*HLA-DRB1*01:03* in patients with inflammatory bowel disease: a genotype–phenotype association study

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Summary

Background The association between *HLA-DRB1*01:03* and severe ulcerative colitis has long been recognised. However, the recent discovery of an association with neutralising auto-antibodies against IL-10 raises new questions about whether this haplotype contributes to other subphenotypes of inflammatory bowel disease (IBD). We sought to systematically reappraise the contribution of *HLA-DRB1*01:03* across the full spectrum of IBD subphenotypes, including multiple disease-related adverse outcomes.

Methods In this genotype–phenotype association study, we used data from patients with IBD of inferred European ancestry from more than 100 UK hospitals who were recruited into the National Institute for Health and Care Research IBD BioResource or the UK IBD Genetics Consortium cohorts between 2005 and 2025. Associations between *HLA-DRB1*01:03* and IBD phenotypes were examined using logistic or linear regression, and adjusted for sex, smoking, diagnosis, follow-up, genetic principal components, six co-inherited HLA alleles, and other significant associations. Time-to-event analyses were performed using Cox regression models.

Findings 43 762 patients with IBD (21 839 with Crohn's disease and 21 923 with ulcerative colitis or IBD unclassified) were included in our analysis. *HLA-DRB1*01:03* carriage was observed in 2009 (4·6%) patients with IBD and associated with multiple severe outcomes in the adjusted models, including colonic resection in patients with Crohn's disease (odds ratio 1·35 [95% CI 1·07–1·69]), colectomy in patients with ulcerative colitis or IBD unclassified (1·99 [1·63–2·43]), perianal disease in both patients with Crohn's disease (1·65 [1·42–1·92]) and patients with ulcerative colitis or IBD unclassified (1·70 [1·27–2·28]), and advanced therapy use in patients with Crohn's disease (1·33 [1·12–1·58]) and patients with ulcerative colitis or IBD unclassified (2·17 [1·86–2·52]). *HLA-DRB1*01:03* was associated with younger-onset ulcerative colitis or IBD unclassified and older-onset Crohn's disease. *HLA-DRB1*01:03* also associated with earlier development of perianal Crohn's disease (hazard ratio 1·61 [95% CI 1·24–2·07]), earlier need for colonic surgery in patients with Crohn's disease (1·43 [1·13–1·82]), and earlier colectomy in patients with ulcerative colitis or IBD unclassified (1·69 [1·33–2·14]). *HLA-DRB1*01:03* carriers initiated advanced therapy earlier (HR 1·37 [95% CI 1·18–1·59] in patients with Crohn's disease and 1·82 [1·53–2·16] in patients with ulcerative colitis or IBD unclassified) and had a higher risk of advanced therapy failure across IBD phenotypes (HR 1·23 [95% CI 1·02–1·50]).

Interpretation *HLA-DRB1*01:03* emerges as a genetic determinant of severe disease in both patients with Crohn's disease and patients with ulcerative colitis. Although further validation is needed, assessing *HLA-DRB1*01:03* carriage might help identify patients who could benefit from more intensive monitoring or earlier use of advanced therapies, aiming to modify the disease course to which they are genetically predisposed.

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Introduction

Crohn's disease and ulcerative colitis are relapsing–remitting immune-mediated inflammatory disorders, which arise from a complex interplay of genetic and environmental factors.[1] Crohn's disease and ulcerative colitis are the principal forms of inflammatory bowel disease (IBD), with a smaller proportion of patients having an indeterminate form (IBD unclassified). The extent, severity, and response to treatment of inflammation in IBD can vary markedly between patients for reasons that are not well understood. By 2035, the overall global prevalence of IBD is anticipated to reach 1%.[2]

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Research in context

Evidence before this study

We searched MEDLINE, Embase, and Google Scholar for studies published between Jan 1, 1990, and Nov 30, 2025, with no language restrictions, using the following search constraints: ("HLA-DRB1*01:03" OR "HLA-DRB1*01:03" OR "HLA DRB1 01:03" OR "DRB1*01:03" OR "HLA-DRB1") AND ("inflammatory bowel disease" OR "IBD" OR "ulcerative colitis" OR "Crohn's disease" OR "Crohn's disease") AND ("surgery" OR "surgical" OR "colectomy" OR "biologic therapy" OR "biologic*" OR "advanced therapy" OR "therapy" OR "treatment" OR "response" OR "outcome*" OR "perianal" OR "extraintestinal manifestation*" OR "arthritis" OR "uveitis" OR "erythema nodosum" OR "primary sclerosing cholangitis" OR "PSC" OR "orofacial granulomatosis"). This search returned 75 papers. Previous studies have identified *HLA-DRB1*01:03* as a susceptibility factor for both ulcerative colitis and Crohn's disease. Beyond disease susceptibility, several associations have been reported between this HLA allele and some subphenotypes of inflammatory bowel disease (IBD), including disease extent, colectomy in patients with ulcerative colitis, and some extraintestinal manifestations. However, many of these studies were underpowered and none of them adequately addressed potential confounding factors (either genetic or clinical). For example, it remains unclear whether the reported association with colectomy in patients with ulcerative colitis is a true effect or driven by more extensive disease. Likewise, a confounding effect of linkage disequilibrium with other HLA alleles has never been systematically examined. Interest in this allele and its links to IBD have been rekindled with the recent discovery of a strong association between *HLA-DRB1*01:03* and development of neutralising auto-antibodies against the immunomodulatory cytokine IL-10. There is therefore urgent need of a comprehensive evaluation of how *HLA-DRB1*01:03* contributes across the full spectrum of IBD phenotypes and disease outcomes.

Added value of this study

We did a comprehensive analysis of the association between *HLA-DRB1*01:03* and a large panel of IBD subphenotypes in two large and deeply phenotyped UK cohorts (collectively comprising more than 43 000 patients). These cohorts—assembled by the National Institute for Health and Care Research IBD BioResource and the UK IBD Genetics Consortium—reflect a UK-wide collaboration involving over 100 hospitals over 20 years, providing a unique opportunity to assess the role of *HLA-DRB1*01:03* in IBD. Using the power of these cohorts, we not only identify novel associations with clinically relevant disease phenotypes, including perianal complications, surgery in patients with Crohn's disease, and the burden and onset of independent severe clinical outcomes, but also refute some previously reported associations, showing that they result from confounding factors (eg, the apparent association with enteropathic arthritis is actually driven by *HLA-B27*). These results clarify the true phenotypic associations of *HLA-DRB1*01:03* and extend the spectrum of associated clinical phenotypes, highlighting the potential of this allele to identify a subset of patients with a greater chance of developing clinically significant complications.

Implications of all the available evidence

We identify *HLA-DRB1*01:03* as the first comprehensive severity allele that is associated with adverse outcomes across the spectrum of IBD subtypes. In patients with IBD, carriage of this allele identifies a subgroup who could be considered for more intensive monitoring and perhaps earlier use of advanced therapies, aiming to modify the disease course to which they are genetically predisposed.

