The Epidemiology of Pendred Syndrome and Viable Treatment Therapies

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Abstract

Pendred Syndrome is a form of syndromic hearing loss characterized by sensorineural hearing loss, inner ear malformations, and irregularities of the thyroid and temporal bone. Pendred Syndrome is predominantly caused by genetic mutations in SLC26A4, but FOXL1 and KCNJ10 may also be involved. Treatment involves using cochlear implantation to target hearing loss, which is associated with positive outcomes. Treatments for other effects of Pendred Syndrome include anticholinergics or benzodiazepines to treat vertigo and levothyroxine for hypothyroid patients. This review compiles the most recent information about Pendred Syndrome, and it provides a summary of the etiology, pathogenesis, and physical effects of the disorder.

1. Introduction

Hearing loss affects 1–3 children in every 1000 [1]–[3]. Hearing loss is often caused by genetic defects that impair the development of proteins in the hearing pathway. It can be classified as nonsyndromic or syndromic. Nonsyndromic hearing loss, not characterized by other signs and symptoms, affects 70% of patients. Syndromic hearing loss occurs when other organ abnormalities are present, such as effects on the kidneys, eyes, or heart [2]. Over 400 syndromes associated with hearing loss demonstrate different phenotypic and genetic heterogeneity [4], [5].

First discovered in 1896 by doctor Vaughan Pendred, Pendred Syndrome (PS) is a form of syndromic hearing loss accounting for 4% of hereditary deafness [6], [7]. PS is characterized by sensorineural hearing loss, inner ear malformation, vestibular dysfunction, thyroid and temporal bone abnormalities, and abnormal organification of iodide. It is an autosomal-recessive disorder that is caused by rare inherited germline mutations in one of three genes: SLC26A4, FOXL1, and KCNJ10 [8], [9].

2. Genetic Causes

2.1 SLC26A4/PDS gene

The SLC26A4 gene consists of 21 exons located at the DFNB4 locus. It encodes the pendrin protein, which comprises 780 amino acids and is a multifunctional exchanger protein found in the thyroid, inner ear, and kidney. A lack of pendrin causes Pendred Syndrome. The SLC26A4 gene, in patients with Pendred Syndrome, the mutation of the gene leads to an intracellular ionic imbalance [10]. SLC26A4 is expressed by an Iodide/Chloride exchange in the thyroid [11] and Cl-/HCO3- exchange in the inner ear [12]. These exchanges occur during late embryonic and early postnatal development of the inner ear [13]. Pendrin also allows bicarbonate transport into the cochlear endolymph, which bathes the inner ear's sensory cells to help convey information about sound, position, and balance [14]. Mutated pendrin may lead to iodide organification defects [15]. Most patients with PS have pathogenic variants and biallelic mutations in the SLC26A4 gene [8], [9]. Biallelic mutations of SLC26A4 are associated with abnormal iodide organification, increased thyroid gland volume, severe hearing loss, and bilateral enlarged vestibular aqueduct. Despite Pendred being characterized as an autosomal-recessive disorder, a single mutated allele of SLC26A4 presents with less severe consequences, and some may have normal iodide organification, normal thyroid gland volume, less severe hearing loss, and bilateral/unilateral EVA. The prevalence of a mutated SLC26A4 gene in PS patients is estimated at around 90%, which marks SLC26A4 as one of the most commonly mutated genes in Pendred Syndrome [16].

SLC26A4 Effect on Thyroid

The thyroidal iodine organification defect common in PS results in the development of a goiter, which later becomes nodular [17]. Typically, potassium perchlorate transports iodide into thyroid folliculocytes across the basolateral membrane. However, in PS, high amounts of iodide are discharged in the thyroid. Despite Scott et al's proposition that normal thyroid function in NSEVA (nonsyndromic enlarged vestibular aqueduct) patients is the consequence of residual activity encoded by mutated SLC26A4 variants [18], analysis of Ito et al [19] concluded that an enlarged thyroid and PS is dependent on the presence of 2 mutant SLC26A4 alleles, and NSEVA is associated with 1 or 0 mutant alleles [16], [20], [21].

SLC26A4 Effect on Auditory System

An Enlarged Vestibular Aqueduct (EVA) is a vestibular aqueduct exceeding 1.5 mm, measured between the common crus and external aperture. While Pendred Syndrome is characterized by the enlargement of the vestibular aqueduct, not all EVA patients have SLC26A4 mutations. In 50% of EVA populations, no mutations of SLC26A4 are detected [19]. Typically, Pendred Syndrome patients display cochlear hypoplasia secondary to a small or absent cochlear nerve, expansion of the scala media (cochlear duct), or an enlargement of the endolymphatic sac and duct [6], [22]–[24]. Due to additional oxidative stress, abnormal cell stretching, and impaired cell-to-cell communication in the stria vascularis, PS is associated with a reduced endocochlear potential [12], [25]–[27].

