J. Endocrinol. Invest. 30: 907-913, 2007

J. Endocrinol. Invest. 30: 907-913, 2007
©2007, Editrice Kurtis.

Two common and three novel PDS mutations in Thai patients with Pendred syndrome

T. Snabboon[1], W. Plengpanich[1], S. Saengpanich[2], S. Sirisalipoch[3], S. Keelawat[4], S. Sunthornyothin[1], W. Khovidhunkit[1], S. Suwanwalaikorn[1], V. Sridama[1], and V. Shotelersuk[5]

Departments of [1]Internal Medicine, [2]Otolaryngology, [3]Radiology, [4]Pathology, and [5]Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

ABSTRACT. Pendred syndrome is an autosomal recessive disorder characterized by congenital sensorineural deafness, goiter, and impaired iodide organification. It is caused by mutations in the PDS gene. Most published mutation studies of Pendred syndrome have dealt with Western populations. In this study, we examined clinical and molecular characteristics of 16 affected individuals in 6 unrelated Thai families. Of all the affected, 100% (16/16) had bilateral deafness, 68.8% (11/16) goiters, and 25% (4/16) hypothyroidism. Follicular thyroid carcinoma and Hürthle cell adenoma were found in affected members of a family, raising the possibility of an increased risk of thyroid carcinoma in Pendred syndrome patients. Sequence analysis of the entire coding region of the PDS gene successfully identified all 12 mutant alleles in these 6 families. The 12 identified mutant alleles constituted 6 distinct mutations including 3 splice site mutations (IVS4-1G>A, IVS7-2A>G, IVS9-1G>A), one frame shift mutation (1548insC) and 2 missense mutations (T67S, H723R). Eight mutations out of 12 were constituted by IVS7-2A>G and 1548insC, each one being present in 4 distinct alleles in our studied group. The identification of these two frequent PDS mutations will facilitate the molecular diagnosis of Pendred syndrome in Thai populations. In addition, three newly identified mutations, T67S, IVS4-1G>A, and IVS9-1G>A, were not observed in 50 unrelated healthy Thai controls.
(J. Endocrinol. Invest. 30: 907-913, 2007)
©2007, Editrice Kurtis

©2007, Editrice Kurtis

INTRODUCTION

Pendred syndrome (OMIM 274600), the most common syndromal form of deafness, is an autosomal recessive disorder associated with sensorineural hearing loss, developmental abnormalities of the inner ear, and goiter (1). The hearing loss, an obligatory sign, is bilateral and mostly at the prelingual stage. Usually, anomalies of the inner ear, such as malformation of the membranous labyrinth with an enlarged vestibular aqueduct (EVA) or a malformation of cochlea referred to as Mondini defect (2, 3), can be identified by either computerized tomography (CT) or magnetic resonance imaging (MRI). The basic defect in thyroid function is defective organification of iodide, which can be demonstrated by the perchlorate discharge test. While most patients are euthyroid, some present with subclinical or overt hypothyroidism. Thyromegaly, present in 50% of reported cases, typically develops during puberty (2). The molecular basis of Pendred syndrome is a mutation of the PDS or SLC26A4 gene, located on the long arm of chromosome 7 (7q31.1). The PDS complementary DNA (cDNA) contains an open reading frame of 2343 bp and encompasses 21 exons (4). The protein encoded by the PDS gene, pendrin, is a member of the Solute Carrier Family 26. It consists of 780 amino-acids (molecular weight 86 kDa) and it is speculated to contain 12 transmembrane domains, and intracellular N- and C-termini. Functionally, pendrin is an anion transporter, expressed in non-sensory and sensory epithelia of the inner ear (5, 6), thyroid follicular cells (7), renal cortical collecting ducts (8), placental trophoblasts (9), uterine endometrium (10), and mammary gland (11).

Key-words: Pendred syndrome, PDS gene, goiter, deafness, perchlorate discharge test.

Correspondence: T. Snabboon, MD, Division of Endocrininology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Chulalongkorn University, Rama IV Road, Patumwan, Bangkok 10330, Thailand.

E-mail: thiti.s@chula.ac.th

Accepted March 23, 2007.

In vivo, pendrin is likely to mediate iodide transport across the apical membrane of thyroid follicular cells and bicarbonate secretion by intercalated cells of renal cortical collecting ducts (7, 12-14)

Nearly 100 mutations of the PDS gene have now been identified (www.medicine.uiowa.edu/pendredandbor/slcMutations.htm) and they are scattered throughout the encoding region. Most of these mutations have been found in single families, however some are recurrent. This may, in part, be the consequence of a founder effect, or of independently recurrent mutations. Most published mutation studies of Pendred syndrome have been performed in the Western population. There are only a few reported cases in East and South Asians (15, 16). In this study, we examined clinical and molecular characteristics of 6 families of Thai ethnic origins with Pendred syndrome.

