Age May Influence the Impact of TRAbs on Thyroid Function and Relapse-Risk in Patients With Graves Disease

Arjola Bano,1,2,3* Earn Gan,1* Caroline Addison,4 Kilimangalam Narayanan,4 Jolanta U. Weaver,1,4 Vasileios Tsatlidis,1 and Salman Razvi1,4

1Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne NE1 3BZ, United Kingdom; 2Departments of Internal Medicine and Epidemiology, Erasmus Medical Center, 3015 GD Rotterdam, Netherlands; 3Institute of Social and Preventive Medicine, University of Bern, 3012 Bern, Switzerland; and 4Queen Elizabeth Hospital, Gateshead Health NHS Foundation Trust, Gateshead NE9 6SX, United Kingdom

ORCiD numbers: 0000-0003-0956-7145 (A. Bano).

Context: Thyrotropin receptor antibodies (TRAbs) play a crucial role in the pathogenesis of Graves disease (GD). However, factors that influence the association of TRAbs with thyroid hormones and relapse risk in GD remain unclear.

Objective: We investigated the associations of TRAbs at diagnosis with thyroid hormones and relapse risk and potential factors that can influence these associations in GD.


Patients and Main Outcome Measures: Three hundred eighty-four consecutive patients with GD who had measurements of TRAbs and thyroid hormones at diagnosis. The association of TRAbs with thyroid hormones and relapse risk was assessed through linear regression and Cox proportional hazard models, adjusted for confounders.

Results: TRAbs were nonlinearly associated with thyroid hormones, following a curve with an initial positive slope and a subsequent flattening ($P < 0.0001$). Higher TRAbs were associated with greater relapse risk [hazard ratio (HR), 1.05 (95% CI, 1.02 to 1.08) per 1-U/L increase]. These associations were modified by age, but not by sex, race, smoking, or thyroid peroxidase antibody levels. In younger participants, increasing TRAbs were associated with higher thyroid hormones and greater relapse risk [HR, 1.13 (95% CI, 1.04 to 1.23) per 1-U/L increase]. In older participants, TRAbs were not associated with thyroid hormones or relapse risk [HR, 0.99 (95% CI, 0.93 to 1.05) per 1-U/L increase.

Conclusions: In GD, age can influence the effect of TRAbs on thyroid function and relapse risk. TRAbs at diagnosis have better predictive value in younger patients with GD. (J Clin Endocrinol Metab 104: 1378–1385, 2019)

Graves disease (GD) is a common autoimmune disorder characterized by thyrotoxicosis, goiter, and, in some patients, ophthalmopathy. In iodine-sufficient areas, it accounts for 70% to 80% of all cases of thyrotoxicosis (1). As in most autoimmune diseases, GD is more frequent in women and can be observed at any age, although its incidence peaks between the fifth and sixth decades (2). No consistent differences by ethnicity in the incidence of GD have been observed, but the disease prevalence is higher in whites and Asians than in Africans (3).

GD is caused by circulating antibodies that bind to and stimulate the thyroid-stimulating hormone receptor (TSHR),...
resulting in increased synthesis and release of thyroid hormones and hypertrophy of thyroid follicular cells. Antibodies against TSHR (TRAbs) are pathognomonic for GD. They are detectable in the serum of ~98% of untreated patients with GD by using a second-generation assay (4) and in an even higher proportion of patients by using a third-generation assay (5). TRAb measurement is useful to differentiate between GD and thyrotoxicosis due to other causes (6). Furthermore, circulating TRAb levels correlate with the clinical course and severity of GD and are useful predictors of relapse risk (7). Although the exact etiology of GD remains largely unclear, it is thought that a complex interaction between genetic and environmental factors in susceptible individuals leads to the breakdown of immune tolerance to thyroid antigens and to the initiation of an immune reaction against TSHR (8).

Antithyroid drugs (ATDs) are widely used to manage Graves thyrotoxicosis and are safe and usually effective, but recurrence is common after their withdrawal; recurrence rates are 40% to 50% in Europe and 70% to 80% in the United States (9). Many risk factors for recurrence of GD after ATD cessation have been identified, including younger age (10), male sex (10), large goiter size (11), biochemical severity of thyrotoxicosis at diagnosis (12), cigarette smoking (6, 10–12), and high TRAb levels, both at diagnosis (13) and at cessation of therapy (7).

