Increased Risk of Autoimmune Disease in Families with Wegener's Granulomatosis

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ABSTRACT. ***Objective.*** The etiology of Wegener's granulomatosis (WG) is unknown. Susceptibility genes for WG that also affect the risks of other autoimmune/inflammatory diseases have been identified, indicating the existence of shared interdisease genetic susceptibilities. To determine the effect, on a population level, of shared susceptibility on disease risk, we assessed the occurrence of autoimmune/inflammatory disease in first-degree relatives of patients with WG.

Methods. In the Swedish Hospital Discharge Register we identified 2288 individuals discharged with the diagnosis of WG between 1970 and 2003. Through linkage to the Swedish Multi-generation Register we identified 787 parents, 1212 siblings, and 3650 children of these patients. From the Register of Total Population we identified 10 controls for each patient with WG, and 65,000 of their first-degree relatives. Through linkage to the nationwide Outpatients Register, we identified autoimmune/inflammatory disease among all relatives. Relative risks were estimated as hazard ratio (HR) using Cox regression. The study period was 2001-2006.

Results. Biological first-degree relatives of patients with WG were at a moderately increased risk of any autoimmune/inflammatory disease (HR 1.32, 95% CI 1.18–1.49), including specific associations with, for example, multiple sclerosis (HR 1.92, 95% CI 1.16–3.16), Sjögren's syndrome (HR 2.00, 95% CI 1.07–3.73), and seropositive rheumatoid arthritis (HR 1.54, 95% CI 1.09–2.19).

Conclusion. Relatives of patients with WG are at increased risk of being diagnosed with other autoimmune/inflammatory diseases, indicating shared susceptibility between WG and other autoimmune/inflammatory disease. (J Rheumatol First Release Oct 1 2010; doi:10.3899/jrheum.091280)

Key Indexing Terms:
WEGENER'S GRANULOMATOSIS AUTOIMMUNE DISEASE FAMILIARITY

Wegener's granulomatosis (WG) is a necrotizing granulomatous systemic vasculitis usually affecting the upper and lower respiratory tract and the kidneys. The disease affects men and women equally and occurs in all age groups with a peak onset in upper middle age. The unknown etiology is thought to harbor interplay of genetic susceptibility and yet-unknown triggering exogenous factors. Two observations support a genetic susceptibility to WG: that the prevalence of WG varies across different ethnic groups[1], and that α-1-antitrypsin deficiency, an autosomal recessive disease[2], is a risk factor for the disease[3,4]. Recent investigations of HLA associations (also implicated as important factors in the susceptibility to autoimmune/inflammatory disease) have revealed that certain alleles are overrepresented among patients with WG[5]. Case reports describe familial occurrence of WG[6,7,8] although we recently noted only a 60% increased risk of WG among first-degree relatives of patients with the disease[9]. Finally, the finding of an association between the 620W functional polymorphism of the PTPN22 gene and the risk of antineutrophil cytoplasmic antibody-positive WG[10] is of particular interest, because this polymorphism has been linked to risk of a series of other autoimmune or inflammatory diseases, including insulin-dependent diabetes mellitus, seropositive rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and autoimmune thyroiditis. However, the effect of this and other susceptibility genes on a population level, i.e., the extent to which autoimmune or inflammatory disease are actually more common in close biological relatives of patients with WG, is unknown.

To better understand the effect of genetic susceptibility in the etiology of WG we therefore assessed the relative risk of chronic autoimmune/inflammatory disease in family members of patients with WG.

MATERIALS AND METHODS

Setting and data sources. The Swedish public healthcare system, the national health and census registers, and the national registration number, allowing for deterministic record linkage, have all been described[11]. We

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used a variety of national, population-based, and virtually complete registers.

The Swedish Hospital Discharge and Outpatient Visits Register contains individual-based information on all inpatient care since 1964, nationwide since 1987. Hospital discharge codes according to the International Classification of Disease (ICD; World Health Organization 1968) versions 7, 8, 9, and 10 are recorded for each individual. Since 2001, this register also covers outpatient visits to specialist care (e.g., an outpatient visit to a rheumatologist), including date of visit and medical diagnosis, coded according to ICD-10.

The Register of Total Population contains information on all residents in Sweden, including national registration number, domicile, and dates of immigration or emigration from Sweden.

