

Specific Association of Type 1 Diabetes Mellitus With Anti-Cyclic Citrullinated Peptide–Positive Rheumatoid Arthritis

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Objective. The co-occurrence of autoimmune diseases such as rheumatoid arthritis (RA) and type 1 diabetes mellitus (DM) has been reported in individuals and families. In this study, the strength and nature of this association were investigated at the population level in a Swedish case–control cohort.

Methods. For this case–control study, 1,419 patients with incident RA diagnosed between 1996 and 2003 were recruited from university, public, and private rheumatology units throughout Sweden; 1,674 matched control subjects were recruited from the Swedish national population registry. Sera from the subjects were

tested for the presence of antibodies to cyclic citrullinated peptide (anti-CCP), rheumatoid factor (RF), and the 620W *PTPN22* allele. Information on a history of diabetes was obtained by questionnaire, telephone interview, and/or medical record review. The prevalence of type 1 DM and type 2 DM was compared between patients with incident RA and control subjects and further stratified for the presence of anti-CCP, RF, and the *PTPN22* risk allele.

Results. Type 1 DM was associated with an increased risk of RA (odds ratio [OR] 4.9, 95% confidence interval [95% CI] 1.8–13.1), and this association was specific for anti-CCP–positive RA (OR 7.3, 95% CI 2.7–20.0), but not anti-CCP–negative RA. Further adjustment for the presence of *PTPN22* attenuated the risk of anti-CCP–positive RA in patients with type 1 DM to an OR of 5.3 (95% CI 1.5–18.7). No association between RA and type 2 DM was observed.

Conclusion. The association between type 1 DM and RA is specific for a particular RA subset, anti-CCP–positive RA. The risk of developing RA later in life in patients with type 1 DM may be attributed, in part, to the presence of the 620W *PTPN22* allele, suggesting that this risk factor may represent a common pathway for the pathogenesis of these 2 diseases.

Autoimmune diseases such as rheumatoid arthritis (RA) and type 1 diabetes mellitus (DM) have been observed to co-occur within individuals and families (1–4). Although the exact etiologies of RA and type 1 DM are unknown, they are likely attributable to a combination of genetic susceptibility and interactions between environmental risk factors and genes. Thus far, one established genetic risk factor is shared by RA and type 1 DM: the 620W allele of the protein tyrosine phosphatase N22 gene (*PTPN22*) (5–9). Other genes involved in the pathogenesis of RA and type 1 DM have

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been identified recently and are under active investigation (6,10–15). Although the association between the *PTPN22* polymorphism and the risk of type 1 DM and RA is established, few population studies have examined the clinical comorbidity between type 1 DM and RA. A recent epidemiologic study provided evidence of a non-significant trend toward an association between RA and diabetes in general (16); however, that study did not stratify subjects according to the presence of antibodies to cyclic citrullinated peptide (anti-CCP) in RA patients or according to the type of diabetes.

It has become increasingly clear that there are distinct subsets of RA, as highlighted in recent studies showing specific genetic and environmental risk factors that differ depending on the presence or absence of anti-CCP and the presence or absence of rheumatoid factor (RF) (17–25). For example, the risk of developing anti-CCP-positive RA was found to be higher in individuals who have the 620W allele of *PTPN22* and the shared epitope (18).

Considering these observations, it follows that a comprehensive assessment of autoimmune comorbidity is needed to take into account established common genetic risk factors as well as genotypic and phenotypic aspects of the diseases under study. We hypothesized that type 1 DM, an autoimmune disease that shares *PTPN22* as a susceptibility gene, may be associated with RA, and that this association may be dependent on the phenotype defined by the presence or absence of anti-CCP antibodies.

PATIENTS AND METHODS

Design overview. The Epidemiological Investigation of RA (EIRA) study is a population-based case-control study of incident cases of RA among patients ages 18–70 years in whom RA was diagnosed between May 1996 and December 2003 in Sweden. More details on the design of the EIRA study are described in reports by Klareskog et al and Stolt et al (17,22). The Ethics Committee of the Karolinska Institute approved the study, and all case and control subjects consented to participate in the study after providing their written informed consent.

Setting and participants. A case was defined as a subject in whom RA was newly diagnosed by his or her rheumatologist and who fulfilled the American College of Rheumatology (formerly, the American Rheumatism Association) 1987 criteria for the classification of RA (26). Cases were recruited from all public rheumatology units and a majority of private rheumatology units throughout Sweden.

