FAMILIAL ASSOCIATIONS FOR RHEUMATOID AUTOIMMUNE DISEASES

Hauke Thomsen1,2,8, Xinjun Li2, Kristina Sundquist2, Jan Sundquist2,3, Asta Försti1,2,4,5, Kari Hemminki1,2,6,7

1Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany;
2Center for Primary Health Care Research, Lund University, Malmö, Sweden;
3Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, CA, USA
4Hopp Children's Cancer Center (KiTZ), German Cancer Research Center (DKFZ), Heidelberg, Germany
5Division of Pediatric Neurooncology, German Cancer Consortium (DKTK), Heidelberg, Germany
6Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany;
7Faculty of Medicine and Biomedical Center in Pilsen, Charles University in Prague, Pilsen, Czech Republic
8Bioinformatics and Biostatistics Working Section, GeneWerk GmbH, 69120 Heidelberg, Germany

Correspondence to: Hauke Thomsen,
GeneWerk GmbH, Im Neuenheimer Feld 582, D-69120 Heidelberg, Germany
Email: hauke.thomsen@genewerk.de

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Running title: Thyroid autoimmune disease
ABSTRACT

Objectives: Previous studies have shown a familial component in rheumatoid arthritis (RA) and in some other rheumatic autoimmune diseases (RAIDs) but because of various study designs the risk estimates for familial risks differ extensively.

Methods: We collected data on patients diagnosed in Swedish hospitals with RA, ankylosing spondylitis (AS), polymyositis/dermatomyositis (PM/DM), Sjogren syndrome (SS), systemic lupus erythematosus (SLE) and systemic sclerosis (Sys, scleroderma) and calculated familial standardized incidence ratios (SIRs) for each of these (concordant) and between them (discordant).

Results: The combined number of RAID patients in the offspring population (for whom SIRs were calculated) was 71,544 and in the whole population the number was 152,714, accounting for 19.8% of all AIDs in Sweden. AS showed the highest concordant familial risk of 18.42, followed by SLE (14.04), SS (8.63), Sys (4.50), PM/DM (4.03) and RA (3.03). There were no sex difference in SIRs. Risks for AS and SLE were 80.28 and 19.53 for persons whose parents and siblings were affected. Discordant risks were far lower than concordant risks but they were significant for RA with all other 5 RAIDs, for SLE and Sys with 4 RAIDs, for AS and SS with 3 RAIDs and for PM/DM with 2 RAIDs, attesting to extensive polyautoimmunity between RAIDs.

Conclusions: The derived familial risks in this nation-wide family study on medically diagnosed RAID are compatible with emerging evidence on the polygenic background of these complex diseases. Novel genetic pathways offer new therapeutic targets that optimally alleviate disease onset in high-risk familial patients and others.

Key messages:

Rheumatoid autoimmune disease patients accounted for 13.8% of all autoimmune diseases in the offspring population.

Concordant familial risks for rheumatoid autoimmune diseases were always clearly higher than the discordant risks.

The result showed extensive familial polyautoimmunity between the rheumatoid autoimmune diseases
INTRODUCTION

Rheumatic autoimmune diseases (RAID) include conditions such as ankylosing spondylitis (AS), polymyositis/dermatomyositis (PM/DM), rheumatoid arthritis (RA), Sjogren syndrome (SS), systemic lupus erythematosus (SLE) and systemic sclerosis (SyS, scleroderma). In industrialized countries their prevalence ranges from the most common one, RA of 1% to the rare ones of PM/DM and SS of some 0.02% (1-4). Most of them, and particularly SLE and SS, are more common in women compared to men, but SyS has no large sex difference and AS is more common in men. In autoimmune diseases (AIDs) dysregulated lymphocytes react against self-antigens by producing autoantibodies and suppressing the normal immune function (5). In RAIDs the misdirected inflammation affects connective tissue, with a preference of spine in AS, skin and muscle in DM/PM, joints in RA, joints and internal organs in SLE, salivary and lacrimal glands in SS and skin and internal organs in SyS (6-8). Diagnosis is based on clinical assessment, supported by investigations, including the finding of autoantibodies in RAIDs, (except for AS lacking autoantibodies). Treatments include a wide and expanding range of pharmacological modalities including anti-inflammatory, cytotoxic, immunomodulating and immunosuppressive agents and B cell-targeted therapies (9-11). Family and twin studies have shown that genetic risk factors contribute to the etiology of RA and some other RAIDs (1, 2, 5, 12-17).

