International Journal of Audiology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iija20

Good cochlear implantation outcomes in subjects with mono-allelic *WFS1*-associated sensorineural hearing loss – a case series

M. L. A. Fehrmann, C. P. Lanting, L. Haer-Wigman, E. A. M. Mylanus, W. J. Huinck & R. J. E. Pennings

To cite this article: M. L. A. Fehrmann, C. P. Lanting, L. Haer-Wigman, E. A. M. Mylanus, W. J. Huinck & R. J. E. Pennings (18 Oct 2024): Good cochlear implantation outcomes in subjects with mono-allelic *WFS1*-associated sensorineural hearing loss – a case series, International Journal of Audiology, DOI: 10.1080/14992027.2024.2411579

To link to this article: https://doi.org/10.1080/14992027.2024.2411579

Published online: 18 Oct 2024.

INTERNATIONAL JOURNAL OF AUDIOLOGY
https://doi.org/10.1080/14992027.2024.2411579

The British Society of Audiology
The International Society of Audiology
NAS NORDIC AUDIOLOGICAL SOCIETY
Taylor & Francis
Taylor & Francis Group

CLINICAL NOTE

Good cochlear implantation outcomes in subjects with mono-allelic *WFS1*-associated sensorineural hearing loss – a case series

M. L. A. Fehrmann[a,b], C. P. Lanting[a,b], L. Haer-Wigman[c], E. A. M. Mylanus[a,b], W. J. Huinck[a,b] and R. J. E. Pennings[a,b]

[a]Department of Otorhinolaryngology, Radboud University Medical Center, Nijmegen, The Netherlands; [b]Donders institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands; [c]Department of Clinical Genetics, Radboud University Medical Center, Nijmegen, The Netherlands;

ABSTRACT

Objective: This study aimed to evaluate long-term cochlear implant (CI) outcomes in individuals with mono-allelic pathogenic variants in WFS1, which is associated with both Wolfram-like syndrome and DFNA6/14/38.

Design: Retrospective case series.

Study sample: Seven CI recipients, ranging from eight months to 58 years of age, were included in the study, including four with Wolfram-like syndrome and three with DFNA6/14/38. A total of ten cochlear implantations were performed among these subjects.

Results: At one-year post-implantation, a mean phoneme score of 90 ± 9% at 65 dB SPL in quiet was found, which remained stable up to ten years post-implantation with a mean phoneme score of 94 ± 6%. Despite these excellent outcomes, one subject achieved no speech recognition with CI and eventually became a non-user. This individual had a prolonged absence of auditory stimulation prior to implantation and encountered multiple challenges during rehabilitation.

Conclusion: Individuals with Wolfram-like syndrome or DFNA6/14/38 demonstrate consistently good outcomes following implantation, which remain stable over time. These findings affirm cochlear implantation as an effective rehabilitation option for these individuals. Furthermore, the stable and good CI outcomes contradict the suggested link between *WFS1*-associated sensorineural hearing loss and auditory neuropathy.

ARTICLE HISTORY
Received 7 May 2024
Revised 23 September 2024
Accepted 26 September 2024

KEYWORDS
Cochlear implant outcomes; hereditary hearing loss; WFS1; wolfram-like syndrome; DFNA6/14/38

Introduction

Hearing loss is a prevalent and commonly diagnosed sensory disorder, with 50-70% of cases linked to genetic factors (Morton and Nance 2006). Hereditary hearing loss can be categorised as syndromic, representing about 30% of cases, or non-syndromic, which accounts for the remaining ~70% (Shearer et al. 1993). Some genes are, however, associated with both syndromic and non-syndromic hearing loss, like the Wolfram syndrome type 1 gene (*WFS1*). *WFS1* is located on chromosome 4p16.1 and encodes the transmembrane protein wolframin (Hofmann et al. 2003). In the inner ear, wolframin is expressed in various cells, including inner and outer hair cells, pillar cells, stria vascularis, spiral ganglion neurons, and vestibular hair cells. The protein is predominantly localised in the canalicular reticulum, which is believed to be involved in the transcellular movements of ions, suggesting a potential role in inner ear ion homeostasis (Cryns et al. 2003).

Pathogenic variants in *WFS1* cause a spectrum of different disorders, including Wolfram syndrome type 1, Wolfram-like syndrome, and DFNA6/14/38 (Barrett et al. 1993). Wolfram syndrome type 1 is caused by biallelic pathogenic variants in *WFS1*, presenting as a progressive neurodegenerative disorder characterised by the onset of diabetes mellitus and optic atrophy before puberty. Additional clinical manifestations may include variable sensorineural hearing loss (SNHL), predominantly affecting high frequencies, diabetes insipidus, neurologic abnormalities, neurogenic bladder, and psychiatric disorders (Barrett et al. 1993; Inoue et al. 1998; Strom et al. 1998; Pennings et al. 2004; Plantinga et al. 2008).

This study, however, focuses on individuals with mono-allelic pathogenic variants in *WFS1*, which is associated with both Wolfram-like syndrome and DFNA6/14/38. Wolfram-like syndrome exhibits a milder phenotype compared to Wolfram syndrome, with optic atrophy and diabetes mellitus typically manifesting after puberty. Additionally, this syndrome is associated with profound SNHL in infancy, predominantly affecting the high frequencies (Barrett et al. 1993; Eiberg et al. 2006). In contrast, DFNA6/14/38 represents a non-syndromic form of SNHL characterised by low-frequency SNHL, typically with a congenital onset (Bespalova et al. 2001; Aldè et al. 2023). All variants associated with Wolfram-like syndrome and DFNA6/14/38 are missense variants or small in-frame deletions located in exon eight, the final and largest exon of *WFS1*. This exon encodes the transmembrane domains and the C-terminal domain of the protein (UniProt Consortium 2021; Hofmann et al. 2003). However, the reason why specific variants lead to wolfram-like syndrome while others result in DFNA6/14/38, as well as the differential frequency effects observed between the two conditions, remains unknown.

CONTACT R. J. E. Pennings Ronald.pennings@radboudumc.nl Department of Otorhinolaryngology, Radboud University Medical Center, Nijmegen, The Netherlands

Cochlear implantation (CI) outcomes in individuals with Wolfram-like syndrome and DFNA6/14/38 have, up to now, only been evaluated in a few cases. Lim et al. recently reviewed CI outcomes in this population and identified ten CI recipients, reporting improved auditory performance (Lim et al. 2023). However, heterogeneous outcome measures made comparisons challenging, and conclusions were drawn based on varying follow-up times. Individuals with wolfram-like syndrome will develop progressive vision deterioration due to optic atrophy, which increases their dependence on auditory perception for communication. Assessing long-term CI performance in these individuals, therefore, is crucial. Moreover, *WFS1*-associated SNHL has been associated with auditory neuropathy in some cases in literature (Sun et al. 2022; Lin et al. 2022). According to the spiral ganglion hypothesis, poor CI performance is expected when the spiral ganglion neurons and/or auditory nerves degenerate over time, while good CI performance is anticipated when only the pre-synaptic cochlea is affected (Eppsteiner et al. 2012). This makes it especially interesting to evaluate long-term CI outcomes, as according to this hypothesis, deterioration of the auditory nerve would lead to a decline in CI performance over time. Therefore, this study aims to assess CI outcomes in Dutch individuals with either Wolfram-like syndrome or DFNA6/14/38 in the short and long term.

Methods

Study design and population

In this retrospective, observational case series, CI recipients were included if they had monoallelic (likely) pathogenic variants in *WFS1* and had at least one year of follow-up following implantation. Subjects were categorised into those with Wolfram-like syndrome and those with DFNA6/14/38 based on their phenotype or that of their affected family members. Individuals with solely SNHL were classified as DFNA6/14/38, while those with optic atrophy were labelled as having Wolfram-like syndrome. Ethical approval for this study was granted by the Medical Ethics Committee (METC) Eastern Netherlands (Reference number: 2021-7501). The requirement for signed informed consent was waived by the ethics committee because all data were collected, saved, analysed, and reported anonymously.

