REPORT

Novel Association in Chromosome 4q27 Region with Rheumatoid Arthritis and Confirmation of Type 1 Diabetes Point to a General Risk Locus for Autoimmune Diseases

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Recently, association of celiac disease with common single-nucleotide polymorphism (SNP) variants in an extensive linkage-disequilibrium block of 480 kb containing the *KIAA1109, Tenr, IL2,* and *IL21* genes has been demonstrated in three independent populations (*rs6822844* $P_{combined} = 1.3 \times 10^{-14}$). The *KIAA1109/Tenr/IL2/IL21* block corresponds to the Idd3 locus in the nonobese diabetic mouse model of type 1 diabetes (T1D). This block was recently found to be associated with T1D in a genomewide association study, although this finding lacks unequivocal confirmation. We therefore aimed to investigate whether the *KIAA1109/Tenr/IL2/IL21* region is involved in susceptibility to multiple autoimmune diseases. We tested SNP *rs6822844* for association with disease in 350 T1D-affected and 1,047 rheumatoid arthritis (RA)–affected Dutch patients and in 929 controls. We replicated the association with T1D ($P = .0006$; OR 0.64 [95% CI 0.50–0.83]), and revealed a similar novel association with RA ($P = .0002$; OR 0.72 [95% CI 0.61–0.86]). Our results replicate and extend the association found in the *KIAA1109/Tenr/IL2/IL21* gene region with autoimmune diseases, implying that this locus is a general risk factor for multiple autoimmune diseases.

Type 1 diabetes (T1D [MIM 222100]), rheumatoid arthritis (RA [MIM 180300]), and celiac disease (CD [MIM 212750]) are common autoimmune diseases (AIDs), each affecting ~1% of the general population. The manifestation and progression of AIDs depend on a combination of multiple genetic and environmental factors, yet the co-occurrence of these three different AIDs in families, or even within single patients, has been reported frequently.[1–3] For instance, 6.2% of patients with T1D also have CD,[4] and 2.8% of first-degree relatives of RA-affected probands have T1D.[1] This overlap in etiology is most likely due to a shared genetic predisposition to autoimmunity. The well-known and major genetic risk factor for all three diseases are the human leukocyte antigen class II genes. Other risk factors in common that have been confirmed in various AIDs are the *PTPN22* (MIM 600716) (in T1D and RA) and *CTLA4* (MIM 123890) (in T1D and CD) genes, where the differences in overlap may point to differences in disease pathways.[5]

The region encompassing *KIAA1109/Tenr/IL2/IL21* is contained in a large block (480 kb) of linkage disequilibrium (LD) recently reported to be a strong genetic factor involved in CD.[6] This block is located on chromosome 4q27 and includes the *IL2* (MIM 147680) and *IL21* (MIM 605384) genes, which are both plausible functional candidate loci for AIDs. *IL2* is a susceptibility gene in the nonobese diabetic (NOD) mouse model of T1D,[7] and association of the *IL2* receptor (*IL2RA* and *CD25* [MIM 147730]) to T1D has been demonstrated in extended cohorts, highlighting the importance of the IL2 pathway in the predisposition to AIDs.[8,9] Both IL2 and IL21 belong to the type 1 cytokine family, share a large degree of homology, and possess pleotropic functions in immune cells.[10,11]

Hence, the association of the *KIAA1109/Tenr/IL2/IL21* gene region with T1D in mouse and with CD in human may reflect a general role for this locus in the etiology of autoimmunity. Given the comorbidity among CD, T1D, and RA, we sought to confirm this hypothesis by testing the most associated CD variant from the U.K. genomewide association (GWA) screen (*rs6822844*) in a Dutch T1D cohort and a Dutch RA cohort.

