

Review

Hereditary Optic Neuropathies: An Updated Review

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Abstract: Hereditary optic neuropathies (HONs) are a class of genetic disorders that may lead to vision loss due to either acute or progressive injury to the optic nerve. Although HONs may commonly manifest as isolated optic atrophy, these disorders can also have a variety of characteristic clinical features and time courses that may narrow the differential diagnosis. While the two most prevalent HONs are Leber Hereditary Optic Neuropathy (LHON) and Dominant Optic Atrophy (DOA), the phenotypic spectrum of these conditions, as well as genetic landscape of less common optic neuropathies, have been better characterized through advances in molecular diagnostic testing. Treatment targeting various pathogenic mechanisms has been investigated, although studies of clinical applicability remain nascent. Present management largely remains supportive. In this review, we discuss the clinical features, molecular diagnosis, current treatment, and future directions for HONs.

Keywords: optic neuropathy; optic atrophy; Leber's hereditary optic neuropathy; dominant optic atrophy



Citation: Lee, S.K.; Mura, C.; Abreu, N.J.; Rucker, J.C.; Galetta, S.L.; Balcer, L.J.; Grossman, S.N. Hereditary Optic Neuropathies: An Updated Review. *J. Clin. Transl. Ophthalmol.* **2024**, *2*, 64–78. <https://doi.org/10.3390/jcto2030006>

Academic Editor: Peter Koulen

Received: 4 March 2024

Revised: 19 June 2024

Accepted: 25 June 2024

Published: 26 June 2024



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1. Introduction

Hereditary optic neuropathies (HONs) represent an important cause of visual impairment in the differential diagnosis of optic atrophy. Ranging from isolated optic atrophy to systemic disease, HONs are defined by retinal ganglion cell degeneration often causing bilateral loss of vision, due to variants in the nuclear or mitochondrial genome [1]. Typical additional clinical features of HONs include dyschromatopsia and central scotomas on visual field evaluation. Through advances in molecular genetic testing technologies, the number of genes associated with HONs has expanded, with the majority of variants disrupting mitochondrial function [2]. HON inheritance patterns are frequently mitochondrial or autosomal dominant, although autosomal recessive and X-linked patterns have been described [3,4]. The availability of next-generation sequencing technologies, such as targeted panels, exome sequencing, and mitochondrial genome sequencing, has allowed for broad and efficient genomic evaluation in common clinical practice. These tools have expanded the number of pathogenic variants of common HONs like Leber Hereditary Optic Neuropathy (LHON) and dominant optic atrophy (DOA), while also advancing understanding of rarer syndromic HONs [5–7]. In this review, we discuss the epidemiology, clinical features, molecular diagnosis, treatment, and future directions for isolated and syndromic HONs.

2. Leber's Hereditary Optic Neuropathy

First described by von Graefe in 1858 [8] and later defined by Leber in detail through four different families in 1871 [9], LHON (Online Mendelian Inheritance in Man [OMIM]:

535000) usually presents as painless, isolated, bilaterally sequential, subacute, central visual loss, most frequently in young men. In 1988, Wallace et al. [10] demonstrated a mitochondrial point mutation in LHON that correlated with its known maternal inheritance. LHON has since been identified as one of the most common mitochondrial diseases with estimated minimum prevalence varying by region from 1 per 31,054 individuals in northeast England to 1 per 68,403 individuals in Australia [11,12]. LHON is a disorder with incomplete penetrance, meaning that an individual may possess a pathogenic variant but not develop symptoms. A 2021 national registry study in Australia found that risk of visual loss among those with an LHON disease-causing variant was 17.5% for males and 5.4% for females [12], which was lower than previously estimated risks of 50% and 10%, respectively [13]. The three most common pathogenic variants associated with LHON are found in three different genes that encode a mitochondrial respiratory chain complex 1 subunit—*MT-ND1* m.3460G>A, *MT-ND4* m.11778G>A, and *MT-ND6* m.14484T>C. They are responsible for approximately 90% of LHON cases worldwide [14], while the other 10% are ascribed to more than 30 other less frequent variants [1]. These genes reside in the genome located within mitochondria rather than the nucleus, and are transmitted maternally. However, variants in nuclear genes, such as *NDUFAF5* (OMIM 612360), *DNAJC30* (OMIM 618202), and *NDUFS2* (OMIM 602985) that are all involved in Complex I assembly and repair, have been recently implicated in LHON phenotypes, often following an autosomal recessive inheritance pattern [6,15–17]. A recent case study of LHON identified a mono-allelic pathogenic variant in *KIF5A* (OMIM 602821), which encodes for a neuronal motor protein heavy chain involved in mitochondrial transport, although autosomal dominant inheritance has not yet been definitely established [18].

