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Influences of Age, Gender, Smoking, and Family History on Autoimmune Thyroid Disease Phenotype

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Context: Both genetic and environmental factors contribute to susceptibility to Graves' disease (GD) and Hashimoto's thyroiditis (HT), as well as disease manifestations.

Objective: The objective of the study was to define how endogenous/environmental factors contribute to variation in phenotype.

Design/Setting: This was a multicenter cohort study.

Patients/Outcome Measures: We prospectively collected clinical/biochemical data as part of the protocol for a United Kingdom DNA collection for GD and HT. We investigated, in 2805 Caucasian subjects, whether age at diagnosis, gender, family history (FH), smoking history, and presence of goiter influenced disease manifestations.

Results: For 2405 subjects with GD, the presence of goiter was independently associated with disease severity (serum free T_4 at diagnosis) ($P < 0.001$). Free T_4 ($P < 0.05$) and current smoking ($P < 0.001$) were both independent predictors of the presence of ophthalmopathy. Approximately half of those with GD (47.4% of females, 40.0% of males) and HT (n = 400) (56.4% of females, 51.7% of males) reported a FH of thyroid dysfunction. In GD, a FH of hyperthyroidism in any relative was more frequent than hypothyroidism (30.1 *vs.* 24.4% in affected females, $P < 0.001$). In HT, a FH of hypothyroidism was more common than hyperthyroidism (42.1 *vs.* 22.8% in affected females, $P < 0.001$). For GD ($P < 0.001$) and HT ($P < 0.05$), a FH was more common in maternal than paternal relatives. The reporting of a parent with thyroid dysfunction (hyper or hypo) was associated with lower median age at diagnosis of both GD (mother with hyperthyroidism, $P < 0.001$) and HT (father with hypothyroidism, $P < 0.05$). In GD and HT, there was an inverse relationship between the number of relatives with thyroid dysfunction and age at diagnosis ($P < 0.01$).

Conclusions: Marked associations among age at diagnosis, disease severity, goiter, ophthalmopathy, smoking, and FH provide evidence for interactions between genetic and environmental/endogenous factors; understanding these may allow preventive measures or better tailoring of therapies. **(*J Clin Endocrinol Metab* 91: 4873–4880, 2006)**

AUTOIMMUNE THYROID DISEASES, comprising Graves' disease (GD) and Hashimoto's thyroiditis (HT), are common, affecting up to 2% of the population (1). There are marked gender differences in prevalence, with reported 5- to 10-fold excesses in females for both diseases (2, 3). There is also a significant clustering of disease in families, with 40–50% of patients reporting another family member with a thyroid disorder (4–6).

Whereas the precise pathogenetic mechanisms are unknown, autoimmune thyroid diseases are believed to reflect a multifactorial mode of inheritance and various environmental triggers (7). Clear evidence of the genetic component has been demonstrated in twin studies for GD based on European populations, with concordance rates ranging from 30–40% in monozygotic twins, compared with 0–7% in dizygotic twins (8, 9), with lower rates reported in the United States (10). For HT, a concordance rate of 55% was observed for monozygotic twins and 0% for dizygotic twins (9). Because the concordance rate for identical twins is clearly less than 100%, these studies indicate the etiological importance of other factors (11). Several environmental factors are relevant including cigarette smoking, psychological stress, iodine intake, intrauterine growth, bacterial and viral infections, and drugs such as interferon (12).

In addition, there is marked variation in disease phenotype in subjects with autoimmune thyroid diseases, *i.e.* disease severity, the presence and size of goiter, and the presence and severity of ophthalmopathy in those with GD. The influence of both environmental and endogenous factors, such as smoking, age, and gender, has been most clearly elucidated for ophthalmopathy in which there is a clear association between risk of development of eye disease and cigarette smoking (13). Smoking is also an independent risk factor for the development of both GD and HT (13, 14). Advancing age and male gender have both been found to be

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Abbreviations: CI, Confidence interval; FH, family history; GD, Graves' disease; HT, Hashimoto's thyroiditis; IQR, interquartile range; NOSPECS, no signs or symptoms; only signs, no symptoms; signs only; proptosis; eye muscle involvement; corneal involvement; sight visual acuity reduction.

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associated with severity of ophthalmopathy in GD (15, 16). There is also some evidence that male gender is associated with increased biochemical severity of GD (17) and that severity of hyperthyroidism decreases with age (18, 19). We have previously reported in a study of 536 GD patients that males were less likely to enter remission after thionamide treatment or to respond to a single dose of radioiodine than females (20). We also reported that younger patients had more severe biochemical hyperthyroidism and larger goiters and were more likely to have a family history (FH) of thyroid disease (20).

As part of the protocol for a large national United Kingdom collection of DNA for studies of genetic susceptibility to autoimmune thyroid diseases, we prospectively and systematically collected clinical data from a cohort of almost 3000 subjects with well-defined autoimmune thyroid disease. To examine the hypothesis that these factors may influence the phenotypic expression of GD and HT, we analyzed our data to investigate whether age at diagnosis, gender, and the presence of goiter influence disease severity; whether age, gender, biochemical severity, and smoking history influence the presence or severity of ophthalmopathy; and finally whether a FH of thyroid disease influences disease phenotype.

