

Familial Associations of Rheumatoid Arthritis With Autoimmune Diseases and Related Conditions

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Objective. In the era of genome-wide association studies, familial risks are used to estimate disease heritability and the likelihood of candidate-gene identification. This study was undertaken to estimate associations of rheumatoid arthritis (RA) with any of 33 autoimmune diseases and related conditions among parents and offspring, singleton siblings, twins, and spouses.

Methods. The Multigeneration Register in Sweden was used as a reliable source of information on Swedish families throughout the last century. Data on autoimmune diseases in individual family members were obtained through linkage to the Hospital Discharge Register. The standardized incidence ratio (SIR) was calculated as a measure of the relative risk of RA in family members of patients with RA or any of 33 other autoimmune diseases or related conditions, as compared with the relative risk of RA in those lacking an affected family member.

Results. Among a total of 447,704 patients, 47,361 were diagnosed as having RA. The SIRs for RA were 3.02 in offspring of affected parents, 4.64 in siblings, 9.31 in multiplex families, 6.48 in twins, and 1.17 in spouses. Significant associations with the familial risk of RA in offspring according to parental proband were observed for ankylosing spondylitis (SIR 2.96), localized scleroderma (SIR 2.40), Sjögren's syndrome (SIR 2.25), systemic lupus erythematosus (SIR 2.13), systemic sclerosis (SIR 1.65), Hashimoto thyroiditis/hypothyroidism

(SIR 1.54), pernicious anemia (SIR 1.53), sarcoidosis (SIR 1.40), psoriasis (SIR 1.36), Wegener's granulomatosis (SIR 1.34), and asthma or polymyalgia rheumatica (SIR 1.32).

Conclusion. This is the first study to compare the familial risks of RA in relation to a large number of autoimmune diseases and related conditions using data from a single population. The high discordant familial risks in this population suggest that there is extensive genetic sharing between RA and the associated diseases.

Rheumatoid arthritis (RA) is a common autoimmune disease with an estimated population prevalence of 1% (1). In autoimmune diseases, dysregulated lymphocytes react against self antigens by producing autoantibodies and suppressing normal immune function; the synovial joints of RA patients are particularly affected (1,2). Studies on twins have shown a higher disease concordance between monozygotic twins as compared with dizygotic twins, consistent with the idea that RA has heritable causes (1); the familial relative risk between siblings has been reported to range between 5 and 10 (3,4). It has been assumed that the HLA locus accounts for close to half of the familial susceptibility (1). Recent genome-wide association (GWA) studies and candidate-gene studies have identified a novel spectra of disease-susceptibility genes for RA (4–6). The HLA association and some of the other susceptibility genes for RA are shared by some other autoimmune diseases (4). Even family studies have noted clustering of other autoimmune diseases in families of RA patients (2,7–11).

Family history is important even in the era of GWA studies, because it is the only population-level indicator of a possible heritable etiology in complex diseases before the susceptibility genes are found (12–14). Familial risks may be considered before gene-finding studies are initiated, in order to estimate the likelihood of success in identifying candidate genes.

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Familial risks can also be considered after obtaining gene profiles, in order to estimate the global significance of the genetic findings (15). In diseases that may share etiology, such as autoimmune diseases, family studies would help to estimate the level of genetic sharing. All family members also share environmental experiences, which can be assessed through disease correlation between spouses (16).

Family studies on complex medical conditions are sensitive to many types of biases, particularly concerning correct and balanced reporting of the condition in the affected family member (the proband case) compared with the unaffected family members (the controls) or in family members whose condition was probably diagnosed decades before the proband case. The biases tend to be nonrandom, in that the affected family member could overreport diseases in his or her relatives, while the unaffected control subject could underreport diseases in his or her relatives, resulting in exaggerated familial risk estimates (17,18).

