The Journal of Laryngology and Otology
January 2000, Vol. **114,** pp. 6–16

Review Articles

Hearing: cracking the code

C. W. R. J. Cremers

Key words: History of medicine; Hearing loss, sensorineural; Genetics, medical

Prologue

Otology started as a specialty in France, by branching out from general surgery almost two centuries ago. Great Britain, Austria and Germany rapidly followed this trend. The Frenchman, Jean Marie Gaspard Itard (1774–1838), published his famous textbook *Traité des Maladies de l'Orielle et de l'Audition* after 20 years of medical practice in Paris.[1] In 1834 Jean Pierre Bonnafont (1805–1891) developed the first otoscope, an instrument for looking into the narrow ear canal.[2] It was a revolutionary design, because light could enter the instrument from the side. Then, via a combination of mirrors, it coincided with the direction in which the physician was looking and lit up the area under examination. It was not until 1896 that an electric light source was attached to the side of the otoscope.[2] Very often, progress in medical science is made possible by technical advances.

The origination of the ear, nose and throat specialty

At the turn of the century ear, nose and throat surgery, or otorhinolaryngology, originated from a combination of otology and laryngology, which themselves had very different backgrounds. The first otologists were surgeons, who were used to employing scalpel and drill, whereas the first laryngologists were physicians who combined their knowledge of the larynx with that of the lungs. The connection between laryngology and otology was rhinology, initially also part of the domain of the laryngologists.

In the 19th century otologists and laryngologists were separate specialists: they had their own clinics and, in the latter part of the century, they also had their own scientific journals. It was not until the turn of the century that the two groups joined forces and became otorhinolaryngologists or, as they are more popularly known ear, nose and throat specialists.

Pioneers in ENT surgery and hereditary deafness

The pioneers in the field of otology showed great interest in the deaf and the deaf and dumb, and consequently in the causes of congenital deafness, which would lead to deaf–mutism if the patient did not receive special education. One of them was the Irish otologist Sir William Wilde (1815–1876), the father of Oscar Wilde. In 1841 he accepted the post of medical commissioner because a census was being held in Ireland. He added a question to the census about the prevalence of deafness in families and, in the course of his duties, managed to make the acquaintance of several families with deafness. In 1853 he drew up their pedigrees and indicated the family members who were deaf. In this way he was the first to describe the direct or dominant pattern of inheritance.[3] In 1858, the famous Berlin ophthalmologist Albrecht von Graefe (1828–1870)[4] published the first description of a syndrome characterized by a combination of congenital deafness and pigmentation of the retina, known at that time as retinitis pigmentosa. In adulthood this disorder leads to blindness. Another Berlin ophthalmologist, Richard Liebreich (1830–1917), continued von Graefe's work and performed a systematic study on this syndrome.[5] He examined 341 deaf people from Berlin, and he was very surprised to find that this syndrome was very common among deaf people with a Jewish background. Congenital deafness was four times more common among Jews (1:368) than among the remaining population (1:1477). He understood that the higher percentage of consanguinity among Jews must be associated with the cause.

In the first half of the 19th century reports had appeared in France on the strikingly high percentage of consanguinity among the parents of deaf children at the schools for the deaf in Poiters and Paris. Owing to the fact that consanguinity between spouses was not unusual at that time, and moreover did not always lead to congenital anomalies, the

Inaugural address presented on acceptance of the Chair of Professor of Otology at the Faculty of Medical Sciences of the University of Nijmegen, the Netherlands, on Friday 16 October 1998.
Accepted for publication: 1 November 1999.

meaning of these observations was not properly understood. The Berlin otologist Arthur Hartmann (1849–1931) published the first description of indirect inheritance, besides the direct inheritance pattern.[6] He based his description of direct inheritance on the autosomal dominant inheritance pattern and his description of indirect inheritance on the autosomal recessive inheritance pattern, as they were defined at the beginning of this century according to the laws formulated by Gregor Johann Mendel (1822–1884) in 1865. The Viennese otologist Adam Politzer (1835–1920) is considered to be the founder of modern scientific otology. He organized and gave courses to 7000 foreign doctors. His *Lehrbuch der Ohrenheilkunde* was first published in 1876.[7] There were five editions and it was translated into English, Italian and Spanish. In the second German edition, published in 1887,[7] Politzer emphasized that heredity was a major cause of deafness. He adopted every detail of the conclusions drawn by Hartmann about the existence of a direct and an indirect pattern of inheritance for deafness.

Animal models for human hereditary deafness and eugenetic tendencies

In 1942, three Dutch physicians, Van Gilse, Hinnen and Nieuwenhuijse,[8] published a book in English about the heredity of ENT diseases. The book gives a good impression of how research was performed into the heredity of deafness during the first half of the 20th century. The authors also made a mathematically based stand against the detrimental aspects of the eugenetic movement that had taken root, particularly in the USA and Germany.[9] There were also extensive descriptions of in-depth histological studies on deaf animals, especially on deaf species of mice known at that time. Very few people realized how important this and later data on these deaf mice would be in the future. One exception was Deol from London.[10–21,49] It is partly through their insight and efforts that the present-day study of candidate genes for hereditary deafness is so successful, but more about that later.

Incidence of hearing loss

Depending on how it is defined, about 10–20 per cent of the Dutch population suffer from hearing impairment. It is an invisible and highly invalidating problem. Hearing impairment is an epidemic disease.[22,23] It does not display itself, but literally withdraws itself, so that others often do not know that it is there.

Sensorineural hearing loss affects half of the population of 80-year-olds and one-third of the population of 70-year-olds.[24–26] One in 750 children is deaf, or becomes deaf in very early childhood.[27–32] This handicap generally has a hereditary cause. In adulthood we do not know how often heredity is responsible for the development of hearing loss.

First description of hereditary syndromes

Thanks to the invention of the ophthalmoscope by Hermann von Helmholtz (1821–1894) at the University of Königsberg in the middle of last century, it became possible to examine the retina of a patient's eye with one's own eye.[2] In contrast, it has never been possible to examine the inner ear in a similar way, which strongly hinders the development of our knowledge about diseases of the inner ear. However, it was possible for physicians to recognize a systematic pattern when inner-ear disease occurred simultaneously with other physical characteristics. This was particularly valid for the previously mentioned example of deafness with a form of blindness that developed in later life. At present this condition is called Usher's syndrome.

Besides studying the causes of hereditary and acquired deafness at schools for the deaf and in regions with an increased incidence of hereditary hearing impairment and deafness, research into hereditary deafness has concentrated chiefly on elucidating the many hereditary deafness syndromes. At present about 450 different, usually rare, hereditary syndromic forms with hearing impairment and deafness have been described.[33] About a dozen of these forms were first observed and described at the University Hospital Nijmegen.[34–51] These syndromes make up only a small minority of the hearing impairment and deafness that have a hereditary cause. In terms of the number of affected adults and children, the non-syndromic hereditary forms constitute by far the largest group.

In the 1960 and 1970s researchers started to distinguish between some forms of generally autosomal dominant hereditary non-syndromic forms of hearing impairment. They could do this only on the basis of the shape of the tone audiogram, combined with familial examination. Besides recognizing the pattern of inheritance, it was important to establish whether the hearing loss was most pronounced in the low tone, mid-tone or high-tone region.[52]

Gene linkage, gene isolation and mutation research

To gain more understanding of the inner ear it is necessary to detect genes which, in a mutated form, cause hereditary deafness. For this purpose we can employ gene-linkage studies and gene isolation. Mutated genes which were responsible for the development of hereditary hearing loss in species of deaf mice also appeared to lead to hereditary forms of deafness in humans.[53] Many of these genes form the building blocks of the inner ear. By means of analogous studies on animal models, we will be able to find out more about the inner ear on a cell-biological level. The title of this address refers to this.

In the 1960 and 1970s gene-linkage studies were sometimes performed on syndromic forms of hearing impairment.[54–56] In the 1980s gene linkage was accomplished for several dozen syndromic forms of hereditary deafness. In the 1990s gene-linkage

https://doi.org/10.1258/0022215001903816 Published online by Cambridge University Press

studies and gene isolation were also applied to non-syndromic forms of hereditary hearing impairment.[52]

For gene-linkage studies about 200 polymorphic DNA markers are used, spread over chromosomes 1–22. By means of systematic analysis we look for one or two of these 200 DNA markers that are inherited with the genetic defect. At present 50 locations in the genome are known to be related to a hereditary form of hearing loss. These 50 locations are always the first to be investigated with gene-linkage studies in a new family with hereditary deafness. If there is no linkage to any of these locations, then the whole set of DNA markers is tested. The availability of far-reaching automation means that an unknown genetic defect can be localized in a period of five to eight weeks. Finding the affected gene takes at least several months.

