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Review

Role of SLC Transporters in Hereditary Hearing Loss

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Hearing loss • Solute carriers • SLC26A4 • Pendred syndrome • SLC transporters

Abstract
This review investigates the role of solute carrier (SLC) transporters in hereditary hearing loss, emphasizing their physiological functions, genetic variations, and contribution to cochlear ion and solute homeostasis. We synthesize the current literature and structural analyses to elucidate transporter mechanisms and their impact on inner ear function. Key findings highlight that loss of function of specific SLC transporters as a consequence of genetic mutation can impair a broad array of physiological processes, ranging from ion transport and fluid volume regulation within the cochlea (SLC26A4), transmitter loading into cochlear ribbon synapses (SLC17A8), cellular uptake of vitamins (SLC19A2, SLC44A4, SLC52A2 and A3), organic cations (SLC22A4), and acetyl-CoA (SLC33A1), and the phenomenon of the cochlear amplifier (SLC26A5), leading to sensorineural hearing loss. These insights underscore the importance of solute transporters in maintaining auditory physiology and reveal molecular pathways underlying hereditary hearing impairments. Understanding SLC transporter dysfunction can inform targeted genetic diagnostics and improve patient outcomes, and ultimately pave the way for the development of therapeutic strategies and personalized interventions for hereditary hearing loss.

Introduction

Hearing loss is the most common sensory disorder and substantially affects the quality of life [1]. According to the WHO, 1 in 5 people, that is, over 1.5 billion people, currently live with some degree of hearing loss; of these, 430 million people suffer from hearing loss in a disabling form. Disabling hearing loss refers to a hearing threshold greater than 35 decibels

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(dB) in the better ear. These figures are projected to increase: in 2050, 1 person in 4, that is, 2.5 billion people, will live with hearing loss, which will be disabling for more than 700 million people [2, 3]. In Europe, roughly 59 million people are reported to live with a degree of hearing loss that affects their daily communication [4].

Many causes may lead to hearing loss, including noise exposure, aging, ototoxic drugs and chemicals, infections, perinatal hypoxia, and trauma [3]. In developed countries, where the contribution of environmental factors is relatively less significant due to better health care, genetic factors play an important role, accounting for at least 50% of cases of hearing loss. Genetic (inherited) hearing loss can be categorized as syndromic (30% of inherited hearing loss forms) or non-syndromic (70% of inherited hearing loss forms). For non-syndromic hearing loss, autosomal recessive inheritance is the most common, accounting for 75-80% of cases; autosomal dominant inheritance accounts for approximately 20% of cases; X-linked, Y-linked, and mitochondrial inheritance account for the remaining 5% of cases [5-7].

In most cases, hearing loss of genetic origin is congenital (present at birth) or has an early onset. If not recognized and treated, this condition can lead to significant developmental, educational, psychological, and social challenges, including delays in speech discrimination (not being able to understand the language) and production (not learning to talk in an intelligible manner), learning deficiencies, inattention, social isolation, and delays in access to rehabilitation programs [8, 9]. Although cases of congenital hearing loss are identified at birth through universal newborn hearing screening programs [10], the early identification of hearing loss with perilingual or early postlingual onset is more challenging.

Genetic hearing loss is a highly heterogeneous condition; a regularly updated, comprehensive list of non-syndromic hearing-loss genes is available on the Hereditary Hearing Loss Homepage [11]. According to this source, the total number of unequivocally established non-syndromic hearing loss genes identified to date is 156, of which 88 cause autosomal recessive and 64 autosomal dominant hearing loss, respectively. In addition, more than 600 syndromes that include hearing loss in the clinical spectrum have been described [12]. Thus, it can be estimated that several hundred genes contribute to hearing loss, making genetic diagnosis a significant clinical challenge.

Mutations in the *GJB2* gene alone, which encodes the protein connexin 26 (Cx26), account for approximately 50% of cases of genetic hearing loss in most world populations [13, 14]. Other genes are rarer. According to many authors, *SLC26A4*, which encodes the anion exchanger SLC26A4/pendrin, ranks second or third [7, 12]. Considering the functions of these two genes, that is, the phenomenon of cochlear potassium recycling for *GJB2* and ion transport in the endolymph for *SLC26A4,* respectively, provides a clear hint at the pathophysiology of hearing loss, which often involves the transport of solutes.

In this review, we provide an overview of the cell- and tissue-level expression, structure, function, physiology, pathophysiology, and genetics of solute carriers (SLCs) associated with genetic hearing loss according to the Deafness Variation Database [15], with a focus on *SLC26A4*. The Deafness Variation Database is a public, expert-curated resource of genetic variation that summarizes all known variants across 224 deafness-associated genes, including non-syndromic and syndromic genes. The scope of this review is to raise awareness among researchers, geneticists, and otolaryngologists of the importance of these transporters in the fundamental physiology of hearing, to identify the molecular mechanisms and physiological pathways involved, and to highlight the gaps in knowledge in this field.

SLC4A11 (BTR1, NaBC1)

The solute carrier family 4 member 11 gene (*SLC4A11*; OMIM #610206; Table 1) encodes an 891-amino-acid integral membrane protein of the SLC4 family, originally identified in 2001 as bicarbonate transporter-related protein 1 (BTR1), also called sodium-coupled borate cotransporter 1 (NaBC1) [16-18]. Initially proposed to function as a bicarbonate

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transporter potentially mediating HCO_3^-, Cl^-, and Na^+ fluxes [16, 19], subsequent studies demonstrated that SLC4A11 supports electrogenic Na^+-dependent transport, including Na^+ and OH^- movement and Na^+/borate cotransport [17, 19]. More recent work indicates that SLC4A11 primarily functions as an electrogenic H^+ transporter activated by NH_3 and alkaline pH [20].

Gene	Protein	Protein function	Functional validation	Hearing loss, non-syndromic	Hearing loss, syndromic (symptoms); inheritance mode
SLC4A11	Bicarbonate transporter-related protein 1 (BTR1); Sodium-coupled borate cotransporter (NaBC1)	Unclear; NH_3/NH_4Cl-stimulated electrogenic H^+ transport; does not transport bicarbonate; Na^+-dependency controversial; probably does not transport borate	Transfected HEK cells and Xenopus oocytes; endogenous transport in bovine corneal endothelial cells. Summarized in [20]	-	Harboyan syndrome (corneal dystrophy with sensorineural deafness); autosomal recessive
SLC17A8	Vesicular glutamate transporter (VGLUT3)	Uptake of glutamate into synaptic vesicles driven by the proton electrochemical gradient	ATP-dependent ^{3}H-glutamate uptake in stably transfected BON[1] cells [215]; H^+-dependent ^{3}H- glutamate uptake in microvesicles from stably transfected PC12 cells [216]; absence of glutamate release from hair cells in knockout mice [217]	DFNA25	-
SLC19A2	Thiamine transporter 1 (THTR1; THT1)	Thiamine (vitamin B1) cellular uptake	Na(+)-independent ^{3}H-thiamine uptake in transfected HeLa cells [58]	-	Thiamin-responsive megaloblastic anemia syndrome (megaloblastic anemia, non-type-I-diabetes mellitus, and sensorineural hearing loss); autosomal recessive
SLC22A4	Organic cation transporter novel 1 (OCTN1)	pH-dependent transport of organic cations, including acetylcholine, carnitine, and ergothioneine	Ergothioneine uptake in stably transfected 293 cells [81]; uptake and efflux of ^{3}H-acetylcholine in OCTN1-reconstituted proteoliposomes [218]; ^{3}H-carnitine uptake in transiently transfected 293 cells [219]	DFNB60	-
SLC26A4	SLC26A4/pendrin	$Cl^-/HCO_3^-/I^-$ anion exchanger	Na^+-independent Cl^- and I^-uptake in Xenopus oocytes or Sf9 insect cells [220]; Cl^-/OH^-, Cl^-/HCO_3^-, and Cl^-/formate exchange in stably transfected 293 cells [221]; bicarbonate secretion in isolated mouse cortical collecting ducts [94]	DFNB4	Pendred syndrome (deafness and goiter); autosomal recessive
SLC26A5	SLC26A5/prestin	Outer hair cell motor protein	Transient capacitive currents in transiently transfected TSA201[2] cells; generation of electromechanical forces in transfected 293 and CHO cells [222]	DFNB61	-
SLC33A1	Acetyl-CoA transporter 1 (AT-1)	Transport of cytosolic acetyl-CoA into the ER lumen	[Ac-^{14}C]Ac-CoA uptake in stably transfected HeLa cells [164]; ^{3}H-CHO Ac-CoA transport in ER membrane fractions of stably transfected CHO cells and reconstituted liposomes [165]	-	Huppke–Brendel syndrome (sensorineural hearing loss, congenital cataracts, developmental delay, intellectual disability, altered copper metabolism); autosomal recessive
SLC44A4	Choline transporter-like protein 4 (CTL4)/thiamine pyrophosphate transporter (TPPT)	Choline uptake in non-neuronal cells; colonic thiamine pyrophosphate (vitamin B1) uptake	Knockdown and overexpression respectively decreased and increased choline uptake in colon and cancer cell lines [176]; ^{3}H-thiamine pyrophosphate in transiently transfected ARPE19[3] cells [175]	DFNA72	-
SLC52A2	Riboflavin transporter RFVT2	Ubiquitous cellular uptake of riboflavin (vitamin B2)	^{3}H-riboflavin transport in transiently transfected 293 cells [182]	-	Brown-Vialetto-Van Laere syndrome (sensorineural hearing loss, bulbar palsy, muscle weakness, optic atrophy, sensory ataxia, and respiratory compromise); autosomal recessive
SLC52A3	Riboflavin transporter RFVT3	Cellular uptake of riboflavin (vitamin B2)	^{3}H-riboflavin transport in transiently transfected 293 cells [182, 223]	-	Brown-Vialetto-Van Laere syndrome (sensorineural hearing loss, bulbar palsy, muscle weakness, optic atrophy, sensory ataxia, and respiratory compromise); autosomal recessive

Table 1. The SLC transporters involved in determining hearing loss according to the Deafness Variation Database [15], protein function, and corresponding clinical phenotype. DFNA, deafness, autosomal dominant; DFNB, deafness, autosomal recessive; SLC, solute carrier. [1]A neuroendocrine cell line secreting serotonin; [2]clones of human embryonic kidney 293 cells that express the simian virus 40 large T-antigen in a stable manner; [3]spontaneously arising retinal pigment epithelia (RPE) cell line

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The *SLC4A11* gene maps to chromosome 20p12 and encodes an approximately 100-kDa protein highly expressed in corneal endothelium and kidney, with additional expression in salivary gland, cochlea, trachea, thyroid, testis, and several brain regions, including hippocampus, cerebral cortex, and choroid plexus [16, 21, 22]. Transcript analyses have also detected expression in the stomach, duodenum, pancreas, and ovary [16, 22].

