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The Gene for Pendred Syndrome Is Located between D7S501 and D7S692 in a 1.7-cM Region on Chromosome 7q

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Pendred syndrome is an autosomal recessive disorder characterized by goiter and congenital deafness. The primary defect is not yet known, although the gene causing Pendred syndrome has been localized very recently on chromosome 7q, a region that also contains a gene responsible for nonsyndromal hearing loss (DFNB4). We confirmed linkage to this chromosome 7 region in five Pendred families originating from different ethnic groups, with a highest cumulative lod score of 8.26 for marker D7S501. In combination with previous reports, our results define a candidate region for the Pendred gene of 1.7 cM flanked by markers D7S501 and D7S692. © 1997 Academic Press

INTRODUCTION

Pendred syndrome (MIM No. 274600) is characterized by the presence of goiter and profound congenital sensorineural hearing loss (Pendred, 1896). Most affected persons are euthyroid, although hypothyroidism is occasionally reported (Batsakis *et al.*, 1962). Hearing impairment is usually congenital and, in nearly all cases, is accompanied by a type of cochlear hypoplasia known as a Mondini defect (Gorlin, 1995). The disease prevalence of Pendred syndrome is estimated at 4–10% among congenitally deaf children, and the frequency varies from 1/15,000 in the British Isles to 1/100,000 in Scandinavia (Gorlin, 1995).

Inheritance is generally considered to be autosomal recessive, and in many families, consanguinity between nonaffected parents can be documented. However, there are some families in which the disease apparently skips generations, and the phenotype varies in affected persons. These intrafamilial differences are consistent

with autosomal dominant inheritance with incomplete penetrance (Illum *et al.*, 1972).

The primary defect responsible for Pendred syndrome is not yet known, although it probably involves the partial failure to convert free iodide into organic iodine in the thyroid gland in Pendred patients (Frazer, 1965; Morgans and Trotter, 1958). The latter process is a complex sequence of metabolic events. During the formation of thyroid hormones, iodide is first oxidized and then covalently bound to thyroglobulin (TG) to form iodotyrosyls by thyroperoxidase (TPO). The iodotyrosyls are subsequently coupled oxidatively into iodothyronines T₃ and T₄ within the matrix of TG (Dumont *et al.*, 1994). The iodine organification defect in Pendred patients is demonstrated with the perchlorate test, which releases free iodine from the thyroid gland and is very common in patients with Pendred syndrome (Illum *et al.*, 1972). TG and TPO are both major components of the iodine organification system. However, biochemical studies failed to find abnormalities in these proteins in Pendred patients (Burrow *et al.*, 1973; Manglabruks *et al.*, 1991; Ljunggren *et al.*, 1973; Niepomniszeze *et al.*, 1978; Cave and Dunn, 1975), and genetic linkage analysis excluded both genes (Coucke *et al.*, 1995; Coyle *et al.*, 1996).

Recently, two groups reported linkage of Pendred syndrome to chromosome 7q31 in an interval of 5.5 and 9.2 cM, respectively (Coyle *et al.*, 1996; Sheffield *et al.*, 1996). In the present study, we confirm the localization of the Pendred syndrome gene to 7q31, provide more evidence for genetic homogeneity, and reduce the candidate region to 1.7 cM.

MATERIALS AND METHODS

Families. The diagnosis of Pendred syndrome was established when individuals presented congenital hearing loss and a palpable goiter. In all five families an abnormal perchlorate test was present in at least one family member. Family 1 originates from Belgium

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and is not consanguineous (Fig 1). Family 2 originates from an isolated small village, Tasobasi, in the South of Turkey. This family is highly consanguineous and includes more than 13 affected individuals (Fig. 1). The family has been subject of a previous clinical study (Kabakkaya *et al.*, 1993). Families 3 and 4 originate from the Netherlands, and the parents of the patients are consanguineous. The two patients from Family 4 have been described extensively (Cremers, 1976). A fifth family lives in Denmark but originates from Lebanon. Patient IV-2 from this family showed no goiter and a normal perchlorate test, although congenital hearing loss was present, and a cochlear defect of the Mondini type was shown by CT scan. Patient IV-3 has congenital hearing loss, a Mondini malformation of the cochlea, an abnormal perchlorate test, but no goiter.

