

Genetic Causes of Sensorineural Hearing Loss

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Genetic deafness is often identified with or without other “syndromic” features (i.e., syndromic vs. non-syndromic deafness). A genetic defect in connexin-26, a gap junction protein present in the inner ear, is thought responsible for nearly half of cases of non-syndromic deafness. Syndromic deafness, although less common, is more often recognized because of other systemic anomalies. The CT scan remains one of the most practical clinical tools in elucidating the causes of hearing loss. Genetic screening for connexin-26 is helpful in some cases.

Introduction. Nearly 1 in 650 infants born in Colorado will have some degree of hearing impairment. As a state, Colorado has always been on the forefront of deafness awareness and rehabilitation. Even before the legislation of Universal Newborn Hearing Screening in Colorado in 1997, most hospitals were voluntarily performing hearing screenings on all newborns. The age of identification of hearing loss has gone from 36 months to 5 months.¹ Now nearly every child born in Colorado with a hearing loss can be rehabilitated by 6 months of age, the goal age for auditory rehabilitation in order to achieve optimal language development.² The future of hearing care, however, lies in better understanding the etiology of hearing loss so as to allow prevention rather than rehabilitation.

Etiologies of Congenital Hearing Loss. Approximately 50 percent of all cases of congenital hearing loss are attributable to environmental factors, such as congenital hyperbilirubinemia, ototoxic medication exposure, neonatal hypoxia, viral infections, and meningitis. The other 50 percent of cases are thought to be inherited, i.e., of genetic causes. Of these hereditary cases,

approximately 30 percent are classified as syndromic — i.e., associated with other recognizable anomalies. (Table 1) There are over 400 named syndromes associated with hearing loss, the associated auditory features being quite variable — sensorineural or conductive, unilateral or bilateral, and progressive or stable. This small subset of hearing loss patients (15 percent of all patients with hearing loss) is the group most readily diagnosed by physicians due to recognizable features other than hearing loss. The other 70 percent of hereditary cases are classified as non-syndromic — i.e., associated without any other recognizable features. This group is the otherwise perfectly normal child with the exception of hearing loss.

The inheritance patterns of non-syndromic genetic deafness are autosomal recessive in 75 percent, autosomal dominant in 22 percent and x-linked in 3 percent of patients. The associated “DeaFNess” genes are designated DFN A (for autosomal dominant genes), DFN B (for autosomal recessive genes) and DFN (for x-linked genes). To date, more than 50 deafness genes have been identified and genetically sequenced, more than half of these identified from syndromic forms of hereditary deafness.



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It is likely that hundreds of genes still await discovery. As a general rule, patients with autosomal recessive inheritance are typically born with bilateral, profound deafness to normal hearing parents. Patients with autosomal dominant inheritance have a variable pattern of severity and progression and more often have hearing-impaired parents. Interestingly, most genetically acquired hearing losses are caused by single-gene defects and no traceable family history is apparent.

Connexin-26 — The most common cause of non-syndromic deafness.

In almost half of children born with severe-profound, non-syndromic, autosomal recessive hearing loss, mutations in a small gene on chromosome 13 named Gap Junction Beta 2 (GJB2) have been identified. In most cases, a single gene base pair deletion (known as 35delG) signals a premature end to protein production rendering this gap junction protein non-functional. GJB2 encodes a protein known as Connexin-26, a gap junction protein present throughout the inner ear, and is

important in potassium concentration regulation.³ The absence of potassium circulation is responsible for the hair cells' inability to generate an action potential in response to sound.