Classic clinical features of LHON include painless, bilateral subsequent central vision loss with one eye initially affected followed by the other eye within several weeks to one year [19]. Vision loss typically manifests as a central or centrocecal scotoma. Simultaneous involvement can occur in up to 25% of cases [20] while unilateral involvement has only rarely been reported [21]. Most cases have onset between 15 and 35 years of age, although male patients have a mean age of onset at 25 years old compared to female patients at 30 years old [1]. Increased male prevalence has been suggested to be due to the role of estrogen in protecting mitochondrial function along with other anatomic and genetic risk factors [14]. Age of onset has been reported as early as 2 years old and as late as 90 years old [22–24]. Children with LHON onset before age 9 have been proposed to have a better visual prognosis relative to those with later onset [22]. Current investigations have not elucidated the reason for the variation in timing of visual loss onset, but differing explanations include environmental triggers, secondary genetic modifiers, and anatomic variability [22,25].

After initial vision loss, LHON has been described as having three stages: subacute, dynamic, and chronic [26]. Figure 1 details the classic characteristics seen in each stage. Asymptomatic carriers can also demonstrate optical coherence tomography (OCT) and fundus changes without evidence of accompanying visual loss [20]. Visual acuities classically plateau around 4 months, with nadir worse than 20/200 (or 6/60) [19]. For patients with initial unilateral onset, bilateral involvement commonly occurs by the end of the subacute stage since the second eye manifests symptoms on average in about 2–3 months. Vision usually stabilizes in the dynamic phase although prior fundus exam changes regress and optic nerve head pallor becomes prominent, especially temporally due to earliest axonal loss in the papillomacular bundle (PMB) [20]. Visual fields and OCT measurements of retinal nerve fiber layer (RNFL) thickness also continue to progress [26]. The chronic phase, occurring after 12 months, is marked by stable severe visual impairment and optic atrophy. Occasionally, patients may experience some degree of spontaneous vision recovery. A more favorable course has been associated with the m.14484T>C variant, though recovery is often incomplete [27].

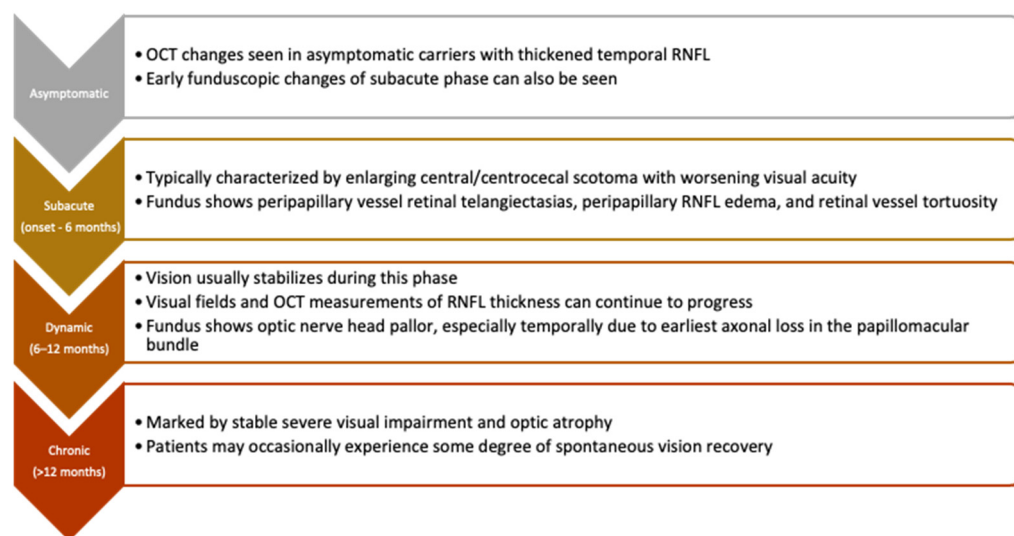


Figure 1. Stages of LHON. OCT, optical coherence tomography; RNFL, retinal nerve fiber layer.

While LHON can be suspected based on patient and family history, molecular genetic diagnostics provides confirmation. Genetic testing strategies may include common pathogenic variant analysis, gene panels, and mitochondrial genome sequencing with or without nuclear exome sequencing. Next generation sequencing relies on DNA fragmentation and amplification of targeted DNA segments by polymerase chain reaction (PCR) [28]. After preparatory modifications, these segments undergo massive parallel sequencing in high-throughput sequencers. Bioinformatic analysis of sequence data determines variants compared to the human genome and compiles a report of the targeted genes. Targeted variant analysis is typically appropriate in evaluating an at-risk individual when there is a known familial pathogenic variant [20]. Worldwide, the m.11778G>A variant is the most common, although the distribution of pathogenic variants can vary by geography as the m.14484T>C and m.3460G>A variants are less common in East Asians compared to non-East Asians [29]. Otherwise, panel-based testing that includes the mitochondrial genome may be considered. Expansion of genetic evaluation to include nuclear genes may be added as first- or second-tier testing depending on the clinical context.