Subjects and Methods

The study cohort comprised 2405 Caucasian subjects with GD (2020 females, 385 males) and 400 with HT (342 females, 58 males) recruited from specialist clinics in Birmingham, Bournemouth, Cambridge, Cardiff, Exeter, Leeds, Sheffield, and Newcastle, United Kingdom, as part of a national program investigating genetic susceptibility to autoimmune thyroid disease. Standard criteria were used for the diagnosis of autoimmune thyroid disease, as described by our group previously (21). GD was defined by the presence of biochemical hyperthyroidism with: 1) a diffuse goiter on a radionuclide or sonographic scan; 2) Graves' ophthalmopathy [no signs or symptoms; only signs, no symptoms; signs only; proptosis; eye muscle involvement; corneal involvement; sight visual acuity reduction (NOSPECS) classification score $\geq$ 2] (22); 3) positive autoantibodies to the TSH receptor; 4) diffuse goiter on physical examination and positive antibodies to thyroglobulin or thyroid peroxidase; or 5) confirmation of a lymphocytic infiltrate in thyroid histology. HT was defined by the presence of biochemical hypothyroidism and positive antibodies to thyroglobulin or thyroid peroxidase, the presence of lymphocytic infiltrate in a fine-needle aspirate, or the presence of a diffuse goiter on physical examination.

Recorded information for each study subject included the age at biochemical diagnosis of thyroid dysfunction and the presence of goiter on physical examination (defined as palpable or visible thyroid enlargement). The biochemical severity of thyroid dysfunction at diagnosis was determined from serum concentrations of free T_4 and TSH, this information being available for 2201 subjects. Information regarding the presence or absence of thyroid antibodies (and antibody titer if positive) was available in 2025. The severity of ophthalmopathy at presentation in those with GD was classified according to the NOSPECS score: 1) mild/absent (NOSPECS 0–1 including lid retraction or lid lag), 2) moderate (NOSPECS 2–3 including periorbital edema and proptosis), or 3) severe (NOSPECS 4–6 including eye muscle involvement/corneal involvement or sight loss).

All subjects were interviewed by a trained research nurse or specialist physician and completed a structured questionnaire seeking smoking history (classified as current smoker, previous smoker, or never smoked) and a FH of thyroid diseases. FH was recorded for first-degree, second-degree, and more distant relatives. A FH of thyroid dysfunction was recorded on the basis of subject recall as being positive for hyperthyroidism or hypothyroidism. If index cases were unsure of the diagnosis in their relatives or if the diagnosis was not clear from administered therapies (antithyroid drugs or radioiodine), then the nature of thyroid dysfunction was recorded as unknown. Family history of nontoxic goiter was also recorded.

All subjects gave informed written consent to participate. The study was approved by a multicenter research ethics committee and corresponding local ethics research committees.

Statistical analysis

Statistical analyses were performed using SigmaStat software (version 3.2; SPSS Science Software U.K. Ltd., Birmingham, UK) and Minitab (version 14; Coventry, UK). The Mann-Whitney test was used for comparison between medians of two groups, *e.g.* median age at diagnosis, median serum free T_4 levels. Two proportion tests were used to compare binomial proportions, *e.g.* prevalence of goiter in males *vs.* females, presence of thyroid eye disease in males *vs.* females. The same test was used to compare prevalence of FH of hyperthyroidism *vs.* FH of hypothyroidism, FH of thyroid disease in maternal *vs.* paternal relatives, and in female *vs.* male relatives. Simple and multiple regression analyses were performed to determine the influence of factors such as age, gender, and presence of goiter on the biochemical severity of thyroid disease. Ordinal and binary logistic regression analyses were performed to determine the association among age, gender, smoking status, and disease severity and ophthalmopathy. Binary logistic regression analysis was also used to assess the association of FH of thyroid dysfunction with disease severity and presence/severity of ophthalmopathy. The strength of association between age at diagnosis of thyroid disease and number of reported relatives with thyroid dysfunction was determined using the Spearman rank order correlation. $P < 0.05$ indicated statistical significance.

Results

Influence of age, gender, and goiter on disease severity

The ages at diagnosis of subjects with GD and HT are shown in Fig. 1. The peak ages for diagnosis were the fourth through sixth decades, and for both GD and HT, the median age at diagnosis was younger for females than males [GD females 41.0 yr (interquartile range [IQR] 31.0–52.0), n = 2020 *vs.* GD males 45.0 yr (33.0–56.0), n = 385, $P < 0.001$; HT females 41.0 yr (31.8–52.0), n = 342 *vs.* HT males 49.0 yr (38.0–60.0), n = 58, $P < 0.01$]. The biochemical severity of thyroid dysfunction at diagnosis (serum free T_4) was similar in females and males with GD [females, median serum free T_4, 44.2 (IQR 31.0–64.8) pmol/liter, n = 1621 *vs.* males 43.0 (32.0–65.0) pmol/liter, n = 305; $P = 0.92$]. However for HT, median serum TSH was higher in males than females [20.9 (9.6–83.9) mIU/liter, n = 46 *vs.* 11.0 (7.0–30.2) mIU/liter, n = 229, $P < 0.01$].

