

ORIGINAL ARTICLE

Shared and Distinct Genetic Variants in Type 1 Diabetes and Celiac Disease

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ABSTRACT

BACKGROUND

Two inflammatory disorders, type 1 diabetes and celiac disease, cosegregate in populations, suggesting a common genetic origin. Since both diseases are associated with the HLA class II genes on chromosome 6p21, we tested whether non-HLA loci are shared.

METHODS

We evaluated the association between type 1 diabetes and eight loci related to the risk of celiac disease by genotyping and statistical analyses of DNA samples from 8064 patients with type 1 diabetes, 9339 control subjects, and 2828 families providing 3064 parent-child trios (consisting of an affected child and both biologic parents). We also investigated 18 loci associated with type 1 diabetes in 2560 patients with celiac disease and 9339 control subjects.

RESULTS

Three celiac disease loci — *RGS1* on chromosome 1q31, *IL18RAP* on chromosome 2q12, and *TAGAP* on chromosome 6q25 — were associated with type 1 diabetes ($P < 1.00 \times 10^{-4}$). The 32-bp insertion-deletion variant on chromosome 3p21 was newly identified as a type 1 diabetes locus ($P = 1.81 \times 10^{-8}$) and was also associated with celiac disease, along with *PTPN2* on chromosome 18p11 and *CTLA4* on chromosome 2q33, bringing the total number of loci with evidence of a shared association to seven, including *SH2B3* on chromosome 12q24. The effects of the *IL18RAP* and *TAGAP* alleles confer protection in type 1 diabetes and susceptibility in celiac disease. Loci with distinct effects in the two diseases included *INS* on chromosome 11p15, *IL2RA* on chromosome 10p15, and *PTPN22* on chromosome 1p13 in type 1 diabetes and *IL12A* on 3q25 and *LPP* on 3q28 in celiac disease.

CONCLUSIONS

A genetic susceptibility to both type 1 diabetes and celiac disease shares common alleles. These data suggest that common biologic mechanisms, such as autoimmunity-related tissue damage and intolerance to dietary antigens, may be etiologic features of both diseases.

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TYPE 1 DIABETES IS CAUSED BY AUTOIMMUNE destruction of the insulin-producing beta cells in the pancreatic islets. The disease affects approximately 0.4% of persons of European origin and is strongly clustered in families. The major susceptibility genes — the HLA class II loci, HLA-DQB1 and HLA-DRB1 on chromosome 6p21 — act in combination with many other non-HLA loci across the genome,^{1,2} with unknown environmental factors playing a major role.³⁻⁶ Celiac disease, which results from an immune, inflammatory reaction in the small intestine to proteins in ingested barley, wheat, and rye gluten, occurs in approximately 0.1% of persons of northern European origin, an estimate that is based on clinically diagnosed symptoms. However, within that population, the prevalence of celiac disease may be as high as 1% on the basis of the highly sensitive and specific test for autoantibodies to tissue transglutaminase.^{7,8} The major susceptibility gene is also HLA-DQB1.^{9,10}

Celiac disease and anti-tissue transglutaminase antibodies occur more frequently in patients with type 1 diabetes than in the general population, depending on the age of the patient; at most, 10% of children and 2% of adults with type 1 diabetes have positive tests for such antibodies.¹¹ An increasing incidence of celiac disease during recent decades has also been reported.⁸ It has been suggested that gluten consumption, along with gut permeability and inflammation, are factors in the development of type 1 diabetes.^{6,12} These results suggest that type 1 diabetes and celiac disease may share some causative genetic and environmental factors.

Genomewide association studies have recently identified eight chromosome regions outside the HLA region as being associated with celiac disease ($P < 5.00 \times 10^{-7}$), findings that probably provide a representative view of the major genetic effects in the northern European population for this disorder.¹⁰ In patients with type 1 diabetes, 15 non-HLA regions have been established to date,^{1,13-15} and two other loci, *IL7R* on chromosome 5p13 and *CD226* on chromosome 18q22, have been implicated in type 1 diabetes and multiple sclerosis.^{1,16,17} It has already been reported that the *SH2B3* locus on chromosome 12q24 is shared between type 1 diabetes and celiac disease, with indications of such sharing in *IL2-IL21* on chromosome 4q27 and *CCR3* on chromosome 3p21.^{9,10} In addition, there is some evidence for association of the established type 1 diabetes loci, *CTLA4* on

chromosome 2q33^{9,18} and *PTPN22* on chromosome 1p13,¹⁹ in celiac disease. In this study, we evaluated the association between all these loci and type 1 diabetes and celiac disease, including the *CCR5* 32-bp insertion-deletion variant that we report here as a type 1 diabetes locus, in order to assess the genetic similarities and differences between these two inflammatory disorders. (See the Glossary and the Methods section in the Supplementary Appendix, available with the full text of this article at www.nejm.org.)