SUBJECTS AND METHODS

Subjects

Six unrelated probands, 1 male and 5 females (age 25-52 yr old), with a clinical diagnosis of Pendred syndrome were identified. They all had sensorineural hearing loss, goiter and positive perchlorate discharge test. We also studied 31 of their family members; 10 (8 males and 2 females, age range 30-62 yr) were found to be affected with clinical features of bilateral sensorineural hearing loss with or without goiter (Table 1). The other 21 who were unaffected were 10 males and 11 females, aged between 9-70 yr. History of consanguineous marriage was denied by all families. An additional 50 unrelated Thai controls were recruited to help determine whether any sequence changes might be a common polymorphism. The study was approved and in compliance with the guidelines set forth by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University.

Clinical study

All 16 affected individuals were evaluated for onset of hearing loss (or the age at which hearing loss was first noted), the presence of vertigo and the average hearing level using an audiometer (Beltone Model 2000, Chicago, IL, USA) in the same sound-insulated chamber for all pure-tone audiometry. Average hearing level was expressed as the average of air conductive threshold at 3 frequencies (500 Hz, 1 kHz, and 2 kHz). The severity of hearing loss was defined as mild (<40 db), moderate (40-70 db), severe (70-90 db), and profound (>90 db). The thyroid function tests (free T_3, free T_4 and 4th generation TSH), were carried out by electrochemiluminescent assay (Elecsys 2010, RoChe Diagnostics GmBH, USA). Thyroid ultrasonography was per-

©2007, Editrice Kurtis

Table 1 - *Phenotypic and genotypic findings in 6 Thai families with Pendred syndrome.*

No.	Sex	Age	Thyroid function status FT_3 (1.6-4.0 pg/ml)	FT_4 (0.8-1.8 ng/dl)	TSH (0.3-4.1 µu/ml)	Goiter	Perchlorate discharge test	Deafness	Genotype	Others
I-1	M	62	2.53	0.41	23.54	MNG	+ (40%)	Severe	IVS7-2A>G, IVS4-1G>A	Follicular thyroid carcinoma
I-2	M	55	3.81	0.99	3.78	No	– (5%)	Severe	IVS7-2A>G, IVS4-1G>A	-
I-3*	M	52	1.94	0.25	35.75	MNG	+ (50%)	Severe	IVS7-2A>G, IVS4-1G>A	Hurthle cell adenoma
II-1*	F	52	3.77	1.12	2.56	MNG	+ (30%)	Profound	IVS7-2A>G, 200C>G	Diabetes mellitus
II-2	M	50	3.12	1.43	3.25	No	N/A	Profound	IVS7-2A>G, 200C>G	Diabetes mellitus
III-1*	F	43	3.11	1.55	2.21	MNG	+ (25%)	Severe	1548insC, IVS9-1G>A	-
IV-1*	F	38	1.96	0.21	22.75	MNG	+ (50%)	Severe	IVS7-2A>G, 2168A>G	-
IV-2	M	37	2.44	1.62	1.95	Diffuse	– (5%)	Profound	IVS7-2A>G, 2168A>G	-
IV-3	V	33	1.99	1.14	2.65	Diffuse	N/A	Profound	IVS7-2A>G, 2168A>G	Ovarian carcinoma
IV-4	F	33	2.18	1.24	3.22	Diffuse	N/A	Profound	IVS7-2A>G, 2168A>G	-
IV-5	M	31	2.22	0.92	3.45	No	N/A	Profound	IVS7-2A>G, 2168A>G	-
V-1*	F	33	2.75	1.32	2.66	Diffuse	+ (20%)	Profound	IVS7-2A>G, 1548InsC	-
VI-1	M	35	3.27	1.64	2.55	Diffuse	N/A	Profound	1548insC, 1548insC	-
VI-2	M	33	2.55	1.42	2.44	No	+ (40%)	Severe	1548insC, 1548insC	-
VI-3	M	30	3.15	1.55	1.98	No	N/A	Severe	1548insC, 1548insC	-
VI-4*	F	25	2.22	0.44	1.45	Diffuse	+ (50%)	Severe	1548insC, 1548insC	-

*: proband; +: positive; –: negative; FT_3: free T_3; FT_4: free T_4; N/A: not available; MNG: multinodular goiter; M: male; F: female.

