

Hypothyroidism and hyperthyroidism

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Summary. Congenital hypothyroidism is a condition in which the thyroid gland does not produce enough thyroid hormones. It occurs in 1:2000-4000 newborns. Common clinical features include decreased activity and increased sleep, feeding difficulty, constipation, prolonged jaundice, myxedematous facies, large fontanels (especially posterior), macroglossia, distended abdomen with umbilical hernia, and hypotonia. Slow linear growth and developmental delay are usually apparent by 4-6 months of age. Without treatment, congenital hypothyroidism leads to severe intellectual deficit and short stature. Congenital hyperthyroidism occurs when the thyroid gland produces too much of the hormone thyroxine, which can accelerate body metabolism, causing unintentional weight loss and a rapid or irregular heartbeat. Hyperthyroidism is very rare and its prevalence is unknown. Common clinical features include unintentional weight loss, tachycardia, arrhythmia, palpitations, anxiety, tremor and sweating. Here we summarize the genes involved in congenital hypo- and hyperthyroidism and the tests we use for genetic analysis. (www.actabiomedica.it)

Key words: congenital hypothyroidism, non-autoimmune hyperthyroidism, thyroxine

Congenital hypothyroidism

Congenital hypothyroidism (CH) is the most common congenital endocrine disorder. It has a prevalence of 1:2000-4000 and is more frequent in females than in males (ratio of 2:1) (1). At birth, clinical features are mild or absent, becoming apparent a few months later. The disorder is characterized by reduced physical activity, increased sleeping periods, feeding difficulties, constipation, jaundice, myxedematous face, wide fontanels, macroglossia, abdominal distention with umbilical hernia, and hypotonia. Developmental and growth delay become evident 4-6 months after birth. Without therapy, the disorder leads to intellectual disability and very short stature (1).

Congenital hypothyroidism can be caused by thyroid dysgenesis (85% of cases) or defects in thyroid hormone biosynthesis (10-15% of cases) (2). Second-

ary congenital hypothyroidism is caused by chronic low levels of thyroid stimulating hormone (TSH) and may be due to congenital hypopituitarism. Peripheral congenital hypothyroidism is caused by defects in the transport, metabolism and action of thyroid hormones, or peripheral resistance to thyroid hormones (3). Congenital hypothyroidism can also be syndromic.

Currently, neonatal screening mainly detects elevated levels of TSH that increase in response to the reduction in thyroid hormone. This screening identifies 90% of cases of CH. Most patients have normal development after treatment with thyroxine. Besides assay of TSH, triiodothyronine (T3) and thyroxine (T4), other diagnostic tests include thyroid scanning with radioactive iodine, thyroid echography, and assay of serum thyroglobulin. These exams can help determine the etiology of the disease and differentiate permanent and transient cases (1,4). Differential

Table 1. Genes associated with congenital hypothyroidism

| Gene | OMIM gene | Disease | OMIM disease | Inheritance | Gene function |
|-----------------|-----------|--|----------------------------|----------------|--|
| <i>THRA</i> | 190120 | CHNG6 | 614450 | AD | Nuclear hormone receptor mediator of T3 biological activity |
| <i>NKX2-1</i> | 600635 | CAHTP | 610978 | AD | Transcription factor for expression of thyroid-specific genes |
| <i>NKX2-5</i> | 600584 | CHNG5 | 225250 | AD | Transcription factor for thyroid organogenesis |
| <i>PAX8</i> | 67415 | CHNG2 | 218700 | AD | Transcription factor for expression of thyroid-specific genes, maintenance of thyroid cell differentiation |
| <i>POU1F1</i> | 173110 | CPHD1 | 613038 | AD, AR | Transcription factor involved in specification of lactotrope, somatotrope and thyrotrope phenotypes in developing anterior pituitary gland |
| <i>GNAS</i> | 139320 | PHP1A PHP1C | 103580 612462 | AD | Activation of adenylate cyclase that regulates thyroid activity |
| <i>SECISBP2</i> | 607693 | Abnormal thyroid hormone metabolism | 609698 | AR | Co-translational insertion of selenocysteine into selenoproteins like type II iodothyronine deiodinase |
| <i>THRB</i> | 190160 | GRTH PRTH | 188570 274300 145650 | AD AR AD | Nuclear hormone receptor for triiodothyronine. Mediation of thyroid hormone activity |
| <i>TRHR</i> | 188545 | Generalized thyrotropin-releasing hormone resistance | 188545 | AR | TRH receptor promoting TSH and prolactin release |
| <i>KAT6B</i> | 605880 | GTPTS SBBYSS | 606170 603736 | AD | Histone acetyltransferase transcriptional activator and repressor, also important for thyroid organogenesis |
| <i>LHX4</i> | 602146 | CPHD4 | 262700 | AD | Early stages of pituitary development |
| <i>TSHB</i> | 188540 | CHNG4 | 275100 | AR | Control of thyroid structure and metabolism |
| <i>TSHR</i> | 603372 | CHNG1 | 275200 | AR | Major controller of thyroid cell metabolism. Receptor for thyrotropin and thyrostimulin |
| <i>TPO</i> | 606765 | TDH2A | 274500 | AR | Central role in thyroid gland function. Generation of thyroxine, T3 |
| <i>SLC5A5</i> | 601843 | TDH1 | 274400 | AR | Uptake of iodine by thyroid |
| <i>DUOX2</i> | 612772 | TDH5 | 274900 | AR | Thyroid hormone synthesis |
| <i>DUOX2</i> | 606759 | TDH6 | 607200 | AR | Thyroid hormone synthesis |
| <i>IYD</i> | 612025 | TDH4 | 274800 | AR | Hydrolysis of thyroglobulin to release iodide |

