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A specific association exists between type 1 diabetes and anti-CCP positive rheumatoid arthritis

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Abstract

Objective—The co-occurrence of autoimmune diseases such as rheumatoid arthritis (RA) and type 1 diabetes (T1D) has been reported in individuals and families. We studied the strength and nature of this association at the population level.

Methods—We conducted a case-control study of 1419 incident RA cases and 1674 controls between 1996 and 2003. Subjects were recruited from university, public and private rheumatology units throughout Sweden. Blood samples were tested for the presence of antibodies to cyclic citrullinated peptide (anti-CCP), rheumatoid factor (RF) and the presence or absence of the 620W *PTPN22* allele. Information on history of diabetes was obtained by questionnaire, telephone interview, and medical record review. The prevalence of T1D and type 2 diabetes (T2D) was compared between incident RA cases and controls and further stratified by anti-CCP, RF status, and the presence of the *PTPN22* risk allele.

Results—T1D was associated with an increased risk of RA, OR 4.9 (95% CI 1.8–13.1), and was specific for anti-CCP+ RA, OR 7.3 (95% CI 2.7–20.0), but not anti-CCP negative RA. Further adjustment for *PTPN22* attenuated the odds ratio for anti-CCP+ RA in individuals with T1D to 5.3 (95% CI 1.5–18.7). No association was observed between RA and T2D.

Conclusion—The association between T1D and RA is specific for a particular RA subset, anti-CCP+ RA. The risk of type 1 diabetics developing RA later in life may be attributed in part to the presence of the 620W *PTPN22* allele, suggesting a common pathway for the pathogenesis of these two diseases.

Conflict of interest statement Authors report no conflicts of interest.

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INTRODUCTION

Autoimmune diseases such as rheumatoid arthritis (RA) and type 1 diabetes (T1D) have been observed to co-occur within individuals and families (1–4). Although the exact etiology of RA and T1D are unknown, it is likely due to a combination of genetic susceptibility and interactions between environmental risk factors and genes. Thus far, there is one established genetic risk factor shared by RA and T1D, the 620W allele of protein tyrosine phosphatase N22 (*PTPN22*) (5–9). Other genes involved in the pathogenesis of RA and T1D have recently been identified and are under active investigation (6,10–15).

Although the association between the *PTPN22* polymorphism and risk of T1D and RA is established, few population studies have examined the clinical co-morbidity between T1D and RA. A recent epidemiologic study provided evidence for a non-significant trend toward an association between RA and diabetes in general, however, did not stratify by antibodies to cyclic citrullinated peptides (anti-CCP) status in RA patients or type of diabetes (16).

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

From the above, it follows that a comprehensive assessment of autoimmune co-morbidity needs to take into account established common genetic risk factors, as well as geno- and pheno-typic aspects of the diseases under study. We hypothesized that type 1 diabetes, an autoimmune disease that shares *PTPN22* as a susceptibility gene, may be associated with rheumatoid arthritis, 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) is a population-based case-control study of incident cases with RA aged 18–70 diagnosed between May 1996 and December 2003 in Sweden. For more details on the EIRA study design, please refer to Stolt and Klareskog, et al (17,22). The Ethics Committee of the Karolinska Institute approved the study and the cases and controls consented to participate in the study after receiving written information.

Setting and Participants

A case was defined as a subject who received a new diagnosis of RA by their rheumatologist and fulfilled the 1987 American College of Rheumatology (ACR) criteria for the classification of RA (26). Cases were recruited from all public and a majority of private rheumatology units throughout Sweden.

For each case, a control, matched by age, sex, and location of residence, was randomly selected from the study base, using the national population registry. If a control 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 which covered a broad range of topics including questions on pre-existing diseases, such as diabetes and treatment for diabetes. Questions pertaining to diabetes specifically asked: "Do you have diabetes?" (yes or no) and

the type of treatment. Treatment categories included: "diet restricted", "oral treatment" or "insulin." Participants were also asked to specify the year of diabetes onset. In total, 1419 cases (96% response rate) and 1674 controls (82% response rate) answered the EIRA questionnaire. Self-reported data on whether a patient had type 1 or type 2 diabetes were not specifically asked in the questionnaire. Ninety-five percent of cases and 51% of controls provided samples for genotyping.

Diabetes validation

We validated subjects' diabetes status by contacting all self-reported diabetics by telephone and administering a diabetes questionnaire (further details on the questionnaire below, *Diabetes classification*) and through medical record review (Figure 1).