The frequency of goiter on examination was higher in GD females than males (81.0%, n = 1637 *vs.* 74.8%, n = 288, $P < 0.001$). Goiter prevalence was also higher in females with HT (54.1%, n = 185 *vs.* 31.0%, n = 18, $P < 0.001$). Presence of goiter was associated with lower median age at diagnosis in both females and males with GD [females with goiter 40.0 yr (30.0–50.0), n = 1637 *vs.* females without goiter 46.0 yr (35.0–56.0), n = 383, $P < 0.001$, males with goiter 43.0 yr (32.0–55.0), n = 288 *vs.* males without goiter 49.0 yr (40.0–58.0), n = 97, $P < 0.01$]. Similar findings were evident for HT [females with goiter 40.0 yr (29.8–52.0), n = 185 *vs.* females without goiter 43.0 yr (32.3–53.3), n = 157, $P = 0.064$, males with goiter 40.0 yr (36.0–50.0), n = 18 *vs.* males without goiter 51.5 yr (42.5–63.0), n = 40, $P < 0.01$]. In those with GD, the presence of goiter was associated with greater disease severity [females with goiter serum free T_4 46.0 (IQR 32.0–67.0) pmol/liter, n = 1347 *vs.* females without goiter 37.7 (27.0–53.7) pmol/

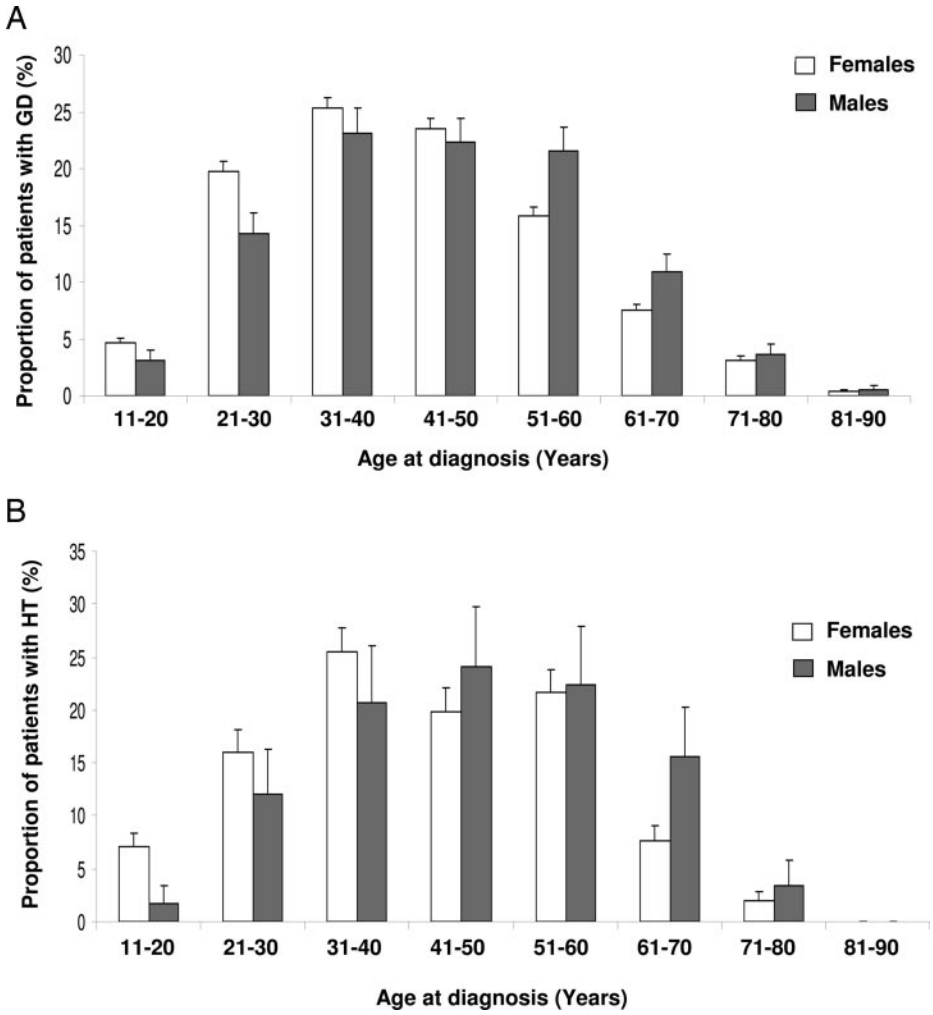

FIG. 1. Age at diagnosis (years) of female and male subjects with GD (A) and HT (B).

liter, n = 274, $P < 0.001$; males with goiter serum free T_4, 44.4 (33.0–66.0) pmol/liter, n = 242 *vs.* males without goiter 38.0 (25.6–55.0) pmol/liter, n = 63, $P < 0.01$]. In subjects with HT, a similar association between the presence of goiter and disease severity (serum TSH) was not observed (data not shown).

