Journal of Translational Autoimmunity 3 (2020) 100058

Contents lists available at ScienceDirect

Journal of Translational Autoimmunity

journal homepage: www.journals.elsevier.com/journal-of-translational-autoimmunity/

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

Hauke Thomsen [a,b,h,*,1], Xinjun Li [b,1], Kristina Sundquist [b], Jan Sundquist [b,c], Asta Försti [a,b,d,e], Kari Hemminki [a,b,f,g]

[a] Division of Molecular Genetic Epidemiology, German Cancer Research Centre (DKFZ), 69120, Heidelberg, Germany
[b] Center for Primary Health Care Research, Lund University, Malmö, Sweden
[c] Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, CA 94305-5705, USA
[d] Hopp Children's Cancer Center (KiTZ), Heidelberg, Germany
[e] Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK), Heidelberg, Germany
[f] Division of Cancer Epidemiology, German Cancer Research Centre (DKFZ), 69120, Heidelberg, Germany
[g] Faculty of Medicine and Biomedical Center in Pilsen, Charles University in Prague, 30605, Pilsen, Czech Republic
[h] GeneWerk GmbH, 69120, Heidelberg, Germany

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 extend 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 [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 [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 [1,3]. These diseases are associated with each other and many other AIDs presenting examples of polyautoimmunity [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 antigenes may be triggers of these

* Corresponding author. Division of Molecular Genetic Epidemiology, German Cancer Research Centre (DKFZ), 69120, Heidelberg, Germany.
E-mail address: hauke.thomsen@genewerk.de (H. Thomsen).
[1] Joint first authorship.

https://doi.org/10.1016/j.jtauto.2020.100058
Received 5 April 2020; Received in revised form 22 May 2020; Accepted 27 May 2020

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			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
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				Wives			
	O	SIR	95% CI		O	SIR	95% CI	
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**

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

diseases, as well as some dramatic psychosocial events [5,6]. Autoimmune thyroid diseases also appear as a side-effect of immunotherapy, which has recently become a promising novel therapeutic modality in the treatment of some cancers [7]. Multiple low-to-moderate-risk susceptibility genes for Graves influence effector pathways, such as thyroglobulin, thyrotropin receptor, protein tyrosine phosphatase nonreceptor type 22, and cytotoxic T-lymphocyte–associated antigen 4; the latter is also associated with Hashimoto thyroiditis [8,9]. Familial risk is known for both of these diseases, also between each other and a few other autoimmune diseases [10,11].

Here we provide a comprehensive follow-up study of familial risks for 29,005 patients with Graves disease and 25,607 with Hashimoto thyroiditis as the first diagnosed AID. A concordant familial risk (i.e. either Graves disease or Hashimoto thyroiditis in two or more family members) was calculated for both of these diseases and a discordant risk (i.e. Graves disease or Hashimoto thyroiditis patients had family members diagnosed with other AIDs) was calculated between these diseases and over 450,000 other medically diagnosed incident patients with 41 other AIDs. In addition to proband- and sex-specific familial risks we present also associations between spouses in order to provide estimates of the contribution of environmental sharing to the familial risk.

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 registers 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 ultrasound 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

Table 2
Discordant familial risks of Graves disease.