Numerous genetic factors have been associated with the development of IBD, including polymorphisms in the human leukocyte antigen (HLA) region.[3–5] The HLA locus is a highly polymorphic, gene-dense region on chromosome 6p21.3, spanning 4 Mb.[6,7] Many genes within this region, particularly HLA class I and II genes, encode antigen-presenting receptors that facilitate adaptive immune responses from T cells and B cells. This process is an essential aspect of vertebrate immunity but can erroneously lead to autoreactivity against self-antigens through mechanisms including molecular mimicry.[8] Notably, the most important shared HLA allele for Crohn's disease and ulcerative colitis susceptibility is *HLA-DRB1*01:03*.[3]

A recent study reported that *HLA-DRB1*01:03* might contribute to IBD through induction of neutralising autoantibodies against the immunomodulatory cytokine IL-10.[9] This could additionally explain the reported association between *HLA-DRB1*01:03* and severe ulcerative colitis requiring hospitalisation or colectomy.[10–12] Beyond disease severity in patients with ulcerative colitis, *HLA-DRB1*01:03* has also been linked with some extraintestinal manifestations and age at diagnosis.[12–14] However, it remains unclear whether these associations are independent or influenced by unaccounted for clinical or genetic confounders, such as disease extent or other HLA alleles. The relationship between *HLA-DRB1*01:03* and the full spectrum of clinically relevant subphenotypes in ulcerative colitis or Crohn's disease has not yet been explored.

In this study, we aimed to leverage a uniquely large and deeply phenotyped IBD cohort to delineate the relationship between *HLA-DRB1*01:03* carriage and a broad range of IBD subphenotypes, including multiple disease-related adverse outcomes.

Methods

Study design, phenotype definition, and quality control

This genotype–phenotype association study used data from two existing IBD biobanks into which patients with

IBD from across the UK had been recruited between 2005 and 2025. Most recently, patients were recruited into the UK National Institute for Health and Care Research (NIHR) IBD BioResource (IBDBR; n=38 628; research ethics committee reference number 15/EE/0286),[15] and previously patients were recruited into the UK IBD Genetics Consortium (UKIBDGC; n=17 527; research ethics committee reference numbers 03/5/012, LREC/2002/6/18, GREC/03/0273, YREC/P12/03, 08/H0202/139, 11/SW/0222, 22/02, 05/Q0502/127, 11/YH/0020, 16/YH/0247, 03/5/012, 05/Q1407/274, 09/H0717/4, and 06/Q2104/9).[5,16] Data on population controls were derived from the INTERVAL study, a randomised trial that recruited 50 000 blood donors in England between 2012 and 2014.[17]

Detailed phenotyping was performed on all participants from the two IBD cohorts. Participants in IBDBR were recruited from more than 100 UK hospitals between 2017 and 2024. Clinical phenotype data were collected from participant medical records at study entry (baseline) together with demographic data, including gender, sex assigned at birth, and ethnicity. Participants were also invited to complete a health and lifestyle questionnaire (appendix p 2). Approximately 28 000 participants from the IBDBR cohort were recruited before 2020 and had their phenotype data refreshed in 2023–25, providing updated clinical information, including treatment outcomes. After quality control within the baseline and refreshed datasets, the two datasets were merged (appendix p 2). Following the merging of the datasets, 38 221 patients from the IBDBR cohort were available for study. Patients with ulcerative colitis and IBD unclassified were analysed together owing to their shared clinical characteristics and closely aligned treatment strategies.[18] Details of the phenotypic data collected and their definitions are provided in the appendix (p 2). In instances of discordant information across phenotype sources (eg, diagnosis change from ulcerative colitis to Crohn's disease), inconsistencies were resolved according to a prespecified hierarchy: phenotypes from the more recent refreshment dataset were accorded highest priority, followed by baseline data entry, and subsequently the baseline health and lifestyle questionnaire responses. The UKIBDGC dataset served as an independent validation cohort; details of the phenotypes and data collection for the UKIBDGC cohort are described elsewhere.[12] Briefly, this included core phenotype data on disease type, age of onset, Montreal classification, surgery and smoking history, treatment, and basic demographic data. A phenotype refresh was applied to a subset of participants from the UKIBDGC cohort in 2020, similarly to the IBDBR cohort.

All participants provided written informed consent.

Quality control on genotype data

Participants from the IBDBR and INTERVAL cohorts were genotyped using the Affymetrix Axiom UK Biobank Array (Affymetrix, Santa Clara, CA, USA) and processed together. Detailed variant and sample quality control steps are provided in the appendix (p 3). Only participants genetically inferred to be of European ancestry based on principal component analysis were included in the analysis. IBDBR duplicated samples (kinship ≥0·345) and first-degree relatives (kinship ≥0·177) were identified, and the sample with the lowest missingness was retained for further analyses. Four genetic principal components (accounting for intra-European population stratification) were selected within this subset.

Participants from the UKIBDGC cohort were genotyped in three batches, each one with a different array.[5] Each batch underwent the same quality control steps as the IBDBR cohort. UKIBDGC duplicated samples and first-degree relatives were removed based on the same strategy as in the IBDBR cohort. Samples from participants already included within the IBDBR cohort and their first-degree relatives were excluded from any further analyses as part of the UKIBDGC cohort.

HLA imputation

We used HLA imputation using attribute bagging to impute classical HLA alleles from the major histocompatibility complex (MHC) region.[19] Pretrained, multi-ethnic reference models based on variants from the Affymetrix Axiom UK Biobank Array were applied to the IBDBR and INTERVAL datasets. Genotyped variants that passed quality control were used for the imputation. In total, seven HLA genes including *HLA-A*, *HLA-B*, *HLA-C*, *HLA-DRB1*, *HLA-DQA1*, *HLA-DQB1*, and *HLA-DPB1* were imputed at four-digit resolution. We applied the same pipeline for HLA imputation in the UKIBDGC dataset. Pretrained, multi-ethnic reference models based on variants from the Affymetrix 500K, Affymetrix 6.0 array, and Human Core Exome version 12 array (Affymetrix, Santa Clara, CA, USA) were applied separately.

Statistical analysis

We adopted a three-stage analytical approach to evaluate the associations between *HLA-DRB1*01:03* and each phenotype. *HLA-DRB1*01:03* was included in all models as a binary variable (carriage *vs* non-carriage). Patients were classified as carriers if they had at least one copy of the *HLA-DRB1*01:03* allele and non-carriers if they had zero copies. This approach was chosen because *HLA-DRB1*01:03* is relatively rare in the population; the number of homozygotes (individuals with two copies) was insufficient to support a meaningful additive or dose–response model.

In the primary analysis (stage 1), using data from the IBDBR dataset, we used logistic regression for categorical outcomes and linear regression for continuous outcomes (age at diagnosis). For categorical variables with more than two levels, pairwise comparisons were performed

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See Online for appendix

by modelling each target category against the reference category separately. Phenotypes shared between patients with Crohn's disease and patients with ulcerative colitis or IBD unclassified, including age at diagnosis, hospital admission, use of advanced therapy, perianal disease, and development of extraintestinal manifestations (psoriasis, enteropathic arthritis, ankylosing spondylitis, primary sclerosing cholangitis, erythema nodosum, iritis or uveitis, orofacial granulomatosis, and pyoderma gangrenosum) were analysed within Crohn's disease and ulcerative colitis or IBD unclassified separately, and in a combined analysis of Crohn's disease and ulcerative colitis or IBD unclassified (we hereafter refer to the latter analysis as IBD combined). Disease-specific phenotypes were analysed only within the corresponding disease group (stoma, location, behaviour, colonic surgery, and small bowel surgery in patients with Crohn's disease; extent and colectomy in patients with ulcerative colitis or IBD unclassified). All primary models were adjusted for sex, smoking status at diagnosis (current, never, or ex-smoker), follow-up time (to account for differences in the duration of follow-up between participants), year of diagnosis (to control for temporal changes in clinical management), and disease diagnosis (only applicable for analysis in IBD combined), as well as four genetic principal components to account for population stratification. To minimise confounding by linkage disequilibrium with other HLA alleles, we included six HLA alleles in linkage disequilibrium with *HLA-DRB1*01:03* (R^2>0·01) as covariates (appendix p 15). Missing values in covariates were imputed based on multivariate imputation (appendix p 3) by chained equations implemented in the mice package in R.[20] False discovery rate correction on p values was applied across all subphenotypes tested in each analysis stage (stage 1, 2, and 3) to derive q values, and associations with q<0·05 were considered statistically significant.

