Supplementary Information B

Intermarker linkage disequilibrium

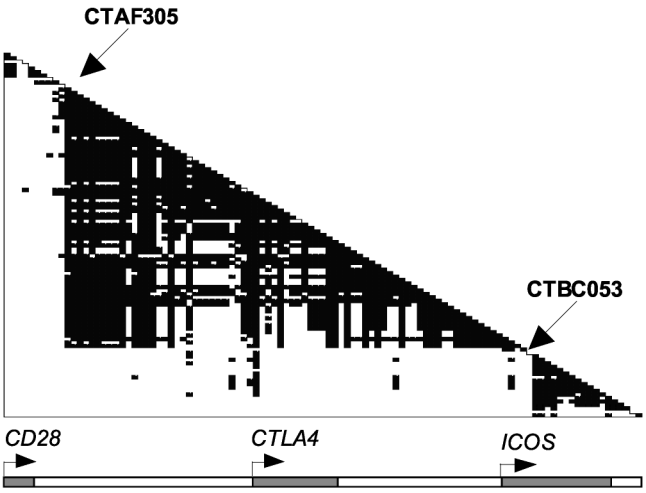


Figure B1 Three blocks of LD in the *CD28-CTLA4-ICOS* region. Pair-wise LD values of D' > 0.8 are shaded. The physical distance between the genes is not to scale. Breaks in LD, or hot spots of recombination, are denoted by arrows, and the marker loci indicated at these breakpoints (CTAF305 and CTBC053).

D' values were calculated for 108 SNPs in all two-SNP combinations using the 652 controls. In contrast to the very strong LD (average D' = 0.84, indicating low levels of historical recombination) between markers in the *CTLA4* block LD was much lower across the hot spots (average D' = 0.29). Alleles of SNPs are more likely to be in LD with alleles of other SNPs if they are close to each other on the chromosome, in the order of 100 kb or less, and the base changes occurred at a similar time in history. Association of alleles on particular chromosomes or haplotypes is eroded by homologous recombination at meiosis between chromosomes carrying different alleles. The pattern of recombination is not uniform along chromosomes and tends to be concentrated in hot spots such that two SNPs flanking a hot spot, one a causal variant, could be next to each other but show very little LD. These recombination hot

spots can create breaks in the pattern of LD. It is, therefore, informative in a systematic approach to association mapping of a causal variant, to analyse the pattern of intermarker LD across the region under analysis.

Detailed description of logistic regression analyses.

1. Graves' disease

The 108 SNPs genotyped in 384 GD cases and 652 controls were analysed using logistic regression [1] (Table B7). CT60 was the most associated marker $P = 1.6 \times 10^{-6}$ (Table B1). The plot of marker disease association, taken as the *P* value of the odds ratio, against sequence position (Fig. B2) showed there were three main peaks of association. Markers were first tested using a model that assumed no particular mode of inheritance then, using a multiplicative model. The adequacy of the model was assessed with a likelihood ratio test. For all loci except the $(AT)_n$-3'UTR the multiplicative model could be used.

The next step was to try to distinguish between the three disease association peaks in terms of which one might harbour the causal variant. Therefore, we chose the most disease-associated SNP from each peak to see if it could explain the association at the other two peaks. This was done with logistic regression in the following way[2]. Consider two loci A and B. To distinguish the effects of A and B we address the question: does locus B add to a model with locus A, or are the effects of locus B explained by locus A? The null hypothesis is, locus A is sufficient to model the data. No specific mode of inheritance is assumed for locus A, so genotype risks of a/A and A/A are modelled relative to the a/a genotype. A one degree-of-freedom trend test is used for locus B, which assumes a multiplicative model for the effects of the individual alleles at locus B.

Table B1: Association of key *CTLA4* SNPs in 384 Graves' disease cases and 672 controls. Odds ratios are calculated from the coefficients of the regression equation[1], and *P*-values are for the null hypothesis of no association of the marker. The typing of the CT60 SNP in 210 GD families helped confirm the validity of the disease association: the G allele was transmitted at 59.4% to affected offspring ($P = 0.023$) and 45.7% to unaffected offspring ($P = 0.35$).

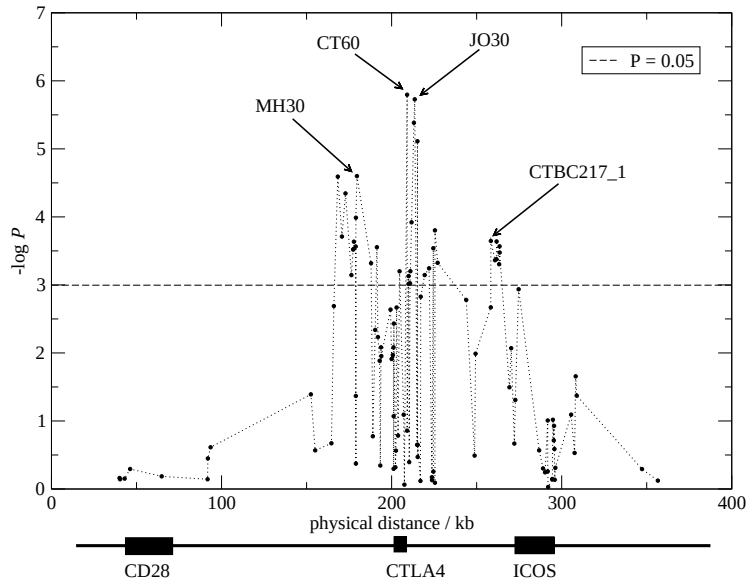
Marker	% Case chromosomes	% Control chromosomes	Odds ratio	95% CI	P value
AF343	81.5	73.5	1.61	1.28-2.02	0.00003
rs1863800	64.1	54.8	1.47	1.22-1.78	0.00005
MH30	64.6	55.0	1.49	1.23-1.80	0.00002
+49G>A	42.4	35.8	1.34	1.11-1.62	0.0021
CT60	63.4	52.3	1.56	1.30-1.88	1.6×10^{-6}
JO31	61.0	50.2	1.54	1.28-1.85	4.1×10^{-6}
JO30	61.5	50.5	1.56	1.29-1.87	1.9×10^{-6}
JO27_1	59.5	49.2	1.53	1.27-1.84	7.7×10^{-6}
CTBC217_1	53.4	44.9	1.40	1.17-1.68	0.00023

