Introduction

Deafness is the most common sensory defect, affecting 1.3-2.3 per 1000 children. Studies based on pupil records in schools for the deaf have attributed about 50% of childhood sensorineural hearing impairment to genetic factors. About 20% to 25% of cases have been assigned to identifiable environmental causes, prenatal, perinatal, or postnatal, whereas 25%-30% are classified as sporadic cases of unknown etiology, composed to some degree of nonsyndromic genetic hearing losses. Advances in diagnosis and therapy including the development of immunizations against infectious agents, which cause hearing loss, should cause a relative increase in the prevalence of genetic sensorineural hearing loss. This relative increase will mandate an increase in the clinicians familiarity with the full spectrum of these disorders.

Heritable forms of hearing loss can be congenital or delayed onset; conductive, sensorineural, or mixed type; mild to profound in degree; progressive or nonprogressive; unilateral or bilateral and symmetrical or asymmetrical in severity and configuration; as well as syndromic or nonsyndromic. The genetic syndromes that include hearing loss are commonly classified according to the other systems involved where as the nonsyndromic hearing disorders have been classified by their audiological characteristics, age of onset, presence or absence of progression, and mode of inheritance. Progress in gene localization and identification of the genes responsible for sensorineural hearing loss should allow future subclassification by the gene involved in these losses. Most authors attribute 75% to 80% of genetic deafness to autosomal recessive genes and 18% to 20% to autosomal dominant genes, with the remainder classified as X-linked, or chromosomal, disorders.

Basic Genetic Principles

Human genes are arranged linearly on 22 pairs of autosomes and one pair of sex chromosomes. Each pair of chromosomes carries a distinctive set of gene loci for which there may be several alternative codes or alleles. The genotype for a specific trait may consist of two identical alleles (homozygous) or two different alleles (heterozygous).
Which alleles are present and how they interact determine the physical expression of the gene or phenotype.

Autosomal dominant inheritance exhibits a vertical pattern of transmission as an affected parent passes the gene to children who are then affected. There is a 50% chance of an affected heterozygote transmitting the gene to each of their children. Alternatively, a new mutation in a gene may be inherited in a dominant fashion, resulting in the offspring being the first affected individual in the family. In some instances, a dominant gene may demonstrate lack of penetrance, so not all persons who are heterozygous for the gene will manifest the disorder. Penetrance is an all or none phenomenon; either there is evidence of the gene expression as demonstrated by certain clinical findings, or there is no evidence of gene expression and the gene is termed nonpenetrant. In contrast, the term expressivity refers to graduations and the degree to which an individual has acquired few, some, or all of the traits associated with a particular gene. Dominant disorders may show variable expressivity, with different family members showing different manifestations of the gene. Phenotypic expression may be modified by environmental influences or interactions with other genes.

The most common pattern of transmission in hereditary hearing loss is autosomal recessive. In the recessive transmission, the parents will most likely have normal or near normal hearing even though they possess the recessive gene. Typically, there is a 25% chance that the offspring will be affected and manifest hearing impairment or deafness. This mode of transmission is characterized by a horizontal pattern of affected individuals when visualized on a pedigree. For a child to exhibit the disorder, both parents must be carriers of the particular gene involved in the disorder.

The X-linked inheritance pattern involves particular genes located on the X chromosome. This type of inheritance more commonly affects males because they possess a single X chromosome and will present phenotypically with any genotypic change in this location. Therefore, an X-linked trait may be carried by a heterozygous female without phenotypic expression, but her sons have a 50% chance of inheriting the gene, which would be expressed in the absence of another X chromosome. The daughters of a female carrier have a 50% chance of being a carrier of the trait. Sons of an affected male with a sex-linked trait will not be affected, whereas all of his daughters will carry the gene. The hallmark of X-linked inheritance is the absence of male-to-male transmission.

Chromosomal abnormalities involving autosomes result from extra or deficient chromosomal material being present in each cell; the phenotypic expression may be severe or even fatal. In patients with trisomy, three copies of a given chromosome are present: trisomy 21 is the least severe, whereas trisomy 13 and trisomy 18 are less common and more severe. Other autosomal trisomies are almost always fatal, as is the presence of a single chromosome (monosomy). Chromosomal deletions or duplications may be present, with the nature and severity of each phenotype depending on the amount and origin of the material involved.

Another rare mode of inheritance for hereditary hearing loss is mitochondrial inheritance, which is caused by a mutation in the small amount of DNA present in the mitochondria of cells. This type of hearing impairment is inherited only through the mother because the mitochondria are transmitted in the cytoplasm of the maternal oocyte. The expression
of mitochondrially inherited hearing impairment varies so greatly that some individuals who do inherit a mutation in the mitochondria DNA possess only a minimal hearing impairment. Involvement in patients with mitochondrial disorders is graded because only a fraction of all mitochondria in a cell may harbor a particular mutation at a given time. A typical mitochondrial disorder may gradually worsen.

