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EDUCATIONAL REVIEW

Hearing loss and renal syndromes

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Abstract The association between ear and kidney abnormalities has long been recognized; however, the connection between these two disparate organs is not always straightforward. Although Alport syndrome is the most well-known, there are over 20 disorders that need to be considered in the differential diagnosis of patients with both ear and kidney abnormalities. Commonalities are present between the kidney and ear in a number of structural proteins, developmentally important transcription factors, ciliary proteins, and channel proteins, and mutations in these pathways can lead to disease in both organ systems. This manuscript reviews the congenital disorders with both hearing and kidney manifestations.

Keywords Sensorineural hearing loss · Alport syndrome · Congenital anomalies of the kidney and urinary tract

Introduction

The association between ear and kidney abnormalities has long been recognized; however, the connection between these two disparate organs is not always straightforward. Although Alport syndrome (AS) is the most well-known, there are over 20 disorders that need to be considered in the differential diagnosis of patients with both ear and kidney abnormalities. Kidney diseases associated with ear abnormalities can include a wide variety of disorders, including glomerulopathies, congenital anomalies of the kidney and urinary tract (CAKUT), ciliopathies, and tubulopathies.

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Normal hearing

Normal hearing requires multiple steps to convert sound waves to nerve signals that the brain can recognize as sound [1]. Sound waves enter the outer ear and cause vibrations of the tympanic membrane that are then amplified via the middle ear bones. Next, the vibrations are transferred to the fluid-filled, spiral-shaped cochlea, which is divided into three compartments: the scala vestibuli (vestibular duct) and scala tympani (tympanic duct), which both contain perilymph, and the scala media (cochlear duct), which contains endolymph (Fig. 1). The stria vascularis is an epithelium that lines the outer wall of the scala media and secretes potassium-rich (157 mM) and sodium-poor (1.3 mM) endolymph fluid compared with the perilymph (potassium 4.2 mM and sodium 148 mM) [2]. The organ of Corti lies on the basilar membrane and is responsible for converting physical sound waves into electrical nerve stimuli. Within the organ of Corti are inner hair cells and outer hair cells. Vibrations within the cochlear fluid are sensed by stereocilia on top of the hair cells, which are stimulated to bend, and lead to the opening of channels that allow movement of potassium across the cell membrane and electrical signal transmission through the auditory nerve to the brain. Abnormalities at any step of this process can lead to hearing loss. Commonalities are present between the kidney and ear in a number of structural proteins, developmentally important transcription factors, ciliary proteins, and channel

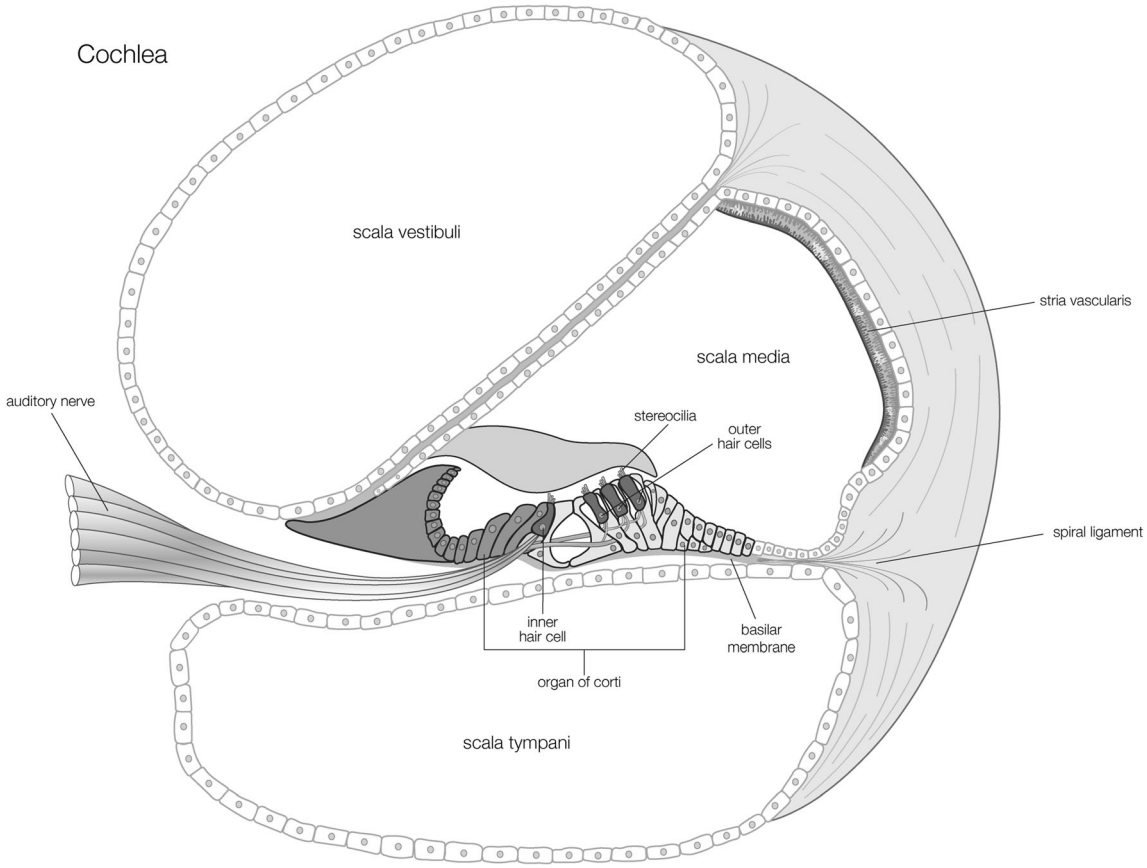

Fig. 1 Cochlear structures involved in normal hearing. For more detail, see the text

proteins, and mutations in these pathways can lead to disease in both organ systems.

