





## ORIGINAL ARTICLE

# Utility of systematic *TSHR* gene testing in adults with hyperthyroidism lacking overt autoimmunity and diffuse uptake on thyroid scintigraphy

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## Summary

**Objective:** Patients with hyperthyroidism lacking autoimmune features but showing diffuse uptake on thyroid scintigram can have either Graves' disease or germline activating TSH receptor (*TSHR*) mutation. It is important to identify patients with activating *TSHR* mutation due to treatment implication, but the overlapping clinical features with Graves' disease make it difficult to discriminate these two conditions without genetic testing. Our study aimed to assess the potential of systematic *TSHR* mutation screening in adults with hyperthyroidism, showing diffuse uptake on thyroid scintigraphy but absence of TSH receptor antibodies (TRAb) and clinical signs of autoimmunity.

**Design:** A cross-sectional study of Caucasian adults with hyperthyroidism, managed at three endocrine centres in the South West, UK, from January 2006 to April 2017.

**Methods:** We recruited 78 adult Caucasian patients with hyperthyroidism showing diffuse uptake on <sup>99m</sup>Tc-pertechnetate thyroid scintigraphy but without TRAb and other autoimmune clinical features of Graves' disease (such as thyroid-associated ophthalmopathy or dermopathy). Genomic DNA of these patients was analysed for variants in the *TSHR* gene.

**Results:** Genetic analysis identified 11 patients with four variants in *TSHR* [p.(Glu34Lys), p.(Asp36His), p.(Pro52Thr) and p.(Ile334Thr)]. None of these variants were pathogenic according to the American College of Medical Genetics and Genomics guideline.

**Conclusions:** Activating *TSHR* mutations are a rare cause of nonautoimmune adult hyperthyroidism. Our study does not support the routine genetic testing in adult patients with hyperthyroidism showing diffuse uptake on scintigraphy but negative TRAb and lacking extrathyroidal manifestations of Graves' disease.

## KEYWORDS

Graves' disease, hyperthyroidism, thyroid scintigraphy, TRAb, *TSHR*

## 1 | INTRODUCTION

Activating TSH receptor (*TSHR*) mutations are a rare cause of nonautoimmune hyperthyroidism, although the true prevalence in adults is unknown.<sup>1-3</sup> The majority of these cases are familial, with autosomal dominant patterns of inheritance, but mutation can also arise de novo.<sup>1,2,4</sup> Identification of these patients has important clinical implications. Hyperthyroidism due to activating *TSHR* mutations does not remit following antithyroid drug treatment, and patients usually require total thyroidectomy or radioiodine ablation as a definitive treatment.<sup>1,2</sup> A genetic diagnosis at the time of first presentation could, potentially, prevent unnecessary and prolonged treatment with antithyroid drugs, as well as reducing the associated morbidity and cost. This would also enable screening immediate family members, leading to earlier identification and treatment of undiagnosed hyperthyroidism.

It is difficult to identify patients with hyperthyroidism due to activating *TSHR* mutation, as their clinical features show significant overlap with Graves' disease. Similar to Graves' disease, presentation is highly variable, from subclinical hyperthyroidism to severe hyperthyroidism,<sup>1,2,5</sup> with ages at presentation ranging from the neonatal period up to 60 years,<sup>1,6</sup> and has a diffuse uptake on thyroid scintigraphy.<sup>2</sup> A family history of thyrotoxicosis is not always present in patients with activating *TSHR* mutation due to variable penetrance and seen in 30% of patients with Graves' disease<sup>7</sup>; thus, it is not very useful in discriminating these two aetiologies. Contrary to Graves' disease, patients with an activating *TSHR* mutation do not have TSHR antibodies (TRAb) or extrathyroidal autoimmune clinical manifestations such as thyroid-associated ophthalmopathy and dermopathy.<sup>1,2</sup> However, around 3%-5% patients with Graves' disease also do not have TRAb when analysed with the second- or third-generation assays,<sup>8,9</sup> and only about 25% will have extrathyroidal manifestations, such as thyroid-associated ophthalmopathy.<sup>10</sup> Altogether these data suggest that it is difficult to identify patients with activating *TSHR* mutation in routine clinical practice without systematic genetic testing. However, utility of this approach is not known. Therefore, we aim to assess the utility of systematic genetic testing for *TSHR* mutations in adults with hyperthyroidism showing diffuse uptake on thyroid scintigraphy but TRAb negative and lacking extrathyroidal manifestations of Graves' disease.