For each case, a control subject, who was matched by age, sex, and location of residence, was randomly selected from the study base, using the national population registry of Sweden. If a control subject declined to participate, was not

traceable, or reported having RA, a new control was selected according to the same algorithm.

Exposure. Cases and controls completed an EIRA questionnaire that covered a broad range of topics, including questions on preexisting diseases such as diabetes, as well as treatment for diabetes. Questions pertaining to diabetes specifically asked, “Do you have diabetes?” In addition, patients were asked to classify the type of diabetes treatment, in categories that included “diet restricted,” “oral treatment,” or “insulin.” Participants were also asked to specify the year of diabetes onset. In total, 1,419 cases (96% response rate) and 1,674 controls (82% response rate) answered the EIRA questionnaire. Data indicating whether a patient self-reported having a specific type of diabetes, either type 1 DM or type 2 DM, were not obtained in the questionnaire. Ninety-five percent of cases and 51% of controls provided serum samples for genotyping.

Diabetes diagnosis. Validation of diagnosis. We validated each subject’s diabetes status by contacting all those with a self-reported diagnosis of diabetes. For this purpose, we contacted the subjects by telephone, administered a diabetes questionnaire (see below for further details), and obtained data through medical record review (Figure 1).

Classification of diabetes. We classified subjects as having type 1 DM or type 2 DM, using 1 of the following methods: 1) telephone interview or questionnaire with specific questions about diabetes history, followed by classification of diabetes type by 2 independent reviewers; 2) chart review of available medical records; or 3) for those subjects for whom data were not available from interview or medical records, application of criteria (for classification of type 1 DM) requiring that the patient be receiving insulin monotherapy and be younger than age 30 years at the time of diabetes diagnosis.

We contacted all subjects with self-reported diabetes by telephone and administered a diabetes history questionnaire. This questionnaire was developed with an endocrinologist at the Karolinska Institute. It contained the following questions: 1) “Do you have diabetes?”; 2) “What type of diabetes do you have?” (response choice: type 1 DM, type 2 DM, or unknown); 3) “How old were you at diagnosis?”; 4) “What treatment were you on at diagnosis?” and 5) “What treatment are you on now?” (response choice: diet restriction only, diet restriction and oral medication, oral medication only, oral medication and insulin, or insulin only). If a subject could not be reached by telephone, a printed version of the questionnaire was mailed to his or her home. Seventeen of the 113 subjects were deceased at the time of the mailing. Of the remaining 96 subjects, 86 responded to the mailed questionnaire (90% response rate).

Two independent reviewers with medical training classified subjects as having type 1 DM or type 2 DM on the basis of responses to the questionnaire. These individuals were blinded to the RA status of the subjects. For 2 subjects, there was discordance between reviewers in the assigned diagnosis. Final classification of diabetes was reached by consensus.

We had access to 44 medical records (39%) among the 113 patients with diabetes self-reported on the EIRA questionnaire. Type 1 DM or type 2 DM was determined by diagnosis code and by the actual wording from the treating physician in the medical record, with reviewers blinded to the RA status of the subjects.

