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HLA-DQ2 is associated with anti-drug antibody formation to infliximab in patients with immune-mediated inflammatory diseases

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Abstract. Brun MK, Bjørlykke KH, Viken MK, Stenvik G-E, Klaasen RA, Gehin JE, et al. HLA-DQ2 is associated with anti-drug antibody formation to infliximab in patients with immune-mediated inflammatory diseases. *J Intern Med.* 2023;**293**:648–655.

Background. Immunogenicity to tumour necrosis factor inhibitors is a significant clinical problem leading to treatment failure and adverse events. The study aimed to assess human leukocyte antigen (HLA) associations with anti-drug antibody (ADAb) formation to infliximab.

Methods. Immune-mediated inflammatory disease patients on infliximab therapy (n = 612) were included. Neutralising ADAb were assessed with a drug-sensitive assay. Next generation sequencing-based HLA typing was performed.

Results. Overall, 147 (24%) patients developed ADAb. Conditional analyses indicated *HLA-DQB1* ($p = 1.4 \times 10^{-6}$) as a primary risk locus. Highest risk of ADAb was seen when carrying at least one of the HLA-DQ2 haplotypes; DQB1*02:01–DQA1*05:01 or DQB1*02:02–DQA1*02:01 (OR 3.18, 95% CI 2.15–4.69 and $p = 5.9 \times 10^{-9}$). Results were consistent across diseases and when adjusting for concomitant immunomodulator. Computational predictions indicated that these HLA-DQ2 haplotypes bind to peptide motifs from infliximab light chain.

Conclusion. A genome-wide significant association between two HLA-DQ2 haplotypes and the risk of ADAb formation to infliximab was identified, suggesting that HLA-DQ2 testing may facilitate personalised treatment decisions.

Keywords: autoimmune disease, gastroenterology, genetics, immunology, immunosuppressive treatment, rheumatology

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Introduction

Tumour necrosis factor inhibitors (TNFi), such as infliximab, have substantially improved outcomes for prevalent chronic immune-mediated inflammatory diseases (IMIDs) like ulcerative colitis (UC),

Crohn's disease (CD), rheumatoid arthritis (RA), spondyloarthritis (SpA), psoriatic arthritis (PsA) and psoriasis (Ps). Still, lack or loss of treatment response resulting in reduced quality of life and potential irreversible organ damage and disability is a significant clinical problem. Formation of anti-drug antibodies (ADAb) is a leading cause of TNFi treatment failure and is also related to adverse events [1, 2].

Identifying patients at risk of developing ADAb is important for treatment strategies to mitigate the formation of ADAb [3]. Two genome-wide association studies (GWAS) have linked HLA-DQA1*05 to ADAb formation in IMID patients treated with therapeutic antibodies [4, 5]. Human leukocyte antigen (HLA) class II alleles have been proposed as the main genetic factor associated with ADAb to TNFi, [6] including the haplotype DRB1*03:01–DQB1*02:01–DQA1*05:01 [7-9]. However, these prior studies have only investigated a few of the classical *HLA* genes. The aim of this study, using data from the Norwegian Drug Monitoring (NOR-DRUM) trials [10, 11], was to comprehensively assess associations between genetic variations in the peptide-binding groove of all classical HLA loci and ADAb formation to infliximab.

Materials and Methods

The study population comprised 612 of the 616 IMID patients treated with infliximab included in the randomised NOR-DRUM trials [10, 11] assessing the effect of therapeutic drug monitoring. Exclusion of four patients was due to lack of either HLA or ADAb assessment. Infliximab trough concentrations and neutralising ADAb (if drug concentrations were <5 mg/L) were assessed using a drug-sensitive assay (Table S1) [3]. The main outcome was presence of ADAb defined as one or more sample with ADAb ≥15 μg/L.

Next generation sequencing-based HLA typing was performed by HistoGenetics LLC (Ossining, NY, USA) on DNA extracted from full blood. Four duplicate samples were included as quality controls, and their HLA genotyping showed full concordance. Genotype success rates were 100% for all HLA loci. Alleles were genotyped at G-group resolution for the loci *HLA-A, -B, -C, -DQA1, -DRB1, -DRB3, -DRB4, -DRB5, -DQB1, -DPB1* and *-DPA1*. Analyses were performed on data trimmed to second field resolution.