Data collection

Demographic data were obtained by reviewing medical records, including gender, use of hearing aids (HA) prior to implantation, age at the time of implantation, and type of implant and electrode used. Additionally, comprehensive vestibular testing outcomes were collected, including rotatory chair testing using electronystagmography (ENG), the video Head Impulse Test (vHIT) to assess the semi-circular vestibular organs, and Vestibular Evoked Myogenic Potential (VEMP) measurements to evaluate otolith function. Furthermore, pre-implantation imaging was reviewed to assess inner ear anatomy.

Genotype and phenotype

The genotype was evaluated by reviewing previous genetic test results. The identified variant(s) in *WFS1*, along with the corresponding protein change(s), type of variant (truncating or missense) were documented. All identified variants were classified according to the ACMG-AMP variant classification guidelines (Richards et al. 2015). No additional genetic analyses were performed. The phenotype was mapped by reviewing medical records, evaluating self-reported age of onset of SNHL, family history, presence of additional symptoms such as optic atrophy and diabetes mellitus, degree of SNHL, and configuration of pure-tone audiograms.

Audiological performance

Audiometric data were also evaluated by reviewing medical records. Hearing assessments were conducted using standard pure tone and speech audiometry in accordance with current local protocols. No additional audiometric tests were performed. The pure tone average (PTA) was determined using thresholds at 500, 1000, 2000, and 4000 Hz ($PTA_{0.5\text{-}4kHz}$). Phoneme scores were assessed in quiet with standard monosyllabic (consonant-vowel-consonant) Dutch word lists (Bosman and Smoorenburg 1995) presented at 65 dB SPL. For both PTA and phoneme scores, aided and unaided scores were measured pre-implantation, while only aided scores were measured post-implantation. The postimplantation $PTA_{0.5\text{-}4kHz}$ and phoneme scores at 65 dB SPL were evaluated at both short-term (one-year post-implantation) and long-term ($\geq$6 years post-implantation). CI-recipients with a phoneme score $<$70% at least one year post-implantation were considered poor performers and were evaluated in more detail.

Not all individuals used hearing aids prior to implantation. We calculated the best-aided PTA and phoneme score to represent the pre-implantation auditory performance. The best-aided scores were related to the scores obtained while using a HA in the implanted ear or to unaided scores in those subjects not using a HA preoperatively. These scores were used to compare pre-implantation hearing performance to post-implantation CI performance.

Compared to adults, children with early-onset SNHL typically undergo a more comprehensive assessment, including Auditory Brainstem Response (ABR) and Otoacoustic Emissions (OAEs). When available, these data were also assessed. Additionally, the newborn hearing screening (NHS) results were evaluated when available. In early-implanted subjects with prelingual SNHL, behavioural observation audiometry (BOA) was used to determine pure tone thresholds pre-implantation and during the one-year follow-up. Speech audiometry could not be performed pre-implantation or at one-year follow-up in these children due to their young age.

Data analysis

Statistical analyses were performed with IBM Statistical Package for the Social Science Statistics (SPSS) 29. A p-value <0.05 was considered statistically significant. The Shapiro-Wilk test was used to assess data distribution for normality, and normally distributed data (e.g. PTA scores, phoneme scores, months/years of follow-up) were presented as mean values with standard deviation (SD). The median with interquartile ranges (IQR) was used to present non-normally distributed data (e.g. age at implantation, self-reported age of onset hearing loss). The mean PTA and phoneme scores at different follow-up moments were compared with the dependent sample t-test. The Mann-Witney U test was used to compare PTA and phoneme scores between subjects with Wolfram-like syndrome and those with DFNA6/14/38.

Results

Study cohort

Following the assessment of inclusion and exclusion criteria, this study included seven CI-recipients with monoallelic (likely) pathogenic variants in *WFS1*, of whom four (57%) were female (Table 1). Four subjects (A, B, C, D) have Wolfram-like syndrome, whereas the remaining three exhibited the DFNA6/14/38 phenotype. In the study cohort, a total of ten cochlear implantations were performed. Among these, four adults received unilateral implantation, while three children underwent bilateral implantation, one of those was performed simultaneously and two sequentially. The age at implantation ranged from eight months till 58 years, with a median of nine years (IQR 3.8-43.5). All subjects exhibited normal vestibular function, and pre-implantation imaging showed normal inner ear anatomy. Genetic testing identified five different missense variants, all located in exon 8 (Table 2). Two of them are classified as likely pathogenic, and three as pathogenic.

Subjects with wolfram-like syndrome

Four subjects were diagnosed with Wolfram-like syndrome. Subject A reported an onset of hearing loss at 18 months. However, she failed NHS on the first two OAE measurements but passed the third session (ABR). An ABR at the age of two years showed thresholds of 60 dB HL in the left ear, while no responses were obtained in the right ear. None of the family members experienced hearing loss. When subject A was twelve years of age, she was diagnosed with optic atrophy. Targeted genetic testing identified the heterozygous p.(Ala684Val) variant in *WFS1*. Her pre-implantation unaided pure tone audiogram showed a flat threshold (Figure 1A1 (left ear) and A2 (right ear)). At 17 years of age, she had no symptoms of diabetes mellitus. She did, however, have a growth hormone deficiency caused by neurosecretory dysfunction, for which she was successfully treated.

Subject B displays severe congenital SNHL without any additional symptoms. He failed NHS with absent OAEs; bilateral thresholds of ≥90 dB HL were found on a later performed ABR. The identified heterozygous pathogenic variant in *WFS1,* p.(Ala684Val), was determined to be a de novo mutation, with no other affected family members, although his parents were not tested. The unaided pre-implantation audiogram obtained with BOA displayed a severe hearing loss with a flat pure tone threshold right (Figure 1B1) and ski-slope SNHL left (Figure 1B2). As of now, the twelve-year-old boy has no visual symptoms or symptoms of diabetes mellitus.

Subject C reported a congenital onset of hearing loss, while none of her family members experienced hearing loss. Through genetic testing, the heterozygous p.(Ala684Val) variant was identified. Additionally, optic atrophy was observed, leading to a subsequent diagnosis of Wolfram-like syndrome. The pre-implantation unaided pure tone audiogram displayed high-frequency SNHL (Figure 1C). She had been using bilateral hearing aids since she was nine months old but ceased using a hearing aid in her to be implanted ear eight years before the implantation procedure. The reason for discontinuation was not reported. Although she does not exhibit symptoms of diabetes mellitus, over the years, she has developed emotional and social problems, as well as a conversion disorder.

Subject D reported severe early-onset SNHL along with optic atrophy, as did his brother and mother. Genetic testing identified the heterozygous p.(Ala684Val) variant as the cause in all affected family members. This family has previously been

Table 1. Subject characteristics.