Hearing loss begins in the first few years of life, and is sensorineural or mixed, typically asymmetric, ranging from mild to profound. Sensorineural hearing loss occurs after inner ear damage. Mixed hearing loss occurs after damage in the outer or middle ear and in the inner ear or the nerve pathway to the brain. Hearing fluctuates downward following head trauma or barotrauma. In 92% of ears with SLC26A4 mutations, hearing loss fluctuation is observed, and some progressed at 1 decibel/year without environmental factors [16], [28], [29]. The type of mutation does not affect the severity of hearing loss, which is associated with the number of mutant alleles. Two mutant alleles result in more significant and fluctuating hearing loss when compared to those with one or zero mutant alleles [16], [20], [29], [30]. Hearing loss is also not associated with the severity of the enlarged vestibular aqueduct, suggesting that endolymphatic hydrops are not responsible for hearing loss [29], [31].

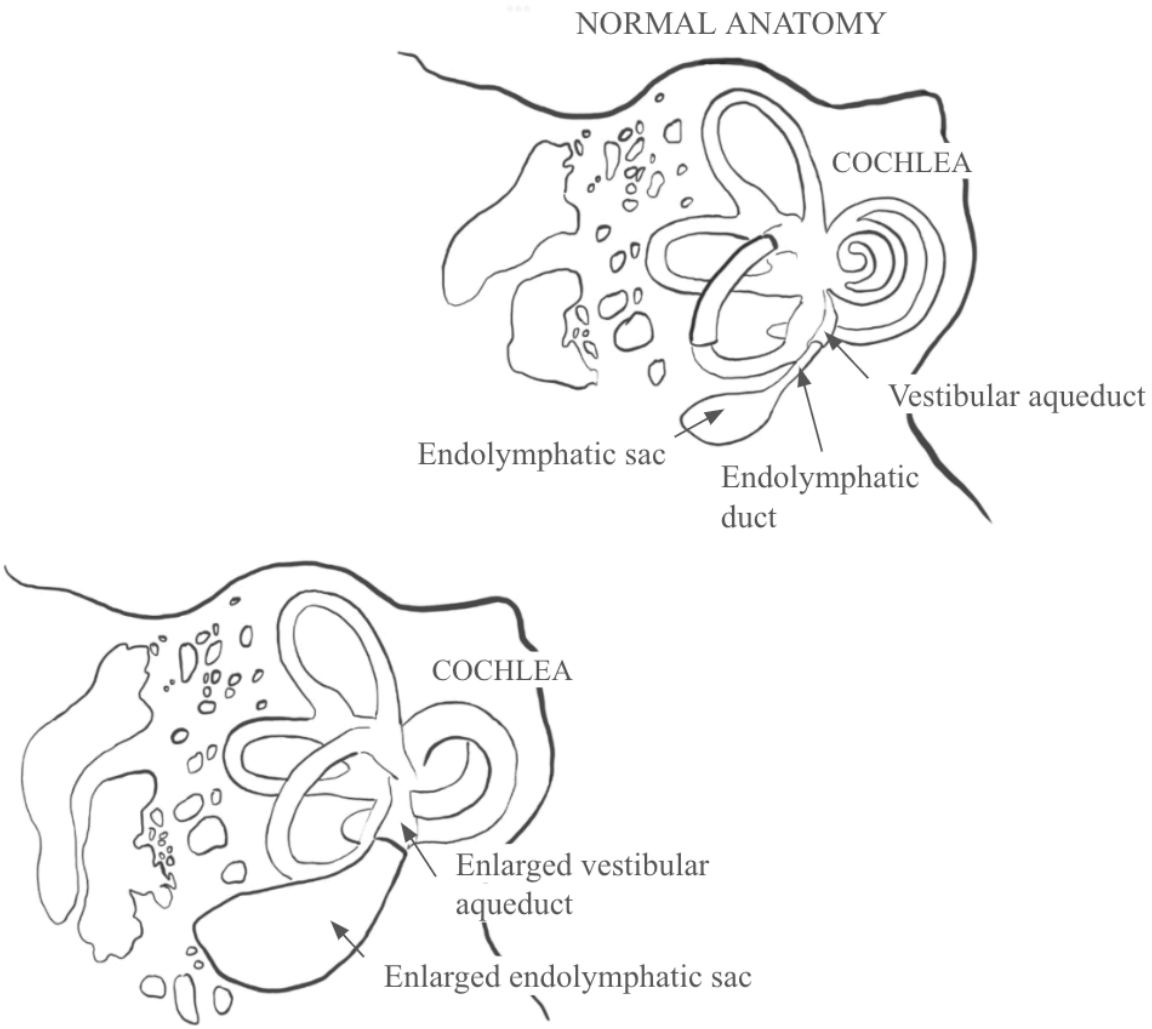

Figure 1: Vestibular aqueduct and endolymphatic sac and duct expressed normally and abnormally. (Reference: [19])