Linkage analysis. Genomic DNA was purified from peripheral blood samples by standard techniques. Microsatellite polymorphisms were taken from the recent genetic map from Généthon (Dib *et al.*, 1996). Polymerase chain reaction amplification and electrophoresis on polyacrylamide gels were performed as described (Hughes, 1993). Two-point linkage analysis was performed using the MLINK program of the LINKAGE 5.1 package (Lathrop and Laouel, 1984). An estimated frequency of 1/100 was used for the disease gene, and penetrance was set at 100%. Allele frequencies were set equal to each other. Lod score calculations in Family 2 were performed without the consanguinity of the parents of sibship B and of the paternal grandparents of sibship D taken into account.

RESULTS

Linkage Analysis

Five families segregating with Pendred syndrome were studied (Fig. 1). We typed these five pedigrees with 10 polymorphic markers from 7q31. All these markers were obtained from the most recent Généthon genetic map (Fig. 2) (Dib *et al.*, 1996). Table 1 summarizes the two-point lod scores for the 10 markers. Cumulative lod scores higher than 3 were obtained for all markers except D7S523. The highest combined lod score of 8.26 was obtained for marker D7S501 at recombination fraction 0. When the lod scores for each of the families were analyzed separately, lod scores higher than 3 were obtained only for Family 2 with a maximum of 4.91 for marker D7S496 at recombination fraction 0. The other four families are too small to yield statistically significant lod scores, but the theoretical maximum lod score was approached for each of the families when the lod scores were calculated with 100% informative markers. Therefore, it is likely that all five families are linked to chromosome 7q. Statistical analysis of the data using HOMOG (Ott, 1991) gave a maximum likelihood under the hypothesis of linkage homogeneity, confirming this assumption.

Haplotype Analysis

To narrow down the candidate region of the Pendred gene, haplotypes were constructed for the 10 markers that were analyzed. As Family 2 is highly inbred, homozygosity mapping was used to delineate the interval containing the Pendred gene. In this family, eight Pendred patients from four related sibships (A–D) were analyzed (Fig. 1). In sibship A, the parents are first cousins, and both patients are homozygous for all 10

markers tested. The parents for sibship B were reported to be consanguineous, but the exact nature of their blood relationship could not be indicated by the family members. The three patients from sibship B are homozygous for four adjacent markers, D7S2453, D7S501, D7S496, and D7S2459. In contradiction to the consanguinity of the parents of sibship C that was reported in a previous study (Kabakkaya *et al.*, 1993), extensive interviews of the family on several occasions in the course of this study revealed no reports of consanguinity between the parents of sibship C. As the father of this sibship has a completely different disease haplotype, he is most likely unrelated to the family and carries an independent Pendred mutation. The parents of sibship D are first cousins, and the paternal grandparents were also reported to be related by family members, although they could not indicate the exact nature of this consanguinity. The patient from sibship D is homozygous for five adjacent markers, D7S2453, D7S501, D7S496, D7S2459, and D7S692. When the disease-carrying chromosome from the unrelated father of sibship C is not taken into account, all the haplotypes of the eight patients in Family 2 are identical for the four adjacent markers D7S2453, D7S501, D7S496, and D7S2459. Under the assumption that the parents of sibship B are consanguineous and have inherited the same mutation from a common ancestor, a historical recombination must have occurred between the Pendred gene and D7S692. This assumption is likely for two reasons. First, several family members confirmed the consanguinity of the parents of sibship B. Second, the three patients of sibship B are homozygous for four adjacent markers, D7S2453, D7S501, D7S496, and D7S2459, that also show several other alleles in the rest of the family. For these reasons, it is more likely that those four adjacent markers are homozygous by descent than that they are homozygous by chance. Under the more likely hypothesis of a single common ancestral disease chromosome, this key recombinant defines the candidate region for the Pendred gene as an interval of 6.9 cM flanked by D7S2446 and D7S692 (Fig. 2).