I would like to discuss a number of examples of such studies, in order to demonstrate how much the outcomes have increased our clinical knowledge of hereditary deafness.

X-recessive progressive mixed hearing loss with stapes ankylosis and perilymphatic gusher during stapes replacement surgery

Conductive hearing loss can be caused by fixation of one or more of the ossicles, including the stapes. The transmission of sound vibrations from the air via the tympanic membrane to the inner ear will be impeded by fixation of the stapes. Otosclerosis is a bone disease of the temporal bone which can cause fixation of the stapes by bone ingrowth. This leads to conductive hearing loss, which can be treated with stapes replacement surgery.[57] With every operation there is a risk of complications, in this case persistent dizziness and exacerbation of the hearing impairment, sometimes even to total deafness and persistent tinnitus.

Perilymph in the cochlea has the same composition as cerebrospinal fluid (CSF). CSF can enter the cranial cavity via two channels, the internal auditory canal and the cochlear aqueduct The latter sometimes becomes blocked as people grow older, but this does not seem to have any detrimental effect. However, when the footplate of the stapes is opened during stapes replacement surgery, CSF can leak via the perilymph from the middle ear and flow outwards through the auditory canal if the connection with the inner ear is too wide. This complication is called a stapes gusher. Fortunately, it is vary rare.

In 1971 the first report appeared on a large pedigree with progressive, mixed hearing loss which chiefly affected the men and was transmitted solely by mothers to their sons.[58] This pattern of heredity is linked with the sex chromosome and is called X-recessive. In three male members of this family who underwent stapes replacement surgery the above-described stapes gusher occurred, and was accompanied by loss of hearing in the operated ear.[59] In the Netherlands we detected three similar cases. Ultimately we were able to identify a large family with these symptoms. At two hospitals a stapes gusher occurred in two second cousins younger than 20 years as a complication of stapes replacement surgery. With the assistance of the family and the records from the Institute for the Deaf in St Michielsgestel, we were able to trace the pedigree of this family, which had many hearing-impaired and deaf males. The pattern of inheritance agreed with the previously mentioned X-recessive pattern. Clinical examination showed that in the internal auditory canal of the sufferers there was bony widening laterally. This abnormality can be detected before surgery by polytomography or, better still, by CT scanning of the internal auditory canal (Figure 1), so that the operation can be cancelled and complications avoided.[62] Audiometry revealed other common characteristics, but they were less specific.[60–63]

Gene-linkage studies were started on this family in the mid-1980s. It was clear that, in view of the X-recessive pattern of inheritance, we only needed to investigate the relatively small X chromosome. At that time a great many DNA markers for the X chromosome were known, in contrast with the non-sex-linked chromosomes. The Institute for Anthropogenetics in Nijmegen is famous for its expertise with the X chromosome. After successful gene linkage,[64] affected families from all over the world agreed to participate. In this way it was possible to indicate *POU3F4* as the gene responsible.[65–68,174]

With the aid of preoperative CT scanning and supplementary genetic studies we were able to prevent several persons with this form of hearing impairment from undergoing surgery. They all appeared to belong to the next generation of our existing pedigree. Scientifically, the identification of the *POU3F4* gene was an important step forwards. For the first time, a gene had been recognized that leads to a progressive form of deafness which has no syndromic characteristics outside the ear.

Usher's syndrome

In 1919 De Wilde from Amsterdam obtained his PhD with a thesis on *Kinship and Heredity in Deaf–Mutism and Retinitis Pigmentosa*.[69] About

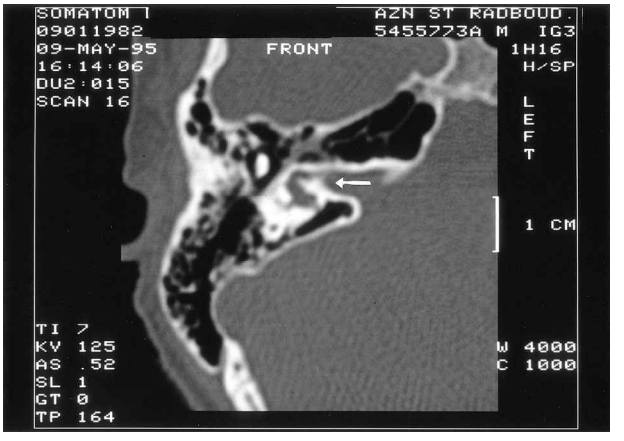

FIG. 1

A too-wide communication between the internal auditory canal and the inner ear is shown by an arrow.

https://doi.org/10.1258/0022215001903816 Published online by Cambridge University Press

half a century earlier similar studies had been performed, chiefly in German.[5,6,70,71] After the discovery of this syndrome in 1858 by the ophthalmologist Albrecht von Graefe[4] and the meticulous study by Liebreich in 1861,[5] several other German teams performed systematic research and recognized this syndrome in other deaf populations, in whom the frequency was lower.[6] In his book *Deaf–Mutism and Education for the Deaf and Dumb,* published in 1880, Arthur Hartmann, an otologist from Berlin, spent a whole chapter describing deaf–blindness. His clinical description of the syndrome, which was characterized by congenital deafness and retinitis pigmentosa, is strikingly accurate. Nevertheless, the subject received little attention in the international literature.

The syndrome was not given the name Usher's syndrome until part-way through the 20th century, after the Scottish ophthalmologist Charles Usher from Aberdeen had described it in his Bowman lecture in 1935.[72] Other German and English contributions were made by Adler[70] and Lee.[71] Usher's syndrome is a strongly invalidating condition with an autosomal recessive pattern of inheritance, which leads to deaf–blindness. The first ophthalmological symptoms in a deaf or hearing-impaired child often do not appear until the age of ten years. By that time the family is usually complete and there is more than one deaf child that will ultimately become deaf and blind. In their PhD theses, Annelies van Aarem[31,73] and Mariette Wagenaar[74,75] have redescribed the clinical symptoms (phenotype) of Usher's syndrome type IIA on the basis of the genotype. They have shown that the hearing loss is progressive, in contrast to the notion that is generally accepted in the literature.[31,73–75] Early diagnosis is only possible by gene-linkage studies with flanking markers or by mutation analysis on the affected gene. In 1922, on the basis of the severity of the hearing loss and on whether or not the patient's sense of balance was functional, Julia Bell concluded that there were two clinical types.[76] At the end of the 1980s international collaboration was achieved, with a genetic laboratory at Boys Town Hospital in Omaha, USA (head: Professor W. Kimberling), to perform gene-linkage studies and later gene isolation with subsequent mutation analysis. This resulted in the two previously mentioned PhD theses on Usher's syndrome from Nijmegen.[31,74] Blood samples were obtained for gene-linkage studies. On the basis of these and other gene-linkage studies it appeared that there were three clinically distinguishable types of Usher's syndrome, namely I^{A-F}, II^{A-B} and III.[71] Types I^{A-F} and II^{A-B} have six and two genetically distinguishable subtypes, respectively.[74,77–83] For types IIA and IB[84,85] – the most common types – the gene has been identified. The mutations vary fairly widely from one part of the world to another, but also sometimes between neighbouring countries.[86] This finding emphasizes the importance of identifying the mutations present in this country. In this way, early diagnosis of this devastatingly invalidating syndrome will soon be within our reach.