Glomerulopathies

Alport syndrome

Alport syndrome (AS) is an inherited disorder that leads to progressive chronic kidney disease, sensorineural deafness, and ocular abnormalities. It is caused by mutations in *COL4A3*, *COL4A4*, and *COL4A5* that encode type IV collagen proteins required for maintenance of the glomerular basement membrane (GBM), cochlear basement membranes, and specific basement membranes in the eye [3, 4]. Affected children present with isolated microscopic hematuria followed by proteinuria and decline in glomerular filtration rate. Affected male subjects with X-linked AS and male and female subjects with autosomal recessive AS develop end-stage kidney disease (ESKD) at a median age of 25 years [5, 6]. Individuals with autosomal dominant AS have a slower progression, with only 50% requiring renal replacement therapy by the age of 50 years [7]. Females with X-Linked AS have a wide variability in outcomes, with some women demonstrating only isolated microscopic hematuria, whereas up to 30% of others develop ESKD by the age of 60 years [8, 9]. Treatment of kidney disease with angiotensin-converting enzyme inhibitors is recommended once proteinuria develops and may slow the progression to ESKD [10, 11].

Newborn hearing screening is normal in individuals with AS; however, high frequency hearing loss becomes apparent in late childhood by audiometry and later progresses into the frequency range of conversational speech. Hearing loss is present in 50% of males with X-linked AS by the age of 15 years and 90% by the age of 40 years [5]. Women with X-linked AS are at a lower risk of hearing loss, with 10% affected by the age of 40 years and 20% by the age of 60 years [9]. The hearing loss in AS has been localized to the cochlea [12]. Within the cochlea, type IV collagen is expressed in the spiral limbus, the spiral ligament, stria vascularis, and in the basement membrane situated between the organ of Corti and the basilar membrane [13–15].

MYH9-related disorders

MYH9-related disorders are rare autosomal dominant macrothrombocytopenias caused by mutations in *MYH9*, the gene encoding nonmuscle myosin IIA. These include Epstein syndrome, Fechtner syndrome, May–Hegglin anomaly, and Sebastian syndrome, which were originally classified as

separate disorders, but appear to be more appropriately classified as *MYH9*-related disorders with variable phenotypes of hearing loss, chronic kidney disease, leukocyte Döhle-like bodies, and cataracts [16].

Renal disease in *MYH9*-related disorders manifests as microscopic hematuria and proteinuria in approximately 30–70% of affected individuals, with a majority diagnosed before the age of 35 years [17]. Renal biopsy findings can be similar to those in AS and these disorders can be misdiagnosed owing to the similarities in clinical presentations and pathological findings. Biopsies early in the disease course demonstrate focal foot process effacement in areas of focal thickening of the GBM. At more advanced stages of disease, GBM thickening is more widespread, with areas of GBM lamellation. Isolated GBM thinning has also been reported [18].

Sensorineural hearing loss may be present in up to 58% of affected families at a mean age of 31 years, although some present in their adolescent years [19]. Although the exact mechanism by which mutations in *MYH9* cause hearing loss are unknown, nonmuscle myosin IIA is known to be expressed in several structures of the inner ear that are important for hearing, including the organ of Corti, the spiral ligament, and the spiral limbus [20].

Fabry disease

Fabry disease is a rare X-linked disorder characterized by accumulation of globotriaosylceramide (Gb3) in lysosomes of various cell types owing to deficiency of the lysosomal enzyme alpha-galactosidase A caused by mutations in the *GLA* gene. This accumulation causes thrombotic and ischemic complications including stroke, cardiac disease, and progressive chronic kidney disease. Additional findings may include hypohidrosis, angiokeratomas, pain in the hands and feet, and corneal opacities. Renal involvement presents as proteinuria, hematuria, and isosthenuria with progressive chronic kidney disease leading to ESKD predominantly in the 3rd to 5th decades of life.

Hearing loss is present in 18–55% of patients with Fabry disease and is predominantly sensorineural [21]. High-frequency hearing loss is detectable in a small percentage of children with Fabry disease [22]. The etiology of hearing loss is unclear. Human autopsy studies and mouse studies have demonstrated atrophy of the stria vascularis and spiral ligament, hair cell loss, and a decrease in the number of spiral ganglion cells [23, 24]. Enzyme replacement therapy does not reverse hearing loss; however, it is unknown whether or not early treatment prevents hearing loss [21].