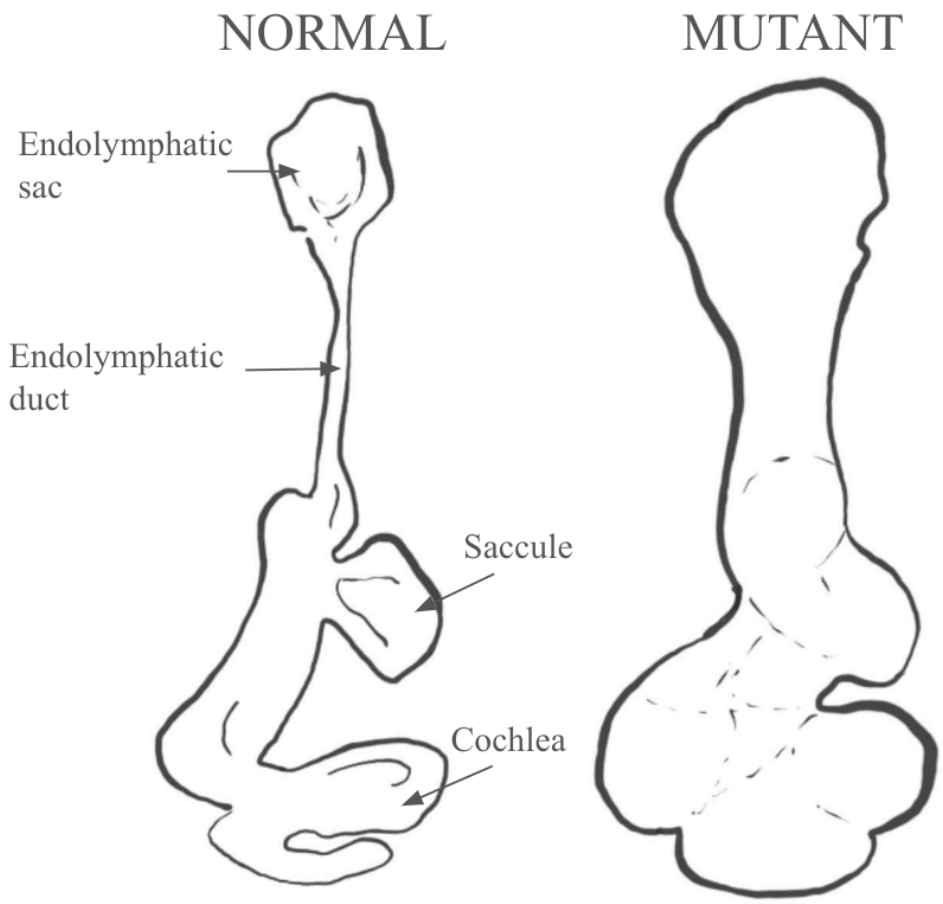

Figure 2: depicts that mutant mice have a larger endolymphatic duct and sac and vestibular aqueduct. Binary transgenic mice have less enlargement compared to mutant mice. (Reference: [13])

