World Journal of Gastroenterology

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World J Gastroenterol 2026 October 14; 32(38): 119677

DOI: 10.3748/wjg.119677

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

OPINION REVIEW

Microbiota signatures and genetic risk in pediatric celiac disease

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Peer review: Externally peer reviewed.
Peer-review model: Single blind
Peer-review report's classification
Scientific quality: Grade B, Grade C, Grade C
Novelty: Grade B, Grade C, Grade C
Creativity or innovation: Grade B, Grade C, Grade C
Scientific significance: Grade B, Grade C, Grade C
P-Reviewer: Tonch-Cerbu AK, Doctorate Student, MD, Romania; Zeng JQ, Academic Fellow, Associate Chief Nurse, China
Received: February 3, 2026
Revised: April 22, 2026
Accepted: May 22, 2026
Published online: October 14, 2026
Processing time: 216 Days and 12.8 Hours

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Abstract

Celiac disease (CD) is a chronic, immune-mediated enteropathy triggered by dietary gluten in genetically susceptible individuals, most commonly those carrying human leukocyte antigen-DQ2 or human leukocyte antigen-DQ8 haplotypes. However, because these haplotypes are prevalent in the general population while only a minority of carriers develop disease, additional factors are likely to contribute to disease onset and progression. In recent years, the gut microbiota has emerged as a potential mediator between host genetic susceptibility and environmental triggers, particularly in pediatric CD. Current evidence suggests that children with CD exhibit reduced microbial diversity, depletion of beneficial commensals, enrichment of proinflammatory taxa, and broader alterations extending to fungal and viral communities. However, these findings remain heterogeneous, largely due to variability in study design, sampling sites, diet, age, and analytical methods. This review examines the interplay between host genetic risk and the intestinal microbiota in pediatric CD, with emphasis on bacterial, fungal, and viral components. Moreover, it highlights the importance of longitudinal, functionally oriented, and multi-omics approaches, particularly in genetically at-risk yet clinically unaffected children, to better clarify causality and identify early microbial markers of disease susceptibility.

Key Words: Gut microbiota; Human leukocyte antigen; Mycobiome; Pediatric celiac disease; Virome

Core Tip: Pediatric celiac disease cannot be explained by host genetics alone. Although human leukocyte antigen-DQ2 and human leukocyte antigen-DQ8 are necessary risk factors in most patients, they do not fully account for disease onset or clinical heterogeneity. Current evidence suggests that the gut microbiota, including bacterial, fungal, and viral communities, may act as a dynamic interface between genetic predisposition and environmental exposures. Longitudinal and functional studies in at-risk children may help define early microbial signatures and improve future risk stratification.

Citation: Akcin R, Saribas S, Kocazeybek B. Microbiota signatures and genetic risk in pediatric celiac disease. *World J Gastroenterol* 2026; 32(38): 119677
URL: https://www.wjgnet.com/1007-9327/full/v32/i38/119677.htm
DOI: https://dx.doi.org/10.3748/wjg.119677

INTRODUCTION

Celiac disease (CD) is a T cell-mediated enteropathy that results from an aberrant immune response to gluten proteins present in wheat, barley, and rye[1,2]. Although it was initially defined as a malabsorption syndrome, CD is now considered a complex, multisystem disease characterized by the presence of specific autoantibodies, mucosal injury, and a broad clinical spectrum[3]. Clinical presentation is particularly heterogeneous in pediatric populations. In addition to gastrointestinal symptoms, such as chronic diarrhea, abdominal distension, and growth retardation, extraintestinal manifestations, such as iron deficiency anemia, decreased bone mineral density, and delayed puberty, are also frequently observed[4]. The global prevalence of pediatric CD is approximately 1%, and the recent observed increase in incidence cannot be attributed solely to advanced diagnostic methods, suggesting a contributory role for early-life environmental factors[4,5].

The pathogenesis of CD involves a dynamic interaction between dietary gluten, genetic predisposition, and dysregulated mucosal immune responses[6]. The high proline and glutamine content of gluten proteins renders them resistant to complete proteolytic digestion, resulting in the accumulation of immunogenic peptides in the small intestine[7]. In this context, intestinal barrier integrity emerges as a critical regulatory threshold. Gliadin-induced zonulin release disrupts tight junctions, leading to increased intestinal permeability and facilitating the translocation of immunogenic gluten peptides across the epithelial barrier into the lamina propria[8,9]. In the lamina propria, gluten peptides are deamidated by tissue transglutaminase 2, which enhances their binding affinity to major histocompatibility complex class II molecules, specifically human leukocyte antigen (HLA)-DQ2 or HLA-DQ8. This interaction promotes activation of CD4+ T cells and the production of proinflammatory cytokines, particularly interferon-γ[10]. Concurrently, increased expression of interleukin-15 in the epithelium enhances the cytotoxic activity of intraepithelial lymphocytes, leading to enterocyte apoptosis, villous atrophy, and crypt hyperplasia[11].