Statistical analysis

Genetic association analyses were performed using Unphased v3.0.13 [12], with a rare allele frequency threshold of 0.01 (101 HLA alleles passed this threshold, Table S2), at both allelic and haplotypic levels. Woolf's method with Haldane correction was used to calculate odds ratios (OR). Svejgaard test was used to assess the degree of independence between associated alleles. Correcting for multiple testing using Bonferroni gave a significance threshold of 0.0005. For HLA amino acid association analyses, BIGDAWG v2.1 was utilized [13].

Cox proportional hazards regression was performed using Stata v16 (StataCorp). The Kaplan–Meier estimator was used to estimate survival functions. Covariates adjusted for were age, sex, diagnosis and use of concomitant immunosuppressive therapy.

Peptide-binding prediction

Amino acid sequences for the infliximab antigen-binding fragment were obtained from the Protein Bank Database, accession number 4g3y. NetMHCIIpan-4.0 was used for HLA peptide-binding predictions for infliximab heavy- and light chain [14], using a peptide length of 15 amino acids. Peptides were annotated as strong or weak binders with the predicted %Rank lower than the thresholds of 1% and 5%, respectively.

The study was approved by the regional ethics committee and registered as a clinical trial (NCT-03074656).

Results

In total, 612 patients (114 UC, 80 CD, 120 RA, 181 SpA, 72 PsA and 45 Ps) were included. Median follow-up time was 51 weeks (IQR 37–87). Infliximab was discontinued in 187 (31%) patients. ADAb formation was detected in 147/612 (24%) patients (UC 27/114 (24%), CD 14/80 (18%), RA 38/120 (32%), SpA 33/181 (18%), PsA 20/72 (28%) and Ps 15/45 (33%)). Patient characteristics are detailed in Table S3 and have been published previously [3, 10, 11].

Conditional analyses indicated that *HLA-DQB1* represented the primary HLA locus association, as there were no residual association signals for the other loci when conditioning on *HLA-DQB1* (Table S4). In contrast, association signals were