The availability of the Multigeneration Register in Sweden provides reliable access to data on Swedish families throughout the last century. This register has been used extensively to study cancers through linkage to the Swedish Cancer Registry, and to study any hospitalized cases of autoimmune disease, including familial autoimmune diseases, and their relationships to cancer (19–25), through linkage to the Hospital Discharge Register. In the present study, we assessed the familial risks of RA among parents and offspring, singleton siblings, twins, and spouses. Both concordant associations within families (RA–RA) and discordant associations with any of 33 other autoimmune diseases and related conditions were studied. With a total patient population of 447,704, of whom 47,361 were diagnosed as having RA, this is the largest family study published on these diseases. Our study has the advantage that all of the results emanated from a single population of patients with medically confirmed autoimmune diseases in a country that maintains high medical standards and has reasonably uniform diagnostic criteria.

PATIENTS AND METHODS

The research database used for this study, a compilation of data on autoimmune diseases among Swedish families, is a subset of the national Swedish MigMed database at the Centre for Family and Community Medicine of Karolinska Institute. The MigMed database was compiled by researchers at Statistics Sweden using data from several national Swedish registers, including the Multigeneration Register. In the MigMed database, persons born in Sweden in 1932 and thereafter (second generation) are registered shortly after birth and are

linked to their parents (first generation). In addition, sibships are defined as part of the second generation. National census data (from 1960 to 1990) and Swedish population register data (from 1990 to 2001) are also incorporated into the database, to obtain information on individuals' socioeconomic status. For the present study, dates of hospitalization for autoimmune diseases during the study period were obtained from the Swedish Hospital Discharge Register (for the years 1964 to 2004). Patients registered as having been hospitalized for an autoimmune disease had stayed at least one night in the hospital, usually in wards with specialists; the Hospital Discharge Register does not include data on outpatient care in hospitals or health care centers.

Diagnoses were reported according to the different versions of the International Classification of Diseases (ICD), with each of the 34 autoimmune diseases and related conditions identified under an ICD-defined group. All linkages with the Hospital Discharge Register were performed using the national 10-digit civic identification number that is assigned to each person in Sweden for his or her lifetime. This number was replaced by a serial number for each person, in order to provide anonymity and to check that each individual was entered only once, at the time of his or her first hospitalization for an autoimmune disease. More than 7.4 million individuals are included in the database of second-generation patients with autoimmune diseases; with inclusion of the parental generation in the database, the total population is 11.5 million.

The calculation of incidence rates (number of cases divided by the number of person-years at risk) in our study population was determined from the start of followup on January 1, 1964 until the first hospitalization for the autoimmune disease, death, emigration, or the closing date of the study (December 31, 2004). Age-specific disease incidence rates were calculated for the whole followup period, divided into five 5-year periods. Standardized incidence ratios (SIRs) were calculated as the ratio of the observed number of cases to the expected number of cases. The expected number of cases was calculated for age group (5-year groups), sex, time period (5-year groups), region, and socioeconomic status-specific standard disease incidence rates. Familial risks were calculated for male and female patients separately according to the proband categories of parents, singleton siblings, or twins affected with concordant (same) or discordant (different) autoimmune diseases, compared with men and women whose relatives were not affected by these conditions.

The familial risks were calculated using cohort methods that have been described previously (26). With this method, families with at least 2 affected siblings contribute each sibling as an individual case, and these are compared with the affected family member in single-case families, using the described person-years calculation. In the rare families in which more than 2 siblings are affected, each sibling is still individually counted as a patient. Spouses were identified from the population older than age 25 years through data on common children. For each SIR value, the 95% confidence intervals (95% CIs) were calculated on the assumption of a Poisson distribution, and these were adjusted for dependence between the sibling pairs (26).

