CURRENT TOPIC

Inherited deafness in childhood—the genetic revolution unmasks the clinical challenge

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Approximately one child per 1000 is diagnosed with severe, profound, or early onset hearing impairment, of whom approximately 50% are thought to have a genetic cause.[1 2] Associated clinical findings, if present and recognised neonatally, often facilitate the identification of a syndrome and the prediction that a hearing problem is likely to be part of the clinical profile. While the presence of such findings affords the recognition of an underlying syndromic diagnosis in up to 30% of hearing impaired individuals, in most children with hearing impairment there are no other clinical findings—that is, the hearing loss is non-syndromic. As most such cases are transmitted in autosomal recessive manner,[3] the finding of hearing loss in the affected child is unexpected, often delayed and, in addition to the obvious social and educational implications, frequently accompanied by parental anxiety for subsequent born siblings or ongoing pregnancies. Faced with such clinical tensions, the paediatrician may rightly wonder whether the recent molecular advances in the genetics of deafness might not benefit hearing impaired patients and their families.

Progress in gene mapping and identification

It is scarcely credible now to recall that less than 10 years ago genetic loci for different forms of hearing loss were just starting to be mapped—initially concentrating on well defined syndromic forms of deafness.[4] Though apt to rapid change, reflecting new advances, the situation in September 1999 identified 31 loci for autosomal dominant non-syndromic forms of hearing loss, designated DFNA 1–31, 28 loci for autosomal recessive forms, designated DFNB 1–28, and six loci for X linked forms, designated DFN 1–6.[5] Since 1997 mutations have been established in 10 genes for autosomal dominant and six genes for autosomal recessive hearing loss with the result that important scientific insights into the biological basis of hearing and deafness in different clinical situations have been recorded. Moreover, identifying the molecular cause of hearing impairment has become a realistic possibility for some patients.

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The genes which cause hearing loss

A wide variety of genetic defects have been established. Some, such as DIAPH1,[6] POU4F3,[7] and the un-named gene causing DFNA5,[8] have, to date, been described in single families with autosomal dominant hearing loss. Thus, it remains unclear whether these families represent unique experiments of nature or whether genetic abnormalities at these loci are epidemiologically significant in the overall hearing impaired population. Other findings have quickly proven to be applicable to a wider range of patients and have signposted fruitful avenues of further research for scientists as well as signalling some important clinical and genetic lessons. Foremost among these genes are atypical myosins, connexins, and ion channelopathies.

Atypical myosin genes

The recognition in 1995 that a type VII myosin gene mutation caused the mouse deafness mutant, shaker-1,[9] put in motion a train of research milestones which have important clinical ramifications. The human homologoue, *MYOVIIA*, maps to human chromosome 11q, to which region three forms of inherited hearing loss were already known to localise. One of these was a form of Usher syndrome type I, an autosomal recessive disorder characterised by profound congenital hearing impairment, associated vestibular disturbance, and progressive retinal degenerative disease commencing towards the end of the first decade of life. It is estimated that about 75% of Usher syndrome type I cases map to this region, and Weil *et al* published evidence that mutation in the human myosin VIIA gene causes the deafness/blindness phenotype in these patients, most likely as a result of the absence of a functional protein.[10] Unsurprisingly, in view of the human phenotype, the shaker-1 mouse mutant has deafness and vestibular problems; however, the main difference is the absence of blindness in the murine model. Accordingly, researchers suspected that there might be other families with autosomal recessive hearing loss in the absence of associated retinal findings whose disease might be a result of mutation at this same locus. These suspicions were well founded, with mutations being identified as the basis of non-syndromic autosomal recessive hearing loss in Chinese[11] and Tunisian[12]

families. Finally, mutation at this same locus was established as the cause of the deafness in a Japanese family with autosomal dominant progressive loss of hearing which was also known to map to this same region of chromosome 11.[13] The mutation in this situation is associated with a less severe phenotype and involves a different part of the protein to those mutations observed in autosomal recessive syndromic and non-syndromic disease.

More recently another myosin gene, *MYO15*, was found to be mutant in the shaker-2 mouse model. The homologous human gene on chromosome 17 mapped to a region in which a non-syndromic form of deafness had been localised by linkage studies; mutation at this locus was subsequently established as the cause of the hearing disturbance in three families.[14]

Connexins

The connexins are a family of genes which have been highly conserved throughout evolution and which appear to play a crucial role in forming gap junctions to facilitate intercellular communication. Mutations at three distinct connexin loci have now been associated with hearing loss resulting in autosomal dominant, recessive, and X linked patterns of disease segregation.[15–18] Linkage data in European populations suggest that 70–80% of families with non-syndromic autosomal recessive hearing loss is because of a single locus on chromosome 13q,[19] mutation in these families involving the connexin 26 gene. These data suggest that, notwithstanding the number of other loci for autosomal recessive hearing impairment, connexin 26 may be the single most prevalent locus for recessively inherited deafness. Further epidemiological support for a high prevalence of deafness owing to connexin 26 mutation is offered by the finding that 37% of individuals with sporadically occurring deafness have identifiable mutations at this locus.[20] These data, based on European populations, are not as striking in the British population in whom preliminary analyses suggest that 10% of sporadically occurring deafness may be attributable to mutation at the connexin 26 locus.[21] Although several different mutations of connexin 26 have been described in deaf patients, one particular mutation, 35delG, is especially common in white populations,[22] while different distributions of mutant allele frequency have been recorded in Ashkenazi Jewish[23] and in Japanese[24] deaf patients. Apart from the importance conferred on this locus by the relatively high prevalence of mutation in deaf individuals, there are preliminary data to suggest that mutation carriers may have some subclinical auditory anomalies, raising the possibility that some cases of age related progressive hearing loss might be a result of the carrier state.[23]