Diabetes classification

We classified subjects as having T1D or T2D by the following three methods: (1) telephone interview or questionnaire with specific questions about diabetes history followed by classification of diabetes by 2 independent reviewers; (2) chart review of available medical records; (3) if data were not available from interview or medical records, subjects on insulin monotherapy whose age was less than 30 at diabetes diagnosis were classified as T1D.

We contacted all self-reported diabetics by telephone and administered a diabetes history questionnaire. This questionnaire was developed with an endocrinologist at the Karolinska Institute with the following questions: (1) Do you have diabetes? Yes/no; (2) What type of diabetes do you have? Type 1/ Type 2/ unknown; (3) How old were you at diagnosis? (4) What treatment were you on at diagnosis? (5) What treatment are you on now? Diet restriction only/ Diet restriction and oral medication/ Oral medication only/ Oral medication and insulin/ Insulin only. If a subject could not be reached by telephone, a print version of the questionnaire was mailed to their home. Seventeen of the 113 subjects were deceased at the time of the mailing. Of the remaining 96 subjects, we received 86 responses (90% response rate).

Two independent reviewers with medical training classified subjects as T1D or T2D based on responses to the questionnaire. These individuals were blinded to the RA status of the subjects. There were 2 subjects where there was discordance in the assigned diagnosis. Final classification of diabetes was reached by consensus.

We had access to 44 medical records of the 113 self-reported diabetics in the EIRA questionnaire (39%). Type 1 and 2 diabetes was determined by diagnosis code and actual wording by the treating physician in the medical record, with reviewers blinded to the RA status of the subjects. We hypothesized that type 1 diabetics could be identified as individuals on insulin monotherapy and had an age at diagnosis less than 30. This age cutoff is generally accepted in the literature to classify T1D (27,28). In contrast, the majority of type 2 diabetics would be diet controlled, likely in combination with oral medications or age \geq 30 and on insulin monotherapy. We tested the positive predictive value (PPV) of this method for classifying T1D against our two methods of classification, chart review and telephone interview.

The PPV of using insulin monotherapy (defined by EIRA questionnaire response) and age <30 at diagnosis of diabetes to classify T1D compared to chart review diagnosis of T1D was 100% (sensitivity 69%, specificity 100%). Similarly, the PPV of insulin monotherapy and age <30 in classifying T1D compared to the telephone interview classification of T1D was 100% (sensitivity 72% and specificity 100%). The agreement between the diagnoses of T1D and T2D was high between chart review and telephone questionnaire (kappa=0.94). Therefore, self-reported diabetics were first classified as T1D or T2D according to their

diagnosis 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 whom we had no medical records available, were classified as T1D if they reported being on insulin monotherapy and had an age at diagnosis of <30 years on the initial EIRA questionnaire (Figure 1).

Laboratory studies

Sera for serologic analysis (99.9 % of cases) were obtained, and tested for the presence of RF and anti-CCP. RF status was determined using nephelometry. Anti-CCP was analyzed with the Immunoscan-RA Mark2 ELISA. Results were corroborated by validation at the clinical immunology laboratory in Uppsala, Sweden. Cases with anti-CCP antibody levels over 25 U/ml were considered positive. DNA was retrieved from 1356 cases and 863 controls, and genotyping for the 620W *PTPN22* allele was performed as previously described and reported (6).

Smoking status

Subjects' smoking status was stratified by "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. For more details on smoking classification, please refer to Stolt, et al (22).

Statistical Analysis

We calculated odds ratios (OR) for RA associated with T1D and T2D, respectively, with 95 % confidence intervals (CI) by means of logistic regression models. We performed stratified analyses according to anti-CCP and RF status among cases. Eighty percent of RF positive cases and 87% of anti-CCP positive 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 <5%), we chose to present results regarding anti-CCP status in the text. 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 former was more precise, only the results of the unmatched analyses adjusted for the matching variables are presented.

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

RESULTS

In total, there were 3093 participants in the study; 1419 incident RA cases and 1674 population based controls. Most subjects were born in Sweden, and 97% of participants reported a Caucasian ancestry. Seventy-one percent of the study population was female and the mean BMI among all subjects was 25.3 (SD 5.17). Characteristics of the study population are presented in Table 1. Controls without genotype data had similar age, sex, geographic distribution and smoking history compared to those with genotype data (data not shown).