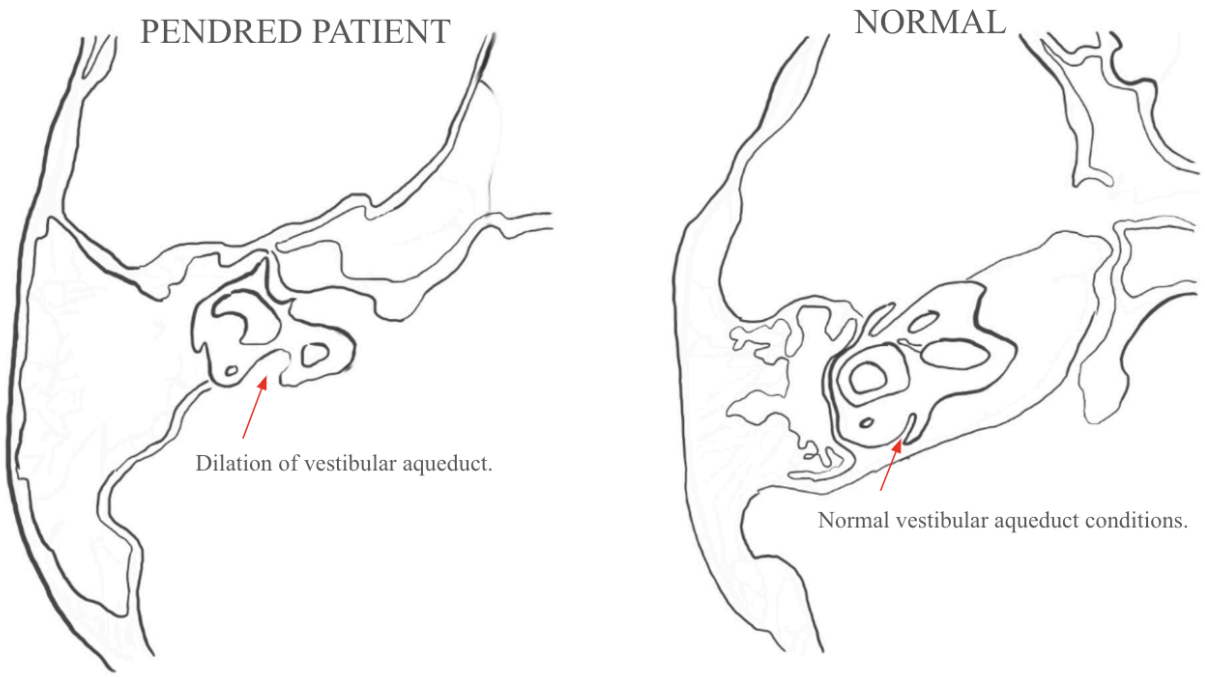

Figure 3: Depicts a normal vestibular aqueduct versus a dilated vestibular aqueduct present in a Pendred patient with mutated EphA2 and SLC26A4. (Reference: [32])

SLC26A4 Mutation Variants

8,647 different mutations of SLC26A4 have been reported, and 487 are classified as pathogenic [33]. The majority of mutations present in Pendred Syndrome are missense mutations, where mutant proteins are retained in the endoplasmic reticulum. Other possible mutations include nonsense mutations, splicing mutations, partial duplications, insertions, and deletions. Highly variable regions of mutations are exon 8, 19, 10, 17, and 15 [34]. These mutations affect iodide transport, which disrupts the protein function due to resulting iodide organification defects [15].

Common mutations include E29Q, V138F, G209V, L236P, IVS8+1 G>A, R409H, T410M, T416P, Y78C, T193I, F355S, L445W, Y530H, S694P, D724N, 2127delT [16].

Effect of Mutated Alleles on the SLC26A4 Genes (Ranked In Severity of Hearing Loss and Inner Ear Malformation)

Gene	Mutated Allele #1	Mutated Allele #2	Mutation Type	Deafness Degree	Evolution	Inner Ear Malformation
SLC26A4	VS8+1 G>A		Splice			EVA
SLC26A4	L117F		Substitution			EVA
SLC26A4	T193I	G209V	Substitution			EVA
SLC26A4	G209V	Y5530H	Substitution			EVA
SLC26A4	L627R		Substitution			EVA
SLC26A4	G209V	L236P	Substitution			EVA
SLC26A4	R409H	L445W	Substitution			EVA
SLC26A4	C565R	T721M	Substitution			EVA+Mondini
SLC26A4	Q421L		Substitution			EVA+Mondini
SLC26A4	M147T	M147T	Substitution		Fluctuating	EVA
SLC26A4	S694P	D724N	Substitution		Fluctuating	EVA
SLC26A4	G740V	Del5nt	Substitution & Deletion		Fluctuating	EVA
SLC26A4	V138F	V138F	Substitution		Fluctuating	EVA+Mondini
SLC26A4	M283I		Substitution	Mild		EVA
SLC26A4	F335L		Substitution	Mild		EVA
SLC26A4	G740V	Del5nt	Substitution & Deletion	Mild	Fluctuating	EVA
SLC26A4	Y530H		Substitution	Severe		EVA
SLC26A4	IVS 14+1 G>A	IVS 18+1G>A	Insertion	Severe		EVA
SLC26A4	IVS12−3 Ins CAGT		Insertion	Severe	Fluctuating	EVA
SLC26A4	T307M; G740V	Y530H	Substitution	Severe	Fluctuating	EVA+Mondini
SLC26A4	T410M		Substitution	Severe	Fluctuating	EVA+Mondini
SLC26A4	IVS 11+1 G>C	V690A	Insertion & Substitution	Severe	Fluctuating	EVA+Mondini
SLC26A4	F355S		Substitution	Severe	Progressive	EVA
SLC26A4	129insC	T721M	Insertion & Substitution	Severe	Progressive	EVA
SLC26A4	S133T	S133T	Substitution	Profound		EVA
SLC26A4	G209V	G209V	Substitution	Profound		EVA
SLC26A4	G209V	G209V	Substitution	Profound		EVA
SLC26A4	V609G		Substitution	Profound		EVA+Mondini
SLC26A4	S391N		Substitution	Profound	Fluctuating	EVA
SLC26A4	E29Q	L445W	Substitution	Profound	Fluctuating	EVA
SLC26A4	T416P	2127 delT	Substitution & Deletion	Profound	Fluctuating	EVA
SLC26A4	Y78C	Y530H	Substitution	Profound	Fluctuating	EVA+Mondini
SLC26A4	M1T	L445W	Substitution	Profound	Fluctuating	EVA+Mondini
SLC26A4	T416P	2127 delT	Substitution & Deletion	Profound	Fluctuating	EVA+Mondini
SLC26A4	IVS8+1 G>A		Splice	Profound	Progressive	EVA
SLC26A4	G209V	G209V	Substitution	Profound	Progressive	EVA
SLC26A4	M147T	M147T	Substitution	Profound	Progressive	EVA
SLC26A4	M147T	M147T	Substitution	Profound	Progressive	EVA
SLC26A4	T193I	G209V	Substitution	Profound	Progressive	EVA
SLC26A4	S28R	S391R	Substitution	Profound	Progressive	EVA
SLC26A4	I199T		Substitution	Profound	Progressive	EVA
SLC26A4	G209V		Substitution	Profound	Progressive	EVA+Mondini
SLC26A4	T99R		Substitution	Profound	Progressive	EVA+Mondini
SLC26A4	IVS1-3-2 A>G	L445W	Insertion & Substitution	Profound	Progressive	EVA+Mondini
SLC26A4	G209V	IVS8+1 G>A	Substitution & Insertion	Profound	Progressive	EVA+Mondini

