Further mutations in brain 4 (P043F) clarify the phenotype in the X-linked deafness DFN3.
Figure 3. Inheritance of alleles for the marker DXS1002 in family 2. Both II₁ and II₂ have inherited the same maternal X chromosome. Affected boys (III₁ and III₂) have also inherited the grandmaternal X chromosome from I₁, as has IV₁. Thus the mutant SSC band observed in II₂, not present in her sister, demonstrates that this is a *de novo* change.

restricted manner. They have gained their name from sequence homology with three mammalian transcription factors Pit-1, Oct-1 and Oct-2, and a *C. elegans* developmental control gene unc-86. Developmental mutants in two of these genes indicate that they have a role in determining cell fate and phenotype; mutations in the gene Pit-1 have been shown to cause pituitary
transition at nucleotide 935 resulting in an alanine to valine substitution in a highly conserved residue of the homeodomain of the predicted protein. This mutation gives rise to a novel AccI restriction site (Fig. 2b), which also arises de novo in individual II2 and cosegregates with the deafness in this family.

The POU domain family of genes are transcription factors, expressed early in development in a temporally and tissue-specific manner, and are involved in the development of the nervous, respiratory, and urogenital systems. The POU domain is conserved across species and is present in every higher eukaryote and in many lower eukaryotes. The POU domain is composed of two subdomains, the POU-specific domain (POUS) and the POU-homeodomain (POUHD), which together form a DNA-binding domain.

In the case of the Snell mouse, a mutant strain with familial autosomal recessive deafness, the mutation in the POU domain gene causes the development of deafness. In humans, the POU domain gene is involved in the development of the inner ear, and mutations in this gene can cause congenital deafness. The POU domain gene is also involved in the development of the heart, and mutations in this gene can cause congenital heart defects.

In conclusion, the POU domain family of genes play a crucial role in the development of the nervous, respiratory, and urogenital systems, and mutations in this gene can cause congenital deafness in humans and other animals.
human and is only the second POU gene which has been confirmed to underlie a human disease, namely a form of X-linked deafness in which there is a developmental abnormality of the cochlea, seen on CT scan as a dislocated and absent bone between the lateral end of the internal auditory meatus and the basal turn of the cochlea together with a dilated internal auditory meatus. Other members of this gene family are numerous and are scattered throughout the genome (10).

POU3F4 is the first gene known to cause non-syndromic deafness in humans. Identification of mutations in the gene in a subset of patients has helped towards a reclassification of non-syndromic X-linked deafness. To date only patients with the bony abnormality of the cochlea have mutations in POU3F4 whereas families that map to Xq13-q21 but have normal cochlear morphology do not. Furthermore, this study confirms that families with mixed deafness and families with sensorineural deafness both have mutations in POU3F4 (7). Thus McKusick’s classification which distinguishes types of non-syndromic X-linked deafness on the audiometric findings alone would appear to need updating based on the results of this work (11). Consequently, DFN3 is not characterized by mixed conductive and sensorineural deafness associated with perilymphatic gusher at stapes surgery, but by profound sensorineural deafness with or without a conductive component associated with a unique developmental abnormality of the ear.

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REFERENCES