METHODS

STUDY SUBJECTS

In our study, patients with type 1 diabetes (www.childhood-diabetes.org.uk/grid.shtml) were under 16 years of age at the time of sample collection, with a mean age at diagnosis of 7.5 years (range, 0.5 to 16).¹ A total of 9339 control samples were obtained from 6164 subjects in the British 1958 Birth Cohort (www.b58cgene.sgul.ac.uk) and from a collection of 3175 blood donors, established by the Wellcome Trust Case Consortium.¹³ The cohort of 2828 families (providing 3064 parent-child trios, consisting of one affected child and two biologic parents) included 468 multiplex families from the Diabetes UK Warren I repository, 331 multiplex families from the Human Biological Data Interchange in the United States, 881 multiplex and simplex families from Finland, 263 multiplex and simplex families from Northern Ireland, 124 simplex families from the Diabetes UK Warren III repository, 350 simplex families from Norway, and 411 simplex families from Romania (www-gene.cimr.cam.ac.uk/todd/dna-refs.shtml).¹ The 2560 patients with celiac disease were recruited throughout England, Scotland, and Wales. DNA was extracted from peripheral-blood samples obtained from 1175 patients recruited from hospital outpatient clinics and from saliva samples obtained from 1385 patients recruited through an advertisement by Celiac UK.

The diagnosis of celiac disease was based on clinical symptoms, a current gluten-free diet, serologic analysis, a biopsy sample of the small intestine, and response to treatment. The mean age at diagnosis was 41.0 years (range, 3 months to 84 years); 75.1% of the patients were female. The Irish collection consisted of 416 patients with celiac disease and 957 control subjects, and the Dutch collection consisted of 507 patients with celiac disease and 888 control subjects.¹⁰ All

patients with type 1 diabetes or celiac disease, control subjects, and parent–child trio families reported their race as white. The relevant research ethics committees approved the study, and written informed consent was obtained from all study subjects or their parents or guardians.

GENOTYPING

We genotyped single-nucleotide polymorphisms (SNPs) from 8 celiac disease loci — *RGS1* on chromosome 1q31, *IL18RAP* on chromosome 2q12, *CCR3* on chromosome 3p21, *IL12A* on chromosome 3q25, *LPP* on chromosome 3q28, *IL2-IL21* on chromosome 4q27, *TAGAP* on chromosome 6q25, and *SH2B3* on chromosome 12q24 — and from 15 type 1 diabetes loci — *PTPN22* on chromosome 1p13, *IFIH1* on chromosome 2q24, *CTLA4* on chromosome 2q33, *IL2-IL21* on chromosome 4q27, *BACH2* on chromosome 6q15, *IL2RA* (*CD25*) on chromosome 10p15, *PRKCQ* on chromosome 10p15, *INS* on chromosome 11p15, *ERBB3* on chromosome 12q13, *SH2B3* on chromosome 12q24, *CTSH* on chromosome 15q24, *CLEC16A* on chromosome 16p13, *PTPN2* on chromosome 18p11, *UBASH3A* on chromosome 21q22, and *CIQTNF6* on chromosome 22q13 (for all gene names, see the Glossary in the Supplementary Appendix). We also genotyped SNPs from *IL7R* on chromosome 5p13, *CD226* on chromosome 18q22, and the 32-bp insertion–deletion variant in *CCR5* on chromosome 3p21.

STATISTICAL ANALYSIS

In our study, $P < 1.00 \times 10^{-4}$ was determined to indicate statistical significance. This approach was conservative because established evidence needed to show that the two diseases being studied have a familial association (cosegregation), a clinical or epidemiologic association, or both and that they share some clinical and biologic phenotypes.^{20,21} We also required that the evidence for the locus association with the first disease be robust and convincing (i.e., $P < 5.00 \times 10^{-7}$ in multiple populations) and that there be robust marker scoring and statistical analyses (see the Supplementary Appendix for details).

