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Large-scale studies of the association between variation at the *TNF*/*LTA* locus and susceptibility to type 2 diabetes

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Abstract *Aims/hypothesis:* The proinflammatory cytokine TNF-α has been implicated in the pathogenesis of insulin resistance and type 2 diabetes, and variation in the gene encoding TNF-α (*TNF*) has shown inconsistent associations with susceptibility to both conditions. Additionally, the coding non-synonymous variant T60N in the neighbouring *LTA* gene has been reported to be associated with type 2 diabetes. The present study aimed to obtain a robust assessment of the role of variation in the tightly linked *TNF*/*LTA* region in diabetes susceptibility by genotyping *TNF* and *LTA* variants in large case-control resources. *Materials and methods:* The G-308A and G-238A *TNF* promoter variants and the *LTA* T60N polymorphism were genotyped in two UK case samples that were ascertained for positive family history and/or early onset of type 2 diabetes (combined n=858) and in 1,257 ethnically matched controls. *Results:* There were no significant associations between the T60N, G-308A or G-238A genotype and type 2 diabetes in the combined analysis (exact Cochran–Mantel–Haenszel statistic for ordered genotypes for T60N, p=0.69; for G-308A, p=0.51; for G-238A, p=0.16). *Conclusions/interpretation:* The present study, one of the largest association analyses yet reported at this locus, provides no evidence that the specific *TNF* or *LTA* variants examined influence susceptibility to type 2 diabetes. More comprehensive studies of the *TNF*/*LTA* locus in substantially larger sample sets are required to establish whether genome sequence variation at this locus truly influences susceptibility to type 2 diabetes.

Keywords Association · Linkage disequilibrium · Tumour necrosis factor · TNF · Lymphotoxin α

Abbreviations ECACC: European Collection of Cell Cultures · EFS: Exeter Family Study · LD: linkage disequilibrium · OR: odds ratio · SNP: single-nucleotide polymorphism · W2P: Warren 2 probands · YT2D: young-onset type 2 diabetes

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Introduction

The aetiology of type 2 diabetes is complex. Although environmental and genetic factors contribute to the variation in individual susceptibility to disease [1], the specific

molecular mechanisms underlying disease development remain uncertain. One area of particular importance relates to the mechanisms responsible for the pathophysiological link between obesity and type 2 diabetes. One possible mechanism involves the release from adipocytes of molecules that influence insulin action in muscle, liver and other insulin-responsive tissues. Several such adipokines have been implicated, much recent interest focusing on the relationship between adipocyte-derived proinflammatory cytokines, such as IL-6 and TNF-α, and the development of insulin resistance and type 2 diabetes [2].

Fluctuations in protein expression may be influenced by variations at the genetic level. The gene encoding TNF-α (*TNF*) lies in the class III region of the MHC on chromosome 6p21.3, as part of a cluster of related genes, including *LTA* and *LTB*. These code for lymphotoxin α and β respectively, other members of the TNF ligand superfamily. A large number of single-nucleotide polymorphisms (SNPs) have been identified within this cluster, but association studies examining the role of *TNF* variation in genetic susceptibility to type 2 diabetes and related phenotypes have focused on two promoter sequence variants at positions −308 and −238 relative to the transcriptional start site. These particular SNPs have previously been implicated in susceptibility to a wide range of inflammatory and infectious disorders [3, 4].

Association studies of these variants in type 2 diabetes and related phenotypes have generated inconsistent results. Such variability in complex trait association studies is well recognised and results from many factors (including locus and allelic heterogeneity, population stratification, multiple testing and variable linkage disequilibrium), of which inadequate sample size is probably the most important [5]. In this respect, it is notable that several of the more recent, larger studies of the −308 variant have generated the strongest positive associations with type 2 diabetes and/or insulin resistance [6–9]. However, none of these studies has examined more than a few hundred subjects. For example, in 490 overweight subjects with impaired glucose homeostasis studied in the Finnish Diabetes Prevention Study, Kubaszek and colleagues [9] reported that the −308A allele was associated with a two-fold increase in conversion from IGT to type 2 diabetes. There have been no large-scale studies of the −238 variant in relation to type 2 diabetes or related phenotypes; the only studies reporting positive associations were of modest size and contradictory in terms of the susceptibility allele [10, 11].

The G-308A and G-238A *TNF* promoter variants have been found to affect transcriptional regulation of the neighbouring *LTA* gene [12]. In addition, a non-synonymous coding polymorphism in *LTA* (T60N, referred to as T26N in some studies) has been associated with myocardial infarction [13]. Recently, evidence implicating the T60N polymorphism with increased susceptibility to type 2 diabetes has emerged from two studies [14, 15] conducted in Danish Caucasian and Japanese individuals.