MH30 was put in the regression model as the best marker for the 5' *CTLA4* peak, and all other markers added to see if a second locus could improve the model. Thirteen SNPs of the 107 tested improved the model (CTAF343, CTAF450_1, CT41, CT57, CT60, JO31, JO30, JO27_1, JO23, JO6_2, JO6_1, JC068sFa, JC068sRb with $P =$ 0.049, 0.024, 0.034, 0.025, 0.012, 0.036, 0.040, 0.022, 0.047, 0.016, 0.042, 0.024, 0.042 respectively). A model using CT60, the best marker from the second peak, was

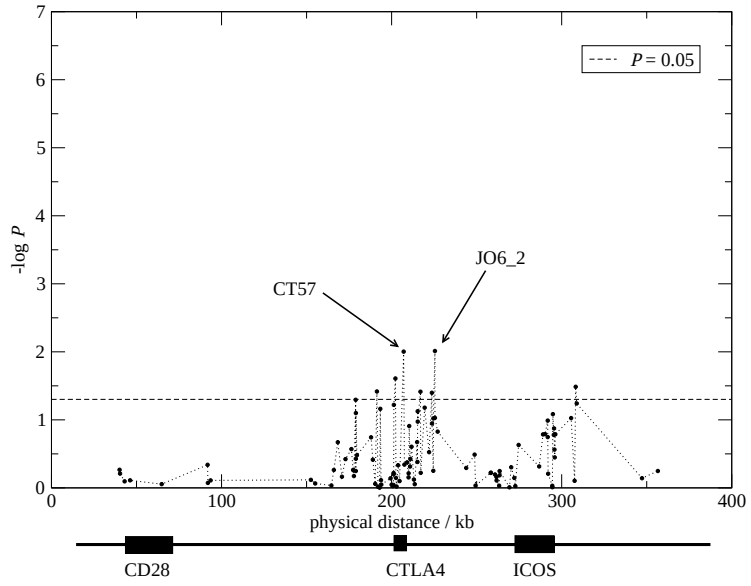
improved by adding any one of eight markers (MH18, CT41, CT57, $(AT)_n$-3'UTR, JO23, JO10, JO6_2, JC068sFa with P = 0.038, 0.006, 0.010, 0.004, 0.039, 0.040, 0.010 and 0.033 respectively, see Fig. B3). Ten markers improved a model with CTBC217_1, the best marker from the third peak (CTAF343, rs1863800, MH30, CT57, CT60, JO31, JO30, JO27_1, JO6_1, JC068sFa with P = 0.008, 0.021, 0.036, 0.018, 0.001, 0.002, 0.004, 0.006, 0.035 and 0.022 respectively). All improvements to the models were at modest levels of significance given that 107 markers were tested, although the P-values were smaller for the CTBC217_1 peak analysis suggesting that it was unlikely to contain the disease variant.

Next, we tested a regression model taking each one of 107 loci in turn and adding the test locus to it. There were thirteen markers that MH30 did not improve (CTAF343, rs1863800, CTAF439_2, MH26, CT60, JO31, JO30, JO27_1, JO8_2, CTBC190, CTBC182_1, CTBC165_3, CTBC165_2). Marker CT60 added significantly to all markers except JO30, JO31 and JO27_1 (Fig. B4). In contrast, CTBC217_1 did not improve a model with any one of 31 markers in it (CTAF322, CTAF343, CTAF371_1, rs1863800, CTAF422, CTAF434_2, CTAF439_1, CTAF439_2, CTAF450_1, CTAF450_4, MH30, MH26, MH18, CT60, JO37_2, JO35, JO34, JO31, JO30, JO27_1, JO18, JO13, JO8_2, JO6_1, JO3, CTBC190, CTBC182_2, CTBC182_1, CTBC165_3, CTBC165_2, CTBC165_1). Therefore, taking the first stage regression results together with these results, the CTBC217_1 peak is unlikely to harbour the causal variant, and the association is probably due to LD with the causal variant residing in either of the other two peaks of association.

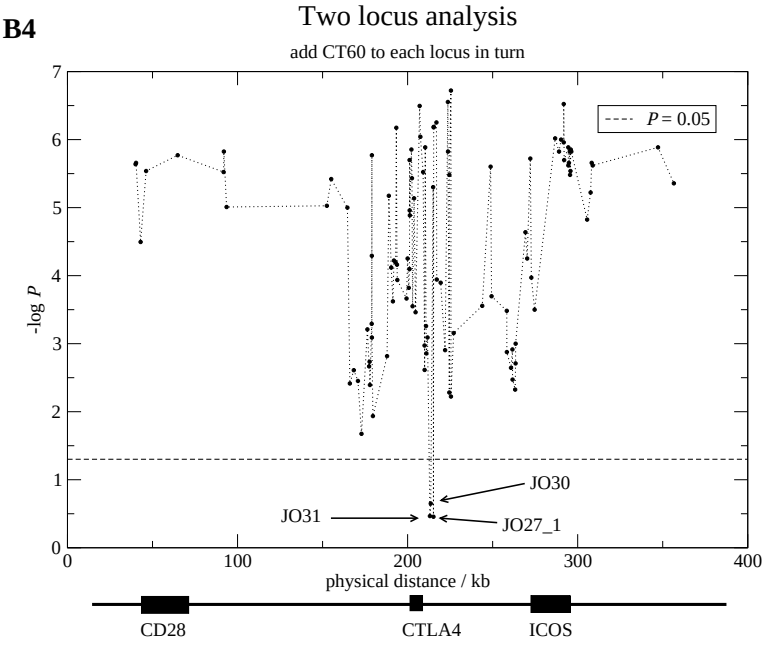
B2


Single locus analysis
P = 0.05
CT60
JO30
MH30
CTBC217_1
-log P
physical distance / kb
CD28
CTLA4
ICOS

B3


Two locus analysis
add each locus in turn to CT60
P = 0.05
JO6_2
CT57
-log P
physical distance / kb
CD28
CTLA4
ICOS