In the sensitivity analysis (stage 2), we restricted the analyses to phenotypes that were significant in stage 1 and refitted the models for these phenotypes with further adjustment for the other significant phenotypes as covariates.

For the significant phenotypes identified in stage 2, we validated their associations in the UKIBDGC cohort, with sex, batch, and four genetic principal components as covariates. We then performed a fixed-effect inverse-variance meta-analysis (stage 3) between the two datasets to estimate the effect sizes (including β for age at

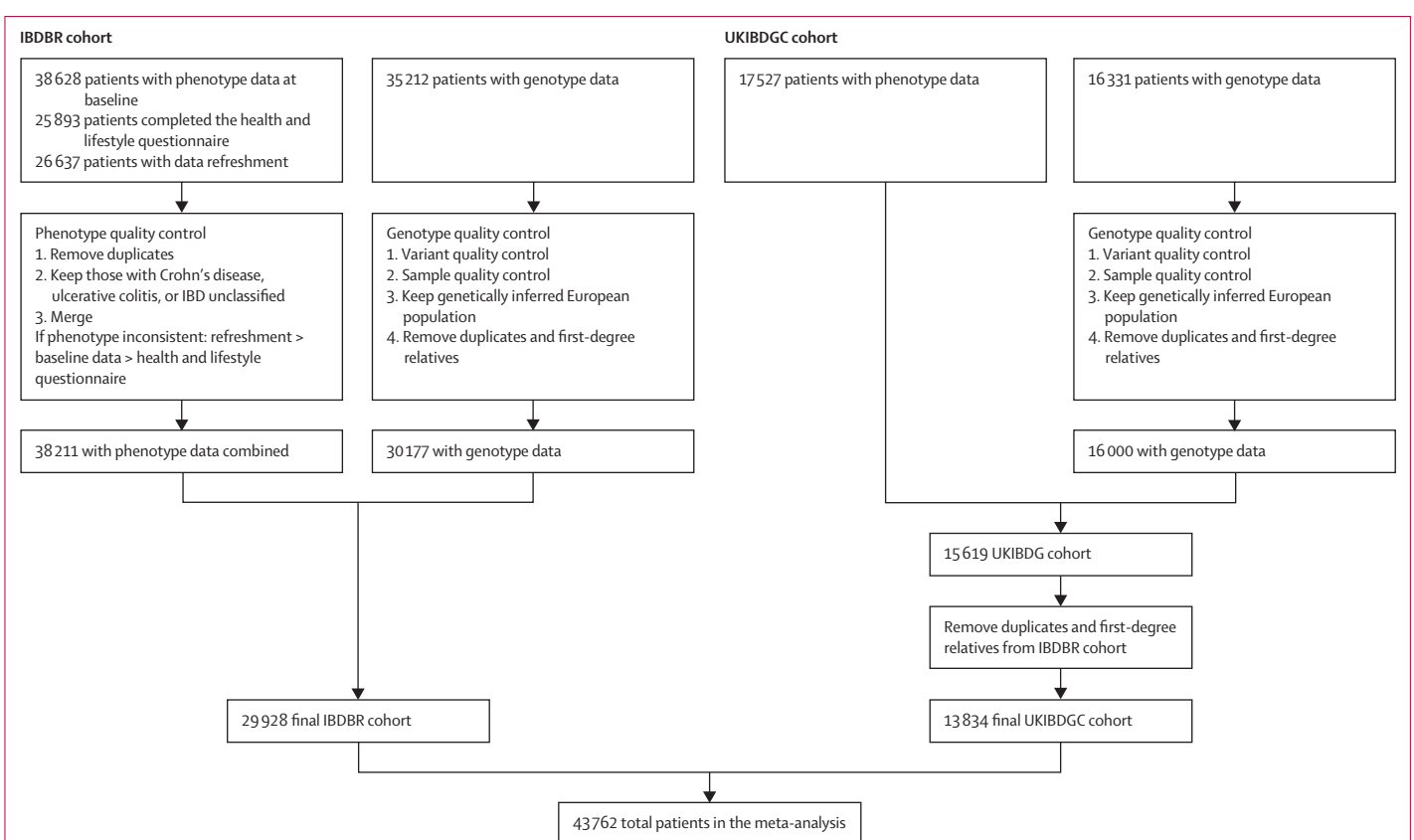

Figure 1: **Quality control flow diagram**
The figure shows the quality control pipeline for both phenotype and genotype data in the IBDBR and UKIBDGC cohorts. IBDBR=Inflammatory Bowel Disease BioResource. UKIBDGC=UK Inflammatory Bowel Disease Genetics Consortium.

diagnosis and odds ratios [ORs] for other phenotypes) and assess heterogeneity based on Cochran's Q test.[21]

For phenotypes that remained significant after multiple test correction in the sensitivity analysis (stage 2), and for which event dates were available, we undertook time-to-event analyses using data from the IBDBR dataset. Hazard ratios (HRs) were estimated using Cox proportional hazards models implemented in the survival package (version 3.8-6) in R.[22,23] The start of follow-up was the date of diagnosis and the end of follow-up was the date of the event or date of last known follow-up (as per data entry). For the analysis of time to first advanced therapy, we included only patients with Crohn's disease diagnosed in or after 2002 and patients diagnosed with ulcerative colitis or IBD unclassified in or after 2008, corresponding to the period when advanced therapy first became available for these diseases in the UK. The same covariate set as in the primary analysis was used. Nominal p value threshold ($p<0·05$) was used to assess statistical significance. The proportional hazards assumption was examined for all Cox models using the Grambsch–Therneau test based on Schoenfeld residuals. Survival probabilities were estimated using the Kaplan–Meier method and presented as survival curves.

To assess the effect of *HLA-DRB1*01:03* on the risk of advanced therapy discontinuation, we did time-to-event analyses in the IBDBR cohort. Treatment discontinuation due to primary non-response or loss of response was defined as the event, and patients who remained on therapy were censored at their last clinical review. The same set of covariates used in the primary analysis was applied. When analysing advanced therapies overall, only the first advanced therapy was considered. For analyses stratified by treatment class (only drugs with enough samples were considered), the first advanced therapy within each class was included. To minimise bias related to limited drug availability, analyses were restricted to patients who initiated the relevant therapy from Jan 1, 2015, onwards, when the first non-anti-TNF advanced therapy, vedolizumab, became available in the UK.

The association between *HLA-DRB1*01:03* and disease severity was assessed using ordinal logistic regression, with patients ordered by the number of severe clinical outcomes. Proportional ORs and p values were estimated using the ordinal package (version 2025.12-29) in R.[24] All analyses were conducted in R version 4.3.1.

Role of the funding source

The funders of the study had no role in study design, data analysis, data collection, data interpretation, or writing of the report.