The term LHON-Plus refers to cases involving further syndromic features, mainly neurological, that can accompany the optic neuropathy [30]. LHON-Plus cases can result from one of the three common pathogenic variants but other less common ones as well [20], and even nuclear DNA variants [6]. Age of onset has been reported as being similar to LHON although several LHON-Plus cases of childhood onset have been described [31,32]. Extraocular neurological symptoms reported include dystonia [33], epilepsy [34], cerebellar ataxia [35], parkinsonism [36], myoclonus [37], peripheral neuropathy [38], and encephalopathy [39]. Cardiac conduction deficits and endocrine-related dysfunction represent non-neurological extraocular symptoms in LHON-Plus [40]. For all of these symptoms, no causative relationship has been established. Harding disease, or the co-occurrence of LHON and multiple sclerosis (MS), is one overlapping LHON-Plus syndrome that can provide a diagnostic challenge as the HON can be overlooked or mistaken for optic neuritis [41]. Adding to the challenge, LHON-Plus can mimic demyelinating diseases like MS or neuromyelitis optica (NMO) rather than coexisting with them [32]. Absence of demyelination was recently reported in a patient with MS-like illness and subclinical optic neuropathy, highlighting this complicated entity [42]. The exact nature between co-existing LHON and MS remains unclear and controversy exists in the literature whether such cases represent co-occurrence of two disorders or a causative relationship [43].

Management of LHON and LHON-Plus centers on genetic counseling and supportive care while definitive medical and gene therapy continues to be investigated in clinical trials. Currently, idebenone is the only approved medication by the European Medicines Agency

for the treatment of LHON. Idebenone is a synthetic analog of coenzyme Q₁₀ that crosses the blood–brain barrier and prevents retinal ganglion cell death by shuttling electrons to bypass Complex I [44]. Within 12 months of LHON onset, treatment should be started at 900 mg daily for at least one year or until improvement plateaus [26]. The RHODOS trial, which included 85 patients with LHON for less than 5 years, did not meet statistical significance in its primary endpoint of best recovery of visual acuity (worse eye at baseline to better eye at study end) when comparing idebenone and placebo over 24 weeks [45]. Secondary endpoints of change in best visual acuity (better eye at baseline to better eye at study end) and change in visual acuity for both eyes were statistically significant in favor of the idebenone group [45]. The RHODOS-OFU study followed up on 60 of these patients at a median of 30 months after the RHODOS trial end and found that the idebenone group only demonstrated a significant improvement in the primary endpoint of change in best visual acuity (better eye at baseline to better eye at study end) in a subgroup analysis including patients with *MT-ND1* m.3460G>A and *MT-ND4* m.11778G>A pathogenic variants, excluding patients with the *MT-ND6* m.14484T>C pathogenic variant [46]. The idebenone group had a statistically significant improvement for the secondary endpoint of change in visual acuity of individual eyes (treated independently) [46]. The LEROS study confirmed idebenone benefit for LHON patients, investigating 199 LHON patients treated with idebenone compared to 372 LHON patients in an external natural history cohort up to 5 years after symptom onset [47]. The primary endpoint of clinically relevant benefit from baseline, satisfied by improving from ‘off-chart’ visual acuity to 1.6 logMAR, improving at least 0.2 logMAR if ‘on-chart’, or maintaining visual acuity less than 1.0 logMAR, was significantly higher after 12 months of idebenone treatment compared to the natural history cohort [47,48]. Further subgroup analysis demonstrated that the treatment effect varied by disease phase and pathogenic variant type. Patients in the chronic phase with the *MT-ND4* m.11778G>A or *MT-ND6* m.14484T>C pathogenic variant demonstrated consistent treatment benefit while patients with the *MT-ND1* m.3460G>A showed little impact. In the subacute/dynamic phase, only patients with the *MT-ND4* m.11778G>A pathogenic variant demonstrated statistically significant treatment benefit [47]. A retrospective study on seven patients with LHON for longer than 5 years found that idebenone treatment improved best corrected visual acuity, although its conclusions are significantly limited by sample size [49]. Recently, the importance of NADPH oxidoreductase I (NQO1) has been highlighted in LHON treatment as patients with variants resulting in low NQO1 levels demonstrate a poorer response to idebenone therapy [50]. The therapeutic landscape for LHON continues to evolve as new treatments are explored, including nutritional interventions, stem cell therapy, and antioxidant therapy [51]. For asymptomatic carriers of LHON, avoiding oxidative stress from smoking, excessive alcohol use, and toxic medications is advised [52]. For all patients with LHON, visual rehabilitation and psychological support should be emphasized.