RESULTS

CELIAC DISEASE LOCI IN TYPE 1 DIABETES

We genotyped samples from 8064 patients with type 1 diabetes and 9339 control subjects and, where appropriate, samples from 2828 families. We chose the nine SNPs with the highest disease

association from the eight non-HLA regions associated with celiac disease¹⁰ (Table 1, and Table 1 in the Supplementary Appendix). Three of these newly analyzed regions — *RGS1* on chromosome 1q31, *IL18RAP* on chromosome 2q12, and *TAGAP* on chromosome 6q25 — showed strong evidence of association with type 1 diabetes ($P < 1.00 \times 10^{-4}$) in case–control and family subjects. Therefore, along with the sharing in *SH2B3* on chromosome 12q24 that was reported previously,¹⁰ four of these eight celiac disease loci are shared with those associated with type 1 diabetes (Fig. 1A). The celiac disease–associated SNPs rs6441961 in *CCR3* and rs6822844 in *IL2-IL21* did not reach the threshold for significance for type 1 diabetes ($P > 1.00 \times 10^{-4}$) (Table 1). The regions *IL12A* on chromosome 3q25 and *LPP* on chromosome 3q28 showed no evidence of association with type 1 diabetes ($P > 0.15$) (Table 1 and Fig. 1D).

Since the association for *CCR3* in the type 1 diabetes case–control analysis ($P = 3.40 \times 10^{-4}$) narrowly missed the threshold for significance and *CCR3* is one of several chemokine receptor genes on chromosome 3p21, we hypothesized that a stronger association with type 1 diabetes might exist owing to a polymorphism in one of the other *CCR* genes in this region, all of which are functional candidates for both diseases. Therefore, we tested the association of two established functional variants, one in *CCR2* (rs1799864, Ile64Val) and the other in *CCR5* (rs333, the 32-bp insertion–deletion variant), which have been reported to be associated with susceptibility to infection with the human immunodeficiency virus (HIV) and with the outcome and treatment of HIV.²² Moreover, polymorphisms of *CCR5* and its ligand, *CCL3L1*, have also been associated with susceptibility to rheumatoid arthritis^{23,24} and with type 1 diabetes in several smaller studies in which the results remain unconfirmed.^{25–28} We did not find any evidence for an association between rs1799864 in *CCR2* and type 1 diabetes (odds ratio, 0.97; 95% confidence interval [CI], 0.89 to 1.06; $P = 0.51$) (Table 2 in the Supplementary Appendix). In contrast, homozygosity of the rs333 32-bp insertion–deletion variant in *CCR5*, which encodes a nonfunctional receptor, was associated with a decreased risk of type 1 diabetes (odds ratio, 0.54; 95% CI, 0.40 to 0.72; $P = 1.88 \times 10^{-6}$ with 2 df). We validated the association in the family collection (relative risk, 0.53; 95% CI, 0.34 to 0.82; $P = 0.009$; $P = 1.81 \times 10^{-8}$ with 2 df for the overall comparison). The *CCR5* insertion–dele-

Table 1. Association Results for Celiac Risk Variants Genotyped in Type 1 Diabetes Case-Control and Family Collections.*

| Candidate Gene and SNP† | Chromosome | Genomewide Association Study of Loci in Celiac Disease† | | Minor Allele | Allele Frequency | | Type 1 Diabetes Results | | Combined P Value‡ | | |
|-------------------------|------------|---|------------------------|--------------|------------------|------------------|--|------------------------|-------------------|-----------------------|-----------------------------------|
| | | Maximum 2421 Case Subjects and 4828 Control Subjects | P value | | case subjects | control subjects | Maximum 8064 Case Subjects and 9339 Control Subjects | odds ratio (95% CI) | | odds ratio (95% CI) | P value |
| RG51 | 1q31 | | | C | 0.166 | 0.182 | 0.89 (0.84–0.95) | 1.23×10 ⁻⁴ | 0.91 (0.82–1.00) | 0.04 | 1.48×10 ⁻⁵ |
| rs2816316 | | 0.72 (0.65–0.79) | 2.58×10 ⁻¹¹ | | | | | | | | |
| IL18RAP§ | 2q12 | | | A | 0.220 | 0.221 | 0.98 (0.93–1.03) | 0.42; 2 df, 0.01 | 0.87 (0.78–0.96) | 0.008; 2 df, 0.006 | 0.15; 2 df, 8.03×10 ⁻⁵ |
| rs917997 | | 1.29 (1.19–1.40) | 8.49×10 ⁻¹⁰ | | | | | | | | |
| CCR3¶ | 3p21 | | | A | 0.321 | 0.301 | 1.09 (1.04–1.14) | 3.40×10 ⁻⁴ | 1.04 (0.95–1.13) | 0.39 | 0.002 |
| rs6441961 | | 1.21 (1.13–1.30) | 3.41×10 ⁻⁷ | | | | | | | | |
| IL12A | 3q25 | | | G | 0.123 | 0.123 | 1.00 (0.93–1.07) | 0.96 | ND | ND | ND |
| rs17810546 | | 1.35 (1.23–1.49) | 1.07×10 ⁻⁹ | | | | | | | | |
| rs9811792 | | 1.21 (1.15–1.32) | 5.24×10 ⁻⁸ | | 0.451 | 0.443 | 1.04 (0.99–1.08) | 0.15 | ND | ND | ND |
| LPP | 3q28 | | | T | 0.451 | 0.456 | 1.00 (0.95–1.04) | 0.82 | ND | ND | ND |
| rs1464510 | | 1.23 (1.15–1.31) | 5.33×10 ⁻⁹ | | | | | | | | |
| IL2-IL21¶¶ | 4q27 | | | T | 0.165 | 0.176 | 0.95 (0.89–1.00) | 0.06 | ND | ND | ND |
| rs6822844 | | 0.71 (0.63–0.80) | 2.82×10 ⁻¹³ | | | | | | | | |
| TAGAP | 6q25 | | | T | 0.414 | 0.437 | 0.92 (0.88–0.96) | 7.90×10 ⁻⁵ | 0.86 (0.80–0.92) | 2.71×10 ⁻⁵ | 7.59×10 ⁻⁹ |
| rs1738074 | | 1.21 (1.13–1.30) | 6.71×10 ⁻⁸ | | | | | | | | |
| SH2B3¶¶ | 12q24 | | | A | 0.544 | 0.484 | 1.28 (1.22–1.35) | 2.72×10 ⁻²⁴ | 1.25 (1.15–1.36) | 5.08×10 ⁻⁸ | 5.62×10 ⁻³¹ |
| rs3184504 | | 1.21 (1.12–1.29) | 1.33×10 ⁻⁷ | | | | | | | | |

