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The Clinical Spectrum of Thyrotropin Receptor Gene (*TSHR*) Mutations

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1. Introduction

Resistance to thyrotropin (RTSH) is a condition in which thyroid cells show reduced sensitivity to TSH. This condition is characterized by elevated serum TSH concentration, a normal or hypoplastic thyroid gland and normal to very low levels of thyroid hormones. Loss-of-function mutations in the TSH receptor gene (*TSHR*) lead to RTSH syndrome, presenting with either congenital hypothyroidism (CH) or subclinical hypothyroidism (Beck-Peccoz et al., 2006; Refetoff, 2003).

CH occurs in about 1 in 3500 live births. Thyroid dysgenesis is responsible for 75% of these cases, dyshormonogenesis for 15%, central hypothyroidism for 5%, and 5% are due to other causes (Grüters et al., 2003; Kratzsch & Pulzer, 2008). Most cases of CH due to thyroid dysgenesis occur sporadically, but 2% of the patients are familial (Castanet et al., 2000, 2001). Dyshormonogenesis is commonly recessively inherited (Park & Chatterjee, 2005). Genes associated with thyroid gland dysgenesis include *TITF1*, *TITF2* and *PAX8* (De Felice & Di Lauro, 2004; Gillam & Kopp, 2001(a); Park & Chatterjee, 2005). Thyroid dyshormonogenesis is caused by genes that are involved in thyroid hormone synthesis including thyroperoxidase (*TPO*), thyroglobulin (*TG*), sodium iodide symporter (*NIS*), pendrin (*PDS*), dual oxidase 2 (*DUOX2*) and its maturation factor (*DUOXA2*), and dehalogenase (*DEHAL1*) (Gillam & Kopp, 2001(b); Grasberger & Refetoff, 2010). Loss-of-function mutations in *TSHR* lead to a spectrum of phenotypes, depending on the mutation's location and severity (Biebermann et al., 2010; De Felice & Di Lauro, 2004). The first report in 1968 of RTSH was of an 8-year-old boy with cretinism in whom the thyroid gland was small in a ^{99m}TC scan and radioiodine uptake was normal (Stanbury et al., 1968). It was only in 1995 that the cause for RTSH syndrome in that case was shown to be a mutation in *TSHR* (Sunthornthepvarakul et al., 1995). Since the first report of CH caused by a *TSHR* mutation, several cases of loss-of-function mutations of *TSHR* have been reported: most are missense mutations, but deletions and insertions have been identified as well (see http: www.hgmd.cf.ac.uk/ac/ gene.php?gene=TSHR and OMIM#275200) (Abramowicz et al., 1997; Alberti et al., 2002; Biebermann et al., 1997, 2010; Bretones et al., 2001; Camilot et al., 2005; Cangul et al., 2010; Clifton-Bligh et al., 1997; De Marco et al., 2009; de Roux et al., 1996; Fricke-Otto et al., 2005; Gagne et al., 1998; Grasberger et al., 2007; Jeziorowska et al., 2006; Jordan et al., 2003; Kanda et al., 2006; Nagashima et al., 2001; Narumi et al., 2009; Narumi et al., 2011; Park et al., 2004;

Richter-Unruh et al., 2004; Rubio et al., 2008; Russo et al., 2000; Sriphrapradang et al., 2011; Sunthornthepvarakul et al., 1995; Sura-Trueba et al.,2009; Tenenbaum-Rakover et al., 2009; Tiosano et al., 1999; Tonacchera et al., 2000, 2001, 2004; Tsunekawa et al., 2006; Wonerow et al., 2001) (Table 1, Fig 1).

2. TSHR: Structure and function

TSH controls thyroid function upon its interaction with the G-protein-coupled TSHR. The family of G-protein-coupled receptors (GPCRs) shares seven transmembrane segments connected by three extracellular and three intracellular loops (ECL and ICL, respectively). Together with the receptors for glycoprotein hormones LH/HCG and FSH, TSHR has a long N-terminal domain that is involved in recognition and binding of the ligand. The *TSHR* gene located on chromosome 14q31 was cloned in 1989 (Libert et al., 1989). It encodes a protein with a large N-terminal ligand-binding extracellular domain, a hepta-helical transmembrane domain and an intracellular domain. The extracellular domain is encoded by the first nine exons and part of exon 10, whereas the transmembrane and intracellular domains are encoded entirely by exon 10. The protein consists of 744 amino acids and the N-terminal ectodomain consists of 398 amino acids composed of eight leucine-rich repeat motifs (Szkudlinski et al., 2002; Van Durme et al., 2006). Similar to other GPCRs, TSHR shares a common mode of intracellular signaling, stimulating the exchange of GDP for GTP on the Gα subunit (Gsα) and phosphoinositol (IP) turnover through Gq coupling. TSH binding to TSHR on the basolateral membrane of the thyroid follicular cells leads to stimulation of secondary-messenger pathways involving these two main pathways: Gs/cAMP, which mediates hormone secretion, thyroid cell growth and differentiation and iodide uptake, and IP/Ca^{+2}, which regulates thyroid hormone synthesis by stimulating iodide organification (Dumont et al., 1992; Vassart & Dumont, 1992; Wonerow et al., 2001). Mutations in *TSHR* result in either gain or loss of receptor function.

