Syndromic Hearing Loss: A Brief Review of Common Presentations and Genetics

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J Pediatr Genet 2018;7:1–8.

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Abstract

Congenital hearing loss is one of the most common birth defects worldwide, with around 1 in 500 people experiencing some form of severe hearing loss. While over 400 different syndromes involving hearing loss have been described, it is important to be familiar with a wide range of syndromes involving hearing loss so an early diagnosis can be made and early intervention can be pursued to maximize functional hearing and speech-language development in the setting of verbal communication. This review aims to describe the presentation and genetics for some of the most frequently occurring syndromes involving hearing loss, including neurofibromatosis type 2, branchio-oto-renal syndrome, Treacher Collins syndrome, Stickler syndrome, Waardenburg syndrome, Pendred syndrome, Jervell and Lange-Nielsen syndrome, Usher syndromes, Refsum disease, Alport syndrome, MELAS, and MERRF.

Keywords
- hearing loss
- syndromic
- sensorineural

Introduction

Congenital hearing loss is one of the most common birth defects worldwide. Estimates show that prelingual congenital hearing loss affects approximately 1 in 1,000 children, with an additional 1 in 1,000 people experiencing postlingual severe hearing loss.[1,2] Roughly 15% of all congenital hearing loss is syndromic.[2,3] While over 400 different syndromes involving some degree of hearing loss have been described, it is important to be familiar with a wide range of syndromes involving hearing loss so an early diagnosis can be made and early intervention can be pursued to establish, preserve, or restore functional hearing to maximize speech-language development in the setting of verbal communication. This review sets out to describe the clinical presentation and most common genetics for some of the most frequently occurring syndromes involving hearing loss.

Autosomal Dominant Syndromes

Neurofibromatosis Type 2

Neurofibromatosis type 2 (NF2, OMIM 101000), is characterized by the development of bilateral vestibular schwannomas (VS) with multiple other meningiomas, optic gliomas, ependymomas, and other spinal tumors.[4] NF2 definitive diagnostic criteria include bilateral VS or family history of NF2 in a first-degree relative, plus either of the following: (1) unilateral VS at age younger than 30, or (2) any two of the following: meningioma, glioma, schwannoma, or juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract.[4] Hearing loss is the most common presenting symptom in NF2 and is usually high frequency and sensorineural.[5,6] Associated findings of facial nerve paresis or paralysis, tinnitus, vertigo, and other balance problems can be seen as well.[4]

NF2 is an autosomal dominant disease, and 50% of children of affected individuals are at risk for developing the disease. Of patients in whom NF2 is diagnosed, 50% present with a family history of NF2. Half of all NF2-affected patients have no family history of NF2 and are considered founder cases.[4] The incidence of NF2 is 1 per 25,000 live births.[7] The NF2 gene (OMIM 607379), located on chromosome 22q12.17, codes for a protein called *Merlin* or *Schwannomin*.[8] This protein is a tumor suppressor that helps correct F-actin cytoskeletal defects found in schwannomas.[9] Several additional genes affecting a wide range of pathways—including angiogenesis, tumor suppression, and vascular endothelial growth factor (VEGF) inhibition,

received
September 21, 2017
accepted after revision
November 29, 2017
published online
January 4, 2018

DOI https://doi.org/10.1055/s-0037-1617454.
ISSN 2146-4596.

to name a few—appear to become deregulated in NF2, though the specific mechanism is not fully understood at this time.[10]

Branchio-Oto-Renal Syndrome

As the name implies, branchio-oto-renal syndrome (BOR) can involve anomalies of the branchial arch system, ears, and renal system. In terms of clinical presentation from an otologic perspective, BOR can have outer, middle, or inner ear manifestations. External ear anomalies include preauricular pits or tags (82%), malformation of the auricle (32%), microtia, and narrowing of the external auditory canal.[11–13] Middle ear anomalies include absence of the oval window, facial nerve dehiscence, decreased size of the middle ear cleft, and fusion, displacement, or underdevelopment of the osicles.[11] Inner ear anomalies include cochlear dysplasia and hypoplasia, enlarged vestibular aqueduct (EVA), and lateral semicircular canal irregularities.[14] Some degree of hearing impairment is seen in up to 90% of patients, most frequently a mixed loss (50%), but sometimes exclusively conductive (30%) or sensorineural (20%).[13] Thirty-five percent of affected individuals experience severe hearing loss, and approximately 25% of individuals have a progressive loss.[13] Most commonly, branchial anomalies are present in roughly half of affected individuals, and typically manifest as lateral cervical fistulae, sinuses, and cysts. Renal anomalies occur in approximately 65% of cases and include agenesis (most commonly), hypoplasia, and dysplasia.[13] Less commonly, lacrimal duct aplasia, short palate, retrognathia, and benign intracranial tumors are seen.[13]

