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

Deborah J Smyth[1], **Vincent Plagnol**[1], **Neil M Walker**[1], **Jason D Cooper**[1], **Kate Downes**[1], **Jennie HM Yang**[1], **Joanna MM Howson**[1], **Helen Stevens**[1], **Ross McManus**[2], **Cisca Wijmenga**[3], **Graham A. Heap**[4], **Patrick C. Dubois**[4], **David G. Clayton**[1], **Karen A Hunt**[4], **David A van Heel**[4], and **John A Todd**[*,1]

[1]Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory, Department of Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge, Addenbrooke's Hospital, Cambridge, CB2 0XY, UK. [2]Department of Clinical Medicine, Institute of Molecular Medicine, Trinity College Dublin, Dublin, Ireland. [3]Genetics Department, University Medical Center and Groningen University, Groningen, 9700 RB Groningen, The Netherlands. [4]Institute of Cell and Molecular Science, Barts and The London School of Medicine and Dentistry, Newark Street, London, E1 2AT, UK.

Abstract

BACKGROUND—The inflammatory disorders type 1 diabetes (T1D) and celiac disease co-segregate in populations, suggesting a common genetic origin. Both are associated with the HLA class II genes on chromosome 6p21, and the present paper tested whether non-HLA loci are shared.

METHODS—We evaluated eight celiac disease risk loci in T1D by genotyping and statistical analyses of 8,064 T1D cases, 9,339 controls and 2,519 families. We also investigated 18 T1D loci in 2,560 celiac disease cases and 9,339 controls.

RESULTS—Three celiac disease loci, listed as chromosome/candidate gene: 1q31/*RGS1*, 2q12/*IL18RAP* and 6q25/*TAGAP*, were associated with T1D ($P < 10^{-4}$). The 3p21/*CCR5* 32 base pair insertion/deletion variant was newly identified as a T1D locus ($P = 1.81 \times 10^{-8}$), and was also associated with celiac disease, as were 18p11/*PTPN2* and 2q33/*CTLA4*, bringing the total loci shared to seven, including 12q24/*SH2B3*. The 2q12/*IL18RAP* and 6q25/*TAGAP* allele associations were in the opposite direction in T1D as compared to celiac disease. Distinct effects included *11p15/INS, 10p15/IL2RA* and 1q13/*PTPN22* in T1D and 3q25/*IL12A* and 3q28/*LPP* in celiac disease.

CONCLUSIONS—Genetic susceptibility to T1D and celiac disease shares common alleles. These data suggest that common biological mechanisms, such as autoimmunity related tissue damage and intolerance to dietary antigens may be a feature of T1D.

Type 1 diabetes (T1D) is caused by autoimmune destruction of the insulin-producing β cells in the pancreatic islets, affecting approximately 0.4% of European populations and strongly

[*]Correspondence to Prof. John Todd Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory, Department of Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge, Addenbrooke's Hospital, Cambridge, CB2 0XY, UK Phone 01223 762101 FAX 01223 762103 john.todd@cimr.cam.ac.uk.

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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 ingested barley, wheat and rye gluten proteins, occurs in 0.1% of northern European-origin populations, an estimate based on clinically-diagnosed symptoms. However, within that population, there may be as much as 1% prevalence, if the highly sensitive and specific test for autoantibodies to tissue transglutaminase is used.7, 8 The major susceptibility gene is also *HLA-DQB1*.9, 10

Celiac disease and anti-tissue transglutaminase antibodies occur more frequently in T1D cases than in the general population, depending on the age of the patients; at most 10% of children and 2% of adults with T1D are positive.11 Increasing incidence of celiac disease over recent decades has also been reported.8 It has been suggested that gluten consumption, and gut permeability and inflammation, are also factors in the development of T1D.6, 12 These results suggest that the etiologies of T1D and celiac disease may share some genetic and environmental factors.