Although the central role of TRAbs in the pathogenesis of GD has been known for several years, it still remains unclear which sociodemographic, environmental, or immunological factors influence their relationship with thyroid function and also affect the risk for relapse. We therefore studied patients with GD in order to (i) investigate the association of TRAb at diagnosis with thyroid hormones and risk for relapse and (ii) explore whether age, sex, race, smoking, or thyroid peroxidase antibody (TPOAb) influence the association of TRAb with thyroid hormones and risk of relapse.

**Material and Methods**

**Patients**

Consecutive patients with hyperthyroidism referred to an outpatient endocrine clinic in Gateshead, England, were included prospectively. All patients provided informed consent to participate in the study. The diagnosis of GD was confirmed after a clinical examination was performed and the typical biochemical picture of low serum TSH and high thyroid hormone levels in the presence of elevated TRAb levels or uniform uptake on Tc99m scans was noted. All patients had TRAb levels measured at diagnosis but Tc99m scans were obtained only if the TRAb levels were negative or borderline (<1.0 U/L or 1.0 to 2.0 U/L, respectively). Clinical and biochemical information was collected at diagnosis and before commencement of ATD. Graves orbitopathy (GO) was noted as present or absent based on clinical guidelines (14). None of the patients included in this analysis were taking any medications that could affect thyroid function. Patients with GD who were pregnant (at diagnosis, during ATD treatment, or during follow-up after ATD cessation) were not included in this analysis. The median (interquartile range) duration of treatment with ATD was 12 (11 to 14) months. Most patients were treated with carbimazole (90.0%).

After the baseline visit, several patients were not included in the follow-up analysis because they were lost to follow-up or moved to a different area (n = 13), opted for definitive treatment with surgery or radioactive iodine (n = 8), did not require ATD treatment because of presentation with subclinical hyperthyroidism (n = 34), or were still continuing treatment with ATD (n = 98). Overall, the baseline characteristics of participants with data available on relapse were similar to those without follow-up data available (Table 1). Relapse was defined as

---

**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Study Participants (n = 384)</th>
<th>Data Available on Relapse Risk (n = 231)</th>
<th>Data Not Available on Relapse Risk (n = 153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>48.0 (35.0–58.0)</td>
<td>50.0 (36.5–60.0)</td>
<td>45 (33–54)</td>
</tr>
<tr>
<td>Women</td>
<td>327 (85.2)</td>
<td>195 (84.4)</td>
<td>132 (86)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>104 (27.1)</td>
<td>64 (27.7)</td>
<td>40 (26.1)</td>
</tr>
<tr>
<td>Former</td>
<td>90 (23.4)</td>
<td>60 (26.0)</td>
<td>30 (19.6)</td>
</tr>
<tr>
<td>Never</td>
<td>190 (49.5)</td>
<td>107 (46.3)</td>
<td>83 (54.2)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>359 (93.5)</td>
<td>217 (93.9)</td>
<td>142 (92.8)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (0.8)</td>
<td>1 (0.4)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>22 (5.7)</td>
<td>13 (5.6)</td>
<td>9 (5.9)</td>
</tr>
<tr>
<td>Active GO</td>
<td>74 (19.3)</td>
<td>43 (18.6)</td>
<td>31 (20.3)</td>
</tr>
<tr>
<td>TPOAb, IU/mL</td>
<td>128.0 (22.9–365.2)</td>
<td>129.2 (26.6–379.9)</td>
<td>124 (10.5–130.2)</td>
</tr>
<tr>
<td>TRAb, U/L</td>
<td>7.0 (3.6–14.3)</td>
<td>7.0 (3.7–13.6)</td>
<td>7.1 (3.2–16.0)</td>
</tr>
<tr>
<td>FT4, pmol/L</td>
<td>39.8 (28.3–58.8)</td>
<td>39.3 (29.1–58.4)</td>
<td>40.0 (23.5–59.4)</td>
</tr>
<tr>
<td>FT3, pmol/L</td>
<td>15.2 (9.7–26.0)</td>
<td>15.1 (10.2–25.4)</td>
<td>16.1 (8.0–27.7)</td>
</tr>
</tbody>
</table>

Data are presented as number (percentage) or median (interquartile range).

