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REVIEW ARTICLE

# Genetic deafness

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## Historical overview

The concept of heredity as a cause of deafness gained acceptance in the last quarter of the 19th century.[1 2] Politzer,[3] writing in 1882, stated that "the most frequent causes of congenital deafness are: hereditary, including direct transmission from the parents as well as indirect transmission from forefathers and marriage between blood relatives". This statement was based upon the work of Arthur Hartmann whose studies were carried out in the Berlin schools for deaf children.[4 5] Hartmann distinguished between direct transmission of deafness from parent to child and indirect transmission, in which he noted a high level of consanguinity. This latter finding was supported by Uchermann's extensive study of Norwegian schools for deaf children.[6] Uchermann showed that consanguinity was four times as high among the parents of deaf children as among the parents of their normally hearing counterparts. Moreover, those areas of Norway with the highest degree of consanguinity were those with the highest prevalence of deafness.

The earliest known author to have recognised that some forms of deafness may be inherited was Schenck.[7] A century later Zacchia, physician to the Pope, recommended that deaf people be precluded from marriage in view of the evidence that their children were similarly afflicted.[8] Although Joseph Adams distinguished between hereditary (dominant) and familial (recessive) disorders, he was of the view that deafness "is rarely if ever hereditary".[9]

In the mid-nineteenth century two men, of diametrically opposed views, served to raise otology from quackery to the level of credible clinical discipline.[10] Wilheim Kramer (1801–1875) did not accept that deafness could be inherited, although he did admit that deaf and dumb children frequently had "numerous deaf mutes among their male or female cousins".[11] In contrast, his eminent Irish contemporary, William Wilde (1815–1876) (fig 1) identified pedigrees with "transmission of the disease by hereditary taint" and distinguished between these and pedigrees where "too close consanguinity among the parents may be looked upon as paramount".[12] Not only did Wilde thus fundamentally identify autosomal dominant and recessive inheritance of deafness, but he further emphasised the excess of males among congenitally deaf patients, much of which is likely to be explained by the X linked form of deafness.[13] Thus, in the context of human genetic disease, the three forms of Mendelian inheritance had been documented by Wilde more than a decade before Mendel published his observations on peas in 1865.

## Inheritance of deafness

Nowadays at least half of severe childhood deafness in a community is attributed to genetic causes,[14] and the approximate prevalence of genetic deafness has been calculated as 1 per 2000.[15] The spectrum of hereditary deafness is broad and ranges from simple deafness without other clinical abnormalities to genetically determined syndromes of a more pleiotropic nature in which deafness is one of a number of clinically recognisable signs, together comprising the syndrome. Approximately 30% of genetically determined deafness is said to occur in syndromic form and 70% in non-syndromic form.[16]

Overall the most common forms of genetic deafness are the autosomal recessive forms, accounting for >75% of cases.[14] Autosomal dominant inheritance accounts for a further 10

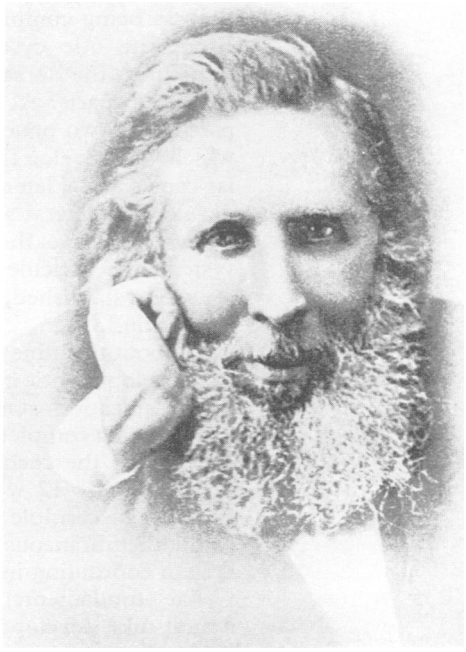

*Figure 1 Sir William Wilde.*

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to 20%[14] of cases, and X linked inheritance for 2 to 3%.[17 18] Deafness may also be a feature of chromosomal aneuploidy[19] or chromosomal deletion,[20 21] as well as of mitochondrial inheritance[22] and of mitochondrially determined predisposition to deafness inducing environmental agents.[23]