3. Gain-of-function mutations in *TSHR*

Germline gain-of-function mutations result in non-autoimmune hyperthyroidism, whereas somatic mutations that constitutively activate *TSHR* result in toxic thyroid nodules. Hyperthyroidism caused by germline mutations in *TSHR* exhibits autosomal dominant inheritance. The mutations are located mainly in exon 10, which encodes the transmembrane region and intracellular tail that constitutively activate TSHR. The phenotype of these patients is characterized by hyperthyroidism with the presence of goiter but the absence of ophtolmopathy, and a lack of thyroid autoantibodies as well as of lymphocytic infiltration in thyroid histology (Van Sande et al., 1995). The clinical spectrum of phenotypes is variable and onset can occur anywhere from birth to adulthood. The presence of either congenital or adulthood-onset hyperthyroidism, multinodular goiter (MNG) and follicular carcinoma has been reported in the same family (Karges et al., 2005). To date, more then 55 germline gain-of-function mutations have been reported, about 14 of them sporadic and the others with familial occurrence (http: www.hgmd.cf.ac.uk/ac/gene.php?gene=TSHR) (Akurin et al., 2008; Davies et al., 2005; Farid et al., 2000; Führer et al., 1997(b); Holzapfel et al., 1997; Karges et al., 2005; Khoo et al., 1999; Tonacchera et al., 1996; Van Sande et al., 1995). Hyperthyroidism in affected individuals is often resistant to the conventional treatment used in Graves' disease, and either radiotherapy or total thyroidectomy is required.

Autonomous benign and malignant toxic thyroid nodules have been shown to result from a variety of somatic mutations leading to constitutive activation of *TSHR* and affecting cell proliferation and cell function. Somatic *TSHR* mutations commonly occur in the transmembrane and ECL domains, but hot spots are the sixth transmembrane domain and the third ICL where the receptor interacts with G-proteins. Toxic adenoma due to TSHR-activating mutations may occur in infancy (Kohn et al., 2009) or even *in utero* (Kopp et al., 1997) (OMIM#2603372) (Davies et al., 2005; Führer et al., 1997(a); Kohn et al., 2009). To date, about 25 different somatic TSHR-activating mutations have been reported manifesting with toxic adenoma, MNG and toxic thyroid carcinoma.

4. Loss-of-function mutations in *TSHR*

About 50 different loss-of-function mutations have been described in *TSHR* (Table 1). Affected individuals are either homozygous, compound heterozygous or heterozygous. The degree of insensitivity to TSH depends on the type and location of the *TSHR* mutation; more severe loss of TSHR function manifests as CH, whereas mild mutations present with euthyroid hyperthyrotropinemia or subclinical hypothyroidism. When both alleles carry mutated receptors with complete lack of function, the result is severe hypothyroidism, commonly presenting at birth, whereas carriers of a mutation on one allele present with compensated hyperthyrotropinemia. The thyroid gland is hypoplastic or invisible in a ^{99m}TC scan; however, in ultasonographic imaging, the gland is shown to be in a normal position and commonly of small size. *TSHR* mutations are distributed all along the receptor. Mutations located in the binding domain result in reduced binding capacity or decreased membrane expression of the receptor. The third ECL and the seventh intracellular domain of *TSHR* are hot spots for gain-of-function mutations, but some inactivating mutations have been identified in this domain as well (Alberti et al., 2002; Grasberger et al., 2007; Tiosano et al., 1999) (Fig. 1).