* Celiac disease loci that met the criteria for genomewide significance ($P < 5.00 \times 10^{-7}$) were tested in type 1 diabetes collections. SNP denotes single-nucleotide polymorphism, and ND not done.
 † Data are from Hunt et al.¹⁰
 ‡ P values were calculated with the use of the Wald test.
 § The 2-df test is reported for P values when there was a significant difference between the model for genotypic effects and that for multiplicative allelic effects so that the multiplicative model was not the appropriate one.
 ¶ These loci have previously been examined for their possible sharing between celiac disease and type 1 diabetes, with strong support for an association in SH2B3 on chromosome 12q24 (same SNP, same allele direction),¹⁰ since this locus is an established risk determinant for type 1 diabetes.¹

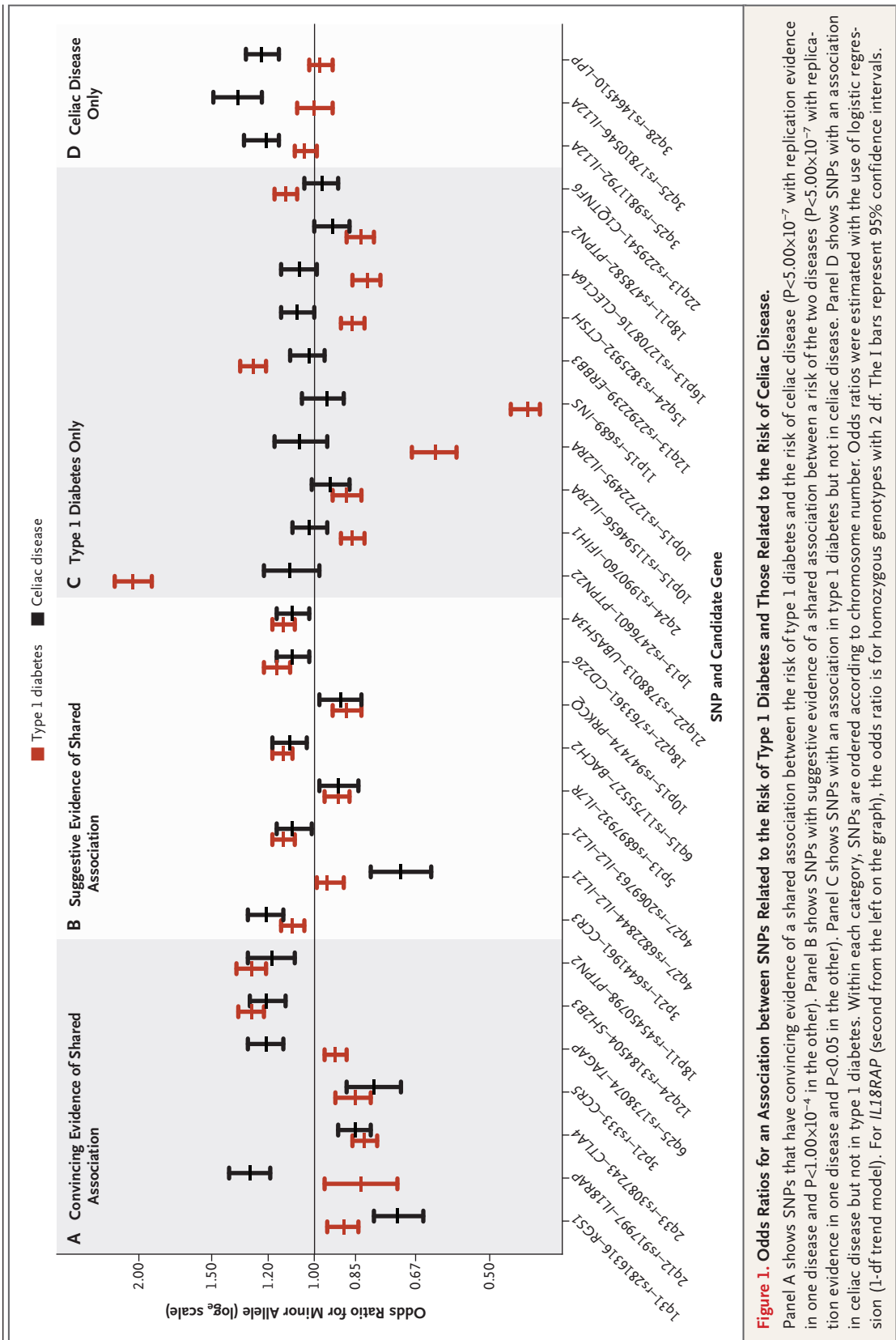


Figure 1. Odds Ratios for an Association between SNPs Related to the Risk of Type 1 Diabetes and Those Related to the Risk of Celiac Disease.

Panel A shows SNPs that have convincing evidence of a shared association between the risk of type 1 diabetes and the risk of celiac disease ($P < 5.00 \times 10^{-7}$ with replication evidence in one disease and $P < 1.00 \times 10^{-4}$ in the other). Panel B shows SNPs with suggestive evidence of a shared association between a risk of the two diseases ($P < 5.00 \times 10^{-7}$ with replication evidence in one disease and $P < 0.05$ in the other). Panel C shows SNPs with an association in type 1 diabetes but not in celiac disease. Panel D shows SNPs with an association in celiac disease but not in type 1 diabetes. Within each category, SNPs are ordered according to chromosome number. Odds ratios were estimated with the use of logistic regression (1-df trend model). For *IL18RAP* (second from the left on the graph), the odds ratio is for homozygous genotypes with 2 df. The 1 bars represent 95% confidence intervals.