In the present study, an estimate of the degree of environmental contribution to the familial risk was obtained on the basis of the risk between spouses. When the risk between spouses was lower than the risk between blood relatives, a

Table 1. Sex-specific and total numbers of hospitalized patients diagnosed as having rheumatoid arthritis or other autoimmune diseases and related conditions

Autoimmune disorder	Men		Women		All	
	No.	%	No.	%	No.	%
Addison's disease	586	0.3	810	0.3	1,396	0.3
Amyotrophic lateral sclerosis	2,865	1.4	2,105	0.9	4,970	1.1
Ankylosing spondylitis	3,673	1.8	1,463	0.6	5,136	1.1
Asthma	72,310	35.1	61,414	25.4	133,724	29.9
Autoimmune hemolytic anemia	366	0.2	438	0.2	804	0.2
Behçet's disease	1,817	0.9	894	0.4	2,711	0.6
Celiac disease	4,100	2.0	6,127	2.5	10,227	2.3
Chorea minor	15	0.01	31	0.01	46	0.01
Chronic rheumatic heart disease	7,017	3.4	6,747	2.8	13,764	3.1
Crohn's disease	9,020	4.4	9,857	4.1	18,877	4.2
Diabetes mellitus (type 1)	29,254	14.2	24,233	10.0	53,487	11.9
Discoid lupus erythematosus	138	0.1	359	0.1	497	0.1
Graves' disease/hyperthyroidism	5,456	2.7	26,387	10.9	31,843	7.1
Hashimoto thyroiditis/hypothyroidism	1,709	0.8	5,776	2.4	7,485	1.7
Immune thrombocytopenic purpura	1,598	0.8	1,679	0.7	3,277	0.7
Localized scleroderma	130	0.1	543	0.2	673	0.2
Lupoid hepatitis	81	0.04	138	0.1	219	0.05
Multiple sclerosis	3,975	1.9	7,168	3.0	11,143	2.5
Myasthenia gravis	923	0.4	1,212	0.5	2,135	0.5
Pernicious anemia	2,788	1.4	2,633	1.1	5,421	1.2
Polyarteritis nodosa	541	0.3	442	0.2	983	0.2
Polymyalgia rheumatica	6,523	3.2	10,999	4.5	17,522	3.9
Polymyositis/dermatomyositis	475	0.2	724	0.3	1,199	0.3
Primary biliary cirrhosis	435	0.2	608	0.3	1,043	0.2
Psoriasis	7,241	3.5	6,857	2.8	14,098	3.1
Reactive arthritis	218	0.1	50	0.02	268	0.1
Rheumatic fever	2,413	1.2	895	0.4	3,308	0.7
Rheumatoid arthritis	14,625	7.1	32,736	13.5	47,361	10.6
Sarcoidosis	4,659	2.3	4,526	1.9	9,185	2.1
Sjögren's syndrome	129	0.1	1,011	0.4	1,140	0.3
Systemic lupus erythematosus	964	0.5	3,874	1.6	4,838	1.1
Systemic sclerosis	2,343	1.1	2,302	1.0	4,645	1.0
Ulcerative colitis	14,210	6.9	11,605	4.8	25,815	5.8
Wegener's granulomatosis	3,218	1.6	5,246	2.2	8,464	1.9
All	205,815	100.0	241,889	100.0	447,704	100.0

genetic contribution was considered likely. For calculations of the risk between twins, the value would be expected to exceed that in singleton siblings, but we did not have data on zygosity; instead, the proportion of monozygotic twins could be estimated using Weinberg's difference method, which is based on the assumption that all different-sex twins are dizygotic (27,28).

RESULTS

The total number of patients with autoimmune diseases in the whole study population was 447,704, as shown by disease type in Table 1. The largest diagnostic groups were asthma ($n = 133,724$), type 1 diabetes mellitus ($n = 53,487$), and RA ($n = 47,361$). In the whole patient population, women outnumbered men, but the sex-specific incidence rates depended on the disease. In men, a >2-fold increase in the incidence of ankylosing spondylitis, Behçet's disease, reactive arthri-

tis, and rheumatic fever was noted in comparison with female patients, whereas in women, discoid lupus erythematosus, Graves' disease/hyperthyroidism, Hashimoto thyroiditis/hypothyroidism, localized scleroderma, RA, Sjögren's syndrome, and systemic lupus erythematosus were more common.

