

insulin resistance is also supported by reported associations of the *INS* VNTR class III allele with a number of conditions in which insulin resistance is a major feature^{2,3}, such as polycystic ovary syndrome and central obesity. Thus, selective peripheral insulin resistance could explain the III/III genotype associations with both larger size at birth and insulin resistance or type 2 diabetes risk. Similarly, in conditions of fetal growth restraint, such as poor nutrition in pregnancy, peripheral insulin resistance may also represent a fetal metabolic adaptation that diverts nutrients to protect brain and skeletal growth *in utero*¹², but may lead to disease in adulthood.

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Deafness linked to DFNA2: one locus but how many genes?

Hereditary hearing impairment shows extreme genetic heterogeneity and more than 40 different loci have been reported. One of these, DFNA2, was localized to chromosome 1p34 on the basis of linkage analysis in two large families with autosomal dominant nonsyndromic hearing loss originating from Indonesia and the United States¹. Subsequently, hearing loss in three additional large families from Belgium and the Netherlands was found to map to the same region².

Two different genes are now reported to be the 'DFNA2' gene. In December's issue of *Nature Genetics*, Jia-Hui Xia and colleagues described two small Chinese families with nonsyndromic autosomal dominant hearing loss in which they found a missense and a nonsense mutation in *GJB3*, which encodes connexin 31 (ref. 3). As *GJB3* is located on chromosome 1p34, it was proposed, in an accompanying *News & Views* that *GJB3* is a good candidate for involvement in DFNA2 families⁴. Extensive sequence analysis of the coding region and the 5' UTR of *GJB3* in

all 5 DFNA2 families revealed no mutations, however (data not shown). A recent report in *Cell* reports the identification of a novel member (*KCNQ4*) of the potassium channel family *KCNQ*, also located on chromosome 1p34. Its authors found its mutation to segregate with hearing loss in a small French family, and claimed the identification of the DFNA2 gene.

Which one of these claims is correct? An obvious point to consider is that DFNA2 (Fig. 1) is the name of a chromosomal locus identified by linkage analysis, rather than a gene. Our analysis indicates that the candidate region delineated by the Indonesian family does not overlap with the candidate region of one of the Dutch families. The candidate regions of the remaining families overlap with both candidate regions (Fig. 1). *KCNQ4* is located in the candidate region of four families (Fig. 1); it is therefore possible that *KCNQ4* is responsible for hearing loss in these 'DFNA2' families, but conclusive data awaits mutation analysis. The centromeric recombinant of the Indonesian family excludes this gene as a

possible candidate gene for hearing loss in this family, suggesting the presence of a third deafness gene in this region.

As both *GJB3* and *KCNQ4* are responsible for nonsyndromic autosomal dominant hearing loss and are present in the DFNA2 region, each of them can be considered to be a 'DFNA2' gene (a hearing loss gene from the DFNA2 region), rather than the 'DFNA2' gene. As nonsyndromic deafness is a paradigm of genetic heterogeneity⁶, the presence of different genes responsible for nonsyndromic deafness in a small chromosomal region is not all that surprising. This situation may not be limited to hearing loss, as two different genes have been suggested at one locus for retinitis pigmentosa^{7,8}, another prime example of genetic heterogeneity. The question posed in our title is therefore legitimate, and DFNA2 may not be the only locus to which it applies.

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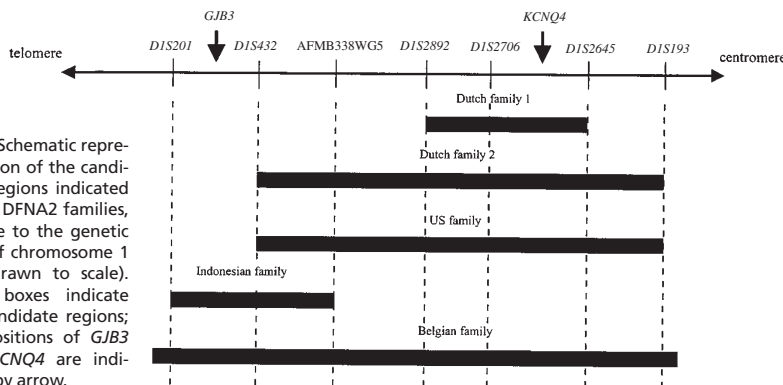


Fig. 1 Schematic representation of the candidate regions indicated by the DFNA2 families, relative to the genetic map of chromosome 1 (not drawn to scale). Black boxes indicate the candidate regions; the positions of *GJB3* and *KCNQ4* are indicated by arrow.