B4


Two locus analysis
add CT60 to each locus in turn
P = 0.05
JO30
JO31
JO27_1
-log P
physical distance / kb
CD28
CTLA4
ICOS

Analysis of the MH30:CT60:CTBC217_1 haplotype also showed that CTBC217_1, and its neighbouring markers in the third peak, are not having an additional effect. Three loci haplotypes were generated for cases and controls, imputing phase from the *a posteriori* distribution using a stochastic version of the EM algorithm. Estimates of odds ratios with confidence intervals were calculated by the multiple imputation method[3]. The three most common MH30:CT60:CTBC217_1 haplotypes were G:G:T, 53% in cases and 44% controls, C:A:C, 35% in cases and 44% in controls and G:G:C, 10% in cases and 8% in controls. Using C:A:C as reference, the G:G:T haplotype has OR = 1.53 with 95% CI [1.26-1.87]. Similarly the G:G:C haplotype has OR = 1.48 with 95% CI [1.06-2.07]. The G:G:C and G:G:T haplotypes have very similar odds ratios and 95% CIs despite the change of allele at CTBC217_1, thus implying neither CTBC217_1 nor any of the markers from peak 3 in strong LD with it, are a primary disease determinant.

Statistical results for the region's previously known markers, –319C>T/CT44, +49G>A/CT42, +1,822T>C/CT55 and $(AT)_n$-3' UTR are given in Table B2. Despite +49G>A/CT42 and +1,822T>C/CT55 having significant *P*-values in a single locus analysis, the two loci analyses with MH30, CT60 or BC217_1 excluded all three SNPs. None of the markers added to a model with MH30 in, whereas MH30 improved a model with any one of these three SNPs in. Similar results were seen with the best markers from the other two peaks, CT60 and BC217_1. Coding the $(AT)_n$-3' UTR as a biallelic marker with the most common allele, allele 1, versus the remaining alleles, the $(AT)_n$-3' UTR was analysed as a single locus and within a two locus model. A model assuming no particular mode of inheritance was required. The $(AT)_n$-3' UTR did not improve a model with MH30 in whereas MH30 did improve a model

with $(AT)_n$-3' UTR in, $P = 0.0078$. However the $(AT)_n$-3'UTR was one of the loci that improved a model with CT60 included, $P = 0.004$. However the $(AT)_n$-3'UTR had a very modest single locus association, P=0.01, and, CT60 improved a model with the $(AT)_n$-3'UTR included (P=0.0001). Hence, the microsatellite is unlikely to be disease causing in a major way.

After our study was completed we located a report[4] on the association of CTLA4 with IgE production, which reported that a SNP 5' of *CTLA4* was associated with bronchial hyperreponsiveness and asthma, -1,147C>T. In the same study +49G>A was associated with total serum IgE levels. We believe that these authors' –1,147C>T SNP corresponds to a SNP we assigned as CT54. In our current study we do not report the genotyping results for CT54 (–1,478G>A) because the results for the locus in the GD case control study showed some evidence of irregular LD patterns and also the SNP is the centre of a the common LINE repeat. This marker was therefore removed from the study. Nevertheless, with the data we have (not shown) CT54 was not associated with GD (P = 0.51, odds ratio = 1.09). Also, CT54 was in strong LD with CT61 ($r^2 = 0.9$) and CT61 is not associated with GD either (Table B7).

Table B2: Exclusion of the four previously known markers in Graves' disease. The $(AT)_n$-3' UTR has been coded as a biallelic marker, the most common allele, allele 1 versus the remaining 25. The most common allele of $(AT)_n$-3'UTR was the lowest size allele. Odds ratios are from the coefficients of the regression equation[1] and *P*-values are for the null hypothesis of no association. Two-locus *P*-values are for the null hypothesis of the second locus not having an additional effect to the first.

Marker	% Case Chromosomes %Control Chromosomes	Odds ratio [95%CI]	Single locus *P*	*P*, add marker to CT60	*P*, add CT60 to marker
–319C>T / CT44	10.7 9.2	1.18 [0.87-1.59]	0.2729	0.7152	$3.7x10^{-6}$
+49G>A / CT42	42.4 35.8	1.34 [1.11-1.62]	0.0021	0.9539	0.0003
+1822T>C /CT55	42.3 34.9	1.38 [1.15-1.68]	0.0006	0.7951	0.0003
	Genotype				
$(AT)_n$-3' UTR	1/1 1/other other/other	1 [ref.] 0.72 [0.50-1.04] 1.11 [0.75-1.64]	0.2475 (1df) 0.0115 (2df)	0.0040 (1df) 0.0114 (2df)	0.0001 (1df) 0.0005 (2df)

The eight SNPs typed in the larger GD dataset, 672 cases and 844 controls, were analysed with logistic regression (Table B3). Two loci from the 5' *CTLA4* peak, MH30 and rs1863800 had $P \sim 10^{-6}$, whereas four loci, CT60, JO31, JO30, JO27_1 from the second peak all had $P \sim 10^{-7}$ (Table B1). The two-locus approach described above, was used to try to distinguish these two peaks. Choosing MH30 as the best locus from the 5' peak, four markers improved the model, CT60, JO31, JO30, JO27_1 with $P = 0.006$, 0.003, 0.008 and 0.006 respectively. CT60 was chosen as the best locus from the second peak and no additional loci were required to model the data. Equally, each of JO30, JO31 or JO27_1 was sufficient to model the data without additional loci and explain the association of the region in this sample. Finally, we added the test locus to each of the remaining seven loci. MH30 did not improve a model with any one of rs1863800, CT60, JO31, JO30 or JO27_1 included.

Conversely, CT60 did not improve a model with JO31, JO30 or JO27_1 included. We can conclude that +49G>A, rs1863800, MH30 and CTAF343 are less likely to be the casual variants in GD than the markers under the CT60 peak. Note however our data is limited by sample size. Rejection of MH30 is due to the lower and higher risks associated with two *rare* haplotypes, G:A:A and G:A:C (Table B4).

