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Pathogenic Variants in the *COCH* Gene That Lead to Hearing Loss and Vestibular Deficit: Update on DFNA9 and Introducing DFNB110

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ABSTRACT

DeaFNess Autosomal Dominant 9 is an autosomal dominant hereditary non-syndromic form of progressive sensorineural hearing loss often associated with vestibular dysfunction. It is caused by over 30 heterozygous pathogenic variants in the *COCH* gene, which encodes cochlin. The DeaFNess Autosomal Dominant 9 p.Pro51Ser variant is the most prevalent cause of adult-onset hereditary hearing loss in Belgium and leads to severe-to-profound sensorineural hearing loss and bilateral vestibulopathy. The recent discovery of homozygous pathogenic variants in the *COCH* gene—leading to loss-of-function of cochlin—has resulted in the designation of a new autosomal recessive disorder called DFNB110. Cochlear implantation should be considered as soon as patients no longer benefit from a hearing aid because all carriers show a natural evolution toward deafness, a condition that is associated with a higher risk of accelerated cognitive impairment. Moreover, cochlear implantation candidates fulfilling the most recent reimbursement criteria in Belgium have better speech understanding after cochlear implantation when compared to the previous reimbursement criteria. Vibrotactile feedback of the gravity vector—provided by a balance belt—can significantly improve balance and mobility for the bilateral vestibulopathy symptoms. A vestibulocochlear implant is a modified research cochlear implantation that—next to capturing hearing—is also able to capture motion. The dominant inheritance pattern and non-haploinsufficiency disease mechanism of DeaFNess Autosomal Dominant 9 indicate that suppressing translation of mutant *COCH* transcripts has high therapeutic potential, which might even prevent hearing impairment. This review will highlight recent insights and future perspectives related to DeaFNess Autosomal Dominant 9 and DFNB110.

Keywords: Auditory, balance disorder, cochlear implants, dysequilibrium, sensorineural hearing loss

Introduction

Hearing impairment is the most frequent sensory deficit in the human population, affecting 1.57 billion people worldwide, with an estimated global economic cost exceeding $981 billion each year.[1,2] Because of our aging population, the number of people with hearing loss has been predicted to increase in the next few decades with a proportionate increase in economic cost.[3] For this reason, the World Health Organization (WHO) has listed hearing loss as a priority disease for research into therapeutic interventions and has suggested that even modest reductions in the overall prevalence or severity of loss can be valuable to reduce disease burden and economic cost.[4,5]

One of the most prevalent forms of hereditary postlingual non-syndromic sensorineural hearing loss (SNHL) in Belgium

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and the Netherlands is DeaFNess Autosomal Dominant 9 (DFNA9).[6] DeaFNess Autosomal Dominant 9 is caused by heterozygous gain-of-function (also called dominant-negative) pathogenic variants (mutations) in the *COCH* gene. This gene codes for the protein cochlin, one of the most abundant proteins in the inner ear, next to collagen. Currently, over 25 pathogenic variants have been identified to cause DFNA9, and each variant has its own phenotype, that is, its own set of observable characteristics (such as SNHL and/or vestibular deficit).[7-9] Only recently, homozygous autosomal recessive inactivating variants in the *COCH* gene have been identified in Belgium.[10] It was effectively the first report worldwide of autosomal recessive variants in the *COCH* gene, a disorder that has now been designated as DFNB110.[10] These pathogenic variants lead to loss-of-function of the *COCH* gene (i.e., cochlin is not produced or in such small amounts that its function is negligible) and homozygote carriers that present with congenital moderate SNHL presumably not associated with vertigo or balance problems. Longer follow-up is needed to identify a long-term impact on vestibular function.[10-12]

Phenotype of DFNA9 and DFNB110

An overview of the different *COCH* mutations causing DFNA9 and DFNB110 and their associated phenotypic appearance can be found in Tables 1 and 2, respectively.[7,10-23] The inheritance pattern is shown in Figure 1.

DFNA9.

Autosomal dominant variants (DFNA9) show some phenotypic variability according to their location in *COCH*, as upstream located variants (Limulus factor C, cochlin, lung gestational protein (LCCL) domain), such as the p.Pro51Ser variant, express with a more delayed onset of SNHL (fourth decade) and with more pronounced vestibular signs compared to the more downstream located variants (von Willebrand factor A-like (vWFA2) domain: onset of SNHL in the second decade; no vestibular signs).[19] The most typical characteristics of DFNA9 are late-onset progressive SNHL combined with vestibular deterioration. Most variants have a limited number of carriers, described in only a few families. The p.Pro51Ser variant, in contrast, is highly prevalent in Belgium and the Netherlands, probably exceeding 1000 carriers. Recently, large-scale prospective phenotyping studies have been initiated to better define its natural evolution.[24,25] The following characteristics have been observed in 111 p.Pro51Ser carriers:

