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ARTICLE

Two frequent missense mutations in Pendred syndrome

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Pendred syndrome is an autosomal recessive disorder characterized by early childhood deafness and goiter. A century after its recognition as a syndrome by Vaughan Pendred, the disease gene (*PDS*) was mapped to chromosome 7q22–q31.1 and, recently, found to encode a putative sulfate transporter. We performed mutation analysis of the *PDS* gene in patients from 14 Pendred families originating from seven countries and identified all mutations. The mutations include three single base deletions, one splice site mutation and 10 missense mutations. One missense mutation (L236P) was found in a homozygous state in two consanguineous families and in a heterozygous state in five additional non-consanguineous families. Another missense mutation (T416P) was found in a homozygous state in one family and in a heterozygous state in four families. Pendred patients in three non-consanguineous families were shown to be compound heterozygotes for L236P and T416P. In total, one or both of these mutations were found in nine of the 14 families analyzed. The identification of two frequent *PDS* mutations will facilitate the molecular diagnosis of Pendred syndrome.

INTRODUCTION

In 1896 Vaughan Pendred first described Pendred syndrome (MIM 274600) as a combination of congenital deafness and goiter (1). Estimations of the frequency of Pendred syndrome vary from 1/15 000 in the British Isles to 1/100 000 in Scandinavia (2). The disease accounts for an estimated 4–10% of congenitally deaf children (2). Most Pendred patients are prelingually deaf and have a type of cochlear malformation known as a Mondini defect (2). A Mondini malformation is characterized by one and a half coils instead of two and a half coils, with the upper two turns forming a common cavity (2). Although most Pendred patients develop a goiter during adolescence or adulthood, nearly every patient is euthyroid (3).

The basic defect in the thyroid is a less efficient organification of iodide (4,5), which can be demonstrated by the perchlorate discharge test (6). In this test, radioactive iodide is given to a patient. One hour later, perchlorate is administered and diffusion of inorganified iodine from the thyroid gland is measured as a drop in thyroid counting rate. An abnormal result is defined as a release of >20% of the radioactive iodide taken up by the thyroid gland.

Pendred syndrome is inherited as an autosomal recessive trait and in many families consanguinity is present (2). The phenotype of Pendred patients, however, can vary within and between families (7).

After Coyle *et al.* (8) and Sheffield *et al.* (9) found linkage between Pendred syndrome and markers on chromosome 7q31, we were able to reduce the Pendred candidate region to 1.7 cM (10). Recently, Everett *et al.* (11) reported the identification of the Pendred gene (*PDS*), with the identification of three different mutations in five Pendred families. *PDS* encodes a putative

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sulfate transporter. The open reading frame of *PDS* is distributed across 21 exons, with the 5 kb mRNA highly expressed in thyroid tissue. In a preliminary experiment, Everett *et al.* (11) were able to PCR amplify the *PDS* gene from a fetal cochlear cDNA library, suggesting that the gene is also expressed in the cochlea. The protein encoded by the *PDS* gene has been named pendrin and is predicted to consist of 780 amino acids (molecular weight 86 kDa). Analysis of the predicted amino acid sequence of pendrin reveals 11 transmembrane domains.

PDS is one of the first disease genes to be identified with the aid of genomic sequence information. Everett *et al.* (11) analyzed the available sequence from a BAC from the Pendred critical region with the GRAIL program (12), which revealed the presence of several putative exons. Comparison of these exons with sequences in GenBank revealed strong homology to the 'down-regulated in adenoma' (*DRA*) gene, which had been previously mapped to the Pendred candidate region (13). *DRA* encodes a sulfate transporter (14) and mutations in this gene cause congenital chloride diarrhea (15). Interestingly, the *PDS* gene maps very close to the *DRA* gene. Both genes are positioned tail-to-tail and separated by only 48 kb, suggesting an evolutionary relationship.

In this study we performed mutation analysis of the *PDS* gene in 14 Pendred families from different ethnic origins. The 14 identified mutations included three frameshift mutations, one splice site mutation and 10 missense mutations. Interestingly, two missense mutations were present in more than half of the families analyzed in this study.