Gene therapy, although not yet used in clinical practice, represents the other major approach to LHON treatment with multiple human clinical trials currently investigating various therapeutic targets. Present approaches employ allotopic expression to address the challenge of delivering genes to the mitochondrial genome. Allotopic expression involves using a viral vector to introduce a mitochondrial gene into the nucleus where it can replicate and be expressed in the cytosol. Engineered with a specific mitochondrial targeting sequence, the subsequent synthesized protein will be transported into the mitochondria by the cell’s own machinery [48]. Most trials have been conducted with unilateral intravitreal injections using the untreated eye as an internal control. Interestingly, bilateral visual acuities improved more than expected given the natural history of the disease and a unilateral injection [53]. The explanation may lie in the transneuronal spread of the viral vector to the contralateral optic nerve and retina, as seen in a nonhuman primate study [53], but further investigation of gene therapy bilateral involvement is required. Bilateral injections have been suggested to have a larger treatment effect than unilateral injection, as seen in the REFLECT trial [54]. Additional genetic techniques, including nuclear and

mitochondrial gene editing [55,56], heteroplasmic shift [57], and direct mitochondrial gene delivery [58], represent potential future avenues of treatment in LHON, notwithstanding the varying ethical, regulatory, and technical challenges of gene therapy.

3. Dominant Optic Atrophy

DOA (OMIM: 165500) is the most common HON with estimated minimum prevalence of 1 in 25,000 in the general population [20]. Described by Batten in 1896 [59] and later confirmed in larger studies by Jaeger [60] and by Kjer [61], DOA typically presents as a painless, insidious bilateral visual loss that follows an autosomal dominant inheritance pattern, although acute vision loss has been reported [62]. In contrast to LHON, males and females are equally affected although there is variable expression between individuals [1]. As in LHON age of onset, this variability likely relates to incompletely understood environmental and genetic factors.

Commonly diagnosed in early life, DOA is characterized by progressive bilateral vision loss, central or centrocecal scotomas, and generalized color vision deficits [7]. Funduscopy findings include optic disc pallor usually temporally or diffusely [1]. Abnormal disc excavation can also occur temporally [63]. Preferential loss of retinal ganglion cells at the PMB is evidenced by reduced RNFL thickness on optic nerve head OCT and blood flow on OCT angiography [7]. Visual acuity loss tends to be less severe than in LHON (usually better than 20/200) but progressive loss over time leads to severe visual impairment by the fifth decade of life for about half of all DOA patients [20].

DOA cases result most frequently from heterozygous variants in the *OPA1* gene located on chromosome 3q29 (OMIM: 605290) [64]. Composed of 30 exons, *OPA1* encodes for eight isoforms of a GTPase protein, complete with a mitochondrial targeting sequence, that assists in mitochondrial fusion, oxidative phosphorylation efficiency, and mitophagy [65]. Thus, while *OPA1* follows an autosomal dominant inheritance pattern and is a nuclear gene, it is considered a mitochondrial disorder, as pathogenic variants affect mitochondrial function. In the over 500 variants in *OPA1* that have been described, two main genetic pathomechanisms have been proposed: haploinsufficiency and dominant negativity [7]. Haploinsufficiency refers to a functional allele's inability to compensate for a null allele's loss of function while dominant negativity occurs when mutated proteins interfere with the remaining wild-type proteins. Splice-site mutations or deletions causing haploinsufficiency may have a less severe phenotype than missense mutations causing a dominant negative effect [66]. Targeted genetic testing again may be useful in the setting of a known familial variant, but broader genomic testing using next-generation sequencing may otherwise be preferred. If causative genes are not found on initial genetic testing strategies or the phenotype is complex, exome or genome sequencing can be helpful in diagnosis [20,66].