BOR is transmitted in an autosomal dominant fashion with penetrance approaching 100%. BOR is seen in approximately 1 in every 40,000 births, but it is noted in roughly 1 out of every 50 profoundly deaf children.[13,15] The EYA1 gene (OMIM 601653), identified at chromosome 8q13.3, has been shown to underlie the disease, with two other genes of the same family, EYA2 (OMIM 601654) and EYA3 (OMIM 601655), as less common causes.[16,17] Relatively recently, two additional genes, SIX1 (OMIM 601205) and SIX5 (OMIM 600963), have been identified to play a role in BOR as well.[18,19] SIX proteins translocate EYA proteins from the cytoplasm to the nucleus. EYAs work as transcriptional coactivators upon recruitment by the SIX protein, and the SIX protein is transformed into a strong transcription activator after interaction with EYA.[20] More specifically, EYA1 and SIX1 products work together to initiate neuronal development of the inner ear and can also induce differentiation of cochlear neurosensory stem cells to hair cells.[20]

Treacher Collins Syndrome

First broadly described by Edward Treacher Collins in 1900, then more completely by Franceschetti and Klein in 1949, Treacher Collins syndrome (TCS) or mandibulofacial dysostosis is a syndrome with characteristic craniofacial abnormalities and conductive hearing loss. Common presenting features include hypoplastic facial bones, particularly the mandible and zygomatic complex, with resulting malocclusion, high-arched palate, and occasional clefting.[21] Downward slanting palpebral fissures, notching of lower eyelids, and decreased eyelashes medial to lid defect are also commonly seen.[21] From an aural and auditory standpoint, auricular malformations are commonly seen, including atresia of the external auditory canals and ossicular anomalies.[21,22] Much variation has been shown in TCS patients with regard to the ossicles and middle ear space in general, including missing or grossly malformed ossicles, ossicular fusion, absent or malformed oval window, and even total absence of the middle ear and epitympanic space.[21,22] These defects predictably lead to conductive hearing impairment, but sensorineural or mixed hearing loss is uncommon.[21–23]

Treacher Collins is transmitted in an autosomal dominant fashion.[24] Incidence is reported at roughly 1 in 50,000, though approximately 50% of cases are believed to be de novo mutations.[21,24–26] Most cases of TCS can be traced to mutations of the TCOF1 (OMIM 606847) gene on chromosome 5q32–33.1, which codes for a protein of uncertain function called *treacle*.[24] Less commonly, mutations in *POLR1D* (OMIM 613715) and *POLR1C* (OMIM 610060) are responsible for TCS, and these genes code for RNA polymerase subunits involved in rRNA transcription.[27,28]

Stickler Syndrome

Stickler syndrome (SS) is an autosomal dominantly inherited disorder of collagen connective tissue with predominantly ophthalmic, orofacial, auditory, and articular manifestations.[29,30] Diagnostic criteria include a congenital vitreous anomaly, and any three of the following: myopia at younger than 6 years of age, rhegmatogenous retinal detachment or paravascular pigmented lattice degeneration, joint hypermobility with abnormal Beighton score, sensorineural hearing loss (SNHL) noted on audiometric assessment, or midline clefting.[29] Micrognathia is seen in up to two-thirds of cases, and when severe leads to Robin sequence.[29,31,32] Clefting can manifest across a broad spectrum, from complete hard and soft palate clefting to bifid uvula or submucous clefting.[30,32,33] Craniofacial anomalies such as hypertelorism, epicanthal folds, flattened midface, short upturned nose, or a long philtrum can be seen as well.[34–36] Conductive, pure sensorineural, and mixed hearing loss have all been reported with SS. Conductive loss in SS typically results from Eustachian tube dysfunction that is frequently seen with craniofacial defects.[32] While incidence of SNHL increases with age, the pathogenesis of SNHL is incompletely understood. Possible mechanisms include alterations in the pigmented epithelium of the inner ear or abnormalities of inner ear collagen from autoantibodies.[31,37] Computed tomography has not shown evidence of gross structural abnormalities.[32] From an ocular standpoint, most SS patients are myopic, but vitreoretinal degeneration, retinal detachment, cataract, and blindness can also occur, with retinal detachment leading to blindness seen in approximately half of SS patients.[29,30]