The Swedish Multi-generation Register[12,13] provides information on vertical and horizontal first-degree relatives (parents, siblings, and children) of Swedish residents born in 1932 or thereafter and alive in 1961 or later. Individuals born before 1932 can only be identified if they were still alive in 1961 and have children born after 1932. Thus, for a hypothetical individual born in 1945 and identified because of WG in 1995, parents, siblings, and children fulfilling the above demographic criteria can be identified. By contrast, for an individual born in 1925, only children fulfilling the above criteria can be identified. The completeness of the register is around 90%, i.e., for eligible individuals, some 90% of their parents can be identified.

The Cause of Death Register includes the date of death and the main and contributory causes of death, coded according to the ICD systems, of all residents who died since 1952.

Patients with WG. In the inpatient register we identified all 2288 individuals discharged with a diagnosis of WG from 1970 through 2003. Fifty-five percent of the patients were men. Mean age at first hospitalization listing WG was 61 years. In previous studies, validation against the underlying medical files has indicated that around 88% of the discharge diagnoses listing WG are indeed correct. The remainder typically represents other vasculitides misdiagnosed as WG[14].

General population controls. For each individual with WG we randomly selected 10 controls from the register of total population, matched for sex, age, marital status, and county of residence (Figure 1). Each control should be alive at the time of identification of the corresponding individual with WG.

Biological and nonbiological first-degree relatives of patients and controls. For 1939 (85%) of the 2288 individuals with WG, we could identify at least 1 first-degree relative. For the statistical analyses, 5649 first-degree relatives of individuals with WG were identified; 787 parents, 1212 siblings, and 3650 children were eligible for followup. Similarly, for 19,606 (85%) of the 22,873 population controls, we identified at least 1 first-degree relative: 7571 parents, 12,698 siblings, and 38,633 children, in total 58,902 relatives of the population controls. Through linkage of the individuals with WG and their controls to the register of total population, we identified spouses (defined by marriage) from 1970 through 2003 (Table 1).

Occurrence of autoimmune diseases among first-degree relatives. To identify cases of autoimmune/inflammatory disease among all first-degree relatives and spouses, we linked those relatives to the Outpatients Visit Register. Through this linkage we identified all outpatient visits (not to general practitioners) listing the ICD code for either of the following conditions: insulin-dependent diabetes, seronegative and seropositive RA, unspecified arthritis, juvenile idiopathic arthritis, psoriatic arthritis, Crohn's disease, ulcerative colitis, hyperthyroidism, Hashimoto's thy-

