Identification of two different mutations in the PDS gene in an inbred family with Pendred syndrome

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Abstract

Recently the gene responsible for Pendred syndrome (PDS) was isolated and several mutations in the PDS gene have been identified in Pendred patients. Here we report the occurrence of two different PDS mutations in an extended inbred Turkish family. The majority of patients in this family are homozygous for a splice site mutation (1143-2A→G) affecting the 3' splice site consensus sequence of intron 7. However, two affected sibs with non-consanguineous parents are compound heterozygotes for the splice site mutation and a missense mutation (1558T→G), substituting an evolutionarily conserved amino acid. The latter mutation has been found previously in two Pendred families originating from The Netherlands, indicating that the 1558T→G mutation may be a common mutation.

Keywords: PDS gene; Pendred syndrome

Pendred syndrome (MIM 274600) is an autosomal recessive disorder with an estimated frequency of 1-8 per 100,000 characterised by prelingual deafness and goitre. Additional abnormalities are an iodide organification defect that can be shown by the perchlorate discharge test, an abnormally developed cochlea (Mondini malformation), and a widened vestibular aqueduct. In 1996, the Pendred syndrome gene was localised on chromosome 7q31, initially in a region of 5.5 cM. This region was then refined and, recently, the Pendred syndrome gene (PDS) was isolated. The gene encodes a transmembrane protein, named pendrin, that is closely related to known sulphate transporters. The homology of pendrin to two other sulphate transporters implicated in human diseases, "down regulated in adenoma" (DRA) involved in congenital chloride diarrhoea, and a sulphate transporter (DTD) involved in diastrophic dysplasia, suggests that the sulphate transporter gene family is clinically important. However, the exact function of pendrin in the thyroid and its involvement in cochlear development remain to be elucidated. To date, 29 different mutations in the PDS gene have been reported in Pendred syndrome patients. Four PDS mutations are found to be recurrent, at least in the western European population (L236P, E384G, T416P, and 1001+1G→Á). Inter-familial as well as intrafamilial clinical variability has been described in Pendred syndrome and recently a PDS mutation has been reported in a family with non-syndromic recessive deafness.

Figure 1 Pedigree of the inbred Pendred syndrome family. Only family members from whom DNA was obtained are numbered. Black bars beneath subjects represent the 1143-2A→G mutation, striped bars represent the 1558T→G mutation, and white bars represent wild type alleles.
Here we report two different PDS mutations, one novel and one previously reported, segregating in an extended inbred Pendred syndrome family originating from a small and isolated Turkish village. The family includes more than 13 affected subjects, all having prelingual hearing loss and a palpable goitre.

In a previous study, linkage analysis with markers flanking the PDS gene showed two different disease haplotypes. Six affected subjects, all with consanguineous parents, were homozygous for the closest flanking markers, whereas two patients with non-consanguineous parents were heterozygous. Several possibilities could explain these results. Firstly, two different mutations segregating on distinct haplotypes could be responsible for Pendred syndrome in this family. Secondly, a single mutation could be responsible for Pendred syndrome, originating from a very distant common ancestor and with different haplotypes evolving from numerous recombinations. A third possibility is the independent occurrence of the same mutation on distinct haplotypes, perhaps as the result of a mutation hot spot.

To identify the PDS mutations in this family, DNA from two patients (V.2 and VI.3) of the pedigree (fig 1) was analysed. Patient V.2, a member of consanguineous branch A, was expected to be homozygous for a PDS mutation, whereas patient VI.3, whose parents are not consanguineous, was expected to be a compound heterozygote (assuming the presence of two different mutations).

Mutation detection of the PDS gene was performed by direct sequencing of PCR products using the ABI PRISM™ BigDye™ Terminator Cycle Sequencing Ready Reaction Kit (Perkin Elmer, Foster City, CA). Genomic DNA was used as template for PCR amplification of DNA segments containing the PDS exons, as described previously. A homozygous A to G substitution was observed at the 3' splice site of intron 7 (1143-2A→G) in patient V.2 (fig 2A). Patient VI.3 was found to be a compound heterozygote for this splice site mutation and a T to G substitution at position 1558 in exon 11 (1558T→G) (fig 2B).

Linkage analysis in this family showed that the 1143-2A→G mutation segregated with Pendred syndrome. All the patients from the
Two different mutations in the PDS gene have been reported for several other disorders,17-19 and it has been suggested that multiple mutations in a single gene may be a relatively common phenomenon in inbred communities.

The identification of two different mutations in this consanguineous family indicates that great care should be taken when inbred families of this type are used for linkage analysis by homozygosity mapping.

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1 Pendred V. Deaf mutism and goitre. Lancet 1896;ii:532.