1) down-sloping SNHL from high toward low frequencies. However, the hearing thresholds at the highest frequencies (6 and 8 kHz) already start to deviate from age-referenced limits at a very young age, that is, ≥18 years (Figure 2);
2) the annual threshold deterioration is about 2.68 dB per year on average for men and 2.97 dB per year for women;
3) around the age of 49 years, p.Pro51Ser carriers on average already reach hearing levels of 40 dB which further deteriorate to 70 dB hearing level around the age of 59 years (Figure 3);
4) the decline of vestibular function starts simultaneously with that of the hearing function;
5) there is a particular decline sequence in all 5 vestibular sensors eventually leading to bilateral vestibulopathy (BV); and
6) there is a high degree of asymmetry in both hearing and vestibular function across the ages. Because age-referenced limits are more stringent for male subjects, they are less likely to be identified at an early stage compared to the female carriers.

DFNB110

It is caused by homozygous loss-of-function variants in *COCH* with autosomal recessive inheritance. Currently, 7 different variants have been identified.[10-12] The phenotype is characterized by down-sloping moderate to severe SNHL from high toward low frequencies presenting at birth or at prelingual age. No vestibular deterioration has been observed yet. Importantly, heterozygous carriers (i.e., one normal *COCH* allele and one null *COCH* allele) preserve normal hearing and vestibular function, which highlights the non-haploinsufficiency of the *COCH* gene as was observed in Coch$^{+/-}$ mouse models.[26] This finding is relevant with regard to gene therapeutic opportunities.

Magnetic Resonance Imaging Findings in DFNA9 Correlate with Caloric Testing and vHIT

At the advanced stage of otovestibular impairment (sixth and seventh decades), typical radiologic signs, that is, reduction or absence of T2-weighted signal on magnetic resonance images, have been observed in one or more semicircular canals in up to 90% of p.Pro51Ser carriers. In 60%, this also corresponds to narrowing or sclerosis on computed tomography (CT) scans mimicking a previous labyrinthitis in one or both labyrinths.[27] This condition was observed in p.Pro51Ser carriers aged older than 42 years and with advanced stages of auditory and vestibular deterioration. Because similar lesions were also observed in 30% of patients presenting advanced stages of otovestibular deterioration due to other etiologies than DFNA9, it has been

Main Points

- DeaFNess Autosomal Dominant 9 (DFNA9) heterozygous pathogenic variants in the *COCH* gene lead to mutant cochlin in the cochlea (gain of function) which results in postlingual sensorineural hearing loss.
- The p.Pro51Ser variant in the *COCH* gene (DFNA9) is the most prevalent cause of adult-onset hereditary hearing loss in Belgium, which leads to severe-to-profound sensorineural hearing loss and bilateral vestibulopathy in all carriers.
- Cochlear implantation (CI) should be considered as soon as patients no longer benefit from a hearing aid because all carriers show a natural evolution toward deafness, a condition that is associated with a higher risk of accelerated cognitive impairment.
- Cochlear implantation candidates fulfilling the most recent reimbursement criteria in Belgium are anticipated to have better speech understanding after CI when compared to the previous reimbursement criteria.
- The dominant inheritance pattern and non-haploinsufficiency disease mechanism of DFNA9 indicate that suppressing translation of mutant *COCH* transcripts has high therapeutic potential, which might even prevent hearing impairment.

Table 1. Overview of Mutations Causing DFNA9 and Their Phenotype

Reference	Domain	Pathogenic Variant	Ethnicity	Age of Onset of Hearing Loss	Vestibular Disorder	Tinnitus
Choi et al (2013)	LCCL	G38D	Korean	N/A	N/A	No
de Kok et al (1999) Fransen et al (2001)	LCCL	P51S	Dutch/Belgian	Fourth to sixth decade	Instability	No
Khetarpal (2000)	LCCL	V66G	USA	Second decade	Ataxic gait	No
Chen et al (2013)	LCCL	G87V	Chinese	Fourth decade	Vertigo, tendency to fall	Yes
Collin et al (2006)	LCCL	G87W	Dutch	Fourth decade	Instability, vertigo, tendency to fall	No
Kemperman et al (2005)	LCCL	G88E	Dutch	Fourth to sixth decade	Instability, vertigo, tendency to fall	No
Dodson et al (2012)	LCCL	P89H	USA	Congenital	N/A	No
Nagy et al (2004)	LCCL	V104del	Hungarian	Fourth decade	Severe vertigo, nausea, vomiting	No
Kamarinos et al (2001)	LCCL	I109N	Australian	Fourth to fifth decade	Unsteady, unable to walk in the dark	No
Pauw et al (2007)	LCCL	I109T	Dutch	Fourth decade	Instability, vertigo, tendency to fall	No
Burgess et al (2016)	LCCL	L114P	Korean	N/A	N/A	No
Robertson et al (1998)	LCCL	W117R	USA, Korean	Third to fifth decade	None	No
Usami et al (2003)	LCCL	A119T	Japanese	Third decade	Recurrent dizziness/ vertigo	No
Hildebrand et al. (2010)	LCCL	F121S	USA	Second to third decade	Balance problems, vertigo, positional nystagmus, dizziness	Yes
Jung et al (2015)	LCCL	V123E	Korean	Fourth to fifth decade	None	No
Gao et al (2013)	vWFA1	C162Y	Chinese	Second decade	None	No
Gallant et al (2013)	vWFA2	I399_ A404del	USA	Third decade	None	Yes
Street et al (2005)	vWFA2	A487P	Italian	Second decade	N/A	No
Yuan et al (2008)	vWFA2	M512T	Chinese	Fourth decade	None	No
Cho et al (2012)	vWFA2	F527C	Korean	Third decade	None	No
Street et al (2005)	vWFA2	C542F	USA	Second decade	None	No
Yuan et al (2008)	vWFA2	C542Y	Chinese	Second to fifth decade	None	Yes
Smits et al (2021)	vWFA2	A438C	Dutch	Second to fifth decade	Variable vestibular dysfunction	Yes

