Familial risks between Graves disease and Hashimoto thyroiditis and other autoimmune diseases in the population of Sweden

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**ARTICLE INFO**

Keywords: Genetics Risk between spouses Discordant risks Polyautoimmunity

**ABSTRACT**

Genetic and family studies have indicated that Graves disease and Hashimoto thyroiditis have a heritable component which appears to be shared to some extent also with some other autoimmune diseases (AIDs). In the present nation-wide study we describe familial risk for Graves disease and Hashimoto thyroiditis identified from the Swedish Hospital Discharge Register (years 1964 through 2012) and the Outpatient Register (2001 through 2012). Family relationships were obtained from the Multigeneration Register and cancers from the Cancer Registry. Familial standardized incidence ratios (SIRs) were calculated for 29,005 offspring with Graves disease and for 25,607 offspring with Hashimoto thyroiditis depending on any of 43 AIDs in parents or siblings. The concordant familial risks for Graves disease and Hashimoto thyroiditis were 3.85 and 4.75, higher for men than for women. The familial risks were very high (11.35, Graves and 22.06, Hashimoto) when both a parent and a sibling were affected. Spousal familial risks were higher for Hashimoto thyroiditis (1.98/1.93) than for Graves disease (1.48/1.50). For Graves disease, 24 discordant AIDs showed a significant association; for Hashimoto thyroiditis, 20 discordant associations were significant. All significant discordant associations were positive for the two thyroid AIDs, with the exception of Hashimoto thyroiditis with Reiter disease. Overall 8 associations were significant only for Graves disease and 6 Hashimoto thyroiditis. The overall high concordant familial risks for Graves disease and Hashimoto thyroiditis suggest a strong genetic contribution to the familial risk. Significant familial associations among more than half of the 43 AIDs attest to the extensive polyautoimmunity among thyroid AIDs.

1. Introduction

Graves disease and Hashimoto thyroiditis are common autoimmune diseases (AIDs) in which autoantibodies interfere with the function of the thyroid gland, in the former causing hyperthyroidism and in the latter hypothyroidism \cite{1,2}. Consequently, the disease mechanisms are different; in Graves disease an antibody (thyroid-stimulating immunoglobulin) mimics the function of thyroid stimulating hormone (TSH), and thus an excessive production of thyroid hormones ensues \cite{1,2}. The initial phase of Hashimoto thyroiditis is characterized by lymphocytic infiltration into thyroid follicles followed by their gradual destruction; antibodies against thyroid peroxidase or thyroglobulin are often found but whether they contribute to the disease mechanism or are consequences thereof remains unestablished \cite{1,3}. These diseases are associated with each other and many other AIDs presenting examples of polyautoimmunity \cite{1,4}. Both of the diseases are much more common in women than in men. For both diseases genetic and environmental causes are thought to be important. Microbial antigens may be triggers of these

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\url{https://doi.org/10.1016/j.jtauto.2020.100058}

Received 5 April 2020; Received in revised form 22 May 2020; Accepted 27 May 2020

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Table 1
Familial risks of the autoimmune diseases Graves and Hashimoto thyroiditis.

|        | Any first-degree relative |        |        |        |
|--------|---------------------------|--------|--------|--------|
|        | All                       | Women  | Men    |
|        | O  SIR  95% CI            | O  SIR  95% CI | O  SIR  95% CI |
| Graves | 1771 3.85 3.67 4.03       | 1450 3.75 3.56 3.95 | 321 4.37 3.90 4.87 |
| Hashimoto thyroiditis | 1255 4.75 4.49 5.02 | 958 4.36 4.09 4.64 | 297 6.68 5.94 7.48 |
|        | Parents only              | Sibling only | Both parent and sibling |
| Graves | 923 3.36 3.15 3.59       | 865 3.86 3.60 4.12 | 52 11.35 8.48 14.90 |
| Hashimoto thyroiditis | 552 3.51 3.22 3.81 | 730 5.52 5.12 5.93 | 52 22.06 16.47 28.94 |

Husbands

| Graves | 88 1.48 1.19 1.82 | 88 1.50 1.20 1.85 |
| Hashimoto thyroiditis | 46 1.98 1.45 2.64 | 46 1.93 1.41 2.57 |

Wives

| Graves | 6.75 6.22 7.31 | 6.75 6.22 7.31 |
| Hashimoto thyroiditis | 5.75 5.22 6.31 | 5.75 5.22 6.31 |

Bold type: 95% CI does not include 1.00.
O = observed number of cases; SIR = standardized incidence ratio; CI = confidence interval.