## 2 | SUBJECTS AND METHODS

### 2.1 | Study participants

We recruited patients from three endocrine centres (Exeter, Plymouth and Torbay) in the South West, England (UK). The inclusion criteria were as follows: age at recruitment >18 years, biochemically confirmed overt or subclinical hyperthyroidism according to the American Thyroid Association guideline,<sup>11</sup> absence of TRAb, diffuse uptake on the thyroid scintigraphy and Caucasian ethnicity. We excluded patients with any extrathyroidal manifestations of Graves'

disease, such as thyroid-associated ophthalmopathy or dermopathy, and patients with any other known cause of hyperthyroidism (eg, toxic nodular disease, thyroiditis and drug-induced thyrotoxicosis).

### 2.2 | Study recruitment

We identified 275 patients from the clinical records who had thyroid scintigraphy and had absence of TRAb from all three centres over 11 years (2006-2017). Local endocrinologists performed TRAb and thyroid scintigraphy at presentation as part of the routine clinical care. The research team reviewed all thyroid scintigraphy to identify patients with diffuse uptake. The clinical records were reviewed to assess the eligibility of these patients. Of the initial 275 potential participants identified, three had died, 41 had decreased or no uptake on scintigraphy, 98 had patchy/localized uptake, two had Graves' ophthalmopathy, and four had drug-related thyrotoxicosis, and they were therefore excluded. All 127 patients who fulfilled the entry criteria were approached and invited to take part in the study, and 78/127 (61%) were recruited (49 refused or were unable to be contacted directly). We estimated the frequency of activating *TSHR* mutation in adults with hyperthyroidism lacking overt autoimmunity and diffuse uptake on thyroid scintigraphy to be ~4.5% based on two previous studies.<sup>12,13</sup> This provided a sample size of 67 to find at least one individual with a mutation at  $P < 0.05$ .

### 2.3 | DNA and data collection

We collected one-off blood or saliva sample for DNA extraction. Demographics and other clinical features were collected from the clinical records. If an individual had multiple episodes of the thyrotoxicosis, the data for the episode during which thyroid scintigraphy and TRAb were performed were used in the study.

All three centres have been using a second-generation enzyme-linked immunoassay from EUROIMMUN AG, Germany, to measure TRAb throughout the study period. Patients with borderline or positive results were excluded from the study (>1.8 IU/L). Thyroid function tests were measured locally as part of routine care by each centre independently. Manufacturers' reference ranges of TSH, free thyroxine (FT4) and free triiodothyronine (FT3) for the assays for each centre were used to confirm biochemical thyrotoxicosis. The nuclear medicine department of each centre performed thyroid scintigraphy according to their local protocol.

NRES Committee North East - Newcastle & North Tyneside, UK, gave ethical approval for the study (IRAS no 153183). All the study participants gave the informed written consent.

### 2.4 | Data analysis

Statistical analysis was conducted using StataSE<sup>®</sup> 15.1 (StataCorp, College Station, TX, USA). The Mann-Whitney *U* test was used for comparing continuous variable, whereas Fisher's exact test was used for comparing categorical variable.

## 2.5 | DNA analysis

Genomic DNA was extracted from peripheral blood or salivary cells using standard procedures in the molecular genetics laboratory, Royal Devon and Exeter Hospital, Exeter, UK. The entire coding region and intron-exon boundaries of all 10 exons of the *TSHR* gene were amplified by polymerase chain reaction and Sanger-sequenced using BigDye Terminator v3.1 cycle sequencing. Sequences were compared to the reference sequence (NM\_000369.2) using Mutation Surveyor software (SoftGenetics, State College, PA, USA). The changes in sequence were assessed and reported according to the American College of Medical Genetics and Genomics (ACMG) guideline.<sup>14</sup>

## 3 | RESULTS

### 3.1 | Study cohort characteristics

The clinical characteristics of the study cohort are shown in Table 1. The median age at diagnosis of hyperthyroidism was 52 years, 76% were female, and 42% had a palpable diffuse goitre. None had thyroid-associated ophthalmopathy, dermopathy or TRAb, all had diffuse uptake on thyroid scintigraphy, and 35% had a family history of thyrotoxicosis.