Gene mapping and localization are used to decode the genes responsible for the ear and hearing. The ultimate goal is for therapeutic or preventative intervention in persons who have genetic hearing loss. The process for determining the precise chromosomal location of a specific gene is called genetic linkage analysis. This technique takes advantage of the phenomenon of crossover whereby genetic material may be randomly exchanged between two members of a chromosome pair during cell meiosis. Two genetic loci are said to be linked when they are sufficiently close together on the chromosome that their alleles are transmitted together more often than expected by chance. If the chromosomal location of one gene is known, the location of the linked locus is determined automatically.

The term genetic heterogeneity implies that different mutations, possibly involving different genes, can result in an identical or similar phenotype. It is possible that a syndrome defined by a set of characteristic traits may be produced by a defect in more than one gene. Genetic heterogeneity has proved to be a major issue in the studies of both syndromic and nonsyndromic hearing loss.

**Inner Ear Structural Malformations**

By week 9 of gestation, the cochlea reaches full growth (2 ¾ turns). Arrest in normal development or aberrant development of inner ear structures may result in hearing impairment. Depending on the timing and nature of the developmental insult, a range of inner ear anomalies can result. Computerized temporal bone imaging techniques reveal that about 20% of children with congenital sensorineural hearing loss have subtle or severe abnormalities of the inner ear. About 65% of such abnormalities are bilateral; 35% are unilateral. On the basis of temporal bone histopathologic studies inner ear malformations have typically been classified into five different groups.

**Michel Aplasia**

Complete agenesis of the petrous portion of the temporal bone occurs in Michel aplasia although the external and middle ear may be unaffected. This malformation is thought to result from an insult prior to the end of the third gestational week. Affected ears are anacusic because of the absence of sensory and neural inner ear structures. These patients have not been helped with conventional amplification or cochlear implantation, but vibrotactile devices have been of some help. Through genetic studies have not been done in humans, but mouse models suggest that a number of different genes can cause this form of aplasia. Autosomal dominant inheritance has been observed, but recessive inheritance is also likely.
Mondini Aplasia

Mondini aplasia involves a developmentally deformed cochlea in which only the basal coil can be identified clearly. The upper coils assume a cloacal form and the interscalar septum is absent. The endolymphatic duct is also usually enlarged. It is postulated that the deformity results from developmental arrest at approximately the sixth week gestation because of the underdeveloped vestibular labyrinth. This anomaly can be inherited in an autosomal dominant fashion and may not be bilateral. It has been described in several other disorders including Pendred’s, Waardenburg’s, Treacher Collins, and Wildervaank’s syndromes. Association of Mondini aplasia with nongenetic etiologies, such as congenital CMV infection, has been reported. The presence of neurosensory structures in most cases warrants an aggressive program of early habilitative intervention, including conventional amplification.

Scheibe Aplasia (Cochlearsaccular dysplasia or pars inferior dysplasia)

The bony labyrinth and the superior portion of the membranous labyrinth, including the utricle and semicircular canals, are normally differentiated in patients with Scheibe aplasia. The organ of Corti is generally poorly differentiated with a deformed tectorial membrane and collapsed Reissner’s membrane, which compromises the scala media. Scheibe aplasia is the most common form of inner ear aplasia and can be inherited as an autosomal recessive nonsyndromic trait. The deformity has been seen in temporal bones of patient with Jervell and Lange-Neilsen, Refsum’s, Usher’s, and Waardenburg’s syndromes as well as in congenital rubella infants. Conventional amplification with habilitative intervention is beneficial in many of these children.

Alexander Aplasia

In Alexander aplasia, cochlear duct differentiation at the level of the basal coil is limited with resultant effects on the organ of Corti and the ganglion cells. Audiometrically these patients have a high frequency hearing loss with adequate residual hearing in the low frequencies to warrant the use of amplification.

Enlarged Vestibular Aqueduct

An enlarged vestibular aqueduct has been associated with early onset sensorineural hearing loss, which is usually bilateral and often progressive and may be accompanied by vertigo or incoordination. This abnormality may also accompany cochlear and semicircular canal deformities. The progressive hearing loss is apparently the result of hydrodynamic changes and possibly labyrinthine membrane disruption. Familial cases have been observed, suggesting autosomal dominant inheritance, but recessive inheritance is also possible. The deformity has also been found in association with Pendred syndrome.
Semicircular Canal Malformations

Formation of the semicircular canals begins in the sixth gestational week. The superior canal is formed first and the lateral canal is formed last. Isolated lateral canal defects are the most commonly identified inner ear malformations identified on temporal bone imaging studies. Superior semicircular canal deformities are always accompanied by lateral semicircular canal deformities, whereas lateral canal deformities often occur in isolation.

Classification of Hereditary Hearing Impairment

Hereditary hearing impairment is classified into nonsyndromic or syndromic forms. Up to 30% of deafness in children can be attributed to syndromic forms. Nonsyndromic hearing impairment is almost exclusively caused by mutations within a single gene and are not associated with any other abnormalities or defects. Hereditary hearing impairment can also be divided into groups by mode of transmission.

