Hereditary deafness and phenotyping in humans

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Hereditary deafness has proved to be extremely heterogeneous genetically with more than 40 genes mapped or cloned for non-syndromic dominant deafness and 30 for autosomal recessive non-syndromic deafness. In spite of significant advances in the understanding of the molecular basis of hearing loss, identifying the precise genetic cause in an individual remains difficult. Consequently, it is important to exclude syndromic causes of deafness by clinical and special investigation and to use all available phenotypic clues for diagnosis. A clinical approach to the aetiological investigation of individuals with hearing loss is suggested, which includes ophthalmology review, renal ultrasound scan and neuro-imaging of petrous temporal bone. Molecular screening of the *GJB2* (*Connexin 26)* gene should be undertaken in all cases of non-syndromic deafness where the cause cannot be identified, since it is a common cause of recessive hearing impairment, the screening is straightforward, and the phenotype unremarkable. By the same token, mitochondrial inheritance of hearing loss should be considered in all multigeneration families, particularly if there is a history of exposure to amino-glycoside antibiotics, since genetic testing of specific mitochondrial genes is technically feasible.

Most forms of non-syndromic autosomal recessive hearing impairment cause a prelingual hearing loss, which is generally severe to profound and not associated with abnormal radiology. Exceptions to this include DFNB2 (*MYO7A*), DFNB8/10 (*TMPRSS3*) and DFNB16 (*STRC*) where age of onset may sometimes be later on in childhood, DFNB4 (*SLC26A4*) where there may be dilated vestibular aqueducts and endolymphatic sacs, and DFNB9 (*OTOF*) where there may also be an associated auditory neuropathy. Unusual phenotypes in autosomal dominant forms of deafness, include low frequency hearing loss in DFNA1 (*HDIA1*) and DFNA6/14/38 (*WFS1*), mid-frequency hearing loss in DFNA8/12 (*TECTA*), DFNA13 (*COL11A2*) and vestibular symptoms and signs in DFNA9 (*COCH*) and sometimes in DFNA11 (*MYO7A*). Continued clinical evaluation of types and course of hearing loss and correlation with genotype is important for the intelligent application of molecular testing in the next few years.

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Hearing impairment is the most common sensory disorder world-wide. When present in an infant, it may have dramatic effects on language

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Table 1 Causes of hearing impairment

Cause	
Genetic (syndromic and non-syndromic)	
	Autosomal recessive
	Autosomal dominant
	X-linked
	Mitochondrial
	Chromosomal, *e.g.* Down syndrome and trisomies 13 and 18, Turner syndrome, 22q11 deletions, mosaic trisomy 8
Environmental	
	Ototoxic medication, *e.g.* aminoglycosides, platinum derivatives
	Prematurity
	Neonatal hypoxia
	Low birth weight
	Severe neonatal jaundice
	Head trauma
	Infection: prenatal, *e.g.* CMV, toxoplasmosis, rubella; postnatal, *e.g.* meningitis
	Noise exposure

acquisition and educational progress. Hearing loss which becomes apparent in later childhood or in adult life may have profound effects upon the social and working lives of those affected.

Causes of hearing impairment are numerous (Table 1) and, in a particular population, the relative contribution of genetic and environmental causes may be determined by social factors such as population structure and consanguinity, infection control and immunisation, and provision of neonatal and postnatal medical care[1]. Thus, in non-industrialised countries, environmental causes of hearing loss may outnumber those that are genetically determined whereas in industrialised countries the importance of the genetic contribution to hearing loss has become more apparent.

Epidemiological surveys of the deaf have consistently shown that about 50% of childhood deafness can be attributed to genetic causes, but all of the surveys have pointed out that the cause cannot be determined in a considerable proportion of individuals[1]. Recent molecular work has demonstrated that in this group of ‘cause unknown’ deafness, genetic causes are common and extremely heterogeneous. Many deaf individuals and their families want to know the cause of their deafness and particularly whether it is genetic. Proven genetic diagnosis may allow for accurate genetic counselling and family planning, carrier testing for relatives, and may provide essential information about environmental risk factors (*e.g.* aminoglycoside antibiotics in those with the A1555G mtDNA mutation, or risk of progression of hearing loss in those with dilated vestibular aqueducts). In addition, precise molecular diagnosis may be important for planning and assessing success of therapies such as cochlear implant[2] or future gene therapy.

The increasing knowledge of the molecular basis of hearing impairment will raise expectations among deaf people and their families that

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the exact cause of their hearing impairment may be determined and understood by genetic analysis. While this may be possible for some families with common causes of genetic hearing impairment or extensive family histories, the complexity of hearing, demonstrated by the underlying molecular heterogeneity, poses considerable problems in aetiological diagnosis in the majority. The aim of this chapter is not to provide an exhaustive description of genes implicated in hereditary deafness, but to describe a clinical approach to diagnosis and genetic testing, with the interested non-specialist in mind.

Epidemiology of hearing impairment

About 1 per 1000 children in the UK is born with a permanent hearing impairment and a similar number develop this during early childhood[3]. As age increases so too does the prevalence of hearing impairment; by the age of 40–50 years, 2.3% of the population experience a hearing loss of greater than 40 dB, and nearly 30% of those over 70 years are similarly affected[4]. Genetic factors are likely to be important in all of these age groups.

About 30% of those with a genetic form of hearing loss present with other clinical features in addition to hearing impairment, as part of a

Table 2 Aetiological investigation of hearing impairment

History	
	Prenatal, perinatal and postnatal factors, infection, prematurity, *etc*
	Family history (at least 3 generations with specific enquiry about consanguinity)
Examination	
	Dysmorphic features
	Special attention to external ears and neck, skin, hair, eyes and digits
Investigations	*(including those which might reveal a syndromic cause)*
	• Serology and culture for congenital infection if child presents early
	• Ophthalmology examination with visual acuity and dilated fundoscopy to look for pigmentary retinopathy, signs of congenital infection or developmental malformation. ERG if pigmentary retinopathy, or history or vestibular examination suggests vestibular failure
	• Urinalysis for blood and protein suggestive or nephritis or nephrotic syndrome
	• Renal ultrasound scan to reveal renal dysplasia (BOR and HDR syndromes[46,95–97])
	• Neuro-imaging CT and/or MRI, to exclude dilated vestibular aqueducts and Mondini malformations or other appearances suggestive of syndrome diagnoses[45–47,98,99]
	• ECG if hearing loss is congenital and severe/profound, to look for prolonged QT interval (especially if there are delayed motor milestones)
	• Audiometry on first degree relatives, to determine whether more than one generation is affected
	• Consider vestibular investigations (hypofunction seen in Usher syndrome type 1, Jervell and Lange-Nielsen syndrome, Pendred syndrome, DFNA9 (*COCH*), DFNA11 (*MYO7A*), DFNB2 (*MYO7A*), DFNB4 (*SLC26A4*), DFNB12 (*CDH23*)

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Table 3 Some of the genes underlying syndromic forms of hearing impairment