Subject	Gender	Diagnosis	Type of inheritance	Age at implantation	cDNA variant*	Protein Variant	Self- reported age of onset HL	Degree HL at time of implantation**	Vestibular function in ear to be implanted***	Deviating anatomy inner ear	Optic atrophy	Diabetes mellitus	Hearing aid in ear to be implanted	Implanted ear	Implanted device
A1	Female	Wolfram-like syndrome	De novo	7 years	c.2051C > T	p.(Ala684Val)	1.5 years	Severe	Normal	–	+	–	+	Left	CI522 slim straight
A2				10 years				Profound	Normal	–			+	Right	CI522 slim straight
B1	Male	Wolfram-like syndrome	De novo	8 months	c.2051C > T	p.(Ala684Val)	0 years	Profound	Normal	–	–	–	+	Right	CI24RE (CA)
B2									Normal	–			+	Left	CI24RE (CA)
C1	Female	Wolfram-like syndrome	De novo	27 years	c.2051C > T	p.(Ala684Val)	0 years	Profound	Normal	–	+	–	–	Left	CI24RE (CA)
D1	Male	Wolfram-like syndrome	Autosomal dominant	58 years	c.2508G > C	p.(Lys836Asn)	9 years	Profound	Normal	–	+	–	+	Right	CI24RE (CA)
E1	Male	DFNA6/14/38	Autosomal dominant	45 years	c.2115G > C	Lys705Asn	0 years	Profound	Normal	–	–	–	–	Left	CI512 (CA)
F1	Female	DFNA6/14/38	Autosomal dominant	43 years	c.2512C > T	p.(Pro838Ser)	<10 years	Profound	Normal	–	–	–	+	Left	AB ultra 3D slim J
G1	Female	DFNA6/14/38	Autosomal dominant	5 years	c.2590G > A	p.(Glu864Lys)	3 years	Profound	Normal	–	–	–	+	Left	CI522 slim straight
G2				8 years					Normal	–			+	Right	CI622 slim straight

HL indi1460cates hearing loss; AB, Advanced Bionics.
*cDNA and protein nomenclature is based on transcript NM_006005.3.
**According to WHO's grades of hearing impairment.
***Comprehensive vestibular testing included rotatory chair testing using electronystagmography (ENG), video head impulse test (vHIT), and vestibular evoked myogenic potential (VEMP).

Table 2. Identified variants in *WFS1* in the study cohort.

	Transcript	cDNA	Protein	Domain	Variant type	Classification	References
M1	NM_006005.3	c.2051C > T	p.(Ala684Val)	ER-luminal domain	Missense	Pathogenic	(Zazo Seco et al. 2017)
M2	NM_006005.3	c.2115G > C	p.(Lys705Asn)	ER-luminal domain	Missense	Pathogenic	(Kunz et al. 2003)
M3	NM_006005.3	c.2508G > C	p.(Lys836Asn)	ER-luminal domain	Missense	Likely pathogenic	(Hogewind et al. 2010)
M4	NM_006005.3	c.2512C > T	p.(Pro838Ser)	ER-luminal domain	Missense	Likely pathogenic	(Velde et al. 2023)
M5	NM_006005.3	c.2590G > A	p.(Glu864Lys)	ER-luminal domain	Missense	Pathogenic	(Duzkale et al. 2013)

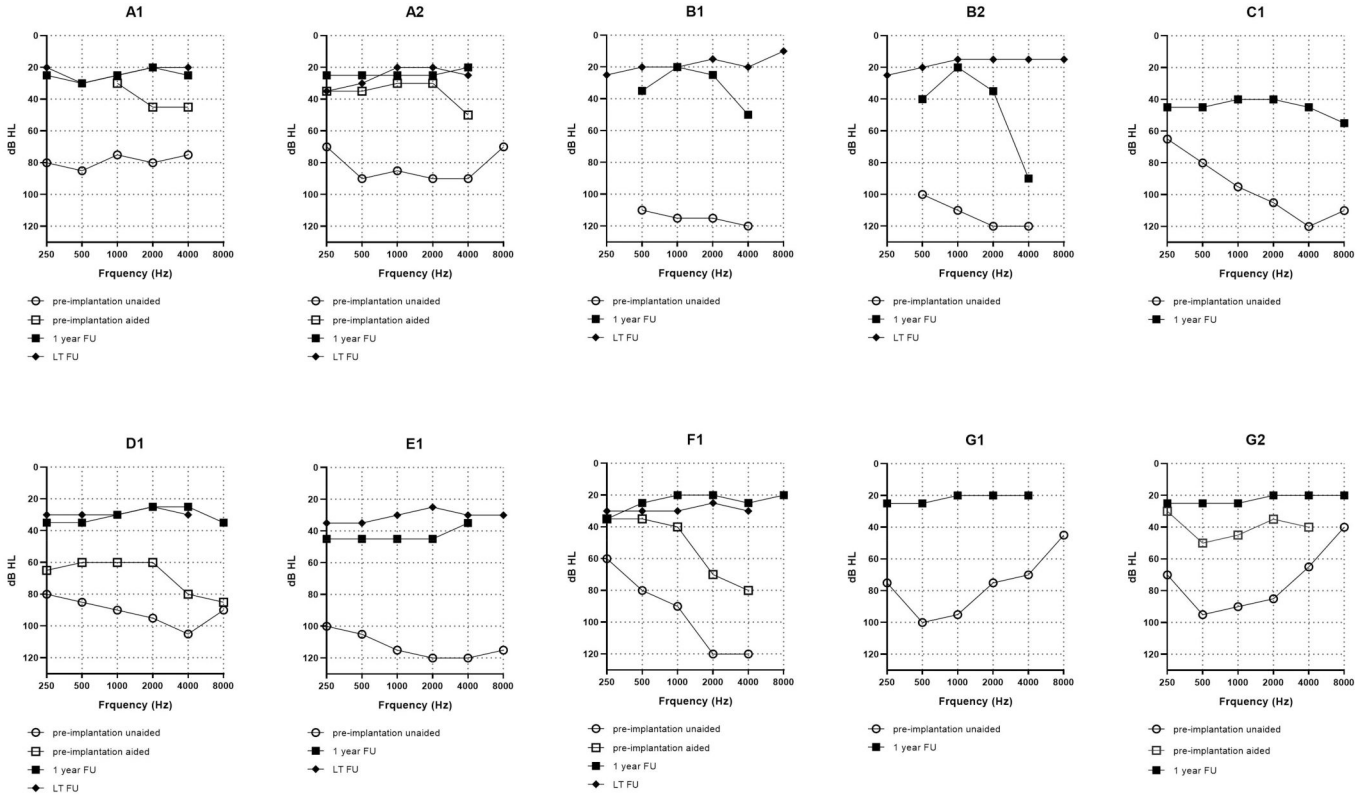

Figure 1. Pure tone audiograms. Pre-implantation unaided and aided pure tone audiograms and post-implantation aided audiograms at both one-year and long-term follow-up. Long-term follow-up audiograms were measured at 10.8 ± 2.7 years post implantation. A1 represents the left ear of subject A, A2 represent the right ear. B1 represents the right ear of subject B, B2 the left ear. G1 represent the left ear of subject G, G2 the right ear.
FU indicates follow-up; LT, long-term.

described by Hogewind et al. (Hogewind et al. 2010). Subject D's pre-implantation pure tone audiogram has a slightly ski-slope configuration (Figure 1D). At his current age of 73, this subject has, besides SNHL and optic atrophy, no symptoms of diabetes mellitus.

Subjects with DFNA6/14/38

Three subjects exhibited the DFNA6/14/38 phenotype. Subject E had congenital hearing loss caused by a segregating heterozygous variant p.(Lys705Asn) in *WFS1*. This variant was found to be associated with SNHL on the paternal side of the family. His pre-implantation unaided pure tone audiogram showed a flat pure tone threshold audiogram (Figure 1E). He solely used a hearing aid in the non-implanted ear and never used a hearing aid at the implanted ear due to physical discomfort while using the hearing aid on that side. Presently, at the age of 64, he does not have any symptoms of optic atrophy or diabetes mellitus. Additionally, none of his affected family members exhibited additional symptoms besides SNHL.

Subject F reported an early onset of hearing loss, which was frequently present in her family, including her brothers and mother. The heterozygous variant p.(Pro838Ser) was identified in *WFS1*. Her pre-implantation audiogram showed a ski-slope pure tone threshold audiogram (Figure 1F). At the age of 44, she has no symptoms of vision loss or diabetes mellitus. Neither her brother nor her mother had any additional symptoms besides SNHL.

