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Co-occurrence of celiac disease and other autoimmune diseases in celiacs and their first-degree relatives

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Abstract

The occurrence of other autoimmune diseases in celiac disease families has not been previously reported in a North American population. We investigated the familial aggregation of rheumatoid arthritis (RA), juvenile rheumatoid arthritis/juvenile idiopathic arthritis (JRA/JIA), hypothyroidism, insulin dependent diabetes mellitus (IDDM), and alopecia areata (AA) among individuals in families with celiac disease (CD). Family history information, obtained from questionnaires from the University of California Irvine Celiac Disease study, was reviewed for reports of RA, JRA/JIA, hypothyroidism, IDDM, and AA in celiac disease cases and their first-degree relatives. Reports of disease were compared with prevalence data from the literature and analyzed by calculating the standardized ratio (SR) with 95% confidence limits. We analyzed: 1) subjects with confirmed celiac disease or dermatitis herpetiformis (205 probands and 203 affected first-degree relatives) and 2) first-degree relatives of celiac disease cases (n=1,272). We found a significantly increased number of cases, relative to the expected number, of IDDM in both groups and hypothyroidism among subjects with celiac disease. JRA/JIA was increased among first-degree relatives of celiacs. These results indicate that the presence of IDDM within our celiac disease families may be due to shared genetic susceptibility predisposing to these diseases or autoimmune diseases in general.

Keywords

autoimmune disease; celiac disease

INTRODUCTION

Celiac disease (CD, gluten-sensitive enteropathy, celiac sprue) is a common autoimmune disease, with estimates that the disease frequency is 0.75% (1:133) in the general population in the US [1], similar to European estimates. CD is caused by sensitivity to the dietary protein

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gliadin, which is present in wheat, and to the related prolamins, secalin in rye and hordein in barley. The term gluten-sensitive enteropathy (GSE) refers to the histologic abnormality of the small intestine, which ranges from minimal lymphocytic infiltration of the intestinal epithelium to severe atrophy of the villi [2]. Occult disease is frequently present with minimal symptoms or signs. CD is familial, with significant morbidity if untreated. CD is one of the most significant causes of chronic malabsorption in children. Complications of CD include lymphoma, osteoporosis, anemia, and seizures.

There have been several reports of co-occurrence of CD and other autoimmune diseases in Europe, with no studies reported in the United States. A significantly increased prevalence of various autoimmune diseases has been reported in individuals with CD as compared to healthy controls [3–10], and a significantly increased prevalence of CD (10–30 fold) has been documented in individuals with varied autoimmune diseases (reviewed in Kumar [11]). The basis for these associations may be that CD and the other diseases share a similar pathogenic autoimmune mechanism or a genetic defect in the same responsible genes [12].

Most studies that have looked at the association of CD with autoimmune diseases have focused on individuals with CD rather than relatives of CD cases. Only two studies, conducted in Italy, specifically looked at the prevalence of autoimmune diseases in relatives of CD cases. In the first study, prevalence of autoimmune diseases was compared in children with CD matched to control children, and in all first- and second-degree relatives of the children with CD and the control children. There was a significantly higher prevalence of autoimmune diseases in the children with CD (7.2%) as compared to the controls (0.8%) and in the relatives of the CD subjects (4.9%) as compared to relatives of the controls (1.1%)[13]. Similarly, Cataldo and colleagues found a significantly higher prevalence of CD in 225 first-degree relatives of 66 children with CD (4.8%) as compared to 232 relatives of controls (0.86%) ($p = 0.028$). Furthermore, the prevalence of autoimmune diseases increased with increasing age of the relatives ($p < 0.0001$) [14].

Large family studies investigating the prevalence of other autoimmune diseases in relatives have not been performed in the US. In this study, we investigated whether RA, JRA/JIA, hypothyroidism, IDDM, and AA are increased in relatives of CD cases, as well as in CD cases themselves.

METHODS

Study sample

Families with CD were studied. These families were previously enrolled in a CD family study under Institutional Review Board (IRB) approvals at the University of California Irvine and the University of Utah. The participants were from the U.S. and Canada, and were ascertained from celiac newsletters, celiac support groups, and physician referral. A family qualified for enrollment if there were two members of the family, excluding parent-child pairs, with biopsy- and/or serology-proven CD. Participation in the study was extended to all first-degree family members of the probands, and then subsequently to all first-degree relatives of other CD cases found in the families. Participants were asked to complete a self-administered questionnaire containing demographic, personal, and family history information. Parents or guardians completed questionnaires for their children. Additional information that was not in the questionnaire was obtained through re-contact of participants and review of medical records, when available.

For this study, we restricted the analyses to families where 10 or more relatives were enrolled. Relatives not in the lineage (spouses) were excluded. The characteristics of the study sample

are listed in Table 1. The study sample consisted of 1,680 individuals from 91 families meeting the criteria (median = 17 individuals per family, range 4–55).