Pendred's syndrome

More than 100 years ago, in 1896, the Englishman Vaughan Pendred[87] described an Irish family with five sons and five daughters. Two of the girls had profound childhood deafness. In addition, at the beginning of puberty they developed a visibly enlarged thyroid gland (Figure 2). In 1927 four further families were described.[88] It had been known for many years that a lack of iodine in the diet could lead to thyroid enlargement and deafness. At the end of the 1950s it became clear that Pendred's syndrome had an autosomal recessive pattern inheritance.[89] In the same period it was found that a metabolic disturbance in the thyroid gland formed the basis of the thyroid abnormality.[90] Free iodine did not bind directly and fully with the thyroid protein thyroglobulin. A new diagnostic test, the perchlorate test, was developed based on this deficient iodine (iodide),-binding capacity. An avalanche of publications with many hundreds of descriptions of Pendred's syndrome followed.[51,91]

The full description of Pendred's syndrome is based on this. Making a diagnosis of Pendred's syndrome is not usually possible until puberty or even later, because hypothyroidism is only occasionally recognized at a younger age.[92,93] By the

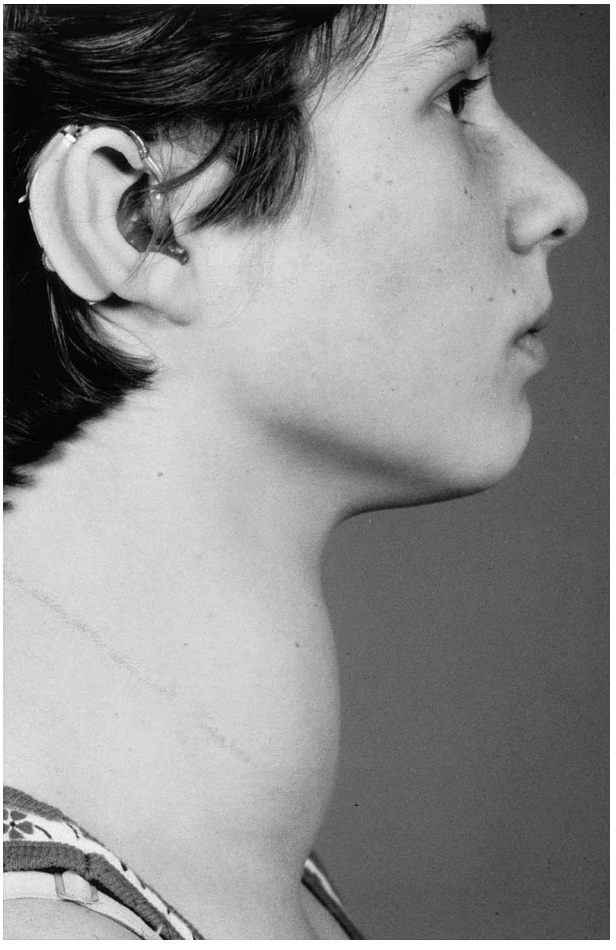

FIG. 2
Girl with an enlarged thyroid gland and impaired hearing having Pendred's syndrome.

https://doi.org/10.1258/0022215001903816 Published online by Cambridge University Press

beginning of the 1990s the gene-linkage techniques had become so powerful that it was believed possible to achieve gene linkage and subsequent isolation. In collaboration with the Department of Medical Genetics of Antwerp University, we started gene-linkage studies on Pendred's syndrome.[94,95] Blood samples were obtained from about 20 families with Pendred's syndrome, chiefly in the Netherlands. However, in Europe we lack large families, each with different blood relationships, and we also lack large families with several affected children. With the aid of families from Islamic populations, other centres successfully accomplished gene linkage. Then various genetic centres were soon able to shorten the portion of chromosome with the affected gene.[94,96–98]

In December 1997 the *PDS* gene was recognized in Bethesda.[99] In view of the existing collaboration, we were able to perform mutation analysis on our Pendred patients[95,100,101] and make a start on rewriting the clinical symptoms.[100,101] With the certainty of mutation analysis, we were able to demonstrate that the hearing loss in nearly all of our patients was strongly progressive in very early childhood, with a deterioration of 7 dB per year and a subsequent slow decline. New computed tomography techniques and magnetic resonance imaging showed that the vestibular aqueduct was widened in the temporal bones of about 30 cases[100–102] (Figures 3, 4).

The vestibular aqueduct is not an open canal but a closed one that connects the inner ear to the subarachnoid cavity. In this aqueduct there is a thin membrane that separates the perilymph in the cochlea from the CSF. During the past 20 years the widened vestibular aqueduct has been recognized. This is characterized by progressive hearing loss, particularly in early childhood. Previously the cause of this syndrome was totally unknown. In these usually isolated cases, mutation analysis of the Pendred gene and the perchlorate test should be able to demonstrate whether the patient has Pendred's syndrome. In the meantime, we have found that children with a widened vestibular aqueduct and Pendred's syndrome do indeed become deaf in the short or long term.[100,101] If they are too deaf for rehabilitation with a powerful hearing aid, it has proved possible to treat them successfully with a cochlear implant. This seems to be the result of their good language acquisition in early childhood before they became hearing impaired. After it has become possible to make an early diagnosis by means of mutation analysis and imaging techniques of the temporal bones, we hope that an effective and reliable surgical technique can be developed to narrow down the widened vestibular aqueduct and consequently prevent the progression in hearing loss. Once again this is an example of how, on the basis of mutation analysis on the affected gene, the clinical picture of a syndrome can be rewritten, with new insights into effective treatment methods.

Non-syndromic autosomal dominant and autosomal recessive hereditary hearing impairment

As gene-linkage techniques became more powerful at the beginning of the 1990s, it also became possible to perform gene-linkage studies on non-syndromic forms of hereditary hearing loss in a worthwhile manner.[52,103–109] These forms of hearing loss could not be recognized as forming part of a syndrome because there were no other accompanying features. This group of non-syndromic forms of hearing loss

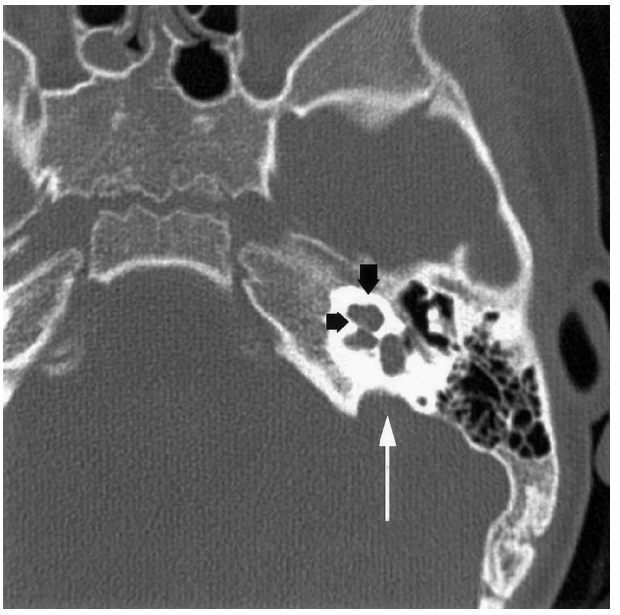

FIG. 3

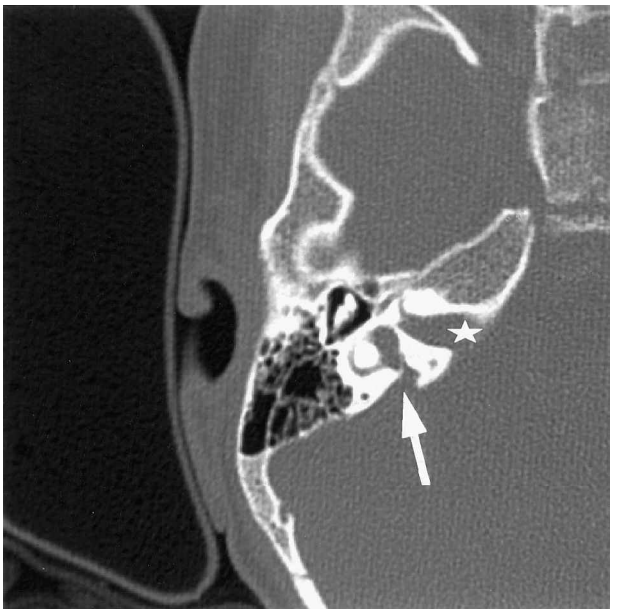

FIG. 4

FIGS. 3 and 4
Enlarged vestibular aqueduct (white arrow) in Pendred's syndrome.

https://doi.org/10.1258/0022215001903816 Published online by Cambridge University Press