Subject G reported an onset of hearing loss at the age of three. However, she failed NHS during the first two sessions due to the absence of OAEs. She reported passing the screening after the third session. Her mother exhibited childhood onset, stable, low-frequency SNHL without symptoms of diabetes mellitus, diabetes insipidus, or optic atrophy. A heterozygous pathogenic variant p.(Glu864Lys) was identified in subject G. The audiogram revealed mainly low-frequency SNHL (Figure 1G1 (left ear) and G2 (right ear)), and today, as expected, the eleven-year-old girl has no symptoms of vision loss or diabetes mellitus.

Cochlear implant outcomes

Ten cochlear implantations were performed in seven subjects. The mean pre-operative unaided $PTA_{0,5\text{-}4kHz}$ of all ten ears was 97 ± 14 dB HL, while the mean pre-operative best-aided $PTA_{0,5\text{-}4kHz}$ was 77 ± 33 dB HL. The mean best-aided $PTA_{0,5\text{-}4kHz}$ significantly improved to 30 ± 9 dB HL at 13 ± 2.4 months post-implantation ($p < 0.001$, $N = 10$ ears; Figure 2A). At 10.8 ± 2.7 years post-

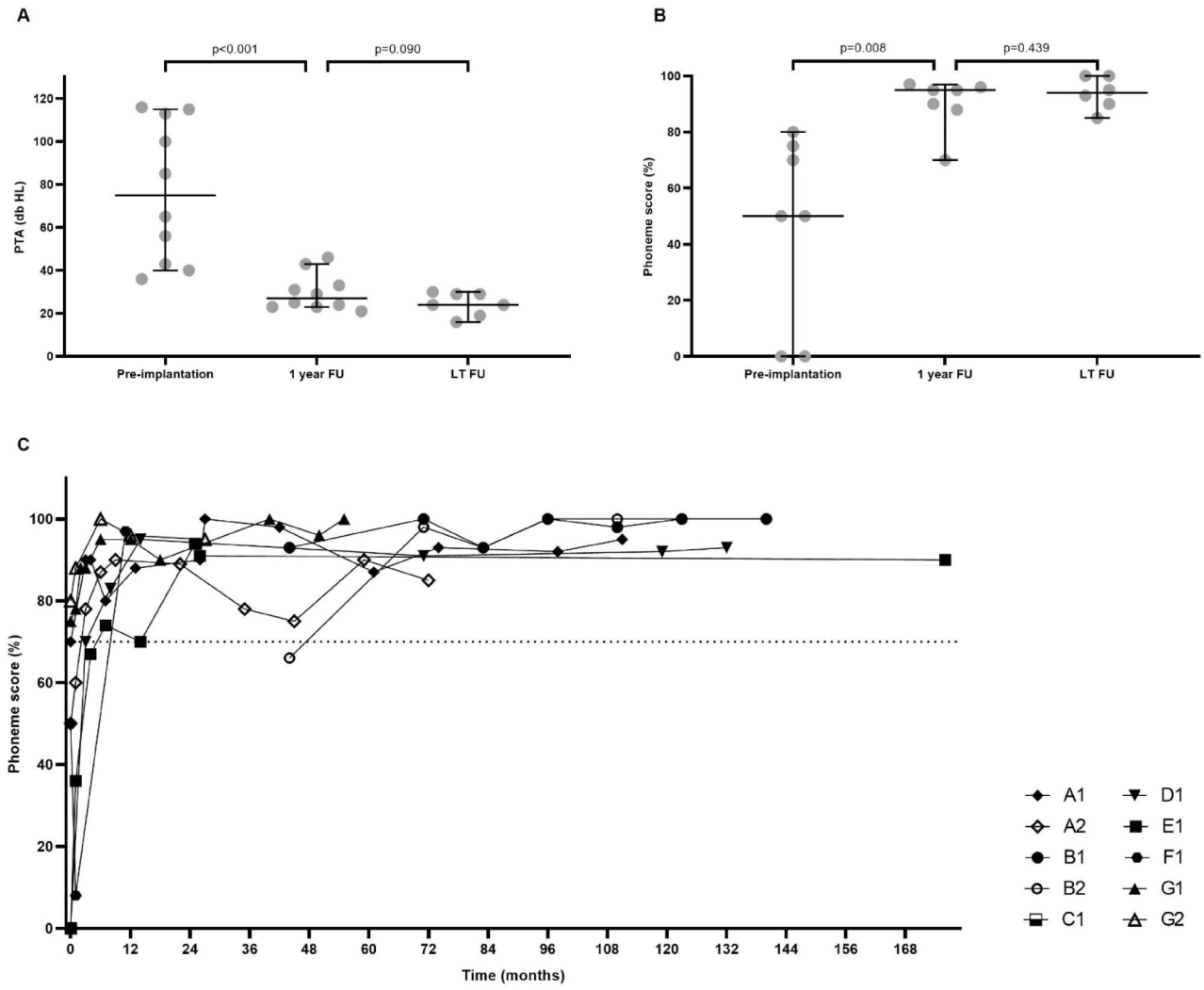

Figure 2. Cochlear implant performance. (A) Boxplot of $PTA_{0,5\text{-}4kHz}$ scores of each ear. Long-term follow-up was measured at 10.8 ± 2.7 years post implantation. (B) Boxplot of phoneme scores at 65 dB SPL in quiet of each ear. Pre-implantation aided phoneme scores were not available in all subjects. Long-term follow-up was measured at 10.8 ± 2.9 years post implantation. (C) Phoneme score at 65 dB SPL in quiet of each ear over the years.
PTA indicates pure tone average; FU, follow-up; LT, long-term.

implantation, the mean $PTA_{0,5\text{-}4kHz}$ remained stable at 24 ± 5 dB HL ($p = 0.090$, $N = 7$ ears).

The pre-implantation unaided phoneme score at 65 dB SPL in quiet was not measurable in the eight tested ears, while this score was 54 ± 29% for the best-aided pre-operative phoneme score. This score improved to 90 ± 9% 12 ± 2 months post-implantation ($p = 0.008$, $N = 7$ ears; Figure 2B). The post-implantation phoneme score remained stable over time (Figure 2C), with at 10.8 ± 2.9 years post-implantation a mean score of 94 ± 6% ($p = 0.439$, $N = 6$ ears).

No significant differences in unaided $PTA_{0,5\text{-}4kHz}$ scores ($p = 0.914$), last-available post-implantation $PTA_{0,5\text{-}4kHz}$ scores ($p = 0.476$), and last-available post-implantation phoneme scores ($p = 0.905$) were observed between subjects with Wolfram-like syndrome and those with DFNA6/14/38.

Poor performer

All subjects achieved phoneme scores ≥70% at 65 dB SPL in quiet (Figure 2C), except for subject C, who became a non-user. This subject reported a congenital onset of hearing loss, with thresholds at ~60 dB HL at the age of two, which deteriorated to 100 dB HL by the age of five. At nine months old, she began using hearing aids in both ears. However, by the age of nineteen, she discontinued the use of a hearing aid in her left ear. At 27, she underwent cochlear implantation on that side. This individual was educated at a school for deaf children and mainly communicated with sign language. Nevertheless, she was able to communicate orally in one-on-one conversations with lip reading support. Given the restricted language-speech development and the significant duration without auditory stimulation in the ear to be implanted, there were modest expectations for improvement in speech recognition post-implantation. The main goal of the implantation was, therefore, for the CI to serve a signalling function and to provide support in oral communication, as her vision deteriorated. Although this subject initially made satisfactory progress in the first months of rehabilitation, she discontinued the use of the CI six months after implantation due to underlying emotional, social and psychiatric problems.