Determining whether or not these variants truly influence diabetes susceptibility and, if so, obtaining a more precise estimate of effect size requires that association analyses be extended to additional, large, well-characterised samples. The aim of the present study was to evaluate the association of the *TNF* G-308A and G-238A promoter SNPs and of the *LTA* T60N variant with type 2 diabetes in one of the largest such studies yet conducted.

Subjects and methods

Subjects

The present study included analysis of two case and two control groups. Clinical characteristics are provided in Table 1. In the first case-control analysis, we compared unrelated type 2 diabetes probands (n=565) from the Diabetes UK Warren 2 sibpair repository (Warren 2 probands; W2P) [16] with 347 random UK population control samples from the European Collection of Cell Cultures (ECACC; Salisbury, UK). For the second comparison, the case sample combines two sets of young-onset type 2 diabetes subjects (YT2D, n=293) with almost identical clinical characteristics: (1) offspring from parent-offspring trios (n=157) ascertained for type 2 diabetes [17]; and (2) young onset

Table 1 Clinical characteristics of the populations studied

Sample group	Sample type	n	Age at diagnosis (cases) or last examination (controls) (years)	BMI (kg/m^2)	WHR	Males (%)
Warren 2 sibpair probands (W2P)	Case	565	55.4 (8.4)	27.7 (4.2) (male) 30.0 (5.6) (female)	0.96 (0.07) (male) 0.87 (0.06) (female)	54.3
Blood donors (ECACC)	Control	347	38.5 (8.2)[a]	–	–	53.1
Young onset type 2 diabetes (YT2D)	Case	293	39.4 (6.9)	31.1 (5.3) (male) 34.3 (8.0) (female)	0.97 (0.06) (male) 0.89 (0.08) (female)	56.3
Exeter family study (EFS)	Control	910	31.6 (5.4)	26.7 (3.8) (male) 27.9 (4.8) (female)[b]	0.88 (0.06) (male) NA (female)[b]	49.9

Continuous data are means (SD)
[a]Age information was available for only 34% of subjects in this group
[b]BMI in females was measured during pregnancy: meaningful measures of WHR not available

(<45 years) type 2 diabetes subjects (n=136) [18]. These cases were compared with 910 unrelated parents from a consecutive birth cohort (the Exeter Family Study; EFS), 825 of whom were normoglycaemic [18]. All case samples are, therefore, strongly selected for inherited type 2 diabetes on the basis of early disease onset and/or positive family history. Other types of diabetes were excluded using a combination of clinical, immunological and genetic criteria, as previously described [16, 17]. Given the position of *TNF* within the MHC (and the potential for linkage disequilibrium [LD] with HLA alleles implicated in islet autoimmunity), it is important to note that we excluded autoimmune diabetes in all cases through standard clinical criteria (including an age of disease onset above 25, insulin independence following diagnosis, no ketoacidosis, no close family history of type 1 diabetes) combined with GAD antibody typing [16, 17]. Confirmation of glycaemic status in the control populations was limited to fasting plasma glucose measures for the EFS samples. All subjects were exclusively of British/Irish origin. Informed consent was obtained from all subjects, and all studies were carried out in accordance with the principles of the Declaration of Helsinki (2000).

SNP genotyping

The two *TNF* variants (G-308A [rs1800629] and G-238A [rs361525]) were genotyped using fluorescence probe-based allele-specific PCR (Amplifluor; Chemicon International, Temecula, CA) [19]. The *LTA* T60N (rs1041981) variant was genotyped by a combination of the Amplifluor [19] and gel-based tetra primer amplification refractory mutation system PCR [20] methods. Overall genotyping success rates were 94.0, 97.6 and 94.7% for the G-308A, G-238A and T60N variants respectively. Based on extensive duplicate genotyping, we estimate an error rate below 1%.

Statistical analyses

SNPs were tested for deviation from Hardy–Weinberg equilibrium in cases and controls separately using HelixTree Genetics Analysis Software (Golden Helix, Bozeman, MT, USA). Genotype and allele frequency distributions were compared by standard contingency table methods using Stata v. 8 (Stata Corporation, College Station, TX, USA). Genotype trend comparisons were also carried out using the Kruskal–Wallis test and the generalised Cochran–Mantel–Haenszel statistic. As necessary, exact p values for these tests were obtained using StatXact 6 (Cytel Software, Cambridge, MA, USA). In addition, logistic regression methods were implemented to allow adjustment for potential confounding or explanatory variables. Pairwise measures of LD were calculated and three-point haplotype frequencies were estimated using the expectation-maximization algorithm in HelixTree (reinitialised several times to ensure convergence). Haplotypic associations were investigated through the haplotype trend regression method [21]. Linear regression was used to examine the relationship between SNP genotype and the normally distributed anthropometric measures (BMI and WHR) using Stata v.8. Statistical significance was designated where $p<0.05$.

