INVITED REVIEW

Genetic variation in thyroid hormone pathway genes; polymorphisms in the TSH receptor and the iodothyronine deiodinases

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Abstract

Serum thyroid parameters show substantial inter-individual variability, in which genetic variation is a major factor. Findings in patients with subclinical hyper- and hypothyroidism illustrate that even minor alterations in serum thyroid function tests can have important consequences for a variety of thyroid hormone-related clinical endpoints, such as atherosclerosis, bone mineral density, obesity, and heart rate. In the last few years, several studies described polymorphisms in thyroid hormone pathway genes that alter serum thyroid function tests. In this review, we discuss the genetic variation in the TSH receptor and iodothyronine deiodinases. We discuss the possible consequences of these studies for the individual patient and also the new insights in thyroid hormone action that can be obtained from these data.

Introduction

Thyroid hormone is essential for growth and differentiation, for the regulation of energy metabolism, and for the physiological function of virtually all human tissues. The production of thyroid hormone is regulated by the classic hypothalamus–pituitary–thyroid axis, whereas the biological activity of thyroid hormone (i.e. the availability of the active hormone triiodothyronine (T3) for the nuclear thyroid hormone receptors) is mainly regulated at the tissue level by the iodothyronine deiodinases and thyroid hormone transporters.

In healthy subjects, serum thyroid parameters show substantial inter-individual variability, whereas the intra-individual variability is within a narrow range (1). This suggests an important influence of genetic variation, in addition to environmental factors such as food or iodine intake, on the regulation of thyroid hormone bioactivity, resulting in a thyroid hormone function set-point that is different for each individual. This notion is supported by a classical twin study that was recently published (2). In this study, heritability accounted for ~65% of the variation in serum thyroid stimulating hormone (TSH), free thyroxine (FT4), and free T3 (FT3) levels. In a Mexican–American population, total heritability in serum thyroid parameters ranged from 26 to 64% of the total inter-individual variation observed (3).

Findings in patients with subclinical hyper- and hypothyroidism illustrate that even minor alterations in thyroid hormone levels (and in thyroid hormone bioactivity) can have important consequences for a variety of thyroid hormone-related clinical endpoints, such as atherosclerosis, bone mineral density, obesity, and heart rate (4–6). In the last few years, several studies described polymorphisms in thyroid hormone pathway genes that result in an altered thyroid hormone bioactivity. Some of these polymorphisms are associated with serum TSH and/or thyroid hormone levels in healthy subjects, and/or with thyroid hormone-related clinical endpoints. As DNA variations are stable throughout life, such genetic effects are likely to have an influence during the lifetime of subjects.

In this review, we discuss the genetic variation in thyroid hormone pathway genes, focusing on the polymorphism studies that have emerged in the last few years. For the sake of brevity, we have focused on single nucleotide polymorphisms (SNPs) in the TSH receptor and iodothyronine deiodinases, since only these genes are presently analyzed for possible associations with serum thyroid hormone levels. Besides their relation with serum thyroid hormone levels, we discuss the effects of these polymorphisms on clinical endpoints such as Graves’ disease and insulin resistance. Furthermore, we discuss the possible consequences of these studies for the individual patient, and also the new insights in thyroid hormone action that can be obtained from these data.

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Polymorphisms in the TSH receptor

Many somatic gain-of-function mutations in the TSH receptor (TSHR) have been described, which result in a phenotype of toxic adenoma or toxic multinodular goiter (7). Germline gain-of-function TSHR mutations that result in congenital hyperthyroidism have also been described. Conversely, germline loss-of-function TSHR mutations are associated with TSH resistance and congenital hypothyroidism (see reference (8) for an illustrative example). However, only three germline TSHR polymorphisms, resulting in amino acid substitutions, have been identified (9–11). Two of these are located in the extracellular domain of the receptor (Asp36His and Pro52Thr) (9, 10), and one is located in the intracellular domain (Asp727Glu) (11) (Fig. 1). In addition, several intronic microsatellite markers and intronic SNPs have been described in TSHR (12–16).

The TSHR-Glu727 allele was associated with lower levels of plasma TSH in a population of healthy blood donors, but had no effect on FT4 (17). Recently, we have confirmed this observation in unrelated study populations (18, 19). This could point toward a higher sensitivity of the variant versus the wild-type TSHR, since less TSH is needed to produce normal FT4 levels. Although there is one in vitro study showing that the TSHR-Glu727 variant results in an increased cAMP response of the receptor to TSH (11), others have not been able to replicate this (20, 21). A different explanation would be that the Asp727Glu polymorphism is linked to another polymorphism elsewhere in the gene. The TSHR-Asp727Glu polymorphism is found to be within a linkage disequilibrium block starting at intron 8 and extending about 10 kb beyond the 3'UTR of the TSHR gene (22).