Subtypes of AID in offspring	Family history of AID	Obs.	SIR	95% CI	
Graves	Addison disease	53	2.24	1.68	2.88
Addison disease	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**
Dermatitis herpetiformis	Graves	**46**	**2.38**	**1.74**	**3.12**
Graves	Diabetes mellitus type I	**141**	**1.78**	**1.50**	**2.08**
Diabetes mellitus type I	Graves	**630**	**1.85**	**1.71**	**2.00**
Graves	Discoid lupus erythematosus	**50**	**1.52**	**1.13**	**1.97**
Graves	Hashimoto thyroiditis	**584**	**2.04**	**1.88**	**2.21**
Hashimoto thyroiditis	Graves	**760**	**1.97**	**1.84**	**2.12**
Graves	Lupoid hepatitis	**74**	**1.30**	**1.02**	**1.61**
Lupoid hepatitis	Graves	**68**	**1.27**	**0.98**	**1.59**
Graves	Myasthenia gravis	**57**	**1.52**	**1.15**	**1.95**
Myasthenia gravis	Graves	**47**	**1.57**	**1.15**	**2.05**
Graves	Pernicious anemia	**127**	**1.94**	**1.61**	**2.29**
Graves	Polymyalgia rheumatica	**395**	**1.12**	**1.01**	**1.23**
Graves	Polymyositis/ dermatomyositis	**42**	**1.58**	**1.14**	**2.10**
Polymyositis/ dermatomyositis	Graves	**32**	**1.47**	**1.00**	**2.02**
Graves	Primary biliary cirrhosis	**56**	**1.36**	**1.03**	**1.74**
Graves	Psoriasis	**1278**	**1.18**	**1.12**	**1.25**
Psoriasis	Graves	**1672**	**1.20**	**1.14**	**1.26**
Reiter disease	Graves	**29**	**1.58**	**1.06**	**2.21**
Graves	Rheumatic fever	**52**	**1.31**	**0.98**	**1.69**
Graves	Rheumatoid arthritis	**1517**	**1.37**	**1.30**	**1.44**
Rheumatoid arthritis	Graves	**883**	**1.28**	**1.19**	**1.36**
Graves	Sarcoidosis	**257**	**1.32**	**1.16**	**1.49**
Sarcoidosis	Graves	**278**	**1.25**	**1.11**	**1.40**
Graves	Sjögrensyndrome	**141**	**1.43**	**1.20**	**1.68**
Sjögrensyndrome	Graves	**109**	**1.24**	**1.02**	**1.48**
Graves	Systemic lupus erythematosus	**141**	**1.71**	**1.44**	**2.00**
Systemic lupus erythematosus	Graves	**120**	**1.50**	**1.24**	**1.78**
Graves	Systemic sclerosis	**57**	**1.66**	**1.26**	**2.12**
Systemic sclerosis	Graves	**36**	**1.38**	**0.97**	**1.87**
Graves	Ulcerative colitis	**577**	**1.15**	**1.06**	**1.25**
Ulcerative colitis	Graves	**859**	**1.19**	**1.11**	**1.27**
Graves	Wegener granulomatosis	**40**	**1.40**	**1.00**	**1.86**

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

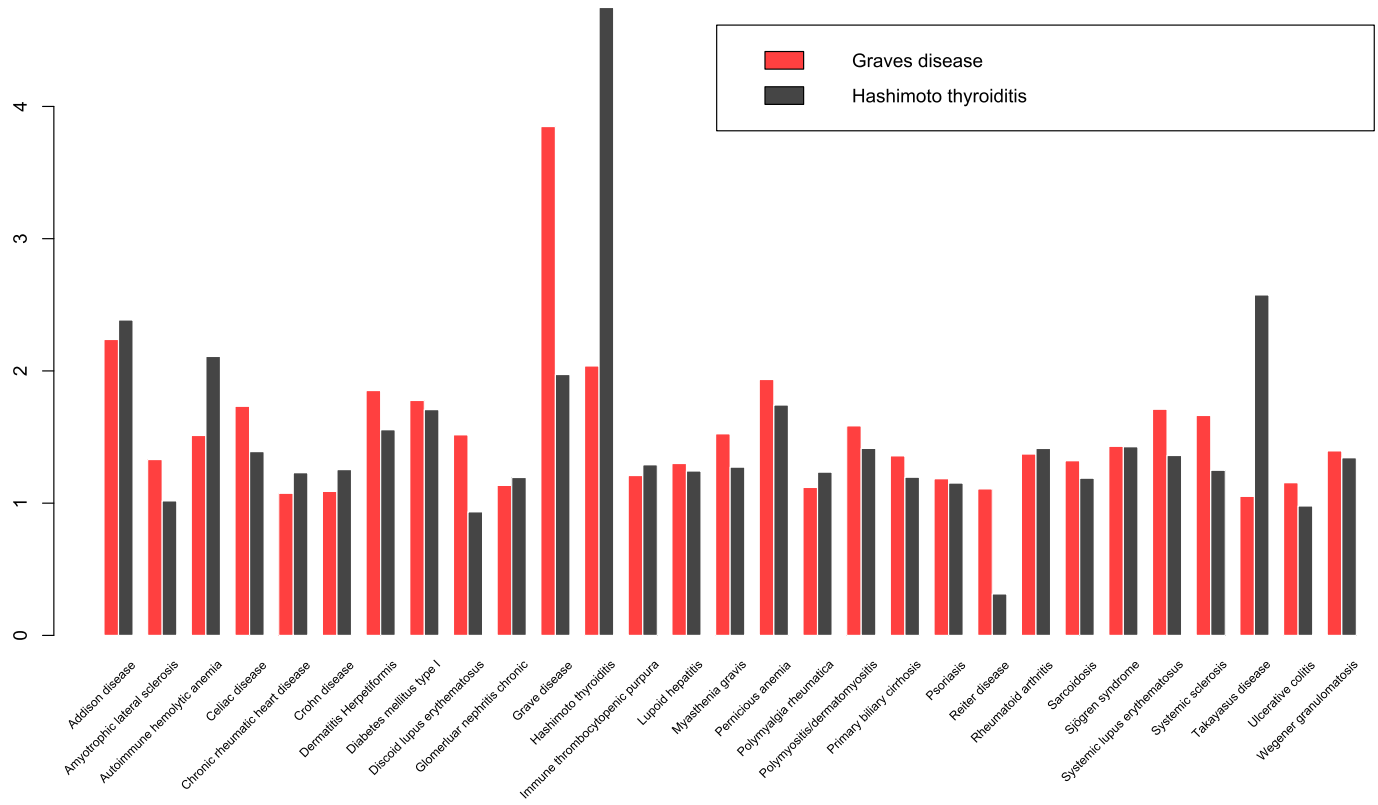
We analyzed familial risks between Graves disease and 42 other AIDs and significant discordant associations are shown in Table 2 shows; significant bidirectional association are also included. The partners with most discordant cases were psoriasis and rheumatoid arthritis. The partner with the highest 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 3
Discordant familial risks of Hashimoto thyroiditis.