(continued on next page)

Table 1 (continued). Genes associated with congenital hypothyroidism

| Gene | OMIM gene | Disease | OMIM disease | Inheritance | Gene function |
|----------------|-----------|--|--------------|-------------|--|
| <i>PROP1</i> | 601538 | CPHD2 | 262600 | AR | Involved in ontogenesis of pituitary gonadotropes, somatotropes, lactotropes and caudomedial thyrotropes |
| <i>SLC26A4</i> | 605646 | PDS | 274600 | AR | Sodium-independent transporter of iodide |
| <i>TG</i> | 188450 | TDH3 | 274700 | AR | Substrate for synthesis of T4 and T3, storage of inactive forms of thyroid hormone and iodine |
| <i>FOXI1</i> | 601093 | PDS | / | AR | Transcription factor for <i>SLC26A4</i> |
| <i>FOXE1</i> | 602617 | Athyroidal/ thyroidal hypothyroidism with spiky hair, cleft palate | 241850 | AR | Thyroid morphogenesis |
| <i>UBR1</i> | 605981 | JBS | 243800 | AR | Degradation of substrate proteins |
| <i>SLC16A2</i> | 300095 | AHDS | 300523 | XLR | Cell import of T4, T3, T2 |

AHDS = Allan-Herndon-Dudley syndrome; CAHTP = choreoathetosis and congenital hypothyroidism with/without pulmonary dysfunction; CHNG = congenital nongonitrous hypothyroidism; CPHD = combined pituitary hormone deficiency; GRTH = generalized thyroid hormone resistance; GTPTS = genitopatellar syndrome; JBS = Johanson-Blizzard syndrome; PDS = Pendred syndrome; PRTH = selective pituitary thyroid hormone resistance; SBBYSS = Ohdo syndrome, SBBYS variant; TDH = thyroid dysmorphogenesis; AD = autosomal dominant; AR = autosomal recessive; XLR = X-linked recessive.

diagnosis should consider chronic fatigue syndrome, depression, dementia and heart failure (5).

Newborns diagnosed with CH should be treated with levothyroxine to ensure normal neurocognitive development. Serum levels of TSH, T4 and T3 should be measured frequently. When babies are treated soon after birth, their prognosis is excellent and their IQ normal (1). Congenital hypothyroidism is usually sporadic, but in 10% of cases it is inherited (6).

Generalized thyroid hormone resistance is a rare genetic disorder caused by a reduced peripheral response to thyroid hormones. The prevalence is 1:40000. In 85% of cases it is caused by mutations in *THRB* (7).

Twenty-five genes are currently known to be associated with congenital hypothyroidism or generalized thyroid hormone resistance (Table 1). Pathogenic variants may be missense, nonsense, splicing or small indels. We use a multi-gene NGS panel to detect nucleotide variations in coding exons and flanking introns of the above genes.

Nonautoimmune hyperthyroidism

Nonautoimmune hyperthyroidism or hereditary hyperthyroidism is a rare form of hyperthyroidism, characterized by excessive thyroid activity. Major symptoms are hyperactivity, anxiety, weight loss, exophthalmos and tachycardia (8). Age of onset is highly variable. Clinical diagnosis is based on observation and measurement of plasma concentrations of thyroid hormone. Differential diagnosis is based on absence of exophthalmos and presence of myxedema, anti-TSH antibodies and lymphocyte infiltration of the thyroid (9). Hyperthyroidism can be treated with drugs that inhibit thyroid activity or with ablation therapy (surgery or radioiodine) (10).

The nonautoimmune hyperthyroidism has autosomal dominant inheritance and is caused by mutations in *TSHR* (OMIM gene: 603373; OMIM disease: 609152, 603373) (9). Prevalence is unknown: very few families (130 patients from 22 families) and

some sporadic cases, especially in Caucasian subjects, have been described (9,11).

Pathogenic variants may be missense, nonsense, splicing or small indels. MAGI uses an NGS panel to detect nucleotide variations in coding exons and flanking introns of *TSHR*.

Conclusions

We created a NGS panel to detect nucleotide variations in coding exons and flanking regions of all the genes associated with hypo- and hyperthyroidism. When one of those suspects is present we perform the analysis of all the genes present in this short article.

In order to have a high diagnostic yield, we developed a NGS test that reaches an analytical sensitivity (proportion of true positives) and an analytical specificity (proportion of true negatives) of $\geq 99\%$ (coverage depth $\geq 10x$).

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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