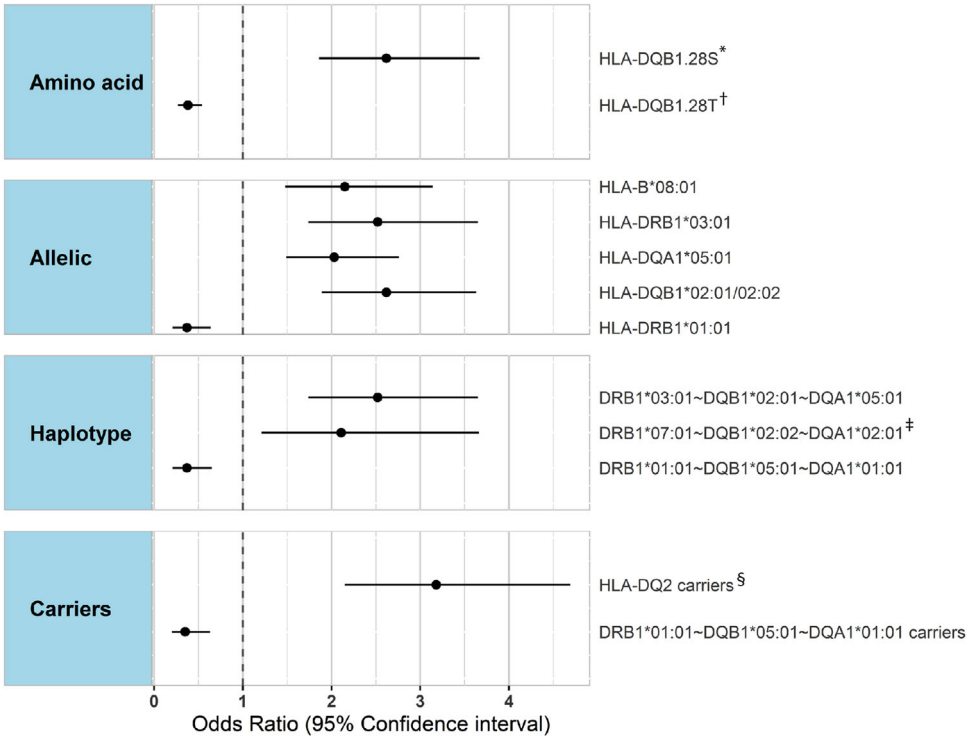

Fig. 1 *Effect sizes for the most significant human leukocyte antigen (HLA) associations to anti-drug antibody (ADAb) formation. Effect sizes are plotted using odds ratio (OR) for analyses on an amino acid, allelic and haplotype level, as well as for carriers/non-carriers of associated haplotypes. Black lines represent 95% confidence intervals (CI).*
**HLA-DQB1 28S represents the amino acids HLA-DQB1 28S, 30S, 37I, 46E, 47F, 52L, 55L, 71K and 74A, which all had the same OR and CI.* † *HLA-DQB1 28T represents the amino acids HLA-DQB1 28T, 46V, 47Y and 52P, which all had the same OR and CI.* ‡ *The haplotype DRB1*07:01–DQB1*02:02–DQA1*02:01 was due to the G-group level HLA typing analysed as DRB1*07:01–DQB1*02:01–DQA1*02:01.* § *HLA-DQ2 carriers represent patients carrying at least one of the two HLA-DQ2 risk haplotypes DQB1*02:01–DQA1*05:01 and DQB1*02:02–DQA1*02:01.*

still present for *HLA-DQB1* when the other loci were conditioned for. The observed locus associations remained after adjusting for age, gender and diagnosis (Table S5).

The risk allele HLA-DQB1*02:01 (representing DQB1*02:01 and DQB1*02:02) showed the strongest association (OR 2.62, 95% confidence interval (CI) 1.89–3.63 and $p = 6.6 \times 10^{-9}$) with ADAb formation (Fig. 1 and Table S2), whereas HLA-DRB1*01:01 was protective (OR 0.37, 95% CI 0.21–0.64 and $p = 0.0004$). Three other risk alleles reached the Bonferroni corrected significance threshold ($p < 0.0005$); HLA-DRB1*03:01 (OR 2.52, $p = 1.1 \times 10^{-6}$), HLA-DQA1*05:01 (OR 2.03, $p = 8.4 \times 10^{-6}$) and HLA-B*08:01 (OR 2.15, $p = 6.8 \times 10^{-5}$). Svejgaard analysis between the class I and class II signals showed that the class II alleles were primarily associated with ADAb formation (Table S6).

Haplotype analyses revealed two risk haplotypes: DRB1*03:01–DQB1*02:01–DQA1*05:01 (OR 2.52, 95% CI 1.74–3.65 and $p = 1.1 \times 10^{-6}$) and DRB1*07:01–DQB1*02:02–DQA1*02:01 (formally analysed as DRB1*07:01–DQB1*02:01–DQA1*02:01) (OR 2.11, 95% CI 1.21–3.66 and $p = 0.008$), and one protective haplotype: DRB1*01:01–DQB1*05:01–DQA1*01:01 (OR 0.37, 95% CI 0.21–0.65 and $p = 0.0005$) (Figs. 1 and 2a–c). Taken together, significantly increased risk for ADAb formation was observed for both HLA-DQ2 haplotypes; DQB1*02:01–DQA1*05:01 and DQB1*02:02–DQA1*02:01.