Abbreviations: FT3, free T3; FT4, free T4.
recurrent hyperthyroidism after ATD cessation. The start date of follow-up was considered the date of ATD cessation. The end date of follow-up was considered the date of relapse, the date of death, or 12 months after ATD cessation, whichever came first.

Biochemical analyses

Thyroid function tests, TRAb, and TPOAb were analyzed by using the Roche Elecsys electrochemiluminescence immunoassay on the Cobas e602 analytical platform. The reference ranges were as follows: TSH (0.4 to 4.0 mU/L), free T4 (FT4) (10 to 25.0 pmol/L), free T3 (FT3) (3.0 to 6.8 pmol/L), TPOAb (<35 U/mL), and TRAb (<1.0 U/L). In our laboratory, the coefficients of variation for all analyses were <5% except for TPOAb, for which it was <10%.

Tc uptake scan

Anterior views of the thyroid were obtained using a gamma camera 20 minutes following injection of 100 MBq 99mTc pertechnetate.

Statistical analyses

Linear regression and Cox proportional hazard models were used to investigate the association of TRAb at diagnosis with thyroid hormones and the risk for relapse. We first investigated the cross-sectional association of TRAb at diagnosis with FT4 and FT3 levels by performing ordinary least-squares linear regression. Restricted cubic splines with three knots were used to allow for potential nonlinearity. Moreover, we investigated the prospective association of TRAb at diagnosis with the risk for relapse by using Cox proportional hazard models. All analyses were tested for potential effect modification by several factors. We separately added product interaction terms of TRAb with age, sex, race, smoking status, and TPOAb levels. Furthermore, we stratified the analyses by age, sex, race, smoking status, and TPOAb levels.

Potential confounders were selected based on biological plausibility and previous literature. All analyses were adjusted for age, sex, race, smoking status, and TPOAb levels. Several sensitivity analyses were performed: (i) To account for a potential influence of GO in our results, we additionally adjusted our analyses for the presence of GO; (ii) we restricted the cross-sectional analysis to participants with data available on relapse; (iii) we additionally adjusted longitudinal analyses for FT4 levels at diagnosis, average daily dose of ATD treatment, and duration of ATD treatment in months; (iv) we extended the follow-up time to 24 months in cases with available data on relapse after 12 months of follow-up; (v) to evaluate the role of age on the bioactivity of TRAb, we performed a post hoc analysis investigating the association of age with FT4/TRAb ratio as a marker of TRAb potency, adjusting for sex, race, smoking status, and TPOAb levels. In addition, we investigated the associations of age with TRAb and FT4 levels, respectively, adjusting for sex, race, smoking status, and TPOAb levels.

The assumption of normally distributed residuals was checked and met. The proportional hazards assumption was assessed by Schoenfeld test and plots. No violation of the proportional hazards assumption was observed. A P value < 0.05 was deemed to indicate statistical significance. Statistical analyses were conducted by using R statistical software (rms package, R Project, Institute for Statistics and Mathematics, R Core Team, version 3.2.2, Vienna, Austria) and SPSS software, version 21 (IBM Corp., Chicago, IL).

Results

Baseline characteristics of 384 eligible participants are presented in Table 1. The median age was 48.0 (interquartile range, 35.0 to 58.0) years; 83.2% of patients were women, 27.1% were current cigarette smokers, 93.5% were white, and 19.3% had active GO. Of these participants, 231 had data available on relapse. During a median follow-up time of 12 (range, 3 to 12) months after ATD cessation, 45 participants (19.5%) relapsed to overt hyperthyroidism.

