Familial hyperthyroidism due to mutations in TSH receptor

Authors: Doctor Diego Russo and Doctor Franco Arturi
Scientific Editor: Prof Sebastiano Filetti

Creation date: October 2004

Dipartimento di Medicina Sperimentale e Clinica, Universita di Catanzaro, Magna Graecia 88100 Catanzaro, Italy. d.russo@unicz.it

Abstract
Familial hyperthyroidism due to mutations in thyroid stimulating hormone (TSH) receptor is a hereditary non-autoimmune hyperthyroidism transmitted as an autosomal dominant trait. It is characterized by the presence of signs and symptoms of hyperthyroidism and diffuse goiter without evidence of an autoimmune etiology. Differential diagnosis is based on the absence of the typical signs of autoimmune hyperthyroidism, such as exophthalmia, myxedema, antibodies anti-TSH receptor and lymphocytic infiltration of the thyroid gland. The incidence is unknown; at present, few families and few sporadic cases with a *de novo TSHR* mutation, mostly from Caucasian populations, have been described The age of onset of hyperthyroidism is highly variable and it may be present in infants or develop in adulthood. Similarly, the size of goiter is variable and it may be minimal or absent in young patients: however, once present, continuous growth is systematically observed. Management is based on drastic ablative therapy (surgery or radioiodine) to control the disease once the patient has become hyperthyroid. The absence of a clear correlation between mutant genotypes and phenotypic expression of the disease limits the prognostic value of genetic testing in families with hereditary non-autoimmune hyperthyroidism. Gain-of-function germline mutations occur preferentially in the transmembrane domain of the TSH-R, resulting in familial non-autoimmune hyperthyroidism. Familial gestational hyperthyroidism is due to a mutant TSH-R which is hypersensitive to chorionic gonadotropin

Keywords
thyroid stimulating hormone receptor (TSH-R), hyperthyroidism, goiter, Gain-of-function germline mutations

Disease name and synonyms
- Familial hyperthyroidism due to mutations in thyroid stimulating hormone (TSH) receptor
- Familial non-autoimmune hyperthyroidism
- Leclere syndrome
- Autosomal dominant toxic thyroid hyperplasia

A different form of hyperthyroidism due to a TSH

receptor mutation is the:
Familial gestational hyperthyroidism

Excluded diseases
Familial autoimmune hyperthyroidism (Graves' disease)

Diagnostic criteria/Definition
Activating germline mutations of the TSH receptor gene are responsible for a familial disease inherited as autosomal dominant trait and characterized by the presence of signs and symptoms of hyperthyroidism and diffuse goiter without evidence of an autoimmune etiology.
A particular activating TSH receptor mutation (K183R) may determine hypersensitivity to Human Chorionic Gonadotropin (hCG) hormone, resulting in the appearance of thyrotoxicosis together with hyperemesis gravidarum during the course of pregnancy.

Differential diagnosis
It is based on the absence of the typical signs of autoimmune hyperthyroidism, such as exophthalmia, myxedema, antibodies anti-TSH receptor and lymphocytic infiltration of the thyroid gland, observed in Graves'disease.

Etiology
The first convincing description of a family in which hyperthyroidism segregates as an autosomal dominant trait in the absence of autoimmunity signs and/or symptoms has been made by Leclere's group in Nancy (Thomas *et al*., 1982).

Table 1.: List of germinal activating mutation of the TSH receptor observed in familial non-autoimmune and sporadic congenital non-autoimmune hyperthyroidism.

Residue	Familial non-autoimmune hyperthyroidism	Sporadic congenital non-autoimmune hyperthyroidism
Ser 281		Ser 281 Asn
Gly 431	Gly 431 Ser	
Met 453		Met 453 Thr
Met 463	Met 463 Val	
Ser 505	Ser 505 Arg	Ser 505 Asn
Val 509	Val 509 Ala	
Val 597		Val 597 Leu
Ala 623	Ala 623 Val	
Leu 629	Leu 629 Phe	
Phe 631		Phe 631 Leu
Thr 632		Thr 632 Ile
Pro 639	Pro 639 Ser	
Asn 650	Asn 650 Tyr	
Asn 670	Asn 670 Ser	
Cys 672	Cys 672 Tyr	

