

Familial hypothyroidism with autosomal dominant inheritance

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Abstract

Three generations of a family with clinical and subclinical hypothyroidism caused by thyroid stimulating hormone (TSH) unresponsiveness are described. Findings were low to normal serum thyroxine, raised serum TSH, and low radioiodine uptake; goitre was notably absent. This family is the first evidence of an autosomal dominant mode of transmission of TSH unresponsiveness and may enable identification of the precise defect by genetic linkage study.

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Hypothyroidism is caused by various pathophysiological mechanisms.¹ Among these, thyroid stimulating hormone (TSH) unresponsiveness is rare and has been reported in only a few isolated patients, two of whom were the product of consanguineous matings.²⁻⁴ This condition has an autosomal recessive mode of inheritance.^{5,6}

We describe a family in which clinical or subclinical hypothyroidism caused by TSH unresponsiveness was observed in three generations, suggesting an autosomal dominant disorder. This family may represent the first evidence of an autosomal dominant TSH receptor defect.

Clinical description

The pedigree of this family is presented in fig 1. The proband (IV.7) was born in 1977 to unrelated parents of Jewish Ashkenazic origin. At the age of 3.8 years, he was referred to our clinic with high TSH and low thyroxine concentrations and a family history of hypothyroidism. He was at the 30th centile for weight and height. On clinical examination there were no signs of either hypothyroidism or goitre. Free thyroxine was 8 pmol/l (normal 11-26 pmol/l) and TSH 100 mU/l (normal 1-4 mU/l). Bone age (according to the Greulich and Pyle atlas) was severely retarded, compatible with 1.3 years of age. Thyroid scan with I¹³¹ showed low iodine uptake, 5% at two hours and 11% at 24 hours (normal 15% and 40%), with the thyroid gland in the normal anatomic site.

Thyroxine treatment was started and TSH and serum thyroxine concentrations progressively became normal. The proband is now 17 years old, well developed, with normal TSH and thyroxine concentrations on 150 mg/day of

thyroxine. Mental development is normal, and hearing tests revealed no abnormalities.

When the patient was first evaluated, we decided to examine the entire family in an attempt to define the mode of inheritance and the pathophysiology of the hypothyroidism. Laboratory tests were performed one month after treatment was stopped for those who were treated; results are summarised in table 1. Affected individuals were defined as those with raised TSH and normal or decreased free thyroxine.

All the affected individuals available for investigation (II.5, III.2, III.3, III.5, IV.1, IV.2, IV.4, IV.6, IV.7) were born after a normal pregnancy with normal birth weight and height. Psychomotor development was also normal, with no cases of mental retardation.

At the time of the patient's first evaluation, none of the children (IV.1, IV.2, IV.4, IV.6, IV.7) showed a classic picture of hypothyroidism, and none except IV.4 had goitre on clinical examination. All the children had normal growth, with weight and height centiles between 25 and 50. Bone age of IV.1 and IV.2 was normal while that of IV.4, IV.6, and IV.7 showed a six to 30 month lag.

IV.4 had previously undergone a thyroid scan with I¹³¹ that showed low iodine uptake, 10.5% at two hours and 5.4% at 24 hours, with normal anatomy. Among the previous generations, III.2 was a known hypothyroid patient who had been on replacement treatment since the age of 6 years. The other affected adults (II.5, III.3, III.5) had no signs of clinical hypothyroidism. II.7 and III.7 live in another country; they are known to have hypothyroidism and are being treated with thyroxine, but we have no detailed history on them. I.1 and I.2 are deceased. II.1, II.2, II.3, II.4, II.8, III.8, and III.9 were not evaluated. They are not known to suffer from hypothyroidism.

To achieve a better understanding of the defect, we conducted further tests. The thyo-

Table 1 Results of thyroid investigations in treated subjects

	Free thyroxine (pmol/l)*	TSH (mU/l)†	Radioiodine uptake	TRH test peak TSH (mU/l)
II.5	13.6	5.5	—	64
III.2	4.0	> 100	—	—
III.3	10.2	10.6	—	> 100
III.5	18.3	34.6	—	> 100
IV.1	8.5	77.0	Low	—
IV.2	6.5	> 100	Low	—
IV.4	11.0	> 100	Low	—
IV.6	15.0	17.8	Low	—
IV.7	8.0	100	Low	—

* Normal 11-26 pmol/l; † normal 1-4 mU/l.