Syndrome	Inheritance	Gene	Type of molecule encoded	Clinical features.
Waardenburg type 1	Autosomal dominant	PAX3	Transcription factor	Abnormal pigmentation of hair, skin and eyes. Dystopia canthorum, hypoplastic alae nasi, short philtrum, synophrys. Deafness in 20%, unilateral or bilateral.
Waardenburg type 2	Autosomal dominant	MITF and others	Transcription factor	Abnormal pigmentation of hair, skin and eyes. Deafness in 40%, unilateral or bilateral. No dysmorphic features.
Waardenburg type 3	Autosomal dominant	PAX3	Transcription factor	Features of type 1 with limb anomalies.
Waardenburg type 4	Autosomal dominant	EDN3, EDNRB SOX10	Endothelin ligand and receptor Transcription factor	Abnormal pigmentation of hair, skin and eyes in addition to Hirschprung's disease.
Treacher Collins	Autosomal dominant	TCOF	Nuclear cytoplasmic transport protein	Down-slanting palpebral fissures, malformation of external (microtia, stenosis and tags) and middle ears, sparse lower eyelashes and colobomata of lower eyelids, malar hypoplasia, cleft palate in some. Deafness may be conductive, sensorineural or mixed.
Branchio-oto-renal	Autosomal dominant	EYA1	Transcriptional activator	Branchial cysts and fistulae, external ear malformations (cup, lop ear or microtia, ear pits) renal dysplasia or hypoplasia. Deafness may be conductive, sensorineural or mixed.
Jervell and Lange-Nielsen	Autosomal recessive	KCNQ1, KCNE1	Ion channel	Profound congenital deafness and prolonged QT interval on ECG leading to syncope and possible sudden death.
Pendred syndrome	Autosomal recessive	SLC26A4	Anion transporter	Congenital deafness and goitre. Thyroid dysfunction, dilated vestibular aqueduct and endolymphatic sacs, Mondini malformation of cochlea may co-exist.
Alport	X-linked dominant Autosomal recessive	COL4A5/6 COL4A3/COL4A4	Structural collagens	Progressive high frequency deafness and nephritis. Anterior lenticonus and macular flecks.
Muckle Wells	Autosomal dominant	CIAS1	Pyrin-like protein involved in apoptosis and inflammation	Arthritis, abdominal pain and urticaria. Progressive deafness. Amyloidosis of AA type causing renal failure.
Non-muscle myosin heavy chain IIA diseases	Autosomal dominant	MYHIIA	Non-muscle myosin heavy chain	Giant platelets and thrombocytopaenia, nephritis, cataracts and hearing loss. Hearing loss is childhood onset, bilateral and progressive.
Norrie	X-linked recessive	NDP	Extracellular matrix protein	Pseudotumour, retinal detachment leading to infantile or congenital blindness. Progressive mental retardation in some and progressive childhood onset hearing loss.

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Table 3 (cont'd from previous page) Some of the genes underlying syndromic forms of hearing impairment

Syndrome	Inheritance	Gene	Type of molecule encoded	Clinical features
Stickler	Autosomal dominant	COL2A1, COL11A1 COL11A2	Structural collagen	Short stature, myopia, arthropathy, mid-face hypoplasia. High frequency progressive sensorineural hearing loss.
Usher type 1B	Autosomal recessive	MYO7A	Motor molecule	Profound congenital deafness, retinitis pigmentosa, vestibular arreflexia.
Usher type 1C	Autosomal recessive	USH1C	PDZ domain protein	Profound congenital deafness, retinitis pigmentosa, vestibular arreflexia.
Usher type 1D	Autosomal recessive	CDH23	Cadherin	Profound congenital deafness, variable retinitis pigmentosa, and variable vestibular function.
Usher type 1E	Autosomal recessive	PCD15	Protocadherin	Profound congenital deafness, retinitis pigmentosa, vestibular arreflexia.
Usher type 2A	Autosomal recessive	USH2A	Extracellular matrix protein	Congenital moderate-to-severe sensorineural hearing loss (normal vestibular function) and retinitis pigmentosa.
Usher type 3	Autosomal recessive	USH3A	Transmembrane protein	Progressive sensorineural hearing loss, normal or absent vestibular function and retinitis pigmentosa.
Bartter syndrome and deafness	Autosomal recessive	BSND	Chloride channel	Polyhydramnios, weight loss, failure to thrive, hypokalaemic hypochloraemic metabolic alkalosis and congenital deafness.
Hypoparathyroidism, deafness and renal dysplasia	Autosomal dominant	GATA3	Transcription factor (zinc finger)	Hypoparathyroidism (hypocalcaemia may be asymptomatic). Renal dysplasia or hypoplasia, but kidneys may rarely be normal. Hearing loss is usually bilateral symmetrical and non-progressive.
Piebaldism and deafness	Autosomal dominant	c-KIT	Tyrosine kinase receptor	Variable frequency of deafness and characteristic depigmentation of skin.
Renal tubular acidosis and deafness	Autosomal recessive	ATPB6B1	Ion pump	Distal renal tubular acidosis, presenting with acute dehydration, vomiting and failure to thrive. Hearing loss is present in a subset of families and is progressive, tending to be severe-to-profound. It is associated with dilated vestibular aqueducts.

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syndrome. It is important to make a syndrome diagnosis because: (i) it is important to monitor the individual and family for known complications and associations of the syndrome, such as renal or eye disease; (ii) inheritance may be clearly defined for many syndromic causes of deafness even if the gene is unknown; and (iii) molecular testing, which may confirm the diagnosis and aid genetic counselling, may be available for many of the commoner syndromes.

Although some syndromes may present in an obvious manner to the clinician, others require specialised investigation and a high index of suspicion in order to make the diagnosis. For these reasons, it is important to examine fully every individual with hearing impairment. Special attention should be paid to facial appearance, including the eyes, appearance of the external ears and neck, the skin (its pigmentation and its quality), and examination of the hands for unusual creases, extra or missing fingers and appearance of the digits. Those organs which cannot be easily seen, such as the eye and the kidney, with which syndromic associations are common, require additional investigations. Table 2 outlines the suggested clinical investigation of patients presenting with hearing impairment. The aim of this is to diagnose syndromic hearing loss, to exclude environmental causes and to build a picture of the phenotype of the hearing loss which may be valuable for directing molecular analysis. Table 3 gives examples of the genes underlying syndromic forms of hearing impairment.

In the remaining 70% of cases, hearing loss is not associated with additional clinical features and is termed 'non-syndromic'. Studies of marriages between the deaf have long indicated that a large number of genes are likely to be involved in human hearing impairment, and estimates have varied considerably[1]. More recent molecular analysis has borne out some of the higher estimates and indeed, to date, more than 40 genes for autosomal dominant deafness and more than 30 for autosomal recessive deafness mapped or cloned, although in some cases the same gene may be responsible for both dominant and recessive deafness[5]. Unsurprisingly, a wide variety of molecules has now been implicated in the causation of human hearing impairment, including transcription factors and activators, motor molecules, extracellular matrix components, cytoskeletal proteins, components of ion channels and gap junctions. These are summarized in Table 4.

For many years, this extreme heterogeneity hampered genetic studies because many different genetic forms of hearing loss give rise to similar clinical phenotypes, preventing the pooling of families in genetic linkage studies. Mapping strategies circumvented these problems by using single, large, dominant families, large consanguineous families and population isolates, where genetic homogeneity is far more likely. Although these approaches have been highly successful in mapping and identifying genes, they give no indication of molecular epidemiology of

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genetic deafness, *i.e.* how much a particular gene contributes to deafness world-wide or in a particular ethnically mixed country. Indeed, preliminary studies indicate that most recessively acting genes, with the exception of *GJB2* (*Connexin 26)*, which encodes for the protein Connexin 26, are small contributors to hereditary deafness as a whole[6]. This means that genetic heterogeneity coupled with relative clinical homogeneity in presentation, require the clinician to use all available phenotypic clues in order to direct molecular testing and determine aetiology.

Autosomal recessive deafness

It is estimated that up to 75–80% of those with non-syndromic genetic hearing impairment have an autosomal recessive cause, 10–15% have an autosomal dominant cause, with the remainder being X-linked, mitochondrial or chromosomal. Autosomal dominant deafness loci are designated DFNA, autosomal recessive loci designated DFNB and X-linked loci, DFN. The loci are numbered according to the order in which they were mapped, DFNA1 being the first autosomal gene mapped in 1992[5].

Most of the recessively inherited forms of hearing impairment cause a phenotypically identical severe to profound, prelingual hearing loss[5], but mutations at a few loci – DFNB2 (MYO7A)[7], DFNB8/10 (*TMPRSS3*)[8] and DFNB16 (*STRC*)[9] – cause a delayed, childhood-onset hearing impairment. Also of note is that hearing loss caused by mutations at DFNB4 (*SLC26A4*) may be associated with dilated vestibular aqueducts and endolymphatic sacs[10], and there may be an associated auditory neuropathy with mutations in DFNB9 (*OTOF*)[11]. In addition, vestibular symptoms have been noted in DFNB2 (*MYO7A*), DFNB4 (*SLC26A4*) and DFNB12 (*CDH23*).

