Chapter 9
Nonsyndromic Deafness: It Ain't Necessarily So

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"It ain't necessarily so" is a song about doubt in George and Ira Gershwin's opera *Porgy and Bess*.

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9.1 Introduction

Improvement in medical technology and a deeper understanding of human disease has lowered the clinical threshold for detecting many disorders, gradually enhancing our ability to identify medically relevant anomalies. Pathology is detected earlier, and with greater precision and finer definition. For instance, diagnoses of diabetes, hypertension, impaired vision, and inner ear abnormalities are occurring at an earlier age because of improved clinical awareness and detection. Concurrently, clinical phenotyping coupled to molecular genetic breakthroughs such as exome and genomic sequencing are accelerating the identification of potentially causative genetic variants that exert a large effect in human disorders. Studies of hereditary hearing loss from different perspectives have benefitted from these technical and conceptual developments.

The inner ear has many highly specialized, delicate, and intricate structures that are functionally unique and necessary for normal hearing. Assuming that unique structures require highly specialized proteins, perhaps limited in expression to the inner ear, it would not have been surprising that inherited abnormalities of such molecular machinery made of proteins expressed exclusively in the inner ear might be expected to cause hearing loss and no other accompanying disorder. When this happens it is referred to as nonsyndromic deafness. Many different recessive and dominant mutant alleles of a variety of genes have been associated with nonsyndromic deafness. However, the assumption that the expression of the "nonsyndromic deafness genes" is largely limited to the inner ear (or at the least not widely expressed in other organ systems) is not strictly correct. It is true that the inner ear is physiologically an exquisitely sensitive structure, composed of startlingly beautiful architectural arrangements of cells that transduce sound to signals then sent to the brain. However, the expression of the majority of macromolecules exploited for this remarkably complex development of the inner ear appears to have been genetically hijacked during the evolution of the auditory system from alternative functions that have remained in many other tissue types. This broad expression of many deafness genes was worrisome for us and offers a cautionary note when assuming a particular hearing loss is nonsyndromic.

Congenital and early onset hearing loss is a common neurosensory deficit that may be associated with other disorders. There are many syndromes that include hearing loss as one feature of a pleiotropic phenotype. The online database Mendelian Inheritance of Man (http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim) lists hundreds of entries that include deafness alone or as one manifestation of a variety of syndromes. For example, Usher syndrome and Jervell and Lange–Nielsen syndrome are disorders involving the eye and heart, respectively, in addition to impaired hearing. These two syndromes are mentioned because progressive loss of vision due to retinitis pigmentosa (RP) may not be obvious in young children, and the life-threatening cardiac conduction defect of Jervell and Lange–Nielsen syndrome is sometimes discovered only posthumously. For a deaf child checking the electrical activity of the heart by an electrocardiogram (EKG) is not yet the

standard of care. An EKG is a quick, easy and inexpensive test and in our opinion should become routine during a pediatric examination of a deaf person.

In contrast to such syndromic forms of hearing loss, nonsyndromic deafness is not accompanied by additional medically significant features, as is often believed at the time of ascertainment and reported in the literature. How might medically relevant issues accompanying hearing loss have been overlooked or ignored? We think that questions addressed to the subjects or relatives may be too narrowly focused on hearing ability. RP or prolongation of the QT cardiac conduction interval (delayed repolarization of the heart detected by an EKG test) are hidden from view, as are many other possible additional clinically relevant features. Hearing loss may be the tip of a clinical iceberg. Lacking a comprehensive physical examination, a strongly held belief that the diagnosis is nonsyndromic deafness may become a self-fulfilling prophecy. Fooling oneself is easy. In science, always doubt you got it right.

Study subjects are often visited where they dwell, which can be a considerable distance from medical staff and not allow for a wide-ranging physical exam to completely characterize the actual phenotype of the study subjects. But even more important, the underlying function of the causative disease gene responsible for hearing loss is likely to be unknown early in a study, further frustrating characterization of the full phenotype. Without knowledge of gene function and expression pattern in the various organ systems, a clinician investigator would need to be thinking of an inordinately large number of relevant questions about organs and tissues throughout the body.

