Kashf Journal of Multidisciplinary Research
Vol: 03 - Issue 01 (2026)
P-ISSN: 3007-1992 E-ISSN: 3007-200X
https://kjmr.com.pk

GENETIC VARIATION IN INNATE IMMUNE GENES SHAPES GUT MICROBIOTA COMPOSITION AND HOST-MICROBE INTERACTIONS: A REVIEW

Mehwish Majeed[1,2], Rabia Sajid[2,3], Alina Sehar[2], *Muhammad Zurgham Akram[1,2]

[1]College of Medicine and Biological Information Engineering Northeastern University Shenyang, Liaoning, 110819, China.
[2]Department of Computer Science, University of Agriculture Faisalabad, Agriculture University Road, 38000, Faisalabad, Pakistan.
[3]College of Basic Medicine, Chongqing Medical University, China.

Corresponding Author: (zurghamakram8@gmail.com)

DOI: (*https://doi.org/10.71146/kjmr809*)

Article Info

Abstract

The gut microbiota is a critical determinant of host immune, metabolic, and epithelial homeostasis, yet the host genetic factors governing inter-individual variation in microbial composition remain incompletely defined. Beyond environmental influences, genetic variation in innate immune pathways has emerged as a key regulator of host-microbiome interactions. Variants in pattern recognition receptors, inflammasome components, antimicrobial peptide genes, and immune-regulatory cytokines modulate microbial sensing, antimicrobial defense, inflammatory tone, and barrier integrity, thereby exerting selective pressures on gut microbial communities. This review systematically synthesizes evidence from human genome-microbiome association studies, twin cohorts, population-based analyses, and mechanistic experimental models to delineate how genetic variation in innate immune genes shapes gut microbiota composition and function. We focus on major innate pathways, including Toll-like receptors, NOD-like receptors, inflammasomes, defensins, and cytokine signaling networks, and summarize their documented effects on microbial diversity, taxonomic structure, and disease-associated dysbiosis. Key methodological challenges such as small genetic effect sizes, environmental confounding, population specificity, and limited causal inference are critically evaluated. Finally, we outline future directions emphasizing longitudinal study designs, multi-omics integration, functional validation, and genotype-stratified interventions. Elucidating innate immune genetic control of the gut microbiota will be essential for advancing precision microbiome medicine and for developing targeted therapeutic strategies for inflammatory, metabolic, and immune-mediated diseases.

Keywords: *Gut microbiota; Innate immunity; Host genetics; Pattern recognition receptors; Dysbiosis; Genome-microbiome interactions.*

1. **Introduction**

The human gastrointestinal tract is colonized by a dense and diverse community of microorganisms whose collective genomes (the gut microbiome) profoundly influence host physiology (Qin et al., 2010; The Human Microbiome Project Consortium, 2012; Thursby & Juge, 2017). Gut microbes contribute to nutrient metabolism, synthesize vitamins, modulate energy balance, and produce bioactive metabolites that signal to host tissues, thereby shaping host metabolic homeostasis (Hou et al., 2022; Nombulelo Mntambo et al., 2025; Rowland et al., 2017). Landmark works such as the Human Microbiome Project and early metagenomic catalogues established the scale and functional potential of the gut microbiome and illustrated that microbial gene content complements the human genome in determining physiological capabilities (Troisi, 2022; Xiao & Kang, 2020).

Beyond metabolism, the gut microbiota is essential for immune system development (Belkaid & Hand, 2014; Gensollen et al., 2016; Hooper et al., 2012). Early-life microbial exposures drive maturation of gut-associated lymphoid tissue, influence the development of regulatory T cells, and calibrate innate and adaptive immune responses; perturbations in these host-microbe dialogues can predispose to immune-mediated and inflammatory diseases later in life (Kühn et al., 1993; Turnbaugh et al., 2006; Yatsunenko et al., 2012). Moreover, decades of ecological and interventional studies have linked alterations in gut community structure to disease susceptibility, including obesity, inflammatory bowel disease, metabolic syndrome, and colorectal cancer, demonstrating that microbial composition and function are clinically consequential (Frank et al., 2007; Ley et al., 2006; Mota et al., 2018; Turnbaugh et al., 2006; Wang, Wang, et al., 2025).

Despite strong environmental influences (diet, drugs, geography, and lifestyle), host factors, notably genetics and immune status, help to determine which microbes colonize and persist. Twin studies demonstrated that some taxa and community features are heritable, suggesting a measurable host genetic contribution to microbiome variation (Goodrich et al., 2016; Goodrich et al., 2014; Lee et al., 2014). Subsequent host genome–microbiome association studies (mGWAS) and meta-analyses have identified specific human loci that correlate with abundances of particular taxa (Wang et al., 2018). Extensive consortium efforts (e.g., MiBioGen, Rühlemann/Kurilshikov, and others) have begun mapping reproducible host genetic effects across cohorts, while also highlighting modest effect sizes and the predominance of environmental drivers (Europe PMC, 2016; Kurilshikov et al., 2021).

