CLINICAL STUDY

Familial risks for hospitalized Graves' disease and goiter

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Abstract

Objectives: Familial clustering of a disease is an indicator of a possible heritable cause, provided that environmental sharing can be excluded. Thus, data on familial risks are important for genetic studies and for clinical genetic counseling.

Design: We carried out a nationwide family study on nontoxic and toxic nodular goiters, and Graves' disease in order to search for familial clustering of these diseases at the population level.

Methods: The Swedish Multigeneration Register on 0–75 year old subjects was linked to the Hospital Discharge Register from years 1987 to 2007. Standardized incidence ratios (SIRs) were calculated for offspring of affected parents and for siblings by comparing to those whose relatives had no hospitalization for thyroid disease.

Results: The number of hospitalized patients in the offspring generations was 11 659 for nontoxic goiter, 9514 for Graves' disease, and 1728 for toxic nodular goiter. Familial cases accounted for 8.2, 5.2, and 2.1% of all patients respectively. The highest familial risk for offspring of affected parents was noted for Graves' disease (SIR 3.87), followed by toxic nodular goiter (3.37) and nontoxic goiter (3.15). Familial risks were higher for affected siblings: toxic nodular goiter (11.66), Graves' disease (5.51), and nontoxic goiter (5.40). Weaker familial associations were observed between the three diseases.

Conclusions: To our knowledge this is a first population-based family study on these thyroid diseases. The observed high familial aggregation for defined thyroid diseases cannot be explained by the known genetic basis, calling for further studies into genetic and environmental etiology of thyroid diseases.

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Introduction

Goiter, the enlargement of the thyroid, is a common finding, particularly in iodine deficient areas (1). Goiter may be nontoxic (simple) or toxic (associated with hyperthyroidism). The estimated population prevalence of overt hyperthyroidism is 0.5–1%, and milder forms are even more common (2, 3). Both goiter and hyperthyroidism, as any thyroid disease, are more common in women than in men (4). Hyperthyroidism or thyrotoxicosis is a hypermetabolic state which may be due to autoimmune Graves' disease, i.e. diffuse goiter, or to a hyperfunctional nodular goiter, related to mutation in the thyroid stimulating hormone receptor (TSHR) gene or other causes (2, 5, 6). According to Swedish studies, Graves' disease is about three times more common than toxic multinodular goiter, with female excess of three- and eight-fold respectively (3). The underlying pathoetiology of autoimmune thyroid diseases comprise gene–environment interactions, between susceptibility genes and environmental triggers (e.g. dietary iodine, psychosocial stress, smoking, and immune modulators). In Graves' disease antibodies

are directed towards various components of the thyroid, including TSHR, resulting in hyperfunction of the tissue. Graves' disease is often associated with other autoimmune diseases, such as systemic lupus erythematosus, Addison's disease and autoimmune polyendocrine syndrome (7–9).

Simple goiter, Graves' disease and toxic nodular goiter are thought to be complex diseases with multifactorial etiology. Genetic susceptibility for Graves' disease and simple goiter is implicated by a higher disease concordance in monozygotic than dizygotic twins (4, 8–11). Several disease susceptibility loci have been identified for Graves' disease, including the human leukocyte antigen (HLA) locus, CTLA-4, CD40, PTPN22, TSH, and TSHR (8, 9, 12–14). For simple goiter, candidate genes with mechanistic links include thyroid peroxidase, thyroglobulin, sodium iodine symporter and TSHR (4).

The availability of a Multigeneration Register in Sweden provides a reliable access to families throughout the last century. This register has been extensively used to study cancers through linkage to the Swedish Cancer Registry and to study any hospitalized diseases through

linkage to the Hospital Discharge Register (15). In the present article we examine familial risks for defined thyroid diseases in offspring of affected parents and in siblings focusing on simple goiter, Graves' disease and toxic nodular goiter.

