

THE DETECTION OF SOMATIC MUTATIONS OF THYROTROPIN RECEPTOR GENE IN FINE NEEDLE BIOPSY SAMPLES FROM THYROID NODULES

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Objective. To evaluate the detection possibility of TSH receptor gene mutation within the third cytoplasmic loop and the sixth transmembrane domain in the cytological material obtained by means of fine needle biopsy of autonomous and non-autonomous nodules.

Methods. The study has been carried out in 16 women with goitre showing no clinical signs of hyperthyroidism. According to the thyroid scintigraphy and serum level of thyrotropin (TSH) the patients were divided into two groups: 1. 6 patients with autonomous nodules; 2. 10 patients with non-autonomous nodules. Genomic DNA has been isolated from the cytological material and the peripheral blood nuclear cells in order to confirm possible somatic character of TSH receptor gene mutations. DNA has been amplified in polymerase chain reaction (PCR) with the use of a specific pair of primers. Purified PCR products have been subjected to further automatic sequencing.

Results. Among 6 autonomous nodules tested one heterozygotic somatic mutation of adenine for cytosine at 1804 nucleotide of TSH receptor gene was detected. This mutation resulted in the change of threonine (codon ACC) at 632 position of TSH receptor protein for proline (codon CCC). Among the non-autonomous nodules one heterozygotic somatic mutation of adenine for cytosine at 1870 nucleotide of receptor TSH gene has been detected. From this mutation followed the change of lysine (codon AAG) at 624 position of the polypeptide chain for glutamine (codon CAG) followed as a consequence.

Conclusions. We emphasize the validity of fine needle biopsy in the detection of somatic mutations in the TSH receptor gene. For the first time the somatic mutation in the TSH receptor gene in a non-autonomous nodule has been reported.

Key words: Thyroid nodules – TSH receptor – Somatic mutations – Fine needle biopsy

The occurrence of focal changes in the thyroid is an essential diagnostic and therapeutic problem. Palpable thyroid nodules are detectable in 4–7 % of the adults only (TAN and GHARIB 1997), while autopsy and ultrasound examinations reveal non-palpable focal changes in thyroid glands in approximately 50 % of the patients (MAZZAFERRI 1993). For proper diagnosis it is of crucial importance to estimate whether the nodule is benign or malignant using all possible diagnostic methods with fine needle biopsy as prior (MAZZAFERRI et al. 1988). Patients with neutral nodular goitre undergo both: surgery and regular treat-

ment with the use of suppressive doses of thyroxine (GHARIB and MAZZAFERRI 1998). Theoretical basis for using thyroxine is based on widely recognised opinion of thyrotropin (TSH) involvement in growth regulation and function of follicular thyroid cells (VAS-SART and DUMONT 1992). Thyrotropin binds to its receptor domain located on the outer side of thyrocyte cell membrane. As a result of ligand binding, the interaction of the receptor with heterotrimeric protein binding guanyl nucleotides (Gs) takes place which further results in the production of cAMP. Subsequently, cAMP stimulates the proliferation of thy-

rocytes including the synthesis and secretion of thyroid hormone. The existence of negative feedback between TSH concentration and cAMP production on the one hand and the process of intensified thyrocytes growth on the other is used in a regular treatment of goitre with thyroxine.

The cause of goitre may be found among all those factors which result in the thyroid enlargement, e.g. iodine deficiency, antithyroid substances, immunological factors, the intrinsic thyrocyte growth potential and follicular replication rate within the same gland being heterogenous (DERWAL 1996).

The new light on the pathogenesis was thrown by PARMA et al. (1993) who detected somatic mutations of TSH gene receptor responsible for constitutive activation of this signal transduction system. These mutations were identified in the third cytoplasmic loop of the receptor. Another type of somatic mutation was found in the same exon of TSH receptor gene obtained by fine needle from hyperactive thyroid adenomas (PORCELLI et al. 1994, 1995). These mutations located within the VI transmembrane domain of the TSH receptor result in its constitutive activation. The above data point to the fact that cAMP generation system may operate even in the absence of TSH and of the changes of its concentration in serum. So far, however, the presence of somatic mutations of TSH gene receptor in non-autonomous thyroid nodules has not been detected.

