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Review article

Delineating Wolfram-like syndrome: A systematic review and discussion of the *WFS1*-associated disease spectrum

Cansu de Muijnck, MD[a,b], *Jacoline B. ten Brink, BSc*[c], *Arthur A. Bergen, PhD*[c,d], *Camiel J.F. Boon, MD, PhD*[b,e], *Maria M. van Genderen, MD, PhD*[a,f,*]

[a] *Department of Ophthalmology, University Medical Center Utrecht, Utrecht, the Netherlands*
[b] *Department of Ophthalmology, Amsterdam University Medical Centers, Amsterdam, the Netherlands*
[c] *Department of Human Genetics, Section Ophthalmogenetics, Amsterdam University Medical Centers, Amsterdam, the Netherlands*
[d] *Queen Emma Center of Precision Medicine, Amsterdam University Medical Centers, Amsterdam, the Netherlands*
[e] *Department of Ophthalmology, Leiden University Medical Center, Leiden, the Netherlands*
[f] *Diagnostic Center for Complex Visual Disorders, Zeist, the Netherlands*

ARTICLE INFO

Article history:
Received 23 June 2022
Revised 23 January 2023
Accepted 30 January 2023
Available online 9 February 2023

Keywords:
WFS1
Wolfram-like syndrome
Hereditary optic neuropathy
Optic atrophy
Autosomal dominant

ABSTRACT

Wolfram-like syndrome (WFLS) is a recently described autosomal dominant disorder with phenotypic similarities to autosomal recessive Wolfram syndrome (WS), including optic atrophy, hearing impairment, and diabetes mellitus. We summarize current literature, define the clinical characteristics, and investigate potential genotype phenotype correlations. A systematic literature search was conducted in electronic databases Pubmed/MEDLINE, EMBACE, and Cochrane Library. We included studies reporting patients with a clinical picture consisting at least 2 typical clinical manifestations of *WSF1* disorders and heterozygous mutations in *WFS1*. In total, 86 patients from 35 studies were included. The most common phenotype consisted of the combination of optic atrophy (87%) and hearing impairment (94%). Diabetes mellitus was seen in 44% of the patients. Nineteen percent developed cataract. Patients with missense mutations in *WFS1* had a lower number of clinical manifestations, less chance of developing diabetes insipidus, but a younger age at onset of hearing impairment compared to patients with nonsense mutations or deletions causing frameshift. There were no studies reporting decreased life expectancy. This review shows that, within the spectrum of *WFS1*-associated disorders or "wolframinopathies," autosomal dominantly inherited WFLS has a relatively mild phenotype compared to autosomal recessive WS. The

* Corresponding author: Maria M. van Genderen, MD, PhD
E-mail address: m.m.vangenderen-3@umcutrecht.nl (M.M. van Genderen).

https://doi.org/10.1016/j.survophthal.2023.01.012

clinical manifestations and their age at onset are associated with the specific underlying mutations in the *WFS1* gene.

1. Introduction

Wolfram syndrome-1 (WS) is a rare autosomal recessive multisystem disorder associated with biallelic mutations in *WFS1*. The estimated prevalence is 1/770,000 in the UK and 1/710,000 in Japan. WS is characterized by optic atrophy (OA), diabetes mellitus (DM), diabetes insipidus (DI) and sensorineural deafness.[5] In addition to the typical phenotype constituting the acronym DIDMOAD, patients may also develop urological, psychiatric, and neurologic symptoms. In 2011, a new WS related disease entity called Wolfram-like syndrome (WFLS) (OMIM# 614296) was described as a syndrome caused by heterozygous mutations in *WFS1*.[A] Clinically, WFLS is characterized by the triad of OA, DM, and hearing impairment (HI). WFLS is distinguished from autosomal recessive WS by its relatively milder phenotype with rather localized sensory symptoms and autosomal dominant (AD) inheritance pattern. As a relatively recently described disorder, there is still a lot unknown about the clinical characteristics of WFLS and the underlying genetic mechanisms.

The *WFS1* gene, implicated in both WFS and WFSL, is a nuclear gene coding for the transmembrane protein wolframin located in the endoplasmic reticulum membrane. Initially, WS patients with a single heterozygous *WFS1* mutations in the coding sequences, were thought to have a second mutation in the untranslated region and introns of the gene. Usually, the latter variants are missed in standard DNA diagnostics strategies. This turned out not be completely true. For example, Eiberg and coworkers[13] described a family with 1 heterozygous mutation in *WFS1* and a clear AD inheritance pattern. Other studies followed and in 2011, WFLS was annotated in OMIM as a separate hereditary disorder.[20,35,A] Although WFLS clinically resembles WS, there are several important differences between the 2. In contrast with WS, patients with WFLS appear to have a different age at onset per symptom, and a generally milder phenotype. Unlike WS, a decreased life expectancy has thus far not been described in WFLS patients.

Despite the increasing number of studies on WFLS, a clear phenotypic description of this disease is not yet available, and there are no known genotype-phenotype correlations. WFLS is a rare hereditary disease, and current literature regarding WFLS consists only of case studies or case series with small cohorts. The phenotypes in these studies vary remarkably from a full-blown WS phenotype to milder phenotypes such as concurrence of DM and moderate HI, without OA or any other systemic manifestations. The mutations in the *WFS1* gene are highly heterogeneous and, thus far, most of the mutations are unique only to single families that have been described.[11] All these factors together pose a challenge in establishing potential genotype-phenotype correlations in WFLS, whereas this knowledge is essential to make accurate prognostic disease predictions.

In this systematic literature review, we aim to provide an overview of current insights about the etiology of WFLS. We describe the clinical features of the disease and assess potential genotype-phenotype correlations. We reanalyzed and summarized the data of 86 WFLS patients reported in the literature, and we propose a model for predicted disease severity based on genotype-phenotype correlations.

2. Materials and methods

2.1. Patients

An electronic literature search was conducted in Pubmed/MEDLINE, EMBACE and Cochrane library databases to identify the relevant studies from 1998 until 2022, by a single reviewer. The following search terms were used: "*WFS1*," "Wolfram-like syndrome," "Wolfram Syndrome," "optic atrophy," "optic neuropathy," "heterozygote," "autosomal dominant," Screening of the abstracts was performed by using web-based systemic review application Rayyan.[33] Inclusion criteria were: a heterozygous mutation in *WFS1* and at least 2 clinical manifestations previously described in the literature associated with *WFS1* mutations. Cases with homozygous or compound heterozygous mutations were considered WS and excluded from this study. Patients with heterozygous *WFS1* mutations and isolated disease manifestations, such as isolated low frequency sensorineural hearing loss, were also excluded, because this clinical presentation does not correspond to the definition of a syndrome. Where possible, we identified patients reported in more than 1 study and combined the data. Only patients with data on age at diagnosis for WFLS or for at least 1 disease manifestation were used in the statistical analysis. When there were no specific age data for the onset of a symptom, age at diagnosis was accepted as the age at onset for that clinical manifestation.

The references in the included studies were screened for additional relevant studies. The list of all the included studies can be found in Supplementary Table 1.[1-4,8,10,12-18,20,22,23,25-32,35-45] A summary of the literature search is presented in Fig. 1.

Informed consent was taken from 1 patient from our own clinical practice whose fundus and optical coherence tomography (OCT) images were used in this paper.