Other glomerular disorders

A number of disorders may manifest as nephrotic syndrome (NS) or proteinuria and hearing loss. Charcot–Marie–Tooth disease is a constellation of inherited neuropathies with variable phenotypes and genetic causes [25]. Mutations in *INF2*, an actin regulatory protein found in podocytes and Schwann cells, cause Charcot–Marie–Tooth disease with focal segmental glomerulosclerosis (FSGS) [26]. INF2 interacts with diaphanous-related formins (mDia), inhibiting mDia-mediated actin polymerization in response to Rho signaling. Affected patients develop steroid-resistant FSGS and peripheral nerve dysfunction at a median age of 18 and 13 years respectively. Hearing loss is an inconsistent phenotype, with ~33% affected by mild to moderate sensorineural hearing loss [26]. The etiology of hearing loss is unclear; however, mDia1 is required for actin cytoskeletal maintenance in the inner ear hair cells [27].

Mutations in several genes associated with the biosynthesis of coenzyme Q10 have been associated with steroid-resistant NS including *COQ2* and *COQ6* [28–30]. Mutations in these genes lead to decreased coenzyme Q10 levels and reduced mitochondrial respiratory enzyme activity. COQ6 is located in podocyte cell processes, Golgi apparatus, stria vascularis, and spiral ligament cells of the inner ear [29]. Mutations in *COQ2* cause collapsing FSGS predominantly in the first decade of life, with increased numbers of mitochondria on EM and variable manifestation of hearing loss [28]. Additional findings may include encephalopathy, hypertrophic cardiomyopathy, and seizures [31]. Mutations in *COQ6* cause onset of steroid resistant NS due to FSGS or diffuse mesangial sclerosis within the first few years of life frequently associated with sensorineural hearing loss [29]. Early diagnosis of mutations in the coenzyme Q10 biosynthetic pathway is important, as early supplementation with coenzyme Q10 may be beneficial.

Mutations in *MTTL1* encoding tRNA-LEU, a mitochondrial-specific transfer RNA, can present with FSGS and sensorineural hearing loss [32, 33]. Patients are variably affected with MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes). Mutations in mitochondrial DNA are one of the most common causes of inherited deafness [34]. It is hypothesized that increased reactive oxygen species might cause damage to inner ear hair cells and cochlear neurons, leading to hearing loss. The pathogenesis of renal injury in individuals with *MTTL1* mutations is unclear.

Cockayne syndrome is a rare autosomal recessive disorder arising from mutations in genes involved in DNA nucleotide excision repair (*ERCC6* and *ERCC8*). It is characterized by growth retardation, cognitive deficits, premature aging, hearing loss, cataracts, retinopathy, sun sensitivity, and dental caries [35]. Renal involvement may include hypertension, proteinuria, and NS or hypoplasia/dysplasia in about 10% of patients, associated with diffuse, homogeneous GBM thickening on EM; however, the pathogenesis is unclear [36]. Sensorineural and/or conductive hearing loss may be present at birth and affects 60–80% of affected individuals [37].

Hearing loss is due to cell loss at multiple sites along the auditory pathways and mimics loss seen in normal aging [35].

Mutation in *CD151* have been reported in several families with sensorineural deafness, nephrotic range proteinuria, and renal failure, epidermolysis bullosa, and beta-thalassemia minor [38]. CD151 is an integral cell membrane protein and forms complexes with integrin α3β1 and α6β1 in the kidney and is required for glomerular and tubular basement membrane assembly [39].

Muckle–Wells syndrome is a rare auto-inflammatory disorder caused by *NLRP3* mutations, leading to overproduction of interleukin-1β, that is characterized by recurrent fever, arthralgias, fatigue, conjunctivitis, and urticarial rash. Sensorineural hearing loss and renal amyloidosis (<10%) are typically late manifestations of this disease [40]. Hearing loss is thought to be due to chronic inflammation of the inner ear and may improve with interleukin-1 blockade [41].

Congenital anomalies of the kidney and urinary tract

Branchio-oto-renal syndrome

Branchio-oto-renal syndrome is a relatively common (estimated incidence of 1:40,000) autosomal dominant disorder with hearing loss, outer ear malformations, and renal anomalies, with a variable penetrance caused by mutations in *EYA1*, *SIX1*, and *SIX5* [42–45]. Causative genes encode transcription co-activators with an effect on a wide array of downstream target genes [46]. EYA1 expression in the developing metanephros is restricted to condensing mesenchymal cells [47]. Congenital anomalies of the kidney and urinary tract can be identified in ~67% and include renal agenesis, hypoplasia/dysplasia, ureteropelvic junction obstruction, and vesicoureteral reflux (VUR) [48]. Hearing impairment is present in over 70% of affected individuals and may be sensorineural, conductive, or mixed [49]. During ear development, *EYA1* expression is observed in differentiating hair cells and in the associated ganglia and appears to be required for differentiation and survival of inner ear cells [47]. Additional phenotypic features may include cleft palate, retrognathia, facial nerve paresis, nonrotation of the gastrointestinal tract, and pancreatic duplication cyst [49].