Results

After quality control, 29928 patients of European ancestry with IBD from the IBDBR cohort were available for analysis (figure 1). Of these, 14958 had Crohn's disease and 14970 had ulcerative colitis or IBD unclassified. Additional details for each IBD subtype are in the appendix (pp 4–5). The UKIBDGC cohort comprised 13834 patients (6881 with Crohn's disease and 6953 with ulcerative colitis or IBD unclassified; appendix pp 4–5). In total, 43762 patients with IBD (21839 with Crohn's disease and 21923 with ulcerative colitis or IBD unclassified) were included in this study. The carriage rate of *HLA-DRB1*01:03* was 4·6% (2009 of 43762) among all patients (appendix p 6).

In the primary analysis of the IBDBR cohort, we identified 12 phenotypes that were significantly ($q<0·05$) associated with *HLA-DRB1*01:03* (figure 2 [stage 1]; appendix p 7). Missing covariate imputation did not bias the result (appendix p 16). Among these phenotypes, eight remained significant after conditioning on each other (Crohn's disease location, age at diagnosis, advanced therapy usage, perianal disease, Crohn's disease colonic surgery, ulcerative colitis colectomy, Crohn's disease upper gastrointestinal involvement, and hospital admission; figure 2 [stage 2]), suggesting that they represent independent associations (appendix p 8). We observed no significant ($p>0·05$) effect size heterogeneity between the IBDBR and UKIBDGC cohorts. All associations were stronger after meta-analysis, other than age at diagnosis (figure 2 [stage 3]; table; appendix p 9). The effects of covariates on disease outcomes are summarised in the appendix (p 17).

In the meta-analysis, we observed a significant association between *HLA-DRB1*01:03* and location in Crohn's disease (figure 2; table), with highest carriage rate (7·4%) in patients with colonic Crohn's disease (appendix p 18). *HLA-DRB1*01:03* was also associated with a lower risk of upper gastrointestinal involvement (OR 0·63 [95% CI 0·46–0·87]). No significant associations were detected between *HLA-DRB1*01:03* and complicated Crohn's disease behaviour (B2 stricturing or B3 penetrating). Regarding age at diagnosis, *HLA-DRB1*01:03* showed heterogeneity of effect, being associated with younger onset ulcerative colitis or IBD unclassified and older onset Crohn's disease (figure 2; table).

We detected a previously unreported association between *HLA-DRB1*01:03* and the development of perianal disease in both patients with Crohn's disease (OR 1·65 [95% CI 1·42–1·92]) and patients with ulcerative colitis or IBD unclassified (1·70 [1·27–2·28]; figure 2; table). This association was detected in both discovery and replication cohorts in patients with Crohn's disease, but could only be assessed in patients with ulcerative colitis in the IBDBR cohort as perianal disease data were not collected in patients with ulcerative colitis in the UKIBDGC cohort. Although perianal involvement in patients with ulcerative colitis or IBD unclassified is unusual, it is a reported feature, affecting up to 5% of patients with ulcerative colitis (734 [4·9%] of 14970 in this study) and is a known feature of patients with defects in

Figure 2: **The effects of *HLA-DRB1*01:03* on IBD subphenotypes at each analysis stage**

The figure shows the estimates and 95% CIs for associations between *HLA-DRB1*01:03* and subphenotypes of Crohn's disease and ulcerative colitis or IBD unclassified (β for age at diagnosis and ORs for all other phenotypes). The left panel shows results from the primary analysis in the Inflammatory Bowel Disease BioResource cohort (stage 1), the middle panel shows results from sensitivity analysis in the Inflammatory Bowel Disease BioResource cohort (stage 2), and the right panel shows results from meta-analysis between the Inflammatory Bowel Disease BioResource and UK Inflammatory Bowel Disease Genetics Consortium cohorts (stage 3). Stage 1 models were adjusted by sex, smoking status at diagnosis, follow-up, year of diagnosis, disease diagnosis (when Crohn's disease and ulcerative colitis and IBD unclassified were combined), genetic principal components, six HLA alleles in linkage disequilibrium with *HLA-DRB1*01:03*: *HLA-C*01:02*, *HLA-B*27:05*, *HLA-B*35:01*, *HLA-DQA1*05:05*, and *HLA-DQB1*05:01*. Additionally, stage 2 models also included the other significant phenotypes per disease subtype (Crohn's disease, IBD combined, or ulcerative colitis or IBD unclassified) as covariates. B1=inflammatory. B2=stricturing. B3=penetrating. E1=proctitis. E2=left-sided. E3=extensive. IBD=inflammatory bowel disease. L1=ileal. L2=colonic. L3=ileocolonic.

IL-10 signalling.[25,26] Notably, we found that previously reported associations between HLA alleles and perianal Crohn's disease[27] were confounded by *HLA-DRB1*01:03* (appendix p 10).

Contrary to reports from previous smaller studies, we found no significant associations between *HLA-DRB1*01:03* and extraintestinal manifestations. Indeed, we showed that previously reported associations with extraintestinal manifestations (appendix p 11), including peripheral arthritis and ocular extraintestinal manifestations, were actually attributable to linkage disequilibrium with other HLA alleles, particularly *HLA-B*27:05*, the most prevalent allele within the *HLA-B*27* group (appendix p 17).

In terms of Crohn's disease outcomes, we identified an association between *HLA-DRB1*01:03* and need for

colonic resection (OR 1·35 [95% CI 1·07–1·69]; figure 2; table). Additionally, in patients with Crohn's disease with perianal disease, *HLA-DRB1*01:03* carriage was associated with increased risk of refractory perianal disease (defined as patients requiring defunctioning ileostomy or proctectomy; OR 1·61 [95% CI 1·03–2·53]). Small bowel surgery or need for stoma (any indication) showed associations in the primary analysis, but these were not significant in sensitivity analyses after conditioning on other significant subtypes (especially disease location; figure 2; appendix p 8). No significant association was observed for hospitalisation for Crohn's disease.

In patients with ulcerative colitis or IBD unclassified, *HLA-DRB1*01:03* was associated with both hospitalisation (OR 1·96 [95% CI 1·67–2·30]) and colectomy (1·99 [1·63–2·43]; figure 2; table), as has been reported previously.[11] Notably, these associations remained significant after correcting for other related phenotypes, including disease extent, highlighting the independent contribution of *HLA-DRB1*01:03* to the development of these outcomes, which has not been previously shown. Indeed, the association with disease extent became non-significant after conditioning on other significant subtypes (figure 2; appendix p 8). Furthermore, we observed that *HLA-DRB1*01:03* was associated with an increased need for advanced therapy in both patients with Crohn's disease (OR 1·33 [95% CI 1·12–1·58]) and patients with ulcerative colitis or IBD unclassified (2·17 [1·86–2·52]; figure 2; table).

In the time-to-event analyses, *HLA-DRB1*01:03* was associated with shorter time from Crohn's disease diagnosis to the documented development of perianal disease (HR 1·61 [95% CI 1·24–2·07]; figure 3; appendix p 12). This was the only analysis for which the proportional hazards assumption was violated (p=0·024), mainly due to patients with very long follow-up times (>30 years). After censoring follow-up at 30 years, no violation was observed (p=0·076), and the effect size remained broadly unchanged (HR 1·66 [95% CI 1·28–2·15]). A similar finding was observed in patients with ulcerative colitis or IBD unclassified, with *HLA-DRB1*01:03* associated with a shorter time to developing perianal disease, but this was not significant, most likely due to the smaller sample size (1·68 [0·87–3·25]; 103 events with date). However, the effect sizes showed no evidence of heterogeneity between ulcerative colitis or IBD unclassified and Crohn's disease (p=0·91). *HLA-DRB1*01:03* was also associated with shorter time to colonic surgery in patients with Crohn's disease (HR 1·43 [95% CI 1·13–1·82]) and a shorter time to colectomy in patients with ulcerative colitis or IBD unclassified (1·69 [1·33–2·14]).