J. Endocrinol. Invest. 30: 907-913, 2007
©2007, Editrice Kurtis.

formed with the ALOKA SSD1000 instrument and a 39mm7.5MHz probe (Aloka Instruments, Tokyo, Japan) to confirm the presence of thyroid goiter or nodule. The potassium perchlorate discharge test was performed in all probands. Three h after the oral administration of iodine-131 (30 μCi), thyroid uptake was performed with Atomlab 950, Biodex Medical System, after which 1 g potassium perchlorate was administered orally. The discharge was determined every hour for 3 h and the test was defined as positive, if exceeding 10%.

Molecular genetic analysis

Informed consent was obtained from the probands and their family members. Genomic DNA was extracted from peripheral blood leukocytes by the phenol-chloroform method. Each of the exons (2-21) of the PDS gene was amplified by PCR using primers and conditions as previously described (4). The genomic novel missense mutation 200C>G in exon 3 was confirmed with a modified sense primer (F3E: 5'-GT TTT CTT GCT TTT TGA CAG TTG TTC AAG AAA GAG AGC CTT TGG TGT GCT GAA G-3') and antisense primer (R3E: 5'-CTA CAG GAA AGA TAC AGG CC-3'). For restriction enzyme analysis of the IVS7-2A>G mutation, a modified sense primer (F8E: 5'-TTG ACA AAC AAG GAA TTA TTA AAA CCA ATG GAG TTT TTA ACA TCT TTT GTT TTA TCT C-3') and antisense primer of exon 8 (R8E: 5'-AGG ACT CTG GTG TTA ACC GT-3') were designed. Sequencing reactions were performed in a MJ Research PTC-225 Peltier Thermal Cycler using an ABI PRISM Big Dye TM Terminator Cycle Sequencing Kits with AmpliTaq DNA polymerase (FS enzyme) (Applied Biosystems), following the protocols supplied by the manufacturer. All mutations have been classified according to the nomenclature recommendations, with the A of the ATG of the initiator Met codon denoted as +1 (17).

Mutation confirmation

We used restriction analysis to confirm the presence of mutations in the PDS gene. Restriction endonucleases (Fermentas, Vilnius, Lithuania) were selected on the basis of whether a mutation created or abolished a restriction site. If it did not, we used modified PCR primers to introduce base substitutions adjacent to a codon of interest thereby creating an artificial restriction site on only one alleic form (wild type or mutant).

RESULTS

Clinical manifestations

The main clinical and biochemical findings of all 16 affected individuals are summarized in Table 1. All had bilateral sensorineural hearing loss during childhood. The degree of deafness was either severe or profound. No vestibular symptom was identified in our patients. Thyroid goiter was found in 11 cases while only 4 developed clinical hypothyroidism. Five cases had deafness without thyroid abnormalities. Thyroid autoantibodies (thyroid microsomal antibody and thyroglobulin antibody) were not found in any of the affected patients. Interestingly, metastatic follicular thyroid carcinoma and Hürthle cell adenoma were noted in family I. Both twins of family IV were affected with clinical Pendred syndrome, while one of them had ovarian cancer. Imaging (high resolution CT) of the inner ear, available only in 2 patients (probands of the families II and IV), re-