Within host determinants, the innate immune system occupies a central role; it is the first line of recognition and response to microbial molecules and thereby actively shapes the gut habitat through multiple mechanisms (Rakoff-Nahoum et al., 2004; Shang et al., 2008) Pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), NOD-like receptors (NLRs), and inflammasome components, detect conserved microbial-associated molecular patterns and trigger signaling cascades that regulate antimicrobial peptide (AMP) production, mucus secretion, epithelial barrier integrity, and cytokine milieus (Takeuchi & Akira, 2010). Reviews of PRR biology and TLR signaling provide a conceptual framework for how variations in these sensors

alter host–microbe communication and downstream ecological selection (Kawai & Akira, 2006; Kawai & Akira, 2010).

Genetic variation in innate immune genes ranges from common single-nucleotide polymorphisms (SNPs) to rare loss-of-function alleles and regulatory variants that affect expression (BURGNER & LEVIN, 2003). A paradigmatic example is NOD2 (CARD15), whose frameshift and missense variants were among the first robust human susceptibility alleles linked to Crohn's disease; NOD2 is highly expressed in Paneth cells and has been implicated in the regulation of Paneth cell α-defensin production and, consequently, in the control of luminal bacterial populations (Cui et al., 2023; Fu et al., 2023). Similarly, inflammasome components (for example, NLRP6) influence colonic IL-18 production and, in mice, have been shown to affect microbial composition and transmissible colitogenic states, illustrating how single-gene perturbations in innate pathways can remodel the microbiota (Elinav et al., 2011; Wlodarska et al., 2014).

Human observational studies and animal experiments together form a growing evidence base linking innate immune genetic variants to microbiome features and disease. Twin and cohort analyses reveal heritable taxa and identify immune-related loci enriched among microbiome-associated variants, while experimental knockouts or gene-targeted models (Nod2−/−, inflammasome component knockouts, defensin perturbations) provide a mechanistic demonstration that altered innate signaling or AMP output changes microbial community structure, mucosal colonization patterns, and disease susceptibility. Still, the field faces challenges of replication, small effect sizes, confounding (especially diet and medication), and population specificity; large meta-analyses and consortium-scale genome wide association study (GWAS) have improved power and reproducibility but underline the complexity of the host-microbiome architecture (Awany et al., 2019; Blekhman et al., 2015; Scepanovic et al., 2019).

Innate immune genes are a primary focus of this review because of their critical influence on microbial ecology and host health. Firstly, the innate immune system continually senses microbial cues at the mucosal surface, and small changes in sensing thresholds or effector outputs can produce selective pressures that favour or suppress particular microbial taxa. Secondly, innate pathways operate upstream of adaptive immunity and of epithelial barrier functions, so genetic variation here can have broad ecological consequences for community composition, colonization resistance, and function. Thirdly, many innate immune variants are clinically linked to inflammatory disorders; therefore, studying their microbiome effects opens direct translational paths toward stratified therapies and microbiome-targeted interventions. Foundational studies in humans and model organisms, and recent large-scale host-genome association efforts, together provide the conceptual and empirical substrate for this focus (Belkaid & Harrison, 2017; Blekhman et al., 2015; Koch, 2014 ;Iliev et al., 2025; Okumura & Takeda, 2017).

In this review, we synthesize current evidence on how genetic variations in key innate immune genes (TLRs, NLRs, inflammasomes, antimicrobial peptides, and immune-regulatory cytokines) influence gut microbiota composition, microbial diversity, and host-microbe interactions. We integrate findings from human cohorts, multi-omic studies, and mechanistic models, highlight methodological challenges in associating host genotype with microbial traits, and outline research

strategies needed to move from association to causation and to exploit innate-genotype-microbiome knowledge for precision therapeutics. The overall conceptual framework is shown in Fig. 1.