In the inner ear, detailed localization studies in the mouse cochlea demonstrated that SLC4A11 is predominantly expressed in fibrocytes of the spiral ligament throughout the cochlear lateral wall (Fig. 1) and in vestibular fibrocytes [17, 19]. In the cochlear lateral wall, spiral ligament fibrocytes play a critical role in maintaining ionic and electrochemical homeostasis in the cochlea, contributing to potassium recycling toward the stria vascularis and to the generation of the endocochlear potential in the scala media, which is essential to hearing function [23].

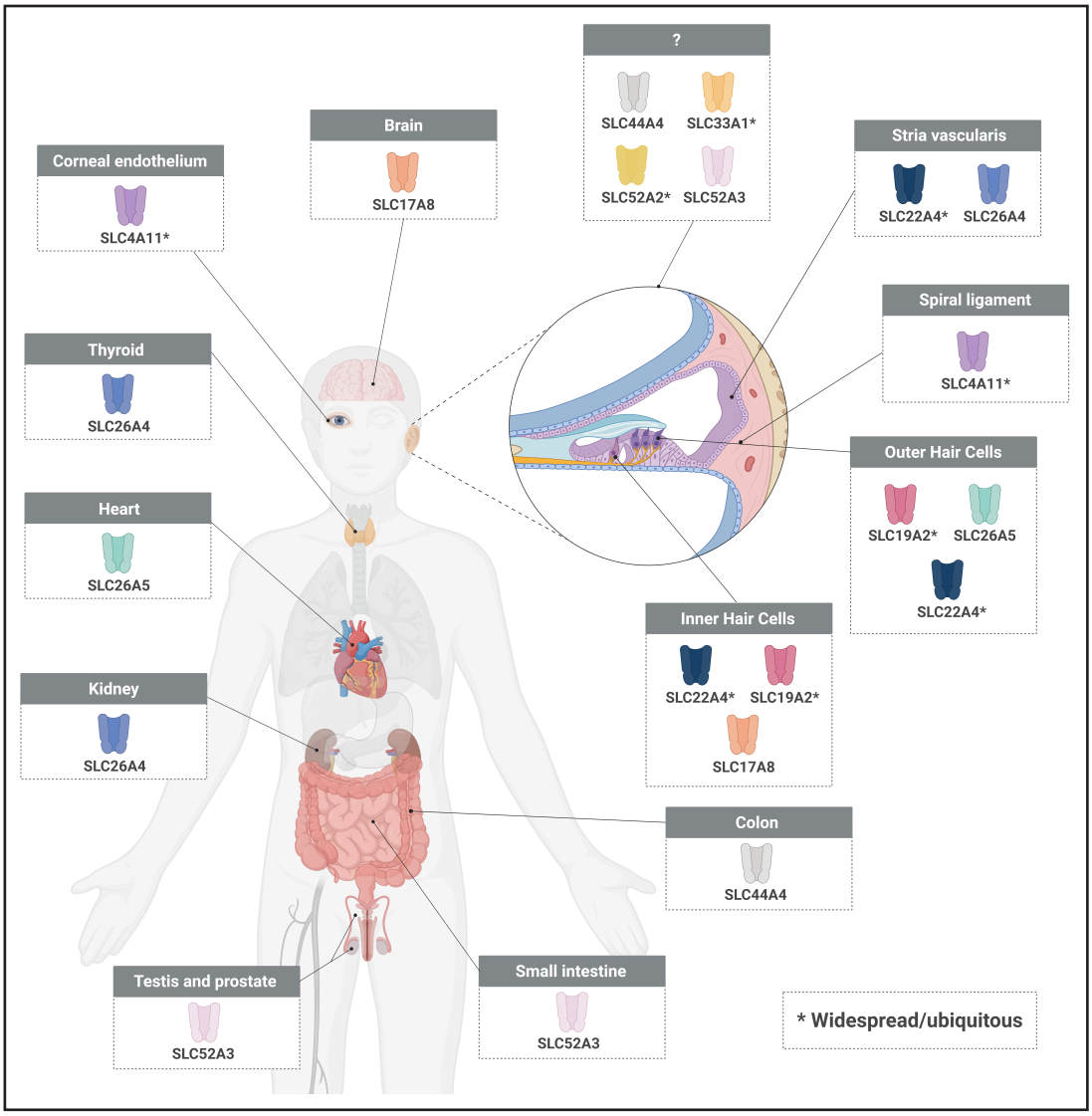

Fig. 1. Tissue expression of the ten SLC transporters implicated in hearing loss. Localization in the inner ear and in tissues important for the syndromic phenotype, or where expression levels are particularly high, is indicated. Transporters for which the expression in the inner ear was not investigated in detail are indicated in the box with a question mark. The asterisks indicate those transporters considered ubiquitous or widespread. For the detailed localization of SLC26A4, refer to Fig. 2.

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Structurally, SLC4A11 is a multi-pass membrane glycoprotein composed of a large cytoplasmic N-terminal domain, a 14-transmembrane-segment core domain, and a short cytosolic C-terminal tail [24]. Cryo-EM analysis of human SLC4A11 revealed a homodimeric architecture capable of adopting inward- and outward-facing conformations; each monomer contains structurally distinct core and gate domains arranged similarly to those of other SLC4 transporters [25]. Structural stability and activity are supported by phosphatidylinositol biphosphate binding at the interface between the cytosolic and transmembrane domains [25]. Proper N-linked glycosylation is required for efficient plasma membrane targeting, and pathogenic variants could impair folding or trafficking, leading to endoplasmic reticulum retention and loss of function [24].

Studies in *Slc4a11* knockout mice illuminated the role of SLC4A11 in the inner ear and other organs. Lopez et al. generated a Slc4a11$^{-/-}$ mouse to specifically investigate the consequences of Slc4a11 deficiency in the sensorineural tissues [17]. The absence of Slc4a11 resulted in significant auditory and vestibular dysfunction, mirroring features of human Harboyan syndrome, which is caused by biallelic pathogenic variants in *SLC4A11*. Mutant mice exhibited elevated ABR thresholds, prolonged response latencies, and reduced waveform amplitudes, indicating impaired neural processing at early stages of cochlear transduction. Higher stimulus intensities were required to evoke responses, and ABR waveforms progressively deteriorated with age, demonstrating a progressive hearing impairment.

Slc4a11 knockout mice were independently generated by Groger et al. through targeted gene inactivation to examine the role of this gene in epithelial ion and fluid transport [19]. This study confirmed Slc4a11 expression in corneal endothelium, the thin descending limb of Henle's loop in the kidney, and fibrocytes of the inner ear. In the cochlea, loss of Slc4a11 led to pronounced morphological alterations in spiral ligament fibrocytes, including intracellular vacuolization and extracellular edema, consistent with disruption of osmotic and ionic homeostasis. Although fibrocyte numbers were preserved, these structural abnormalities impaired lateral wall function and significantly reduced the endocochlear potential. Notably, endolymphatic potassium concentration remained largely unchanged despite the marked reduction in electrical potential. These findings demonstrate that SLC4A11 is essential for the generation and maintenance of the endocochlear potential rather than for the direct regulation of potassium concentration in cochlear fluids, thereby explaining the hearing impairment observed in knockout animals.

In addition to its role in the inner ear, SLC4A11 is required for epithelial ion and fluid balance in multiple organs. In the corneal endothelium, SLC4A11 prevents morphological changes by maintaining sodium chloride balance; loss of function disrupts ion homeostasis, leading to stromal edema, corneal thickening, and progressive visual impairment. In the kidney, SLC4A11 expression in the thin descending limb of Henle's loop supports sodium handling and urine concentration; Slc4a11-deficient mice exhibit impaired urinary concentrating ability, increased urine volume, and altered sodium transport [19]. However, except in extremely rare cases, renal dysfunction is generally not observed in humans with SLC4A11-related disease, suggesting possible species-specific differences, modifier genes, or epigenetic modifications [26].

Biallelic pathogenic variants in *SLC4A11* cause autosomal recessive corneal endothelial dystrophy (CHED, formerly CHED2; phenotype MIM number #217700) and corneal dystrophy with sensorineural deafness (CDPD, CDPD1, or Harboyan syndrome; phenotype MIM number #217400), the latter characterized by corneal endothelial dystrophy associated with progressive sensorineural hearing loss [27, 28]. Variants in *SLC4A11* have also been implicated in autosomal dominant late-onset Fuchs endothelial corneal dystrophy-4 (FECD4; phenotype MIM number #613268) [29, 30]. Pathogenic variants in the *SLC4A11* gene disrupt protein folding and membrane trafficking, resulting in intracellular retention and absence of functional protein at the cell surface [29-31]. The progressive sensorineural hearing loss reported in Harboyan syndrome resembles the auditory dysfunction and reduced endocochlear potential observed in Slc4a11-deficient mice [17, 19, 27].

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Increasing evidence from corneal endothelial models indicates that SLC4A11 deficiency is associated with mitochondrial dysfunction, oxidative stress, impaired autophagy, and ER stress, suggesting that oxidative and metabolic stress responses may participate in SLC4A11-related cellular dysfunction in addition to altered ion homeostasis [32-34].

Although no gene therapy approaches are currently available for *SLC4A11*-associated hearing loss, adeno-associated virus (AAV)-mediated rescue studies in Slc4a11-deficient CHED mouse models support the therapeutic potential of *SLC4A11* gene replacement strategies for corneal disease [35, 36]. However, whether comparable approaches could be adapted to the inner ear remains unexplored.