Eight chromosome regions outside the HLA region have recently been associated with celiac disease using the genome wide association (GWA) approach and achieving genome-wide statistical support at $P < 5 \times 10^{-7}$, probably providing a representative view of the major genetic effects in the northern European population for this disorder 10 (Methods and Glossary). In T1D, 15 non-HLA regions have been established to date 1, 13-15 (Methods and Glossary) and two other loci, 5p13/*IL7R* and 18q22/*CD226,* have been implicated in T1D and multiple sclerosis.1, 16, 17 It has already been reported that the 12q24/*SH2B3* locus is shared between T1D and celiac disease, and possibly loci 4q27/*IL2-IL21* and 3p21/*CCR3*.9, 10 In addition, there is some evidence for association of the established T1D loci, 2q33/*CTLA4*9, 18 and 1p13/*PTPN22, 19* in celiac disease. In the present report, we evaluated the association of all these loci in T1D and celiac disease, including the *CCR5* 32 base pair insertion/deletion variant that we report here as a T1D locus, in order to assess the genetic similarities and differences between these two inflammatory disorders.

METHODS

Subjects

The T1D cases (www.childhood-diabetes.org.uk/grid) were under 16 years of age at the time of sample collection (mean age at diagnosis = 7.5 years, range 0.5 – 16 years).1 The control samples (n = 6,164) are from the British 1958 Birth Cohort (www.b58cgene.sgul.ac.uk); and from a collection of blood donors (n = 3,175), established by the Wellcome Trust Case Consortium.13 The family collection consisted of 455 Diabetes UK Warren 1 families; 250 Northern Irish families; 243 USA families from the Human Biological Data Interchange; 411 Romanian families; 360 Norwegian families and 800 Finnish families.1 The 2,560 celiac disease patients were recruited throughout England, Scotland and Wales. DNA was extracted from peripheral blood for 1,175 persons recruited from hospital outpatient clinics, and from saliva DNA for 1,385 persons recruited via Coeliac UK advertisement. Diagnosis of celiac disease was based on clinical symptoms, current gluten free diet, serology, small intestinal biopsy and response to treatment. Mean age at diagnosis was 41.0 years (range 3 months - 84 years), and 75.1% were female. The Irish collection consisted of 416 celiac cases and 957 controls, and the Dutch collection of 507 celiac cases and 888 controls.10 All cases (T1D and celiac disease) controls and families self-reported as white ethnicity. The relevant research ethics committees approved the study, and written informed consent was obtained from the participants, or their parents/guardian for those too young to consent.

Genotyping

SNPs were genotyped from eight celiac disease loci: chromosome 1q31/candidate gene *RGS1*, 2q12/*IL18RAP*, 3p21/ *CCR3*, 3q25/*IL12A*, 3q28/*LPP*, 4q27/*IL2-IL21*, 6q25/*TAGAP* and 12q24/*SH2B3* and 15 T1D loci: 1p13/ *PTPN22*; 2q24/*IFIH1*; 2q33/*CTLA4*; 4q27/*IL2-IL21;* 6q15/*BACH2;* 10p15/*IL2RA/CD25*; 10p15/*PRKCQ;* 11p15/*INS*; 12q13/*ERBB3*; 12q24/*SH2B3*; 15q24/*CTSH;* 16p13/*CLEC16A*, 18p11/*PTPN2*; 21q22/*UBASH3A* and 22q13/*C1QTNF6* [see Glossary for full gene names]. SNPs from 5p13/*IL7R*, 18q22/*CD22* and 3p21/*CCR5* were also genotyped.

Statistical Analysis

In our study we claim "significance" when $P<10^{-4}$; this approach is conservative because the two disorders being studied must have established evidence that they have a familial (co-segregation) and/or clinical-epidemiological association (i.e., more or less cases of one occur in the patient population of the other disease), and the two diseases share some clinical and biological phenotypes 20, 21. We also required that the evidence for the locus association with the first disease is robust and convincing, i.e., $P < 5 \times 10^{-7}$ in multiple populations, and there be robust marker scoring and statistical analyses (Supplemental Appendix).

