

THE ROLE OF SLC26A4 MUTATIONS IN PENDRED SYNDROME: A GENETIC APPROACH TO HEARING AND THYROID DISORDERS

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ABSTRACT

Pendred syndrome is a genetic disorder characterized by sensorineural hearing loss and goiter, which can lead to hypothyroidism. This review article aims to unravel the genetic puzzle behind this syndrome. Pendred syndrome is one of the well-known syndromic forms of hereditary hearing loss, representing 30% of cases associated with health issues affecting various systems in the body. The syndrome is caused by malfunction in the pendrin protein, which is responsible for ion transport in the thyroid, kidney, and inner ear. The SLC26A4 gene encodes pendrin, and mutations in this gene have been identified as the root cause of Pendred syndrome. Clinical manifestations include progressive and fluctuating hearing loss, inner ear abnormalities such as enlarged vestibular aqueduct and Mondini dysplasia, and goiter. Understanding the genetic basis of Pendred syndrome is crucial for accurate diagnosis and tailored treatment plans.

INTRODUCTION

One of the most prevalent disorders of sensory systems is hereditary hearing loss (HHL). Heterogeneity on three distinct levels—clinical, genetic, and allelic—define it. About 70% of HHL are recognised as non-syndromic HHL as it lacks further clinical manifestations. Syndromic HHL refers to the other 30% of cases, which are associated with health issues affecting the musculoskeletal, digestive, endocrine, neurological, urogenital, cardiovascular, or integumentary systems. Pendred syndrome (PS), Usher syndrome, Waardenburg syndrome, Jervell and Lange-Nielsen syndrome are among the well-known syndromes. PS is the most widely used among them (Chouchen, Mahfood, Alobathani, Eldin Mohamed, & Tlili, 2021).

A relatively common autosomal recessive disorder, Pendred syndrome (PDS) is genetic

disease that is characterized by sensorineural congenital deafness and goiter which can lead to hypothyroidism. (Wémeau et al., 2017) This association of deafness and goiter was first described by Vaughan Pendred in 1896. Morgans and Trotter then first demonstrated that patients with Pendred syndrome have a partial iodide organification defect. (Kopp et al., 2011). PDS is due to malfunction in pendrin, the apical protein (transporter of anion) which mediates chloride (Cl⁻), bicarbonate (HCO₃⁻) hydroxide (OH⁻), and iodide (I⁻) exchange. Pendrin expression in the thyroid and significantly, in the inner side of ear to maintain the potential of endocochlear in the kidney. (Mey, Bille, et al., 2019)

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The *SLC26A4* gene that encodes pendrin, is mainly expressed in the thyroid gland, kidney and inner ear. Pendrin is exclusively localized at the apical membrane of follicular cells facing the colloid. In normal thyroids, where it functions as a Cl^-/I^- exchanger involved in apical iodide efflux to the lumen (Mey, Muhamad, et al., 2019; Pourahmadiyan et al., 2019). Dysfunction of transport of ion affects organification of iodide for the hormone of thyroid biosynthesis that results in goitre, which differentiates it from non-syndromic EVA. However, the majority of patients remain euthyroid. (Li et al., 2020) Two genes, *KCNJ10* and *FOXI1*, have been investigated for their role in the PDS disease spectrum and it has been proposed that digenic mutations in both *SLC26A4* and either *FOXI1* or *KCNJ10* may cause Pendred syndrome. (Klarov et al., 2022)

British physician Vaughan Pendred testified on "the curious relationship of deaf-mutism and goiter occurring in two people of large members of the family". Two sisters who lived in an Irish household with 10 Children had the phenotype. He highlighted that there was no clinical evidence of hypothyroidism as well as that the diagnosis were not explicable by an iodine shortage. Initial studies by Dr. Pendred revealed that goitre and hearing loss coexist, typically occurring in adolescents and childhood. Cases of this disorder started to cluster among families by 1967, indicating that it was genetic. Subsequent research conducted in the 1970s highlighted the connection between thyroid failure and Pendred syndrome, specifically pointing to an iodine organification deficiency that causes goitre.

A significant discovery made in 1997 revealed the root cause was a variant of the *SLC26A4* gene, which encodes for the pendrin protein essential for thyroid iodine transport. Efforts were made in the years that ensued to determine pendrin's function, which revealed that it helps with iodine transportation for the synthesis of thyroid hormones. In the early 2000s, medical professionals became aware of the range of Pendred syndrome symptoms and used genetic testing to make a precise diagnosis. (*Analysis of clinical characteristics of thyroid phenotype in Pendred syndrome based on multiple databases,*

n.d.-a; *Pendred syndrome-100 years of underascertainment?*, 1997)

The identification of temporal bone abnormalities, including EVA and Mondini dysplasia, in individuals with Pendred syndrome contributes to our understanding of the disease and its impact on auditory function. By recognizing and addressing these structural abnormalities, healthcare professionals can develop tailored treatment plans and interventions to optimize the hearing outcomes and overall quality of life for individuals with Pendred syndrome.

Clinical Features of Pendred Syndrome

The primary clinical indicator of Pendred syndrome is sensorineural deafness. Usually, the loss of hearing is associated with inner ear malformations, hearing loss, vestibular dysfunction, and thyroid abnormalities. (Nlm Citation et al., 1998) (Vázquez-Román et al., 2022). Less frequently, the hearing impairment occurs later in childhood and worsens gradually; this can be made worse by exposure to acoustic or barotraumas. The impairment is bilateral, though asymmetry may be present. The hearing loss in Pendred syndrome is described as progressive and fluctuating. This means that the severity of hearing loss may worsen over time, and it can vary or fluctuate in intensity even within short periods. (Honda & Griffith, 2022). (Al-Zaidi et al., 2023)

Pendred syndrome patients have an inner ear abnormality that includes an enlarged Vestibular Aqueduct (EVA) and occasionally a Mondini cochlea. The cochlear twists and the intermediate septum are either totally or partially replaced by a hollow filled with fluid in the Mondini malformation. (Honda et al., 2022; Mey, Muhamad, et al., 2019) These abnormalities are commonly observed in individuals with Pendred syndrome and contribute to the clinical manifestations of the condition. The vestibular aqueduct is a bony canal that connects the inner ear to the cranial cavity. In Pendred syndrome, the vestibular aqueduct is often enlarged, which can be detected through imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI). This enlargement is referred to as enlargement of the vestibular aqueduct (EVA). EVA is a characteristic