Methods

A thyroid disease research database was constructed by linking several national Swedish registers, based on the MigMed 2 datasets at Center for Primary Health Care Research, Malmö, Lund University. Statistics Sweden provided the Multigeneration Register where persons born in Sweden in 1932 and later (second generation) were linked to their parents (first generation), registered shortly after birth. Families could be defined by linking all the children to their parents. Sibships can only be defined for the second generation. Linkages were carried out to national census data, in order to obtain individual socioeconomic status. The final links were made by adding individual data from the Swedish Hospital Discharge Register that records data on all discharges after a minimal stay of one night with dates of hospitalization and diagnoses since 1964 with a complete nationwide coverage since 1986. A flowchart of the linkages has been published elsewhere (15). All linkages were performed by the use of the individual national identification number that is assigned to each person in Sweden for their lifetime. This number was replaced by a serial number for each person in order to provide anonymity. The serial number was used to check that each individual was only entered once, for his or her first appearance with a defined diagnosis. Over 3.5 million families were included in this database in which the second generation had reached age 75 years at the end of the follow-up, spanning from 1987 to 2007.

Thyroid diseases were retrieved from hospital discharges reported according to different versions of the International Classification of Diseases (ICD), 9th (1987–1996) and 10th (1997–2007) versions. Parental cases were also included from earlier ICD, starting from year 1964. The individual variables controlled for in the analysis include gender, age at diagnosis (categorized in 5-year intervals), socioeconomic status (six groups: farmers; unskilled/skilled workers; white collar workers; professionals; self-employed;

all others) and region (three groups: large cities, Stockholm, Gothenburg and Malmö; Southern Sweden; Northern Sweden), allowing adjustment for regional differences in hospitalization. Familial cases were defined as patients who have more than one family members (parents or sibling) with the same disease. Person-years were calculated from start of follow-up on January 1, 1987 until hospitalization/diagnosis of disease, death, emigration, or closing date, December 31, 2007. Standardized incidence ratios (SIRs, indirect method of standardization) were calculated for familial risks as the ratio of observed (O) to expected (E) number of cases. The observed number was first retrieved and then compared with the number that would have been expected (E) if the cohort had the same covariate-specific incidence from defined thyroid disease. The expected number of cases was calculated for age, sex, period, region, and socioeconomic status-specific standard incidence rates (16). Based on the assumption of a Poisson distribution, the 95% confidence intervals (CI) for SIRs were calculated and rounded to the nearest two decimals. Separate familial risks were calculated for offspring whose parents were affected (sibling not affected), for siblings (parents not affected) and for offspring whose parents and at least another sibling were affected. Genetic modes of inheritance were searched by using these three types of probands.

Separate analyses were also performed according to gender and age at hospitalization of offspring to explore the possible risk differences. Spouse correlation with either the husband or the wife as the proband was carried out to detect the effect of environmental sharing in the adulthood.

Results

The numbers of the covered familial and sporadic thyroid disease patients (in offspring generation) and median ages of diagnosis are shown in Table 1. Nontoxic nodular goiter and Graves' disease were the most common diagnoses both as familial and sporadic diseases. The familial cases accounted for 8.2% of nontoxic goiter, 5.2% for Graves' disease, and 2.1% for toxic nodular goiter. Among offspring diagnosed with nontoxic goiter, 93.5% (898/961) had one, 5.7% (55/961) had two and 0.8% (8/961) had three or

Table 1 Number of cases and median age of diagnosis (year) and incidence rate (per 100 000 per years) for familial and sporadic cases among offspring from 1987 to 2006.

Disease	All	Familial		Sporadic	
	Number of cases	Number of cases (%)	Median age of diagnosis	Number of cases	Median age of diagnosis
Nontoxic goiter	11 659	961 (8.2)	45	10 698	47
Graves' disease	9514	497 (5.2)	32	9017	37
Toxic nodular goiter	1728	37 (2.1)	48	1691	47

Table 2 Standardized incidence ratio (SIR) for nontoxic goiter in offspring when parents, siblings or parents and siblings were hospitalized for thyroid disease.