Therefore, the aim of our study was to evaluate the validity of aspiration fine needle biopsy for the detection of somatic mutations of TSH gene receptor in thyroid nodules and to estimate their frequency within the third cytoplasmic loop and the sixth transmembrane domain in cytological material from autonomous and non-autonomous thyroid nodules.

Subjects and Methods

Patients. The study was approved by the Ethical Committee, Pomeraniam Medical Academy. The first group of patients consisted of 6 women (age range 24–29 years) with autonomous nodules classified as hot nodules by scintigraphy (Tc^{99m}) and decreased TSH level by ultrasensitive IRMA assay (<0.3 mU/l). The second group consisted of 10 women (age range 27–49 years) with scintigraphically warm (6 patients) or cold nodules (4 patients) and normal TSH level

(0.3–5.6 mU/l). The samples for genomic DNA isolation were obtained by fine needle biopsy (FNB) and the histological examination of that also showed benign character of nodular tissue in all cases.

DNA isolation. In each patient, the genomic DNA was isolated from the cytological material obtained from thyroid nodules and from peripheral blood cells. Cytological material from FNB was placed in a sterile test tube and preserved at -20°C for further analysis. Peripheral blood nuclear cells (PBNC) were obtained by concentration gradient (Gradisol L, Polfa, Kutno) centrifugation of 10 ml venous blood taken in EDTA. Genomic DNA from FNB and PBNC was isolated using SDS-proteinase K method and subsequent phenol extraction (SAMBROOK et al. 1989) and placed in 18 and 200 μl of TE buffer, respectively.

Detection of the TSH receptor gene mutations in thyroid nodules. The TSH cDNA was amplified in PCR with oligonucleotides: 5'-ACCGAGAC-CCCTCTTGCTCT-3' (bases: 1820–1839) as a sense primer (TSHR-D) and 5'-AGTTGCTAACAGTGATGAGAGGCT-3' (bases 2052–2075) as an antisense primer (TSHR-E) (PORCELLINI et al. 1994). The product of amplification with this pair of primers was a segment (256 bp in length) of TSHR gene sequence from the second to third extracytoplasmic loop comprising the third intracytoplasmic loop and the transmembrane domain (NAGAYAMA et al. 1989). DNA samples (5 μl from FNB or 200 ng from PBNC) were amplified in the solution of 100 μl final volume containing 30 pM of each primer, 2.5 mM of the deoxyribonucleotide (dATP, dTTP, dCTP, dGTP; Promega), 50 mM KCl, 20 mM Tris-HCl (pH 8.4), 1.5 mM MgCl_2 , 10 mg/ml of nuclease free bovine serum albumin and 2.5 units Taq DNA polymerase (Boehringer, Mannheim). The thermal profile used on a Perkin Elmer/Cetus thermal cycler consisted of an initial denaturation at 94°C for 3 min followed by denaturation at 94°C for 30 sec, annealing for 1 min at 60°C and extension at 72°C for 1 min for 38 cycles for FNB-DNA or 35 cycles for PBNC-DNA. After PCR, 10 μl loading buffer (40 % sacharose, 0.25 % bromophenol blue and xylene cyanol) was added to each sample, the amplification products being then checked for the predicted sizes and visualized by electrophoresis in 2 % agarose gel stained with ethidium bro-

