Surprising news: a putative sulfate transporter is defective in Pendred’s syndrome

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The cloning of the gene involved in the pathogenesis of Pendred’s syndrome has been eagerly awaited since linkage was reported to chromosome 7q22–31.1 in 1996 (1, 2). What could cause sporadic goiter with impaired iodine organification along with congenital sensorineural deafness? The association of these signs was first described by Vaughan Pendred in 1898, in a family in which two of five children were deaf mutes and had large goiters (3). Subsequent reports on families with Pendred’s syndrome, many of them highly inbred, suggested an autosomal recessive mode of inheritance (4, 5). As first demonstrated by Morgans and Trotter in 1958, the administration of perchlorate to these patients results in a partial discharge of radiolabeled iodide from the thyroid, indicating an impaired organification of this trace element into thyroglobulin (6). However, despite these thyroid abnormalities, most Pendred patients are euthyroid, excluding hypothyroidism as a cause of the deafness. The sensorineural deafness is typically associated with a malformation of the inner ear, referred to as Mondini cochlea, in which the apical cochlear turns are replaced by a single cavity. The expression of both deafness and goiter development is variable among affected individuals. Deafness is most commonly present at birth, but may only become apparent during childhood. The incidence of Pendred’s syndrome is thought to be as high as 7.5 to 10 in 100 000 individuals, and it has been estimated to account for about 10% of the cases with hereditary deafness (7). This defines Pendred’s syndrome as the most common form of syndromic deafness.

The initial reports on linkage to 7q22–31.1 were confirmed in subsequent studies and demonstrated genetic homogeneity, indicating that the syndrome is caused by mutations within the same gene (8, 9). Importantly, these studies also excluded the possibility that the genes encoding thyroglobulin (chromosomal location 8q24), thyroperoxidase (2p25), or the thyroid hormone receptor α (17q11.2) and β (3p24.3) are directly involved in the pathogenesis of the syndrome. Who could then be the culprit? There was wide room for speculation and the candidates included structural proteins, ion-channels, transcription factors or possibly an NADPH-oxidoreductase involved in H₂O₂ generation. Others felt that Pendred’s syndrome might be caused by a contiguous gene defect. The latter hypothesis obtained some support by the fact that an independently mapped locus associated with hereditary deafness, DFNB4, is located within the same genetic region.

Everett and colleagues put an end to these speculations and provided us with a surprising answer: the gene found to be defective in patients affected by Pendred’s syndrome encodes a putative sulfate transporter (10). By studying additional consanguineous kindreds, these investigators further refined the critical region from about 1.7 to a genetic distance of 1.1 centiMorgans. Subsequently, this region was physically mapped and systematically sequenced. Analysis of seven candidate genes, three of them previously known, were negative. The eighth gene submitted to mutational analysis was found to be mutated in individuals with Pendred’s syndrome and consequently was called the Pendred syndrome gene (PDS).

The PDS cDNA contains an open reading frame of 2343 bp and encompasses 21 exons. The predicted gene product, called pendrin, is a highly hydrophobic 780 amino-acid protein with eleven putative transmembrane domains. On the basis of its high homology to several sulfate transporters found in yeast, plants, and animals, pendrin is thought to exert a similar functional role. However, the formal proof for this assumption is still pending. The closest relatives of the PDS gene are the human DRA (down-regulated in adenoma) and the DTD (diastrophic dystrophia) genes. Notably, DRA is telomerically oriented in a head-to-tail arrangement in close vicinity to PDS, suggesting an ancient gene duplication. DRA encodes an intestine-specific sulfate transporter which is mutated in congenital chloride diarrhea (11, 12). Mutations in the DTD gene can result in various subtypes of chondrodysplasias caused by impaired development and stability of connective tissues (13, 14).

As demonstrated by Northern analysis, PDS gene expression is almost exclusively found in the thyroid gland. Only weak signals were demonstrated in adult and fetal kidney, as well as in fetal brain. PDS expression was also found to be positive by probing a human cochlear cDNA library.

Analysis of the PDS gene in five kindreds with Pendred’s syndrome led to the identification of three distinct mutations resulting in disruption of a highly
conserved region or premature truncations of the protein. Consistent with the autosomal recessive mode of inheritance, affected individuals were homozygous and obligate carriers heterozygous for the respective mutations, while non-carriers or unrelated controls were homozygous for the wild-type sequence. This mode of transmission, together with the profound alterations of the protein caused by the detected mutations, confirm that PDS is indeed the gene responsible for the peculiar phenotype found in Pendred’s syndrome.

It will now be exciting to learn how this putative sulfate transporter exerts its roles both in the ear and the thyroid. PDS defines a new class of deafness genes, a category which has dramatically expanded over the last few years (15, 16). Does pendrin play a role in inner ear development, does it have a role in inner ear function? Endocrinologists ponder on the role of pendrin in development, does it have a role in inner ear function? Pendred syndrome maps to chromosome 7q21–34 and is caused by an intrinsic defect in thyroid iodine organification. Nature Genetics 1997 40 48–54.

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