SLC17A8 (VGLUT3)

Solute carrier family 17, member 8 (SLC17A8; Table 1), also called vesicular glutamate transporter (VGLUT3), is a member of the SLC17 family of vesicular anion transporters that mediates the uptake of glutamate into synaptic vesicles in specific neuronal populations. The human *SLC17A8* gene (OMIM ID *607557) is associated with autosomal dominant deafness DFNA25 (phenotype MIM number #605583) [37].

Within the inner ear, VGLUT3 is strongly expressed in cochlear inner hair cells (IHCs), where it localizes to synaptic vesicles at ribbon synapses contacting spiral ganglion neurons and is largely absent from outer hair cells [37-39] (Fig. 1). Expression analyses in rodent models and human tissue show that SLC17A8/VGLUT3 is also present in selected central neurons, including subsets of serotonergic and cholinergic neurons in the brainstem, hippocampus, and basal ganglia, indicating broader roles in modulatory neurotransmission outside the auditory periphery [40, 41].

VGLUT3 is an integral membrane protein with a predicted topology of 12 transmembrane helices, an N-terminus and C-terminus oriented cytoplasmically, and luminal loops that contribute to the substrate translocation pathways, consistent with the canonical SLC17 transporter fold [42, 43]. High-resolution structures of VGLUT3 itself are not yet available, but homology models of VGLUT1/2 and the recent cryo-EM structures of the related SLC17A5 transporter Sialin support a conserved SLC17 fold operating by an alternating-access mechanism [44], in which conformational changes allow glutamate to bind on the cytosolic side and be released into the vesicle lumen, driven by the proton electrochemical gradient [43, 45].

In the inner ear, VGLUT3 loads glutamate into synaptic vesicles of inner hair cells, enabling rapid, phase-locked synaptic transmission to spiral ganglion neurons that is required for faithful encoding of sound onset and intensity [37, 46]. In the absence of functional VGLUT3, inner hair cells can generate receptor potentials but fail to release sufficient glutamate, leading to a near-complete loss of auditory brainstem responses and a primary synaptic form of deafness despite preserved outer hair cell electromotility [46, 47]. Outside the ear, VGLUT3 functions as a vesicular glutamate transporter in subsets of serotonergic raphe neurons, cholinergic interneurons, and other specialized neuronal populations where it supports glutamate co-release and fine-tunes synaptic plasticity, nociception, and motor control; however, these roles have not yet been clearly linked to human SLC17A8-related disease [40, 41, 48].

Pathogenic variants in *SLC17A8* cause autosomal dominant, nonsyndromic sensorineural hearing loss DFNA25, characterized clinically by post-lingual onset, high-frequency-predominant loss, and gradual progression [37, 49]. The original two unrelated families described with DFNA25 carried a missense mutation (p.A211V) that segregated with hearing loss and was absent in controls, establishing SLC17A8 as the causal gene [37].

Knockout mouse models lacking *Slc17a8* recapitulate a profound auditory deficit with absent or severely reduced auditory brainstem responses, normal distortion-product otoacoustic emissions, and preserved hair-cell morphology, supporting a primary synaptopathy at the inner hair cells-spiral ganglion synapse [37, 46]. More recently,

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homozygous knock-in mice carrying the DFNA25-associated VGLUT3 p.A211V variant have been characterized in greater detail [50]. These animals show progressive hearing loss accompanied by collapse and fusion of inner hair-cell stereocilia bundles, reductions and later distortions of ribbon synapses, and an increased rate of sustained exocytosis at remaining synaptic ribbons, indicating combined defects in mechano-transduction and synaptic transmission [50]. Together with the null-mouse data demonstrating profound deafness, preserved outer hair-cell function, and primary synaptic failure at inner hair cell–spiral ganglion neuron synapses [37], these functional studies support a primary synaptopathy and hair-cell structural pathology as key mechanisms of SLC17A8-related hearing loss. Consistent with these findings, zebrafish mutants lacking Vglut3 ("asteroid") exhibit absent vestibulo-ocular and acoustic startle reflexes, loss of postsynaptic action currents in acousticolateralis neurons, and a reduction in ribbon-associated synaptic vesicles in hair cells, confirming that VGLUT3 is essential for quantal synaptic transmission at hair-cell ribbon synapses [51]. This synaptopathic mechanism, in which impaired vesicular glutamate loading at inner hair cell ribbon synapses leads to primary failure of afferent neurotransmission, is distinct from the ion-homeostasis defects caused by mutations in other SLC transporters, yet functionally converges on disrupted cochlear signal transduction and progressive degeneration of hair cell–neuron communication [52].

Proof-of-concept gene therapy studies targeting *VGLUT3* have demonstrated that cochlear delivery of *Vglut3* can restore auditory function in Slc17a8-deficient mice [46]. In congenitally deaf *Vglut3* knockout mice, adeno-associated virus serotype 1 (AAV1)–mediated expression of VGLUT3 in inner hair cells restored auditory brainstem response thresholds within approximately 2 weeks and partially reversed synaptic ribbon abnormalities at the inner hair cell–spiral ganglion synapse [46]. More recent AAV8-based studies extended rescue to adult mice, including 5-week, 8-week, and 20-week *Vglut3* knockout animals, with recovery detectable as early as day 1 after treatment and sustained improvement in hearing and synaptic morphology [47, 53, 54].

Human DFNA25 is typically isolated (nonsyndromic), inherited in an autosomal dominant pattern (DFNA), and not associated with vestibular or systemic abnormalities in most reported cases. Audiograms in affected individuals usually show down-sloping high-frequency sensorineural hearing loss with relatively preserved low-frequency thresholds in the early stages and progression toward mid-frequency involvement over time [37, 55].

Expanded cohort studies and next-generation sequencing over the last decade have confirmed that *SLC17A8* variants (Table 2) are a rare cause of dominant nonsyndromic hearing loss, with only a small number of additional families identified worldwide. Screening of Korean and other East Asian families with DFNA has identified both missense and splice-site variants in *SLC17A8*, including novel alleles uncovered by whole-exome sequencing, and has emphasized that *SLC17A8* mutations explain only a minor fraction of hereditary hearing loss in these populations [49, 56, 57].

Table 2. Number of variants detected in the SLC genes described in this review and their classification regarding pathogenicity according to ClinVar [224]. Classification is made according to standard criteria established by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) [225] based on population data, computational predictions, functional studies, and segregation studies. Variants indicated as "pathogenic" or "likely pathogenic" are not necessarily implicated in hearing loss

Gene	Number of variants	Pathogenic/likely pathogenic (% of total for the gene)	Benign/likely benign (% of total for the gene)	Uncertain significance/conflicting classifications (% of total for the gene)
SLC4A11	1323	210 (15.9%)	762 (58%)	351 (26%)
SLC17A8	381	13 (3.4%)	128 (34%)	240 (63%)
SLC19A2	553	90 (16.3%)	234 (42%)	229 (41%)
SLC22A4	205	16 (7.8%)	90 (44%)	99 (48%)
SLC26A4	1987	798 (40%)	687 (35%)	502 (25%)
SLC26A5	351	41 (11.7%)	149 (42%)	161 (46%)
SLC33A1	308	27 (8.8%)	111 (36%)	170 (55%)
SLC44A4	320	8 (2.5%)	144 (45%)	168 (52%)
SLC52A2	648	104 (16.0%)	233 (36%)	311 (48%)
SLC52A3	568	83 (14.6%)	225 (40%)	260 (46%)

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SLC19A2 (Thiamine Transporter 1)

The solute carrier 19, member 2 (SLC19A2; Table 1), also known as thiamine transporter 1 (THTR1; THT1), is a high-affinity transporter for the cellular uptake of thiamine (vitamin B1) [58]. The protein is encoded by the corresponding gene *SLC19A2* (OMIM ID *603941), located on the long arm of chromosome 1 at position 24.2 (1q24.2) [59]. The gene contains 6 exons and extends to approximately 22.5 kb. It produces the 55.4 kD protein consisting of 497 amino acids. The protein is expressed at the plasma membrane and has 12 transmembrane helices; its N- and C-termini are located in the cytosol. The cryo-electron microscopy structure of SLC19A2 in the inward-facing conformation in complex with either thiamine or pyridoxine (vitamin B6) was recently determined. A comparison of the outward- and inward-facing SLC19A2/A3 structures revealed a transport mechanism involving a rocker-switch movement, although the driving force of transport remained unclear [60]. After transport into the cell, thiamine is converted into derivatives, mostly thiamine pyrophosphate (TPP), which functions as a coenzyme in several metabolic reactions, e.g., the oxidative decarboxylation of pyruvate and α-ketoglutarate, both of which are essential for energy production by the citric acid cycle [61]. Accordingly, SLC19A2 is expressed in nearly all tissues, but predominantly in cardiac and skeletal muscle, as well as in the brain, kidney, liver, lung, and the digestive tract [58, 62].

Mutations in the *SLC19A2* gene are rare (prevalence <1/1.000.000) and can cause thiamin-responsive megaloblastic anemia syndrome (TRMA; phenotype MIM number 249270), which is inherited in an autosomal recessive manner [63-65]. Fewer than 100 cases worldwide have been reported. Common types of mutations involve missense, nonsense, and frameshift variants. With modern gene analysis methods, new variants are continuously detected (Table 2).

As the name TRMA implies, the syndrome is characterized by the triad of megaloblastic anemia, non-type-I-diabetes mellitus, and sensorineural hearing loss [66]. Symptoms typically manifest in early childhood but can be treated with very high doses of thiamine, because a certain amount of thiamine can enter the cell even in the absence of a functional transporter [67, 68]. Anemia and diabetes can be improved or at least stabilized, whereas sensorineural hearing loss, once manifested, is generally irreversible and does not respond to thiamine therapy [66, 68].

In the cochlea, SLC19A2 is expressed in both inner and outer hair cells, with stronger expression in inner hair cells [62] (Fig. 1). In a mouse model with disruption of the *SLC19A2* gene, loss of inner hair cells, an extremely rare type of sensorineural histopathology, was observed after 1-2 weeks on a low-thiamine diet (2 mg/kg). The exact pathophysiological mechanism of this selective inner hair cell loss is unclear [69]. However, when maintained on higher oral thiamine intake (≥3 mg/kg), hearing loss could be prevented in these mice. Studies in humans are rare. Amatuzzi et al. and Slack et al. described selective inner hair cell loss in human temporal bone specimens from premature infants, which was associated with premature birth and anemia. Thiamine deficiency (non-genetic) was discussed as a possible cause [70, 71]. These studies underscore the fundamental role of thiamine in preserving the integrity of inner hair cells.