Regression analysis indicated that for GD, a lower age at diagnosis was associated with higher serum free T_4 at diagnosis ($P < 0.001$). The presence of goiter was similarly associated with higher free T_4 ($P < 0.001$), whereas gender was not ($P = 0.63$). For HT, neither age at diagnosis ($P = 0.32$) nor presence of goiter ($P = 0.98$) or gender ($P = 0.50$) was associated with serum TSH concentration.

We subsequently performed a multiple regression analysis simultaneously analyzing the influence of age, gender, and the presence of goiter on the biochemical severity of GD. This demonstrated that goiter was an independent predictor of disease severity ($P < 0.001$), whereas a lower age ($P = 0.11$) and patient's gender ($P = 0.37$) were not independent predictors (age × gender, $P = 0.54$) ($R^2 = 0.03$). In contrast, in HT, goiter ($P = 0.80$), lower age ($P = 0.20$), and gender ($P = 0.08$) were not independent predictors of severity (serum TSH) ($R^2 = 0.02$).

Influence of age, gender, smoking, and disease severity on Graves' ophthalmopathy

Moderate or severe thyroid eye disease (NOSPECS score of ≥2) was documented in similar proportions of females (51.5%, n = 1040) and males (52.7%, n = 203, $P = 0.65$) with GD. A higher proportion of males had severe ophthalmopathy (NOSPECS score 4–6) (30.4%, n = 117) than females

TABLE 1. NOSPECS classification score of Graves' ophthalmopathy in female and male subjects

NOSPECS classification score	Females		Males	
	Percentage (n)	Median age, yr (IQR)	Percentage (n)	Median age, yr (IQR)
0–1 (absent/mild)	48.5 (980)	40.0 (30.0–51.0)	47.5 (183)	43.0 (32.0–55.0)
2–3 (moderate)	30.2 (610)	40.0 (30.0–50.0)	22.0 (85)	39.0 (31.8–49.0)
4–6 (severe)	21.3 (430)	44.0 (33.0–54.0)	30.4 (117)	52.0 (40.0–59.0)

Median age at diagnosis is also displayed for each group.

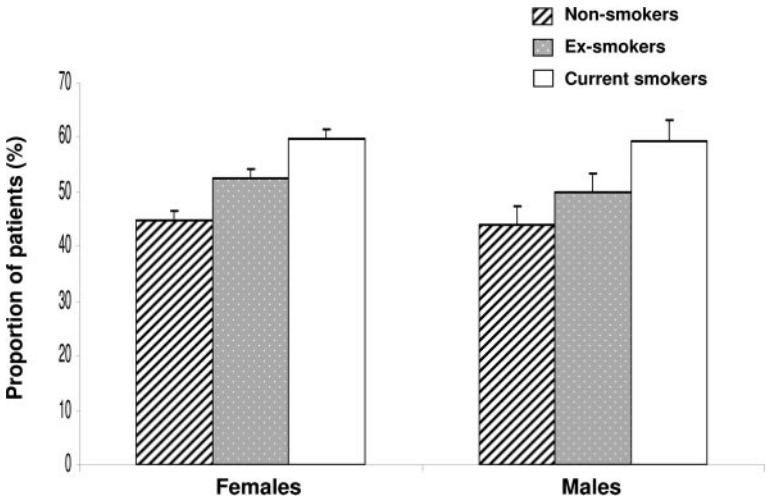

FIG. 2. Proportion of GD patients with ophthalmopathy (NOSPECS score ≥ 2), compared among nonsmokers (n = 317 females and n = 47 males), ex-smokers (n = 208 females and n = 44 males), and current smokers (n = 332 females and n = 73 males) for subjects for whom this information was available.

(21.3%, n = 430) ($P < 0.001$). The median age at diagnosis of GD was higher in those with severe ophthalmopathy for both males and females ($P < 0.05$) (Table 1).

A similar percentage of current smokers was noted for females and males for both GD (females 27.5%, n = 555, males 31.4%, n = 121, $P = 0.12$) and HT (females 17.3%, n = 59, males 20.1%, n = 12, $P = 0.55$). Figure 2 displays the distribution of subjects with ophthalmopathy, depending on their smoking status. A 2-fold increased risk of ophthalmopathy (NOSPECS score ≥ 2) was evident in current smokers [adjusted odds ratio 1.83, 95% confidence interval (CI) 1.49–2.25, $P < 0.001$], with an increased risk also present in ex-smokers, compared with nonsmokers (adjusted odds ratio 1.34, 95% confidence interval 1.07–1.67, $P < 0.01$).