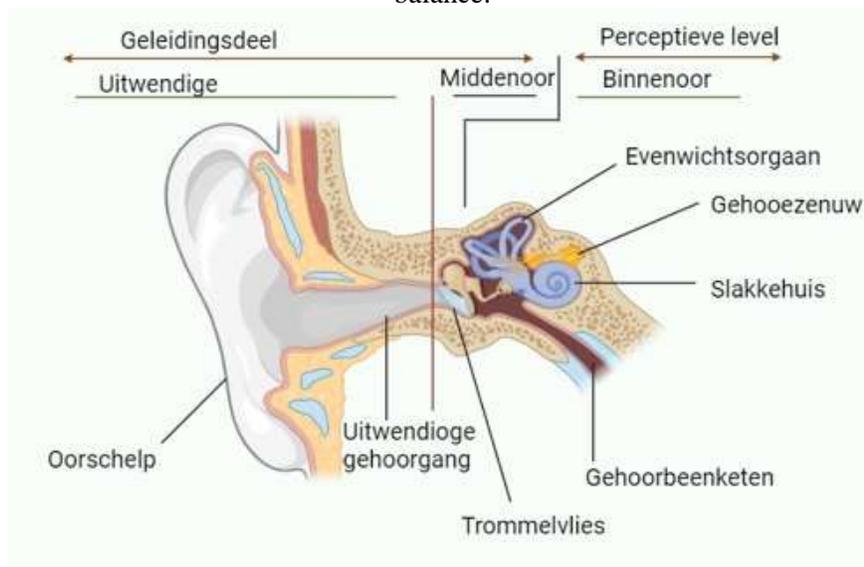
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finding in Pendred syndrome and can be bilateral or unilateral.

In addition to EVA, some individuals with Pendred syndrome may also exhibit Mondini dysplasia. Mondini dysplasia is a specific type of malformation of the cochlea, which is the spiral-shaped structure in the inner ear responsible for hearing. In Mondini dysplasia, the cochlea is characterized by incomplete development and abnormal shape, resulting in a shorter cochlear structure with fewer turns than normal. These temporal bone abnormalities, such as EVA and Mondini dysplasia, can contribute to the sensorineural hearing loss observed in Pendred

syndrome. The enlarged vestibular aqueduct can predispose individuals to fluctuations in hearing loss, as changes in fluid pressure within the inner ear can affect the function of sensory hair cells responsible for hearing. Due to increased newborn hearing testing requirements, a newborn's hearing impairment may now be identified during screening. Otoacoustic Emission (OAE) and Auditory Brainstem Response (ABR) testing can be used to formally diagnose hearing loss. (*Analysis of clinical characteristics of thyroid phenotype in Pendred syndrome based on multiple databases*, n.d.-b)

Figure: Anatomy of the ear, illustrating the outer, middle, and inner ear structures involved in hearing and balance.



Another key characteristic of Pendred syndrome is the presence of goiter, which refers to the enlargement of the thyroid gland. Goiter in Pendred syndrome typically manifests during the second decade of life, although the exact timing can vary among individuals. The size of the goiter can also range from mild to more pronounced, depending on factors such as iodide intake and the specific impact of the genetic mutation on pendrin function. (Honda & Griffith, 2022)

The thyroid gland is a butterfly-shaped gland located in the neck, and its primary function is to produce hormones that regulate metabolism and growth in the body. In Pendred syndrome, the enlargement of the thyroid gland is thought to be

related to the disrupted function of pendrin, which is expressed in the thyroid gland. Pendrin plays a role in the transport of iodide, an essential component for thyroid hormone synthesis.

The impaired transport of iodide caused by mutations in the SLC26A4 gene leads to alterations in thyroid hormone production and regulation. These disruptions can result in the enlargement of the thyroid gland. The severity of goiter can vary among individuals with Pendred syndrome. Factors such as iodide intake and the specific genetic mutation can influence the size and growth of the goiter. Regular monitoring of thyroid function and imaging studies, such as ultrasound, may be performed to assess the size and

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progression of the goiter over time.(Abeal, 2008).Weight gain, bowel issues, rough hair and skin, low energy, drowsiness, a protruding abdomen, a drop in body temperature, delayed growth, and intellectual disability are the disease's clinical signs. Since there is presently no approved treatment for this medical condition, it is of the utmost significance to look into the genetic components that contribute to it.(Al-Zaidi et al., 2023)

Pendred syndrome exhibits variability in the development of goiter and hypothyroidism among affected individuals.(Scott et al., 2000) The severity of these conditions is influenced, in part, by nutritional iodide intake. Low iodide intake can lead to hypothyroidism, while high iodide intake usually results in a euthyroid state. It is worth noting that pendrin expression in the kidney also functions as a chloride/bicarbonate exchanger, but its impact on renal function appears to be less significant compared to its roles in the inner ear and thyroid gland. (Kopp & Bizhanova, 2011)

Temporal bone abnormalities, particularly enlargement of the vestibular aqueduct (EVA) or Mondini dysplasia, are common findings in individuals with Pendred syndrome (PDS). The prevalence of temporal bone abnormalities in PDS can vary depending on the population studied and the diagnostic criteria used.Studies have reported that approximately 80-90% of individuals with PDS exhibit temporal bone abnormalities, with EVA being the most common finding. EVA refers to the enlargement of the bony canal that connects the inner ear to the brain. It is often associated with other malformations of the inner ear, such as Mondini dysplasia, which involves incomplete cochlear development.

It's worth noting that the presence or absence of temporal bone abnormalities doesn't necessarily correlate with the severity of hearing loss or other symptoms in PDS. Some individuals with PDS may have normal temporal bone structure despite having significant hearing impairment, while others may have mild hearing loss despite the presence of temporal bone abnormalities.

In the early days of PDS specification, clinical indicators alone were used to make the diagnosis (e.g., temporal bone deformities, goitre, thyroid

failure, and deafness). But since the primary gene responsible for the disease, SLC26A4, was identified, diagnostic techniques have advanced, and it is now feasible to identify the molecular cause of the patient's illness. The need of a thorough clinical evaluation is underscored by the fact that PDS patients exhibit significant levels of clinical variability and that there is still a limited identification percentage of PDS-causing mutations.