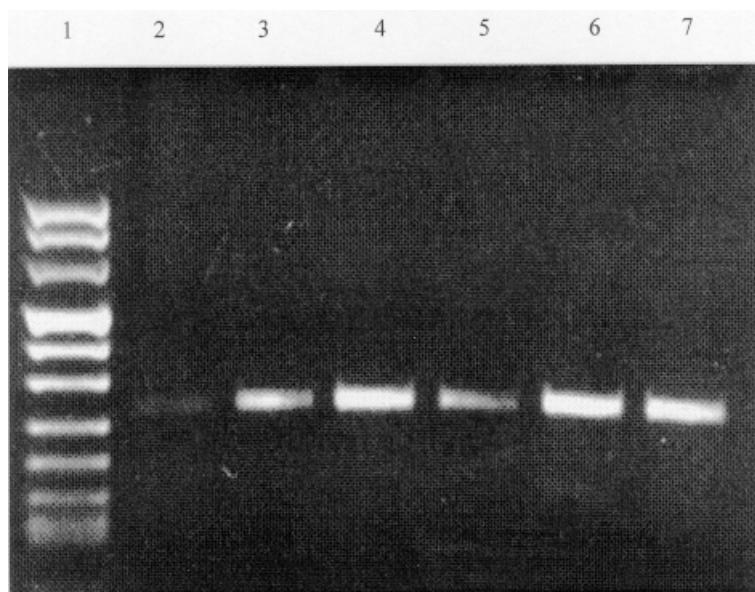


Fig. 1 Column 1: DNA molecular weight marker VIII (Boehringer, Mannheim, Germany); columns 2-7: TSH-R PCR products from genomic DNA isolated from FNB samples of thyroid nodules.

mide. To record the results, pictures of the gels were taken in UV light with DS-34 Camera (Polaroid). The PCR products of good quality were then subjected to automatic sequencing, separated from unused primers, purified on Microcon 100 microconcentrators (Amicon) filters and sequenced in Model 373 Sequencing System (Applied Biosystems) by means of DNA Sequencing Kit, Dye Terminator Cycle Sequencing Ready Reaction with AmpliTaq DNA polymerase (Perkin-Elmer).

Results

The amount of genomic DNA obtained by FNB from thyroid nodule of each patient was sufficient for further examination using PCR method (Fig. 1). For each patient the same fragment of TSH receptor gene was also amplified by PCR using genomic DNA isolated from PBNC as a template.

By sequencing of both PCR products only in thyroid cells the heterozygous mutation of adenine for cytosine at 1894 nucleotide of TSH receptor gene has been found in one out of 6 patients with autonomous nodules only. As a consequence of such mutation, threonine (codon ACC) at 632 position of TSH-R polypeptide chain has been changed for proline (codon CCC) (Fig. 2).

In one out of 6 patients with non autonomous nodules the heterozygous mutation of adenine into cytosine at 1870 nucleotide of TSH receptor gene has been detected. The change of lysine (codon AAG) at 624 position of TSH receptor protein for glutamine (codon CAG) followed from such mutation (Fig. 3). Both mutations have been of somatic character since they occurred in DNA of thyroid cells and have not been detected in PBNC-DNA (Fig. 2 and 3).

Discussion

First reports about hyperfunctioning thyroid nodules with somatic mutations of TSH receptor gene resulting in the constitutive activation of transduction system were reported by PARMA et al. (1993). Such mutations were found in 3 out of 11 hyperfunctioning adenomas in the third cytoplasmic loop of the TSH receptor gene which concerned T to C transition in two cases resulting in the replacement of aspartic acid by glycine at position 619, and in one case in contiguous base substitution GC to TA which resulted in the replacement of alanine 623 by isoleucine. In the same exon of TSH receptor gene PORCELLINI et al. (1994) found another type of somatic mutation leading to its constitutive activation. Those mutations referred to 3 codons of three ami-