Other than *OPA1*, numerous genes have been implicated in DOA, with most affecting mitochondrial function and dynamics [66]. A recent retrospective study on a French cohort of 2186 probands identified *WFS1* (OMIM 606201), *ACO2* (OMIM 100850), and *SPG7* (OMIM 607259) as the next three most common nuclear genes affected in individuals with HONs [5]. These results roughly aligned with a later study in an Italian cohort with 1097 probands although *AFG3L2* (OMIM 604581) was more common than *SPG7* [67]. In the French study, late onset of HON after 60 years of age, presumably due to more moderate variants, was restricted to four genes: *OPA1*, *WFS1*, *ACO2*, and *MFN2* (OMIM 608507) [5]. *WFS1* and *MFN2* will be further described below. *ACO2* encodes for aconitase 2, which participates in the second step of the Krebs cycle where citrate is isomerized into iso-citrate [68]. *SPG7* and *AFG3L2* encode for proteins forming a mitochondrial matricial AAA protease complex involved in *OPA1* protein processing [69]. Table 1 highlights the *ACO2*-related DOA cases described in the literature. Recessive pathogenic variants in *ACO2* have previously been described in infantile cerebellar-retinal degeneration and isolated optic atrophy, and the recessive cases of optic atrophy have been shown to have worse visual acuity than the dominant ones [68]. Interestingly, compared to *OPA1*-related DOA, *ACO2*-related DOA shows higher nasal RNFL and ganglion cell layer thickness albeit with

similar visual function [70]. This may indicate a differing pathogenic mechanism compared to *OPA1* variants. In contrast, *AFG3L2*-related DOA demonstrates a similar phenotype to *OPA1*-related DOA with respect to visual acuity, RNFL thickness, and rates of extraocular symptoms, supporting the proposed mechanism of an *OPA1* processing defect [70]. *SPG7* pathogenic variants are thought to have the same mechanism as *AFG3L2* variants due to the dimeric relationship between the respective encoded proteins.

Table 1. *ACO2*-related DOA cases in literature.

Number of Cases	Age at First Diagnosis of OA Symptoms	Extraocular SYMPTOMS	Reference
50 individuals	0–63	Yes, 12%	Charif [68] (2021)
1 individual	26	No	Neumann [71] (2020)
1 individual	Unknown	No	Weisschuh [72] (2024)
23 individuals *	34.7 (mean)	Yes, 13%	Amore [70] (2024)

* Some initially reported in Charif [68] (2021).

Similar to the LHON disease spectrum, DOA-Plus refers to multisystemic features in addition to optic atrophy, mainly musculoskeletal and neurologic. These syndromic phenotypes may include deafness, myopathy, spastic paraplegia, chronic progressive external ophthalmoplegia, ataxia, parkinsonism, and dementia [73–78], and account for about 20% of all DOA cases [78]. DOA-Plus most commonly arises from *OPA1* variants, especially missense mutations [79]. Interestingly, a large meta-analysis found that DOA-Plus syndromes due to *OPA1* were more likely to be maternally inherited, while isolated DOA was more likely to be paternally inherited [79]. DOA-Plus can also be seen with mutations in other genes including *WFS1* [80], *MFN2* [81], and *OPA3* (OMIM 606580) [82]. To emphasize the complexity of DOA genetics, compound heterozygous mutations in *OPA1* can lead to a Behr-related syndrome presenting with early-onset optic neuropathy, spinocerebellar degeneration, peripheral neuropathy, pyramidal signs, and developmental delay [83]. The variable expressivity adds to the challenge of genotype–phenotype correlation and clinical recognition of specific genetic syndromes.

Treatment modalities of DOA overlap greatly with LHON although they remain under investigation as no preventative or curative therapies have yet been approved by major regulatory agencies for clinical practice. Unlike LHON, there is not typically spontaneous recovery of vision in DOA [1]. Due to its positive benefit in LHON, idebenone has been theorized to benefit patients with DOA as well [84]. A recent phase II clinical trial showed a significant but minor increase in best recovery of visual acuity after 12 months of 900 mg idebenone, although the small number of patients and absence of control group limited the study's evidence [85]. Other ongoing clinical trials for DOA are investigating regenerative treatment through stem cell injections [84], while gene therapies targeting different mechanisms of *OPA1* variants have been explored in preclinical studies with promising results but limited applicability [86,87]. Much of the paradigm of treating DOA lies in translation from LHON treatments, but future study is required before clinical approval.

4. Charcot–Marie–Tooth Disease

Charcot–Marie–Tooth (CMT) disease is a broad group of hereditary neuropathies that can cause optic atrophy along with peripheral sensorimotor neuropathies. Due to differing classification systems and phenotypic heterogeneity seen in individuals possessing pathogenic variants in the *MFN2* gene that encodes mitofusin 2, the general term *MFN2*-related hereditary motor and sensory neuropathy (*MFN2*-HMSN) is currently preferred. *MFN2*-HMSN encompasses what has previously been referred to as CMT2A2A, CMT2A2B, and HMSN6 [88]. *MFN2*-HMSN is the most common axonal CMT disease, accounting for 30–40% of genetically diagnosed axonal CMT disease [89]. It is characterized by greater lower extremity involvement than upper extremity involvement, motor deficits worse than

sensory defects, and optic atrophy [90]. Usually inherited in autosomal dominant fashion, the median age of onset is 12 years old, ranging from one year to the sixth decade [88]. It has been estimated that only 7% of autosomal dominant and 20% of the rarer autosomal recessive form of *MFN2*-HMSN present with optic atrophy [88].