Discussion

Mono-allelic pathogenic variants in *WFS1* are associated with both Wolfram-like syndrome and DFNA6/14/38. CI outcomes in

these individuals have been evaluated in a few cases, reporting overall improved auditory performance (Lim et al. 2023). However, this conclusion was based on heterogeneous outcome measures and varying, overall short follow-up durations. As *WFS1*-associated SNHL has been associated with auditory neuropathy (Sun et al. 2022; Lin et al. 2022), evaluating long-term CI outcomes is interesting since a decline in CI performance can be anticipated when the auditory nerve deteriorates over time. This study, therefore, focused on evaluating CI outcomes in CI recipients with either Wolfram-like syndrome or DFNA6/14/38. In our cohort of seven subjects in which ten cochlear implantations were performed, we found overall good CI outcomes in both the short-term and long-term. This emphasises that cochlear implantation in *WFS1*-associated hearing loss is not impaired by auditory nerve dysfunction.

Genotype and phenotype in wolfram-like syndrome and DFNA6/14/38

Both Wolfram-like syndrome and DFNA6/14/38 result from mono-allelic pathogenic variants in *WFS1*, which can be autosomal dominantly inherited or occur de novo. Lim et al. reported 80 probands with SNHL associated with heterozygous pathogenic variants in *WFS1*. Among these, 43 individuals (54%) exhibited a dominant inheritance pattern, while 16 individuals (20%) had hearing loss caused by de novo variants. The inheritance pattern was unknown in 21 individuals (26%) (Lim et al. 2023). In our study, a distinct dominant inheritance pattern was evident within the families of four subjects (subjects D, E, F, and G). Three subjects (A, B, and C) were the only affected individuals in their families, suggesting a de novo pathogenic variant. They all had the same p.(Ala684Val) variant, a known de novo variant hotspot (Rendtorff et al. 2011; Kobayashi et al. 2018; Guan et al. 2020).

All variants in *WFS1* associated with Wolfram-like syndrome and DFNA6/14/38 are either missense variants or small, in-frame deletions located in exon eight, encoding the transmembrane domains and the C-terminal domain of the protein (13; Hofmann et al. 2003). All cases in the present study had a missense *WFS1* variant in exon eight. The reason why specific variants result in Wolfram-like syndrome while others lead to DFNA6/14/38 so far remains unclear. In our study, we differentiated between Wolfram-like syndrome and DFNA6/14/38 based on the phenotype of the subjects and their affected family members.

Wolfram-like syndrome

Wolfram-like syndrome is characterised by the triad of SNHL, optic atrophy, and diabetes mellitus but can also manifest with neurological symptoms, psychiatric symptoms, urological symptoms, and diabetes insipidus (de Muijnck et al. 2023). Three subjects (A, C, and D) exhibited the Wolfram-like syndrome phenotype with SNHL combined with optic atrophy but without any signs of diabetes mellitus. This is in line with the findings from the systematic by de Muijnck et al., which demonstrated that 47% of individuals with Wolfram-like syndrome exhibit SNHL combined with optic atrophy. In contrast, the triad of SNHL, optic atrophy, and diabetes mellitus is observed in only 7% of affected individuals (de Muijnck et al. 2023).

Subjects A and C carry the p.(Ala684Val) variant, associated with Wolfram-like syndrome in multiple families (Rendtorff et al. 2011; Mets et al. 2010; Alías et al. 2022; Grenier et al. 2016). Hence, it is likely that subject B, a currently twelve-year-old boy carrying this same variant, may also develop optic atrophy over time. Subject C, in addition to SNHL and optic atrophy, also exhibited psychiatric symptoms, a feature observed in 16% of the individuals with Wolfram-like syndrome. Furthermore, Subject A presented, besides SNHL and optic atrophy, a growth hormone deficiency described in one other individual with Wolfram-like syndrome and the p.(Ala684Val) variant (de Muijnck et al. 2023).

The p.(Lys836Asn) variant identified in subject D was previously reported by Mair et al. in a family with Wolfram-like syndrome, although with a different nucleotide change (c.2508G > C versus c.2508G > T) (Mair et al. 2022). Kobayashi et al. presented three subjects with a heterozygous c.2508G > C (p.(Lys836Asn)) variant in *WFS1*. In their study, the 41-year-old subject and an eleven-year-old child showed no optic atrophy, while this information was unavailable for the other subject (aged 67). Although optic atrophy is typically diagnosed within the first two decades in most individuals with Wolfram-like syndrome, a gradual decrease in the age of diagnosis is observed until the eighth decade (de Muijnck et al. 2023). While the subjects described by Kobayashi et al. may still develop optic atrophy, subject D and his two affected family members reported ages of onset of ophthalmological complaints at eleven, ten, and thirty years (Hogewind et al. 2010).

DFNA6/14/38

DFNA6/14/38 presents as a non-syndromic form of SNHL, primarily affecting the lower frequencies (Bespalova et al. 2001). Subject G's unaided pre-implantation audiograms clearly indicated low-frequency SNHL. The eleven-year-old girl has no symptoms of optic atrophy or diabetes mellitus. Furthermore, her mother exhibits low-frequency SNHL without any additional symptoms, which is suggestive of DFNA6/14/38. The identified p.(Glu864Lys) variant in subject G has been previously described in individuals with solely SNHL and individuals with SNHL along with optic atrophy (Eiberg et al. 2006; Kobayashi et al. 2018; Guan et al. 2020; Fukuoka et al. 2007).

Subjects E and F both exhibited the phenotype of DFNA6/14/38, featuring SNHL solely. Additionally, none of their affected family members exhibited additional symptoms besides SNHL. However, subjects E and F's unaided pre-implantation audiograms do not show the typically low-frequency SNHL but rather display a flat and ski-slope configuration, respectively. Subject E carries the p.(Lys705Asn), previously identified in a German family with DFNA6/14/38 (Kunz et al. 2003). The p.(Pro838Ser) variant in subject F has also been described in another Dutch DFNA6/14/38 family (Velde et al. 2023).

Cochlear implantation outcomes in wolfram-like syndrome and DFNA6/14/38

The outcomes following CI in individuals with Wolfram-like syndrome and DFNA6/14/38 have only been evaluated in a limited number of cases. In most cases, CI was reported to be successful, resulting in improved speech perception and PTA scores (Table 3) (Lim et al. 2023; Lin et al. 2022; Hogewind et al. 2010; Rendtorff et al. 2011; Guan et al. 2020; Alías et al. 2022). While many of these studies had short follow-up durations, three studies also reported favourable long-term outcomes (Lin et al. 2022; Rendtorff et al. 2011; Alías et al. 2022). This is in line with our study in which we found excellent outcomes, in both short-term

Table 3. Cochlear implant recipients with mono-allelic pathogenic variants in WFS1.

