Journal of Inflammation Research

Dovepress
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REVIEW

Identifying Genetic Factors Influencing the Development of Anti-Drug Antibodies in Inflammatory Bowel Disease: A Scoping Review

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Abstract: Biologic therapies such as infliximab and adalimumab have transformed the management of inflammatory bowel disease. However, many patients experience primary or secondary loss of response, often due to the development of anti-drug antibodies. The cause of anti-drug antibody formation is thought to be influenced by genetic variations, with human leukocyte antigen alleles—particularly HLA-DQA1*05—emerging as consistent risk factors for immunogenicity, but other candidate variants may also be of importance. To explore the role of genetic predictors in anti-drug antibody development, we systematically reviewed the literature. A search of Medline, Embase, and the Cochrane Library identified 1944 records, of which 27 studies met inclusion criteria. Across these studies, HLA-DQA1*05 carriage was repeatedly associated with higher antibody formation, lower drug levels, treatment failure, and secondary loss of response. Other HLA alleles and FCGR3A variants were also linked to increased risk, while some haplotypes appeared protective. Findings varied depending on the drug, genetic background, and patient population. The role of concomitant immunomodulator therapy was inconsistent, though some genotypes appeared to benefit. Overall, HLA-DQA1*05 and FCGR3A variants are the most reliable predictors of immunogenicity, particularly in infliximab-treated patients. Future work should prioritize large, multi-ethnic prospective studies with standardized antibody measurements and integrated pharmacogenomic approaches to establish clinical utility.

Keywords: Crohn's disease, ulcerative colitis, biologics, immunogenicity, HLA-DQA1*05, FCGR3A

Introduction

Inflammatory bowel disease (IBD), primarily consisting of Crohn's disease (CD) and Ulcerative colitis (UC), is a chronic relapsing immune-mediated disorder of the gastrointestinal tract triggered by genetic and environmental factors.[1] The therapeutic management of IBD focuses on inducing and maintaining remission while minimizing the risk of adverse events, as no curative treatment currently exists.[2]

Anti-tumor necrosis factor (TNF) antibodies such as infliximab (IFX) and adalimumab (ADL) have revolutionized IBD therapy. But alternative biologics like vedolizumab (VDZ) (anti-integrin) and ustekinumab (UST) (anti-IL-12/23) are also available.[3,4] Despite their efficacy, response failure to anti-TNF therapy is common.[5] About 10–40% of patients will lose response in the induction state as primary non-responders.[6,7] And loss of response (LOR) within the first year of treatment referred to as secondary LOR will occur in 24–46% of patients.[8] A major contributor to LOR is the formation of anti-drug antibodies (ADAs) referred to as immunogenicity.[8,9] Immunogenicity reduces drug levels, increases infusion reactions, and lowers remission rates.[10] Studies show that concomitant use of immunomodulators may mitigate ADA development[11–13] but carries additional risk of adverse events, opportunistic infections and malignancies.[14,15]

Genetic predisposition appears to play a key role in ADA formation and LOR.[16] Variants in human leukocyte antigen (HLA) alleles, particularly HLA-DQA1*05, have been consistently associated with increased risk of immunogenicity, as

Received: 1 October 2025
Accepted: 28 November 2025
Published: 17 December 2025

demonstrated in the "Personalized Anti-TNF Therapy in Crohn's Disease study" (PANTS).[11] These findings were confirmed by meta-analyses.[17,18] Genetic variations in HLA genes influence immunogenicity by altering the peptide-binding grooves of HLA molecules and thereby modifying antigen presentation to T-cells. This modification affects T-cell activation and the likelihood of ADA formation and thereby shaping individual differences in treatment response and immunogenic risk.[19] Evidence also suggests variants of the Fcγ receptor type IIIA (FCGR3A) as a possible risk factor for ADA development, increased IFX clearance, LOR and relapse risk.[20,21] Other candidate variants include polymorphisms in the *TNFα* gene and the *CD96 locus*, which also may be related to ADA formation.[22,23] In contrast, studies of UST and VDZ have so far not confirmed an association between genetic variations and the formation of ADAs or drug levels.[24,25] This may relate to their mechanisms of action. UST and VDZ are directed against distinct molecular targets with UST targeting IL-12/23 and VDZ selectively binding the α4β7 integrin.[26,27] The differences in UST and VDZ molecular targets, compared to IFX and ADL may lead to distinct genetic interactions and immunogenic epitopes. Consequently, the genetic basis for ADA development may differ from that of IFX and ADL, potentially contributing to their comparatively lower immunogenicity.[28]

Current approaches often detect ADAs only after LOR, highlighting the need for predictive tools. Understanding genetic contribution to ADA formation could improve risk stratification, treatment choice, and inform personalized strategies to minimize immunogenicity. Yet, evidence remains heterogeneous due to differences in study design, cohorts, genotyping, and ADA assays. This scoping review therefore aims to systematically synthesize current findings on genetic factors determinants of ADA development in IBD patients receiving biologics, clarify key concepts, and identify gaps to guide future research and clinical application.

Methods

The review was conducted as a scoping review in accordance with the methodological framework guidelines for scoping reviews,[29] with the purpose of providing an overview of what is known about how genetic variations influence ADA development as well as knowledge gaps in the field. Due to heterogeneity of studies in terms of design and analytical methods, neither a systematic review nor a meta-analysis was considered feasible. This is also why a formal critical appraisal or risk-of-bias was not conducted. Thus, the review was conducted with the aim to map the scope and characteristics of existing evidence rather than to evaluate study quality or to assess the internal validity of individual studies. The protocol was preregistered in the Open Science Framework (OSF) with the OSF registration DOI 10.17605/OSF.IO/9GWR2.[30]

Review Question

This scoping review aims to identify and summarize evidence on genetic factors associated with ADA development in patients with IBD treated with biologics.

Research Questions

1. Which genes, alleles, or polymorphisms have been studied in relation to ADA development in IBD treatment?
2. Does the type of biologic therapy influence ADA development?

Inclusion and Exclusion Criteria

Inclusion criteria were defined according to the PCC Framework

Population (P): Patients diagnosed with IBD, including Crohn's disease and Ulcerative Colitis, treated with biological agents (ie, monoclonal antibodies produced by biotechnological methods), with no other limitations on the study population.

Concept (C): ADA formation (immunogenicity) against biological agents and the potential influence of genetic factors.

Context (C): All health care settings and study types (eg, clinical trials, cohort studies, case-controls), without geographic restrictions or limitations on publication date.

Only publications written in English were considered eligible. Conference abstracts, editorials, commentaries, and letters were excluded.

Search Strategy

We systematically searched MEDLINE (via Ovid), EMBASE (via Ovid), and the Cochrane Library using controlled vocabulary (MeSH/Emtree) and free-text terms related to IBD, biologic therapy, ADAs, and genetic factors. All searches were reviewed by at least two independent reviewers. The search strategy was iteratively refined and repeated based on feedback from the research team. Key publications were identified, and their query strings and MeSH terms were compared with ours to ensure the development of the most sensitive search strategy possible for our research question. Full search strings for each electronic database are available in Supplementary Tables 1–3.

Selection of Included Studies

Search results were imported into Covidence, where duplicates were automatically removed. In the first stage of screening, titles and abstracts were independently reviewed by at least two reviewers (FCH, EB, MTK). Excluded protocols and conference abstracts were hand-searched to identify corresponding full-text publications. Publications deemed potentially relevant based on title and abstract were retrieved in full text. Full-text screening was likewise conducted independently by two members of the research team (FCH, EB), and articles were evaluated in detail against the predefined inclusion criteria. Any conflicts or disagreements were resolved through discussion within the research team, and, when necessary, by consensus with a senior researcher.