Questionnaire data

The primary source of data for this study was a self-administered questionnaire, which included demographic information (date of birth, current age, sex, vital status), and medical history information on the respondent and first-degree family members for diagnoses including CD, RA, JRA/JIA, AA, hypothyroidism, and/or IDDM. Only data on blood relatives were included. A total of 1,014 questionnaires were reviewed from the 91 families (median = 9 questionnaires per family, range 1–38). Each questionnaire provided information on multiple family members, however not all individuals completed a questionnaire. Therefore, data were based on self-report, self-report and family history report; or only family history report. Of the questionnaires reporting an autoimmune disease, 60.5% were self-report or report of a parent on a minor child, 9.0% were a sibling report, 13.1% were an adult offspring report, 4.8% were a report from a parent of an adult offspring, and 12.6% were reports from two first-degree relatives. To ensure that family history and self-report data were as accurate as possible, participants were telephoned to verify each disease reported on a questionnaire. In the instances where reports from relatives differed, all family members reporting the diseases were contacted. We successfully reached 84% of those targeted for recontacting. Reports that could not be verified were excluded, so that we may have excluded some true diagnoses. Additional information was collected including age at diagnosis of the disease, symptoms, diagnostic modality, and type of treatment. This information enabled us to distinguish JRA/JIA from RA, and in a limited number of those with hypothyroidism, to identify those specifically diagnosed with Hashimoto's thyroiditis.

We only included a diagnosis of CD if it was documented with a small bowel biopsy pathology report consistent with CD and/or a positive serological testing with IgA anti-endomysial antibody (EMA) and IgA tissue transglutaminase (tTG) antibody documented from medical records or diagnosed by our study. Other individuals in our study sample may have CD but did not have a verified diagnosis or were not yet identified as having CD. When date of birth or age was unknown, age was estimated based on ages of first-degree relatives (n=32, 1.9%).

Data Analysis

Two groups were analyzed: 1) all subjects with confirmed CD (n = 408) and 2) all first-degree relatives of CD cases (n=1272). We compared the observed prevalence of RA, JRA/JIA, AA, hypothyroidism, and IDDM with expected prevalence based on available general population data (Table 2). These comparisons were performed separately for the two groups (CD group and first-degree relatives group). To test our hypotheses, we calculated standardized ratios (SR) as the ratio of observed cases in our two groups to the expected number based on prevalences in published reports (Table 2) and 95% confidence intervals (CI).[15].

RESULTS

We investigated the prevalence of IDDM, RA, JRA, AA, and hypothyroidism in celiac disease cases and their first degree relatives in North American families. A total of 184 autoimmune diseases were reported on questionnaires. We were able to verify 120 (65%) of these reports through telephone recontact and included these 120 in the analyses. For these 120 diagnoses, we were able to obtain medical records for 58 (48%) of the diagnoses (medical records were obtained from 1 of 10 RA, 1 of 4 JRA, 44 of 76 thyroid, 12 of 24 IDDM, and 0 of 7 alopecia cases). The medical records confirmed the diagnoses in 58 cases, suggesting that verified self-reports are reliable. We were unable to contact the subjects for 22 reports (12%) and for another 17 reports (9%), the family member had too little detail to confirm the diagnosis. Therefore,

we may have under-reported the total number of autoimmune diseases, specifically by 22 cases for thyroiditis, 8 cases for RA, 5 cases for IDDM, and 4 cases for AA. For five questionnaire self-reports of RA and nine questionnaire reports of relatives, when we called to verify and asked specific questions, the initial report was incorrect (8%) and the contact reported it was osteoarthritis. There were an additional 9 questionnaire reports (5%) of relatives where the individual with the reported disease did not confirm the diagnosis, with the error for hypothyroidism (5 cases), AA (3 cases), and IDDM (1 case).

In the 408 CD cases (group 1), 59 autoimmune diseases were verified in 54 individuals. Five individuals reported two autoimmune diseases in addition to CD. As shown in Table 3, we observed a significantly increased prevalence of hypothyroidism (40 cases ≥12 years of age observed compared to 17.5 expected; SR of 2.3, CI 1.6–3.0), and of IDDM at any age and diagnosed at less than 20 years [SR of 10.0 (CI 5.3–16.7) and 10.9 (CI 5.1–19.8) respectively]. The prevalence of RA was not significantly different than expected. There were only three cases of AA reported, too few to adequately assess the prevalence, and no cases of JRA.

In the 1,272 first-degree relatives of CD cases, a total of 62 autoimmune diseases were reported in 58 individuals. Four individuals reported two autoimmune diseases. We observed a significant increase in IDDM at any age (SR 3.2, CI 1.7–5.3) and in those diagnosed at less than 20 years of age (SR 4.0, CI 2.0–7.0) (Table 4). The prevalence of JRA/JIA at any age was significantly higher than expected (SR 5.7; CI 1.5–12.7), and was higher at less than 17 years of age but the SR was not significant. There was no increase in the prevalence of RA, AA, or hypothyroidism. In fact, the observed number of individuals with hypothyroidism was lower than expected (Table 4).

The number of autoimmune diseases reported per family was evaluated to determine if some families carry a larger burden of disease than others. A total of 53 (58.2%) families reported having an autoimmune disease. In order to account for family size, the burden of disease in these families was calculated as the percent of family members with autoimmune diseases. The mean percentage of autoimmune diseases in these families was 10% with a range of 2–45% (Table 5). Therefore, some families had a much higher percentage of family members with autoimmune diseases than others.