Hearing impairment caused by mutation in GJB2 (DFNB1) – a common cause of non-syndromic recessive and sporadic deafness

Epidemiological surveys of the deaf suggested that non-syndromic hearing loss was genetically heterogeneous, and that there was unlikely to be a single major gene involved. The discovery of *GJB2* and the subsequent realisation that it is a common cause of hearing impairment in many populations[12–18] was largely unexpected, although there was some previously published evidence of this in haplotype analysis of small families with non-syndromic deafness[19,20]. The gene *GJB2* encodes a gap junction protein known as Connexin 26. There is now good evidence that up to 50% of recessive non-syndromic hearing loss may be

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Table 4 Cloned genes involved in non-syndromic hearing impairment

Locus	Name (gene)	Predicted functions	Phenotype of hearing loss (*denotes unusual phenotype)
DOMINANT GENES			
DFNA1 5q31	Diaphanous (HDIA1)	Cytokinesis and cell polarity	*Postlingual, low frequency. Onset 1st–2nd decade but rapidly progressive to involve all frequencies
DFNA2 1p34	Connexin 31 (GJB3)	Gap junction protein	Postlingual, high frequency. Onset 20–40 years. May cause deafness with auditory and peripheral neuropathy; also causes erythrokeratodermia variabilis (no deafness)
	KCNQ4 (KCNQ4)	Voltage gated potassium channel	Post-lingual, high frequency. Onset 10–30 years
DFNA3 13q12 (see also DFNB2)	Connexin 26 (GJB2)	Gap junction protein	See text. Prelingual, mainly high frequency, severe to profound or postlingual mild/moderate high frequency, onset 10–20 years. May also cause palmoplantar keratoderma, Vohwinkel's syndrome, or keratitis ichthyosis deafness (KID) syndrome
	Connexin 30 (GJB6)	Gap junction protein	Mid-high frequency (age of onset not stated)
DFNA5 7p15	ICERE-1 (ICERE-1)	Unknown	Postlingual high frequency onset age 5–15 years
DFNA6 4p16 (DFNA6/14/38 now confirmed to be same locus)	Wolframin (WFS1)	Unknown	See text. *Prelingual, low frequency. Onset 5–15 years with minimal progression except due to presbyacusis. No vestibular abnormalities, normal radiology
DFNA8/12 11q22-21	α-Tectorin (TECTA)	Structural component of tectorial membrane	See text. *Prelingual, mid-frequency. One family with high frequency progressive HI, and possibly delayed motor milestones[76]
DFNA9 14q12-13	Cochlin (COCH)	Extracellular matrix protein	See text. *Postlingual, high frequency, progressive with Menière-like symptoms
DFNA10 6q22-q23	EYA4 (EYA4)	Transcriptional activator	Postlingual, all frequencies, progressive. Onset 20–60 years
DFNA11 11q12-q21	Myosin 7A (MYO7A)	Motor molecule (unconventional myosin)	Postlingual, all frequencies, progressive. Onset 1st–2nd decade. Variable asymptomatic vestibular dysfunction.
DFNA12 11q 22-21 (see DFNA8) DFNA13 6p21	Collagen 11A2 (COL11A2)	Structural molecule	See text. *Prelingual, mid/high frequency, progressive. 'Cookie bite' picture on audiogram
DFNA15 5q31	POU4F3 (POU4F3)	Transcription factor	Postlingual, all frequencies, progressive. Onset 20–40 years
DFNA17 22q12.2-13.3	MYH9 (MYH9)	Non-muscle myosin heavy chain	Postlingual, high-frequency. Onset by 10 years, moderate-to-severe by 30 years. Cochleosaccular degeneration
DFNA22 6q13	Myosin 6 (MYO6)	Motor molecule (unconventional myosin)	Postlingual, all frequencies, progressive. Onset 8–10 years
DFNA36 (see also DFNB7/11)	TMC1 (TMC1)	Transmembrane protein	Postlingual, initially high frequency, rapidly progressive across all frequencies. Onset in 1st decade. Or postlingual, slowly progressive. Onset 30–50 years
DFNA38 (see DFNA6)			

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Table 4 Cloned genes involved in non-syndromic hearing impairment (continued from previous page)

Locus	Name (gene)	Predicted functions	Phenotype of hearing loss (*denotes unusual phenotype)
RECESSIVE GENES			
DFNB1 13q12	Connexin 26 (GJB2)	Gap junction protein	See text. Prelingual, usually severe to profound (can be variable)
DFNB2 11q13.5	Myosin 7A (MYO7A)	Motor molecule (unconventional myosin)	Prelingual, severe-to-profound with reduced or absent vestibular function; *or variable age of onset (birth to 16 years) profound some with vertigo. Allelic with type 1B Usher
DFNB3 17p11.2	Myosin 15 (MYO15)	Motor molecule (unconventional myosin)	Prelingual, profound
DFNB4 7q13	Pendrin (SLC26A4)	Anion transporter	*Prelingual, sloping with profound high frequency hearing loss. May be progressive. Frequently associated with dilated vestibular aqueducts and endolymphatic ducts and sacs. Allelic with Pendred syndrome.
DFNB7/11 9q13-21 (see DFNA36)	TMC1 (TMC1)	Transmembrane protein	Prelingual, profound
DFNB8/10 21q22	TMPRSS3 (TMPRSS3)	Serine protease	Childhood onset (10–12 years) with profound losses across all frequencies within 4–5 years. Or prelingual profound
DFNB9 2p22	Otoferlin (OTOF)	Component of s synaptic vesicle	Prelingual, profound. *May be associated auditory neuropathy[11]
DFNB12 10q21	Otocadherin (CDH23)	Cell adhesion protein	Prelingual profound. Some families with atypical late onset retinitis pigmentosa and borderline vestibular dysfunction. Allelic with type 1D Usher
DFNB16 (possible second gene at 15q15)	Stereocilin (STRC)	Stereocilia protein	Early childhood onset (3–5 years), all frequencies moderate-to-severe (more severe in higher frequencies). Non-progressive. Or prelingual profound
DFNB18 11p15.5	Harmonin (USH1C)	PDZ domain protein	Prelingual profound (no vestibular pathology in non-syndromic cases). *Suspect if enteropathy (indicative of contiguous gene deletion). Allelic with type 1C Usher
DFNB21 11q22	α-tectorin (TECTA)	Structural component of tectorial membrane	Prelingual severe to profound
DFNB22 16p12.2	Otoancorin (OTOA)	Anchoring protein between acellular gels and non-sensory cells	Prelingual, moderate-to-severe
DFNB29 21q22	Claudin 14 (CLDN14)	Tight junction protein	Prelingual, profound
	Connexin 43 (GJA1)	Gap junction protein	Prelingual, profound
Note. The gene responsible for DFNB13 (uncloned at present) is reported to cause severe progressive sensorineural hearing loss.			
X-LINKED GENES			
DFN1 Xq22	Deafness dystonia protein (DDP)	Mitochondrial import protein	Postlingual but rapidly progressive in early childhood. Deafness is presenting symptom but may later be associated with dystonia, visual disability and mental impairment. *Suspect if X-linked agammaglobulinaemia (indicative of contiguous gene deletion)
DFN3 Xq13-21	POU3F4 (POU3F4)	POU domain transcription factor	Profound congenital deafness (mixed or pure sensorineural) with vestibular hypofunction. *Characteristic CT scan appearance[83]. Suspect if choroideremia and mental retardation (indicative of contiguous gene deletion)

Adapted from Van Camp and Smith[5].

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accounted for by mutations in this gene in Caucasian and European populations[12,13]. In European, North American and Mediterranean populations, the most common mutation is a deletion of a single guanine nucleotide in a series of six guanines known as 35delG[18,20]. This mutation may account for 70% of mutant alleles of *GJB2* and the carrier frequency of this mutation alone is estimated at around 1 in 51 overall in Europe, but is considerably higher in some populations[12,13,21]. Originally, this mutation was thought to be a deletion hot-spot, but more recent evidence has suggested that it may be due to a founder effect, *i.e.* an ancient mutation which has become wide-spread possibly due to some undefined heterozygote advantage[22].