The patients with T1D were retrieved from the Kolibri T1D cohort, which includes 350 patients with juvenile-onset T1D (median age 8.7 years [range 1–17 years]). The cohort was collected consecutively after diagnosis by pediatricians in the southwestern part of the Netherlands between 1995 and 1999. The diagnosis was made accord-

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Table 1. Frequency of SNP *rs6822844* in Controls ($n = 929$), Patients with T1D ($n = 350$), and Patients with RA ($n = 1,047$)

		Patients with T1D			Patients with RA		
rs6822844	Control Counts (%)	Counts (%)	OR (95% CI)	*P*	Counts (%)	OR (95% CI)	*P*
Allele G	1,506 (81.5)	585 (87.3)	1 (ref)	...	1,739 (85.9)	1 (ref)	...
Allele T	342 (18.5)	85 (12.7)	.64 (.50–.83)	.0006	285 (14.1)	.72 (.61–.86)	.0002
GG	613 (66.3)	258 (77.0)	1 (ref)	...	748 (73.9)	1 (ref)	...
GT	280 (30.3)	69 (20.6)	.59 (.44–.80)	.0014	243 (24.0)	.71 (.58–.87)	.0009
TT	31 (3.4)	8 (2.4)	.67 (.31–1.44)	...	21 (2.1)	.56 (.32–.99)	...

NOTE.—ref = Reference. The number of dropouts was 5 in controls, 14 in patients with T1D, and 35 in patients with RA. Reported *P* values were obtained with 1-df test for allelic effect and 2-df test for genotyping effect.

ing to International Society of Pediatric and Adolescent Diabetes and World Health Organization criteria. The RA group comprised two independent cohorts from Groningen ($n = 408$) and Nijmegen ($n = 639$). The characteristics of patients with RA in the Nijmegen cohort have been described elsewhere.[12] All the patients were given diagnoses in accordance with American College of Rheumatology (ACR) criteria for RA,[13] had a disease duration of >1 year, and had no history of using disease-modifying antirheumatic drugs or biological agents before presentation. The patients with RA in the Groningen cohort were recruited from the outpatient clinic of the Department of Rheumatology, University Medical Center Groningen (UMCG). All patients were given diagnoses in accordance with ACR criteria[13] and had rheumatoid factor (RF)–positive and/or RF-erosive RA. Patients with T1D and RA were first compared with a panel of 929 unrelated Dutch controls who were genotyped and presented in the replication GWA study for CD.[6] All the patients and controls gave their informed consent, and the medical ethics committees of the University Medical Center Utrecht, the UMCG, and the Radboud University Nijmegen Medical Center approved the respective original studies.

Genotyping was performed using TaqMan technology. SNP genotyping assays for PCR were supplied by Applied Biosystems, as described elsewhere.[6] The DNA samples were processed in 384-well plates. Each plate contained 8 negative controls and 16 genotyping controls (4 duplicates of four different CEPH samples). In the control group, the frequencies of all the SNPs were in Hardy-Weinberg equilibrium. Hardy-Weinberg equilibrium was tested by comparing the expected and observed genotypes in a 2×3 χ^2 table. Odds ratios (ORs) were calculated, and the CIs were approximated using Woolf's method with Haldane's correction.[14]

The *rs6822844* G→T SNP was tested in 350 patients with early-onset T1D and in 1,047 patients with RA. We saw a decrease in frequency of the *rs6822844**T allele in both T1D (12.7%) and RA (14.1%) groups compared with controls (18.5%); this is similar to our earlier result for CD in the Dutch population (12.4%).[6] The association was significant in both T1D ($P = .0006$; OR 0.64 [95% CI 0.50–0.83]) and RA ($P = .0002$; OR 0.72 [95% CI 0.61–0.86]) (table 1).

While we were performing this study, the results of a GWA study of T1D became available.[15] One of the reported loci was on 4q27 and contained the *KIAA1109/Tenr/IL2/IL21* gene region. A follow-up replication study indicated moderate association of SNPs in the *KIAA1109/Tenr/IL2/IL21* gene region with T1D.[8] We compared the SNPs from the T1D GWA study with the haplotype-tagging (ht) SNPs that we used for replicating the CD GWA results and observed that the most T1D-associated SNP (*rs3136534* A→C) was in complete LD with one of the SNPs included in the CD screen (*rs4505848* A→G) ($r^2 = 1$; LOD 32.26 [HapMap data]), where the *rs3136534**A allele corresponds to *rs4505848**A and *rs3136534**C corresponds to *rs4505848**G. The haplotype structure and LD in the region were investigated using HapMap data[16] with the Haploview application.[17]