RESULTS

Mutation detection

To detect mutations in the *PDS* gene of Pendred patients, we PCR amplified and sequenced each of the 21 exons (11) from one affected individual of 14 anamnestically unrelated Pendred families. In family 1, two patients (II.1 and III.1) were analyzed, as the structure of the pedigree suggested the presence of three mutations (Fig. 1). Table 1 summarizes the clinical and molecular data for all 14 families. In these 14 families, originating from seven countries, 14 different mutations were found, including three frameshifts, one splice site mutation and 10 missense mutations (Table 2). A specific restriction enzyme assay was developed to facilitate the analysis of the remaining family members from whom DNA was available (Table 2).

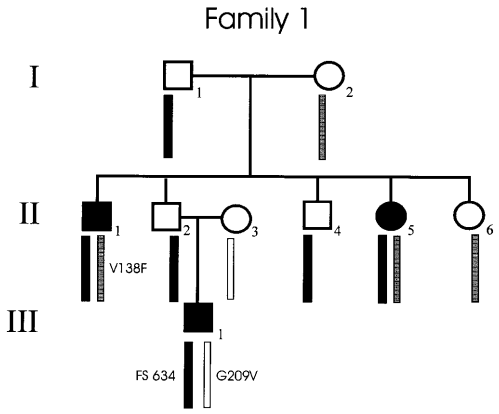


Figure 1. Pedigree of Belgian family 1. Bars below the family markers indicate the segregation of the mutation.

Three different frameshift mutations leading to a premature stop codon were found (Tables 1 and 2). Two of these (FS 400 and FS 383) lead to a truncated protein with only the first eight transmembrane domains (Fig. 2). The FS 634 mutation, however, results in a pendrin protein containing all transmembrane domains (Fig. 2), but lacking the 146 amino acids at the C-terminus.

Table 1. Characteristics of *PDS* mutations in the Pendred families

Family	Origin	Early childhood deafness	Goiter	Abnormal perchlorate test	Consanguinuity	PDS mutations
1	Belgium	3/3	2/3	NP for II.1 and II.5; normal for III.1	No	G209V, FS634, V138F
2	Holland	1/1	1/1	1/1	Yes	**L236P**
3	Holland	1/1	1/1	1/1	No	L445W, H723R
4	Lebanon	3/3	1/3	2/3	Yes	FS400
5	Holland	2/2	2/2	2/2	Yes	**T416P**
6	Holland	2/2	1/2	1/2	No	FS383, **T416P**
7	Turkey	1/1	1/1	1/1	No	D271H, R409H
8	Holland	1/1	1/1	1/1	No	**L236P**, G139A
9	USA	1/1	1/1	1/1	No	C565Y, **L236P**
10	Denmark	1/1	0/1	1/1	No	**L236P**, **T416P**
11	Belgium	1/1	1/1	1/1	Yes	**L236P**
12	Holland	1/1	1/1	1/1	No	**L236P**, **T416P**
13	Holland	1/1	1/1	1/1	No	**L236P**, **T416P**
14	India	2/2	2/2	NP	Yes	1142+1G→A

NP, test was not performed; FSx, frameshift mutation in which x is the position of the first altered amino acid.
The two recurrent mutations are in bold type.

Table 2. Characteristics of *PDS* mutations in the Pendred families

Protein change	Protein domain	Sequence change	Exon	PCR primers	Mutation confirmation	Family
V138F	TR3	636G→T	4	exon4-s[1]–exon4-as[1]	Sequencing	1
G139A	TR3	640G→C	5	exon5-s[1]–exon5-as[1]	Sequencing	8
G209V	TR4	850G→T	6	exon6-s[1]–exon6-as[1]	*Hin*fI cuts WT	1
L236P	EL3	931T→C	6	exon6-s[1]–exon6-as[1]	*Alu*fI cuts WT	2, 8, 9, 10–13
D271H	EL3	1035G→C	7	1035-F1m[2]-1035-R1[2]	*Bcl*I cuts mutant	7
FS383	IL4	1370delC	9	exon9-s[1]–exon10-as[1]	*Bst*NI cuts WT	6
FS400	TR9	1421delT	10	exon9-s[1]–exon10-as[1]	Sequencing	4
R409H	EL5	1450G→A	10	exon9-s[1]–exon10-as[1]	Sequencing	7
T416P	EL5	1470A→C	10	exon9-s[1]–exon10-as[1]	*Ban*II cuts mutant	5, 6, 10, 12, 13
L445W	TR10	1558T→G	11	exon11-s[1]–exon11-as[1]	Sequencing	3
C565Y	C-terminus	1918G→A	15	1918-F1[2]–1918-R1m[2]	*Ssp*I cuts mutant	9
FS634	C-terminus	2122delA	17	2122-F1[2]–2122-R1m[2]	*Mbo*II cuts mutant	1
H723R	C-terminus	2392A→G	19	exon19-s[1]–exon19-as[1]	Sequencing	3
Unknown	Unknown	1142+1G→A	5′ intron 7	exon7-s[1]–exon8-as[1]	Sequencing	14

