Commentary | Open Access

Journal of Translational Genetics and Genomics

Zhang et al. J Transl Genet Genom. 2026;10:468-72 DOI:10.20517/jtgg.2026.69

CAIT cells and TRA clonotypes: emerging immunological candidates for IBD therapy

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Citation: Zhang XP, Zhou YY. CAIT cells and TRA clonotypes: emerging immunological candidates for IBD therapy. *J Transl Genet Genom.* 2026;10:468-72. https://dx.doi.org/10.20517/jtgg.2026.69

Received: 5 Jun 2026
First Decision: 17 Jul 2026
Revised: 29 Jul 2026
Accepted: 11 Aug 2026
Published: 25 Aug 2026

Academic Editor: Houfeng Zheng
Copy Editor: Tong Wang
Production Editor: Tong Wang

BACKGROUND

Inflammatory bowel disease (IBD) is a group of chronic, non-specific intestinal inflammatory disorders, including ulcerative colitis (UC) and Crohn's disease (CD)[1,2]. Currently, IBD affects approximately 7 million people globally, causing a severe financial and medical burden on both patients and society[3,4]. The treatment of IBD has developed from conventional anti-inflammatory drugs (5-aminosalicylates and corticosteroids) and immunosuppressants (thiopurines) to biologics targeting specific inflammatory pathways [anti-tumor necrosis factor-alpha (TNF-α), anti-integrin, interleukin-12/23 (IL-12/23) inhibitors] and small molecules [Janus kinase (JAK) inhibitors]. However, there is still approximately 40%-70% of patients who face insufficient response, loss of response, or intolerance in UC[5]. There is still further work to be done to satisfy the clinical demands. Finding new and more potent therapy targets becomes more important than ever. With the rapid development of immunotherapy, T-cell abnormalities play a crucial role in IBD, making the hunt for effective immunological targets in IBD increasingly important[6,7]. Different T cells have distinct roles and functions throughout the body. One crucial protein for T cells is the T-cell receptor (TCR). The αβ heterodimer of the TCR, which is the primary receptor type for the majority of mature T cells, is made up of the α chain encoded by the T cell receptor alpha (TRA) gene and the β chain transcribed by the T cell receptor beta (TRB) gene.

MAJOR RESEARCH FINDINGS

Recently, a large multicenter study titled 'Multi-centered T cell repertoire profiling identifies alterations in the immune repertoire of individuals with IBD across different disease stages' was published in *Genome Medicine*[8]. This study systematically examined the TRA repertoire of 1,732 people, covering the entire course of IBD: patients who had not received therapy at diagnosis, those who had received treatment, and those who had been diagnosed for more than 20 years. This study design makes it possible to distinguish between immunological signals driven by therapy and those that are inherent to the disease.

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The subpopulation of unconventional Crohn's-associated invariant T (CAIT) cells was first discovered and described by Rosati *et al.* in 2022[9]. Nevertheless, no additional explanation was provided about the function and possible relevance of these cells in that study. Subsequent related investigations led by Minervina *et al.* reported that CD1d antibodies can identify and prevent the activation of CAIT cells, although the reason for this *in vivo* proliferation is still unknown[10].

Here, they found that CAIT cells are considerably more prevalent in CD patients with penetrating illness, ileal involvement, and positive anti-Saccharomyces cerevisiae antibodies (ASCA). Furthermore, CAIT expansion is a stable immunological character of CD since it is evident at the time of CD diagnosis and continues to be significant even after 20 years of medication treatment. From a clinical perspective, these results indicate that CAIT can serve as both a disease-associated biomarker and a therapeutic target of CD.

In contrast, mucosal-associated invariant T (MAIT) cells were consistently reduced in the peripheral blood of patients with IBD. Both UC and CD patients showed lower MAIT-cell levels compared with healthy controls. This reduction was largely independent of treatment status and correlated with demographic and disease-related factors, including age, sex, and disease stage. This suggests that MAIT reduction is a marker of IBD-associated immunological disorder, though its directionality (protective vs. pathological) remains to be clarified.

Perhaps most exciting for the field is the identification of 25 CD-associated and 27 UC-associated TRA clonotypes via an unbiased statistical framework and cross-cohort meta-analysis[8]. Notably, the majority of CD-associated clonotypes were grouped into CAIT, *TRAV29-01/TRAVJ06-01*, and MAIT-like clusters. The *TRAV8* family, the *TRAV10-01/TRAJ30-01* cluster, and a few additional clusters were the main sources of UC-associated clonotypes. What makes this finding particularly valuable is the distinct clustering patterns between CD and UC, which suggest different antigen-driven immune responses underlying these two conditions. This raises the possibility that these clonotype signatures could aid in differentiating CD from UC in diagnostically challenging cases, especially in pediatric or atypical presentations[11].