In addition to having a greater overall need for advanced therapy, patients carrying *HLA-DRB1*01:03* had a shorter time from diagnosis to commencing their first advanced therapy (figure 3). This effect was more pronounced in patients with ulcerative colitis or IBD unclassified than in patients with Crohn's disease (HR 1·82 [95% CI 1·53–2·16] *vs* 1·37 [1·18–1·59]; heterogeneity p=0·015).

We next considered whether *HLA-DRB1*01:03* carriage might affect the response to advanced therapies, specifically the need to discontinue treatment due to primary non-response or loss of response. *HLA-DRB1*01:03* carriers were more likely to discontinue their first advanced therapy than non-carriers (HR 1·23 [95% CI 1·02–1·50]; figure 4A), which was especially true for first anti-TNF (1·27 [1·03–1·55]) and first JAK inhibitors (1·90 [1·19–3·55]; figure 4B), even though the JAK inhibitor cohort was smaller and thus less powered. These associations were consistently observed in both patients with Crohn's disease and patients with ulcerative colitis or IBD unclassified but there was no detectable association between *HLA-DRB1*01:03* and discontinuation of anti-integrin or anti-IL-12/23 therapies (appendix pp 13, 20).

Finally, we assessed whether *HLA-DRB1*01:03* carriage might influence the cumulative development of adverse clinical outcomes. We defined strata based on the number of significantly associated adverse outcomes in the sensitivity analysis, including the need for advanced therapy, hospital admission (only for ulcerative colitis and IBD unclassified), colectomy, and perianal disease.

	Effect* (95% CI)	p value†
Crohn's disease		
Location: L1 *vs* L2	0·53 (0·44 to 0·63)	$4·10 \times 10^{-12}$
Location: L3 *vs* L2	0·59 (0·50 to 0·70)	$1·89 \times 10^{-9}$
Age at diagnosis	1·96 (0·91 to 3·01)	$2·46 \times 10^{-4}$
Advanced therapy: yes *vs* no	1·33 (1·12 to 1·58)	$9·97 \times 10^{-4}$
Perianal disease: yes *vs* no	1·65 (1·42 to 1·92)	$6·75 \times 10^{-11}$
Colonic surgery: yes *vs* no	1·35 (1·07 to 1·69)	$9·99 \times 10^{-3}$
Upper gastrointestinal involvement: yes *vs* no	0·63 (0·46 to 0·87)	$4·71 \times 10^{-3}$
Ulcerative colitis or IBD unclassified		
Age at diagnosis	−2·40 (−3·4 to −1·36)	$5·82 \times 10^{-6}$
Advanced therapy: yes *vs* no	2·17 (1·86 to 2·52)	$6·43 \times 10^{-24}$
Colectomy: yes *vs* no	1·99 (1·63 to 2·43)	$2·28 \times 10^{-11}$
Hospital admission: yes *vs* no	1·96 (1·67 to 2·30)	$1·70 \times 10^{-15}$
Perianal disease	1·70 (1·27 to 2·28)	$8·84 \times 10^{-4}$

Only significant phenotypes identified in the IBDBR cohort (stage 2) were considered. IBD=inflammatory bowel disease. IBDBR=Inflammatory Bowel Disease BioResource. L1=ileal. L2=colonic. L3=ileocolonic. UKIBDGC=UK Inflammatory Bowel Disease Genetics Consortium. *β for age at diagnosis (linear regression), odds ratio for all other phenotypes (logistic regression). Effect sizes from IBDBR were adjusted by sex, smoking status at diagnosis, follow-up, year of diagnosis, disease diagnosis (when Crohn's disease and ulcerative colitis and IBD unclassified were combined), genetic principal components, six HLA alleles in linkage disequilibrium with *HLA-DRB1*01:03*: *HLA-C*01:02*, *HLA-B*27:05*, *HLA-B*35:01*, *HLA-DQA1*05:05*, and *HLA-DQB1*05:01*; effect sizes from UKIBDGC were adjusted by sex, batch and genetic principal components. †Meta-analysis p value; two-sided test; no significant effect-size heterogeneity (p_{het}>0·05) was observed for any of the phenotypes.