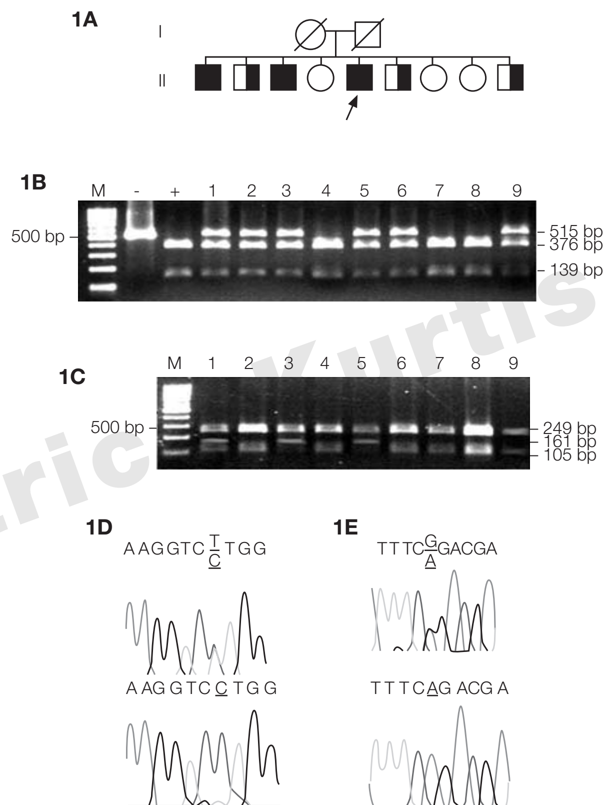

Fig. 1 - *Family I. 1A) Pedigree of family I: Affected patients are indicated by solid symbols. Heterozygous individuals are indicated by half-filled symbols. Normal individuals are indicated by empty symbols. The arrow indicates the proband. 1B) Restriction enzyme analysis of the IVS4-1G>A mutation. Each lane represents the individual in the above pedigree. M represents the 100-bp marker. The size of the PCR products of exon 5 is 515 bp (–). After Eco47I treatment, two restriction products of 376 and 139 bp of the wild type were found in controls (+) and in all tested individuals while the undigested 515 bp fragments of the mutant allele were found in lanes 1, 2, 3, 5, 6, and 9. 1C) Restriction enzyme analysis of IVS7-2A>G mutation. Each lane represents the individual in the above pedigree. With modified sense primer (F8E) and antisense primer of exon 8 (R8E), the size of PCR product is 410 bp (not shown). After DdeI treatment, three restriction products of 249, 105, and 56 bp of the wild-type allele (all lanes) and 249 and 161 bp (lanes 1, 3, and 5) of the IVS7-2A>G mutants were produced. The 56-bp bands were not shown. 1D) The antisense sequence of the PDS gene, exon 5, of the proband showing the heterozygous IVS4-1G>A change (upper panel), compared to that of a control (lower panel). 1E) The sense sequence of PDS exon 8 of proband showing the IVS7-2A>G change (upper panel), compared to that of a control (lower panel).*

©2007, Editrice Kurtis

©2007, Editrice Kurtis.

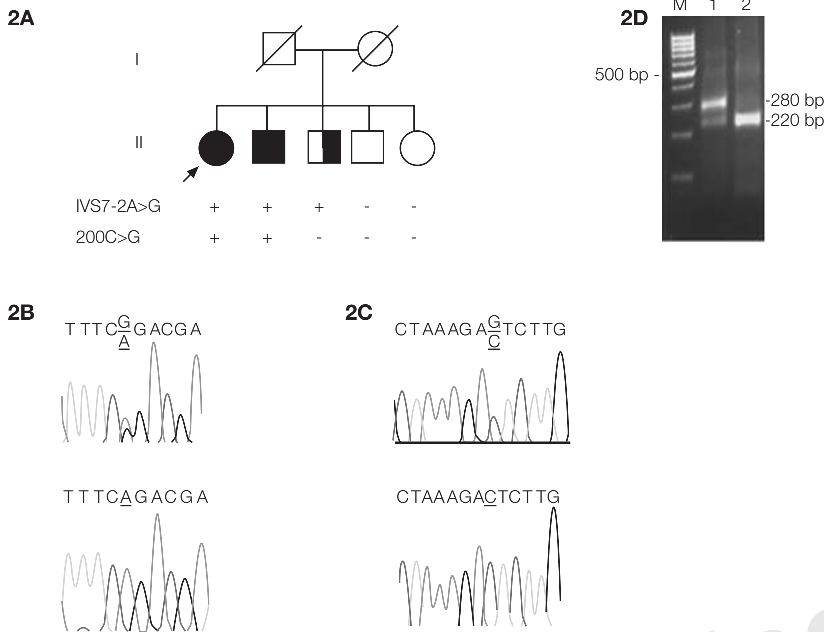

Fig. 2 - *Family II. 2A) Pedigree. 2B) The sense sequence of exon 8 of the proband showing the IVS7-2A>G mutation (upper panel), compared to a control (lower panel). 2C) The sense sequence of exon 3 of the PDS gene of the proband showing the heterozygous 200C>G mutation (upper panel), compared to that of a control (lower panel). 2D) With a modified sense primer (F3E) to detect a 200C>G mutation and a reverse primer of exon 3 (R3E), the size of PCR product is 280 bp. After BpiI treatment, two restriction products of 220 and 60 bp in the wild-type and undigested 280 bp in the 200C>G mutant were produced in lane 1 of the proband, while only the 220- and 60-bp bands were seen in controls (lane 2). The 60-bp band was not shown. M represents the 100-bp marker.*

©2007, Editrice Kurtis

vealed enlarged vestibular aqueducts, 2.5 and 2.7 mm in diameters at the midpoint between the common crus and the external aperture (18).