Haplotype analysis of Families 1, 3, and 4 confirms the candidate region determined in Family 2. A recombination between D7S2446 and the Pendred gene in patient II-1 from Family 1 confirms the exclusion of the region centromeric to D7S2446, whereas recombinations with D7S523 in Families 3 and 4 confirm that the Pendred gene is located centromeric to D7S523 (Figs. 1 and 2).

DISCUSSION

In this study we confirm the localization of the Pendred gene to chromosome 7q31 by linkage analysis and homozygosity mapping in five families with Pendred syndrome. The highly consanguineous Family 2, originating from Turkey, contains at least 13 Pendred pa-

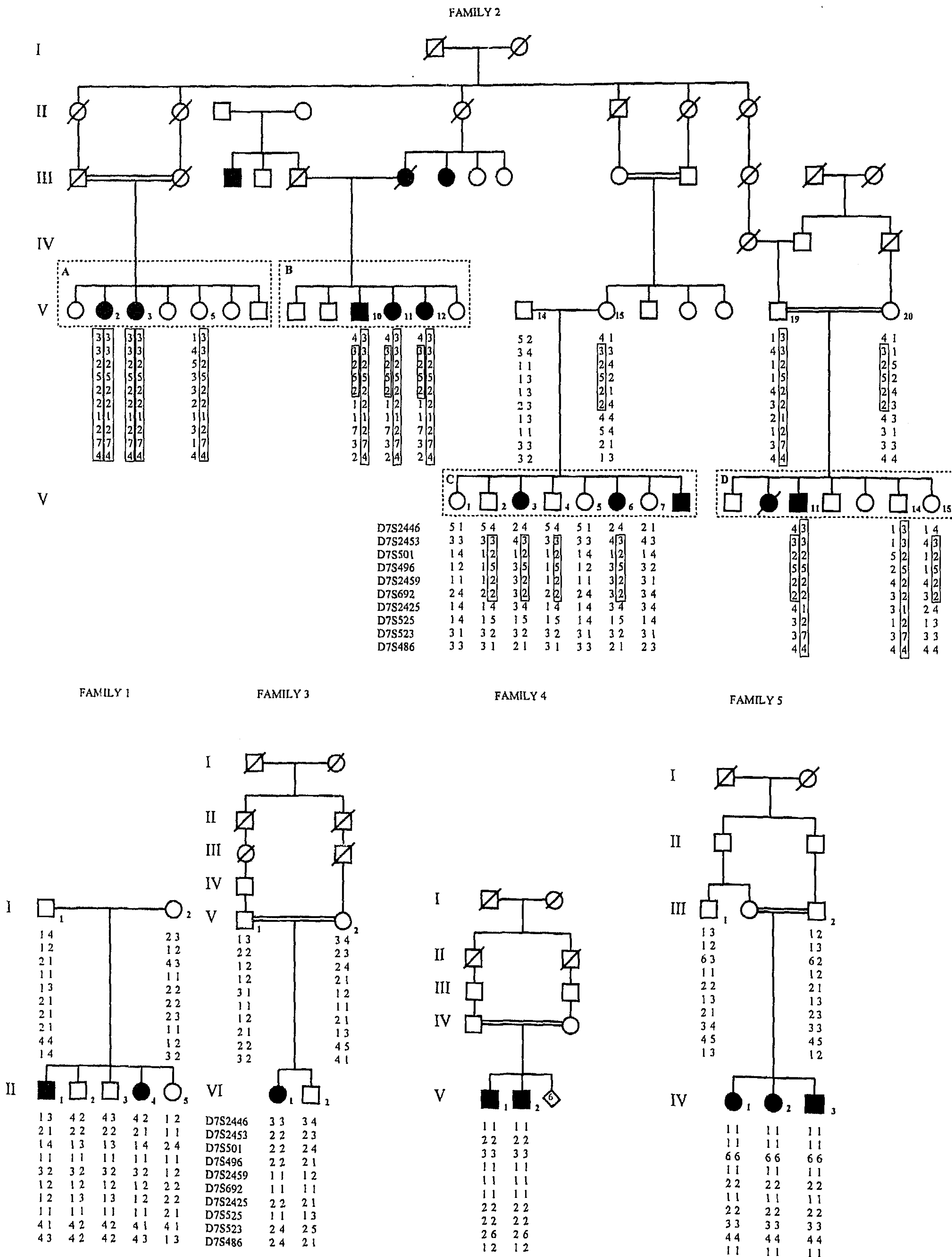


FIG. 1. Pedigrees of the five Pendred families. Only family members included in the linkage study were numbered. In Family 2, individuals IV-2, IV-3, V-3, V-6, and V-11 correspond to patients 5, 4, 1, 2, and 6, respectively, in the original paper (Kabakkaya *et al.*, 1993).