Nearly 70 different nonsyndromic deafness genes have been reported to date (http://dnalab-www.uia.ac.be/dnalab/hhh/). How many of these different nonsyndromic deafness disorders, in reality, are syndromic remains to be determined. Early in a study of hereditary deafness, this can be an inherently difficult issue to resolve. For all these reasons, classification of human hereditary hearing loss as nonsyndromic should be considered provisional until there is adequate understanding of the normal function and expression pattern of a deafness gene that can then guide a focused clinical evaluation.

Functional studies can be technically difficult, especially when a gene expresses multiple mRNA splice isoforms, which is common for eukaryotic genes. Meticulous functional studies are also expensive and resource intensive. As a consequence, crucial mechanistic information about gene function that might inform a clinician about where to focus a physical examination often follows many years after disease gene identification. And that has meant a delay between disease gene discovery and expanded clinical insight concerning hitherto unrecognized syndromic manifestations.

A few published examples of mistaken assignment of hereditary deafness as nonsyndromic are described briefly, including an instance from our own recent work. In this chapter we also emphasize that most of the studies of hereditary hearing loss were initiated with the ascertainment of affected subjects from families where marriages often occur within the ethnic group (endogamy), from community isolates, or from large consanguineous families living almost exclusively outside of Western countries. In many countries study subjects often live far from

sophisticated medical resources. Family ascertainment is tough work that is the bedrock for identification of the many novel mutated genes responsible for this monogenic disorder, and is underappreciated. In addition, ascertaining families segregating hereditary disorders is not hypothesis driven research and attracts support with difficulty. At times our own personal funds have subsidized this critically important first step of locating large families for molecular genetic studies.

9.2 Nonsyndromic Deafness

In the 1980s restriction fragment length polymorphism (RFLP) markers allowed genetic mapping of Mendelian disorders, although the process was sluggish by today's standards. Studies were initiated to map the chromosomal locations (loci) for human syndromic and nonsyndromic deafness genes. To achieve statistical significance, genetic linkage studies required large families with several affected and unaffected participants, and achieved stronger results when parents and grandparents were included. In Western countries there have been many opportunities to ascertain large families segregating nonsyndromic deafness as an autosomal dominant trait (DFNA). However, large families segregating autosomal recessive deafness (DFNB) are rare in the United States and Europe.

Large families or community isolates segregating recessive deafness were first studied in Bali, India, Saudi Arabia, Iran, Turkey, Tunisia, and Pakistan. Given these locations, it was uncertain if the mutated deafness genes, once discovered, would have relevance in Western countries. During this time, there was a concern that families ascertained in remote locations would reveal mutant genes that would turn out to be private to particular ethnic groups, and it was possible that the knowledge gained would contribute little clinically relevant information toward an understanding of deafness in the United States or Europe. In the absence of molecular genetic data it was not possible to refute such concerns. However, it seemed likely that basic knowledge about how hearing happens would expand through functional studies of the genes causing deafness, even if the mutations discovered were private and their clinical relevance limited to non-Western populations.

This matter was settled when it was shown that hereditary deafness in Western countries was caused by mutant alleles of nearly all the same deafness genes identified through studies of families in non-Western countries. This was also true for deafness genes segregating in community isolates and even in families living in a centuries-old Balinese village. It was the best of all possible outcomes. The vast majority of mutated genes associated with recessive deafness segregating in these families ascertained from remote areas were also found among individuals with hearing loss worldwide. For example, mutations of *MYO15A* encoding unconventional myosin XVA (Probst et al., 1998; Wang et al., 1998) were first discovered through studies of deaf and hearing individuals living in Bengkala, Indonesia (Friedman et al., 1995), and are now reported to be associated with recessive deafness in North and South America, the Middle East, Asia, and Europe (Nal et al., 2007) (Table 9.1).