Molecular genetic results

Sequence analyses of the entire coding regions of the PDS gene encompassing exons 2-20 and a portion of exon 21 successfully identified all of the 12 mutations in our 6 families.

Affected members of family I were compound heterozygous for a previously reported transition A to G in the splice acceptor site of intron 7 (IVS7-2A>G) (19) and a novel splice site mutation in intron 4 (IVS4-1G>A). This novel mutation, which created an additional restriction site in the amplicon, was confirmed by restriction analysis using an Eco47I enzyme (Fig. 1).

In family II, the index patient was a compound heterozygote for the IVS7-2A>G mutation and a novel transversion 200C>G in exon 3 of the PDS gene resulting in substitution of threonine to serine (T67S). This mutation was confirmed by a restriction enzyme analysis using an amplicon generated with a modified sense primer (F3E), an antisense primer for exon 3 (R3E) and a restriction site for enzyme BpiI (Fig. 2). It was not found in 50 unrelated Thai controls. Her affected brother had both the mutant alleles while her non-affected brother carried only one.

The proband of family III was found to be compound heterozygote for a 1548insC in exon 14 resulting in a stop codon 29 amino acids downstream (15) and a transition of G to A in the splice site of intron 9 (IVS9-1G>A). This novel IVS9-1A>G mutation created a new restriction site for the enzyme BspTI which facilitated an independent confirmation of this splice site mutation (Fig. 3). Her non-affected sisters and daughter were found to be heterozygous for this mutation.

In family IV, all the 5 affected siblings were compound heterozygous for the mutations IVS7-2A>G and a transversion 2392A>G in exon 19 resulting in substitution of histidine to arginine (H723R) (20). Specifically, the IVS7-2A>G was from their father, while the H723R was from their mother (Fig. 4).

The proband of family V was compound heterozygous for the mutations IVS7-2A>G and the 1548insC in exon 14 (Fig. 4). All 4 affected siblings of family VI were either homozygous or hemizygous for a frame shift mutation, 1548insC, in exon 14. Their mother and the daughter of a brother of the proband were heterozygous for the mutation (Fig. 4).

DISCUSSION

We report the clinical and molecular features of 16 Thai patients in 6 families with Pendred syndrome. All 6 probands manifested the triad clinical symptoms of classical Pendred syndrome: bilateral sensorineural hearing loss, goiter, and a positive per-

J. Endocrinol. Invest. 30: 907-913, 2007
©2007, Editrice Kurtis.

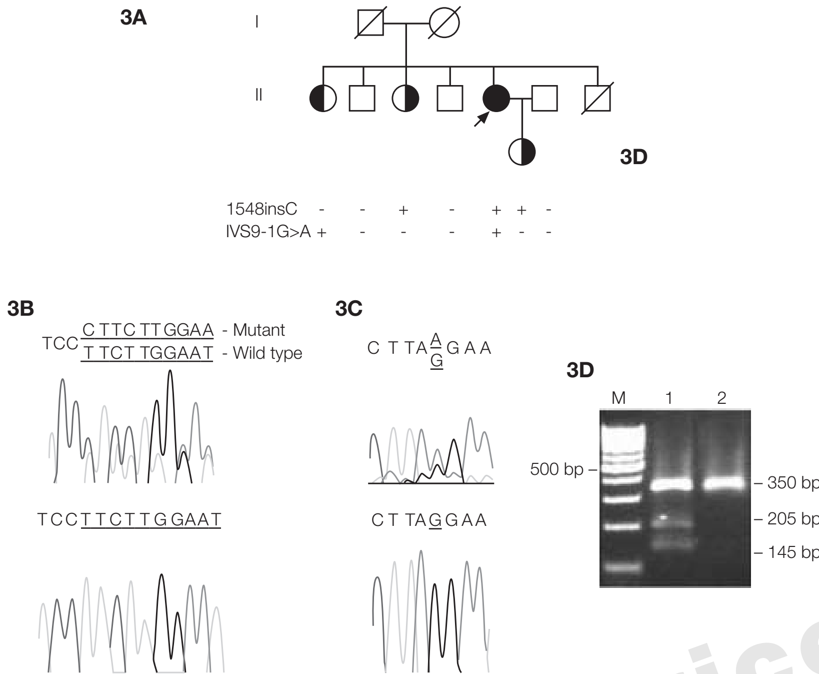

Fig. 3 - *Family III. 3A) Pedigree. 3B) The sense sequence of exon 14 of the proband showing the 1548insC mutation (upper panel), compared to that of a control (lower panel). 3C) The sense sequence of exon 10 of the PDS gene of the proband showing the IVS9-1G>A mutation (upper panel), compared to that of a control (lower panel). 3D) The size of PCR product of exon 10 is 350 bp. After BspTI treatment, the undigested 350 bp in wild-type and two restriction products of 205 and 145 bp of the IVS9-1G>A mutant allele were produced in lane 1, while only the 350-bp band was seen in lane 2 of control. M represents the 100-bp marker.*