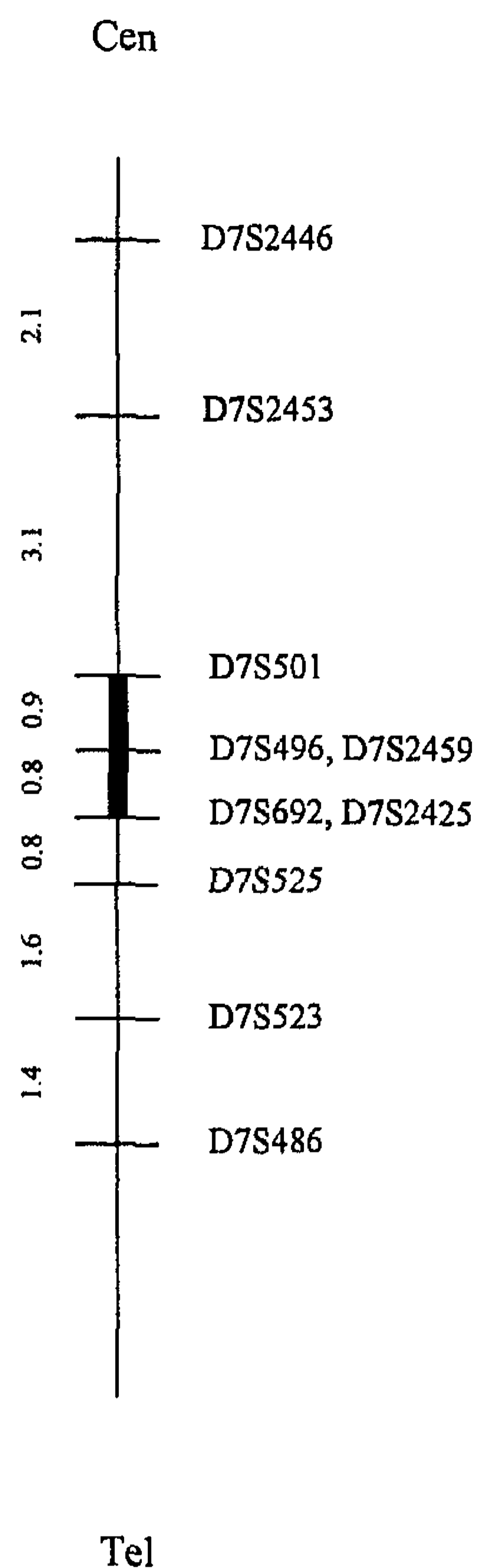


FIG. 2. Linkage map of the markers used in the analysis. The genetic distances between the markers are indicated in centimorgans. The candidate region for Pendred syndrome is indicated by the bold line.

tients and is therefore very useful for linkage analysis, yielding lod scores higher than 3 with chromosome 7 markers. The other four families, of which three are consanguineous, are much smaller. However, they are probably also linked to this region based upon the homozygosity in the patients of the consanguineous Families 3, 4 and 5 and the positive lod score of 0.98 for Family 1.

Combining previously reported data (Coyle *et al.*, 1996; Sheffield *et al.*, 1996) with our own data, we could narrow the candidate region to 1.7 cM between markers D7S501 and D7S692. However, it should be noted that both flanking markers are based on a single recombinant. The proximal flanking marker D7S501 recombinates with the Pendred gene in a patient from a small pedigree, published in a previous study (Coyle *et al.*, 1996). The distal flanking marker D7S692, which comes from the analysis of Family 2 (sibship B) in this study, is based on the assumption that the parents of sibship B are consanguineous and have inherited the same mutation from a common ancestor.

