9, and OPA3 are related to both recessive and dominant forms of OA. Due to the genetic variability, we refer to this condition as "autosomal OA" throughout this review.