ORIGINAL ARTICLE

A Novel Mutation of SLC26A4 Gene In an Iranian Family with Pendred Syndrome

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In the diagnosis of Pendred syndrome, assessment of individuals by molecular analysis of the SLC26A4 gene is recommended. Here we report a novel mutation in the SLC26A4 gene as revealed by denaturing high performance liquid chromatography (DHPLC) and DNA sequencing of the entire coding region of the SLC26A4 gene in five members of an Iranian family affected with Pendred syndrome. This is the first report of the molecular investigation of Pendred syndrome in Iran and the first report of the R79X mutation.

Key Words: Pendred syndrome, congenital deafness, SLC26A4, R79X, mutation analysis, Iran

Introduction

Pendred syndrome accounts for 1 to 10% of hereditary hearing loss in various world populations. It is the most common form of the syndromic hearing loss associated with thyroid dysfunction.[1]

Although deficiency of the interscalar septum in the distal coils of the cochlea (Mondini deformity) has been found to be common, it is probably not a constant feature of Pendred syndrome.[2] It has been stated that enlargement of the vestibular aqueduct, a radiologic marker, should be considered as the most likely presentation of Pendred syndrome.[3]

To assess deficiency in the bony interscalar septum of the cochlea (Mondini deformity) and to evaluate the (VA) Vestibular Aqueduct, high resolution computed tomography (CT) of temporal bones in the coronal and axial planes is performed. On the other hand, Magnetic Resonance Imaging (MRI) is used to examine enlargement of the endolymphatic sac and duct in association with a large VA.[2,3]

Patients suffering from undiagnosed Pendred syndrome often present with congenital hearing loss, but thyroid dysfunction could go undetected, might not arise until later in life or could even be compensated hypothyroidism. Indeed, thyroid dysfunction in Pendred syndrome varies and many patients remain euthyroid.[4] For this reason, due to the nonspecific nature of the perchlorate discharge test,[5] the gold-standard investigation for Pendred syndrome, molecular analysis of the SLC26A4 gene in the assessment of indi-

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viduals with severe to profound congenital hearing loss, is recommended.[6]

The SLC26A4 gene is located on chromosome 7q31 and contains 21 exons (Fig.1).[7] The encoded protein is pendrin, which is composed of 12 transmembrane domains.[7,8] The SLC26A4 gene has a relatively restricted pattern of expression, with SLC26A4 mRNA detected only in the thyroid, inner ear, and kidney. An autosomal recessive locus for non-syndromic deafness designated DFNB4 also maps to 7q31, the same region as SLC26A4 gene. Mutations of the SLC26A4 gene are causative for both Pendred syndrome (MIM 274600) and DFNB4 (MIM 600791).[9] The aim of this study was to determine the molecular cause of Pendred in the family studied.

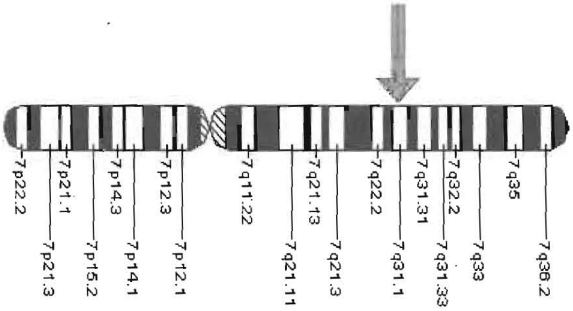

Fig. 1. The SLC26A4 gene location; the gene is located on the long (q) arm of chromosome 7 at 7q31.1.

Case Report

A 40-year-old male presented with hereditary sensory neural hearing loss with symptoms of hypothyroidism and goiter, at 38 years of age, detected by isotope scanning and ultrasonography. On physical examination, other organs abnormalities of the cardiovascular, central nervous system and of the skin were seen. There was no history of any other disorders related to hearing loss or usage of any medications resulting in hearing

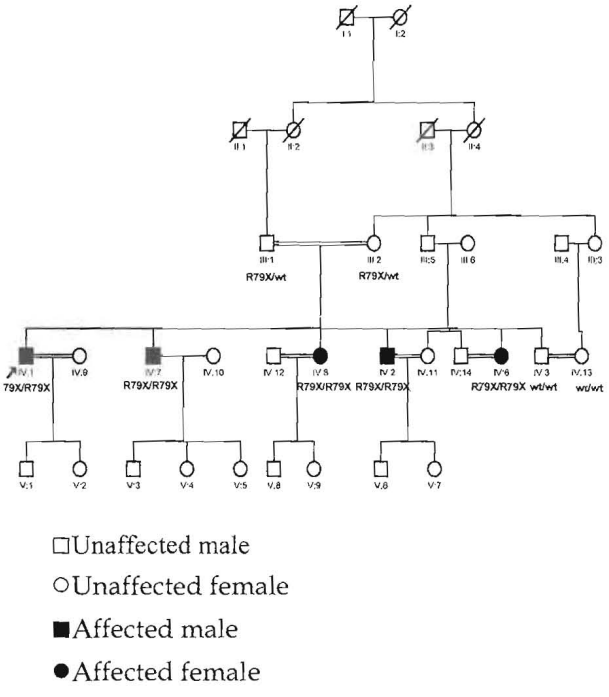

Fig. 2. Pedigree of the family (wt: wild type)

impairment. The patient had 5 siblings (Fig.2).