2.2. Genotype classification

Patients were assigned to 2 genotype classes based on the type of mutation and expected consequence on protein production. Genotype A was defined as loss of function muta-

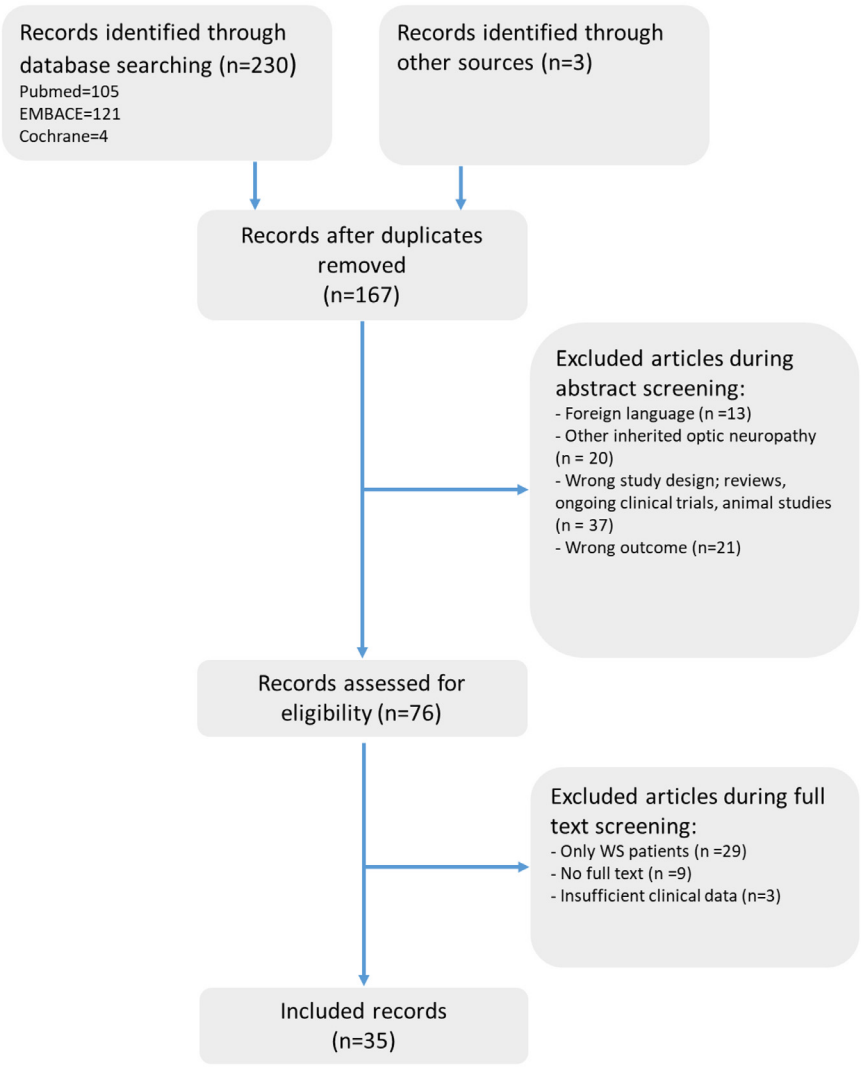

Fig.1 – Flow diagram for literature search and article selection.

tions that include all nonsense mutations and out-frame deletion/insertions causing frameshifts resulting in a premature stop codon. One splice site variant that was predicted to cause a premature stop codon was also included. The genotype A mutations most likely results in RNA nonsense-mediated decay and thus protein depletion. We defined genotype B as a group of missense mutations and small in-frame deletions/insertions (<15 base). These mutations are predicted to be dominant-negative as a result of in a defective or shortened "toxic" protein.

2.3. *Statistical analysis*

Demographic, clinical and genetic data of the patients were extracted from the articles and collected using Excel 2016 (Microsoft, Redmond, WA). Statistical analyses were performed with SPSS statistical software (version 28.0 for Windows, SPSS Inc., Chicago, IL) and R Software: R4.1.2 (http://www.r-project.org/). Missing data were handled based on pairwise deletion. Frequency of the clinical manifestations between different genotypes was assessed with Chi-square test; age at onset was compared across the groups with Mann-Whitney U test. Logistic regression was used to calculate the odds ratio for developing clinical manifestations based on genotype classes. For visual acuity (VA), best VA out of 2 eyes was used for statistical analysis. In all statistical tests, P-values of 0.05 or less were considered significant.

3. Results

3.1. *Patients*

In total we collected clinical and genetic data of 86 WFLS patients from 35 studies. Fifteen out of 35 studies were case reports consisting of only 1 pedigree with AD *WFS1* mutations. Twenty out of 35 were small case series or cohort studies consisting of a mixed group of WFLS and WS patients. In only 8 studies, the term WFLS was used for patients with AD *WFS1* mutations. The descriptions of the corresponding phenotype in the other studies were as follows: WS,[2,3,14,30,37,41] AD *WFS1*-related disorder,[1,8,38] ADOA,[13] and AD optic neuropathy and

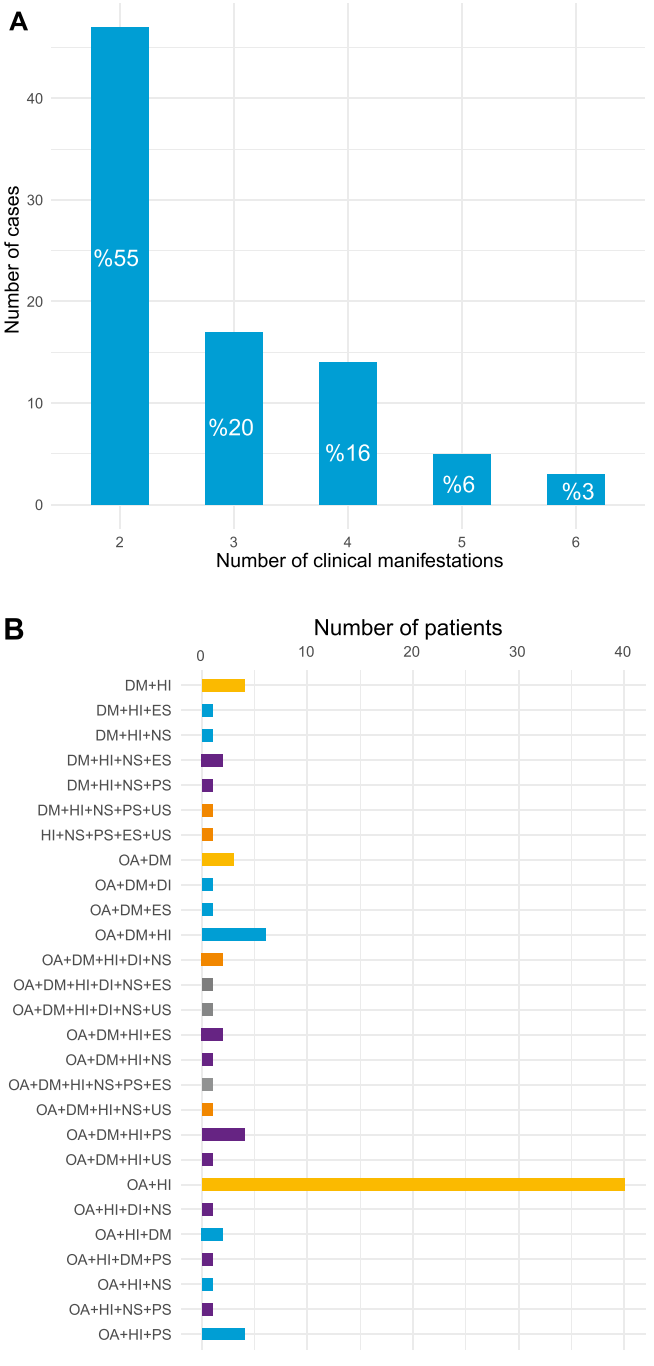

Fig. 2 – *A*: The number of clinical manifestations in WFLS patients. *B*: Frequency distribution of different combinations of clinical manifestations. OA = optic atrophy; DM = diabetes mellitus; HI = hearing impairment; DI = diabetes insipidus; ES = endocrine symptoms other than DM; NS = neurological symptoms; US = urological symptoms; PS = psychiatric symptoms.