Most available data on the subject of genetic deafness concentrate on congenital or prelingual deafness. Deafness of later onset is frequently likely to reflect genetic factors but precise reliable data are currently lacking.[24] Indeed epidemiological data on the prevalence of hearing disorders in the population are only now coming to hand following the first large scale survey of this problem since 1947.[25 26] Early indications suggest that 15 to 20% of the population have a significant hearing impairment (>25 dB, average 0·5 to 4 kHz, better ear).[27] While otosclerosis is recognised as a genetically determined cause of post-lingual deafness,[28 29] as are several syndromic forms of deafness, such as Alport's disease, Alstrom's disease, and Refsum's disease, other genetic aspects of aetiological importance in post-lingual deafness remain to be identified.

## Embryology of the inner ear

Most of the published data on genetic deafness relate to pathological and histopathological studies in man and in other mammals. Before attempting to interpret these or draw any conclusions relevant to human genetic deafness, it is essential to be conversant with the basic sequence of events involved in the embryology of the cochlea.

The membraneous inner ear is of ectodermal derivation. At three weeks an ectodermal thickening, the otic placode, appears on the lateral surface of the head. Subsequently the placode invaginates, forming the otic pit, which grows downwards into the underlying mesoderm. As the surface ectoderm closes over the otic pit, the otic cyst is formed, the process being complete by about four weeks. From the otic cyst develop two primitive structures, the dorsal (vestibular) and ventral (cochlear) parts. At six weeks the vestibular part forms two pouches, a dorsal pouch from which will develop the two vertical semicircular canals and a lateral pouch from which will develop the lateral semicircular canal. By the nine week stage the basis of the vestibular system, the utricule and semicircular canals, are well established, but the cochlear system lags behind.[30 31]

At about this time the mesoderm enveloping the developing otic cyst becomes cartilaginous and ossification starts at approximately 16 weeks, being completed by the third trimester. Meanwhile the cochlear system starts to develop and, by 12 weeks, the two and a half turns are discernible with further development of the membraneous elements of the cochlear system continuing into the second trimester.

The fundamental importance of normal neural tube development for correct otic cyst development in the mammal has long been appreciated.[32–34] More recent evidence suggests that melanocytes, derived from the neural crest, have an important role in the normal development of the stria vascularis and endocochlear potential within the membraneous system of the cochlea,[35] a normal endocochlear potential being of crucial importance in the physiology of hearing.

Bearing these considerations in mind, it is hardly surprising that the phylogenetically older vestibular system appears more resistant to disease than the later developing cochlea. It is the cochlea which is the more sensitive to rubella, measles, and mumps damage and equally it is the cochlea alone which is the seat of most genetically determined hearing loss.

## Temporal bone pathology in deafness

Four main classes of abnormality have been described as a result of temporal bone studies in deaf human subjects[36 37]: (1) Michel type, characterised by total underdevelopment of the inner ear; (2) Mondini type (more correctly Mundini[38]), in which the cochlea appears as a single basal turn with the rest of the cochlea comprising a single sac, as if to suggest interrupted development. Vestibular structures may be similarly underdeveloped, though several cases are known where this abnormality was accompanied by a normal vestibular labyrinth[39]; (3) Bing-Siebenmann type, in which the bony labyrinth is well formed but the membraneous labyrinth is not developed; (4) Scheibe (cochleosaccular) type, in which the underdevelopment is restricted to the membraneous cochlea and saccule only, but the vestibular part of the ear is functional.

The latter is thought to be the most common form of abnormality in deafness of genetic origin. However, no direct relationship exists between pathological class and mode of inheritance.