Table: **Meta-analysis between the IBDBR and UKIBDGC cohorts (stage 3)**

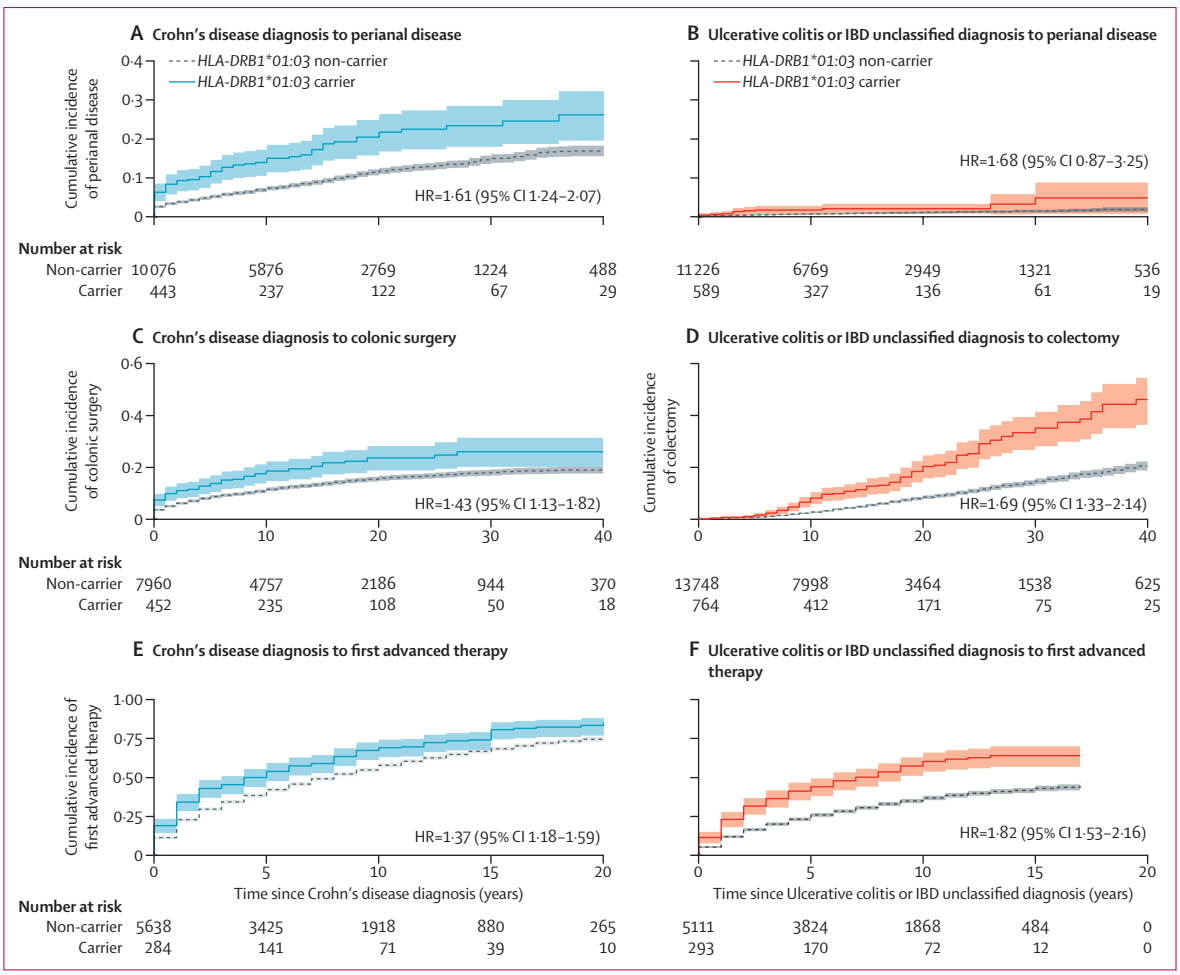

***Figure 3*: Time-to-event analyses**

Time-to-event analyses from diagnosis of IBD until the diagnosis of perianal disease in patients with Crohn's disease (A) or ulcerative colitis or IBD unclassified (B). Time-to-event analyses from diagnosis of IBD until colonic surgery in patients with Crohn's disease (C) or to colectomy in patients with ulcerative colitis or IBD unclassified (D). Time-to-event analyses from diagnosis of IBD until first advanced therapy in patients with Crohn's disease (E) or ulcerative colitis or IBD unclassified (F). The models were adjusted by sex, smoking status at diagnosis, follow-up, year of diagnosis, disease diagnosis (when Crohn's disease and ulcerative colitis or IBD unclassified were combined), genetic principal components, six HLA alleles in linkage disequilibrium with *HLA-DRB1*01:03*: *HLA-C*01:02*, *HLA-B*27:05*, *HLA-B*35:01*, *HLA-DQA1*05:05*, and *HLA-DQB1*05:01*. Data shown are from patients from the IBD BioResource cohort. HR=hazard ratio. IBD=inflammatory bowel disease.

Patients were categorised into five groups according to whether they had none, one, two, three, or four of these outcomes. Consistent with the concordant direction of effect observed across individual outcomes, a significant effect of *HLA-DRB1*01:03* was detected on the number of adverse outcomes in both patients with colonic Crohn's disease (OR 2·37 [95% CI 1·90–2·96]) and patients with ulcerative colitis or IBD unclassified (2·65 [2·32–3·02]; appendix p 14). A modest association was observed in patients with ileal Crohn's disease (1·41 [1·05–1·89]). The carriage rate of *HLA-DRB1*01:03* in patients with ulcerative colitis or IBD unclassified with all four outcomes was 11 [19·6%] of 56, compared with only 183 [2·9%] of 6268 in patients without a single severe outcome (figure 5). When restricting an association analysis to patients without any adverse outcomes, we still observed a significant difference in carriage rates between patients with IBD and population controls ($p<0·001$ for all subtypes; appendix p 21), implying that the previously described association between *HLA-DRB1*01:03* and IBD susceptibility is not completely attributable to disease severity. This pattern remained similar when restricting the analysis to patients with at least 10 years of follow-up (appendix p 22).

Discussion

To our knowledge, this is the largest genotype–phenotype study to date in patients with IBD, comprising 43762 patients. Leveraging the power of this cohort, we explored the contribution of *HLA-DRB1*01:03* to clinically relevant subphenotypes of IBD. We were able to extend, clarify, or refute previously reported associations,

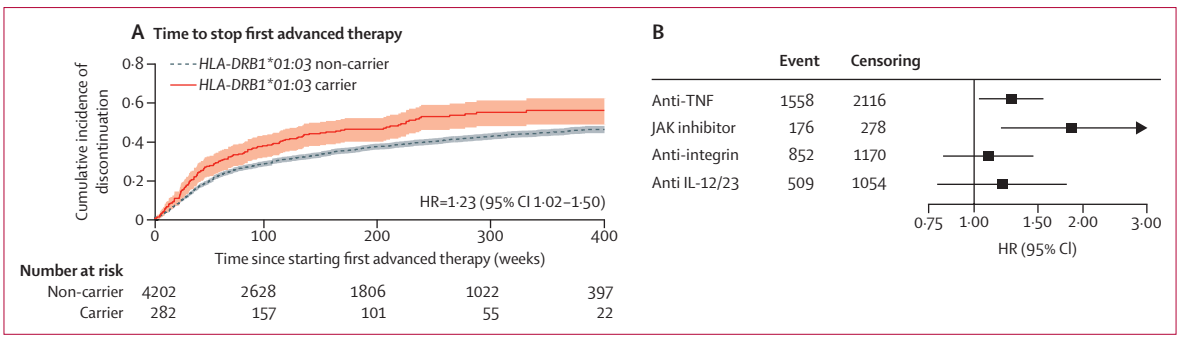

Figure 4: **Effect of *HLA-DRB1*01:03* on advanced therapy discontinuation**
(A) Time-to-event analysis from initiation of first advanced therapy until its discontinuation due inadequate response across all drug classes. (B) Risk of needing to discontinue the first advanced therapy stratified by drug class. The models were adjusted by sex, smoking status at diagnosis, follow-up, year of diagnosis, disease diagnosis (when Crohn's disease and ulcerative colitis or IBD unclassified were combined), genetic principal components, six HLA alleles in linkage disequilibrium with HLA-DRB1*01:03: *HLA-C*01:02*, *HLA-B*27:05*, *HLA-B*35:01*, *HLA-DQA1*05:05*, and *HLA-DQB1*05:01*. Data shown are from patients from the IBD BioResource cohort. IBD=inflammatory bowel disease. HR=hazard ratio.

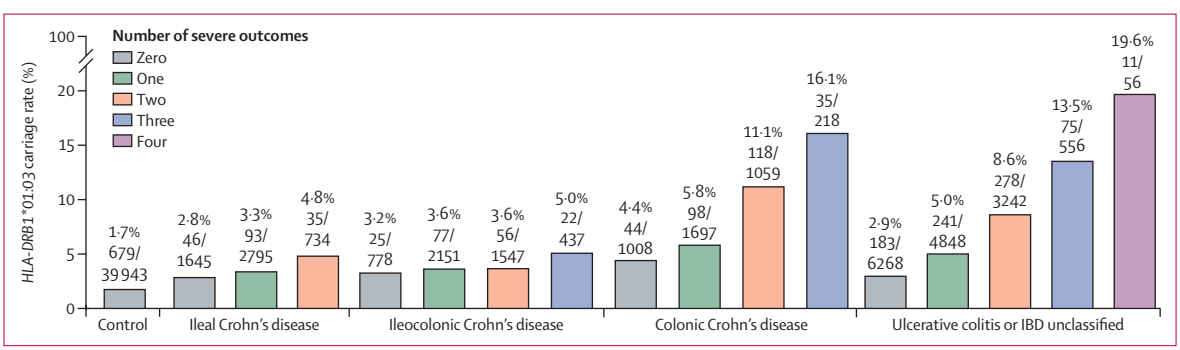

Figure 5: **Effect of *HLA-DRB1*01:03* on cumulative severe outcomes in IBD**
Comparison of *HLA-DRB1*01:03* carriage between patients with different numbers of severe outcomes. In patients with Crohn's disease, the severe outcomes were requirement for advanced therapy, requirement for colonic surgery, and perianal disease. In patients with ulcerative colitis or IBD unclassified, the severe outcomes were requirement for advanced therapy, requirement for colectomy, perianal disease, and hospitalisation. Data shown are patients from the IBD BioResource cohort. Population controls are from the INTERVAL cohort. IBD=inflammatory bowel disease.

showing that *HLA-DRB1*01:03* is a bona fide severity allele associated with more aggressive disease in both Crohn's disease and ulcerative colitis. The clinical phenotype of *HLA-DRB1*01:03* carriers was characterised by a greater burden of adverse outcomes, including perianal disease, need for surgery, need for advanced therapy, and hospitalisation. Moreover, these individuals were less likely to respond to, or have sustained remission from, anti-TNF and JAK inhibitor treatments, necessitating their discontinuation.