2. Methods

AID patients were identified from the Swedish Hospital Discharge Register (years 1964 through 2012, full national coverage from 1986 onwards) and the Outpatient Register (2001 through 2012). Only the first AID diagnosis was included. Of a total of 769,991 patients, 51% were identified from Inpatient Register and 49% from Outpatient Register. Various revisions of the International Classification of Diseases (ICD) codes were used for AIDs as described elsewhere [12]. Family relationships were obtained from the Multigeneration Register, containing the Swedish population in families and spanning more than a century [13].

As family members, only first-degree relatives of offspring-parent pairs and siblings in ‘the offspring generation’ were considered; ‘the offspring generation’ was born after 1931 and ‘the parental generation’ was born any time earlier. By year 2012, the offspring generation reached age 80 years; siblings can be defined only in the offspring generation. For the parental generation there was no age limits. Information from the registries was linked at the individual level via the national 10-digit civic registration number. In the linked dataset, civic registration numbers were replaced with serial numbers to ensure the anonymity of all individuals.

In Sweden the treatment of thyroid AIDs is concentrated to specialist wards [14]. The diagnostics of Graves disease has been based was screened by measuring antibodies to thyrotrophin receptor antibody and thyroid peroxidase antibody [14]. For Hashimoto thyroiditis typical ultrason sound pattern and the presence of antithyroid antibodies have been used.

Standardized incidence ratios (SIRs) were calculated for the offspring generation as the ratio of observed to expected number of cases. The expected numbers were calculated for all individuals without a first-degree family history of a specific AID, and the rates were standardized by 5-year-age, gender, period (5 years group), socioeconomic status and residential area. The 95% confidence interval (95%CI) of the SIR was calculated assuming a Poisson distribution. Separate SIRs were calculated for offspring when only parent, only sibling or parent and sibling were probands, i.e., they were diagnosed with concordant AID. In analysis of discordant AIDs bidirectional (i.e., Graves-Hashimoto and Hashimoto-Graves) associations were considered.

The study was approved by the Ethical Committee of Lund University.

3. Results

The number of Graves disease patients in the offspring generation (to whom risks were calculated) was 29,005 with a mean diagnostic age (i.e., first hospital contact) of 41.4 years; considering also their parents the total number was 53,214. Offspring with Graves disease had 1771 (6.1%) first-degree relatives (parents or siblings) also diagnosed with Graves disease. For Hashimoto thyroiditis the numbers were 25,607 (mean age 37.8 years) and 40,718; 1255 (4.9%) first-degree relatives were diagnosed with Hashimoto thyroiditis. The total AID population amounted to 519,180 patients in the offspring generation of 8.5 million; thus 6.1% of the population were diagnosed with AIDs. When also the parental generation was included the total number of AID patients was 769,991. In this population Graves disease accounted for 6.9% of all AIDs compared to 5.3% for Hashimoto thyroiditis.

3.1. Concordant familial risks

Familial risks for the AIDs are shown in Table 1 for offspring whose first-degree relatives (parents or siblings) were diagnosed with concordant AID. The overall familial risks for Graves disease and Hashimoto thyroiditis were 3.85 and 4.75, higher for men than for women but only the difference for Hashimoto thyroiditis (female 4.36 vs male 6.68) was significant, i.e., 95%CIs did not overlap. In the middle row of Table 1, familial risks for AIDs are shown separately for offspring whose parents, siblings or both were diagnosed with concordant AIDs. Risks for siblings were higher than for offspring of affected parents, and the difference in SIRs was higher (5.52 vs. 3.51) in Hashimoto thyroiditis. Both AIDs...
reached very high risks of 11.35 (Graves) and 22.06 (Hashimoto) in multiplex families (both a parent and a sibling affected). Spousal familial risks were calculated for a husband given a concordant AID in the wife and vice versa (bottom of Table 1). The SIRs were higher for Hashimoto thyroiditis (1.98/1.93) than for Graves disease (1.48/1.50) but the differences between these were not significant.