Data Extraction

Data extraction was conducted by one member of the research group and cross-checked by another member of the team. Discrepancies were resolved by consensus. A predefined Excel-based extraction sheet was used to capture study characteristics (eg, design, sample size, genetic variants, treatments, duration, demographics).

Synthesis of Results

Data analysis was narrative and aimed at presenting an overview of the evidence highlighting key patterns and relationships, supported by descriptive summaries of study characteristics and findings. Results are presented according to the specific drug, with associations between genetic factors and ADA development reported in relation to the treatment administered. However, some studies did not provide a clear stratification of their findings according to specific drugs, hence the results of these studies will be presented together. The results of the studies investigating only IFX or only ADL will be presented separately.

Results

A total of 1,944 records were identified, of which 174 duplicates were removed. After screening 1,770 records, 1648 records were excluded, primarily due to wrong patient population (did not report data on IBD patients) or did not report on ADA formation and genetic associations, while 122 full-text articles were assessed for eligibility. The Cohen's Kappa coefficients were calculated to be 0.86 for title and abstract screening and 0.98 for full-text screening. Twenty-seven studies, published between 2009 and 2025, met the inclusion criteria and were included in the review (Figure 1).

Characteristics of Included Studies

Key characteristics are summarized in Table 1. Seven studies reused cohorts from prior publications where two of the studies used the same patient cohort from PANTS.[24,31–36] 17 studies were conducted in Europe,[19,21,22,25,31,33–44] five in America,[24,32,45–47] four in China[23,48–50] and one in South Korea.[51] Study design included 17 retrospective cohort studies,[19,22,33,35,36,39–42,44–51] four prospective cohort studies,[21,25,31,43] one cross-sectional study,[23] one case-control study,[38] one Genome-Wide Association Study (GWAS),[37] one study used data derived from an RCT study,[32] one study was an extended analysis to one of the other included studies[34] and one study was described as a post-hoc analysis.[24] Most cohorts included both CD and UC and two of them included a small population of IBD unclassified as well.[38,47] Eleven studies were limited to CD patients[23,31,32,34,37,40,42,48–51] with one study focusing solely on small bowel CD.[50] One study did not distinguish between CD and UC,[43] and two studies included mixed immune-mediated inflammatory disease (IMIDs) population without disease specific results.[33,43] As for the patient population, most studies

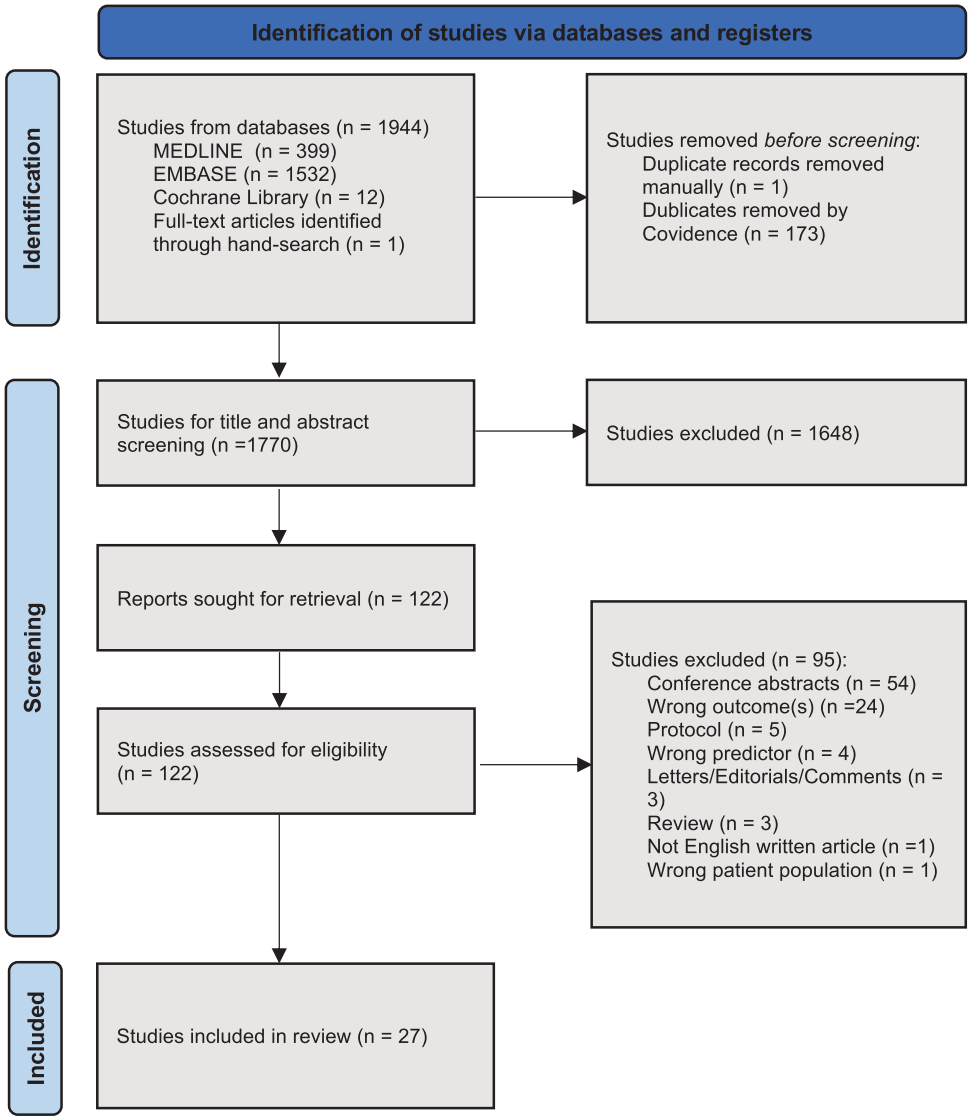

Figure 1 PRISMA flowchart illustrating the stages of a systematic search, showing the number of studies identified, screened, assessed for eligibility and included in the final review including reasons for exclusion.

reported on adults, while six studies reported exclusively on pediatric patients.[22,32,39,44,48,51] Data on HLA-DQA1*05 were provided in 20 of the studies; seven of them also presented data on other HLA Class II alleles, variants of the TNFα gene or FCGR3A. Three studies reported on FCGR3A,[21–23] one study on polymorphisms in the TNFα-gene,[43] one study investigated the CD96 locus,[37] one study the DNA methylation,[40] one study the NUDT15[51] while one study provided data on IgG1 allotypes.[42]

Type of Biologic Agent and Concomitant Therapy

Among anti-TNFα agents, most studies included patients treated with both IFX and ADL, whereas nine studies reported exclusively on IFX[22,23,33,42,45,48–51] and two studies exclusively on ADL.[35,37] Only one study focused solely on Ustekinumab,[24] and one study investigated all four biologics; however, results regarding Ustekinumab were not reported due to a limited sample size.[25] The use of concomitant immunomodulators or corticosteroids varied substantially between studies. Prevalence and type of concomitant therapy are reported in Table 1. The proportion of patients receiving concomitant therapy was not reported in 7 studies.[33–37,44,47] In two studies, concomitant therapy was defined as an exclusion criteria.[23,43]

Table 1 Characteristics of Participants, ADA Determination, Genetic Variants and Key Findings in the Included Studies