Subject	Gender	Diagnosis	Type of inheritance	Age at implantation	cDNA variant*	Protein Variant	Self- reported age of onset HL	Degree HL at time of implantation**	Configuration audiogram	Optic atrophy	Diabetes mellitus	pre-implantation hearing performance	post-implantation hearing performance	Last follow-up
A1	Female	Wolfram-like syndrome	De novo	7 years	c.2051C > T	p.(Ala684Val)	1.5 years	Severe	Flat	+	–	$PTA_{0,5\text{-}4kHz}$: 40 Phoneme score: 70%	$PTA_{0,5\text{-}4kHz}$: 24 Phoneme score: 95%	9 years
A2				10 years				Profound	Flat			$PTA_{0,5\text{-}4kHz}$: 36 Phoneme score: 50%	$PTA_{0,5\text{-}4kHz}$: 24 Phoneme score: 85%	6 years
B1	Male	Wolfram-like syndrome	De novo	8 months	c.2051C > T	p.(Ala684Val)	0 years	Profound	Flat	–	–	$PTA_{0,5\text{-}4kHz}$: 116	$PTA_{0,5\text{-}4kHz}$: 19 Phoneme score: 100%	12 years
B2									Flat			$PTA_{0,5\text{-}4kHz}$: 113	$PTA_{0,5\text{-}4kHz}$: 16 Phoneme score: 100%	12 years
C1	Female	Wolfram-like syndrome	De novo	27 years	c.2051C > T	p.(Ala684Val)	0 years	Profound	High-frequency	+	–	$PTA_{0,5\text{-}4kHz}$: 100	$PTA_{0,5\text{-}4kHz}$: 29	12 years
D1	Male	Wolfram-like syndrome	Autosomal dominant	58 years	c.2508G > C	p.(Lys836Asn)	9 years	Profound	High-frequency	+	–	$PTA_{0,5\text{-}4kHz}$: 65 Phoneme score: 0%	$PTA_{0,5\text{-}4kHz}$: 29 Phoneme score: 93%	11 years
E1	Male	DFNA6/14/38	Autosomal dominant	45 years	c.2115G > C	p.(Lys705Asn)	0 years	Profound	Flat	–	–	$PTA_{0,5\text{-}4kHz}$: 115 Phoneme score: 0%	$PTA_{0,5\text{-}4kHz}$: 30 Phoneme score: 90%	15 years
F1	Female	DFNA6/14/38	Autosomal dominant	43 years	c.2512C > T	p.(Pro838Ser)	<10 years	Profound	High-frequency	–	–	$PTA_{0,5\text{-}4kHz}$: 56 Phoneme score: 50%	$PTA_{0,5\text{-}4kHz}$: 23 Phoneme score: 97%	1 year
G1	Female	DFNA6/14/38	Autosomal dominant	5 years	c.2590G > A	p.(Glu864Lys)	3 years	Profound	Low-frequency	–	–	$PTA_{0,5\text{-}4kHz}$: 85 Phoneme score: 75%	$PTA_{0,5\text{-}4kHz}$: 25 Phoneme score: 100%	5 years
G2				8 years					Low-frequency			$PTA_{0,5\text{-}4kHz}$: 43 Phoneme score: 80%	$PTA_{0,5\text{-}4kHz}$: 28 Phoneme score: 95%	2 years
Lim et al. SH486 (15)	Male	DFNA6/14/38	De novo	56	c.1544_1545insA	p.(Phe515LeufsTer28	4 years	Profound	High-frequency	–	–	Monosyllabic words: 28%	Monosyllabic words: 60%	3 months
Lim et al. SH550 (15)	Female	NA	De novo	29 months	c.2051C > T	p.(Ala684Val)	1 year	Severe	Flat	–	–	CAP 1	CAP 3	3 months
Rendtorff et al. VI:7 (22)	Male	Wolfram-like syndrome	Autosomal dominant	57 years	c.2051C > T	p.(Ala684Val)	NA	Profound	High-frequency	+	NA	$PTA_{0,5\text{-}4kHz}$: 84	$PTA_{0,5\text{-}4kHz}$: 34	16 years
Rendtorff et al. VI:9 (22)	Female	Wolfram-like syndrome	Autosomal dominant	77 years	c.2051C > T	p.(Ala684Val)	NA	NA	High-frequency	+	NA	"Outcome was questionable due to old age, general medical frailty and inability to perform relevant training efforts after CI treatment".		
Guan et al. #1 (24)	Male	NA	De novo	<3 years	c.2051C > T	p.(Ala684Val)	2 years	Profound	Flat	–	–	"Four probands underwent CI treatment before age three and their language ability improved after surgery".		
Guan et al. #2 (24)	Male	NA	De novo	<3 years	c.2051C > T	p.(Ala684Val)	1 year	Profound	Flat	–	–			
Guan et al. #3 (24)	Male	NA	De novo	<3 years	c.2051C > T	p.(Ala684Val)	2 years	Profound	Flat	–	–			
Guan et al. #4 (24)	Male	NA	De novo	<3 years	c.2051C > T	p.(Ala684Val)	8 months	Profound	Flat	–	–			
Lin et al. #1 (17)	Female	NA	De novo	2.6 years	c.2051C > T	p.(Ala684Val)	0 years	Profound	Flat	NA	NA	$PTA_{0,5\text{-}4kHz}$: 90	$PTA_{0,5\text{-}4kHz}$: 23 WRS at 35 db HL: 92%	3.8 years
Alías et al. #1 (27)	Female	Wolfram-like syndrome	De novo	3 years	c.2051C > T	p.(Ala684Val)	<1.6 years	Profound	Flat	+	–	$PTA_{0,5\text{-}4kHz}$: 116	$PTA_{0,5\text{-}4kHz}$: 20 Speech recognition: 70%	9 years
				10 years				Profound	flat			$PTA_{0,5\text{-}4kHz}$: 116	$PTA_{0,5\text{-}4kHz}$: 20 Speech recognition: 65%	3 years

HL indicates hearing loss; PTA indicates pure tone average; NA: not available; CAP: categories of auditory perception; CI: cochlear implant; WRS: word recognition score.
*cDNA and protein nomenclature is based on transcript NM_006005.3.
**According to WHO's grades of hearing impairment.
***Tested with electronystagmography (ENG) which was performed with vestibular caloric, and rotary chair testing.

and long-term, with phoneme scores of respectively 90 ± 9% and 94 ± 6%. No significant difference was observed in post-implantation phoneme scores between subjects with Wolfram-like syndrome and those with DFNA6/14/38. Although speech perception outcomes in noise were not tested, the outcomes of this study indicate that cochlear implantation is a successful type of rehabilitation for individuals with *WFS1*-associated SNHL.

Less favourable CI outcomes in individuals with *WFS1*-associated SNHL have been reported in one subject by Rendtorff et al. Although specific details are not provided, they noted that in one individual, outcomes were questionable due to advanced age, general medical frailty, and challenges in proper rehabilitation (Rendtorff et al. 2011). Our study identified one subject with unfavourable outcomes, which ultimately became a non-user (subject C). This subject ceased using a hearing aid in her (to be) implanted ear eight years before the implantation. Consequently, she experienced a long-term absence of auditory stimulation, which is known to lead to profound changes in the structure and function of the central auditory system (Syka 2002). As a result, she faced challenges in developing speech understanding post-implantation. Nevertheless, she initially made satisfactory progress within the first months of rehabilitation, but difficulties in rehabilitation occurred due to underlying emotional, social, and psychiatric problems. It is known that psychosocial issues can negatively impact speech recognition following CI (Shin et al. 2015). Although the goal of implantation in this subject was for the CI to have a signalling function, we, nevertheless, have to conclude that the outcomes did not match the anticipated outcome pre-implantation.

To better predict CI outcomes, Eppsteiner et al. proposed the spiral ganglion hypothesis. This hypothesis suggests that good CI outcomes are anticipated when the pre-synaptic structures in the cochlea are affected, while poorer CI performance is expected when the spiral ganglion neurons and/or auditory nerve (i.e. the post-synaptic structures) are affected (Eppsteiner et al. 2012). Although the substantiation of the spiral ganglion hypothesis is currently limited, our study, demonstrating overall excellent outcomes following CI in subjects with *WFS1*-associated SNHL, aligns with this hypothesis, as wolframin has a predominant role in inner ear ion homeostasis (Cryns et al. 2003). However, in a few cases, *WFS1*-associated SNHL has been associated with auditory neuropathy (Sun et al. 2022; Lin et al. 2022), characterised by the absence or abnormalities in auditory brainstem responses, with preserved activity of the hair cells (Starr et al. 1996). The clinical findings in two children in our study, with absent OAEs and detectable ABR response, do not align with the criteria for auditory neuropathy. Moreover, the stable long-term CI outcomes in our subjects contradict the presence of auditory neuropathy.