Figure 4: (Reference: [16]).

Variants in mutations also reflect ethnic differences. Three founder mutations in SLC26A4 have been identified in Caucasians, which are c.707T>C, c.1246A>C, and c.1001+ 1G>A mutations. The majority of mutations reported in China included the C.919-2 A>G mutation and C.2168A>G mutation. In South America and North America mutations C.1826T>G and C.1001 + 1G>A are more common, whereas C.2168A>G mutations are present in Koreans [35]. Recently, CEVA (Caucasian EVA) has been discovered to be a recessive mutant allele that is present in a pathogenic variant of SLC26A4, and is generally identified in Caucasian patients. CEVA includes 12 variants in introns or intergenic regions upstream of SLC26A4 [36].

In one case study, a patient was found with a compound heterozygosity variant in a mutated C.1174A>T. This affects amino acid position 535-729 in the STAS domain that affects protein function. In another patient with EVA, p.V690A, a missense mutation, was located on the same amino acid position, however there was no functional defect. One combination of compound heterozygosity (both parent genes harbor different mutations) present in SLC26A4 is the C.1341 + 1G>C mutation and the C.2069T>C, which are classified as disease-causing mutations, or DM. Using these classifications, enlarged vestibular aqueduct syndrome can be detected during neonatal hearing screening [16].

Ephrins and Pendrin

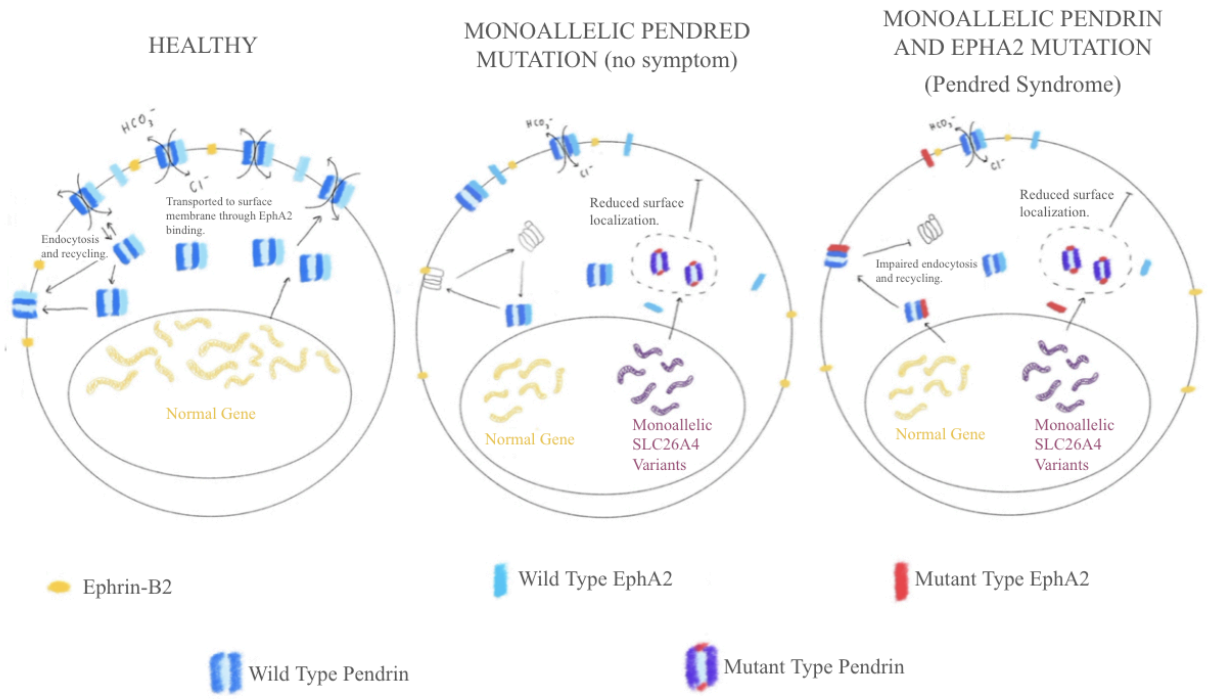

Figure 5: Illustrates effects of SLC26A4 and EphA2 mutations exhibited in Pendred Syndrome (Reference: [32])