4.1 Prevalence of loss-of-function mutations

The exact prevalence of inactivating *TSHR* mutations is not known. A prevalence of 4.3% biallelic *TSHR* mutations was found among 134 Japanese infants with CH (Narumi et al., 2009). Among 38 children with non-autoimmune subclinical hypothyroidism, 11 (29%) were carriers of *TSHR* mutations (Nicoletti et al., 2009). A prevalence of 12% *TSHR* mutations was shown in 42 subjects with non-autoimmune isolated hyperthyrotropinemia in Italy; all were with familial occurrence (Tonacchera et al., 2004). Camilot et al. (2005) identified 13 patients with heterozygous mutations (11%) out of 116 pediatric patients with asymptomatic euthyroid hyperthyrotropinemia. A rate of 0.6% for carriers of W546X-mutated *TSHR* was identified in Welsh euthyroid individuals (Jordan et al., 2003). We found up to 2.4% carriers of two known mutations in a highly consanguineous population in the northern region of Israel (Tenebaum-Rakover et al., 2009). Moreover, the coexistence of two different novel mutations of *TSHR* in each of two separate clans has been shown (Sriphrapradang et al., 2011). In view of these data, it may be speculated that the occurrence of inactivating *TSHR* mutations in certain populations is not so rare, and therefore screening for *TSHR* mutations is indicated in cases with non-autoimmune subclinical hypothyroidism in those populations.
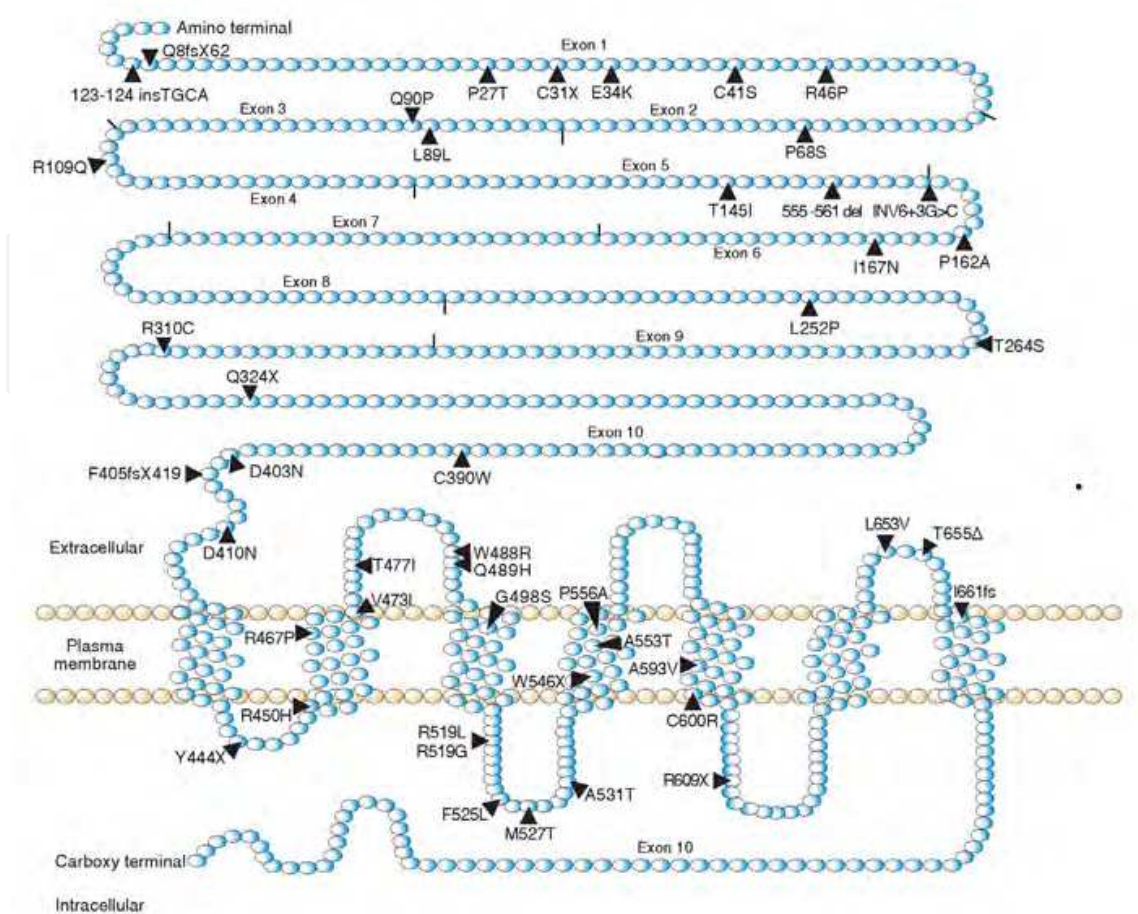
Fig. 1. Scheme of TSHR with known loss-of–function mutations