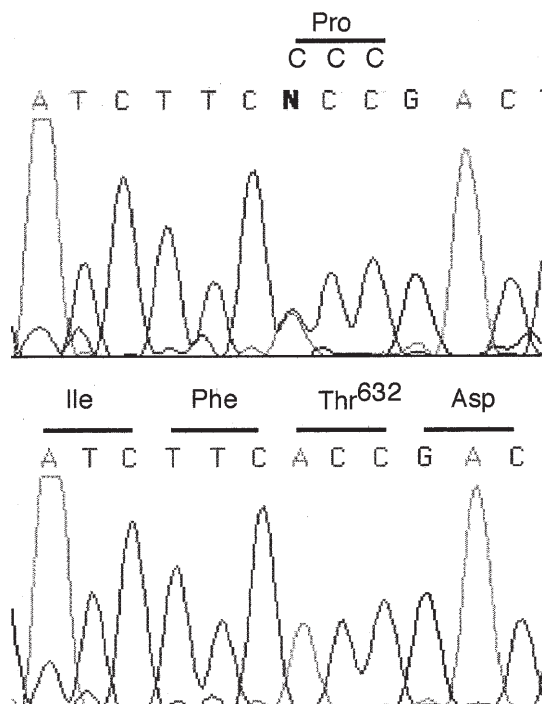


Fig. 2 Sequence analysis of a somatic mutation A 1894 C of the TSH-R gene. Upper panel: fragment of DNA from thyroid nodule; lower panel: fragment of DNA from leukocytes of the same patient.

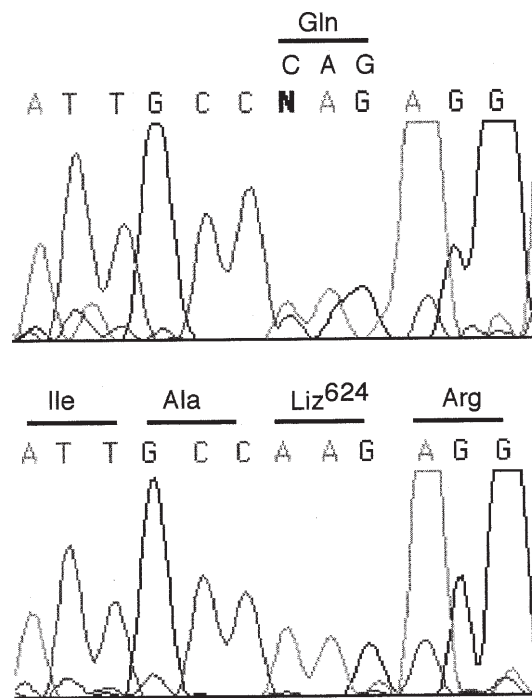


Fig. 3 Sequence analysis of a somatic mutation A 1870 C of the TSH-R gene. Upper panel: fragment of DNA from thyroid nodule; lower panel: fragment of DNA from leukocytes of the same patient.

no acids in the sixth transmembrane domain resulted respectively following changes: 1. phenylalanine to cysteine at 631 position of TSH-R chain, 2. threonine to isoleucine at 632 position (resulting from G to A transition), 3. aspartic acid to glutamic acid (C to A transition) or tyrosine (G to A transition) at 633 position of the chain. In summary, so far the presence of somatic mutations in 7 out of 11 hyperfunctioning nodules has been found (three at 632 and 633 positions and one at 631 position of TSH-R sequence).

Further studies of toxic nodules not only confirmed the frequent occurrence of somatic mutation of the TSH receptor gene in areas described above, but also revealed their presence in other positions of the TSH-R chain. Thus, PARMA et al. (1995) reported somatic mutations in 9 out of 11 toxic adenomas and described two new locations in the first and second extracytoplasmic receptor loop at 486 position (isoleucine for phenylalanine or methionine in two different nodules) and at 568 position (change of isoleucine for threonine). HOLZAPFEL et al. (1997)

described somatic mutations in 3 out of 6 toxic adenomas and found further new location at 630 position (isoleucine for leucine). PARMA et al. (1997) found 27 (82 %) mutations among 33 autonomous nodules including two new mutations: at 629 position (leucine for phenylalanine) and the deletion of 12 bases (removal of the 658-661 codons of C-terminal part of the third extracytoplasmic loop). FUEHRER et al. (1997) reported 15 somatic mutations (48 %) out of 31 toxic adenomas including two new changes at 656 position (valine for phenylalanine) and the deletion of 27 bases of the third intracytoplasmic loop (loss of 9 amino acids – codons from 613 to 621). TONACCHERA et al. (1998) showed that among patients with toxic nodular goitre mutations occurred in 13 out of 17 toxic nodules (76 %) including one at 639 position (proline for serine) which was described for the first time.

