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INFLUENCE OF GUT MICROBIOTA ALTERATIONS ON THE ONSET AND PROGRESSION OF CELIAC DISEASE

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Abstract

The intestinal microbiota plays a pivotal role in the ontogeny and regulation of the mucosal immune system and may exert a protective influence against immune-mediated pathologies. Celiac disease (CD), a chronic autoimmune enteropathy precipitated by the ingestion of gluten-containing proteins in genetically susceptible individuals, has been increasingly associated with dysbiosis perturbations in the gut microbial community structure. Emerging cross-sectional analyses delineating microbial profiles of CD patients versus healthy controls have uncovered significant compositional disparities; however, the causal relationship between microbiome alterations and disease etiology remains inadequately resolved. Experimental investigations employing bacterial isolates derived from individuals with CD have demonstrated that specific microbial taxa may potentiate aberrant immunological responses to gluten, exacerbating intestinal inflammation, whereas certain commensals appear to confer immunomodulatory or protective effects. Additionally, both host genetic predispositions—particularly HLA-DQ2/DQ8 haplotypes—and environmental exposures during early postnatal development have been correlated with early-life microbial colonization patterns and longitudinal microbiota trajectories that may influence CD susceptibility. Epigenetic regulatory mechanisms, including DNA methylation, histone modification, and non-coding RNAs, have also emerged as influential determinants of gut microbiota configuration and functional output. These mechanisms may serve as molecular mediators linking gene-environment interactions to microbiome-driven immunopathogenesis in CD. This review synthesizes current evidence on the interplay between host genomics, environmental modulators, and epigenetic regulation in shaping gut microbial ecosystems and explores their collective implications for celiac disease onset, progression, and clinical management. A deeper understanding of these interdependent factors will inform the development of targeted microbiota-based therapeutic interventions and precision medicine approaches aimed at modulating host-microbe interactions to attenuate CD pathology.

INTRODUCTION

Contemporary scientific discourse increasingly acknowledges the pivotal role of the gut microbiota defined as the complex community of microorganisms inhabiting the human gastrointestinal tract in maintaining systemic health through the regulation of metabolic functions and the preservation of immune homeostasis [1]. The initial acquisition and subsequent development of this microbial consortium are essential for the maturation and functional efficiency of the host immune system [2]. It plays a central role in establishing appropriate immune responses against pathogenic entities while simultaneously promoting tolerance toward innocuous antigens, such as dietary constituents and commensal microbial species. The gut microbiome constitutes a highly adaptable and interactive ecosystem that is modulated by an intricate interplay of host genetic determinants and extrinsic environmental influences, including dietary intake, pharmaceutical exposure, and lifestyle factors. These factors collectively shape both the compositional diversity and functional output of the microbial community. Under physiological conditions, the microbiota exists in a state of eubiosis, which is positively correlated with immune balance and intestinal integrity [3]. However, this equilibrium is vulnerable to disruption by adverse environmental stimuli or intrinsic perturbations, resulting in dysbiosis a condition marked by an aberrant microbial configuration, often characterized by a disproportionate increase in potentially pathogenic taxa and a reduction in beneficial commensals with anti-inflammatory capacities.

A growing body of research has established a strong correlation between dysbiosis and the impairment of immune regulatory mechanisms, thereby increasing susceptibility to various immune-mediated disorders, including celiac disease (CD). CD is a multifactorial, chronic enteropathy mediated by immune mechanisms and is triggered by the ingestion of gluten in individuals carrying specific genetic risk alleles. Despite the genetic predisposition, the relatively low incidence of CD among carriers of susceptibility alleles underscores the significance of additional environmental and microbial factors in disease onset and progression. Significant alterations in the gut microbial composition of CD patients, when compared with healthy individuals, have been consistently documented, indicating a potential etiological or modulatory role of the microbiota [4]. Furthermore, emerging evidence from observational and mechanistic studies suggests that early-life factors and environmental exposures that influence microbiota composition may concurrently modulate the risk of developing CD. Recent experimental findings, including those derived from murine models, have demonstrated that certain bacterial taxa associated with CD in human cohorts exhibit pro-inflammatory effects capable of exacerbating intestinal pathology, thereby reinforcing the hypothesis that microbial agents can act as disease-promoting factors. Although comprehensive clinical validation remains necessary, preliminary intervention trials involving probiotic bifidobacterial strains have yielded encouraging results, suggesting that such microbial therapeutics may contribute to the restoration of gut homeostasis and symptomatic improvement in CD patients [5]. These findings highlight the therapeutic potential of microbiota-targeted interventions as complementary strategies to conventional dietary management in enhancing health outcomes and quality of life among affected individuals.