Characteristics of deafness associated with Connexin-26 include bilateral, severe-profound deafness discovered either at birth or in early childhood and rarely gets worse. The 35delG mutation is found in 3 percent of the population, but 2 copies of GJB2 need to be defective to produce deafness. Overall, this genetic defect is responsible for ~20 percent of childhood deafness. This finding has raised considerable interest in genetic screening since most Connexin-26 defects are passed on in an autosomal recessive pattern. This means that those who are *carriers*, or heterozygotes, carry only one defective Connexin-26 gene and typically have normal hearing. Those with 2 copies of the defective gene, or homozygotes, are hearing impaired. Genetic screening is now readily available to detect a mutated Connexin-26 gene. This not only allows identification of the cause of a child's hearing

Table 1. Common Causes of Congenital (Inherited) Hearing Loss

ENVIRONMENTAL (50%)	<ul style="list-style-type: none"> • Viral (CMV, Rubella, Measles, Herpes) • Neonatal jaundice • Bacterial meningitis • Ototoxins (Gentamycin, Chemotherapy) • Hypoxic brain injury
GENETIC (50%)	
Non-Syndromic (70%)	<ul style="list-style-type: none"> • Autosomal Dominant (DFNA genes) • Autosomal Recessive (DFNB genes) • X-linked (DFN genes) • Mitochondrial (rare)
Syndromic (30%)	<ul style="list-style-type: none"> • Usher Syndrome • Pendred Syndrome • Alport Syndrome • Waardenburg Syndrome • Jervell and Lange-Neilsen Syndrome • Branchio-Oto-Renal (BOR) Syndrome

loss, but also can determine the carrier state in the parents. This can be influential in family planning, in that if both parents are found to be carriers, 25 percent of their children will be homozygotes and, as a result, hearing impaired.

Enlarged Vestibular Aqueduct Syndrome — *The most common structural deformity of the inner ear.* Enlarged Vestibular Aqueduct (EVA) syndrome is usually associated with some degree of hearing loss in the affected ear, noted either at birth or later in childhood. A typical story is that of a child who sustains a sudden loss of hearing following head trauma (which may be relatively minor), strenuous exertion or a sudden change in barometric pressure. Hearing loss occurs in a progressive, step-wise fashion and profound deafness is, unfortunately, a common end result.

The EVA is a congenital anomaly of the temporal bone whereby the normally narrow passage from the endolymphatic sac to the inner ear is abnormally large. This allows inappropriate communication of cerebrospinal fluid (CSF) pressure into the inner ear, damaging the membranous labyrinth. The diagnosis of EVA is made with a CT scan of the temporal bone, showing a diameter of more than 1.5 mm at the mid portion of the duct. (*Figure 1*) On gross visual inspection, the diameter of the aqueduct should be no larger than the lumen of the adjacent posterior semi-circular canal. The incidence of EVA in the pediatric hearing loss population is roughly 7 percent, much more commonly seen bilaterally than unilaterally.⁴

There is currently no treatment for EVA. It is important, however, to counsel parents about avoidance of head trauma in patients with EVA syndrome, as this is the

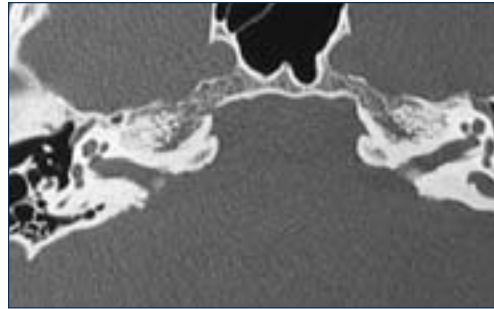


Figure 1.

only method of prevention of future hearing loss in this population. Unfortunately, patients with bilateral EVA syndrome will often go progressively deaf and require consideration of cochlear implantation when candidacy occurs.

Recognizable Forms of Hearing Loss.

Syndromic Hearing Loss. Even though syndromic hearing loss represents only 20 percent of genetic causes of hearing loss, it is important to be aware of the common forms. This is especially important in identifying co-morbidities, such as visual loss, renal failure, heart defects, etc. The information below will outline a few of the common forms of syndromic hearing loss.

Autosomal Dominant Syndromic Hearing Loss. Waardenburg Syndrome.