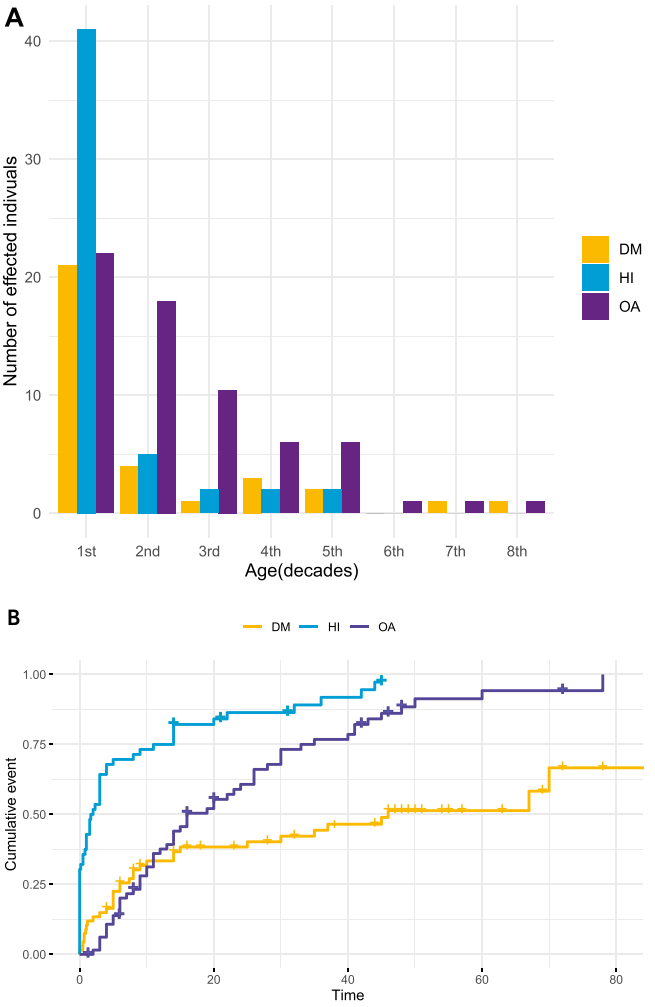

Fig. 3 – *A*: Onset of clinical manifestations per decade. *B*: Cumulative risk of developing clinical manifestations per age. DM = diabetes mellitus; HI = hearing impairment; OA = optic atrophy. .

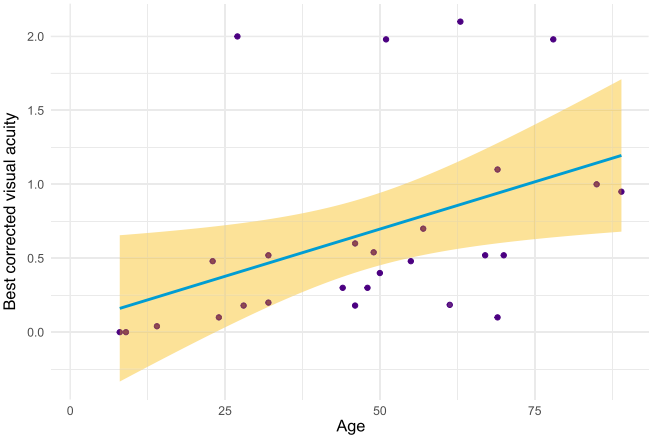

Fig. 4 – Visual acuity per age. BCVA = best corrected visual acuity, by LogMAR.

Table 1 – Demographics of the included patients.

Demographics	Subjects, n = 86
Age*, mean ± SD (range)	35.6 ± 22.6 (1–89)
Sex, n (%)	
Female	49 (57%)
Male	37 (43%)
Country of origin	
USA	9 (11%)
Denmark	7 (8%)
China	4 (5%)
The Netherlands	4 (5%)
Japan	4 (5%)
France	3 (4%)
UK	3 (4%)
Italy	2 (2%)
Greece	2 (2%)
Palestine	1 (1%)
Iran	1 (1%)
Sweden	1 (1%)
Not reported†	44 (51%)

* Age at last examination.
† Cases where the country of origin is not mentioned by authors.

deafness associated with WFS1.[20] Thirteen patients were reported in multiple studies.

We excluded some patients even though they fulfilled the inclusion criteria for the following reasons: 9 patients from the study of Chaussenot and coworkers[8] were not included because the authors classified these patients as autosomal recessively inherited cases in spite of monoallelic mutations. Authors of this study advocated that in the absence of a second variant they could not confirm the deleterious effect of the mutations in these cases. Although these patients were eligible for inclusion according to our criteria, we decided to favor the concerns of the authors in the original article and did not include these patients. The patients who were reported to have AD inheritance in the same study were included. Two patients from the articles of De Franco and coworkers[10] and Prochazkova and coworkers[34] were excluded because the phenotypic features with prominent morphological anomalies including Peter's anomaly, megalocornea, micropthalmia, bilateral microcornea, iris coloboma and atresia of external auditory canal were not typical for *WFS1* mutations, and could result from additional genetic abnormalities. Also, genetic testing for chromosomal anomalies was not performed in these studies. One patient in the study of Soares and coworkers[40] was also not included because the *WFS1* variant that this patient harbored was located in 5′ untranslated region of *WFS1* mRNA, which was predicted to be a polymorphism by *in silico* analysis tools (Mutation Taster, http://www.mutationtaster.org).

Demographics of the patients are summarized in Table 1.

3.2. *Clinical characteristics of Wolfram-like syndrome*

HI was the most common disease manifestation (94%) followed by OA (87%), DM (44%), neurological symptoms (19%), psychiatric symptoms (16%), endocrine symptoms other than DM (11%), urological symptoms (6%) and DI (7%). Most patients (55%) had at least 2 clinical manifestations out of the aforementioned 8 symptom categories. The combination of OA and HI, without obvious additional disease manifestations, was by far the most common phenotype in the cohort, occurring in 47% of reported WFLS patients. In Fig. 2A the number of clinical manifestations in WFLS patients is presented. Fig. 2B shows a detailed frequency distribution of the different clinical manifestation combinations.

In most cases, HI was the first disease manifestation, generally presenting in the first decade (median age at onset: 1.5; range: 0–44), followed by DM a few years later (median age at onset: 6; range: 0–70), and OA in the second decade (median age at onset: 15; range: 2–78). The order of developing OA, DM, and HI per decade is presented in Fig. 3A.

The probability of developing OA, HI and DM is calculated with Kaplan Meier method and presented in Fig. 3B with a cumulative hazard plot. The probability of developing HI increased sharply in the first decade and reached a plateau at the age of 14 (30% probability of developing HI at birth, 52% at the age of 2, and 82% at the age of 14). The risk of developing DM was highest in the first 2 decades (34% at the age of 10, 38% at the age of 16) The curve for OA was less steep (32% at the age of 10, 51% at the age of 16), and there was no clear plateau until the age of 50, with a probability of 92% having OA at this age.

HI had the most consistent onset time. Among the 53 patients with known age at onset data for HI, 80% received the HI diagnosis in the first decade (Fig. 3). Seventeen patients were reported to have congenital hearing loss, and 21 patients received the diagnosis of HI before the age of 1. Data regarding the type of HI were reported in 15 cases: 5 out of 15 had low frequency sensorineural HI, 6 had high frequency sensorineural HI, and 4 had mixed/profound HI.[8,12,13,15,17,20,22] Most patients needed hearing aids in the form of cochlear implants with a variable degree of improvement.