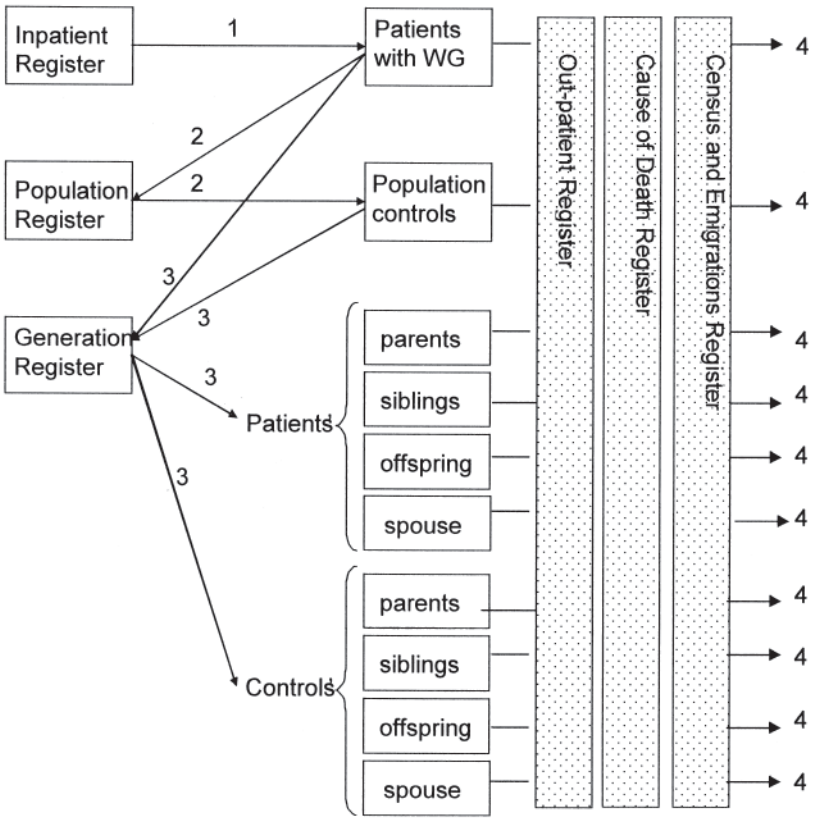

Figure 1. Register linkage procedure. 1. Identification of patients with Wegener's granulomatosis (WG). 2. Identification of population controls. 3. Identification of first-degree relatives and spouses of patients and controls. 4. Links to identify autoimmune disease and vital status for all subjects.

Table 1. Characteristics of the first-degree relatives and spouses of the cohort of Swedish patients with Wegener's granulomatosis, and first-degree relatives and spouses of general population controls. Observed age distributions of the different generations are affected by truncation in the registers in which index persons born before 1932 can only contribute with offspring.

Relationship	Relatives of patients with WG			Relatives of Controls		
	N	M/F, %	Age at Start of Followup (IQR)	N	M/F, %	Age at Start of Followup (IQR)
Parents	787	42/58	73 (58–82)	7571	41/59	73 (59–83)
Siblings	1212	50/50	52 (42–58)	12,698	50/50	53 (43–59)
Children	3650	52/48	42 (32–51)	38,633	51/49	42 (30–51)
Spouses	428	35/65	52 (45–57)	4512	37/63	52 (45–58)

IQR: interquartile range.

roidism, hypothyroidism, multiple sclerosis, Sjögren's syndrome, SLE, WG, ankylosing spondylitis, and unspecified spondylopathy (Table 2). We restricted this search to the Outpatients Visit Register rather than the Hospital Discharge Register because a majority of patients with the chosen disorders would have been treated only on an outpatient basis. This is contrary to what we have previously found concerning patients with WG, who during our earlier study periods in general all had at least 1 inpatient-care period[14]. This restriction also avoids any bias resulting from different thresholds for hospitalization in families with versus families without cases of WG. All identified first-degree relatives and spouses were linked to the Register of Total Population and to the Cause of Death Register. Among the 98,166 unique individuals in the study, 1324 (1.3%) were lost to followup or had to be excluded because of data ambiguities precluding followup.

For juvenile idiopathic arthritis, unspecified spondylopathy, and Hashimoto thyroiditis we found only 1, 1, and 3 cases, respectively, so those diseases were not analyzed separately but were included in the definition of "any" autoimmune/inflammatory disease.

Followup and statistical methods. To assess the association between exposure (being a first-degree relative of a patient with WG versus a first-degree relative of a control) and outcome (occurrence of autoimmune/inflammatory disease in the first-degree relative), we fit Cox proportional hazard ratio (HR) models, treating the first-degree relatives as a cohort, using attained age as the time scale, and adjusting for sex of the first-degree relative. With the start of followup beginning January 1, 2001, relative risks are presented as HR of outpatient visits registered for autoimmune inflammatory disease, estimated from Cox regression. Followup ended at the first observed autoimmune inflammatory disease, date of death, date of emigration or end of study period (December 31, 2006), whichever came first. Since very few subjects were lost during the followup between 2001 and 2006, the overwhelming majority of individuals were followed through the entire study period. We fit separate models for the outcome of each autoimmune/inflammatory disease as well as the combined outcome of any autoimmune inflammatory disease, and separately for each type of relationship (parents, siblings, children, and spouses) and for the combined group of all first-degree relatives (parents + siblings + children). Because the outcome (autoimmune inflammatory disease) among different relatives of one and the same patient with WG (or healthy control) can be considered correlated, we also calculated standard errors and associated 2-sided 95% CI using robust standard errors. In our data for relatives, the autoimmune/inflammatory diseases observed in different generations may to some extent be due to age differences in the available data. We therefore also fit complementary models analyzing different attained ages during followup: 1–49 years,

Table 2. Occurrence and relative risks of autoimmune/inflammatory diseases among first-degree relatives of patients with Wegener's granulomatosis (WG) and among first-degree relatives of matched general population controls. Except for total numbers, data are hazard ratio and 95% CI.