SS has an autosomal dominant inheritance pattern and is caused by mutations in the *COL2A1* (OMIM 120140), *COL11A2* (OMIM 120290), or *COL11A1* (OMIM 120280) genes that encode for the constituent proteins of type II and type XI collagen.[38–40] Type I SS (STL1) (OMIM 108300) is caused by mutations in *COL2A1*.[38] This phenotype includes the classic ocular findings with a "membranous" vitreous, and often, palate deformities are seen. Patients with STL1 have either

normal hearing or only a mild impairment.[41] Type II SS (STL2) (OMIM 604841) results from missense mutations in *COL11A2*, and interestingly, no ocular anomalies are seen in STL2 as the causative gene is not expressed in the vitreous.[40] Hearing loss in STL2 is moderate.[41] Type III SS (STL3) (OMIM 184840) is caused by mutations in *COL11A2*.[40] Of note, autosomal recessive forms of SS with phenotype similar to STL3 exist due to mutations of COL9A1 (STL4) (OMIM 614134) and COL9A2 (STL5) (OMIM 614284), though palate defects are rarely seen.[42,43] Patients with STL3 tend to have moderate to severe hearing loss in childhood, and generally do not have the vitreous irregularities seen in STL1.[41]

Waardenburg Syndrome

Waardenburg syndrome (WS) refers to a condition affecting pigmented cells in various locations of the body, including the stria vascularis of the cochlea.[44,45] WS is subdivided into four distinct types. Type I WS (WS1) (OMIM 193500) is characterized by dystopia canthorum, an involuntary displacement of the inner canthi and lacrimal puncti giving the impression of a widened nasal bridge.[44,45] Additional features often include heterochromia iridium (pale blue eye), white forelock, synophrys, broad nasal root, hypoplasia of the alae nasi, patent metopic suture line, and a square jaw.[44–46] Hearing impairment is seen in between one-third and two-thirds of WS1 patients.[47,48] In type II WS (WS2, OMIM 193510), presentation is largely the same as WS1 without dystopia canthorum.[48] Congenital deafness is seen in just over half up to as many as 85% of WS2 patients.[47,48] Type III WS (WS3) (OMIM 148820), also known as Klein–Waardenburg Syndrome, has similar presentation as WS1, with the addition of musculoskeletal abnormalities such as limb and digit defects.[49] Type IV WS (WS4) (OMIM 277580), also known as Shah–Waardenburg Syndrome or Waardenburg–Hirschsprung disease has similar presentation to WS1 with the addition of Hisrchsprung's disease features (aganglionic megacolon).[50]

Initially, WS (all variants taken together) had an estimated prevalence of 1 in 42,000, but more recent studies estimate the prevalence is closer to 1 to 2 per 20,000 with an incidence of 1 to 2 per 8,400.[45,51] WS1 is caused by mutations in *PAX3* (OMIM 606597), which is expressed in neural crest cells in early development, and melanocytes, including those in the stria vascularis, can thus be absent in WS1 patients.[45] PAX3 also plays a role in limb bud development, so it is believed to be responsible for WS3 phenotypic findings.[45] While there is a greater degree of heterogeneity in the underlying genetics of WS2 phenotypic individuals, mutations in the *microphthalmia* (*MITF*) (OMIM 156845) gene, a transcription factor that, like PAX3, plays a role in melanocyte development have been found in roughly 15% of affected individulas.[45,52] Mutations in SNAI2 (OMIM 602150) transcription factor involved in neural crest cell migration, have also been shown to cause WS2.[53] Endothelin 3 (*EDN3*) (OMIM 131242), endothelin receptor B (*EDNRB*) (OMIM 131244), and *SOX10* (OMIM 602229) genes have been rarely associated with WS2, but mutations of each of the three genes is more commonly seen in WS4.[52–55] WS1 and WS3 are always thought to be autosomal dominant, while WS2 is mostly dominant with rare cases of autosomal recessive inheritance being seen, and WS4 is thought to always be recessive.[49,52,53,55–57]