The number of individual diseases reported per family was also evaluated. Out of 53 families reporting disease, 27 families had two or more individuals reported to have an autoimmune disease (Table 6).

DISCUSSION

In our study of CD families, we investigated whether there is an increase in the co-occurrence of other autoimmune diseases in individuals with CD and their first-degree relatives. The increased risk of acquiring an autoimmune disease may be due to genetic susceptibility for both diseases, an environmental trigger able to initiate both diseases, the presence of one autoimmune disease that alters or affects the body so that it is susceptible to another disease, or some undiscovered mechanism [16]. We found a significantly increased number of observed cases of hypothyroidism and IDDM among individuals with CD. We also noted a larger number of cases of JRA/JIA and IDDM in first-degree relatives of CD cases than expected based on published prevalence studies. We did not observe an increased number of RA or AA cases than expected in either group.

Autoimmune diseases among CD cases

In this study, the overall burden of the five autoimmune diseases (RA, JRA/JIA, AA, IDDM, hypothyroidism) in CD cases was 15%, which is higher than the estimated population

prevalence of 3–5% [17,18]. We only looked at a subset of the greater than 20 identified autoimmune diseases included in the total prevalence studies of autoimmune diseases, which likely resulted in an underestimate of total burden of autoimmune diseases in our sample. Our results are in agreement with previously published reports in which the prevalence of autoimmune diseases was significantly higher in CD cases than in healthy, age-matched controls. In one study of children, the prevalence of autoimmune disease was 14% in celiacs versus 2.8% in controls ($p < 0.000001$), with the most common autoimmune disease being IDDM [3]. In adult CD patients and controls, the prevalence of autoimmunity was three-fold higher in one study [4], and there were significantly more endocrine disorders, IDDM, RA, and Sjögren's syndrome in the cases than the controls in a second study [5].

Previous reports have found an increased prevalence of IDDM among CD patients in the range of 2.5–5% and of thyroid disease among CD patients of about 10–15% [7–9,19–21]. The total observed number of reports of IDDM (12 cases) and hypothyroidism (42 cases) among CD cases in our study are significantly increased above the expected numbers based on prevalence studies from the literature, similar to what has been previously reported. The vast majority of cases of hypothyroidism were likely due to Hashimoto's thyroiditis, as it has been reported that 90% of hypothyroid cases in an iodine sufficient area are due to Hashimoto's thyroiditis [22]. In this study, we did not have sufficient data to assign a diagnosis of Hashimoto's thyroiditis except in six cases.

We did not find an increased number of observed cases of CD with RA, JRA/JIA, or AA, relative to expected numbers. There have been a few studies focused on the prevalence of RA among CD patients, but similar to our results, the rates have been similar to those in the general population [10,23–26]. The majority of patients with RA have the HLA-DR4 subtype (associated with the HLA-DQB1*0302 allele of DQ8) [27,28]. Because the number of CD patients with DQ8 is only about 5%, an association with RA in our smaller sample of CD patients with DR4 may not have been evident. In addition, some studies have reported that the incidence of RA is decreasing and both comparison studies may be an overestimate of the true disease burden [29,30]. In our sample, no individuals with CD reported being diagnosed with JRA/JIA. Previous studies have reported a prevalence of JRA/JIA co-occurring with CD in children of approximately 3–7% [31,32]. CD may be diagnosed at any age and given the young age of onset of JRA/JIA it is possible that some individuals in our study sample with JRA/JIA have not yet developed or been diagnosed with CD. It is also possible that children in our sample have been diagnosed with CD, but have yet to be diagnosed with JRA/JIA. JRA/JIA is rare and the study sample is small, so it is very possible that there will be cases in this set. We found no association of AA and CD, even though AA is associated with the CD susceptibility allele, HLA-DQB1*0201 [33]. There have been a few case reports of the co-occurrence of AA and CD [34,35].

Autoimmune diseases among first-degree relatives of CD cases

Family studies allow for the opportunity to study the aggregation of disease and assist in the determination of disease etiology. Aggregation of disease in families may be explained by the sharing of genetic susceptibility factors or environmental factors, which predispose to disease. Some studies have found a positive association of probands with a specific autoimmune disease, such as IDDM, and autoimmune diseases as a whole among their first- and second-degree family members [36,37]. Among our first-degree family members, we had an overall burden of the studied autoimmune diseases of 4.9%, which is similar to the population prevalence of 3–5%. However, we only studied a subset of autoimmune diseases and therefore may have underestimated the total burden of autoimmune disease. We found a significantly increased number of relatives than expected for IDDM (SR = 3.2 and SR = 4.0) in comparison

to expected numbers derived from the two published studies, Table 3. We found a significantly increased number of observed cases relative to expected in all ages for JRA/JIA (SR = 5.7).

Standardized ratios less than 1.0 were found for RA in two of the three comparisons, and we identified no males with JRA/JIA. There are several reasons this may have occurred. Given that many autoimmune diseases are rare, our study may have been underpowered to evaluate these diseases. The lack of knowledge and understanding about these conditions in our families may have resulted in underreporting. Issues of bias in reporting and selection, as outlined in the limitations sections, may have resulted in an under identification of additional disease cases. It is also possible that there is not an association of these conditions in CD families.