EphA2 is another gene implicated in the development of PS. Typically, Pendrin is a binding partner of EPHA2. EPH receptors interact with plasma-membrane-bound ephrin ligands. Ephrins are categorized into two subclasses, A subclass (ligands for GPI-anchored EphA receptors) and B subclass (ligands for EphB1-6 tyrosine kinase receptors). EphB/ephrin-B2 is responsible for regulating vascular endothelial growth factor receptors such as VEGFR, which are responsible for transmembrane protein localization and compartmentalization of cells in epithelial tissue formation. Loss of ephrin-B2 results in abnormalities in the inner ear, disrupting cell proliferation, cell survival, folding of the endolymphatic epithelium, and abnormally formed otoconia [37].

As SLC26A4 is responsible for making Pendrin, a mutated SLC26A4 will impact protein EPHA2's function. EphA2-null and ephrin-B2 deficient mice both exhibit abnormal structures in

epithelial tissues and mislocalization of pendrin in the inner ear and thyroid [32]. However, stimulation of EphA2 and ephrin-B2 causes EphA2 and pendrin to move inside the cell from the outer membrane. This leads to a weaker self-activation of EphA2 compared to when activated with ephrin-A1. Due to EphA2's inability to bind with ephrin-B2, it results in a failure of ephrin-B2 to induce internalization of pendrin. PS patients that bear a mono-allelic mutation of SLC26A4 will typically have point mutations that lead to amino acid substitution in EPHA2 [32].

EphA2 knock-out mice have an enlarged lumen, a decreased thickness of the stria vascularis, and a thyroid goiter, which are all present in PS patients [32]. EFNB2 (inner ear epithelial cell gene) encodes ephrin-B2 (responsible for the growth and morphogenesis of the endolymphatic sac and duct of the inner ear). EFNB2-deficient mice have vestibular-behavioral dysfunction and abnormal endolymph homeostasis, similar to Pendred symptoms [37].

Typically, EphA2 receptors are exclusively activated by ephrin-A; however, if EphA2 is superimposed to EphA4 in a complex with ephrin-B2, EphA2 gains the ability to bind to ephrin-B2 [37].

EPHA2 Mutations in Pendred Syndrome Patients

Missense mutations of the EphA2 gene responsible for Pendred syndrome patients include *SLC26A4*: c.1300G>A (p.434A>T), *EPHA2*: c.1063G>A (p.G355R) and *SLC26A4*: c.1229C>A (p.410T>M), *EPHA2*: c.1532C>T (p.T511M).

2.2 FOXL1

1.4% of PS patients are suspected to have a mutated FOXI1 gene. Some heterozygous variants of FOXI1 are c.77C>T (p.Thr226Ile), c.812G>A(p.Arg271His), c.812G>A(p.Arg271His), which are all rare variants [38]. PS patients have one heterozygous mutation in each of FOXIL and SLC26A4, observed in the SLC26a4+/- and FOXL1+/- double heterozygous mouse model of [38].

The FoxL1 gene is responsible for regulating the transcription of SLC26A4 on the endolymphatic sac and duct. In a Foxl1-null mouse with EVA and deafness, pendrin was only

expressed in the cochlea and vestibular labyrinth. This suggests that pendrin expression in the endolymphatic sac is needed for normal hearing [39].

Gene	Symptoms	Percentage of Participants With A Mutated FOXL1 Gene	Population Origin	Sources
FOXL1	EVA+Mondini Dysplasia	6/372	US/Sweden	Yang et al., 2007
FOXL1	Bilateral EVA	0/38	Taiwan	Wu et al., 2010
FOXL1	EVA	0/44	Australia	Mercer, Mutton & Dahl, 2011
FOXL1	Bilateral EVA & Inner Ear Malformation	1/14	Italy	Cirello et al., 2012
FOXL1	EVA	0/8	China	Lai et al., 2012
FOXL1	Inner Ear Malformation	0/15	China	Chen et al., 2012
FOXL1	Nonsyndromic EVA	0/33	China	Chai et al., 2013
FOXL1	Sensorineural hearing loss	1/29	US	Pique, Lynn M. et al
	Frequency of Pendred Patients With Mutated FOXL1:	***8/553 (1.4%)***		

Figure 6: Effects of Mutations on the FOXL1 Gene & Frequency of Pendred Patients With FOXL1 Mutation (References: [38], [40]–[46])