Although Pendred syndrome affects thyroid and hearing worldwide, regional variations exist in its incidence. Most frequent in East Asia, where it can affect up to 1 in 10,000 individuals, it is most likely caused by a particular gene mutation known as c.919-2A>G. While the frequency is significantly lower in Europe (1 in 40,000), the spectrum of mutations implicated is greater. With estimates of 1 in 100,000 to 200,000, the Americas and Africa experience the least, in part because there has been little research on their unique genetic environment. These differences are influenced by several variables, such as founder effects, difficulties in diagnosing conditions, and availability of genetic testing. Sufficient diagnosis and assistance for individuals with Pendred syndrome depend on ongoing study and awareness, since understanding prevalence aids in the distribution of healthcare resources and directs genetic counselling.According to literature data, the detection rate of at least one mutation ranges between 25–50% .In a report ,it was identified that 20.8% of all the patients,an overall *SLC26A4*-mutations carriers rate of 41.7%. (Mey, Bille, et al., 2019; Mey, Muhamad, et al., 2019).

Genetic Basis:

The SLC26A4 gene is located on chromosome 7q31 and consists of 21 exons extending along 57,175 bp. It encodes a protein called pendrin, which is an anion transporter. This gene is expressed in a variety of tissues, including the inner ear and thyroid gland .Pendrin, encoded by the SLC26A4 gene, is responsible for transporting sulfate ions across cell membranes. This transport activity is crucial for maintaining the ion balance within the inner ear and thyroid. Mutations in the SLC26A4 gene can lead to impaired pendrin function, affecting the balance of ions and leading

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to the characteristic symptoms of Pendred syndrome, including hearing loss and thyroid dysfunction (Li et al., 2020) SLC26A4 gene mutations are unvaryingly associated with hearing loss and malformations in inner ear, like the enlargement, bending of the membranous labyrinth (enlarged endolymphatic duct and sac, EED and EES) and of the bony structures. The specific types and locations of mutations in the SLC26A4 gene can influence the severity and clinical features of Pendred syndrome. (Li et al., 2020) Moreover, despite the recessive inheritance of this disease, in some patients with PS the mutational analysis of SLC26A4 gene fails to identify two disease-causing mutations or identify a monoallelic mutation. For these cases, the involvement of other genes can be postulated. (Chow et al., 2017; Hulander et al., 2003)

Other than SLC26A4, the transcription activator gene FOXI1 has been identified as upstream regulator of SLC26A4 transcription. The FOXI1 gene is a transcription factor that plays a vital role in the development of the inner ear, including the formation of the otic vesicle. It is expressed during early embryogenesis and is critical for the proper development of the structures of the inner ear. FOXI1 is required for the proper formation of the otic vesicle, which gives rise to the structures of the inner ear, including the cochlea and vestibular system. It regulates the expression of other genes involved in inner ear development, contributing to the establishment of the normal inner ear structure. Mutations in the FOXI1 gene have been identified in some individuals with Pendred syndrome. These mutations can disrupt the normal function of FOXI1, leading to hearing loss. Moreover, 2 DNA binding domains (FOXI1-DBD 1 and 2) are required for FOXI1-mediated transcriptional activation of SLC26A4. One allelic variant in FOXI1-DBD, interfering with FOXI1 binding and completely abolishing FOXI1-mediated transcriptional activation, (Klarov et al., 2022; Landa et al., 2013)

The KCNJ10 gene is involved in regulating ion transport in the thyroid gland. The gene KCNJ10 encodes an inwardly rectifying potassium (K^+) channel, expressed in a wide variety of tissues but most importantly in the case of Pendred syndrome, in the cochlear stria vascularis which maintains the

endocochlear potential and K^+ -homeostasis. Variants of KCNJ10 have also been considered as a risk factor for seizure susceptibility in genetic association studies and biallelic mutations in KCNJ10 in humans are known to cause a syndromic form of hearing loss. (Abeal, 2008; Klarov et al., 2022; Pique et al., 2014). The GJB2 gene encodes a protein called connexin 26, which forms gap junctions between cells. Variations in the GJB2 gene have been implicated in various forms of hearing loss, including some cases of Pendred syndrome. These variations may act in combination with mutations in other Pendred syndrome-associated genes to contribute to the overall phenotype. (Chow et al., 2017) Nearly one percent of individuals may have PDS due to mutations in other genes, such as FOXI1, KCNJ10, or EPHA2. (Tesolin et al., 2021)

SLC26A4 Gene and Pendred Syndrome

Pendred syndrome is considered a complex genetic disease that can be inherited monogenically or digenically. Biallelic mutations (M2) in the SLC26A4 gene have been identified as a hallmark of Pendred syndrome. These individuals often exhibit incomplete partition type II of the cochlea, enlarged endolymphatic sacs, and vestibular aqueducts. However, approximately 50% of patients with Pendred syndrome have only monoallelic mutations (M1) in SLC26A4, indicating the involvement of other deafness-related genes. Monoallelic mutations (M1) or the absence of mutations (M0) in SLC26A4 result in greater variability in inner ear morphology. Individuals with M1 or no detectable SLC26A4 mutations have less severe hearing loss and more diverse inner ear morphology. This suggests the existence of a digenic inheritance pattern in Pendred syndrome. In individuals with Pendred syndrome, the severity and variability of inner ear morphology and hearing loss are associated with the number of mutations in the SLC26A4 gene.

At location 7q22.3 on chromosomal number 7, the SLC26A4 gene is found. This gene is related to the category of solute carriers (SLC), which is made up of 433 distinct genes. With 780 amino acids, it spans approximately 160 kilobases and it has 21 exons. The anion transporter pendrin, which carries

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iodine and chlorine ions, is encoded by this gene. (Cirello et al., 2012)

At least two synonymous and eight nonsynonymous SNPs are present in the SLC26A4 coding region. Nonsynonymous SNPs are located at pendrin amino acids 9 (serine leucine), 188 (valine isoleucine, Spanish), 189 (serine→alanine, African- - American), 301 (proline leucine, African- f American), 324 (asparagine tyrosine, African-American and sub-Saharan African), 609 (valine glycine, African-American and sub-Saharan African), 687 (asparagine tyrosine, African-American and European) and two in amino acid 740 (glycine→serine, African-American, sub-Saharan African and European; glycine valine, Spanish)(Wémeau & Kopp, 2017)