Sixty-two subjects (4.4% of all cases) with RA self-reported pre-existing diabetes while 51 controls (3.1% of all controls) reported pre-existing diabetes (p= 0.05). Using the algorithm based on our telephone interview and medical record review (see Methods, Diabetes classification), 25 subjects had T1D (20 cases and 5 controls), while 88 subjects had T2D (42 cases and 46 controls).

The median age at onset of T1D was 21 years (range 2 to 44 years), and the mean duration of T1D at RA onset was 25 years. Median age at onset of T2D was 57 (range 30 to 69 years), and the mean duration of T2D at RA onset was 6 years, with no significant difference in duration between cases and controls. In the telephone interview (n=86) and the chart-validated subset (n=44), median age at onset for T1D was 23 years (range 2 to 44 years) for both groups. For those without chart or telephone interview data (n=16), median age at onset of T1D was 18 years (range 2 to 28 years).

Overall, self-reported diabetes was associated with a modest increased risk of RA, OR 1.4 (95% CI 2.0–2.2). When stratified by T1D and T2D, the increased risk was limited to T1D (OR 4.9, 95% CI 1.8–13.1) rather than to T2D, (OR 1.1, 95% CI 0.7–1.6) (Table 2). When stratified by anti-CCP status, the increased risk associated with T1D was entirely observed in anti-CCP positive RA (OR 7.3, 95% CI 2.7–20.0) rather than anti-CCP negative RA (OR 1.3, 96% CI 0.3–7.0). T2D was neither associated with anti-CCP positive nor with anti-CCP negative RA. Similar 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 T1D and anti-CCP positive RA. Further adjustment for the presence of the 620W *PTPN22* allele attenuated the odds ratio for developing anti-CCP positive RA among individuals with T1D, from 7.3 to 5.3 (Table 3).

To test the robustness of the above associations based on self-reported diabetes in the entire dataset, we performed a series of sensitivity analyses: (A) To test the algorithm used to define type of diabetes, we performed analyses on the subset subjected to the chart review (39% of all self-reported diabetes in the study population). Based on the actual diabetes type recorded in the medical record, the above observed association between T1D and risk of anti-CCP positive RA was similar (OR 11.7, 95% CI 2.6–52.7), whereas other combinations of diabetes (T1D/T2D) and RA (anti-CCP positive/negative) revealed no association (data not shown). (B) To assess whether insulin rather than T1D was driving the association with RA, we assessed the risk of RA in those subjects who reported diabetes and were treated with insulin in combination with oral medication and/or diet restrictions (presumed to have type 2 diabetes treated with insulin). No association was seen (OR 1.0, 95% CI 0.3–3.6, 7 exposed cases vs. 8 exposed controls).

DISCUSSION

Our study showed a significant association between T1D and RA. The association is not general, but rather 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 with previous studies demonstrating that the *PTPN22* polymorphism is a risk factor for T1D as well as for anti-CCP positive RA (3,6,18). Although the risk of anti-CCP positive RA was attenuated after adjusting for *PTPN22* (OR decreasing from 7.3 to 5.3), our data suggests that other genetic and/or environmental factors could contribute to the association between T1D and RA. Since RF and anti-CCP are highly correlated in RA, the association between T1D and RA was also specific for RF positive RA and not RF negative RA. There was no association between any subset of RA and T2D.

A recent study by Simard et al., suggested a non-significant association between diabetes and RA (16). There are several reasons for the apparent discrepancy between their results and those of our study. They conducted a cross-sectional analysis and did not analyze T1D and T2D as separate groups, nor did they distinguish between anti-CCP positive and negative RA (or between RF positive and negative RA). Their study also included a smaller number of patients with RA and diabetes (in total 144 patients with RA, 24 of which had concurrent diabetes). The study was conducted in the United States on a population with a mean age of 73, where diabetes has a prevalence of approximately 18.5% in individuals ages 65–74, of which an estimated 90–95% have T2D (29).

Analyzing diabetics as one group, when the majority are type 2 diabetics, a group where there presumably is no association with RA would dilute a significant association seen with type 1 diabetics and risk of RA and specifically, anti-CCP positive RA. Their overall association of 1.2 is comparable to our overall risk of 1.4 (95% CI 1.0–2.1).