Autoimmune diseases within CD families

The burden of disease was not the same in all of our families. Out of 91 families that met inclusion criteria, approximately half reported autoimmune diseases (58%). When the families reporting disease were examined, the size of the family was not related to the number of diseases reported. We had a range of 2–45% of individuals reported with disease in these families. It appears that some families may be more susceptible to autoimmune diseases than other families.

We also evaluated whether the specific disease or diseases reported were different within a family. Within families, the number of different autoimmune diseases reported was most often one or two. In the 27 families with more than one relative reporting disease, the specific autoimmune disease in the family members was the same in 10 families. In 16 families, there were two autoimmune diseases and in 1 family there were 4 autoimmune diseases. There may have been other autoimmune diseases that were not investigated in this study.

It is well-documented that many autoimmune diseases are associated with alleles in genes in the major histocompatibility complex (MHC) [22]. In many of these diseases, an association with specific alleles of either MHC class I or class II genes has been documented, as with the association of DQ2 (DQA1*05/DQB1*02) and DQ8 (DQA1*0301/DQB*302) in CD and DR4 (HLA-DRB1*0401, *0404, *0405, *0408) in RA [27,28,38–41]. However, these genetic associations only predispose a person to the development of disease but are not sufficient by themselves to cause the disease.

In our families, individuals with CD and their first-degree relatives reported significantly more cases of IDDM than expected. The individuals in our families with IDDM may share HLA alleles and other unknown genetic susceptibility factors, which may predispose them to both IDDM and CD. CD and IDDM are reported to be associated with the same HLA susceptibility alleles, but not all individuals with these susceptibility alleles develop both diseases. Greater than 90% of individuals with CD or IDDM have the DQ2 (DQA1*0501/DQB1*0201) or DQ8 (DQA1*0301/DQB*302) haplotype, which are reported to be susceptibility loci for CD and IDDM, but in studies of patients with IDDM only about 2.5–5% of patients also developed CD [19–21,39,42,43]. This demonstrates that there are other unidentified susceptibility factors.

A pathogenetic model proposed for some autoimmune diseases is that multiple genes may act independently of each other or may interact through functionally related pathways to lead to the pathogenesis of the disease [22]. It is possible that individuals with autoimmune diseases also share non-MHC genes predisposing to autoimmune conditions. For example, the PTPN22 gene has been reported to be associated with susceptibility to RA and JRA/JIA and the MDR1 gene has been shown to confer risk for Crohn's disease and ulcerative colitis [44–46]. A combination of MHC and non-MHC genes in the etiology of CD and autoimmune diseases is likely, but the precise interaction of these to increase disease susceptibility is still unclear. The disease associations in our study could also be related to common environmental exposure or

a combination of factors [47]. Environmental factors that have been implicated as risk factors for autoimmune disease are infection, vaccines, smoking, diet, exposure to ultraviolet light, and stress [48].

Limitations of the study

We were limited by the availability of prevalence studies for the diseases we studied and the ethnicity of the CD families (99.7% non-Hispanic Caucasian) may not have been well-matched to published populations for the specific disease. Second, with low prevalence rates for a disease and/or age group, SR estimates were not precise. For most of the diseases, we relied on self-reports and reports from first-degree relatives rather than medical records, which may have resulted in some inaccuracies. However, in general, studies have shown that self-report and family history are accurate [49–52]. When the first-degree relative is a parent versus a sibling, the reporting accuracy typically is higher [53]. We found that for the 58 cases for whom we had medical records, the diagnoses were confirmed, suggesting that verified self-reports are reliable. The questionnaires were not designed to be a specific tool for the assessment of autoimmune diseases other than CD, and a number of diagnoses may have been missed or erroneously reported. To decrease the likelihood of over-reporting, we did not include reports about first-degree relatives if we were unable to re-contact the family member reporting. Therefore, some reports of disease were omitted. We had medical records to verify diagnoses for 48% of disease reports. These records were primarily for hypothyroidism and IDDM, so reports of these diseases may be more accurate than reports of RA, JRA, and AA.

Conclusion

The results of this first North American study support the hypothesis that there is an increased occurrence of autoimmune diseases in CD families relative to the general population. In the set of CD cases (group 1), 13.2% of individuals had at least one autoimmune disease. In the first-degree relatives of CD cases (group 2), 4.6% of individuals had at least one autoimmune disease. Individuals with CD are more likely to report an autoimmune disease than first-degree relatives. It may be that individuals with CD are more susceptible to autoimmune diseases due to a shared genetic factor(s). An individual with one autoimmune disease also may be more susceptible to develop additional disease(s). For IDDM, the observed number of affecteds was significantly higher than expected among both CD cases and first-degree relatives. In addition, an increased number of cases of hypothyroidism were observed in individuals with CD (SR > 1.0 with 95% CI excluding unity for 3 of the 4 estimates). A significant increase in the number of first-degree relatives with JRA/JIA was observed (SR = 5.7). Given these findings, a genetic association with other autoimmune diseases in our CD families is plausible. Further studies to evaluate our entire study sample and replication in another set of celiac families are needed.