Autosomal Dominant Disorders

The identification of autosomal dominant disorders is facilitated by a positive family history reflecting a classical dominant inheritance pattern and recognizable phenotype. In reality, the variation in expressivity of dominant genes leads to different phenotypic characteristics being present in various affected members of the same family. Decreased penetrance is also commonly seen in autosomal dominant traits and causes an obligate carrier to not have any detectable phenotypic expression. An affected individual may have a new mutation that is causing the disorder so that their family history is negative. They then will transmit the gene to their offspring in an autosomal dominant fashion.

Waardenburg Syndrome

Waardenburg syndrome may account for 3% of childhood hearing impairment and is the most common form of inheritable congenital deafness. The incidence of Waardenburg syndrome is 1 in 4000 live births. There is a significant amount of variability of expression in this syndrome. There may be unilateral or bilateral sensorineural hearing loss in patients and the phenotypic expressions may include pigmentary anomalies and craniofacial features. The pigmentary anomalies include: white forelock (20-30% of cases), heterochromia irides, premature graying, and vitiligo. Craniofacial features that are seen in Waardenburg syndrome include dystopia canthorum, broad nasal root, and synophrys. All of the above features are variable in appearance. There are three different forms of Waardenburg syndrome, which can be distinguished clinically. Type 1 is characterized by congenital sensorineural hearing impairment, heterochromia irides, white forelock, patchy hypopigmentation, and dystopia canthorum. Type 2 is differentiated from type 1 by the absence of dystopia canthorum, whereas type 3 is characterized by microcephaly, skeletal abnormalities, and mental retardation, in addition to the features associated with type 1. Sensorineural hearing loss is seen in 20% of
patients with type 1 and in more than 50% of patients with type 2. Essentially all cases of type 1 and type 3 are caused by a mutation of the PAX3 gene on chromosome 2q37. This genetic mutation ultimately results in a defect in neural crest cell migration and development. About 20% of type 2 cases are caused by a mutation of the MITF gene (microphthalmia transcription factor) on chromosome 3p. Waardenburg syndrome has also been linked to other genes such as EDN3, EDNRB, and SOX10.

**Stickler Syndrome**

Stickler syndrome is characterized clinically by cleft palate, micrognathia, severe myopia, retinal detachments, cataracts, and marfinoid habitus. Significant sensorineural hearing loss or mixed hearing loss is present in about 15% of cases, whereas hearing loss of lesser severity may be present in up to 80% of cases. Eustation tube dysfunction occurs secondarily to the cleft palate and results in conductive hearing loss. Ossicular abnormalities may also be present. Most cases of Stickler syndrome can be attributed to mutations in the COL2A1 gene found on chromosome 12 which causes premature termination signals for a type II collagen gene. Additionally, changes in the COLIIA2 gene on chromosome 6 have been found to cause the syndrome.

**Branchio-oto-renal Syndrome**

Branchio-oto-renal syndrome is estimated to occur in 2% of children with congenital hearing impairment. The syndrome involves branchial characteristics including ear pits and tags or cervical fistula and renal involvement ranging from agenesis and renal failure to minor dysplasia. Seventy-five percent of patients with branchio-oto-renal syndrome have significant hearing loss. Of these, 30% are conductive, 20% are sensorineural, and 50% demonstrate mixed forms. Recently, mutations in a drosophila gene EYA1 have been shown to cause the syndrome. The encoded protein is a transcriptional activator. The gene in humans has been located on chromosome 8q.

**Treacher Collins Syndrome**

Treacher Collins syndrome consists of facial malformations such as malar hypoplasia, downward slanting palpebral fissures, coloboma of the lower eyelids, hypoplastic mandible, malformations of the external ear or the ear canal, dental malocclusion, and cleft palate. The facial features are bilateral and symmetrical in Treacher Collins syndrome. Conductive hearing loss is present 30% of the time, but sensorineural hearing loss and vestibular dysfunction can also be present. Ossicular malformations are common in these patients. The syndrome is transmitted autosomal dominant with high penetrance. However, a new mutation can be present in as many as 60% of cases of Treacher Collins syndrome. The gene responsible for Treacher Collins syndrome is TCOF1 which is located on chromosome 5q and produces a protein named treacle, which is operative in early craniofacial development. There is considerable variation in expression between and within families indicating that other genes can modify the expression of the treacle protein.
Neurofibromatosis