Autosomal Recessive Syndromes

Pendred Syndrome

Pendred syndrome (OMIM 274600) is an autosomal recessive disorder characterized by sensorineural deafness, goiter, and a partial defect in iodide organification.[58] First described in the literature by Pendred in 1896, deafness is often the presenting symptom, and in the majority of cases the deafness is prelingual.[47,59,60] Accompanying the sensorineural deafness are inner ear malformations including enlargement of the endolymphatic system, often seen on imaging as an EVA.[61] Some patients also have been shown to have a Mondini malformation, where only the basal one and a half turns are present instead of the typical coiled scala.[62] Thyroid enlargement can vary widely from normal thyroid to significant goiter that can impinge upon the airway.[63] Normally, less than 10% of radioiodide accumulated in thyrocytes are not rapidly organified into thyroglobulin for the purpose of thyroid hormone synthesis. In contrast, patients with Pendred syndrome lose more than 15% thus indicating an impaired iodide organification.[59,62] Despite the variation in iodide organification, most patients with Pendred are euthyroid unless they have deficient dietary iodine.[64]

Pendred syndrome is inherited in an autosomal recessive fashion and results from a mutation of the PDS/SLC26A4 gene (OMIM 605646) on chromosome 7.[65] The affected gene codes for an ion transporter protein named pendrin, most abundantly expressed in the thyroid, inner ear, and kidney.[64,65] In Pendred syndrome, the SLC26A4 mutation is biallelic, but EVA can be observed in nonsyndromic hearing loss if there is homozygosity for the *SLC26A4* wild-type or only one mutated allele.[64,66] Overall, it is estimated that Pendred syndrome accounts for up to 10% of hereditary hearing loss with and incidence of 7.5 to 10 in 100,000.[62,63]

Jervell and Lange-Nielsen Syndrome

Jervell and Lange-Nielsen syndrome (JLNS) was first described in 1957 by Jervell and Lange-Nielsen in a Norwegian family in which four of six siblings had congenital deafness, marked prolongation of the QT interval, and multiple syncopal attacks induced by exercise or emotion.[67,68] JLNS is inherited in autosomal dominant fashion. QT prolongation without congenital deafness may be inherited in dominant or recessive fashion, and the more common dominant disease is known as Romano–Ward syndrome.[69] Mutations of the KCNQ1 gene (JLNS1) (OMIM 607542) on chromosome 11 and mutations of the KCNE1 gene (JLNS2) (OMIM 176261) on chromosome 21 have been shown to result in the JLNS phenotype, each affecting ion transport channels in the heart and the inner ear.[69–71] Though prevalence of JLNS is low at 0.21%, malignant courses are known to result in sudden death at a young age. Additionally, as treatment of the disease with β-blockers can reduce rates of sudden death from 71 to 6%, early identification is critical.[68,72]

Usher Syndromes

Though clinical presentation can vary widely, Usher syndromes are classically characterized by SNHL and retinitis pigmentosa.[73] While the genetics of the Usher syndromes have much heterogeneity, there are three known clinical subtypes.[74] Type 1 Usher syndrome (USH1) is the most severe, with congenital bilateral SNHL, constant vestibular dysfunction, and prepubertal retinitis pigmentosa.[74] Vestibular dysfunction in USH1 patients usually presents clinically as delays in motor development, with delay in sitting up unsupported and inability to walk younger than age 18 months.[75] As vision worsens over time, USH1 patients also develop more severe gait disturbances.[75] The retinopathy appears as a loss of night vision and a restriction of the visual field during childhood, and eventually, as a visual acuity loss that rapidly progresses to blindness.[74] Type 2 Usher syndrome (USH2) is notable for less severe deafness, absence of vestibular symptoms, and generally later onset of vision loss, typically around the age of puberty.[74] Type 3 Usher syndrome (USH3) much less common, but it is characterized by progressive hearing loss and occasional vestibular dysfunction in addition to retinitis pigmentosa around puberty.[74,76] In all three subtypes, cataracts may develop in addition to retinitis pigmentosa.[77]