Disease (ICD10)	Total Number of Affected Relatives/ Controls	Children	Siblings	Parents	All Biological First-degree Relatives	Spouses
Any autoimmune/inflammatory disease*	345/2697	1.30 (1.12–1.51)	1.32 (1.04–1.67)	1.42 (1.07–1.89)	1.32 (1.18–1.49)	1.02 (0.67–1.55)
Hypothyroidism (E03)	17/134	0.96 (0.44–2.09)	0.99 (0.36–2.74)	3.66 (1.43–9.37)	1.31 (0.79–2.17)	0.65 (0.09–4.94)
Hyperthyroidism (E05)	19/180	1.16 (0.64–2.11)	1.59 (0.67–3.76)	0.30 (0.04–2.19)	1.08 (0.68–1.73)	1.04 (0.25–4.43)
Insulin-dependent diabetes (E10)	57/512	1.14 (0.80–1.62)	0.85 (0.45–1.60)	1.76 (0.98–3.16)	1.16 (0.89–1.52)	1.91 (0.85–4.29)
Multiple sclerosis (G35)	18/97	2.06 (1.16–3.65)	1.11 (0.26–4.64)	2.55 (0.55–11.82)	1.92 (1.16–3.16)	2.42 (0.52–11.21)
Crohn's disease (K50)	18/130	1.50 (0.82–2.75)	1.01 (0.31–3.28)	1.76 (0.51–6.09)	1.42 (0.87–2.33)	1.12 (0.15–8.64)
Ulcerative colitis (K51)	32/287	1.12 (0.71–1.78)	1.37 (0.61–3.04)	0.94 (0.22–4.02)	1.15 (0.79–1.70)	**
Psoriatic arthritis (L40.5)	72/531	1.24 (0.89–1.73)	1.57 (1.01–2.44)	1.82 (0.95–3.49)	1.41 (1.10–1.81)	1.34 (0.62–2.93)
All inflammatory polyarthritis combined	74/514	1.66 (1.11–2.49)	2.04 (1.15–3.62)	0.88 (0.46–1.67)	1.45 (1.12–1.87)	0.60 (0.19–1.93)
Rheumatoid arthritis RF+ (M05)	38/249	1.41 (0.84–2.38)	2.50 (1.42–4.41)	0.87 (0.38–2.02)	1.54 (1.09–2.19)	0.57 (0.08–4.26)
Rheumatoid arthritis RF– (M06)	12/115	1.41 (0.68–2.95)	0.35 (0.05–2.59)	1.11 (0.34–3.66)	1.07 (0.59–1.94)	1.19 (0.15–9.33)
Other inflammatory polyarthritis (M13)	24/164	1.72 (1.04–2.85)	1.79 (1.10–2.91)	0.55 (0.07–4.13)	1.56 (1.01–2.43)	0.43 (0.06–3.11)
Sjögren's syndrome (M35.0)	12/61	2.36 (0.97–5.72)	1.49 (0.45–4.99)	2.15 (0.60–7.73)	2.00 (1.07–3.73)	**
Systemic lupus erythematosus (M32)	7/42	1.85 (0.72–4.77)	**	3.69 (0.69–19.85)	1.71 (0.77–3.80)	**
WG (M31.3)	4/14	2.60 (0.56–12.04)	2.10 (0.25–17.46)	**	2.98 (0.99–8.97)	**
Ankylosing spondylitis (M45)	10/61	2.14 (0.92–4.97)	1.75 (0.41–7.45)	**	1.69 (0.81–3.50)	**

* Juvenile rheumatoid arthritis, unspecified spondylitis, and Hashimoto thyroiditis, n = 5, are not analyzed separately but included in "any." ** Too few events to calculate hazard ratio and CI.

50–74 years, and ≥ 75 years at first diagnosis registration with the outcome diagnosis. The Cox regression models were estimated using SAS software version 9.2[15]. All statistical tests were considered significant on the 2-sided 5% level of significance.

Chart review and disease characteristics. Through review of the medical charts of a subgroup of the index individuals with WG, we validated the diagnosis of WG against the American College of Rheumatology (ACR) criteria[16], and when available also confirmed the diagnosis by histology. This validation was done for all patients (n = 68) who had a first-degree relative registered with RA or unspecified arthritis. Among the autoimmune/inflammatory diseases of the first-degree relatives of patients with WG, we validated the diagnosis among all individuals registered with either RA (ICD 10 code M05 and M06) against the ACR criteria[17] or other and unspecified inflammatory polyarthritis (M13). To assess the correctness also of the inflammatory polyarthritis diagnosis among the first-degree relatives of the population controls (the linkage identified 514 individuals with RA or unspecified inflammatory polyarthritis), a random subset (n = 70) of these were also subjected to a similar chart review.