For GD, binary logistic regression indicated that serum free T_4 at diagnosis ($P < 0.05$) and being a current smoker ($P < 0.001$) were both independent predictors of the presence of ophthalmopathy. However, age at diagnosis ($P = 0.17$), gender ($P = 0.69$), or being an ex-smoker ($P = 0.76$) were not independent predictors of ophthalmopathy.

Family history of thyroid disease and influence on age of presentation and disease severity

Approximately half of all subjects in the cohort with either GD (females 47.4%, n = 957 of 2020; males 40.0%, n = 154 of 385) or HT (females 56.4%, n = 193 of 342; males 51.7%, n = 30 of 58) reported a FH of thyroid dysfunction. When cases in relatives of thyroid disease of unknown diagnosis and goiter were included, the overall prevalences of positive FH were higher but remained similar in females and males (GD females 53.7%, n = 1085 of 2020, GD males 47%, n = 181 of 385; HT females 61.1%, n = 209 of 342, HT males 51.7%, n = 30 of 58). Subjects with HT were more likely to have a FH of thyroid dysfunction (55.5%, n = 222) than those with GD (46.2%, n = 1110) ($P < 0.001$).

For subjects with GD (Table 2), a FH of hyperthyroidism among any relative was reported more frequently than a FH of hypothyroidism, with significant differences evident for females (30.1%, n = 625 *vs.* 24.4%, n = 493, $P < 0.001$). In males, the difference was not significant. This difference between FH of hyperthyroidism and hypothyroidism was

TABLE 2. Prevalence of thyroid dysfunction and median age at diagnosis (and IQR) according to reported FH of thyroid dysfunction in subjects with GD

	Females with GD (n = 2020)		Males with GD (n = 385)	
	Hyperthyroidism (n)	Hypothyroidism (n)	Hyperthyroidism (n)	Hypothyroidism (n)
Affected mother	8.2% (n = 165) 38.0 yr (30.0–47.3)[a]	8.6% (n = 174) 34.0 yr (27.0–45.0)[a]	9.1% (n = 35) 41.0 yr (35.5–52.8)	8.8% (n = 34) 38.5 yr (33.0–49.0)[b]
Affected father	1.9% (n = 39) 39.0 yr (29.0–44.5)[c]	1.1% (n = 22) 33.5 yr (28.0–39.0)[c]	2.1% (n = 8) 45.0 yr (24.5–49.0)	0.5% (n = 2) 23.5 yr (23.0–24.0)[b]
Affected sibling(s)	7.2% (n = 145) 40.0 yr (31.8–49.0)	7.0% (n = 141) 44.0 yr (34.0–53.0)	6.5% (n = 25) 57.0 yr (39.8–59.3)	5.2% (n = 20) 48.0 yr (42.0–53.0)
Affected relatives excluding parents and siblings	19.3% (n = 389) 36.0 yr (29.0–47.0)[a]	12.4% (n = 250) 35.0 yr (27.0–45.0)[a]	12.0% (n = 46) 40.0 yr (26.0–53.0)[c]	9.6% (n = 37) 39.0 yr (25.8–51.5)[c]
Any affected relative	30.1% (n = 625) 38.0 yr (30.0–48.0)[a]	24.4% (n = 493) 37.0 yr (28.0–47.0)[a]	25.5% (n = 98) 41.0 yr (31.0–53.0)[b]	20.3% (n = 78) 40.0 yr (29.0–52.0)[c]
No FH	46.3% (n = 935) 43.0 yr (33.0–54.0)	46.3% (n = 935) 43.0 yr (33.0–54.0)	52.3% (n = 204) 47.0 yr (35.5–57.0)	52.3% (n = 204) 47.0 yr (35.5–57.0)

Median ages of subjects with FH of thyroid dysfunction were compared with median ages of those with no FH of thyroid disease.
[a] $P < 0.001$ (Mann-Whitney rank sum test).
[b] $P < 0.05$ (Mann-Whitney rank sum test).
[c] $P < 0.01$ (Mann-Whitney rank sum test).

TABLE 3. Prevalence of thyroid dysfunction and median age at diagnosis (and IQR) according to reported FH of thyroid dysfunction in subjects with HT