The positive predictive value of insulin monotherapy and age < 30 in classifying T1D was 100% when compared against medical record review and telephone interview. However, the sensitivity of this classification was 69% compared to chart review and 72% compared to telephone interview. This could lead to misclassification where type 1 diabetics are considered type 2 diabetics. We therefore, conducted a subset analysis on the diabetes diagnosis obtained from medical records where misclassification is minimized. This analysis suggested a similar risk of type 1 diabetics developing anti-CCP positive RA (OR 11.7, 95% CI 2.6–52.7). This subset analysis concurs 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 new onset incident RA cases. To classify diabetes, we employed two methods, medical record review and contacting all available self-reported diabetics over the telephone and administering a diabetes questionnaire. In addition, we discriminated between anti-CCP positive from anti-CCP negative RA. Previous studies have shown this to be of importance since the two 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 T1D and RA, there are major clinical differences between subjects with T1D and T2D that could potentially explain the association seen in our study. Individuals with T1D are exposed to elevated glucose levels and exogenous insulin much longer than T2D. To test this alternative explanation, we performed subset analyses assessing the risk of RA in individuals exposed to insulin as treatment for T2D. No increased risk of RA was observed in this group, although 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 pre-existing disease at the time of diagnosis of RA and who had their charts reviewed and/or completed a diabetes questionnaire actually had diabetes.

Another limitation to this study was the relatively small number of diabetics 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%) for which the prevalence in our control study population (3.1%) concurs with the estimated national prevalence proportion (31,32). This also suggests that

the prevalence of diabetes seen in our study population is not a consequence of healthy participant bias.

A smaller percentage of controls were genotyped than cases for *PTPN22*. If the probability to be genotyped is related to diabetes this may result in biased relative risk estimates. To assess this we compared characteristics of the control group which were genotyped and those who were not. There was no significant difference seen in general (sex, age, area of residence, smoking and BMI), and there was no relation 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 T1D (11,13,14,33,34). The known genetic risk factors for T1D include loci in the major histocompatibility complex region HLA DQB1, -DQA1, -DRB1, in the insulin locus (INS), in the insulin gene 2 (IDDM2), cytotoxic T-lymphocyte associated protein (*CTLA-4*), and 620W *PTPN22* allele (11,33,34). Recent genome-wide analyses have also identified *KIAA0350*, interferon induced helicase region (*IFIH1*), and new chromosome regions on 4q27, 12q13, 16p13, 12q24, and 18p11 as potential T1D susceptibility loci (11,34,35). The single-nucleotide polymorphism (SNP) rs6822844 at chromosome 4q27 region has recently been shown to be associated with RA (35).

Other established genetic risk factors other than the 620W *PTPN22* allele for RA include the shared epitope (SE) of the HLA-DRB1 allele, *CTLA-4*, 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 for 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 SE alleles, and the 620W *PTPN22* allele as well as the TRAF-1-C5 associate alleles, have been specifically associated with anti-CCP positive RA (17–19).

Our results emphasize that further studies of co-morbidities and shared susceptibility factors between different immune mediated inflammatory diseases, should be performed taking subsets of the diseases into account such anti-CCP positive vs. anti-CCP negative RA. With the expanding knowledge and information we have 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 common molecular pathways involved in the etiology of the diseases. Further investigation of the susceptibility genes and other risk factors for T1D merit investigation as potential risk factors for anti-CCP/RF positive RA and may ultimately provide more insight into the etiology of autoimmunity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