Named after a Dutch eye doctor named Petrus Johannes Waardenburg who noticed that people with differently colored eyes often had a hearing impairment, Waardenburg Syndrome is one of the most commonly recognized hearing loss syndromes. This syndrome affects the body in 3 recognizable ways: hearing, pigmentation irregularities of the skin, hair and eyes, and facial structure. Patients will often have 2 different colored eyes (usually one blue and one brown eye), a prominent white forelock of hair extending backward

Figure 1.
Axial CT of the Temporal bone in a patient with a normal vestibular aqueduct (right ear) and an enlarged vestibular aqueduct (left ear) with associated hearing loss.

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and dystopia canthorum (apparent widening of the nasal bridge). Waardenburg syndrome occurs in approximately 2 per 100,000 births and is estimated to account for 2 percent of all cases of congenital hearing loss in the United States.⁵ There are 4 types of Waardenburg syndrome (WS1-4): nearly all are inherited in an autosomal dominant fashion, yet fortunately not all will have a hearing loss. Most WS phenotypes (largely from PAX3 and MITF mutations) are the result of improper melanocyte (pigment) differentiation. Melanocytes are necessary in the stria vascularis for normal cochlear function.

Branchio-oto-renal Syndrome.

Branchio-oto-renal (BOR) syndrome accounts for 2 percent of causes of congenital deafness, with a prevalence of 2.5 of every 100,000 births. The inheritance pattern is autosomal dominant and is associated with hearing loss, ear pits, branchial (neck) cysts or fistulas and kidney anomalies. Nearly 90 percent of BOR patients have a hearing loss, the degree (mild-profound) and progressiveness (stable or progressive) is rather unpredictable however. Ear pits are found in 80 percent of cases and branchial cleft anomalies in the neck are seen in 60 percent of cases. Kidney anomalies are found in 67 percent of cases and usually are mild, although occasionally progress to renal failure. The gene in question is EYA1, a transcription factor whose role in the inner ear still remains poorly understood.⁶

Neurofibromatosis type II. As opposed to Neurofibromatosis type I (consisting of café au lait spots, axillary and inguinal freckling, multiple discrete dermal neurofibromas, and iris Lisch nodules), type II Neurofibromatosis (NFII) commonly

occurs with hearing loss. NFII is an autosomal dominant trait affecting 2.5 in 100,000 people. Nearly every patient with NFII shows evidence of bilateral acoustic neuromas (AN), with other intracranial neoplasms and posterior subcapsular cataracts occurring in many patients. Patients present with tumors by age 30 and therefore NFII is thought of as an adult-onset disease. Bilateral acoustic neuromas are often diagnosed in childhood now with the use of MRI screening for patients in high-risk families.

Autosomal Recessive Syndromic Hearing Loss. Usher Syndrome.

Usher syndrome is the most common cause of deafness with blindness, with a prevalence of 4.4 per 100,000 people. It is estimated that about 10 percent of all children with sensorineural hearing loss have Usher syndrome, with a asymptomatic carrier rate of roughly 1 out of 70 individuals. Characteristic features are progressive, bilateral hearing loss and progressive blindness due to retinitis pigmentosa.⁷

There are 3 types of Usher syndrome: type 1 (USH1) patients are profoundly deaf at birth and develop visual loss by age 10, type 2 (USH2) have moderate-severe hearing loss at birth and develop less severe visual loss in their teens and type 3 (USH3) have normal hearing at birth and develop progressive hearing loss and blindness during their teens or early adulthood.

At this time, genetic testing for Usher syndrome is done only as part of research projects, since Usher syndrome is not caused by a single genetic defect. So far, 11 Usher genes have been mapped: 7 for type I, 3 for type II and 1 for type 3. The most studied gene so far causing USH1 is myosin VIIa, a protein necessary for the development and

maintenance of inner ear hair cells. The absence of normal Myosin VIIa prevents normal hair cell auditory signaling.