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REFERENCES

1. Fasano A, Berti I, Gerarduzzis T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. Arch Intern Med 2003;163(3):286–292. [PubMed: 12578508]
2. Trier, Js. Celiac sprue. N Engl J Med 1991;325(24):1709–1719. [PubMed: 1944472]
3. Ventura A, Magazzu G, Greco L. Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease. SIGEP Study Group for Autoimmune Disorders in Celiac Disease. Gastroenterology 1999;117(2):297–303. [PubMed: 10419909]

4. Sategna Guidetti C, Solerio E, Scaglione N, et al. Duration of gluten exposure in adult coeliac disease does not correlate with the risk for autoimmune disorders. Gut 2001;49(4):502–505. [PubMed: 11559646]
5. Collin P, Reunala T, Pukkala E, et al. Coeliac disease--associated disorders and survival. Gut 1994;35 (9):1215–1218. [PubMed: 7959226]
6. Ludvigsson JF, Ludvigsson J, Ekbom A, et al. Celiac disease and risk of subsequent type 1 diabetes: a general population cohort study of children and adolescents. Diabetes Care 2006;29(11):2483–2488. [PubMed: 17065689]
7. Counsell CE, Taha A, Ruddell WS. Coeliac disease and autoimmune thyroid disease. Gut 1994;35(6): 844–846. [PubMed: 8020817]
8. Velluzzi F, Caradonna A, Boy MF, et al. Thyroid and celiac disease: clinical, serological, and echographic study. Am J Gastroenterol 1998;93(6):976–979. [PubMed: 9647032]
9. Hakanen M, Luotola K, Salmi J, et al. Clinical and subclinical autoimmune thyroid disease in adult celiac disease. Dig Dis Sci 2001;46(12):2631–2635. [PubMed: 11768252]
10. Lubrano E, Ciacci C, Ames PR, et al. The arthritis of coeliac disease: prevalence and pattern in 200 adult patients. Br J Rheumatol 1996;35(12):1314–1318. [PubMed: 9010064]
11. Kumar V, Rajadhyaksha M, Wortsman J. Celiac disease-associated autoimmune endocrinopathies. Clin Diagn Lab Immunol 2001;8(4):678–685. [PubMed: 11427410]
12. Strober, W. Gluten-sensitive enteropathy. In: King, R.; Rotter, JI.; Motuslky, AG., editors. Genetic Basis of Common Diseases. New York: Oxford University Press; 1992. p. 279-304.
13. Petaros P, Martelossi S, Tommasini A, et al. Prevalence of autoimmune disorders in relatives of patients with celiac disease. Dig Dis Sci 2002;47(7):1427–1431. [PubMed: 12141796]
14. Cataldo F, Marino V. Increased prevalence of autoimmune diseases in first-degree relatives of patients with celiac disease. J Pediatr Gastroenterol Nutr 2003;36(4):470–473. [PubMed: 12658037]
15. Kelsey, JL.; Douglas Thompson, W.; Evans, Alfred S. Methods in Observational Epidemiology. New York City: Oxford: Oxford University Press; 1986.
16. Sloka JS, Phillips PW, Stefanelli M, et al. Co-occurrence of autoimmune thyroid disease in a multiple sclerosis cohort. J Autoimmune Dis 2005;2:9. [PubMed: 16280086]
17. Jacobson DL, Gange SJ, Rose NR, et al. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol 1997;84(3):223–243. [PubMed: 9281381]
18. Becker KG, Simon RM, Bailey-Wilson JE, et al. Clustering of non-major histocompatibility complex susceptibility candidate loci in human autoimmune diseases. Proc Natl Acad Sci U S A 1998;95(17): 9979–9984. [PubMed: 9707586]
19. Buysschaert M, Tomasi JP, Hermans MP. Prospective screening for biopsy proven coeliac disease, autoimmunity and malabsorption markers in Belgian subjects with Type 1 diabetes. Diabet Med 2005;22(7):889–892. [PubMed: 15975104]
20. Baptista ML, Koda YK, Mitsunori R, et al. Prevalence of celiac disease in Brazilian children and adolescents with type 1 diabetes mellitus. J Pediatr Gastroenterol Nutr 2005;41(5):621–624. [PubMed: 16254520]
21. Fraser-Reynolds KA, Butzner JD, Stephure DK, et al. Use of immunoglobulin A-antiendomysial antibody to screen for celiac disease in North American children with type 1 diabetes. Diabetes Care 1998;21(11):1985–1989. [PubMed: 9802755]
22. Rose, NR.; Mackay, Ian R. The Autoimmune Diseases. In: Rose, NR.; Mackay, Ian R., editors. The Autoimmune Diseases. Third Edition. San Diego, CA: Academic Press; 1998.
23. O'Farrelly C, Marten D, Melcher D, et al. Association between villous atrophy in rheumatoid arthritis and a rheumatoid factor and gliadin-specific IgG. Lancet 1988;2(8615):819–822. [PubMed: 2902267]
24. Francis J, Carty JE, Scott BB. The prevalence of coeliac disease in rheumatoid arthritis. Eur J Gastroenterol Hepatol 2002;14(12):1355–1356. [PubMed: 12468957]
25. Luft LM, Barr SG, Martin LO, et al. Autoantibodies to tissue transglutaminase in Sjogren's syndrome and related rheumatic diseases. J Rheumatol 2003;30(12):2613–2619. [PubMed: 14719202]