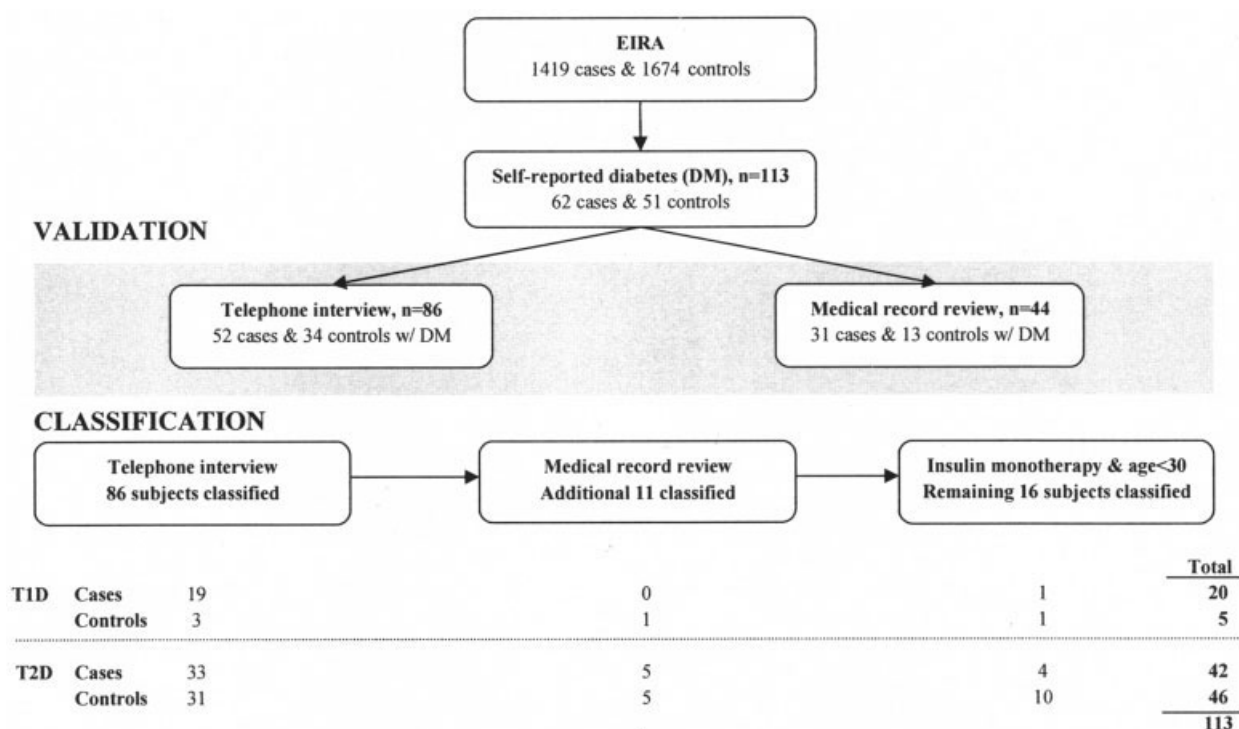


Figure 1. Validation and classification of self-reported type 1 (T1D) and type 2 (T2D) diabetes mellitus (DM) from the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) questionnaire.

We hypothesized that patients with type 1 DM could be identified as those who were receiving insulin monotherapy and whose age at diagnosis was <30 years. This age cutoff is generally accepted in the literature as a criterion for classification of type 1 DM (27,28). In contrast, the majority of patients with type 2 DM would be receiving a controlled diet regimen, likely in combination with oral medications or being age ≥ 30 years and receiving insulin monotherapy.

We tested the positive predictive value (PPV) of this method for classifying type 1 DM against our 2 other methods of classification, chart review and telephone interview. The PPV of using the criteria for classification of type 1 DM in which patients were required to be receiving insulin monotherapy (defined by EIRA questionnaire response) and being age <30 years at the time of diagnosis of diabetes, as compared with classification of type 1 DM by chart review diagnosis, was 100% (sensitivity 69%, specificity 100%). Similarly, the PPV of a patient receiving insulin monotherapy and being age <30 years at the time of diagnosis as the classification criteria for type 1 DM, as compared with telephone interview for classification of type 1 DM, was 100% (sensitivity 72%, specificity 100%).

The agreement (kappa statistic) between chart review and telephone questionnaire for the diagnosis of type 1 DM or type 2 DM was high ($\kappa = 0.94$). Therefore, those with self-reported diabetes in our study were first classified as having type 1 DM or type 2 DM according to the diagnosis determined via the extended telephone questionnaire ($n = 86$). Of the remaining 27 subjects who did not respond to the telephone questionnaire, 11 had a chart review diagnosis

available and were classified according to their medical records. The remaining 16 who did not respond to the telephone interview and for whom we had no medical records available were classified as having type 1 DM if they reported being on a regimen of insulin monotherapy and being younger than age 30 years on the initial EIRA questionnaire (Figure 1).

Laboratory studies. Sera for serologic analyses (99.9% of cases) were obtained and tested for the presence of RF and anti-CCP. RF status was determined using nephelometry. Anti-CCP positivity was determined with an Immunoscan-RA Mark2 enzyme-linked immunosorbent assay. Results were corroborated by validation at the clinical immunology laboratory in Uppsala, Sweden. Cases with anti-CCP antibody levels higher than 25 units/ml were considered positive for anti-CCP. DNA was retrieved from the serum samples of 1,356 cases and 863 controls, and genotyping for the 620W *PTPN22* allele was performed as previously described (6).