Clinically, patients with *MFN2*-HMSN usually develop motor deficits before loss of vision, although isolated vision loss with no other neurological deficits has been reported [91]. Progressive bilateral vision loss with optic nerve pallor characterizes the ophthalmic findings, with decreased color vision, impaired ocular motility, and abnormal visual evoked potentials (VEP) having been described in the literature [92]. Typical visual acuity is 20/200 or worse, although visual recovery is possible and correlated with later age of onset [2]. The predominant findings of peripheral neuropathy, limb deformities, and length-dependent weakness are typically more severe with earlier onset than other CMT diseases [89].

MFN2 encodes for a 757-amino acid long transmembrane GTPase protein on the outer mitochondrial membrane that is involved in mitochondrial fusion reactions. Various loss-of-function pathogenic variants like p.Arg94Gln and p.Thr105Met inhibit this process while others like p.Arg364Trp, through gain-of-function mechanisms, cause mitochondrial hyperfusion [89]. Patients with p.Arg364Trp tend to have severe, early-onset disease, and cases have been described with optic atrophy, but patients with other pathogenic variants can demonstrate similar features [90]. An understanding of which mutations cause optic atrophy has not yet been fully elucidated, regardless of pathomechanism. About 90% of affected individuals with *MFN2*-HMSN possess a single heterozygous variant consistent with an autosomal dominant inheritance pattern, though biallelic variants have been reported in some cases [89]. Other genes responsible for CMT-associated optic atrophy continue to be identified, often affecting mitochondrial function or even myosin [93]. Typical molecular genetic diagnosis relies on panel, exome, or genome sequencing.

There are no currently available disease-modifying treatments for *MFN2*-HMSN. Management focuses on supportive care and surveillance of individual symptoms. For optic atrophy, this includes low vision aids, school accommodations for children, and assistive devices [88]. Musculoskeletal follow-up can help with physical therapy and many patients benefit from foot orthotics, wheelchairs, and other mobility aids. Multimodal pain control can be achieved through nonsteroidal anti-inflammatory agents, tricyclic antidepressants, carbamazepine, or gabapentin [88].

5. Wolfram Syndrome

Wolfram syndrome is a rare neurodegenerative disorder characterized by non-autoimmune early onset diabetes mellitus and optic atrophy that was first described in 1938 [94]. Historically, it was also described as DIDMOAD, standing for diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy (OA), and deafness (D). Typically diagnosed before 15 years of age, prevalence has been hard to estimate, although various studies have determined it to range from 1 in 54,478 in the Sicilian Messina district to 1 in 805,000 in North India, thought to be influenced by rates of consanguinity [95,96]. Wolfram syndrome classically results from autosomal recessive mutations in the *WFS1* gene and prognosis remains poor with mean age of death at 30 years old, usually due to respiratory failure secondary to brainstem atrophy [97]. Autosomal dominant mutations in *WFS1* have been more recently described in a clinical entity called Wolfram-like syndrome, characterized by optic atrophy, diabetes mellitus, and hearing impairment [98]. In a recent retrospective study of 37 patients with *WFS1*-associated optic neuropathy, 19 patients had dominant *WFS1* mutations. Interestingly, all 19 patients had OCT signs of outer plexiform layer cleft-like lamination and thickening, an evidently pathognomonic finding in dominant *WFS1* variants and an identifier of great diagnostic value [98]. Patients with autosomal dominant variants had a better visual prognosis than their recessive counterparts [98].

Optic atrophy in Wolfram syndrome presents as bilateral central vision acuity loss with loss of color vision. Vision loss is progressive although normally of faster trajectory than in DOA [99]. Structurally, a recent retrospective study of 25 Wolfram syndrome patients and

33 *OPA1*-related DOA found that the pattern of retinal ganglion cell (RGC) loss in Wolfram syndrome differs from a classic mitochondrial optic neuropathy [100]. Using OCT RNFL and ganglion cell layer thicknesses, they found that Wolfram syndrome patients suffered RGC axonal thinning about a decade before RGC cellular body atrophy compared to the relative stability of DOA patients after initial RGC loss [100]. Tonic pupils have also been reported in Wolfram syndrome [101]. The other pillar of clinical presentation, diabetes mellitus, usually develops around 6 years of age with lower insulin requirements and better glycemic control than Type 1 diabetes mellitus [97]. Diabetes insipidus and deafness are less common than optic atrophy and diabetes mellitus but still remain major features of the classic presentation. Despite not being originally described as part of Wolfram syndrome, neurological, urological and psychiatric symptoms can also occur, suggesting the need for careful follow-up of multiple systems [97].