Table 9.1 Selected genes underlying human syndromic and nonsyndromic deafness mentioned in this chapter[a]

Syndrome	Locus	Chromosomal location	Gene	Comments
Chudley–McCullough (CMCS)	*DFNB32 DFNB82*	1p13.3	*GPSM2*	G-protein signaling modulator, unknown function in the ear
Deafness–dystonia–optic neuropathy	*MTS*	Xq22.1	*TIMM8A*	Essential for import of proteins into the mitochondrion inner membrane
Jervell and Lange–Nielsen	*JLNS1*	11p15.5-p15.4	*KCNQ1*	Potassium voltage-gated channel, KQT-like subfamily, member 1, mediates secretion of K^+ from stria vascularis marginal cells into scala media
Perrault	*DFNB81*	19p13.3	*CLPP*	Chambered protease, highly conserved mitochondrial protein
	PRLTS1	5q23.1	*HSD17B4*	17-β-hydroxysteroid dehydrogenase IV, enzyme involved in peroxisomal fatty acid β-oxidation
	PRLTS2	5q31.3	*HARS2*	Histidyl tRNA synthetase, highly conserved mitochondrial protein
	LARS2	3p21.31	*LARS2*	Leucyl-tRNA synthetase, mitochondrial protein
Usher, type 1	*USH1B*	11q13.5	*MYO7A*	Myosin VIIA, actin-based motor required for stereocilia function
	USH1C	11p15.1	*USH1C*	Harmonin, scaffolding protein required for stereocilia function
	USH1D	10q22.1	*CDH23*	Cadherin 23, component of the stereocilia tip link
	USH1F	10q21.1	*PCDH15*	Protocadherin 15, component of the stereocilia tip link
	USH1G	17q25.1	*USH1G*	Sans, scaffolding protein required for stereocilia function
	USH1J	15q25.1	*CIB2*	Calcium- and integrin-binding protein 2
Nonsyndromic deafness				
	DFNB1	13q12	*GJB2*	Connexin 26, gap junctions for intercellular communication
	DFNB3	17p11.2	*MYO15A*	Myosin motor protein 15 essential for stereocilia elongation and maintenance
	DFNB12	10q21-q22	*CDH23*	Cadherin 23, component of the tip link
	DFNB72	19p13.3	*GIPC3*	GAIP C-terminus-interacting protein 3, essential for survival of hair cells and spiral ganglion
	DFNB81	19p13.3	*CLPP*	Chambered protease, highly conserved mitochondrial protein

[a]Modified from Tables 1 and 3 of Griffith and Friedman (2014)

As of 2012, approximately 100 nonsyndromic recessive deafness loci have been genetically mapped using consanguineous families ascertained in non-Western countries. There are several reasons why India and Pakistan in particular have been troves of immense scientific value for geneticists studying monogenic disorders. Schools for the hearing impaired are good starting points to identify affected members of large families. In many countries in Asia and the Middle East, individuals marry relatives, often their first cousins. Generations of consanguineous marriages or endogamy within a community bring together mothers and fathers who are carriers (heterozygotes) of the same recessive mutations. Their progeny have a one in four chance of being homozygous for a particular recessive mutant allele. In a sufficiently large family, the location of the causative allele can be mapped to a chromosome using a genome-wide homozygosity mapping strategy (Friedman et al., 1995), and the gene eventually identified. Among many consanguineous families there is a tradition of large sibships and members frequently live close to one another. A shared environment helps to rule out major contributions of extrinsic factors to a phenotype. In addition, family members often are genuinely interested in understanding the reasons for their hearing loss and generously participate in basic research studies when direct benefits are not promised and evidence-informed therapies are not close at hand.

9.3 Rhetoric and Reality

Human nonsyndromic deafness can be caused by any one of a great many different large-effect mutant genes. A skeptic might ask about other clinically relevant issues considered and ruled out before accepting an assertion that a hearing impaired individual has no other co-segregating features indicative of a known or novel syndrome. Already there are a few reports where the initial supposition of nonsyndromic deafness was just the beginning of an evolving diagnosis.