Molecular analysis of the DNA obtained from the blood of the affected member from this family, showed the presence of an activating mutation in the transmembrane segments of the TSH receptor (Duprez *et al*., 1994). Several studies confirmed that activating germline mutations in the TSH receptor may be considered the cause of such a disease (Table1).
Constitutively activating germline mutations in the TSH receptor act as gain-of-function events. They exert –even in heterozygotes- a continuous stimulation of both growth and differentiation of the thyrocytes, resulting in thyroid diffuse hyperplasia and hyperproduction of thyroid hormones. Mutations are mostly located in the third intracellular loop and the sixth transmembrane domain of the receptor, but they have been detected also in the remaining portions, including the extracellular region (Corvilain *et al.*, 2001). Despite of their position in the receptor molecule, all activating mutations would shift the equilibrium towards active receptor conformations, which activate the cAMP-dependent, and sometimes even the Ca-PI-dependent signal transduction pathways. The age of onset and the clinical features of the disease are highly variable, so that other factors, including genetic background and iodine intake, may modulate the phenotypical expression (Russo *et al.*, 1997; Corvilain *et al.*, 2001; Kopp *et al.*, 2001; Arturi *et al.*, 2003). In addition, there has been described also a family with non-autoimmune hyperthyroidism with no evidence of TSH receptor mutations (Aoshima *et al.*, 2000).
Familial forms are always transmitted in an autosomal dominant mode, according to the Mendelian laws. The absence of a clear correlation between mutant genotypes and phenotypic expression of the disease currently limits the prognostic value of genetic testing in families with hereditary non-autoimmune hyperthyroidism.
Few sporadic cases have been also described, when a *de novo* germline activating TSH receptor occurs early in the fœtal or perinatal period of life, determining a sporadic congenital non-autoimmune hyperthyroidism (Corvilain *et al.*, 2001; Kopp, 2001) (Table 1). This disorder must be suspected when there is no maternal history of Graves' disease. In this case, no other family members are affected, but the disease will be transmitted to the sons in an autosomal dominant mode, according to the Mendelian laws. The phenotype, in these cases, is more severe.
Familial gestational hyperthyroidism, first described in 1998 in a family with dominant inheritance of hyperthyroidism occurring only during pregnancy (Rodien *et al.*, 1998), is believed to be caused by a gain-of-function mutation of the TSH receptor responsible for

hypersensitivity to hCG. Thus, when the hCG levels are high, as during pregnancy, the consequent hyperfunction of the receptor (independent of TSH levels) determine an increased synthesis of thyroid hormones resulting in thyrotoxicosis.

Clinical description
Familial hyperthyroidism due to mutations in TSH receptor is characterized by the presence of a diffuse goiter associated to the common signs of hyperthyroidism in the absence of clinical, serological and histological signs of autoimmune thyroid disease (Thomas *et al*., 1982; Leclere *et al*., 1997). Common features of the patients with familial non-autoimmune hyperthyroidism include the absence of clinical (ophthalmopathy and dermopathy) or biological signs of autoimmunity (circulating anti-thyroglobulin, anti-thyroperoxidase and anti-TSH receptor antibodies). Besides, no intrathyroid lymphocyte infiltrates of the thyroid gland are present at surgery. The hyperthyroidism may vary from mild or subclinic to severe. The age of onset of hyperthyroidism is highly variable and it may be present in infants or develop in adulthood. Similarly, the size of goiter is variable and it may be minimal or absent in young patients: however, once present, continuous growth is systematically observed.
The onset of hyperthyroidism, the entity of the symptoms and the size of goiter may vary in carriers of a different TSH receptor mutation and also in carriers of the same mutation in a given kindred (Fuhrer et al., 1999; Arturi et al., 2002). These differences are commonly observed in dominant diseases; it is likely that the resultant phenotype reflects differences in the genetic background of affected individuals as well as environmental factors like the amount of iodide or the presence of goitrogens in the diet.
In the Familial gestational hyperthyroidism, only during the pregnancy the affected family members present the signs of severe thyrotoxicosis associated to hyperemesis gravidarum, while, when non-pregnant, they are clinically and biologically euthyroid.

Diagnostic methods
Diagnosis is established on clinical grounds associated with laboratory tests. Beside the signs and symptoms of hyperthyroidism, absence of exophthalmia and myxedema typical of Graves' disease arises the suspect, when a family history is documented, of the disease. Laboratory tests consist of hormones (free T3, free T4 and TSH) and antibodies (circulating anti-thyroglobulin, anti-thyroperoxidase and anti-TSH receptor) evaluation. The latter, by excluding the autoimmune nature of the disorder, make the diagnosis almost certain: up to now, only in one family with such a clinical picture no TSH receptor mutations were detected (Aoshima *et al.*, 2000). The presence of a mutation, however, requires the sequencing of the *TSHR* gene from the DNA extracted by the lymphcytes of the patient. On our knowledge, there are no available sources for commercial testing. Many research laboratories overall the world can perform genetic testing on a research basis.