Power

Assuming no enrichment of cases for familiality and early onset, the sample sizes genotyped in the present study would have (for α=0.05 and odds ratio [OR]=1.3 under a multiplicative model) 56% power to detect an effect at G-238A and 94% power at G-308A. If allowance is made, under realistic models [22, 23], for the increase in susceptibility allele frequency to be expected when, as in the present study, cases have been selected for familiality and early onset, these power values rise to 91 and >99%, respectively. In the specific case of T60N, where previous evidence [14, 15] supports a recessive effect (amino acids NN vs. T/−; genotypes AA vs. C/−), the present study has only 41% power to detect the effect size (OR 1.24) detected by Hamid and colleagues in unselected cases [14]. However, once again, allowance for the effects of case selection leads to power estimates of >99.9% for detection of the OR seen in the Danish early onset case subset (OR=1.99), or, more conservatively, 97% for an OR of 1.50.

Results

Genotype distributions at the three variants are detailed in Table 2. None of the variants deviated significantly from

Table 2 T60N, G-308A and G-238A genotype distributions in the sample groups under study: *n* (%)

T60N: W2P vs. ECACC, p=0.76, YT2D vs. EFS, p=0.31, combined p=0.69
G-308A: W2P vs. ECACC, p=0.41, YT2D vs. EFS, p=0.90, combined p=0.51
G-238A: W2P vs. ECACC, p=0.04, YT2D vs. EFS, p=0.86, combined p=0.16

Genotype	W2P Case	ECACC Control	YT2D Case	EFS Control
T60N CC	202 (38.6)	129 (37.8)	102 (36.1)	344 (40.2)
T60N CA	251 (48.0)	164 (48.1)	143 (50.5)	398 (46.5)
T60N AA	70 (13.4)	48 (14.1)	38 (13.4)	114 (13.3)
−308 GG	310 (61.5)	222 (64.5)	174 (64.0)	557 (64.1)
−308 GA	173 (34.3)	107 (31.1)	87 (32.0)	284 (32.7)
−308 AA	21 (4.2)	15 (4.4)	11 (4.0)	28 (3.2)
−238 GG	470 (83.9)	303 (88.9)	234 (85.4)	765 (86.0)
−238 GA	87 (15.5)	37 (10.8)	40 (14.6)	119 (13.4)
−238 AA	3 (0.5)	1 (0.3)	0 (0.0)	6 (0.7)

Table 3 Estimated *LTA/TNF* haplotype frequencies (%) in the sample groups under study

T60N/–308/–238 haplotype	W2P (%) Case	ECACC (%) Control	YT2D (%) Case	EFS (%) Control
C-G-G	55.4	56.4	53.5	57.1
A-A-G	20.2	19.0	19.7	19.3
A-G-G	15.8	18.5	19.0	16.1
C-G-A	6.8	5.2	7.4	6.7
A-G-A	<0.1	<0.1	<0.1	<0.1
C-A-A	<0.1	<0.1	<0.1	<0.1
C-A-G	<0.1	<0.1	<0.1	<0.1
A-A-A	<0.1	<0.1	<0.1	<0.1

Hardy–Weinberg equilibrium in any of the case or control groups. There were no significant associations between the T60N or the G-308A genotypes and type 2 diabetes in either case-control comparison or in the combined analysis (exact Cochran–Mantel–Haenszel statistic for ordered genotypes for T60N, p=0.69; for G-308A, p=0.51). There was a borderline significant association between the G-238A SNP genotypes and type 2 diabetes in the first case-control analysis (W2P vs. ECACC, Kruskal–Wallis test p=0.042), but this finding was not replicated in the second case-control data set (YT2D vs. EFS, p=0.86). Adjustment for gender, age, BMI and WHR (where such data were available) failed to generate any significant SNP associations with type 2 diabetes.

There was evidence of LD between pairs of the three SNPs when the D′ metric was used (D′ value of at least 0.73 in the two control groups). However, the alternative r^2 measure, which more usefully reflects the extent to which each variant can act as a proxy for the other in association studies, revealed minimal disequilibrium (r^2<0.02) between the two *TNF* SNPs and only moderate LD between the T60N polymorphism and G-308A (r^2~0.4). Estimated haplotype frequencies for the different sample groups are depicted in Table 3. No significant haplotypic associations with diabetes were observed.