4.2 Clinical characteristics

Loss-of-function mutations manifest with a variable clinical spectrum of phenotypes. Severe uncompensated RTSH presents with CH, partially compensated RTSH manifests with subclinical hypothyroidism, and fully compensated RTSH presents with euthyroid hyperthyrotropinemia or even normal thyroid function. The diagnosis of TSHR defect is based on the absence of thyroid antibodies, a lack of goiter, measurable serum thyroglobulin, and familial occurrence of hyperthyrotropinemia or hypothyroidism. CH is commonly detected by TSH-based neonatal screening but may missed by total T_4 (TT_4)-based screening since, in many cases, TT_4 levels are within the normal range at birth (Table 1). The degree of CH is variable and depends on the genotype. Severe forms manifest as overt CH (Bretones et al., 2001; Gagne et al., 1998; Jeziorowska et al., 2006; Park et al., 2004; Tonacchera et al., 2000), moderate forms as hypothyroidism identified by neonatal screening without clinical symptoms of hypothyroidism (Abramowicz et al., 1997; Jordan et al., 2003), and mild forms present with hyperthyrotropinemia and normal thyroid hormones (de Roux et al., 1996; Nagashima et al., 2001; Narumi et al., 2009; Tenenbaum-Rakover et al., 2009). Gagne et al. (1998) described a case of CH with persistent neonatal jaundice, myxedematous facies, large fontanelle and absence of ossification centers of the knee on x-rays, indicating severe prenatal deficiency of thyroid hormone. Most of the described cases of CH are detected by neonatal screening with elevated TSH and normal TT_4 levels, but without any

clinical symptoms or signs of hypothyroidism (de Roux et al., 1996; Tenenbaum-Rakover et al., 2009). Nevertheless, L-T$_4$ therapy is initiated in most cases to prevent future consequences of untreated CH. At the age of 2 to 3 years, when L-T$_4$ is withdrawn, thyroid hormones remain low in the severe mutations (Abramowicz et al., 1997; Biebermann et al., 1997; Tonacchera et al., 2000); however in milder mutations, despite extremely elevated TSH, thyroid hormone levels are normal, indicating compensated hypothyroidism (Clifton-Bligh et al., 1997; Tenenbaum-Rakover et al., 2009). ^{99m}TC scan commonly reveals a normal or hypoplastic gland but in some cases, an absence of thyroid gland has been demonstrated, suggesting thyroid agenesis (Table 1). The presence of detectable thyroglobulin as well as the demonstration of a thyroid gland in the normal position in ultrasonographic imaging exclude thyroid agenesis and indicate a diagnosis of RTSH. In a few reports, an enlarged thyroid gland has been described (de Roux et al., 1996; Grasberger et al., 2007). Inactivating *TSHR* mutations at older ages present with either subclinical hypothyroidism or euthyroid hyperthyrotropinemia without thyroid autoantibodies. The affected patients are commonly identified by routine laboratory tests and are asymptomatic. Most of the described cases are heterozygous for *TSHR* mutations, but biallelic mutations have been reported as well (Kanda et al., 2006; Russo et al., 2000; Sriphrapradang et al., 2011; Tenenbaum-Rakover et al., 2009; Tonacchera et al., 2001, 2007).

4.3 Mechanism of loss-of-function mutations

The mechanism leading to loss-of-function of TSHR includes abnormal binding affinity, abnormal receptor synthesis, accelerated degradation, defective receptor targeting to the cell membrane and abnormal signal transduction (Tao, 2006). Mutations may exert their activity by causing protein misfolding, misassembly or aberrant oligomerization. Loss-of-function mutations are located all along the TSHR (Biebermann et al., 2010) (Fig 1). The function of TSHR is assessed *in vitro* by cAMP response, IP accumulation, TSH binding and cell-surface expression of the mutated receptor. The analysis is performed with COS-7 cells transfected with the mutant receptor. Each mutation has a different effect on binding capacity, membrane expression and cAMP and IP accumulation, depending on its type and location along the *TSHR*. In *in-vitro* studies, it has been shown that *TSHR* mutations differ in their effect on the Gs and Gq pathways, which may lead to more severe loss of one pathway compared to the other (Claus et al., 2005). The third ECL represents an important domain for intermolecular TSHR signal transduction and single amino acids play different roles in receptor folding and cAMP and IP signaling (Claus et al., 2005). We identified a biallelic L653V mutation located in the third ECL in three sisters presenting with marked hyperthyrotropinemia and increased thyroid radioiodine uptake (Grasberger et al., 2007). Normal ligand binding, slightly reduced cell expression and mildly reduced basal and stimulated cAMP accumulation with markedly reduced IP formation were found in *in-vitro* studies using transfected COS-7 cells. These *in-vitro* findings explained the phenotype of the affected subjects manifesting compensated hyperthyrotropinemia concomitant with increased iodide uptake, and this was the first report to provide *in-vivo* evidence of the important role of the IP/Ca^{+2} pathway in the regulation of thyroid hormone synthesis. Narumi et al. (2011) recently reported two patients with CH and high iodide uptake harboring biallelic *TSHR* mutations (R450H+T145I in one and R450H+I166fs in the other), supporting our previous findings. They termed this apparently discrepant phenotype nonclassic TSH resistance.