	Females with HT (n = 342)		Males with HT (n = 58)	
	Hyperthyroidism (n)	Hypothyroidism (n)	Hyperthyroidism (n)	Hypothyroidism (n)
Affected mother	5.0% (n = 17) 41.0 yr (30.8–50.5)	18.1% (n = 62) 35.0 yr (29.0–49.0)[a]	3.4% (n = 2) 39.0 yr (38.0–40.0)	20.0% (n = 11) 47.0 yr (36.3–51.5)[b]
Affected father	2.0% (n = 7) 36.0 yr (34.0–55.8)	5.0% (n = 17) 29.0 yr (19.0–42.0)[c]	n = 0	8.6% (n = 5) 23.0 yr (23.0–40.0)[a]
Affected sibling(s)	3.5% (n = 12) 48.0 yr (34.5–56.5)	8.5% (n = 29) 42.0 yr (32.3–54.3)	5.2% (n = 3) 40.0 yr (37.8–61.0)	10.3% (n = 6) 36.5 yr (30.0–40.0)[a]
Affected relatives excluding parents and siblings	15.0% (n = 51) 37.0 yr (29.0–49.8)[a]	22.5% (n = 77) 33.0 yr (26.8–43.0)[c]	10.3% (n = 6) 46.0 yr (37.0–58.0)	20.0% (n = 11) 39.0 yr (31.5–52.0)[a]
Any affected relative	22.8% (n = 78) 39.5 yr (31.0–51.0)[a]	42.1% (n = 144) 37.0 yr (29.0–49.0)[c]	15.5% (n = 9) 40.0 yr (37.8–52.0)[b]	43.1% (n = 25) 39.0 yr (30.0–50.5)[c]
No FH	38.9% (n = 133) 48.0 yr (35.0–56.3)	38.9% (n = 133) 48.0 yr (35.0–56.3)	48.3% (n = 28) 55.5 yr (46.0–65.0)	48.3% (n = 28) 55.5 yr (46.0–65.0)

Median ages of subjects with FH of thyroid dysfunction were compared with median ages of those with no FH of thyroid disease.
[a] $P < 0.01$ (Mann-Whitney rank sum test).
[b] $P < 0.05$ (Mann-Whitney rank sum test).
[c] $P < 0.001$ (Mann-Whitney rank sum test).

not evident when examining first-degree relatives only but was evident when more distant family members were also considered. In HT (Table 3), a FH of hypothyroidism in any relative was reported more frequently than a FH of hyperthyroidism, this difference being evident in first-degree as well as more distant relatives (females with hyperthyroid relative 22.8%, n = 78 *vs.* females with hypothyroid relative 42.1%, n = 144, $P < 0.001$; males with hyperthyroid relative 15.5%, n = 9 *vs.* males with hypothyroid relative 43.1%, n = 25, $P < 0.001$).

For subjects with GD, a reported FH of thyroid disease was more common in maternal relatives than paternal relatives (GD females with affected maternal relatives 34.1%, n = 688 *vs.* affected paternal relatives 14.3%, n = 288, $P < 0.001$; GD males with affected maternal relatives 31.9%, n = 123 *vs.* affected paternal relatives 8.8%, n = 34, $P < 0.001$). The same pattern was seen in HT (HT females with affected maternal relatives 39.2%, n = 134 *vs.* affected paternal relatives 18.1%, n = 62, $P < 0.001$; HT males with affected maternal relatives 31.0%, n = 18 *vs.* affected paternal relatives 13.8%, n = 8, $P < 0.05$). For females and males with GD and HT, the most commonly reported family member with thyroid disease was the mother (Tables 2 and 3).

We next investigated the effect of FH on age at onset of both GD and HT. The reporting of a parent with thyroid dysfunction in females with GD was associated with lower median age at diagnosis when compared with GD females without a parental history (Table 2). For males with GD, a positive association of parental thyroid dysfunction was confined to hypothyroidism. For those with HT, a similar influence of parental thyroid dysfunction was confined to parental hypothyroidism, which was also associated with reduction in median age at diagnosis (Table 3).

Those with GD with a reported FH of thyroid disease had a lower median age at diagnosis, compared with those without a FH of thyroid disease [GD females with FH, 38.0 yr (29.0–48.0), n = 957 *vs.* no FH 43.0 yr (33.0–54.0), n = 935, $P < 0.001$; GD males with FH, 41.0 yr (31.0–53.0), n = 154 *vs.* no FH, 47.0 yr (35.5–57.0), n = 204, $P < 0.01$]. Median age at diagnosis was also lower in HT in those who had a positive FH of thyroid dysfunction, compared with those with no FH of thyroid dysfunction [HT females with FH 38.0 yr (29.0–

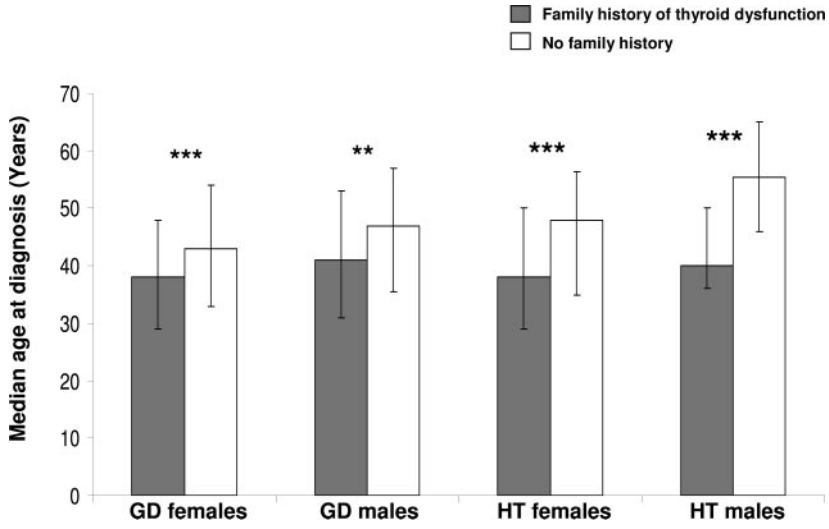

FIG. 3. Median age (and IQR intervals) at diagnosis in subjects with GD and HT divided according to the presence or absence of a family history of thyroid dysfunction. ***, $P < 0.001$; **, $P < 0.01$, comparing positive and negative family history.