Table B3: Association of *CTLA4* SNPs in Graves' disease (672 cases and 844 controls). Odds ratios were calculated from the coefficients of the regression equation[1], and *P*-values are for the null hypothesis of no association of the marker.

Marker/ allele	Case chromosomes (%)	Control chromosomes (%)	Odds ratio	95% confidence interval	*P* value
CTAF343/C	80.5	74.3	1.44	1.20 - 1.72	0.00007
rs1863800/C	64.9	56.0	1.45	1.24 - 1.68	1.19×10^{-6}
MH30/G	64.9	56.0	1.45	1.25 - 1.68	1.02×10^{-6}
+49/G	44.0	37.1	1.34	1.16 - 1.56	0.0001
CT60/G	63.4	53.2	1.51	1.31 - 1.75	2.72×10^{-8}
JO31/G	61.0	50.9	1.49	1.29 - 1.73	8.35×10^{-8}
JO30/G	61.2	51.2	1.49	1.29 - 1.73	7.26×10^{-8}
JO27_1/T	58.7	49.6	1.46	1.25 - 1.69	9.47×10^{-7}

Previously, authors speculated that +49G>A or the $(AT)_n$-3' UTR might be the GD etiological variant, but our regression analyses indicated that they are not. This is illustrated by analysis of haplotypes across the LD block. The distribution of the MH30:+49G>A:CT60 haplotype in cases and controls, shows there are only three common haplotypes, C:A:A, G:G:G and G:A:G (Table B4). The C:G:G and C:A:G haplotypes differ at +49G>A, yet they have the same positive risk compared to the protective T:A:A haplotype thus indicating +49G>A is not having an additional

effect. MH30 and CT60 were then assessed for haplotype specific effects using logistic regression. A model that included both CT60 and MH30 genotypes was compared to a model in which CT60 and MH30 had phased genotypes, to see if phase information improved the model. No haplotype specific effects were found.

Table B4: Odds ratios of MH30:+49G>A:CT60 3-marker haplotypes in Graves' disease (672 cases and 844 controls).

3-marker haplotype	Frequency		Odds ratio	95% confidence intervals
	Cases	Controls		
C:A:A	0.346	0.435	1 (reference)	
G:G:G	0.436	0.367	1.53	1.29-1.80
G:A:G	0.191	0.161	1.51	1.22-1.86
G:A:A	0.019	0.031	0.78	0.47-1.29
C:A:G	0.004	0.002	3.70	0.46-29.72

Finally the mode of inheritance of CT60 was evaluated with a logistic regression approach. For a full dominance effect to be observed, the risk of the A/G genotype would be approximately equal to the G/G genotype risk. (These risks would have a value greater than one when A/A is taken as reference.) The dominance hypothesis was formally tested with a χ^2 test. In both the initial GD dataset of 652 controls (P=0.0024) and, the extended GD dataset of 844 controls (P = 0.0013) the mode of inheritance of CT60 did not fit a full dominant or recessive model, and was not inconsistent with a multiplicative model.

2. Type 1 diabetes

The ten SNPs typed in 3,671 T1D families were analysed using the same general strategy as for the GD data sets. However, since these studies are family-based, we generated "pseudo-controls" by conditioning upon parental genotype and considering the possible genotypes that could have been passed to offspring. This facilitated the use of conditional logistic regression but robust variance estimates were necessary to allow for non-independence of sibs. These methods are described in detail elsewhere[2]. Single locus results are given in Table 1 of the main text, *P* values and percentage transmissions under the TDT are also given for comparison. Again there were two peaks of association. MH30 was the best marker from the 5' *CTLA4* peak and JO30 the best marker from the second peak both with $P \sim 10^{-6}$. The *ICOS* SNP, CTIC154_1, was not associated. Neither was another SNP, JC068sFa, 11.8 kb 3' of *ICOS* in 1,999 T1D families ($P = 0.97$).

Again two-locus regression analysis clearly rejected +49G>A as the causal SNP and suggested that CTAF343 and JO31 were also unlikely to be involved. A model with +49G>A was improved by MH30 and CT60, $P = 0.0002$ and 0.0002 respectively, but +49G>A did not improve models with either MH30 or CT60 included. Choosing MH30 as the best SNP from the 5' *CTLA4* peak, each of the other loci were added to see if they improved the model. No loci improved the model. Similarly no loci improve a model with CT60 included. Conversely, adding MH30 to each locus in turn, improves models with CTAF343, +49G>A and JO31 included, P=0.0101, 0.0018 and 0.0112, respectively. CT60 also improves models with CTAF343, +49G>A and JO31 included, P=0.0052, 0.0016 and 0.0126, respectively.

The JO31 result was unexpected because JO31 was not excluded in the GD study. A case pseudo-control analysis of the T1D family data, by individual population provided an explanation. A rare CT60:JO31 haplotype, G:T, at about 2% frequency in the UK population showed no association with disease in UK T1D families, or in the UK GD case-control dataset. However, in all the non-UK populations, from Finland, Norway, Romania and the USA, there was an increased frequency of this haplotype in cases compared to pseudo-controls (Table B5). Since the T allele of JO31 is associated with low disease risk, the positive disease association of the CT60*G:JO31*T haplotype in the non-UK sets would have led to its exclusion in the regression analysis. Nevertheless, this result requires replication. Very large samples are needed because evidence for or against a marker being the causal variant comes from rare haplotypes. An additional informative approach may be to search for populations with different frequencies of these haplotypes.

Table B5: Frequencies of the CT60*G:JO31*T haplotype, in T1D families from five different populations.

Population	Frequency in cases % (count)	Frequency in pseudo-controls % (count)
UK	2.1 (38)	2.2 (104)
Norway	2.1 (12)	1.6 (25)
Romania	6.6 (26)	4.8 (51)
USA	2.6 (25)	1.9 (48)
FIN	1.6 (34)	1.1 (69)

Table B6: Association of *CTLA4* SNPs by population in T1D families. The relative risks (RR) are calculated from the coefficients of the regression equation[1], and the *P*-values are for the null hypothesis of no association of the SNP.