The connexin 26 gene is easy to screen for mutation, in particular for the recurrent 35delG mutation which has been documented in large scale studies. Some observers have drawn attention to the uncertainties which surround the current understanding of connexin 26—for instance hearing impairment ranging from moderate to profound has been recorded in patients homozygous for the 35delG mutation[22]—urging caution in the application and interpretation of data and their implementation in the clinical setting. However, it deserves to be said that similar situations are by no means unusual in clinical genetics and the unavailability of an immediate "counsel of perfection" does not mean that patients and families cannot benefit from testing of the connexin 26 locus at this time. Indeed it is fair to say that many families have already benefited from the identification of a connexin 26 mutation as the basis of deafness in their child and the inherent recognition of the autosomal recessive nature of that disorder.

Ion channelopathies and deafness

While the recent identification of mutation in an H^+-ATPase gene as the basis of disease in patients with renal tubular acidosis and sensorineural deafness is likely to apply to only a small number of deaf patients,[25] it represents another landmark associating deafness with disordered ion transfer and follows fast on the identification of mutations predicted to alter chloride and iodide transport as the basis of Pendred syndrome.[26] While the traditional textbook profile of Pendred syndrome patients as the combination of deafness and goitre has had to be reassessed in light of the fact that only 33% of cases develop goitre by the age of 10 years,[27] the recognition that most affected individuals have dilatation of the vestibular aqueduct on neuroradiological investigation[28] has offered clinicians a way of identifying these patients at an early age. Nonetheless, the absence of an agreed approach to investigation of the deaf patient and uniform access to specialised neuroradiology, means that many cases currently go unrecognised through childhood.[29] Neither is the molecular approach to diagnosis a panacea to the problem of diagnosis of the condition. Apart from the large size of the gene, with consequent time and technical challenges posed by mutation detection, over 35 mutations, distributed throughout the gene, have been identified to date; many clinically certain cases are known for whom one or both mutations have not been identifiable using current technical approaches. However, the example of Pendred syndrome represents a valuable experience which confirms that patient recognition and case identification for molecular diagnostics are best achieved when careful clinical assessment and laboratory analysis proceed in parallel with one another, the clinical findings enabling the clinician to direct the energies of laboratory staff most appropriately.

The clinical challenge

It would appear that the proliferation of new scientific data with respect to the genetic aetiology of deafness has the potential to alter current clinical practices and to modify approaches to investigation, management and, possibly even, treatment. However, in order to achieve this ideal much more is required. Even

if unlimited laboratory resources were available, the current understanding of the phenotypes of the different forms of genetic deafness is insufficient to guide laboratory investigators towards the "most likely locus" in an individual case. Moreover, an observed molecular change at that locus does not necessarily mean that the basis of the hearing impairment has been indisputably established. For instance, as confirmed by the experience of several groups working with connexin 26, there are many patients for whom only one mutation can be established. Do these patients have hearing impairment consequent on connexin 26 mutation? In deaf sibships it may be possible to establish the statistical likelihood that the connexin 26 gene is the mutant locus and that the second mutation is simply refractory to current approaches to mutation analysis. However, in the singleton case—the most common situation clinically—the possibility that the patient is a coincidental carrier of a connexin 26 mutation but is deaf because of mutation at some other locus cannot be discarded. Indeed there may even prove to be rare examples where the carrier state of an autosomal recessive form of deafness might interact with the carrier state of another form of autosomal recessive deafness to give a combined affected phenotype, as has been observed in other forms of genetic disease, notably retinitis pigmentosa.[30]

As is suggested by the experience of Pendred syndrome, the best approach is an integrated one, in which the molecular data are considered in the context of all other data—clinical, family, audiometric, vestibular, and neuroradiological. In order to create that context for the interpretation of molecular data of deafness loci, much more is required by way of information as to the relative frequencies of the different mutant deafness genes in our hearing impaired population. Studies which aim to achieve this goal also offer investigators an opportunity to evaluate the different modalities of audiometric investigation currently available to see whether any clues as to audiological characteristics of specific locus identified deafness emerge. Such data will also help establish or refute the role of the carrier state in progressive hearing loss.[23] The role of neuroradiology of the inner ear as an adjunct to audiometric investigation will also need evaluation, not least for the service provision implications which detailed neuroradiological investigation of congenitally deaf patients would involve. Studies addressing these issues are required to inform the sensible introduction of new genetic information into clinical management of deaf patients over the next decade and will assist clinicians in identifying those clinical, audiometric, and neuroradiological characteristics which appertain to each form of inherited non-syndromic deafness. These detailed phenotypic evaluations will govern future generations of clinical geneticists, audiological physicians, and paediatricians in guiding laboratory colleagues as to which of the multitude of genes for deafness is most likely to be worth evaluating by mutation analysis in an individual case.

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