		Concordant				Discordant				
		O	SIR	95% CI		O	SIR	95% CI		
Proband type										
All										
Parent only	Nontoxic goiter	568	3.15	2.90	3.42	Graves' disease	235	2.24	1.96	2.54
						Toxic nodular goiter	105	2.43	1.99	2.94
Sibling only	Nontoxic goiter	351	5.40	4.85	5.99	Graves' disease	53	1.27	0.95	1.66
						Toxic nodular goiter	30	3.20	2.16	4.57
Parent and sibling	Nontoxic goiter	42	11.38	8.20	15.40	Graves' disease	5	4.23	1.33	9.94
						Toxic nodular goiter	1	12.25	0.00	70.23
Age at hospitalization < 50 years										
Parent only	Nontoxic goiter	409	3.33	3.01	3.67	Graves' disease	134	2.13	1.79	2.53
						Toxic nodular goiter	62	2.61	2.00	3.35
Sibling only	Nontoxic goiter	200	6.01	5.20	6.90	Graves' disease	33	1.27	0.88	1.79
						Toxic nodular goiter	16	3.35	1.91	5.45
Parent and sibling	Nontoxic goiter	35	15.74	10.95	21.90	Graves' disease	5	5.94	1.88	13.98
						Toxic nodular goiter	1	19.59	0.01	112.28
Age at hospitalization ≥ 50 years										
Parent only	Nontoxic goiter	159	2.27	2.35	3.23	Graves' disease	101	2.39	1.95	2.91
						Toxic nodular goiter	43	2.21	1.60	2.98
Sibling only	Nontoxic goiter	151	4.76	4.03	5.58	Graves' disease	20	1.26	0.77	1.94
						Toxic nodular goiter	14	3.05	1.66	5.13
Parent and sibling	Nontoxic goiter	7	4.78	1.89	9.90	Graves' disease	0			
						Toxic nodular goiter	0			

O, observed; SIR, standardized incidence ratio; CI, confidence interval. Bold type, 95% CI does not include 1.00.

more family members diagnosed with the same disease. Among 497 familial offspring with Graves' disease, only 12 were found to have two family members diagnosed with the same disease; all others had one concordant family member. All of the 37 familial cases with toxic nodular goiter had only one family member diagnosed with the same disease. The median ages at

diagnosis between familial and sporadic diagnoses were only different for Graves' disease, 32 and 37 years respectively.

Familial risks were adjusted for a number of variables, including age, socioeconomic status, region, gender, and period and these will not bias the results. Familial risks for nontoxic goiter are shown in Table 2 in three

Table 3 Standardized incidence ratio (SIR) for Graves' disease in offspring when parents, siblings or parents and siblings were hospitalized for thyroid disease.

Proband type		Concordant				Discordant				
		O	SIR	95% CI		O	SIR	95% CI		
All										
Parent only	Graves' disease	312	3.87	3.45	4.32	Nontoxic goiter	173	1.15	0.99	1.34
						Toxic nodular goiter	66	2.30	1.78	2.93
Sibling only	Graves' disease	173	5.51	4.72	6.40	Nontoxic goiter	53	1.33	1.00	1.74
						Toxic nodular goiter	20	3.40	2.07	5.26
Parent and sibling	Graves' disease	12	11.91	6.13	20.88	Nontoxic goiter	4	1.63	0.42	4.22
						Toxic nodular goiter	0			
Age at hospitalization <50 years										
Parent only	Graves' disease	260	4.31	3.80	4.86	Nontoxic goiter	147	1.20	1.02	1.41
						Toxic nodular goiter	44	2.26	1.64	3.04
Sibling only	Graves' disease	153	6.46	5.48	7.57	Nontoxic goiter	30	1.23	0.83	1.76
						Toxic nodular goiter	15	4.12	2.30	6.81
Parent and sibling	Graves' disease	12	14.27	7.34	25.01	Nontoxic goiter	1	0.58	0.00	3.33
						Toxic nodular goiter	0			
Age at hospitalization ≥50 years										
Parent only	Graves' disease	52	2.56	1.91	3.36	Nontoxic goiter	26	0.93	0.61	1.37
						Toxic nodular goiter	22	2.37	1.48	3.59
Sibling only	Graves' disease	20	2.60	1.58	4.02	Nontoxic goiter	23	1.49	0.94	2.24
						Toxic nodular goiter	5	2.23	0.70	5.24
Parent and sibling	Graves' disease	0				Nontoxic goiter	3	4.11	0.78	12.18
						Toxic nodular goiter	0			