RESULTS

Celiac Disease Loci in Type 1 Diabetes

We genotyped in 8,064 T1D cases and 9,339 controls, and where appropriate, in 2,519 parent-child trio families, the nine SNPs with the highest disease association from the eight non-HLA celiac disease regions 10(Table 1; Supplementary Table 1). Three of these newly analyzed regions showed strong evidence of association ($P < 10^{-4}$; Methods) with T1D in case-control and family sample sets, 1q31/*RGS1*, 2q12/*IL18RAP* and 6q25/*TAGAP* (Table 1; Supplementary Table 1). Therefore, along with the 12q24/*SH2B3* sharing reported previously,10 four of these eight celiac loci are shared with T1D (Fig. 1, A). The celiac disease-associated SNPs/variants of 3p21/*CCR3*/rs6441961 and 4q27/IL2-IL21/rs6822844 did not reach our statistical threshold in T1D ($P > 10^{-4}$; Table 1). The regions 3q25/*IL12A* and 3q28/*LPP* showed no evidence of association with T1D ($P > 0.147$; Table 1; Fig 1, D).

Since the 3p21/*CCR3* association in the T1D case-control at $P = 3.40 \times 10^{-4}$ (Table 1) just failed to reach our threshold for statistical significance, and *CCR3* is one of several chemokine receptor genes on chromosome 3p21, we hypothesized that a stronger T1D association might exist due to a polymorphism in one of the other CCR genes in this region, all of which are functional candidates for both diseases. We, therefore, tested the association of two established functional variants, one in the CCR2 gene (rs1799864/ Ile64Val) and the other in *CCR5* (rs333, the 32 base pair insertion/deletion), which have been reported to be associated with susceptibility to HIV infection, its outcome and treatment.22 Moreover, polymorphisms of *CCR5* and its ligand, *CCL3L1*, have also been associated with susceptibility to rheumatoid arthritis,23 and for *CCR5* with T1D in several smaller studies. 24-28 We did not find any evidence for an association between *CCR2*/rs1799864 and T1D ($P = 0.506$; Table 2). Homozygosity of the *CCR5*/rs333 deletion allele, which encodes a non-functional receptor, in contrast, was associated with decreased T1D risk, odds ratio (OR) = 0.54, (95% confidence interval (CI) = 0.40-0.72), $P = 1.88 \times 10^{-6}$ (2-df)(Table 2). We validated the association in the family collection relative risk (RR) = 0.53 (95% CI = 0.34-0.82), $P = 9.10 \times 10^{-3}$, and overall the combined results gave $P = 1.81 \times 10^{-8}$ (Table 2). The *CCR5* insertion/deletion rs333 is located 62 kb away from the *CCR3*/rs6441961 SNP, with $D' = 0.98$ and $r^2 = 0.05$, and logistic regression analysis indicated that the potential T1D association with *CCR3*/rs6441961 is not due to linkage disequilibrium with

CCR5/rs333: *CCR5*/rs333 added to *CCR3*/rs6441961, $P = 3.39 \times 10^{-5}$, and in the reverse analysis, adding *CCR3*/rs6441961 to *CCR5*/rs333 gave $P = 7.6 \times 10^{-3}$.

Type 1 Diabetes Loci in Celiac Disease

We analysed the 18 loci that have been associated with T1D, including the *CCR5* deletion/rs333 variant (Table 2) and the 12q24/*SH2B3* locus previously recognised to be shared between the two diseases, in celiac disease by genotyping 19 SNPs and the *CCR5*/rs333 variant in 2,560 celiac cases and comparing the results with those from the 9,339 controls (Table 3; Supplementary Table 4; Fig 1). The most significantly associated loci were *CTLA4*/rs3087243 and *CCR5*/rs333 ($P = 1.26 \times 10^{-6}$ and 9.18×10^{-6}, respectively), indicating that these two regions are likely to be true effects, a conclusion supported by previous reports that these loci have been associated with both disorders and other immune-mediated diseases.9, 18, 23, 26 Markers in the *CCR5* and *CCR3* genes were independently associated with celiac disease: in a logistic regression analysis *CCR5*/rs333 added to *CCR3*/rs6441961, $P = 1.00 \times 10^{-3}$, and in the reverse analysis, adding *CCR3*/rs6441961 to *CCR5*/rs333 gave $P = 0.0127$. These results indicate two or more causal variants or genes in this chemokine gene rich region of chromosome 3p21.