Subtypes of AID in offspring	Family history of AID	Obs.	SIR	95% CI	
Hashimoto thyroiditis	Addison disease	**47**	**2.39**	**1.75**	**3.12**
Addison disease	Hashimoto thyroiditis	**35**	**2.04**	**1.42**	**2.77**
Hashimoto thyroiditis	Autoimmune hemolytic anemia	**16**	**2.11**	**1.20**	**3.27**
Hashimoto thyroiditis	Celiac disease	**242**	**1.39**	**1.22**	**1.57**
Celiac disease	Hashimoto thyroiditis	**504**	**1.59**	**1.46**	**1.74**
Hashimoto thyroiditis	Chronic rheumatic heart disease	**163**	**1.23**	**1.05**	**1.43**
Hashimoto thyroiditis	Crohn disease	**325**	**1.25**	**1.12**	**1.39**
Crohn disease	Hashimoto thyroiditis	**348**	**1.24**	**1.11**	**1.37**
Hashimoto thyroiditis	Dermatitis herpetiformis	**25**	**1.56**	**1.01**	**2.22**
Hashimoto thyroiditis	Diabetes mellitus type I	**191**	**1.71**	**1.47**	**1.96**
Diabetes mellitus type I	Hashimoto thyroiditis	**431**	**1.65**	**1.49**	**1.80**
Hashimoto thyroiditis	Glomerular nephritis chronic	**126**	**1.19**	**0.99**	**1.41**
Glomerular nephritis chronic	Hashimoto thyroiditis	**105**	**1.22**	**1.00**	**1.46**
Hashimoto thyroiditis	Graves	**760**	**1.97**	**1.84**	**2.12**
Hashimoto thyroiditis	Immune thrombocytopenic purpura	**87**	**1.29**	**1.03**	**1.58**
Immune thrombocytopenic purpura	Hashimoto thyroiditis	**95**	**1.25**	**1.01**	**1.51**
Pemphigus	Hashimoto thyroiditis	**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**
Primary biliary cirrhosis	Hashimoto thyroiditis	**25**	**1.63**	**1.05**	**2.33**
Hashimoto thyroiditis	Psoriasis	**1075**	**1.15**	**1.08**	**1.22**
Psoriasis	Hashimoto thyroiditis	**1078**	**1.22**	**1.15**	**1.29**
Hashimoto thyroiditis	Reiter disease	**4**	**0.31**	**0.08**	**0.70**
Hashimoto thyroiditis	Rheumatoid arthritis	**1148**	**1.41**	**1.33**	**1.50**
Rheumatoid arthritis	Hashimoto thyroiditis	**631**	**1.51**	**1.39**	**1.63**
Hashimoto thyroiditis	Sarcoidosis	**191**	**1.19**	**1.03**	**1.36**
Hashimoto thyroiditis	Sjögren syndrome	**114**	**1.43**	**1.18**	**1.70**
Hashimoto thyroiditis	Systemic lupus erythematosus	**89**	**1.36**	**1.09**	**1.66**
Systemic lupus erythematosus	Hashimoto thyroiditis	**74**	**1.49**	**1.17**	**1.84**
Hashimoto thyroiditis	Takayasu disease	**6**	**2.57**	**0.93**	**5.05**
Takayasu disease	Hashimoto thyroiditis	**5**	**2.57**	**0.81**	**5.32**