### 3.2. Discordant familial risks

We analyzed familial risks between Graves disease and 42 other AIDs and significant discordant associations are shown in Table 2 shows; significant bidirectional association are also included. The partners with most discordant cases were psoriasis and rheumatoid arthritis. The partner with the highest risk was dermatitis herpetiformis (2.38), followed by Addison disease (2.24) and Hashimoto thyroiditis (2.04). Overall, 24 discordant AIDs showed a significant association, many of them in both directions. No significant sex differences were observed and results are not shown.

#### Table 2

| Subtypes of AID in offspring | Family history of AID | Obs. | SIR | 95% CI |
|-----------------------------|-----------------------|------|-----|--------|
| Graves                      | Addision disease      | 53   | 2.24| 1.68  | 2.88  |
| Graves                      | Graves                | 47   | 1.76| 1.29  | 2.29  |
| Graves                      | Amyotrophic lateral sclerosis | 127 | 1.33| 1.11  | 1.57  |
| Graves                      | Celiac disease        | 268  | 1.73| 1.53  | 1.95  |
| Celiac disease              | Graves                | 759  | 1.86| 1.73  | 2.00  |
| Crohn disease               | Graves                | 472  | 1.10| 1.00  | 1.20  |
| Graves                      | Dermatitis herpetiformis | 39  | 1.85| 1.32  | 2.48  |
| Graves                      | Dermatitis             | 46   | 2.38| 1.74  | 3.12  |
| Graves                      | Diabetes mellitus type I | 141 | 1.78| 1.50  | 2.08  |
| Graves                      | Discoid lupus erythematous | 50  | 1.52| 1.13  | 1.97  |
| Graves                      | Hashimoto thyroiditis | 584  | 2.04| 1.88  | 2.21  |
| Graves                      | Lupoid hepatitis       | 760  | 1.97| 1.84  | 2.12  |
| Graves                      | Myasthenia gravis      | 68   | 1.27| 0.98  | 1.59  |
| Graves                      | Myasthenia gravis      | 57   | 1.52| 1.15  | 1.95  |
| Graves                      | Pernicious anemia      | 47   | 1.57| 1.15  | 2.05  |
| Graves                      | Polymyalgia rheumatica | 127 | 1.94| 1.61  | 2.29  |
| Graves                      | Polymyositis/dermatomyositis | 955| 1.12| 1.01  | 1.23  |
| Graves                      | Polyositis/dermatomyositis | 42  | 1.58| 1.14  | 2.10  |
| Graves                      | Primary biliary cirrhosis | 32  | 1.47| 1.00  | 2.02  |
| Graves                      | Psoriasis              | 56   | 1.36| 1.03  | 1.74  |
| Graves                      | Psoriasis              | 1278 | 1.18| 1.12  | 1.25  |
| Graves                      | Rheumatoid arthritis   | 1672 | 1.20| 1.14  | 1.26  |
| Graves                      | Reiter disease         | 29   | 1.58| 1.06  | 2.21  |
| Graves                      | Rheumatoid arthritis   | 52   | 1.31| 0.98  | 1.69  |
| Graves                      | Rheumatoid arthritis   | 1517 | 1.37| 1.30  | 1.44  |
| Graves                      | Sarcoïdosis            | 883  | 1.28| 1.19  | 1.36  |
| Graves                      | Sarcoïdosis            | 257  | 1.32| 1.16  | 1.49  |
| Graves                      | Sjogrensyndrome        | 278  | 1.25| 1.11  | 1.40  |
| Graves                      | Sjogrensyndrome        | 141  | 1.43| 1.20  | 1.68  |
| Graves                      | Systemic lupus         | 109  | 1.24| 1.02  | 1.48  |
| Graves                      | Systemic lupus         | 141  | 1.71| 1.44  | 2.00  |
| Graves                      | Systemic lupus         | 120  | 1.50| 1.24  | 1.78  |
| Graves                      | Systemic lupus         | 57   | 1.66| 1.26  | 2.12  |
| Graves                      | Systemic lupus         | 36   | 1.38| 0.97  | 1.87  |
| Graves                      | Systemic lupus         | 577  | 1.15| 1.06  | 1.25  |
| Graves                      | Systemic lupus         | 859  | 1.19| 1.11  | 1.27  |
| Graves                      | Systemic lupus         | 40   | 1.40| 1.00  | 1.86  |