Study of other ethnic groups has shown that different mutations may be more common. For example, the 167delT mutation is the most prevalent mutation found in the Ashkenazi Jewish population with a probable carrier frequency of 3–4%, again possibly due to a founder effect[16,23]. In East Asian populations, the 235delC mutation is the most common mutation[17] and three mutations, W24X, W77X and Q124X, have been found commonly in families from different parts of the Indian subcontinent[24].

Not only is mutation in *GJB2* a common cause of non-syndromic recessive deafness, but mutations have been also been found in a significant number of sporadic cases – consistent with autosomal recessive inheritance[14,15]. Estimates vary, but between 10–30% of individuals with severe-to-profound non-syndromic hearing impairment of unknown cause have been shown to harbour mutations in this gene. Molecular analysis of *GJB2* in hearing-impaired individuals is simplified by the fact that this is a small gene consisting of two exons, only one of which codes for the protein, Connexin 26. Therefore, analysis of the gene in the diagnostic setting is relatively straightforward. This is a powerful argument for offering *GJB2* screening as part of the routine aetiological work-up in the diagnosis of all cases of non-syndromic deafness of unknown cause (Table 5). A further argument for offering *GJB2* testing on a wide-spread basis is the observation that the phenotype of hearing impairment caused by mutations in this gene is rather unremarkable, implying that one cannot select patients for analysis based on clinical phenotype[25]. There are no associated vestibular abnormalities or abnormality on the CT scan of the temporal bone. The deafness caused by mutations in *GJB2* is frequently severe or profound, but there can be considerable variation in severity even within families[23,26–28]. Deafness is usually stable, but progression has been reported[25,29]. Onset is nearly always pre-lingual, but not necessarily congenital, and it is possible that hearing may be normal at birth and progress rapidly during the first few months of life[30]. This implies that some babies with mutations in *GJB2* may pass new-born hearing screening but become profoundly deaf during infancy.

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Table 5 Rationale of routine *GJB2 (Connexin 26)* mutation screening in all cases of non-syndromic hearing impairment where cause is unknown

	Common cause of hearing impairment
	Phenotype unremarkable and variable
	Small coding region
	Common mutations in some ethnic groups
	Enables accurate genetic information to be given to families
Disadvantages	
	Counselling difficulties with missense and heterozygous mutations

GJB2 may also be a rare cause of autosomal dominant deafness, both syndromic and non-syndromic (DFNA3)[31]. Phenotypes described include mild-to-profound hearing impairment, which is commonly progressive in nature, and may be associated with varying skin phenotypes including palmoplantar keratoderma (caused by the missense mutations G59A, R75W and DE42), Vohwinkel syndrome (associated with D66H), and keratitis-ichthyosis-deafness (KID, associated with D50N, G12R and S17F mutations)[32–36]. It would, therefore, seem sensible to screen the gene in individuals with deafness associated with epidermal defects. Interestingly, the R75W mutation appears to cause a variable skin phenotype since in some families it is reported to cause deafness with palmoplantar keratoderma, but in others the skin symptoms may be very mild or absent[33,37]. However, the missense mutations, W44C and C202F, definitely appear to cause non-syndromic deafness at the DFNA3 locus[5,31]. The role of the M34T allele in hearing loss is contentious since experimental studies show that there is a functional effect on the Connexin 26 molecule[38,39], but genetic studies now cast doubt on whether this is clinically significant[40,41].

Once *GJB2* analysis has been completed in the individual whose hearing loss is of unknown cause, there are very few further avenues for molecular investigation in small families or isolated cases at the present time. Recent data suggest that other recessive genes, with the exception of *SLC26A4*, contribute fairly equally to non-syndromic recessive deafness at least in Caucasian sibling pairs[6].

Hearing impairment caused by SLC26A4 (DFNB4/Pendred syndrome) – a significant cause of familial dilated vestibular aqueducts

Pendred syndrome describes the association of congenital deafness and goitre inherited in an autosomal recessive manner. Decades ago, Fraser estimated that mutations in this gene, giving rise to classical Pendred syndrome, may account for 5–10% of those with prelingual hearing

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impairment[42]. More recently, it has become apparent that the clinical presentation of individuals with mutations in this gene is highly variable. Features may range from those with classical Pendred syndrome presenting with goitre and prelingual profound sensorineural hearing loss, to those with absence of goitre, normal biochemical thyroid function and normal organification of iodine as demonstrated on a perchlorate discharge test, in whom the hearing impairment presents as non-syndromic. The most frequent presentation of the hearing loss is sensorineural, profound and prelingual but there may be a history of fluctuating progressive hearing loss that affects mainly the high frequencies[43]. Vestibular dysfunction has been demonstrated in a high proportion of individuals although not all are symptomatic. The major clue to diagnosis in an individual without overt goitre is, however, neuro-imaging. Enlargement of the vestibular aqueduct is the commonest abnormality which may be present in up to 80% of those with the disorder and in some cases there may also be a Mondini cochlea (1.5 cochlear turns instead of the normal 2.5)[44,45]. Dilatation or enlargement of the vestibular aqueducts is by no means diagnostic of Pendred syndrome, since these have been demonstrated in other genetic forms of hearing impairment including branchio-oto-renal syndrome and renal tubular acidosis with deafness[46,47]. However, in the absence of these syndromes where dilatation of the vestibular aqueduct and deafness is familial, there is a high chance of finding a mutation in the *SLC26A4* gene but a rather lower mutation pick-up rate in isolated cases[44].

PDS, the protein product of *SLC26A4*, is an anion transporter[48–50], expressed in the endolymphatic duct and sac from embryonic day 13 onwards and in non-sensory parts of the utricle, saccule and cochlea where it may be involved regulation and resorption of endolymph[51,52]. This is an attractive hypothesis since a protein involved in inner-ear fluid homeostasis might account for fluctuating hearing loss observed in individuals with mutations in the gene and for enlargement of the vestibular aqueduct and endolymphatic duct contained within it.

Many mutations have been described throughout the coding region of the gene including some which appear to be common[53,54]. Initial reports described a genotype–phenotype correlation based on functional study of chloride and iodide uptake by PDS transfected *Xenopus* oocytes[49,55]. Data suggested that mutations associated with full-blown Pendred syndrome cause a complete loss of transport whereas variants reported in those with non-syndromic deafness showed residual transport function. However, more recent assays of iodide efflux using transiently transfected mammalian cells, failed to show any correlation of mutation type with transport function and phenotype[56]. This is in keeping with the situation seen in human families in which there maybe clear phenotypic variation between siblings with the same mutation.

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Autosomal dominant non-syndromic deafness

Most forms of autosomal dominant non-syndromic deafness are difficult to distinguish phenotypically. The majority of autosomal dominant genes are associated with hearing impairment that is post-lingual in onset, often beginning before the age of 20 years. Some forms, however, notably DFNA4, DNFA9 and DFNA10 are associated with hearing impairment starting somewhat later during the third and fourth decades. Mutations at the DFNA6/14/38 locus as well as those associated with the DFNA9 locus tend to have distinguishable clinical phenotypes, and DFNA12, DFNA13 and DFNA21 are characterised by mid-frequency hearing impairment.

WFS1 gene mutations (DFNA6/14/38) – a common cause of familial low frequency hearing loss

Mutations at only two loci are known to cause low-frequency sensorineural hearing loss; individuals from a single large Costa-Rican family with mutations at the DFNA1 locus have a rapidly progressive, fully penetrant form of hearing impairment in which affected individuals become profoundly deaf across all frequencies by the fourth decade of life[57].

In contrast to the DFNA1 phenotype, mutations at DFNA6/14/38 (caused by mutations in the gene *WFS1*) show overall mild progression consistent with presbyacusis[58–60]. Affected individuals show fully penetrant, early-onset, low-frequency hearing impairment which is bilateral and symmetrical. There is good speech discrimination and sometimes the hearing impairment may be asymptomatic as hearing at and below 2 kHz is predominantly affected. With the onset of presbyacusis, there is some flattening of the audiogram or even down-sloping configuration in older people. In a family from Newfoundland, the age of onset of hearing impairment was reported as the second decade although affected children could be identified before school age by an 'S-shaped' pure tone audiogram[59]. By the age of 40 years, hearing impairment was moderate-to-severe across all frequencies with males appearing to be more severely affected than females.