The onset of DM was also in the first decade in the majority of cases (64%). Data on insulin dependency was available for 20 cases: 18 out 20 had insulin-dependent DM, and the remaining 2 were managed by oral medication only. Two patients had positive anti-GAD and anti-ZnT8 antibodies, suggesting an autoimmune component in the development of DM in these patients.[15,39] One patient was reported to have DM1 without further information on antibody status.[28]

DI, one of the typical clinical manifestations of WS, was seen only in 6 out of 86 patients (7%). Median age at onset for DI was 11 years. Four out of 6 patients with DI showed also the full DIDMOAD (DI, DM, OA, and deafness) phenotype. Age data regarding the onset for other symptoms were scarce in the original publications and therefore not included in the further analysis. A detailed list of all the reported neurological, psychological, urological and endocrine symptoms can be found in Supplementary Tables 1 and 2.

3.3. *Ophthalmic characteristics of Wolfram-like syndrome*

OA was the most common ophthalmological manifestation in the WFLS cohort, occurring in 87% of patients. Most patients received the diagnosis of OA in the first decade (32%), and there was a more gradually decreasing pattern in the diagnosis throughout the years compared to the nonocular clinical

manifestations (Fig. 3A). Diagnosis of OA in all patients was made by direct fundus examination. In some cases, findings of additional examinations such as OCT, visually evoked potentials, or magnetic resonance imaging were reported. In some asymptomatic patients OA was only detected during an ophthalmologic checkup because of a diagnosis of WS or WFLS in family members.[35]

Cataract was the second most common ophthalmologic manifestation in the study cohort and was described in 16 out of 86 (19%) patients. Four of these 16 patients were reported to have congenital cataract, and 4 other patients were diagnosed with cataract in early childhood. For the other patients data on the age at diagnosis was not available, but based on the age data at the time of the original study, 3 patients must have been diagnosed with cataract before the age of 25, and 1 patient before the age of 45. Four patients with older ages were described as age-related cataracts in the original studies. One patient who was not included in these numbers had chlorpromazine-related cataracts.[35] Four patients out of 86 (5%) had glaucoma; 3 of whom had also congenital cataract that could have played a role in the development of glaucoma. One patient in the study cohort had recurrent retinal detachments, 1 patient had strabismus, 1 patient had nystagmus, 1 patient had vertical gaze palsy, 2 patients had epiretinal membrane, one patient had high myopia, whereas another patient had high hyperopia. One patient developed diabetic retinopathy. The mean VA was 0.64 ± 0.64 (0–2.1) LogMAR (Snellen equivalent: mean 0.2, range 0–1.0). A scatter plot of age versus VA can be seen in Fig. 4. Longitudinal data on VA were available only in 1 patient; therefore, we could not perform an analysis on the degree of VA deterioration over the years.

In 17 patients, an OCT finding thus far considered specific for heterozygous *WFS1* mutations was described, i.e., lamination of the outer plexiform layer. These patients had an outer plexiform layer which consisted of 2 hyperreflective bands separated by a hyporeflective zone (Fig. 5).[25,27,28] In 4 studies, authors reported a decreased thickness of the retinal ganglion cell layer and retinal nerve fiber layer on the OCT.[25,26,28,39] Patient-specific data on the sectoral distribution of the decreased thickness were limited. In 1 study with a relatively larger cohort, investigators reported that the decrease in the thickness of peripapillary retinal nerve fiber layer was most prominent in the temporal and inferior quadrants.[28]

There were limited data available for color vision, electrophysiological studies and visual fields. A summary of visual functions is presented in Table 2.

3.4. *Genetic analysis*

3.4.1. *Disease-associated WFS1 variants*

A total of 33 different disease-causing *WFS1* gene variants were reported. The majority of these mutations were missense (n = 72, 84%), nonsense (n = 6, 7%), in-frame deletions (n = 4, 5%), out-frame deletions (n = 2, 2%), insertions (n = 1, 1%), and a splice-site variant (n = 1, 1%). Almost all variants were located in exon 8 (n = 84, 98%), with majority of them affecting the C-terminal domain of the wolframin protein. Fig. 6 shows a representation of the wolframin protein and the mutation locations at protein level.

For 9 out of 34 *WFS1* variants, functional studies were carried out that assessed the effect of the mutation(s) on protein level. Four variants (p.Asn325_Ile328del, p.Glu809Lys, p.Glu830Ala, p.His313Tyr) showed a dominant negative effect in functional studies with increased aggregation of unfolded proteins resulting in endoplasmic reticulum stress. The remainder of the variants (c.460+1G>A, p.Tyr528Leufs*15, p.Trp690fs706*116, p.Gly780Ser, p.Ala684Val), showed decreased protein production to different degrees.

P.Ala684Val was the most commonly described *WFS1* variant in the reported studies (n = 29, 34%). All WFLS patients with this variant had both OA and HI, with HI diagnosed in all cases before the age of 3. A chi-square test showed that subjects with the p.Ala684Val variant developed less frequently DM compared to the rest of the cohort (17% vs. 57%, X2 (1, N = 76) = 11.9, P = 0.001). Two patients with this mutation had mild cognitive dysfunction. One patient had growth hormone deficiency, 2 patients depression, and 1 patient had epilepsy. No urological symptoms or progressive neurological symptoms were reported for this group.

3.4.2. *Genotype-phenotype correlations*

For the classification of patients and genotype groups, see materials and methods above. We classified 10 patients (12%) as genotype class A and 76 patients (88%) as genotype class B. A Mann-Whitney *U* test indicated that patients in genotype class A had an older age at onset for HI (median 12.5 years vs. 1.5 years for genotype class A and B respectively, $U = 35$; $P = 0.032$). They also appeared to develop a higher number of disease manifestations (median of 4 manifestations vs. 2 manifestations, $U = 218$; $P = 0.016$) compared to genotype class B. There was no statistically significant difference between the 2 genotype classes in age at onset of OA (median of 13 years vs. 15 years for genotype class A and B respectively, $U = 292$; $P = 0.562$) or DM (median of 6 years vs. 8.5 years for genotype class A and B respectively, $U = 114$; $P = 0.872$). A logistic regression analysis corrected for age was performed to calculate the odds of developing different disease manifestations based on genotype class. Patients with genotype class A were more likely to develop DI (odds ratio = 61.2 [95% CI: 5.3–705.5], Wald=10.8, P = 0.001) compared to genotype class B. Genotype class A was also predictive for the more likely development of neurological symptoms (odds ratio = 5.4 [95% CI: 1.1–25.3], Wald = 4.6, P = 0.031); There was no statistically significant difference in the likelihood of developing other clinical manifestations such as OA, DM, HI, urological, endocrine, or psychiatric symptoms between the different genotype classes.