Among the environmental triggers emphasized in the pathogenesis of CD, the gut microbiota has recently emerged as an important component. The gut microbiota constitutes a dynamic and complex ecosystem that plays a central role in the development and functional maturation of the immune system, maintenance of oral tolerance, and preservation of intestinal barrier integrity[12]. Alterations in gut microbiota composition, particularly during early life, may critically influence the onset and clinical course of CD in individuals with genetic predisposition such as HLA-DQ2/DQ8[13]. Studies conducted in pediatric patients with CD have consistently indicated dysbiosis characterized by reduced gut microbiota diversity, enrichment of proinflammatory bacterial species, and depletion of beneficial commensal bacteria compared with healthy individuals[13,14]. These changes are suggested to influence disease pathogenesis by increasing the immunogenicity of gluten peptides and modulating mucosal immune responses[14]. Moreover, microbiota differences observed among individuals with shared genetic backgrounds but divergent phenotypes (for example, siblings discordant for CD) further highlight the complex interaction between genetic predisposition and environmental factors [15].

In this context, this review aims to address the interaction between genetic predisposition and environmental factors in pediatric CD, with a particular focus on the gut microbiota, and to discuss the current literature from this perspective. Although the decisive role of genetic susceptibility in CD pathogenesis is established, the factors underlying incomplete penetrance and clinical heterogeneity remain incompletely understood. At this point, the gut microbiota emerges as a critical interface between genetic predisposition and environmental triggers. Accordingly, this review evaluates changes in microbiota composition in pediatric CD, particularly in genetically similar but phenotypically distinct individuals. In addition, the potential role of the microbiota as a biomarker and its interaction with host genetic factors will be discussed in terms of future research directions.

GENETIC PREDISPOSITION: THE HLA-DQ2/DQ8 AXIS AND BEYOND

The genetic basis of CD is primarily determined by polymorphisms in the HLA class II region[16]. In particular, HLA-DQ molecules play a central role in modulating disease susceptibility[16]. Among these, HLA-DQ2.5 (DQA1*05:01-DQB1* 02:01) and HLA-DQ8 (DQA1*03-DQB1*03:02) haplotypes represent the strongest genetic risk factors, while HLA-DQ2.2 (DQA1*02:01-DQB1*02:02) is associated with a lower and context-dependent risk[16-18]. Approximately 90%-95% of

patients with CD carry the HLA-DQ2.5 heterodimer, while most of the remaining individuals are HLA-DQ8-positive[16,19]. However, these haplotypes are present in approximately 30%-40% of the general population, and only a small proportion of carriers develop CD, indicating that HLA predisposition is necessary but not sufficient for disease development[20].

Importantly, the effect of HLA genotype extends beyond its mere presence or absence. Allelic dose and specific combinations critically influence disease risk and clinical severity. In particular, the copy number of the *DQB1**02 allele is an important parameter associated with both increased susceptibility and greater phenotypic severity[21]. Studies in pediatric cohorts demonstrate that HLA-DQ2.5 carriage, particularly in the presence of DQB1*02 homozygosity, is associated with a higher risk of CD, earlier age of onset, and more severe histological damage[21,22]. In contrast, HLA-DQ8 and HLA-DQ2.2 confer lower, but still significant, levels of risk[23]. These findings suggest that genetic susceptibility in CD follows a multilayered, combinatorial, and dose-dependent structure rather than a simple binary framework.

Although the strongest genetic associations in CD are linked to HLA-DQ2.5 and HLA-DQ8, in recent years, certain HLA variants beyond this DQ2/DQ8 axis have been discussed for their potential contributions to disease susceptibility [23]. For example, HLA-DQ7.5 (DQA1*05:05-DQB1*03:01) has been associated with CD in some populations and has been reported within the distribution of risk haplotypes, particularly in pediatric cohorts. However, large-scale screening studies have shown that confirmed CD is rare in individuals who are DQ2/DQ8-negative but DQ7-positive; therefore, the clinical utility of including this variant in routine screening algorithms remains unclear. Moreover, current evidence is still insufficient to establish a definitive role for DQ7.5 in CD pathogenesis[24-26]. Similarly, although clinical data on HLA-DQ9 (DQA1*03-DQB1*03:03) are limited, the identification of gluten-specific T-cell responses restricted by DQ9 suggests that this haplotype contributes to disease susceptibility in certain subgroups[25,26]. While extended HLA genotyping is not routinely required, it may be considered in certain pediatric cases that are HLA-DQ2/DQ8-negative but exhibit strong clinical and serological suspicion of CD[24]. Further studies are needed to clarify the roles of HLA-DQ7 and HLA-DQ9 not only in terms of disease susceptibility but also with regard to their potential effects on age at onset, clinical severity, histological damage, and long-term prognosis[24]. Although current evidence suggests that the effects of these variants are limited or secondary, it is also possible that, in reality, they may assume supportive or indirect roles alongside DQ2 and DQ8 that have not yet been fully defined.