We previously reported two independent T1D associations within the *PTPN2* region marked by the SNPs rs1893217 and rs478582.1 Resequencing of the *PTPN2* gene, genotyping and analyses identified a SNP rs45450798 in high linkage disequilibrium with rs1893217 ($r^2 = 0.97$) that replaces rs1893217 as the most associated SNP in the *PTPN2* region. Logistic forward regression analysis revealed that rs45450798 explained the association at rs1893217 and combined with rs478582 explains the T1D association of the *PTPN2* chromosome region (Supplementary Table 3). In the celiac disease cases, the *PTPN2* SNP rs45450798 just failed to pass our threshold of $P \leq 10^{-4}$ ($P = 2.61 \times 10^{-4}$; Table 1). Therefore, we analysed 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 ($P = 0.045$; Supplementary Table 5). Combined with the fact that *PTPN2* has also been associated with the inflammatory bowel disease, 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 eight to 11.

Six other regions showed nominal evidence at $P < 0.05$ of association with celiac disease. The currently most associated SNP for T1D in the 4q27/*IL2-IL21* region, rs2069763, (a synonymous SNP in exon 1 of *IL2*) is weakly associated with celiac disease ($P = 0.018$) indicating that while this region is linked to both diseases the genetic variants are different. The remaining regions are: 5p13/*IL7R* ($P = 7.23 \times 10^{-3}$), 6q15/*BACH2* ($P = 2.78 \times 10^{-3}$), 10p15/*PRKCQ* (P = 0.0178), 18q22/*CD226* ($P = 0.0133$) and 21q22/U*BASH3A* ($P = 8.88 \times 10^{-3}$). Figure 1 illustrates the combined results of Tables 1 and 3, with 14 loci showing some evidence for co-localisation, seven of which are convincing: 1q31/*RGS1*, 2q12/*IL18RAP*, 2q33/*CTLA4*, 3p21/*CCR5*, 6q25/*TAGAP*, 12q24/*SH2B3*, and 18p11/*PTPN2*. At least five showed distinct differences (Figure 1, C and D), namely a strong association in one disease, and no or little evidence for association in the other (11p15/*INS*, 1p13/*PTPN22*, 10p15/*IL2RA*, 3q28/*LPP* and 3q25/*IL12A*).

DISCUSSION

The results presented here and reported recently elsewhere1, 10, 14, 15 indicate that one may be confident in 21 non-HLA loci in T1D and 11 in celiac disease (Fig. 1), of which four are newly identified loci in T1D (1q31/*RGS1*, 2q12/*IL18RAP*, 3p21/*CCR5* and 6q25/*TAGAP;* Tables 1 and 2) and of which two are new for celiac disease, 3p21/*CCR5* and 18p11/*PTPN2*. Further, the results provide convincing confirmation of the importance of the

2q33/*CTLA4* region (Table 3). 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 co-segregate, the prior odds of 1000:1 against there being a true association at any locus tested 20 is too conservative.

Four alleles, 1q31/*RGS1*, 2q33/*CTLA4*, 12q24/*SH2B3* and 18p11/*PTPN2*, 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 (Supplementary Appendix); nor is the use of a common set of controls a problem since we have consistent results from families (Supplementary Appendix).

The minor alleles of the SNPs 2q12/*IL18RAP* rs917997 and 6q25/*TAGAP* rs1738074 were negatively associated with T1D (Table 1),with the effects in the opposite direction to the previous celiac disease findings (Table 1).10 These results may be interpreted in two ways: the causal variants in these two regions have opposite biological effects in T1D and celiac disease, or that there are different causal variants for each disease in each region with the typed marker SNPs tagging these causal variants. For the 2q12/*IL18RAP* and 6q25/*TAGAP* regions we have found no evidence so far in T1D GWA studies13, 15 for a second loci within these regions (data not shown). Moreover, there is precedent for a causal variant having opposing effects in different diseases. For example, the minor allele of 1p13/*PTPN22* variant Arg620Trp 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 the T1D and celiac disease patients. In contrast, for 4q27 our current data indicate that different causal variants are involved, perhaps affecting different genes, in T1D and celiac disease. 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 in order to identify all of the most associated variants.