Conflicting data are also available regarding the response of the TSHR-Pro52Thr variant to TSH stimulation (23–25). This might reflect the subtle effects of these polymorphisms. The TSHR-Pro52Thr and -Asp36His polymorphisms were not associated with changes in serum TSH or iodothyronine levels in healthy blood donors. However, this could be attributable to the low allele frequency of these SNPs (6 and 0.6% respectively) resulting in a lack of power.

No data on polymorphisms resulting in a relative loss of function of the TSHR are yet available. Subjects with a heterozygous loss of function mutation appear to have a dominant transmission of partial TSH resistance, which is due to intracellular entrapment and reduced maturation of the wild-type TSHR by the inactive mutants (26). Similarly, polymorphisms resulting in a relative loss of function could have an impact via this mechanism, and possibly account for some of the so-called ‘euthyroid outliers’ with elevated TSH determinations.

Besides effects on serum thyroid hormone levels, polymorphisms in the TSHR may also have effects on the development of autoimmune thyroid disease. The TSHR gene is located on chromosome 14q31, an area in which a Graves’ disease susceptibility locus (GD-1) has been mapped (27). The GD-1 locus is
specifically linked to Graves’ disease, but not Hashimoto’s thyroiditis or autoimmune thyroid disease in general. Several case-control studies have been carried out analyzing the possible association between one or more of the previously mentioned TSHR polymorphisms and autoimmune thyroid disease. An overview of the 14 studies up to 2002 that analyzed the possible association of TSHR polymorphisms with Graves’ disease has been presented by Ban et al. (28).

All studies analyzing the TSHR-Pro52Thr or Asp36His variant showed no association, apart from one in which an association of the TSHR-Pro52Thr variant with Graves’ disease was described in US Caucasian females (n = 100 females with autoimmune thyroid disease versus 69 controls) (29). These same authors later described two subjects who were homozygous for the Thr52 allele and had normal thyroid function tests, on the basis of which they suggested that the variant receptor is able to respond normally to TSH (23). Obviously, more subtle effects of this polymorphism cannot be excluded by the last study. In a multiethnic (Chinese, Malays, and Indians) cohort of patients with Graves’ disease, TSHR-Asp36His was absent, and TSHR-Pro52Thr and -Asp727Glu were not associated with Graves’ disease (30). Unfortunately, no data are presently available if the two variants in the extracellular domain of the receptor show altered binding of thyroid-stimulating antibodies. Nor are any data available regarding altered binding or altered cAMP response of the variant TSH receptor to a different TSHR ligand termed thyrostimulin that has recently been identified (31).

Three case-control studies in Caucasians showed no association between the TSHR-Asp727Glu polymorphism and Graves’ disease (11, 28, 32). However, meta-analysis of these three studies (28), as well as a study in Russian patients (n = 78 vs 93 controls), showed a weak association of the variant receptor with Graves’ disease (33, 34). These Graves’ patients showed a significantly higher frequency of the TSHR-Glu727 allele than did healthy subjects (33, 34). A recent transmission disequilibrium test (TDT) study in Russian families showed that the D2-Thr92Ala (see below) and TSHR-Asp727Glu polymorphisms are in weak linkage disequilibrium (35), and that the D2-Ala92/TSHR-Glu727 haplotype allele was preferentially transmitted from parents to affected siblings with Graves’ disease (35). However, TDT is not the best design to analyze linkage disequilibrium.

A recent study in Japanese patients with autoimmune thyroid disease showed that several SNPs in intron 7 of the TSHR gene are significantly associated with Graves’ disease (14). Another polymorphism in intron 4 of TSHR was associated with Graves’ disease in a multi-ethnic population of patients from Singapore (30). Recently, a study in which common haplotype tagging SNPs in TSHR were analyzed showed a significant association of intronic SNPs in one linkage disequilibrium block with Graves’ disease (22).

These data together suggest that genetic variation in TSHR is, albeit weakly, associated with the development of Graves’ disease, but it is yet unclear whether the associated polymorphisms are functional or whether they are linked to functional variants elsewhere in the gene or in the nearby genome that are still to be discovered. Meta-analysis, detailed linkage disequilibrium analysis, and haplotype tagging approaches (as well as the HapMap project, www.hapmap.org) should be able to resolve this issue (36).