Genetic predisposition in CD is not limited to the HLA region alone. Genome-wide association studies have revealed numerous non-HLA loci related to immune regulation, T-cell differentiation, epithelial barrier integrity, and cytokine signaling that contribute to the risk of CD[27]. These loci constitute a broader immunogenetic background that influences an individual's threshold for loss of tolerance to gluten[28]. Therefore, the genetic background of CD cannot be reduced to a single HLA axis but instead exhibits a multilayered structure shaped by the contributions of both HLA and non-HLA genetic factors[27]. This genetic predisposition determines disease development through its interaction with environmental factors, among which the gut microbiota has emerged as an important component of this interaction[13]. Indeed, the microbiota is considered a key mediator in the translation of genetic background into disease phenotype by regulating immune responses and maintaining gluten tolerance[12,13].

ROLE OF THE GUT MICROBIOTA IN PEDIATRIC CD

The gut microbiota plays an important role in the development of the immune system, the maintenance of intestinal barrier integrity, and the metabolic functions of the host from early childhood[29]. In healthy children, this system is characterized by a eubiotic balance that supports immune tolerance[30]. It has also been reported that the microbiota shifts towards a dysbiotic direction in pediatric CD[30-35]. Generally, an increase in the relative abundance of *Proteobacteria*, *Bacteroides spp*., *Escherichia coli* and other Gram-negative taxa has been observed[30-35]. In contrast, a decrease in beneficial commensals such as *Bifidobacterium* and *Lactobacillus* has been reported[30,31,34,35]. However, these findings should not be interpreted as representing a consistent microbial signature specific to pediatric CD. Microbiota profiles can vary depending on age, diet, disease course, treatment status, sample type (stool, duodenal biopsy, *etc*.) and analysis methods[36-38]. Therefore, the microbiota should be considered not only as a consequence of disease, but also as a dynamic component that interacts with host factors and can contribute to the prognosis and clinical heterogeneity of the disease[32,33,36-38].

Table 1 summarizes the major bacterial changes reported in pediatric CD and the possible functional effects associated with these changes[13,30,31,34,36,39-49]. However, the findings presented in the table should not be interpreted as a fixed and universal microbiota profile for all studies. Differences reported between studies may be affected by methodological variables such as sample size, age distribution, gluten-free diet status, sample type used, and analysis platform[13,30,31,34,36,39-49]. In particular, stool samples and duodenal biopsies do not provide the same biological information[13,30,31,34,36,39-49]. While stool samples provide a more practical and convenient sample type for longitudinal follow-up, duodenal biopsies can provide information about the mucosal-associated microbial niche more directly related to celiac pathology[13,30,31,34,36,39-49]. Therefore, Table 1 should be considered not as a definitive taxonomic signature for pediatric CD, but rather as a brief synthesis of bacterial patterns that are recurring in different studies but may vary depending on the context.

At this point, functional interpretation of the microbiota is increasingly recognized as more informative than diversity measurements alone[29]. Indeed, even in studies where no differences in overall diversity are detected, significant distinctions may be observed in the relative abundance of specific taxa or in microbial metabolite profiles[32]. According to research by Leonard *et al*[50], in children at risk for CD, changes in microbiota and metabolic structure may begin approximately 18 months before the disease is clinically diagnosed. In contrast, some birth cohort analyses have not

Table 1 Taxonomic changes and functional effects in pediatric celiac disease

Bacterial taxon/group	Reported change	Context/condition	Sample type	Possible functional consequence	Nature of evidence
Bifidobacterium spp.	Decrease	Active CD; may change after GFD	Mostly stool	Decreased SCFA production and interleukin-10-related tolerogenic response; weakened barrier support	Clinical cohort findings + mechanistic support
Lactobacillus spp.	Decrease	Active CD; strain-dependent effect	Stool; *in vitro* studies	Reduced gluten peptide hydrolysis capacity; increased inflammatory stimulation	Clinical cohort findings + *in vitro*/functional support
Bacteroides spp.	Increase/variable	Active CD; GFD effect may vary	Stool; duodenal biopsy in some studies	Increased permeability and proinflammatory cytokine responses	Clinical cohort findings + mechanistic interpretation
Proteobacteria	Increase	Active inflammation/dysbiosis	Stool; duodenal biopsy in some studies	Increased oxidative stress, epithelial damage, and inflammation	Clinical cohort findings + mechanistic support
Escherichia coli	Increase	Active CD; strain-dependent	Stool; duodenal biopsy in some studies	Increased virulence-associated epithelial damage and T-cell activation	Clinical cohort findings + strain-dependent support
Staphylococcaceae	Increase	Some pediatric CD cohorts	Mostly stool	Increased dysbiosis, inflammation, and symptom burden	Limited clinical observation
Akkermansia spp.	Decrease/variable	Barrier function; influenced by GFD/age	Mostly stool	Reduced mucus layer and barrier support	Mechanistic support + limited CD-specific findings

CD: Celiac disease; GFD: Gluten-free diet; SCFAs: Short-chain fatty acids.

identified similarly strong distinctions. These differences suggest that the effect of the microbiota may not be fixed at a single time point but may become more evident during specific developmental windows[45,50]. Therefore, in microbiota research related to CD, longitudinal follow-up appears to be substantially more valuable than a single time-point analyses[45,50].