4. Discussion

In this systematic review we describe the clinical and genetic characteristics of WFLS, an autosomal dominantly inherited syndrome caused by heterozygous mutation in *WFS1*. We also established genotype-phenotype correlations. WFLS patients in our cohort showed variable phenotypic features. Compared to autosomal recessive WS, clinical presentation of the AD WFLS was different in many aspects. First, HI was the most common disease manifestation in our WFLS study population,

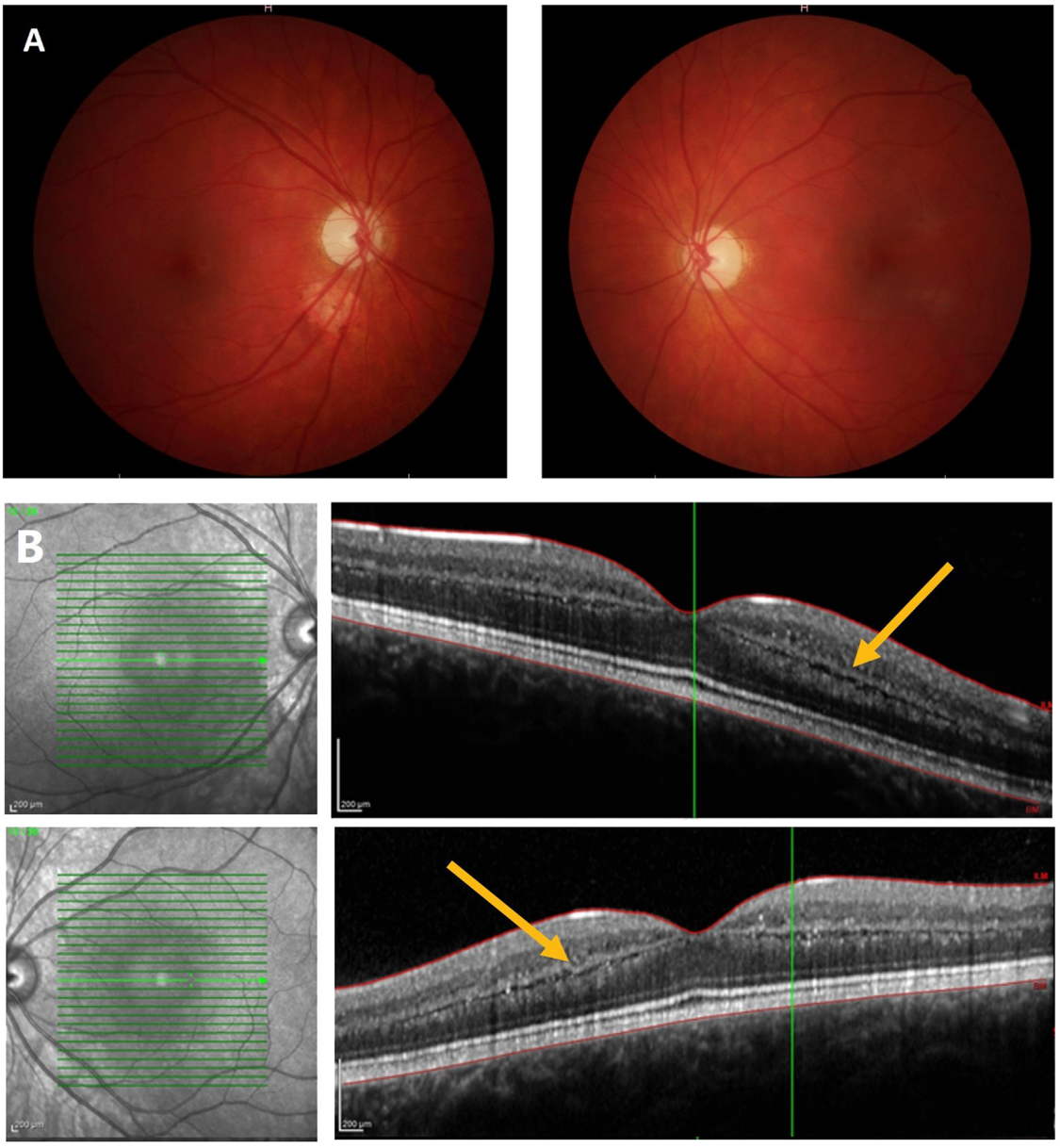

Fig. 5 – *A*: Fundus image of a patient with WFLS (p.Ala684Val) and optic atrophy. *B*: Macular OCT of the same patient with bilateral laminated outer plexiform layer (OPL).

whereas DM is known as one of the major disease manifestations in WS. The prevalence of HI (94%) in our WFLS population also appears remarkably higher than the previous report of 48% in WS by de Heredia and coworkers[11] in their systematic review on 392 WS patients. Second, the median age at onset for developing HI was 1.5 years in WFLS, whereas it is approximately 13-14 years for WS in studies with large cohorts.[11,37] Third, there was a relatively high prevalence of cataract (19%) in the WFLS study population. Although the prevalence of cataract in WS has to date not been reported in large cohorts, this number is much higher than the estimate (1%) of Euro-wabb (European Registry for Wolfram, Alström, Bardet-Biedl and other Rare Diabetes Syndromes) for WS.[B] In 1 study, Hoekel and coworkers[19] reported that 22% (5/23) of WS patients had cataract, but in this study genotypic data of the subjects were not reported, and it is unclear whether patients with heterozygous mutations were also included.

Another interesting ophthalmologic finding in the study cohort was the lamination of the outer plexiform layer. This phenomenon was described so far by 2 research groups and seems to be observed only in heterozygous mutations in *WFS1*.[25,27,28] The exact mechanisms underlying this OCT finding are yet to be discovered but the authors of the first study reporting this finding suggest a pathologic process in the Müller cells. Although more studies are needed to confirm the authenticity of this finding in monoallelic state, for the timing being, it appears to be a promising ophthalmologic finding in

Table 2 – Summary of visual functions.

Visual functions	Findings	Number of patients with available data, n (% in n = 86)
BCVA (mean, median, [range])*	0.64, 0.48 [0–2.1]	28 (33%)
Color vision (n, finding as stated in original study)	4, normal 2, reduced 2, marked abnormality in protan and deutan axes 1, abnormal 1, failed	10 (12%)
VEP (n, finding as stated in original study)	3, delayed response 1, extinct monocular 1, normal	5 (6%)
Visual fields (n, finding as stated in original study)	6, normal 3, enlarged blind spot 2, extensive defects in all quadrants 1, abnormal 1 bilateral nasal defects 1, superotemporal and inferonasal defects	14 (16%)

* LogMAR.

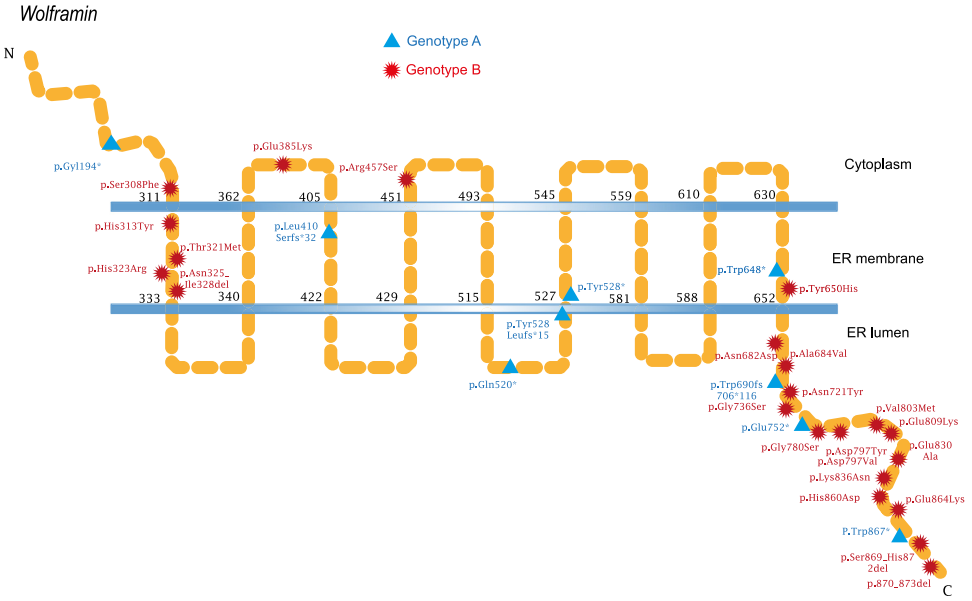

Fig. 6 – Location of disease-associated *WFS1* gene variants on protein level. c.460+1G>A splice-site variant is not demonstrated on this figure.

the differential diagnosis of WFLS in patients with suspicion of IONs.