2.3 KCNJ10

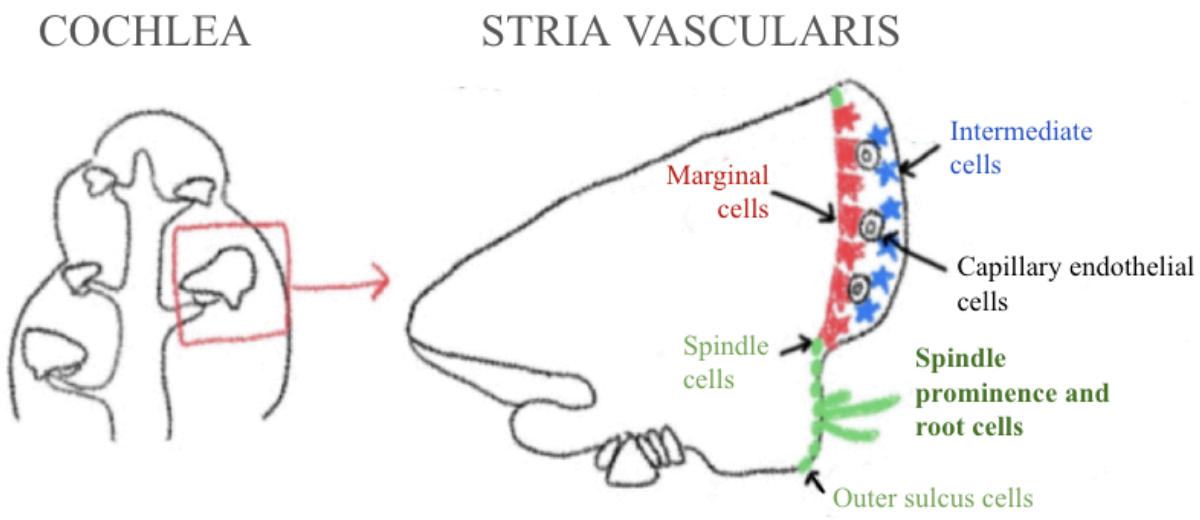

Figure 7: Depicts KCNJ10 and Pendrin expression in the cochlea. KCNJ10 is expressed in intermediate cells inside the stria vascularis. Pendrin is expressed in spindle cells, spiral prominence epithelial cells, root cells, and outer sulcus epithelial cells. (Reference: [10])

3.6% of Pendred Syndrome is caused by a single mutated KCNJ10 gene (1). The frequency of KCNJ10 mutations is inflated by the inclusion of Chinese and Italian probands, since *KCNJ10* variant c.812G>A (p.Arg271His) may be a polymorphism in the Chinese population [38].

Mutations in the KCNJ10 gene can also be associated with SLC26A4 mutations. A possible scenario is double heterozygosity, where the Pendred patient carries single mutations in both SLC26A4 and KCNj10. The harmful interaction of mutated SLC26A4 and KCNJ10 results in inner-ear dysfunction. Pathogenic SLC26A4 mutations result in hypofunction or haploinsufficiency, which results in a reduced expression of KCNJ10, causing a reduced supply of K+ to marginal cells in the stria vascularis [25]. The reduced supply of K+ ions results in fluctuating and progressive hearing loss [20], [48], [49]. This suggests that if strial expression could be maintained through controlling endolymph pH levels or limiting oxidative stress through medical therapy, further hearing loss could be prevented [10].

Possible mutation combinations include a p.R348C / + in KCNJ10 and c.919-2a→G/+ in SLC26A4, which results in an enlarged vestibular aqueduct. Another case is p.P194H / + in KCNJ10 and p.F335L / + in SLC26A4, which results in an enlarged vestibular aqueduct and Mondini dysplasia [38].

Gene	Symptoms	Percentage of Participants With A Mutated KCNJ10 Gene	Population Origin	Sources
KCNJ10	EVA+Mondini dysplasia	2/89	China/US/Canada	Yang et al., 2007
KCNJ10	EVA+Mondini dysplasia	0/44	Australia	Mercer, Mutton & Dahl, 2011
KCNJ10	Bilateral Inner Ear Malformation / family history of Pendred Syndrome / goiter	3/14	Italy	Cirello et al., 2012
KCNJ10	Inner Ear Malformation	0/15	China	Chen et al., 2012
KCNJ10	Nonsyndromic EVA	1/33	China	Chai et al., 2013
KCNJ10	Sensorineural Hearing Loss	2/29	US	Pique, Lynn M. et al
	Frequency of Pendred Patients With Mutated KCNJ10	***8/224 (3.6%)***		

Figure 8: Effect of Mutations on the KCNJ10 Gene & Frequency of Pendred Patients With KCNJ10 Mutation (References: [38], [40], [42], [43], [45], [46]).