O, observed; SIR, standardized incidence ratio; CI, confidence interval. Bold type, 95% CI does not include 1.00.

mutually exclusive proband types: parent only, sibling only, and parent and sibling (multiplex). The concordant (same disease subtype in family members) risks according to these proband types were 3.15, 5.40, and 11.38 respectively. The familial risk for nontoxic goiter in offspring increased with the number of family members of same disease, being 3.94 (95% CI: 3.69–4.21) for one affected family member, 10.84 (95% CI: 8.16–14.11) for two and 46.08 (95% CI: 19.68–91.24) for three or more family members. The *P* value for the trend test was <0.01. Those with a hospitalization before age 50 showed a higher risk, with significant SIRs of 3.33, 6.01 and 15.74 respectively. Affected offspring in multiplex families accounted for 4.3% of all familial cases. Nontoxic goiter associated somewhat stronger with toxic nodular goiter than with Graves' disease. SIRs were similar for male and female cases (data not shown).

The familial risk for Graves' disease in offspring of affected parents was 3.87, in siblings it was 5.51 and in multiplex families it was 11.91 (Table 3). Higher familial risk was observed among younger age (<50 years) at hospitalization, i.e. 4.31 for parental history only, 6.46 for sibling history only, and 14.27 for both respectively. Offspring with two concordant family members had a higher familial risk than those with only one concordant family member (8.89 (95% CI: 4.57–15.57) vs 4.52 (95% CI: 4.13–4.94)). Similar SIRs were observed for men and women (data not shown). Affected offspring in multiplex families accounted for 2.4% of all familial cases. As a discordant disease, toxic nodular goiter associated with Graves' disease.

The familial risk for toxic nodular goiter in offspring of affected parents was 3.37 and in siblings it was 11.66; no multiplex families were found (Table 4). The overall familial risk for offspring diagnosed with one concordant family member was 4.97 (95% CI: 3.50–6.86). Neither age at hospitalization nor gender was observed to be associated with increased familial risk among concordant cases (data not shown for gender). As a discordant disease, toxic nodular goiter associated with both nontoxic goiter and Graves' disease.

We estimated risk for concordant and discordant Graves' disease and goiter among spouses to explore the contribution of shared environment. A significantly increased risk observed among discordant cases was not observed for either husband or wife as proband. As for concordant cases, the highest risk (SIR=1.48, 95% CI: 1.07–2.01) was observed for male Graves' patients whose wives were probands (data not shown).

In order to check for diagnostic accuracy and diagnostic shifts, we determined the numbers of subsequent hospitalizations for the three diseases among all patients (offspring and parents). When nontoxic goiter was the first hospitalization, 8.7% of the patients visited hospital a second time for the same reason; only 0.6 and 0.5% of them were diagnosed with Graves' disease and toxic nodular goiter respectively in the subsequent hospitalization. Over 20% of Graves' disease and toxic nodular goiter patients were hospitalized for a second time for the same disease; Graves' disease was followed by toxic nodular goiter in 3.1% of the patients while the reverse order took place in 6.1% of the patients (Table 5).

Table 4 Standardized incidence ratio (SIR) for toxic nodular goiter in offspring when parents, siblings or parents and siblings were hospitalized for thyroid disease.