Table 3 shows the significant discordant bidirectional associations for Hashimoto thyroiditis. The partner with the highest risk was Takayasu disease (2.57), followed by Addison disease (2.39), autoimmune hemolytic anemia (2.11) and pemphigus (2.05). The association Hashimoto-Reiter disease was significantly decreased (0.31) as the only negative association found. Overall, 20 discordant AIDs showed a significantly increased association, and also for many both of the bidirectional associations were significant.

Significant associations for Graves disease and Hashimoto thyroiditis with concordant and discordant AIDs are shown in Fig. 1. The comparison of Tables 2 and 3 reveals that 8 associations were significant only for Graves, including amyotrophic lateral sclerosis, discoid lupus erythematosus, lupoid hepatitis, myasthenia gravis, polymyositis/dermatomyositis, systemic sclerosis, ulcerative colitis and Wegener granulomatosis. Similarly 6 discordant association were significant only for Hashimoto thyroiditis, including autoimmune hemolytic anemia, chronic rheumatic heart disease, glomerular nephritis chronic, immune thrombocytopenic purpura, pemphigus and Takayasu disease. Reiter disease showed a significant opposite association, positive with Graves disease and negative with Hashimoto thyroiditis. No significant sex differences were observed.



Fig, 1. Significant familial associations for Graves disease and Hashimoto thyroiditis with concordant and discordant autoimmune diseases. The SIR were calculated to Graves disease or Hashimoto thyroiditis. Discordant associations are shown for both when at least one is significant. P-values are shown on top of the bars.

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 polyhalogenatated 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, diagnostics of thyroid AID would almost invariable 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. This is consistent with a recent review on thyroid AIDs referring them to 'tallest tree in the forest of 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. Asta Försti: Conceptualization, Writing - Reviewing and Editing. Kari Hemminki: Conceptualization, Writing - original draft.

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.