Linkage of Pendred syndrome to chromosome 7q31 has been found now in 19 families from different ethnic origins. Our study includes 5 families originating from Belgium, The Netherlands (2 families), Turkey, and

Lebanon. Coyle *et al.* (1996) reported linkage in 11 families of British origin and 1 from Asia, and Sheffield *et al.* (1996) proved linkage in 2 families of Arab origin. There is no indication for genetic heterogeneity in any of these 19 families, although most of these families are too small to prove linkage independently. These results suggest that the locus on chromosome 7q may be the only locus for Pendred syndrome. Because only a limited number of families have been analyzed so far, additional linkage studies should be performed to prove genetic homogeneity. This is important if genetic diagnosis is requested by small families affected with the disease.

Three other hereditary diseases have been mapped to the Pendred chromosomal region: nonsyndromal autosomal recessive deafness DFNB4 (Baldwin *et al.*, 1995), cystic fibrosis (CF) (Riordan *et al.*, 1989), and congenital chloride diarrhea (CLD) (Kere *et al.*, 1993). The candidate regions for DFNB4 and CLD are identical and are bounded by flanking markers D7S501 and D7S523. Both markers were mapped a few centimorgans proximal to the CF gene (Kere *et al.*, 1993). This means that the Pendred candidate region determined in this study is entirely located inside the candidate region of DFNB4 and CLD. To our knowledge, no genes with a known function in hearing or thyroid metabolism have been mapped to this region, which would make them obvious candidate genes for Pendred syndrome. Although CLD and Pendred syndrome probably map to the same region by chance, the colocalization of DFNB4 and Pendred syndrome might not be coincidental. It has been shown that a single gene can be responsible for both syndromic and nonsyndromic deafness, as mutations in the myosin VIIA gene give rise to Usher syndrome (Weil *et al.*, 1995) as well as nonsyndromal deafness (DFNB2) (Ayadi *et al.*, 1996). As no perchlorate test was performed in the DFNB4 family, and the size of the goiter is variable in Pendred syndrome, thyroid problems might have remained undetected in the DFNB4 family. Alternatively, it is possible that certain mutations in the same gene lead to a combined defect of iodine organification and deafness, while other mutations lead only to deafness. On the other hand only one of the three patients from Family 5 had all typical abnormalities of Pendred syndrome (deafness, Mondini malformation, goiter, abnormal perchlorate test), whereas one sibling had no goiter and two siblings had a normal perchlorate test. This intrafamilial clinical variability shows that the diagnosis of Pendred syndrome can be missed and that cases might be classified as nonsyndromic deafness.

The relatively small region of 1.7 cM containing the Pendred gene will make it possible to use positional cloning techniques to isolate the Pendred gene. This will be an important step in the elucidation of the molecular pathology of the syndrome. The gene identification will also clarify whether Pendred syndrome and DFNB4 are allelic or not and lead to a better under-

TABLE 1
Two-Point Lod Scores between Pendred Syndrome and Markers Located on Chromosome 7q