Cross-sectional association of TRAb at diagnosis with thyroid hormones

TRAbs at diagnosis were nonlinearly associated with FT4 levels ($P < 0.0001$) (Fig. 1a) and FT3 levels ($P < 0.0001$) (Fig. 2a), following a curve with an initial positive slope and a subsequent flattening ($P$ for nonlinearity $= 0.0003$ and 0.007, respectively). The association was independent of age, sex, race, smoking status, and TPOAb levels. Additional adjustments for the presence of GO provided consistent results. Also, results remained similar after we restricted the analysis to participants with data available on relapse. In the cross-sectional analyses of TRAb at diagnosis with FT4 and FT3, we found differences by age ($P$ for interaction $= 0.0008$ and 0.0006, respectively) but no differences by sex, race, smoking status, and TPOAb levels. Further stratification by age tertiles showed differences among categories (Fig. 1b and 2b). In the youngest participants (i.e., those age 17 to 39 years, first tertile of age) and the middle-aged group (i.e., those age 40 to 54 years, second tertile of age), TRAb levels at diagnosis were positively associated with higher FT4 and FT3 concentrations in a linear manner ($P$ for nonlinearity $= 0.05$) (Fig. 1b and 2b). In the oldest participants (i.e., those age 55 to 92 years, third tertile of age), TRAb at diagnosis < 10 U/L was positively associated with FT4 and FT3 levels in a linear manner, but there were no significant changes in FT4 or FT3 levels with TRAb at diagnosis > 10 U/L (Fig. 1b and 2b). Interaction terms of TRAb with sex, race, smoking status, and TPOAb levels were not statistically significant in relation to FT4 ($P$ for interactions $= 0.5, 0.9, 0.6$, and 0.3, respectively) and FT3 ($P$ for interactions $= 0.1, 0.7, 0.7, 0.1$, respectively). After further stratification by sex, race, smoking status, and TPOAb levels, we did not observe meaningful differences in the direction or magnitude of the associations across categories. In our post hoc analyses, age was not associated with TRAb levels ($P = 0.2$) or FT4/TRAb ratio as a marker of TRAb potency ($P = 0.8$). Increasing age was associated with lower FT4 levels at diagnosis [$\beta = -0.29$ (95% CI, $-0.43$ to $-0.16$)] per 1-year increase in age; $P < 0.0001$.

Downloaded from https://academic.oup.com/jcem/article/104/5/1378/5224751 by guest on 24 October 2021
Prospective association of TRAb at diagnosis with risk for relapse

Higher TRAb levels at diagnosis were associated with a higher risk for relapse, independent of age, sex, race, smoking status, and TPOAb levels [hazard ratio (HR), 1.05 (95% CI, 1.02 to 1.08) per 1-U/L increase in TRAb; \( P = 0.001 \)] (Fig. 3a, Table 2). No evidence of nonlinearity was observed. Results did not change after additional adjustments for the presence of GO [HR, 1.05 (95% CI, 1.02 to 1.08) per 1-U/L increase in TRAb]. Results remained similar after additional adjustment for FT4 levels at diagnosis, average daily dose of ATD treatment, and duration...
of ATD treatment [HR, 1.06 (95% CI, 1.02 to 1.09) per 1-U/L increase in TRAb] or after extension of the follow-up time to 24 months [HR, 1.04 (95% CI, 1.01 to 1.08) per 1-U/L increase in TRAb]. Of 231 patients with GD, we observed 66 relapses (28.6%) after extending the follow-up time to 24 (interquartile range, 12 to 24) months.

In the prospective analyses of TRAb at diagnosis with the risk for relapse, we found significant differences by age (P for interaction = 0.01), but no differences by sex, race, smoking status, or TPOAb levels. Further stratification by age tertiles showed differences among categories (Fig. 3b). In the youngest participants (i.e., those age 18 to 41 years, first tertile of age) and the middle-aged
group (i.e., those age 42 to 56 years, second tertile of age), higher TRAb at diagnosis were associated with a higher risk for relapse [HR, 1.13 (95% CI, 1.04 to 1.23) per 1-U/L increase in TRAb (P = 0.005); HR, 1.05 (95% CI, 1.01 to 1.09) per 1-U/L increase in TRAb (P = 0.01), respectively] (Table 2). In the oldest participants (i.e., those age 57 to 90 years, third tertile of age), TRAb at diagnosis was not associated with the risk for relapse [HR, 0.99 (95% CI, 0.93 to 1.05) per 1-U/L increase in TRAb; P = 0.7] (Table 2). Interaction terms of TRAb with sex, race, smoking status, and TPOAb levels were not statistically significant (P for interactions = 0.3, 0.9, 0.9, and 0.8, respectively). After further stratification by sex, race, smoking status, and TPOAb levels, we did not observe meaningful differences in the direction or magnitude of the associations across categories.