Environmental Determinants Shaping Gut Microbiota Composition & Celiac Disease Susceptibility

A multitude of environmental factors exert substantial influence on both the ontogeny of gut microbiota and the risk trajectory for developing celiac disease (CD), as outlined in conceptual models such as Figure 1 [6]. These external determinants, particularly those encountered during the early stages of life, play a critical role in microbial colonization and ecosystem maturation. Disruptions during these critical windows of microbial establishment are increasingly associated with heightened vulnerability to immune-mediated diseases. The intestinal microbiota, a highly dynamic and plastic ecosystem, undergoes significant temporal evolution in response to age-related developmental changes and environmental exposures, including diet, pharmaceutical agents, and perinatal conditions [7]. During infancy, the microbial milieu is particularly

susceptible to fluctuations, with compositionally unstable profiles that gradually stabilize and diversify following the introduction of solid foods. Longitudinal microbiome analyses indicate that this maturation process follows a non-stochastic, highly ordered progression, culminating around the age of 2 to 3 years with the formation of a stable, adult-like microbial community structure [8].

One of the primary determinants of neonatal gut microbial assembly is gestational age at birth [9]. In preterm neonates, immaturity of host physiology significantly alters the trajectory of microbial succession [10]. Conversely, in term infants, the mode of delivery and early nutritional practices (e.g., breastfeeding versus formula feeding) appear to be predominant modulators of initial microbial composition. Infants delivered via cesarean section demonstrate reduced maternal microbial transmission particularly of taxa such as Bacteroides and Bifidobacterium resulting in diminished bacterial diversity. This altered colonization pattern has been hypothesized to partially account for the elevated incidence of CD observed among children born via elective cesarean section [11]. Breastfeeding has been identified as a fundamental ecological force shaping neonatal gut microbiota, with implications for long-term immune health. Comparative studies between breast-fed and formula-fed infants reveal that human milk selectively promotes the dominance of Bifidobacterium species, which may constitute up to 90% of the infant fecal microbiome. This effect is largely attributed to the presence of nondigestible oligosaccharides in breast milk, which exert bifidogenic (prebiotic) activity, modulating the microbial landscape toward an immunoregulatory phenotype. In contrast, formula-fed infants harbor more diverse yet less functionally specialized microbial communities. Upon cessation of breastfeeding and the initiation of weaning, a marked shift in the microbiota occurs characterized by increased prevalence of genera such as Bacteroides, Roseburia, Clostridium, and Anaerostipes signaling a transition toward an adult-like enterotype [12].