- 1. Agrawal S, Desai MP. Simultaneous occurrence of type I diabetes mellitus and juvenile rheumatoid arthritis. Indian Pediatr. 2003; 40(6):568–571. [PubMed: 12824669]
- 2. Munakata Y, Kodera T, Saito T, Sasaki T. Rheumatoid arthritis, type 1 diabetes, and Graves' disease after acute parvovirus B19 infection. Lancet. 2005; 366(9487):780. [PubMed: 16125597]
- Somers EC, Thomas SL, Smeeth L, Hall AJ. Autoimmune diseases co-occurring within individuals and within families: a systematic review. Epidemiology. 2006; 17(2):202–217. [PubMed: 16477262]
- Zonana MF, Reyes E, Weisman AK. Coexistence of four autoimmune diseases in one patient: the kaleidoscope of autoimmunity. J Clin Rheumatol. 2002; 8(6):322–325. [PubMed: 17041402]
- Chelala C, Duchatelet S, Joffret ML, Bergholdt R, Dubois-Laforgue D, Ghandil P, et al. PTPN22 R620W functional variant in type 1 diabetes and autoimmunity related traits. Diabetes. 2007; 56(2): 522–526. [PubMed: 17259401]
- Plenge RM, Padyukov L, Remmers EF, Purcell S, Lee AT, Karlson EW, et al. Replication of putative candidate-gene associations with rheumatoid arthritis in >4,000 samples from North America and Sweden: association of susceptibility with PTPN22, CTLA4, and PADI4. Am J Hum Genet. 2005; 77(6):1044–1060. [PubMed: 16380915]
- Begovich AB, Carlton VE, Honigberg LA, Schrodi SJ, Chokkalingam AP, Alexander HC, et al. A missense single-nucleotide polymorphism in a gene encoding a protein tyrosine phosphatase (PTPN22) is associated with rheumatoid arthritis. Am J Hum Genet. 2004; 75(2):330–337. [PubMed: 15208781]
- Raychaudhuri S, Remmers EF, Lee AT, Hackett R, Guiducci C, Burtt NP, et al. Common variants at CD40 and other loci confer risk of rheumatoid arthritis. Nat Genet. 2008; 40(10):1216–1223. [PubMed: 18794853]
- Criswell LA, Pfeiffer KA, Lum RF, Gonzales B, Novitzke J, Kern M, et al. Analysis of families in the multiple autoimmune disease genetics consortium (MADGC) collection: the PTPN22 620W allele associates with multiple autoimmune phenotypes. Am J Hum Genet. 2005; 76(4):561–571. [PubMed: 15719322]
- Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007; 447(7145):661–678. [PubMed: 17554300]
- Hakonarson H, Grant SF, Bradfield JP, Marchand L, Kim CE, Glessner JT, et al. A genome-wide association study identifies KIAA0350 as a type 1 diabetes gene. Nature. 2007; 448(7153):591– 594. [PubMed: 17632545]
- Nistico L, Buzzetti R, Pritchard LE, Van der Auwera B, Giovannini C, Bosi E, et al. The CTLA-4 gene region of chromosome 2q33 is linked to, and associated with, type 1 diabetes. Belgian Diabetes Registry. Hum Mol Genet. 1996; 5(7):1075–1080. [PubMed: 8817351]
- 13. Plenge RM, Seielstad M, Padyukov L, Lee AT, Remmers EF, Ding B, et al. TRAF1-C5 as a Risk Locus for Rheumatoid Arthritis -- A Genomewide Study. N Engl J Med. 2007