DFNA9, DeaFNess Autosomal Dominant 9; LCCL, Limulus factor C, cochlin, lung gestational protein; vWFA2, von Willebrand factor A-like.

hypothesized that these typical radiologic signs may be associated with the condition of advanced hearing and vestibular deterioration itself rather than with DFNA9.[28]

A potential hypothesis is that progressive accumulation of fibrous tissue deposits toward the semicircular canals' membranous ampulla might decrease cupula impedance, and therefore, the convective current of the endolymph produced by caloric irrigation (or in real life, angular acceleration in the axis of the semicircular canal) does not stimulate vestibular hair cells to send an afferent signal. The cupula is obstructed in its movement without the need for vestibular hair cell degeneration. The origin of this fibrous tissue remains elusive, although it seems unlikely that deposits would be produced in the cochlea and travel through the small-bore ductus reuniens and the saccular duct. Progressive degeneration of the membranous labyrinth in the utricle might be more likely to produce proteins that dislocate and accumulate at the level of the cupula and eventually prevent the cupula from detecting angular acceleration of endolymph.

Table 2. Overview of Mutations Causing DFNB110 and Their Phenotype

Reference	Domain	Pathogenic Variant	Ethnicity	Age of Onset of Hearing Loss	Vestibular Disorder
Janssensdevarebeke et al (2018)	LCCL	R98X	Belgian/Moroccan	Congenital	None
Mehregan et al (2019)	LCCL	L39X	Iranian	Prelingual	None
Booth et al (2020)	LCCL	R91G	Middle Eastern	Congenital	None
Booth et al (2020)	LCCL	K147X	European	Congenital	None
Booth et al (2020)	vWFA1	V191R	European	Congenital	None
Booth et al (2020)	vWFA1	E211X	Pakistan	Prelingual	None
Danial-Farran et al (2021)	vWFA2	c.984_985dup	Christian Arab	Congenital	N/A

LCCL, Limulus factor C, cochlin, lung gestational protein; vWFA2, von Willebrand factor A-like.

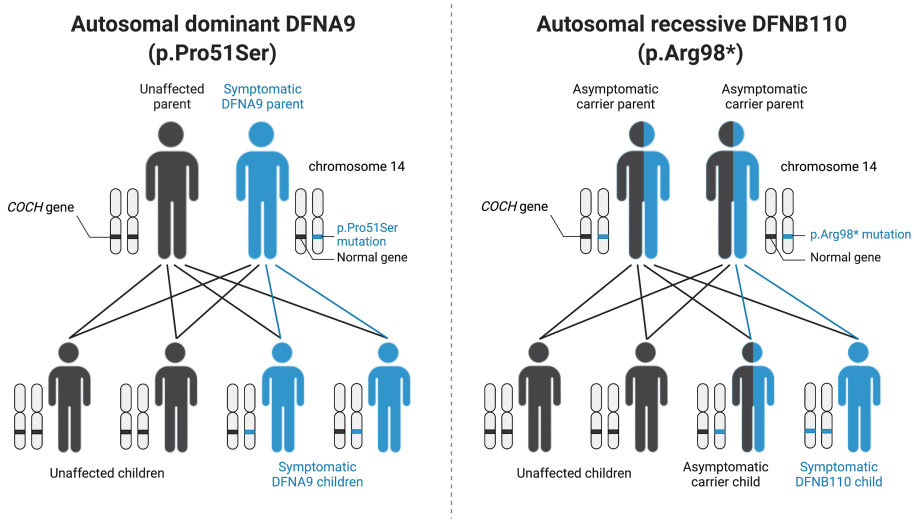

Figure 1. Inheritance patterns of DFNA9 (p.Pro51Ser) and DFNB110 (p.Arg98*). DFNA9, DFNA9, DeaFNess Autosomal Dominant 9.

Functional correlations have been observed between fibrous tissue deposits and vestibulo-ocular reflex measurements including caloric response and video head impulse testing.[28,29] Further research is needed to identify the histopathological correlate of these findings and what the implications are, for example, vestibulo-cochlear implantation (CI).