The numbering of amino acids and nucleotides is according to Everett *et al*. (11).
TR, transmembrane domain; WT, wild-type; EL, extracellular loop; IL, intracellular loop; FSx, frameshift mutation in which x is the position of the first altered amino acid.
[1]See Everett *et al.* (11).
[2]See Table 3.

In consanguineous family 14, a homozygous G→A transition in the first nucleotide of intron 7 (1142+1G→A) was identified. Determining the effect of this splice site mutation was not possible as the *PDS* gene is not expressed in blood cells, which was the only tissue available for this patient.

A total of 10 missense mutations were identified. The location of these mutations in the pendrin protein and their effect on the protein is given in Table 2. Two frequent *PDS* mutations (L236P and T416P) were identified. The L236P mutation was found in seven families (Tables 1 and 2) and occurred twice in the homozygous state and five times in the heterozygous state. L236P changes a non-conserved leucine to a proline. This leucine is part of an extracellular loop (EL3; see Table 2) between transmembrane domains 5 and 6 (Fig. 2). Another frequent mutation, T416P, was found in five families, once in the homozygous state and four times in the heterozygous state (Tables 1 and 2). T416P changes a conserved threonine residue into a proline. The threonine at position 416 is located in an extracellular loop (EL5; see Table 2) between transmembrane domains 9 and 10 (Fig. 2). To exclude that these two mutations are frequent in the general population (and thus represent polymorphisms), 48 unrelated control samples of Belgian origin (i.e. 96 chromosomes) were analyzed for L236P and T416P. In no instance was either mutation detected.

Haplotype comparison

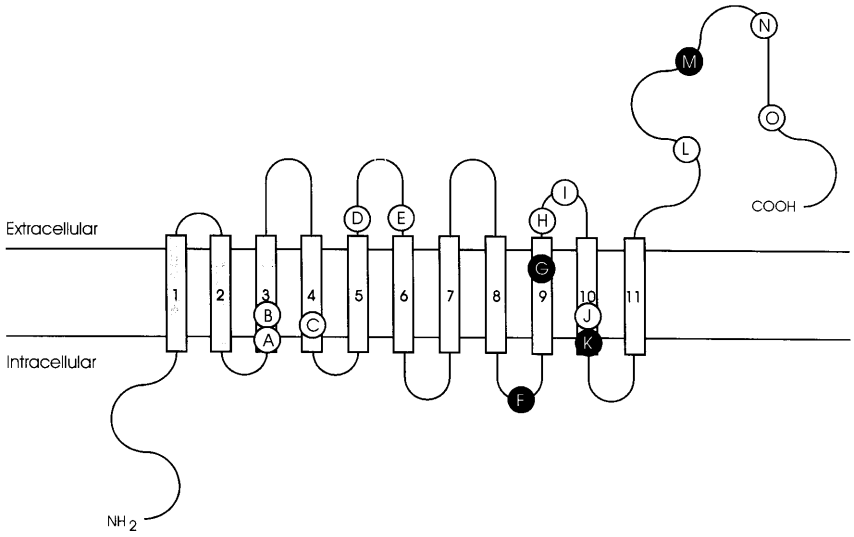
To investigate if common ancestral chromosomes accounted for one or both frequent mutations, we compared the disease haplotypes in these families. In a few instances, the linkage phase could not be determined and two possibilities remain for the linked allele. As shown in Figure 3, there is significant haplotype sharing among the families carrying the L236P mutation. Most likely, all patients in these families have inherited this mutation from a common founder.