Familial risks in offspring according to mutually exclusive proband categories (parent only, singleton sibling only, parent and sibling, twins, and spouses) are shown in Table 2. When a parent was diagnosed as having RA, the SIR for RA in offspring was 3.02. The significant SIRs for RA in offspring according to parental proband were 2.96 for ankylosing spondylitis, 2.40 for localized scleroderma, 2.25 for Sjögren's syndrome, 2.13 for systemic lupus erythematosus, 1.65 for systemic sclerosis, 1.54 for Hashimoto thyroiditis/hypothyroidism, 1.53 for pernicious anemia, 1.40 for sarcoidosis, 1.36 for

Table 2. Familial standardized incidence ratio (SIR) for rheumatoid arthritis (RA) in relation to other autoimmune diseases and related conditions according to disease in the proband*

Proband disease	Parent only			Sibling only			Both parent and sibling			Twins			Spouses		
	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI
Addison's disease	5	1.05	0.33–2.48	2	0.52	0.03–2.69	0	–	–	1	9.26	0.00–75.06	10	1.28	0.61–2.36
Amorphous lateral sclerosis	22	0.76	0.47–1.15	12	1.51	0.55–3.74	0	–	–	0	–	–	58	1.03	0.78–1.33
Ankylosing spondylitis	41	2.96	2.12–4.02†	41	1.83	0.93–3.51	1	3.82	0.00–21.92	0	–	–	34	1.03	0.72–1.45
Asthma	572	1.32	1.22–1.43†	301	1.47	0.92–2.32	31	1.67	1.14–2.38†	2	0.43	0.03–2.24	701	1.04	0.96–1.12
Autoimmune hemolytic anemia	9	1.92	0.87–3.65	0	–	–	0	–	–	0	–	–	7	0.98	0.39–2.03
Behçet's disease	10	0.93	0.44–1.72	15	1.79	0.70–4.18	0	–	–	1	4.30	0.00–34.84	14	0.80	0.44–1.34
Celiac disease	12	1.25	0.65–2.20	28	1.65	0.77–3.37	0	–	–	0	–	–	15	0.92	0.51–1.53
Chorea minor	0	–	–	0	–	–	0	–	–	0	–	–	0	–	–
Chronic rheumatic heart disease	112	1.14	0.94–1.38	10	0.80	0.27–2.10	0	–	–	0	–	–	187	1.15	0.99–1.32
Crohn's disease	35	0.93	0.64–1.29	79	1.18	0.66–2.09	2	2.16	0.20–7.96	2	1.22	0.08–6.35	71	1.03	0.81–1.30
Diabetes mellitus (type 1)	133	1.11	0.93–1.32	194	1.43	0.87–2.33	6	2.07	0.75–4.54	1	0.34	0.00–2.74	213	0.96	0.84–1.10
Discoid lupus erythematosus	2	0.90	0.09–3.33	3	1.94	0.26–8.12	0	–	–	0	–	–	7	2.00	0.79–4.14
Graves' disease/hyperthyroidism	173	1.16	0.99–1.35	104	1.27	0.74–2.18	3	1.28	0.24–3.79	2	0.89	0.06–4.62	220	1.17	1.02–1.34†
Hashimoto thyroiditis/hypothyroidism	73	1.54	1.21–1.94†	23	1.71	0.76–3.62	0	–	–	0	–	–	49	0.90	0.67–1.20