We also genotyped the *rs4505848* A→G SNP in our cohorts of patients with T1D and RA and found a slight increase of the *rs4505848**G allele in patients with T1D (36.2%) and RA (37.1%) compared with controls (34.9%). Although the observed difference in allele frequency was not significant in either T1D ($P = .53$; OR 1.06 [95% CI

Table 2. Frequency of SNP *rs4505848* in Controls ($n = 929$), Patients with T1D ($n = 350$), and Patients with RA ($n = 1,047$)

		Patients with T1D			Patients with RA		
rs4505848	Control Counts (%)	Counts (%)	OR (95% CI)	*P*	Counts (%)	OR (95% CI)	*P*
Allele A	1,180 (65.1)	417 (63.8)	1 (ref)	...	1,270 (62.9)	1 (ref)	...
Allele G	632 (34.9)	237 (36.2)	1.06 (.88–1.28)	.53	750 (37.1)	1.10 (.97–1.26)	.15
AA	380 (41.9)	144 (44.0)	1 (ref)	...	396 (39.2)	1 (ref)	...
AG	420 (46.4)	129 (39.4)	.81 (.62–1.07)	.03	478 (47.3)	1.09 (.90–1.32)	.34
GG	106 (11.7)	54 (16.5)	1.35 (.93–1.97)	...	136 (13.5)	1.23 (.92–1.64)	...

NOTE.—ref = Reference. The number of dropouts was 23 in controls, 23 in patients with T1D, and 37 in patients with RA. Reported *P* values were obtained with 1-df test for allelic effect and 2-df test for genotyping effect.

Table 3. Haplotype Analysis of SNPs *rs4505848, rs11732095, rs6822844, rs4492018,* and *rs1398553*

Haplotype	Control Counts (%)	Patients with RA			Patients with T1D			Patients with CD		
		Counts (%)	OR (95% CI)	*P*	Counts (%)	OR (95% CI)	*P*	Counts (%)	OR (95% CI)	*P*
GAGGA	536 (29.1)	636 (31.2)	1	Ref	192 (29.0)	1	Ref	312 (31.1)	1	Ref
AAGAG	409 (22.2)	433 (21.2)	.89 (.75–1.07)	.21	161 (24.3)	.91 (.71–1.16)	.45	216 (21.5)	.91 (.73–1.13)	.38
AATGG	343 (18.6)	283 (13.9)	.70 (.57–.85)	.00025	87 (13.2)	.71 (.53–.95)	.018	124 (12.4)	.62 (.49–.80)	.00016
AAGGG	213 (11.6)	293 (14.3)	1.16 (.94–1.43)	.17	81 (12.2)	1.07 (.79–1.44)	.70	150 (15.0)	1.21 (.94–1.56)	.14
AGGGG	154 (8.3)	176 (8.6)	1.04 (.81–1.33)	.76	49 (7.5)	.90 (.63–1.29)	.52	91 (9.0)	1.02 (.76–1.37)	.92
GAGGG	101 (5.4)	108 (5.3)	.90 (.67–1.21)	.49	41 (6.2)	1.15 (.77–1.70)	.54	61 (6.1)	1.04 (.74–1.47)	.84
AAGGA	67 (3.6)	71 (3.5)	.89 (.63–1.27)	.53	43 (6.5)	1.72 (1.13–2.62)	.01	34 (3.4)	.88 (.57–1.36)	.54

NOTE.—Combined frequency of haplotypes presented is >98%. Ref = reference.

0.88–1.28]) or RA ($P = .15$; OR 1.10 [95% CI 0.97–1.26]), it did show a trend similar to that reported for the U.K. T1D-affected population (OR 1.11)[8,15] (table 2).

We further investigated the haplotypes of the *KIAA1109/Tenr/IL2/IL21* gene region by typing three additional ht SNPs: *rs11732095, rs4492018,* and *rs1398553*. The combined five SNPs tag seven haplotypes of the block in which *rs6822844* is located. These haplotypes have a combined frequency of >98%. Interestingly, *rs6822844* is a perfect proxy for the AATGG haplotype, which is the most associated haplotype in all three diseases with haplotype frequencies of ~13% in cases versus 18.6% in controls (table 3).