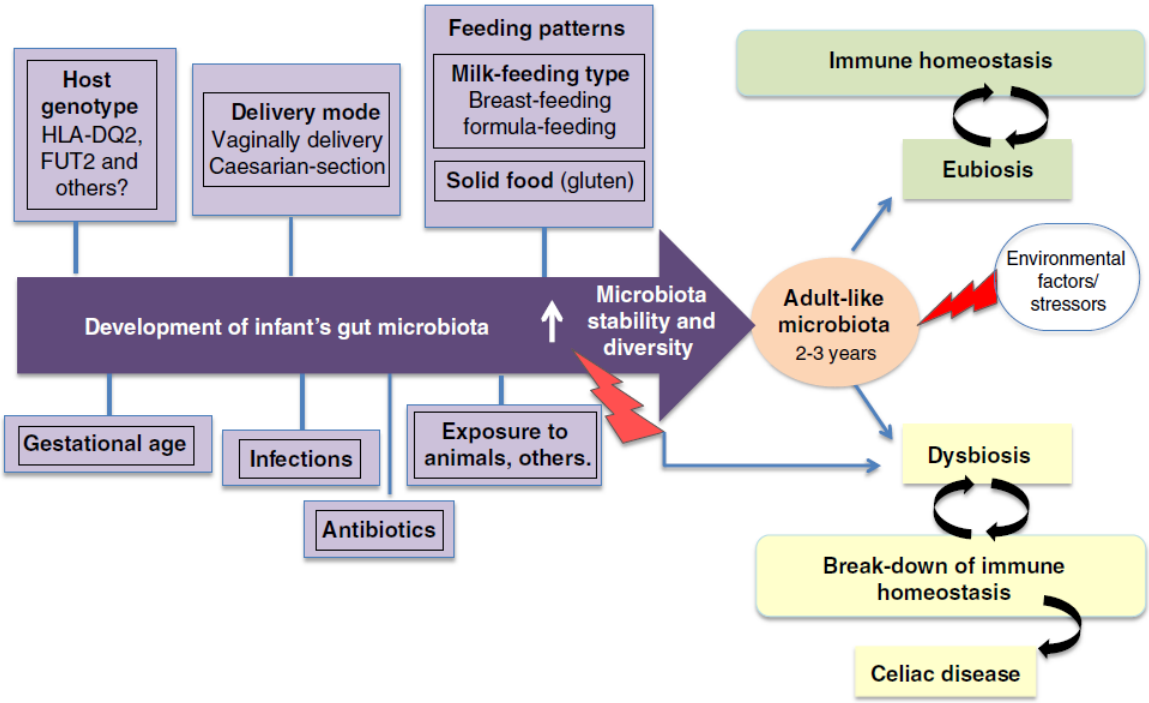

Fig 1. Schematic factors impact the gut microbiota & celiac disease (Cenit, M. C et.al)

Epidemiological evidence has suggested that extended breastfeeding duration, particularly when sustained during the introduction of dietary gluten, may delay or reduce CD onset. Retrospective case-control

studies and meta-analyses, such as the one conducted by Akobeng et al., have reinforced this association, which mirrors protective trends observed in other immune-related pathologies. This protective mechanism was initially attributed to the immunomodulatory potential of bifidobacteria enriched by breast milk, given their observed depletion in both diagnosed CD patients and genetically predisposed infants [13]. However, more recent prospective studies have failed to consistently replicate these findings, thereby challenging earlier assumptions. Current research endeavors aim to resolve these discrepancies, with attention to breast milk compositional variability and unaccounted confounding variables in prior epidemiological studies. The transition to complementary feeding further catalyzes microbial diversification, gradually steering the gut ecosystem toward greater taxonomic complexity [14]. Despite this recognized influence, the specific role of weaning patterns on CD pathogenesis remains inconclusive. Initial studies posited that introducing gluten between 4 and 6 months of age could facilitate immunological tolerance and mitigate CD risk; however, subsequent randomized controlled trials have not substantiated significant differences in CD incidence based on the timing of gluten exposure within the first year of life [15]. Although it is well established that a gluten-free diet significantly alters gut microbiota composition in adults, its effect during early developmental stages on CD susceptibility remains poorly understood. Additional environmental triggers, such as infectious diseases, have also been implicated in modulating CD risk in genetically predisposed individuals. Ivarsson et al. reported seasonal variation in CD incidence, with higher prevalence among children born in summer months suggesting that exposure to infectious agents during critical developmental windows may potentiate immune dysregulation. Antibiotic administration, frequently associated with infection management, has emerged as another major perturbing factor. Antibiotics can induce substantial dysbiosis by reducing microbial diversity and promoting the overgrowth of opportunistic pathogens (e.g., Enterobacteriaceae) and antibiotic-resistant strains, thus undermining mucosal immune equilibrium. Specific classes of antibiotics exert variable impacts; however, those that disrupt anaerobic commensals are particularly deleterious. In the context of CD, several studies have drawn associations between early antibiotic exposure and increased disease risk. Dysbiosis resulting from antimicrobial intervention is posited to compromise immune tolerance mechanisms, thus facilitating pathogenic responses to gluten antigens. Recent findings further substantiate the notion that gastrointestinal infections and antibiotic use within the first year of life significantly correlate with the early onset of CD, likely via alterations in the gut microbial ecosystem [16].