Type of mutations		Phenotype	US	99mTC- scan	TSH (mIU/l)	TT₄ (µg/dl)	FT₄ (nmol/l)	Age*	Treatment	Reference
123-124 insTGCA	wt	SCH	NA	NA	NA	NA	NA	NA	NA	Camilot et al., 2005
Q8fsX62	wt	SCH	Normal	NA	6.6	NA	7.5	13 y	Yes	Tonacchera et al., 2007
P27T	wt	SCH	NA	NA	NA	NA	NA	NA	NA	Camilot et al., 2005
C31X	wt	SCH	Hypoplasia	NA	8.3		NA	NA	Yes	Nicoletti et al., 2009
E34K	wt	CH	NA	NA	NA	NA	NA	NA	NA	Camilot et al., 2005
C41S	F525L	CH	NA	Normal	129	NA	22	19 d	No	de Roux et al., 1996
C41S	wt	SCH	Normal	Normal	4.7-12.8	NA	19.3	30 d	NA	Alberti et al., 2002; Camilot et al., 2005
R46P	wt	SCH	NA	NA	NA	NA	NA	NA	NA	Camilot et al., 2005
P68S	wt	SCH	Normal	Normal	Slightly elevated	NA	Normal	Variable	No	Tenenbaum-Rakover et al., 2009
L89L+Q90P	P264S	CH	Normal	Low trapping	72	11.5	NA	3 w	Yes	Sriphrapradang et al., 2011
R109Q	wt	SCH	NA	NA	NA	NA	NA	NA	NA	Camilot et al., 2005
R109Q	W546X	CH	Normal	Normal	92	NA	10	8 w	Yes	Clifton-Bligh et al., 1997
555-561del	wt	SCH	NA	NA	6.5	NA	NA	NA	NA	Camilot et al., 2005
IVS6+3G>C	T655Δ	CH	Hypoplasia	Absent	1390	NA	<2.5	15 d	Yes	Gagne et al., 1998
P162A	P162A	CH, CH, SCH	NA	Normal	89, 99, 13.4	NA	12,NA, 10.7	14,NA, 47 y	Yes,NA,No	de Roux et al., 1996; Camilot et al., 2005; Tonacchera et al., 2004
P162A	wt	SCH	Normal	NA	3.8-8.6	NA	8.8	38 y	Yes	Tonacchera et al., 2007; Camilot et al., 2005
P162A	I167N	CH	NA	Normal	47	9.2		16 d	Yes	Sunthornthepvarakul et al., 1995
P162A	C600R	SCH	Hypoplasia	Normal	46	NA	13.4	25 y		Alberti et al., 2002
L252P	wt	SCH	Normal	NA	8.6	NA	12.7	34 y	NA	Tonacchera et al., 2004; Camilot et al., 2005
R310C	R310C	SCH	Normal	Normal	6.8	NA	14.2	63 y	Yes	Russo et al., 2000
Q324X	D410N	CH	NA	Slightly enlarged	44	NA	20	13 d	Yes	de Roux et al., 1996
C390W	F405 fsX419	CH	Hypoplasia	NA	89	6.0	8.2	Newborn	Yes	Biebermann et al., 1997
D403N	wt	SCH	NA	NA	NA	NA	NA	NA	NA	Camilot et al., 2005
C390W	W546X	SCH	NA	Slightly enlarged	34	NA	12.9	55 d	Yes	de Roux et al., 1996