Decreased cellular thiamine uptake and impaired energy metabolism may result in mitochondrial dysfunction, which can lead to oxidative stress. Accordingly, studies have shown that SLC19A2 dysfunction leads to elevated oxidative stress, e.g., in brain and pancreatic β-cell mitochondria, contributing to neurodegeneration and diabetes, respectively [72-74].

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SLC22A4 (OCTN1)

The solute carrier family 22, member 4 gene (*SLC22A4*, OMIM *604190; Table 1), also known as organic cation transporter novel 1 (OCTN1), encodes a 551-amino-acid membrane transporter involved in pH-dependent transport of organic cations across biological membranes [75-77].

Consistent with its function as a membrane transporter, OCTN1 is predicted to contain 12 α-helical transmembrane domains, with intracellular N- and C-termini. The protein also features a large glycosylated extracellular loop between transmembrane domains 1 and 2, as well as a substantial intracellular loop between transmembrane domains 6 and 7 that includes predicted phosphorylation sites [75].

SLC22A4 is widely expressed in several human tissues, including the brain, small intestine, liver, kidney, and immune cells [76, 78]. Importantly, expression has also been reported in the inner ear. Immunofluorescence studies detected SLC22A4 in cochlear hair cells and in endothelial cells of capillaries of the stria vascularis (Fig. 1), where it is primarily localized to the apical membrane [75, 76]. More recent experimental data further strengthen these findings. In mouse cochlear tissue, OCTN1 expression was observed in several key structures, including the organ of Corti, spiral ganglion neurons, and the stria vascularis, although with varying intensity across regions. The specificity of this expression pattern was confirmed by immunohistochemistry on cochlear explants [79]. Together, these observations indicate that OCTN1 is consistently expressed in functionally relevant regions of the inner ear.

Functionally, OCTN1 mediates the transport of various substrates, including organic cations such as acetylcholine, as well as carnitine, which plays a key role in the transport of fatty acids into mitochondria [76]. In addition, it transports ergothioneine, a naturally occurring antioxidant that contributes to cellular protection against oxidative stress [80, 81]. This range of substrates suggests that OCTN1 may be involved in both metabolic processes and cellular defense mechanisms.

The involvement of SLC22A4 in hearing loss was first reported by Ben Said et al., who identified a homozygous missense variant, c.338G>A (p.Cys113Tyr), in Tunisian families affected by nonsyndromic sensorineural hearing loss [75]. The condition was subsequently designated DFNB60, although this disease phenotype is currently not included in OMIM. The identified variant results in the substitution of a highly conserved cysteine residue with tyrosine at position 113 in the OCTN1 transporter. This residue is located within the first extracellular loop and is predicted to contribute to disulfide bond formation, proper protein folding, and protein stability. Functional *in vitro* studies demonstrated that the p.Cys113Tyr substitution impairs correct targeting of OCTN1 to the apical plasma membrane in polarized epithelial cells and significantly reduces substrate uptake, supporting the functional importance of this region [75].

In the Tunisian families reported by Ben Said et al. [75], the homozygous p.Cys113Tyr variant co-segregated with nonsyndromic hearing loss and was proposed to represent a founder mutation. The association was later supported by an independent study performed by Chiereghin et al. [76] in a large consanguineous Moroccan family, in which the same homozygous variant was identified through genome-wide linkage analysis and exome sequencing. In this family, all affected individuals carried the p.Cys113Tyr variant in the homozygous state. However, one homozygous sibling showed normal hearing, indicating incomplete penetrance of the phenotype [76].

Differences in clinical presentation were also observed between the two cohorts. In the Tunisian families described by Ben Said et al. [75], hearing loss was prelingual and severe to profound, whereas in the Moroccan family reported by Chiereghin et al. [76], it was postlingual, moderate to profound in severity, and progressive in at least one affected individual. These observations suggest that additional genetic, environmental, or modifier factors may influence disease expression. Nevertheless, current evidence linking *SLC22A4* to hearing loss remains limited to a small number of families carrying the same variant, and

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additional clearly pathogenic variants have not yet been consistently reported.

Findings from animal models complicate the interpretation of these results. In *Slc22a4* knockout mice analyzed by the International Mouse Phenotyping Consortium, no significant differences in auditory brainstem responses (ABR) were observed compared to wild-type controls, indicating the absence of a clear hearing phenotype [76]. This discrepancy between human genetic data and mouse models raises important questions regarding the role of SLC22A4 in hearing. It is possible that the identified variant does not fully account for the observed phenotype or that additional modifying factors are required for disease manifestation. Alternatively, species-specific differences or compensatory mechanisms in mice may mask the functional consequences of SLC22A4 deficiency.

Therefore, SLC22A4 should currently be considered a potential but still provisional hearing-loss gene requiring further genetic and functional validation.

Given its ability to transport ergothioneine, OCTN1 has also been implicated in cellular responses to oxidative stress. Ergothioneine is a sulfur-containing antioxidant that accumulates in tissues exposed to high metabolic demand and oxidative challenge, where it contributes to reactive oxygen species (ROS) scavenging and protection against oxidative damage. Experimental studies have shown that OCTN1-mediated ergothioneine uptake enhances cellular resistance to oxidative injury, reduces intracellular ROS accumulation, and supports mitochondrial function under stress conditions. These observations suggest that SLC22A4 may indirectly contribute to redox homeostasis and cytoprotective mechanisms in the inner ear, a tissue known to be highly vulnerable to oxidative stress–related damage [78, 79, 81].

The SLC26 family of multifunctional solute transporters and channels

The SLC26 gene family of solute carriers comprises 10 genes and 1 pseudogene; the genes encode proteins that primarily function as multifunctional anion exchangers or channels, allowing the movement of various anions, including chloride, bicarbonate, sulfate, oxalate, formate, and iodide, across cell membranes. Owing to their functional versatility and widespread expression or tissue-specificity, SLC26 transporters play fundamental roles in several physiological processes, ranging from ion uptake and secretion across epithelia to the regulation of systemic and fluid compartment pH and volume [82, 83]. SLC26A4 and SLC26A5 are involved in the development of hearing loss in humans, and will be detailed in the following.

SLC26A4/pendrin

Expression

The solute carrier family 26, member 4 gene (*SLC26A4*; OMIM ID *605646; Table 1) encodes the anion exchanger SLC26A4, also known as pendrin, or PDS, identified in 1997 [84].

In the inner ear, SLC26A4 is expressed on the apical membrane of specialized epithelial cells of the cochlea (Fig. 2), endolymphatic sac and duct, and vestibular labyrinth. In the cochlea, SLC26A4 is found in the cochlear lateral wall, both outside and inside the *stria vascularis*. Outside the *stria vascularis*, prominent SLC26A4 expression is detected in the root cells [85, 86] and on the apical membrane of epithelial cells of the outer sulcus and spiral prominence [85, 86]. Within the *stria vascularis,* other cell types that express SLC26A4 are the spindle-shaped cells [85-88].

In the endolymphatic sac and duct, SLC26A4 is expressed on the apical membrane of mitochondria-rich cells [85, 89], which are primarily involved in vectorial ion transport and consequent fluid reabsorption [90].

In the vestibular labyrinth, SLC26A4 is found in the apical membrane of vestibular transitional cells, which are non-sensory epithelial cells surrounding the macula in the

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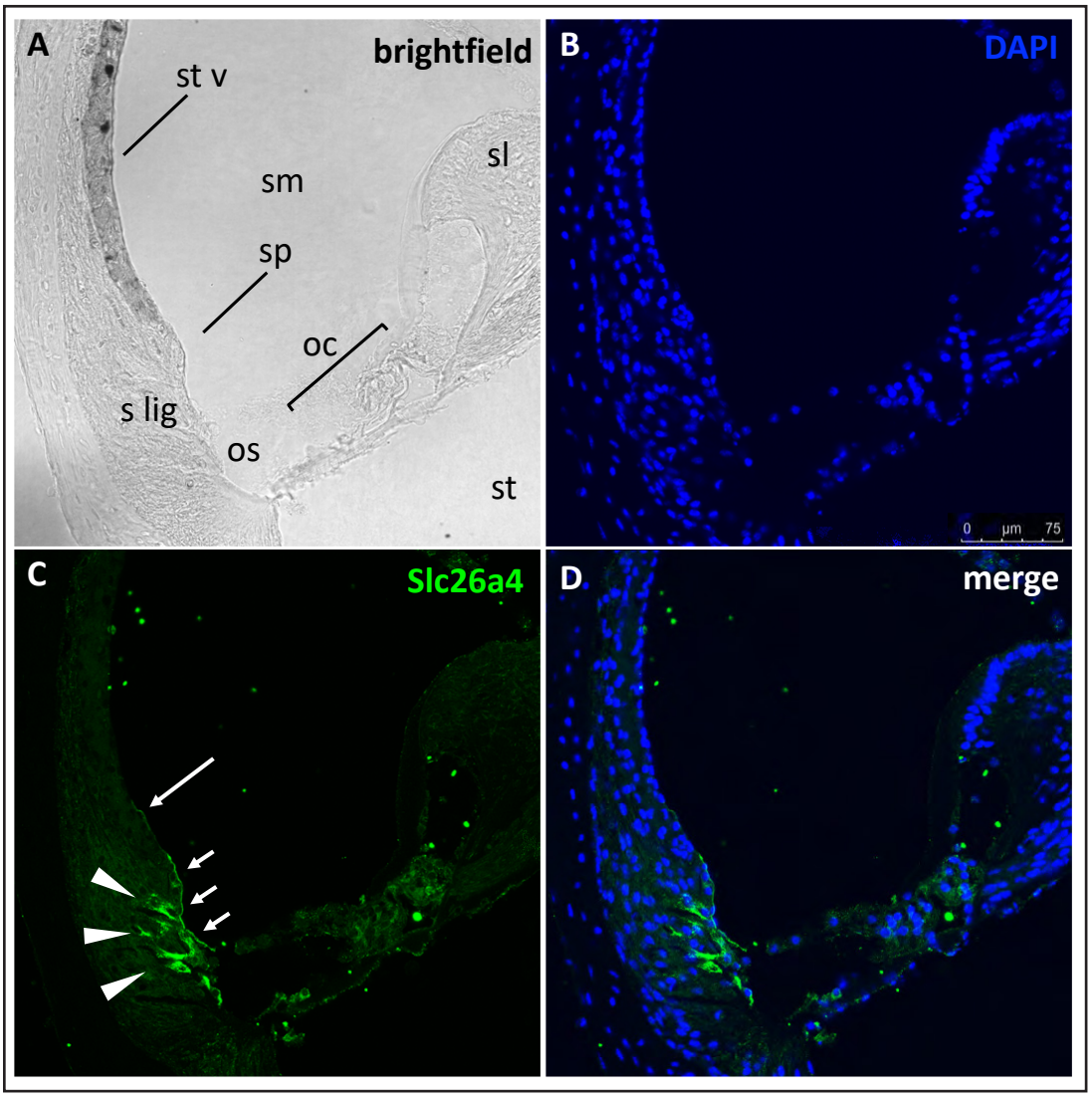