From a mechanistic perspective, the role of the microbiota in the pathogenesis of pediatric CD is not limited solely to changes in microbial composition[37]. These changes, along with their effects on epithelial barrier dysfunction, antigen processing, and mucosal immune response, should be evaluated in conjunction with host genetics[37]. Intestinal barrier dysfunction can increase susceptibility to CD[13,31]. Alterations in microbial metabolites, short-chain fatty acids, can affect the maintenance of tight junctions between epithelial cells and mucosal immune tolerance[13,31]. Disruption of this balance may contribute to increased epithelial permeability *via* the zonulin axis and facilitate the passage of gliadin peptides into the lamina propria[13,32,38]. Moreover, the microbiota can alter the antigenic load by directly affecting the processing of gluten peptides[32,38]. While some *Lactobacillus* strains can break down gluten peptides into less immunogenic forms, some bacteria convert them into more immunogenic products[7,37]. This suggests that the microbiota is an active modulator that can shape the intensity of gliadin-induced antigenic stimulus[51-53]. In addition, the microbiota can influence mucosal immune polarization, leading to increased inflammatory responses specific to CD [13,31,32,38]. Dysbiosis can contribute to increased inflammatory Th1/Th17 responses, weakened Treg-mediated immune tolerance, and disrupt tolerogenic balance in the gut by promoting interleukin-15-related immune activation[51,53]. Therefore, in pediatric CD, the microbiota should be considered as a dynamic biological interface that interacts with host genetics and shapes disease risk not only through compositional changes but also through functional outcomes such as barrier permeability, antigen processing, and immune polarization. In this context, the fundamental question should not only be "which microbial compositions are changing"? but also "how does the microbiota interact with host genetics, and what functions does the microbiota play in this disease"?

Some studies have identified significant changes in the microbiota of pediatric celiac patients compared to healthy individuals[39]. However, some studies have reported that there is no significant difference, only limited statistical differences[50]. Notably, some studies have yielded quite remarkable data. Olivares *et al*[54] demonstrated that HLA-DQ2 positivity can affect the gut microbiota in early childhood and therefore play an important role in the development of CD risk. By contrast, a longitudinal analysis by Leonard *et al*[55] suggested that significant changes in the microbiota may occur before the clinical onset of pediatric CD. In addition, in the study by Zafeiropoulou *et al*[43], no significant difference was found in terms of alpha diversity between pediatric celiac patients and the control group. Conversely, significant microbial differences at the taxon level have been identified in association with pediatric CD. In this context, when these data reported by Zafeiropoulou *et al*[43], Olivares *et al*[54] and Leonard *et al*[55] are evaluated, rather than being conflicting results, it suggests that genetic predisposition, microbiota, microbial changes and colonization in early childhood should be considered as components that evolve and influence each other over time in the development of pediatric CD.

As summarized in Table 2[43,54-57], microbiota research in pediatric CD is highly heterogeneous. However, considering the results of the researchers listed in Table 2, we believe there may be several reasons for this heterogeneity.

Table 2 Comparative summary of microbiota studies in pediatric celiac disease

Ref.	Focus area	Key findings	Statistical significance/status
Zafeiropoulou *et al* [43]	New diagnosis *vs* GFD	No difference in diversity; GFD effect is dominant	Significant signature in taxon abundance
Olivares *et al*[54]	Early life and HLA	Impact of HLA-DQ2 on microbial colonization	Significance at the initial stage
Leonard *et al*[55]	Longitudinal risk monitoring	Microbial shifts occurring 18 months prior to diagnosis	Strong longitudinal significance
El Mouzan *et al*[56]	Bacteria + virus + fungi	Bacteria and virus combination as a robust diagnostic tool	High AUC value (0.818)
Salamon *et al*[57]	Bacteria + fungi + HLA	Intermediate microbiota form in siblings; influence of DQ8/DQ2.2	Significant difference in beta diversity

GFD: Gluten-free diet; HLA: Human leukocyte antigen; AUC: Area under the curve.