Townes–Brocks syndrome

Townes–Brocks syndrome is an autosomal dominant disorder due to mutations in *SALL1* (encoding a zinc finger protein thought to act as a transcriptional repressor) that is characterized by the triad of imperforate anus, dysplastic ears, and thumb malformations [50]. SALL1 is expressed in the metanephric mesenchyme in the developing kidney and is required for ureteric bud invasion in kidney development [51]. Approximately 42% of affected individuals have renal anomalies that may include renal agenesis, hypoplasia/dysplasia, or cystic kidneys [52]. Hearing loss or dysplastic outer ears are observed in 65% of individuals with Townes–Brocks syndrome. Malformations in the malleus and incus have been identified in some patients with Townes=Brocks syndrome, leading to conductive hearing loss [53]. *SALL1* mutations also frequently lead to inner ear dysfunction and sensorineural hearing loss; however, the mechanisms are unclear [54]. Additional clinical findings may include club feet, toe malformations, genitourinary anomalies, and congenital heart disease.

CHARGE syndrome and Abruzzo–Erickson syndrome

The CHARGE syndrome is a rare disorder including coloboma, heart defects, choanal atresia, retardation of growth or development, genitourinary malformations, and ear anomalies due to a mutation in *CHD7*, a transcriptional regulator required for normal neural crest migration [55]. One patient with this phenotype has also been reported with a mutation in *SEMA3E*, encoding developmental neural guidance molecules [56]. Significant renal anomalies are uncommonly associated, but may include dysplasia, renal agenesis, or horseshoe/ectopic kidney. Genital hypoplasia occurs in 50–70% of individuals [57]. Either conductive or sensorineural hearing loss can occur in CHARGE syndrome. Typically, the lateral semicircular canals are absent; however, dysplasia of all semicircular canals and the cochlea can be observed [57].

Abruzzo–Erickson syndrome has been referred to as X-linked CHARGE syndrome and is caused by mutations in *TBX22*, a transcription factor [58]. Additional findings may include cleft palate and radial synostosis [59].

Other syndromes

A number of mutations in other genes are associated with very rare syndromes, with hearing loss, and with congenital anomalies of the kidney and urinary tract, and are summarized in Table 1.

Ciliopathies

Cilia are membrane-enclosed hair-like cell organelles that are found on the apical surface of many cells, including renal tubular cells. The broad range of phenotypes observed in ciliopathies demonstrates the presence of cilia in all organ systems. They function as chemo-, mechano- and osmosensors and mediate many pathways essential for organ development, including left–right organization of the internal organs [60]. Genetic disorders of primary cilia are a frequent cause of childhood renal disease, which is frequently cystic in

Table 1 Renal syndromes associated with hearing loss

Name	Gene	Inheritance	Renal/genitourinary findings	Extrarenal findings	Hearing loss frequency (%)
CAKUT					
Abruzzo–Erickson syndrome	*TBX22*	XL	Horseshoe kidney	Coloboma, cleft palate, hypospadias, short stature	Male: >80 Female: rare
Barakat syndrome	*GATA3*	AD?	Renal dysplasia, steroid-resistant nephrosis	Hypoparathyroidism	100
Baraitser–Winter syndrome	*ACTB*, *ACTG1*	AD	Hydronephrosis, horseshoe, ectopic kidney	Dysmorphic facial features, iris or retinal coloboma	30–43
Branchio-oto-renal syndrome	*EYA1*, *SIX1*, *SIX5*	AD	Renal hypoplasia/dysplasia, 5–10% ESKD	Variable penetrance; external ear anomalies, branchial fistulae or cysts	70
CHARGE syndrome	*SEMA3E*, *CHD7*	AD	Dysplasia, renal agenesis, ectopy	Coloboma, choanal atresia, genital anomalies, ear anomalies	70–90
Fronto-metaphyseal dysplasia	*FLNA*	XL	Hydronephrosis, hydroureter	Skeletal anomalies, cleft palate	Male: >95 Female: rare
Leopard/Noonan syndrome	*PTPN11*, *RAF-1*, *BRAF*, *MAP2K1*	AD	Unilateral renal agenesis	Multiple lentigines, conduction abnormalities, abnormal genitalia, pulmonic stenosis	20
Neurodevelopmental disorder with or without anomalies of the brain, eye, or heart	*RERE*	AD	VUR, hypospadias, cryptorchidism	Developmental delay, eye abnormalities, congenital heart defects	28
Townes–Brocks syndrome	*SALL1*	AD	Renal hypoplasia/dysplasia	Imperforate anus, limb defects	65
Wolfram syndrome	*WFS1*	AR	Hydronephrosis, neurogenic bladder	Diabetes mellitus, optic atrophy, diabetes insipidus	66
Zellweger syndrome	*PEX1*	AR	Hydronephrosis, cortical cysts	Severe neurological dysfunction, craniofacial abnormalities, liver dysfunction	>75
Ciliopathies					
Alstrom syndrome	*ALMS1*	AR	Tubulointerstitial nephropathy	Retinitis pigmentosa, obesity, diabetes mellitus	88
Bardet–Biedl	*BBS1*, *BBS2*, *ARL6* (BBS3), *BBS4*, *BBS5*, *MKKS* (BBS6), *BBS7*, *TTC8* (BBS8), *BBS9*, *BBS10*, *TRIM32* (BBS11), *BBS12, MKS1* (BBS13), *CEP290* (BBS14), *WDPCP* (BBS15), *SDCCAG8* (BBS16), *LZTFL1* (BBS17), *BBIP1* (BBS18), and *IFT27* (BBS19)	AR	Polyuria/polydipsia, cysts, tubulointerstitial nephropathy	Obesity, retinopathy, polydactyly, developmental delay, diabetes mellitus, hypogonadism	11–50
Glomerular disease					
Alport syndrome	*COL4A3*, *COL4A4*, *COL4A5*	AR, AD, XL	Hematuria, proteinuria, ESKD	Eye abnormalities (anterior lenticonus, maculopathy)	XL male: 80–90 XL female: 20