Fig. 2. Immunohistochemistry of the mouse inner ear showing Slc26a4 expression. Cochlear cryosections from adult CBA/J mice have been probed with a customized rabbit anti-Slc26a4 antibody [226], counterstained with DAPI, and imaged by confocal microscopy (Leica TCS SP5II AOBS, Leica Microsystems, Wetzlar, Germany, equipped with an HCX PL APO CS 40x/1.25 oil immersion objective). A, brightfield image; B, cell nuclei; C, Slc26a4 signal; and D, merged image. The arrowheads and short arrows in panel C indicate Slc26a4 expression in root cells and epithelial cells of the outer sulcus and spiral prominence, respectively. The long arrow indicates Slc26a4 expression in the spindle-shaped cells within the stria vascularis. Oc, organ of Corti, os, outer sulcus, sl, spiral limbus, s lig, spiral ligament, sm, scala media, sp, spiral prominence, st, scala timpani, st v, stria vascularis.

saccule and utricle and the ampulla in the cupula of the semicircular canals [86, 89], and are thought to regulate the ion composition of the endolymph and the activity of neighboring cells via other pathways [91].

Outside the inner ear, SLC26A4 is also found in the thyroid and kidney (Fig. 1). In the thyroid, SLC26A4 is expressed at extremely high levels and is immunolocalized on the apical membrane of thyroid follicular cells, facing the colloidal lumen [92, 93]. In the mammalian kidney nephron, SLC26A4 is detected in a subset of cells within the late distal convoluted tubule and at the apical pole of beta and non-alpha non-beta intercalated cells of the cortical collecting duct and connecting tubule [94-96].

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Other organs and tissues that express SLC26A4 include the mammary gland [97], the placenta [98], the liver [99], and, at low levels, Sertoli cells [100] and secretory non-ciliated airway cells; in the latter, it is upregulated in various inflammatory conditions (reviewed in [101]).

SLC26A4 Protein Structure

While remaining elusive for decades due to the inherent difficulties of crystallizing highly hydrophobic membrane proteins, the SLC26A4 structure was recently resolved by cryo-electron microscopy by two independent research groups. Liu et al. described mouse SLC26A4 as a homodimer with three distinct states: a symmetric inward-open, a symmetric outward-open, and an asymmetric dimer comprising one inward-open protomer and one outward-open protomer. Based on this, the authors proposed an inverted alternate-access transport mechanism, in which the two protomers transport ions in opposite directions, consistent with electroneutral anion exchange. Each protomer is composed of an N-terminal domain, a transmembrane domain including 14 transmembrane domains organized into the core and the gate region, a sulfate transporter and anti-sigma factor antagonist domain (STAS), and a C-terminal domain, not dissimilar from our former predictions [102]. The core region would accommodate the ion-binding pocket and rotate relative to the gate region via an elevator-like mechanism to release the bound ion and recruit the counterion. Most of the dimerization interface is represented by STAS domains, with the STAS domain of one protomer coming into contact with the STAS and the transmembrane domain of the other protomer [103].

Wang et al. determined the structures of Slc26a4 from *Sus scrofa* in the presence of either Cl^-, I^-, HCO_3^-, or in the apo-state [104]. In contrast to the findings of Liu et al., these authors describe two anion-binding sites in each protomer, which are both involved in ion exchange and can allocate the same anion, suggesting a transport stoichiometry different from a 1:1 electroneutral exchange. Interestingly, these authors also resolved the Slc26a4 structure in complex with niflumic acid, which we first reported as an SLC26A4 inhibitor [105], and long remained the only known inhibitor of this transporter until the identification of tetrahydropyrazolopyridine and pyrazolothiophenesulfonamide inhibitors with high-throughput screenings by the Verkman lab [106, 107].

SLC26A4 Protein Function

The understanding of SLC26A4 protein function arises from seminal studies of ion transport in heterologous expression systems (summarized in [102]) and morphological and physiological studies in *Slc26a4* knockout mice and other genetically modified mice expressing hypomorphic Slc26a4 variants or with inducible Slc26a4 expression [89, 108]. Slc26a4 global knockout mice or mice expressing pathogenic Slc26a4 variants p.S408F, c.919-2A>G, or human SLC26A4 p.H723R manifest profound deafness with abnormal dilation of the inner ear compartments and variable vestibular dysfunction [108-111]. Slc26a4 p.L236P knock-in mice show similar vestibular and anatomical pathological findings, but hearing loss varies from mild to profound [112].

In the inner ear, SLC26A4 functions as an anion exchanger, excreting bicarbonate in the extracellular fluid and reabsorbing chloride. While long considered electroneutral by us and others [113, 114], recent reports suggest that the anion exchange may be electrogenic [115]. The earliest pathophysiological event observed in mice due to a lack of Slc26a4 during embryonic development is the enlargement of the lumen of all inner ear compartments, a consequence of a lack of fluid reabsorption in the endolymphatic sac due to a failure of chloride reabsorption via SLC26A4 [90, 116, 117].

Another essential function of SLC26A4 is the regulation of endolymph pH by bicarbonate secretion [118]. The enlargement of inner ear compartments and acidification of the endolymph as a consequence of SLC26A4 dysfunction generate a cascade of events culminating in loss of endocochlear potential and degeneration of the sensory cells of the organ of Corti, which ultimately lead to hearing loss [86, 118-121].

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In the vestibular system, we and others observed the precipitation of giant otoconia in the saccule and utricle of mouse models of Slc26a4 dysfunction, which explains the vestibular symptoms in these mice and in patients. Lack of Slc26a4 activity with consequent acidification and increase in Ca^{++} concentration in the vestibular endolymph would explain this phenomenon [108, 109, 122].

The function of SLC26A4 in the thyroid has been controversial for decades. At present, it is generally accepted that SLC26A4 permits the iodide efflux from the thyrocyte to the follicular lumen, which is essential for the biosynthesis of thyroid hormones [123, 124]. Although thyroid size and blood thyroid hormone levels are normal in mouse models for Slc26a4 dysfunction, histological analysis of the thyroid gland of the Slc26a4 p.S408F mouse model revealed defective morphology with many atrophic follicles [125], suggesting a possible contribution of hypothyroidism in the development of hearing phenotypes.

In the kidney, SLC26A4 reacts to metabolic alkalosis via renal base (bicarbonate) excretion into the urine and chloride reabsorption. Hence, SLC26A4 is critically involved in the regulation of systemic acid-base homeostasis and NaCl balance, with major implications in the control of vascular volume and systemic blood pressure, and therefore represents a promising and novel drug target for treatment of severe edematous states and hypertension [126, 127].

Hearing Loss Linked to SLC26A4

Patients harboring biallelic pathogenic sequence alterations (mutations) in the *SLC26A4* gene develop autosomal recessive sensorineural non-syndromic hearing loss type B4 (DFNB4; phenotype MIM number 600791) or Pendred syndrome (phenotype MIM number 274600) [128, 129]. Both these conditions are characterized by bilateral hearing loss associated with inner ear malformations, i.e., an enlarged vestibular aqueduct (EVA; Fig. 3) with dilated endolymphatic sac and duct, with or without a cochlear incomplete partition type II (Mondini cochlea). Vestibular dysfunction, manifested as dizziness and balance disorders, can be present. DFNB4 and Pendred syndrome are among the most common non-syndromic and syndromic forms of genetic hearing loss, respectively, and EVA is the most common inner ear malformation [7, 130].

Hearing loss typically has an early onset; residual hearing may be present at birth, but it is lost before or around the time of language acquisition. In these cases, hearing loss is severe to profound. A second patient group exhibits fluctuating and progressive hearing loss that presents later in life [129].

In Pendred syndrome, patients also exhibit a partial iodide organification defect in the thyroid and may develop subclinical or overt hypothyroidism with or without goiter. The thyroid phenotype becomes apparent around puberty. The gold standard for the identification of thyroid dysfunction in this context, and hence the discrimination between non-syndromic and syndromic SLC26A4-related hearing loss, is the perchlorate discharge test, which is positive in Pendred syndrome patients and indicates a defect in iodide organification on thyroglobulin [131]. The reason some individuals manifest the full spectrum of the syndrome, whereas others do not, is currently unknown; the types of mutations and residual SLC26A4 function do not account for phenotypic variability. It has been postulated that environmental factors, such as dietary iodide intake [131], and genetic or epigenetic factors, may play a role. Likewise, it is not understood why not all patients exhibit vestibular symptoms.

Due to the function of SLC26A4 in the kidney in alkali excretion, Pendred syndrome/DFNB4 patients are particularly prone to developing life-threatening metabolic alkalosis under conditions of alkali loading, such as diuretic therapy or persistent vomiting [132, 133].