©2007, Editrice Kurtis

chlorate discharge test (21). Concordant with previous published series, most of our affected patients were euthyroid and about 2/3 had goiters (1, 3). False negative results of the perchlorate discharge test were noted in subjects, I-2 and IV-2 (Table 1). Intra-familial phenotypic variations especially in the thyroid manifestation were identified in affected patients in family I, II, IV, and VI. Modifier genes or environmental factors such as iodine supplementation may modulate the phenotypic effect of PDS mutations, especially the thyroid gland affection (22). Even though inner ear imaging study was not obtained on all of our patients, EVA was found in both of our cases who underwent the study. No data were available about the progressive nature of the hearing defect in our affected patients. Of note is the presence of follicular thyroid carcinoma and Hürthle cell adenoma in affected patients in family I. There are only few studies investigating an association between thyroid carcinoma and Pendred syndrome (23, 24). This may be in line with an increased incidence of thyroid carcinomas in patients with untreated congenital hypothyroidism caused by dyshormonogenesis (25). Long-standing stimulation of the thyroid gland by TSH may result in multistep progression from polyclonal hyperplasia to an increasingly aggressive carcinoma (26, 27). Interestingly, ovarian carcinoma was found in an affected member of family IV. An association between ovarian cancer and Pendred syndrome, however, has never been reported.

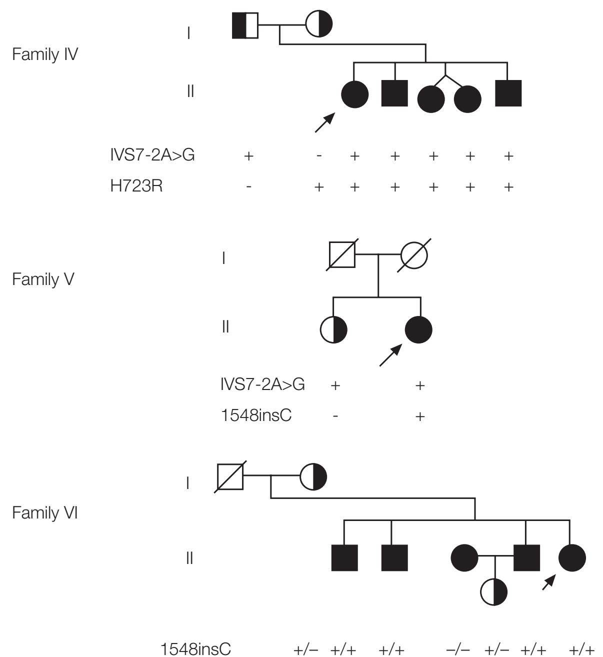

Fig. 4 - *Pedigree and molecular analysis of families IV, V and VI. "+" and "–" indicate presence and absence of the mutant allele, respectively.*

Sequencing of the entire coding region of the PDS gene successfully identified all 12 mutant alleles of these 6 families. The 12 identified mutant alleles constituted 6 distinct mutations including 3 splice site mutations (IVS4-1G>A, IVS7-2A>G, IVS9-1G>A), 1 frame shift mutation (1548insC) and 2 missense mutations (T67S, H723R). IVS7-2A>G and 1548insC were each composed of 4 mutant alleles comprising 8 out of 12 mutants. Therefore, mutational analysis directed at these 2 common mutations may identify the majority mutant alleles in the Thai population. IVS7-2A>G and H723R have previously been found in East Asian populations as the prevalent alleles accounting for a majority of observed PDS mutations (15, 21, 28). 1548insC was also reported in deaf probands from Mongolia (15). In Japan, most of the patients were either homozygous or compound heterozygous for H723R, a mutation which accounts for 75% of the mutations in Japanese families with EVA with and without classical Pendred syndrome (16, 29, 30), while the incidence of this mutation is low in Western countries. The detection of these mutations in multiple probands from different Asian populations suggested that it might have arisen on a common ancestral founder chromosome. Haplotype analyses of these mutations are required to verify this hypothesis. We did not detect any of the eight mutations (G209V, L236, IVS8+1G>A, E384G, T416P, L445W, Y530H, T721M) most commonly reported among Western patients (21, 31-34).
Three novel mutations were identified in our study. Two of them were splice site mutations, IVS4-1G>A and IVS9-1G>A. The third one was a missense mutation, 200C>G (T67S). The fact that it was not found in 50 unrelated Thai controls (100 alleles) and that it segregated with the Pendred phenotype within family II supports its etiologic role.
In conclusion, we reported 3 novel mutations, T67S, IVS4-1G>A, and IVS9-1G>A, extending the total number of confirmed PDS mutations to more than 100. In addition, this study suggests that IVS7-2 A>G and 1548insC seem to be particularly prevalent in the Thai population. The spectrum of the PDS mutations revealed in this study will constitute a significant and relevant tool for an effective molecular diagnosis of a category of disease caused by this gene in the Thai population. However, if these particularly frequent mutations are not detected, sequencing of the whole coding regions will be required.