Proband type		Concordant				Discordant			
		O	SIR	95% CI		O	SIR	95% CI	
All									
Parent only	Toxic nodular goiter	21	3.37	2.08	5.16	Nontoxic goiter	57	2.19	1.66 2.84
						Graves' disease	40	2.60	1.85 3.54
Sibling only	Toxic nodular goiter	16	11.66	6.64	18.97	Nontoxic goiter	27	2.85	1.88 4.15
						Graves' disease	21	3.46	2.14 5.29
Parent and sibling	Toxic nodular goiter	0				Nontoxic goiter	4	7.61	1.98 19.67
						Graves' disease	0		
Age at hospitalization <50 years									
Parent only	Toxic nodular goiter	16	5.14	2.93	8.36	Nontoxic goiter	35	2.06	1.44 2.87
						Graves' disease	22	2.54	1.59 3.85
Sibling only	Toxic nodular goiter	5	8.05	2.54	18.94	Nontoxic goiter	11	2.57	1.28 4.62
						Graves' disease	13	3.69	1.96 6.33
Parent and sibling	Toxic nodular goiter	0				Nontoxic goiter	2	6.91	0.65 25.41
						Graves' disease	0		
Age at hospitalization ≥50 years									
Parent only	Toxic nodular goiter	5	1.60	0.51	3.77	Nontoxic goiter	22	2.44	1.53 3.70
						Graves' disease	18	2.67	1.58 4.23
Sibling only	Toxic nodular goiter	11	14.63	7.26	26.28	Nontoxic goiter	16	3.08	1.75 5.01
						Graves' disease	8	3.14	1.34 6.21
Parent and sibling	Toxic nodular goiter	0				Nontoxic goiter	2	8.46	0.80 31.11
						Graves' disease	0		

O, observed; SIR, standardized incidence ratio; CI, confidence interval. Bold type, 95% CI does not include 1.00.

Table 5 Numbers of subsequent hospitalizations after a first thyroid disease.

First hospitalization		Subsequent hospitalization	
Diagnosis	Number of patients	Diagnosis	Number of patients (%)
Nontoxic goiter	48 604	Nontoxic goiter	4239 (8.7)
		Graves' disease	301 (0.6)
		Toxic nodular goiter	255 (0.5)
Graves' disease	33 994	Graves' disease	8047 (23.7)
		Nontoxic goiter	351 (1.0)
		Toxic nodular goiter	1046 (3.1)
Toxic nodular goiter	9505	Toxic nodular goiter	1998 (21.0)
		Nontoxic goiter	276 (2.9)
		Graves' disease	583 (6.1)

Discussion

There are previous family data on goiter and Graves' disease but these are based on a few numbers of cases and for goiter they are very old; for toxic goiter no specific studies have been conducted (6, 9, 17–19). Familial risk is a good estimate of disease heritability, calculated as the ratio of the prevalence of the disease in siblings of affected individuals compared with the prevalence of the disease in the general population. The novel aspect of the present study is that we can define familial risks in the distinct thyroid diseases in a systematic way in a single population of a whole nation. However, there are limitations to the study, for example, that the diagnostics may have changed over the years, which was the reason that we started the follow-up of the offspring population in 1987, after which time the diagnostic codes were relatively uniform and many up-to-date diagnostic tests were in place. Although we have no objective way of evaluating the overall diagnostics accuracy, the high observed risks would have been unlikely without high precision. The diagnostic accuracy in the Hospital Discharge Register has been referred to as being 88–90% on the main diagnoses (20). Hyperthyroidism is almost always leading to hospitalizations in Sweden (3, 21) and the 43 500 identified patients with hyperthyroidism give a crude population prevalence of 0.5% (the Swedish population was 8.8 million in the middle of the study period); however, this figure is an underestimation of the prevalence because many patients could have been diagnosed before the start of the follow-up in year 1987. Graves' disease was over three times more common than toxic multinodular goiter in accordance with previous studies (3, 21). For nontoxic goiter hospitalizations are not equally regular and the present 48 600 patients with this diagnosis are likely to be a subgroup.