Smoking status. Subjects' smoking status was stratified as "ever smoker" or "never smoker." An ever smoker was defined as an individual who had ever smoked cigarettes. A never smoker was someone who had never smoked cigarettes. More details on smoking classification are provided in the study by Stolt et al (22).

Statistical analysis. We calculated odds ratios (ORs) and 95% confidence intervals (95% CIs) to determine the likelihood of an association of RA with type 1 DM or type 2 DM, by means of logistic regression models. We further performed analyses stratified according to anti-CCP and RF status among cases. Eighty percent of RF-positive RA cases

and 87% of anti-CCP-positive RA cases were positive for both RF and anti-CCP. Since the results from cases stratified by anti-CCP and RF status were similar (point estimates differed by <5%), we chose to present only the results for anti-CCP status in the text, while the results pertaining to RF status are shown in the Tables.

All analyses were adjusted for the matching factors of age, sex, and location of residence. Further adjustments were made for known and possible confounding factors, such as smoking, body mass index (BMI), and the 620W *PTPN22* genotype. We performed both unmatched analyses (unconditional logistic regression) and matched analyses (conditional logistic regression). The point estimates for the unmatched and matched analyses were in close agreement. Since the data obtained by unconditional logistic regression analyses were more precise, only the results from the unmatched analyses, adjusted for the matching variables, are presented.

The SAS software package, version 9.1 (SAS Institute, Cary, NC) was used to calculate ORs and 95% CIs.

RESULTS

In total, there were 3,093 participants in the study, of whom 1,419 were incident RA cases and 1,674 were population-based controls. Most subjects were born in Sweden, and 97% of participants reported having a Caucasian ancestry. Seventy-one percent of the study population was female, and the mean \pm SD BMI among all subjects was 25.3 ± 5.17 kg/m². Characteristics of the study population are presented in Table 1. Controls without genotype data had similar age, sex, geographic distribution, and smoking history as compared with those with genotype data (data not shown).

Sixty-two patients with RA (4.4% of all cases) self-reported a diagnosis of diabetes as a preexisting disease, while 51 controls (3.1% of all controls) self-reported a preexisting diagnosis of diabetes ($P = 0.05$). Using the algorithm of classification based on our telephone interview and medical record review, 25 subjects had type 1 DM (20 cases and 5 controls), while 88 subjects had type 2 DM (42 cases and 46 controls).

The median age at onset of type 1 DM was 21 years (range 2–44 years), and the mean duration of type 1 DM at the time of RA onset in the cases was 25 years. The median age at onset of type 2 DM was 57 years (range 30–69 years), and the mean duration of type 2 DM at the time of RA onset in the cases was 6 years, with no significant difference in duration of diabetes between cases and controls. In the telephone interview subset ($n = 86$) and the chart-validated subset ($n = 44$), the median age at onset of type 1 DM was 23 years (range 2–44 years) for both cases and controls. For those without available chart or telephone interview data ($n =$

Table 1. Characteristics of the cases and controls*

	Cases (n = 1,419)	Controls (n = 1,674)
Female sex	1,012 (71)	1,188 (71)
Age		
18–29 years	106 (7)	143 (8)
30–39 years	176 (12)	225 (13)
40–49 years	251 (18)	308 (18)
50–59 years	475 (33)	543 (32)
60–70 years	411 (29)	455 (27)
BMI†		
0–20 kg/m ²	101 (7)	120 (7)
20–25 kg/m ²	654 (46)	804 (48)
25–30 kg/m ²	475 (33)	550 (33)
>30 kg/m ²	188 (13)	198 (12)
Smoker‡		
Ever	869 (61)	913 (55)
Never	432 (30)	625 (37)
Serology§		
RF+	927 (65)	–
Anti-CCP+	857 (60)	–
Genetics, presence of <i>PTPN22</i> ¶	390 (28)	197 (12)

* Values are the number (%) of subjects. BMI = body mass index.

† Information on weight was missing for 1 case and 2 controls.

‡ Information on smoking was missing for 118 cases and 136 controls.

§ Information on rheumatoid factor (RF) status was available for 1,418 cases; information on anti-cyclic citrullinated peptide (anti-CCP) status was available for 1,401 cases.

¶ Genetic information was available for 1,356 cases and 863 controls.