However, there are also some reports about substantially lower frequency or even their total absence of mutations in autonomous thyroid nodules. Thus, RUSSO et al. (1995) found them in only 8 % (3/37),

TAKESHITA et al. (1997) in only 2 % (1/45) and PIN-
DUCCIU et al. (1998) found no somatic mutations in
15 toxic adenomas.

It may be concluded that so far 27 somatic muta-
tions of the TSH receptor gene in 12 different chain
positions have been described, whilst some locations
are preferred, especially at sixth transmembrane seg-
ment, in which 44 % of mutations described so far
are localised (PARMA et al. 1997). In our study we
found one mutation at 632 position, described earlier,
out of 6 autonomous nodules (17 %). We have
found, however, the change of threonine for proline
and not for isoleucine as reported earlier by PORCEL-
LINI (1994). The reasons for such diverse frequency
occurrence of somatic mutations in the TSH recep-
tor gene in autonomous nodules can be sought in
ethnic differences (more often in Caucasians than in
Japanese), methodological (investigation of a part of
exon 10 or application of methods less sensitive than
sequencing) and geographic differences connected
with the access to iodine (mutations are described
mostly in the areas with iodine deficiency) (TAKESH-
ITA et al. 1995; PARMA et al. 1997; TONACCHERA et al.
1998).

As far as we are aware, the presence of TSH-R
gene mutations in non-autonomous thyroid nodules
has not been described yet. Among 10 of our pa-
tients with such nodules there was only one case of
heterozygous mutation at 624 position of the TSH
receptor with a consecutive change of lysine for
glutamine. In addition, it should be emphasized that
the mutation at 624 position has not yet been de-
scribed. There are rare cases in the literature con-
cerning mild non-autonomous nodules in which so-
matic mutations of the TSH receptor gene have been
described. Thus, MATSUO et al. (1993) tested 20 mild
nodules from neutral multinodular goitre and 37 fol-
licular adenomas, however poor clinical characteris-
tics and the use of a less sensitive SSCP (Single
Strand Conformational Polymorphism) method does
not allow any unambiguous conclusions. Similar
conclusions may be drawn by ESAPA et al. (1997) who
examined 66 mild thyroid nodules.

We cannot yet ascertain that the mutation found
in our study led to the constitutive activation of the
receptor with the consecutive overproduction of
cAMP, because in order to confirm such phenome-
non the cAMP concentration should have been mea-

sured in basal conditions and after the TSH stimula-
tion of mutated receptor-transfected COS cells as
described by PORCELLINI et al. (1997). Second muta-
tion in our material at 632 position concerning au-
tonomous nodule is surely of constitutive character,
which was confirmed by other authors using the *in*
vitro COS model (PORCELLINI et al. 1994, FUEHRER et
al. 1997).

The mutations found in our study were of somatic
character, since we did not notice any changes of TSH
receptor chain sequence in genomic DNA isolated
from peripheral blood nuclear cells. Other authors
also confirmed somatic character of the mutation
(PORCELLINI et al. 1994; PARMA et al. 1993). If the
fine needle biopsy is used for mutation search, con-
firmation of somatic character of the change using
PBNC-DNA as the template for PCR may be
achieved by means of a lower number of punctures
and their restriction only to nodular area without any
biopsy of extra-nodular tissue. The amount of DNA
obtained from fine needle aspiration is sufficient to
molecular analysis with the use of PCR and subse-
quent automatic sequencing. Good quality PCR prod-
ucts visualised in agarose gels and the sequencing
results confirm the opinion thoroughly. Thus, the use
of FNB can be of great importance in early detec-
tion of thyroid nodules leading finally to thyrotoxi-
cosis and can also enable further proper treatment.