TABLE I
NON-SYNDROMIC AUTOSOMAL DOMINANT HEREDITARY HEARING LOSS

Locus	Chromosomal localization	Year	Gene cloned	Year
DFNA1	5q31	1992[117]	*HDIA1*	1997[118]
DFNA2	1p34	1994[119]	*GJB3(C×31),KCNQ4*	1999[120,121]
DFNA3	13q12	1994[122]	*GBJ2(C×26)*	1998[123]
DFNA4	19q13	1995[124]	–	–
DFNA5	7p15	1995[125]	*DFNA5*	1998[126]
DFNA6	4p16.3	1995[127]	–	–
DFNA7	1q21-q23	1995[128]	–	–
DFNA8/DFNA12	11q22-24	1995[129,130]	*TECTA*	1998[131]
DFNA9	14q12-q13	1996[132]	*COCH*	1998[133]
DFNA10	6q22-q23	1996[134]	–	–
DFNA11	11q12.3-q21	1996[135]	*MYO7A*	1997[136]
DFNA13	6p21-p22	1997[137]	*COL11A2*	1999[138]
DFNA14	4p16	1997[139]	–	–
DFNA15	5q31	1998[140]	*POU4F3*	1998[140]
DFNA16	2q24	1998[141]	–	–
DFNA17	22q	1998[142]	–	–
DFNA18	3q22	1998[143]	–	–
DFNA19	10	1998[144]	–	–
DFNA20	reserved	–	–	–
DFNA21	6p21	1999[145]	–	–
DFNA22	reserved	–	–	–
DFNA23	reserved	–	–	–
DFNA24	reserved	–	–	–
DFNA25	reserved	–	–	–
DFNA26[a]	5p11	–	–	–
DFNA27	reserved	–	–	–
DFNA28	reserved	–	–	–

[a]Unpublished (Smith *et al.*)

and deafness affect far more people with hearing impairment than the group with a syndromic form. The forms of hereditary deafness that were distinguished on the basis of gene linkage received a letter/number code in chronological order. DFNA stands for autosomal dominant (Table I), DFNB stands for autosomal recessive (Table II) and DFN stands for X- or Y-linked hereditary forms (Table III) of non-syndromic hearing loss. About one dozen hereditary mitochondrial syndromic and non-syndromic forms of hereditary hearing loss have been identified.[52,163] Over a period of five years we have discovered about 50 new and different non-syndromic forms of hearing loss. Owing to the rapidity of

TABLE II
NON-SYNDROMIC AUTOSOMAL RECESSIVE HEREDITARY HEARING LOSS DFNB1-26

Locus	Chromosomal localization	Year	Gene cloned	Year
DFNB1	13q12	1994[146]	*GJB2 (C×26)*	1997[147]
DFNB2	11q13.5	1994[148]	*MYO7A*	1997[149,150]
DFNB3	17p11.2-q12	1995[151]	*MYO15A*	1998[152]
DFNB4	7q31	1995[153]	*PDS*	1998[154]
DFNB5	14q12	1995[155]	–	–
DFNB6	3p14-p21	1995[156]	–	–
DFNB7	9q13-q21	1995[157]	–	–
DFNB8	21q22	1996[158]	–	–
DFNB9	2p22-p23	1996[159]	*OTOF*	1999[160]
DFNB10	21q22.3	1996[161]	–	–
DFNB11	9q13-q21	1996[162]	–	–
DFNB12	10q21-q22	1996[163]	–	–
DFNB13	7q34-36	1998[164]	–	–
DFNB14	7q31	1998[165]	–	–
DFNB15	3q21-q25 and 19p13	1997[166]	–	–
DFNB16	15q21-q22	1997[167]	–	–
DFNB17	7q31	1998[168]	–	–
DFNB18	11p14-15.1	1998[169]	–	–
DFNB19	18p11	1998	–	–
DFNB20	11q25	1998[170]	–	–
DFNB21	11q	1999[171]	*TECTA*	1999[171]
DFNB22	reserved	–	–	–
DFNB23[a]	10p11.2-q21	–	–	–
DFNB24[a]	11q23	–	–	–
DFNB25[a]	4p15.3-q12	–	–	
DFNB26	reserved	–	–	–

[a]Unpublished (R. Smith *et al.*)

https://doi.org/10.1258/0022215001903816 Published online by Cambridge University Press

TABLE III
NON-SYNDROMIC X-LINKED HEREDITARY HEARING LOSS

Locus	Chromosomal localization	Year	Gene cloned	Year
DFN1[a]	Xq22	1995[172]	DDp	–
DFN2	Xq22	1996[173]	–	–
DFN3[b]	Xq21.1	1995[174]	POU3F4	1995[174]
DFN4	Xp21.2	1994[175]	–	–
DFN5	Withdrawn	–	–	–
DFN6	Xp22	1996[176]	–	–
DFN7	Withdrawn	–	–	–
DFN8	Reserved	–	–	–

[a]Later recognized as syndromic.
[b]Mixed hearing impairment.

these developments and the fact that new gene linkage is often found in a new family, it can be expected that in the next few years several dozen more new hereditary forms of hearing loss will be recognized. This explosion of new knowledge will lead to our finding out more about the genes responsible. In this way we will learn about the building blocks of the inner ear, and we will gain more insight into their position and the role they play in the total functioning of the inner ear.[110] At present it is believed that about 1000 genes are involved in the build-up and function of the inner ear.

At the same time the first genes have been identified that, in a mutated form, are responsible for non-syndromic forms of early childhood deafness. In the Mediterranean countries one of these genes, connexin-26, appears to be responsible for half of the cases of early childhood deafness.[111,112] Connexin-26 is a fairly small protein, which means that research into mutated forms will be simple and reasonably cheap. As a consequence, the early diagnosis of hereditary deafness in a young hearing-impaired or deaf child has become reality. In view of the speed of recent developments, it can be expected that important new discoveries will be made very soon. We can conclude that the secret code which determines how the inner ear functions will indeed be cracked in the near future.[110,113,114]

The meaning of diagnosing the often unsuspected hereditary cause of deafness at an early stage is of great importance for the child and the parents.

It is now a question of making this new knowledge accessible on a sufficiently large scale for clinical practice.

References

1 Itard JMG. *Traité des Maladies de l'Oreille et de l'Audition,* Part I pp 1–296, Part II pp 1–522. Paris: Méquignon-Marvis, 1821
2 Weir N. *Otolaryngology: an Illustrated History.* London: Butterworths, 1990
3 Wilde WR. *Practical Observations on Aural Surgery and the Nature and Treatment of Diseases of the Ear.* Philadelphia: Blanchard and Lea. London: Churchill, 1853
4 Von Graefe A. Vereinzelte Beobachtungen und Bemerkungen: exceptionelles erhalten des Gesichtsfeldes bei Pigmentenartung der Netzhaut. *Von Graefe's Arch Ophthalmol* 1858;**4:**250–3
5 Liebreich R. Abkunft aus Ehen unter Blutsverwandten als Grund von Retinitis pigmentosa. *Dtsch Arch Klin Med* 1861;**13:**53–5
6 Hartmann A. *Taubstummheit und Taubstummenbildung nach den voorhanden quellen sowie nach eigenen Beobachtungen und Erfahrungen.* Stuttgart: Verlag Ferdinand Enke, 1880
7 Politzer A. *Lehrbuch der Ohrenheilkunde für practische Ärtze und Studierenden.* Stuttgart: Ferdinand Enke, 1876; 2nd edn 1887
8 van Gilse PHG, Hinnen AB, Nieuwenhuijse AC. *Heredity in Diseases in the Field of Oto-rhino-laryngology.* Bibliographia Genetica Deel XIII, No. 4, pp 301–424. 's Gravenhage: Martinus Nijhoff, 1942
9 Ruben RJ. The history of the genetics of hearing impairment. *Ann NY Acad Sci* 1991;**630:**5–15
10 Deol MS. The anomalies of the labyrinth on the mutants varitint-Waddler, Shaker-2 and Jerker in the mouse. *J Genet* 1954;**52:**562–88
11 Deol MS. The auditory and development of the mutants pirouette, shaker-1 and waltzer in the mouse. *Proc Roy Soc Lond Ser B* 1956;**145:**206–13
12 Deol MS, Robins MW. The spinner mouse. *J Hered* 1962;**53:**133–6
13 Deol MS. The origin of the abnormalities of the inner ear in Dreher mice. *J Embryol Exp Morphol* 1964;**12:**727–33
14 Deol MS. The abnormalities of the inner ear in Kreisler mice. *J Embryol Exp Morphol* 1964;**12:**474–90
15 Deol MS. A new gene affecting the morphogenesis of the vestibular part of the inner ear in the mouse. *J Embryol Exp Morphol* 1996;**16:**543–58
16 Deol MS. Inherited diseases of the inner ear in man in the light of studies on the mouse. *J Med Genet* 1968;**5:**137–57
17 Deol MS. The relationship between abnormalities of pigmentation and of the inner ear. *Proc Roy Soc Lond Ser B* 1970;**175:**201–17
18 Deol MS. An experimental approach to the understanding and treatment of hereditary syndromes with congenital deafness and hypothyroidism. *J Med Genet* 1973a;**10:**235–42
19 Deol MS. Congenital deafness and hypothyroidism. *Lancet* 1973b;**2:**105–6
20 Deol MS. Deficiencies of the inner ear in the mouse and their origin. *Colloq Int CNRS* 1976;**266:**163–71
21 Brown KS, Bergsma DR, Barrow MV. Animal models of pigment and hearing abnormalities in man. *Birth Defects* 1971; OAS VII no. 4 102–9
22 Parving A. Epidemiology of genetic hearing impairment. In: Martini A, Read A, Stephens D, eds. *Genetics and Hearing Impairment.* London: Whurr, 1996
23 Grote JJ. Slechthorendheid een vergeten volksgezondheidsprobleem. *Ned Tijdschr Geneeskd* 1992;**136:**2404–6
24 Pederson KE. Presbyacusis. An epidemiological study. Dissertation, University of Göteborg, 1990
25 Davis A. The prevalence of hearing impairment and reported hearing disability among adults in Great Britain. *Int J Epidemiol* 1989;**18:**911–7
26 Morton ME. Genetic epidmiology of hearing impairment. *Ann NY Acad Sci* 1991;**630:**16–31