Individuals with biallelic pathogenic variants in *SLC26A4* invariably develop hearing loss with an EVA. However, in Caucasian cohorts, approximately 25% of patients with EVA have only one *SLC26A4* pathogenic variant, and 50% have no identifiable variants. Finding the missing pathogenic allele(s) and the underlying pathogenic mechanism in these patients remains a diagnostic challenge [130, 134-136]. Potential digenic inheritance of Pendred syndrome/DFNB4 involving a pathogenic monoallelic variant in *SLC26A4* and a pathogenic monoallelic

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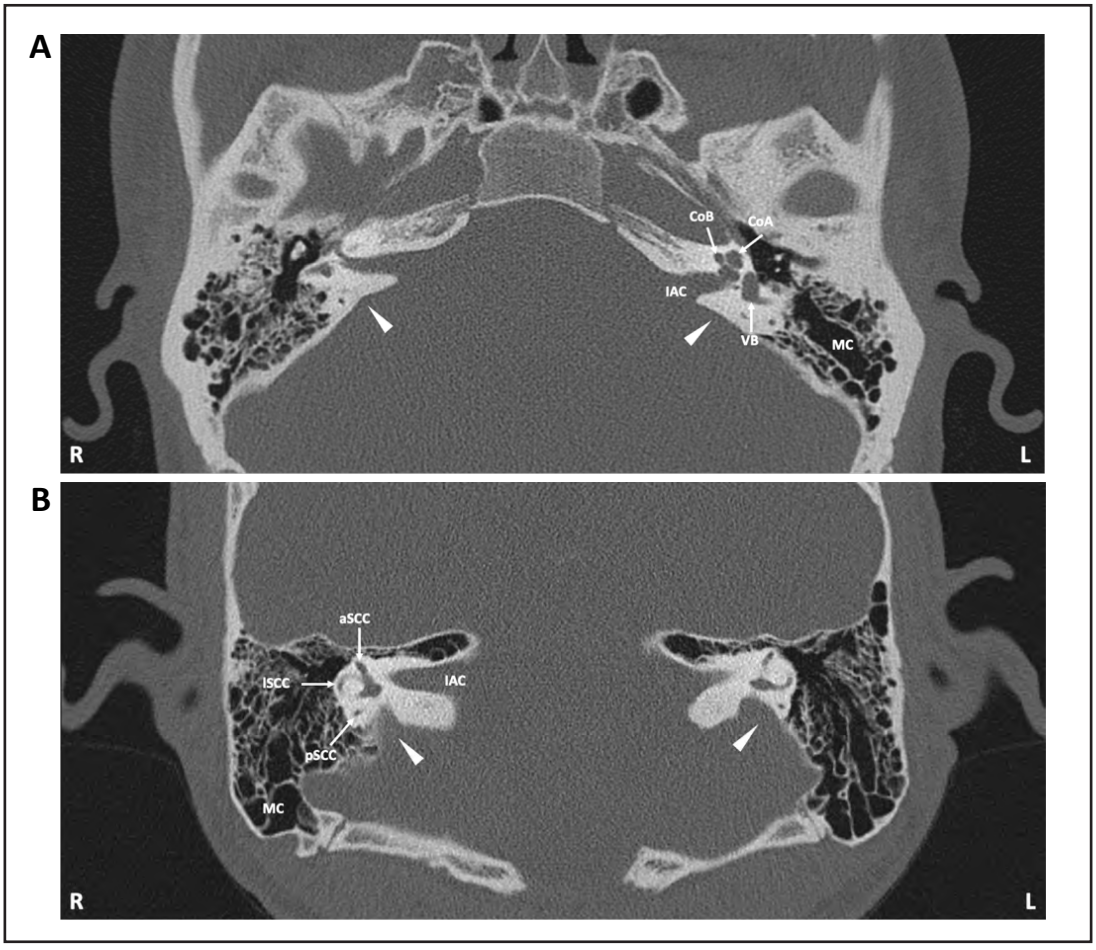

Fig. 3. A, computed tomography of the temporal bones of a normal hearing adult. Axial plane, bone window: Unremarkable findings with no signs of enlarged vestibular aqueduct (arrowhead). B, computed tomography of the temporal bones of a 7-year-old male patient with hearing loss and biallelic pathogenic homozygous variants in the SLC26A4 gene coding for protein variant p.Y78C. The patient (patient #681), his clinical findings, and the molecular features of the SLC26A4 protein variant have been described in our recent publication [135]. Axial plane, bone window: Prominent bilateral enlarged vestibular aqueduct (arrowhead). aSCC, anterior semicircular canal; CoA, cochlear apex; CoB, cochlear basal turn; IAC: internal acoustic canal; L, left; lSCC: lateral semicircular canal; MC: mastoid cavity; pSCC: posterior semicircular canal; R, right; VB, vestibulum.

variant in another gene, such as *FOXI1*, *KCNJ10,* or *EPHA2*, has been suggested to explain the missing heritability, but it is a rare occurrence and was not unequivocally established in all cases (discussed in [137]). A haplotype of 12 SNPs in linkage disequilibrium, common in Caucasians, and postulated to lie in *SLC26A4* regulatory regions, may be causative if found *in trans* with an *SLC26A4* monoallelic pathogenic variant [134]. The role of deep intronic variants, undetected by conventional methods that focus on sequencing exons, is beginning to emerge [138]. In addition, the role of variants in the promoter or other regulatory regions warrants further investigation. The gene diagnostics of EVA in patients with no *SLC26A4* identifiable variants is even more complex, as genes other than the acknowledged EVA genes, dominant genes, syndromic genes with incomplete penetrant traits, epigenetic factors, or even environmental factors may play a role [135, 137, 139].

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SLC26A5/prestin

Protein Expression, Structure, and Function

The solute carrier family 26, member 5 gene (*SLC26A5*; OMIM ID *604943; Table 1) encodes the motor protein of cochlear outer hair cells SLC26A45, also known as prestin (PRES), identified in 2000 [140].

In the inner ear, prestin is highly expressed in the basolateral plasma membrane of outer hair cells, which are motile, while it is absent in inner hair cells, which are not motile (Fig. 1). It is not found in apical stereocilia and the cuticular plate of the outer hair cells. Its ear expression is unique for mammals [141, 142].

Although classically considered to be expressed exclusively in the outer hair cells of the inner ear, a recent report showed that prestin is also abundant in mouse and human cardiomyocytes (Fig. 1), where it would serve as an elastic element to amplify the sarcomere contraction system based on actin and myosin [143].

The structure of human prestin and various prestin orthologs was recently revealed by cryo-EM. Prestin is a homodimer, of which the conformation varies depending on the bound anion; each protomer is constituted by 14 alpha-helix transmembrane domains, organized to form a gate domain and a core domain, and an intracellular C-terminal STAS domain composed of a core of five beta-sheets surrounded by 5 alpha-helices, similar to what seminal studies from Battistuta´s group determined by X-ray crystallography [144-148].

Though prestin is a transmembrane protein and belongs to a family of anion transporters, it does not transport ions across the plasma membrane. Instead, it is an incomplete anion transporter that undergoes conformational changes in response to changes in cell transmembrane potential, thereby altering cell length – a long-known phenomenon called electromotility, which is at the basis of the mechanism of cochlear amplification of the mammalian inner ear [149, 150]. Stimulation or inhibition of outer hair cells by upward or downward deflections of the basilar membrane, respectively, leads to depolarization or hyperpolarization of their transmembrane potential, due to the opening or closure of the mechanotransduction (MET) cation channel. This leads to the shortening or elongation of these cells, respectively (reviewed in [151]). These changes in the length of outer hair cells are the consequence of changes in the conformation of prestin from a contracted to an expanded state. Prestin conformation changes are primarily controlled by intracellular chloride; chloride binding induces a contracted state, while in the absence of chloride, an expanded state is stabilized [146]. Changes in the length of the outer hair cells amplify the movements of the basilar membrane, which, in turn, amplify the stimulation of the outer hair cells themselves in a positive feedback loop. The conformational changes of prestin resemble an elevator-like movement of the gate domain on the core domain, similar to what was described for SLC26A4 and other SLC26 transporters (see chapter SLC26A4/pendrin), but failing to reach a full outward-facing conformation, consistent with prestin´s inability to drive transmembrane ion fluxes [152]. Interestingly, salicylate, which notably leads to reversible sensorineural hearing loss in high doses, can occupy the chloride-binding pocket and lock prestin in the expanded state, thereby impeding outer hair cell electromotility [146, 147].

Hearing Loss Linked to SLC26A5

Ablation of the *SLC265* gene in mice led to shortened outer air cells lacking electromotility, prominent auditory brainstem recording (ABR) threshold shifts of 45–65 dB, distortion product otoacoustic emissions (DPOAEs) threshold shifts of 45–55 dB, but intact mechano-electrical transduction, i.e., normal activity of the MET cation channel, unequivocally linking prestin to outer hair cell somatic electromotility and to the mechanism of cochlear amplification [153]. These findings were later confirmed in knock-in mice expressing variants of prestin designed *in silico* to affect protein function [154].

Although prestin is expected to be required for functional outer hair cells and normal hearing in humans, the clinical significance of reported putative pathogenic alleles is uncertain.

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Prestin putatively causes autosomal recessive sensorineural non-syndromic hearing loss type B61 (DFNB61; phenotype MIM number 613865). This assumption was based on the identification of a 5'-UTR splice acceptor mutation (IVS2-2A>G) in exon 3 of the prestin gene in two unrelated families with recessive non-syndromic deafness [155]. However, the pathogenicity of this specific variant was later confuted by population studies [156] and animal studies [157].

Mutai et al. described two siblings with early-onset moderate-to-severe sensorineural hearing loss and compound heterozygous variants in the *SLC26A5* gene, encoding the p.W70X and p.R130S protein variants [158]. Mice homozygous for prestin variant p.R130S suffer from hearing loss, in agreement with the altered function of the protein in cell-based assays [159, 160]. Not surprisingly for such a short truncation of the protein, p.W70X exhibits pathogenic features in cell culture. $Slc26a5^{p.R130S/-}$ mice, which harbor only one functional *SLC26A5* allele coding for the prestin variant p.R130S, have been used as a model for human DFNB61, as they mimic the genotype of p.W70X/p.R130S compound heterozygous patients. These mice exhibit dramatically reduced DPOAEs and premature outer hair cell loss, thus confirming the pathogenicity of patients' genotype [161].

It is striking that so few pathogenic variants have been described to date in this large gene with such an important role in hearing; pending additional family segregation and population frequency studies of novel variants, which may strengthen the genotype-phenotype correlation, the link between prestin pathogenic variants and hereditary hearing loss remains provisional.