tion, rs333, is located 62 kb centromeric from the rs6441961 SNP in *CCR3* ($D'=0.98$, $r^2=0.05$), and logistic-regression analysis indicated that the potential association with type 1 diabetes with rs6441961 in *CCR3* was not due to linkage disequilibrium with rs333 (rs333 added to rs6441961, $P=3.39\times 10^{-5}$; in reverse analysis, rs6441961 added to rs333, $P=0.008$).

TYPE 1 DIABETES LOCI IN CELIAC DISEASE

We analyzed the associations of the 18 loci that have been associated with type 1 diabetes in celiac disease (including the *CCR5* insertion-deletion, rs333, and the *SH2B3* locus on 12q24 that was previously recognized to be shared between the two diseases) by genotyping 19 SNPs and the rs333 variant in *CCR5* in 2560 patients with celiac disease. We then compared the results with those from 9339 control subjects (Table 2 and Fig. 1, and Table 3 in the Supplementary Appendix). The loci with the most significant associations were *CTLA4* (rs3087243) with an odds ratio of 0.85 ($P=1.26\times 10^{-6}$) and *CCR5* (rs333) with an odds ratio of 0.79 ($P=9.18\times 10^{-6}$). The findings in these two regions indicated that these are probably true effects, a conclusion supported by previous reports that these loci have been associated with both type 1 diabetes and celiac disease and other immune-mediated diseases.^{9,18,23-28}

Markers in *CCR5* and *CCR3* were independently associated with celiac disease (in logistic-regression analysis, rs333 added to rs6441961, $P=0.001$; in reverse analysis, rs6441961 added to rs333, $P=0.01$). These results indicate that there are two or more causal variants or genes in this region of chromosome 3p21, which is rich in chemokine and chemokine receptor genes.