Lim et al. observed in their review that the molecular genetic aetiology in CI-recipients with *WFS1*-associated SNHL clustered around three pathogenic variants (p.(Phe515LeufsTer28), p.(Ala684Val), and p.(Lys836Asn)), suggesting a narrow molecular aetiological spectrum. Additionally, they proposed p.(Ala684Val) as a strong CI marker, as this variant was present in 81.8% of their identified CI recipients with mono-allelic *WFS1*-associated hearing loss (Lim et al. 2023). However, whether this observation is coincidental is debateable. This particular variant was also the most commonly recognised in their dataset and is frequently identified due to being a known de novo mutational hotspot (Rendtorff et al. 2011; Kobayashi et al. 2018; Guan et al. 2020). Our study identified five variants among the CI recipients, including the p.(Ala684Val) and p.(Lys836Asn) variants.

Conclusion and future perspectives

In this case series, including seven subjects (ten ears) with either Wolfram-like syndrome or DFNA6/14/38, we observed good outcomes that remained stable over many years. This indicates that CI is a recommended form of rehabilitation for these individuals. Our findings contradict the suggested association between *WFS1*-associated SNHL and auditory neuropathy, as our subjects had absent OAEs with detectable ABR responses and no decline in CI performance over time. Current study represents the largest cohort assessing CI performance in this population using homogeneous outcome measurements and evaluating outcomes during different follow-up moments. Nevertheless, larger study cohorts are necessary to further confirm our findings.

Disclosure statement

The authors report there are no competing interest to declare.

Funding

This study was sponsored by Cochlear Ltd. as an independent investigator-initiated research study.

Data availability statement

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

References

Aldè, M., G. Cantarella, D. Zanetti, L. Pignataro, I. La Mantia, L. Maiolino, S. Ferlito, P. Di Mauro, S. Cocuzza, J. R. Lechien, et al. 2023. "Autosomal Dominant Non-Syndromic Hearing Loss (DFNA): A Comprehensive Narrative Review." *Biomedicines* 11 (6):1616. https://doi.org/10.3390/biomedicines11061616.

Alías, L., M. López de Heredia, S. Luna, N. Clivillé, L. González-Quereda, P. Gallano, J. de Juan, A. Pujol, S. Diez, S. Boronat, et al. 2022. "Case Report: De Novo Pathogenic Variant in WFS1 Causes Wolfram-Like Syndrome Debuting with Congenital Bilateral Deafness." *Frontiers in Genetics* 13:998898. https://doi.org/10.3389/fgene.2022.998898.

Barrett, T., L. Tranebjærg, R. Gupta, L. McCarthy, N. D. Rendtorff, D. Williams, et al. 1993. *WFS1 Spectrum Disorder*, edited by M. P. Adam, J. Feldman, G. M. Mirzaa, R. A. Pagon, S. E. Wallace, and L. J. H. Bean. Seattle, WA: University of Washington.

Bespalova, I. N., G. Van Camp, S. J. Bom, D. J. Brown, K. Cryns, A. T. DeWan, A. E. Erson, K. Flothmann, H. P. Kunst, P. Kurnool, et al. 2001. "Mutations in the Wolfram Syndrome 1 Gene (WFS1) are a Common Cause of Low Frequency Sensorineural Hearing Loss." *Human Molecular Genetics* 10 (22):2501–2508. https://doi.org/10.1093/hmg/10.22.2501.

Bosman, A. J., and G. F. Smoorenburg. 1995. "Intelligibility of Dutch CVC Syllables and Sentences for Listeners with Normal Hearing and with Three Types of Hearing Impairment." *Audiology: official Organ of the International Society of Audiology* 34 (5):260–284. https://doi.org/10.3109/00206099509071918.

Cryns, K., S. Thys, L. Van Laer, Y. Oka, M. Pfister, L. Van Nassauw, R. J. H. Smith, J.-P. Timmermans, and G. Van Camp. 2003. "The WFS1 Gene, Responsible for Low Frequency Sensorineural Hearing Loss and Wolfram Syndrome, is Expressed in a Variety of Inner Ear Cells." *Histochemistry and Cell Biology* 119 (3):247–256. https://doi.org/10.1007/s00418-003-0495-6.

de Muijnck, C., J. Brink, A. A. Bergen, C. J. F. Boon, and M. M. van Genderen. 2023. "Delineating Wolfram-Like Syndrome: A Systematic Review and Discussion of the WFS1-Associated Disease Spectrum." *Survey of Ophthalmology* 68 (4):641–654. https://doi.org/10.1016/j.survophthal.2023.01.012.

Duzkale, H., J. Shen, H. McLaughlin, A. Alfares, M. A. Kelly, T. J. Pugh, B. H. Funke, H. L. Rehm, and M. S. Lebo. 2013. "A Systematic Approach

to Assessing the Clinical Significance of Genetic Variants." *Clinical Genetics* 84 (5):453–463. https://doi.org/10.1111/cge.12257.

Eiberg, H., L. Hansen, B. Kjer, T. Hansen, O. Pedersen, M. Bille, T. Rosenberg, and L. Tranebjaerg. 2006. "Autosomal Dominant Optic Atrophy Associated with Hearing Impairment and Impaired Glucose Regulation Caused by a Missense Mutation in the WFS1 Gene." *Journal of Medical Genetics* 43 (5):435–440. https://doi.org/10.1136/jmg.2005.034892.

Eppsteiner, R. W., A. E. Shearer, M. S. Hildebrand, A. P. Deluca, H. Ji, C. C. Dunn, E. A. Black-Ziegelbein, T. L. Casavant, T. A. Braun, T. E. Scheetz, et al. 2012. "Prediction of Cochlear Implant Performance by Genetic Mutation: The Spiral Ganglion Hypothesis." *Hearing Research* 292 (1-2): 51–58. https://doi.org/10.1016/j.heares.2012.08.007.

Fukuoka, H., Y. Kanda, S. Ohta, and S. I. Usami. 2007. "Mutations in the WFS1 Gene are a Frequent Cause of Autosomal Dominant Nonsyndromic Low-Frequency Hearing Loss in Japanese." *Journal of Human Genetics* 52 (6):510–515. https://doi.org/10.1007/s10038-007-0144-3.

Grenier, J., I. Meunier, V. Daien, C. Baudoin, F. Halloy, B. Bocquet, C. Blanchet, C. Delettre, E. Esmenjaud, A. Roubertie, et al. 2016. "WFS1 in Optic Neuropathies: Mutation Findings in Nonsyndromic Optic Atrophy and Assessment of Clinical Severity." *Ophthalmology* 123 (9):1989–1998. https://doi.org/10.1016/j.ophtha.2016.05.036.

Guan, J., H. Wang, L. Lan, Y. Wu, G. Chen, C. Zhao, D. Wang, and Q. Wang. 2020. "Recurrent de Novo WFS1 Pathogenic Variants in Chinese Sporadic Patients with Nonsyndromic Sensorineural Hearing Loss." *Molecular Genetics & Genomic Medicine* 8 (8):e1367. https://doi.org/10.1002/mgg3.1367.

Hofmann, S., C. Philbrook, K. D. Gerbitz, and M. F. Bauer. 2003. "Wolfram Syndrome: Structural and Functional Analyses of Mutant and Wild-Type Wolframin, the WFS1 Gene Product." *Human Molecular Genetics* 12 (16): 2003–2012. https://doi.org/10.1093/hmg/ddg214.

Hogewind, B. F., R. J. Pennings, F. A. Hol, H. P. Kunst, E. H. Hoefsloot, J. R. Cruysberg, and C. W. Cremers. 2010. "Autosomal Dominant Optic Neuropathy and Sensorineual Hearing loss Associated with a Novel Mutation of WFS1." *Molecular Vision* 16:26–35.