16), the median age at onset of type 1 DM was 18 years (range 2–28 years).

Overall, self-reported diabetes was associated with a modest increased risk of RA (OR 1.4, 95% CI 1.0–2.1). When the analysis was stratified by type of DM, the increased risk of RA was limited to those with type 1 DM (OR 4.9, 95% CI 1.8–13.1) rather than to those with type 2 DM (OR 1.1, 95% CI 0.7–1.6) (Table 2).

When the analysis was stratified by anti-CCP status, the increased risk of RA associated with type 1 DM was observed entirely in those with anti-CCP–

Table 2. Risk of developing rheumatoid arthritis according to the type of diabetes mellitus (DM)

	No. exposed cases/ no. exposed controls	OR (95% CI)*	
		Model 0	Model 1
All diabetes	62/51	1.4 (1.0–2.1)	1.3 (0.9–2.0)
Type 1 DM†	20/5	4.9 (1.8–13.1)	4.8 (1.8–12.9)
Type 2 DM†	42/46	1.1 (0.7–1.6)	1.0 (0.6–1.5)

* Odds ratios (ORs) and 95% confidence intervals (95% CIs) were determined by unconditional logistic regression analysis adjusted for age, sex, and location of residence (model 0) or for age, sex, location of residence, smoking, and body mass index (model 1).

† Type of DM was assigned by either telephone questionnaire, chart review, or requirement of being on a regimen of insulin monotherapy and being age <30 years.

Table 3. Association between type 1 and type 2 diabetes mellitus (DM) and risk of developing rheumatoid arthritis, stratified by anti-CCP and RF status with successive adjustment for potential confounding factors*

Type of DM, anti-CCP/RF status	No. exposed cases/ no. exposed controls	OR (95% CI)†		
		Model 0	Model 1	Model 2
Type 1				
All	20/5	4.9 (1.8–13.1)	4.8 (1.8–12.9)	3.5 (1.0–12.1)
Anti-CCP+	18/5	7.3 (2.7–20.0)	7.3 (2.6–20.2)	5.3 (1.5–18.7)
Anti-CCP–	2/5	1.3 (0.3–7.0)	1.3 (0.2–6.9)	1.1 (0.2–6.7)
RF+	19/5	7.1 (2.6–19.2)	7.0 (2.6–19.2)	5.1 (1.5–17.8)
RF–	1/5	0.7 (0.1–5.8)	0.7 (0.1–5.7)	0.6 (0.1–5.6)
Type 2				
All	42/46	1.1 (0.7–1.6)	1.0 (0.6–1.5)	1.1 (0.6–1.8)
Anti-CCP+	22/46	0.9 (0.6–1.6)	0.9 (0.5–1.6)	1.0 (0.6–1.9)
Anti-CCP–	20/46	1.3 (0.7–2.2)	1.1 (0.6–1.9)	1.1 (0.6–2.2)
RF+	27/46	1.1 (0.7–1.8)	1.0 (0.6–1.7)	1.2 (0.7–2.1)
RF–	15/46	1.0 (0.6–1.9)	0.9 (0.5–1.7)	0.9 (0.5–1.9)

* Anti-CCP = anti-cyclic citrullinated peptide; RF = rheumatoid factor.

† Odds ratios (ORs) and 95% confidence intervals (95% CIs) were determined by unconditional logistic regression analysis adjusted for age, sex, and location of residence (model 0), for age, sex, location of residence, smoking, and body mass index (BMI) (model 1), or for age, sex, location of residence, BMI, and *PTPN22* status among a subset of study subjects (1,356 cases and 863 controls) (model 2).

positive RA (OR 7.3, 95% CI 2.7–20.0) rather than in those with anti-CCP–negative RA (OR 1.3, 95% CI 0.3–7.0). Type 2 DM was not associated with either anti-CCP–positive or anti-CCP–negative RA. Similar risk associations were found when cases were stratified by RF status (Table 3).

Adjustment (in addition to age, sex, and location of residence) for smoking and BMI did not significantly alter the association between type 1 DM and anti-CCP–positive RA. Further adjustment for the presence of the 620W *PTPN22* allele attenuated the risk of developing anti-CCP–positive RA among individuals with type 1 DM, from an OR of 7.3 to an OR of 5.3 (Table 3).