Study ID (First Author and Publication Year)	Study Design	Total Sample Size and by Anti-TNF-drug (n)	Type and Prevalence of IBD (n)	Concomitant Therapy (Prevalence (%) and Type)	Total ADA Frequency (%); Assay Type (Drug-Sensitive or Drug-Tolerant)	Genetic Variant/Locus/ SNP; Frequency of Genetic Variant (%)	Outcome Measures (Risk of Immunogenicity in Relation to Genetic Variant)
Adler 2025[32]	Derived from an RCT	207 IFX: 70.5% ADL: 28%	CD: 100%	MTX: 51.7% Placebo: 46.9%	16% - IFX: 19%, ADL: 7%; Drug-sensitive and drug-tolerant	HLA-DQA1*05; 43%	IFX: (OR 2.86, 95% CI 1.13–7.26, p = 0.027) ADL: (p = 0.64). Total: (OR 1.96, 95% CI 0.90–4.31, p = 0.09)
Aterido 2019[37]	Observational cohort study (GWAS study)	150 ADL: 100%	CD: 100%	Not reported	14.5% Discovery stage, 3.4 replication stage; Drug sensitive	CD96 locus/SNP rs9828223; Not reported	Discovery: OR 20.2 (95% CI 5.57–73.27), p = 1.88×10^{-9}. Replication: OR 1.16 (95% CI 1.09–1.23), p = 0.044.
Bangma 2020[38]	Case-control	279 IFX: 72.8% ADL: 27.2%	CD: 79.9% UC: 17.2% IBD-U: 2.9%	47%; Type of IMM not specified	27%; drug-tolerant*	HLA-DQA1*05 /SNP: rs2097432	HLA-DQA1*05 carriage showed increased risk of immunogenicity (OR 1.65, 95% CI 0.95–2.85), did not reach significance in multivariate analysis (p = 0.075).
Brun 2023b [33]	Retrospective observational study	612 IFX: 100% (194 (31.8%) with IBD)	CD: 41.2% UC: 58.8%	Not reported	CD: 18% UC: 24%; Drug-sensitive	HLA-DQ2; 46.9%	Strongest risk allele: HLA-DQB1*02:01/02:02 (OR 2.62, p = 6.6×10^{-9}). Protective allele: HLA-DRB1*01:01 (OR 0.37, p = 0.0004).
Cheli 2023[39]	Retrospective cohort study	79 IFX: 72.2% ADL: 27.8%	CD: 70.9% UC: 29.1%	IFX 39.2%: steroid exposure: 11.4% steroid + mesalazine 5.1%, AZA+steroid 2.5% AZA+mesalazine 6.3% ADL 15.2%: steroid exposure 1.3% steroid + mesalazine 1.3% AZA+mesalazine 3.8%	10.1%; Drug-sensitive	HLA-DQA1*05 /SNP rs2097432; 68% HLA-DQA1 rs2097432T; 56%	No significant association with ADA risk and HLA-DQA1*05 carriage (OR 4.1, 95% CI 0.49–35, p = 0.19). HLA-DQA1 rs2097432 Carriers associated with ADA formation (χ^2 p = 0.04), logistic regression did not reach significance (OR 6.7, 95% CI 0.79–56, p = 0.07).

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https://doi.org/10.2147/JIR.S546252

Table 1 (Continued).

Study ID (First Author and Publication Year)	Study Design	Total Sample Size and by Anti-TNF-drug (n)	Type and Prevalence of IBD (n)	Concomitant Therapy (Prevalence (%) and Type)	Total ADA Frequency (%); Assay Type (Drug-Sensitive or Drug-Tolerant)	Genetic Variant/Locus/ SNP; Frequency of Genetic Variant (%)	Outcome Measures (Risk of Immunogenicity in Relation to Genetic Variant)
Chokshi 2024[46]	Retrospective cohort study	67 IFX: 65.7% ADL: 34.3%	CD: 68.7% UC: 31.3%	HLA carriers 13%, HLA non-carriers 21%; Type not reported	HLA carrier: 15% HLA non-carrier: 6%; Assay type not reported	HLA-DQA1*05; 56%	3 HLA-DQA1*05 carriers vs 1 noncarrier developed high ADA titers requiring cessation ($p = 0.61$).
Colombel 2024[24]	Post hoc analysis in patients from the pivotal Phase 3 IM-UNITI (CD) and UNIFI (UC) studies	675 Ustekinumab: 100%	CD: 50.8% UC: 49.2%	IM-UNITI (CD): 32.7% UNIFI (UC): 31.1%; Type not reported	IM-UNITI (CD): 3.4% UNIFI (UC): 5.4%; Drug-tolerant*	HLA-DQA1*05; IM-UNITI (CD): 43.2%, UNIFI (UC): 39.2%	ADA formation was low overall (4.1% at week 44; 3.4% IM-UNITI patients, 4.5% in UNIFI patients). No significant association between HLA-DQA1*05 carriage and ADA positivity in either cohort.
Curci 2021[22]	Retrospective Cohort study	76 IFX: 100%	CD: 65.8% UC: 34.2%	Total 39.5%; Glucocorticoid 6.6% Aza 38.2% Glucocorticoid 5.3% MTX 1.3%	56.5%; Not reported if drug-sensitive /drug-tolerant	FCGR3A rs396991 (559 A > C); Wt 43.4%, Het 38.2%, Var 18.4% TNFα SNP rs1800629 (−308 G > A); Wt 77.6%, Het 19.8%, Var 2.6%	V allele carriers had increased risk of ADA vs FF genotype (HR 7.3, $p = 0.01$). No significant association between TNFα genotype and ADA risk.
Domingues 2025[25]	Single-center, prospective cohort study	100 IFX: 51% ADL: 21% UST: 10% VDZ: 18%	CD: 67% UC: 33%	26%; Type not reported	CD patients HLA-positive: 28% (7 out of 25), UC patients HLA-positive: 25% (3 out of 12). Patients treated with Anti-TNF therapy: HLA-positive 14%, HLA-negative 21%. Drug-tolerant	HLA-DQA1*05; 43% (CD: 36%, UC: 46%)	No statistical data provided. HLA-DQA1*05 carriage was not significantly associated with ADA development, clinical remission, drug levels, or therapeutic persistence overall.

Doherty 2020[34]	Extended analysis of the study by Sazonovs (Data from PANTS)	1240 Number of patients on either IFX or ADL is not reported	CD: 100%	Not reported	Not reported	HLA-DQA1*05 variants: *05:01, *05:03, *05:05 Associated beta chain variants: HLA-DQB1*02 :01HLA-DQB1*03:01 Associated DRB1 variants: HLA-DRB1*03 :01 HLA-DRB1*11 :01; Frequency of each variant not reported	**IFX**: HLA-DQA105:01, HLA-DQB102:01, HLA-DRB1*03:01 (HR ~1.9–2.0, $p < 5 \times 10^{-9}$). HLA-DQA105:05, HLA-DQB103:01, HLA-DRB1*11:01 (HR 1.28–1.41, p = 0.004–0.056). **ADL**: HLA-DQA105:05, HLA-DQB103:01, HLA-DRB1*11:01 (HR 1.5–2.9, $p < 0.001$). No significant association of HLA-DQA105:01, HLA-DQB102:01, or HLA-DRB1*03:01 with adalimumab immunogenicity.
Hu 2021[48]	Retrospective Cohort study	62 IFX: 100%	CD: 100%	5-ASA: 93.5% Aza: 12.9% MTX: 1.6% None: 6.5%	25.8%; Drug-sensitive*	TNFRSF1A (rs4149570), TNFRSF1B (rs3397 and rs1061624), TLR4 (rs5030728), TLR2 (rs3804099), IL6 (rs10499563), IL17A (rs2275913), IL10 (rs1800872 and rs3024505), and HLADQA1 (rs2097432); Prevalence of each variant not reported	TNFRSF1B rs3397 CC genotype significantly associated with earlier ADA development ($p < 0.001$). No significant associations for 9 other SNPs with ADA development.

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Table 1 (Continued).