Firstly, different dietary habits and environmental/cultural exposures can significantly affect microbiota composition[58,59]. Importantly, the type of sample used can significantly alter the results[58,59]. While stool samples mostly reflect the luminal/fecal microbiota, duodenal biopsies can provide information about microbial communities closer to the small intestinal mucosa[58,59]. Thirdly, age ranges are particularly critical in pediatric age groups. This is because the microbiota, immune system and intestinal barrier are still developing in childhood[58,59]. Therefore, even one year of age can lead to significant biological differences in terms of microbial composition and immune maturation[58,59]. Finally, the sequencing and analysis methods used can also cause variability in the results. 16S rRNA gene sequencing, shotgun metagenomics, metatranscriptomics or different platforms may differ in terms of taxonomic resolution, read length, error profile and functional interpretation capacity[58,59]. Therefore, when evaluating the results of different studies, not only the reported microbial changes but also the study population, sample type, age distribution, and methodological approach used should be considered.

Although research in pediatric CD has long focused on bacterial composition, this approach is increasingly recognized as insufficient[60]. The gut ecosystem encompasses not only bacteria but also fungi, viruses, and particularly bacteriophages, all of which contribute to host-microbe interactions[61]. While the intestinal mycobiome has historically been considered a secondary extension of bacterial dysbiosis in pediatric CD, current evidence challenges this approach[62,63]. Despite representing only a small proportion of the total microbial load, the intestinal fungal community may be important in pathogenesis due to its extensive interactions with the mucosal immune system[64]. Therefore, fungi should not be considered merely as an "accompanying change" but as an active biological layer that may influence immune tolerance, sustain inflammation, and modulate the overall microbial ecosystem[57,61]. Particularly in the pediatric population, evaluating early fungal alterations, potentially preceding disease onset, represents a promising area of research for identifying biomarkers of the preclinical phase[50,55,64].

Within this framework, *Candida* species represent one of the most prominent groups in the pediatric CD mycobiome [57]. In particular, the molecular mimicry hypothesis, proposed based on the structural similarity between gliadin peptides and hyphal wall protein 1 expressed by *Candida albicans*, suggests that fungal components act not only as consequences of inflammation but also as potential triggers in the loss of tolerance to gluten[65]. According to this model, antibody response generated during fungal exposure may facilitate cross-reactivity to gliadin in genetically predisposed children, thereby lowering the immunological threshold and contributing to early stages of CD pathogenesis[65-67]. Similarly, an increase in *Saccharomyces cerevisiae* abundance may be interpreted not merely as a compositional shift but as an indicator of inflammation associated with anti-*Saccharomyces cerevisiae* antibody responses and intestinal fungal dysbiosis[68]. In contrast, a decrease in certain commensal or ecologically balancing species such as *Pichia kudriavzevii* may reflect weakened protective microbial competition and a loss of fungal diversity[69]. Additionally, enrichment of fungal groups such as *Tricholomataceae* and *Saccharomycetaceae* observed in some studies suggests a characteristic fungal restructuring of the fungal community in pediatric CD, whereas the detection of *Pneumocystis jirovecii* at low levels may indicate a distinct fungal niche selection within the duodenal mucosa[70,71].

The findings summarized in Table 3 demonstrate that in pediatric CD, the fungal community may also be a complementary layer of disease-associated microbial changes[57,65,69-75]. Nevertheless, current data are still limited, and it is not clear whether fungal changes are the cause or consequence of the disease or a reflection of a broader disruption in the gut ecosystem[57,65,69-75]. Accordingly, fungal profile should not be considered as a definitive disease signature on its own, but rather as a component to be evaluated together with study design, sample type, disease activity and bacterial microbiota findings[69,74]. One of the important studies in this area was conducted by Salamon *et al*[57], who made a comparison based on 16S and internal transcribed spacer 1 between children with CD, unaffected siblings and healthy controls. This study is important because it shows that the fungal community is a variable that should not be overlooked in pediatric CD and that bacteria-focused analyses alone may be limited in explaining all the changes in the gut ecosystem[57].

Therefore, the clinically relevant question is whether the gut microbiota, particularly the fungal profile, can serve as an early biomarker before the onset of CD? At present, a definitive answer to this question is not possible. However, current evidence supports the potential utility of longitudinal microbiota monitoring, especially in genetically at-risk yet clinically healthy children - such as unaffected siblings - for improving early disease prediction[55,59].

Table 3 Fungal taxa alterations and their pathophysiological implications in celiac disease