50.0), n = 193 *vs.* no FH 48.0 yr (35.0–56.3), n = 133, $P < 0.001$; HT males with FH 40.0 yr (36.0–50.0), n = 30 *vs.* no FH 55.5 yr (46.0–65.0), n = 28, $P < 0.001$] (Fig. 3).

For subjects with GD, further analysis revealed a significant inverse relationship between the total number of reported relatives with thyroid dysfunction and median age at diagnosis (GD females, R = −0.16, $P < 0.001$; GD males, R = −0.14, $P < 0.01$). The number of reported relatives with thyroid dysfunction was also associated with lower median age at diagnosis for HT (HT females, R = −0.25, P=<0.001; HT males, R = −0.49, $P < 0.001$) (Table 4).

A positive FH of thyroid dysfunction was not associated with either the presence or severity of ophthalmopathy in GD. Similarly, a positive FH was not associated with a difference in disease severity at presentation for either GD or HT (data not shown).

Discussion

The present study used a unique cohort of almost 3000 well-characterized subjects with clearly defined autoimmune thyroid diseases to demonstrate marked associations between several factors such as age and FH of thyroid diseases as well as cigarette smoking and the phenotypic features of GD and HT.

We have shown that in those with GD, the median age at diagnosis was lower in females than males and that more women than men had goiter evident on physical examination. The presence of goiter was associated with a lower age at diagnosis and more biochemically severe disease. Multiple regression analysis demonstrated that goiter was similarly associated with disease severity, whereas age and gender did not exert independent effects. These findings agree with our own previous smaller study of 536 GD patients in which we reported that those younger than 40 yr at diagnosis had more severe disease than those presenting later (20), as well as being in agreement with a small Japanese study (18). Goiter prevalence has previously been reported to be inversely related to age at diagnosis of hyperthyroidism (23), although that study also included toxic nodular hyperthyroidism. The present finding that goiter independently predicts disease severity is plausible in that goiter may be a surrogate marker of the severity of the autoimmune process.

In HT, women again had a significantly lower age at diagnosis than men, with severity (serum TSH at presentation) being higher in males than females, speculatively because males may present later, as recorded for other diseases (24). As in GD, goiter was associated with a lower age at diagnosis, but in contrast to GD, goiter was not associated with severity. However, none out of gender, goiter presence, and age independently predicted biochemical severity of hypothyroidism in a multiple regression analysis, in contrast to GD, even though these diseases may represent part of a spectrum of thyroid autoimmunity (25).

When we examined the influence of age, gender, smoking, and severity of GD on the presence/severity of ophthalmopathy, we found that a higher proportion of males than females had severe ophthalmopathy (despite a similar prevalence of smoking) and that the median age at diagnosis was higher in those with severe ophthalmopathy. These findings agree with a smaller study of 101 subjects attending a thyroid-eye disease clinic in whom there was a positive relationship between age and severity of ophthalmopathy and in whom males had a greater disease severity score (15). Whereas that study examined a selected group, as did one further study with similar findings (16), a gender influence was also apparent in previous studies that reported a lower female to male prevalence in ophthalmopathy, compared with GD as a whole (26, 27). The reason for these gender and age associations with ophthalmopathy are unclear. We previously reported that males with GD are less likely to enter remission after antithyroid therapy, perhaps because of poorer compliance and biochemical control (20). The latter may contribute to the relatively higher prevalence of severe ophthalmopathy.

As expected, we found a clear relationship between smoking and ophthalmopathy, the greatest relative risk being in current smokers, with an intermediate risk in ex-smokers. In contrast to the severity of ophthalmopathy, the presence of ophthalmopathy was not independently associated with gender or age, but an independent association with current smoking was confirmed by binary logistic regression analysis, as was the severity of hyperthyroidism. Several studies now provide good evidence that smoking is a risk factor for not only development of GD itself but also, specifically, development of ophthalmopathy, a metaanalysis providing an odds ratio for development of GD with ophthalmopathy of 4.4 (95% CI 2.88–6.73), compared with GD overall of 1.90 (95% CI 1.42–2.55) (28). The mechanisms underlying this are unclear, although links between smoking and rheumatoid arthritis (29) and Crohn's disease (30) suggest a generalized stimulation of autoimmunity. The risk of ophthalmopathy has also been linked before with severity of hyperthyroidism in a report (31) that the probability of development/worsening of ophthalmopathy was directly related to serum T_3

TABLE 4. Median age (and IQR) at diagnosis of GD and HT in subjects divided according to the total number of reported relatives with thyroid dysfunction