26. Lundin KE, Scott H, Hansen T, et al. Gliadin-specific, HLA-DQ(alpha 1*0501,beta 1*0201) restricted T cells isolated from the small intestinal mucosa of celiac disease patients. J Exp Med 1993;178(1): 187–196. [PubMed: 8315377]
27. Michalski JP, McCombs CC, Arai T, et al. HLA-DR, DQ genotypes of celiac disease patients and healthy subjects from the West of Ireland. Tissue Antigens 1996;47(2):127–133. [PubMed: 8851726]
28. Fernandez-Arquero M, Figueredo MA, Maluenda C, et al. HLA-linked genes acting as additive susceptibility factors in celiac disease. Hum Immunol 1995;42(4):295–300. [PubMed: 7558913]
29. Linos A, Worthington JW, O'Fallon WM, et al. The epidemiology of rheumatoid arthritis in Rochester, Minnesota: a study of incidence, prevalence, and mortality. Am J Epidemiol 1980;111(1):87–98. [PubMed: 7352462]
30. Doran MF, Pond GR, Crowson CS, et al. Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period. Arthritis Rheum 2002;46(3):625–631. [PubMed: 11920397]
31. Lepore L, Martelossi S, Pennesi M, et al. Prevalence of celiac disease in patients with juvenile chronic arthritis. J Pediatr 1996;129(2):311–313. [PubMed: 8765635]
32. Stagi S, Giani T, Simonini G, et al. Thyroid function, autoimmune thyroiditis and celiac disease in juvenile idiopathic arthritis. Rheumatology (Oxford) 2005;44(4):517–520. [PubMed: 15695302]
33. Barahmani N, de Andrade M, Slusser JP, et al. Major histocompatibility complex class I chain-related gene A polymorphisms and extended haplotypes are associated with familial alopecia areata. J Invest Dermatol 2006;126(1):74–78. [PubMed: 16417220]
34. Barbato M, Viola F, Grillo R, et al. Alopecia and coeliac disease: report of two patients showing response to gluten-free diet. Clin Exp Dermatol 1998;23(5):236–237. [PubMed: 10233613]
35. Corazza GR, Andreani ML, Venturo N, et al. Celiac disease and alopecia areata: report of a new association. Gastroenterology 1995;109(4):1333–1337. [PubMed: 7557104]
36. Anaya JM, Castiblanco J, Tobon GJ, et al. Familial clustering of autoimmune diseases in patients with type 1 diabetes mellitus. J Autoimmun. 2006
37. Prahalad S, Shear ES, Thompson SD, et al. Increased prevalence of familial autoimmunity in simplex and multiplex families with juvenile rheumatoid arthritis. Arthritis Rheum 2002;46(7):1851–1856. [PubMed: 12124869]
38. Green PHR, Bana Jabri. Celiac Disease. Annual Review Medicine 2005;57:14.1–14.15.
39. Alaedini A, Green PH. Narrative review: celiac disease: understanding a complex autoimmune disorder. Ann Intern Med 2005;142(4):289–298. [PubMed: 15710962]
40. Roudier J. Association of MHC and rheumatoid arthritis. Association of RA with HLA-DR4: the role of repertoire selection. Arthritis Res 2000;2(3):217–220. [PubMed: 11094433]
41. Fugger L, Svejgaard A. Association of MHC and rheumatoid arthritis. HLA-DR4 and rheumatoid arthritis: studies in mice and men. Arthritis Res 2000;2(3):208–211. [PubMed: 11094431]
42. Redondo MJ, Fain PR, Eisenbarth GS. Genetics of type 1A diabetes. Recent Prog Horm Res 2001;56:69–89. [PubMed: 11237226]
43. Tanure MG, Silva IN, Bahia M, et al. Prevalence of Celiac Disease in Brazilian Children with Type 1 Diabetes Mellitus. J Pediatr Gastroenterol Nutr 2006;42(2):155–159. [PubMed: 16456407]
44. van Oene M, Wintle RF, Liu X, et al. Association of the lymphoid tyrosine phosphatase R620W variant with rheumatoid arthritis, but not Crohn's disease, in Canadian populations. Arthritis Rheum 2005;52(7):1993–1998. [PubMed: 15986374]
45. Urcelay E, Mendoza JL, Martin MC, et al. MDR1 gene: susceptibility in Spanish Crohn's disease and ulcerative colitis patients. Inflamm Bowel Dis 2006;12(1):33–37. [PubMed: 16374256]
46. Hinks A, Barton A, John S, et al. Association between the PTPN22 gene and rheumatoid arthritis and juvenile idiopathic arthritis in a UK population: further support that PTPN22 is an autoimmunity gene. Arthritis Rheum 2005;52(6):1694–1699. [PubMed: 15934099]
47. Khoury, MJ.; Beaty, Terri H.; Cohen, Bernica H. Fundamentals of Genetic Epidemiology. In: Kelsey, JL.; Marmot, Michael G.; Stolley, Paul D.; Vessey, Martin P., editors. Monographs In Epidemiology and Biostatistics. Vol. 22. New York: Oxford University Press; 1993.
48. Shepshelovich D, Shoenfeld Y. Prediction and prevention of autoimmune diseases: additional aspects of the mosaic of autoimmunity. Lupus 2006;15(3):183–190. [PubMed: 16634374]