Nevertheless, the 32 base pair insertion/deletion in *CCR5* (rs333), which causes 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* (Table 3) and *CCR5* (Table 2), 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 the pancreatic lymph nodes, which have been linked to insulitis and β-cell destruction.32 In recent-onset T1D patients alterations in the levels of CCR5 ligands, CCL3 (MIP-1α) and CCL4 (MIP-1β) have been reported.33 In the NOD mouse model of T1D, CCR5 and its ligand CCL4 have multiple reported significant roles in the disease development. 34

There are, however, distinct differences in genetic susceptibility between the two diseases, including at 1p13*/PTPN22*, 10p15/*IL2RA* and 11p15/*INS* (Table 1), and although there are shared T1D and celiac disease predisposing alleles at the HLA-DQB1 gene, there are distinguishing *HLA-DQB1* genotype differences (Supplementary Appendix). One possibility is that there is a common autoimmunity-inflammatory genetic background, 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 T1D 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 in T1D; thus, one might speculate that bovine insulin in infant feeds could enhance anti-insulin responses,3 particularly if there are genetically-determined defects in oral tolerance predisposing to T1D. Conversely, genes classified as autoimmunity genes, because they are associated with T1D, contribute to celiac disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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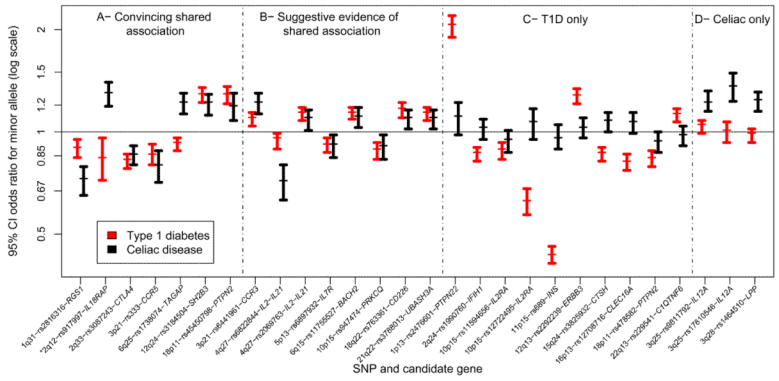

Figure 1.

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Table 1

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

Celiac disease loci meeting genome wide significance criteria ($P < 5\times10^{-7}$), which have been reported previously,10 were tested in T1D collections.

Genome-wide Association Study Loci in Celiac Disease Hunt *et al. 10*				Type 1 Diabetes Results							
							Maximum 8,064 cases and 9,339 controls		2,519 parent-child-trios		
Chromosome/ Candidate gene	**SNP**	**Maximum 2,421 cases and 4,828 controls OR 95% CI**	***P*-value**	**Minor allele**	**Allele Frequency cases**	**Allele Frequency controls**	**OR 95% CI**	***P***	**RR 95% CI**	***P***	$P_{combined}$
1q31/*RGS1*	rs2816316	0.72 (0.65-0.79)	2.58×10^{-11}	C	0.166	0.182	0.89 (0.84-0.95)	1.23×10^{-4}	0.91 (0.82-1.00)	0.0436	1.48×10^{-5}
2q12/*IL18RAP*	rs917997	1.29 (1.19-1.40)	8.49×10^{-10}	A	0.220	0.221	0.98 (0.93-1.03)	0.416 0.0122 (2-df)	0.87 (0.78-0.96)	8.35×10^{-3} 6.50×10^{-3} (2-df)	0.151 8.03×10^{-5} (2-df)
3p21/*CCR3**	rs6441961	1.21 (1.13-1.30)	3.41×10^{-7}	A	0.321	0.301	1.09 (1.04-1.14)	3.40×10^{-4}	1.04 (0.95-1.13)	0.386	1.95×10^{-3}
3q25/*IL12A*	rs17810546 rs9811792	1.35 (1.23-1.49) 1.21 (1.15-1.32)	1.07×10^{-9} 5.24×10^{-8}	G G	0.123 0.451	0.123 0.443	1.00 (0.93-1.07) 1.04 (0.99-1.08)	0.960 0.147	N/A N/A		N/A N/A
3q28/*LPP*	rs1464510	1.23 (1.15-1.31)	5.33×10^{-9}	T	0.451	0.456	1.00 (0.95-1.04)	0.820	N/A		N/A
4q27/*IL2-IL21**	rs6822844	0.71 (0.63-0.80)	2.82×10^{-13}	T	0.165	0.176	0.95 (0.89-1.00)	0.0559	N/A		N/A
6q25/*TAGAP*	rs1738074	1.21 (1.13-1.30)	6.71×10^{-8}	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}
12q24/*SH2B3**	rs3184504	1.21 (1.12-1.29)	1.33×10^{-7}	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}