We previously reported two independent associations with type 1 diabetes within the *PTPN2* region marked by the SNPs rs1893217 and rs478582.¹ Resequencing of the *PTPN2* gene, genotyping, and analyses identified SNP rs45450798 in high linkage disequilibrium with rs1893217 ($r^2=0.97$), so rs45450798 replaces rs1893217 as the most strongly associated SNP in the *PTPN2* region. Logistic forward regression analysis revealed that rs45450798 explained the association at rs1893217 and, combined with rs478582, explained the association with type 1 diabetes of the *PTPN2* chromosome region (Table 4 in the Supplementary Appendix). In the patients with celiac disease,

the significance of the association of *PTPN2* SNP rs45450798 ($P=2.61\times 10^{-4}$) narrowly missed the threshold of $P<1.00\times 10^{-4}$ (Table 2). Therefore, we analyzed the available but unpublished data for the two independent case-control sample sets from Ireland and the Netherlands, obtaining consistent support for the association of *PTPN2* rs1893217 with celiac disease ($P=0.045$) (Table 6 in the Supplementary Appendix). Given the fact that *PTPN2* has also been associated with another inflammatory disorder, Crohn's disease,²⁹ it is highly likely that *PTPN2* is also a celiac disease locus, bringing the total of non-HLA celiac disease loci from 8 to 11.

Six other regions showed nominal evidence of association with celiac disease ($P<0.05$). The most strongly associated SNP for the risk of type 1 diabetes in the *IL2-IL21* region on chromosome 4q27, rs2069763 (a synonymous SNP in exon 1 of *IL2*), is weakly associated with celiac disease ($P=0.02$), which indicates that although this region is linked to both diseases, the genetic variants are different. The remaining regions are *IL7R* on chromosome 5p13 ($P=0.007$), *BACH2* on chromosome 6q15 ($P=0.003$), *PRKCCQ* on chromosome 10p15 ($P=0.02$), *CD226* on chromosome 18q22 ($P=0.01$), and *UBASH3A* on chromosome 21q22 ($P=0.009$). Figure 1 illustrates the combined results of Tables 1 and 2, with 15 loci showing some evidence for colocalization (assuming two susceptibility variants in the *IL2-IL21* region on chromosome 4q27); of these, 7 have convincing evidence: *RGS1* on chromosome 1q31, *IL18RAP* on chromosome 2q12, *CTLA4* on chromosome 2q33, *CCR5* on chromosome 3p21, *TAGAP* on chromosome 6q25, *SH2B3* on chromosome 12q24, and *PTPN2* on chromosome 18p11. At least five showed distinct differences — namely, a strong association in one disease and no or little evidence for association in the other disease (*INS* on chromosome 11p15, *PTPN22* on chromosome 1p13, *IL2RA* on chromosome 10p15, *LPP* on chromosome 3q28, and *IL12A* on chromosome 3q25) (Fig. 1C and 1D).

DISCUSSION

Our findings and those reported previously^{1,10,14,15} provide convincing evidence that 21 non-HLA loci are associated with type 1 diabetes and 11 non-HLA loci are associated with celiac disease. Of

these loci, we have identified three celiac disease loci as having an association with type 1 diabetes (*RGS1*, *IL18RAP*, and *TAGAP*) and two type 1 diabetes loci as having an association with celiac disease (*CCR5* and *PTPN2*). Furthermore, our results provide confirmation of the importance of the *CTLA4* region on chromosome 2q33. Seven of these chromosome regions are shared between the two diseases, suggesting that for an investigation of shared loci in two diseases that are known to cosegregate, the previous odds of 1000:1 against there being a true association at any tested candidate gene^{20,21} is too conservative (Supplementary Appendix).

Four alleles — *RGS1* on chromosome 1q31, *CTLA4* on chromosome 2q33, *SH2B3* on chromosome 12q24, and *PTPN2* on chromosome 18p11 — show the same direction of association in the two diseases, constituting evidence for shared causal variants. We know that this is not due to bias in ascertainment of the cases, nor is the use of a common set of control subjects a problem since we have consistent results from our family-based analyses (Supplementary Appendix).

The minor alleles of the SNPs rs917997 (*IL18RAP* on chromosome 2q12) and rs1738074 (*TAGAP* on chromosome 6q25) were negatively associated with type 1 diabetes, whereas these minor alleles were positively associated with celiac disease.¹⁰ These results may be interpreted in two ways: the causal variants in these two regions may have opposite biologic effects in type 1 diabetes and celiac disease, or there may be different causal variants for each disease in each region with the typed marker SNPs tagging these causal variants. For the regions of *IL18RAP* on chromosome 2q12 and *TAGAP* on chromosome 6q25, we have found no evidence for a second locus within these regions in genomewide association studies of type 1 diabetes^{13,15} (data not shown). Moreover, there is precedent for a causal variant having opposing effects in different diseases. For example, the minor allele of *PTPN22* variant Arg620Trp on chromosome 1p13 predisposes a person to many immune-mediated diseases but is protective for Crohn's disease.³⁰ Hence, we favor the possibility that the causal variants have opposite effects in patients with type 1 diabetes and celiac disease. In contrast, for chromosome 4q27, our data indicate that different causal variants are involved in type 1 diabetes and celiac

disease, perhaps affecting different genes. The important immune-response genes, *IL-2*³¹ and *IL-21*, are strong functional candidates. Before we can draw further conclusions, all the regions discussed here must be thoroughly resequenced from multiple persons to ascertain a complete catalogue of polymorphisms, followed by further genotyping to identify all the variants with the most association.