In the families carrying the T416P mutation, haplotype sharing is also present, albeit to a lesser extent. However, the comparison is complicated by the fact that the linkage phase cannot be determined in family 10, as the family contains only one patient and no DNA is available from the parents. All five families with the T416P mutation share the same allele for marker D7S2459, which is located in an intron of the *PDS* gene. The frequency for this allele (150 bp) is 20%, as determined in CEPH pedigrees (http://www.genethon.fr/). Therefore, a founder effect is also likely for the T416P mutation.

DISCUSSION

In this study we identified a spectrum of mutations in *PDS*, the gene responsible for Pendred syndrome, in 14 anamnestically unrelated Pendred families. Ten of these families originate from Western Europe (The Netherlands, Belgium and Denmark). In addition, one family comes from the USA, one from Lebanon, one from Turkey and one from India. In all nine non-consanguineous families two discrete mutations were found, while a single mutation was encountered in every consanguineous family. This suggests that Pendred syndrome is genetically homogeneous and caused by a single gene in virtually all cases.

The 14 mutations consist of three frameshift mutations, one splice site mutation and 10 missense mutations, demonstrating the allelic heterogeneity of Pendred syndrome. Most (11 out of 14) of these mutations were private mutations occurring in a single family. The FS 400 mutation found in family 4 is also present in three Arab families living in northern Israel (11). As family 4 originates from Lebanon, it is possible that the FS 400 mutation is common in the Middle East Arab population.



Mutation	
A	V138F
B	G139A
C	G209V
D	L236P
E	D271H
F	FS 383
G	FS 400
H	R409H
I	T416P
J	L445W
K	FS 446 / Aberrant splicing
L	C565Y
M	FS 634
N	F667C
O	H723R

Figure 2. Structure of the pendrin protein with indication of the position of all known *PDS* mutations. As the effect of the 1142+1G→A splice site mutation on the pendrin protein is not yet known, this mutation is not included in this figure. Mutations G, K and N were described by Everett *et al*. (11). White encircled letters indicate missense mutations, black encircled indicate frameshifts or splice site mutations.

Two mutations, L236P and T416P, proved to be particularly frequent, as they were present in nine of the 14 families. We looked at 96 control chromosomes for each of these mutations and did not find their occurrence in a single instance. Haplotype analysis (Fig. 3) revealed a partial shared haplotype between families of each group. The families carrying the frequent mutations originate from Western Europe and the USA and these mutations were not detected in the families from Lebanon, Turkey or India. Although the frequency of the mutations remains to be determined in other populations, it is possible that they will be frequent only in patients with ancestors originating from Europe.

The 14 identified *PDS* mutations are most probably disease causing. The FS 383, FS 400 and FS 634 mutations lead to a frameshift resulting in a truncated protein. The splice site mutation in family 14 changes a G at a position in the 5′ splice consensus sequence that is 100% conserved. We calculated that the CV value (16) for this splice site dropped from 0.928 (normal sequence) to 0.76 (mutated sequence). Such a mutation almost always leads to aberrant splicing, either by exon skipping or the use of a cryptic splice site (17). However, the exact effect on the mRNA needs to be determined by RT-PCR. Significant *PDS* expression has only been convincingly demonstrated in the thyroid (11), which was not available from this patient and RT-PCR amplification of the *PDS* gene from lymphoblast mRNA has not been successful (data not shown).

Six of the 10 missense mutations (V138F, G139A, G209V, D271H, T416P and L445W) replace amino acids that are conserved among several other related sulfate transporter genes from different species, suggesting their importance in pendrin function. The four missense mutations at non-conserved positions are L236P, C565Y, R209H and H723R. It cannot be excluded that these changes are polymorphisms rather than