Fungal taxon/group	Reported change	Context/condition	Sample type	Possible functional consequence	Nature of evidence
Candida spp./C. albicans	Increase	Pediatric CD; potential immune cross-reactivity	Stool; duodenal biopsy in some studies	Molecular mimicry *via* hyphal wall protein 1; possible gliadin cross-reactivity and immune activation	Clinical observation + mechanistic hypothesis
Saccharomyces cerevisiae	Increase/variable	Fungal dysbiosis; inflammation-associated context	Mostly stool	ASCA-related immune response; marker of intestinal fungal dysbiosis	Clinical observation + immunological association
Tricholomataceae	Increase	Pediatric CD-associated fungal signature	Fecal samples	Possible marker of altered fungal community structure	Study-dependent clinical observation
Saccharomycetaceae	Increase	Family-level fungal shift in CD	Mostly stool	Fungal ecosystem imbalance; possible dysbiosis marker	Clinical observation + ecological interpretation
Pichia kudriavzevii	Decrease	Loss of commensal fungal diversity	Mostly stool	Reduced protective microbial competition; weakened fungal ecosystem balance	Limited clinical observation + ecological interpretation
Pneumocystis jirovecii	Decrease	Duodenal mucosal fungal profile	Duodenal biopsy	Possible altered mucosal fungal niche; unclear functional relevance	Study-dependent mucosal finding
Fungal community overall	Altered/variable	Active CD, at-risk siblings, and preclinical context	Stool; duodenal biopsy in some studies	Barrier regulation, antigenic environment, T-cell polarization, and immune tolerance	Clinical cohort findings + mechanistic support

CD: Celiac disease; ASCA: Anti-*Saccharomyces cerevisiae* antibodies.

In light of the available data, fungi in pediatric CD should no longer be considered merely a "neglected minor component", but rather a promising layer of research that may reflect early interactions between genetic predisposition, epithelial barrier dysfunction, and immune activation[69,70].

The virome, particularly bacteriophages, represents another underexplored microbial layer in pediatric CD[75]. Because bacteriophages infect bacteria rather than host cells, their effects on host are largely indirect, mediated through modulation of bacterial community structure and function[75]. Therefore, they may contribute to either to stabilization of the gut microbiota or, conversely, to propagation of dysbiosis[76,77]. However, the directionality of these effects in pediatric CD remains unclear and warrants further research[77].

Available data suggest that the virome composition in children with CD differs from that of healthy controls[77]. El Mouzan *et al*[56] reported that newly diagnosed pediatric CD cases exhibited increased abundance of certain agents such as *Enterobacteria* phage mEpX1/mEpX2 and human polyomavirus 2, alongside decreased levels of *Lactococcus* phage ul36 and *Streptococcus* phage Abc2 in stool samples. Notably, although no marked differences were observed in Shannon alpha diversity or Bray-Curtis beta dissimilarity, these findings at the level of differential abundance support the possibility of "viral dysbiosis"[77]. This suggests that the effect of the virome in CD is better understood not through overall diversity but through selective increases or decreases of specific viral members[77].

Beyond bacteriophages, early-life exposure to eukaryotic viruses may also play a role in CD pathogenesis[78]. Cohort data indicating that enterovirus exposure increases the risk of celiac autoimmunity suggest that viral infections create transient inflammatory windows that facilitate the loss of tolerance to gluten[78,79]. However, it remains unclear whether such viruses truly act as primary triggers of disease or as accompanying factors that accelerate pre-existing immunological vulnerability[80].

AUTHOR'S PERSPECTIVE AND FUTURE RESEARCH DIRECTIONS

To date, research on the gut microbiota in pediatric CD has been largely shaped around descriptions of bacterial dysbiosis [30,33]. However, this framework appears increasingly insufficient, particularly for explaining early and preclinical stages of disease development[81]. During childhood, the immune system, epithelial barrier, and microbial ecosystem are still undergoing dynamic maturation; consequently, even minor changes in the intestinal environment may lead to pronounced biological consequences[36,61,64]. Therefore, in pediatric CD, the microbiota may be more accurately considered not merely as an "accompanying variable" but as an active biological interface between genetic predisposition and environmental triggers[16,31,50].

For this reason, the role of the mycobiome warrants reconsideration in particular. Although historically treated as a secondary extension of bacterial dysbiosis, the effects of fungal components on intestinal homeostasis may not fit within such a passive framework[64,69]. In early life, fungal communities may have the potential to influence epithelial barrier integrity, mucosal antigen presentation, and T-cell polarization[64,69]. In particular, species such as *Candida* and *Saccharomyces* can exhibit either tolerogenic or proinflammatory effects depending on host and environmental context, suggesting that the mycobiome in CD functions not as a fixed "beneficial" or "harmful" factor but rather as a dynamic

regulator of immune imbalance[64,67,69]. In genetically predisposed children, these effects may influence the delicate threshold between maintenance and breakdown of gluten tolerance[10,16].

Similarly, the gut virome, and especially bacteriophages, represents another important yet underexplored layer in pediatric CD[60,80]. Phages predominantly influence host cells indirectly by selective reshaping bacterial communities [75-77]. Therefore, their potential role in CD should be considered in terms of which bacterial networks are supported or suppressed, and how this, in turn, affects mucosal immune balance[75-77]. In particular, phage-mediated modulation of commensal bacteria associated with Th17 responses may have downstream effects on the Th17/Treg balance[16,38]. Although CD has classically been defined primarily through the Th1 axis, considering that Th17 responses may also contribute to disease immunobiology, phages may represent one of the less visible ecological regulators influencing this balance[16,25,38,76].