The researchers identified two novel variants of SLC26A4 that exhibited altered intracellular localization and impaired maturation. This gene has been found to contain more than 300 mutations. The thyroid, kidney, and ear are all affected by a genetic defect in this gene.(Al-Zaidi et al., 2023),The SLC26A4 gene is involved in molecular functions such as sulphate channel activity, bicarbonate, chloride, iodide, sulphate, and oxalate transmembrane transporter activity, and secondary active sulphate transmembrane transporter activity. It also affects biological processes like ion transport (sulphate, mineral anions, bicarbonate, iodide, and oxalate), pH regulation, particularly intracellular pH, membrane potential regulation, transmembrane transport (anion, chloride, and sulphate), regulation of protein localization, and sensory perception of sound. Studies have also revealed that the SLC26A4 gene is a crucial component of the membrane and is actively present in the plasma membrane and extracellular exosome.(Al-Zaidi et al., 2023)

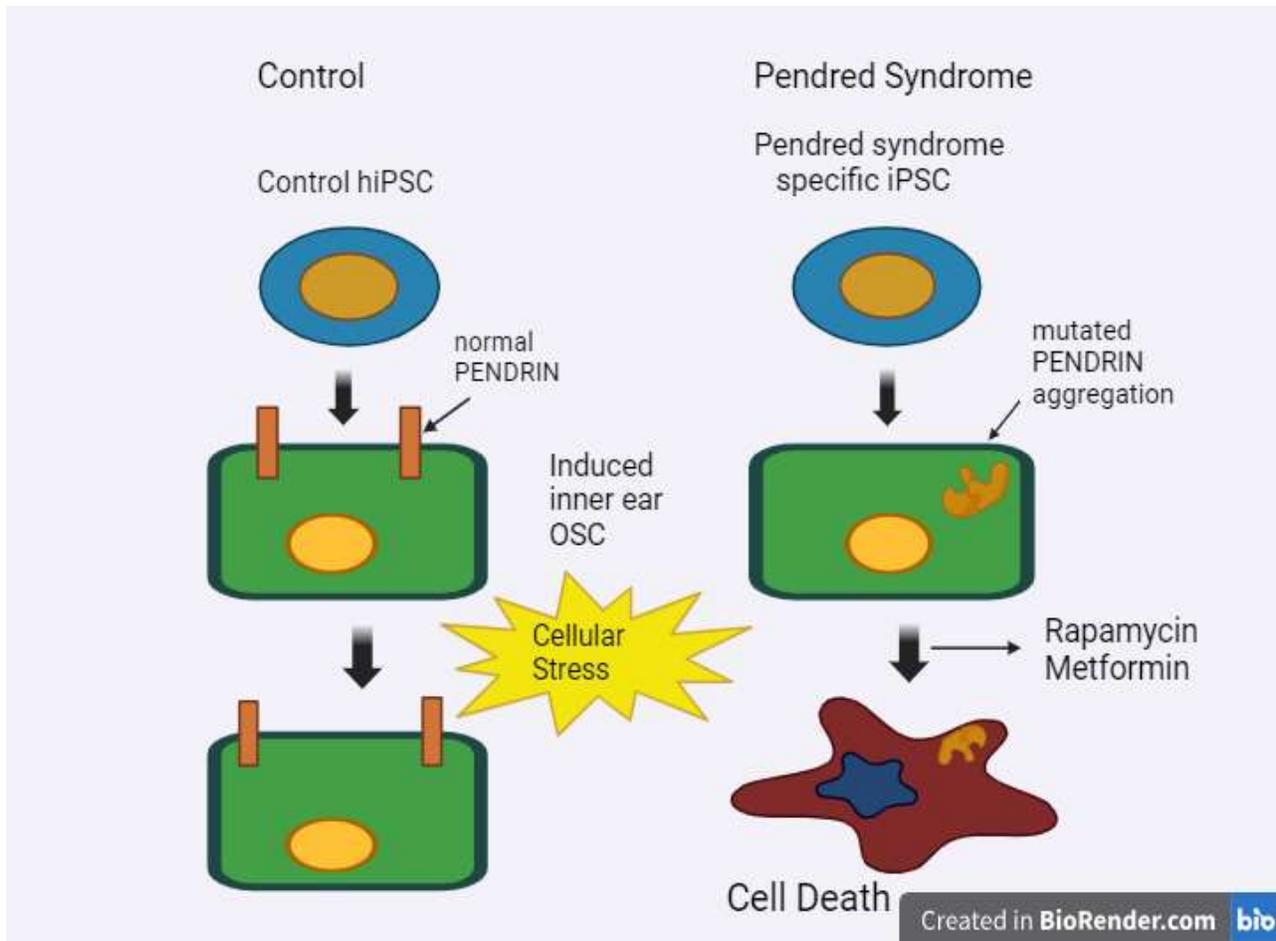
The mechanism by which SLC26A4 mutations affect the inner ear and thyroid involves impaired anion transport and disrupted thyroid hormone synthesis and secretion. In the inner ear, mutations in the SLC26A4 gene can lead to decreased or altered function of pendrin, resulting in imbalances

in ion concentrations in the endolymph. This disruption in ion homeostasis can affect the function and survival of sensory hair cells, leading to hearing loss. In the thyroid gland, SLC26A4 mutations can impair the transport of iodide into the follicular cells, hindering thyroid hormone synthesis. As a result, there can be reduced levels of circulating thyroid hormones, leading to hypothyroidism. The enlarged thyroid gland observed in Pendred syndrome, known as goiter, is thought to be a compensatory response to the impaired iodide transport.

The pendrin protein plays a crucial role in transporting sulfate ions (SO₄²⁻) and other anions across cell membranes. In the inner ear, pendrin is expressed in the cells of the cochlea and the vestibular system. It is responsible for maintaining the ion homeostasis in the fluid-filled compartments of the inner ear, such as the endolymph and perilymph. Proper ion balance is essential for the normal functioning of sensory hair cells and the transmission of auditory signals. In the thyroid gland, pendrin is expressed in the follicular cells, which are responsible for the synthesis and secretion of thyroid hormones. Pendrin helps transport iodide ions (I⁻) into the follicular cells, a critical step in the production of thyroid hormones. Iodide is taken up from the bloodstream and transported into the follicular cells, where it undergoes further processing to produce thyroid hormones, including thyroxine (T₄) and triiodothyronine (T₃).

This image compares healthy inner ear hair cells to damaged ones from individuals with Pendred syndrome, a genetic hearing loss disorder. Both oxidative stress and cellular stress appear to contribute to the damage. Rapamycin and metformin, medications with potential protective effects, are also shown.