#### Table 3

| Subtypes of AID in offspring | Family history of AID |Obs. | SIR | 95% CI |
|-----------------------------|-----------------------|------|-----|--------|
| Hashimoto thyroiditis       | Addision disease      | 47   | 2.39| 1.75  | 3.12  |
| Hashimoto thyroiditis       | Addison disease       | 35   | 2.04| 1.42  | 2.77  |
| Hashimoto thyroiditis       | Autoimmune            | 16   | 2.11| 1.20  | 3.27  |
| Hashimoto thyroiditis       | Hemolytic anemia      | 242  | 1.39| 1.22  | 1.57  |
| Hashimoto thyroiditis       | Celiac disease        | 504  | 1.59| 1.46  | 1.74  |
| Hashimoto thyroiditis       | Chronic rheumatic     | 163  | 1.23| 1.05  | 1.43  |
| Hashimoto thyroiditis       | Heart disease         | 325  | 1.25| 1.12  | 1.39  |
| Hashimoto thyroiditis       | Crohn disease         | 348  | 1.24| 1.11  | 1.37  |
| Hashimoto thyroiditis       | Dermatitis             | 25   | 1.56| 1.01  | 2.22  |
| Hashimoto thyroiditis       | Dermatitis herpetiformis | 191 | 1.71| 1.47  | 1.96  |
| Hashimoto thyroiditis       | Diabetes mellitus type I | 431 | 1.65| 1.49  | 1.80  |
| Hashimoto thyroiditis       | Glomerular nephritis   | 126  | 1.19| 0.99  | 1.41  |
| Hashimoto thyroiditis       | Chronic               | 105  | 1.22| 1.00  | 1.46  |
| Hashimoto thyroiditis       | Graves                 | 760  | 1.97| 1.84  | 2.12  |
| Hashimoto thyroiditis       | Immune                | 87   | 1.29| 1.03  | 1.58  |
| Hashimoto thyroiditis       | Immune thrombocytopenic purpura | 95 | 1.25| 1.01  | 1.51  |
| Hashimoto thyroiditis       | Immunopurpura          | 14   | 2.05| 1.12  | 3.26  |
| Hashimoto thyroiditis       | Pernicious anemia      | 74   | 1.74| 1.37  | 2.16  |
| Hashimoto thyroiditis       | Polymyalgia rheumatica | 292 | 1.23| 1.10  | 1.38  |
| Hashimoto thyroiditis       | Rheumatoid arthritis   | 631  | 1.51| 1.39  | 1.63  |
| Hashimoto thyroiditis       | Sjogren syndrome      | 114  | 1.43| 1.18  | 1.70  |
| Hashimoto thyroiditis       | Systemic lupus         | 89   | 1.36| 1.09  | 1.66  |
| Hashimoto thyroiditis       | Sjogrensyndrome        | 74   | 1.49| 1.17  | 1.84  |
| Hashimoto thyroiditis       | Takayasu disease       | 6    | 2.57| 0.93  | 5.05  |
| Hashimoto thyroiditis       | Takayasu disease       | 5    | 2.57| 0.81  | 5.32  |
4. Discussion

This is the first comprehensive analysis of familial risks between thyroid AIDs and other AIDs, with the advantages that all family relationships were complete and accurate, cases were medically diagnosed, usually at the specialist level, and the scope was nation-wide, guaranteeing a large patient population of 769,991 and possibility to include even rare AIDs among the total of 43 [14,15]. In the 0 to 80 year offspring generation 6.1% were diagnosed with AID. Also including the parental generation, Graves disease accounted for 6.9% and Hashimoto thyroiditis for 5.3% of all AIDs. Among offspring with Graves disease, 6.1% of their parents and siblings were diagnosed with same disease while for Hashimoto thyroiditis the proportion was only 4.9%.