Immune thrombocytopenic purpura	10	1.38	0.66–2.55	9	1.44	0.46–3.88	0	–	–	0	–	–	17	1.26	0.73–2.03
Localized scleroderma	10	2.40	1.14–4.43†	3	2.20	0.29–9.19	0	–	–	1	65.36	0.02–529.85	2	0.40	0.04–1.48
Lupoid hepatitis	2	3.33	0.31–12.24	0	–	–	0	–	–	0	–	–	4	3.61	0.94–9.33
Multiple sclerosis	26	0.80	0.52–1.17	44	1.10	0.57–2.09	0	–	–	1	1.23	0.00–10.00	72	1.14	0.89–1.44
Myasthenia gravis	11	1.24	0.62–2.23	11	2.02	0.71–5.14	0	–	–	0	–	–	14	0.84	0.46–1.42
Pernicious anemia	77	1.53	1.21–1.91†	5	1.56	0.35–5.20	0	–	–	0	–	–	60	0.92	0.70–1.19
Polyarteritis nodosa	10	1.73	0.82–3.19	4	2.20	0.40–8.03	0	–	–	0	–	–	12	1.16	0.60–2.04
Polymyalgia rheumatica	156	1.32	1.12–1.54†	38	1.24	0.62–2.41	1	2.08	0.00–11.93	1	1.52	0.00–12.36	166	0.93	0.79–1.08
Polymyositis/dermatomyositis	6	1.29	0.46–2.82	2	0.64	0.04–3.33	0	–	–	0	–	–	10	1.14	0.54–2.10
Primary biliary cirrhosis	5	0.77	0.24–1.80	1	0.48	0.00–3.91	0	–	–	0	–	–	7	0.68	0.27–1.41
Psoriasis	82	1.36	1.08–1.69†	97	2.01	1.15–3.46†	0	–	–	1	0.77	0.00–6.22	118	1.14	0.94–1.36
Reactive arthritis	1	2.03	0.00–11.66	2	1.84	0.12–9.57	0	–	–	0	–	–	1	1.04	0.00–5.97
Rheumatic fever	18	1.40	0.83–2.22	12	1.06	0.39–2.63	0	–	–	0	–	–	24	0.94	0.60–1.41
RA	833	3.02	2.82–3.23†	418	4.64	2.98–7.23†	54	9.31	6.99–12.16†	15	6.48	2.56–15.15†	489	1.17	1.07–1.28†
Sarcoidosis	53	1.40	1.05–1.84†	51	1.44	0.76–2.69	0	–	–	2	2.11	0.14–10.99	60	0.99	0.75–1.27
Sjögren's syndrome	11	2.25	1.11–4.03†	8	2.44	0.74–6.84	0	–	–	0	–	–	7	0.94	0.37–1.95
Systemic lupus erythematosus	40	2.13	1.52–2.90†	37	2.77	1.38–5.41†	0	–	–	1	3.68	0.00–29.85	29	1.04	0.70–1.50
Systemic sclerosis	32	1.65	1.13–2.33†	21	1.99	0.87–4.32	0	–	–	1	3.88	0.00–31.42	37	1.12	0.79–1.55
Ulcerative colitis	58	0.94	0.71–1.22	122	1.31	0.77–2.21	0	–	–	3	1.35	0.18–5.64	124	1.04	0.86–1.23
Wegener's granulomatosis	102	1.34	1.09–1.63†	7	1.45	0.41–4.25	0	–	–	0	–	–	91	0.98	0.79–1.20
All	2,742	1.55	1.49–1.61†	1,704	1.73	1.17–2.57†	98	2.76	2.24–3.37†	35	1.46	0.72–2.88	2,930	1.06	1.02–1.09†
All except RA and asthma	1,337	1.26	1.20–1.33†	985	1.43	0.95–2.15	13	1.17	0.62–2.01	18	1.06	0.44–2.38	1,740	1.03	0.99–1.08

* Observed values are the observed number of cases of RA in a family member according to each proband disease. The SIRs, along with 95% confidence intervals (95% CIs), are calculated as the ratio of the observed number of cases of RA to the expected number of cases of RA.