SNP	**UK** RR [95% CI] *P*-value	**Finland** RR [95% CI] *P*-value	**USA** RR [95% CI] *P*-value	**Romania** RR [95% CI] *P*-value	**Norway** RR [95% CI] *P*-value
CTAF343	1.09 [0.96-1.23] 0.1955	1.21 [1.02-1.42] 0.0255	1.27 [1.06-1.52] 0.0096	1.20 [0.87-1.64] 0.2659	1.32 [1.01-1.74] 0.0433
rs1863800	1.07 [0.96-1.19] 0.2336	1.18 [1.04-1.34] 0.0130	1.27 [1.07-1.51] 0.0064	1.23 [0.99-1.53] 0.0609	1.36 [1.06-1.73] 0.0142
MH30	1.08 [0.97-1.20] 0.1779	1.17 [1.05-1.30] 0.0049	1.25 [1.04-1.50] 0.0166	1.34 [1.05-1.72] 0.0195	1.23 [0.99-1.53] 0.0317(2df)
+49G>A	1.05 [0.95-1.17] 0.3216	1.09 [0.97-1.22] 0.1383	1.11 [0.92-1.35] 0.2548	1.19 [0.91-1.55] 0.1983	1.10 [0.88-1.38] 0.3818
CT60	1.09 [0.98-1.21] 0.1254	1.14 [1.02-1.27] 0.0186	1.22 [1.03-1.45] 0.0218	1.17 [0.94-1.45] 0.1576	1.21 [0.98-1.50] 0.0809
JO31	1.07 [0.95-1.21] 0.2512	1.16 [1.03-1.30] 0.0174	1.13 [0.95-1.35] 0.1777	1.14 [0.90-1.44] 0.2641	1.17 [0.94-1.44] 0.1585

JO30	1.10 [0.98-1.23] 0.0776	1.28 [1.10-1.49] 0.0014	1.25 [1.04-1.50] 0.0151	1.19 [0.88-1.60] 0.2606	1.21 [0.96-1.51] 0.0996
JO27_1	1.07 [0.95-1.19] 0.2657	1.24 [1.08-1.43] 0.0028	1.32 [1.10-1.58] 0.0025	1.03 [0.79-1.34] 0.8480	1.25 [1.01-1.54] 0.0378
CTIC154_1	1.09 [0.87-1.36] 0.0720(2df)	1.08 [0.89-1.32] 0.4210	1.09 [0.82-1.45] 0.5365	1.10 [0.68-1.76] 0.7010	1.27 [0.81-2.00] 0.2971

By considering the appropriate "interaction" terms in the regression, we found that genotype associations were consistent over populations. Table B6 gives the genotype associations by population. Like in the combined dataset neither +49G>A or CTIC154_1 are associated in any individual population. MH30 is associated in all populations except the UK, while CT60 is associated in just the Finnish and USA populations. However all 95% confidence intervals of the relative risks overlap for each locus across populations including the combined dataset.

Finally, the MH30:CT60 haplotype was analysed for haplotype-specific effects in addition to the MH30 and CT60 genotypes. There was evidence for haplotype-specific effects (P= 0.003) but this was based on two rare haplotypes. The two largest populations in the study, the UK and the Finnish datasets, were analysed separately for haplotype specific effects. Phase was only important in the UK dataset (P=0.001) and not the Finnish, P=0.5499. The fact that this haplotype-specific effect was only seen in the UK dataset and arises from two rare haplotypes requires verification in

even larger data sets. Rare haplotypes may possibly exist with different functional CTLA-4 gene variants.

A single causative common disease SNP is the most likely explanation for the association of the region with GD. However, the T1D CTLA-4 gene effect was significantly weaker (OR ~ 1.2) than in GD (OR ~ 1.5). Thus, to detect the effect at least four times more subjects would be required in T1D than in GD. This is one possible reason why the 5' and 3' peaks of association flanking *CTLA4* could not be distinguished in T1D. Alternatively, there could be more than one SNP involved in T1D, or the T1D causal SNP is in the 5' *CTLA4* peak and not in the 3' *CTLA4* CT60 peak. However, the results of the expression analyses presented, do not support a major functional role for the 5' SNPs in modulating CTLA-4 gene transcription.

For reference we provide allele frequencies, odds ratios with 95% confidence intervals, and *P* values for all 108 SNPs typed in the Graves' case-control study (Table B7).

Table B7: Association of 108 SNPs and the $(AT)_n$-3'UTR in 384 Graves' disease cases and 652 controls. Their positions in our database are also given. Odds ratios are calculated from the coefficients of the regression equation[1], and *P*-values are for the null hypothesis of no association of the marker.

1 CD28p5_1Rb *P*=0.69

Position: 40021

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	593	78.0	972	77.3	1.05	0.84	1.30
T	167	22.0	286	22.7			

2 rs1879877 *P*=0.72

Position: 40304

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	168	22.2	280	22.8	1.04	0.83	1.30
G	590	77.8	946	77.2			

3 rs1181390 *P*=0.70

Position: 42985

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	160	22.0	260	21.3	1.04	0.84	1.29
G	566	78.0	962	78.7			

4 rs1181388 *P*=0.51

Position: 46260

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	654	86.7	1127	87.8	1.09	0.84	1.42
A	100	13.3	157	12.2			

5 CD28ex3F *P*=0.65

Position: 64820

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	152	20.0	247	19.2	1.05	0.84	1.32
T	608	80.0	1041	80.8			

6 rs1863800 *P*=0.72

Position: 91798

Alleles	Case	%	Control	%	Odds ratio	95%CI	
A	216	28.9	357	28.1	1.04	0.85	1.26
G	532	71.1	913	71.9			

7 rs1181425V *P*=0.36

Position: 91941

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	219	28.8	346	26.9	1.10	0.90	1.34
A	541	71.2	940	73.1			

8 rs1181426V *P*=0.24

Position: 93552

Alleles	Case	%	Control	%	Odds ratio	95%CI	
A	187	28.9	330	26.4	1.14	0.92	1.41
C	459	71.1	918	73.6			

9 CTAF185 *P*=0.041

Position: 152511

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	224	29.4	327	25.2	1.23	1.01	1.50
T	538	70.6	971	74.8			

10 CTAF212 *P*=0.27

Position: 155073

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	147	19.5	227	17.6	1.14	0.91	1.43
T	605	80.5	1065	82.4			