ACKNOWLEDGMENTS

The authors thank Dr. Wanla Kulwichit and Professor Dr. Henry Wilde for invaluable input to this study. The study was supported by the Anandamahidol research fund and Molecular research fund of Chulalongkorn University, and Thailand research fund.

REFERENCES

1. Reardon W, Coffey R, Chowdhury T, et al. Prevalence, age of onset, and natural history of thyroid disease in Pendred syndrome. J Med Genet 1999, 36: 595-8.
2. Phelps PD, Coffey RA, Trembath RC, et al. Radiological malformations of the ear in Pendred syndrome. Clin Radiol 1998, 53: 268-73.
3. Prasad S, Kölln KA, Cucci RA, Trembath RC, Van Camp G, Smith RJ. Pendred syndrome and DFNB4-mutation screening of SLC26A4 by denaturing high-performance liquid chromatography and the identification of eleven novel mutations. Am J Med Genet A 2004, 124: 1-9.
4. Everett LA, Glaser B, Beck JC et al. Pendred syndrome is caused by mutations in a putative sulphate transporter gene (PDS). Nat Genet 1997, 17: 411-22.
5. Everett LA, Morsli H, Wu DK, Green ED. Expression pattern of the mouse ortholog of the Pendred's syndrome gene (Pds) suggests a key role for pendrin in the inner ear. Proc Natl Acad Sci U S A 1999, 96: 9727-32.
6. Yoshino T, Sato E, Nakashima T, et al. Distribution of pendrin in the organ of Corti of mice observed by electron immunomicroscopy. Eur Arch Otorhinolaryngol 2006, 263: 699-704.
7. Yoshida A, Taniguchi S, Hisatome I, et al. Pendrin is an iodide-specific apical porter responsible for iodide efflux from thyroid cells. J Clin Endocrinol Metab 2002, 87: 3356-61.
8. Royaux IE, Suzuki K, Mori A, et al. Pendrin, the protein encoded by the Pendred syndrome gene (PDS), is an apical porter of iodide in the thyroid and is regulated by thyroglobulin in FRTL-5 cells. Endocrinology 2000, 141: 839-45.
9. Bidart JM, Lacroix L, Evain-Brion D, et al. Expression of Na^+/I^- symporter and Pendred syndrome genes in trophoblast cells. J Clin Endocrinol Metab 2000, 85: 4367-72.
10. Suzuki K, Royaux IE, Everett LA, et al. Expression of PDS/Pds, the Pendred syndrome gene, in endometrium. J Clin Endocrinol Metab 2002, 87: 938-41.
11. Rillema JA, Hill MA. Prolactin regulation of the pendrin-iodide transporter in the mammary gland. Am J Physiol Endocrinol Metab 2003, 284: E25-8.
12. Soleimani M, Greeley T, Petrovic S, et al. Pendrin: an apical $Cl^-/OH^-/HCO_3^-$ exchanger in the kidney cortex. Am J Physiol Renal Physiol 2001, 280: F356-64.
13. Royaux IE, Wall SM, Karniski LP, et al. Pendrin, encoded by the Pendred syndrome gene, resides in the apical region of renal intercalated cells and mediates bicarbonate secretion. Proc Natl Acad Sci U S A 2001, 98: 4221-6.
14. Gillam MP, Sidhaye AR, Lee EJ, Rutishauser J, Stephan CW, Kopp P. Functional characterization of pendrin in a polarized cell system. Evidence for pendrin-mediated apical iodide efflux. J Biol Chem 2004, 279: 13004-10.