Persons with neurofibromatosis will have café-au-lait spots and multiple fibromas. Cutaneous tumors are most common, but the central nervous system, peripheral nerves, and viscera can be involved. Mental retardation, blindness, and sensorineural hearing loss can result from central nervous system tumors. Neurofibromatosis is classified as types 1 and 2. Neurofibromatosis type 1 is more common with an incidence of about 1:3000 persons. Type 1 generally includes many café-au-lait spots, cutaneous neurofibromas, plexiform neuromas, pseudoarthrosis, Lisch nodules of the iris, and optic gliomas. Acoustic neuromas are usually unilateral and occur in only 5% of affected patients. Hearing loss can also occur as a consequence of a neurofibroma encroaching on the middle or inner ear, but significant deafness is rare. The expressed phenotype may vary from a few café-au-lait spots to multiple disfiguring neurofibromas. Type 1 is caused by a disruption of the NF1 gene (a nerve growth factor gene) localized to chromosome 17q11.2. Neurofibromatosis type 2, which is a genetically distinct disorder, is characterized by bilateral acoustic neuromas, café-au-lait spots, and subcapsular cataracts. Bilateral acoustic neuromas are present in 95% of affected patients and are usually asymptomatic until early adulthood. Deletions in the NF2 gene (a tumor suppressor gene) on chromosome 22q12.2 cause the abnormalities associated with neurofibromatosis type 2. Both types of neurofibromatosis are inherited as autosomal dominants with high penetrance but variable expressivity. High mutation rates are characteristic of both types of the disorder.

Otosclerosis

Otosclerosis is caused by proliferation of spongy type tissue on the otic capsule eventually leading to fixation of the ossicles and producing conductive hearing loss. Hearing loss may begin in childhood but most often becomes evident in early adulthood and eventually may include a sensorineural component. Otosclerosis appears to be transmitted in an autosomal dominant pattern with decreased penetrance, so only 25% to 40% of gene carriers show the phenotype. The greater proportion of affected females points to a possible hormonal influence. Recent statistical studies suggest a role for the gene COLIA1 in otosclerosis, and measles viral particles have been identified within the bony overgrowth in otosclerotic foci, raising the possibility of an interaction with the viral genome.

Osteogenesis Imperfecta

Osteogenesis imperfecta is characterized by bone fragility, blue sclera, conductive, mixed, or sensorineural hearing loss, and hyperelasticity of joints and ligaments. This disorder is transmitted as an autosomal dominant with variable expressivity and incomplete penetrance. Two genes for osteogenesis imperfecta have been identified, COLIA1 on chromosome 17q and COLIA2 on chromosome 7q. The age at which the more common tarda variety becomes clinically apparent is variable. Van der Hoeve’s syndrome is a subtype in which progressive hearing loss begins in early childhood.
Nonsyndromic Autosomal Dominant Hearing Loss

Autosomal dominant modes of inheritance account for 15% of cases of nonsyndromic hearing loss. Autosomal dominant forms of deafness in humans involve DNFA loci and also include an array of chromosomes. Konigsmark and Gorlin described several types of nonsyndromic, autosomal dominant hearing loss. Congenital, severe nonprogressive hearing impairment actually represents more than one disorder, with several different genes having been localized.

Dominant Progressive Hearing Loss

Dominant progressive hearing loss is a type of nonsyndromic, noncongenital sensorineural hearing loss, variable in age of onset and rate of progression. It is inherited in an autosomal dominant pattern. Age of onset can vary from early childhood in some families to early adulthood in others. Presymptomatic gene carriers may demonstrate elevated thresholds for stapedial reflexes and positive signs for recruitment. Eventually the disease progresses to the level of severe to profound hearing loss. More than 12 genes causing dominant progressive hearing loss have been localized. Konigsmark and Gorlin defined four types of dominant progressive hearing loss: early onset, high frequency, midfrequency, and low frequency. Heterogeneity has been documented for each subtype as exemplified by four types of high frequency dominant progressive hearing loss identified by audiogram configuration within family groups. The frequency of dominant progressive hearing loss or of the subtypes in the general population is unknown because past epidemiologic studies have failed to distinguish it from otosclerosis or other causes of noncongenital hearing loss. Given the extensive genetic heterogeneity, information on pathogenesis from small samples of individuals, or from individual families, may not generalize over a greater population of dominant, progressive hearing loss patients.

Recessive Disorders

The most common pattern of transmission of hereditary hearing loss is autosomal recessive, compromising 80% of cases of hereditary deafness. Half of these cases represent recognizable syndromes. A clinician may be confronted by a single affected child in a family with no known history of the disorder, making differentiation between a recessively inherited disorder and a nongenetic disorder extremely difficult. Most reports regarding the etiology of childhood hearing loss attribute a significant proportion of hearing losses in study populations to undetermined causes, many of which are undoubtedly undetected autosomal recessive disorders. Identification of recessive syndromes, which include hearing loss, necessitates a diligent search by clinicians for the other syndromic components.