Interestingly, prestin may play a role in hearing loss with pathogenic mechanisms other than genetics. The *SLC26A5* gene contains a thyroid hormone response element, indicating that decreased protein expression and distribution of prestin can participate in determining hearing loss in the context of congenital hypothyroidism [162]. Congenital hypothyroidism is a recognized risk factor for sensorineural hearing loss, affecting up to 20% of patients [163].

SLC33A1

The solute carrier family 33, member 1 gene (*SLC33A1*; OMIM:603690; Table 1) encodes the ubiquitous acetyl-CoA transporter 1 (AT-1), an integral membrane protein of the endoplasmic reticulum (ER) that mediates the transport of cytosolic acetyl-CoA into the ER lumen in exchange for free lumenal CoA [164, 165].

Structurally, AT-1 is an integral ER membrane protein predicted to contain 12 transmembrane helices. Recently, a high-resolution cryo-electron microscopy (cryo-EM) structure of human SLC33A1 bound to acetyl-CoA was published, revealing the N-terminal and C-terminal transmembrane helices TM1–6 and TM7–12, respectively, organized into two lobes accommodating a central cavity hosting the ligand [166]. Thus, the structural insights further support the functional role of SLC33A1 as an acetyl-CoA transporter.

The SLC33A1-mediated transport of acetyl-CoA into the ER lumen is essential for the O-acetylation of gangliosides as well as the post-translational modification (N-lysine acetylation) of luminal and membrane proteins, which is fundamental for protein folding, maturation, and ultimately proper function of the secretory pathway [165]. In addition to its central role in protein acetylation, AT-1 is also crucial for maintaining ER homeostasis and cellular proteostasis. When AT-1 activity is impaired, the acetylation capacity of the ER is reduced, leading to increased ER stress and alterations in autophagy pathways [165, 167]. Accordingly, AT-1 is considered essential for cell viability, as it regulates key ER functions that become particularly critical under stress conditions.

This essential cellular role is also reflected in human disease phenotypes. Monoallelic pathogenic sequence alterations in *SLC33A1* have been identified in patients with autosomal dominant spastic paraplegia 42 (SPG42; phenotype MIM number 612539) [168, 169], where haploinsufficiency has been suggested as a disease mechanism. In contrast, biallelic loss-of-

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function variants lead to a more severe multisystem disorder known as Huppke–Brendel syndrome (phenotype MIM number 614482).

The association between SLC33A1 and hearing loss is primarily described in the context of Huppke–Brendel syndrome, a rare autosomal recessive disorder. This condition is characterized by sensorineural hearing loss, congenital cataracts, severe developmental delay, intellectual disability, and additional neurological and systemic abnormalities, including altered copper metabolism in some cases, and premature death [170]. In affected individuals, hearing loss is early-onset and consistently occurs as part of a broader syndromic phenotype rather than as an isolated feature [171]. Therefore, SLC33A1-related hearing loss is best classified as autosomal recessive, syndromic sensorineural hearing loss.

Further insight into SLC33A1 function is provided by animal models. In the study by Peng et al., mice heterozygous for the point mutation p.S113R in AT-1, which has been associated with the familial form of spastic paraplegia SPG42, were viable but at the age of 10-12 months exhibited neurological abnormalities, including motor deficits, neurodegeneration, and abnormal activation of autophagy. These mice also showed increased inflammation and susceptibility to infections. In contrast, homozygous animals died during the early embryonic phase (E8–E8.5), highlighting the essential role of AT-1 for proper development [172]. Notably, hearing function was not specifically assessed in these mice, limiting conclusions about the role of SLC33A1 in the inner ear. However, the fact that, in patients with Huppke–Brendel syndrome, hearing loss occurs in combination with widespread systemic abnormalities suggests that auditory dysfunction is likely a consequence of a generalized cellular defect rather than a cochlear-specific mechanism.

SLC44A4

The solute carrier family 44, member 4 (SLC44A4; OMIM *606107; Table 1), also called choline transporter-like protein 4 (CTL4), thiamine pyrophosphate transporter (TPPT), chromosome 6 open reading frame 29 (C6ORF29), is a member of the SLC44 family, which is known to encode five different CTLs [173, 174]. The gene is located on the short arm of chromosome six, band 21, sub-band 33 (6p21.33).

SLC44A4/CTL/TPPT permits choline transport and, consequently, the acetylcholine (ACh) synthesis in non-neuronal cell lines and facilitates the colonic thiamine pyrophosphate (TPP) uptake [175, 176]. It is a transmembrane protein that contains 10 to 13 transmembrane domains and is N-glycosylated at multiple sites, which is reported to be vitally important for its function [175, 177]. So far, no tertiary structure of the protein has been resolved.

In human tissues, SLC44A4 is highly expressed in the colon (Fig. 1), prostate, and trachea, while moderate expression is observed in the lung and stomach [175]. Furthermore, Slc44a4 expression was found in the central nervous system and the inner ear and lateral line neuromasts of zebrafish [178]. However, no expression in the human brain or spinal cord was found [175].

To our knowledge, no reports on SLC44A4 expression in the human inner ear have been published (Fig. 1). Nevertheless, alterations in the amino acid sequence of SLC44A4 have been reported as a potential cause of hearing loss (phenotype MIM 617606; Deafness, autosomal dominant 72; DFNA72) in one family. Ma et al. described a p.M156V substitution in the SLC44A4 protein sequence in a Chinese family with autosomal-dominant postlingual non-syndromic mid-frequency hearing loss. This variant co-segregated with hearing loss in all eight affected family members but was not found in 13 unaffected relatives, supporting pathogenicity [178]. As this study is the only report of SLC44A4-linked hearing loss, the relationship between this phenotype and the gene is still provisional [179]. Of note, p.M156V is not included in the eight SLC44A4 variants classified so far as pathogenic or likely pathogenic (Table 2).

While cell culture-based studies showed that SLC44A4 knockdown significantly decreased ACh synthesis in lung and colon cancer cells [176], a study on a Slc44a4 global

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knockout mouse model showed that thiamine pyrophosphate (TPP) uptake in the colon of these mice was almost completely inhibited [180]. Unfortunately, hearing measurements in this knockout mouse model were not reported. However, Slc44a4 knockout zebrafish showed abnormal numbers of small, fused, and misplaced otoliths, a smaller inner ear, and a defective balance system, which was concluded to be the cause of the abnormal swimming behavior [178]. Finally, after evaluating the escape reflex at different sound intensities, the study concluded that Slc44a4 knockout affects hearing in zebrafish. Hearing loss in zebrafish is widely acknowledged as highly representative of hearing loss in humans, as most of the human hearing loss genes have a direct counterpart in zebrafish [181]. However, obvious differences in the anatomy of the hearing organs between zebrafish and humans would require validation of the findings in a mammalian model. In addition, because sequence alterations in SLC44A4 have been linked to hearing loss in only one family, the evidence for a connection between SLC44A4 and hearing loss in humans remains limited, and more research is needed to draw conclusions about this causal relationship.

SLC52A2 and SLC52A3

Solute carrier family 52, member 2 (*SLC52A2*; OMIM *607882) and member 3 (*SLC52A3*; OMIM *613350) genes code for riboflavin transporters SLC52A2/RFVT2 and SLC52A3/RFVT3, respectively (Table 1). These transporters are expressed in different tissues, with SLC52A2/RFVT2 being ubiquitously expressed but most abundant in the nervous system and SLC52A3/RFVT3 being mostly expressed in the testis, intestine, and prostate [182] (Fig. 1).

RFVT2 and RFVT3 are small membrane proteins of ~50 kDa in size that consist of 11 transmembrane helices (TM1-11), of which TM1-6 form the N-domain, and TM7-11 form the C-domain, exhibiting an asymmetric 6 + 5 topology. The cryo-EM structures of human RFVT2 and RFVT3 captured in two distinct functional states in complex with riboflavin revealed a "rocker-switch" alternating-access transport mechanism, with RFVT3 activity stimulated by low pH [183].

Defects in either of the two transporters result in riboflavin deficiency in several tissues, with very severe consequences, especially affecting the nervous system. Deletion of either gene causes embryonic or neonatal lethality in the mouse model [184, 185]. According to the International Mouse Phenotyping Consortium, heterozygous mice exhibit increased or absent auditory brainstem response thresholds [186]. However, most *in vitro* studies are carried out using patient-derived iPSCs [187, 188].

Riboflavin is a water-soluble vitamin belonging to the B-class of vitamins (Vitamin B2 complex). It is rapidly converted intracellularly into flavin cofactors, such as flavin mononucleotide (FMN) or flavin adenine dinucleotide (FAD). Both cofactors are incorporated in several proteins, collectively defined as flavoproteome [189], most of which are involved in the electron transfer and redox reactions in the mitochondria. From *in vitro/ex vivo* studies on patient-derived iPSCs, it appears that oxidative phosphorylation may be preserved, while mitochondrial fusion and mitophagy are impaired, disrupting the functional mitochondrial network throughout the normal cell cycle [187] and eventually leading to the generation of ROS. Other flavoproteins are involved in the activation of B-class vitamins, chromatin modification, apoptosis, and cytoskeleton organization [189, 190]. Due to the central role of flavoproteins in key cellular processes, defects in riboflavin transport are associated with a wide range of symptoms, particularly in high-energy-demanding tissues such as the nervous system and the inner ear.

The collection of symptoms associated with defective riboflavin transporters is commonly defined as Brown-Vialetto-Van Laere syndrome (BVVLS) types 1 and 2 (phenotype MIM numbers #211530 and #614707, respectively) and Fazio-Londe (FL) syndrome (phenotype MIM number #211500) [191], more recently collectively renamed riboflavin transporter deficiencies (RTDs). Both syndromes are characterized by autosomal recessive inheritance and are uniquely associated with defects in the two transporters.