## Correlations between temporal bone pathology and genetic deafness

As they involve abnormalities of bone, Michel and Mondini types may be diagnosed radiologically.[40] Although some residual hearing, particularly in the low frequencies, has been documented in association with the normal basal cochlear coil of the Mondini deformity,[38] this is unlikely to be a universal finding.[41–43] The Mondini deformity is rare in genetic forms of deafness, but is seen in the autosomal dominant condition of branchio-oto-renal syndrome and in the autosomal recessive condition of Pendred's syndrome. Michel abnormality is not a consistent finding in genetic deafness.

Indeed, as few as 20% of congenitally deaf patients have radiologically detectable abnormalities of the inner ear.[41] For these reasons detailed radiological examination of the ear is difficult to justify in all cases of genetic deafness. Cochlear lesions apart, the other inner ear lesions which benefit from CT scans of the cochlea are those in which congenital abnormalities of the labyrinth are associated with cerebrospinal fluid (CSF) fistulae. Clinically

such labyrinthine abnormalities present as CSF otorrhoea, CSF rhinorrhoea, recurrent episodes of meningitis, or stapes 'gusher' at surgery.[40 44] The value of CT scanning in X linked deafness associated stapes 'gusher' has been shown[45] and similar investigation is likely to be of predictive value in preoperative identification of other patients at risk of this surgical complication.[21]

Temporal bone studies in human subjects with genetic deafness indicate that lesions confined to the membraneous cochlea are the most common form of pathology[24] and these are generally of the Scheibe type. Accordingly, blanket cochlear CT scanning in genetic deafness is likely to give a disappointing yield.

## Correlations between genetic deafness in man and animal models

More than 70 different mutations are known to affect the inner ear of the mouse[46] and 151 forms of inherited deafness have been documented in man by drawing distinctions, some more justified than others, between different pedigrees.[24] Many of the inner ear abnormalities observed in mice appear to be grossly similar to abnormalities documented in man and suggest that the responsible mouse mutations are candidates for specific forms of genetic deafness in man. Unlike colleagues working with mice, the human geneticist has rarely been in a position to relate specific abnormalities to the effects of a particular gene. The number of human pedigrees with known inner ear pathology in all affected members is small and when families whose deafness is ostensibly similar on clinical grounds differ in respect of temporal bone pathology, differentiation tends to be made between them on this basis. Mouse studies have, however, shown that the same gene may produce a wide variety of clinical and pathological abnormalities.[47 48] This probably reflects the genetic background factors against which the gene is being expressed. For this reason attempts to relate specific inner ear abnormalities on a one to one basis to particular single gene causes of deafness in man are liable to be disappointing and misleading. Moreover, this observation is important in understanding the limitations of phenotype studies as a guide to shared genotype in the study of human deafness.[49]

Notwithstanding the limitations of the relationship between inner ear abnormalities and specific genes in man, it has been possible to define certain similarities between human hereditary inner ear abnormalities and those in mice. Broadly speaking such abnormalities in the mouse may be of three distinct types.[50]

(1) Morphogenetic, which includes all cases of structural abnormality and corresponds to the Michel and Mundini defects in man. As with Michel and Mundini abnormalities in man, asymmetry is a frequent finding between the two ears in affected cases.

(2) Neuroepithelial, characterised by a primary organ of Corti abnormality and a variable degree of vestibular degeneration. No strict corresponding form is described in the classification of temporal bone findings in man.[37]

(3) Cochleosaccular, characterised by a primary lesion involving the stria vascularis and corresponding to the Scheibe abnormality in man (fig 2).

There may be certain benefits from an interspecific comparative system such as this. Classifying animal models of deafness in this manner may facilitate the future selection of appropriate models for study of comparable forms of genetic deafness in man. It also defines a better framework for classifying temporal bone findings in human cases. Although the limitations of this approach are formidable, nevertheless expanding our knowledge in this area may help identify mechanisms common to both species which are important in the development of normal hearing and genetically determined aberrations thereof. Other avenues of insight into these same mechanisms are likely to be provided by mouse mutants which are not thought to be murine counterparts of human hearing disorders but rather serve as models of interrupted developmental biology of the ear. Study of such mutants should elucidate several of the factors important in normal cochlear development.