Study ID (First Author and Publication Year)	Study Design	Total Sample Size and by Anti-TNF-drug (n)	Type and Prevalence of IBD (n)	Concomitant Therapy (Prevalence (%) and Type)	Total ADA Frequency (%); Assay Type (Drug-Sensitive or Drug-Tolerant)	Genetic Variant/Locus/SNP; Frequency of Genetic Variant (%)	Outcome Measures (Risk of Immunogenicity in Relation to Genetic Variant)
Ioannou 2025[47]	Retrospective Cohort study	Total cohort: 2225 (1495 (67.2%) with IBD), 404 (18.2%) patients exposed to IFX+ADL Data on immunogenicity in 320 (14.4%) patients	CD: 56.4% UC: 41.3% IBD-U: 2.3%	Not reported	Total 29.7% IFX: 21.9% ADL: 10%; Drug-tolerant	HLA-DQA1*05 SNP rs2097432; 23%	No significant association with immunogenicity and IFX. ADL significant under a dominant model for both HLA-DQA1*05 (OR 4.06 (95% CI 1.37–13.49) P: 1.53 10^{-2a}) and Rs2097432 (OR 6.19 (95% CI 1.99–22.74) P: 2.90 10^{-3a}) For anti-TNFs overall (HLA-DQA1*05 p = 0.035; rs2097432 p = 0.002).
Kim 2022[51]	Retrospective observational study	143 IFX: 100%	CD: 100%	Aza 100%	Normal metabolizers: 11.6% Intermediate metabolizers: 3.2%; Drug-sensitive	NUDT15; NUDT15 normal metabolizers 78.3%, intermediate metabolizers 21.7%.	Intermediate metabolizers significantly lower risk of LOR (HR 0.23, p = 0.048) and better infliximab durability (96.8% vs 80.4%, p = 0.027) compared with normal metabolizers. ATI positivity strongly associated with LOR (HR 3.82, p < 0.001) and reduced IFX durability (HR 4.28, p = 0.001).
Lin 2023[40]	Retrospective Cohort study	385 IFX: 51.4% ADL: 48.6%	CD: 100%	Immunomodulators or Steroid 35.3%; Type of IMM not specified	Not reported	DNA methylation (HLA-DQA1*05); frequency not reported	4999 DMPs identified after anti-TNF treatment; most significant at SOCS3 (p = 1.91×10^{-41}). HLA-DQA1*05: 8 DMPs associated with carrier status, but no direct association with ADA development.

Lopez De-La-Cruz 2025[41]	Retrospective Cohort study	408 IFX: 51.6% ADL: 48.3%	CD: 70.8% UC: 29.1%	Corticosteroid therapy total 82.8% Combination therapy >6 months 47.6% Aza 42.4% Mcp 1.5% MTX 3.7%	24%; Drug-sensitive	HLA-DQA1. Alleles studied: HLA-DQA1*01; 62.7% HLA-DQA1*02; 34.8% HLA-DQA1*03; 25% HLA-DQA1*04; 3.9% HLA-DQA1*05; 43.3% HLA-DQA1*06; 1.0%	HLA-DQA1*05 and infliximab use were independent predictors (OR 3.44 and OR 4.64, respectively). Stratified: HLA-DQA1*05 predicted immunogenicity to infliximab only (OR 6.63, 95% CI 1.53–37.35). HLA-DQA1*05 carriage = independent risk factor for LOR to anti-TNF (aHR 1.80, 95% CI 1.21–2.67). HLA-DQA1*03 carriage = protective factor against LOR (aHR 0.42, 95% CI 0.20–0.88). HLA-DQA1*05 + *03 together = ~2.5-fold increased risk of LOR.
Magdelaine-Beuzelin 2009[42]	Retrospective cohort study	118 IFX: 100%	CD: 100%	Corticosteroids: 44.9% Aza/mcp 47.5% MTX 2.5% Mesalamine 42.4%	61.9%;Drug-sensitive	IGHG1: 50.8%, CH1-359 genotype: 73.3%, G1m phenotype: 11.9%	No significant association between IGHG1 CH1 359g/a genotype (G1m1, G1m3, G1m17 allotypes) and ADA formation in Crohn's disease patients on infliximab.
Hernandez 2024[19]	Observational retrospective study	200 IFX: 54.4% ADL: 45.5%	CD: 60.5% UC: 39.5%	92.9%; Type of IMM not specified	20.5%; Drug-sensitive	HLA-DQA1*05; 35% (IFX: 36%, ADL: 34%)	HLA-DQA1*05 carriage increased risk of ADAs (35.7% vs 12.3%, $p < 0.001$). Multivariate: HLA-DQA1*05 increased risk of ADAs up to 7-fold (HR ≈ 1.94–25.9), drug withdrawal (HR 2.73, $p < 0.001$) and treatment intensification (HR 2.16, $p = 0.002$).
Miler 2021[43]	Prospective Cohort Study	112/66 with IBD IFX: 66.1% ADL: 33.9%	CD+UC: 58.9% [50]	Concomitant therapy was an exclusion criterion	Frequency not reported; Drug-sensitive	TNF-a-238 rs361525 (GG, GA/AA) TNF-a-308 rs1800629 (GG, GA/AA); frequency not reported	No associations between TNF-α polymorphisms and ADA development, drug trough levels, or switching biologic.
Pau 2025[44]	Retrospective observational study	65 IFX: 75.4% ADL: 24.6%	CD: 49.2% UC: 44.6% Very early onset: 6.2%	Not reported	IFX: 6.5%, ADL: 6.25%; Drug-sensitive	HLADQA1*05 rs2097432; 58%	No significant association between HLA-DQA1*05 genotype/allele and anti-drug antibody (ADA) development in IFX, ADA, or pooled anti-TNF groups (all $p > 0.5$).

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Table 1 (Continued).

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Reppell 2024[35]	Retrospective Cohort Study (building on work from the SERENE CD and UC studies)	1100 ADL: 100%	CD: 36.2% UC: 63.8%	Not reported	33.3%; Drug-sensitive*	HLA-DQA1*05:05; 20% HLA-DRB1*01:02; 2% HLA-DRB1*11:01; 11% HLA-DQB1*03:01; 25% HLA-DQA1*01:02; 21% HLA-B*14:02; 2% HLA-C*08:02; 3%	HLA-DQA1*05:05: HR 1.54 (p = 7.2E-8), increased risk of ADA; effect stronger after adjustment (HR 1.76, p = 2.0E-10). HLA-DRB1*01:02: stronger effect (HR 2.61, p = 1.39E-5; adjusted HR 3.16, p = 2.9E-7). HLA-DQA1*01:02 protective effect HR 0.72 (p = 2.5E-4)
Romero-Cara 2018[21]	Prospective cohort study	103 IFX: 64.1% ADL: 35.9%	CD: 77.7% UC: 22.3%	Aza 35% Mcp 2.9% MTX 4.9% None 57.3%	12.6% CD: 13.8% UC: 8.7% Anti-IFX: 16,7% Anti-ADL: 5.4%; Drug-sensitive	FCGR3A V158F; FF:38.8%, FV: 44.6% VV: 15.5% CD: 37.5% FF, 46.3% FV. 16.3% VV UC: 43.5% FF, 45.5% FV, 13% VV	IFX: VV carriers much higher ADA risk vs FF +FV (41.7% vs 11.1%; p = 0.01). ADL: trend toward higher ADA risk in VV vs FF +FV (25% vs 3.0%; p = 0.066). FCGR3A VV genotype significantly increased risk of ADA development (37.5% vs 10.6% FV and 5% FF; p = 0.004) VV carriers had a 6-fold higher risk of ADA formation (OR 6.08, 95% CI 1.16–31.84, p = 0.032).