† The 95% CI does not include 1.00, indicating a significant association.

psoriasis, 1.34 for Wegener's granulomatosis, and 1.32 for asthma or polymyalgia rheumatica. The risk of RA in offspring in relation to any autoimmune disease in a parent was 1.55, but it decreased to 1.26 when RA and asthma cases were removed from the analysis.

In these analyses, the ages of the parents were not limited to a specific range, whereas all offspring were younger than age 73 years. Thus, to enable a comparison with the risks between siblings, the above analyses were repeated by limiting the parental age to 72 years (results not shown). In offspring, the SIRs were somewhat increased, and even though the numbers of cases were reduced, almost all of the associations that were significant in offspring of affected parents remained significant in siblings. The SIR for RA in siblings when a parent was diagnosed as having RA was 3.45, while the other significant SIRs in siblings according to parental proband were 3.03 for ankylosing spondylitis, 2.93 for localized scleroderma, 2.36 for systemic lupus erythematosus, 2.54 for Sjögren's syndrome, 1.74 for pernicious anemia, 1.78 for Hashimoto thyroiditis/hypothyroidism, 1.41 for polymyalgia rheumatica, and 1.37 for asthma. The SIRs in siblings when a parent was diagnosed as having psoriasis (1.28) or Wegener's granulomatosis (1.30) were of borderline significance, whereas the association with RA in a sibling when a parent was diagnosed as having sarcoidosis (1.05) was no longer significant.

Because of the age structures of the parent and offspring populations, the number of singleton siblings with any autoimmune disease was only 1,704, as compared with the larger group of 2,742 affected offspring of affected parents. Thus, only familial risks for concordant RA (SIR 4.64), RA-psoriasis (SIR 2.01), and RA-systemic lupus erythematosus (SIR 2.77) were significant in singleton siblings. However, the SIRs for the discordant diseases RA-ankylosing spondylitis and RA-asthma in singleton siblings were of borderline significance (lower 95% CIs >0.90).

When both a parent and a sibling were diagnosed as having RA (multiplex families), the SIR for RA was 9.31. When a parent and a sibling were diagnosed as having asthma, the SIR for RA was 1.67. Among twins, only the familial risk for concordant RA (SIR 6.48) was significant; among the twins studied, only one pair was of opposite sex, and therefore the SIRs were mainly based on the risk in monozygotic twins. The familial risk for concordant RA was also significant among spouses (SIR 1.17). However, an equally strong association was observed for RA-Graves' disease/hyperthyroidism among spouses.

The question of sex-specific familial associations was addressed by comparing the familial risk between sons of affected fathers and daughters of affected moth-

ers (results not shown). For RA, there was no difference in familial risk by sex, since the SIR for RA in male family members was 3.41 (90 affected pairs) compared with a SIR for RA of 3.22 in female family members (492 affected pairs). For most discordant associations between RA and other autoimmune diseases and related conditions, sex-specific SIRs did not differ. The apparent exceptions were the SIR for RA when a parent was diagnosed as having localized scleroderma (in women, SIR 3.29, 95% CI 1.49–6.29, 9 affected pairs; in men, no affected pairs), polymyalgia rheumatica (in women, SIR 1.57, 95% CI 1.27–1.92, 95 affected pairs; in men, SIR 0.89, 10 affected pairs), Sjögren's syndrome (in women, SIR 2.44, 95% CI 1.04–4.83, 8 affected pairs; in men, no affected pairs), or Wegener's granulomatosis (in women, SIR 1.47, 95% CI 1.11–1.91, 56 affected pairs; in men, SIR 0.76, 6 affected pairs). The numbers of these cases were small, and the 95% CIs overlapped.