11 CTAF305 *P*=0.21

Position: 164591

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	628	86.5	1119	88.4	1.19	0.90	1.58
C	98	13.5	147	11.6			

12 CTAF322 *P*=0.0020

Position: 166028

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	305	43.1	634	50.4	1.33	1.11	1.60
T	403	56.9	624	49.6			

13 CTAF343 *P*=2.5e-05

Position: 168351

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	139	18.5	338	26.5	1.61	1.28	2.01
T	613	81.5	936	73.5			

14 CTAF371_1 *P*=0.00019

Position: 170812

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	312	40.8	641	49.3	1.41	1.17	1.69
T	452	59.2	659	50.7			

15 rs1863800 *P*=4.5e-05

Position: 172898

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	469	64.1	709	54.8	1.47	1.22	1.78
T	263	35.9	585	45.2			

16 CTAF422 *P*=0.00072

Position: 176345

Alleles	Case	%	Control	%	Odds ratio	95%CI	
A	296	40.4	615	48.4	1.36	1.14	1.63
G	436	59.6	655	51.6			

17 CTAF434_2 *P*=0.00030

Position: 177356

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	451	59.0	654	50.8	1.39	1.16	1.67
A	313	41.0	634	49.2			

18 CTAF439_1 *P*=0.00030

Position: 177655

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	311	40.9	629	49.1	1.40	1.16	1.68
T	449	59.1	651	50.9			

19 CTAF439_2 *P*=0.00023

Position: 177823

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	448	59.4	654	51.0	1.41	1.17	1.69
G	306	40.6	628	49.0			

20 CTAF450_1 *P*=0.00027

Position: 178883

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	266	36.8	575	45.2	1.41	1.17	1.71
T	456	63.2	697	54.8			

21 CTAF450_2 *P*=0.043

Position: 178957

Alleles	Case	%	Control	%	Odds ratio	95%CI	
A	427	60.0	808	64.5	1.22	1.01	1.48
C	285	40.0	444	35.5			

22 CTAF450_3 *P*=0.42

Position: 178987

Alleles	Case	%	Control	%	Odds ratio	95%CI	
A	627	84.5	1092	85.8	1.11	0.86	1.42
G	115	15.5	180	14.2			

23 CTAF450_4 *P*=0.00010

Position: 179014

Alleles	Case	%	Control	%	Odds ratio	95%CI	
A	273	36.3	576	45.1	1.44	1.20	1.74
T	479	63.7	702	54.9			

24 MH30 *P*=2.5e-05

Position: 179587

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	483	64.6	701	55.0	1.49	1.23	1.80
C	265	35.4	573	45.0			

25 MH26 *P*=0.00048

Position: 187926

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	503	65.7	683	57.8	1.40	1.16	1.69
G	263	34.3	499	42.2			

26 MH23 *P*=0.17

Position: 188942

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	155	20.4	225	17.9	1.17	0.94	1.46
A	603	79.6	1033	82.1			

27 MH20 *P*=0.0046

Position: 190352

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	428	56.5	796	62.6	1.32	1.09	1.60
A	330	43.5	476	37.4			

28 MH18 *P*=0.00028

Position: 191345

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	488	64.0	699	55.9	1.41	1.17	1.71
C	274	36.0	551	44.1			

29 MH17 *P*=0.0058

Position: 191965

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	337	44.5	484	38.4	1.30	1.08	1.58
C	421	55.5	776	61.6			

30 MH15 ***P*=0.013**

Position: 192965

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	435	57.2	802	62.7	1.27	1.05	1.53
G	325	42.8	478	37.3			

31 MH14 ***P*=0.45**

Position: 193354

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	727	95.7	1219	94.9	1.18	0.76	1.82
A	33	4.3	65	5.1			

32 MH13_2 ***P*=0.0083**

Position: 193754

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	339	45.2	494	39.3	1.29	1.07	1.56
C	411	54.8	762	60.7			

33 MH13_1 ***P*=0.011**

Position: 193963

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	337	44.8	477	39.2	1.28	1.06	1.55
A	415	55.2	739	60.8			

34 MH3 ***P*=0.023**

Position: 199366

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	327	44.8	493	38.0	1.34	1.11	1.62
C	403	55.2	803	62.0			

35 MH2 ***P*=0.012**

Position: 200008

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	329	44.3	488	38.9	1.28	1.05	1.55
A	413	55.7	768	61.1			

36 MH1 ***P*=0.011**

Position: 200678

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	402	55.2	755	60.9	1.29	1.06	1.56
C	326	44.8	485	39.1			

37 CT50 (-1765T>C) ***P*=0.0083**

Position: 201114

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	343	44.8	506	39.0	1.29	1.07	1.55
C	423	55.2	790	61.0			

38 CT51 (-1722T>C) ***P*=0.50**

Position: 201157

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	705	91.8	1202	92.6	1.12	0.80	1.57
C	63	8.2	96	7.4			

39 CT52 (-1661A>G) ***P*=0.085**

Position: 201218

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	153	20.0	217	16.9	1.22	0.97	1.53
A	611	80.0	1065	83.1			

40 CT53 (-1577G>A) ***P*=0.0037**

Position: 201302

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	493	64.7	743	58.2	1.32	1.09	1.59
A	269	35.3	533	41.8			

41 CT41 (-658C>T) ***P*=0.48**

Position: 202221

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	686	91.5	1112	92.4	1.12	0.81	1.57
T	64	8.5	92	7.6			

42 CT44 (-319C>T) ***P*=0.27**

Position: 202560

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	677	89.3	1157	90.8	1.18	0.88	1.59
T	81	10.7	117	9.2			

43 +49G>A ***P*=0.0021**

Position: 202927

Alleles	Case	%	Control	%	Odds ratio	95%CI	
A	442	57.6	835	64.2	1.34	1.11	1.62
G	326	42.4	465	35.8			

44 CT43 (923C>T) ***P*=0.16**

Position: 203801

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	632	82.5	1048	84.9	1.18	0.93	1.50
T	134	17.5	186	15.1			