Inoue, H., Y. Tanizawa, J. Wasson, P. Behn, K. Kalidas, E. Bernal-Mizrachi, M. Mueckler, H. Marshall, H. Donis-Keller, P. Crock, et al. 1998. "A Gene Encoding a Transmembrane Protein is Mutated in Patients with Diabetes Mellitus and Optic Atrophy (Wolfram Syndrome)." *Nature Genetics* 20 (2):143–148. https://doi.org/10.1038/2441.

Kobayashi, M., M. Miyagawa, S.-Y. Nishio, H. Moteki, T. Fujikawa, K. Ohyama, H. Sakaguchi, I. Miyanohara, A. Sugaya, Y. Naito, et al. 2018. "WFS1 Mutation Screening in a Large Series of Japanese Hearing Loss Patients: Massively Parallel DNA Sequencing-Based Analysis." *PloS One* 13 (3):e0193359. https://doi.org/10.1371/journal.pone.0193359.

Kunz, J., B. Marquez-Klaka, S. Uebe, A. Volz-Peters, R. Berger, and P. Rausch. 2003. "Identification of a Novel Mutation in WFS1 in a Family Affected by Low-Frequency Hearing Impairment." *Mutation Research* 525 (1-2):121–124. https://doi.org/10.1016/s0027-5107(02)00265-8.

Lim, H. D., S. M. Lee, Y. J. Yun, D. H. Lee, J. H. Lee, S. H. Oh, and S. Y. Lee. 2023. "WFS1 Autosomal Dominant Variants Linked with Hearing Loss: Update on Structural Analysis and Cochlear Implant Outcome." *BMC Medical Genomics* 16 (1):79. https://doi.org/10.1186/s12920-023-01506-x.

Lin, P.-H., H.-P. Wu, C.-M. Wu, Y.-T. Chiang, J. S. Hsu, C.-Y. Tsai, H. Wang, L.-H. Tseng, P.-Y. Chen, T.-H. Yang, et al. 2022. "Cochlear Implantation Outcomes in Patients with Auditory Neuropathy Spectrum Disorder of Genetic and Non-Genetic Etiologies: A Multicenter Study." *Biomedicines* 10 (7):1523. https://doi.org/10.3390/biomedicines10071523.

Mair, H., N. Fowler, M. E. Papatzanaki, P. Sudhakar, and R. S. Maldonado. 2022. "Novel Missense WFS1 Variant Causing Autosomal Dominant Atypical Wolfram Syndrome." *Ophthalmic Genetics* 43 (4):567–572. https://doi.org/10.1080/13816810.2022.2068038.

Mets, R. B., S. B. Emery, M. M. Lesperance, and M. B. Mets. 2010. "Congenital Cataracts in two Siblings with Wolfram Syndrome." *Ophthalmic Genetics* 31 (4):227–229. https://doi.org/10.3109/13816810.2010.516056.

Morton, C. C., and W. E. Nance. 2006. "Newborn Hearing Screening–A Silent Revolution." *The New England Journal of Medicine* 354 (20):2151–2164. https://doi.org/10.1056/NEJMra050700.

Pennings, R. J., P. L. Huygen, J. M. van den Ouweland, K. Cryns, L. D. Dikkeschei, G. Van Camp, and C. W. Cremers. 2004. "Sex-Related Hearing Impairment in Wolfram Syndrome Patients Identified by Inactivating WFS1 Mutations." *Audiology & Neuro-Otology* 9 (1):51–62. https://doi.org/10.1159/000074187.

Plantinga, R. F., R. J. E. Pennings, P. L. M. Huygen, R. Bruno, P. Eller, T. G. Barrett, B. Vialettes, V. Paquis-Fluklinger, F. Lombardo, C. W. R. J. Cremers, et al. 2008. "Hearing Impairment in Genotyped Wolfram Syndrome Patients." *The Annals of Otology, Rhinology, and Laryngology* 117 (7):494–500. https://doi.org/10.1177/000348940811700704.

Rendtorff, N. D., M. Lodahl, H. Boulahbel, I. R. Johansen, A. Pandya, K. O. Welch, V. W. Norris, K. S. Arnos, M. Bitner-Glindzicz, S. B. Emery, et al. 2011. "Identification of p.A684V Missense Mutation in the WFS1 Gene as a Frequent Cause of Autosomal Dominant Optic Atrophy and Hearing Impairment." *American Journal of Medical Genetics. Part A* 155a (6): 1298–1313. https://doi.org/10.1002/ajmg.a.33970.

Richards, S., N. Aziz, S. Bale, D. Bick, S. Das, J. Gastier-Foster, W. W. Grody, M. Hegde, E. Lyon, E. Spector, et al. 2015. "Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology." *Genetics in Medicine: official Journal of the American College of Medical Genetics* 17 (5):405–424. https://doi.org/10.1038/gim.2015.30.

Shearer, A. E., M. S. Hildebrand, A. M. Schaefer, R. J. H. Smith, et al. 1993. *Genetic Hearing Loss Overview*, edited by M. P. Adam, J. Feldman, G. M. Mirzaa, R. A. Pagon, S. E. Wallace, and L. J. H. Bean. Seattle, WA: University of Washington.

Shin, M.-S., J.-J. Song, K.-H. Han, H.-J. Lee, R.-M. Do, B. J. Kim, and S. H. Oh. 2015. "The Effect of Psychosocial Factors on Outcomes of Cochlear Implantation." *Acta Oto-Laryngologica* 135 (6):572–577. https://doi.org/10.3109/00016489.2015.1006336.

Starr, A., T. W. Picton, Y. Sininger, L. J. Hood, and C. I. Berlin. 1996. "Auditory Neuropathy." *Brain: a Journal of Neurology* 119 (Pt 3) (3):741–753. https://doi.org/10.1093/brain/119.3.741.

Strom, T. M., K. Hörtnagel, S. Hofmann, F. Gekeler, C. Scharfe, W. Rabl, K. D. Gerbitz, and T. Meitinger. 1998. "Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness (DIDMOAD) Caused by Mutations in a Novel Gene (Wolframin) Coding for a Predicted Transmembrane Protein." *Human Molecular Genetics* 7 (13):2021–2028. https://doi.org/10.1093/hmg/7.13.2021.

Sun, L., Z. Lin, J. Zhang, J. Shen, X. Wang, and J. Yang. 2022. "Genetic Etiological Analysis of Auditory Neuropathy Spectrum Disorder by Next-Generation Sequencing." *Frontiers in Neurology* 13:1026695. https://doi.org/10.3389/fneur.2022.1026695.

Syka, J. 2002. "Plastic Changes in the Central Auditory System After Hearing Loss, Restoration of Function, and During Learning." *Physiological Reviews* 82 (3):601–636. https://doi.org/10.1152/physrev.00002.2002.

UniProt Consortium. 2021. "UniProt: The Universal Protein Knowledgebase in 2021." *Nucleic Acids Research*. 49 (D1):D480–d9. https://doi.org/10.1093/nar/gkaa1100.

Velde, H. M., X. J. J. Huizenga, H. G. Yntema, L. Haer-Wigman, A. J. Beynon, J. Oostrik, S. A. H. Pegge, H. Kremer, C. P. Lanting, R. J. E. Pennings, et al. 2023. "Genotype and Phenotype Analyses of a Novel WFS1 Variant (c.2512C > T p.(Pro838Ser)) Associated with DFNA6/14/38." *Genes* 14 (2):457. https://doi.org/10.3390/genes14020457.

Zazo Seco, C., M. Wesdorp, I. Feenstra, R. Pfundt, J. Y. Hehir-Kwa, S. H. Lelieveld, S. Castelein, C. Gilissen, I. J. de Wijs, R. J. Admiraal, et al. 2017. "The Diagnostic Yield of Whole-Exome Sequencing Targeting a Gene Panel for Hearing Impairment in The Netherlands." *European Journal of Human Genetics: EJHG* 25 (3):308–314. https://doi.org/10.1038/ejhg.2016.182.