27 Martin JAM, Bentzen O, Colley JRT, Hennebert D, Holm C, Iurato S, *et al.* Childhood deafness in the European community. *Scand Audiol* 1981;**10:**165–74

28 Parving A. Epidemiology of hearing loss and aetiological diagnosis of hearing impairment in childhood. *Int J Pediatr Otorhinolaryngol* 1983;**5:**151–5

29 Parving A. Congenital disability–epidemiology and identification: a comparison between two health authority districts. *Int J Pediatr Otorhinolaryngol* 1993;**27:**29–46

30 Davis A, Parving A. Towards appropriate epidemiology data on childhood hearing disability: a comparative European study of birth cohorts 1982–1988. *J Audiol Med* 1994;**3:**35–47

31 van Aarem A. *Heterogeneity in the Usher Syndrome.* Academisch Proefschrift Katholieke Universiteit Nijmegen, 1996

32 Graaf de R, Knippers EWA, Bijl RV. Prevalentie en relevante achtergrondkenmerken van doofheid en ernstige slechthorendheid in Nederland. *Nederland Tijdschr Geneeskd* 1998;**142:**1819–23

33 Gorlin RJ, Toriello HV, Cohen MM. *Hereditary Hearing Loss and its Syndromes.* New York: Oxford University Press, 1995

34 Cremers CWRJ, ter Haar BGA, van Rens TJG. The Nathalie syndrome. A new hereditary syndrome. *Clin Genet* 1975;**8:**330–40

35 Cremers CWRJ, Philipsen VMJG, Mali JHW. Deafness, ichthyosiform erythroderma, corneal involvement, photophobia and dental dysplasia. *J Laryngol Otol* 1977;**91:**585–90

36 Cremers CWRJ. Autosomal recessive non-syndromal progressive sensorineural deafness in childhood. A separate clinical and genetic entity. *Int J Pediatr Otolaryngol 1979;***1:**193–9

37 Cremers C, van Rijn P, ter Haar B. Autosomal recessive progressive high-frequency sensorineural deafness in childhood. *Arch Otolaryngol* 1987;**113:**1319–32

38 Teunissen E, Cremers CWRJ. An autosomal dominant inherited syndrome with congenital stapes ankylosis. *Laryngoscope* 1990;**100:**380–4

39 Marres HAM, Cremers CWRJ. Congenital conductive or mixed deafness, preauricular sinus, external ear anomaly and commissural lip pits: An autosomal dominant inherited syndrome. *Ann Otol Rhinol Laryngol* 1991;**100:**928–32

40 Kumar S, Marres HAM, Cremers CWRJ, Kimberling WJ. Autosomal-dominant branchio-otic (BO) syndrome is not allelic to the Branchio-Oto-Renal (BOR) gene at 8q13. *Am J Med Genet* 1998;**76:**895–401

41 Brunner HG, Smeets B, Smeets D, Nelen M, Cremers CWRJ, Ropers HH. Molecular genetics of X-linked hearing impairment. *Ann NY Acad Sci* 1991;**630:**176–91

42 Manni JJ, Huygen PLM, Noten JFP, Kuijpers W. Eight cranial nerve dysfunction in hyperostosis cranialis interna. *Acta Otolaryngol* 1992;**112:**75–82

43 Verhagen WIM, Huygen PLM, Bles W. A new autosomal dominant syndrome of idiopathic progressive vestibulo-ocular dysfunction with middle-age onset. *Acta Otolaryngol* 1992;**112:**899–906

44 Mariman ECM, Beersum SEC van, Cremers CWRJ, Struycken PM, Ropers HH. Fine mapping of a putatively imprinted gene for familial non-chromaffin paragangliomas to chromosome 11q13.1: evidence for genetic hyeterogeneity. *Hum Genet* 1995;**95:**56–62

45 Van Schothorst EM, Van Beersum SEC, Jansen JC, Van der Mey AGL, Green JS, Cremers CWRJ, *et al. Genetic Heterogeneity Analysis of Hereditary Paragangliomas shows that the Large Majority are due to PGL1 at 11q22-q23.*Thesis, University of Leiden, 1998;53–61

46 Brunner HG, Beersum SEC van, Warman ML, Olsen BR, Ropers HH, Mariman ECM. A Stickler syndrome gene is linked to chromosome 5 near the COL11A2 gene. *Hum Mol Genet* 1994;**9:**1561–4

47 Ensink R, Brunner H, Cremers CWRJ. Maxillofacial dysostosis: X-linked or X-recessive? *Genet Couns* 1997;**8:**285–90

48 Ensink RJH, Verhoeven K, Marres HAM, Huygen PLM, Padberg GWAM, Laakter H, *et al.* Early onset sensorineural hearing loss and late onset neurologic complaints caused by a mitochondrial mutation at position 7472. *Arch Otolaryngol Head Neck Surg* 1998;**124:**886–91

49 Kunst H, Marres H, Huygen P, Van Camp G, Joosten F, Cremers C. Autosomal dominant non-syndromic low-frequency sensorineural hearing impairment linked to chromosome 4p16 (DFNA14). *Audiology* 1999;**38:**165–73

50 Kunst H, Marres H, Huygen P, van Duijnhoven G, Cremers F, Cremers C. Non-syndromic autosomal dominant progressive non-specific mid-frequency sensorineural hearing impairment with childhood to late adolescence onset (DFNA13). *Clin Otolaryngol* 1998: (submitted)

51 Kunst H, Marres H, Huygen P, Van Camp G, Huybrechts C, Cremers C. A new type of non-progressive non-syndromic autosomal dominant mid- and highfrequency sensorineural hearing impairment. *Am J Otol* 1998: (submitted)

52 Kunst H, Marres H, Camp van G, Cremers C. Non-syndromic autosomal dominant sensorineural hearing loss. A new field of research. *Clin Otolaryngol* 1998;**23:**9–17

53 Brown SDM, Steel KP. Mouse models for human hearing impairment. In: Martini A, Read A, Stephens D, eds. *Genetics and Hearing Impairment.* London: Whurr, 1996:53–6

54 Fraser GR. Association of congenital deafness with goitre (Pendred's syndrome). *Ann Hum Genet* 1965;**28:**201–48

55 Arias S. Genetic heterogeneity in the Waardenburg syndrome. *Birth Defects* OAS 1971; VII no. 4: 87–101

56 Cremers CWRJ, Fikkers-van Noord M. The earpits–deafness syndrome. Clinical and genetic aspects. *Int J Pediatr Otorhinolaryngol* 1980;**2:**309–22