Incidence
It is unknown; at present, few families and few sporadic cases with a *de novo TSHR* mutation, mostly from Caucasian populations, have been described (Corvilain *et al.*, 2001; Kopp, 2001), but it should be considered that, in the absence of genetic screening, it may be easily confused with Graves' disease with negative thyroid peroxidase antibodies (TSAb).
Familial gestational hyperthyroidism due to TSH receptor mutations has been described so far only in one family (Rodien *et al.*, 1998).

Genetic counseling
It may apply when the genetic alteration is well documented. It must be pointed out that the risk of hyperthyroidism is 50% of the kindred (according to Mendelian way of inheritance), but the disease is easily manageable, and the treatment is curative.

Prenatal diagnosis
It is not considered relevant.

Management including treatment
Hyperthyroidism may be resolved only by a radical treatment because there is no chance that a spontaneous remission of the disease would occur.
A common observation in the cases described to date is the need for drastic ablative therapy (surgery or radioiodine) to control the disease once the patient has become hyperthyroid. Indeed, in patients who underwent partial thyroidectomy a high rate of relapse has been observed.

Unresolved questions and comments
- Existence of other genetic factors?
- Phenotype-genotype correlations?

References
Aoshima H, Yoshida T, Kobayashi S, Mizushima Y, Kawai S (2000). Genomic DNA analysis of thyrotropin receptor in a family with hereditary hyperthyroidism. Endocr. J. 47, 365-372.
Arturi F, Chiefari E, Tumino S, Russo D, Squatrito S, Chazenbalk G, Persani L, Rapoport B, Filetti S (2002). Similarities and differences in the phenotype of members of an Italian family

with hereditary non-autoimmune hyperthyroidism associated with an activating TSH receptor germline mutation. J. Endocrinol. Invest. 25, 696-701.

Arturi F, Scarpelli D, Coco A, Sacco R, Bruno R, Filetti S, Russo D (2003). Thyrotropin receptor mutations and thyroid hyperfunctioning adenomas ten years after their first discovery: unresolved questions. Thyroid 13, 341-343.

Corvilain B, Van Sande J, Dumont JE, Vassart G (2001). Somatic and germline mutations of the TSH receptor and thyroid diseases. Clin. Endocrinol. (Oxf) 55, 143-158.

Duprez L, Parma J, Van Sande J, Allgeier A, Leclere J, Schvartz C, Delisle MJ, Decoulx M, Orgiazzi J, Dumont J, Vassart G (1994). Germline mutations in the thyrotropin receptor gene cause non-autoimmune autosomal dominant hyperthyroidism. Nat Genet. 7, 396-401.

Fuhrer D, Mix M, Wonerow P, Richter I, Willgerodt H, Paschke R (1999). Variable phenotype associated with Ser505Asn-activating thyrotropin-receptor germline mutation. Thyroid 9, 757-761.

Kopp P (2001). The TSH receptor and its role in thyroid disease. Cell. Mol. Life Sci. 58, 1301-1322.

Leclere J, Bene MC, Aubert V, Klein M, Pascal-Vigneron V, Weryha G, Faure G (1997). Clinical consequences of activating germline mutations of TSH receptor, the concept of toxic hyperplasia. Horm. Res. 47, 158-162.

Rodien P, Bremont C, Sanson ML, Parma J, Van Sande J, Costagliola S, Luton JP, Vassart G, Duprez L (1998). Familial gestational hyperthyroidism caused by a mutant thyrotropin receptor hypersensitive to human chorionic gonadotropin. N. Engl. J. Med. 339, 1823-1826.

Russo D, Arturi F, Chiefari E, Filetti S (1997). Molecular insights into TSH receptor abnormality and thyroid disease. J. Endocrinol. Invest. 20, 36-47.

Thomas JS, Leclere J, Hartemann P, Duheille J, Orgiazzi J, Petersen M, Janot C, Guedenet JC (1982). Familial hyperthyroidism without evidence of autoimmunity. Acta Endocrinol. (Copenh) 100, 512-518.