*HLA-DRB1*01:03* is a well-established susceptibility allele for both Crohn's disease and ulcerative colitis, which has recently been linked to the development of anti-IL-10 auto-antibodies.[9] Disrupting IL-10 signalling, for example by damaging missense mutations in *IL10* or its receptor, is known to cause severe, early-onset IBD with perianal involvement.[28] This pathogenic mechanism could potentially explain the previously reported need for surgery and hospitalisation in patients with ulcerative colitis who carry *HLA-DRB1*01:03*.[11] Our study both extends and clarifies our understanding of the association between *HLA-DRB1*01:03* and clinically important outcomes in Crohn's disease and ulcerative colitis or IBD unclassified, and highlights the relevance of this allele to disease severity and trajectory.

Notably, this is the first study to show an association between *HLA-DRB1*01:03* and perianal Crohn's disease (which affects approximately 25% of patients with Crohn's disease), as well as perianal disease in ulcerative colitis, which is a much rarer but recognised complication that is also a feature of IL-10 disruption.[28] This is an important discovery because perianal disease is often difficult to treat, carries a high morbidity, and has previously been identified as a priority area for IBD research.[29] In clinical practice, *HLA-DRB1*01:03* carriers could receive personalised education regarding perianal disease risk and the importance of early symptom reporting to allow proactive treatment escalation. Strikingly, our data also show that previously reported associations between perianal Crohn's disease and the HLA region are attributable to linkage disequilibrium with *HLA-DRB1*01:03*,[27] rather than representing independent genetic effects. Conversely, our data show that the previously reported associations between *HLA-DRB1*01:03* and extraintestinal manifestations are actually due to linkage disequilibrium with other HLA alleles, especially *HLA-B*27:05*.[13,14] These findings

underscore the importance of careful fine-mapping within the MHC region to disentangle true causal signals from correlated genetic alleles.

Similar to the potentially confounding effect of linkage disequilibrium between genetic variants, any correlation between clinical phenotypes could also result in a false discovery in association studies. For example, we show that the previously reported association between *HLA-DRB1*01:03* and disease extent in patients with ulcerative colitis was not significant after conditioning on other phenotypes (colectomy and hospitalisation), perhaps reflecting ascertainment bias in previous smaller cohorts. However, the association with colectomy in patients with ulcerative colitis remained significant after correcting for other phenotypes, illustrating that this is an independent effect. Notably, our study extended this observation, showing a novel association with the need for colonic surgery in patients with Crohn's disease. This association appeared to be specific to colonic disease, with no equivalent association observed for small bowel surgery, which is clinically plausible given that small bowel surgery is often performed for indications other than treatment-refractory severe disease, including fibrostenotic Crohn's disease.[30]

Other than surgery, *HLA-DRB1*01:03* carriers more frequently required advanced therapies, including biologics, and (ulcerative colitis-related) hospitalisation, which have been used as indicators of disease severity previously. Moreover, we show that *HLA-DRB1*01:03* is associated with more frequent non-response to, or loss of response to, advanced therapy, particularly anti-TNF and JAK inhibitors, suggesting that carriers of this allele represent a particularly difficult-to-treat subgroup.

Previous studies have shown little overlap between genetic contributions to disease susceptibility and disease progression across multiple diseases,[31–33] but recent evidence suggests that the genetic burden of IBD susceptibility might be associated with disease severity, especially in patients with ulcerative colitis.[34] Our findings suggest that *HLA-DRB1*01:03* exerts independent effects on both IBD susceptibility and disease severity, and further support a role for genetics in shaping the clinical course of IBD. This underscores the need for large-scale genome-wide association studies to identify additional genetic determinants of disease severity, and to characterise their interplay with established IBD susceptibility loci.

Our study had several limitations. Due to data availability, our analyses were restricted to patients with IBD who were of European ancestry. Recent studies have reported higher colectomy rates in ulcerative colitis and higher incidence of perianal Crohn's disease in south Asian populations compared with individuals of European descent.[35] Because *HLA-DRB1*01:03* frequency varies across populations, further studies will be required to evaluate its contribution in non-European populations. Another limitation is that HLA alleles were inferred by imputation rather than directly typed. Misclassification is therefore possible, although current imputation methods have been shown to achieve high accuracy for relatively common alleles. Missing covariates were also imputed, although the effect sizes remained consistent before and after imputation, suggesting that this did not bias the primary results. Additionally, the use of structured data limits our ability to expand these analyses beyond the phenotype fields collected within each cohort, although the use of data collection forms that were rigorously developed and validated by expert IBD clinicians should ensure that the most relevant characteristics were captured. Changes in IBD management over time—from a traditional step-up approach to a top-down strategy of early use of advanced therapies—could have affected the results, but all models were adjusted for year of diagnosis to account for changes in treatment patterns. For the advanced therapy discontinuation analysis, only patients initiating treatment from 2015 onwards were included to capture the modern era of biosimilars and newer biologic classes, although it remains feasible that treatment discontinuation could reflect differences in disease severity between drug classes. Notably, the JAK inhibitor cohort was less well powered than some of the other cohorts, which should be considered when interpreting the results, even though the direction and magnitude of effect were consistent with the difficult-to-treat phenotype observed with other drug classes in *HLA-DRB1*01:03* carriers. Finally, although testing for *HLA-DRB1*01:03* could have potential clinical utility, further validation work is required before pharmacogenetic testing for this allele can enter clinical practice, specifically relating to cost-effectiveness, predictive performance, and modelling of the additional burden on genetic laboratories.

In summary, using a deeply phenotyped cohort of more than 43 000 patients with IBD, we show that *HLA-DRB1*01:03* is a bona fide severity allele and a genetic determinant of more aggressive disease in both Crohn's disease and ulcerative colitis. These analyses reveal independent contributions to multiple adverse clinical outcomes, including perianal disease, IBD course, need for major surgery, and requirement for advanced therapy. A key next step will be to establish whether *HLA-DRB1*01:03* carrier status could be used—alone or in combination with other parameters—to help guide treatment decisions in IBD, for example in identifying patients who might benefit from early advanced therapy use. Moreover, its association with anti-IL-10 antibodies raises the possibility that B-cell-directed therapies could be effective in treatment-refractory *HLA-DRB1*01:03* carriers.

Contributors

QZ: conceptualisation, formal analysis, visualisation, methodology, writing the original draft, review, and editing. ES, MTS, BZ, CR, and NJW: conceptualisation, methodology, writing the original draft, review, and editing. JC: resources, review, and editing. OEG: formal analysis. LK: resources and data curation. LP: resources and project administration. CAA and TA: conceptualisation, methodology, funding acquisition, and supervision. HU: resources and conceptualisation.