RESULTS

Occurrence and relative risk of autoimmune/inflammatory diseases. Of the patients with WG, 6.5% had a first-degree relative who had at least 1 registration with any of the specified autoimmune/inflammatory diseases registered during the study period (2001-2006). Of the controls, 4.8% had such a relative. Based on this, biological first-degree relatives of patients with WG were at an overall and statistically significant 32% increased risk of any autoimmune/inflammatory disease (HR 1.32, 95% CI 1.18–1.49; Table 2). With respect to specific autoimmune inflammatory diseases, statistically significant increased risks were observed for multiple sclerosis (HR 1.92, 95% CI 1.16–3.16), Sjögren's syndrome (HR 2.00, 95% CI 1.07–3.73), psoriatic arthritis (HR 1.41, 95% CI 1.10–1.81), and for the combined group of all inflammatory polyarthritic diseases (HR 1.45, 95% CI 1.12–1.87). The combined group harbored increased risks for seropositive RA (HR 1.54, 95% CI 1.09–2.19) and non-RA inflammatory polyarthritides (HR 1.56, 95% CI 1.01–2.43), but not for seronegative RA (HR 1.07, 95% CI 0.59–1.94; Table 2).

Repeating the analyses among the different generations, we found that among children there was a statistically significantly increased risk of multiple sclerosis (HR 2.06, 95% 1.16–3.65) and any inflammatory polyarthritis (HR 1.66, 95% CI 1.11–2.49). Among siblings, increased risks were noted for seropositive RA (HR 2.46, 95% CI 1.39–4.34) and any inflammatory polyarthritis (HR 1.81, 95% CI 1.11–2.95). Overall, no increased risk of autoimmune/ inflammatory disease was noted among spouses (Table 2).

Validation of the WG diagnosis suggested that 80% of the WG diagnoses fulfilled the ACR criteria for WG (and in 80% of these the diagnosis was also confirmed by histology). Over 90% of all diagnoses of an inflammatory polyarthritide (RA M05 or M06, or other inflammatory polyarthritis, M13) were correct, similarly so among relatives of index patients and among relatives of controls.

DISCUSSION

The overall increased risk of autoimmune/inflammatory disease among first-degree relatives of patients with WG in our study was estimated to HR 1.32 (95% CI 1.18–1.49), but varied among the different autoimmune/inflammatory diseases and across the different generations under study, possibly indicating effect modification by attained age. For instance, we found statistically significantly increased risks of seropositive RA among siblings (HR 2.46, 95% CI 1.39–4.34), and of multiple sclerosis among offspring (HR 2.06, 95% CI 1.16–3.65; Table 2).

Importantly, although our results reflect relative risks during the defined study period of 6 years, the observed absolute occurrence is likely to represent underestimations of the true lifetime risks of the outcomes under study. Nevertheless, our findings mean that 6.5% of the relatives of patients with WG and 4.8% of the relatives of the control group have an autoimmune/inflammatory disease. This can be compared to current estimates of the prevalence of autoimmune disease in a US population of 5%–8% when including more than 80 recognized disorders and 3%–5% when including fewer than 24 diseases[18]. The observed overall relative risk of autoimmune/inflammatory disease in relatives of patients with WG is comparable to findings in relatives of patients with multiple sclerosis, among whom an overall risk of 1.2 (95% CI 1.1–1.4) has been reported[19]. The observed overall association is also of similar magnitude as that reported in surveys of autoimmune/inflammatory disease in families of patients with SLE[20,21].

In our study, the risk for WG among first-degree relatives of patients with the disease was estimated at HR 2.98 (95% CI 0.99–8.97). In terms of estimated CI, this estimate is no different from that reported in our previous assessment (HR 1.56, 95% CI 0.35–6.90)[9]. In fact, the addition of 1 single case would have made the 2-point estimates essentially identical. It should also be remembered that the age composition and generations under study were somewhat different in the 2 assessments, as was the method of outcome assessment. Even so, the clinically relevant conclusion remains, i.e., that the absolute risk of WG in first-degree relatives of patients with WG is very low.