Type of mutations		Phenotype	US	99mTC-scan	TSH (mIU/l)	TT₄ (µg/dl)	FT₄ (nmol/l)	Age*	Treatment	Reference
D410N	wt	SCH	Normal	NA	8.7	NA	12	31 y	Yes	Tonacchera et al., 2007
Y444X	Y444X	CH	Hypoplasia	Hypoplasia	68	NA	8.4	7 y	Yes	Jeziorowska et al., 2006
R450H	T145I	CH	NA	High ^{125}-I uptake	53.8	NA	7.7	Newborn	Yes	Narumi et al., 2011
R450H	G498S	CH	Hypoplasia	Normal	66.8	NA	8.8	12.9	Yes	Nagashima et al., 2001
R450H	V473I	SCH	Normal	NA	12.8	NA	15.5	NA	NA	Tsunekawa et al., 2006
R450H	R519C	SCH	NA	NA	22.9	8.4	NA	NA	NA	Tsunekawa et al., 2006
R450H	R519G	SCH	NA	NA	38.1	8.9	NA	NA	NA	Tsunekawa et al., 2006
R450H	I661fs	CH	Normal	High ^{125}-I uptake	178	NA	3.9	Newborn	Yes	Narumi et al., 2011
L467P	wt	SCH	Normal	Low uptake	9.6	NA	14	5 y	NA	Alberti et al., 2002
T477I	T477I	CH	Hypoplasia	Hypoplasia	NA	NA	<undetectable	22 y	Yes	Tonacchera et al., 2000
W488R	wt	SCH	NA, Normal	NA	NA	NA	NA	NA	NA	Camilot et al., 2005; De Marco et al., 2009
Q489H	Q489H	CH	Absent	Absent	180		1	Newborn	Yes	Sura-Trueba et al., 2009
M527T	wt	SCH	NA	NA	NA	NA	NA	NA	NA	Camilot et al., 2005
A531T	A531T	CH	Normal	NA	33	NA	16.8	NA	NA	Cangul et al., 2010
W546X	W546X	CH	Normal	Absent	126	NA	7	Newborn	Yes	Jordan et al., 2003
A553T	A553T	CH	Hypoplasia	Absent	>130	1.2	4.8	4 d	Yes	Abramowicz et al., 1997; Cangul et al., 2010
A553T	W546X	CH	Hypoplasia	Absent	160	1.4		Newborn	Yes	Park et al., 2004
P556A	P556A	CH	Absent	Absent	>100	NA	5.2	3 m	Yes	Cangul et al., 2010
A593V	A593V	SCH, CH	Normal	NA	18.9-33	7.0	NA	7 y, Newborn	Yes	Fricke-Otto et al., 2005
R609X	R609X	CH	Hypoplasia	Absent	>100	NA	1.2-7.0	Newborn	Yes	Tiosano et al.,1999; Richter-Unruh et al., 2004
L653V	L653V	CH+SCH	Slightly enlarged	High ^{131}-I uptake	53	NA	Normal	10 y	No	Grasberger et al., 2007
T655Δ	wt	SCH	Normal	Normal	14.9	NA	14.1	23 d	NA	Alberti et al., 2002

* At diagnosis; NA, not available; CH, congenital hypothyroidism, SCH, sub-clinical hypothyroidism; y, years; w, weeks; d, days; wt, wild type; US, ultrasonographic imaging

Table 1. Summary of the *TSHR* loss-of-function mutations

4.4 Heterozygosity for loss-of-function mutations

Heterozygous subjects carrying loss-of–function mutations in *TSHR* are commonly mildly affected, presenting with euthyroid hyperthyrotropinemia but with variable expressivity (Camilot et al., 2005; Sriphrapradang et al., 2011; Tenenbaum-Rakover et al., 2009). Heterozygotes are typically diagnosed with slightly increased TSH but normal free T_4 (FT_4) levels. At least one case of neonatal hypothyroidism has been reported as well (Camilot et al., 2005). In *in-vitro* models expressing the combination of wild-type and mutated *TSHR*, it has been shown that basal and TSH-stimulated cAMP production are reduced compared to cells transfected with wild-type receptor, albeit less severely than in biallelic mutations. These *in-vitro* studies are consistent with the dominant-negative effect of the mutated receptor on the activity of the wild type and explain the mild phenotype of the carriers (Calebiro et al., 2005; Tenenbaum-Rakover et al., 2009). The dominant-negative effect of the mutated receptor may result in reduction of cAMP accumulation, as well as reduced membrane cell-surface expression of the receptor and retention in intracellular compartments (Calebiro et al., 2005).