Genetic Determinants of Gut Microbiota and Coeliac Disease (CD) Risk

In addition to environmental influences on the composition of the human gut microbiota, a growing body of literature underscores the pivotal role of host genetic architecture in shaping microbial communities. Earlier investigations, particularly studies involving monozygotic and dizygotic twins, have demonstrated that the gut microbiota of monozygotic twin's exhibit significantly greater similarity compared to that of dizygotic twins. This observation strongly supports the heritable component of microbiota configuration. Subsequent twin studies, such as the comprehensive analysis conducted by Goodrich et al., have elucidated specific microbial taxa whose relative abundances are modulated by host genetic factors, distinguishing them from those predominantly governed by environmental exposures [17]. Notably, host genetic determinants have been implicated in regulating microbial composition via genes involved in immune-microbial signaling pathways. Several loci associated with inflammatory bowel disease (IBD) susceptibility have been correlated with distinct alterations in gut microbial ecology, often involving genes encoding pattern recognition receptors and immunological modulators.

Evidence from large-scale initiatives such as the Human Microbiome Project further reveals significant associations between host single nucleotide polymorphisms (SNPs) and variations in microbial taxa. These genomic variants are linked with modulations in alpha diversity and are implicated in pathophysiological traits, including immune-mediated disorders and metabolic syndromes.

Additionally, genes involved in innate immunity and mucosal tolerance have shown enrichment in microbiome-correlated pathways, suggesting a genetically orchestrated mechanism underpinning microbial-host interactions [8]. Historically, the most well-characterized genetic risk factor for coeliac disease (CD) resides within the human leukocyte antigen (HLA) complex, particularly the HLA-DQ2 alleles. These alleles encode molecules central to antigen presentation and are instrumental in the aberrant immune response to gluten peptides. However, genome-wide association studies (GWAS) have expanded this framework by identifying over thirty-nine non-HLA loci associated with CD, many of which are involved in mucosal immunity and microbial sensing. The dysregulation of these genes potentially perturbs host-microbial equilibrium, contributing to immune dysregulation observed in CD pathogenesis [19].

Emerging evidence highlights the synergistic effect of genetic predisposition and early-life environmental factors particularly feeding practices in shaping the neonatal gut microbiota. Infants carrying the high-risk HLA-DQ2/8 genotype exhibit distinctive microbial profiles, especially when breastfed. This includes elevated proportions of Firmicutes and Proteobacteria and reduced levels of Actinobacteria, notably Bifidobacterium species. Although the precise mechanisms by which HLA genotypes modulate microbial colonization remain elusive, the immunological role of HLA in antigen discrimination is likely instrumental [20]. In parallel, host genetic regulation of intestinal glycosylation patterns has garnered attention for its role in establishing microbial niches. Fucosylated glycans, expressed on intestinal epithelial cells (IECs), are critical substrates for mutualistic bacterial species and confer protection against pathogenic colonization. The FUT2 gene encodes an enzyme essential for fucosylation and the synthesis of secretory ABO(H) antigens. FUT2-deficient mice exhibit increased vulnerability to gastrointestinal infections, while in humans, polymorphisms resulting in a non-secretor phenotype have been associated with various infectious and inflammatory diseases, including an elevated risk of CD. This phenotype correlates with reduced microbial diversity and diminished populations of beneficial bacteria such as Bifidobacterium spp [21].

Further investigation into host-immune regulation has identified the role of innate lymphoid cells (ILCs), particularly group 3 ILCs (ILC3s), in modulating epithelial fucosylation. IL-22, a cytokine produced by ILC3s in response to commensal organisms, upregulates FUT2 expression in IECs. Concurrently, IL-22 enhances the secretion of antimicrobial peptides and defensins, thus reinforcing epithelial barrier function. Microbial signals are also integral to the maturation of ILC populations and their cytokine output, establishing a reciprocal regulatory axis. This suggests that IL-22-driven pathways possibly impaired in CD due to FUT2 mutations or dysbiosis could offer therapeutic avenues for restoring mucosal integrity. In recent years, the intersection of host genetics, epigenetic modulation, and microbial dynamics has emerged as a novel paradigm in gut immunity regulation [23]. Epigenetic mechanisms such as DNA methylation and histone modification not only influence microbial composition but are also modulated by microbial metabolites. For example, short-chain fatty acids (SCFAs), the byproducts of microbial fermentation of dietary fibers, inhibit histone deacetylases (HDACs), leading to altered gene expression in host immune cells.