Impact on Cognition and Incident Dementia

Since the world's population has been dramatically growing and aging, a rising number of people are not only confronted with hearing impairment and vestibular loss but also with cognitive impairment and dementia. A cure or disease-modifying therapy remains currently unknown. A significant association between SNHL and cognitive functioning has been demonstrated in multiple studies.[30,31] Hearing-impaired individuals have a 24% increased risk of accelerated cognitive decline and incident dementia.[32] Because of its high relative risk (RR of 1.9) and prevalence (occurring in 32% of individuals aged 55 years and older), hearing loss has been identified as a significant modifiable risk factor for dementia.[30,33] Due to their close anatomical relationship in the inner ear, there is a high occurrence of hearing loss in people with vestibular dysfunction and vice versa. Vestibular dysfunction, affecting 1 in every 5 older adults, is also associated with cognitive impairment and may even contribute to the onset of Alzheimer's disease, the largest cause of dementia.[34] Although SNHL and BV are associated with cognitive decline, no studies have been reported yet on the impact of DFNA9 on cognition and incident dementia.[35]

Cochlin Physiology and Pathophysiology in the Inner Ear

The *COCH* gene is located at the long arm of chromosome 14 and encodes for cochlin. This protein contains an N-terminal signal peptide (SP), an LCCL domain, 2 vWFA domains, and 2 short intervening domains (ivd).[8,9,36]

Cochlin is expressed in the spiral ligament and spiral limbus of the cochlea and in the area of the stromal fibrocytes in the cristae.[37,38] A recent study identified a role for cochlin in determining calcium carbonate ($CaCO_3$) crystallization on the surface of vestibular epithelia.[39] Abnormal otolith crystallization could potentially explain the reduced magnetic resonance imaging T2 signal observed (rarely even ossification on CT-scan) in the semicircular canals of p.Pro51Ser carriers with severe-to-profound SNHL and BV.

The *LCCL domain*, consisting of a central alfa helix wrapped by 2 beta sheets, has a strong homology with an endotoxin-sensitive serine proteinase (called Factor C) involved in the immune response in the horseshoe crab Limulus where it