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Pendred syndrome can result from various types of mutations, including deletions, insertions, and point mutations. The mutations in the *SLC26A4* gene can be classified into different types, including missense mutations, nonsense mutations, frameshift mutations, splice site mutations, and large deletions or insertions. Missense mutations involve a change in a single DNA base, resulting in the substitution of one amino acid with another in the pendrin protein. Nonsense mutations introduce a premature stop codon, leading to a truncated and nonfunctional protein. Frameshift mutations occur when the addition or deletion of DNA bases shifts the reading frame, altering the entire amino acid sequence downstream of the mutation. Splice site mutations affect the correct splicing of the gene, resulting in abnormal protein production. Large deletions or insertions involve the loss or addition of a significant portion of the *SLC26A4* gene, leading to disruption of the gene's function. ("pds," n.d.)

The specific mutation a person carries can influence the severity and clinical features of Pendred syndrome. Some mutations may result in a complete loss of pendrin function, leading to more severe impairments in hearing and thyroid function. Other mutations may cause a partial loss of pendrin function, resulting in milder phenotypes. Additionally, the presence of certain mutations in the *SLC26A4* gene has been associated with the occurrence of a specific inner ear malformation known as Mondini dysplasia, characterized by abnormal cochlear development. (Bizhanova & Kopp, 2010)

Common mutations in the *SLC26A4* gene associated with Pendred syndrome include the c.919-2A>G splice site mutation, the c.2168A>G (p.H723R) missense mutation, and the c.1174delT (p.Leu392fs) frameshift mutation. These mutations can disrupt the structure or function of the pendrin protein, impairing its ability to transport ions effectively.

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Genotype-phenotype correlations in Pendred syndrome are complex, and variable expressivity is observed. This means that individuals with the same mutation can exhibit different clinical manifestations and degrees of severity. Factors such as the specific genetic alteration, environmental factors, and other genetic modifiers contribute to the variability in the phenotype. (Abeal, 2008)

In a research, researchers collected clinical data, performed computed tomography (CT) scans, and conducted audiometric examinations on the participants. Among the 165 patients, CT scans revealed an incomplete partition of the cochlea (IP-1 and IP-2) in six individuals, either in isolation or combined with an enlarged vestibular aqueduct (EVA) anomaly. Molecular genetic analysis was performed on these six patients, focusing on the coding regions of the SLC26A4, FOXI1, and KCNJ10 genes. In the SLC26A4 gene, the researchers identified several pathogenic variants, including c.85G>C p.(Glu29Gln), c.757A>G p.(Ile253Val), c.2027T>A p.(Leu676Gln), and c.2089+1G>A (IVS18+1G>A). They also found the variant c.441G>A p.(Met147Ile), which was previously reported as a variant with uncertain significance but was determined to be potentially pathogenic using *in silico* evidence.

No causative variants were found in the FOXI1 and KCNJ10 genes, and there was no evidence of digenic inheritance involving these genes and monoallelic SLC26A4 variants. And it was found that biallelic SLC26A4 variants were present in 66.7% of patients with IP-1, IP-2, IP-2+EVA, and isolated EVA. Among the SLC26A4-biallelic patients, various types of incomplete partition of the cochlea were observed, with IP-2+EVA being the most common anomaly. This finding has important implications for cochlear implantation, as IP-2 anomaly does not carry an increased risk of "gushers" and recurrent meningitis. (Klarov et al., 2022)

Thyroid dysfunction in Pendred syndrome is believed to be a result of the absence of functional pendrin. Pendrin functions as a chloride/iodide exchanger, facilitating the efflux of iodide from the follicular cells into the colloid lumen. This process is essential for the synthesis of thyroid hormones. In PDS, the loss of pendrin disrupts the normal

iodide transport, leading to impaired thyroid hormone synthesis and subsequent goiter formation. The histopathological features of PDS thyroids have been studied to understand the effects of pendrin deficiency. Studies have reported the presence of hyperplastic changes in the thyroid architecture of PDS patients. However, the expression of thyroid-specific markers, such as thyroglobulin (Tg), thyroid peroxidase (TPO), and thyroid transcription factor-1 (TTF-1), showed only slight changes.

In addition to the absence of pendrin, alternative iodide transporters have been investigated for their compensatory role in PDS thyroids. Studies have found increased expression of iodide channels such as CLC-5, ANO-1, and CFTR in diffuse hyperplastic areas of PDS thyroids compared to highly cellular follicular nodules. This suggests that these alternative iodide transporters may attempt to compensate for the loss of pendrin and maintain iodide transport. Another aspect explored is the presence of primary cilia (PC) in thyroid follicular cells. PC are sensory organelles involved in various cellular processes. In PDS thyroids, alterations in ciliogenesis and changes in the normal ciliary pattern have been observed. The loss of pendrin may be associated with disrupted ciliogenesis, contributing to the morphological changes in PDS thyroids. (Vázquez-Román et al., 2022)

In the kidney, SLC26A4 is expressed in type B as well as in non-A and non-B intercalated cells of the distal convoluted tubule, connecting the tubule and cortical part of the collecting duct. SLC26A4 mRNA expression has also been detected in the endometrium, placenta, prostate, CNS, trachea, pituitary gland and Sertoli cells. (Wémeau & Kopp, 2017)

FOXI1 Gene and Inner Ear Development

The FOXI1 gene, located on chromosome 5q34, encodes a transcription factor that is essential for the expression of the pendrin protein. Some patients with Pendred syndrome have heterozygous mutations in the FOXI1 gene, which impair its ability to activate SLC26A4 transcription. This suggests a connection between mutations in FOXI1 and the development of Pendred syndrome and EVA in humans. (Abeal,

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2008)Foxi1 is an upstream regulator of a chloride/iodide transporter known as pendrin. The absence of Foxi1 leads to a lack of pendrin expression in the endolymphatic duct/sac epithelium. This, in turn, results in defective chloride ion resorption in the endolymphatic duct/sac epithelium. The dysfunction in ion resorption could contribute to the expansion of the endolymphatic compartment and the development of deafness observed.(Wu et al., 2010)Furthermore, the researchers propose that the regulation of pendrin by Foxi1 may involve a specific type of endolymphatic cell called FORE (forkhead-related) cells. These cells express Foxi1, Pds (the gene associated with Pendred syndrome), Coch, and Jag1. Mutations in the FOXI1 gene in humans could potentially lead to a Pendred syndrome-like deafness.(Hulander et al., 2003)

In a study aimed to investigate the potential genetic factors contributing to PDS. The researchers screened 107 individuals with one known mutation in the SLC26A4 gene using a technique called Multiplex Ligation-dependent Probe Amplification (MLPA). They specifically looked for large deletions or duplications in the SLC26A4 gene. They found a heterozygous deletion in exons 4-6 in only one individual, accounting for approximately 1% of the missing mutations in the studied group.