Table 1 (continued)

Name	Gene	Inheritance	Renal/genitourinary findings	Extrarenal findings	Hearing loss frequency (%)
Charcot–Marie–Tooth	*INF2*	AD	Proteinuria, FSGS	Distal muscle weakness and atrophy, distal sensory loss	33
Cockayne syndrome	*ERCC6*, *ERCC7*	AR	Proteinuria, CKD	Growth retardation, neurological abnormalities, premature aging, cataracts, retinopathy	60–80
Coenzyme Q10 deficiency	*COQ6*, *COQ2*	AR	Nephrotic syndrome (FSGS, DMS)	Encephalopathy, hypertrophic cardiomyopathy, seizures	>90
Fabry disease	*GLA*	XL	Hematuria, proteinuria, ESKD	Stroke, cardiac disease, acroparesthesias, angiokeratomas, hypohidrosis	18–55
MELAS syndrome	*MTTL1*	Mitochondrial	Proteinuria, FSGS	Mitochondrial encephalopathy, lactic acidosis, stroke-like episodes	75
Muckle–Wells syndrome	*NLRP3*	AD	Amyloidosis	Recurrent fever, arthralgias, fatigue, urticarial rash	80–99
MYH-9 related disorders (Epstein, Fechtner syndromes)	*MYH9*	AD	Hematuria, proteinuria, ESKD	Macrothrombocytopenia, leukocyte inclusions, cataracts	58
Nephropathy with pretibial epidermolysis bullosa and deafness	*CD151*	?	Nephrotic range proteinuria, ESKD	Epidermolysis bullosa, beta thalassemia major	66
Tubular disorders					
Bartter syndrome type IV	*BSND* (or double heterozygous *CLCNKA* and *CLCNKB*)	AR	Polyuria, hypokalemic salt-wasting tubulopathy, CKD		>90
Combined oxidative phosphorylation deficiency	*RMND1*	AR	Dysplasia, RTA	Hypotonia, liver dysfunction, lactic acidosis, encephalopathy	Unknown
Distal renal tubular acidosis with progressive nerve deafness	*ATP6B1*, *ATP6N1B*	AR	Distal RTA, nephrocalcinosis		66
EAST syndrome (SESAME syndrome)	*KCNJ10*	AR	Polyuria, sodium and potassium wasting	Seizures, ataxia, developmental delay	80–99
Pendred syndrome	*SLC26A4* (or double heterozygous *SLC26A4* and *FOXI1*)	AR	No renal phenotype at baseline, but may have hypovolemia and metabolic alkalosis when exposed to alkali load or thiazides	Goiter	100

AD autosomal dominant, *AR* autosomal recessive, *CAKUT* congenital anomalies of the kidney and urinary tract, *CHARGE* coloboma, heart defects, choanal atresia, retardation of growth or development, genitourinary malformations, and ear anomalies, *CKD* chronic kidney disease, *EAST* epilepsy ataxia sensorineural-deafness tubulopathy, *ESKD* end stage kidney disease, *FSGS* focal segmental glomerulosclerosis, *MELAS* mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, *RTA* renal tubular acidosis, *SESAME* sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance, *VUR* vesicoureteral reflux, *XL* X-linked

nature. Primary cilium dysfunction alters spatial organization of the cells (planar cell polarity) and therefore cellular growth and development, possibly via deranged Wnt signaling [61]. This leads to cystic kidneys and often many extra-renal defects. Examples of renal ciliopathies include autosomal recessive and dominant polycystic kidney disease, von Hippel–Lindau disease, tuberous sclerosis, and the medullary cystic kidney disease–nephronophthisis complex. The Bardet–Biedl and Alstrom syndromes are ciliopathies causing renal disease and deafness in addition to sharing other phenotypic characteristics, such as retinitis pigmentosa, obesity, and diabetes mellitus. In addition to primary cystic kidney disease, affected individuals may develop secondary renal dysfunction due to diabetes and hypertension.