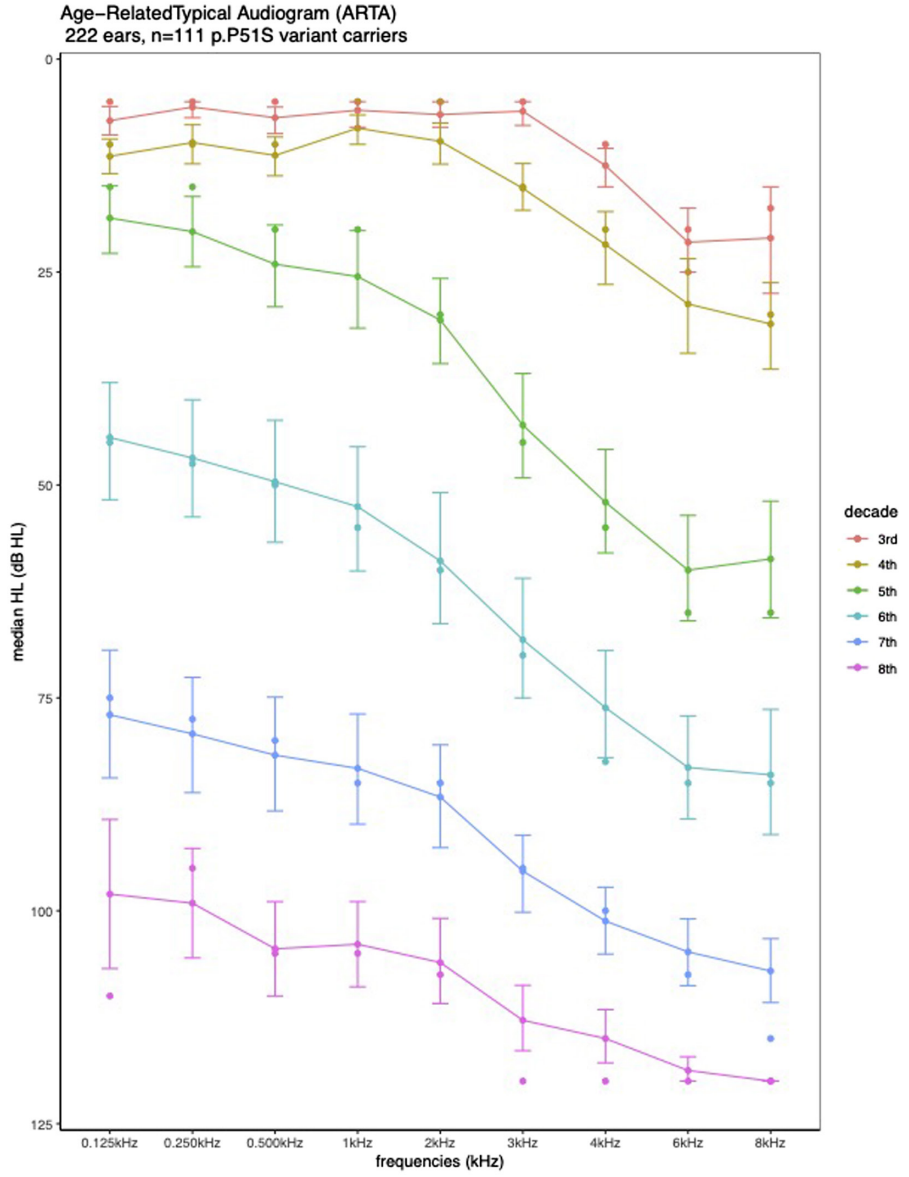

Figure 2. Age-related typical audiograms of 111 p.Pro51Ser carriers, which represents the predicted decline of hearing thresholds across ages for each frequency from 0.125 to 8 kHz, using a non-linear regression model for predicting the relationship between age and hearing threshold as a measure of hearing decline. The 95% confidence intervals were added (binaural averaged thresholds). It confirms the primary decline at the highest frequencies (third decade) and the rapid decline over the following decades.

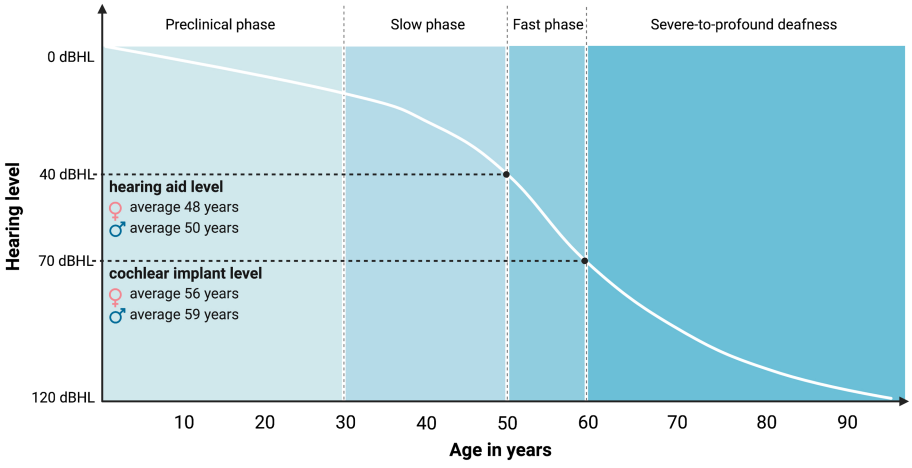

Figure 3. Graphical representation of hearing decline estimations based on JanssensdeVarebeke et al (24).

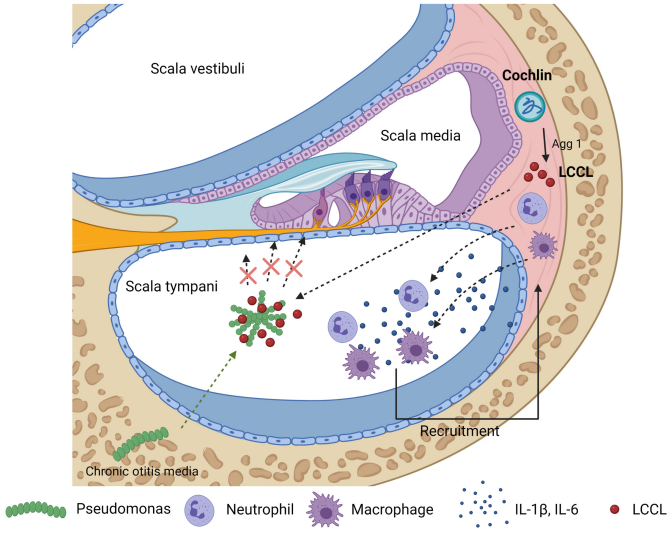

Figure 4. Illustration of how the cleaved cochlin LCCL domain enhances the innate immune response in the inner ear by aggregating infiltrated bacteria and recruiting innate immune cells, protecting the organ of Corti from bacterial invasion. Created using BioRender.com, modified from Jung et al (42).

serves as an antibacterial peptide.[21,40,41] The role of the LCCL domain in the antibacterial immune system of the inner ear has recently been identified (Figure 4). During bacterial infection, the N-terminal LCCL is cleaved by aggrecanase-1 in the extracellular matrix (ECM) of the spiral ligament and secreted into the scala tympani. Once in the scala tympani perilymph, LCCL segregates and entraps invading bacteria by direct interaction, as well as enhancement of recruitment of inflammatory cells and cytokine production. This enriched innate immunity protects essential auditory structures, such as the organ of Corti, from bacterial invasion.[42] The *vWFA2 domain* of cochlin has a structure similar to other vWFA domains: a central beta sheet of 6 strands, flanked by 3 and 4 helices. It has a metal ion-dependent adhesion site motif, which plays an important role in structural stability and ligand binding in vWFA domain-containing proteins.[13] The vWFA domains are generally believed to be involved in maintaining ECM structure due to their affinity for type I, type II, and type IV collagens.[40,42,43]