DISCUSSION

To our knowledge, this is the first attempt to assess the familial risk of RA in relation to a large number of autoimmune diseases and related conditions using unified data. The use of hospitalized cases may offer advantages and disadvantages in etiologic studies. Hospitalization may involve selection bias, in which family members of patients who are hospitalized may preferentially seek hospitalization. However, such selection should be largest among cohabiting spouses, and no evidence of this effect was noted; the largest correlation between spouses was 1.17 for concordant RA. Another limitation would be that not all affected family members are hospitalized, in which case the numbers of hospitalizations would be decreased and would probably preferentially include only those patients with severe disease at presentation. In the case of RA, it has been estimated that up to 75% of Swedish patients have been hospitalized for RA at one time or another (29,30). A crude prevalence of hospitalization can be estimated by dividing the number of RA patients (47,361) by 8.5 million (the Swedish population over the study period minus the number of persons lacking family links), yielding a crude prevalence of hospitalization for RA of 0.56%; this is 80% of the assumed true population prevalence of RA (0.7%) in Sweden (31).

The advantages of using hospitalized cases include the ability to recruit patients on a nationwide basis, and high diagnostic accuracy. Hospitalizations normally require a doctor's pass from a primary care clinic. Thus, each hospitalized patient is seen by at least 2 medical doctors, of whom the practitioner in the hospital is likely to be a specialist. For autoimmune dis-

eases, diagnostic techniques and standards are concentrated in hospitals with specialized staff and diagnostic facilities. Accordingly, an ad hoc study on close to 1,000 hospitalized RA patients found that ~90% of the patients fulfilled the American College of Rheumatology (formerly, the American Rheumatism Association) criteria for RA (31,32). Moreover, ~61% of the RA patients identified in the present study were hospitalized with a diagnosis of RA multiple times. These data are informative in terms of confirming the diagnostic accuracy (90%) and sensitivity (~75%) of an RA diagnosis in Swedish hospitals.

Such data are not available on most of the 33 other diseases covered by the present study, but ad hoc studies on some of the diseases are available. The diagnostic accuracy for hospitalized cases of ulcerative colitis and Crohn's disease has previously been estimated by comparing hospital discharge data with regional registry data, including individually reviewed patient data, which yielded a concordance for diagnosis of the specific inflammatory bowel disease of 96% (21). As other quality indicators, we have reported that only 0.18% of patients with ulcerative colitis were diagnosed as having Crohn's disease in a subsequent discharge, and more than one-half of the patients had been discharged multiple times with a repeated diagnosis of inflammatory bowel disease (33,34). Moreover, in a previous study, it was shown that among Swedish patients diagnosed as having asthma in 1987, one-half of the patients were later hospitalized at least once, and 18% were hospitalized at least 4 times, with the same diagnosis of asthma (28). According to one study, all patients in Sweden diagnosed as having type 1 diabetes mellitus have been hospitalized, and in a study of celiac disease, a correct diagnosis was made in >85% of discharged patients (35,36). Diagnostic accuracy of close to 90% for Wegener's granulomatosis has been reported in the hospital discharge registry (37).

Thus, we would emphasize that any misclassification of diagnosis would be likely to decrease the familial risks, leading to null results. Moreover, for studies of the present kind, correct classification of cases would be preferred over maximal coverage, as long as the effects of selection bias on the patient population are kept in mind.

It was not surprising that the familial relative risks were highest for concordant RA in family members, being 3.02 in offspring of affected parents (3.45 when parental age was limited to 72 years), 4.64 in siblings, 6.48 in twins, and 9.31 in individuals with an affected parent and sibling. The risk of RA in siblings, 4.64, is consistent with the risk of RA, 4.38, reported in

an Icelandic study (3). However, less recent literature cites higher risks in siblings, probably because of selection and reporting biases, as discussed elsewhere (14). The recent Wellcome Trust Case Control Consortium study on 7 diseases cited a sibling risk of 5–10 for RA (4).