Bardet–Biedl syndrome

Bardet–Biedl syndrome (BBS) is characterized by polydactyly, learning difficulties, and hypogonadism in addition to the features listed above. Polydactyly (and perhaps brachydactyly and syndactyly) may be the only early feature; thus, diagnosis is often delayed until later in childhood. Obesity is particularly common and most develop blindness by the second or third decade because of an atypical retinitis pigmentosa with early macular involvement [62]. Data on deafness in BBS is often incomplete, although a series of 109 cases reported hearing loss in 21% of patients, mostly because of a conductive pattern (chronic otitis media), although 3 patients had unexplained sensorineural deafness [63]. Up to 50% of adults with BBS had subclinical sensorineural deafness in another series [64]. The renal phenotype is variable, with structural malformations common, although a cystic tubulopathy similar to nephronophthisis is typical. It is a rare disorder with a variable prevalence, ranging from 1 in 13,500 among the Bedouin peoples of Kuwait to 1 in 100,000 and 1 in 160,000 in North America and Switzerland respectively [6]. It is a heterogenous genetic condition, generally inherited in an autosomal recessive pattern. Mutations in at least 19 genes are associated with the syndrome, with those in *BBS1* the most common, followed by *BBS10* (Table 1) [63, 65]. The BBS proteins form a complex, the BBSome, which is involved in cilia targeting and assembly. *MKKS* (BBS6) is expressed in inner hair cells and outer hair cells of the cochlea and mutations may impair function of the kinocilium, which is important for cochlear development [64, 66]. A study of 350 cases of BBS from a UK registry found that 31% of children and 42% of adults had CKD. It also noted that a severe phenotype was likely with the presence of two truncating mutations and a BBS10 (versus BBS1) mutations [65].

Alstrom syndrome

Alstrom syndrome is an autosomal recessive disorder caused by mutations in the *ALMS1* gene, the protein of which is found in the cilium basal body. It shares many clinical features of BBS including cone–rod dystrophy and childhood obesity, although there is no polydactyly, hypogonadism or learning difficulty [67]. The hearing loss in individuals with Alstrom syndrome is sensorineural in origin. It is recognized that altered planar cell polarity in the inner ear disrupts orientation of the stereociliary bundles, mechanosensing organelles of hair cells, which may explain the pathogenesis of the deafness in Alstrom syndrome [68]. A myriad of urological problems are frequently reported. Consistent with BBS, the renal disease appears to be predominantly due to interstitial fibrosis in cases in which biopsies are performed [69]. Life expectancy is often greatly reduced because of dilated cardiomyopathy, liver disease, and restrictive lung disease.

Tubulopathies

There are several rare genetic syndromes that share the phenotypes of deafness and renal tubular dysfunction. These syndromes are mostly due to co-localization of electrolyte channels in the cochlea and renal tubular cells. In contrast to ciliopathies, where renal impairment may occur because of tubulointerstitial fibrosis, these syndromes feature various metabolic phenomena caused by altered tubular cell function (Fig. 2).

Bartter syndrome

Bartter syndrome (BS) is a group of autosomal recessive disorders caused by mutations in various ion transport mechanisms of the thick ascending limb of the loop of Henle. It is characterized by hypokalemia, metabolic alkalosis, often hypercalciuria and hyperreninemia due to hyperplasia of the juxtaglomerular apparatus. These metabolic features mimic those seen with the chronic use of loop diuretics. In types I, II, and III BS respectively, the altered channels are the Na-K-2Cl co-transporter (coded by *SLC12A1*), the luminal potassium channel ROMK (coded by *KCNJ1*), and the basolateral chloride channel ClC-Kb (coded by *CLCNKB*) [70]. Deafness is not a feature of these conditions.

Bartter syndrome with sensorineural deafness (BS type IV) is due to the loss of function mutations in *BSND* [71–73], coding Barttin, a protein that co-localizes to the basolateral membrane of the loop tubular cells and the inner ear epithelia [73]. Barttin is critical for both the ClC-Ka and ClC-Kb channels. These channels have an overlapping function; thus, the complete phenotype requires defects in both the ClC-Ka and ClC-Kb channels, explaining the milder disease seen in BS type III (preserved ClC-Ka activity). Aside from *BSND* mutations affecting barttin, simultaneous mutations of genes coding ClC-Ka and ClC-Kb cause a similar phenotype [74], termed BS type IVb. This also explains why deafness is not