The exact function of cochlin is not fully understood but as mutations in the *COCH* gene can cause DFNA9 and DFNB110, which are characterized by progressive SNHL (and often vestibular dysfunction in case of DFNA9), it is believed that cochlin is critical for maintaining auditory function.[42] Accumulation of cochlin in the eye has been demonstrated to be associated with glaucoma.[44] As both the anterior eye chamber and the perilymph space of the ear contain fluid, it is speculated that cochlin may have a function in maintaining the shear stress and ion homeostasis of these fluids by interacting with collagen II to build up the ECM.[40,42-44] In the vestibular organ, cochlin is believed to have a role in the structural homeostasis of the vestibule by acting in concert with the bundles of fibrillar collagen II.[45]

An overview of histopathological findings observed in different mutations causing DFNA9 can be found in Table 3.[9,16,26,37,46-49] Fibrocyte degeneration in the spiral ligament is specifically implicated because of the native *COCH* expression in fibrocytes. Mutant cochlin has been found to aggregate and render the extracellular matrix cytotoxic to fibrocytes.

Is DFNA9 Linked with Menière's Disease or Autoimmune Inner Ear Disease?

Patients with DFNA9 share some aspects of the symptomatology observed in patients affected by Menière's disease (MD) including episodes of vertigo, tinnitus, aural fullness, and SNHL. These symptoms are congruent with the MD diagnostic criteria, and because of the positive family history, p.Pro51Ser carriers were often diagnosed as familial MD until the discovery of the *COCH* gene.[50] In contrast, MD patients do not carry pathogenic variants in the *COCH* gene. Cochlin upregulation (and collagen IV downregulation) has been observed in the vestibular end organs from definite MD patients when compared to normal human vestibular end organs.[50,51]

Cochlin has been associated with autoimmune inner ear disease (AIED), a rare disease accounting for less than 1% of all cases of hearing impairment or dizziness.[45] Autoimmune inner ear disease is characterized by a rapidly progressive, often fluctuating, bilateral SNHL over a period of weeks to months.[51] Significantly higher serum levels of anti-cochlin antibodies have been found in AIED patients compared with patients with noise- or age-related hearing loss and healthy controls suggesting an active immune response to the *COCH* protein.[45,52] Also, T-cell responses to cochlin have been reported in AIED patients implicating cochlin in the pathogenesis of AIED.[52]

Although cochlin may be implicated in the pathophysiology of MD and AIED, there is no known correlation with pathological variants in the *COCH* gene, that is, DFNA9 or DFNB110.

Current Treatments and Future Perspectives

Hearing Aids and Cochlear Implantation

Hearing rehabilitation in patients with SNHL includes acoustic hearing aids to amplify sounds for patients with mild-to-moderate SNHL and unilateral CI for cases of severe-to-profound SNHL for whom amplification does no longer lead to meaningful speech perception.[53] Despite histopathological evidence of spiral ganglion degeneration, we have demonstrated earlier that CI in DFNA9 patients results in improvements of speech understanding equivalent to other etiologies of postlingual SNHL.[54] Due to the increased risk of incident dementia in patients with severe-to-profound SNHL, CI should be offered as soon as hearing aids do not offer adequate speech understanding.[34,35,55-62] Recently, a retrospective cohort study was performed by Huinck et al[63] analyzing speech recognition scores in quiet and quality of life of 164 CI recipients 1 year after CI. The objective of this study was to compare a group of patients who fulfilled conservative criteria (>85 dBHL Fletcher index 0.5-1-2 kHz and phoneme scores with hearing aids < 30%) and the remaining group of patients who were outside this conservative criteria (the expanded criteria, similar to the 2019 criteria for reimbursement of CI in Belgium). They observed that patients who qualified for CI using the expanded criteria had better speech recognition performance and quality of life, which is likely due to an earlier transition from hearing aid to CI.

Table 3. Overview of Histopathological Findings Observed in Different Mutations Causing DFNA9