Pendred Syndrome. It is estimated that 10 percent of all children with congenital hearing loss have Pendred syndrome. The cardinal features of Pendred syndrome are a thyroid goiter and congenital sensorineural hearing loss. Hearing loss is usually bilateral and profound, (although some forms are found to be mild and progressive), and is inherited in an autosomal recessive fashion. The enlarged thyroid is often euthyroid (normally functional) and becomes apparent during early puberty or in adulthood. The diagnosis of Pendred syndrome is usually made with a perchlorate discharge test, using radioactive iodine displacement by potassium perchlorate. A discharge of >10 percent is abnormal and indicates a lack of organification of iodine in the thyroid.

The underlying defect appears to be in the SLC26A4 gene, encoding the protein Pendrin, resulting in an abnormality in iodide and chloride transport. Pendred syndrome is more recently found to be associated with congenital otic capsule defects, present in 85 percent of cases.⁸ The 2 most common anomalies are an Enlarged Vestibular Aqueduct (EVA) and the Mondini deformity (incomplete cochlear coiling). The prominent association of the EVA and Pendred syndrome should prompt the Otologist to perform a perchlorate discharge test on all patients with an EVA since Penred syndrome follows a known inheritance pattern (AR) unlike EVA syndrome. EVA without associated Penred syndrome has no known inheritance pattern to date. Genetic screening is possible although not readily available outside of research centers.

Jervell and Lange-Nielson Syndrome.

This is a rare syndrome with a prevalence of 1 out of every 250,000 and is inherited in an autosomal recessive pattern. It is important to be aware of Jervell and Lange-Nielsen syndrome (JLNS) because of its associated fatal cardiac dysrhythmias otherwise not identified by many physicians. The classic presentation of JLNS is a deaf child who experiences syncopal episodes during periods of exercise, fright or emotional stress. These syncopal episodes often culminate in sudden death, with half of untreated patients dying before age 15. Often a family history is present of other deaf family members dying in their youth. The diagnosis is confirmed with a routine electrocardiogram.

The defective gene responsible for JLNS produces an abnormal voltage-gated potassium channel in both the heart and cochlea (KCNQ1). Malfunction of these channels in the stria vascularis causes deafness by failure to maintain an adequate potassium concentration in the scala media. Malfunction of these channels in the heart results in abnormal depolarization and repolarization of cardiac myocytes and a prolonged QT interval.

X-linked Recessive Deafness. Alport Syndrome.

Alport syndrome is characterized by renal, cochlear and ocular dysfunction with an inheritance pattern largely X-linked (80 percent), but occasionally autosomal recessive (15 percent) and autosomal dominant (5 percent). The prevalence of Alport syndrome is 2 per 100,000 people. The hearing loss of Alport syndrome is never seen at birth, with progressive hearing loss usually detected in late childhood and 90 percent showing profound deafness by age 40. In its early stages, the hearing deficit is detectable only by audiometry, with a

bilateral high frequency pattern of loss noted. Because most of Alport syndrome inheritance is X-linked, boys are much more commonly affected. In affected males, hearing loss progresses to affect all speech frequencies.

The clinical hallmark of Alport syndrome is microscopic hematuria. Nearly 20 percent of children evaluated by pediatric nephrologists for isolated microhematuria are diagnosed with Alport syndrome. Proteinuria is ultimately seen as the child progresses to end-stage renal failure, often by age 35.⁹ In addition, visual loss is found in many patients with the pathognomonic finding of anterior lenticonus making the diagnosis certain.

The genetic defect apparent in the eye, ear and kidney defects is attributable to COL4A, a type IV collagen gene. There is no readily available genetic screening test for a carrier state. If, however, a boy is diagnosed with Alport syndrome, his mother is usually a carrier and can pass the mutation on to 50 percent of her other male children. She should also have a urinalysis to identify microhematuria, indicating a heterozygosis. If she develops proteinuria or early renal failure, a nephrology evaluation should be sought.

What should be the work-up for a child with hearing loss? There is no standard algorithm that one follows when working up a child with a hearing loss. Once hearing loss is detected, it is important to explain to parents that there is little they could have done to prevent it and that hearing loss can often be effectively rehabilitated. It is crucial to offer rehabilitation within 6 months of life to help optimize auditory development and language acquisition.