3. Treatment

3.1 Cochlear Implantation

A cochlear implant helps generate sound perception in the brain, and a cochlear implant system has an external and internal part. The external part contains a microphone, a speech processor, a battery, and a transmitter, which detects sound from the environment and delivers it to the internal part. The internal device (implanted between the muscle and bone under the ear)

receives transmitted signals sent from the external part and stimulates the cochlea through electrical impulses [50].

Cochlear implantation is frequently referred to as the “treatment of choice” for patients with severe-to-profound sensorineural hearing loss [51]–[53]. Patients must have no anatomical contraindications to be considered for implantation [50]. Absolute indications of cochlear implantation are observed in patients with acute hearing loss after meningitis, deafness, severe visual impairment, and sudden bilateral hearing loss [50].

Cochlear implantation in Pendred Syndrome patients with severe to profound hearing loss results in positive outcomes, with proven benefits in speech perception and speech intelligibility [54]–[56].

Demir et al. concluded that vestibular aqueduct diameter and inner-ear malformations have no impact on audiological outcomes after cochlear implantation [55]. Studies demonstrated that children with SLC26A4 mutations have better outcomes than those with genetically undiagnosed hearing loss, since genetic consequences in Pendred syndrome are in the inner ear, rather than the auditory nerve and central auditory pathways [54], [57]–[59].

Studies support that cochlear implantation should occur before the age of 3.5 years [54], especially in children with fluctuating hearing loss so that speech and language development should not be impaired [60], [61]

One complication of cochlear implantation is the cerebrospinal fluid “gusher”, or the egress of clear fluid upon cochleostomy. However, there are no effects of meningitis or auditory outcomes [62].

3.2 Enlarged Vestibular Aqueduct Treatment

No treatment exists to reduce hearing loss associated with an enlarged vestibular aqueduct. To prevent hearing loss from becoming more severe, patients should avoid head injury by wearing

head protection and avoiding situations that lead to extreme, rapid changes in air pressure such as scuba diving or hyperbaric oxygen treatment [63].

Patients who are experiencing vertigo can be treated with anticholinergics or benzodiazepines. These medications are able to modify the intensity of symptoms by suppressing the vestibular aqueduct [64].

3.3 Hypothyroidism Treatment

Hypothyroidism refers to thyroid hormone deficiency. Overt hypothyroidism is diagnosed once the thyroid-stimulating hormone (TSH) concentrations are above the reference range (0–4-4–0 mIU/L) and free thyroxine concentrations are below the reference range. Mild and subclinical hypothyroidism is defined once the TSH concentrations are above the reference range and free thyroxine concentrations are within the normal range [65].

Symptoms of hypothyroidism include an increase in body-max index, low metabolic rate, fatigue, shortness of breath, muscle weakness, dry skin, hair loss, deterioration of kidney function, and neuropathy. Hypothyroidism has also been reported to cause cochlear dysfunction and decreased hearing [66].

Currently, the preferred treatment for hypothyroidism is levothyroxine monotherapy in solid formulation taken on an empty stomach. The optimal daily dose is 1.5-1.8 μg per kg of body weight [53], [67], [68]. Patients with low body weight or older patients will not be able to withstand dose changes, since it can have substantial effects on serum TSH concentrations [66].

The target of treatment is to normalize TSH concentrations and help with physical and mental complaints [69]. However, 35-60% of patients do not reach the target range of TSH after treatment due to overtreatment or undertreatment [69], [70]. 6% of patients experience

undertreatment (TSH concentrations below 0-1 mIU/L) and 10% experience overtreatment (10-0 mIU/L) [71].

An explanation for persistent complaints after levothyroxine monotherapy could be the treatment itself. This therapy ensures adequate concentrations of circulating thyroxine that are converted to triiodothyronine by deiodination of deiodinase 1 and deiodinase 2. Meanwhile, in euthyroid patients, 20% of circulating triiodothyronine is converted from direct thyroidal secretion [71]–[73].

Another treatment method is using combined levothyroxine-liothyronine therapy. This therapy helps patients with a preference for combination therapy or an improved metabolic profile, however other than that, there are generally no other improved outcomes [74]–[76].

4. Conclusion

It will be important for the otolaryngology field to continue searching for direct strategies to ameliorate Pendred Syndrome abnormalities, due to its rareness. Due to the mutation of the SLC26A4 gene, the lack of pendrin results in unbalanced ion levels. Inner ear malformations affect hearing, and iodide organification defects cause an enlarged thyroid gland. While these symptoms are typically present in most Pendred patients, there is a high clinical variability in the severity of the symptoms, which exacerbates inability to find sufficient treatment.

There is no specific treatment for Pendred Syndrome. Depending on the extent of hearing loss, Pendred Syndrome patients may work to reduce the severity of hearing loss through cochlear implantation or hearing aids. Due to malformations present in the inner ear, patients should avoid head injuries to prevent any worsening of impairment or vertigo.

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