Usher Syndrome

Usher’s syndrome has a prevalence of 3.5 per 100,000 population and affects about one half of the 16,000 deaf and blind persons in the United States. Sensorineural hearing loss
and retinitis pigmentosa characterize the syndrome. Genetic linkage analysis studies demonstrated Usher syndrome to be genetically heterogeneous, with three distinct subtypes, distinguishable on the basis of severity or progression of the hearing loss and the extent of vestibular system involvement. Usher type 1 patients have congenital bilateral profound hearing loss and absent vestibular function; type 2 patients have moderate losses and normal vestibular function. Patients with type 3 demonstrate progressive hearing loss and variable vestibular dysfunction and are found primarily in the Norwegian population. Linkage analysis studies reveal at least 5 different genes for type 1 and at least 2 for type 2. Only type 3 appears to be due to just one gene. Ophthalmologic evaluation is an essential part of the diagnostic work up, and subnormal electroretinographic patterns have been observed in children as young as 2 to 3 years of age, before retinal changes are evident fundoscopically. Early diagnosis of Usher syndrome can have important rehabilitation and educational planning implications for an affected child.

**Pendred Syndrome**

Pendred’s syndrome includes thyroid goiter and profound sensorineural hearing loss. Hearing loss is progressive in about 15% of patients. The majority of patients present with bilateral moderate to severe sensorineural hearing impairment, with some residual hearing in the low frequencies. The hearing loss is associated with abnormal iodine metabolism resulting in generally an euthyroid goiter, which usually becomes clinically detectable at about 8 years of age. The perchlorate discharge test shows abnormal organification of nonorganic iodine in these patients and is needed for definitive diagnosis. Radiological studies reveal that most patients have Mondini aplasia or enlarged vestibular aqueduct. Recessive inheritance is seen in many families, whereas others show a dominant pattern with variable expression. A gene for Pendred syndrome was localized to chromosome 7q in a number of families with a consistent autosomal recessive inheritance pattern. Mutations in the PDS gene, which codes for the pendrin protein, a sulfate transporter, have been shown to cause this disorder. Treatment of the goiter is with exogenous thyroid hormone.

**Jervell and Lange-Neilsen Syndrome**

Jervell and Lange-Neilsen syndrome is a rare syndrome that consists of profound sensorineural hearing loss and syncopal episodes resulting from a cardiac conduction defect. Electrocardiography reveals large t waves and prolongation of the QT interval, which may lead to syncopal episodes as early as the second or third year of life. The cardiac component of this disorder is treated with beta-adrenergic blockers such as propranolol. An electrocardiogram should be performed on all children with early onset hearing loss of uncertain etiology. Genetic studies attribute one form of Jervell and Lange-Neilsen syndrome to homozygosity for mutations affecting a potassium channel gene (KVLQT 1) on chromosome 11p15.5, which are thought to result in delayed myocellular repolarization in the heart. The gene KCNE1 has also been shown to be responsible for the disorder.
Recessive Nonsyndromic Hearing Loss

Konigsmark and Gorlin divided nonsyndromic recessive sensorineural hearing loss into three subtypes. These are congenital severe-to-profound, congenital moderate, and early onset. The early onset subtype usually progresses rapidly from onset at age 1 ½ years to profound loss by age 6. The congenital severe-to–profound type is most prevalent, and genetic heterogeneity is confirmed by the likelihood that offspring of parents with clinically identical recessive hearing loss will have normal hearing. Genetic linkage studies have identified at least 15 gene loci for recessive nonsyndromic hearing loss. The gene DFNB2 on chromosome 13q may be the most common and has been identified as connexin 23. Another gene, DFNB1, also found on chromosome 13 codes for a connexin 26 gene gap junction protein. The connexin 26 protein plays an important role in auditory transduction. Expression of connexin 26 in the cochlea is essential for audition. Although many genes may be implicated in recessive nonsyndromic hearing loss, it is likely that most of them are rare, affecting one or a few inbred families.

Sex-Linked Disorders

X-linked dominant and recessive inheritance is rare, accounting for only 1% to 2% of cases of hereditary hearing impairment. It may constitute about 6% of nonsyndromic profound losses in males.

Norrie Syndrome

Norrie syndrome is a sex-linked disorder that includes congenital or rapidly progressive blindness, development of pseudoglioma, opacification, and ocular degeneration resulting in microphthalmia. One third of affected patients have onset of progressive sensorineural hearing loss beginning in the second or third decade. A gene for Norrie syndrome has been localized to chromosome Xp11.4, where studies have revealed deletions involving contiguous genes. A number of families have shown variable deletions in this chromosomal region.

Otopalatodigital Syndrome

Otopalatodigital syndrome includes hypertelorism, craniofacial deformity involving supraorbital area, flat midface, small nose, and cleft palate. Patients are short statured with broad fingers and toes that vary in length, with an excessively wide space between the first and second toe. Conductive hearing loss is seen due to ossicular malformations. Affected males manifest the full spectrum of the disorder and females may show mild involvement. The gene has been found to be located on chromosome Xq28.

Wildervaank Syndrome

Wildervaank’s syndrome is comprised of the Klippel-Feil sign involving fused cervical vertebrae, sensorineural hearing or mixed hearing impairment, and cranial nerve 6 paralysis causing retraction of the eye on lateral gaze. This syndrome is seen most commonly in female because of the high mortality associated with the X-linked dominant
form in males. Isolated Klippel-Feil sequence includes hearing impairment in about one third of cases. The hearing impairment is related to bony malformations of the inner ear.