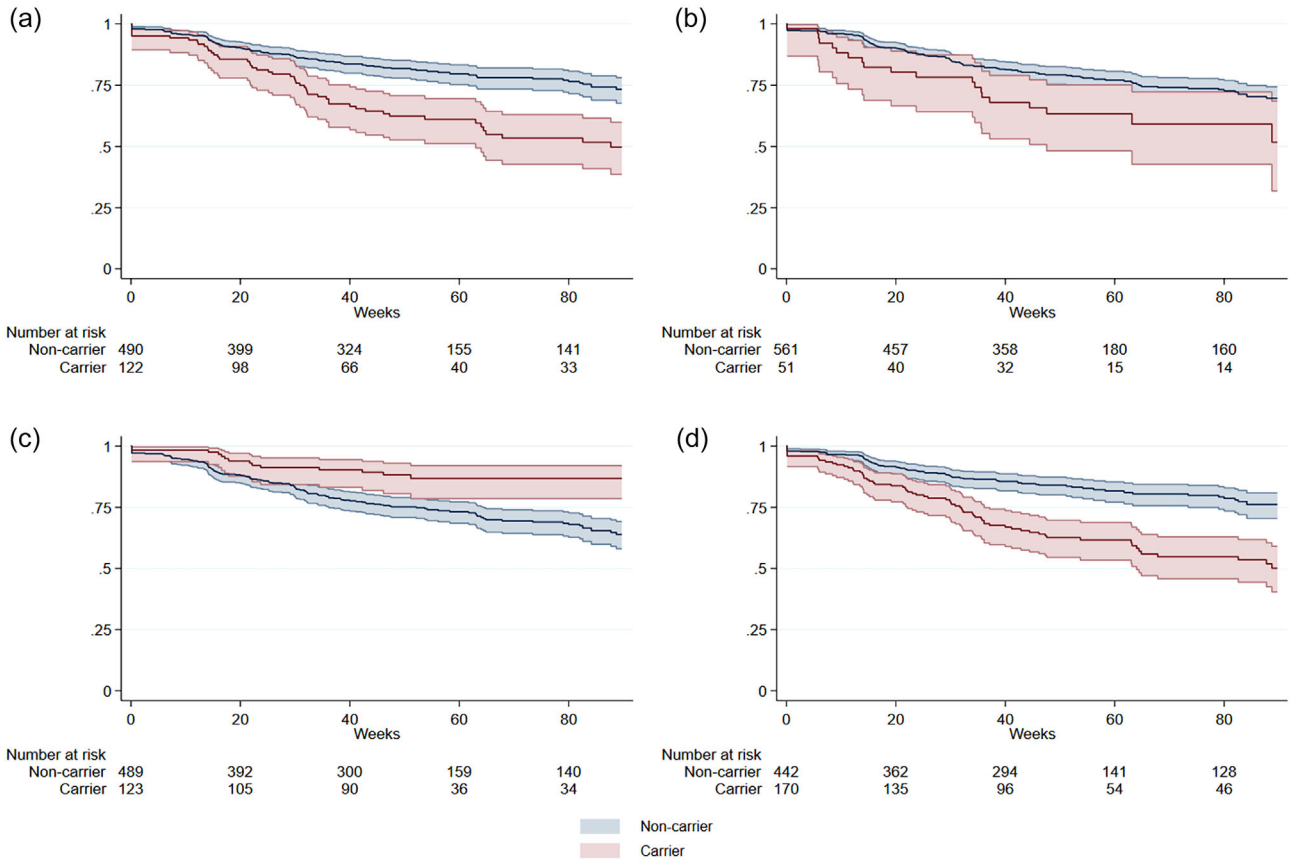

Fig. 2 *Kaplan–Meier survival curves of time to anti-drug antibody (ADAb) formation (weeks) for significant DRB1–DQB1–DQA1 haplotypes and HLA-DQ2. Y-axis indicates proportion of patients without ADAb. Red colour denotes carriers of the haplotype, blue colour denotes non-carriers of the haplotype. Human leukocyte antigen (HLA) typing was at G-group resolution and trimmed to second field resolution for analyses. (A) Patients carrying the risk haplotype DRB1*03:01–DQB1*02:01–DQA1*05:01. (B) Patients carrying the risk haplotype DRB1*07:01–DQB1*02:02–DQA1*02:01 (analysed as DRB1*07:01–DQB1*02:01–DQA1*02:01). (C) Patients carrying the protective haplotype DRB1*01:01–DQB1*05:01–DQA1*01:01. (D) Patients carrying at least one of the two HLA-DQ2 risk haplotypes.*

Table 1. Multivariable cox regression analyses of time to anti-drug antibody (ADAb) formation[a]

	ADAb formation, $n = 147/612$	
	HR (95% CI)	p Value
HLA-DQ2 risk haplotypes[b]	2.54 (1.82–3.56)	<0.001
Age	1.01 (1.00–1.02)	0.08
Female sex	1.38 (0.97–1.96)	0.08
Diagnosis		
Rheumatoid arthritis	1	1
Ulcerative Colitis	0.59 (0.33–1.04)	0.07
Crohn's disease	0.43 (0.22–0.83)	0.01
Psoriatic arthritis	0.76 (0.44–1.33)	0.34
Spondyloarthritis	0.47 (0.27–0.82)	<0.01
Psoriasis	0.90 (0.47–1.74)	0.75
Concomitant immunosuppressive therapy[c]	0.66 (0.46–0.96)	0.03

Results are presented as hazard ratios (HR) with 95% confidence intervals (CI). Patients withdrawn from the study or discontinued infliximab were censored at the time of last study visit or 12 weeks after the last infliximab infusion.
Abbreviations: ADAb, antidrug antibodies; HLA, human leukocyte antigen.
[a]Defined as anti-drug antibodies (ADAb) ≥15 μg/L.
[b]HLA-DQ2 risk haplotypes include DQB1*02:01–DQA1*05:01 and DQB1*02:02–DQA1*02:01.
[c]Concomitant immunosuppressive therapy includes methotrexate and thiopurine use at baseline.