The critical point here is that fungal and viral components should be considered within a combined model, not as separate microbial entities independent of bacteria. In general, the current literature on pediatric CD focuses mostly on a specific microorganism. Some studies evaluate bacterial composition, others fungal profile, and still others virome patterns separately. However, the gut microbiota is not simply the sum of isolated groups of microorganisms. The microbiota is a dynamic ecosystem in which bacteria, fungi, and viruses interact with each other. Therefore, the multi-kingdom approach proposed in this opinion review aims to evaluate the interrelationships of microbial changes within the gut ecosystem and their functional consequences reflected in the host immune response, rather than interpreting microbial changes individually in pediatric CD. As shown in Figure 1A, host genetic predisposition is a fundamental basis. Along with bacteria, fungi, and viruses, it can shape epithelial barrier integrity, the antigenic environment, cytokine balance, and the Th17/Treg axis. Another unique aspect of this model is that it also examines how the functional outputs of microorganisms interact with host genetics. Bacterial and fungal gene expression profiles, metabolite production, surface antigens, and secreted proteins can influence HLA-mediated antigen presentation, the immunogenicity of gluten peptides, and the maintenance of mucosal tolerance. Therefore, in addition to well-known genetic risk factors such as HLA-DQ2 and HLA-DQ8, it is necessary to investigate how less studied subtypes such as HLA-DQ7 and HLA-DQ9, which are thought to play a role in celiac susceptibility, interact with the microbial ecosystem. In this context, the multi-kingdom model conceptualized in Figure 1A aims to answer the questions: "Which genes do these microorganisms express, which proteins or metabolites do they produce, and what immunological consequences do these products have in a genetically susceptible host"?

One of the most important aspects of this holistic model we propose is that biological changes associated with the disease can be monitored before the disease develops. In this respect, we consider healthy siblings of pediatric celiac patients to be a special group for understanding the preclinical phase of the disease. These children are not entirely randomly selected healthy controls. Healthy siblings share a common genetic predisposition, similar environmental exposures, and dietary conditions with their siblings who have CD. However, they do not have clinically active CD either. Therefore, healthy siblings can be considered a potential bridge between genetic predisposition and clinical disease. Indeed, some studies show that the microbiota profiles of these individuals may differ from both healthy controls and their siblings with CD, suggesting that they may be an intermediate form carrying early ecological and immunological changes associated with susceptibility to the disease[57,63]. As shown in Figure 1B, this group can offer a unique window for evaluating transitional signatures that may emerge before clinical disease develops. Longitudinal monitoring of healthy siblings and the simultaneous assessment of bacterial, fungal, and viral components within a multi-kingdom framework will be of considerable importance. In addition, metabolites, proteins, surface antigens, and gene expression profiles produced by microorganisms should be considered together with host genetic predisposition. Thus, healthy siblings of celiac patients should be considered not only as a control group, but also as an intermediate biological model that allows us to understand the transition process between genetic predisposition, microbial ecosystem changes, and immune response.

Similarly, the holistic model we propose reinforces the importance of preclinical monitoring and early risk assessment. Although shotgun metagenomics, metatranscriptomics, metabolomics, and other omics approaches offer powerful tools for understanding the compositional and functional structure of the gut microbiota, applying these analyses for routine clinical screening or early diagnosis is not yet feasible. High cost, technical infrastructure requirements, complexity of data analysis, and lack of standardization are the main limitations in this field. Accordingly, for now, multi-omics approaches should be considered not as direct clinical tests, but rather as research-based tools to elucidate the preclinical biology of pediatric CD and to identify more applicable biomarkers for future use. If specific bacterial, fungal, viral, or metabolic signatures are later confirmed to be associated with disease risk, this information could pave the way for the development of simpler, more targeted, and cost-effective biomarker panels. Such an approach can contribute to earlier identification of at-risk children, more precise biological monitoring, and the development of targeted preventive strategies in the future.

CONCLUSION

In pediatric CD, the key issue is not merely to demonstrate the presence of alterations in the microbiota but to determine in which children, at what stage of the disease, and within which immunogenetic context these changes become relevant. Within this framework, evaluating fungal profiles, bacteriophage dynamics, and immune balance not as separate entities but as components of a single, integrated disease model may provide a more explanatory approach. Such a model suggests that, against a background of genetic predisposition, multi-kingdom microbial interactions may shape the epithelial barrier and mucosal immune responses, thereby influencing the direction of preclinical disease.