We also examined the relationship between the three variants and available type 2 diabetes-related continuous traits. Although there were nominally significant associations at T60N for BMI and WHR in the male cases, these were not replicated in female cases or in the EFS controls (in whom analysis was restricted to males, as the females were pregnant).

Discussion

In this, the largest study yet performed of the relationship between *TNF* variation and type 2 diabetes, we have found no significant evidence for an association between variation around this locus and susceptibility to type 2 diabetes. No significant effect was detected at the G-308A or G-238A variants in these cases, loaded for familiality and early-onset type 2 diabetes. In addition, no effect on disease risk was observed for the *LTA* coding non-synonymous variant T60N.

Assessment of these data in the light of previous findings is not straightforward. Association studies at this locus display a chequered pattern of results, which is typical of much of the association literature [1, 5]. At the G-308A variant, it is notable that several of the recent, larger studies (though the largest of these has only 700 subjects) have provided the most convincing evidence for positive associations with diabetes and/or insulin resistance [6–9]. However, the present study found no significant association between this variant and type 2 diabetes. Whilst meta-analysis might, in principle, be expected to provide a more conclusive answer, the value of such an approach is seriously compromised by the heterogeneity of subject ascertainment and outcome phenotypes (type 2 diabetes, insulin sensitivity, insulin secretion, etc.) in the studies to date. In contrast, there have been relatively few studies of the relationship between the G-238A variant and metabolic phenotypes: the two studies reporting positive associations [10, 11] were contradictory (in the direction of the association) and compromised by modest sample size. This is, therefore, the first well-powered study (estimated power, given case selection enrichment, of 91% for OR=1.3 under a multiplicative model and α=0.05) to explore the role of this variant in metabolic disease.

Associations between a non-synonymous *LTA* variant (T60N) and type 2 diabetes have recently been reported in Danish and Japanese subjects [14, 15]. In these studies, the rare homozygous T60N (AA) genotype was found to be associated with increased risk of disease. The present study has not corroborated these findings. Although the present sample is a little smaller than those studied previously [14], the UK cases examined were strongly selected for inherited type 2 diabetes on the basis of early disease onset and/or positive family history. This enrichment has a substantial effect on study power (see Subjects and methods, Power) [22, 23]. Indeed, the Danish study reported a much increased OR for the AA genotype when only early-onset cases were considered [14]. This conflicting evidence will only be resolved by additional studies in larger data sets from these and other ethnic groups.

The functional effects of the *TNF* promoter variants are complex: indeed, there is evidence to indicate that their primary regulatory effect is not on *TNF* expression at all, but on *LTA* [12]. Interestingly, in a recent genome-wide association scan conducted in Japanese subjects, Ozaki and colleagues found that variation in *LTA* was highly associated with myocardial infarction [13]. Subsequently, the same group have shown that galectin-2, which is thought to modify lymphotoxin α secretion, may also be implicated in myocardial infarct susceptibility [24]. *TNF* variants may therefore, in principle, be exerting their effects via *LTA* as well as *TNF* expression, effects that may reflect both direct transcriptional control and LD with functional variants in these adjacent genes. Such complex functional and LD relationships could be contributing to the inconsistency of the association findings reported to date.

It is important to note that this gene cluster lies in the midst of the MHC. As LD between *TNF* and major HLA loci has been reported [8], the strong impact of HLA variation on type 1 diabetes and on latent autoimmune diabetes of adulthood [25] raises the possibility that some of the observed associations between *TNF*/*LTA* variation and type 2 diabetes reflect latent autoimmunity (present in up to 10% of unselected type 2 diabetes populations [26]). In the present study, we used several complementary strategies to exclude subjects with type 1 diabetes and latent autoimmune diabetes of adulthood from the case populations. Differences in the extent to which latent autoimmunity is detected and excluded may contribute to the differences in the evidence for association with type 2 diabetes at this locus.

The present study does not add to the evidence implicating *TNF*/*LTA* variation in the development of type 2 diabetes. More comprehensive studies featuring a denser array of SNPs genotyped across this locus in considerably larger sample sizes will be required for a definitive assessment. Available data indicate that the haplotypic structure of this locus is complex and that a substantial number of SNPs will need to be typed so as to tag the majority of common variation [27]. With the availability of large collaborative studies, information on the local LD structure and improved genotyping methods, such a study should be feasible in the near future.

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