Familial AIDs have been extensively studied using a number of different designed with vastly differing results. A review published in 2013 surveyed the literature on 5 common AIDs, including RA and SLE, and summarized the results of 44 studies. The review concluded: “Thus, further studies of familial autoimmunity will help in increasing the knowledge about the common mechanisms of autoimmunity” (13). Following such recommendations, we used the Swedish medical records on the 6 RAIDs and calculate familial risks for each of these (concordant) and between them (discordant). Data are presented as proband- and sex-specific familial risks.

METHODS

SAID 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) with any diagnostic codes for SAIDs. 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. If a patient was treated only in the primary care, they were missed from the analysis. However, in view of diagnostic verification and treatment planning, such cases were probably very few (see the first paragraph of Discussion). Various revisions of the International Classification of Diseases (ICD) codes were used for AIDs as described elsewhere (18). Family relationships were obtained from the Multigeneration Register, containing the Swedish population in families and spanning more than a century (19). 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. For the family history, a register-based definition was used without consideration of the timing of the diagnoses among family members as it was shown to be preferable in terms of case numbers (20). 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. The study was approved by the Ethical Committee of Lund University.
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 (i.e., essentially for the whole Swedish population), and the rates were standardized by 5-year-age, gender, period (5 years group), socioeconomic status and residential area. The follow-up was started in year 1964 and continued through year 2012. 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 SAID. In analysis of discordant SAIDs bidirectional (i.e., RA-AS and AS-RA) associations were considered.

RESULTS

The number of RAID patients in the offspring generation (to whom risks were calculated) was 46,256 with a mean diagnostic age (i.e., first hospital contact) of 48.2 years; considering also their parents the total number was 112,958 (Table 1). PM/DM presented the smallest number of patients 1384 in the offspring generation and 2668 including the parental generation. Among the offspring patients, AS and SLE were the youngest patients (28.5 and 39.4 years) and SS patents were the oldest (53.5 years). The total AID population amounted to 519,180 patients in the offspring generation of 8.5 million. Thus RA accounted for 8.9% of all AIDs and was diagnosed in 0.54% of the offspring population. Jointly RAID patients numbered 71,544 in the offspring population and 152,714 in the whole population, accounting for 13.8% and 19.8% of all AIDs, respectively.

Concordant familial risks

Familial risks for the RAIDs are shown in Table 2 for offspring whose first-degree relatives (parents or siblings as probands) were diagnosed with concordant RAID. The SIRs differed widely. AS showed the highest risks, 16.12 when parents, 16.57 when siblings, and 80.28 when parents and siblings were probands. Next in rank was SLE, with the respective SIRs of 13.30, 13.55 and 19.53. For RA the risks were 2.64, 2.89 and 7.17. For PM/DM only the sibling risk of 7.39 was significant. None of the SIRs between parents-offspring and siblings were significant (i.e., the 95%CI s overlapped).

Sex specific familial risks are shown in Table 3 using any first-degree relatives as probands. The ranking order from Table 2, led by AS with familial risk of 18.42, and followed by SLE (14.04), SS (8.63), SyS (4.50), PM/DM (4.03) and RA (3.03). There was no single sex difference in SIR s. For RA the male and female SIRs differed only marginally (2.93 vs 3.07). For SS and SLE with a large female excess of cases, female risk was slightly higher for SS (8.96 vs 5.57) but male risk was slightly higher in SLE (15.39 vs 13.83).

We calculated also risk between spouses but the case number were low for RAIDs other than RA. For RA, the SIR was 1.16 (N=593, 95%CI 1.07-1.26).

Discordant familial risks

We analyzed familial risks between the 5 discordant RAIDs in Table 4. RA was associated with all other 5 RAIDs, SIRs ranging from 1.35 to 2.08. SLE and SyS associated with 4 RAIDs each; SIRs ranged from 1.80 to 3.61 for SLE and from 1.75 to 2.71 for SyS. AS and SS associated with 3 RAIDs each; SIRs ranged from 1.58 to 1.69 for AS and from 1.78 to 2.83 for SS. PM/DM associated with RA (1.35) and SLE (2.28).

We analyzed also sex-specific discordant associations but as none of these were significant results are not shown.
Summarizing concordant and discordant associations

Significant associations for the 6 RAIDs are shown in Fig. 1. The concordant risk of AS is prominent, compared to its modest discordant risks. This is in contrast to RA and SyS with smaller differences between concordant and discordant risks. RA was the significant proband partner with the 5 other RAIDs; i.e., the SIR were reciprocally increased with RA and other RAIDs. Disregarding associations of RA, AS was only associated with SyS and PM/DM only with SLE; SS, SLE and SyS we all reciprocally associated.