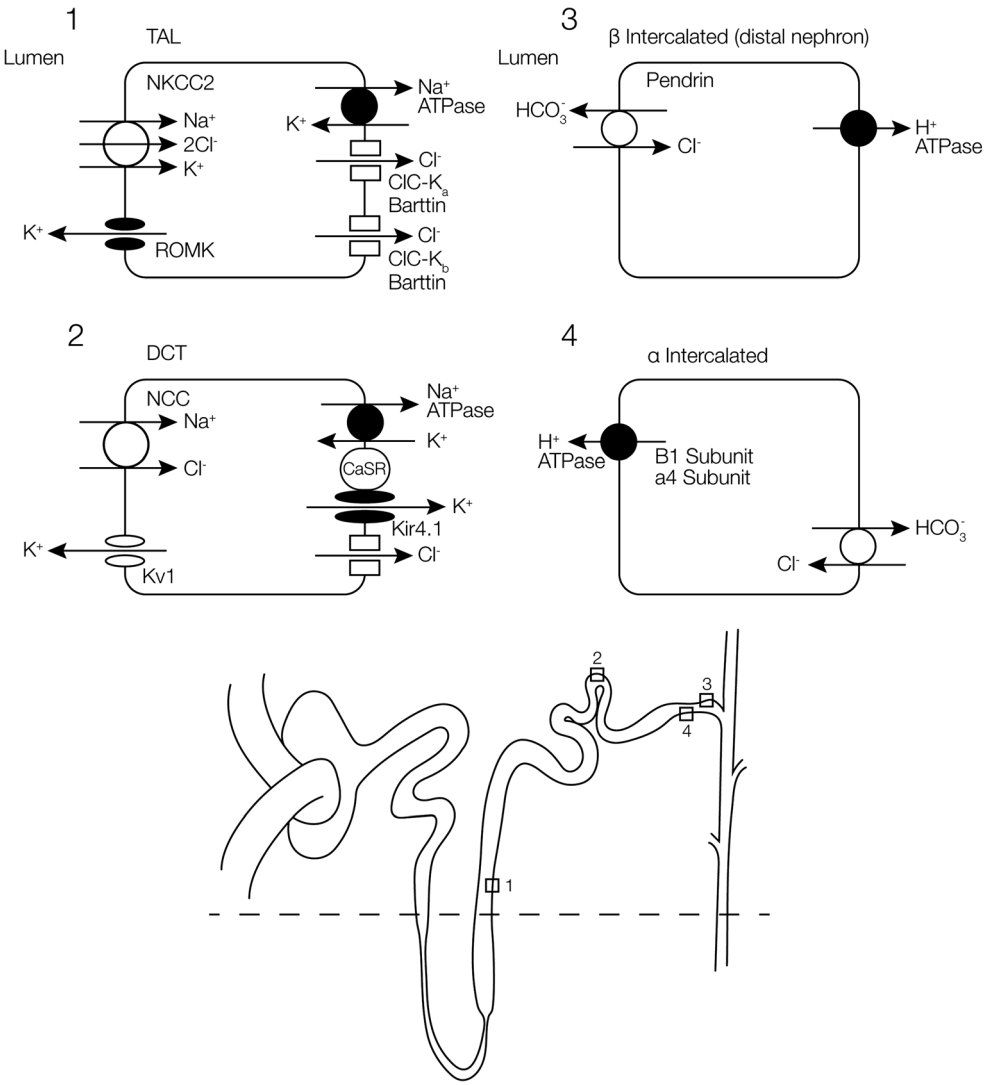

Fig. 2 Localization of tubular channels affected in renal and hearing syndromes. **a** Abnormalities in barttin, critical for function of the basolateral chloride channels in the thick ascending limb of the loop of Henle, cause Bartter syndrome. **b** Abnormalities in Kir4.1, an inward rectifying potassium channel in the distal convoluted tubule, cause EAST syndrome. **c** Abnormalities in pendrin, a sodium-independent chloride–bicarbonate exchanger on the apical membrane of β-intercalated cells of the distal nephron, cause Pendred syndrome. **d** Abnormalities in the B1 and a4 subunits of H^+-ATPase in α-intercalated cells cause distal renal tubular acidosis with deafness. *TAL* thick ascending limb, *ROMK* renal outer medullary potassium channel, *DCT* distal convoluted tubule, *NCC* sodium-chloride co-transporter, *CaSR* calcium sensing receptor

a feature of BS type III (only ClC-Kb is affected). The phenotype of BS type IV is generally that of severe salt-losing nephropathy and early sensorineural deafness. There is often an antenatal presentation with polyhydramnios in the mother and neonatal volume depletion in the infant. Type IV disease may also demonstrate progressive renal dysfunction more commonly than other BS subtypes. This phenotypic variability may be modified by the particular causative mutation in *BSND* [71].

EAST syndrome

The EAST syndrome is an autosomal recessive condition caused by mutation in the *KCNJ10* gene, coding for an inward rectifying potassium channel. This channel, Kir4.1, is expressed on the basolateral membrane of the distal nephron, from the macula densa to the early cortical collecting duct. It is expressed in the spinal cord and brain, where it may maintain membrane resting potential and modulate cell excitability [75]. It is also found in the cochlea, where it is involved in the generation of endolymph. Loss of function mutations in *KCNJ10* are characterized by epilepsy, ataxia, moderate sensorineural deafness, and tubulopathy leading to a salt-losing nephropathy similar to BS (with hypokalemia, metabolic alkalosis, and normal blood pressure) [76]. It was described by Scholl et al. as SESAME syndrome with features of seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance [77]. Neurological features include generalized seizures in infancy, delayed psychomotor development, ataxia with a progressive axonal neuropathy, and hypomyelination [77]. The salt-wasting and hypokalemic state may be explained by impaired function of the distal convoluted tubular cells due to mutant Kir4.1, as basolateral potassium recycling is critical for Na-Cl reabsorption [78].

Combined oxidative phosphorylation deficiency-11

Combined oxidative phosphorylation deficiency is a group of rare autosomal recessive disorders with multisystemic

features. Loss-of-function mutations in mitochondrial translation genes cause the syndrome, with the *RMND1* gene being responsible for combined oxidative phosphorylation deficiency-11 [78]. Features include seizures, encephalopathy, hypotonia, liver disease, lactic acidosis, and death in infancy. Additionally, hearing loss and renal failure in the context of a tubulopathy have also been described [78, 79]. Other renal phenotypes reported include dysplastic kidneys and renal tubular acidosis [79], but the pathogenesis of the renal involvement remains unclear given the rarity of the condition.