## Clinical genetics and deafness

Given the aetiological heterogeneity of genetic deafness and the complexity of possible mechanisms underlying this heterogeneity, it is not surprising that genetic counselling for deafness continues to be empirical. The statistical basis of such counselling in regard to deafness has been authoritatively reviewed elsewhere.[51–53] Perhaps the main role of the clinical geneticist is in attempting to recognise syndromic forms of deafness and provide appropriate counselling for other family members on the basis of the diagnosis. Diagnostic possibilities may be suggested by the history and clinical examination which may be further refined by reference to an authoritative database.[54] Frequently special procedures may be required to confirm a syndrome diagnosis and reference to a guide to the appropriate investigation of isolated cases of hearing loss may be helpful.[55 56]

Perhaps the area of greatest confusion relates to the value of the audiogram not only in relation to phenotype definition but also as a screening measure for gene carriers. Several different forms of non-syndromic genetic deafness have been delineated on the basis of audiogram findings[24] but the validity of these findings as a guide to shared genotype remains unproven. Indeed the only study which has evaluated the audiogram in affected members of a number of families with apparently the same form of non-syndromic genetic deafness has shown no reliable correlation between audiogram and genotype.[57]

Syndrome related autosomal recessive forms of deafness have been said to be characterised by a preferential high tone loss of hearing.[18] In contrast the hearing loss in X linked recessive non-syndromic deafness has been said to give a

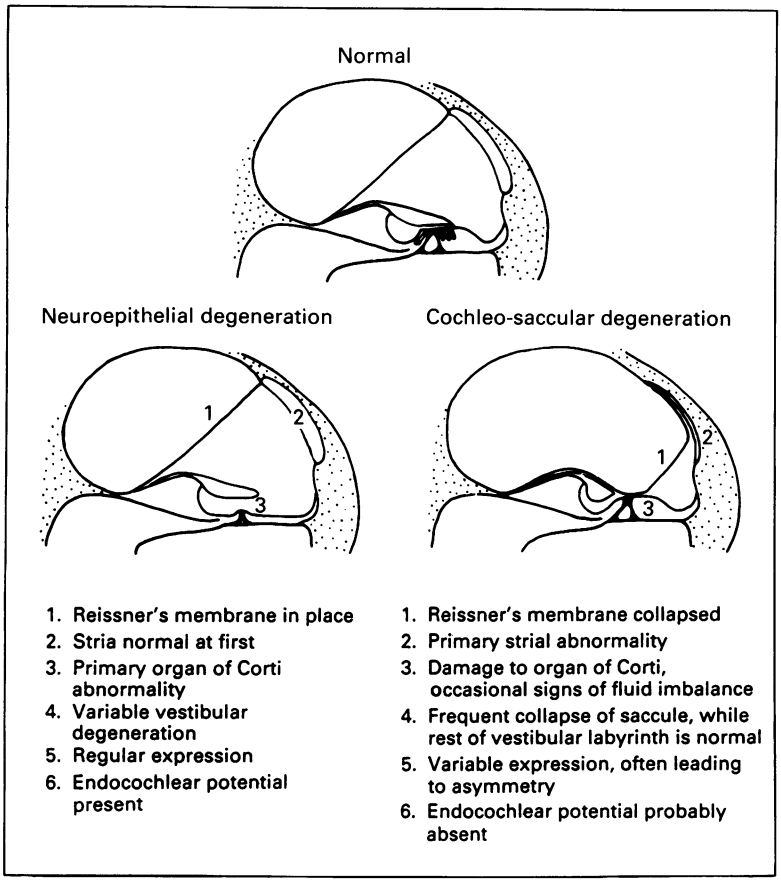


*Figure 2 Cochlear duct sections showing normal animal (top), neuroepithelial degeneration (bottom left), and cochleosaccular degeneration (bottom right).*

flat audiogram.[17] However, X linked deafness appears to be a heterogenous disorder[58 59] and general remarks as to audiogram pattern are unlikely to be helpful. One way of evaluating the audiogram is to look at the consistency of pattern and degree of hearing loss in a single group of patients likely to be genetically homogeneous. Such a group is Pendred's syndrome, in which condition audiogram involvement may vary from profound hearing loss through all frequencies to minimal loss of function.[18] Other authors have evaluated the audiogram as a means of discriminating between aetiologically different forms of deafness but have not found it a reliable tool.[60]