### 3.2 | Analysis of *TSHR* variants

Genetic analysis identified 11 patients with four variants in *TSHR* (Table 2). None of these variants were novel or pathogenic according to the ACMG guideline.<sup>14</sup> p.(Glu34Lys), p.(Asp36His) and p.(Pro52Thr) were definitely benign according to the ACMG guideline. All the variants were outside the mutational hot spot for the disease (transmembrane domain) and present in the larger control population (gnomAD version 2.0, n ~ 137 000)<sup>15</sup> at a frequency incompatible with rare monogenic disease (Table 2). Furthermore, two of these variants, p.(Asp36His) and p.(Pro52Thr), were seen previously in patients with Graves' disease with TRAb and ophthalmopathy.<sup>16-18</sup> The p.(Glu34Lys) variant was seen in an individual with congenital hypothyroidism and the probands' mother with Graves' disease (Table 2).<sup>19</sup> Both p.(Glu34Lys) and p.(Asp36His) had in vitro evidence of normal or low activity.<sup>18,19</sup> These data together suggest that these are not activating pathogenic variants.

### 3.3 | Analysis of *TSHR* variant p.(Ile334Thr)

p.(Ile334Thr) variant was not reported in the literature. It is classified as a likely benign variant according to the ACMG guideline.<sup>14</sup> The variant is in the extracellular domain outside the mutation hot

Clinical characteristics	Whole cohort N = 78	Patients without TSHR variant, n = 67	Patients with benign TSHR variant, n = 11	P
Age at diagnosis (y)	52.4 (43.8-69.5)	51.6 (42.4-67.9)	60.6 (51.9-73.1)	0.13
Female (%)	59 (76)	51 (76)	8 (73)	1
Duration since the presentation with thyrotoxicosis at the time of recruitment (y)	2.7 (1-4.8)	2.8 (1-4.7)	2.6 (1-6.5)	0.81
Hyperthyroidism (%)				
Overt hyperthyroidism	75 (95)	64 (96)	11 (100)	1
Subclinical hyperthyroidism	3 (5)	3 (4)	0	
Presence of goitre (%)	33 (42)	25 (37)	8 (73)	0.05
Family history of hyperthyroidism (%)	27 (35)	22 (33)	5 (45)	0.5
Thyroid-associated ophthalmopathy or dermopathy (%)	0	0	0	
Presence of TSH receptor antibodies (%)	0	0	0	
Diffuse uptake on thyroid scintigraphy (%)	78 (100)	67 (100)	11(100)	
Treatment of hyperthyroidism				
Antithyroid drug	61 (78)	51 (76)	10 (91)	0.76
Radioiodine ablation <sup>a</sup>	15 (19)	14 (21)	1 (9)	
Total thyroidectomy <sup>a</sup>	2 (3)	2 (3)	0	

**TABLE 1** Clinical characteristics of the study cohort

Median (IQR) for age at diagnosis and duration. N (%) for the others. P-value is for comparison between patients with or without TSH receptor (TSHR) variant.

<sup>a</sup>All patients had antithyroid drug prior to these treatments.

**TABLE 2** TSH receptor (*TSHR*) variants identified in the study cohort

<i>TSHR</i> variants	No. of patients	Exon	Location of variant	No. and freq. of heterozygotes in control population (gnomAD), all ethnicity	No. and freq. of heterozygotes in control population (gnomAD), European (non-Finnish)	No. of homozygotes in gnomAD	In vitro activity of variant in literature	Phenotype previously reported in literature	ACMG classification of variants
c.100G>A, p.(Glu34Lys) (rs45499704)	1	1	Extracellular	60/137 988 (0.043%)	41/62 742 (0.065%)	1	Low (19)	Proband with congenital hypothyroidism and mother with Graves' disease (19)	Benign
c.106G>C, p.(Asp36His) (rs61747482)	2	1	Extracellular	1439/137 892 (1.04%)	1146/62 646 (1.83%)	12	No impact (18)	TRAb-positive Graves' disease (18)	Benign
c.154C>A, p.(Pro52Thr) (rs2234919)	7	1	Extracellular	15 958/137 484 (11.6%)	7092/62 256 (11.3%)	1071	-	Graves' disease with ophthalmopathy (16, 17)	Benign
c.100IT>C, p.(Ile334Thr) (rs553893026)	1	10	Extracellular	5/123 129 (0.004%)	2/55 855 (0.003%)	0	-	-	Likely benign

spot, not conserved and seen in five patients in gnomAD (Table 2). Based on the frequency of this variant in gnomAD, for this variant to be pathogenic, monogenic disease would have to be seen in one in 5000 population, which is far more common than the estimated prevalence of hyperthyroidism due to activating *TSHR* mutations (~<1:15 000 children in Denmark).<sup>12,20</sup> None of the previously published pathogenic activating *TSHR* mutations are seen in gnomAD. Furthermore, the proband with this variant in our study was diagnosed at 60 years of age and had no family history of thyrotoxicosis. She also remitted after 18 months of antithyroid drug treatment which is unlikely if she had activating *TSHR* gene mutation.