Sazonovs 2020[31]	Prospective Cohort Study	1240 IFX: 59.8% ADL: 40.2%	CD: 100%	Aza: IFX: 27.3% ADL: 15.8%Mcp: IFX: 4.6%, ADL: 2.6%MTX: IFX: 4.0%, ADL: 1.9% tacrolimus: IFX: 0.2%, ADL: 0 none: IFX: 23.7%, ADL: 19.8% Steroids: IFX: 17.7%, ADL: 10.7%	44% at 12 months, 62% at 36 months; Drug-sensitive + drug-insensitive	HLA-DQA1*05; 39%	Adalimumab: HR 1.89 (95% CI 1.32–2.70) Infliximab: HR 1.92 (95% CI 1.57–2.33) No heterogeneity (P_{het} = 0.91) By therapy type: Monotherapy: HR 1.75 (95% CI 1.37–2.22) Combination with immunomodulator: HR 2.01 (95% CI 1.57–2.58) No heterogeneity (P_{het} = 0.14)
Spencer 2024[36]	Retrospective Cohort study	415 IFX: 55.4% ADL: 44.6%	CD: 88.4% UC: 11.6%	Not reported	15%; Drug-tolerant	HLA-DQA1*05 (presence of rs2097432 AG or GG variant); 40%	HLA-DQA1*05 carrier status independently increased risk of ADA formation (OR 1.9, 95% CI 1.4–2.8, p < 0.001). Each additional Pharmacokinetic risk factor (HLA-DQA1*05 or clearance) doubled likelihood of ADA formation (OR 2.16, 95% CI 1.7–2.7).
Wang 2024[49]	Retrospective Cohort study	345 IFX: 100%	CD: 100%	42.9%; Type not specified	49.28%; Drug-sensitive	HLA-DQA1*05 A > G (rs2097432)	HLA-DQA1*05 G allele significantly increased risk of ADA formation (HR = 1.65, 95% CI 1.18–2.30, p = 0.003), LOR (HR = 2.55, 95% CI 1.78–3.68, p < 0.001) and Discontinuation (HR = 2.21, 95% CI 1.59–3.06, p < 0.001)
Wilson 2020[45]	Retrospective Cohort study	262 IFX: 100%	CD: 58.0% UC: 42.0%	Combination therapy 66.4% Glucocorticoid exposure 86.3% Immunomodulator exposure 90.5%	12.98%; Drug-sensitive	HLADQA1*05 AA: 59.9%, HLADQA1*05 AG 29.8%, HLADQA1*05 GG 10.3%	HLA-DQA1*05 risk of ADA formation (adjusted HR = 7.29, 95% CI 2.97–17.91, p = 1.46×10^{-5}), LOR (HR = 2.34, 95% CI 1.41–3.88, p = 0.001), Discontinuation (HR = 2.27, 95% CI 1.46–3.53, p = 2.53×10^{-4})
Wu 2024[50]	Retrospective Cohort study	106 IFX: 100%	Small bowel CD: 100%	Aza 14.2%	HLA-carriers: 34.4% HLA non-carriers: 18.9%; Drug-tolerant	HLA-DQA1*05 rs2097432; 30.2%	HLA-DQA1*05 risk of ADA formation: COX regression model 1: odds ratio [OR] = 2.337, 95% confidence interval [CI] = 1.026–5.319, p = 0.043, Model 2: OR = 2.337, 95% CI = 1.026–5.320, p = 0.043)

(*Continued*)

https://doi.org/10.2147/JIR.S546252

Table 1 (Continued).

Study ID (First Author and Publication Year)	Study Design	Total Sample Size and by Anti-TNF-drug (n)	Type and Prevalence of IBD (n)	Concomitant Therapy (Prevalence (%) and Type)	Total ADA Frequency (%); Assay Type (Drug-Sensitive or Drug-Tolerant)	Genetic Variant/Locus/SNP; Frequency of Genetic Variant (%)	Outcome Measures (Risk of Immunogenicity in Relation to Genetic Variant)
Zhu 2023[23]	Cross sectional study	104 IFX: 100%	CD: 100%	Exclusion criterion	53.85%; Drug-sensitive*	HLA-DQA1*05 (rs2097432); 19.71%FCGR3A (rs396991); 34.13%	HLA-DQA1*05 (rs2097432) carriers vs non-carriers (71.1% vs 43.9%, p = 0.01). Logistic regression: OR = 2.94 (95% CI 1.19–7.30, p = 0.02). FCGR3A (rs396991) variant allele CC/AC vs AA (64.9% vs 40.4%, p = 0.01). Logistic regression: OR = 2.94 (95% CI 1.24–6.96, p = 0.01).

Notes: *Other assay than ELISA used to detect ADAs.

Abbreviations: IFX, Infliximab; ADL, Adalimumab, UST, Ustekinumab; VDZ, Vedolizumab; IBD, Inflammatory bowel disease; CD, Crohn's disease; UC, Ulcerative Colitis; IBD-U, Inflammatory bowel disease unclassified; LOR, Loss of response; ADA, Anti-drug antibody; OR, Odds ratio; HR, Hazard ratio; CI, Confidence interval; IMM, immunomodulators, MTX, methotrexate; Aza, Azathioprine; mercaptopurine, Mcp; Wt, Wild type; Het, Heterozygote; Var, Variant.

Method of ADA Determination

Most studies employed Enzyme-Linked Immunosorbent Assay (ELISA) for ADA detection (see Table 1); however, other methodologies such as bridging-ELISA, radioimmunoassay, electrochemiluminescence assay, and immunochromatographic assay were also used. Sixteen studies used different ELISA methods described as drug-sensitive assays, where only free antibodies are detected and the signal is reduced if drug concentrations are high, as drug-antibody complexes are not detected. In contrast, five studies used drug-tolerant assays, which are designed to minimize drug interference and detect antibodies even in the presence of circulating drugs.[24,25,36,38,47] Two studies used both types of assays,[32,50] and one study reported the use of both drug-sensitive and drug-insensitive assay methods.[31] In some papers, details of the assay like cut-off values and assay type (drug-sensitive, drug-tolerant, drug-insensitive), were incomplete or not reported at all.

HLA-DQA1*05 and Risk of Immunogenicity in Infliximab and Adalimumab Treated Patients

Most of the included studies investigated the HLA-DQA1*05 and the association with immunogenicity in IFX and ADL-treated patients. Eight studies found a comparable risk of ADA formation, irrespective of the biological agent,[19,25,31,36,38,40,44,46] whereas five studies reported differences in immunogenicity frequency between IFX and ADL (Table 2).[32,34,39,41,47]

Three studies found the HLA-DQA1*05 to be a strong genetic determinant of anti-TNF immunogenicity in both IFX and ADL treated patients and that HLA-DQA1*05 carriage significantly increased the risk of ADA development.[19,31,36] One study reported a genome-wide significant association between HLA-DQA1*05 and immunogenicity to biologics, with carriage of a single allele associated with increased risk (HR 1.90, $p = 5.9 \times 10^{-13}$). Immunogenicity rates were

Table 2 Effect of Investigated Genetic Variants in Relation to ADA Development in Relation to Anti-TNF Therapy Based on Data from Table 1

Genetic Variant	IFX	ADL	UST	VDZ
*HLA-DQA1*05*	+	+	0	0
*HLA-DQA1*05:01*	+	0	?	?
*HLA-DQA1*05:05*	+	+	?	?
*HLA-DQB1*02:01*	+	0	?	?
*HLA-DRB1*01:02*	?	+	?	?
*HLA-DRB1*03:01*	+	0	?	?
*HLA-DRB1*11:01*	+	+	?	?
FCGR3A V158F (V allel)	+	(+)	?	?
TNFRSF1B rs3397 (CC)	+	0	?	?
TNFα SNP (rs1800629)	0	0	?	?
CD96 Locus	?	+	?	?
IgHG1	0	?	?	?
NUDT15	(+)	?	?	?
DNA methylation	0	0	?	?