Mutation analysis studies of the *WFS1* gene have shown that it is a common cause of dominantly inherited low frequency hearing loss[60], but not of sporadic, low-frequency hearing impairment[61]. The lower mutation pick-up rate in simplex cases suggests that there may be other non-genetic causes as well as genetic causes. It should be noted that mutations in the same gene cause Wolfram syndrome or DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy and deafness

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inherited in an autosomal recessive manner)[62]. Mutations which cause Wolfram syndrome appear to be, in the most part, inactivating and tend to be spread throughout the gene. In contrast, the heterozygous missense mutations associated with low-frequency sensorineural hearing impairment tend to be non-inactivating and cluster at the C-terminal protein domain, an observation which may simplify mutation analysis of the 8 exons of the gene[61]. In summary, it is probably worthwhile screening the *WFS1* gene in cases of low-frequency sensorineural hearing impairment where there is a positive family history.

Hearing impairment caused by mutations in the COCH gene (DFNA9) – familial progressive vestibulocochlear dysfunction with 'Menière-like' symptoms

The clinical presentation of mutations in this gene is remarkable in its consistency. Most families have presented at 40–60 years of age with a progressive autosomal dominant sensorineural hearing loss[63]. The exception to this is the family reported by Robertson *et al* in which the age of onset was somewhat younger, at 20–40 years of age[64]. Initially, high frequencies are affected but progression ultimately involves all frequencies so that severe-to-profound loss is seen by 60–80 years. However, the most notable feature is that of the vestibular symptoms, which may be present in some or all affected family members. Many individuals report a feeling of unsteadiness, difficulty walking in the dark, on uneven ground or up and down steps and vertigo has been reported in some individuals although it is not present in all. In some families, vestibular dysfunction has shown complete penetrance[63] but reduced penetrance in others[64–66]. The episodes of vertigo, tinnitus, aural fullness and progressive hearing impairment are reminiscent of symptoms of Menière's disease.

Endolymphatic hydrops, a characteristic of Menière's disease, has been confirmed in one patient histopathologically. Histopathological examination in the original DFNA9 families is said to have a unique appearance[67] with degeneration and acellularity of the spiral ligament, spiral limbus and stroma of the cristae and maculae, and replacement by eosinophilic acellular material. The actual function of the *COCH* gene product is, however, unknown, although it is likely to be a secreted protein[64].

The clinical presentation of this disorder does differ from classical Menière's disease in which the hearing loss usually begins as low-frequency as opposed to high-frequency in DFNA9. Meticulous clinical characterisation of this disorder has been described by Bom *et al* in a large Dutch family[68]. The progression of vestibular involvement was clearly documented and vestibular areflexia was found from the age of

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47 years onwards, whereas younger individuals showed either severe hyporeflexia or unilateral caloric areflexia. In summary, it would appear that familial progressive hearing loss associated with progressive vestibular dysfunction is a good indication for mutation screening of the *COCH* gene.

Mid-frequency hearing loss (mutations at DFNA12, DFNA13 and DFNA21)

COL11A2 **(DFNA12)**

Mutations at three deafness loci (DFNA12, DFNA13 and DFNA21) are characterised by hearing impairment that affects the mid-frequencies.

Mutations at the locus DFNA13, in the *COL11A2* gene, give rise to a mid-frequency, or U-shaped ('cookie-bite') hearing loss with no significant progression beyond presbyacusis[69,70], which eventually produces a flattened audiogram[71]. Most individuals noted hearing problems 20–40 years of age, although actual age of onset may have been prelingual in some families. Study of a Dutch family revealed that about half of the mutation carriers also had caloric abnormalities[71]. It should be noted that mutations in the same gene, COL11A2, may cause Stickler syndrome without eye involvement. However, detailed clinical evaluation of the families described above confirms that their hearing impairment is non-syndromic.

Detailed clinical evaluation of a family with hearing impairment linked to DFNA13, but without a known mutation, again showed mid-frequency hearing impairment which became apparent at about the age of 30 years, but there was no evidence for congenital or prelingual onset. Speech had developed normally in all cases. Vestibular function as assessed by bithermal calorics was intact in most cases[72].

Studies of the hearing impaired *Col11a2*$^{-/-}$ mouse have shown that the tectorial membrane appeared to be thicker and less compacted than normal, due to disorganization of the type 2 collagen fibrils, which were not arranged in their usual parallel, evenly spaced manner[70]. It has been hypothesized that the type XI collagen is needed in the tectorial membrane for even spacing between type 2 collagen fibrils, the major collagen in the tectorial membrane. *Col11a2* mRNA was observed in vestibular sensory areas, compatible with the vestibular findings in some of the human families. Thus structural disorganization of the tectorial membrane appears to cause congenital, permanent hearing impairment, which is stable and affects the mid-frequencies predominantly.

Although the phenotype of mid-frequency hearing loss caused by mutations in this gene is more distinctive than many other autosomal dominant non-syndromic forms of hearing loss, the gene is large, consisting of 67 exons; therefore, prior linkage probably needs to be established in a family before mutation screening can be offered.

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TECTA (DFNA8/12)

It is interesting to note that another component of the tectorial membrane, tectorin, causes a form of autosomal dominant deafness with a similar phenotype. Mutations in the zona pellucida domain of the *TECTA* gene, which encodes α-tectorin, also cause prelingual non-progressive, mid-frequency hearing impairment[73–75]. However, mutations in a different domain, the zonadhesin-like domain, cause autosomal dominant progressive high frequency hearing impairment which may be prelingual or postlingual in onset[76,77]. Homozygous loss of function mutation of *TECTA* may also result in the phenotype of severe-to-profound non-syndromic autosomal recessive hearing loss[78], DFNB21.

DFNA21

Mutation at the DFNA21 locus, mapped to 6p21-22, also may give rise to progressive non-syndromic mid-frequency sensorineural hearing impairment, with an age of onset estimated at around 3–4 years[79]. The gene responsible has not yet been identified.

Maternally inherited hearing impairment

The importance of maternally inherited hearing impairment, due to mutations in the mitochondrial genome, has only come to light in the last decade or so[80,81]. Mitochondria are intracellular organelles which are responsible for the generation of energy through oxidative phosphorylation. They contain their own DNA (mtDNA), which encodes 13 mRNAs (components of five enzymatic complexes necessary for oxidative phosphorylation), two rRNAs and twenty-two tRNAs. At fertilization, only the ovum contributes mitochondria to the zygote and; therefore, mutations in the mitochondrial genome are only inherited through the maternal line and are never transmitted by the father. Usually all the mitochondrial chromosomes in a cell carry identical copies of mtDNA (homoplasmy), but some mutations may be heteroplasmic (wild-type and mutant mitochondria in the same cell). Random distribution of mutations between cells following cell division may lead to differences in mutational loads between different cells and tissues.

Estimates of the contribution made by mitochondrial genes to inherited deafness vary between populations. Mitochondrial genes appear to be a rare cause of prelingual hearing loss[83], although data suggest that a considerable proportion of post-lingual hearing loss may be maternally inherited (T Hutchin, personal communication)[82,84].

A comprehensive description of the biology and phenotypes associated with mitochondrial hearing impairment is beyond the scope of this review and is available elsewhere[82,83], but suffice it to say that hearing

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impairment may be non-syndromic or syndromic and varies greatly in severity and age of onset even within families. Other systems which may be involved tend to include organs and tissues with a high energy requirement such as muscle, central nervous system, retina, heart, and gut, besides the ear. Symptoms such as ataxia, seizures, hypotonia, myopathy, ophthalmoplegia, optic atrophy, cardiomyopathy, retinopathy and endocrinopathies often occur in mitochondrial diseases (*e.g.* MERRF, MELAS, Pearson syndrome, Kearns-Sayre syndrome and maternally inherited diabetes and deafness). The hearing loss associated with these conditions tends to be of childhood or early adult onset, to involve high frequencies and is often progressive[81]. The hearing impairment appears to be cochlear in origin due to loss of outer hair cell function, and successful cochlear implantation indicates that the cochlear nerve is unaffected.