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Typical symptoms associated with BVVLS include sensorineural hearing loss, bulbar palsy, muscle weakness, optic atrophy, sensory ataxia, and respiratory compromise. FL syndrome is characterized by similar symptoms, excluding hearing loss [191]. SLC52A2 has been associated only with BVVLS, whereas SLC52A3 has also been involved in FL syndrome [191]. Most symptoms develop early in life, usually before age 10. Later onset has been reported in patients carrying SLC52A3 pathogenic variants [192, 193]. Other than the age of onset, there is no significant difference in symptoms between individuals carrying pathological variants in SLC52A2 or SLC52A3; therefore, for genetic diagnosis, it is recommended to sequence both genes. So far, the third member of the family, SLC52A1, has not been associated with any syndrome [194].

So far, 648 and 568 variants have been reported in SLC52A2 and SLC52A3, respectively (Table 2). The identified variants are distributed throughout the entire coding sequence and include nonsense, missense, splicing donor and acceptor, and indel variants [191, 195, 196]. *In vitro* assays of some of the identified variants showed that in most of the cases the genetic alteration leads to retention of the misfolded polypeptide in the intracellular compartment and in the ER, but some variants do show correct trafficking to the plasma membrane, hinting at a defect in the riboflavin transport itself [197-202]. Only in one case, an mRNA instability was described as a consequence of an SLC52A2 single-nucleotide variant [203].

Despite hearing loss being one of the most common, and often the first, symptoms detected in individuals affected by different forms of RTDs, the audiological findings are seldom reported and investigated [204]. Based on available reports, the hearing defect associated with pathogenic variants in SLC52A2 and SLC52A3 is characterized by profound-to-severe hearing loss and auditory neuropathy spectrum disorder (ANSD) [196]. Affected individuals typically show intact otoacoustic emissions, indicating functional outer hair cells, but abnormal or absent brain stem responses and impaired speech perception.

The established intervention consists of riboflavin supplementation at high doses (up to 80mg/kg/day), which leads to stabilization or even improvement of most symptoms and prevents disease progression [205, 206]. The treatment is an effective life-saving measure, and it is safe, with no report of toxicity communicated so far. Regarding the hearing phenotype, although riboflavin supplementation does not generally improve the hearing defect [79, 207, 208], partial recovery of hearing function has been reported in some cases. Foley et al. report an improvement in the audiometric testing from a threshold of 80 dB at 8 kHz to 40-55 dB after 3 months of 50 mg/kg/day of riboflavin supplementation [197]. Mutlu and colleagues also reported a case of a 6-year-old who showed improvement in hearing function, from profound hearing loss to a hearing threshold of 30 dB, measured by free-field audiometry, after 20 months of high-dose riboflavin supplementation. Hearing and speech discrimination further improved with the implementation of hearing aids [209]. Regardless of whether riboflavin supplementation improves the hearing phenotype, most individuals affected by RTDs are good candidates for cochlear implant and show hearing and speech improvements similar to those of implanted patients with other forms of sensorineural hearing loss [204, 210].

Comparative analysis of the mechanisms of action across SLC families implicated in hearing loss

Although the SLC members described here are involved in seemingly diverse physiological pathways, including inorganic ion homeostasis (SLC26A4 and SLC4A11), glutamate neurotransmitter loading into ribbon synapses (SLC17A8), cellular uptake of essential solutes including vitamin B1 (SLC19A2 and SLC44A4) and B2 (SLC52A2/A3), organic cations (SLC22A4), and acetyl-CoA (SLC33A1), and the phenomenon of the cochlear amplifier (SLC26A5), some commonalities can be identified concerning the mode of transport and pathophysiological mechanisms. All are solute transporters except SLC26A5. Among the transporters, there are anion exchangers (SLC26A4), uniporters (vesicular SLC17A8,

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SLC52A2/A3), co-transporters (SLC19A2, SLC22A4, SLC44A4), and antiporters (SLC33A1).

Although dysfunction of all these SLC transporters leads to sensorineural hearing loss, the pathophysiological mechanisms range from cochlear synaptopathy (SLC17A8), deranged endolymph pH and volume homeostasis (SLC26A4), loss of outer hair cell electromotility (SLC26A5), oxidative stress (SLC22A4), and metabolic dysfunction (SLC19A2, SLC33A1, SLC52A2/A3). Although oxidative stress is seen as a major pathophysiological event in the context of SLC22A4 dysfunction due to the lack of cellular uptake of the dietary antioxidant ergothioneine, the production of ROS may arise from metabolic impairment and consequent mitochondrial dysfunction (SLC4A11, SLC19A2, SLC52A2/A3) or as a downstream consequence of a complex chain of deregulatory events. For example, in *Slc26a4* knockout mice, oxidative stress has been detected in the stria vascularis, which can lead to impaired expression of K^+ channels essential in the generation of the endocochlear potential [86].

Oxidative stress may, in principle, cause ER stress; these two phenomena are intimately connected in a feedback loop, as excess ROS disrupts protein folding in the ER, while prolonged ER stress subsequently generates more ROS [211]. Thus, apart from SLC33A1 dysfunction causing ER stress as a direct consequence of impaired acetyl-CoA transport activity into the ER, ER stress can also arise from oxidative stress in the context of dysfunction of various SLCs, as detailed above. ER stress can also represent a common event caused by the production of misfolded SLC pathogenic protein variants, independent of oxidative stress. These hypotheses, however, and the extent to which they contribute to the pathophysiology of individual SLCs, require further investigation.

Clinical implications and outlook

Investigations into these solute carriers, particularly their function, distribution, and localization across tissues, contribute to a deeper understanding of the links among disease mechanisms, clinical symptoms, and potential treatments. Regarding genetic diagnostics, the SLC transporters mentioned here should be included in WES and WGS panels, as precise identification of the causative gene and inheritance pattern is of the utmost importance for genetic counseling of the affected patient and their family. In addition, clinical implications vary depending on the specific affected gene and its impact on solute carrier function. It must be considered that in syndromic forms of hearing loss, other organ systems are affected, requiring specific interventions. For example, in the case of an *SLC26A4* mutation (Pendred syndrome), hypothyroidism or kidney dysfunction may be present, requiring regular laboratory follow-up to detect early signs of the need for hormone supplementation or measures to prevent metabolic alkalosis. Hearing loss and other symptoms, if present, can fluctuate, worsen over time, and result in residual hearing loss. Awareness of this can help plan an adequate intervention.

In vitamin transport deficiency syndromes, e.g., SLC52A2/3 and SLC19A2 dysfunction, symptoms can be treated by high-dose supplementation of riboflavin and thiamine, respectively. Early diagnosis by genetic screening is essential to prevent long-term damage and disabilities.

In auditory synaptopathy, e.g., with SLC17A8 dysfunction, patients experience sensorineural hearing loss due to disrupted transmission of the electrical signal from the cochlea to the auditory nerve and brain. Independent of the degree of hearing loss, patients often do not achieve sufficient speech comprehension, even with high-performance hearing aids, and therefore are candidates for cochlear implants [212]. Currently, cochlear implants are considered the state-of-the-art intervention for severe-to-profound hearing loss and deafness, provided that an intact auditory nerve is present.

Although no SLC-specific gene therapy has yet been attempted in clinical trials, clinical progress in inner-ear gene therapy for other deafness genes, especially *OTOF*, indicates that this approach is becoming increasingly feasible in humans and may provide a future translational framework for SLC-associated hearing loss [213, 214].

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Conclusion

To conclude, eight SLC families and ten SLC family members participate in building the genetic basis of hereditary hearing loss. Thus, the transport of solutes, not only including ions, but also vitamins, acetyl-CoA, choline, and glutamate neurotransmitter, appears to be fundamental for the physiology of hearing. SLC dysfunction due to genetic mutation determines non-syndromic (SLC17A8, SLC22A4, SLC26A5, SLC44A4) and syndromic (SLC4A11, SLC19A2, SLC33A1, SLC52A2, SLC52A3) forms of hearing loss, or both (SLC26A4) (Table 1). While the inheritance pattern of the syndromes caused by these genes is autosomal recessive in all cases, isolated deafness can have both autosomal dominant (SLC17A8, SLC44A4) and autosomal recessive (SLC22A4, SLC26A4, SLC26A5) inheritance patterns (Table 1). Among SLC genes, SLC26A4 is the most commonly implicated in hearing loss, with 798 pathogenic/likely pathogenic variants identified to date (Table 2). In contrast, SLC44A4, SLC17A8, and SLC22A4 are associated with rare forms of hearing loss, as reflected by the relatively low number of pathogenic/likely pathogenic variants detected (Table 2). For all these forms of hearing loss, there is no cure; whether supplementation with high-dose thiamine or riboflavin can effectively prevent or stabilize hearing loss in cases involving SLC19A2 and SLC52A2/SLC52A3, respectively, is not predictable.

Recent advances in next-generation sequencing technologies enable the identification of an increasing number of gene variants at a speed that outpaces their interpretation. For some genes (for example, *SLC17A8*, Table 2), the number of variants with unknown significance or conflicting pathogenicity classifications even exceeds the number of variants for which pathogenicity has been assigned or excluded; for *SLC22A4*, *SLC26A5*, and *SLC44A4*, the association with hearing loss in humans remains provisional due to the limited number of cases which have been studied; thus, more research to strengthen the genotype-phenotype correlation of these specific genes and corresponding gene variants is needed.

Although cryo-EM structures have been obtained recently for many of the SLC transporters covered in this review, illuminating their transport mode and structure-function relationships, high-resolution structures are missing for SLC17A8, SLC22A4, and SLC44A4.

Some of these SLC transporters appear to be particularly enigmatic. For example, the inner ear expression of SLC44A4 was never determined; hearing measurements in the existing knockout mouse model were not reported. Both these relatively simple tests would strengthen the provisional link between SLC44A4 and hearing loss.

Even regarding the most studied of these transporters, SLC26A4, many questions remain unanswered. Why some patients manifest the full spectrum of Pendred syndrome, and some others do not, remains to be unequivocally established; the same applies to the vestibular dysfunction. The function of SLC26A4 in the thyroid and the possible transport of iodide under physiological conditions remain long-standing enigmas that have yet to be fully resolved. Whether the possible contribution of SLC26A4 regulatory factors can explain the clinical phenotype in patients with monoallelic SLC26A4 pathogenic variants and the underlying mechanisms still needs to be elucidated. Determining whether SLC26A4 and other SLC transporters can represent realistic therapeutic targets for hearing loss remains a challenging question and an open field of investigation.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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