	GD females	GD males	HT females	HT males
No FH	43.0 yr (33.0–54.0)[a] n = 935	47.0 yr (35.5–57.0)[b] n = 204	48.0 yr (35.0–56.3)[a] n = 133	55.5 yr (46.0–65.0)[a] n = 28
One relative	40.0 yr (30.0–49.0) n = 579	41.0 yr (32.0–53.0) n = 95	42.0 yr (33.0–53.0) n = 114	44.5 yr (38.0–50.0) n = 18
Two or more relatives	36.0 yr (28.8–47.0) n = 378	41.0 yr (30.3–53.0) n = 59	33.0 yr (26.0–43.0) n = 79	36.5 yr (25.0–48.0) n = 12

Age at diagnosis was correlated with the number of affected relatives using the Spearman rank order correlation.
[a] $P < 0.001$.
[b] $P < 0.01$.

concentration before treatment, regardless of treatment with radioiodine, surgery, or antithyroid drugs; although, in contrast to the present study, there was no predictive value of serum T_4. The present finding of an association between ophthalmopathy and severity of GD is plausible in that more severe hyperthyroidism is likely to reflect a more potent autoimmune process, predisposing to a wider spectrum of manifestations.

Evidence from family and twin data reinforced by molecular genetic studies provides convincing support for a genetic basis to both GD and HT (9, 11). As might be expected, approximately half of our cohort reported a relative with thyroid dysfunction (either hyperthyroidism or hypothyroidism), with greater proportions reporting a FH of all types of thyroid disease, including goiter and unspecified thyroid disorders. Our prevalence rates are consistent with a number of studies reporting a family history in 50–60% of index cases with autoimmune thyroid disease (4, 32).

In an attempt to quantify the degree of family clustering, the method of Risch (33) can be applied to calculate the lambda(s), *i.e.* the risk to the second sibling when the first already has disease, divided by the population prevalence for disease. Crude estimates for lambda(s) for autoimmune thyroid diseases, at between 10 and 15 (34, 35), are similar to those for other common diseases such as type 1 diabetes (36). Assuming a population prevalence of 0.5–0.8% for GD in the United Kingdom (2) and because 5.1% of our subjects (n = 130) reported a second sibling with disease, we can confirm lambda(s) of 6.5–10 for GD. Similarly for HT, with a population prevalence of 1.0% (2), our data provide lambda(s) of 6.5 (n = 25 with affected second sibling, 2.99%). These data not only support a polygenic, multifactorial inheritance pattern reflecting low-risk alleles at multiple loci but also help to explain why it has proved difficult to identify specific susceptibility loci because the size of data sets needed are greater than those so far collected.

It was notable that GD subjects were more likely to have a relative with hyperthyroidism than hypothyroidism and vice versa in HT. This supports the hypothesis that whereas GD and HT represent a spectrum of autoimmune diseases, the risk factors including genetic effects are, at least in part, disease specific. An example of this is the recently reported genetic association of the TSH receptor gene with GD but not HT (37).

Interestingly, a positive FH of thyroid dysfunction was associated with a lower median age at diagnosis for both GD and HT, and the greater the number of affected relatives, the greater this effect. These observations may reflect earlier recognition of thyroid disease in subjects with a known FH of thyroid disorders. They could also reflect ascertainment bias because of the preferential identification of family members of different ages with simultaneous disease onset, whereas the apparent parental influence could be spurious if early-onset GD in the parent affected fertility. An alternative explanation is that of genetic anticipation, reported in type 1 diabetes (38), rheumatoid arthritis (39), multiple sclerosis (40), and inflammatory bowel disease (41). Consistent with the present findings, Yaturu *et al.* (42) reported that the age of onset of type 2 diabetes was 6 yr earlier in those with a positive FH, compared with those without; furthermore, the age of onset of those with affected siblings was not different from those without, as in the present study. The possibility of genetic anticipation has been explored before in a recent study of the age of onset of GD in affected parent-child pairs (43). Children were found to be younger than their parents at diagnosis in 25 of 33 pairs investigated.

A limitation of our data was the self-reported nature of the FH, without verification by case-note review. There is evidence that there is a high sensitivity for self-reported hyperthyroidism and hypothyroidism, although specificity is lower (44). Whereas no study has examined the accuracy of reporting of thyroid dysfunction among family members of index cases, it might be expected that our FH data would reflect underreporting rather than overreporting of the prevalence of thyroid diseases in family members.

In summary, we have demonstrated that gender, age, and family and smoking history variously have marked associations with disease phenotypes in autoimmune thyroid diseases, such as the presence of ophthalmopathy in those with GD and the biochemical severity of thyroid dysfunction. These findings provide some insight into the complex interactions between genetic factors, which account for a major part of disease susceptibility, and environmental/endogenous factors. Better understanding of these factors, and how they impact both on disease manifestations and also on response to treatments, should facilitate tailoring of therapies, *e.g.* for those at particular risk of complications such as ophthalmopathy or, ideally, preventive measures to subjects at particular risk based on their FH.

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