57 Shea JJ. Fenestration of the oval window. *Ann Otol Rhinol Laryngol* 1958;**67:**932–51

58 Nance WE, Setleff R, Mcleod A, Sweeney A, Cooper C, McConnell F. X-linked mixed deafness with congenital fixation of the stapedial footplate and perilymphatic gusher. *Birth Defects OAS* 1971;VII,no.4:64–9

59 Glasscock ME. The stapes gusher. *Arch Otolaryngol* 1973;**98:**82–91

60 Cremers CWRJ, Hombergen GCJH, Wentges RThR. Perilymphatic gusher and stapes surgery. A predictable complication? *Clin Otolaryngol* 1983;**8:**235–40

61 Cremers CWRJ, Huygen PLM. Clinical features of female heterozygotes in the X-linked mixed deafness syndrome (with perilymphatic gusher during stapes surgery). *Int J Pediatr Otorhinolaryngol* 1983;**6:**179–85

62 Cremers CWRJ, Hombergen GCJH, Scaff JJ, Huygen PLM, Volkers WS, Pinckers AJLG. X-linked progressive mixed deafness with perilymphatic gusher during stapes surgery. Preoperatively identifiable specific features. *Arch Otolaryngol* 1985;**11:**249–54

63 Cremers CWRJ. Audiological features of the X-linked progressive mixed deafness syndrome with perilymphatic gusher during stapes surgery. *Am J Otol* 1985;**6:**243–6

64 Brunner HG, van Bennekom CA, Lambermon EMM, Oci TL, Cremers CWRJ, Wieringa BW, *et al.* The gene for X-linked progressive mixed deafness with perilymphatic gusher during stapes surgery (DFN_3) is linked to PGK. *Hum Genet* 1988;**80:**337–40

65 Huber I, Bitner-Glindzicz M, de Kok YJM, Maarel van der SM, Ishikawa-Brush Y, Monaco AP, *et al.* X-linked mixed deafness (DFN3): cloning and characterization of the critical region allows the identification of novel microdeletions. *Hum Mol Genet* 1994;**3:**1151–4

66 Huber I. *Cloning of a gene underlying X-linked Mixed Deafness.* Academisch Proefschrift Katholieke Universiteit, 1995

67 Kok de YJM, Maarel van der SM, Bitter-Glindzicz M, Huber I, Monaco AP, Malcolm S, *et al.* Associations between X-linked deafness and mutations in the Pou domain Gene Pou 3F4. *Science* 1995;**267:**685–8

68 van der Maarel SM. *Cloning of a Gene for X-linked Deafness (DFN3). Cloning of a Candidate Gene for X-linked Mental Retardation.* Academisch Proefschift Katholieke Univresiteit Nijmegen, 1997

69 Wilde De Pa. *Verwantschap en Erfelijkheid bij Doofstomheid en Retinitis Pigmentosa.* Academisch Proefschrift Universiteit van Amsterdam, Uitg F van Rossum, 1919

70 Adler H. Beobachtungen und Bermerkungen über das Sehen der Taubstummen. *Klin Mbl Augenheilkd* 1876;**14:**64–70

71 Lee CG. Notes on the ophthalmic conditions of deafmutes. *Br Med J* 1883;**2:**1184

72 Usher CH. The Bowman lecture: on a few hereditary eye affections. *Trans Ophthalmol Soc UK* 1935;**55:**164–70

73 Aarem A van, Huygen PLM, Pinckers AJLG. Stable and progressive hearing loss in type 2A Usher syndrome. *Ann Otol Rhinol Laryngol* 1996;**105:**962–7

74 Wagenaar M. *Usher syndrome. Genotype and Phenotype Correlations.* Academisch Proefschrift Katholieke Universiteit Nijmegen (in press)

75 Wagenaar M, van Aarem A, Huygen PLM. Kimberling WJ, Cremers CWRJ. Hearing impairment related to age in Usher syndrome type IB and IIA. *Arch Otolaryngol* 1999;**125:**441–5

76 Bell J. Retinitis pigmentosa and allied diseases. In: Pearson K, ed. *The Treasury of Human Inheritance.* London: Cambridge University Press 1922;**2:**1–29

77 Kimberling WJ, Weston MD, Möller C, *et al.* Localization of Usher syndrome type IIA to chromosome 1q. *Genomics* 1990;**7:**245–9

78 Kaplan J, Gerber S, Bonnaeu D, *et al.* A gene for Usher syndrome type I (USA IA) maps to chromosome 14q. *Genomics* 1992;**14:**979–87

79 Kimberling WJ, Möller C, Davenport SLH, *et al.* Linkage of Usher syndrome type I gene (USHIB) to the long arm of chromosome 11. *Genomics* 1992;**14:**988–94

80 Smith RJH, Lee EC, Kimberling WJ, *et al.* Localization of two genes for Usher syndrome type I to chromosome 11. *Genomics* 1992;**14:**995–1002

81 Wayne S, Der Kaloustian VM, Schloss M, *et al.* Localization of the Usher ID gene (USHD) to chromosome 10. *Hum Mol Genet* 1996;**10:**1689–92

82 Chaib H, Kaplan J, Gerber S, *et al.* A newly identified locus for Usher syndrome type I, USHIE, maps to chromosome 21q21. *Hum Mol Genet* 1997;**6:**27–31

83 Wayne S, Lowry RB, McLeod DR, Knaus R, Farr C, Smith RJH. Localization of the Usher syndrome type IF (USHIF) to chromosome 10. *Am J Hum Genet* 1997;**4**(suppl)

84 Weil D, Blanchard S, Kaplan J, *et al.* Defective myosin VIIA responsible for Usher syndrome type IB. *Nature* 1995;**374:**60–1

85 Eudy JD, Weston MD, Yao SF, *et al.* Mutation of a gene encoding a protein with extracellular matrix motifs in Usher syndrome type IIa. *Science* 1998;**280:**1753–6

86 Weston MD, Kelley PM. Overneck LD, *et al.* Myosin VIIA mutation screening in 189 Usher syndrome IB patients. *Am J Hum Genet* 1996;**59:**1074–83

87 Pendred V. Deaf mutism and goitre. *Lancet* 1896;**11:**532

88 Brain WR. Hereditary in simple goitre. *Q J Medi* 1927;**20:**303–19

89 Deraemaeker R. Congenital deafness and goiter. *Am J Hum Genet* 1956;**8:**253–6

90 Morgans ME, Trotter WR. Association of congenital deafness with goitre. The nature of the thyroid defect. *Lancet* 1958;**1:**607–9

91 Fraser GR. Deafness with goiter (Pendred's syndrome). In *The Causes of Profound Deafness in Childhood.* Baltimore: John Hopkins University Press, 1976:11–35

92 Cremers CWRJ. Het syndroom van Pendred. Een autosomal recessief syndroom met doofheid en een synthesestoornis in de schildklier. *Tijdschr Kingergeneeskd* 1976;**44:**89–9

93 Cremers CWRJ. Het syndroom van Pendred. *Ned Tijdschr Geneeskd* 1977;**121:**1202–5

94 Coucke P, Camp van, Demirhan O, *et al.* The gene for Pendred syndrome is located between D7S501 and D7S692 in a 1.7 cM region on chromosome 7q. *Genomics* 1997;**40:**48–54

95 Van Hauwe P, Everett LA, Coucke P, *et al.* Two frequent missense mutations in Pendred syndrome. *Hum Mol Genet* 1988;**7:**1099–104

96 Sheffield VC, Kraiem Z, Beck JC, *et al.* Pendred syndrome maps to chromosome 7q21 and is caused by an intrinsic defect in thyroid iodine organification. *Nature Genet* 1996;**124:**424–6

97 Coyle B, Coffey R, Armour JA, *et al.* Pendred syndrome (goitre and sensorineural hearing loss) maps to chromosome 7 in the region containing the nonsyndromic deafness gene DFNB4. *Nature Genet* 1996;**124:**421–3

98 Gausden E, Goyle B, Armour JAL, *et al.* Pendred syndrome: evidence for genetic homogeneity and further refinement of linkage. *J Med Genet* 1997;**34:**126–9

99 Everett LA, Glaser B, Beck JC, *et al.* Pendred syndrome is is caused by mutations in a putative sulphate transporter gene (PDS). *Nature Genet* 1997;**17:**411–22