Notes: + = increased risk of ADA, 0 = effect not significant, ? = Association not investigated, (+) = Trend towards effect but not significant.
Abbreviations: IFX, infliximab; ADL, Adalimumab; UST, Ustekinumab; VDZ, Vedolizumab.

https://doi.org/10.2147/JIR.S546252

lower with ADL compared to IFX (HR 3.21, $p = 1.2 \times 10^{-28}$), although no significant difference in the effect of HLA-DQA1*05 between the two anti-TNF agents was observed (HR 1.92 for IFX and HR 1.89 for ADL).[31] One of the studies reported that HLA-DQA1*05 also increased risk of drug withdrawal (HR 2.73, $p < 0.001$) and treatment intensification (HR 2.16, $p = 0.002$), thus carriage strongly predisposed to immunogenicity (HR ≈ 1.94–25.9), lower trough levels and secondary LOR.[19] Another study found that high baseline clearance of anti-TNF agents (>0.326 L/day) also increased ADA risk (OR 2.3, 95% CI 1.7–3.4, $p < 0.001$), concluding that HLA-DAQ1*05 and high clearance of anti-TNF agents might be independent predictors of immunogenicity (OR 2.16, 95% CI 1.7–2.7).[36]

Three studies found an association between HLA-DQA1*05 carriage and an increased risk of immunogenicity, but the results did not reach significance.[25,38,46] Carriage of HLA-DQA1*05 was found to be common in IBD patients but showed no overall impact on ADA risk, remission, drug levels or persistence across IFX, ADL or pooled anti-TNF groups.[25] Another study reported that ADA-related discontinuations were more frequent among carriers, but the difference was not statistically significant.[46] One study investigated changes in DNA methylation in carriers of HLA-DQA1*05 and the association with ADAs. The study identified eight DNA methylation profiles associated with carrier status but found no direct association with ADA development.[40]

Two studies in pediatric IBD populations reported that carriers of HLA-DQA1*05 had an increased risk of ADA formation, with a strong predictive value for LOR and treatment discontinuation with IFX; however, the association did not reach statistical significance.[32,39] Another study investigating a pediatric cohort found that carriage of HLA-DQA1*05 was common (58%), but not significantly associated with ADA formation against IFX or ADL.[44] No association with ADA formation was observed in ADL-treated pediatric patients ($p = 0.64$),[32] suggesting that genetic influence may differ between drugs.[32,39]

One study reported that HLA-DQA1*05 predicted immunogenicity (OR 6.63, 95% CI 1.53–37.35) and increased risk of LOR (HR 1.80, 95% CI 1.21–2.67), particularly in IFX-treated patients. Carriers of both HLA-DQA1*05 and HLA-DQA1*03 had an elevated risk of LOR (~2.5-fold) and adverse events, whereas HLA-DQA1*03 appeared to be protective in ADL-treated patients.[41] Another study found that HLA-DQA1*05 rs2097432 was significantly associated with immunogenicity in ADL-treated patients (HLA-DQA1*05 $p = 0.015$ and rs2097432 $p = 0.003$), especially among patients of European ancestry; no significant association was observed with IFX, although both variants remained significantly associated with ADA development across anti-TNF agents (HLA-DQA1*05 $p = 0.035$; rs2097432 $p = 0.002$).[47]

One study reported that the risk of ADA development was allele- and drug-specific. For IFX, immunogenicity was primarily associated with HLA-DQA1*05:01, HLA-DQB1*02:01, and HLA-DRB1*03:01 (HR ~1.9–2.0, $p < 5 \times 10^{-9}$), whereas for ADL it was associated with HLA-DQA1*05:05, HLA-DQB1*03:01, and HLA-DRB1*11:01 (HR 1.5–2.9, $p < 0.001$). Cross-associations were weaker and not statistically significant.[34]

Risk of Immunogenicity and Treatment with Infliximab

HLA-Alleles

HlA-DQA1*05

Among studies investigating immunogenicity in IFX-treated patients, all found an association with the HLA-DQA1*05 genotype. Two studies found that the HLA-DQA1*05 G allele significantly increased the risk of ADA formation (HR = 1.65, 95% CI 1.18–2.30, $p = 0.003$)[49] (adjusted HR = 7.29, 95% CI 2.97–17.91, $p = 1.46 \times 10^{-5}$),[45] LOR and treatment discontinuation and strongly predict these outcomes in IFX-treated IBD patients.[45,49] One study investigating patients with small-bowel CD also found HLA-DQA1*05 as an important risk factor for ADA formation, and that carriage of the allele doubled the risk of ADA formation in IFX-treated patients with small-bowel CD.[50] The study by Zhu et al also found that HLA-DQA1*05 (rs2097432) GG/AG carriers had higher ADA formation vs non-carriers (OR 2.94). Furthermore, they found that double carriers of HLA-DQA1*05 and the non-HLA genotype FCGR3A additively increased the ADA risk by 10-fold.[23]

Other HLA Class II Alleles

The study by Brun et al suggested that a combination of HLA-DQA1 and DQB1 alleles encoding HLA-DQ2 may represent the primary association with the development of ADAs to IFX. The study identified HLA-DQB1 as the key

locus driving the association and that HLA-DQB1*02:01/02:02 (DQ2 alleles) were the strongest genetic predictors of ADAs across IMID patients (OR 2.62, $p = 6.6 \times 10^{-9}$).[33]

Protective Alleles/Haplotypes

One study found the HLA-DRB1*01:01- DQB1*05:01-DQA1*01:01 to be protective, suggesting an alternate antigen-presentation pathway (OR 0.37, p = 0.0004).[33] Another study found HLA-DQA1*03 carriage to be a protective factor against LOR (HR 0.42, 95% CI 0.20–0.88).[41]

Non-HLA Variants

FCGR3A Polymorphisms

Three studies investigated the FCGR3A genotype and risk of ADA formation in IFX-treated patients.[21–23] All studies found an increased risk of ADA development and concluded that FCGR3A is a strong predictor of ADA development (Table 2). Two of the studies investigating FCGR3A V158F found that carriers of the V allele had poorer response, lower drug levels and higher ADA risk (HR 7.3, p = 0.01),[22] (OR 6.08, 95% CI 1.16–31.84, p = 0.032)[21] compared to FF/FV carriers.[21,22] One of the studies found that the FCGR3A SNP was significantly associated with LOR at induction and maintenance, while another one found that ADA formation was associated with lower IFX trough levels. Thus, VV carriers were more likely to require dose intensification.[21] The study by Zhu et al investigated the FCGR3A rs396991 found carriers of variant allele CC/AC had higher ADA formation compared to AA carriers and that ADA formation was strongly associated with lower drug levels (OR = 2.94, 95% CI 1.24–6.96, p = 0.01). Further, they concluded that carriers of both FCGR3A SNP and HLA-DQA1*05 had additively increased risk of ADA development (~10-fold).[23]

TNFα Promoter Variants

Among studies investigating variants in TNFα genotype, only one found an association with ADA risk in one of ten studied SNPs in pediatric patients. They found that the TNFRSF1B rs3397 CC genotype was significantly associated with earlier ADA development ($p < 0.001$) and was a strong genetic risk factor for ADA development in pediatric CD patients treated with IFX. However, they found no significant associations for nine other SNPs with ADA development.[48] Three papers investigated the TNFα rs1800629 SNP and found no significant risk of ADA production according to the TNFα genotype, clinical response or IFX drug levels.[22,23,43] The study by Miler et al also investigated TNFα rs361525 and did not find an association to ADA development. The same study investigated the TNFα genotypes in ADL treated patients but did not differentiate the therapies in the results. The study by Zhu et al also investigated two other TNFα SNP (rs767455, rs1061622) and found no association with risk of ADA formation.[23]