To test the robustness of these associations that were based on self-reported diabetes in the entire data set, we performed a series of sensitivity analyses. To test the algorithm used to define the type of diabetes, we performed analyses on the subset assigned the diagnosis by medical chart review (39% of all subjects with self-reported diabetes in the study population). Based on the actual diabetes type recorded in the medical record, the association between type 1 DM and the risk of anti-CCP–positive RA was similar to that observed for the entire data set (OR 11.7, 95% CI 2.6–52.7), whereas other combinations of diabetes (type 1 DM/type 2 DM) and RA (anti-CCP positive/anti-CCP negative) revealed no association (data not shown).

To assess whether insulin, rather than type 1 DM classification, was driving the association with RA, we assessed the risk of RA in those subjects who reported

having diabetes and being treated with insulin in combination with oral medication and/or diet restrictions (presumed to have type 2 DM treated with insulin). No association of insulin treatment with the risk of RA was observed (OR 1.0, 95% CI 0.3–3.6; 7 exposed cases versus 8 exposed controls).

DISCUSSION

Our study results show a significant association between type 1 DM and RA. The association is not general, but rather is specific for a particular subset of RA, anti-CCP–positive RA. Part of this association could be attributed to the presence or effect of the 620W *PTPN22* allele, which corroborates the findings from previous studies in which the *PTPN22* polymorphism has been determined to be a risk factor for type 1 DM as well as for anti-CCP–positive RA (3,6,18). Although the risk of anti-CCP–positive RA was attenuated after adjusting for the presence of *PTPN22* (OR decreasing from 7.3 to 5.3), our data suggest that other genetic and/or environmental factors could contribute to the association between type 1 DM and RA. Since the presence of RF and positivity for anti-CCP antibodies are highly correlated in RA, the association between type 1 DM and RA was also found to be specific for RF–positive RA, and not for RF–negative RA. There was no association between any subset of RA and type 2 DM.

In a recent study by Simard and Mittleman, the

results suggested a nonsignificant association between diabetes and RA (16). There are several reasons for the apparent discrepancy between their results and the findings in our study. Simard and Mittleman conducted a cross-sectional analysis and did not analyze type 1 DM and type 2 DM as separate groups, nor did they distinguish between anti-CCP-positive and anti-CCP-negative RA (or between RF-positive and RF-negative RA). Moreover, the study also included a smaller number of patients with RA and diabetes (in total, 144 patients with RA, 24 of whom had concurrent diabetes). In addition, their study was conducted in the US in a population with a mean age of 73 years, in which the prevalence of diabetes is ~18.5% in individuals ages 65–74 years, of whom an estimated 90–95% have type 2 DM (29). Analysis of patients with diabetes as one group when the majority of patients have type 2 DM, in whom there is presumably no association with RA, would dilute the significant association seen between type 1 DM and the risk of RA, specifically with anti-CCP-positive RA. The overall type 1 DM–RA risk association of 1.2 observed in the study by Simard and Mittleman is comparable with the overall association of 1.4 (95% CI 1.0–2.1) observed in our study.

The PPV for classifying type 1 DM by requiring that a patient be receiving insulin monotherapy and be age <30 years was 100% when compared with classification by medical record review or by telephone interview. However, the sensitivity of this classification was 69% as compared with classification by chart review, and 72% as compared with classification by telephone interview. This could lead to misclassification, in which type 1 DM might be considered to be type 2 DM. We therefore conducted a subset analysis of the diabetes diagnosis that was obtained from medical record review, a method in which misclassification is minimized. The results from this subset analysis suggested a similar risk of developing anti-CCP-positive RA among patients diagnosed as having type 1 DM by medical record review (OR 11.7, 95% CI 2.6–52.7). These findings from the subset analysis concur with the association seen in the entire study population.

The strengths of our study include the population-based setting, the large number of RA cases, the high participation rate (96% among cases and 82% among controls), and the use of incident cases of new-onset RA. To classify diabetes, we used 2 methods, medical record review and contacting all available subjects with self-reported diabetes by telephone or by administering a diabetes questionnaire. In addition, we discriminated anti-CCP-positive RA from anti-CCP-negative RA;

previous studies have shown this distinction to be of importance, since the 2 subgroups are associated with specific, but different, genetic and environmental risk factors and interactions between them (17–19,21–25,30). Finally, we incorporated genotype information on *PTPN22*, a shared genetic susceptibility loci, into our model.