DISCUSSION

Incidence data for common diseases are liable to biases depending on the source of data origin (hospital, hospital discharge or insurance data etc), diagnostic criteria and level of reporting (21). Family studies are adding another level of complexity, because family histories are usually obtained anecdotally by interview; reporting accuracies even for relatively well defined diseases, such as cancer, show high variability, let alone for diseases, such as AID, where diagnostic criteria (such as ICD codes) have changed over time (22-24). In the Swedish Multigeneration Register the national family relationships are unbiased and complete (19). The advantages of using relatively recent national hospital discharge and outpatient data include high diagnostic accuracy (21). As hospitalizations in Sweden normally require a doctor’s pass from the primary care, thus each patient is seen at least by two medical doctors, of whom the one in the hospital is likely to be a specialist (2). An ad hoc study on close to 1000 hospitalized RA patients found that some 90% of the patients fulfilled the RA criteria of the American College of Rheumatology (25).

To emphasize the above point about fallacies in family data on AID, some examples can be taken from the review of five common AIDs by Cardenas-Roldan and coworkers (13). They list three US studies reporting familial risks on concordant RA (the results are given as a relative risk, incidence among first-degree family members compared to population incidence): 2.0, 7.8 and 18.7. Our SIR was 3.03. Two studies reported risks of SLE in RA families: 64 and 28; our SIR was 2.08. Two studies reported risks of RA in SLE families: 390 and 225; our SIR was 1.80. We have no possibility to explain such high reported familial risks, but high risks would be compatible with Mendelian genetic background, characterized by high-penetrant genes causing disease in every generation. In contrast, RAIDs are typically non-Mendelian complex diseases on a polygenic background (26). A polygenic background would imply that the frequencies of risk alleles is widely distributed in the population which has been used to calculate polygenic risk scores based on the number of risk alleles (27). The high overall risk for AS and SLE may imply particularly strong polygenic influence with more than 100 known genes, and in AS by the HLA allele B27 and its subtypes and in SLE non-HLA genes (28, 29).

Polygenic models predict that families with many risk alleles show a high familial risk which was commensurate with the results in families where both a parent and a sibling were affected (SIR 80.28 in AS and 7.17 in RA). Complex diseases also have environmental risk factors, for which we showed evidence through spouse correlation in RA. The SIR was however modest of 1.16, and for the other RAIDs spousal case numbers were small for reliable risk estimation. Considering the large sex differences in the incidence of some RAIDs, it was surprising that no single familial risk showed sex-specific difference.

Polyautoimmunity is a common feature of many AIDs, and particularly among rheumatoid and thyroid AIDs (30, 31). The present results attest to shared familial risks between RAIDs, as RA was associated with all other RAIDs, and SLE and SyS were associate with 4/5 discordant RAIDs. Genetic basis of such pleiotropy is partially understood through extensively shared low-risk genes (32-36). A recent genome-wide meta-analysis of autoantibody positive RAIDs (i.e., all others of the present study but
AS) revealed 26 independent non-hla significantly associated genetic risk loci (37). Extensive genetic sharing was evident in that 85% of the associated variants were shared by at least three diseases. Many of the shared loci were related with immune processes such as interferon signaling and B- and T-cell related immune functions, offering possible therapeutic targets (37). Some studies have pointed out greater sharing of risk loci among the autoantibody positive or among seronegative diseases than between these two groups (26, 38). In line with this paradigm, AS had only three modest discordant associations (ranging from 1.45 to 1.69) although its concordant risk of 18.42 was the highest observed; our study included only AS as an autoantibody negative disease.

The strengths of the study were overall large numbers of patients diagnosed in a standard way in a high-level health care system accessible to the population at large without economic barriers. Limitations include low patients numbers for rare RAIDs and the relatively short follow-up time (2001-2012) of patients from the Outpatient Register. We had no primary care data, which however guaranteed a defined level of diagnostic accuracy, provided by the specialist wards.

In summary, the present study showed that RAID patients accounted for 13.8% all AIDs in the offspring population and 19.8% the whole population. RA alone accounted for 8.9% of all AIDs the offspring population and it was diagnosed in 0.54% of this population. The results provided conclusive quantitative familial risk estimates for and between RAIDs. Concordant familial risks were high for all RAIDs, but particularly for AS and SLE. The discovery of multiple genetic pathways underlying these diseases has pointed out novel therapeutic targets which may help disease intervention in family members at an early stage. The result showed extensive familial polyautoimmunity between these diseases but also specificity in that the concordant familial risks were always clearly higher than the discordant ones.