45 CT55 (1822T>C) ***P*=0.00063**

Position: 204700

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	325	42.3	442	34.9	1.39	1.15	1.68
C	443	57.7	826	65.1			

46 CT57 ***P*=0.081**

Position: 207073

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	763	99.3	1281	98.5	2.28	0.85	6.16
A	5	0.7	19	1.5			

47 CT59 ***P*=0.86**

Position: 207534

Alleles	Case	%	Control	%	Odds ratio	95%CI	
A	6	0.8	11	0.9	1.09	0.40	2.98
G	746	99.2	1253	99.1			

48 (AT)n-3' UTR ***P*=0.25 (1df)**

Position: 208256 - 208295

Alleles	Case	%	Control	%	Odds ratio	95%CI	
1	306	42.0	521	44.6	1.11	0.92	1.37
others	422	58.0	647	55.4			

***P*=0.01(2df)**

Genotype	Odds ratio	95%CI	
1/1	1.0 (ref)		
1/others	0.72	0.50	1.04
others/others	1.12	0.75	1.65

49 CT60 (6230G>A) ***P*=1.6e-06**

Position: 209108

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	469	63.4	676	52.3	1.56	1.30	1.88
A	271	36.6	616	47.7			

50 CT61 (6249G>A) ***P*=0.14**

Position: 209127

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	615	80.5	1048	83.2	1.19	0.95	1.49
A	149	19.5	212	16.8			

51 JO37_3 ***P*=0.00097**

Position: 209970

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	321	42.8	457	35.6	1.38	1.14	1.66
A	429	57.2	827	64.4			

52 JO37_2 ***P*=0.00074**

Position: 210012

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	323	43.0	439	35.5	1.38	1.15	1.67
A	429	57.0	799	64.5			

53 JO37_1 ***P*=0.40**

Position: 210360

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	160	21.2	246	19.6	1.10	0.88	1.37
A	594	78.8	1006	80.4			

54 JO36 ***P*=0.00095**

Position: 210860

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	474	62.9	889	69.9	1.39	1.14	1.69
A	280	37.1	383	30.1			

55 JO35 ***P*=0.00063**

Position: 211051

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	279	36.8	384	29.6	1.41	1.16	1.71
C	479	63.2	912	70.4			

56 JO34 ***P*=0.00012**

Position: 211735

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	473	62.6	884	70.7	1.47	1.21	1.79
A	283	37.4	366	29.3			

57 JO31 ***P*=4.1e-06**

Position: 213120

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	290	39.0	590	49.8	1.54	1.28	1.85
G	454	61.0	594	50.2			

58 JO30 ***P*=1.9e-06**

Position: 213595

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	466	61.5	629	50.5	1.56	1.29	1.87
A	292	38.5	617	49.5			

59 JO27_2 ***P*=0.22**

Position: 215010

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	168	22.6	256	20.3	1.14	0.92	1.42
C	576	77.4	1008	79.7			

60 JO27_1 ***P*=7.7e-06**

Position: 215189

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	439	59.5	615	49.2	1.53	1.27	1.84
C	299	40.5	635	50.8			

61 JO26_2 ***P*=0.34**

Position: 215318

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	550	75.5	973	77.5	1.11	0.90	1.37
C	178	24.5	283	22.5			

62 JO26_1 ***P*=0.22**

Position: 215349

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	180	24.7	279	22.2	1.14	0.92	1.41
C	550	75.3	977	77.8			

63 JO23 ***P*=0.76**

Position: 216953

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	114	15.2	187	14.7	1.04	0.81	1.34
A	636	84.8	1085	85.3			

64 JO22 ***P*=0.0015**

Position: 217128

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	472	64.3	907	71.0	1.38	1.13	1.69
C	262	35.7	371	29.0			

65 JO18 ***P*=0.00072**

Position: 219436

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	409	57.3	623	49.4	1.38	1.14	1.66
C	305	42.7	639	50.6			

66 JO13 ***P*=0.00057**

Position: 222056

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	475	63.8	874	71.2	1.42	1.16	1.73
C	269	36.2	354	28.8			

67 JO10 ***P*=0.67**

Position: 223672

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	579	79.3	1019	80.1	1.05	0.84	1.32
G	151	20.7	253	19.9			

68 JO9 ***P*=0.74**

Position: 223754

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	605	82.7	1042	83.2	1.04	0.82	1.33
C	127	17.3	210	16.8			

69 JO8_2 ***P*=0.00029**

Position: 224538

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	415	57.5	613	49.0	1.41	1.17	1.70
C	307	42.5	637	51.0			

70 JO8_1 ***P*=0.55**

Position: 224554

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	159	21.8	258	20.6	1.07	0.86	1.33
C	571	78.2	992	79.4			

71 JO6_2 ***P*=0.81**

Position: 225487

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	140	19.7	254	20.2	1.03	0.81	1.31
C	570	80.3	1006	79.8			

72 JO6_1 ***P*=0.00016**

Position: 225494

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	259	36.3	353	28.3	1.48	1.21	1.82
A	455	63.7	895	71.7			

73 JO3 ***P*=0.00047**

Position: 227090

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	410	56.9	616	48.7	1.39	1.15	1.67
A	310	43.1	648	51.3			

74 CTBC358 ***P*=0.0017**

Position: 243864

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	167	22.3	370	28.5	1.40	1.13	1.73
G	583	77.7	926	71.5			

75 CTBC313 ***P*=0.32**

Position: 248785

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	126	16.8	193	15.1	1.13	0.89	1.43
C	626	83.2	1089	84.9			

76 CTBC305 ***P*=0.010**

Position: 249366

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	248	34.1	365	28.7	1.30	1.06	1.59
C	480	65.9	907	71.3			

77 CTBC217_2 ***P*=0.0021**

Position: 258326

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	275	36.2	379	29.7	1.36	1.12	1.66
A	485	63.8	895	70.3			

78 CTBC217_1 *P*=0.00023

Position: 258341

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	407	53.4	568	44.9	1.40	1.17	1.68
C	355	46.6	696	55.1			

79 CTBC190 *P*=0.00043

Position: 260796

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	390	52.7	573	44.6	1.38	1.15	1.66
C	350	47.3	713	55.4			