CLINICAL SIGNIFICANCE

The results of this study have significant clinical value and can be assessed from four different perspectives. First, CAIT cells represent a potential therapeutic target. Since CD1d is a non-polymorphic antigen-presenting molecule that restricts CAIT cells, most CD patients may benefit from CAIT-targeted therapy [such as CD1d-blocking antibodies or CAIT-depleting chimeric antigen receptor (CAR)-T cells] without requiring customized human leukocyte antigen (HLA) matching. This is a critical advantage over conventional T-cell targets that are HLA-restricted and patient-specific.

Second, CAIT expansion may serve as a disease-associated biomarker for disease phenotype and severity. The association between increased CAIT-cell levels and ileal disease, stricturing or penetrating behavior, and ASCA positivity suggests that CAIT cells may help identify patients with a more aggressive CD phenotype. Clinically, this could inform treatment intensity at diagnosis, guiding more aggressive therapies for patients with high CAIT levels. CAIT-based immune profiling could potentially contribute to disease stratification, prognostic assessment, and therapeutic decision-making in the future.

Third, the identification of CD- and UC-associated TRA clonotypes provides a valuable foundation for precision immunotherapy. These clonotypes may reflect disease-relevant antigen recognition events and could serve as direct targets for clonotype-specific depletion, immune modulation, or antigen-directed

regulatory T-cell approaches. Beyond their therapeutic relevance, these findings also deepen our understanding of the immunological heterogeneity of IBD. The distinct clustering patterns suggest that CD and UC may be driven by qualitatively different immune stimuli.

Finally, this study is consistent with the broader development of cellular immunotherapy in immune-mediated diseases. In 2025, the *New England Journal of Medicine* reported successful treatment of a patient with refractory UC using CD19 CAR T-cell therapy[12]. Although that report involved a different cellular target and disease context, it provided important proof of concept that cell-directed immune interventions may be feasible in severe IBD. This study further extends this concept by identifying CAIT cells as a potential disease-relevant cellular target in CD.

LIMITATIONS AND AREAS FOR IMPROVEMENT

Despite its impressive research findings, the study has several limitations that merit consideration. First, the study was based primarily on peripheral blood samples, whereas the most pathogenic T-cell populations in IBD are likely to reside in the intestinal mucosa, particularly within the lamina propria. Therefore, paired analyses of peripheral blood and intestinal tissue will be essential to determine whether CAIT expansion in blood accurately reflects mucosal immune activity[13].

Second, the findings may not be fully generalizable to pediatric IBD. Approximately 10% of IBD cases have childhood onset, and the present study did not detect significant CAIT expansion in its pediatric CD cohort[8]. This raises important questions about age-dependent differences in T-cell repertoire development and disease pathogenesis. Larger pediatric IBD cohorts are needed for verification.

Third, all analyzed cohorts were of European ancestry. Validation in non-European populations is needed to determine whether CAIT expansion is a universal immunological feature of CD or whether it varies according to genetic background, environmental exposure, microbiome composition, or regional disease phenotype, which is critical to establish global generalizability.

Fourth, although the study identified disease-associated TRA clonotypes, the antigens recognized by these clonotypes remain largely unresolved. Functional confirmation will be necessary to establish whether these cells directly contribute to disease pathogenesis or instead represent secondary immune responses to chronic inflammation.

CONCLUSION AND FUTURE DIRECTIONS

The work by this study significantly broadens our understanding of T-cell immunity in IBD. Through systematic TRA repertoire profiling across multiple cohorts and disease stages, the study identifies CAIT-cell expansion as a persistent and clinically relevant immune signature of CD. It also provides a valuable repertoire-level resource of disease-associated TRA clonotypes for future mechanistic and translational studies.

CAIT cells represent a rational candidate target for antibody-mediated blockade, selective cellular depletion, or other immune-modulating strategies in refractory CD. However, before CAIT-directed therapies can be translated into clinical practice, further studies are needed to define the antigen specificity, tissue distribution, functional phenotype, and pathogenic contribution of CAIT cells.

Future research should integrate high-throughput antigen discovery, single-cell transcriptomics, paired TCR sequencing, and matched intestinal mucosal sampling. Such approaches will help distinguish causal immune drivers from inflammation-associated bystanders.

Overall, this study illustrates the power of multi-cohort, unbiased TCR repertoire analysis in uncovering hidden immune drivers of complex inflammatory diseases. As immunotherapy continues to evolve, precision targeting of pathogenic immune cell populations may become an increasingly important strategy for improving outcomes in patients with IBD.

DECLARATIONS

Authors' contributions

Wrote the manuscript and has directly accessed and verified the underlying data reported in the manuscript: Zhang XP

Revised the manuscript: Zhou YY

Both authors had full access to all the data in the study and accepted responsibility to submit for publication.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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