Interestingly, a reported RA association with *PTPN22*-1858T, another general autoimmune risk factor, was preferentially observed in the subgroup of patients with RF-positive RA[18]; similarly, linkage to the *PTPN22* region is also limited to families with RF-positive RA.[19] We investigated whether the association in our RA group was dependent on the presence of RF. Information about RF was available for 776 individuals genotyped for *rs6822844,* of whom 664 had RF-positive RA. We did not observe a significant difference in association between the RF-positive and RF-negative groups, although the protective effect in the RF-positive group was moderately stronger than in the RF-negative group (OR 0.71 [95% CI 0.59–0.87] and OR 0.89 [95% CI 0.61–1.29], respectively) (table 4).

To estimate overall association of the studied SNPs with AIDs in the Dutch population, we then pooled all the Dutch patients with T1D, RA, and CD into one group (Dutch AIDs), which was compared with controls. This group was then included in a meta-analysis with recently published data from a U.K. and Irish CD genome-scan study presented elsewhere,[6] with use of a random-effect model. There was no significant heterogeneity among the studies. In total, 6,236 patient chromosomes and 5,812 control chromosomes were included in the meta-analysis. Overall, a meta-analysis of our findings showed a consistently lower frequency of the *rs6822844**T allele (random model test for an overall effect, $P < .00001$). It yielded a 1.5-fold decrease (95% CI 1.36–1.69) in risk of AIDs in carriers (OR 0.67 [95% CI 0.59–0.74]) (fig. 1).

In this study, we have identified the 4q27 *KIAA1109/Tenr/IL2/IL21* gene region as a general autoimmune locus, since we have shown genetic association with three AIDs—namely, CD, T1D, and RA. These results were corroborated by the recent report of a GWA study of T1D.[15] The *KIAA1109/Tenr/IL2/IL21* block is characterized by extremely strong LD that shows a very similar pattern in the different populations studied (HapMap CEU, Dutch, U.K., and Irish).[6] Four SNPs, all in strong LD with each other, tag the same haplotype and show strong association with CD in multiple populations. Other common SNPs located in the *KIAA1109/Tenr/IL2/IL21* gene region have shown strong association with T1D in a recent GWA study.[15] However, a large replication study of T1D in a U.K. population reported only moderate association with *rs3136534,* the most associated SNP in the study.[8] *rs4505848* is a perfect proxy for *rs3136534* ($r^2 = 1$), and it was included in both the CD GWA study and the replication analysis. In the three CD-affected populations tested, this proxy SNP was related to only a moderate increase in the frequency of the G allele compared with controls (*P* value is nonsignificant in Dutch, U.K., and Irish cohorts).[6] When we investigated the T1D proxy SNP *rs4505848* in our AIDs cohort, we did not detect significant associations with either

Table 4. Frequency of SNP *rs6822844* in Patients with RF-Positive ($n = 664$) and RF-Negative ($n = 112$) RA Compared with Controls

rs6822844	Control Counts (%)	RF Positive			RF Negative		
		Counts (%)	OR (95% CI)	*P*	Counts (%)	OR (95% CI)	*P*
Allele G	1,506 (81.5)	1,143 (86.1)	1 (ref)	…	187 (83.5)	1 (ref)	…
Allele T	342 (18.5)	185 (13.9)	.71 (.59–.87)	.0006	37 (16.5)	.89 (.61–1.29)	.47
GG	613 (66.3)	491 (73.9)	1 (ref)	…	79 (70.5)	1 (ref)	…
GT	280 (30.3)	161 (24.2)	.72 (.57–.90)	.0028	29 (25.9)	.82 (.52–1.28)	.63
TT	31 (3.4)	12 (1.8)	.51 (.26–.99)	…	4 (3.6)	1.20 (.43–3.31)	…

NOTE.—ref = Reference.