Marker		Recombination fraction						
		0.00	0.01	0.05	0.10	0.20	0.30	0.40
D7S2446	Family 1	$-\infty$	-3.02	-1.60	-0.99	-0.44	-0.17	-0.04
	Family 2	2.91	3.01	2.96	2.61	1.74	0.90	0.28
	Family 3	0.82	0.78	0.64	0.47	0.21	0.07	0.02
	Family 4	1.28	1.24	1.09	0.90	0.56	0.27	0.09
	Family 5	1.20	1.17	1.06	0.91	0.64	0.39	0.17
	Total	$-\infty$	3.18	4.15	3.90	2.71	1.46	0.52
D7S2453	Family 1	0.68	0.65	0.53	0.38	0.15	0.03	0.00
	Family 2	4.29	4.18	3.73	3.18	2.08	1.11	0.39
	Family 3	0.70	0.67	0.56	0.43	0.23	0.10	0.03
	Family 4	1.18	1.14	1.00	0.82	0.50	0.24	0.07
	Family 5	1.18	1.15	1.04	0.89	0.62	0.37	0.16
	Total	8.03	7.79	6.86	5.70	3.58	1.85	0.65
D7S501	Family 1	0.98	0.95	0.82	0.67	0.38	0.16	0.03
	Family 2	4.19	4.09	3.67	3.14	2.10	1.17	0.45
	Family 3	0.73	0.69	0.56	0.40	0.17	0.06	0.01
	Family 4	1.18	1.14	1.00	0.82	0.50	0.24	0.07
	Family 5	1.18	1.15	1.04	0.89	0.62	0.37	0.16
	Total	8.26	8.02	7.09	5.92	3.77	2.00	0.72
D7S496	Family 1	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Family 2	4.91	4.78	4.25	3.60	2.34	1.24	0.44
	Family 3	0.65	0.61	0.49	0.34	0.14	0.05	0.01
	Family 4	1.10	1.06	0.92	0.75	0.45	0.21	0.07
	Family 5	0.78	0.77	0.75	0.69	0.53	0.35	0.16
	Total	7.44	7.22	6.41	5.38	3.46	1.85	0.68
D7S2459	Family 1	0.07	0.07	0.06	0.05	0.03	0.01	0.00
	Family 2	4.89	4.76	4.25	3.61	2.36	1.26	0.44
	Family 3	0.67	0.63	0.50	0.36	0.15	0.05	0.01
	Family 4	1.10	1.06	0.92	0.75	0.45	0.21	0.07
	Family 5	0.78	0.77	0.75	0.69	0.53	0.35	0.16
	Total	7.51	7.29	6.48	5.46	3.52	1.88	0.68
D7S692	Family 1	0.07	0.07	0.06	0.05	0.03	0.01	0.00
	Family 2	3.96	3.87	3.48	2.97	1.93	1.00	0.33
	Family 3	0.48	0.46	0.38	0.29	0.15	0.07	0.02
	Family 4	1.10	1.06	0.92	0.75	0.45	0.21	0.07
	Family 5	1.05	1.02	0.90	0.76	0.49	0.26	0.08
	Total	6.66	6.48	5.74	4.82	3.05	1.55	0.50
D7S2425	Family 1	0.98	0.95	0.82	0.67	0.38	0.16	0.03
	Family 2	1.13	1.29	1.44	1.33	0.90	0.47	0.14
	Family 3	0.65	0.61	0.49	0.34	0.14	0.05	0.01
	Family 4	1.01	0.98	0.84	0.68	0.40	0.19	0.06
	Family 5	1.14	1.11	1.00	0.86	0.59	0.35	0.15
	Total	4.91	4.94	4.59	3.88	2.41	1.22	0.39
D7S525	Family 1	0.07	0.07	0.06	0.05	0.03	0.01	0.00
	Family 2	1.65	1.78	1.86	1.68	1.14	0.61	0.22
	Family 3	0.73	0.69	0.56	0.40	0.17	0.06	0.01
	Family 4	1.18	1.14	1.00	0.82	0.50	0.24	0.07
	Family 5	0.40	0.39	0.33	0.25	0.14	0.05	0.01
	Total	4.03	4.07	3.81	3.20	1.98	0.97	0.31

TABLE 1—Continued

Marker		Recombination fraction						
		0.00	0.01	0.05	0.10	0.20	0.30	0.40
D7S523	Family 1	0.37	0.37	0.33	0.28	0.19	0.09	0.03
	Family 2	1.15	1.30	1.45	1.36	0.98	0.55	0.20
	Family 3	-0.12	-0.11	-0.05	-0.02	0.01	0.00	0.00
	Family 4	0.06	0.09	0.15	0.18	0.14	0.07	0.02
	Family 5	1.05	1.02	0.91	0.77	0.50	0.26	0.08
	Total	2.51	2.67	2.79	2.57	1.82	0.97	0.33
D7S486	Family 1	0.98	0.95	0.82	0.67	0.38	0.16	0.03
	Family 2	1.82	1.94	2.06	1.93	1.37	0.73	0.24
	Family 3	-0.12	-0.11	-0.07	-0.04	0.01	0.01	0.00
	Family 4	0.09	0.11	0.18	0.19	0.15	0.08	0.02
	Family 5	1.21	1.18	1.06	0.92	0.64	0.39	0.17
	Total	3.98	4.07	4.05	3.67	2.55	1.37	0.46

standing of inner ear development and thyroid functioning.

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