There was a history of similar symptoms in two of his brothers (48 and 43 years old) and two sisters (45 and 21 years old). The affected individuals had congenital hearing loss and adult onset thyroid dysfunction. The age of onset for thyroid dysfunction varied in these affected siblings (Table.1). We did not perform CT scan or MRI to rule out mondini deformity and VAE (Vestibular Aqueduct Enlargement). There was no information about thyroid function status prior to development of hypothyroidism.

The parents' marriage was consanguineous (first cousins). The SLC26A4 gene was sequenced and we identified a novel mutation due to a nucleotide substitution (235C>T) (Fig.3.) in the third exon of SLC26A4 gene which results in a stop codon (R79X) (Fig. 4).

Table1. Clinical characteristics of study cases

Clinical characteristics	Patient: oneIV:7	Patient: two IV:8	Patient: three IV:2	Patient: four IV:1	Patient: five IV:6
Age of cases	48	45	43	40	21
Age of onset of hypothyroidism	28	24	24	38	14
Age of onset of hearing impairment	Infancy	Infancy	Infancy	Infancy	Infancy
Severity of deafness	Severe-profound	Severe-profound	Severe-profound	Severe	Moderately
Uni-or bilateral deafness	Bilateral SNHL	Bilateral SNHL	Bilateral SNHL	Bilateral SNHL	Bilateral SNHL
Type of Hearing Loss	Non-progressive	Non-progressive	Non-progressive	Non-progressive	Non-progressive
Imaging tests to rule out Mondini deafness and VAE	Not yet	Not yet	Not yet	Not yet	Not yet

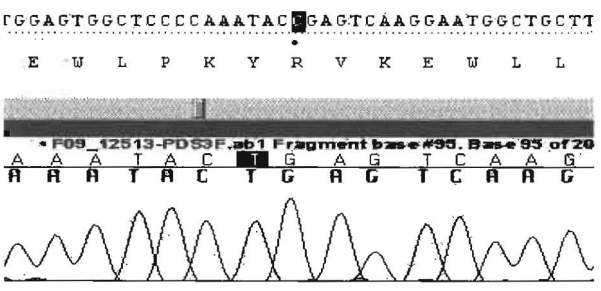

Fig.3. Location of 235C>T mutation

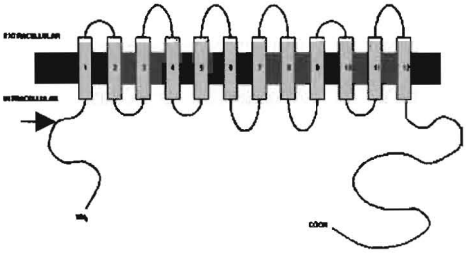

Fig.4. Location of the R79X mutation in pendrin protein

Discussion

This case report is an attempt to highlight the importance of considering Pendred syndrome in the differential diagnosis of those patients with congenital hearing impairment and especially mutation analysis in patients suspected of having Pendred syndrome. The molecular diagnosis of this family has led to the identification of a novel mutation, higher to unreported in other populations. Because population-specific differences are not uncommon, and the rate of consanguineous marriage in Iran is high, 38.6 for overall and 27.9 for first cousin marriages,[10] it is important that the mutation spectrum of this gene to be investigated further in our population. This patient had been initially diagnosed with congenital hearing loss but only upon detection of hypothyroidism and goiter at age 38, was a diagnosis of Pendred syndrome suspected. Pendred syndrome, the most common syndromic form of deafness, is an autosomal recessive disorder associated with developmental abnormalities of the cochlea, sensorineural hearing loss, and diffuse thyroid enlargement (goiter) caused by mutations in the SLC26A4 gene. Mutations in this gene also cause non-syndromic deafness, DFNB4, as well as enlarged vestibular aqueduct syndrome (EVA).[11] Everett et al. found that the

SLC26A gene encodes a 780-amino acid (86 kD) protein, an anion transporter known as Pendrin. Pendrin is closely related to a number of sulfate transporters and contains 12 transmembrane proteins.[6]

To date, 90 mutations have been found in the SLC26A4 gene, four of which (L236P, IVS8+1G>A, T416P, and H723R) account for approximately 60% of the total Pendred genetic load.[8]

Functional studies by Scott et al. suggest that the observed phenotype correlates with the degree of residual function of the encoded protein, Pendrin. Thus, mutations that result in no residual transport function appear to be associated with the Pendred phenotype; minimal transport ability prevents thyroid dysfunction but not the (Sensorineural Hearing Loss) SNHL and temporal bone anomalies that characterize DFNB4.[12]