As mentioned above, much genetic heterogeneity exists in the Usher syndromes. USH2 is generally accepted as being the most common phenotype, but exact estimates of ratios of USH1:USH2 vary.[73,78] Though there are at least 13 different genes accounting for the three different clinical subtypes of Usher syndrome, 2 of these, USH1B (OMIM 276900) and USH2A (608400), account for up to 80% of all Usher syndrome cases (see ►**Table 1** for a more detailed list of Usher syndrome genes).[78] USH1B is caused by a mutation in the MYO7A gene (OMIM 276903) on chromosome 11, and this subtype is believed to account for three quarters of all USH1.[79] MYO7A codes for myosin-VIIa, an unconventional member of the large superfamily of myosin motor proteins that move on cytoplasmic actin filaments present, among other places, on the inner and outer hair cells in the organ of Corti.[73,79,80] USH2A is the most common form of USH2 and has been shown to result from a mutation in the *USH2A* gene on chromosome 1.[81,82] *USH2A* codes for "Usherin," a putative extracellular matrix protein.[82] Incidence was historically believed to be approximately 4.4 in 100,000, which represents 3 to 6% of congenitally deaf persons in the United States, but more recent evidence suggests that number may be far too small, with actual incidence closer to 1 in 6,000.[83,84]

Table 1 Summary of covered syndromes

Mode of inheritance	Syndrome	Locus/Gene	OMIM number
Autosomal dominant	Neurofibromatosis 2	NF2	607379
	Branchio-oto-renal syndrome	EYA1	601653
		EYA2	601654
		EYA3	601655
		SIX1	601205
		SIX5	600963
	Treacher Collins	TCOF1	606847
		POLR1D	613715
		POLR1C	610060
	Stickler syndrome	STL1/COL2A1	120140
		STL2/COL11A2	120290
		STL3/COL11A1	120280
		STL4/COL9A1	614134
		STL5/COL9A2	614284
	Waardenburg syndrome	PAX3	606597
		MITF	156845
		SNAI2	602150
		EDN3	131242
		EDNRB	131244
		SOX10	602229
Autosomal recessive	Pendred syndrome	PDS/SLC26A4	605646
	Jervell and Lange–Nielsen syndrome	JLNS1/KCNQ1	607542
		JLNS2/KCNE1	176261
	Usher syndrome	USH1B/MYO7A	276903
		USH1C	605242
		USH1D/CDH23	605516
		USH1E	602097
		USH1F/PCDH15	605514
		USH1G/SANS	607696
		USH1H	612632
		USH1J/CIB2	605564
		USH1K	614990
		USH2A	608400
		USH2C/ADGRV1	602851
		USH2D/WHRN	607928
		USH3A/CLRN1	606397
		USH3B/HARS	142810
	Refsum disease	PHYH/PAHX	602026
		PEX7	601757
X-linked dominant	Alport syndrome	COL4A5	303630
		COL4A3	120070
		COL4A4	120131
Mitochondrial	MELAS	MTTL1	590050
	MERRF	MTTK	590060

Abbreviations: MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; OMIM, Online Mendelian Inheritance in Man.