49. Brix TH, Kyvik KO, Hegedus L. Validity of self-reported hyperthyroidism and hypothyroidism: comparison of self-reported questionnaire data with medical record review. Thyroid 2001;11(8):769–773. [PubMed: 11525270]
50. Gaff CL, Aragona C, MacInnis RJ, et al. Accuracy and completeness in reporting family history of prostate cancer by unaffected men. Urology 2004;63(6):1111–1116. [PubMed: 15183962]
51. Marder K, Levy G, Louis ED, et al. Accuracy of family history data on Parkinson's disease. Neurology 2003;61(1):18–23. [PubMed: 12847150]
52. Bergmann MM, Jacobs EJ, Hoffmann K, et al. Agreement of self-reported medical history: comparison of an in-person interview with a self-administered questionnaire. Eur J Epidemiol 2004;19(5):411–416. [PubMed: 15233312]
53. Bensen JT, Liese AD, Rushing JT, et al. Accuracy of proband reported family history: the NHLBI Family Heart Study (FHS). Genet Epidemiol 1999;17(2):141–150. [PubMed: 10414557]
54. Kiessling U, Doring E, Listing J, et al. Incidence and prevalence of juvenile chronic arthritis in East Berlin 1980–1988. J Rheumatol 1998;25(9):1837–1843. [PubMed: 9733469]
55. von Koskull S, Truckenbrodt H, Holle R, et al. Incidence and prevalence of juvenile arthritis in an urban population of southern Germany: a prospective study. Ann Rheum Dis 2001;60(10):940–945. [PubMed: 11557650]
56. Andersson Gare B, Fasth A, Andersson J, et al. Incidence and prevalence of juvenile chronic arthritis: a population survey. Ann Rheum Dis 1987;46(4):277–281. [PubMed: 3592782]
57. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002;87(2):489–499. [PubMed: 11836274]
58. Canaris GJ, Manowitz NR, Mayor G, et al. The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160(4):526–534. [PubMed: 10695693]
59. Bjoro T, Holmen J, Kruger O, et al. Prevalence of thyroid disease, thyroid dysfunction and thyroid peroxidase antibodies in a large, unselected population. The Health Study of Nord-Trondelag (HUNT). Eur J Endocrinol 2000;143(5):639–647. [PubMed: 11078988]
60. Forouhi NG, Merrick D, Goyder E, et al. Diabetes prevalence in England, 2001-estimates from an epidemiological model. Diabet Med 2006;23(2):189–197. [PubMed: 16433718]
61. Safavi KH, Muller SA, Suman VJ, et al. Incidence of alopecia areata in Olmsted County, Minnesota, 1975 through 1989. Mayo Clin Proc 1995;70(7):628–633. [PubMed: 7791384]
62. Safavi K. Prevalence of alopecia areata in the First National Health and Nutrition Examination Survey. Arch Dermatol 1992;128(5):702. [PubMed: 1575541]

Table 1

Sample characteristics of selected families and individuals studied

Number of families with ≥ 2 CD probands	91
Total study sample (in 91 families)	1,680
Probands	205
Relatives with confirmed CD	203
Relatives without CD	1,272
Median number of individuals per family (range)	17 (4–55)
Groups for analysis	
Group 1 – CD cases (median age)	408 (42.0 years)
Group 2 – Relatives of CD cases (median age)	1,272 (34.0 years)

Table 2

Disease prevalence studies for comparison

Study	Date	Type of study	Age	Population	% Prevalence
RA					
U.S. Minnesota [29]	1950–1974	record review	> 15	U.S.	female = 1.3 male = 0.6 both = 1.2
Jacobson [17]	1965–1996	literature review	> 16	U.S., Canada, Europe	0.86
JRA/JIA					
Kiessling [54]	1980–1988	record review	≤ 16	German	0.020
Von Koskull [55]	1995	doctor reported	≤ 16	German	0.015
Andersson [56]	1993	Pop'n-based; epidemiological	all ages	Sweden	0.056
Hypothyroidism					
National Health and Nutrition Examination [57]	1988–1994	survey	≥ 12	U.S. (C 39.2%; H 28.2%; AA 28%; Oth 4.3%)	4.6
Colorado [58]	1995	health fair	> 18	U.S.	9.5
HUNT [59]	1995–1997	questionnaire	> 19	Norway	female = 4.8 male = 0.9
IDDM					
Forouhi [60]	2001	Pop'n-based; epidemiological	all ages	England	0.3
Jacobson [17]	1965–1996	literature review	< 20	U.S., Canada, Europe	0.2
AA					
Minnesota [61]	1975–1989	Retrospective pop'n- based; descriptive	all ages	U.S.	0.1–0.2
First Nat'l Health and Nutrition Examination Survey [62]	1971–1974	physician survey and exam	all ages	U.S.	2.0