WFS1 encodes for wolframin, a transmembrane protein on the endoplasmic reticulum (ER), that participates in mitochondrial interaction regulation, apoptosis signaling, and the ER stress response. Wolframin deficiency compromises axonal integrity, which aligns with the observed RGC axonal loss on OCT imaging [99,100]. Molecular genetic testing through multi-gene panels or comprehensive genomic testing confirms the diagnosis in patients with suggestive clinical findings [102]. Genetic advances have both added to and complicated the understanding of Wolfram syndrome as many pathogenic variants have been found for the classic phenotype, but other non-classic phenotypes have also been described. Other phenotypes have been referred to as Wolfram-like syndromes or “wolframinopathies” [102], emphasizing the spectrum of Wolfram syndromes.

There are no currently available therapies to prevent or cure Wolfram syndrome. Idebenone may have potential benefit for visual recovery given its mitochondrial dysfunction, but no prospective studies have investigated the coenzyme Q₁₀ derivative [103]. Various proposed therapies include drugs targeting ER stress, ER calcium stabilizers, gene therapy, and stem cell therapy with clinical trials underway for repurposing valproic acid and dantrolene sodium [104]. The rarity of the disease coupled with timing of disease progression has made it challenging to conduct clinical trials with adequate results. In the absence of curative treatment, patients receive supportive care, often from multidisciplinary specialists to manage syndromic manifestations [102].

6. Friedreich Ataxia

Friedreich ataxia (FRDA) is an autosomal recessive neurodegenerative disorder caused by biallelic pathogenic variants in the *FXN* gene (OMIM 606829), typically abnormal GAA repeat expansions within the first intron, which impairs *FXN* gene expression or leads to its mRNA deficit. FRDA is characterized by early-onset progressive gait and limb ataxia with varying additional neurologic and non-neurologic findings [105]. It is the most common autosomal recessive spinocerebellar ataxia, with a prevalence of 1 in 50,000 people worldwide [106]. Most patients have no symptomatic vision loss, but optic neuropathy is a common cause of afferent visual impairment and is frequently appreciated on detailed exam [107].

Optic neuropathy in FRDA is slowly progressive, with low-contrast acuity decreasing linearly over time [108]. Many patients are visually asymptomatic, although rapid loss of vision has been reported [105]. Other ophthalmic symptoms include ocular motility dysfunction, macro-saccadic oscillations, and frequent square-wave jerks [106]. On OCT, there is classically scattered loss of retinal ganglion cells, but the PMB thickness is preserved, suggesting a different pathogenesis than LHON or DOA [109]. Bilateral abnormal VEP are common and demonstrate conduction delay associated with progressive nerve fiber loss [106]. Other clinical features include dysarthria, scoliosis, areflexia, sensory loss, and cardiomyopathy [110].

Fraixin, the protein encoded by the *FXN* gene, primarily resides on the inner mitochondrial membrane contributing to mitochondrial electron transport and iron metabolism. Fraixin deficiency due to the common GAA repeat expansion or pathogenic small nu-

cleotide variants that impair oxidative stress defense mechanisms [106]. The diagnosis of FRDA relies on clinical features and molecular genetic confirmation. Polymerase chain reaction testing can be used to amplify the GAA repeats to establish the genetic diagnosis. While most patients have homozygous mutations, about 4% of patients demonstrate compound heterozygosity with GAA expansion and a point mutation [111]. Recently, the FDA approved omaveloxolone, an NRF2 activator, for the treatment of FRDA based on the MOXIe clinical trial where persistent benefit was demonstrated with few adverse events compared to placebo [112,113]. As the first FDA-approved FRDA treatment, omaveloxolone represents a landmark development in mitochondrial-directed therapy. Gene therapy for FRDA remains in various stages of preclinical and clinical trials, targeting the *FXN* gene to increase frataxin levels [114]. Current management of FRDA involves a multidisciplinary supportive approach. Regular neurologic and neuro-ophthalmic follow-up can help monitor symptoms and support low-vision care.