OR = odds ratio, 95% CI = 95% confidence intervals, RR = relative risk, N/A = not attempted.

* These loci have previously been examined for their possible sharing between celiac disease and T1D, with strong support for 12q24/*SH2B3* sharing (same SNP, same allele direction),10 since this locus is an established T1D risk determinant.1 The 2-df test is reported when there was a significant difference between genotypic effects model and the multiplicative allelic effects model such that the multiplicative model is not the appropriate one (Methods).

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Table 2

Association Results in Type 1 Diabetes for *CCR5* and *CCR2* Variants

SNP	Allele/ genotype	Maximum 8,064 Cases and 9,339 Controls: frequency n (%) cases	Maximum 8,064 Cases and 9,339 Controls: frequency n (%) controls	Maximum 8,064 Cases and 9,339 Controls: OR (95% CI)	Maximum 8,064 Cases and 9,339 Controls: *P*-values 1-df 2-df	2,519 Parent-child Trios: frequency n (%) cases	2,519 Parent-child Trios: frequency n (%) parents	2,519 Parent-child Trios: RR (95% CI)	2,519 Parent-child Trios: *P*-values 1-df 2-df	Combined *P* 1-df 2-df
3p21/*CCR5*	del	814 (10.33)	1,155 (11.90)	0.85 (0.80-0.92)	5.72×10^{-6}	309 (10.06)	503 (10.67)	0.90 (0.75-1.09)	0.116	1.49×10^{-6}
rs333	ins/ins	6,320 (80.23)	7,554 (77.83)	1.00 (reference)		2,496 (80.65)	1,887 (80.13)	1.00 (reference)		
del32	ins/del	1,487 (18.88)	1,994 (20.54)	0.89 (0.82-0.96)		572 (18.48)	433 (18.39)	0.97 (0.86-1.10)		
	del/del	70 (0.89)	158 (1.63)	0.54 (0.40-0.72)	1.88×10^{-6}	27 (0.87)	35 (1.49)	0.53 (0.34-0.82)	9.10×10^{-3}	1.81×10^{-8}
3p21/*CCR2*	A	582 (7.50)	564 (7.68)	0.97 (0.89-1.06)	0.506	N/A				
rs1799864	G/G	6,641 (85.57)	6,262 (85.32)	1.00 (reference)						
Ile64Val	A/G	1,074 (13.86)	1,027 (13.99)	0.99 (0.90-1.08)	0.556					
	A/A	44 (0.57)	50 (0.68)	0.80 (0.53-1.21)						

OR = odds ratio, 95% CI = 95% confidence intervals, RR = relative risk, N/A = not attempted

A 2-df test is reported as there was a significant difference between genotypic effects model and the multiplicative allelic effects model.