9.3.1 X-Linked Nonsyndromic Deafness DFN1 Is Deafness–Dystonia–Optic Neuropathy Syndrome

X-linked genes account for only a few percent of all cases of inherited hearing loss. In 1960, a four-generation Norwegian family was described that segregated early-onset, progressive, nonsyndromic neurosensory deafness consistent with an X-linked pattern of inheritance (Mohr & Mageroy, 1960) and designated DFN1 (X-linked nonsyndromic deafness). There was an initial clinical evaluation of the seven affected males in this family, all of whom were described as just having hearing loss. However, when this family was restudied, extensive intrafamilial phenotypic variation was observed among affected males including progressive loss of vision, mental deterioration, dystonia, ataxia, and hip fractures in addition to the

postlingual progressive hearing loss (Tranebjaerg et al., 1995). Some female carriers also seemed to manifest focal dystonias (Swerdlow & Wooten, 2001). The hearing loss component of this syndrome (DDON; deafness–dystonia–optic neuropathy syndrome; previously named Mohr–Tranebjaerg syndrome, MTS; MIM 304700) was due to degeneration of cochlear neurons observed in temporal bone specimens (Bahmad et al., 2007) (Table 1).

Linkage analysis was conducted and the *DDON* locus was mapped to Xq22 (Tranebjaerg et al., 1995). Subsequently, a variety of pathogenic mutations of *TIMM8A* (translocase of the *i*nner *m*itochondrial *m*embrane *8A*) were shown to cause DDON (Jin et al., 1996; Engl et al., 2012). *TIMM8A* mediates selective import of proteins from the cytosol to the inner mitochondria membrane (Koehler et al., 1999; Roesch et al., 2002). DDON syndrome is therefore a disorder of defective mitochondrial protein import. But the pathophysiology that accounts for the pleiotropy of DDON remains somewhat of a mystery when there are apparently phenotypically normal tissues and organs that also have substantial respiratory demands. An inner ear conditional *Timm8a1* mutant mouse or other animal models of DDON syndrome should provide insight. Nearly 20 years ago, the thesis that Tranebjaerg and co-authors stressed was the necessity of implementing detailed clinical evaluations of study subjects when a novel deafness gene is identified.

9.3.2 Nonsyndromic Deafness DFNB82 Is Chudley–McCullough Syndrome

A large Palestinian family segregating profound deafness as a recessive trait was ascertained in the West Bank and the phenotype was genetically mapped to a novel locus on chromosome 1p (Shahin et al., 2010) (Table 1). Subsequently, a homozygous nonsense mutation (p.Arg127X) of *GPSM* was reported as the cause of hearing loss DFNB82 initially reported to be nonsyndromic (Walsh et al., 2010). A Turkish family also segregating deafness was reported to be homozygous for a p.Gln562X allele of *GPSM* (Yariz et al., 2012). Subsequently, recessive mutations of *GPSM* were reported to be associated with Chudley–McCullough syndrome (CMS; MIM 604213). CMS is characterized by hearing loss and a prominent although partial failure in the development of the corpus callosum, an anatomic defect of the brain that appears not to translate into any obvious or consistently contemporaneous abnormalities. However, in two of the twelve affected subjects pharmacologically controlled seizures were present, a disorder known to be associated with corpus callosum defects (Doherty et al., 2012).

Because CMS subjects were found to have two mutant alleles of *GPSM in trans*, Doherty and coauthors used brain imaging to re-examine some of the deaf DFNB82 subjects. The Palestinian affected individuals and three Turkish deaf subjects all had brain abnormalities consistent with CMS. In these subjects there were no obvious developmental or behavioral deficits that might have indicated the possibility of additional clinically relevant features beyond hearing loss, the phenotype

used for ascertainment. How many other study subjects reported to have nonsyndromic deafness actually have a new syndromic form of hearing loss that was overlooked or ignored?