In natural development of toxic nodular goitre,
thyrocytes diversity in reference to their inner po-
tential growth, the activity of iodine transportation
and thyroid peroxidase seem to be of main impor-
tance (DERWAHL 1996; STUDER et al. 1995). Thus, ir-
respective of the clonal nature of the nodule (mono-
clonal or polyclonal) it can be either hot or even cold.
Since the proliferation rate is higher within the nod-
ule than in extranodular tissue, mutations are more
frequent in the first cases (DERWAHL 1996). It seems
that the mutation of TSH receptor gene or other genes
in signal transduction cascade could be of major
importance in the stimulation of hyperfunction of
the nodule, contrary to previous opinion claiming
its primary role in tumorigenesis process (DERWAHL
1996). However, experimental *in vitro* research de-
finitely showed that the somatic mutations of the TSH
receptor gene resulted in its activation followed by
the increase of cAMP concentration and subsequent
stimulation of growth, differentiation and thyrocytes

function (VASART and DUMONT 1992). The presence of mutations in neutral nodules and the possibility of their identification by molecular analysis in FNB material can partially explain the resistance of some nodules to the treatment with suppressive thyroxine doses both for nodules which are neutral *per se* and for nodules which are only an intermediate stage in the development of toxic nodule. The available data (MORITA et al. 1989; CELANI 1993) show that only 30 % of neutral nodules are prone to 50 % volume reduction as a reaction to thyroxine administration. The mutations of the TSH receptor gene cannot be the only cause of treatment resistance; other mutations of oncogenes ras and gsp which are believed to be responsible for thyroid tumorigenesis should also be taken into account (KOPP et al. 1994). MATSUO et al. (1993) and ESAPA et al. (1997) showed the presence of single mutations of alpha Gs protein chain in neutral thyroid nodules.

It may be concluded that the FNB of thyroid nodules followed by molecular analysis of thyroid DNA is very useful in the search for somatic mutations of the TSH receptor gene. Therefore, the detection of TSH-R gene mutation causing the constitutive activation of signal transduction cascade may predict the resistance for suppressive thyroxine treatment. In addition, it can be helpful in the individual choice-therapy of neutral nodular goitre.

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BOOK REVIEW

INTERNATIONAL TEXTBOOK OF DIABETES MELLITUS

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Honorary Editor: **H. Keen** (London), Second Edition, Volume I and II, 1827 pages, John Wiley & Sons,
Chichester 1997

This is an excellent result of the giant project to bring together all present knowledge on diabetes presented by 188 outstanding experts and cut into more than 100 subject headings. The topics discussed in this king size manual include a broad spectrum of aspects from the molecular genetics, morphology, physiology, molecular basis of insulin action and immunopathogenesis, to the diagnosis, epidemiology, dietary management, drug treatment, implantable pumps, islet transplantation, glucose sensors, self monitoring (blood glucose, glycated hemoglobin, lipids), computer-assisted education of diabetic patient, special problems in management (brittle diabetes, childhood, pregnancy, aging), acute disturbances (hypoglycemia, ketoacidosis, infections, surgery, vascular events), chronic microvascular (nephropathy, retinopathy, peripheral neuropathy etc.) and macrovas-

cular complications (coronary heart disease, clotting disorders, hypertension), diabetic foot and public health problems (organisation of care in various continents, economics of diabetes, social rights, primary prevention).

At the same time, such broad spectrum of topics defines the broad spectrum of the readers and professions (physicians of all medical fields, social workers, economists, biochemists, pharmacologists etc.) which may benefit from this diabetes bible. This comprehensive work, in addition to excellent and valuable scientific and medical information, presents up to date references and high quality of technical arrangements including up to additional 300 pages of indexes facilitating to find any subtopic on advancing broad field of diabetes.

Pavel Langer