IGHG1 Allotypes

One study investigated the association between IGHG1 allotypes and risk of ADA formation in IFX-treated patients, but found no significant association and concluded that ADA development in CD patients is not driven by IgG1 allotype mismatch.[42]

NUDT15 Polymorphisms

One study investigated treatment outcome between NUDT15 normal and intermediate metabolizers in pediatric patients with CD in IFX therapy, including NUDT15 polymorphisms related to LOR. They found that ADA positivity was strongly associated with LOR (HR 3.82, $p < 0.001$) and reduced IFX durability (HR 4.28, p = 0.001). NUDT15 intermediate metabolizers had a significantly lower risk of LOR (HR 0.23, p = 0.048) and better IFX durability (96.8% vs 80.4%, p = 0.027) compared with normal metabolizers.[51]

Risk of Immunogenicity and Treatment with Adalimumab

HLA-Alleles

Only one study investigated ADL as the only biological agent and the risk of immunogenicity. The study found that HLA-DQA1*05:05 (HR 1.54, p = 7.2E-8) and HLA-DRB1*01:02 are strong, independent genetic predictors of ADA formation and low ADL concentrations. They found that HLA-DRB1*01:02 carriers had an even stronger association

(HR 2.61, p = 1.39E-5; adjusted HR 3.16, p = 2.9E-7) with low and very low concentrations and that nearly all patients with persistent low concentrations developed ADAs.[35]

Non-HLA Variants

FCGR3A Polymorphisms

The FCGR3A V158F polymorphism and the association with ADA formation in ADL-treated patients were investigated by one study.[21] The study found a higher proportion of patients with ADA formation in the VV genotype compared to FF or FV carriers. The difference was significant and allele-dose dependent (25% vs 3.0%; p = 0.066). When restricting the analysis to ADL patients, a trend toward a higher ADA risk was observed in VV genotype compared to FF+FV genotypes.

CD96 Locus

One study[37] reported on a significant association between genetic variation at the CD96 locus (SNP rs9828223) and the production of ADAs in CD (Discovery: OR 20.2 95% CI 5.57–73.27 p = 1.88×10^{-9}; Replication: OR 1.16 95% CI 1.09–1.23 p = 0.044). The same study found a significant association between the clinical response to ADL and genetic variation at the CD96 locus (OR = 1.77, 95% CI, 1.09–5.02, p = 0.019).

Risk of Immunogenicity and Treatment with Ustekinumab

In Ustekinumab-treated IBD patients, HLA-DQA1*05 carriage was not associated with ADA development and was not significantly associated with ADA positive status regardless of baseline immunomodulator use or anti-TNF treatment failure [24]. Secondly, drug levels, clinical response, and treatment persistence were not influenced by HLA status in Ustekinumab-treated patients.[24,25]

The study by Colombel et al found overall ADA formation to be low (3.4% in CD patients, 4.5% in UC patients) and found no significant difference between the type of IBD and HLA-DQA1*05 carrier status.[24]

Risk of Immunogenicity and Treatment with Vedolizumab

Only one study investigated Vedolizumab in 18 patients; seven patients were HLA-DQA1*05 positive, and 11 patients were HLA-DQA1*05 negative. None of the patients developed ADAs.[25]

Associations to ADA Formation in Anti-TNF Monotherapy vs Combination Therapy with Immunomodulators

The results of the studies investigating concomitant immunomodulation therapy and HLA-DQA1*05 were not consistent across studies. Three studies found that combination therapy with an immunomodulator did not result in any outcome differences between the groups; thus, there was no difference in immunogenicity risk from concomitant immunosuppressant therapy, time to biologic start, or dose optimization by HLA status.[19,25,39] One study found that carriage of HLA-DQA1*05 almost doubled the rate of ADAs independent of immunomodulator use for both IXF and ADL.[31] Two studies found immunomodulator comedication to be a protective factor for ADA formation and that absence of immunomodulation therapy was associated with higher immunogenicity.[33,38] One study found a protective trend in both carriers and non-carriers, but not statistically significant.[45] Combination therapy with immunomodulators was in one study reported to reduce ADA risk and was suggested to mitigate genetic risk, especially in ADL-treated patients, but was not statistically conclusive.[45]

One study found that combination therapy had opposite effects depending on genotype: protective in wild-type (improved remission and reduced LOR) and harmful in carriers (increased risk of LOR, earlier ADA development, earlier LOR).[49] Another study found no interaction effect with HLA status but found the strongest genetic effect in patients with higher ADA risk while using ADL without immunomodulators.[35] A study investigating combination therapy with methotrexate (MTX) and anti-TNF therapy in pediatric patients found that HLA-DQA1*05 carriers without MTX had highest treatment failure, while MTX reduces both treatment failure and immunogenicity, with a particularly protective in HLA-DQA1*05 negative patients.[32] None of the studies investigating FCGR3A found an association in ADA development and concomitant use of immunomodulators irrespective of patients were treated with IFX or ADL.[21–23]

Differences in ADA Development According to IBD Type

Among studies including both CD and UC patients, not all reported immunogenicity rates stratified by disease type.[36,39,41,44,45] The studies investigating the FCGR3A polymorphism found no significant effect on IBD type and the risk of ADA development.[21–23] Two studies did not find a difference in disease type and immunogenicity between carriers and non-carriers of the investigated genetic variant.[25,46] Two studies found that ADA frequencies were higher in UC patients than in CD patients,[35,47] and another study reported that CD patients had a lower risk of immunogenicity than UC patients.[38]

ADA Formation in Pediatric vs Adult Cohorts

Of the studies investigating SNPs of the TNFα genotype, one studied the association to ADA production in pediatric patients, while the other studies only used adults in their cohort. The study focusing on pediatric patients found a significant association between one TNFα SNP (rs3397),[48] but no association was found in the studies investigating adults.[22,23,43] Among studies investigating FCGR3A, only one study focused on pediatric patients, but it found the same association with immunogenicity and carriage of the FCGR3A variant as in adult cohorts.[21,23] Three studies investigated the HLA-DQA1*05 allele in pediatric cohorts. All studies found an increased risk of immunogenicity among carriers, but results did not reach statistical significance.[32,39,44] These findings are consistent with the results of studies investigating adult cohorts, where increased risk of ADAs was reported but with results not being significant.[25,38,46]

Discussion

The purpose of this scoping review was to investigate genetic factors and risk of immunogenicity in IBD patients treated with biologics. Mapping the available evidence across 27 included studies, we found that carriage of HLA-DQA1*05 is consistently associated with an increased risk of immunogenicity, particularly in patients treated with IFX, with downstream effects on drug levels, treatment discontinuation, and LOR. In ADL–treated patients, findings were more variable, suggesting drug- and allele-specific effects; however, the overall trend still supports a role of HLA-mediated risk (Table 2). Results on FCGR3A variants were also associated with higher ADA risk, lower trough levels, and reduced response across both adult and pediatric cohorts. Other variants (eg, TNFα, IGHG1, CD96, NUDT15) showed more context-specific or inconsistent associations. Protective haplotypes (eg, HLA-DQA1*03, HLA-DRB1*01:01-DQB1*05:01-DQA1*01:01) were also identified, highlighting complexity in HLA-driven risk.