- Remmers EF, Plenge RM, Lee AT, Graham RR, Hom G, Behrens TW, et al. STAT4 and the risk of rheumatoid arthritis and systemic lupus erythematosus. N Engl J Med. 2007; 357(10):977–986. [PubMed: 17804842]
- Ueda H, Howson JM, Esposito L, Heward J, Snook H, Chamberlain G, et al. Association of the Tcell regulatory gene CTLA4 with susceptibility to autoimmune disease. Nature. 2003; 423(6939): 506–511. [PubMed: 12724780]
- Simard JF, Mittleman MA. Prevalent rheumatoid arthritis and diabetes among NHANES III participants aged 60 and older. J Rheumatol. 2007; 34(3):469–473. [PubMed: 17183622]
- Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum. 2006; 54(1):38–46. [PubMed: 16385494]
- Kallberg H, Padyukov L, Plenge RM, Ronnelid J, Gregersen PK, van der Helm-van Mil AH, et al. Gene-gene and gene-environment interactions involving HLA-DRB1, PTPN22, and smoking in two subsets of rheumatoid arthritis. Am J Hum Genet. 2007; 80(5):867–875. [PubMed: 17436241]
- Lee HS, Irigoyen P, Kern M, Lee A, Batliwalla F, Khalili H, et al. Interaction between smoking, the shared epitope, and anti-cyclic citrullinated peptide: a mixed picture in three large North American rheumatoid arthritis cohorts. Arthritis Rheum. 2007; 56(6):1745–1753. [PubMed: 17530703]
- 20. van der Helm-van Mil AH, Wesoly JZ, Huizinga TW. Understanding the genetic contribution to rheumatoid arthritis. Curr Opin Rheumatol. 2005; 17(3):299–304. [PubMed: 15838240]
- Padyukov L, Silva C, Stolt P, Alfredsson L, Klareskog L. A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. Arthritis Rheum. 2004; 50(10):3085–3092. [PubMed: 15476204]
- 22. Stolt P, Bengtsson C, Nordmark B, Lindblad S, Lundberg I, Klareskog L, et al. Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based casecontrol study, using incident cases. Ann Rheum Dis. 2003; 62(9):835–841. [PubMed: 12922955]
- Stolt P, Kallberg H, Lundberg I, Sjogren B, Klareskog L, Alfredsson L. Silica exposure is associated with increased risk of developing rheumatoid arthritis: results from the Swedish EIRA study. Ann Rheum Dis. 2005; 64(4):582–586. [PubMed: 15319232]
- 24. Suzuki A, Yamada R, Chang X, Tokuhiro S, Sawada T, Suzuki M, et al. Functional haplotypes of PADI4, encoding citrullinating enzyme peptidylarginine deiminase 4, are associated with rheumatoid arthritis. Nat Genet. 2003; 34(4):395–402. [PubMed: 12833157]
- 25. van der Helm-van Mil AH, Verpoort KN, Breedveld FC, Huizinga TW, Toes RE, de Vries RR. The HLA-DRB1 shared epitope alleles are primarily a risk factor for anti-cyclic citrullinated peptide antibodies and are not an independent risk factor for development of rheumatoid arthritis. Arthritis Rheum. 2006; 54(4):1117–1121. [PubMed: 16572446]
- Arnett FC. Revised criteria for the classification of rheumatoid arthritis. Bull Rheum Dis. 1989; 38(5):1–6. [PubMed: 2679945]
- 27. Finne P, Reunanen A, Stenman S, Groop PH, Gronhagen-Riska C. Incidence of end-stage renal disease in patients with type 1 diabetes. Jama. 2005; 294(14):1782–1787. [PubMed: 16219881]
- Mayfield J. Diagnosis and classification of diabetes mellitus: new criteria. Am Fam Physician. 1998; 58(6):1355–1362. 1369–1370. [PubMed: 9803200]
- 29. CDC. Diabetes Data and Trends. Department of Health and Human Services. 2007
- Bengtsson C, Nordmark B, Klareskog L, Lundberg I, Alfredsson L. Socioeconomic status and the risk of developing rheumatoid arthritis: results from the Swedish EIRA study. Ann Rheum Dis. 2005; 64(11):1588–1594. [PubMed: 15843455]
- Berger B, Stenstrom G, Chang YF, Sundkvist G. The prevalence of diabetes in a Swedish population of 280,411 inhabitants. A report from the Skaraborg Diabetes Registry. Diabetes Care. 1998; 21(4):546–548. [PubMed: 9571340]
- Berger B, Stenstrom G, Sundkvist G. Incidence, prevalence, and mortality of diabetes in a large population. A report from the Skaraborg Diabetes Registry. Diabetes Care. 1999; 22(5):773–778. [PubMed: 10332680]

- She JX, Marron MP. Genetic susceptibility factors in type 1 diabetes: linkage, disequilibrium and functional analyses. Curr Opin Immunol. 1998; 10(6):682–689. [PubMed: 9914216]
- Todd JA, Walker NM, Cooper JD, Smyth DJ, Downes K, Plagnol V, et al. Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. Nat Genet. 2007; 39(7):857–864. [PubMed: 17554260]
- 35. Zhernakova A, Alizadeh BZ, Bevova M, van Leeuwen MA, Coenen MJ, Franke B, et al. Novel association in chromosome 4q27 region with rheumatoid arthritis and confirmation of type 1 diabetes point to a general risk locus for autoimmune diseases. Am J Hum Genet. 2007; 81(6): 1284–1288. [PubMed: 17999365]
- 36. Cha S, Choi CB, Han TU, Kang CP, Kang C, Bae SC. Association of anti-cyclic citrullinated peptide antibody levels with PADI4 haplotypes in early rheumatoid arthritis and with shared epitope alleles in very late rheumatoid arthritis. Arthritis Rheum. 2007; 56(5):1454–1463. [PubMed: 17469103]
- Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis Rheum. 1987; 30(11):1205–1213. [PubMed: 2446635]
- Iwamoto T, Ikari K, Nakamura T, Kuwahara M, Toyama Y, Tomatsu T, et al. Association between PADI4 and rheumatoid arthritis: a meta-analysis. Rheumatology (Oxford). 2006; 45(7):804–807. [PubMed: 16449362]
- 39. Lee HS, Remmers EF, Le JM, Kastner DL, Bae SC, Gregersen PK. Association of STAT4 with Rheumatoid Arthritis in the Korean population. Mol Med. 2007
- 40. Plenge RM, Cotsapas C, Davies L, Price AL, de Bakker PI, Maller J, et al. Two independent alleles at 6q23 associated with risk of rheumatoid arthritis. Nat Genet. 2007; 39(12):1477–1482. [PubMed: 17982456]

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Validation and classification of self-reported diabetics from the EIRA questionnaire.