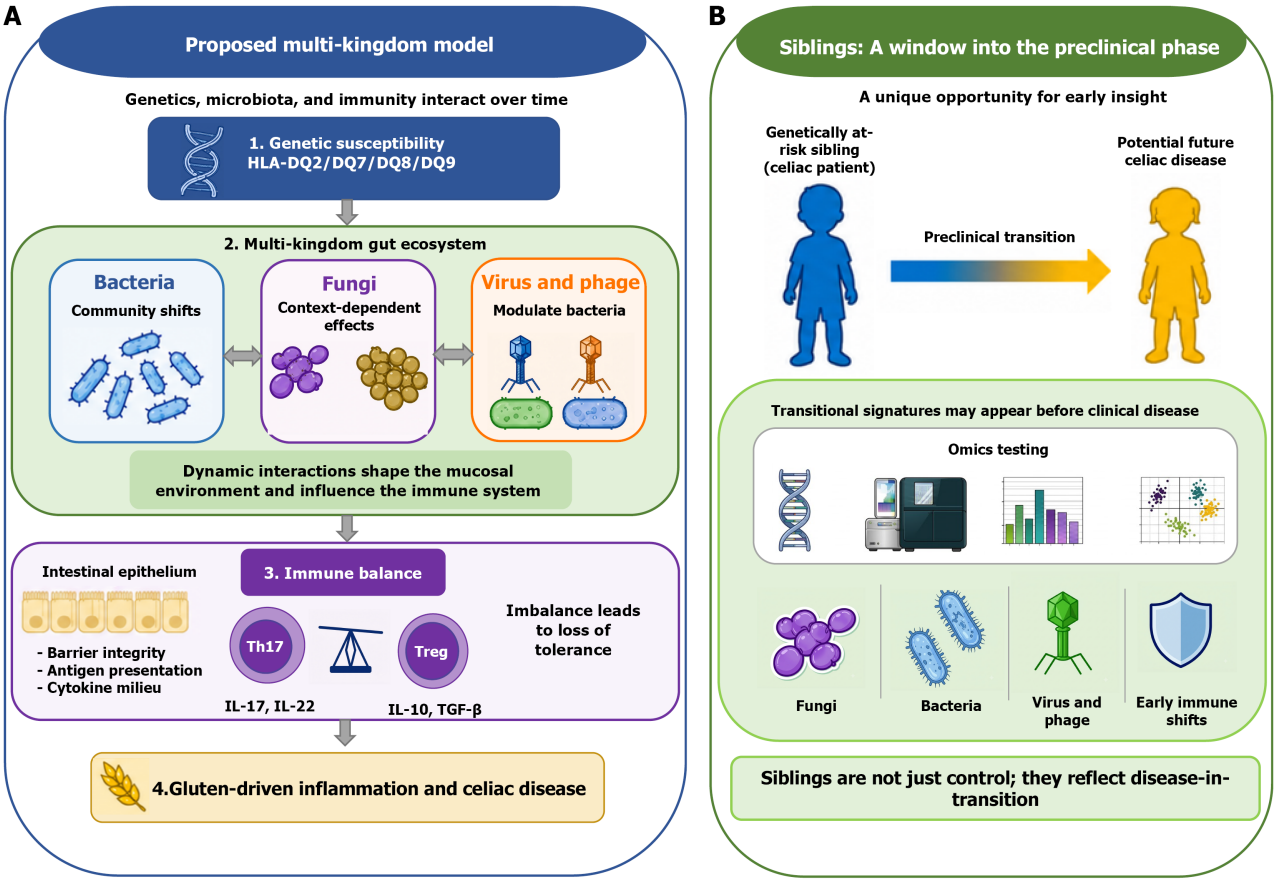

Figure 1 Proposed multi-kingdom model of pediatric celiac disease and the role of at-risk siblings. A: Genetic susceptibility interacts with bacterial, fungal, and viral components to modulate immune homeostasis and promote loss of gluten tolerance; B: Unaffected siblings may represent a preclinical window characterized by early microbial and immunological signatures relevant for risk stratification. HLA: Human leukocyte antigen; IL: Interleukin; TGF: Transforming growth factor.

In particular, integrated microbial-immune patterns identified in genetically predisposed yet clinically unaffected children hold significant potential for early risk assessment. While maintaining appropriate caution, it can be suggested that this approach offers a stronger conceptual framework for advancing early diagnosis, improving risk stratification, and guiding the development of future preclinical intervention strategies in pediatric CD. Therefore, the next step in the field should be not only to describe dysbiosis but also to identify which integrated microbial-immune signals truly reflect disease risk.

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FOOTNOTES

Specialty type: Gastroenterology and hepatology

Country of origin: Türkiye

Author contributions: Akcin R, Saribas S, and Kocazeybek B contributed to this paper; Kocazeybek B designed the overall concept; Akcin R contributed to the writing, discussion and design of the manuscript; Saribas S contributed to the editing the manuscript, illustrations, and review of literature. All authors have read and approved the final manuscript.

AI contribution statement: AI tools (Google Gemini) were used only for limited language assistance and editorial support, while the scientific content, interpretations, and intellectual framework of the manuscript were entirely developed by the authors.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

S-Editor: Hu XY
L-Editor: A
P-Editor: Zhang YL

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