One challenge in the detection of WFLS cases with heterozygous mutations in *WFS1* during the literature search was that diverse terminology was used to describe these patients. WS,[2,3,14,30,37,41] AD *WFS1*-related disorder,[1,8,38] ADOA[13] and AD optic neuropathy and deafness associated with WFS1[20] were some of the terms used in the literature. This variation in terminology causes suboptimal accessibility to the available information, especially in the case of a rare disease such as WFLS. A consensus on the terminology is needed for better understanding of the spectrum of *WFS1*-associated disorders or "wolframinopathies," and making the information on this disease more accessible.

In this study, we considered a comparatively "mild" phenotype to be a phenotype with few to no systemic manifestations. Impaired vision and hearing loss are clearly severe symptoms and often have a highly detrimental impact on

quality of life; however, they are not associated with a shortened life span. We therefore chose to label them "mild," in contrast to "severe" syndromic manifestations, such as neurologic and psychiatric symptoms, DM, and DI that have been associated with increased mortality. Neurological symptoms are a leading cause of shortened lifespan in WS, as death around the fourth decade is often from respiratory failure resulting from brainstem atrophy. We did not observe differences in the type of neurological symptoms between this cohort and the previously reported WS cohorts; however, in WS patients, neurological symptoms can be seen in up to 62%, and DI in up to 73% of cases.[5] Among the WFLS patients assessed in this review, these numbers were much lower, particularly for DI (DI 7%, NS 19%). There were only 2 patients reported as deceased at the time of the original study (at the age of 63 and 45, cause of death unknown).[17,35] Eighty-four patients were still alive during the original studies. It is currently still unknown if there is an increased mortality rate and shorted life span in WFLS, as compared to the normal population.

The typical phenotype in the current study population of WFLS patients was the combination of OA and HI. This phenotype shows striking similarities to another well-known inherited optic neuropathy, namely dominant OA. Dominant OA is most commonly caused by mutations in the *OPA1* gene, and in a smaller proportion of patients the *OPA3* gene, and is the most common inherited optic neuropathy. When deafness is added to the phenotype, it is sometimes referred to as DOAD. In a recent study, Charif and coworkers[7] performed genetic analysis in a French cohort of 1102 patients with clinical suspicion of inherited optic neuropathies. In this study, *WFS1* (12%) was the third most commonly mutated gene in patients with AD inherited optic neuropathies, after *OPA1* (41%) and *ACO2* (17%). Interestingly, in this cohort, AD mutations in *WFS1* were as common as autosomal recessive *WSF1* mutations (n = 23 for both). Our data combined with those of Charif and coworkers[7] underline the importance of *WFS1* mutation testing not only for patients with typical juvenile onset OA and a DM phenotype, but also for patients with clinical suspicion of AD inherited optic neuropathy, especially if accompanied by other phenotypic features such as HI. It is possible that some patients with heterozygous *WFS1* variants receive a clinical diagnosis of dominant OA without genetic confirmation. This may imply that the number of autosomal dominantly inherited disease-causing *WFS1* variants among these populations may have been underestimated due to underdiagnoses.

In this study, we assigned patients to 2 different, simple and straightforward genotype classes. Although the age at onset of any symptom was not statistically significantly different between the 2 genotype classes, there were some clear differences in disease manifestations and disease progression. In general, genotype class A followed a remarkably similar pattern to classic WS: all patients developed OA before the age of 20, and all but one patient was diagnosed with DM before the age of 10. Also, all but one patient with DI belonged to genotype class A. A striking pattern was also observed in the development of HI. Patients in genotype class A developed HI typically between the age of 10–20 years, like WS, whereas a large proportion of the patients in genotype class B had congenital hearing loss or developed HI before the age of 5. There were no congenital HI cases in genotype class A. Furthermore, patients with genotype class A developed on average more disease manifestations than patients with genotype class B. All these observations suggest a more severe phenotype in genotype class A, which contains nonsense and frameshift mutations with premature stop codon, overlapping with WS. However, 1 important point to take into consideration in the interpretation of these observations is the large difference in currently available sample sizes of genotype classes A and B, which can lead to over- or underestimation of certain statistical results. The differences in onset of clinical manifestations between the genotypic groups can be described more accurately when more extensive future studies on larger patient cohorts are available. A summary of the differences between genotype classes A and B can be seen in Fig. 7.

Although most patients with missense variants in *WFS1* in our study only had OA and HI, there were several patients with missense variants who presented with more severe phenotypes, including for example extensive neurological abnormalities. Examples of such *WFS1* variants are p.Glu809Lys and p.His313Tyr; however, the number of patients with these specific variants was limited in the patient cohort of this study population (7 out of 76 patients with missense mutations) and not every patient with these variants showed an equally severe phenotype. This makes it difficult to attribute with certainty specific phenotypes to these *WFS1* variants. Nonetheless, it is important to point out the existence of this striking spectrum of phenotypes within the same genotype class. Details of the specific phenotype per *WFS1* variant can be found in Supplementary Table 1.

Patients with the p.Ala684Val variant in the *WFS1* gene constituted a special group in our study population. This was the most common variant reported so far, but it is important to note that most cases in this study are from European populations and the high prevalence of p.Ala684Val in this study may not apply to other ethnic populations. Patients with the p.Ala684Val variant (genotype class B) had almost exclusively the typical phenotype of congenital or very early diagnosed HI (all cases $<$ 3 years of age) and later onset OA (14 out of 29 cases $\geq$ 16 years). DM was only seen in 5 out of 29 patients, and 2 of these patients had proven anti-GAD and anti-ZnT8 antibodies and was thus classified as autoimmune DM1. Patients with the p.Ala684Val variant rarely had other systemic manifestations, and if present, these manifestations were milder compared to classic WS. Therefore, this specific *WFS1* variant appears to be associated with a relatively mild WFLS phenotype in heterozygous state.

The p.Ala684Val variant was also previously reported in compound heterozygous state in WS and in single heterozygous state for isolated hereditary hearing loss.[22,31] In one of the studies included in this review, Rendtorff and coworkers[35] described a family with 2 siblings diagnosed with WS as a result of compound heterozygous variants in *WFS1*, whereas their parents carried each a single heterozygous variant. The mother carried a p.V415del variant and was asymptomatic, and the father who carried the p.Ala684Val variant had a WFLS phenotype with HI (at age 3 years) and late onset OA (at age 41 years). Similar phenotypic patterns with mixed AD and recessive traits were also observed with other *WFS1* mutations in several other studies.[21,24,31,41] These findings all together raises the question whether WS and WFLS are truly differ-