Table 1

Characteristics of cases and controls

	Cases, n=1419	Controls, n=1674
Sex (%)		
Female	1012 (71)	1188 (71)
Age (%)		
18–29	106 (7.5)	143 (8.5)
30–39	176 (12.5)	225 (13.5)
40–49	251 (18)	308 (18.5)
50-59	475 (33)	543 (32.5)
60–70	411 (29)	455 (27)
BMI (%)*		
0-20	101 (7)	120 (7)
20-25	654 (46)	804 (48)
25-30	475 (33)	550 (33)
>30	188 (13)	198 (12)
Smokers (%) †		
Ever	869 (61)	913 (55)
Never	432 (30)	625 (37)
Serology (%) [‡]		
RF+	927 (65)	
anti-CCP+	857 (60)	
Genetics(%) $^{\delta}$		
PTPN22	390 (27)	197 (12)

Percentages reflect the number of individuals testing positive/total individuals in the case or control group

*Information on weight was missing in 1 case and 2 controls

 $^{\dagger} \mathrm{Information}$ on smoking was missing in 118 cases and 136 controls

 ‡ RF status was available for 1418 cases; anti-CCP status was available for 1401 cases

[§]Genetic information was available for 1356 cases and 863 controls

Table 2

Diabetes by type and risk for developing RA

	N exposed cases / controls	OR (95% CI) [‡]	OR (95% CI) §
All diabetes	62/51	1.4 (1.0–2.1)	1.3 (0.9–2.0)
Type 1 diabetes $*$	20/5	4.9 (1.8–13.1)	4.8 (1.8–12.9)
Type 2 diabetes*	42/46	1.1 (0.7–1.6)	1.0 (0.6–1.5)

* Subjects' diabetes type assigned either by telephone questionnaire, chart review or insulin monotherapy and age <30

 $t_{\rm Unconditional logistic regression analysis adjusted for age, sex, location of residence$

 $^{\$}$ Unconditional logistic regression analysis adjusted for age, sex, location of residence, smoking and BMI

Table 3

Association between Type 1 and 2 diabetes and risk of developing RA stratified by anti-CCP and RF status with successive adjustment for potential confounding factors

Type of diabetes	RF/anti-CCP status	N exposed cases/controls	Model 0 [*] OR (95% CI)	Model 1 $^{\uparrow}$ OR (95% CI)	Model 2 [#] OR (95% CI)
Type 1	All	20/5	4.9 (1.8–13.1)	4.8 (1.8–12.9)	3.5 (1.0–12.1)
Type 1	Anti-CCP+	18/5	7.3 (2.7–20.0)	7.3 (2.6–20.2)	5.3 (1.5–18.7)
Type 1	Anti-CCP-	2/5	1.3 (0.3–7.0)	1.3 (0.2–6.9)	1.1 (0.2–6.7)
Type 1	RF+	19/5	7.1 (2.6–19.2)	7.0 (2.6–19.2)	5.1 (1.5–17.8)
Type 1	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)
Type 2	Anti-CCP+	22/46	0.9 (0.6–1.6)	0.9 (0.5–1.6)	1.0 (0.6–1.9)
Type 2	Anti-CCP-	20/46	1.3 (0.7–2.2)	1.1 (0.6–1.9)	1.1 (0.6–2.2)
Type 2	RF+	27/46	1.1(0.7-1.8)	1.0 (0.6–1.7)	1.2 (0.7–2.1)
Type 2	RF	15/46	1.0 (0.6–1.9)	0.9 (0.5–1.7)	0.9 (0.5–1.9)
* Model 0: Unconditic	onal logistic regression an	nalysis adjusted for age, sex, l	ocation of residence		
$\dot{ au}_{ m Model}$ 1: Unconditic	onal logistic regression a	nalysis adjusted for age, sex, l	ocation of residence, smokin	ıg, and BMI	

 ${}^{\sharp}\!Model$ 2: Model 1 plus PTPN22 status among a subset of EIRA (1356 cases and 863 controls)