**Discussion**

In a prospective cohort study of patients with GD, we found that TRAb levels at diagnosis were positively associated with circulating thyroid hormones and relapse risk. These associations were modified by age but not by sex, race, smoking, or TPOAb. Importantly, increasing
The competition-based assays detect TRAb in serum by assays in use are competition-based or functional assays. and undergone several improvements (6). Current TRAb past few decades, TRAb assayshave evolved substantially and the choice of treatment and the course of interpretation of thyroid parameters in older patients be a good predictor of relapse risk in the older patients with GD. The aging process has a complex role on the pathophysiology of GD. The onset of GD at younger ages has been linked with an increased degree of thyrotoxicosis (15) and increased relapse risk (7, 13, 16). These results are not surprising, given that TRAbs can directly stimulate thyroid epithelial cells and lead to various degrees of Graves thyrotoxicosis. Our study extends these previous findings by showing that the effect of TRAbs on thyroid function and risk for relapse can essentially depend on age. Indeed, we observed a gradual change in the pattern of the associations throughout aging. This suggests that there is no specific inflection point for age, but the effect of TRAb levels on relapse risk changes gradually with increasing age. In addition, our data exhibit good concordance between FT4 and FT3 with regard to their association with TRAbs and the modifying effect of age. The aging process has a complex role on the physiologic process is unlikely to have affected TRAb bioactivity. On the other hand, our study had extensive and detailed information on covariates, including exposures, outcomes, and potential confounders.

Several limitations should also be considered. The follow-up time of our study was restricted to a maximum of 12 months. However, our results remained consistent after we extended the follow-up time to 24 months in cases where data were available. Another limitation is that we had no information on whether TRAbs were stimulatory, inhibitory, or neutral. Nevertheless, the lack competing for binding of the TSH receptor with a known ligand, whereas the functional assays detect cAMP production in cells incubated with the patient’s sera. The third generation of TRAb competition-based assay, which was used in our study, has high sensitivity and specificity in diagnosing GD but does not differentiate the stimulating from the blocking or neutral variety. Older age might lead to altered TRAb bioactivity and/or increase the non-stimulatory to stimulating autoantibody ratio. However, our post hoc analyses did not show a link between age and TRAb levels or FT4/TRAb ratio, suggesting that the aging process is unlikely to have affected TRAb bioactivity. On the other hand, our post hoc analyses revealed a negative association of age with FT4 levels independent of TRAb concentrations, indicating a milder degree of biochemical thyrotoxicosis in older people with GD. It is therefore likely that aging may modify the response of the thyroid gland to stimulation. Indeed, aging is known to alter the set point of the hypothalamus-pituitary-thyroid axis (20).

Even in euthyroid persons, older age has been related to increasing circulating TSH without substantial changes in FT4 concentrations (21). This suggests that in older people, the thyroid gland may become less responsive to stimulation by TSH (22). Similar to TSH, TRAbs also target the TSHR in the thyroid gland. Thus, it can be assumed that in older patients with GD, the TSHR and the thyroid gland may become less responsive to TRAbs stimulation. Interestingly, our data suggest that the association of TRAbs with FT4 and FT3 levels across the oldest age tertile consistently diverges at a TRAb level of ~10 U/L. One explanation may be that the thyroid gland of older individuals becomes less responsive to stimulation only at relatively high TRAb levels. However, additional studies are warranted to clarify the exact mechanisms through which aging influences the action of TRAbs on the thyroid gland.

This study found an effect modification by age on the associations of TRAb at diagnosis with thyroid hormones and relapse risk in GD. Our well-characterized study sample was adequately powered to inform the predictive value of TRAbs in relapse of GD. Another strength is the prospective study design. Baseline measurements of thyroid function and TRAb levels were collated before the evaluation of relapse risk. Moreover, we had extensive and detailed information on covariates, including exposures, outcomes, and potential confounders.