For discordant diseases in the present study, offspring had an increased risk of RA when parents were hospitalized for ankylosing spondylitis (SIR 2.96), localized scleroderma (SIR 2.40), Sjögren's syndrome (SIR 2.25), systemic lupus erythematosus (SIR 2.13), systemic sclerosis (SIR 1.65), Hashimoto thyroiditis/hypothyroidism (SIR 1.54), pernicious anemia (SIR 1.53), sarcoidosis (SIR 1.40), psoriasis (SIR 1.36), Wegener's granulomatosis (SIR 1.34), polymyalgia rheumatica (SIR 1.32), or asthma (SIR 1.32). Highly discordant associations (those with SIRs >1.5) might suggest that there is extensive genetic sharing. Asthma showed a significant, but relatively low, association with RA (SIR 1.32); however, the association was stronger in families in which a parent and a sibling were probands (SIR 1.67).

In previous studies, familial aggregation of RA and many other autoimmune diseases, including systemic lupus erythematosus, Sjögren's syndrome, and ankylosing spondylitis, has been reported (8,11,38). A haplotype of the STAT-4 gene has been associated with the familial risk of both RA and systemic lupus erythematosus (6). Variants around the PTPN22 gene have been associated with RA, type 1 diabetes mellitus, and Crohn's disease. The CTLA-4 gene was associated with RA and other autoimmune diseases (4). However, the familial risks conferred by these loci would be small, and they would probably not be detectable, even in studies of the present size (4). The high familial risk of RA of 9.31 found in multiplex families would probably be associated with relatively high-risk genes, such as high-penetrant HLA alleles.

In order to compare the risks between the offspring of affected parents and siblings, the parental age was limited to 72 years, consistent with the age in the offspring population. A clearly higher familial risk in siblings than in offspring of affected parents would suggest that there is a contribution of recessive genetic effects or shared childhood environmental effects. The SIRs in offspring increased somewhat when the probands were younger; for example, for RA, the SIR increased from 3.02 to 3.45. Thus, this risk remained well below the SIR of 4.64 in siblings, which could imply that there are recessive genetic effects or shared childhood environmental effects. A large difference was noted for the discordant association between RA and psoriasis when comparing the risks in offspring of affected par-

ents (SIR 1.28) and those in siblings (SIR 2.01), also suggesting a contribution of recessive effects.

Hospitalization for RA was more than twice as common for female patients as for male patients; nevertheless, the familial SIRs were equal between son–father and daughter–mother pairs, implying that familial risk was a constant multiplier over the background rate of RA. Using the present sample size, most other discordant familial SIRs showed no large difference by sex, with the apparent exception of RA–localized scleroderma, RA–polymyalgia rheumatica, RA–Sjögren’s syndrome, and RA–Wegener’s granulomatosis, all of which showed higher risks in female family members. Because both RA and these 4 discordant autoimmune diseases were more common in women, and therefore male disease pairs were few or nonexistent, it is not possible to make strong statements about sex-specific associations.

The Wellcome Trust Case Control Consortium study on 7 diseases is a witness to the timeliness of the present approach (4). The report summarized their 24 positive GWA findings as follows: 9 loci for Crohn’s disease (cited sibling risk ~17–35), 7 loci for type 1 diabetes mellitus (cited sibling risk ~15), 3 loci for RA (cited sibling risk ~5–10), 3 loci for type 2 diabetes mellitus (cited sibling risk ~3), 1 locus for bipolar disorder (cited sibling risk ~7–10), 1 locus for coronary heart disease (cited sibling risk ~2–7), and none for hypertension (cited sibling risk ~2.5–3.5). As would be expected, the likelihood of finding significant genetic effects appeared to be proportional to the sibling risk as a surrogate of heritability. Therefore, identification of reliable familial risks will be a helpful roadmap for guiding genome scans into the postgenomic era.

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AUTHOR CONTRIBUTIONS

Dr. Hemminki had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Hemminki, K. Sundquist.

Acquisition of data. J. Sundquist, K. Sundquist.

Analysis and interpretation of data. Hemminki, Li.

Manuscript preparation. Hemminki, J. Sundquist, K. Sundquist.

Statistical analysis. Hemminki, Li, J. Sundquist, K. Sundquist.

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