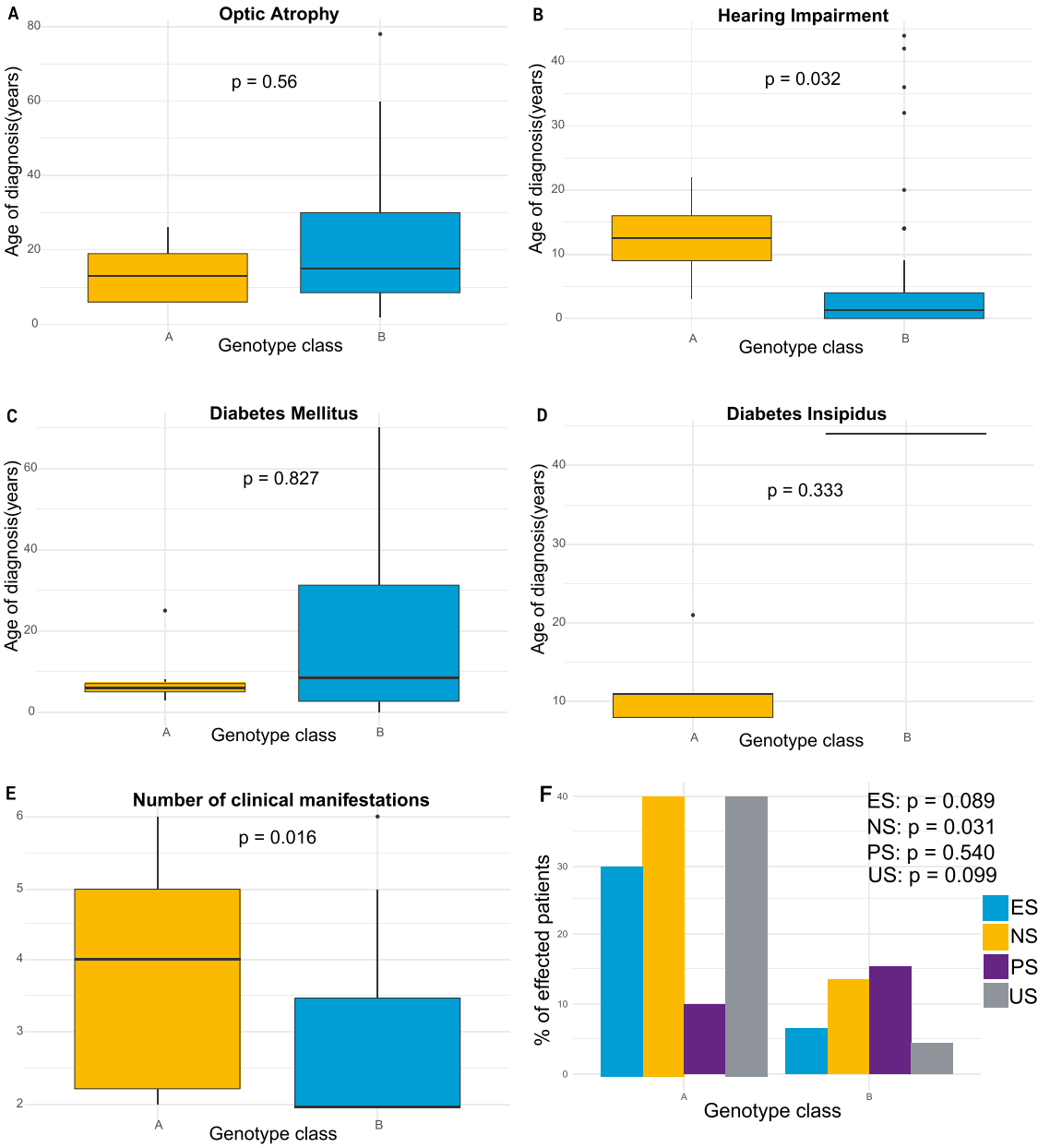

Fig. 7 – A-E: Boxplots demonstrating the age at onset data for different disease manifestations across genotype classes. *A*: Optic atrophy. *B*: Hearing impairment. *C*: Diabetes mellitus. *D*: Diabetes insipidus. *E*: Number of clinical manifestations per patient across genotype classes. *F*: Percentage of affected individuals with other clinical manifestations across genotype classes. ES = endocrine symptoms other than diabetes mellitus; NS = neurological symptoms; PS = psychiatric symptoms; US = urological symptoms.

ent disease entities with different mode of inheritances, or whether they are members of a spectrum of the same autosomal recessive disease that segregates in a recessive manner but shows reduced penetrance of the mutation in the heterozygous state. This could explain the asymptomatic heterozygous family members in many WS families. Another possibility is that *WFS1*-related disease is an AD disease with a variable penetrance, and a more severe phenotype in the case of biallelic *WFS1* mutations, such as is the case in *OPA1*- and *OPA3*-related inherited optic neuropathies. Heterozygous mutations in *OPA1* and *OPA3* can cause isolated optic neuropathy, in some cases accompanied by HI or cataract, but homozygote mutations lead to the progressive neurodegenerative disorders Behr syndrome (*OPA1*) and Costeff syndrome (*OPA3*), respectively, with more severe phenotypes. In Fig. 8, we present a disease model and an overview of phenotype severity based on mutation types in *WFS1*-related disorders.

Whether WFLS is a truly AD disease or not, the variety in the mode of inheritance poses a challenge for genetic counselling and follow up of the asymptomatic patients with

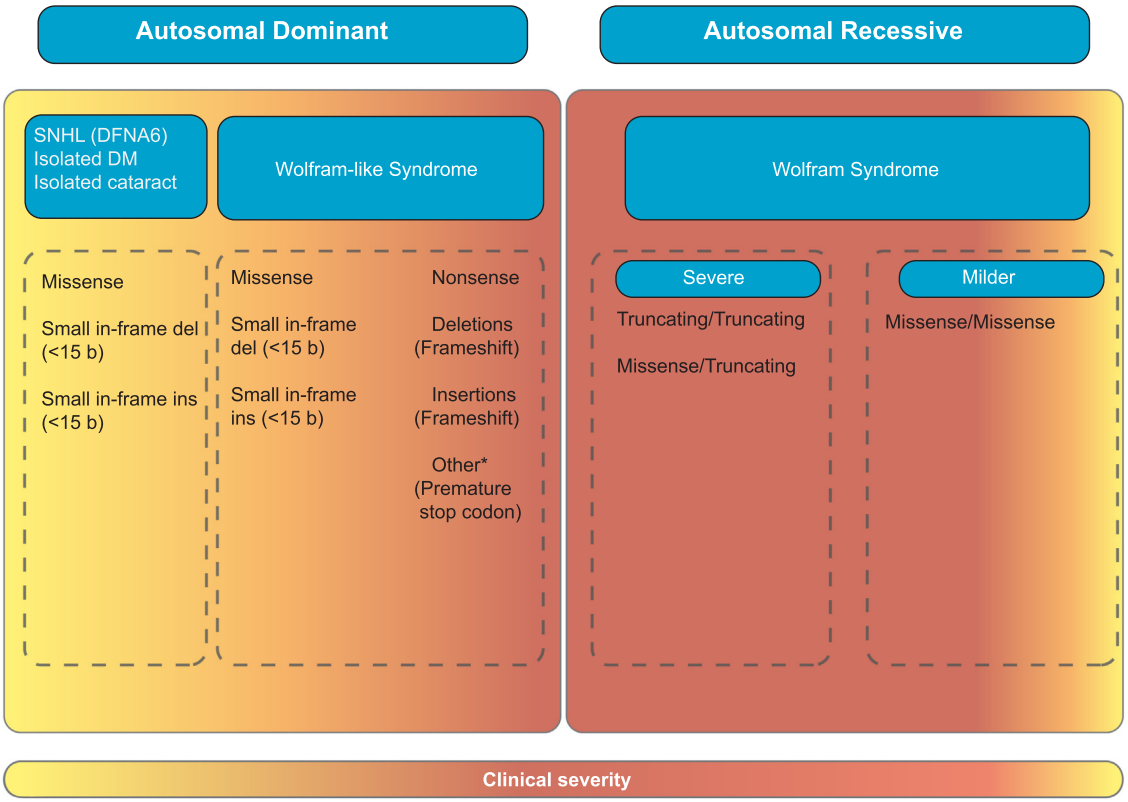

Fig. 8 – Overview of phenotypic severity based on mutation type and mode of inheritance in *WFS1*-related disorders. SNHL = isolated sensorineural hearing loss; type DFNA6 = deafness, autosomal dominant,6; DM = diabetes mellitus. *Truncating intronic, regulatory or splice-site variants such as c.460+1G>A.

heterozygous variants in *WFS1*. Although there are currently insufficient data in the literature to advocate routine diagnostic check-up for WS-related symptoms in patients with asymptomatic heterozygous *WFS1* variants, clinicians should be aware of less severe forms of clinical manifestations in this group. This is especially important for the management of treatable disease manifestations such as DM.