A number of mitochondrial mutations have been described which give rise to non-syndromic hearing impairment. The most important of these is the A1555G mutation in the 12SrRNA gene, which was originally described in a large Arab-Israeli family demonstrating maternally inherited deafness[80,81]. Most of the affected individuals had early onset severe to profound hearing loss in infancy, although other family members had adult onset hearing loss and some had normal hearing. It has subsequently been shown that the deafness phenotype in this family is probably modified by an unknown autosomal gene on chromosome 8[87]. In other cases, this mutation has been reported in families where there is deafness following exposure to aminoglycosides[84,88,89] in which case the age of onset of deafness in exposed individuals is younger[84]. Aminoglycoside-induced hearing impairment appears to be particularly common in some countries. For example, in one region of China, 25% of deaf mutes associated their hearing loss with aminoglycoside exposure, and where deafness was familial, transmission was compatible with maternal inheritance[90]. The A1555G mutation appears to be highly prevalent among Spanish deaf individuals where it is found in 27% of multigeneration families (with and without aminoglycoside exposure)[84], and also in Japanese where 10% of profoundly deaf individuals without aminoglycoside exposure carry the mutation[91]. A second mutation, 961delT, has also been associated with aminoglycoside induced deafness[92].

Other mutations, A7445G, 7472insC, T7510C and T7511C, in the tRNA$^{Ser(UCN)}$ gene, have been reported to cause non-syndromic hearing impairment, although A7445G has also been reported with palmoplantar keratoderma[93], and 7472insC with ataxia and myoclonus[94].

In summary, non-syndromic mitochondrial deafness should be considered in all multigeneration families, with and without exposure to aminoglycoside antibiotics, unless there is reliable documentation of transmission of deafness from a male. Syndromic mitochondrial deafness may underlie symptoms in multiple organ systems.

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Conclusions

Thorough investigation of the aetiology of hearing loss is necessary for accurate genetic counselling and for the implementation and assessment of any future gene therapy. Investigation of non-syndromic deafness should include analysis of *GJB2* since it is the most common cause of inherited hearing loss and its clinical presentation is unremarkable. However, genetic heterogeneity underlying syndromic and non-syndromic deafness greatly complicates further genetic testing and diagnosis in small families and sporadic cases of deafness. Until genetic testing for large numbers of genes becomes cheaper, faster and less labour-intensive, clinicians must rely on the few audiological, vestibular and radiological clues that may suggest mutation at a particular locus. Detailed clinical description of the effects of gene mutations is an important part in realising the full potential.

Key points for clinical practice

- Characterize the hearing loss (audiology, vestibular tests and radiology)
- Rigorously exclude syndromic causes of hearing impairment, by history, examination and specialised investigation (ophthalmology, renal ultrasound, neuro-imaging)
- Consider *GJB2* mutation screen in all non-syndromic cases with unknown aetiology (common cause of hearing loss with few clinical pointers)
- Always consider mitochondrial inheritance in multigeneration families unless there is clear evidence of transmission from a male

References

1 Morton NE. Genetic epidemiology of hearing impairment. *Ann NY Acad Sci* 1991; **630:** 16–31
2 Green GE, Scott DA, McDonald JM *et al.* Performance of cochlear implant recipients with GJB2-related deafness. *Am J Med Genet* 2002; **109**: 167–70
3 Fortnum HM, Summerfield AQ, Marshall DH. Prevalence of childhood hearing impairment in the United Kingdom and implications for universal neonatal hearing screening: questionnaire based ascertainment study. *BMJ* 2001; **323**: 536–40
4 Davis AC. *Hearing in Adults.* London: Whurr, 1995
5 Van Camp G, Smith RJH. *Hereditary Hearing Loss.* Homepage at <http://www.uia.ac.be/dnalab/hhh>
6 Navarro-Coy N, Hutchin TP, Conlon HE *et al.* The relative contribution of mutations in the DFNB loci to congenital/early childhood non-syndromal hearing impairment/deafness. *J Med Genet* 2001; **38**: S38
7 Liu XZ, Walsh J, Mburu P *et al.* Mutations in the myosin VIIA gene cause non-syndromic recessive deafness. *Nat Genet* 1997; **16**: 188–90

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8 Veske A, Oehlmann R, Younnus F *et al.* Autosomal recessive non-syndromic deafness locus (DFNB8) maps on chromosome 21q22 in a large consanguineous kindred from Pakistan. *Hum Mol Genet* 1996; **5**: 165–8
9 Verpy E, Masmoudi S, Zwaenepohl I *et al.* Mutations in a new gene encoding a protein of the hair bundle cause non-syndromic deafness at the DFNB16 locus. *Nat Genet* 2001; **29**: 345–9
10 Phelps PD, Coffey RA, Trembath RC *et al.* Radiological malformations of the ear in Pendred syndrome. *Clin Radiol* 1998; **53**: 268–73
11 Rogers RJ, Kelley P, Keats BJB *et al.* Otoferlin mutations in non-syndromic recessive auditory neuropathy families. *Molecular Biology of Hearing and Deafness Meeting*. Bethesda, MD, 2001 (abstract 67)
12 Denoyelle F, Weil D, Maw MA *et al.* Prelingual deafness: high prevalence of a 30delG mutation in the *connexin 26* gene. *Hum Mol Genet* 1997; **6**: 2173–7
13 Zelante L, Gasparini P, Estivill X *et al.* *Connexin 26* mutations associated with the most common form of non-syndromic neurosensory autosomal recessive deafness (DFNB1) in Mediterraneans. *Hum Mol Genet* 1997; **6**: 1605–9
14 Estivill X, Fortina P, Surrey S *et al.* *Connexin-26* mutations in sporadic and inherited sensorineural deafness. *Lancet* 1998; **351**: 394–8
15 Lench N, Houseman M, Newton V *et al.* *Connexin-26* mutations in sporadic non-syndromal sensorineural deafness. *Lancet* 1998; **351**: 415
16 Morell RJ, Kim HJ, Hood LJ *et al.* Mutations in the *connexin 26* gene (GJB2) among Ashkenazi Jews with non-syndromic recessive deafness. *N Engl J Med* 1998; **339**: 1500–5
17 Abe S, Usami S, Shinkawa H *et al.* Prevalent *connexin 26* gene (GJB2) mutations in Japanese. *J Med Genet* 2000; **37**: 41–3
18 Green GE, Scott DA, McDonald JM *et al.* Carrier rates in the Midwestern United States for GJB2 mutations causing inherited deafness. *JAMA* 1999; **281**: 2211–6
19 Maw MA, Allen-Powell DR, Goodey RJ *et al.* The contribution of the DFNB1 locus to neurosensory deafness in a Caucasian population. *Am J Hum Genet* 1995; **57**: 629–35
20 Gasparini P, Estivill X, Volpini V *et al.* Linkage of DFNB1 to non-syndromic neurosensory autosomal recessive deafness in Mediterranean families. *Eur J Hum Genet* 1997; **5**: 83–8
21 Gasparini P, Rabionet R, Barbujani G *et al.* High carrier frequency of the 35delG deafness mutation in European populations. Genetic Analysis Consortium of GJB2 35delG. *Eur J Hum Genet* 2000; **8**: 19–23
22 Van Laer L, Coucke P, Mueller RF *et al.* A common founder for the 35delG GJB2 gene mutation in connexin 26 hearing impairment. *J Med Genet* 2001; **38**: 515–8
23 Lerer I, Sagi M, Malamud E *et al.* Contribution of *connexin 26* mutations to non-syndromic deafness in Ashkenazi patients and the variable phenotypic effect of the mutation 167delT. *Am J Med Genet* 2000; **95**: 53–6
24 Rickard S, Kelsell DP, Sirimana T *et al.* Recurrent mutations in the deafness gene GJB2 (connexin 26) in British Asian families. *J Med Genet* 2001; **38**: 530–3
25 Denoyelle F, Marlin S, Weil D *et al.* Clinical features of the prevalent form of childhood deafness, DFNB1, due to a connexin-26 gene defect: implications for genetic counselling. *Lancet* 1999; **353**: 1298–303
26 Mueller RF, Nehammer A, Middleton A *et al.* Congenital non-syndromal sensorineural hearing impairment due to connexin 26 gene mutations – molecular and audiological findings. *Int J Pediatr Otorhinolaryngol* 1999; **50**: 3–13
27 Cohn ES, Kelley PM, Fowler TW *et al.* Clinical studies of families with hearing loss attributable to mutations in the connexin 26 gene (GJB2/DFNB1). *Pediatrics* 1999; **103**: 546–50
28 Wilcox SA, Saunders K, Osborn AH *et al.* High frequency hearing loss correlated with mutations in the GJB2 gene. *Hum Genet* 2000; **106**: 399–405
29 Cohn ES, Kelley PM. Clinical phenotype and mutations in connexin 26 (DFNB1/GJB2), the most common cause of childhood hearing loss. *Am J Med Genet* 1999; **89**: 130–6
30 Green GE, Smith RJ, Bent JP *et al.* Genetic testing to identify deaf newborns. *JAMA* 2000; **284**: 1245
31 Denoyelle F, Lina-Grande G, Plauchu H *et al.* Connexin 26 linked to dominant deafness *Nature* 1998; **393**: 319–20