C = Caucasian H = Hispanic AA = African American Oth = Other

Table 3

Prevalence of other autoimmune diseases in CD cases, including both probands and relatives with CD

Disease/Comparison tudies*	n	# observed (%)	Female:male ratio	Median age dx (range)	# expected	Standardized ratio (95% CI)
RA	408	2 (0.5)	Only females	64 (58–70)		
Study 1 [29]						
Female age > 15	203	2 (1.0)			2.6	0.8 (0.7–2.3)
Male age > 15	152	0 (0.0)			1.9	no reported cases
[Female + Male] age > 15	355	2 (0.6)			4.3	0.5 (0.0–1.3)
Study 2 [17] age > 16 yrs	353	2 (0.6)			3.0	0.7 (0.2–1.9)
JRA/JIA	408	0				
Study 1 [55] age ≤ 16 yrs	408	0			0.06	no reported cases
Study 2 [56]	408	0			0.22	no reported cases
Study 3 [54] age ≤ 16 yrs	408	0			0.08	no reported cases
Hypothyroidism	408	42 (10.3)	2.8:1	40.5 (5–82)		
Study 1 [57] age ≥ 12	381	40 (10.5)			17.5	2.3 (1.6–3.0)
Study 2 [58] age > 18	343	39 (11.4)			32.6	1.2 (0.8–1.6)
Study 3 [59]						
female > 19 yrs	191	27 (14.1)			9.2	2.9 (1.9–4.2)
male > 19 yrs	143	11 (7.7)			1.3	8.5 (4.1–14.1)
IDDM	408	12 (2.9)	1.4:1	9 (4–25)		
Study 1 [60]	408	12 (2.9)			1.2	10.0 (5.3–16.7)
Study 2 [17] age < 20 yrs	408	9 (2.2)			0.8	10.9 (5.1–19.8)
AA	408	3 (0.7)	1:2	39 (21–63)		
Study 1 [61]	408	3 (0.7)			0.4	7.5 (1.3–18.0)
					0.8	3.8 (0.6–9.0)
Study 2 [62]	408	3 (0.7)			8.2	0.4 (0.1–0.9)
Total number of diseases	408	60 (14.7)	2.2:1	35 (5–82)		

* all ages unless specified

Table 4

Prevalence of autoimmune diseases in first-degree relatives of CD probands (Group 2)

Disease and Comparison Studies*	n	# observed (%)	Female:male ratio	Median age dx (range)	# expected	Standardized ratio (95% CI)
RA	1272	8 (0.6)	8:0	47.5 (18–71)		
Study 1 [29]						
Female age > 15	498	8 (1.6)			6.5	1.2 (0.5–2.2)
Male age > 15	512	0 (0.0)			3.1	no reported cases
[Female + Male] age > 15	1010	8 (0.8)			12.1	0.7 (0.3–1.2)
Study 2 [17] age > 16 yrs	995	8 (0.8)			8.6	0.9 (0.4–1.7)
JRA/JIA	1272	4 (0.3)	3:1	10.5 (4–17)		
Study 1 [55] age ≤ 16 yrs	1272	1 (0.07)			0.2	5.3 (0.0–19.6)
Study 2 [56]	1272	4 (0.3)			0.7	5.7 (1.5–12.7)
Study 3 [54] age ≤ 16 yrs	1272	1 (0.07)			0.2	4.0 (0.0–19.6)
Hypothyroidism	1272	34 (2.7)	29:5	42.5 (12–78)		
Study 1 [57] age ≥ 12 yrs	1082	34 (2.7)			49.8	0.7 (0.5–0.9)
Study 2 [58] age > 18 yrs	953	34 (2.7)			90.5	0.4 (0.2–0.5)
Study 3 [59]						
female > 19 yrs	457	29 (2.3)			21.9	1.3 (0.9–1.9)
male > 19 yrs	480	5 (0.4)			4.3	1.2 (0.3–2.4)
IDDM	1272	12 (0.9)	1:3	11.5 (4–25)		
Study 1 [60]	1272	12 (0.9)			3.8	3.2 (1.7–5.3)
Study 2 [17] Age < 20 yrs	1272	10 (0.8)			2.5	4.0 (2.0–7.0)
AA	1272	4 (0.3)	1:3	32.0 (19–41)		
Study 1 [61]	1272	4 (0.3)			1.7 – 3.3	2.4 (0.8–6.8) 1.2 (0.4–3.6)
Study 2 [62]	1272	4 (0.3)			33.0	0.1 (0.0–0.3)
Total number of diseases	1272	62 (4.9)	1.6:1	27 (4–78)		

*All ages unless specified

Table 5

Autoimmune disease burden per family

Disease prevalence (%)	# families
1–5	13
6–10	19
11–20	15
> 20	6

Table 6

Number of different autoimmune diseases reported in the 27 families

Characteristics	# families
Families with only 1 individual reported with a disease	26*
Families with > 1 individual reported with disease	27
Number of different diseases reported in the family	
1	10
2	16
4	1

* Includes one individual in a family with two autoimmune diseases