MP: conceptualisation, methodology, funding acquisition, supervision, review, and editing. NAK: resources and supervision. LF and JCL: conceptualisation, methodology, writing the original draft, review and editing, and supervision. CB, RL, SM, HR, HT, RM, MeT, PR, BH, NMN, FM, MaTaylor, MG, OT, SK, SVH, SS, AH, CWL, TR, and CAL: resources. QZ and LF accessed and verified the data. All authors had access to the final study data, reviewed and approved the final report, take full responsibility for the accuracy of the data and the statistical analysis, and agreed with the decision to submit for publication. The corresponding author had final responsibility for the decision to submit for publication.

Declaration of interests

AH received consulting and honoraria fees from AbbVie, Bristol Myers Squibb, Alfasigma, AstraZeneca, Johnson & Johnson, Pfizer, Takeda, Celltrion, Roche, and Eli Lilly; is a governing board member of European Crohn's and Colitis Organisation; and is a research committee member for Crohn's and Colitis UK. BH has received grants or contracts from the National Institute for Health and Care Research (NIHR). BZ has received honoraria fees from Takeda; support to attend meetings from Alfasigma, Lilly, AbbVie, and Falk Pharma; and fees from AstraZeneca. CAA has received consulting fees from BridgeBio and Genomics; honoraria from GSK; support to attend meetings from Wellcome Trust and GeneMappers; and is a director of Anderson Genomics Consultancy. CAL has received grants or contracts from Janssen, Takeda, AbbVie, AstraZeneca, Eli Lilly, Orion, Pfizer, Roche, Sanofi Aventis, UCB, Biogen, Genentech, Bristol Myers Squibb, GSK, Merck Sharp and Dohme, Medical Research Council, Helmsley Charitable Trust, Wellcome Trust, Crohn's & Colitis UK, NIHR Newcastle Biomedical Research Centre, EU Innovative Medicines Initiative, and Open Targets and European Bioinformatics Institute; consulting fees from Janssen, Bristol Myers Squibb, MSD, Takeda, and Polaroid Therapeutics; support for attending meetings or travel from Tillotts Pharma UK, Janssen, British Society of Gastroenterology, International Organisation of IBD, United European Gastroenterology, and the European Crohn's and Colitis Organisation; participation on a data safety monitoring board or advisory board for Mitochondrial Anti-oxidant therapy to Resolve Inflammation in Ulcerative Colitis; was secretary for the British Society of Gastroenterology; and steering committee and board member for IBD UK. CWL has received consulting fees from AbbVie, Takeda, Pfizer, Janssen, Merck, Gilead, Alfasigma, GSK, Eli Lilly, Novartis, Celltrion, Amgen, Samsung Bioepis, Fresnius Kabi, and Tillotts; and honoraria from AbbVie, Takeda, Pfizer, Janssen, Merck, Gilead, Alfasigma, GSK, Eli Lilly, Novartis, Celltrion, Amgen, Samsung Bioepis, Fresnius Kabi, and Tillotts. CR has received grants or contracts from OPEN-Targets, Nova Pharmaceuticals, and La Car MDx; and support for attending meetings from Eli Lilly. ES has received honoraria from Takeda, Lilly, and Dr Falk; and support for attending meetings from Takeda, Lilly, and Dr Falk. HU has received support from the Leona M and Harry B Helmsley Charitable Trust, Medical Research Council CoRE Exposome Immunology, and Oxford Biomedical Research Centre; grants from Johnson & Johnson and Eli Lilly; and has a patent on HLA diagnostics in IBD. JC has served as a paid speaker for Lilly; has received travel grants from Johnson & Johnson and Takeda; and has served as an advisory board member for AbbVie. JCL has received grants or contracts from Kenneth Rainin Foundation Research Grant, Medical Research Council/Merck Sharp & Dohme Alliance Research Grant, and Lifearc idea-to-innovation research grant; has received consulting fees from Johnson & Johnson, Enhanced Genomics, Pasithea, and Isomorphic Labs; honoraria from Johnson & Johnson and AbbVie; and has patents planned, issued, or pending (GB2304900.0: Methods of Treatment of Inflammatory Diseases). MP has received grants from Helmsley Trust, AstraZeneca, and Crohn's & Colitis UK. MTS has received support for attending meetings from Takeda; and participation on a data safety monitoring board or advisory board for Teva and Dr Falk Pharma. NAK has received grants from Pharmacosmos; consulting fees from Johnson & Johnson, Bristol Myers Squibb, Falk, AbbVie, Sandoz, Falk, and Pharmacosmos; honoraria from Johnson & Johnson, AbbVie, Tillotts, and Pharmacosmos; support for attending meetings from Johnson & Johnson, AbbVie, and Lilly; and was Chair of British Society of Gastroenterology IBD Clinical Research Group until November, 2025. NMN has received honoraria from AbbVie, Bristol Myers Squibb, Celltrion, Ferring, Johnson & Johnson, Lilly, Pfizer, Pharmacosmos, and Takeda; support for attending meetings from Celltrion, Dr Falk, Johnson & Johnson, Pharmacosmos, and Tillotts; and participation on a data safety monitoring board or advisory board for AbbVie, Bristol Myers Squibb, Pfizer, and Takeda. NJW has received support from the NIHR through an Academic Clinical Fellowship (August, 2021, to September, 2023); and support to attend educational events from the British Society of Gastroenterology, Takeda Pharmaceuticals, Ferring Pharmaceuticals, and the Falk Foundation. OEG had stock options in Novo Nordisk and Vertex Pharmaceuticals during the past 36 months. RL has received a grant from Crohn's & Colitis UK (project grant FA2025–8); and has received conference attendance support from Ferring pharmaceuticals, Tillotts Pharma UK, and Dr Falk Pharma. RM has received honoraria from Dr Falk; and support for attending meetings from Dr Falk, Alphasigma, and Tillotts. SS has received grants from AbbVie, Johnson & Johnson, and Olympus; consulting fees from Eli Lilly, Johnson & Johnson, and Celltrion; honoraria from Eli Lilly, AbbVie, Celltrion, Johnson & Johnson, and Takeda; and support for attending meetings from Eli Lilly, Celltrion, and AbbVie. TA has received grants from MAST Group, Nova Laboratories, and LaCAR MDx (Belgium); consulting fees from Amgen, Eli Lilly, Janssen, and Celltrion; honoraria from AbbVie, Takeda, Janssen, and Eli Lilly; and support for attending meetings from Tillotts and Lilly. TR has received grants from AbbVie and Takeda; consulting fees from AbbVie, AstraZeneca, Boehringer-Ingelheim, Bristol Myers Squibb, Domain Therapeutics, Eli Lilly, Ferring, Gilead, GSK, Heptares, Janssen, MSD, Novartis, Pfizer, Roche, Scientia, Takeda, and UCB; and is a member of United European Gastroenterology Society and European Crohn's and Colitis Organisation. All other authors declare no competing interests.

Data sharing

Genotype data from UKIBDGC have been deposited in the European Genome-phenome Archive (https://ega-archive.org), which is hosted by the European Bioinformatics Institute and the Centre for Genomic Regulation, and are available under accessions EGAD00000000005, EGAS00000000084, and EGAS00001000924. These data can be accessed by application to, and following approval by, the Sanger Data Access Committee. Genotype and phenotype data from IBDBR are available via the NIHR BioResource (https://www.ibdbioresource.nihr.ac.uk/), subject to approval of a research proposal by the NIHR BioResource Data Access Committee and the completion of a signed data access agreement.

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