The proportion of familial cases decreased from 8.2% for nontoxic goiter, to 5.2% for Graves' disease and 2.1% for toxic nodular goiter. These proportions could be an underestimation, particularly for nontoxic goiter caused

by the exclusion of outpatients and/or incomplete coverage of parents before 1987. The proportions depend in part on the population prevalence of the condition. In the present analysis we wanted to examine familial clustering by using three types of probands: 'parent only', 'sibling only', and 'parent and sibling' in order to deduce the possible inheritance and penetrance modes. Dominant and recessive effects could be distinguished by a higher risk for siblings than for offspring of affected parents. However, a similar effect would be caused by environmental sharing in childhood, which could be, for example, iodine deficiency. Thus, even though for all the three conditions sibling risks exceeded those for offspring of affected parents, the data should be interpreted with caution; yet, it should be noted that for toxic nodular goiter the difference in risks was remarkably higher, 11.66, for siblings, compared to 3.37 for offspring of affected parents. No multiplex families were noted for this condition but for nontoxic goiter these accounted for 4.3% of the familial cases and showed a familial risk of 11.38; for Graves' disease multiplex families accounted for 2.4% of the familial cases with a familial risk of 11.91. Multiplex families are likely to be carriers of high or moderate penetrance genes. It may be pointed out that the familial risks for the present thyroid diseases were higher (SIRs for offspring of affected parents over 3.0 and for siblings over 5.0) than those reported in this database for other common diseases, such as cardiovascular diseases, stroke and cancer (all around 2) but they were lower than those found for non-thyroid endocrine diseases (many subtypes exceeding well over 10) (22, 23).

The concordant familial risks for offspring with the three conditions were remarkably uniform, ranging between 3.17 (nontoxic goiter) and 3.78 (Graves' diseases); for these conditions even sibling risks were almost equal, 5.40 and 5.51. Moreover, the risks were increased depending on the number of affected family members. It should be noted that familial risks for these defined thyroid diseases could be an underestimation because of the exclusion of outpatients that may lead to non-differential misclassification for both probands and cases, especially for nontoxic goiter diseases with more cases in outpatient settings. This might lead to suggestion that the familial risks are shared, however, this was not the case because the discordant familial risk were always much lower than the concordant ones. Nontoxic goiter shared familial effects with toxic nodular goiter but not much with Graves' disease. On the other hand, toxic nodular goiter shared familial associations with both nontoxic goiter and Graves' disease. However, the same individuals were only rarely diagnosed with two different diseases; the most common combination was the first hospitalization for toxic nodular goiter and the second one for Graves' disease in 6.1% of the patients. It is not unexpected that discordant diseases in the patient's same organ are

diagnosed somewhat more often than expected because of the past history of the disease and access to the medical surveillance.

The familial risk of Graves' disease is lower than the one previously reported in small studies. Sibling risks have been estimated at 11.6 for Graves' disease, based on nine affected sibling pairs (24). Interestingly, even if some success has been reached in gene/locus identification studies for autoimmune thyroid diseases (8, 9, 12, 14), most of the shown genotype relative risks (odds ratios) are low, below 2.0. Thus, their contribution to familial risk is marginal. Probably, the identified variants do not capture all the genetic effects of the tagged gene or that the tagged genes do not convey large genetic effect (25, 26). Notably, less success has been reported with euthyroid goiters or those without autoimmune manifestations; recently, a thyroid transcription factor-1 mutation was linked to multinodular goiter and papillary thyroid cancer (27).

This population-level study showed high familial aggregation for defined thyroid diseases. Shared lifestyle among family members seems to explain only a small proportion of familial Graves' disease and goiter susceptibility. Familial Graves' disease and goiter are more likely to be due to heritable than environmental effects. Most of the clustering cannot be explained by the known genetic basis of these diseases, suggesting promising prospects for gene finding studies. However, the known and unknown environmental factors may interact with the susceptibility genes which may complicate gene finding studies, calling for, firstly, large study populations and, secondly, consideration of heterogeneity of environmental exposure and diseased phenotype.

The present results should give reliable risk estimates for hospitalized thyroid disease patients and their relatives, differentiating proband and age of onset. The particularly high risks in families with several affected individuals should be considered in the counseling. Moreover, one thyroid disease in a family member may increase the susceptibility of another family member to another thyroid disease.

Declaration of interest

I declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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