Furthermore, the study explored the involvement of another gene, FOXI1, in PDS. They sequenced the coding regions of the FOXI1 gene in 29 individuals and identified one novel sequence change. The frequency of FOXI1 variants in PDS individuals was found to be low, at 1.4%.Based on their findings and previous research, the authors concluded that large deletions and duplications in the SLC26A4 gene and mutations in FOXI1 play limited roles in the development of PDS. They suggest that other genetic factors are likely contributing to the condition. (Pique et al., 2014)

KCNJ10 Gene and Thyroid Dysfunction

The KCNJ10 gene, also known as the inwardly rectifying potassium channel Kir4.1, is located on chromosome 1q23.2. 1 channel, expressed in a wide variety of tissues but most importantly in the case of Pendred syndrome, in the cochlear stria vascularis which maintains the endocochlear

potential and K⁺homeostasis .It encodes a protein that plays a crucial role in maintaining the electrical balance and function of cells by allowing the selective flow of potassium ions across cell membranes. The KCNJ10 gene is primarily expressed in the brain, inner ear, and kidneys.(Wangemann et al., 2004)

In a research the researchers used mice that either had a functional SLC26A4 gene (SLC26A4^{+/+}) or lacked the gene (SLC26A4^{-/-}). They examined the expression of pendrin and other proteins using immunocytochemistry and quantitative RT-PCR. They also measured the endocochlear potential and the endolymphatic potassium (K⁺) concentration.The findings of the study revealed that pendrin protein was present in various regions of the cochlea, including spiral prominence cells, spindle-shaped cells of stria vascularis, outer sulcus, and root cells. In mice lacking the Slc26a4 gene, the volume of endolymph (fluid in the inner ear) was increased, and the tissue masses in areas normally occupied by specific fibrocytes were reduced.

Importantly, the Slc26a4^{-/-} mice lacked the endocochlear potential, which is generated by the K⁺ channel KCNJ10 localized in intermediate cells. The absence of KCNJ10 protein expression was observed in these mice, despite the presence of KCNJ10 mRNA. The stria vascularis, a tissue critical for maintaining the endocochlear potential, exhibited hyperpigmentation, indicating unalleviated free radical damage.The study also found that the expression of membrane proteins necessary for K⁺ secretion, such as the K⁺ channel KCNQ1, the Na⁺/2Cl⁻/K⁺ cotransporter SLC12A2, and the gap junction GJB2, was unaffected in Slc26a4^{-/-} mice. Additionally, the endolymphatic K⁺ concentrations were normal. Based on these observations, the researchers concluded that dysfunction of pendrin leads to a loss of KCNJ10 protein expression and subsequently the loss of the endocochlear potential, which may be the direct cause of deafness in Pendred syndrome.

In the context of Pendred syndrome, which is characterized by hearing impairment, goiter, and enlarged vestibular aqueducts (EVA), the KCNJ10 gene has been of interest as a potential contributor to the disorder. Mutations in KCNJ10 have been

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hypothesized to affect the ion balance in the inner ear, leading to hearing loss and vestibular abnormalities seen in Pendred syndrome.

However, the specific role of KCNJ10 mutations in the development of Pendred syndrome is still not fully understood. The research suggests that two variants of the KCNJ10 gene, p.Arg271Cys and p.Arg18Gln, were found in a few patients with Pendred syndrome. These variants were considered polymorphisms rather than disease-causing mutations based on their frequency in the general population. This implies that these variants are likely not directly contributing to the development of Pendred syndrome in these individuals. (Landa et al., 2013)

Other Genes Associated with Pendred Syndrome

The GJB2 gene provides instructions for producing a protein called connexin 26, which is a component of gap junctions. Gap junctions are specialized channels that allow direct communication and exchange of ions and small molecules between neighboring cells. In the context of the inner ear, connexin 26 plays a critical role in the transmission of sound signals.

Mutations in the GJB2 gene can disrupt the normal functioning of connexin 26, leading to impaired gap junction communication between cells in the inner ear. This disruption can interfere with the transmission of sound signals from the hair cells of the cochlea to the auditory nerve and ultimately result in hearing loss. GJB2 mutations do not play a significant role in causing Pendred syndrome. Studies have shown that mutations in both GJB2 and SLC26A4 can co-occur in some individuals with Pendred syndrome. This combined effect might exacerbate the hearing loss symptoms.

However, the role of GJB2 in this context is considered modulatory, meaning it influences the severity of hearing loss rather than being the primary cause of the syndrome. GJB2 itself does not directly cause Pendred syndrome. However, GJB2 mutations can be present in some individuals with Pendred syndrome and may contribute to the severity of hearing loss. (Al-Zaidi et al., 2023)

In a study, EPHA2 and SLC26A4 were shown to be potential Pendred syndrome causative genes. In

certain pathogenic variants of pendrin, the localization of pendrin is disturbed due to a protein complex that EphA2 forms with pendrin. Furthermore, individuals with a mono-allelic mutation of SLC26A4 are found to have point mutations in the EPHA2 gene that result in amino acid substitution. Ephrin-B2 attaches itself to EphA2, causing internalisation and a mild induction of EphA2 autophosphorylation by pendrin. With pendrin, the discovered EphA2 mutations reduce ephrin-B2-induced EphA2 internalisation but not ephrin-A1-induced EphA2 internalisation. The Eph/ephrin system has an unanticipated role in epithelial function, as revealed by the results. (Li et al., 2020)

In a research focussing on identifying the genetic mutations associated with Pendred syndrome in a Malaysian family. The researchers performed whole exome sequencing on two sisters diagnosed with Pendred syndrome and their unaffected parents. The results revealed that both sisters inherited monoallelic mutations in two known Pendred syndrome genes, SLC26A4 and GJB2, from their father. They also inherited a deafness-related gene called SCARB2 from their mother. Additionally, a compound heterozygosity involving the DUOX2 gene was identified in both sisters, which was inherited from both parents.