## 4 | DISCUSSION

Our study identified that the systematic assessment for activating *TSHR* mutations in adult patients with hyperthyroidism with diffuse uptake on scintigraphy, negative TRAb and absence of extrathyroidal manifestations of Graves' disease (such as thyroid-associated ophthalmopathy or dermopathy) did not identify a single case. Our study, therefore, is unable to support the routine genetic testing for *TSHR* mutations in these patients.

This is the largest study in adult Caucasian patients with hyperthyroidism with diffuse goitre and lacking overt autoimmunity, and we did not find any individuals with a pathogenic variant in the *TSHR* gene. Our study results differ from a previous study in adult Japanese hyperthyroid patients with diffuse goitre and without TRAb (n = 89).<sup>13</sup> This study found activating *TSHR* mutations in four patients, giving a prevalence of 4.5%. This discrepancy in the results may be due to different populations characteristics; for example, our study participants were older, median age 52 vs 40 years.<sup>13</sup> The high frequency in the Japanese population may be due to founder effects as seen in other monogenic diseases in this population.<sup>21</sup> The negative results in our study may also be due to a type II error (false negative), although we were powered to detect a 4.5% frequency with 95% confidence. This suggests that the accurate assessment of prevalence of activating *TSHR* mutation in adult Caucasian patients may need a larger sample size. For example, Nishihara et al found only 89 patients with diffuse goitre and lacking overt autoimmunity from 24 623 hyperthyroid patients referred to them over 9 years.<sup>13</sup>

Our results suggest that routine screening for *TSHR* gene may not be a useful practice in adult Caucasian patients with hyperthyroidism lacking overt autoimmunity and diffuse goitre due to the rarity of the disease. The European Thyroid Association (ETA) have previously issued recommendations on when and whom to select for genetic testing for *TSHR*.<sup>3</sup> One-third of our cohort had a family history of thyrotoxicosis, and fulfilled the ETA criteria for genetic testing for *TSHR* mutation.<sup>3</sup> Our results do not support routine genetic testing in adult onset hyperthyroidism even in the presence of family history of thyrotoxicosis; however, it may be useful for families with multigenerational history of thyrotoxicosis. Our results are not applicable to children, and these patients should

be evaluated for activating *TSHR* mutation as per the guideline.<sup>3</sup> This is supported by the study in Danish children that showed 6% of children with nonautoimmune hyperthyroidism have activating *TSHR* mutation.<sup>12</sup>

We acknowledge several study limitations: we only recruited 61% patients from the eligible cohort, and a larger sample size would have increased the power to identify a lower frequency of activating *TSHR* mutation. We did not have data on Doppler thyroid ultrasound or thyroid-stimulating immunoglobulin to exclude Graves' disease. Although these two tests would have reduced the number of eligible patients, it would not have changed the results of our study due to the inclusive nature of our study eligibility criteria. We excluded patients with multinodular goitre in our study as it is seen in <15% of individual with activating *TSHR* mutation. This along with relatively common occurrence of nongenetic multinodular goitre in adult population would have provided very low positive predictive value of multinodular goitre to identify *TSHR* mutation.<sup>2</sup> We also did not take the treatment history of patients (eg, relapse after antithyroid drug treatment) into consideration when selecting potential participants as we wanted to establish the utility of genetic testing at the time of diagnosis during routine clinical care.

In conclusion, our systematic assessments of adult Caucasian patients with hyperthyroidism showed that activating *TSHR* gene mutations are a rare cause of nonautoimmune hyperthyroidism. Our results do not support the routine genetic testing for adult patients with hyperthyroidism showing diffuse uptake on scintigraphy but lacking autoimmune features of Graves' disease.

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## CONFLICT OF INTEREST

The authors report no conflict of interests that could be perceived as prejudicing the impartiality of the research reported.

## AUTHORS' CONTRIBUTIONS

KAP and BV designed the study; wrote the first draft of the manuscript, which was modified by all authors; and are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. KAP, BK, VP researched data. KAP, BK, AA, TB, AT, SC, ID helped in data collection and study recruitment. CT did the genetic analysis. All authors contributed to the discussion and reviewed or edited the manuscript.

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