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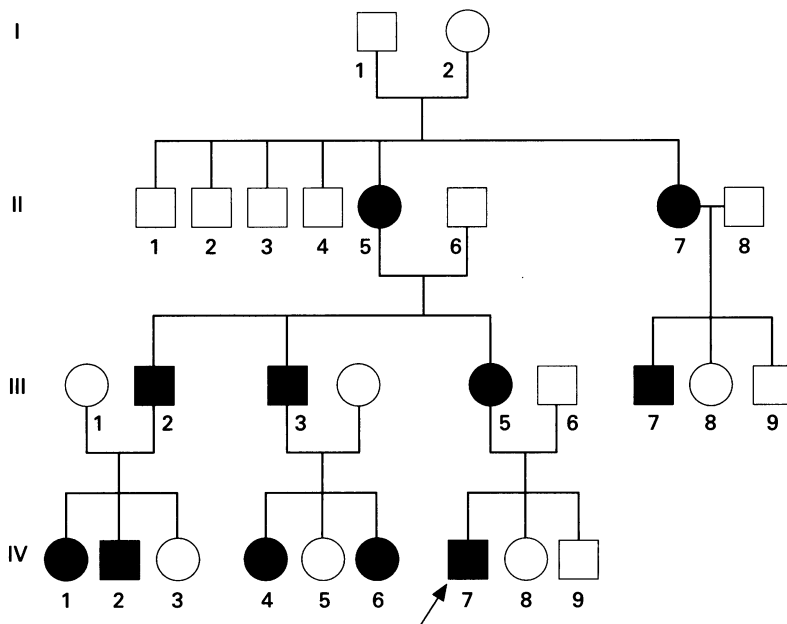


Figure 1 Pedigree of the family.

trophin releasing hormone (TRH) test, performed on II.5, III.3, and III.5, elicited a high TSH response. Thyroid scan with I^{131} , performed on IV.1, IV.2, and IV.6, showed low uptake (3.8%, 12%, and 9% at 24 hours, respectively), with normal anatomic position of the gland. Thyroid antibodies and antinuclear antibodies were negative in all cases. HLA typing was not contributory.

A TSH bioassay of all the members of the family was carried out in FRTL-5 cells, a line of differentiated rat thyroid cells (generously provided by Dr Ambesi-Impombato, Naples, Italy). The assay was done according to the method of Bidey *et al.*⁷ Results showed that the TSH activity of this family was within normal limits. Further evaluation of the defect by administration of bovine TSH was not performed for ethical reasons.⁵ All the members of the family refused a thyroid biopsy.

Discussion

In the family presented, the disease was characterised by low to normal serum thyroxine, raised serum TSH, and low radioiodine uptake. Expression was variable, with no severely affected individuals. The most outstanding feature was the absence of goitre (apart from one case) despite the high serum TSH concentration, which made a diagnosis of a congenital defect in thyroid iodide transport or organification unlikely.^{1,8}

The absence of goitre and of thyroid antibodies also ruled out an autoimmune

disorder. Congenital non-goitrous hypothyroidism has been occasionally described as familial⁸ with a possible autosomal recessive mode of inheritance. In the family presented, hypothyroidism was obviously transmitted as an autosomal dominant trait.

Based on the *in vitro* studies in FRTL-5 cells, we concluded that the TSH bioactivity was within the normal range, and as such, the defect must lie somewhere between the TSH receptor binding site and receptor cyclase binding protein. This was in agreement with the relatively mild phenotype observed in this family, as expected for a receptor defect.

Stanbury *et al.*,² Codaccioni *et al.*,³ Medeiros-Neto *et al.*,⁴ and Sunthornthepvarakul *et al.*⁹ described sporadic cases of TSH unresponsiveness, apparently inherited as an autosomal recessive trait.

Our family constitutes the first evidence of an autosomal dominant mode of transmission of TSH unresponsiveness. This family therefore demonstrates possible genetic heterogeneity for this specific type of hypothyroidism. With the recent progress in gene mapping of the TSH receptor (chromosome 14q31),¹⁰ this family may enable identification of the precise defect by genetic linkage study. We are currently in the process of DNA collection from an appropriate number of family members to examine the possibility of an abnormality in TSH receptor function.

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