TSHR is not only expressed in the thyroid, but also in adipose tissue (37), brain (38), orbital tissue (37, 39), lymphocytes (40), and bone (41). Evidence is accumulating for direct effects of TSH via the TSHR on these tissues. TSH is able to induce proliferation and inhibit differentiation in cultured rat pre-adipocytes (42), and TSHR knockout mice have a severe phenotype of osteoporosis, independent of their thyroid hormone levels (41). Genetic variation in TSHR may thus not only be important for the development of autoimmune thyroid disease (more specifically Graves’ disease), but may also be associated with more common clinical endpoints such as osteoporosis (19), either via its influence on thyroid hormone levels, or via direct effects of TSH on bone.

### Polymorphisms in the iodothyronine deiodinases

No patients with inactivating mutations in any of the iodothyronine deiodinases have yet been described. Whether this means that these mutations are not compatible with life, that they have little or no consequences, or that they result in unexpected phenotypes is unclear. Based on the phenotypes of mice with targeted deletions of D1, D2, or D3, the most severe effects would be expected of mutations in D3 (43–45). In the last few years, several polymorphisms in deiodinases have been described (17, 46, 47) (Fig. 1). Based on the physiological role of the three different deiodinases (48) (Table 1), one can speculate about the possible consequences of polymorphisms in these enzymes. D1 is present in liver, kidney, and thyroid, and plays a key role in the production of the active hormone T3 from T4 and in the clearance of the metabolite reverse T3 (rT3) (48, 49). D2 is present in brain, pituitary, brown adipose tissue, thyroid, skeletal muscle, aortic smooth muscle cells, and osteoblasts; D2 mRNA has also been detected in the human heart (48). In tissues such as the brain, D2 is important for local production of T3, whereas D2 in skeletal muscle may also contribute to plasma T3 production. D3 is present in brain, skin, placenta, pregnant uterus, and various fetal tissues, and is induced in critical illness (48, 50). D3 is the major T3 and T4 inactivating enzyme and
contributes to thyroid hormone homeostasis by protecting tissues from excess thyroid hormone. The T3/rT3 ratio is considered to be a sensitive indicator of the peripheral metabolism of thyroid hormone, being positively influenced by D1 and D2 and negatively by D3. This ratio is also relatively independent of thyroidal T4 production and of variations in serum binding proteins. In addition to genetic variation, the peripheral metabolism of thyroid hormone can be influenced by factors such as iodine deficiency, nutritional status, and disease.

**D1**

Recently, two polymorphisms in D1 (D1-C785T and D1-A1814G) that affect the serum T3/rT3 ratio in healthy subjects have been identified (17) (Fig. 1). The D1-C785T allele is associated with higher levels of rT3 and with a lower T3/rT3 ratio. Based on the function of D1 (Table 1), it was speculated that the D1-785T variant results in a decreased activity of D1. The D1-1814G allele was associated with a higher T3/rT3 ratio, suggesting that the D1-1814G variant may result in increased activity (17). Since both polymorphisms are located in the 3'-UTR of the mRNA, a change in the stability of the mRNA is an attractive explanation for their effect. Alternative explanations include an altered folding of the mRNA, in particular of the selenocysteine insertion sequence (SECIS), which is necessary for the incorporation of a selenocysteine residue in the catalytic center of the protein (48), or linkage with other polymorphisms in the coding sequence or in regulatory regions of the gene. Functional testing and haplotype analysis will be necessary to resolve this issue. Although the D1-785T variant is not associated with serum rT3 levels in a population of 350 elderly men (age > 70 years), its association with lower levels of T3 in this elderly population supports the hypothesis of a lower activity of D1 in carriers of this polymorphism (51). The difference in associations found in the healthy blood donors and the elderly men might be explained by the difference in age, with means of 46 vs 77 years respectively. In young subjects, a decreased T3 production by D1 may be masked by the production of serum T3 by skeletal muscle D2. Throughout adult life, skeletal muscle size and strength gradually decline, resulting in a decrease in D2-expressing skeletal muscle. Furthermore, rT3 levels increase with age, and degradation of the D2 protein is accelerated when it is exposed to its own substrates T4 and rT3 (52). Although it has been shown that D1 activity also decreases during aging (53), the relative contribution of D2 to serum T3 production may be less important in the elderly than in young subjects. This would mean that D1 has a relatively greater contribution to serum T3 production at advanced ages (51) (Fig. 2). In line with this hypothesis is the recent publication of a polymorphism in a short open reading frame (ORFa) in the 5'-UTR of D2, which has been shown to be an important regulatory element (47, 54) (Fig. 2). This polymorphism (D2-ORFa-Gly3Asp) is associated with the serum T3/T4 ratio in young, but not elderly, subjects (47). Also supporting this hypothesis is the association of the D1-C785T polymorphism with both serum T3 and rT3 levels in an unrelated third population, with an average

**Table 1** Physiological role in thyroid hormone metabolism, tissue distribution, and substrate preference of the three human iodothyronine selenodeiodinases (D1–D3).