**Alport Syndrome**

Alport syndrome involves hearing loss associated with renal impairment of varying severity. The renal disease may cause hematuria in infancy, but usually remains asymptomatic for several years before the onset of renal insufficiency. The hearing loss may not become clinically evident until the second decade of life. Dialysis and renal transplantation have proved important therapeutic advances in the treatment of these patients. Genetic heterogeneity had been confirmed for Alport’s syndrome. The gene on the X-chromosome has been identified as \textit{COL4A5}, which codes for a certain form of type IV collagen. When a genetic mutation occurs, connecting structures in both the inner ear and kidney become increasingly fragile, resulting in progressive hearing impairment and kidney disease. Defects in two other collagen genes, \textit{COL4A3} and \textit{COL4A4}, also have been found to cause Alport’s syndrome and are inherited in an autosomal recessive manner. Autosomal type IV collagen gene mutations result in an autosomal dominant inheritance pattern, but males are still more severely affected.

**Nonsyndromic X-Linked Hearing Loss**

Most of the X-linked genes responsible for hereditary hearing impairment have yet to be elucidated. At least 6 loci on the X-chromosome for nonsyndromic hearing loss are known. Two types of nonsyndromic, X-linked severe sensorineural hearing loss have been described. These are an early onset rapidly progressive type and a moderate slowly progressive type. X-linked nonsyndromic hearing impairment is even more uncommon than X-linked syndromic deafness. The hearing impairment is of prelingual onset and characterized by one of two forms. X-linked fixation of the stapes with perilymphatic gusher associated with mixed hearing impairment has been localized to the DNF3 locus, which encode the \textit{POU3F4} transcription factor. This gene is located close to a gene causing choroideremia, and deletion of these genes produces the contiguous gene syndrome of choroideremia, hearing loss, and mental retardation. Preoperative CT scanning can be used to detect predictive findings, such as an enlarged internal auditory canal with thinning or absence of bone at the base of the cochlea. X-linked forms of hearing impairment also may involve congenital sensorineural deafness. Both forms of nonsyndromic hearing impairment have been linked to Xq13-q21.2. Researchers have also identified a X-linked dominant sensorineural hearing impairment associated with the Xp21.2 locus. The auditory impairment in affected males was congenital, bilateral, sensorineural, and profound, affecting all frequencies. Adult carrier females demonstrated bilateral, mild to moderate high frequency sensorineural hearing impairment of delayed onset.

**Multifactorial Genetic Disorders**

Some disorders appear to result from a combination of genetic factors interacting with environmental influences. Examples of this type of inheritance associated with hearing loss include clefting syndromes, involving conductive hearing loss, and the
microtia/hemifacial microsomia/Goldenhar spectrum. Goldenhar’s syndrome has been described as autosomal dominant in some families, although this may simply represent clustering. Findings in this syndrome include preauricular tags/pits, vertebral anomalies such as hypoplastic or hemivertebrae in the cervical region, epibulbar dermoids, and coloboma of the upper lid. Other conditions believed to represent multifactorial inheritance are increased susceptibility to hearing loss and hyperlipidemia.

**Autosomal Chromosomal Syndromes**

Middle ear and mastoid disease are often observe in Down syndrome children, but sensorineural hearing loss may also be present. Trisomy 13, which is often lethal in the newborn period, can have significant sensorineural hearing loss in the survivors. Turner’s syndrome, monosomic for all or part of one X chromosome, presents generally in female as gonadal dysgenesis, short stature, and often webbed neck or shield chest. They will also have sensorineural, conductive, or mixed hearing loss, which can be progressive and may be the first evidence of the syndrome in prepubertal females.

**Mitochondrial Disorders**

Hearing loss can occur as an additional symptom in a range of mitochondrial syndromes. Mitochondria are small organelles in the cytoplasm of the cells. Mutation in the mitochondrial genome can affect energy production through adenosine triphosphate synthesis and oxidative phosphorylation. Tissues that require high levels of energy are particularly affected. Typically, mitochondrial diseases involve progressive neuromuscular degeneration with ataxia, ophthalmoplegia, and progressive hearing loss. Disorders such as Keams-Sayre, MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke), MERRF (myoclonic epilepsy with ragged red fibers) and Lebers hereditary optic neuropathy are all mitochondrial disorders. All of these disorders have varying degrees of hearing loss. Mitochondrial inheritance is different from the inheritance pattern seen with nuclear genes. Sperm transmit little or no mitochondria so nearly the entire contribution of mitochondria to the offspring is from the egg. If the mother is homoplasmic for a mitochondrial mutation, all of the offspring (male and female) will be affected. A condition involving diabetes, hearing loss, and stroke had been attributed to a mitochondrial deletion. Several other mitochondrial mutations have been found to produce enhanced sensitivity to the ototoxic effects of aminoglycosides. Screening for these mutations would be indicated in maternal relatives of persons showing hearing loss in response to normal therapeutic doses of aminoglycosides.