References

[1] S. Bliddal, C.H. Nielsen, U. Feldt-Rasmussen, Recent advances in understanding autoimmune thyroid disease: the tallest tree in the forest of polyautoimmunity, F1000Res 6 (2017) 1776.
[2] A. Antonelli, P. Fallahi, G. Elia, F. Ragusa, S.R. Paparo, I. Ruffilli, et al., Graves' disease: clinical manifestations, immune pathogenesis (cytokines and chemokines) and therapy, Best Pract. Res. Clin. Endocrinol. Metabol. (2020) 101388.
[3] F. Ragusa, P. Fallahi, G. Elia, D. Gonnella, S.R. Paparo, C. Giusti, et al., Hashimotos' thyroiditis: epidemiology, pathogenesis, clinic and therapy, Best Pract. Res. Clin. Endocrinol. Metabol. (2019) 101367.
[4] P. Fallahi, G. Elia, F. Ragusa, I. Ruffilli, S. Camastra, C. Giusti, et al., The aggregation between AITD with rheumatologic, or dermatologic, autoimmune diseases, Best Pract. Res. Clin. Endocrinol. Metabol. (2019) 101372.
[5] S.K. Shukla, G. Singh, S. Ahmad, P. Pant, Infections, genetic and environmental factors in pathogenesis of autoimmune thyroid diseases, Microb. Pathog. 116 (2018) 279–288.
[6] J. Luty, K. Ruckemann-Dziurdzinska, J.M. Witkowski, E. Bryl, Immunological aspects of autoimmune thyroid disease - complex interplay between cells and cytokines, Cytokine 116 (2019) 128–133.
[7] M. Dougan, M. Pietropaolo, Time to dissect the autoimmune etiology of cancer antibody immunotherapy, J. Clin. Invest. 130 (2020) 51–61.
[8] Y. Hwangbo, Y.J. Park, Genome-wide association studies of autoimmune thyroid diseases, thyroid function, and thyroid cancer, Endocrinol. Metab. (Seoul) 33 (2018) 175–184.
[9] D. Vejrazkova, J. Vcelak, E. Vaclavikova, M. Vankova, K. Zajickova, M. Duskova, et al., Genetic predictors of the development and recurrence of Graves' disease, Physiol. Res. 67 (2018). S431-s9.
[10] K. Hemminki, X. Li, J. Sundquist, K. Sundquist, The epidemiology of Graves' disease: evidence of a genetic and an environmental contribution, J. Autoimmun. 34 (2010) J307–J313.
[11] M. Dittmar, C. Libich, T. Brenzel, G.J. Kahaly, Increased familial clustering of autoimmune thyroid diseases, Hormone Metab. Res. = Hormon- und Stoffwechselforschung = Hormones et metabolisme 43 (2011) 200–204.
[12] K. Hemminki, A. Forsti, K. Sundquist, J. Sundquist, X. Li, Familial associations of monoclonal gammopathy of unknown significance with autoimmune diseases, Leukemia 30 (2016) 1766–1769.
[13] K. Hemminki, J. Ji, A. Brandt, S.M. Mousavi, J. Sundquist, The Swedish Family-Cancer Database 2009: prospects for histology-specific and immigrant studies, Int. J. Canc. 126 (2010) 2259–2267.
[14] M. Abraham-Nordling, K. Byström, O. Törring, M. Lantz, G. Berg, J. Calissendorff, et al., Incidence of hyperthyroidism in Sweden, Eur. J. Endocrinol. 165 (2011) 899–905.
[15] J.F. Ludvigsson, E. Andersson, A. Ekbom, M. Feychting, J.L. Kim, C. Reuterwall, et al., External review and validation of the Swedish national inpatient register, BMC Publ. Health 11 (2011) 450.
[16] C. Carter, The inheritance of congenital pyloric stenosis, Br. Med. Bull. 17 (1961) 251–254.
[17] F. Vogel, A. Motulsky, Human Genetics: Problems and Approaches, Springer, Heidelberg, 1996.
[18] C. Frank, M. Fallah, J. Sundquist, A. Hemminki, K. Hemminki, Population landscape of familial cancer, Sci. Rep. 5 (2015) 12891.
[19] K. Hemminki, X. Li, K. Sundquist, J. Sundquist, Familial risks for common diseases: etiologic clues and guidance to gene identification Mutat, Res. Rev. 658 (2008) 247–258.
[20] M. Weires, J.L. Bermejo, J. Sundquist, K. Hemminki, Clustering of concordant and discordant cancer types in Swedish couples is rare, Eur. J. Canc. 47 (2011) 98–106.
[21] J.H. Cho, P.K. Gregersen, Genomics and the multifactorial nature of human autoimmune disease, N. Engl. J. Med. 365 (2011) 1612–1623.
[22] P.S. Ramos, L.A. Criswell, K.L. Moser, M.E. Comeau, A.H. Williams, N.M. Pajewski, et al., A comprehensive analysis of shared loci between systemic lupus erythematosus (SLE) and sixteen autoimmune diseases reveals limited genetic overlap, PLoS Genet. 7 (2011), e1002406.
[23] Y.R. Li, J. Li, S.D. Zhao, J.P. Bradfield, F.D. Mentch, S.M. Maggadottir, et al., Meta-analysis of shared genetic architecture across ten pediatric autoimmune diseases, Nat. Med. 21 (2015) 1018–1027.
[24] S.M. Tajuddin, U.M. Schick, J.D. Eicher, N. Chami, A. Giri, J.A. Brody, et al., Large-scale exome-wide association analysis identifies loci for white blood cell traits and pleiotropy with immune-mediated diseases, Am. J. Hum. Genet. 99 (2016) 22–39.
[25] P.J. Law, A. Sud, J.S. Mitchell, M. Henrion, G. Orlando, O. Lenive, et al., Genome-wide association analysis of chronic lymphocytic leukaemia, Hodgkin lymphoma and multiple myeloma identifies pleiotropic risk loci, Sci. Rep. 7 (2017) 41071.
[26] I.B. Wu, R.A. Schwartz, Reiter's syndrome: the classic triad and more, J. Am. Acad. Dermatol. 59 (2008) 113–121.
[27] G.A. Brent, Environmental exposures and autoimmune thyroid disease, Thyroid 20 (2010) 755–761.