Reference	Mutation	Histopathology Cochlea	Histopathology Vestibular System
Wang et al (2016)	L114P	Acellularity of spiral ligament, distal end of osseous spiral lamina, and base of spiral limbus 50% loss of SGN, some loss of IHC and OHC Deposit of amorphous deposits in spiral ligament, spiral osseous, and limbus	Atrophy of neuroepithelium semicircular canals, maculae sacculi, and utriculi Amorphous deposit in mesenchymal tissue between cribrose area and neuro-epithelium Loss of 50% of Scarpa ganglion cells, degeneration of distal vestibular dendritic fibres
Khetarpal et al (1991) Burgess et al (2016)	G88E	Widespread and diffuse degeneration of the spiral ligament and the spiral limbus and replacement by an eosinophilic, uniformly staining, acellular material Variable losses of IHC and OHC, severe loss of peripheral processes of SGN, loss of SGN	Loss of cellularity of the stroma of maculae and cristae and replacement by an eosinophilic, acidophilic homogeneous substance Severe loss of sensory hair cells, 50% loss of Scarpa ganglions, severe loss of dendritic fibers Otolithic membranes show an irregular granular degenerative change with basophilic staining deposits
Robertson et al (2006)	P51S	Abundant extracellular eosinophilic aggregates throughout the spiral ligament, spiral limbus, and osseous spiral lamina Loss of fibrocytes in spiral ligament and spiral limbus Degeneration of organ of Corti and neural processes in osseous spiral lamina	Abundant eosinophilic deposition present in ampullary stroma with reduction and atrophy of stromal fibrocytes Degeneration of sensory epithelium of the crista, atrophy of ampullary nerve
Khetarpal et al (1991) Burgess et al (2016) Khetarpal (2000)	V66G	Acidophilic homogeneous deposits were noted in the spiral ligaments, limbi, and the spiral laminae There is a severe loss of fibrocytes of the limbus and spiral ligament. Scattered loss of outer hair cells is apparent, the stria vascularisis normal. Loss of SGN, total atrophy of cochlear dendrites in the basal turn, and about 60% in the middle and apical turns were noted A marked excess of a branched microfibrillar/ filamentous structure that fills up the extracellular spaces of the spiral ligament was observed Absence of major fibrillar type II collagen bundles.	Acellularity of stromata of the maculae and cristae Eosinophilic acidophilic deposits in stroma of cristae and maculae. Also, in cribrose area of vestibular nerve Severe loss of hair cells in all cristae and maculae, 50% loss of vestibular neurons
Burgess et al (2016)	W117R	Severe loss of cellularity of the spiral ligament and spiral limbus with replacement by an eosinophilic acellular material Stria vascularis shows partial atrophy Loss of hair cells, severe loss of nerve fibres in the osseous spiral lamina	Loss of cellularity of the stroma of maculae and cristae and replacement by an eosinophilic, acidophilic homogeneous substance Loss of Scarpa ganglions, loss of hair cells in all vestibular end organs

DFNA9, DeaFNess Autosomal Dominant 9; IHC, inner hair cells; OHC, outer hair cells; SGN, spiral ganglion neuron

Vestibular Rehabilitation, Sensory Addition, and Vestibulocochlear Implantation

The symptoms of vestibular loss like imbalance and oscillopsia (the illusory movement of the environment due to loss of gaze stabilization) are currently mainly treated with physical therapy. Unfortunately, physical therapy only has a low yield in BV patients (like DFNA9 patients).[64] Therefore, apart from disease-modifying therapies, 2 other treatment strategies are currently evaluated: sensory addition[65] and a vestibulocochlear implant.[66] Regarding sensory addition, a "balance belt" was developed, which provides vibrotactile feedback of the gravity vector, using a belt worn around the waist. This belt was able to significantly improve balance and mobility in patients with BV. However, the effect on oscillopsia still needs to be determined.[67] A vestibulocochlear implant, or "artificial balance and hearing organ," might be a more comprehensive treatment. This device involves a modified cochlear implant which, next to capturing hearing, is also able to capture motion. Hearing and motion information is then processed and transformed into electrical stimuli. These electrical stimuli are delivered to the vestibulocochlear nerve branches, using surgically implanted electrodes.[68] It was demonstrated that the vestibulocochlear implant is able to influence posture, effectively activate vestibular mediated

reflexes, and provide a functional benefit in patients with BV in a research setting.[69-71] Taking these results into account, a vestibulocochlear implant seems to be a promising treatment strategy in the near future.[72]

Toward Disease-Modifying Therapies Such as Antisense Oligonucleotides?

Recently, innovative inner ear therapies, including in vivo gene therapy, have been reported in rodents as well as in human clinical trials in order to (partially) reverse SNHL by regenerating for example hair cells.[73] In case of autosomal dominant progressive adult-onset SNHL, the aims of future innovative inner ear therapies could be to reverse the symptomatology and to cure the disease, to stabilize or slow down the evolution of symptoms from an annual deterioration rate of 3 dBHL per year to 1 dBHL per year, comparable to presbyacusis.[74] In light of the DFNA9 pathophysiology, suppressing the production of mutant cochlin proteins has high therapeutic potential. Relieving the cochlea from the burden of these toxic proteins, even partially, may halt or delay disease progression. DeaFNess Autosomal Dominant 9 is a particularly interesting disorder for the development of such a therapeutic strategy.