9.3.3 Perrault Syndrome Not Nonsyndromic Deafness (DFNB81)

It was easy to assume hearing loss is nonsyndromic when we didn't ask spot-on questions. The study subject is certainly not at fault. Who would have thought there was a relationship between hearing loss and infertility when we genetically mapped deafness segregating in Pakistani family PKDF291? Family PKDF291 has four deaf female siblings, two normal hearing sibs, and normal hearing parents (Rehman et al., 2011). After discovering the pathogenic mutation causing deafness in this family, but before publishing this observation, William Newman in Manchester, UK identified a different mutation of the *CLPP* gene in a family segregating Perrault syndrome, a genetically heterogeneous disorder (Jenkinson et al., 2013). Perrault syndrome is a sex-influenced, autosomal recessive disorder characterized by sensorineural hearing loss in males and females, and gonadal dysgenesis only in females (Pierce et al., 2011). Armed with this information, the next step was to revisit members of the DFNB81 family and ask questions about fertility and request relevant tests for the levels of serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), progesterone, and estradiol. Affected females of family PKDF291 were found to have the hormonal aberrations expected in Perrault syndrome. Interestingly, if the affected members of family PKD291 were instead males, nonsyndromic deafness would have correctly described the phenotype. On the other hand, females homozygous for the mutation had no menses and in effect are postmenopausal at a very young age (Jenkinson et al., 2013). The functional nexus between hearing loss and ovarian dysgenesis in Perrault syndrome remains an open question.

9.4 Allelic Mutations Can Cause Nonsyndromic or Syndromic Deafness

There are now several published examples of different mutations of the same gene causing syndromic deafness or nonsyndromic deafness, a heretical supposition a few decades ago. Such clinical heterogeneity results from the variable downstream impact of different mutations in the same gene. The severity of the phenotype is presumably directly related to the degree of gene disablement, while genetic modifier variants in the background (Riazuddin et al., 2000; Schultz et al., 2005) and environmental factors may also have a significant impact on the fully evolved phenotype, for better or for worse. A few examples illustrate this point.

Usher syndrome accounts for the majority of inherited human deaf-blindness. The defining features of the most severe presentation of Usher syndrome are hearing loss, peripheral vestibular areflexia, and progressive loss of vision due to retinitis pigmentosa (RP) that becomes noticeable in the second decade of life. Usher syndrome is inherited as a recessive disorder. Even knowing the molecular details of a mutated Usher syndrome gene may make it challenging to predict precisely the ultimate phenotype in young hearing impaired human subjects.

Christine Petit's group genetically mapped the nonsyndromic deafness locus DFNB12 to chromosome 10q21-22 (Chaib et al., 1996) while that same year, Richard Smith and colleagues (Wayne et al., 1996) reported that an Usher syndrome locus (*USH1D*) genetically mapped to roughly the same chromosomal interval. Our group then reported that some alleles of *CDH23* encoding cadherin 23 can cause only nonsyndromic deafness DFNB12 while other presumably more disabling mutations of *CDH23* cause Usher syndrome 1D (Bork et al., 2001). This observation is now well supported by reports from other investigators. A similar genotype–phenotype correlation was found for mutations of some of the other Usher syndrome genes including *USH1C*, *PCDH15*, and *CIB2*. Our working hypothesis is that loss of gene function (null mutation) results in Usher syndrome while hypomorphic alleles spare vision but cause hearing loss (Schultz et al., 2011). Why vision is maintained and hearing lost with some hypomorphic alleles of Usher syndrome genes is an unanswered, experimentally challenging question.

Without an eye examination by an ophthalmologist, the early signs of RP can be easily overlooked in a juvenile. A young deaf person with two predicted pathogenic missense mutations of an Usher gene may wish to know if vision will also be lost. The following examples illustrate this situation. Nonsyndromic deafness in the Ashkenazi Jewish population is predominantly caused by one particular recessive founder mutation (c.167delT) of *GJB2* (Morell et al., 1998). This frameshift mutation ablates the function of connexin 26 and is associated with well-documented nonsyndromic deafness DFNB1.

In the Ashkenazi Jewish community there is also a recessive founder mutation (p.R245X) of *PCDH15* that appears invariably to cause the most severe form of Usher syndrome (Ben-Yosef et al., 2003). In a young person, homozygosity for p.R245X may be incompletely diagnosed as nonsyndromic deafness (Brownstein et al., 2004). As an example, the underlying reasons for hearing loss were sought for 20 young Ashkenazi Jewish adolescents who were previously diagnosed with nonsyndromic deafness that was known to not be due to the c.167delT mutation of *GJB2* or any other mutant allele of *GJB2*. Subsequently, when the *PCDH15* gene was sequenced, 2 of the 20 children were found to be homozygous for p.R245X, foreshadowing loss of vision. The diagnosis of deafness was certainly correct, but incomplete, while early indications of impending vision loss due to RP was overlooked. The standard of care for young deaf *GJB2*-negative Ashkenazi Jewish children should now include an ophthalmological evaluation even if there is no family history of Usher syndrome.