The concordant familial association of Hashimoto thyroiditis (4.75) exceeded that for Graves disease (3.85). Sibling risks were higher than risks between offspring and parents, which suggests that recessive genetic effects or shared childhood environmental effects may influence disease causation. Increased risks between spouses attested to the existence of environmental influence (see below). The very high risks in multiplex (parent and sibling affected) families imply the role for relatively high-penetrant genes. For both diseases male SIRs were higher than female ones although for Graves disease the sex difference was only of borderline significance. The phenomenon of a stronger familial effect in the gender of lower background incidence has resemblance to "the Carter effect", described for pyloric stenosis [16,17]. However, this was not observed for any of the discordant associations but these rarely show such a female excess in incidence comparable to thyroid AIDs. Compared to many other diseases, such as cancer and cardiovascular disease, for which the SIRs are typically 2.0, the present concordant familial risks of 4.75 and 3.85 are relatively high [18,19]. Spousal correlation for cancers is detectable essentially only for lung cancer [20]. Even with the detected correlation between spouses (see below) the results indicate to the overwhelming importance of germline genetics in explaining familial risk.

Considering the SIR of 3.85 for concordant associations for Graves disease it is quite remarkable that some of the highest discordant association reached SIRs over 2.0, including those with dermatitis herpetiformis (2.38), Addison disease (2.24) and Hashimoto thyroiditis (2.04). For Hashimoto thyroiditis, with a concordant association of 4.75, the discordant association where relatively lower than in Graves disease, i.e., Takayasu disease (2.57), Addison disease (2.39), autoimmune hemolytic anemia (2.11) and pemphigus (2.05). Notably, Addison disease was a highly significant partner for both thyroid AIDs.

Polyautoimmunity is a common feature of thyroid AIDs and the genetic basis of such pleiotropy is partially understood [1,4]. Genetic associations of low-penetrance loci are extensively shared between AIDs [8, 21–24]. In a study on pediatric AIDs over 70% of the significant genetic loci were shared by at least 3 AIDs [23]. The direction of allelic effects have been identical while opposite effects such as found in hematologic neoplasms have been rare [25]. The present data provide strong evidence towards similar directions in shared familial risks because only a single opposite association (Reiter disease) reached even a nominal significance in comparison of all 43 AIDs with each other. Why Reiter disease would show opposite associations is not known and chance is not possible to exclude. Reiter disease is also known as reactive arthritis, which presents as a triad of conjunctivitis, urethritis and arthritis occurring after an infection; it shows a high male excess [26]. For Graves disease, 24 discordant AIDs showed a significant association, and for many both of the bidirectional associations were significant. For Hashimoto thyroiditis, 20 discordant AIDs showed a significantly increased association, and also for many both of the bidirectional associations were significant. Overall 8 associations were significant only for Graves and 6 for Hashimoto thyroiditis.

We found significant spouse correlations for these diseases, almost 2.0 for Hashimoto thyroiditis and 1.50 for Graves disease, most likely pointing to environmental risk factors. We had no information on
multiple AIDs in the spousal pairs because the study was limited to the first incident AID in each individual. Autoimmune thyroid diseases are known to have many environmental triggers and contributing factors, including infections, dietary iodine, selenium and polyhalogenated environmental contaminants, which can interfere with thyroid function; spouses may also share dramatic psychosocial events [5,6,27]. Consanguinity would be an unlikely explanation of spousal sharing because the population is outbred. The result could be extrapolated to other European populations with approximately similar genetic constitution.

Limitations of the study include the relatively short follow-up time (2001–2012) of patients from the Outpatient Register; thus if they have been diagnosed earlier as outpatients and never visited a hospital again for thyroid AID they would have remained unidentified. Also if patients were treated only in primary care they were missed; however, diagnosticks of thyroid AID would almost invariably require a visit to a hospital.

In conclusion, the present study provided conclusive quantitative familial risk estimates for thyroid AIDs and other AIDs. Significant familial associations among more than half of the 43 AIDs attest to the extensive polyautoimmunity (1). The demonstrated spouse correlation in the familial risk indicated a role for the shared environmental risk factors. Nevertheless the overall high concordant familial risks for Graves disease and Hashimoto thyroiditis, particularly for multiplex families suggest a strong genetic contribution to the familial risk.

CRediT author statement
Hauke Thomsen: Methodology, Software, Formal analysis, Visualization, Writing - Reviewing and Editing. Xinjun Li: Software, Formal analysis. Kristina Sundquist: Data curation. Jan Sundquist: Data curation. H. Thomsen et al. Journal of Translational Autoimmunity 3 (2020) 100058

Declaration of competing interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement
The study was supported by the European Union’s Horizon 2020 research and innovation programme, grant No 856620.

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