Antisense oligonucleotides (AONs or ASOs in short) present a promising treatment paradigm for DFNA9. Antisense oligonucleotides are short, synthetic pieces of single-stranded RNA and/or DNA nucleotides that act on RNA molecules. A subclass of AONs, called gapmers, is composed of a mixture of DNA and RNA nucleotides that, upon binding to the mRNA, recruit an RNA-cleaving enzyme (RNase H1). In view of this method of action, the AON is often explained to patients as a molecular band-aid. Figure 5 gives a graphical presentation of how AONs can work in DFNA9.

The use of gapmers to induce sequence-specific mRNA cleavage offers a promising treatment strategy for DFNA9. Gapmer AONs have been recently designed that can specifically lower the levels of mRNA molecules that encode p.Pro51Ser mutant cochlin, while leaving those encoding the wild-type (normal) protein intact.[75] To translate these findings to future application in DFNA9 patients, it is important to first investigate how gapmer AONs behave in the mammalian inner ear, if they can indeed delay or avoid the development of hearing loss. Due to the transient effect of synthetic AONs, a safe and efficient method for repeated delivery to the cochlea is needed. There is encouraging evidence that AONs can diffuse over the round window membrane.[75] Further investigations are needed into the intratympanic delivery of AONs and the development of gene therapeutic strategies with a similar goal.

Attitudes Toward Current Treatments and Future Disease-Modifying Therapies

According to the 2017 EuroTrak data, the hearing loss prevalence in Belgium is 11.5% in adults (11.8% in the Netherlands), while the hearing aid adoption rate is only 30.6% in adults (41.1% in the Netherlands).[76-79] Congenital bilateral severe-to-profound SNHL is readily identified at a very young age using neonatal hearing screening and the CI rate in children is high. In contrast, potential adult CI candidates are more reserved

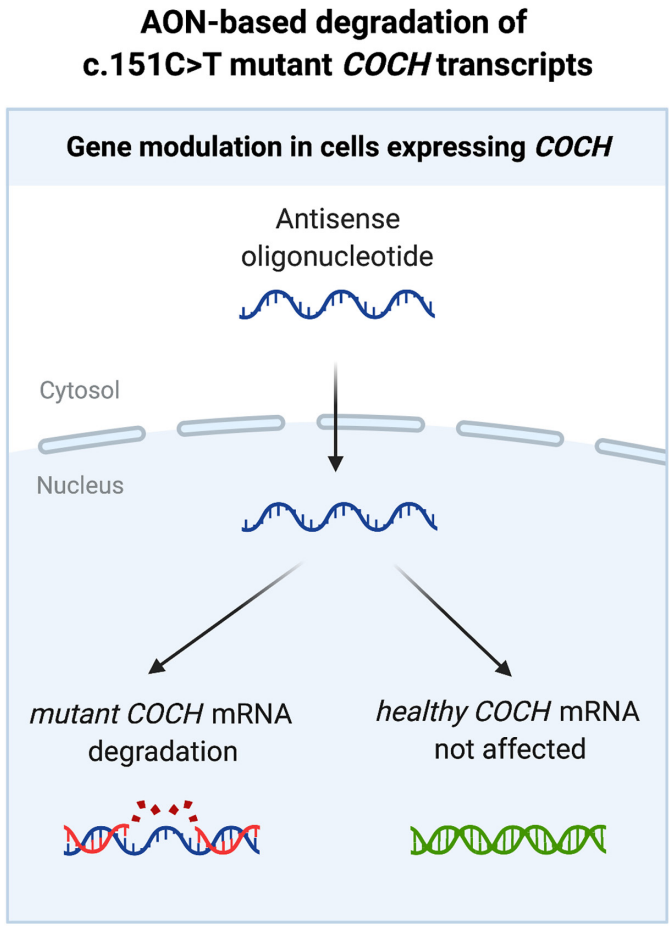

Figure 5. Mechanism of action of antisense oligonucleotides at mRNA level of COCH demonstrating the principle of allele-specificity, that is, target the mutated COCH allele and leave the wild-type (normal) COCH allele intact. Created using BioRender.com.

to adopt this treatment strategy, with less than 10% of those with severe-to-profound bilateral SNHL receiving a CI. This low rate is widespread, regardless of geographical location, and is independent of how health services are organized and country-specific economic output.[80]

The low adoption rates of hearing aids as well as CI raised the question whether or not p.Pro51Ser carriers would present similar behavior to potential gene therapy trials. If disease-modifying therapies would become available for DFNA9 and related autosomal dominant hearing disorders at a certain stage (e.g., clinical trial), we need to consider the attitudes of the patients who suffer from this disease. Therefore, a survey was performed to test various hypothetical scenarios for willingness to participate in future clinical trials involving potential innovative therapies for DFNA9.[81] Overall, most patients would likely consider participation in future innovative inner ear therapy trials, even if it would only slow down the decline of hearing and vestibular function. DeaFNess Autosomal Dominant 9 is a highly relevant population: the awareness of pre-symptomatic carriers of their medical family history, the impact of DFNA9 on hearing and vestibular impairment in daily life as experienced by their next of kin, and the knowledge that they are at risk of carrying the pathogenic variant.

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