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32 Heathcote K, Syrris P, Carter ND *et al.* A connexin 26 mutation causes a syndrome of sensorineural hearing loss and palmoplantar hyperkeratosis (MIM 148350). *J Med Genet* 2000; **37**: 50–1
33 Richard G, White TW, Smith LE *et al.* Functional defects of Cx26 resulting from a heterozygous missense mutation in a family with dominant deaf-mutism and palmoplantar keratoderma. *Hum Genet* 1998; **103**: 393–9
34 Rouan F, White TW, Brown N *et al.* Trans-dominant inhibition of connexin-43 by mutant connexin-26: implications for dominant connexin disorders affecting epidermal differentiation. *J Cell Sci* 2001; **114**: 2105–13
35 Maestrini E, Korge BP, Ocana-Sierra J *et al.* A missense mutation in connexin 26, D66H, causes mutilating keratoderma with sensorineural deafness (Vohwinkel's syndrome) in three unrelated families. *Hum Mol Genet* 1999; **8**: 1237–43
36 Richard G, Rouan F, Willoughby CE *et al.* Missense mutations in GJB2 encoding *Connexin-26* cause the ectodermal dysplasia keratitis-ichthyosis-deafness syndrome. *Am J Hum Genet* 2002: **70**: 1341–8
37 Loffeld A, Kelsell DP, Moss C. Palmoplantar keratoderma and sensorineural deafness in an 8-year-old boy: a case report. *Br J Dermatol* 2000: **143**: 38
38 White TW, Deans MR, Kelsell DP *et al.* Connexin mutations in deafness. *Nature* 1998; **394**: 630–1
39 Martin PE, Coleman SL, Casalotti SO *et al.* Properties of connexin 26 gap junctional proteins derived from mutations associated with non-syndromal hereditary deafness. *Hum Mol Genet* 1999; **8**: 2369–76
40 Griffith AJ, Chowdhry AA, Kurima K *et al.* Autosomal recessive non-syndromic neurosensory deafness at DFNB1 not associated with the compound-heterozygous GJB2 (connexin 26) genotype M34T/167delT. *Am J Hum Genet* 2000; **67**: 745–9
41 Marlin S, Garabedian EN, Roger G *et al.* Connexin 26 gene mutations in congenitally deaf children: pitfalls for genetic counseling. *Arch Otolaryngol Head Neck Surg* 2001; **127**: 927–33
42 Fraser GR. Association of congenital deafness with goitre (Pendred's syndrome): a study of 207 families. *Ann Hum Genet* 1965; **28**: 201–49
43 Luxon LM, Cohen M, Coffey R *et al.* Neuro-otological abnormalities in Pendred syndrome. *Int J Audiol* 2002; In press
44 Reardon W, O'Mahoney CF, Trembath R *et al.* Enlarged vestibular aqueduct: a radiological marker of Pendred syndrome, and mutation of the PDS gene. *Q J Med* 2000; **93**: 99–104
45 Cremers CW, Admiraal RJ, Huygen PL *et al.* Progressive hearing loss, hypoplasia of the cochlea and widened vestibular aqueducts are very common features in Pendred's syndrome. *Int J Pediatr Otorhinolaryngol* 1998; **45**: 113–23
46 Chen A, Francis M, Ni L *et al* Phenotypic manifestations of branchio-oto-renal syndrome. *Am J Med Genet* 1995; **58**: 365–70
47 Berettini S, Forli F, Franceschini SS, Ravecca F, Massimetti M, Neri E. Distal renal tubular acidosis associated with isolated large vestibular aqueduct and sensorineural hearing loss. *Ann Otol Rhinol Laryngol* 2002; **115**: 385–91
48 Everett LA, Glaser B, Beck JC *et al.* Pendred syndrome is caused by mutations in a putative sulphate transporter gene (PDS). *Nat Genet* 1997; **17**: 411–22
49 Scott DA, Wang R, Kreman TM, Sheffield V, Karniski LP. The Pendred syndrome gene encodes a chloride iodide transporter. *Nat Genet* 1999; **21**: 440–3
50 Royaux IE, Wall SM, Karniski LP *et al.* Pendrin, encoded by the Pendred syndrome gene, resides in the apical region of renal intercalated cells and mediates bicarbonate secretion. *Proc Natl Acad Sci USA* 2001; **98**: 4221–6
51 Everett LA, Morsli H, Wu DK *et al.* Expression pattern of the mouse ortholog of the Pendred's syndrome gene (PDS) suggests a key role for pendrin in the inner ear. *Proc Natl Acad Sci USA* 1999; **96**: 9727–32
52 Everett LA, Belyantseva IA, Noben-Trauth K *et al.* Targeted disruption of mouse PDS provides insight about the inner-ear defects encountered in Pendred syndrome. *Hum Mol Genet* 2001; **10**: 153–61
53 Coyle B, Reardon W, Herbrick JA *et al.* Molecular analysis of the PDS gene in Pendred syndrome. *Hum Mol Genet* 1998; **7**: 1105–12

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54 Campbell C, Cucci RA, Prasad S *et al.* Pendred syndrome, DFNB4, and PDS/SLC26A4 identification of eight novel mutations and possible genotype-phenotype correlations. *Hum Mutat* 2001; **17**: 403–11

55 Scott DA, Wang R, Kreman TM *et al.* Functional differences of the PDS gene product are associated with phenotypic variation in patients with Pendred syndrome and non-syndromic hearing loss (DFNB4). *Hum Mol Genet* 2000; **9**: 1709–15

56 Taylor JP, Metcalfe RA, Watson PF *et al.* Mutations of the PDS gene, encoding pendrin, are associated with protein mislocalization and loss of iodide efflux: implications for thyroid dysfunction in Pendred syndrome. *J Clin Endocrinol Metab* 2002; **87**: 1778–84

57 Lynch ED, Leon PE. Non-syndromic dominant DFNA1. *Adv Otorhinolaryngol* 2000; **56**: 60–7

58 McGuirt WT, Lesperance MM, Wilcox ER, Chen AH, Van Camp G, Smith RJH. Characterization of autosomal dominant non-syndromic hearing loss loci: DFNA4,6,10 and 13. *Adv Otorhinolaryngol* 2000; **56**: 84–96

59 Young TL, Ives E, Lynch E *et al.* Non-syndromic progressive hearing loss DFNA38 is caused by heterozygous missense mutation in the Wolfram syndrome gene WFS1. *Hum Mol Genet* 2001; **10**: 2509–14

60 Bespalova IN, Van Camp G, Bom SJ *et al.* Mutations in the Wolfram syndrome 1 gene (WFS1) are a common cause of low frequency sensorineural hearing loss. *Hum Mol Genet* 2001; **10**: 2501–8

61 Cryns K, Pfister M, Pennings RJ *et al.* Mutations in the WFS1 gene that cause low frequency sensorineural hearing loss are small non-inactivating mutations. *Hum Genet* 2002; 110: 389–94

62 Barrett TG, Bundey SE, Macleod AF. Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. *Lancet* 1995; **346**: 1458–63