Worldwide, pediatricians, otolaryngologists, and audiologists are more alert for the possibility of Usher syndrome in young individuals of any ethnicity with hearing

loss, especially among children who exhibit delayed independent ambulation (walking), a condition possibly indicative of a vestibular dysfunction. Early indications of RP can be detected as a small deviation from a normal electroretinogram (ERG) in a young person. An ERG can detect electrical responses from photoreceptors (rods and cones) in the eye and other cell types of the retina. Timely habilitation of hearing through cochlear implantation of otherwise profoundly deaf Usher syndrome children often provides sufficient hearing when later loss of vision precludes sign language and lip reading.

An obvious question arose as to the phenotypic consequence of a person who has one DFNB12 mutation of *CDH23* on one chromosome and an Usher syndrome allele of *CDH23* on the other chromosome (referred to as the *trans*-configuration). Will this person develop RP? Is a nonsyndromic deafness allele of *CDH23* phenotypically recessive or phenotypically dominant to an Usher syndrome allele of *CDH23*? Although the number of subjects in the study was small, Schultz and co-authors addressed this question by characterizing the phenotype of individuals who were compound heterozygotes for an Usher allele and a DFNB12 allele of *CDH23*. The conclusion from this study is that such persons did not have a vestibular dysfunction nor did they develop RP. However, they were deaf. Therefore, a DFNB12 allele is phenotypically dominant to an USH1 allele in the eye and vestibular system. Although at present there is no assay for cadherin 23 function in the retina, it was proposed that one DFNB12 mutation of *CDH23* provides sufficient residual cadherin 23 function for normal retinal and vestibular labyrinth function but, because the subjects were deaf, this is inadequate for inner ear function. The genotype–phenotype relationship for mutations of *CDH23* is reason for optimism that a therapy can be developed to prevent or slow the progression of RP as partial function of defective cadherin 23 seems to be sufficient to preserve vision (Schultz et al., 2011).

9.5 Summary

We predict that there will be more examples of incompletely diagnosed nonsyndromic deafness in which the hearing loss, upon closer clinical examination, will be just one feature of a more complex phenotype. Intellectual flexibility and continuous conversation between subjects, basic scientists and clinicians will help to clarify these situations over time. In part, clues will come from in vitro functional analyses of deafness genes as well as detailed in vivo studies of mouse models. Admittedly, mouse models do not always recapitulate the full phenotypic spectrum of human syndromic forms of deafness. Although not necessarily so, one tipoff that the mutant phenotype may be more complex than just hearing loss alone is a wide pattern of expression of the wild type gene beyond the auditory system. Surprisingly, nearly ubiquitous expression of several presumably nonsyndromic deafness genes appears to be the rule rather than the exception (Schultz et al., 2009).

Our own recent experience, and the published examples described in the preceding text, suggests to us that quick pronouncements of the nonsyndromic nature of an

inherited hearing loss might better be tempered with a degree of uncertainty commensurate with the depth of the initial clinical investigation, which is often sparse. In our case, the focus has been on hearing and vision, and thus the phenotype was nonsyndromic deafness or Usher syndrome. In the fullness of time, how many of the nearly hundred genes associated with nonsyndromic deafness will turn out to actually cause a syndromic form of hearing loss? Before revisiting affected individuals, a goal will be to empower collaborating clinicians with focused biological insight about pathologic and normal "deafness gene" functions from comprehensive studies of cognate mouse models. Germane clinical data beyond the auditory system can then be gathered. Correct and complete science is partial repayment for the generosity of human subjects in our studies and a prerequisite for contributions to the body of published knowledge that withstands the test of time.

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