80 CTBC182_2 *P*=0.00042

Position: 261654

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	343	47.6	695	56.0	1.39	1.15	1.66
G	377	52.4	545	44.0			

81 CTBC182_1 *P*=0.00023

Position: 261714

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	356	46.7	706	55.2	1.40	1.17	1.68
C	406	53.3	574	44.8			

82 CTBC165_3 *P*=0.00050

Position: 263248

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	399	52.4	566	44.4	1.38	1.15	1.65
A	363	47.6	710	55.6			

83 CTBC165_2 *P*=0.00027

Position: 263483

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	353	46.8	704	55.2	1.40	1.17	1.68
C	401	53.2	572	44.8			

84 CTBC165_1 *P*=0.00033

Position: 263524

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	360	47.1	707	55.3	1.39	1.16	1.67
G	404	52.9	571	44.7			

85 CTBC106 ***P*=0.032**

Position: 269287

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	579	76.0	1018	80.2	1.26	1.02	1.55
C	183	24.0	252	19.8			

86 CTBC099 ***P*=0.0085**

Position: 270311

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	566	76.1	1046	81.2	1.33	1.08	1.64
A	178	23.9	242	18.8			

87 CTBC078 ***P*=0.21**

Position: 272165

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	660	87.3	1150	89.1	1.19	0.90	1.57
C	96	12.7	140	10.9			

88 CTBC073 ***P*=0.049**

Position: 272763

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	176	23.8	242	19.9	1.24	1.00	1.53
C	564	76.2	976	80.1			

89 CTBC053 ***P*=0.0012**

Position: 274679

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	185	24.9	233	18.5	1.42	1.15	1.76
C	559	75.1	1027	81.5			

90 CTIC065 ***P*=0.27**

Position: 286757

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	172	22.9	263	20.8	1.13	0.91	1.40
T	580	77.1	1003	79.2			

91 IC082R ***P*=0.50**

Position: 289026

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	614	83.9	1098	85.0	1.09	0.85	1.41
A	118	16.1	194	15.0			

92 CTIC098 ***P*=0.57**

Position: 290240

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	631	84.1	1087	85.1	1.08	0.83	1.39
T	119	15.9	191	14.9			

93 CTIC114_1 ***P*=0.098**

Position: 291787

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	694	92.0	1150	89.8	1.30	0.95	1.79
T	60	8.0	130	10.2			

94 CTIC114_2 ***P*=0.55**

Position: 291796

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	126	16.6	198	15.6	1.08	0.84	1.38
C	634	83.4	1072	84.4			

95 CTIC114_3 ***P*=0.93**

Position: 292024

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	183	24.9	318	24.8	1.01	0.82	1.25
A	551	75.1	966	75.2			

96 CTIC142_1 ***P*=0.71**

Position: 294465

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	479	63.5	784	62.7	1.04	0.86	1.25
T	275	36.5	466	37.3			

97 CTIC142_2 ***P*=0.72**

Position: 294506

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	186	24.9	322	25.6	1.04	0.84	1.28
A	560	75.1	934	74.4			

98 CTIC142_3 ***P*=0.096**

Position: 294834

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	692	91.8	1142	89.5	1.30	0.95	1.77
A	62	8.2	134	10.5			

99 CTIC148 ***P*=0.19**

Position: 295363

Alleles	Case	%	Control	%	Odds ratio	95%CI	
T	63	8.2	129	10.0	1.23	0.90	1.68
A	703	91.8	1167	90.0			

100 CTIC154_1 ***P*=0.12**

Position: 295528

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	692	92.3	1153	90.2	1.29	0.93	1.79
T	58	7.7	125	9.8			

101 CTIC154_2 ***P*=0.26**

Position: 295766

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	62	8.2	125	9.7	1.20	0.87	1.64
A	692	91.8	1161	90.3			

102 CTIC154_3 ***P*=0.73**

Position: 295911

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	563	75.1	968	75.7	1.04	0.84	1.28
A	187	24.9	310	24.3			

103 CTIC159 ***P*=0.49**

Position: 296277

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	120	16.3	193	15.1	1.09	0.85	1.41
C	618	83.7	1083	84.9			

104 JC034sR ***P*=0.081**

Position: 305558

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	305	41.8	467	37.8	1.18	0.98	1.43
A	425	58.2	767	62.2			

105 JC058sR ***P*=0.30**

Position: 307611

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	183	24.2	281	22.3	1.13	0.90	1.41
A	573	75.8	981	77.7			

106 JC068sFa ***P*=0.022**

Position: 308240

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	326	42.7	489	37.7	1.25	1.03	1.51
G	438	57.3	807	62.3			

107 JC068sRb ***P*=0.042**

Position: 308831

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	413	56.9	786	61.4	1.22	1.01	1.47
C	313	43.1	494	38.6			

108 JC473sR_4 ***P*=0.51**

Position: 347248

Alleles	Case	%	Control	%	Odds ratio	95%CI	
C	291	38.0	496	39.4	1.07	0.88	1.29
A	475	62.0	762	60.6			

109 JC569sF ***P*=0.75**

Position: 356561

Alleles	Case	%	Control	%	Odds ratio	95%CI	
G	396	52.1	655	52.8	1.03	0.86	1.24
A	364	47.9	585	47.2			

Names in parentheses of SNPs used by Johnson *et al*. (*Nature Genet* **29,** 233-237 (2001))

References

1. Clayton, D. C. *Handbook of statistical genetics* (ed.s Balding, D. J., Bishop, M. & Cannings, C.) 519-540 (Wiley, Chichester, 2001).
2. Cordell, H. J. & Clayton, D. C. A unified stepwise regression procedure for evaluating the relative effects of polymorphisms within a gene using case/control or family data: application to HLA in type 1 diabetes. *Am J Hum Genet* **70**, 124-141 (2002).
3. Rubin, D. B. *Multiple imputation for non-response in surveys*. *(*Wiley, Chichester, 2001).
4. Howard, T.D. et al. Fine mapping of an IgE-controlling gene on chromosome 2q: analysis of *CTLA4* and *CD28*. *J Allergy Clin Immunol* **110,** 743-751 (2002).