Distal renal tubular acidosis with progressive nerve deafness

Distal renal tubular acidosis (RTA) with progressive nerve deafness is another rare autosomal recessive condition caused by mutations in the *ATP6B1* gene. This gene codes for the B1 subunit of H^+-ATPase, which co-localizes to the apical surface of α-intercalated cells of the distal nephron and the endolymphatic sac of the cochlea. The deafness is presumably caused by impairment of endolymphatic pH homeostasis with alkalinization of endolymph leading to altered hair cell function [80]. The presentation is usually in childhood with failure to thrive and a tubulopathy manifested by hyperchloremic metabolic acidosis (type 1 distal RTA), hypokalemia and hypercalciuria, often with nephrocalcinosis and stone disease [80]. Although alkali therapy may help the systemic pH, it has no impact on hearing loss.

Mutations in the *ATP6N1B* gene, coding for the a4 subunit of H^+-ATPase, also cause distal RTA, but deafness was not thought to be a consequence [81]. However, reports have emerged of later onset deafness occurring with *ATP6N1B* mutations when individuals were followed up into adulthood [82, 83]. In some cases, childhood deafness has also been reported, demonstrating the genetic and phenotypic variability of distal RTA with progressive nerve deafness [83].

Pendred syndrome

Pendrin is a sodium-independent chloride–bicarbonate exchanger found in the inner ear and thyroid, where it regulates acid/base in the endolymphatic sac and iodide transport respectively. It is also found on the apical membrane of β intercalated cells in the distal nephron, where it mediates bicarbonate secretion and chloride absorption [84]. Pendred syndrome is an autosomal recessive disorder caused by mutation in the *SLC26A4* gene, which encodes pendrin. The phenotype is that of sensorineural deafness and goiter, as described by Vaughan Pendred [85].

Pendrin is upregulated in metabolic alkalosis, which attenuates the alkalosis by secreting bicarbonate. However, patients with Pendred syndrome generally have no electrolyte or acid/base disturbance at baseline, possibly because pendrin and the Na-Cl co-transporter (NCC) cross-compensate for each other. Pendrin appears to have minimal influence on Na-Cl reabsorption in the steady state, but may be critical when NCC is inactivated. This explains why patients with Pendred syndrome may develop profound hypovolemia, hypokalemia, and hypochloremic metabolic alkalosis if exposed to thiazide diuretics [86] or an alkali load. It also explains why mice with double pendrin/NCC gene knockouts display a similar phenotype [87].

It is notable that mutations in *SLC26A4* may cause isolated deafness often with an enlarged vestibular aqueduct. Moreover, many patients with the Pendred phenotype lack a mutation in *SLC26A4*, suggesting additional undiscovered genetic causes. Cases of Pendred syndrome have also been described with homozygous mutations in *SLC26A4* and in *FOXI1*, a gene that regulates *SLC26A4*, again highlighting the genetic heterogeneity of the condition [88].

Multiple choice questions (answers are provided following the reference list)

1. A 17-year-old boy has sensorineural hearing loss, hematuria, and proteinuria with GBM thickening on electron microscopy, and thrombocytopenia. Mutation in which of the following genes is the most likely cause of his symptoms?

   a) *COL4A5*
   b) *COL4A3*
   c) *MYH9*
   d) *COQ2*
   e) *CD151*

2. A 1-year-old boy has small dysplastic kidneys, triphalangeal thumbs, and a history of imperforate anus corrected in the neonatal period. What is the child's most likely underlying diagnosis?

   a) Townes–Brocks syndrome
   b) Branchio-oto-renal syndrome
   c) CHARGE syndrome
   d) Abruzzo–Erickson syndrome
   e) Wolfram syndrome

3. A 5-year-old has sensorineural deafness, hypokalemia, metabolic alkalosis, and polyuria. Mutation in which of the following genes is likely to be the cause of his symptoms?

   a) *SLC12A1* (Na-K-2Cl co-transporter)
   b) *KCNJ1* (ROMK potassium channel)
   c) *KCNJ10* (Kir4.1 potassium channel)
   d) *BSND* (Barttin)
   e) *ATP6B1* (B1 subunit of H^+-ATPase)

4. A 16-year-old boy with recently diagnosed X-linked Alport syndrome has proteinuria (1.5 g/day), normal blood pressure, and eGFR of 85 ml/min/1.73 m^2. What treatment should be initiated to slow the progression of chronic kidney disease?

   a) Calcineurin inhibitor
   b) Calcium channel blocker
   c) Beta blocker
   d) Thiazide diuretic
   e) ACE inhibitor

5. An 8-year-old girl has steroid-resistant nephrotic syndrome and FSGS on kidney biopsy. Treatment with coenzyme Q10 should be initiated if a mutation is identified in which of the following genes?

   a) *COQ2*
   b) *MTTL1*
   c) *INF2*
   d) *CD151*
   e) *COL4A5*

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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Answers

1. c; 2. a; 3. d; 4. e; 5. a