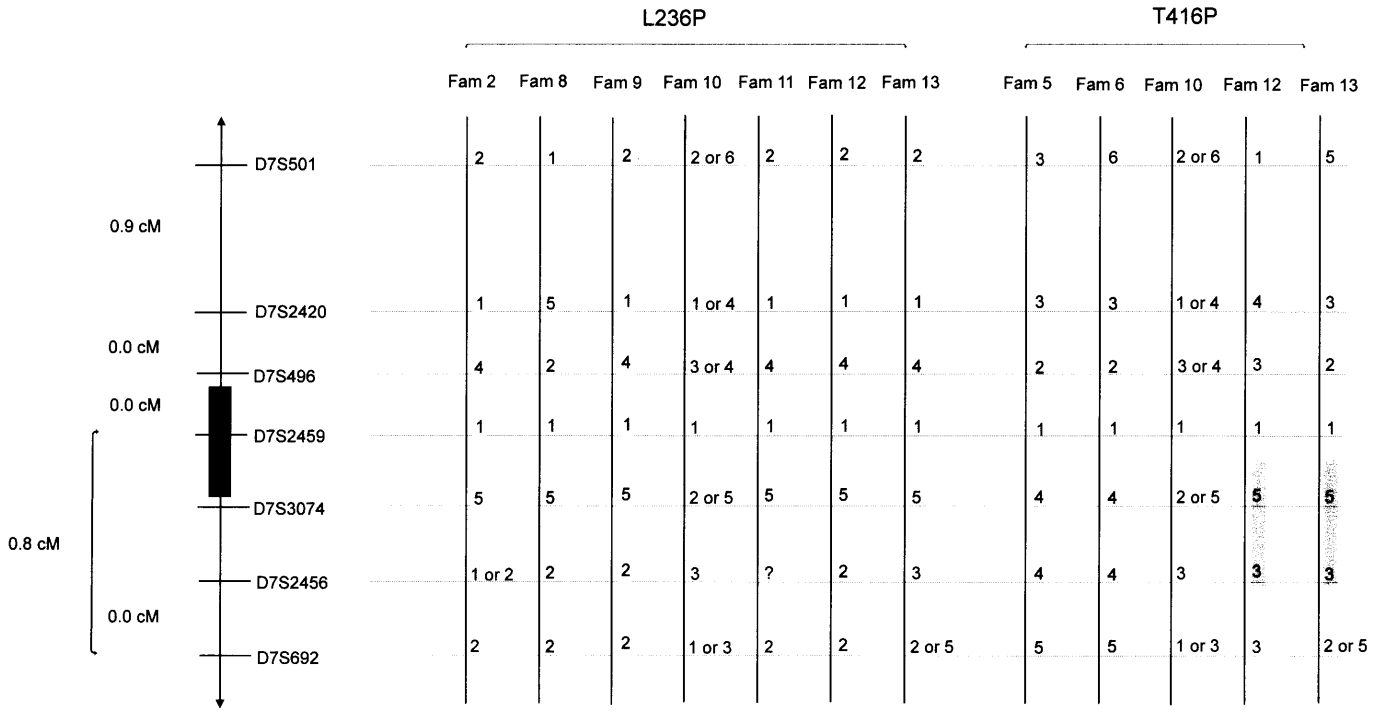


Figure 3. Haplotype analysis in Pendred families with frequent *PDS* mutations. The haplotype for genetic markers closely linked to the *PDS* gene is given for families with the L236P mutation and with the T416P mutation. Shaded boxes indicate shared alleles. Intermarker distances are shown on the left. The black box indicates the position of the *PDS* gene relative to the genetic markers.

disease-causing mutations. However, we did not find any other mutation in the *PDS* coding region in patients of the respective families, although the disease-causing mutation could be located in other regions of the gene, such as the promoter, which were not screened for mutations.

It is possible that the 640G→C change not only results in a G139A change, but also in aberrant splicing of the *PDS* mRNA, as this mutation occurs immediately adjacent to the 5′ splice site of intron 5. The mutation changes the CV value of this splice site (16) from 0.87 (normal sequence) to 0.74 (mutated sequence). However, the exact effect of this mutation on the mRNA could not be determined.

The G209V substitution, found in patient III.1 of family 1 (Fig. 1), changes an amino acid that is conserved in all 14 known sulfate transporter family members. Since this is a conservative substitution (both amino acid residues belong to the same group of non-polar amino acids), one could argue that this does not reflect the disease-causing mutation. This 18-month-old patient has currently only non-syndromic deafness and does not display any thyroid dysfunction. Nonetheless, in the light of the evolutionary conservation at this amino acid position, it seems likely that G209V is disease causing.