<table>
<thead>
<tr>
<th></th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
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</thead>
<tbody>
<tr>
<td>Function</td>
<td>Plasma T3 production, rT3 clearance</td>
<td>Local and plasma T3 production</td>
<td>T3 and T4 clearance, rT3 production</td>
</tr>
<tr>
<td>Tissue distribution</td>
<td>Liver, kidney, thyroid</td>
<td>Brain, pituitary, BAT, thyroid, skeletal muscle, heart, aortic smooth muscle, osteoblasts</td>
<td>Brain, skin, placenta, fetal tissues, critically ill liver and skeletal muscle</td>
</tr>
<tr>
<td>Substrate preference</td>
<td>rT3 &gt; T4 = T3</td>
<td>T4 &gt; rT3</td>
<td>T3 &gt; T4</td>
</tr>
</tbody>
</table>

T3, triiodothyronine; T4, thyroxine; rT3, reverse triiodothyronine; BAT, brown adipose tissue.

![Figure 2](image-url) Illustration of the proposed model in which the relative contribution of D2 to serum triiodothyronine (T3) production decreases with an increase in age, based on the different associations of D1 and D2 polymorphisms with serum iodothyronines in one younger (left arrow, 46 years) and two elderly populations (right two arrows, 69 and 77 years respectively). T4, thyroxine.
Haplotypic association studies have shown that the D1-C785T and D1-A1814G polymorphisms appear on different haplotype alleles (17, 51). The haplotype allele containing D1-C785T is not only associated with changes in serum iodothyronine levels, but also with increased levels of free insulin-like growth factor-I (IGF-I) in two unrelated populations (51). This was substantiated by the association of this haplotype allele with several IGF-I-related endpoints, such as increased muscle strength and muscle mass (51). As IGF-I has a stimulatory effect on D1 expression (55), these higher levels of free IGF-I might be seen as an adaptation to normalize D1 activity in carriers of the D1a-T haplotype allele. Conversely, thyroid hormone stimulates the expression of IGF-binding protein-I (IGFBP-I) in human hepatoma cells (56). A lower activation of thyroid hormone by liver D1 could result in lower levels of IGFBP-1, and thus a higher level of free IGF-I (51), as the majority of IGFBP-1 might be involved (64). Although D2 activity does not differ between different cells that are transfected with the D2-92Thr or the D2-92Ala variant (17, 58), a lower activity of D2 has been reported in muscle and thyroid homogenates of carriers of the D2-Ala92 allele (58). This suggests that the consequences of the D2-Thr92Ala polymorphism are caused by linkage with another polymorphism. Haplotypic analysis has shown that the D2-Thr92Ala polymorphism and the previously mentioned D2-ORFa-Gly3Asp polymorphism appear on different haplotype alleles (47). So far, there is no evidence of any relationship between the D2-ORFa-Gly3Asp polymorphism and insulin resistance.

Based on the expression pattern of D2, and since D2 is crucial in the regulation of local T3 concentrations, one can speculate about other possible consequences of these and other D2 polymorphisms. Guo et al. studied the relation of the Dio2 gene with mental retardation in iodine-deficient areas of China in a case-control study (n = 96 vs 331 controls) (65). They found a positive association of two intronic D2 polymorphisms (but not of D2-Thr92Ala) with mental retardation in these areas (65), and concluded that genetic variation in D2 may determine the risk of developing mental retardation in an iodine-deficient area, probably by affecting the local amount of T3 available in the brain (65). Appelhof et al. addressed the questions whether genetic variation in the Dio2 gene is a determinant of well-being and neurocognitive functioning in hypothyroid patients on levothyroxine substitution, and whether D2 polymorphisms were associated with a preference for T4/T3 combination therapy over substitution with T4 alone (66). No differences in well-being, neurocognitive functioning or appreciation of T4/T3 combination therapy were detected in these thyroid hormone-replaced hypothyroid patients (66).

D2

D2 is important in the production of local T3, but D2 in skeletal muscle also contributes to serum T3 production (48, 57). The above-mentioned association of D2-ORFa-Gly3Asp with the serum T3/T4 ratio also points toward an important role of D2 in serum T3 production (47, 51).