**Evaluation and Genetic Counseling**

Genetic counseling should be tailored to provide information to parents about their child’s hearing loss etiology and about expected pattern of inheritance of any genetic disorder. The prerequisite for meaningful counseling must be a diligent search for etiology of the hearing loss. It is important to obtain a detailed family history. A positive history includes history of family members who were under 30 years of age when they developed hearing impairment or required a hearing aid. They should be asked about hereditary traits that may be associated with syndromic hereditary hearing impairment.
These would include a white forelock of hair, premature graying, different colored eyes, kidney abnormalities, night blindness, severe farsightedness, childhood cardiac arrhythmias, or a sibling with sudden cardiac death. Previous audiologic data acquired from the patient and other family members should be reviewed. The prenatal, perinatal, and postnatal medical history should be carefully reviewed and a thorough physical examination should be carried out. Look for features that are a variant from normal or dysmorphic, as they provide clues to syndromes. Starting from the face, notice any asymmetry of the facial bones, skin tags, the head shape, and presence of unusual hair colors or texture. Note eye slant, iris color, vision limitations, intercanthal distance, cataracts, and retinal findings. Examine the pinnae for asymmetry in shape between the right and left ears, malposition of the pinnae, presence of preauricular pits or skin tags, and for the external auditory canal size, patency, or tortuosity. Inspect the neck for thyromegaly or branchial anomalies. A skin examination should detect areas of hypopigmentation and café-au-lait spots. Extremities should be checked for aberrant digit size, shape, or number, and syndactyly. Gait and balance should be noted to test the vestibular system.

Audiologic evaluation should be undertaken in all cases of suspected hereditary hearing impairment, and should include the parents and siblings of the individual. For infants and younger patients, electrophysiologic tests such as the auditory brain stem response, stapedial reflex, and otoacoustic emission can be done. An audiogram that is U-shaped or cookie bite should alert the clinician to hereditary hearing loss. Vestibular function tests can be helpful in the diagnosis of patients with Usher syndrome.

Depending on the history and physical findings, further evaluations, such as imaging or laboratory studies, may be indicated. All children diagnosed with hearing loss should have a urinalysis to assess for proteinuria and hematuria. Other tests should be ordered as appropriate, for example, thyroid function tests and electrocardiogram in suspected Pendred’s and Jervell and Lange-Neilsen syndrome, respectively. Other studies that may need to be pursued include electroretinograms and perchlorate discharge test. Radiographic studies should be ordered on a case-by-case basis. A CT scan can help to visualize cochlear abnormalities, internal auditory canal aberrations, and cochlear dysplasia. MR imaging with gadolinium enhancement is the study of choice in patients with a family history of Neurofibromatosis type 2. MR is also used when the hearing loss is progressive but the CT scan is normal. At completion of an intensive and sometimes expensive evaluation, the specific etiology of a hearing loss still may remain uncertain.

Consultation with a clinical geneticist is recommended when hereditary hearing loss is suspected. They can assist in making the diagnosis when the findings are equivocal or subtle, and can provide guidance to the parents in terms of prognosis and future offspring, and determine what other diagnostic studies are needed. The geneticist may be able to confirm nonsyndromic hereditary hearing loss.
A complete genetic evaluation should consider prognosis and recurrence risk. Counseling regarding the recurrence risks for autosomal dominant disorders must take into account the degree of penetrance that usually characterizes the particular gene. The chance of inheriting the disorder can range from 50% in fully penetrant genes to less in decreased penetrance genes. Children of parents who are heterozygous for an autosomal recessive disorder gene have a 25% chance of having the disorder and a 50% chance of being a carrier. The recurrence risk for the future offspring of a child with recessively inherited deafness depends on the genetic status of their mate. Heterozygotic carriers of a recessive gene also run low recurrence risks, estimated at about 1:100, depending on the frequency with which the specific gene is found in the general population. Male offspring of a maternal carrier of an X-linked recessive disorder are at 50% risk of being affected, and female offspring of the same mother are at 50% risk of being a carrier. An affected male will pass the gene to all of his daughters, but to none of his sons. The recurrence risk for multifactorial disorders can be quite low, as would the risk for chromosomal disorders if both parents were normal karyotypes. The risk of a mitochondrial disorder will depend on whether the mother is homoplasmic or heteroplasmic and on whether other genetic or nongenetic factors are necessary for expression.

Bieber and Nance developed empiric risk factor tables to assist in determining recurrence risks. Useful information for a clinician to remember is that the range of recurrence risk for future offspring cited for a family with an only child, who has an unexplained hearing loss, is 10% to 16%. Each additional normal hearing child born to such a family would decrease the probability that the disorder has a genetic etiology and thus decrease the recurrence risk. Likewise if another child is born to the same family and has a hearing impairment then the recurrence risk increases because the possibility of a genetic component causing the hearing loss is increased.