HLA-DQ2 carrier frequency was 46.9% in patients with ADAb formation versus 21.7% in patients without ADAb (OR 3.18, 95% CI 2.15–4.69 and $p = 5.9 \times 10^{-9}$) (Figs. 1 and 2d). This observation was consistent across disease phenotypes (Table S7) and when adjusting for immunosuppressive comedication (Adjusted hazard ratio (HR) 2.54, 95% CI 1.82–3.56 and $p < 0.001$) (Table 1), and other possible confounders including smoking (Table S8). Immunosuppressive comedication was a protective factor for ADAb formation (HR 0.66, 95% CI 0.46–0.96 and $p = 0.03$) (Table 1 and Fig. S1).

The amino acids most significantly associated with an increased risk of ADAb formation (OR 2.62, 95% CI 1.86–3.67 and $p = 3.4 \times 10^{-9}$) were located within the peptide-binding groove encoded by the HLA-DQB1 locus (Fig. 1). All these amino acid variants are encoded by the DQB1*02:01 and *02:02 alleles (analysed jointly as DQB1*02:01). The most significant amino acids associated with reduced risk of ADAb (OR 0.38, 95% CI 0.27–0.54 and $p = 3.4 \times 10^{-9}$) were also located within the *HLA-DQB1* peptide-binding groove (Fig. 1) and are encoded by several alleles, such as HLA-DQB1*05:01, -DQB1*03:01 and -DQB1*03:02.

Predicted sequence motifs for antigen-presentation by the two HLA-DQ2 molecules, encoded by DQB1*02:01–DQA1*05:01 and DQB1*02:02–DQA1*02:01, were largely overlapping (Fig. S2). Predictions for infliximab light chain showed that DQB1*02:01–DQA1*05:01 and DQB1*02:02–DQA1*02:01 share nine strong binder peptides, encompassing the following two core-peptide sequences INTVESEDI and VYACEVTHQ. For infliximab heavy chain, binding predictions showed that DQB1*02:01–DQA1*05:01 and DQB1*02:02–DQA1*02:01 only had weak binder peptides. The binding predictions of infliximab for the protective DQB1*05:01–DQA1*01:01 showed only weak binding peptides for both heavy- and light chain.

DISCUSSION

In this large study of IMID patients on infliximab therapy, we demonstrated an association between two HLA-DQ2 haplotypes and risk of ADAb formation with consistency across all six diagnoses. Presence of at least one of the HLA-DQ2 haplotypes increased the risk of ADAb formation two to five times, and this association reached the genome-wide significance level ($p < 5 \times 10^{-8}$). An association with two separate haplotypes encoding the DQ2 molecule has, to our knowledge, not been demonstrated previously.

We identified a combination of *HLA-DQA1* and *-DQB1* alleles encoding HLA-DQ2 as the likely primary association with ADAb to infliximab. Associations between alleles in the HLA class II region and ADAb formation have previously been shown in GWAS and retrospective studies, most often reported for DQA1*05 and/or DRB1*03 alleles [4, 5, 7–9]. The apparent inconsistency between earlier data and the present study may be due to less comprehensive HLA typing in prior studies [4, 5, 7, 8], and the strong linkage disequilibrium between the HLA class II genes that needs to be acknowledged in the analyses [15]. Moreover, previous GWAS have assessed risk of ADAb formation across

various biologic agents and have not accounted for that mechanisms of immunogenicity may differ between biologic agents with different molecular compositions [4, 5]. Importantly, the present study has taken into consideration that HLA-DQ molecules are heterodimers consisting of the α chain encoded by *HLA-DQA1*, and the β chain encoded by *HLA-DQB1*, which together form the peptide-binding groove, and thus analysed the risk of ADAb formation for these two loci in combination. Additionally, variation between different ADAb assays could complicate comparability between studies.

