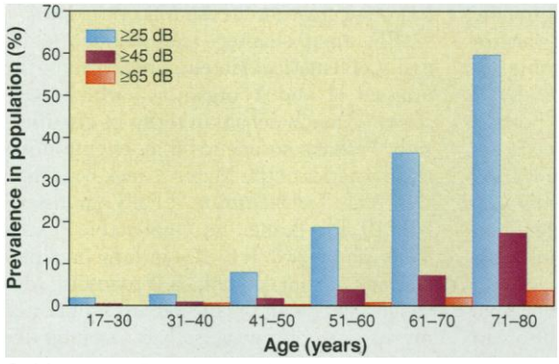
RESEARCH: HUMAN GENETICS

# Progress in Progressive Hearing Loss

Karen P. Steel

Progressive hearing loss impairs a staggeringly large proportion of our population (see chart at right) (*1*). Sixteen percent of adults and more than one-third of those over 60 years old have a hearing loss of 25 decibels or more and so might benefit from wearing a hearing aid. Learning sign language is not an option for these people, and social withdrawal is their all-too-frequent response. Yet we know almost nothing about the reasons for this progressive loss, other than that it is likely highly heterogeneous and is a result of both genetic and environmental influences. Any clue to its genetic basis is useful, so the report on page 1950 of this issue that a mutation in the transcription factor *POU4F3* causes progressive hearing impairment in a large Israeli family is welcome news (*2*).




**Golden ears.** Prevalence of hearing impairment in better ear. [Data from (*1*)]

Sensory hair cells in the inner ear are exquisitely sensitive mechanoreceptors that sport a precise array of specialized microvilli, the stereocilia, at their upper surface. These hair cells can detect sound vibrations, which move the stereocilia as little as a single angstrom. Fine extracellular "tip links" join each stereocilium to its neighbor, and it is likely that these tip links directly open a transducer channel when stretched by the deflection of the stereocilia array (see photo at lower right) (*3*, *4*). This sensitive arrangement at the top of each hair cell requires a precise molecular architecture that needs constant maintenance, and so it would not be surprising for a transcription factor to participate in the maintenance schedule. *Pou4f3* (otherwise known as *Brn3.1* or *Brn3c*) is expressed in adult hair cells of mice, supporting the suggestion that it may be required for continued maintenance (*5*). Both repair of damage and preventive maintenance must be especially important to mature mammalian cochlear hair cells, because they have never been shown to regenerate: We are born with all the cochlear hair cells we are ever to possess.

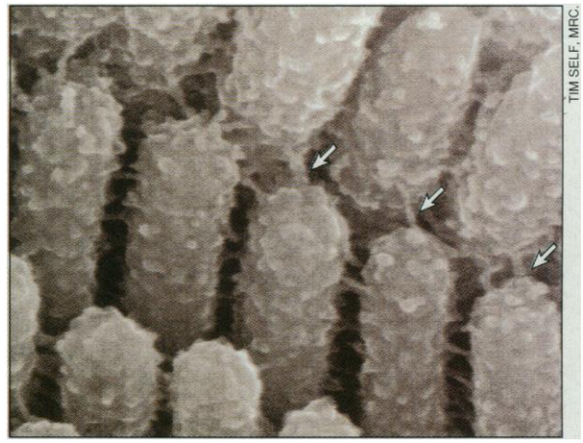
The authors describe a large family with autosomal dominant hearing loss that begins in young adulthood (*2*). Linkage analysis defined a 25-centimorgan region of chromosome 5q as the locus of the disease, and comparison with the mouse genome suggested that *POU4F3* might lie in this region. Mice with a targeted disruption of this gene were already known to show early hair cell loss. Indeed, an 8–base pair segment was found to be deleted from the *POU4F3* gene in affected individuals in this family.

POU-domain transcription factors contain a POU homeodomain and a POU-specific domain, both of which participate in DNA binding. In affected individuals, the deletion in the gene would truncate any protein produced, removing the vital third helix of the homeodomain required for DNA sequence recognition. Within the predicted deleted region is an isoleucine residue that confers repressor properties on another member of the POU family, *POU4F2* (*6*). Thus, the deletion would clearly have a serious effect on the properties of any protein product, but whether the observed hearing loss is attributable to haploinsufficiency or to a dominant negative effect remains to be demonstrated.

Why does it take 18 years or more for the first signs of hearing loss to appear? There may be complex interactions between environmental insults and the ability of the hair cell to repair itself, and the delay in onset may reflect the time needed to accumulate sufficient knocks and scrapes to be noticed as a functional impairment. Alternatively, there are many changes in cellular processes with age, and what may be an adequate degree of *POU4F3* activity for normal development and function of hair cells in a deletion-carrying youngster may prove limiting if other components of the maintenance process decline with age. For example, a generalized decline in mitochondrial efficiency might interact with reduced *POU4F3* activity. *POU4F3* itself might show declining expression with age, which would be exacerbated by haploinsufficiency in affected individuals, bringing forward the age of onset of hearing loss.

Mice carrying one copy of a deleted *Pou4f3* gene show no signs of hearing impairment compared with wild-type mice, even up to 24 months of age; this observation has been used to argue against haploinsufficiency as an explanation for the progressive hearing loss in the Israeli family (*2*). However, it may be that 24 months is simply too little time for any effect to be seen. A detailed study of the sensitivity of the heterozygous mutant mouse to noise or other damaging agents might help to elucidate differences in susceptibility that could be explained by haploinsufficiency. If there are interactions of *Pou4f3* function with other cellular repair processes that decline with age, as hypothesized above, these other processes may be revealed as modifier loci when the mouse knockout is placed on different genetic backgrounds. Both approaches could prove powerful in elaborating the mechanisms that damage and repair hair cells and may open up new possibilities for intervention to prevent hearing loss in humans.