The perchlorate discharge test, used in the diagnosis of Pendred syndrome, is nonspecific, and, in the absence of alternative means of confirming the diagnosis, its sensitivity is unknown.[5,6] Reardon et al. (1997) used the mapping of the Pendred syndrome gene to 7q to identify pedigrees and assessed the prevalence of clinical parameters of the disease in affected individuals. Cosegregation between disease and the locus on 7q was found in 36 familial cases. Clinical and investigative findings were compared in 18 index cases versus 18 affected siblings. The overall prevalence of goiter was 73%. The prevalence was higher in index cases (94%) than in siblings (56%), many of whom had not previously been diagnosed with the condition. One perchlorate discharge test was false-negative (2.9%). Radiologic malformations of the cochlea were identified in 86% of cases. Researchers in this study concluded that securing a diagnosis of Pendred syndrome may be difficult, especially in a single case.[13]

Over ninety different types of mutations have been reported in the SLC26A4 gene so far, most of which have been identified within western populations,[8,11] though molecular investigation of Pendred syndrome has not been reported in our country.

Our previous study regarding the epidemiology of GJB2 gene mutations among the autosomal recessive non-syndromic deaf (ARNSD) showed that prevalence of GJB2-realted deafness is 16.7% in our population which is significantly different from reports published on Western populations. In addition, novel mutations have been found among these patients which have not been reported in other populations.[14,15] Further studies on the prevalence of SLC26A4 gene mutations in our population are required due to the fact that SLC26A4 gene mutations cause ARNSD without goiter as well.[11] We also suggest that mutation detection in the diagnosis of Pendred syndrome be applied to patients with the clinical indication of Pendred syndrome as a part of patient management.

Acknowledgement

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References

1. Batsakis JG, Nishiyama RH. Deafness with sporadic goiter. Pendred's syndrome. Arch Otolaryngol. 1962;76:401-6.
2. Phelps PD, Coffey RA, Trembath RC, Luxon LM, Grossman AB, Britton KE, et al. Radiological malformations of the ear in Pendred syndrome. Clin Radiol. 1998;53(4):268-73.
3. Reardon W, OMahoney CF, Trembath R, Jan H, Phelps PD. Enlarged vestibular aqueduct: a radiological marker of pendred syndrome, and mutation of the PDS gene. QJM. 2000;93(2):99-104.
4. Burrow GN, Spaulding SW, Alexander NM, Bower BF. Normal peroxidase activity in Pen-

dred's syndrome. J Clin Endocrinol Metab. 1973;36(3):522-30.
5. Fraser G. Deafness with goiter (Pendred's syndrome) Baltimore: The John Hopkins University Press, 1976. Coyle B, Reardon W, Herbrick J.-A, Tsui L-C, Gausden E, Lee J, et al. Molecular analysis of the PDS gene in Pendred syndrome (sensorineural hearing loss and goitre). Hum Mol Genet. 1998;7:1105-12.
6. Coyle B, Reardon W, Herbrick JA, Tsui LC, Gausden E, Lee J, et al. Molecular analysis of the PDS gene in Pendred syndrome. Hum Mol Genet. 1998;7(7):1105-12.
7. Everett LA, Glaser B, Beck JC, Idol JR, Buchs A, Heyman M, Adawi F, Hazani E, Nassir E, Baxevanis AD, Sheffield VC, Green ED. Pendred syndrome is caused by mutations in a putative sulphate transporter gene (PDS). Nat Genet. 1997;17 (4):411-22.
8. Saadat M, Ansari-Lari M, and Farhud D.D. Consanguineous marriage in Iran Annals of Human Biology 2004; 31: 263-9.
9. Scott DA, Wang R, Kreman TM, Sheffield VC, Karniski LP. The Pendred syndrome gene encodes a chloride-iodide transport protein. Nat Genet. 1999;21(4):440-3.
10. Saadat M, Ansari-Lari M, Farhud DD. Consanguineous marriage in Iran. Ann Hum Biol. 2004;31(2):263-9.
11. Park HJ, Shaukat S, Liu XZ, Hahn SH, Naz S, Ghosh M, 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(4):242-8.
12. Scott DA, Wang R, Kreman TM, Andrews M, McDonald JM, Bishop JR, et al. Functional differences of the PDS gene product are associated with phenotypic variation in patients with Pendred syndrome and non-syndromic hearing loss (DFNB4). Hum Mol Genet. 2000;9(11):1709-15.
13. Reardon W, Coffey R, Phelps PD, Luxon LM, Stephens D, Kendall-Taylor P, et al. Pendred syndrome--100 years of underascertainment? QJM. 1997;90(7):443-7.
14. Najmabadi H, Nishimura C, Kahrizi K, Riazalhosseini Y, Malekpour M, Daneshi A, et al. GJB2 mutations: passage through Iran. Am J Med Genet A. 2005;133(2):132-7.
15. Najmabadi H, Cucci RA, Sahebjam S, Kouchakian N, Farhadi M, Kahrizi K, et al. GJB2 mutations in Iranians with autosomal recessive non-syndromic sensorineural hearing loss. Hum Mutat. 2002; 19(5):572.