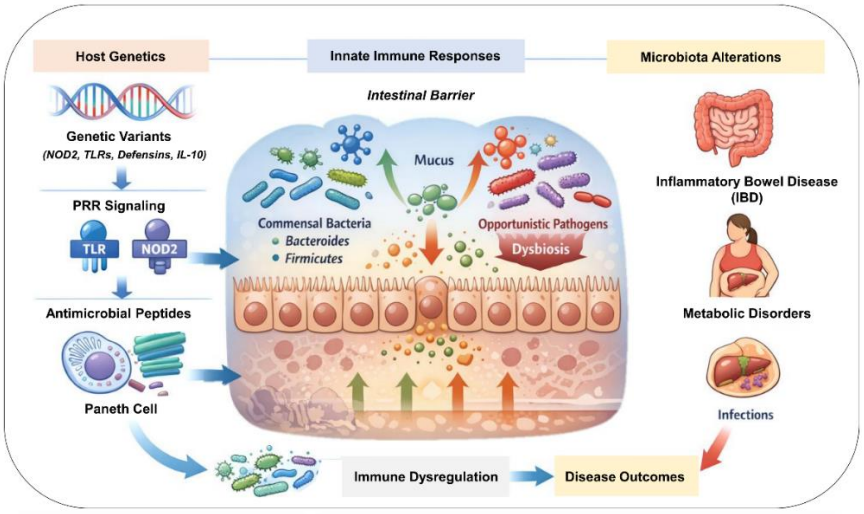

Fig. 1. Integrative overview of host genetic regulation of gut microbiota through innate immune pathways. Genetic variation in innate immune genes, including PRRs (e.g., TLRs, NOD2), AMP pathways, and regulatory cytokines, affects microbial sensing, barrier integrity, and antimicrobial defense. These variations shape the composition of the gut microbiota, and disruptions can lead to dysbiosis, immune imbalance, and an increased risk of inflammatory, metabolic, and infectious diseases.

2. Literature search and selection

A systematic literature search was conducted to identify studies examining the relationship between genetic variation in innate immune genes and gut microbiota composition. Electronic databases, including PubMed/MEDLINE, Web of Science, Scopus, and Embase, were searched up to the time of manuscript preparation. The search strategy combined controlled vocabulary and free-text terms related to the gut microbiome, innate immunity, and host genetics, including “gut microbiota,” “innate immunity,” “pattern recognition receptors,” “Toll-like receptors,” “NOD-like receptors,” “inflammasome,” “antimicrobial peptides,” “cytokines,” “genetic variation,” “polymorphism,” “SNP,” and “copy number variation.” Reference lists of relevant articles and reviews were manually screened to identify additional eligible studies.

Studies were included if they investigated associations between innate immune genetic variation and gut microbiota composition or function in humans, or if they employed experimental animal or in vitro models to assess causal mechanisms. Eligible studies used microbiome profiling approaches such as 16S rRNA gene sequencing or shotgun metagenomics and included original research articles, large-scale genome-microbiome association studies, or high-quality meta-

analyses. Non-intestinal microbiome studies, articles lacking genetic or immune relevance, conference abstracts, and non-English publications were excluded.

Data extracted included study design, population or model system, genes examined, type of genetic variation, microbiome profiling method, and principal findings. Owing to methodological heterogeneity, a narrative synthesis approach was applied. Study quality was assessed qualitatively based on cohort size, replication, control of confounders, and reproducibility across cohorts, informing interpretation of evidence strength.

3. Overview of innate immunity in the gut

3.1. Innate immune system in intestinal homeostasis

The intestinal tract represents the largest interface between the external environment and the host, harbouring a dense microbial ecosystem while simultaneously functioning as an immunological organ that must distinguish between harmless commensals and harmful pathogens. Maintaining homeostasis in this complex environment requires a coordinated innate immune network consisting of the physical epithelial barrier, pattern recognition receptors (PRRs), antimicrobial effectors, and cytokine-mediated signaling. The mechanisms by which genetic variation in pattern recognition receptors disrupts microbial sensing and promotes dysbiosis are illustrated in Fig. 2.

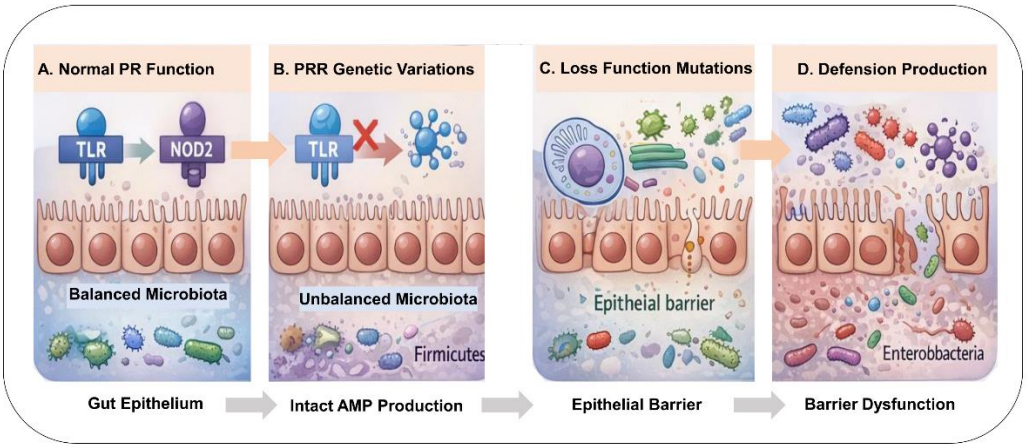

Fig. 2. Genetic variation in pattern recognition receptors disrupts microbial sensing and promotes dysbiosis. Under homeostatic conditions, pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) and NOD2, recognize microbial ligands and support balanced immune signaling, antimicrobial peptide production, and epithelial barrier integrity. Genetic variants, particularly loss-of-function mutations, impair microbial recognition and downstream signaling, thereby reducing immune tolerance, altering antimicrobial responses, and expanding pathobionts such as Enterobacteriaceae, ultimately leading to microbial dysbiosis and barrier dysfunction.