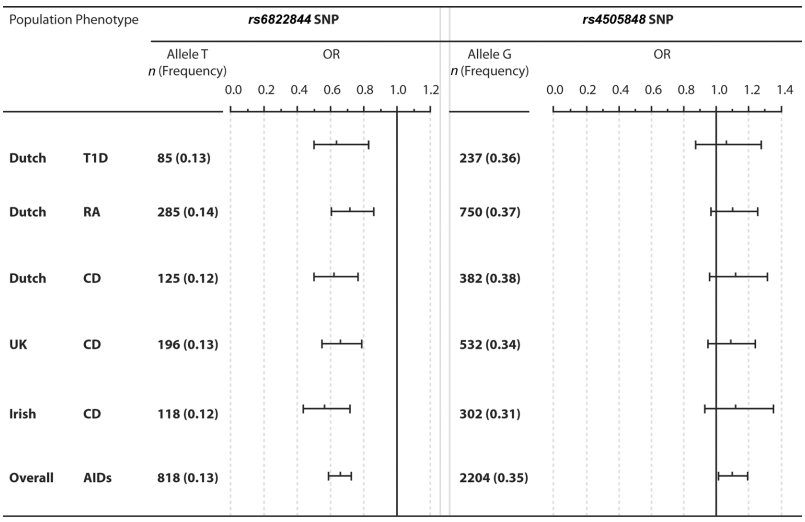

Figure 1. The frequency of *rs6822844* and *rs4505848* alleles in Dutch AIDs cohorts and controls and in a meta-analysis of Dutch, U.K., and Irish AIDs cohorts. Dutch AIDs cohorts include T1D (n = 670), CD (n = 1,012), and RA (n = 2,024). Data for the U.K. and Irish cohorts were extracted from the work of van Heel et al.[6] n = Number of chromosomes. ORs and the corresponding 95% CIs were estimated using a random-effect model. Vertical lines represent no effect (i.e., disease risk = 1).

T1D or RA, although there was a similar increase in frequency of the G allele in both groups (fig. 1). Our haplotype analysis showed that a single haplotype shows consistent association with the majority of the decreased risk for AID. The *rs6822844**T allele differentiates this haplotype perfectly from the others, indicating that, in our data set, this allele is the best proxy for the unknown disease variant. Further investigation of this region, including comprehensive detection and testing of all variants, is required to pinpoint the underlying disease variant.

The 4q27-associated block contains four genes: *KIAA1109, Tenr, IL2,* and *IL2*. The extensive LD within this block means that none of these genes could be excluded by genetic methods from being the causal one. The two genes *IL2* and *IL21* are both plausible functional candidates as genetic modifiers of autoimmunity. The importance of the *IL2* pathway in T1D is underpinned by recent findings that have shown that regulatory variants in the *IL2* gene modify the predisposition to organ-specific AID in NOD mice.[7] The *IL2* receptor (*CD25*) is also a proven T1D-susceptibility locus that has recently been reported to be associated with RA.[15] These considerations highlight the importance of the IL2 pathway in autoimmunity.

IL21 is involved in both cell-mediated and humoral responses and has a pleiotropic effect on a variety of immune and nonimmune cells.[10] A crucial role of IL21 in autoimmune pancreatic B-cell destruction was demonstrated in NOD mice,[20] and a contribution from IL21 to the progression of lupus in mouse models has also been reported.[21,22] IL21 has a crucial role in regulation of antibody production. The role of IL21 in eliminating autoreactive B cells through apoptosis suggests that dysregulation of IL21-IL21 receptor signaling might contribute to the development of antibody-mediated AIDs.[10]

In conclusion, we have now shown association of T1D and RA with the *KIAA1109/Tenr/IL2/IL21* region. Summarizing our findings with previous data about the association of 4q27 with CD and T1D leads us to conclude that the *KIAA1109/Tenr/IL2/IL21* region is a general autoimmune risk locus.

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Web Resources

The URLs for data presented herein are as follows:

HapMap, http://www.hapmap.org/ (for information about SNPs and LD in population controls)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for T1D, RA, CD, *PTPN22, CTLA4, IL2, IL21,* and *CD25*)

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