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DISCLOSURE STATEMENT:
The authors have declared no conflicts of interest.

LEGEND TO FIGURE

Fig. 1. Familial associations of concordant and discordant RAIDs. Statistically significant associations are shown by star. P-values are shown by stars on top of the bars.
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Table 1. Number of cases of autoimmune diseases in offspring (N=8517416) and in the total population, 1964-2012

| Subtype                                | No. of events in the study population | No. of events in total of population | % males |
|----------------------------------------|---------------------------------------|--------------------------------------|---------|
|                                        | No.  | %     | Mean age | No.   |         |          |
| Total                                  | 519180 | 38.8 ± 19.5 | 769991 | 40.2 |
| Ankylosing spondylitis                 | 11226 | 2.2  | 39.6 ± 13.7 | 15097 | 65.6 |
| Polymyositis/dermatomyositis           | 1384  | 0.3   | 44.6 ± 20.9 | 2668  | 46.3 |
| Rheumatoid arthritis                   | 46256 | 8.9   | 48.2 ± 17.0 | 112958 | 29.5 |
| Sjögren syndrome                       | 5754  | 1.1   | 53.5 ± 13.1 | 8971  | 9.3  |
| Systemic lupus erythematosus           | 5201  | 1.0   | 39.4 ± 15.8 | 9566  | 16.1 |
| Systemic sclerosis                     | 1723  | 0.3   | 47.3 ± 16.5 | 3454  | 21.4 |
### Table 2. Familial risks of concordant autoimmune diseases

|                      | Parents only |          |          | Sibling only |          |          | Both parent and sibling |          |          |
|----------------------|--------------|----------|----------|--------------|----------|----------|-------------------------|----------|----------|
|                      | O  | SIR  | 95% CI  | O  | SIR  | 95% CI  | O  | SIR  | 95% CI  |
| Ankylosing spondylitis| 371 | 16.12 | 14.52 | 17.84 | 509 | 16.57 | 15.17 | 18.08 | 53 | 80.28 | 60.12 | 105.06 |
| Polymyositis/dermatomyositis | 1  | 1.35 | 0.00 | 7.72 | 4  | 7.39 | 1.92 | 19.11 | 0  |      |      |      |
| Rheumatoid arthritis  | 3163 | 2.64  | 2.55  | 2.73 | 1945 | 2.86  | 2.74  | 3.00 | 297 | 7.17  | 6.38  | 8.04  |
| Sjögren syndrome      | 68  | 8.01  | 6.22  | 10.16 | 107 | 9.41  | 7.71  | 11.37 | 2  | 24.69 | 2.33  | 90.81 |
| Systemic lupus erythematosus | 118 | 13.30 | 11.01 | 15.93 | 94  | 13.55 | 10.95 | 16.58 | 2  | 19.53 | 1.84  | 71.83 |
| Systemic sclerosis    | 5   | 4.28  | 1.35  | 10.06 | 4   | 3.92  | 1.02  | 10.13 | 0  |      |      |      |

Bold type: 95% CI does not include 1.00.

O = observed number of cases; SIR = standardized incidence ratio; CI = confidence interval
| AID                          | Both Genders | Men | Women |       |       |
|-----------------------------|--------------|-----|-------|-------|-------|
|                             | SIR          | Obs | P     | SIR   | Obs   | P     | SIR  | Obs   | P     |
| Ankylosing spondylitis      | 18.42        | 868 | 17.21 | 19.66 | 0.00  | 17.47 | 543  | 16.03 | 18.97 | 0.00  |
| Polymyositis/dermatomyositis| 4.03         | 5   | 1.27  | 8.35  | 0.00  | 5.77  | 3    | 1.09  | 14.15 | 0.01  |
| Rheumatoid arthritis        | 3.03         | 5418| 2.95  | 3.11  | 0.00  | 2.94  | 1611| 2.80  | 3.08  | 0.00  |
| Sjögren syndrome            | 8.63         | 158 | 7.34  | 10.03 | 0.00  | 5.57  | 10   | 2.65  | 9.55  | 0.00  |
| Systemic lupus              | 14.04        | 204 | 12.18 | 16.03 | 0.00  | 15.30 | 32   | 10.46 | 21.07 | 0.00  |
| Systemic sclerosis          | 4.50         | 9   | 2.04  | 7.91  | 0.00  | 2.22  | 1    | 0.00  | 8.70  | 0.75  |