This review has a number of strengths and limitations. It is a thorough systematic review of all currently available clinical and genetic data on WFLS, identifying genotype/phenotype correlations for the first time. Limitations of the study relate to relatively low patient numbers, differences in clinical examinations, and difference in DNA analysis across samples: several included studies in this review are case reports with low evidence levels. The amount of data reported differs between publications, and the age at diagnosis for a disease manifestation may not always reflect the onset accurately, due to the different clinical practices across the countries where the studies originate from. Different techniques were used for genetic analysis and not all the studies performed complimentary quantitative DNA analyses to exclude large deletions, which makes exclusion of a second mutation difficult in some cases. Yet, considering the limited number of publications on WFLS, we believe that the population of this study reflects the current knowledge of WFLS in the literature.

With regard to our inclusion criteria for this systematic review, we chose to focus on the syndromic AD *WFS1*-related disease WFLS, whereas there are also other well-known AD phenotypes associated with variants in the *WFS1* gene, such as low-frequency SNHL. One might argue that considering the gradual onset pattern of syndromic diseases, these patients with isolated symptoms may also develop other symptoms in the future, and excluding these patients might give a biased view of the disease. We encountered no isolated OA cases with heterozygous mutations in the literature during the screening process of this study. There are very few studies on isolated DM and cataract in heterozygous *WFS1*, making it difficult to estimate the risk of progression to syndromic disease based on the available data. For SNHL, there are multiple studies with relatively large cohorts and well-defined pedigrees with multiple generations that indicate a truly isolated disease.[6,9] Considering the difficulties in estimating the real chance of developing syndromic disease, we decided to exclude the patients with isolated symptoms. Limiting our study cohort to syndromic AD WFLS was also in line with our primary aim to describe the AD *WFS1* associated OA, considering this ophthalmic manifestation was so far only described in the syndromic state in AD mutations of *WFS1*.

Many questions about the spectrum of *WFS1*-related hereditary disease remain yet unanswered. What is the exact inheritance pattern? Are WFS and WFSL truly 2 different

entities, or are they different clinical manifestations of the same genetic disease? Recent studies and our findings may support the latter. Why do heterozygous *WFS1* variants that generally result in milder phenotypes appear to cause earlier-onset HI in WFLS compared to WS with biallelic mutations? Could it be that a dominant negative effect of missense variants has a more toxic effect on the cochlea than haploinsufficiency resulting from nonsense variants? Why are different tissues (more) affected among different individuals? The answers of these questions may be found for instance in the different roles of wolframin in different development stages, or tissue and organ specific pathophysiological processes. More functional and clinical studies are needed to identify the exact pathophysiological mechanisms within the different organs affected in WFLS and WS.

5. Conclusion

WFLS has generally a milder phenotype in comparison to WS, with only few patients having severe systemic manifestations such as DI or neuropsychiatric symptoms. The most characteristic and common disease manifestations of WFLS are OA and HI, followed by DM. Cataract is also a relatively common ophthalmic manifestation in WFLS. Patients with disease-associated missense variants in the *WFS1* gene tend to have a milder phenotype than those with truncating mutations, but with an earlier onset of HI. The p.Ala684Val variant is the most commonly described *WFS1* variant thus far in WFLS, and is associated with a comparatively mild phenotype with OA and HI without systemic manifestations. More studies with larger cohorts are needed to further improve our understanding of the clinical characteristics, inheritance pattern and the genotype-phenotype correlations of the *WFS1*-associated disease. Studies in *in vitro* and *in vivo* disease models may shed further light on the pathogenesis of this intriguing spectrum of 'wolframinopathies', as we propose to call them.

6. Method of literature search

We conducted a literature search in PubMed/MEDLINE, EMBACE and Cochrane Library. The search query for Pubmed was "((optic neuropathy) OR (optic neuropathy[Title/Abstract]) OR (optic atrophy[Title/Abstract]) OR (optic atrophy)) AND ((“Wolfram Syndrome”[Mesh]) OR (DIDMOAD) OR (DIDMOAD Syndrome) OR (DIDMOADUD) OR (DIDMOADUD[Title/Abstract]) OR (DIDMOAD Syndrome[Title/Abstract]) OR (DIDMOAD[Title/Abstract]) OR (Wolfram Syndrome[Title/Abstract]) OR (WFS1[Title/Abstract]) OR (WFS1) OR (Wolfram-like syndrome) OR (Wolfram like syndrome) OR (Wolframlike syndrome)) AND ((autosomal dominant) OR (autosomal dominant[Title/Abstract]) OR dominant OR (dominant[Title/Abstract]) OR heterozygote OR (heterozygote[Title/Abstract]))". For EMBACE we used the following query: "(optic neuropathy OR optic atrophy) AND (“Wolfram Syndrome” OR (DIDMOAD) OR (DIDMOAD Syndrome) OR (DIDMOADUD) OR WFS1 OR (Wolfram-like syndrome) OR (Wolfram like syndrome) OR (Wolframlike syndrome)) AND ((autosomal dominant) OR dominant OR heterozygote)". The included studies were published between 1999 and 2022. We screened the English abstracts of all the studies in foreign languages. Three articles were identified during manual citation searching.

Key references

Eiberg H, Hansen L, Kjer B, Hansen T, Pedersen O, Bille M, et al. Autosomal dominant optic atrophy associated with hearing impairment and impaired glucose regulation caused by a missense mutation in the WFS1 gene. J Med Genet 43 (5):435–40, 2006.

Although this study is not the first study describing a case with WFLS phenotype and a heterozygote mutation in WFS1, it is the first study underlining the autosomal dominant inheritance in WFS1 related disease with multiple phenotypic features.

Majander A, Jurkute N, Burté F, Brock K, João C, Huang H, et al. WFS1-Associated optic neuropathy: genotype phenotype. correlations and disease progression. Am J Ophthalmol 241: 9–27, 2022

Rendtorff ND, Lodahl M, Boulahbel H, Johansen IR, Pandya A, Welch KO, et al. Identification of p.A684V missense mutation in the WFS1 gene as a frequent cause of autosomal dominant optic atrophy and hearing impairment. Am J Med Genet A 155 (6):1298–313, 2011.

The highest number of included patients come from these 2 studies, with 19 and 12 patients respectively.

Disclosures

The authors have no conflicts of interest to disclose.

Funding

This study was funded by Bartiméus Fonds, the Netherlands with grant number 1219277. The funder was not involved in the study design; collection, analysis and the interpretation of data or the writing process.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.survophthal.2023.01.012.

CRediT authorship contribution statement

Cansu de Muijnck: Investigation, Formal analysis, Writing – original draft, Visualization. **Jacoline B. ten Brink:** Investigation. **Arthur A. Bergen:** Supervision, Writing – review & editing. **Camiel J.F. Boon:** Conceptualization, Writing – review & editing. **Maria M. van Genderen:** Conceptualization, Methodology, Writing – review & editing.

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