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Table 3

Association Results of Type 1 Diabetes Loci Tested in Celiac Disease

Type 1 diabetes loci/candidate gene		Minor allele	Type 1 Diabetes Maximum 8,064 Cases and 9,339 Controls		MAF	MAF	MAF	Celiac Disease Maximum 2,560 Cases and 9,339 Controls	
			OR (95% CI)	*P*-value	UK controls	T1D cases	Celiac disease cases	OR (95% CI)	*P*-value
1p13/*PTPN22*	rs2476601	T	2.05 (1.90-2.20)	1.13×10^{-88}	0.095	0.178	0.106	1.09 (0.98-1.22)	0.130
2q24/*IFIH1*	rs1990760	G	0.86 (0.82-0.90)	2.13×10^{-10}	0.389	0.351	0.397	1.02 (0.95-1.09)	0.547
2q33/*CTLA4*	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}
3p21/*CCR5*	rs333	del	0.85 (0.80-0.92)	5.87×10^{-6} 1.93×10^{-6} (2df)	0.119	0.103	0.095	0.79 (0.71-0.88)	9.18×10^{-6}
4q27/*IL2*	rs2069763	T	1.13 (1.08-1.18)	1.28×10^{-7}	0.329	0.358	0.346	1.09 (1.01-1.16)	0.0180
5p13/*IL7R*	rs6897932	A	0.89 (0.84-0.94)	4.13×10^{-4}	0.274	0.255	0.254	0.91 (0.84-0.97)	7.23×10^{-3}
6q15/*BACH2*	rs11755527	G	1.13 (1.09-1.18)	8.57×10^{-9} 4.37×10^{-11} (2df)	0.465	0.495	0.491	1.10 (1.03-1.18)	2.78×10^{-3}
10p15/*PRKCQ*	rs947474	G	0.88 (0.83-0.93)	1.48×10^{-5}	0.187	0.171	0.173	0.90 (0.83-0.98)	0.0178
10p15/*IL2RA*	rs12722495 rs11594656	G A	0.62 (0.57-0.68) 0.87 (0.83-0.93)	1.74×10^{-30} 2.03×10^{-6}	0.113 0.246	0.072 0.222	0.120 0.234	1.06 (0.95-1.17) 0.94 (0.87-1.01)	0.316 0.091
11p15/*INS*	rs689	A	0.42 (0.41-0.46)	8.93×10^{-195} 1.86×10^{-202}(2df)	0.293	0.151	0.286	0.95 (0.89-1.03)	0.201
12q13/*ERBB3*	rs2292239	A	1.31 (1.22-1.34)	5.79×10^{-22}	0.352	0.407	0.359	1.02 (0.96-1.10)	0.498
12q24/*SH2B3*	rs3184504	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}
15q24/*CTSH*	rs3825932	C	0.86 (0.82-0.90)	4.62×10^{-10}	0.318	0.287	0.334	1.07 (1.00-1.14)	0.0559
16p13/*CLEC16A*	rs12708716	G	0.81 (0.77-0.86)	3.19×10^{-13}	0.351	0.306	0.365	1.06 (0.99-1.14)	0.120
18p11/*PTPN2*	rs478582 rs45450798	G G	0.83 (0.79-0.88) 1.28 (1.21-1.36)	8.83×10^{-12} 1.15×10^{-16}	0.449 0.166	0.408 0.202	0.432 0.191	0.93 (0.87-1.00) 1.18 (1.08-1.30)	0.0408 2.61×10^{-4}
18q22/*CD226*	rs763361	A	1.16 (1.10-1.22)	1.56×10^{-8}	0.471	0.503	0.491	1.09 (1.02-1.16)	0.0133
21q22/*UBASH3A*	rs3788013 *	A	1.13 (1.08-1.18)	3.09×10^{-8}	0.433	0.465	0.454	1.08 (1.01-1.15)	8.88×10^{-3}
22q13/*C1QTNF6*	rs229541	T	1.12 (1.07-1.17)	6.96×10^{-7}	0.428	0.455	0.424	0.97 (0.91-1.04)	0.423

The T1D results have all been published previously 1, 14, 15, except for *CCR5* rs333, *PTPN2* rs45450798 and *IL2RA* rs12722495 (Supplementary Tables 3 and 4).

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* rs3788013 is in $r^2 = 1$ with rs876498 from Concannon et al.14 in the British case-control samples. OR = odds ratio, 95% CI = 95% confidence intervals, MAF = minor allele frequency. The MAF was estimated in a maximum of 9,339 controls, maximum of 8,064 T1D cases, and maximum of 2,560 celiac cases. The 2-df test is reported when there was a significant difference between genotypic effects model and the multiplicative allelic effects model.