Identification of the DRB1*07:01–DQB1*02:02–DQA1*02:01 risk haplotype is a novel finding, whereas DRB1*03:01–DQB1*02:01–DQA1*05:01 has also been suggested to be a risk haplotype in an extended analyses of a prior GWAS [5, 9]. The association between this haplotype, known as the autoimmune haplotype [16], and ADAb formation, may indicate a common vulnerability due to an overactive or unregulated immune system. The strong association between the two HLA-DQ2 haplotypes and ADAb formation was robust across diseases, suggesting that the molecular mechanisms of immunogenicity are not disease specific. Furthermore, the influence of HLA-DQ2 on ADAb formation was independent of other risk factors for ADAb, including use of concomitant immunosuppressive medication [3]. Of note, concomitant immunosuppressive medication was an independent protective factor, suggesting that comedication mitigates the formation of ADAb, also for patients carrying the HLA-DQ2 risk haplotypes.

To further investigate the association between ADAb formation and HLA-DQ2 encoding haplotypes, we performed amino acid analyses. Several associated amino acid positions encoded by *HLA-DQB1*, mainly affecting peptide-binding pocket 4 (β28 and β74) or pocket 7 (β28, β47 and β71), were observed. These two pockets are not reported to be affected by polymorphisms in the *HLA-DQA1* gene [17]. Furthermore, both HLA-DQ2 molecules encoded by the ADAb associated alleles were predicted to strongly bind infliximab peptides for presentation to T cells. Hence, our data suggest a primary role for HLA-DQ in ADAb formation to infliximab. However, we cannot exclude that additional HLA genes contribute to the formation of ADAb, as this likely is a complex trait involving several genetic and environmental factors.

Biological relevance of HLA-DQ2 in the process of ADAb formation was supported by peptide-binding analyses for infliximab. The amino acid sequences within the peptide-binding groove of the HLA molecule affect antigen specificity and are thought to be of particular importance in development of ADAb [6, 18]. Peptide-binding predictions for infliximab showed that the HLA-DQ2 molecules share two strong core binder peptide sequences. The INTVESEDI core-peptide sequence is located near the TNFα binding site on infliximab [19]. According to the published sequences for the TNFi (infliximab, adalimumab, golimumab and certolizumab pegol), the INTVESEDI sequence is specific for infliximab. VYACEVTHQ is, however, common for all TNFi monoclonal antibody light chain constant domains and is not likely to be involved in the generation of specific and clinically relevant ADAb. In contrast, the observed protective haplotype DQB1*05:01–DQA1*01:01 was predicted to lack the potential to strongly bind infliximab peptides.

Major strengths of this study are the use of high-resolution sequence-based genotyping of all classical HLA loci and the large number of patients with IMIDs included. In contrast, prior studies have used HLA imputation and indirect tagging strategies and have included patients on various biologic agents [4, 5, 20]. Sequencing-based HLA genotyping is considered the gold standard as it reduces ambiguity and is not influenced by differences in imputation probabilities for HLA alleles. Importantly, we have taken into consideration the complexity of the multiallelic HLA region and the functional biology of HLA molecules when interpreting the results. All patients received the same drug, ADAb was measured consecutively in all patients, and the retention rate was very high.

Limitations of this study include HLA genotyping performed with G-group resolution, which does not allow differentiation between alleles that share the same DNA sequence (and thus the same amino acid sequence) in the peptide-binding groove. However, we believe that the peptide-binding groove is most essential in ADAb formation. Individual patient groups are small in this study, and these data encourage further replication studies to provide even better risk estimates for ADAb formation in different patient groups.

In conclusion, we found HLA-DQ2 to be a strong risk factor for ADAb formation to infliximab. From

a clinical point of view, the identification of novel biomarkers to identify patients at risk of immunogenicity is important to guide treatment strategies, predict therapeutic efficacy, minimize side-effects and enable personalised medicine. This novel finding provides promise for incorporation of HLA-DQ2 testing in future algorithms to facilitate personalised treatment decisions and may have potential to improve outcomes for the large number of patients treated with infliximab as well as reduce risk of adverse effects such as infusion reactions.

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Conflict of interest statement

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or material support: All authors. *Final approval*: All authors.

Data availability statement

The data underlying this article are available in the article and in its online supplementary material.

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Supporting Information

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