**Conclusion**

Diagnosis, prognosis, and estimation of recurrence risk are components of a complete genetic evaluation of a child with suspected genetic hearing loss. Precise diagnosis, that is, delineation of the phenotype, is essential, and a diligent search for etiology should be undertaken, including search for occult syndromic components. Review of clinical and laboratory data by a clinician skilled in pattern recognition can lead to identification of a syndrome or family pattern useful in predicting the likely clinical course of the disorder. An accurate diagnosis also enhances the accuracy of recurrence-risk estimates.
References


Addendum:

1994 Position Statement of when to perform hearing screening if universal screening is not available

I. Neonates through 28 days
   - family hx of hereditary childhood SNHL
   - in utero infection c TORCH
   - craniofacial anomalies
   - birthweight < 1500 grams
   - hyperbilirubinemia
   - ototoxic meds
   - bacterial meningitis
   - Apgars 0 to 4 at 1 minute or 0 to 6 at 5 minutes
   - on ventilator > 5 days

II. Infants 29 days - 2 years
    - parent concern, developmental delay
    - bacterial meningitis
    - head trauma assoc c LOC or skull fracture
    - ototoxic meds
    - recurrent or persistent otitis media c effusion for atleast 3 months

III. Indicators for delayed onset SNHL
    - family history hereditary childhood hearing loss
    - in utero infection c CMV, rubella, syphilis, herpes or toxoplasmosis
    - neurodegenerative disorders
    * This group requires hearing evaluation every 6 months until age 3 years
Referral Indicators

- child’s nonverbal development may be used as yardstick for lang
development
- 0 to 3 months: child should startle at loud noises
- 3 to 6 months: turn head toward sounds and babble
- 6 to 10 months: responds to their name and understands simple words
- 10 to 15 months: responds to simple commands and imitates simple words
- even a deaf child may babble
- 12 months
  - child has little interest communicating with caregiver
  - should be able to understand single, familiar words s non-
    linguistic clues
- 24- 36 months
  - child says fewer than 50 words
  - no combination of any words
  - should be able to understand simple 2 or 3 word phrases
- 36 months
  - combinations of 3 or more words is norm for this age group
  - child expected to have multi-word sentences
  - may test comprehension c certain tests
- 4 y/o
  - unable to carry on conversation of “here and now” topics with
    sentence 3 or more words

General Recurrence Risk Rate

Risk of child being affected:

One parent deaf other child nl hearing
- Range from negligible to 50%
- overall risk is 6%
- one deaf parent and one deaf sibling 40% risk of HL for
  subsequent offspring

Two deaf parents
- 100% if have identical auto recessive disorders
- 50% if one parent has auto dominant disorder
- overall risk 10%
- one deaf child raises risk to 60% encountered syndromic causes
Evaluation of SNHL by Grundfast in Bluestone and Stool

Universal Screening
- all infants prior to age 3 months
- screening of high risk only misses up to 50% children c SNHL until school age

Best if divide pt into categories by age
I. neonate to 6 weeks
II. infant: 6 weeks to 2 years
III. preschool: > 2 to 5 years
IV. school age: > 5 to 10 years
V. pre to adol: > 10 to 17 years

Background information

Gestational History
- embryo most susceptible from 3 to 10 weeks gestation
- exposure to TORCH infections
- IV abx
- endocrine disorders in mother

Perinatal Hx
- screening of high risk pts only, misses 50% children c SNHL
- some evidence that auditory system is selectively vulnerable to brief episodes hypoxia at birth
- ICU stay > 5 days
- Kernicterus

A- affected family member
B- bilirubin (> 15mg/100ml)
C- Congenital rubella or other infection
D- Defects of ENT
S- small at birth (< 1500 grams)

Family Hx
- SNHL in relative is assoc c dominant inheritance
- ask if family member needed hearing aid prior to age 30

Physical Exam
- evaluate eyes for abnormalities
- close evaluation for any minor developmental anomalies
- pigmentary abnormalities

Lab Evaluation
TORCH titers
- CMV needs to be tested w/I first 3 weeks o/w may
actually be post-natal exposure
- persistent elevation of viral titers is suggestive of an intrauterine infection
- a deaf child that fails to develop AB to Rubella after vaccination; the etiology may be secondary to congenital rubella infection

Syphilis
- need to check FTA-abs, IgG

Urinalysis
- looking for protein and blood in urine

Thyroid testing
- if suspect Pendred
- may need to perform perchlorate test

EKG
- abnl in Jervell Lange and Refsum but is low yield

Chromosomal analysis
- identification of AD SNHL not seen in relatives
- mother has h/o of miscarriages
- child has multiple cong anomalies not identified as a syndrome
- majority of hereditary SNHL is secondary to point mutations; therefore genetic analysis not that beneficial

X:Rays
CT
- 80% of neonates c HL do not have a morphogenetic defect
- indicated for children > 3 to look for developmental abnl of temporal bone to help explain hearing loss esp if pt is experiencing a progressive loss

Diligent Search with state of art techniques proves inconclusive 30 to 40% of the time (B&Sp.642)