©2007, Editrice Kurtis

J. Endocrinol. Invest. 30: 907-913, 2007
©2007, Editrice Kurtis.

15. Park HJ, Shaukat S, Liu XZ, et al. Origins and frequencies of SLC26A4 (PDS) mutations in east and south Asians: global implications for the epidemiology of deafness. J Med Genet 2003, 40: 242-8.
16. Usami S, Abe S, Weston M, Shinkawa H, Van Camp G, Kimberling WJ. Non-syndromic hearing loss associated with enlarged vestibular aqueduct is caused by PDS mutations. Hum Genet 1999, 104: 188-92.
17. Antonarakis SE. Recommendations for a nomenclature system for human gene mutations. Nomenclature Working Group. Hum Mutat 1998, 11: 1-3.
18. Colvin IB, Beale T, Harrop-Griffiths K. Long-term follow-up of hearing loss in children and young adults with enlarged vestibular aqueducts: relationship to radiologic findings and Pendred syndrome diagnosis. Laryngoscope 2006, 116: 2027-36.
19. Coucke PJ, Van Hauwe P, Everett LA, et al. Identification of two different mutations in the PDS gene in an inbred family with Pendred syndrome. J Med Genet 1999, 36: 475-7.
20. Van Hauwe P, Everett LA, Coucke P, et al. Two frequent missense mutations in Pendred syndrome. Hum Mol Genet 1998, 7: 1099-104.
21. Yong AM, Goh SS, Zhao Y, Eng PH, Koh LK, Khoo DH. Two Chinese families with Pendred's syndrome—radiological imaging of the ear and molecular analysis of the pendrin gene. J Clin Endocrinol Metab 2001, 86: 3907-11.
22. Pfarr N, Borck G, Turk A, et al. Goitrous congenital hypothyroidism and hearing impairment associated with mutations in the TPO and SLC26A4/PDS genes. J Clin Endocrinol Metab 2006, 91: 2678-81.
23. Abs R, Verhelst J, Schoofs E, De Somer E. Hyperfunctioning metastatic follicular thyroid carcinoma in Pendred's syndrome. Cancer 1991, 67: 2191-3.
24. Bidart JM, Mian C, Lazar V, et al. Expression of pendrin and the Pendred syndrome (PDS) gene in human thyroid tissues. J Clin Endocrinol Metab 2000, 85: 2028-33.
25. Vickery AL Jr. The diagnosis of malignancy in dyshormonogenetic goiter. Clin Endocrinol Metab 1981, 10: 317-35.
26. Camargo R, Limbert E, Gillam M, et al. Aggressive metastatic follicular thyroid carcinoma with anaplastic transformation arsing from a long-standing goiter in a patient with Pendred's syndrome. Thyroid 2001, 11: 981-8.
27. Medeiros-Neto G, Gil-Da-Costa MJ, Santos CL, et al. Metastasis thyroid carcinoma arising from congenital goiter due to mutation in the thyroperoxidase gene. J Clin Endocrinol Metab 1998, 83: 4162-6.
28. Scott DA, Wang R, Kreman TM, et al. Functional differences of the PDS gene products are associated with phenotypic variation in patients with Pendred syndrome and non-syndromic hearing loss (DFNB4). Hum Mol Genet 2000, 9: 1709-15.
29. Kitamura K, Takahashi K, Noguchi Y, et al. Mutations of the Pendred syndrome gene (PDS) in patients with large vestibular aqueduct. Acta Otolaryngol 2000, 120: 137-41.
30. Tsukamoto K, Suzuki H, Harada D, Namba A, Abe S, Usami S. Distribution and frequencies of PDS (SLC26A4) mutations in Pendred syndrome and nonsyndromic hearing loss associated with enlarged vestibular aqueduct: a unique spectrum of mutation in Japanese. Eur J Hum Genet 2003, 11: 916-22.
31. Coyle B, Reardon W, Herbrick JA, et al. Molecular analysis of the PDS gene in Pendred syndrome. Hum Mol Genet 1998, 7: 1105-12.
32. Campbell C, Cucci RA, Prasad S, et al. Pendred syndrome, DFNB4, and PDS/SLC26A4 identification of eight novel mutations and possible genotype-phenotype correlations. Hum Mutat 2001, 17: 403-11.
33. Albert S, Blons H, Jonard L, et al. SLC26A4 gene is frequently involved in nonsyndromic hearing impairment with enlarged vestibular aqueduct in Caucasian populations. Eur J Hum Genet 2006, 14: 773-9.
34. Lopez-Bigas N, Melchionda S, de Cid R, et al. Identification of five new mutations of PDS/SLC26A4 in Mediterranean families with hearing impairment. Hum Mutat 2002, 20: 77-8.

©2007, Editrice Kurtis