Up to now, 16 different mutations in the *PDS* gene have been discovered (11; this study). Figure 2 is a graphical presentation of the position of these mutations in the pendrin protein. Mutations have been found in four transmembrane regions, two extracellular loops, one intracellular loop and in the C-terminal extracellular region, suggesting that there is no clustering of the mutations in any particular domain of the *PDS* gene. On the other hand, it should be noted that the four frameshift mutations (Fig. 2) and the splice site mutations, which probably all lead to a truncated protein, are located at the C-terminus of the pendrin protein, leaving a significant portion of the protein intact. It might be possible that a complete lack of pendrin is incompatible with life.

Knowledge of mutations in *PDS* will aid functional studies of the pendrin protein. Furthermore, with the identification of frequent mutations in the *PDS* gene, the diagnosis of Pendred syndrome will be facilitated. This is particularly the case for those mutations that can be detected by simple restriction enzyme-based screening methods.

MATERIALS AND METHODS

Subjects

Of the 14 Pendred families analyzed in this study, six have been described before and eight are unpublished. Families 1, 2, 4 and 5 have been described by Coucke *et al.* (10). Families 3 and 5 have been previously reported by Cremers (18). Table 1 summarizes the ethnic origin and the clinical data for the Pendred families, including the presence of early childhood deafness, goiter and the results of the perchlorate test. All Dutch families were ascertained by the University Hospital of Nijmegen. Some noteworthy clinical aspects of these families and the results of CT scanning of the temporal bone (when performed) are reported below.

Family 1 is a non-consanguineous family and originates from Belgium. Part of this family has already been described (10). Recently, individual II.2 had a congenitally deaf son (individual

III.1). No goiter was present at the age of 18 months and the boy had a normal perchlorate test.

Interestingly, an intrafamilial clinical variation exists in families 4 and 6. Although all three patients from family 4 are prelingually deaf and have a Mondini malformation of the cochlea, the presence of goiter and the results of the perchlorate test are variable. The oldest patient has a goiter (examined at age 13) and an abnormal perchlorate test, her sister (examined at age 8) has no goiter but the perchlorate test was abnormal and her brother (examined at age 9) has no goiter and a normal perchlorate test.

In family 6, there is also variation in goiter and the outcome of the perchlorate test. One patient has a small goiter (examined at age 13) but a normal perchlorate test, while her affected sister has an abnormal perchlorate test but no goiter (examined at age 15).

In the Belgian patient of family 11, CT scanning revealed a partial fusion of the basal and apical coil of the cochlea, without the typical characteristics of a Mondini malformation and a widened vestibular aqueduct.

Mutation analysis

Mutation analysis was performed by genomic exon sequencing. All 21 exons were PCR amplified by intragenic primers and sequenced as described before (11). To enable rapid screening for the *PDS* mutations, we developed specific restriction enzyme assays for most of the mutations. If the mutation destroyed or created a restriction site for a commercially available restriction enzyme, we amplified the respective *PDS* sequence of all the family members and digested it with the respective restriction enzyme. If no suitable restriction site was created or destroyed by the mutation, we designed a modified primer containing a mismatch that, together with the mutation, artificially introduces a site for a commercially available restriction enzyme. Table 2 describes the restriction enzymes used to identify the different mutations. Table 3 describes which primers were used for the modified PCR experiments. PCR products were purified using the Sephaglas™ BandPrep kit (Pharmacia) before digestion. The digestion was carried out using 10–12 U restriction enzyme according to the manufacturer's specifications. If no suitable restriction enzyme was available, confirmation of the mutation in the remaining family members was performed by sequencing.

Table 3. Sequences of primers used for modified PCR to detect *PDS* mutations

Mutation	Primer name	Sequence
C565Y	1918-F1m	gtaattaaatacttgaggcttg
	1918-R1m	aatacttactgtggacttgaaa
D271H	1035-R1	gttggctccatatgaaatggc
	1035-F1m	tattggtgataccaatcttgat
FS634	2122-F1	tcataagtgatgctgtttcaac
	2122-R1m	ccaatccacttgaatctctctt

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ABBREVIATIONS

CV, consensus value; del, deletion; FS, frameshift.

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