The first polymorphism described in any of the deiodinases was D2-Thr92Ala (46) (Fig. 1). Although this polymorphism does not seem to be associated with serum iodothyronine levels, it has been associated with insulin resistance in three different populations (46, 58, 59). The mechanism behind this association is yet unclear, but it might involve expression of D2 in skeletal muscle and/or in (brown) fat in humans (48). T3 stimulates the transcription of the muscle/fat-specific insulin-sensitive glucose transporter GLUT4 (60). In addition, thyroid hormone augments catecholamine-stimulated lipolysis (61), and a particular inactivating thyroid hormone receptor α mutation results in insulin resistance in mice (62). A decreased D2 activity in insulin-sensitive tissues such as adipose tissue and skeletal muscle, resulting in a decreased availability of local T3, may thus explain the association of D2-Thr92Ala with relative insulin resistance (46, 58, 59). Furthermore, it was recently shown that administration of bile acids to mice can increase energy expenditure, and thereby prevent obesity and insulin resistance via the induction of D2 (63). Alternatively, hypothalamic D2, which regulates the T3 content of brain stem neurons projecting to white adipose tissue, may be involved (64). Although D2 activity does not differ between different cells that are transfected with the D2-92Thr or the D2-92Ala variant (17, 58), a lower activity of D2 has been reported in muscle and thyroid TSHR and the iodothyronine deiodinases that affect mental retardation in these areas and other D2 polymorphisms. Guo et al. studied the relation of the Dio2 gene with mental retardation in iodine-deficient areas of China in a case-control study (n = 96 vs 331 controls) (65). They found a positive association of two intronic D2 polymorphisms (but not of D2-Thr92Ala) with mental retardation in these areas (65), and concluded that genetic variation in D2 may determine the risk of developing mental retardation in an iodine-deficient area, probably by affecting the local amount of T3 available in the brain (65). Appelhof et al. addressed the questions whether genetic variation in the Dio2 gene is a determinant of well-being and neurocognitive functioning in hypothyroid patients on levothyroxine substitution, and whether D2 polymorphisms were associated with a preference for T4/T3 combination therapy over substitution with T4 alone (66). No differences in well-being, neurocognitive functioning or appreciation of T4/T3 combination therapy were detected in these thyroid hormone-replaced hypothyroid patients (66).

D3

Until now, only one polymorphism has been identified in D3 (D3-T1546G), located in the 3'UTR (17). This polymorphism does not result in altered thyroid hormone levels in healthy individuals. D3 plays an important role in thyroid hormone homeostasis in critical illness and during fetal development, providing protection against thyroid hormone excess (50, 67). Possible effects of this polymorphism on development and under pathophysiological conditions therefore remain to be investigated in future studies. A major obstacle in these studies is that the D3 gene is an imprinted gene, with preferential expression from the paternal allele, as has been studied in a mouse model (43). Therefore, the effects of polymorphisms in the Dio3 gene on thyroid hormone homeostasis depend on the parental origin of the variant allele.

Concluding remarks and future perspectives

Here, we have discussed several polymorphisms in TSHR and the iodothyronine deiodinases that affect
serum thyroid hormone levels and/or have effects on thyroid hormone-related physiological endpoints. These polymorphism studies are important for several reasons. First, new insight can be obtained about the physiological function of thyroid hormone pathway genes. The hypothesis regarding a relative decrease in the contribution of D2 to serum T3 production (Fig. 2), based on the different associations of D1 and D2 polymorphisms in younger and elder populations, is an example of this (17, 51), as is the role of D2 activity in the development of insulin resistance (46, 47, 58). Second, genetic variation is important in inter-individual variation in thyroid hormone bioactivity (1–3). It seems that each individual has a different, genetically determined thyroid function set-point, and that small variations around this set-point, even within the normal range, can have important consequences on, for example, body weight (6). A better selection of subjects, by excluding subjects with autonomous thyroid nodules (68, 69), and standardized (regarding time of day) and perhaps multiple TSH measurements to better define an individual’s set-point (1), would increase the power of such association studies. This raises the possibility of estimating an individual’s set-point based on his/her genetic make-up of thyroid hormone pathway genes. The decision of whether a patient with subclinical changes in thyroid parameters should be treated might then be made on that individual patient’s normal values. In addition, the decision to treat patients with subclinical thyroid disease is based on the risk of these patients developing complications. If the genetic profile makes a patient more vulnerable, then this might be an indication to initiate treatment in an earlier phase.

In addition to peripheral metabolism of thyroid hormone by the deiodinases, transmembrane transport of iodothyronines and expression of thyroid hormone receptors are other key processes in the regulation of thyroid hormone bioactivity. Surprisingly, no studies have yet been published investigating the association of polymorphisms in these transporters and receptors with clinical endpoints. This area of research remains to be explored, and it is likely that exciting new insights will be obtained in the upcoming years.

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