Nevertheless, the 32-bp insertion–deletion in *CCR5* (rs333), which causes a loss of expression of the receptor,²² could well be the actual functional, causal variant involved. The disease associations of the two chemokine receptor genes, *CCR3* and *CCR5*, suggest the central importance of lymphocyte trafficking in these organ-specific diseases. The development and anatomy of the small intestine and pancreas are close, and the gut immune system shares close connections with pancreatic lymph nodes, which have been linked to insulinitis and destruction of beta cells.³² In patients with recent-onset type 1 diabetes, alterations in levels of two *CCR5* ligands, *CCL3* (MIP-1 α) and *CCL4* (MIP-1 β), have been reported.³³ In the NOD mouse model of type 1 diabetes, *CCR5* and its ligand *CCL4* have multiple reported roles in the development of disease.³⁴

However, there are distinct differences in genetic susceptibility between patients with type 1 diabetes and those with celiac disease, including differences in *PTPN22* on chromosome 1p13, in *IL2RA* on chromosome 10p15, and in *INS* on chromosome 11p15. Although there are shared predisposing alleles at the *HLA-DQB1* gene for type 1 diabetes and celiac disease, there are distinguishing differences in the *HLA-DQB1* genotype (Supplementary Appendix). One possibility is that there is a common genetic background with respect to autoimmunity and inflammation and that further combinations of more disease-specific variation at HLA and non-HLA genes, in interaction with epigenetic and environmental factors, determine the final clinical outcomes.

Our results support further evaluation of the hypothesis that cereal and gluten consumption might be an environmental factor in type 1 diabetes, leading to the alteration of the function of the gut immune system and its relationship with the pancreatic immune system.^{6,12,32,35} Furthermore, insulin and its precursors are major targets of the T and B lymphocyte autoreactive response

Table 2. Association Results of Type 1 Diabetes Loci Tested in Celiac Disease.*

| Gene and SNP | Chromosome | Minor Allele | Type 1 Diabetes | | Minor Allele Frequency† | | Celiac Disease | | |
|--------------|------------|--------------|--|---|--------------------------|-------------------------------|------------------------------|--|-----------------------|
| | | | Maximum 8064 Case Subjects and 9339 Control Subjects <i>odds ratio (95% CI)</i> | <i>P value‡</i> | British Control Subjects | Type 1 Diabetes Case Subjects | Celiac Disease Case Subjects | Maximum 2560 Case Subjects and 9339 Control Subjects <i>odds ratio (95% CI)</i> | <i>P value</i> |
| PTPN22 | 1p13 | | | | | | | | |
| rs2476601 | | T | 2.05 (1.90–2.20) | 1.13×10 ⁻⁸⁸ | 0.095 | 0.178 | 0.106 | 1.09 (0.98–1.22) | 0.13 |
| IFIH1 | 2q24 | | | | | | | | |
| rs1990760 | | G | 0.86 (0.82–0.90) | 2.13×10 ⁻¹⁰ | 0.389 | 0.351 | 0.397 | 1.02 (0.95–1.09) | 0.55 |
| CTLA4 | 2q33 | | | | | | | | |
| rs3087243 | | A | 0.82 (0.78–0.86) | 1.27×10 ⁻¹⁴ | 0.452 | 0.405 | 0.411 | 0.85 (0.80–0.90) | 1.26×10 ⁻⁶ |
| CCR5 | 3p21 | | | | | | | | |
| rs333 | | del | 0.85 (0.80–0.92) | 5.87×10 ⁻⁶ ; 2 df, 1.93×10 ⁻⁶ | 0.119 | 0.103 | 0.095 | 0.79 (0.71–0.88) | 9.18×10 ⁻⁶ |
| IL2-IL21 | 4q27 | | | | | | | | |
| rs2069763 | | T | 1.13 (1.08–1.18) | 1.28×10 ⁻⁷ | 0.329 | 0.358 | 0.346 | 1.09 (1.01–1.16) | 0.02 |
| IL7R | 5p13 | | | | | | | | |
| rs6897932 | | A | 0.89 (0.84–0.94) | 4.13×10 ⁻⁴ | 0.274 | 0.255 | 0.254 | 0.91 (0.84–0.97) | 0.007 |
| BACH2 | 6q15 | | | | | | | | |
| rs11755527 | | G | 1.13 (1.09–1.18) | 8.57×10 ⁻⁹ ; 2 df, 4.37×10 ⁻¹¹ | 0.465 | 0.495 | 0.491 | 1.10 (1.03–1.18) | 0.003 |
| PRKCQ | 10p15 | | | | | | | | |
| rs947474 | | G | 0.88 (0.83–0.93) | 1.48×10 ⁻⁵ | 0.187 | 0.171 | 0.173 | 0.90 (0.83–0.98) | 0.02 |
| IL2RA | 10p15 | | | | | | | | |
| rs12722495 | | G | 0.62 (0.57–0.68) | 1.74×10 ⁻³⁰ | 0.113 | 0.072 | 0.120 | 1.06 (0.95–1.17) | 0.32 |
| rs11594656 | | A | 0.87 (0.83–0.93) | 2.03×10 ⁻⁶ | 0.246 | 0.222 | 0.234 | 0.94 (0.87–1.01) | 0.09 |