63 Kamarinos M, McGill J, Lynch M, Dahl H. Identification of a novel COCH mutation, I109N, highlights the similar clinical features observed in DFNA9 families. *Hum Mutat* 2001; **17**: 351

64 Robertson NG, Lu L, Heller S *et al.* Mutations in a novel cochlear gene cause DFNA9, a human non-syndromic sensorineural deafness with vestibular dysfunction. *Nat Genet* 1998; **20**: 229–303

65 Fransen E, Verstreken M, Verhagen WI *et al.* High prevalence of symptoms of Menière's disease in three families with a mutation in the COCH gene. *Hum Mol Genet* 1999; **8**: 1425–9

66 de Kok YJ, Bom SJ, Brunt TM *et al.* A Pro51Ser mutation in the *COCH* gene is associated with late onset autosomal dominant progressive sensorineural hearing loss with vestibular defects. *Hum Mol Genet* 1999; **8**: 361–6

67 Merchant SN, Linthicum FH, Nadol JB. Histopathology of the inner ear in DFNA9. *Adv Otorhinolaryngol* 2000; **56**: 212–7

68 Bom SJ, Kemperman MH, De Kok YJ *et al.* Progressive cochleovestibular impairment caused by a point mutation in the *COCH* gene at DFNA9. *Laryngoscope* 1999; **109**: 1525–30

69 De Leenheer EM, Kunst HH, McGuirt WT *et al.* Autosomal dominant inherited hearing impairment caused by a missense mutation in COL11A2 (DFNA13). *Arch Otolaryngol Head Neck Surg* 2001; **127**: 13–7

70 McGuirt WT, Prasad SD, Griffith AJ *et al.* Mutations in COL11A2 cause non-syndromic hearing loss (DFNA13). *Nat Genet* 1999; **23**: 413–9

71 Kunst H, Huybrechts C, Marres H *et al.* The phenotype of DFNA13/COL11A2: non-syndromic autosomal dominant mid-frequency and high-frequency sensorineural hearing impairment. *Am J Otol* 2000; **21**: 181–7

72 Ensink RJ, Huygen PL, Snoeckx RL, Caethoven G, Van Camp G, Cremers CW. A Dutch family with progressive autosomal dominant non-syndromic sensorineural hearing impairment linked to DFNA13. *Clin Otolaryngol* 2001; **26**: 310–6

73 Verhoeven K, Van Laer L, Kirschhofer K *et al.* Mutations in the human alpha-tectorin gene cause autosomal dominant non-syndromic hearing impairment. *Nat Genet* 1998; **19**: 60–2

74 Kirschhofer K, Kenyon JB, Hoover DM *et al.* Autosomal-dominant, prelingual, non-progressive sensorineural hearing loss: localization of the gene (DFNA8) to chromosome 11q by linkage in an Austrian family. *Cytogenet Cell Genet* 1998; **82**: 126–30

75 Govaerts PJ, De Ceulaer G, Daemers K *et al.* A new autosomal-dominant locus (DFNA12) is responsible for a non-syndromic, midfrequency, prelingual and non-progressive sensorineural hearing loss. *Am J Otol* 1998; **19**: 718–23

76 Alloisio N, Morle L, Bozon M *et al.* Mutation in the zonadhesin-like domain of alpha-tectorin

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associated with autosomal dominant non-syndromic hearing loss. *Eur J Hum Genet* 1999; **7**: 255–8
77 Balciuniene J, Dahl N, Jalonen P *et al.* Alpha-tectorin involvement in hearing disabilities: one gene – two phenotypes. *Hum Genet* 1999; **105**: 211–6
78 Mustapha M, Weil D, Chardenoux S *et al.* An alpha-tectorin gene defect causes a newly identified autosomal recessive form of sensorineural pre-lingual non-syndromic deafness, DFNB21. *Hum Mol Genet* 1999; **8**: 409–12
79 Kunst H, Marres H, Huygen *et al.* Non-syndromic autosomal dominant progressive non-specific mid-frequency hearing impairment with childhood to late adolescence onset (DFNA21). *Clin Otolaryngol* 2000; **25**: 45–54
80 Prezant TR, Agapian JV, Bohlman H *et al.* Mitochondrial ribosomal RNA mutation associated with both antibiotic-induced and non-syndromic deafness. *Nat Genet* 1993; **4**: 289–94
81 Hutchin TP, Haworth I, Higashi K *et al.* A molecular basis for human hypersensitivity to aminoglycoside antibiotics. *Nucleic Acids Res* 1993; **21**: 4174–9
82 Hutchin TP, Thompson KR, Parker M, Newton V, Bitner-Glindzicz M, Mueller RF. Prevalence of mitochondrial DNA mutations in childhood/congenital onset non-syndromal sensorineural hearing impairment. *J Med Genet* 2001; **38**: 229–31
83 Hutchin TP, Cortopassi GA. Mitochondrial defects and hearing loss. *Cell Mol Life Sci* 2000; **57**: 1927–37
84 Estivill X, Govea N, Barcelo E *et al.* Familial progressive sensorineural deafness is mainly due to the mtDNA A1555G mutation and is enhanced by treatment of aminoglycosides. *Am J Hum Genet* 1998; **62**: 27–35
85 Van Camp G, Smith RJ. Maternally inherited hearing impairment. *Clin Genet* 2000; **57**: 409–14
86 Tono T, Ushisako Y, Kiyomizu K *et al.* Cochlear implantation in a patient with profound hearing loss with the A1555G mitochondrial mutation. *Am J Otol* 1998; **19**: 754–7
87 Bykhovskaya Y, Estivill X, Taylor K *et al.* Candidate locus for a nuclear modifier gene for maternally inherited deafness. *Am J Hum Genet* 2000; **66**: 1905–10
88 Fischel-Ghodsian N, Prezant TR, Bu X, Oztas S. Mitochondrial ribosomal RNA gene mutation in a patient with sporadic aminoglycoside toxicity. *Am J Otolaryngol* 1993; **14**: 399–403
89 Usami S, Abe S, Kasai M *et al.* Genetic and clinical features of sensorineural hearing loss with the 1,555 mitochondrial mutation. *Laryngoscope* 1997; **107**: 483–90
90 Hu DN, Qiu WQ, Wu BT *et al.* Genetic aspects of antibiotic induced deafness: mitochondrial inheritance. *J Med Genet* 1991; **28**: 79–83
91 Usami S, Abe S, Akita J *et al.* Prevalence of mitochondrial gene mutations among hearing impaired patients. *J Med Genet* 2000; **37**: 38–40
92 Casano RA, Johnson DF, Bykhovskaya Y *et al.* Inherited susceptibility to aminoglycoside ototoxicity: genetic heterogeneity and clinical implications. *Am J Otolaryngol* 1999; **20**: 151–6
93 Sevior KB, Hatamochi A, Stewart IA *et al.* Mitochondrial A7445G mutation in two pedigrees with palmoplantar keratoderma and deafness. *Am J Med Genet* 1998; **75**: 179–85
94 Tiranti V, Chariot P, Carella F *et al.* Maternally inherited hearing loss, ataxia and myoclonus associated with a novel point mutation in mitochondrial $tRNA^{Ser(UCN)}$ gene. *Hum Mol Genet* 1995; **4**: 1421–7
95 Bilous RW, Murty G, Parkinson DB *et al.* Autosomal dominant familial hypoparathyroidism, sensorineural deafness, and renal dysplasia. *N Engl J Med* 1992; **327**: 1069–74
96 Van Esch H, Groenen P, Nesbit MA *et al.* GATA3 haplo-insufficiency causes human HDR syndrome. *Nature* 2000; **406**: 419–22
97 Muroya K, Hasegawa T, Ito Y *et al.* GATA3 abnormalities and the phenotypic spectrum of HDR syndrome. *J Med Genet* 2001; **38**: 374–80
98 Phelps PD, Reardon W, Pembrey M, Bellman S, Luxon L. X-linked deafness, stapes gushers and a distinctive defect of the inner ear. *Neuroradiology* 1991; **33**: 326–30
99 Bamiou DE, Phelps P, Sirimanna T. Temporal bone computed tomography findings in bilateral sensorineural hearing loss. *Arch Dis Child* 2000; **82**: 257–60

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