Clustering of diseases within families may be explained by shared genes, shared environmental exposures, or interactions between these factors. Apart from shared genetic susceptibility, the familial aggregation observed, for example with multiple sclerosis (for which several "risk-genes" have been identified[22], none of which has been reported in WG[23]), raises the possibility of common environmental risk factors. In the case of multiple sclerosis, smoking, hypovitaminosis D, and Epstein-Barr virus infection have been put forward as possible exogenous triggers[24,25], while environmental risk factors for WG remain to be confirmed. An increased risk of autoimmune disease in families with multiple sclerosis has been reported[18,26]; however, in neither of

these 2 patient questionnaire studies was WG included among the autoimmune diseases selected for survey. In the event of shared environmental risk factors, spouses of patients might be at an increased risk. In our study, the overall increased risk for autoimmune/inflammatory disease among first-degree relatives was not mirrored among spouses (relative risk 0.94), and thus does not offer direct support for any major role of shared environment (at least not during ages that are typically shared between spouses).

With respect to RA, the PTPN22 R 620W allele has been identified as a risk factor for anticyclic citrullinated peptide-positive RA[27], as well as for WG, and may represent a partial explanation for our results (we did not find an increased risk for seronegative RA). RA and WG in the same patient has been described as very rare[28]. In our study, no patient had both. The concept of shared genetic pathways between different autoimmune diseases can also be supported by the finding of STAT4 in SLE, RA, and systemic sclerosis[29,30,31,32]; however, any association with STAT4 has not been described in WG. Our finding of increased risks of autoimmune/inflammatory disease among first-degree relatives of patients with WG strengthens the concept that genetic pathways are shared between the different diseases. Further investigation, also including shared phenotypic expression and prognosis, would add to the understanding of why autoimmune/inflammatory diseases form clusters, and also to the causes of autoimmune/inflammatory disease[33].

When interpreting our results, several strengths and weaknesses of our study should be kept in mind. The nationwide population-based setting allowed us to identify a large cohort of patients with WG and a large set of control subjects from the general population. The setting also allowed an unbiased and independent identification of relatives and spouses and of autoimmune/inflammatory disease among these, based on prospectively recorded data. Although our study design limited the index patients to individuals discharged with WG from inpatient care, the vast majority of Swedish patients with WG were, at least once during the study period 1970-2003, hospitalized with the disease or because of diagnostic (kidney biopsy) or therapeutic procedures (e.g., cyclophosphamide infusion), as indicated in a previous study from our group[34]. By contrast, many of the autoimmune inflammatory diseases under study are currently typically not managed on an inpatient basis. The use of outpatient data for the assessment of these diseases therefore served to increase sensitivity and decrease bias from familial differences in thresholds for hospitalization rather than true occurrence of disease. At the time of our initial assembly of the WG cohort, data on nonprimary outpatient care were not available for use, which is why the index cohort of patients is based on hospitalizations and stretches through 2003 rather than 2006. The use of outpatient data and the chart review is a particular strength compared to other register-based assessments of familial comorbidity. For instance, in a recent publication on familial associations of RA with other autoimmune conditions, including WG, a 40% increased risk for the disease was noted among children of parents with RA, but this result was based on hospitalization data only, did not distinguish between seropositive and seronegative RA, and did not include chart review[35].

Our study, which used chart review of 68 of the patients with WG, suggested a somewhat higher proportion of misclassification of the WG diagnosis compared to previous chart reviews of a total of about 160 patients with WG from the same cohort[9,14,34]. This misclassification is, however, more likely to result in an underestimation rather than an overestimation of the relative risks. By contrast, the same chart review indicated a very high diagnostic correctness of the arthritic disease among relatives (a similarly high fraction, 90%, among relatives of patients with WG and population controls). The lack of individual data on the accuracy of the other autoimmune/inflammatory diseases under study is a limitation of our study.

In this large population-based study, we found that first-degree relatives of patients with WG are at increased risk of autoimmune/inflammatory diseases such as hypothyroidism, multiple sclerosis, and inflammatory polyarthritis including seropositive RA, compared to relatives of population controls, indicating a moderate effect of shared susceptibilities to WG and other autoimmune/inflammatory diseases on a population level.

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