What of the role of *Pou4f3* in hair cell development? Mice homozygous for a tar-




**The better to hear you with.** Photos of hair cells with their precise arrays of stereocilia bundles.

The author is at the Medical Research Council, Institute of Hearing Research, Nottingham NG7 2RD, UK. E-mail: karen@ihr.mrc.ac.uk

geted deletion of the gene show early loss of hair cells (*7*, *8*), but a careful electron microscopic investigation is still needed to establish how far these hair cells can proceed in their differentiation. At least one molecular marker specific for hair cells, myosin VIIA, is expressed in immature hair cells in the homozygous mutants, which suggests that some differentiation can occur in the absence of *Pou4f3* (*9*). *Pou4f3* seems to be required for the continued differentiation and survival of hair cells at early stages, as well as for the long-term maintenance and repair of hair cells in adults (as shown by the Israeli family).

The *POU4F3* transcription factor joins myosin VIIA and diaphanous as molecules that, when defective, can result in nonsyndromic progressive hearing loss. All have been reported in the past few months (*10*, *11*). Two mitochondrial mutations, in the 12*S* rRNA and $tRNA^{Ser(UCN)}$ genes, also predispose to age-related hearing loss (*12*, *13*). The A1555G mutation of the 12*S* rRNA gene may be particularly common as a cause of progressive hearing loss in some populations, even in the absence of exposure to aminoglycosides, a drug to which carriers of this same mutation are extremely sensitive (*14*). Many human syndromes show late-onset progressive hearing loss as one of the manifestations, and some of the genes responsible have been identified (*15*, *16*). Furthermore, many inbred mouse strains progressively lose cochlear function, and a start has been made in localizing the relevant genes (*17*). Mice lacking the nociceptin receptor show an increased susceptibility (compared with wild-type mice) to noise-induced hearing loss shortly after exposure to a loud sound, implicating this receptor in the cochlea's protective or recovery mechanisms (*18*). Finally, various growth factors and similar agents can protect laboratory mammals when administered together with an otherwise damaging drug or noise.

All these observations suggest that time is running out on progressive hearing loss, and that a molecular understanding and intervention strategy may be closer than we think.

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**TRANSCRIPTION**

# Promoter Logic

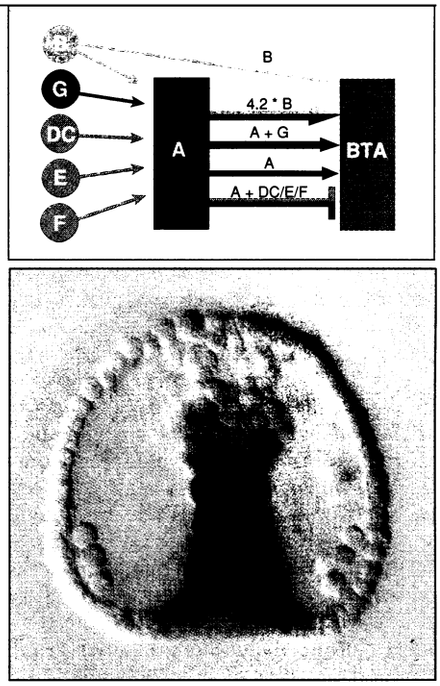

Gregory A. Wray


As animal embryos develop, genes are transcribed in strikingly complex patterns. Single genes can be expressed in several distinct domains, each of which is precisely delineated in space, time, and by level. Not surprisingly, a complicated regulatory apparatus is needed to exert this degree of control. The regulatory regions for animal genes (called promoters) typically span a few hundred to several thousand bases of DNA. Scattered through these promoters can be dozens of regulatory elements of various kinds that act as binding sites for distinct transcription factors (*1*). In some promoters, regulatory elements are grouped into "modules," each of which drives a discrete portion of the overall expression profile of the gene or prevents transcription at inappropriate times and places.

The presence of a particular regulatory element within a promoter reveals very little about how it influences the expression of a given gene. Instead, extensive experimental analyses are needed to decipher how the various regulatory elements within a promoter work together to modulate transcription. To do this, a normal or modified region of a promoter is fused to a reporter gene and introduced into an embryo, where it is exposed to the shifting array of transcription factors that modulate the expression of the endogenous gene. The resulting pattern of reporter gene expression can reveal, for instance, whether a particular regulatory element can activate or repress transcription at a specific time and place. Because of the complexity of most promoters, multiple experiments of this kind are needed to gain even a rough overview of how an expression pattern is generated.

In spite of considerable investigation of the function of animal promoters, general principles have remained frustratingly elusive. There is little logic apparent in the organization of regulatory elements, and even less in the way that they interact to regulate gene expression. The same regulatory element may activate transcription in one promoter and repress it in another, and the consequences of experimentally combining regulatory elements is rarely predictable. Furthermore, comparisons among the handful of well-characterized promoters have not yet revealed many functional similarities (*1*). Evidently, there are many ways to switch a gene on or off or to modulate levels of transcription. The impression one gets is that each promoter is a haphazard and unique assemblage of regulatory elements—able to get the job done, but not elegantly.

It therefore comes as a surprise to discover a promoter that operates in a logical




**A genetic computer.** The promoter of *Endo16* acts like a logic circuit (**top**) to determine expression of the gene (**bottom**).


The author is in the Department of Ecology and Evolution, State University of New York, Stony Brook, NY, 11794–5245, USA. E-mail: gwray@life.bio.sunysb.edu