5. Genotype-phenotype association

The phenotype of the affected subjects correlates with the severity of the mutation, which is dependent on its location and type, and whether it is mono- or biallelic. Most of the described cases reveal a direct association between the severity of the mutation and the phenotype, which is reflected by the extent of increase in TSH and decrease in FT_4 levels. The more severe mutations manifest in infancy with persistent CH, while the mild monoallelic mutations manifest as asymptomatic mild hyperthyrotropinemia. We identified 33 subjects carrying two novel *TSHR* gene mutations (P68S and L653V) in a large consanguineous kindred occurring as homozygous L653V (5 subjects), heterozygous P68S (4 subjects), heterozygous L653V (20 subjects), and compound heterozygous L653V/P68S (4 subjects). Our finding in a large cohort of affected members enabled us to assess the genotype-phenotype association. All homozygotes and compound heterozygotes presented with compensated RTSH, 9 out of 24 heterozygotes showed mild hyperthyrotropinemia and the others had normal TSH values. The clinical results were supported by *in-vitro* studies in which the L653V-mutated *TSHR* resulted in more severely impaired signal transduction than the other genotype combinations. However, large variability was found to exist between affected members. Among those with the homozygous L653V mutation, one child had CH and the other four, aged 3 to 20 years, had markedly elevated TSH, but FT_4 levels were within the normal range; among the heterozygous members for the two different mutations, variable hyperthyrotropinemia was observed, with a few of the affected subjects showing normal thyroid function (Tenenbaum-Rakover et al., 2009).

6. Outcome

Despite several reports of patients affected with *TSHR* mutations, there are limited data on the long-term outcome of this condition. In subjects with *TSHR* mutations, it has been shown that TSH levels remain stable and they do not develop hypothyroidism; in

contrast, in autoimmune thyroid disease (AITD), overt hypothyroidism commonly develops over the years. In our abovementioned large cohort of affected family members, cross-sectional analysis showed neither a decrease nor an increase in TSH levels with age, suggesting stable compensated RTSH with an appropriately adjusted set point of pituitary-thyroid feedback (Tenenbaum-Rakover et al., 2009). In contrast to subclinical hypothyroidism in the context of AITD, the thyroidal compensation in mild to moderate RTSH is expected to be clinically stable with no progression toward true hypothyroidism or spontaneous regression toward normal TSH levels. Patients with homozygous or compound heterozygous mutations who are detected in infancy by neonatal screening to have CH may have normal FT_4 levels despite elevated TSH levels after L-T_4 withdrawal and in these patients, L-T_4 replacement may not be needed. In contrast, development of overt hypothyroidism at the age of 15 years was shown in a patient homozygous for the R540H mutation who presented with compensated hypothyroidism in infancy (Mizuno et al., 2009), but not in an additional four subjects with the same genotype after long-term follow-up. Asymptomatic heterozygotes for *TSHR* mutations have normal or slightly elevated TSH levels with negative thyroid antibodies (Camilot et al., 2005). However, coexistence of thyroid autoantibodies has been reported in some cases of compensated RTSH, leading to overt hypothyroidism (Tonacchera et al., 2001). It is possible that carriers of *TSHR* mutations are at increased risk for AITD. TSHR is involved in AITD, TSH-stimulating autoantibodies in Graves' disease and TSH-blocking antibodies in Hashimoto thyroiditis. Therefore, it has been speculated that modification of TSH structure by the mutated receptor may lead to AITD (Tonacchera et al., 2001). Fluctuation of TSH levels from slightly above normal to normal values have been observed in some cases by us and others (Tenenbaum-Rakover et al., 2009; Tonacchera et al., 2001). In view of the variability in outcome among affected individuals, careful long-term follow-up is recommended.

7. Treatment

The question of whether to treat patients with *TSHR* mutations with L-T_4 is a matter of debate (Utiger, 1995). In cases with loss-of-function mutations in *TSHR* presenting with CH, early initiation of L-T_4 therapy is recommended to prevent late-effect consequences of hypothyroidism as in other etiologies of CH. However, withdrawal of L-T_4 at the age of 2 to 3 years revealed transient hypothyroidism in some cases, putting the need for lifelong replacement therapy into question (Alberti et al., 2002; Tenenbaum-Rakover et al., 2009). Euthyroid hyperthyrotropinemia caused by *TSHR* mutations with mild to moderate loss of function maintains stable compensated RTSH and may not necessitate thyroid hormone replacement. Moreover, most patients with RTSH do not present with symptoms of hypothyroidism or with biochemical parameters of uncompensated hypothyroidism, such as elevated CPK and liver enzymes and hyperlipidemia (Tenenbaum-Rakover et al., 2009). The presence of normal FT_4 levels argues against the need for replacement treatment, especially when inadvertent overtreatment, producing subclinical hyperthyroidism, can have undesirable effects (Samuels et al., 2008). In our long experience, no clinical benefit has been observed with L-T_4 therapy. Contrasting with this approach, it has been shown that some subjects with RTSH have a slight decrease in FT_4 levels compared to controls, although

remaining within the normal range, which may point to subclinical hypothyroidism in these affected patients. In addition, the possibility of secondary pituitary enlargement in patients with extreme hyperthyrotropinemia may support L-T$_4$ replacement therapy. In view of the variability of phenotypes in different types of mutations, as well as between individuals with the same genotypes, it is recommended that careful follow-up and cautious administration of L-T$_4$ be considered based on individual thyroid hormone levels in the clinical context.