100 Cremers CWRJ, Bolder C, Admiraal RJC, *et al.* Progressive senso loss and a widened vestibular aqueduct in Pendred syndrome. *Arch Otolaryngol* 1998;**124:**501–5

101 Cremers CWRJ, Admiraal RJC, Huygen PLM, *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* 1988;**45:**113–23

102 Phelps PD, Goffey RA. Trembath RS, *et al.* Radiological malformations of the ear in Pendred syndrome. *Clin Radiol* 1998;**53:**268–73

103 Van Camp G, Willems PJ, Smith RJH. Nonsyndromic hearing impairment: unparalleled heterogeneity. *J Hum Genet* 1997;**60:**758–64

104 Martini A, Read A, Stephens D, eds. *Genetics and Hearing Impairment.* London: Whurr, 1996

105 Martini A, Milani M, Rosignolo M, Mazzoli M, Prosser S. Audiometric patterns of genetic non-syndromal sensorineural hearing loss. *Audiology* 1997;**36:**228–36

106 Cremers PFM. Genetic causes of hearing loss. *Opin Neurobiol* 1998 (in press)

107 Ruben RJ, Van de Water RR, Steel KP, eds. *Genetics of Hearing Impairment. Ann NY Acad Sci* 1991;**630:**1–331

108 Zbar RIS, Ramesh A, Srisailapathy CRS, Fukushima K, Wayne S, Smith RJH. Passage to India: the search for genes causing autosomal recessive nonsyndromal hearing loss. *Otolaryngol Head Neck Surg* 1998;**118:**333–7

109 Van Camp G, Smith RJH. Hereditary hearing loss homepage. (http://dnalab-www.uia.ac.be/dnlab/hhh.html)

110 Pennisi E. The architecture of hearing. The cloning of a string of genes that, when mutated, cause deafness without any other symptoms is opening a view of the inner workings of the auditory system and how it develops. *Science* 1997;**278:**1223–4.

111 Cremers CWRJ, Stinckens Chr. Connexin-26 en niet syndromaal autosomaal recessief overervende vroegkinderlijke doofheid. *Ned Tijdschr Geneeskd* 1998;**142:**1625–6

112 Zelante L, Gasparini P, Estivill X, *et al.* Connexin-26 mutations associated with the most common form of nonsyndromic neurosensory autosomal recessive deafness (DFNB1) in Mediterraneans. *Hum Mol Genet* 1997;**6:**1605–9

113 Bussoli TJ, Steel KP. The molecular genetics of inherited deafness–current and future applications. *J Laryngol Otol* 1998;**112:**523–30

114 Petit C. Genes responsible for human hereditary deafness: symphony of a thousand. *Nature Genet* 1996;**14:**385–91

115 Lewis Th. *Clinical Science. Illustrated by Personal Experiences.* London: University College Hospital Department, 1934

116 Andrews, McMeel. *Words of Wisdom.* Kansas City: Aeriel Books, 1992

117 Leon PE, Raventos H, Lynch E, Morrow J, King MC. The gene for an inherited form of deafness maps to chromosome 5q31. *Proc Natl Acad Sci USA* 1992;**89:**5181–4
118 Lynch ED, Lee MK, Morrow JE, Welsh PL, Leon PE, King MC Nonsyndromic deafness DFNA1 accoaited with mutation of a human homolog of the *Drosophila* gene diaphanous. *Science* 1997;**278:**1315–8
119 Coucke P, Van Camp G, Djoyodiharjo B, *et al.* Linkage of autosomal dominant hearing loss to the short arm of chromosome 1 in two families. *N Engl J Med* 1994;**331:**425–31
120 Xia J, Liu C, Tang B, *et al.* Mutations in the gene encording gap junction protein β-3 associated with autosomal dominant hearing impairment. *Nature Genet* 1998;**20:**370–3
121 Kubisch C, Schroeder B, Friedrich T, *et al.* KCNQ4, a novel potassium chanel expressed in sensory outer hair cells, is mutated in dominant deafness. *Cell* 1999;**96:**437–46
122 Chaib H, Lina-Granade G, Guilford P, *et al.* A gene is responsible for a dominant form of neurosensory non-syndromic deafness maps to the NSRD1 recessive deafness gene interval. *Hum Mol Genet* 1994;**3:**2219–22
123 Denoyelle F, Lina-Granade G, Plauchu H, *et al.* Connexin 26 gene linked to a dominant deafness (Letter). *Nature* 1998;**393:**319–20
124 Chen AH, Ni L, Fukushima K, Marietta J, *et al.* Linkage of a gene for dominant non-syndromic deafness to chromosome 19. *Hum Mol Genet* 1995;**4:**1073–6
125 Van Camp G,Coucke P, Balemans W, *et al.* Localization of a gene for non-syndromic loss (DFNA5) to chromosome 7p15. *Hum Mol Genet* 1995;**4:**2159–63
126 Van Laer L, Huizing EH, Verstreken M, *et al.* Nonsyndromic hearing impairment is associated with a mutation in DNA5. *Nature Genet* 1998;**20:**194–7
127 Lesperance MM, Hall JW, Bess FH, *et al.* A gene for autosomal dominant nonsyndromic hereditary hearing impairment maps to 4p16.3. *Hum Mol Genet* 1995;**4:**1967–72
128 Fagerheim T, Nilsson O, Raeymaekers P, *et al.* Identification of new locus for autosomal dominant non-syndromic hearing impairment (DFNA&) in a large Norwegian family. *Hum Mol Genet* 1996;**5:**1187–91
129 Kirschhofer, *et al.* Molecular Biology of Hearing and Deafness Meting in Bethesda, 6–8 October 1995. Abstracts pp 100
130 Verhoeven K, Van Camp G, Govaerts PJ, *et al.* A gene for autosomal dominant nonsyndromic hearing loss (DFNA12) maps to chromosome 11q22-24. *Am J Hum Genet* 1997;**60:**1168–73
131 Verhoeven K, Van Laer L, Kirschhofer K, *et al.* Mutations in the human alpha-tectorin gene cause autosomal dominant non-syndromic hearing impairment. *Nature Genet* 1998;**19:**60–2
132 Manolis EN, Yandavi N, Nadal JB, *et al.* A gene for non-syndromic autosomal dominant progressive postlingual sensorineural hearing loss maps to chromosome 14q12-13. *Hum Mol Genet* 1996;**5:**1047–50
133 Robertson NG, Lu L, Heller S, *et al.* Mutations in a novel cochlear gene cause DFNA9, a human nonsyndromic deafness with vestibular dysfunction. *Nature Genet* 1998;**20:**299–303
134 O'Neill ME, Marietta J, Nishimura D, *et al.* A genautosomal dominant late-onset progressive non-syndromic hearing loss, DFNA10, maps to chromosome 6. *Hum Mol Genet* 1996;**5:**853–6
135 Tamagawa Y, Kitamura K, Ishida, T, *et al.* A gene for a dominant form of non-syndromic sensorineural deafness (DFNA11) maps within the region containing the DFNB2 recessive deafness gene. *Hum Mol Genet* 1996;**5:**849–52
136 Liu XZ, Walsh J, Tamagawa Y, *et al.* Autosomal dominant non-syndromic deafness caused by a mutation in the myosin VIIA gene. *Nature Genet* 1997;**17:**268–9
137 Brown MR, Tomek MS, van Laer L, *et al.* A novel locus for autosomal dominant nonsyndromic hearing loss, DNFA13, maps to chromosome 6p. *Am J Hum Genet* 1997;**61:**924–7
138 McGuirt WT, Prasad SD, Griffth AJ, *et al.* Mutation in *COL11A2* causes non-syndromic hearing impairment (DFNA13). *Nature Genet* 1999;**23:**413–9
139 Van Camp G, Kunst H, Flothman K, *et al.* A gene for autosomal dominant hearing impairment (DFNA14) maps to a region on chromosome 4p16.3 that is non-overlapping with the DFNA6 locus. *J Med Genet* (in press)
140 Vahava O, Morell R, Lynch ED, *et al.* Mutation in transmission factor POU4F3 associated with inherited progressive hearing loss in humans. *Science* 1998;**279:**1950–5
141 Fukushima K, Kasai N, Ueki Y, *et al.* A gene for fluctuating, autosomal dominant non-syndromic hearing loss, *DFNA16,* maps to chromosome 2q24. *Am J Hum Genet* (in press)
142 Lalwani AK, Luxford WM, Mhatre AN, Attaie M, Wilcox ER, Castelein CM. A new locus for nonsyndromic hereditary hearing impairment, DFNA17, maps to chromosome 22 and represents a gene for cochleosaccular degeneration. *Am J Hum Genet* 1999b;**64:**318–23
143 Boensch D, Scheer P, Storch P, Neumann C, Deufel T, Lamprecht-Dinnesen A. Mapping of a further type of autosomal dominant, non-syndromic hearing impairment (DFNA18) to chromosome 3q22. *Am J Hum Genet* 1998;**63(Suppl):**A282
144 Green G, Whitehead S, Van Camp G, Smith RJH. Identification of a new locus – DFNA19 – for dominant hearing impairment (abstract). The Molecular Biology of Hearing and Deafness Meeting, Bethesda, Maryland, 8–11 October 1998
145 Kunst H, Marres H, Huygen P, *et al.* Non-syndromic autosomal dominant progressive mid-frequency sensorineural hearing impairment with childhood to late adolescence onset linked to DFNA21. *Clin Otolaryngol* (in press)
146 Guilford P, Ben-Arab S, Blanchard S, *et al.* A non-syndromic form of neurosensory, recessive deafness maps to the pericentrometri region of chromosome 13q *Nature Genet* 1994;**6:**24–8
147 Kelsell DP, Dunlop J, Stevens HP, *et al.* Connexin 26 mutations in hereditary non-syndromic sensorineural deafness. *Nature* 1997;**387:**80–3
148 Guilford P, Ayadi H, Blanchard S, *et al.* A human gene responsible for neurosensory, non-syndromic recessive deafness is a candidate homologue of the mouse sh-1 gene. *Hum Mol Genet* 1994;**3:**989–93
149 Liu XZ, Walsh J, Mburu P, *et al.* Mutations in the myosin VIIA gene cause non-syndromic recessive deafness. *Nature Genet* 1997;**16:**188–90
150 Weil D, Kussel P, Blanchard S, *et al.* The autosomal recessive isolated deafness, DFNB2 and the Usher IB syndrome are allelic defects of the myosin-VIIA gene. *Nature Genet* 1997;**16:**191–3
151 Friedman TB, Liang Y, Weber JL, *et al.* A gene for congenital, recessive deafness DFNB3 maps to the pericentromeric region of chromosome 17. *Nature Genet* 1995;**9:**86–91
152 Wang A, Lyang Y, Fridell RA, *et al.* Association of unconventional myosin MYO15 mutations with human nonsyndromic deafness DFNB3. *Science* 1998;**280:**1447–51
153 Baldwin CT, Weiss S, Farrer LA, *et al.* Linkage of congenital, recessive deafness (DFNB4) to chromosome 7q31 and evidence for genetic heterogeneity in the Middle eastern Druze population. *Hum Mol Genet* 1995;**4:**1637–42
154 Li XC, Everett LA, Lalwani AK, *et al.* A mutation in PDS causes non-syndromic recessive deafness. *Nature Genet* 1998;**18:**215–7
155 Fukushima K, Ramesh A, Srisailapathy CR, *et al.* Consanguineous nuclear families used to identify a new locus for recessive non-syndromic hearing loss on 14q. *Hum Mol Genet* 1995;**4:**1643–8
156 Fukushima K, Ramesh A, Srisailapathy CR, *et al.* An autosomal recessive nonsyndromic form of sensorineural hearing loss maps to 3p-DFNB6. *Genome Res* 1995;**5:**305–8