In addition to shared genetic risk factors for type 1 DM and RA, there are major clinical differences between patients with type 1 DM and those with type 2 DM that could potentially explain the association observed in our study. Patients with type 1 DM are exposed to elevated glucose levels and exogenous insulin much longer than those with type 2 DM. To test this alternative explanation, we performed a subset analysis that assessed the risk of RA in individuals exposed to insulin as treatment for type 2 DM. No increased risk of RA was observed in this group, although the numbers of exposed subjects were small.

Although recall bias is a potential threat to the validity of case-control studies, our validation study showed that 100% of cases and controls who reported diabetes as a preexisting disease at the time of diagnosis of RA and who underwent chart review and/or completed a diabetes questionnaire actually had diabetes. Another limitation to this study was the relatively small number of patients with diabetes in the study, leading to the wide confidence intervals around our point estimates. Therefore, although a highly significant association was seen, the exact quantification of the risk is somewhat uncertain. This situation was difficult to avoid, given the low prevalence of diabetes in the Swedish population (3.2%) and given that the prevalence in our control study population (3.1%) is in concurrence with the estimated national prevalence proportion (31,32). This also suggests that the prevalence of diabetes observed in our study population is not a consequence of selection bias skewed toward healthy participants.

A smaller percentage of controls than cases was genotyped for *PTPN22*. If the probability of being genotyped is related to diabetes, this may result in biased relative risk estimates. To assess this, we compared characteristics of the control group of subjects who were genotyped with those of the controls who were not genotyped. No significant differences were seen, in general, for sex, age, area of residence, smoking, and BMI, and there was no relationship between diabetes and the probability of being genotyped.

With recent breakthroughs in our ability to identify susceptibility loci in genome-wide scans, increasing

numbers of loci are being identified as risk factors for RA and type 1 DM (11,13,14,33,34). The known genetic risk factors for type 1 DM include loci in the major histocompatibility complex region (HLA-DQB1, DQA1, and DRB1), in the insulin locus, in the insulin gene *IDDM2*, in the *CTLA4* gene, and in the 620W *PTPN22* allele (11,33,34). Recent genome-wide analyses have also identified *KLAA0350*, the interferon-induced helicase region *IFIH1*, and new chromosome regions on 4q27, 12q13, 16p13, 12q24, and 18p11 as potential type 1 DM susceptibility loci (11,34,35). The single-nucleotide polymorphism rs6822844 at chromosome 4q27 was recently shown to be associated with RA (35).

Other established genetic risk factors for RA, other than the 620W *PTPN22* allele, include the shared epitope of the HLA-DRB1 allele, *CTLA4*, and the peptidyl arginine deiminase gene *PADI4* in Asian populations (6,15,19,24,36–38). More recently, genome-wide scans have identified new loci associated with increased susceptibility to RA, including *STAT4* and *TRAF1-C5* (encoding tumor necrosis factor receptor-associated factor 1) and complement component 5, and an allele at 6q23 (13,14,39,40). Of these genetic risk factors, the HLA-DRB1 shared epitope alleles and the 620W *PTPN22* allele, as well as the *TRAF1-C5*-associated alleles, have been specifically associated with anti-CCP-positive RA (17–19).

Our results emphasize that further studies of comorbidities and shared susceptibility factors between different immune-mediated inflammatory diseases should be performed, with subsets of the diseases, such as anti-CCP-positive RA versus anti-CCP-negative RA, taken into account. With the expanding knowledge and new information being obtained about genetic associations for diseases, comparative studies incorporating genetic and environmental risk factors into the analysis of complex diseases may lead to a better understanding of the common molecular pathways involved in the etiology of the diseases. Further investigation of the susceptibility genes and other risk factors for type 1 DM are warranted, to allow identification of potential risk factors for anti-CCP-positive/RF-positive RA, and may ultimately provide more insight into the etiology of autoimmunity.

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AUTHOR CONTRIBUTIONS

Dr. Klareskog and Alfredsson had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Liao, Klareskog, Askling, Alfredsson.

Acquisition of data. Gunnarsson, Källberg, Ding, Plenge, Padyukov, Askling, Alfredsson.

Analysis and interpretation of data. Liao, Gunnarsson, Källberg, Ding, Plenge, Karlson, Klareskog, Askling, Alfredsson.

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Statistical analysis. Liao, Gunnarsson, Ding, Alfredsson.

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