8. Differential diagnosis

The diagnostic work-up of RTSH should exclude *PAX8* mutations, which are characterized by thyroid dysgenesis associated with kidney abnormalities (Grüters et al., 2003; Park & Chatterjee, 2005), and mutations in guanine nucleotide binding subunit 1 (*GNAS1*), which encodes Gsα subunit and causes pseudohypoparathyroidism (PHP) type Ia. The latter inactivating mutations in Gsα lead to a syndrome of resistance to multiple hormones, including TSH (Mantovani et al., 2002). Another form of RTSH is an autosomal dominantly inherited disease characterized by euthyroid hyperthyrotropinemia, for which the specific gene has not yet been identified. This condition has been linked to a locus on chromosome 15q25.3-26.1 (Grasberger et al., 2005(b)). In many of the cases with clinical characteristics of RTSH, no mutations have been found in *TSHR,* suggesting that additional genes are involved in RTSH syndrome (Xie et al., 1997). Bigenic defects in thyroid-synthesis pathways have been recently described. Coexistence of mutations in *TPO* (Sriphrapradang et al., 2011) and *GNAS* (Lado-Abeal et al., 2011), in addition to mutations in *TSHR*, has been reported in the same individuals. In those reports, the coexistence of mutated *TPO* and *TSHR* in the same individuals belonging to the same kindred did not aggravate the severity of the RTSH phenotype (Sriphrapradang et al., 2011); similar observations were made for the presence of a monoallelic *TSHR* mutation coexisting with a *GNAS* mutation (Lado-Abeal et al., 2011). It is therefore suggested that in cases where *TSHR* mutations do not explain the phenotype, additional genes that are involved in thyroid hormone synthesis be screened. RTSH must be differentiated from AITD (Ross, 2000), the most common cause of subclinical hypothyroidism in the adult population. The presence of autoantibodies as well as a typical hypoechogenic pattern of the thyroid in ultasonographic imaging support the diagnosis of AITD. This is important from a clinical standpoint since in RTSH, hyperthyrotropinemia is almost always stable while in AITD, hypothyroidism develops with time in about 30% of the cases.

9. Conclusion

To date, about 50 different *TSHR* mutations have been reported presenting with a spectrum of phenotypes ranging from overt CH to mild euthyroid hyperthyrotropinemia. Subjects with euthyroid hyperthyrotropinemia commonly have stable TSH levels and do not develop overt hypothyroidism with time. The phenotype correlates with the genotype as the latter is reflected by the severity of hyperthyrotropinemia and the decrease in FT$_4$ levels. Screening for *TSHR* mutations should be considered in individuals with apparent non-autoimmune subclinical hypothyroidism. In view of the variability in phenotypes and in outcome among individuals in this condition, careful long-term follow-up is recommended and replacement

therapy should be considered on an individual basis according to thyroid hormone levels in the clinical context.

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11. References

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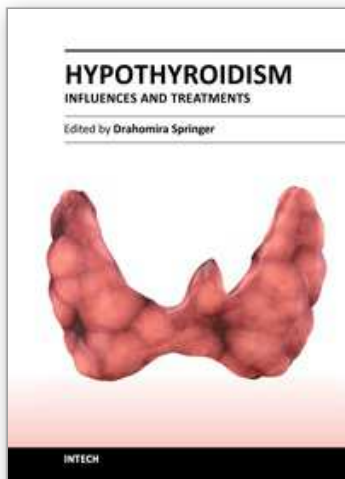
Hypothyroidism - Influences and Treatments
Edited by Dr. Drahomira Springer

Hypothyroidism is the most common thyroid disorder and it is significantly more frequent than presented - millions of people suffer from this disease without knowing it. People with this condition will have symptoms associated with slow metabolism. Estimates of subclinical hypothyroidism range between 3 to 8 %, increasing with age, whereas it more likely affects women than men. About 10% of women may have some degree of thyroid hormone deficiency. Hypothyroidism may affect lipid metabolism, neurological diseases or other clinical conditions. The book includes studies on advancements in diagnosis, regulation and replacement therapy, thyroid ultrasonography and radioiodine therapy for hypothyroidism. "Hypothyroidism - Influences and Treatments" contains many important specifications, results of scientific studies and innovations for endocrine practice.

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