7. Other Hereditary Optic Neuropathies

There have been numerous other isolated and syndromic optic neuropathies reported with varying mutations in genes both previously described and newly explored. Autosomal recessive optic atrophy is early-onset with severe vision impairment caused by pathogenic variants in *TMEM126A* (OMIM 612988), *RTN4IP1* (OMIM 610502), *YME1L* (OMIM 607472), and previously mentioned *ACO2* [20,115–118]. Pathogenic variants in *TIMM8A* (OMIM 304700) cause the Mohr–Tranebjaerg deafness–dystonia–optic atrophy X-linked syndrome [119]. Optic atrophy has been reported to present with multiple spinocerebellar ataxia types including Type 1, Type 5, and Type 7 [120,121]. A number of other syndromes or variations of previously mentioned syndromes exist, albeit in rarity, that are beyond the scope of this review. Many of these conditions are characterized by mitochondrial dysfunction, complex genotype–phenotype relations, and limited disease-modifying treatment modalities.

8. Genetic Counseling

For all HONs, genetic counseling is an important part of enabling patients to understand their disorder. Regardless of inheritance pattern, comprehensive genetic counseling can be helpful in determining risk of other relatives as well as risk of transmission in future children. Prenatal genetic counseling is complex, including the opportunities and limitations associated with assisted reproductive technologies, and is best conducted by a certified genetic counselor using a non-judgmental approach [1]. Information about the HONs will continue to evolve to reflect ongoing investigative efforts, but it is imperative that patients receive adequate genetic counseling to facilitate informed decision making and supportive care for both themselves and at-risk family members.

9. Discussion

The HONs are a diverse group of genetic disorders that continue to be better understood through genetic advances and clinical studies. The theme of mitochondrial dysfunction in terms of bioenergetics, oxidative stress management, and organelle relationships plays a central role in contributing to the clinical picture of optic atrophy. LHON and DOA represent the two major HONs that commonly present with isolated optic atrophy, but an increasing awareness of “plus” syndromes and accessibility of genetic testing has led to a fuller description of syndromic manifestations. This phenotypic variability is only further emphasized in the spectrum of Wolfram disease, *MFN2*-HMSN, and FRDA. For rarer HONs, it is a testament to the advances in molecular genetic diagnostics that an ever-increasing list of genes and variants are being identified [122]. The sheer magnitude of genetic variants responsible for optic atrophy, including ones that have not yet been delineated, provides a complex yet necessary task for future study. Genetic databases for HONs are the start to coupling computational biology with clinical medicine to refine genotype–phenotype matches [7]. Large, prospective studies could help better elucidate

the natural history of HONs to characterize phenotypic variability and provide valuable baseline data for treatment trials [1].

Developing disease-specific treatment remains the most impactful future action in the field. Idebenone is currently available in Europe but has not yet been approved for LHON by the Food and Drug Administration in the United States. Besides idebenone, gene therapy clinical trials are underway, although disease rarity and rate of progression can make obtaining results difficult. For LHON, the unexpected bilateral improvement after unilateral injection must be further explored as clinical trials using the contralateral eye as internal control can lose validity [48]. Additional studies on combination idebenone and gene therapy could also offer valuable insights into LHON. Disease-modifying therapies for rarer optic atrophy entities, such as Wolfram syndrome or *MFN2*-HMSN, have mostly been preclinical, underscoring an area where human clinical trials can greatly benefit patients with no currently available treatments. Omaveloxolone, as the first FDA-approved FRDA treatment, represents an exciting development, although its impact on FRDA optic neuropathy requires further study. Regenerative medicine, namely stem-cell therapy, is another exciting frontier for HON treatment as it targets a common pathway of retinal ganglion cell recovery [123]. It is important that ethical and regulatory guidelines continue to be refined as therapy progresses, so that advances in technology do not outpace ethical concerns nor are potential treatments limited by lack of regulatory approval.

HONs remain a dynamic area as new technology and treatment options evolve. Our understanding of genetic, epigenetic, and environmental factors steadily improves our knowledge about the phenotypic expression of different HONs. For clinicians, recognition of common clinical features and careful molecular diagnostic testing can distinguish HONs from other causes of optic neuropathy, prompting accurate and timely management. The rapid progress in genetic and molecular understanding of HONs offers hope for additional future preventative and curative treatments for these rare but vision-altering disorders.

Author Contributions: Conceptualization, S.L.G. and S.N.G.; writing—original draft preparation, S.K.L.; writing—review and editing, S.N.G., C.M., N.J.A., J.C.R., S.L.G. and L.J.B.; supervision, S.N.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: Dr. Balcer serves as the Editor-in-Chief of the Journal of Neuro-ophthalmology. The other authors have no disclosures.

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