Refsum Disease

Refsum disease (OMIM 266500) is characterized by peripheral polyneuropathy, cerebellar ataxia, retinitis pigmentosa, and ichthyosis.[85] There are also commonly elevated protein levels in the cerebrospinal fluid without an increase in the number of cells in the cerebrospinal fluid.[86] Late sequelae of the disease can include cardiac arrhythmias and progressive postlingual SNHL than can become severe.[87] Patients with Refsum disease have elevated levels of phytanic acid due to a deficiency of the peroxisomal enzyme phytanoyl-CoA hydroxylase, which converts phytanic acid to α-hydroxyphytanic acid.[87,88] Originally, it was thought that all forms of Refsum's disease resulted from mutations to the PHYH/PAHX gene (OMIM 602026) on chromosome 10, which code for this α hydroxylase.[86,89] More recently, however, mutations to the PEX7 gene (OMIM 601757) on chromosome 6 were shown to play a role in approximately 1 in 10 cases of Refsum disease secondary to defects in plasmalogen synthesis and peroxisomal thiolase.[87,90] Though a rare disease with incidence estimated at 1 per 1 million, it is important to recognize this syndrome as dietary modification can slow or prevent hearing loss as well as palliating or reversing some of the other clinical symptoms, such as ichthyosis.[90]

Other Disorders

Alport Syndrome

Alport syndrome (AS, OMIM 301050) was first described in 1927 by A. Cecil Alport with the hallmark findings of hemorrhagic nephritis, hearing loss, and vision changes.[91] Most cases of AS are transmitted in X-linked dominant fashion, though some autosomal recessive and dominant forms also exist.[92] Clinical diagnosis can be made if four of the following diagnostic criteria are met: family history of hematuria, high-frequency progressive SNHL, ocular changes including anterior lenticonus and/or macular flecks, and glomerular basement membrane changes.[93] As would be expected in a largely X-linked syndrome, males are typically affected more significantly than females, with most males progressing to end-stage renal disease by their early 20s.[94] Anterior lenticonus that results from inability of the lens to hold its shape can result in myopia.[95,96] Though the exact mechanism of SNHL in AS is yet undetermined, bilateral progressive high-frequency loss is seen in most cases.[95–97] In X-linked males, 50% have some hearing loss at age 15 and 90% have hearing loss by age 40.[98] Early hearing loss often portends worse renal damage. Nearly all patients with the recessive form of the disease develop early hearing loss, regardless of gender, and it is usually progressive.[99]

Incidence of AS is approximately 1 in 53,000.[100] Mutations to the α subunits of Type IV collagen cause AS, typically interrupting the 3 to 4-5 complex in cellular basement membranes.[101] In X-linked AS, comprising roughly 65 to 80% of cases, this is due to the mutation of the COL4A5 gene (303630) which codes for the α5 subunit of type IV collagen.[92,101,102] Some controversy exists as to the proportion of AS that is autosomal recessive versus dominant, but each is caused by varying proportions of defects in the COL4A3 (OMIM 120070) and COL4A4 (OMIM 120131) genes, affecting the α3 and α4 subunits of type IV collagen, respectively.[92,102]

Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-Like Episodes

This mitochondrial syndrome typically presents with normal early development, short stature, nausea, migraines, seizures, and alternating hemiparesis, hemianopia, or cortical blindness.[103] Hearing loss can present in approximately 30% of patients, may occasionally be the only presenting symptom, and it is typically a bilateral, progressive sensorineural loss.[103–105] Histopathologic analysis shows severe atrophy of the stria vascularis in mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) patients.[105] MELAS (OMIM 540000) is caused by point mutations in the $tRNA^{Leu(UUR)}$ (MTTL1) gene (OMIM 590050), with the A3243G transition as the most common mutation.[106,107] This mutation encodes a defective transfer RNA.[107]

Myoclonic Epilepsy with Ragged-Red Fibers

Another mitochondrial syndrome, MERRF (OMIM 545000) presents with myoclonic epilepsy, ataxia, dementia, optic atrophy, hearing loss, short stature, and neuropathy.[104,106] Hearing loss is present in roughly half of patients.[104,108] MERRF is caused by point mutations in the $tRNA^{(lys)}$ (MTTK) gene (OMIM 590060) most often with an A8344G translocation, again leading to defective transfer RNA.[108,109]

Syndromic hearing loss affects roughly 3 out of every 10,000 live births.[2,3] With this prevalence, it is imperative that one remain vigilant for early signs or symptoms that may be serve as clues of multisystem problems to come. While this review does not aim to be comprehensive, it is our hope that it may be utilized both to guide early intervention to establish, preserve, or restore hearing for patients as well as to spur early engagement with an interdisciplinary team to minimize or delay syndrome-associated morbidity.

Conflict of Interest
None.

Funding
None.

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