Several limitations should also be considered. The follow-up time of our study was restricted to a maximum of 12 months. However, our results remained consistent after we extended the follow-up time to 24 months in cases where data were available. Another limitation is that we had no information on whether TRAbs were stimulatory, inhibitory, or neutral. Nevertheless, the lack

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>1.05 (1.02–1.08)</td>
<td>0.001</td>
</tr>
<tr>
<td>P for interaction with age</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>First tertile of age</td>
<td>1.13 (1.04–1.23)</td>
<td>0.005</td>
</tr>
<tr>
<td>Second tertile of age</td>
<td>1.05 (1.01–1.09)</td>
<td>0.01</td>
</tr>
<tr>
<td>Third tertile of age</td>
<td>0.99 (0.93–1.05)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, race, smoking status, and TPOAb levels at diagnosis. HRs are denoted per one-unit (U/L) increase in TRAb.

TRAb levels were associated with higher concentrations of thyroid hormones and increased relapse risk in younger patients (age < 55 years, first and second tertiles of age) but not in older patients (age ≥ 55 years, third tertile of age). The associations of TRAb at diagnosis with thyroid hormones and relapse risk changes gradually with increasing age. In addition, our data exhibit good concordance between FT4 and FT3 with regard to their association with TRAbs and the modifying effect of age. The aging process has a complex role on the pathophysiology of GD. The onset of GD at younger ages has been linked with an increased degree of thyrotoxicosis (17, 18) and greater risk for relapse (10, 19). In our study, older patients with TRAb levels > 10 U/L had a milder degree of biochemical thyrotoxicosis than younger patients. For example, TRAb levels of 40 U/L in a younger patient were associated with an FT4 of ~80 pmol/L, whereas the same TRAb levels resulted in an FT4 of ~50 pmol/L in an older person with GD. Furthermore, our data suggest that circulating TRAb levels may not be a good predictor of relapse risk in the older patients with GD. Therefore, we recommend a more cautious interpretation of thyroid parameters in older patients with GD. The choice of treatment and the course of follow-up may also be influenced by these findings.

TRAbs are autoantibodies that bind to the TSHR with a stimulating, blocking, or neutral effect. During the past few decades, TRAb assays have evolved substantially and undergone several improvements (6). Current TRAb assays in use are competition-based or functional assays. The competition-based assays detect TRAb in serum by

---

**Table 2. Association of TRAb at Diagnosis With Risk for Relapse**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>1.05 (1.02–1.08)</td>
<td>0.001</td>
</tr>
<tr>
<td>P for interaction with age</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>First tertile of age</td>
<td>1.13 (1.04–1.23)</td>
<td>0.005</td>
</tr>
<tr>
<td>Second tertile of age</td>
<td>1.05 (1.01–1.09)</td>
<td>0.01</td>
</tr>
<tr>
<td>Third tertile of age</td>
<td>0.99 (0.93–1.05)</td>
<td>0.7</td>
</tr>
</tbody>
</table>
of an association between age and FT4/TRAβ ratio suggests that age does not influence TRAb potency. Finally, given the observational character of our study, we cannot rule out the possibility of residual confounding.

In summary, our study provides insights into the influence of age on the predictive value of TRAbs in GD. TRAbs at diagnosis may have a better predictive value in younger patients than in older patients with GD, in terms of biochemical parameters and relapse risk. This conclusion can help inform clinical decision in GD. Future studies need to confirm our results in other populations of patients with GD. Also, the exact mechanisms that underlie our findings must be further investigated.

Acknowledgments

Financial Support: A.B. was supported by an exchange fellowship from the European Thyroid Association. E.G. was supported by a National Institute for Health Research Academic Clinical Lectureship.

Correspondence and Reprint Requests: Salman Razvi, MD, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne NE1 3BZ, United Kingdom. E-mail: salman.razvi@ncl.ac.uk.

Disclosure Summary: The authors have nothing to disclose.

References