Toll-like receptors (TLRs), which recognize conserved microbial motifs, are subject to epigenetic regulation to prevent excessive immune activation. Under homeostatic conditions, methylation-mediated downregulation of TLR4 expression mitigates hyperresponsiveness to commensals. However, aberrant TLR signaling has been observed in CD, with some studies reporting increased duodenal expression of TLR2 and TLR4 in paediatric patients [24]. Moreover, disruptions in the expression of TOLLIP, a negative regulator of TLR pathways, have also been noted. These alterations, which occur independently of genetic mutations in the coding regions, point to the involvement of epigenetic dysregulation. Collectively, these findings illuminate the multifaceted genetic and epigenetic framework that orchestrates gut microbiota composition and function. The interplay between host genetic predisposition, immune regulation, and microbial ecology is central to the pathogenesis of CD. Further elucidation of these pathways may facilitate the development of targeted interventions aimed at

restoring microbial and immunological homeostasis in genetically susceptible individuals [25].

FUTURE RECOMMENDATION

Future research on the complex interplay between genetic predisposition and gut microbiota in celiac disease should focus on a multidimensional and integrative approach to improve early detection, prevention, and personalized treatment strategies. Longitudinal cohort studies involving genetically susceptible individuals particularly carriers of HLA-DQ2 and HLA-DQ8 alleles should be conducted from birth through adulthood to monitor the dynamic changes in gut microbial composition, dietary exposures, and immune responses. These studies could provide crucial insights into early microbial and immunological markers predictive of disease onset. In parallel, functional investigations into specific gene-microbiome interactions, especially involving non-HLA genes like FUT2, IL-22, and CCR9, are essential to unravel the molecular mechanisms by which host genetics influence microbial colonization, mucosal immunity, and intestinal homeostasis. This could be facilitated through advanced techniques such as CRISPR-based gene editing, metagenomic sequencing, and transcriptomic profiling. Additionally, the identification and validation of microbiome-based biomarkers may offer promising non-invasive tools for early diagnosis and risk stratification in predisposed individuals. Personalized microbiome-targeted therapies such as custom-tailored probiotics, prebiotics, or synbiotics based on an individual's genetic and microbial profile should be explored to restore eubiosis and reinforce gut barrier integrity, potentially delaying or preventing disease progression. Furthermore, integrating multi-omics data including genomics, proteomics, and metabolomics into a systems biology framework will enable a comprehensive understanding of the gene-environment-microbiota axis and reveal novel therapeutic targets. Public health initiatives should also be developed to promote awareness and preventive practices among high-risk populations, emphasizing the importance of early-life factors such as breastfeeding, birth delivery mode, and cautious antibiotic use. Collectively, these strategies will contribute to the development of a personalized, predictive, and preventive healthcare model, ultimately enhancing clinical outcomes and quality of life for individuals at risk of celiac disease.

CONCLUSION

Growing scientific evidence highlights a complex and dynamic relationship between our genes and the gut microbiota in the development of celiac disease. While environmental factors such as diet and early-life exposures clearly influence how the gut microbiome is formed, our genetic makeup, especially genes in the HLA region like HLA-DQ2 and HLA-DQ8, plays a critical role in shaping the types of microbes that thrive in our gut from an early age. Research has also identified many non-HLA genes associated with celiac disease risk, many of which are involved in how the body detects and responds to microbes, keeps the gut lining intact, and regulates inflammation. One example is the FUT2 gene, which affects how sugars are displayed on the gut lining a feature that microbes use to attach and interact with the host. Certain variations in this gene have been linked to lower microbial diversity and a higher risk of gut-related issues. The immune system is also deeply involved in this relationship; molecules like IL-22, produced by special immune cells, help maintain a healthy gut environment by supporting the growth of beneficial bacteria and defending against harmful ones. Interestingly, the conversation between genes and microbes doesn't stop their microbial by-products like short-chain fatty acids can actually influence how our genes are expressed, especially those involved in immune function. This suggests a powerful two-way connection where genes shape the microbiome, and the microbiome, in turn, affects gene activity and immune balance. Altogether, these insights show that disruptions whether from our genes, environment, or a combination of both can lead to imbalances in the gut microbiome and trigger the immune reactions seen in celiac disease. Understanding this gene-microbiome-immune system triangle offers promising potential for developing personalized treatments that focus on restoring microbial balance and supporting immune health in people who are genetically at risk.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this study

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