Our findings align with prior systematic reviews and meta-analyses that have also highlighted a strong association between HLA-DQA1*05 and risk of ADA development in anti-TNF treated patients;[17,18,52] however, these studies did not report on other genetic variations that might be associated with risk of immunogenicity and in the meta-analysis by Solitano et al they focused on IMID instead of IBD.[17] Our review suggests that FCGR3A variants also present a higher risk of ADA development, this was also concluded in another review examining how genetic variations and polymorphisms predict response to biologic therapy. The review additionally synthesized data on other genetic variants—such as HLA-DRB1, polymorphisms in immune-pathway genes (eg, TLR2, TLR9), and cytokine-related genes (IL-6, IL-1B)—thereby expanding the evidence base for variants that may influence immunogenicity.[53] However, evidence regarding other genetic variations still remains limited, highlighting the need for further exploration before definitive conclusions can be drawn. For newer biologics as Ustekinumab and Vedolizumab, available evidence suggests a low risk of immunogenicity, but with a limited number of studies investigating these biologics solid conclusions cannot be made.

The studies conclude that there is an association between especially HLA-DQA1*05 and FCGR3A, particularly in IFX treated patients and it is therefore relevant to discuss the clinical relevance of these findings. The population frequencies of these genetic variants are estimated at 31–46% for HLA-DQA1*05[19], while the prevalence of FCGR3A variants appears to be allele-dependent but generally remains relatively high.[54,55] This should be taken into account when considering the implementation of routine pre-treatment testing for the relevant genetic variants, as such testing mayguide treatment optimization and therapy selection. Furthermore, it's important to evaluate the associated costs and the availability of assays for clinical use. Commercial assays already exist, which suggests that implementation in routine practice is feasible. One of the included studies calculated a number needed to genotype to estimate how many

patients would test positive for a predictive variant before treatment initiation, and among these, how many would subsequently develop an adverse event (immunosuppression or immunogenicity)[1]. Before permanent recommendations on pre-treatment genotyping can be made, further research is required to clarify how many patients would meaningfully benefit and to assess the associated costs.

Most studies investigate the genetic risk of HLA-DQA1*05 in relation to immunogenicity; however, other HLA alleles and different SNPs across the genetic variants are also examined, which complicates comparisons across studies. In addition to examining various genetic variants, the studies also employ different outcome measures for their results, which similarly complicates the comparison of studies and the findings regarding ADA risk; this is also why we chose not to conduct a meta-analysis. Moreover, not all studies specify the prevalence of ADA formation in carriers vs non-carriers of the investigated variant.

Evidence on concomitant immunomodulators was mixed. Combination therapy with immunomodulators is known to reduce treatment failure and LOR.[9] Among studies included in this review, evidence on the interaction between immunomodulator use and carriage of HLA-DQA1*05 is inconsistent. For FCGR3A variants, no interaction with co-therapy with immunomodulators was observed across studies. The high variability in results from no effect to clear protective benefits, and in some cases, genotype-dependent risks, highlights the complexity of the interactions between genetic variants and drug and complicates comparison of studies.

While evidence indicates that ADAs may lead to LOR, reduced drug levels, treatment discontinuation and dose intensification, interpretation remains challenging as methods used for ADA measurement, including assay type and cut-off values, varies considerably across studies and immunogenicity definitions are highly dependent on these methodological differences. The divergent associations between immunogenicity and genetic variant carriage may be explained by methodological heterogeneity in ADA determination, this variability complicates comparison across studies and limits the strengths of conclusions regarding genetic determinants of immunogenicity. The use of drug-sensitive assays for ADA determination poses important limitations, as results are influenced by drug concentration. This increases the risk of false negatives in treated patients and may therefore underestimate the true immunogenicity burden, complicating the interpretation and comparison of findings across studies.[56] Drug-tolerant assays may detect higher frequencies of ADAs; however, these assays also capture total antibodies, including those bound to drug, which may not be neutralizing or clinically relevant. In addition, heterogeneity in the definitions of LOR and treatment failure, as well as follow-up duration and timing of ADA measurement, further complicating cross-study comparisons.[57]

The included studies were predominantly retrospective, which limits control over missingness, and covariate detail increases risk of bias. Furthermore, some of the included studies used data from patient cohorts from previously published studies (eg, COMBINE,[58] PANTS,[11] SERENE,[59,60] NORDRUM,[61,62] IM-UNIFI[63]/UNITI[64]) which may compound issues of variable data completeness and overlapping populations.

Most studies focused on adult cohorts, thus, evidence in pediatric populations remains limited. Although similar genetic trends were reported, statistical significance was less frequent, which highlights the need for larger, well-powered studies to clarify the role of genetic factors in pediatric populations.

The review has several strengths. First, the study is based on a comprehensive and up-to-date literature search. In addition, no restrictions were applied regarding research setting, or study design. A further strength of this review is the high level of inter-rater agreement, with Cohen's kappa values of 0.86 for title and abstract screening and 0.98 for full-text screening, indicating almost perfect agreement. Nonetheless, certain limitations should be acknowledged. The depth of the review is partly limited by the fact that data extraction was performed by a single reviewer. Second, this review is a study-level synthesis, which makes it unable to explore all other factors that may influence drug clearance or the effectiveness of biological agents. Furthermore, the exclusion of non-English studies may have introduced bias.

Although a formal risk of bias analysis was not performed, several limitations across the included studies should be noted. Most studies were retrospective which limits control over missing data and covariate detail. Second, heterogeneity in genotyping methods, ADA measurement techniques (drug-sensitive vs drug-tolerant), applied cut-off values, timing of sampling, and definitions of LOR, all of which contribute to divergent findings. Thus, complicating comparison across studies and limits the ability to draw firm conclusions. Additionally, many studies involved relatively small sample sizes, reused cohorts from prior publications, or focused predominantly on associations in populations of Caucasian origin or

ancestry, limiting generalizability. Furthermore, the review was not conducted as a meta-analysis. Therefore, no quantitative synthesis was performed. These observations underscore existing evidence gap and highlight the need for more standardized and systematically designed research in this field and guide future research directions. Findings of this review should therefore be interpreted as a descriptive summary rather than providing definitive effect estimates.

Conclusion

This review demonstrates that evidence highlights HLA-DQA1*05 and FCGR3A as the most consistent predictors of immunogenicity and that these genetic factors are strongly associated with ADA formation, LOR and drug level reductions – particularly in IFX-treated patients. Results for ADL remain more variable, while data for Ustekinumab and Vedolizumab is very limited. Given relatively high prevalence of the genetic variations and ADA development during IFX and ADL therapy, evaluating these polymorphisms is clinically relevant. Routine testing may guide treatment optimization and therapy selection. As commercial assays are available, implementation is feasible. The use of concomitant therapy to prevent ADA formation is uncertain. Given substantial heterogeneity across studies, future work should focus on large, prospective, multi-ethnic cohorts with standardized ADA measurement and integrated pharmacogenomic analysis to refine predictive models and enable precision use of biologics in IBD.

Author Contributions

All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

FCH – Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Writing - original draft, writing - review and editing.

EB – Formal analysis, Investigation, writing - review and editing.

MTK – Formal analysis, Investigation, writing - review and editing.

CS – Conceptualization, Investigation, Methodology, Project administration, Writing - review and editing.

MA – Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing - review and editing.

Data Sharing Statement

Data are available from the corresponding author upon reasonable request.

Funding

No funding was received for the research, authorship and/or publication of this article.

Disclosure

CS reports grants from Takeda and personal fees from MSD, Janssen outside the study, and MA reports personal fees from Celltrion, Abbvie, Johnson&Johnson and Eli Lilly, as well as financial support from Takeda outside the study. The authors have no other conflicts of interest to declare.

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