Mutations in the SLC26A4 gene are considered the hallmark of Pendred syndrome. The document reports that both affected sisters inherited monoallelic mutations in SLC26A4 from their father. One specific mutation identified is ENST00000265715:c.1343C > T, resulting in the amino acid change p.Ser448Leu. These mutations are associated with the development of sensorineural deafness, enlargement of the vestibular aqueduct (EVA), and incomplete iodide organification.

The sisters also inherited a monoallelic mutation in the GJB2 gene from their father. The specific mutation identified is ENST00000382844:c.368C > A, resulting in the amino acid change p.Thr123Asn. Mutations in GJB2 have been linked to both syndromic and non-syndromic forms of hearing loss, including Pendred syndrome. The exact mechanism by which GJB2 mutations contribute to Pendred syndrome is not described in the document.

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The affected sisters inherited a deafness-related gene mutation, SCARB2, from their mother. The specific mutation identified is ENST00000264896:c.914C > T, resulting in the amino acid change p.Thr305Met. SCARB2 mutations have been associated with various forms of deafness. It suggests that this heterozygous mutation in combination with the mutations in SLC26A4 and GJB2 may be causative for the deafness observed in the sisters.

Both sisters share a compound heterozygosity involving the DUOX2 gene. Specifically, two mutations were identified: ENST00000603300:c.1588A > T, resulting in the amino acid change p.Lys530*, and c.3329G > A, resulting in the amino acid change p.Arg1110Gln. These mutations were inherited from both parents. DUOX2 mutations have been associated with thyroid dysfunction. In the case of Pendred syndrome, the presence of these mutations may be correlated with the early onset of goiter.

The researchers postulated that the combination of these three heterozygous mutations (SLC26A4, GJB2, and SCARB2) may contribute to deafness in the affected individuals and warrants further investigation. They also suggested that the compound heterozygous DUOX2 mutations may be correlated with early onset of goiter, a common symptom of Pendred syndrome. In silico tools were used to predict that all the identified mutations were deleterious.

The study concludes that Pendred syndrome in this particular family could be a polygenic disorder resulting from a combination of heterozygous mutations in SLC26A4, GJB2, and SCARB2, which are associated with deafness, as well as compound heterozygous DUOX2 mutations, which are associated with thyroid dysfunction.(Chow et al., 2017)

Diagnostic Approaches

Over the past 10 years, molecular-genetic research in otolaryngology has advanced efficiently, particularly in the areas of otology and brain and cervical tumours. Now, the fundamental research findings are beginning to be used in the clinic. The field of otology has made significant progress in comprehending auditory function. As more and more genes are discovered, the syndromic and non-

syndromic types of hereditary hearing impairment can be further classified according to the underlying genetic abnormalities. The ability to diagnose syndromic hearing loss early has been enhanced. Molecular genetic analysis is still challenging and time-consuming, though. At the moment, only those who may have Pendred syndrome, which is the most common syndrome including hearing loss, are routinely searched for mutations in the related gene SLC26A4. The non-syndromic types of hereditary hearing loss are caused by a wide range of genes and mutations. The most often occurring gene is gap-junction-protein beta2, which codes for connexin 26. In situations of congenital hearing loss, a molecular-genetic investigation of connexin 26 is provided. Sequencing of Wolfram-syndrome gene 1 in familial low-frequency hearing loss is another analysis that has been used in the clinic. Most families with this kind of impairment appear to include members who carry this gene. In the therapeutic realm, gene therapy is not yet an option for treating hearing loss. Molecular-genetic research has shed more light on the many stages involved in the carcinogenesis of head and neck cancer. Clinical uses include creating prognostic indicators and risk profiles for tumour development, as well as creating novel genetic therapy-based treatment plans.(Gürtler, 2003)

The inheritance pattern for PDS is autosomal recessive. Every brother or sister of an affected person has three different chances at conception: 25% to be affected, 50% to be unaffected carrier, and 25% to be unaffected and not a carrier. Genetic testing before pregnancy for embryos at elevated risk, preimplantation genetic testing, and carrier screening for at-risk family members are all feasible when the pathogenic variants unique to the family are identified.

As a result of challenges in diagnosing PDS, the degree of phenotypic variability (i.e., isolated hearing loss versus multisystem involvement), the goiter's often delayed onset and reduced penetrance, and the absence of pathognomonic findings, the true incidence of hereditary hearing loss has not been established, despite initial estimates placing its incidence at 7.5%. Still, PDS is considered to be one of the most prevalent types of syndromic deafness, while mutations in

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SLC26A4 have been identified as the second most common cause of autosomal recessive non-syndromic sensorineural hearing loss globally. (Pique et al., 2014)

Studying the molecular basis of Pendred syndrome and the function of pendrin has provided valuable insights into the pathophysiology of the inner ear, thyroid hormone synthesis, and chloride/bicarbonate exchange in the kidney. By understanding the role of pendrin in these processes, researchers have gained a better understanding of the mechanisms underlying Pendred syndrome and related disorders, contributing to improved diagnosis, treatment, and management strategies for affected individuals. (Kopp & Bizhanova, 2011)

A more sensitive functional assay to detect partial loss-of-function mutations in the SLC26A4 gene, which is associated with Pendred syndrome (PS) and nonsyndromic hearing loss.

The functional assay involved a fluorometric analysis to assess the activity of the SLC26A4 protein. The assay aimed to measure the transport function of the protein, specifically its ability to transport certain ions across cellular membranes.

In the assay, cells were transfected with plasmids containing the normal or mutant forms of the SLC26A4 gene. These cells were then exposed to a fluorescent dye that is taken up by cells when the SLC26A4 protein is active and capable of ion transport. The fluorescence emitted by the dye was measured using a fluorometer.

By comparing the fluorescence levels of cells expressing the normal SLC26A4 protein with those expressing mutant forms, researchers were able to determine the functional impact of the mutations. If a mutation resulted in a partial loss of function, the fluorescence levels would be lower compared to the normal protein but higher than cells with severe loss-of-function mutations.