Serial Audiometry. It is important to assess the degree of hearing loss on a frequent basis to establish whether progression of loss is noted. In the first year of life, hearing assessment (usually with a combination of Auditory Brainstem Response, Otoacoustic Emissions and behavioral testing) is often performed every 3 to 4 months after a diagnosis of hearing loss is established. Thereafter, serial audiometry every 4 to 6 months is often advised during the preschool years to assess for hearing changes. Once a child is in school, audiometry is often performed every 6 to 12 months to ensure undetected, progressive hearing loss does not interfere with academic performance. When the child is considered an appropriate candidate, assistive listening devices, a hearing aid or a cochlear implant should be considered.

Imaging. Even in the emerging era of sophisticated genetic testing, a CT scan of the temporal bones remains one of the most useful tests ordered in the evaluation of childhood hearing loss. This study allows a detailed assessment of the structure of the inner ear, assessing otic capsule dysplasias. A CT scan effectively evaluates the 2 most common temporal bone deformities: an enlarged vestibular aqueduct and a Mondini deformity (hypoplastic cochlea).¹⁰ If a CT abnormality is noted, the physician can give advice on the nature of the hearing loss and can counsel the family regarding hearing loss progression (in the case of an enlarged vestibular aqueduct).

Although MRI of the temporal bone is appealing because of the lack of associated radiation, the detail of the inner ear is not universally adequate for otic capsule evaluation. That said, gadolinium-enhanced MRI is routinely ordered to assess family members with NF-2 to rule out acoustic neuromas.

Laboratory Studies. Screening blood tests add little to the work up of childhood hearing loss.¹¹ Blood tests directed by clinical suspicion show higher value. For instance, if an enlarged vestibular aqueduct is noted, a perchlorate discharge test is useful to evaluate for Pendred syndrome. Similarly, if progressive high frequency hearing loss is noted in a boy, a urinalysis is useful to evaluate for Alport syndrome. Rarely, if a family history of childhood cardiac death is noted in a child with profound deafness, an EKG is useful to evaluate for Jervell and Lange-Nielson syndrome.

Ophthalmology Evaluation. The usefulness of a pediatric ophthalmology evaluation is not to be underestimated. Although it is rare to identify syndromic hearing loss with an eye exam (Usher syndrome with retinitis pigmentosa), it is valuable to exclude common conditions such as myopia that can be corrected in a child already afflicted with one sensory deficit (hearing loss).

Genetic Testing. The availability of genetic screening for the Connexin-26 mutation over the past 5 years has changed how we think about the work up of childhood hearing loss. This gene mutation represents the largest percentage of non-syndromic deafness and at least 20 percent of childhood deafness overall.¹¹ Screening that was previously performed in a research setting and taking weeks to months to perform has now migrated to the private sector with results available within days. The value of this genetic information is that it can preclude the need for further work up and identify the child for future genetic counseling. Since Connexin-26 is passed in an autosomal recessive pattern, a geneticist

referral can help the patient identify the chance of passing hearing loss to offspring. The routine referral to a geneticist in the absence of other “syndromic” features is of limited value and is often made on a case-by-case basis.

Conclusion. The genetic causes of hearing loss continue to be discovered. Although frustrating for the physician to vaguely define a childhood hearing loss as “genetic,” it is important for us to recognize some of the common “syndromic” features that define many causes of hearing loss. In the majority of cases, however, children have no identifiable features that lead to suspicion for a syndrome. In these cases, nearly half of children will have a relatively newly identified genetic mutation in Connexin-26. This genetic defect is readily identifiable through genetic screening and may offer significant value in parental counseling in the evaluation of the severe-profoundly deaf child. In addition to genetic screening, a CT of temporal bones and selected laboratory screening can be useful in detecting some forms of syndromic hearing loss. Regardless of the etiology, prompt identification, early intervention and serial audiometry is crucial in all cases of childhood hearing loss.

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