157 Jain PK, Fukushima K, Deskmukh D, *et al.* A human recessive neurosensory nonsyndromic hearing impairment locus is potential homologue of murine deafness (dn) locus. *Hum Mol Genet* 1995;**4:**2391–4

158 Veske A, Oehlmann R, Younus F, *et al.* Autosomal recessive nonsyndromic deafness locus (DFNB8) maps on chromosome 21q22 in a large consanguineous kindred from Pakistan. *Hum Mol Genet* 1996;**5:**165–8

159 Chaib H, Place C, Salem N, *et al.* A gene responsible for a sensorineural nonsyndromic recessive deafness maps to chromosome 2p22-23. *Hum Mol Genet* 1996;**5:**155–8

160 Yasunaga S, Grati M, Cohen-Salmon M, *et al.* A mutation in OTOF, encoding otoferlin, a FER-1-like protein, causes DFNB9, a nonsyndromic form of deafness. *Nature Genet* 1999;**21:**363–9

161 Bonne-Tamir B, De Stefano AL, Briggs CE, *et al.* Linkage of congenital recessive deafness (gene DFNB10) to chromosome 21q22.3. *Am J Hum Genet* 1996;**58:**1254–9

162 Scott DA, Carmi R, Elbedour K, Yosefsberg S, Stone EM, Sheffield VC. An autosomal recessive nonsyndromic hearing loss locus identified by DNA pooling using two inbred Bedouin kindreds. *Am J Hum Genet* 1996;**59:**385–91

163 Chaib H, Place C, Salem N, *et al.* Mapping of DFB12, a gene for a non-syndromal autosomal recessive deafness, to chromosome 10q21-22. *Hum Mol Genet* 1996;**5:**1061–4

164 Mustapha M, Chardenoux S, Nieder A, *et al.* A sensorineural progressive autosomal recessive form of isolated deafness, DFNB13, maps to chromosome 7q34-q36. *Eur J Hum Genet* 1998;**6:**245–50

165 Mustapha M, Salem N, Weil D, El-Zir E, Loiselet J, Petit C. Identification of a locus on chromosome 7q31, DFNB14, responsible for prelingual sensorineural nonsyndromic deafness. *Eur J Hum Genet* 1998;**6:**548–51

166 Chen A, Wayne S, Bell A, *et al.* New gene for autosomal recessive on-syndromic hearing loss maps to either chromosome 3q or 19p. *Am J Med Genet* 1997;**71:**467–71

167 Campbell DA, McHale DP, Brown KA, *et al.* A new locus for non-syndromal, autosomal recessive, sensorineural hearing loss (DFNB16) maps to human chromosome 15q21-q22. *J Med Genet* 1997;**34:**1015–7

168 Greinwald JH, Wayne S, Chen AH, *et al.* Localization of a novel gene for nonsyndromic hearing loss (DFNB17) to chromosome region 7q31. *Am J Med Genet* 1998;**78:**107–13

169 Jain PK, Lalwani AK, Li XC, *et al.* A gene for recessive nonsyndromic sensorineural deafness (DFNB18) maps to the chromosomal region 11p14-p15.1 containing the Usher syndrome type IC gene. *Genomics* 1998;**50:**290–2

170 Moynihan L, Houseman M, Newton V, Mueller R, Lench N. DFNB20: a novel locus for autosomal recessive, nonsyndromal sensorineural hearing loss maps to chromosome 11q-25-qter. *Eur J Hum Genet* 1999;**7:**243–6

171 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

172 Tranebjaerg L, Schwartz C, Eriksen H, *et al.* A new X linked recessive deafness syndrome with blindness, dystonia, fractures, and mental deficiency is linked to Xq22. *J Med Genet* 1995;**32:**257–63

173 Tyson J, Bellman S, Newton V, *et al.* Mapping of DFN2 to Xq22. *Hum Mol Genet* 1996;**5:**2055–60

174 De Kok YJ, Geurds MP, Sistermans EA, Usmany M, Vlak JM, Wieringa B. Production of native creatine Kinase B in insect cells using a baculovirus expression vector. *Mol Cell Biochem* 1995;**143:**59–65

175 Lalwani AK, Brister JR, Fex J, *et al.* A new nonsyndromic X-linked sensorineural hearing impairment linked to Xp21,2.*Am J Hum Genet* 1994;**55:**685–94

176 De Castillo I, Villamar M, Sarduy M, *et al.* A novel locus for nonsyndromic sensorineural deafness (DFN6) maps to chromosome Xp22. *Hum Mol Genet* 1976;**5:**1383–7

Address for correspondence:
Prof dr C. W. R. J. Cremers,
Keel-, Neur, en Oorheelkunde,
Radboud west,
Philips van leydenlaan 15,
Postbus 9101,
6500 HN Nijmegen,
The Netherlands.

https://doi.org/10.1258/0022215001903816 Published online by Cambridge University Press