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### Table 4: Familial risks for discordant rheumatoid AID

| Subtypes of AID in offspring | Family history of AID                      | SIR  | Obs. | 95% CI   | P     |
|------------------------------|-------------------------------------------|------|------|----------|-------|
| Ankylosing spondylitis       | Polymyositis/dermatomyositis              | 1.45 | 14   | 0.79     | 2.31  | 0.17 |
| Ankylosing spondylitis       | Rheumatoid arthritis                      | 1.61 | 638  | 1.48     | 1.73  | 0.00 |
| Ankylosing spondylitis       | Sjögren syndrome                          | 1.58 | 57   | 1.19     | 2.01  | 0.00 |
| Ankylosing spondylitis       | Systemic lupus erythematosus              | 1.35 | 41   | 0.97     | 1.79  | 0.06 |
| Ankylosing spondylitis       | Systemic sclerosis                         | 1.69 | 21   | 1.05     | 2.50  | 0.02 |
| Polymyositis/dermatomyositis| Ankylosing spondylitis                    | 1.05 | 6    | 0.38     | 2.05  | 0.92 |
| Polymyositis/dermatomyositis| Rheumatoid arthritis                      | 1.35 | 73   | 1.06     | 1.68  | 0.01 |
| Polymyositis/dermatomyositis| Sjögren syndrome                          | 0.67 | 3    | 0.13     | 1.65  | 0.55 |
| Polymyositis/dermatomyositis| Systemic lupus erythematosus              | 2.28 | 9    | 1.03     | 4.00  | 0.02 |
| Polymyositis/dermatomyositis| Systemic sclerosis                         | 1.26 | 2    | 0.12     | 3.60  | 0.80 |
| Rheumatoid arthritis         | Ankylosing spondylitis                    | 1.92 | 340  | 1.72     | 2.13  | 0.00 |
| Rheumatoid arthritis         | Polymyositis/dermatomyositis              | 1.47 | 60   | 1.12     | 1.87  | 0.00 |
| Rheumatoid arthritis         | Sjögren syndrome                          | 1.69 | 243  | 1.49     | 1.91  | 0.00 |
| Rheumatoid arthritis         | Systemic lupus erythematosus              | 2.08 | 264  | 1.83     | 2.33  | 0.00 |
| Rheumatoid arthritis         | Systemic sclerosis                         | 1.35 | 71   | 1.06     | 1.68  | 0.01 |
| Sjögren syndrome             | Ankylosing spondylitis                    | 1.38 | 31   | 0.94     | 1.91  | 0.07 |
| Sjögren syndrome             | Polymyositis/dermatomyositis              | 0.94 | 5    | 0.30     | 1.94  | 0.90 |
| Sjögren syndrome             | Rheumatoid arthritis                      | 1.78 | 409  | 1.61     | 1.95  | 0.00 |
| Sjögren syndrome             | Systemic lupus erythematosus              | 2.83 | 46   | 2.07     | 3.71  | 0.00 |
| Sjögren syndrome             | Systemic sclerosis                         | 2.20 | 15   | 1.23     | 3.46  | 0.00 |
| Systemic lupus erythematosus| Ankylosing spondylitis                    | 1.26 | 28   | 0.84     | 1.77  | 0.23 |
| Systemic lupus erythematosus| Polymyositis/dermatomyositis              | 2.42 | 11   | 1.20     | 4.06  | 0.00 |
| Systemic lupus erythematosus| Rheumatoid arthritis                      | 1.80 | 346  | 1.62     | 2.00  | 0.00 |
| Systemic lupus erythematosus| Sjögren syndrome                          | 3.61 | 61   | 2.76     | 4.58  | 0.00 |
| Systemic lupus erythematosus| Systemic sclerosis                         | 3.39 | 20   | 2.07     | 5.04  | 0.00 |
| Systemic sclerosis            | Ankylosing spondylitis                    | 2.22 | 15   | 1.24     | 3.49  | 0.00 |
| Systemic sclerosis            | Polymyositis/dermatomyositis              | 1.30 | 2    | 0.12     | 3.73  | 0.77 |
| Systemic sclerosis            | Rheumatoid arthritis                      | 1.75 | 117  | 1.45     | 2.08  | 0.00 |
| Systemic sclerosis            | Sjögren syndrome                          | 2.60 | 14   | 1.42     | 4.14  | 0.00 |
| Systemic sclerosis            | Systemic lupus erythematosus              | 2.71 | 13   | 1.44     | 4.38  | 0.00 |