| INS | 11p15 | A | 0.42 (0.41–0.46) | 8.93×10^{-195} ; 2 df, 1.86×10^{-202} | 0.293 | 0.151 | 0.286 | 0.95 (0.89–1.03) | 0.20 |
|------------|-------|---|------------------|--|-------|-------|-------|------------------|-----------------------|
| rs689 | | A | | | | | | | |
| ERBB3 | 12q13 | A | 1.31 (1.22–1.34) | 5.79×10^{-2} | 0.352 | 0.407 | 0.359 | 1.02 (0.96–1.10) | 0.50 |
| rs2292239 | | A | | | | | | | |
| SH2B3 | 12q24 | A | 1.28 (1.22–1.35) | 2.72×10^{-24} | 0.485 | 0.549 | 0.523 | 1.15 (1.08–1.23) | 2.85×10^{-5} |
| rs3184504 | | A | | | | | | | |
| CTSH | 15q24 | C | 0.86 (0.82–0.90) | 4.62×10^{-10} | 0.318 | 0.287 | 0.334 | 1.07 (1.00–1.14) | 0.06 |
| rs3825932 | | C | | | | | | | |
| CLEC16A | 16p13 | G | 0.81 (0.77–0.86) | 3.19×10^{-13} | 0.351 | 0.306 | 0.365 | 1.06 (0.99–1.14) | 0.12 |
| rs12708716 | | G | | | | | | | |
| PTPN2 | 18p11 | G | 0.83 (0.79–0.88) | 8.83×10^{-12} | 0.449 | 0.408 | 0.432 | 0.93 (0.87–1.00) | 0.04 |
| rs478582 | | G | | | | | | | |
| rs45450798 | | G | 1.28 (1.21–1.36) | 1.15×10^{-16} | 0.166 | 0.202 | 0.191 | 1.18 (1.08–1.30) | 2.61×10^{-4} |
| CD226 | 18q22 | | | | | | | | |
| rs763361 | | A | 1.16 (1.10–1.22) | 1.56×10^{-8} | 0.471 | 0.503 | 0.491 | 1.09 (1.02–1.16) | 0.01 |
| UBASH3A | 21q22 | | | | | | | | |
| rs3788013§ | | A | 1.13 (1.08–1.18) | 3.09×10^{-8} | 0.433 | 0.465 | 0.454 | 1.08 (1.01–1.15) | 0.009 |
| C1QTNF6 | 22q13 | | | | | | | | |
| rs229541 | | T | 1.12 (1.07–1.17) | 6.96×10^{-7} | 0.428 | 0.455 | 0.424 | 0.97 (0.91–1.04) | 0.42 |

* The results with respect to type 1 diabetes have all been published previously,^{1,14,15} except for rs333 in *CCR5*, rs45450798 in *PTPN2*, and rs12722495 in *IL2RA* (Tables 2, 4, and 5 in the Supplementary Appendix).

† The minor allele frequency was estimated in a maximum of 9339 control subjects, 8064 patients with type 1 diabetes, and 2560 patients with celiac disease.

‡ The 2-df test is reported for P values when there was a significant difference between the model for genotypic effects and that for multiplicative allelic effects so that the multiplicative model was not the appropriate one.

§ In the British case-control samples, rs3788013 is in complete linkage disequilibrium ($r^2 = 1$) with rs876498.¹⁴

in type 1 diabetes. Thus, one might speculate that bovine insulin in infant foods could enhance anti-insulin responses,³ particularly if there are genetically determined defects in oral tolerance predisposing to type 1 diabetes. Conversely, genes that are classified as autoimmunity genes, because they are associated with type 1 diabetes, contribute to celiac disease.

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