This assay provided a more sensitive method to detect subtle impairments in the activity of the SLC26A4 protein caused by specific mutations. It allowed researchers to identify partial loss-of-function mutations that may have been missed by other conventional assays. (Cirello et al., 2012)

Previously, the candidate gene screening method was the only method available to identify disease-causing mutations due to limitations in genomic

sequencing technologies. Next-generation sequencing technologies have made it possible to do genome-wide screening at a reasonable cost. Whole exome sequencing (WES) is the best option among them as it exclusively looks at coding regions, which include around 85% of the mutations that cause illness. Genes for other uncommon disorders have also been successfully discovered using WES. (Chow et al., 2017)

Treatment and Management

Management of Pendred syndrome typically involves a multidisciplinary approach, including hearing aids or cochlear implants for hearing loss, monitoring and management of thyroid function, and careful evaluation and counseling for individuals and families regarding the potential genetic implications. (Pryor et al., 2005) (Eshraghi et al., 2020) The variability of deafness in Pendred syndrome, including cases of late onset, suggests that pendrin dysfunction may not be the direct cause of deafness. It is possible that pendrin dysfunction contributes to changes in the expression levels of proteins critical for maintaining normal hearing function. The researchers emphasize the importance of identifying the genes responsible for Pendred syndrome to facilitate early detection, precise molecular diagnosis, and effective family planning for the management of heritable deafness.

the researchers found that the audiograms of patients carrying SLC26A4 mutations exhibited a characteristic slope at the medium and high frequencies. This correlation suggests that specific mutations in the SLC26A4 gene may have an impact on the pattern and severity of hearing loss in individuals with PDS.

Audiograms are graphical representations of a person's hearing ability across different frequencies. In the case of PDS patients with SLC26A4 mutations, the audiograms showed a distinct slope, indicating that the degree of hearing loss varied depending on the frequency of sound. This finding provides new insights into the auditory manifestations of PDS and suggests that certain mutations in the SLC26A4 gene may influence the specific frequencies at which hearing loss is most pronounced. (Wémeau & Kopp, 2017)

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In a research conducted retrospectively and included three groups of patients: the Pendred group, the enlarged vestibular aqueduct (EVA) group, and a reference group with an unknown cause of hearing impairment. Speech perception was measured using a phonetically balanced word list, and quality of life was assessed using the Nijmegen Cochlear Implant Questionnaire. The results showed that children with Pendred syndrome who received cochlear implants had better speech perception compared to the reference group. However, there was no significant difference in speech perception between the Pendred group and the EVA group. Adults with Pendred syndrome performed similarly to the reference group in terms of speech perception. Post-implantation, there was a significant improvement in several subdomains of quality of life, including basic sound perception, advanced sound perception, speech production, and activity limitations.

The study concluded that cochlear implantation can provide speech perception benefits for children with Pendred syndrome. However, adults with Pendred syndrome may have similar outcomes to those with other causes of hearing impairment. The findings suggest that patients with Pendred syndrome can be considered comparable to those with EVA in terms of expected speech perception performance after cochlear implantation. (Van Nierop et al., 2015a)

In a study conducted a retrospective case series involving nine pediatric patients with Pendred syndrome who underwent cochlear implantation at a tertiary academic medical center between 2003 and 2017. All patients included in the study had bilateral sensorineural hearing loss ranging from mild-to-profound to severe-to-profound and had been using hearing aids prior to the implantation procedure. Preoperative imaging results revealed that all patients exhibited bilateral enlarged vestibular aqueducts, which is a characteristic feature of Pendred syndrome. Additionally, eight out of the nine patients had cochlear dysplasia equivalent to Incomplete Partition II, indicating abnormalities in the development of the cochlea.

Despite the presence of these inner ear malformations, the study reported successful

implantation of cochlear electrodes in all patients with minimal complications. The surgical procedure was able to be completed without significant issues or adverse events. The post-operative audiological outcomes of the patients were positive and favorable. Cochlear implantation proved to be an effective and successful treatment option for severe-to-profound hearing loss in children with Pendred syndrome, particularly for those who experienced limited benefit from traditional hearing aids. The implants provided substantial improvements in hearing and enabled the patients to benefit from speech and cognitive development.

Moreover, it emphasized the importance of early intervention with cochlear implantation in children with Pendred syndrome. (Van Nierop et al., 2015b) By receiving cochlear implants at an early age, these children were able to achieve speech and cognitive development comparable to that of individuals with normal hearing. This allowed them to participate in mainstream educational settings and facilitated their learning and communication abilities. Therefore, cochlear implantation is a viable and effective treatment option for severe-to-profound hearing loss in children with Pendred syndrome. Despite the presence of inner ear malformations, successful implantation can be achieved with positive post-operative audiological outcomes. Early intervention with cochlear implants enables these children to develop speech and cognitive skills similar to their peers with normal hearing, promoting their educational and overall developmental outcomes. (Patterson, Gonzalez, & Carron, 2021)

The severity of goiter and hypothyroidism in Pendred syndrome is influenced by the nutritional iodide intake. Low iodide intake exacerbates the impaired iodide transport and organification, leading to more pronounced goiter and hypothyroidism. Adequate or high iodide intake can partially compensate for the deficiency in pendrin function, resulting in a milder or euthyroid state. In terms of management, individuals with Pendred syndrome who develop hypothyroidism, a condition characterized by an underactive thyroid, are typically treated with a standard thyroid hormone-replacement regimen. This helps restore

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normal thyroid hormone levels and can help prevent or reduce the growth of the goiter. In some cases, surgical intervention in the form of total or partial thyroidectomy may be necessary if the goiter becomes significantly large or causes other complications.

It is important for individuals with Pendred syndrome to receive appropriate medical care and monitoring to address the goiter and any associated thyroid dysfunction. This may involve collaboration between endocrinologists, geneticists, and other healthcare professionals to ensure comprehensive management and optimize the individual's thyroid health and overall well-being

Conclusion

The identification of the SLC26A4 gene as the underlying cause has provided valuable insights into the pathology of this syndrome. The malfunction of pendrin, encoded by the SLC26A4 gene, disrupts ion transport in the thyroid, kidney, and inner ear, leading to the clinical manifestations observed in Pendred syndrome. The presence of inner ear abnormalities, such as enlarged vestibular aqueduct and Mondini dysplasia, contributes to the hearing loss experienced by affected individuals. Additionally, goiter development is linked to the impaired function of pendrin in the thyroid gland. Accurate diagnosis of Pendred syndrome requires a comprehensive assessment of clinical features, genetic testing, and imaging studies. While there is currently no approved treatment for Pendred syndrome, understanding its genetic components paves the way for future research and potential targeted therapies. Further studies are needed to explore the variability in goiter development and hypothyroidism among affected individuals, as well as to improve the overall quality of life for individuals with Pendred syndrome

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