With regard to the carrier state in autosomal recessive deafness there have been several studies attempting to identify audiological characteristics of such patients. Wildervanck[61] performed audiograms on normally hearing consanguineous couples who were the parents of at least two deaf children and could not find any abnormality in the parental audiograms. A subsequent report indicated 'peculiarities' of hearing in almost all parents of children with presumed autosomal recessive deafness.[62] It was unclear whether these 'peculiarities' were sufficiently similar in all cases to form the basis of a carrier detection test. Similar techniques of Bekesy audiometry and stapedial reflex examination have been used by other authors but without observing significant findings.[60]

The benefits of audiological tests as an aid to genetic counselling in autosomal dominant non-syndromic deafness are better documented. In general, dominant deafness is said to be milder than recessive.[18] Reduced penetrance and variable expressivity of autosomal dominant non-syndromic deafness genes are well documented[18] and, for this reason, audiograms of first degree relatives of index cases are usually undertaken, although the sensitivity and specificity of such testing is open to question.

## Genetic counselling in deafness

In the USA 90% of deaf adults marry another deaf person and, in view of this assortive mating, genetic counselling may often be appropriate to persons whose deafness may be non-genetic in aetiology. Perhaps nowhere in genetic counselling is an appreciation of cultural factors said to be more important.[63–65] Many deaf patients have no desire to be cured and are hostile to any suggestion that the aim of counselling is to prevent deafness. Thus, the counsellor may find his/her personal views being challenged by the preference of a deaf couple to have deaf children. These cultural considerations aside, several other general phenomena have been observed in relation to genetic counselling in deaf communities. Questionnaires have been successfully used to elucidate aspects of medical, pregnancy, and family history which may influence counselling. Limited knowledge of family history is frequently observed and may necessitate contacting other family members, with the proband's consent, for relevant details. Moreover the collection of data relevant to counselling may be limited by educational and communication factors.

These phenomena have been well documented in the USA as a result of the genetics service programme established in 1984 at Galludet University, an institution for deaf students. Though valuable in highlighting factors unique to this population which would not be observed otherwise, it is unclear how generally applicable they may be to less educationally privileged, less culturally aware groups of deaf people elsewhere. Similar studies outside this highly selective group are needed to facilitate a balanced overview of the more general situation.

## Molecular genetics and deafness

Several methods of investigating genetic deafness have been outlined. Irrespective of whether this group of conditions is approached clinically, histologically, radiologically, audiologically, or by means of animal model correlation, the problem of non-specificity remains unsurmounted. In terms of applying linkage analysis and other tools of modern genetics to deafness this non-specificity in the clinical and investigative findings of conditions which are genetically distinct means that it has not been possible to define a genetically homogeneous patient group. Accordingly the strategies

which have met with such spectacular success in other human genetic diseases have had their impact limited to well defined clinical subtypes of genetic deafness, such as Waardenburg syndrome,[66] Usher syndrome,[67 68] Treacher Collins syndrome,[69] and X linked deafness.[70] Comparative gene mapping represents one such tack. Knowledge of the chromosomal location of a deafness causing mouse mutation may be exploited to predict the likely chromosomal location of the human homologue.[71] The identification of loci in mice responsible for mutations whose effects are confined to the auditory system offers a possible basis for genetic analysis of non-syndromic deafness in many.[72 73] Homologous human genes may then be isolated and evidence of their possible involvement in deafness sought. While this approach to overcoming the problems of heterogeneity may seem cumbersome, it is clear that innovative approaches are required if progress in identifying the genetic basis of non-syndromic deafness is to be made. Nevertheless, the technology of molecular genetics is the most sophisticated method yet applied to genetic deafness and must, with imaginative use, represent the best chance of resolving the genetic complexities inherent to the group of conditions.

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