3.1.1. Epithelial barrier

The epithelial monolayer of the gut constitutes the first line of defense, functioning as a semipermeable physical barrier that limits direct microbial contact with underlying tissues

(Antonio Di Sabatino et al., 2023; Takiishi et al., 2017). Specialized epithelial cells (absorptive enterocytes, mucus-secreting goblet cells, and antimicrobial peptide-producing Paneth cells) and intercellular tight junctions collectively maintain barrier integrity and segregate luminal microbes from the systemic immune system. Disruption of this barrier alters microbial ecology and predisposes to inflammation and disease (Arumugam et al., 2025; Fukata & Arditi, 2013; Gieryńska et al., 2022).

3.1.2. Pattern Recognition Receptors (PRRs)

PRRs are germline-encoded sensors that detect conserved microbial-associated molecular patterns (MAMPs). Major PRR families in the gut include TLRs, NOD-like receptors (NLRs), C-type lectin receptors, and cytosolic nucleic acid sensors (Chen et al., 2025; Rolland et al., 2024). Upon engagement of a MAMP, PRRs initiate intracellular signaling cascades that modulate host defence, cytokine production, and epithelial responses, thereby shaping microbial composition and host-microbe interactions (Chu & Mazmanian, 2013; Muniz et al., 2012).

3.1.3. Antimicrobial Peptides (AMPs)

Antimicrobial peptides are small cationic molecules secreted primarily by Paneth cells and epithelial surfaces that exert direct microbicidal activity and modulate microbial community structure (Kim, 2014; Ra & Bang, 2024). Families such as defensins and cathelicidins are expressed constitutively or after PRR stimulation and regulate commensal and pathogenic populations. Dysregulated AMP expression alters ecological niches and can shift the microbiota toward pathogenic states (Ra & Bang, 2024; Yao et al., 2024).

3.1.4. Cytokine signaling

Innate immune activation in the gut also triggers production of cytokines and chemokines (e.g., Interleukin-1 beta (IL-1β), Interleukin-18 (IL-18), tumor necrosis factor alpha (TNF-α), and interleukin-22 (IL-22)) by epithelial and immune cells. These mediators coordinate local immune responses, recruit effector cells, promote barrier repair, or maintain tolerance (Garlanda et al., 2025; Ohara et al., 2024; Wang, Gong, et al., 2025). Cytokine signaling is critical not just for pathogen clearance, but for regulating baseline crosstalk with the microbiota itself. Perturbations in cytokine networks often parallel alterations in microbial communities in diseases such as inflammatory bowel disease and metabolic disorders (Marek Vebr et al., 2023; Ohara et al., 2024; Shirin Manshouri et al., 2024; Zurgham & Mehwish, 2025).

Together, these components constitute a dynamic innate immune network that both restricts inappropriate microbial invasion and supports a symbiotic relationship with commensal microbiota, maintaining intestinal integrity and overall host health.

3.2. Genetic variation in innate immune genes

Genetic variation in innate immune genes represents a fundamental source of inter-individual differences in immune responses and, by extension, gut microbiota composition. These variants can alter host sensing, effector functions, and downstream immune regulation.

3.2.1. Single Nucleotide Polymorphisms (SNPs)

SNPs are the most common form of genetic variation and can influence gene function by altering amino acid sequences or by affecting regulatory elements that control gene expression.60 Innate

immune genes such as Toll-like receptor 4 (TLR4), nucleotide-binding oligomerization domain-containing protein 2 (NOD2), and interleukin-23 receptor (IL23R) harbour well-characterized SNPs that modulate signal transduction and disease susceptibility (e.g., TLR4 Asp299Gly) (Cheng et al., 2015; Giambra et al., 2023). These variations can consequently shape individual differences in gut microbiota composition and host immune responses.

3.2.2. Loss-of-function mutations

More severe than SNPs, loss-of-function mutations altogether abolish the normal protein activity (Chigozie et al., 2025; Yamaguchi et al., 2017). A classic example is NOD2 mutations (e.g., R702W, G908R, L1007insC), which impair bacterial peptidoglycan recognition and are strongly associated with Crohn's disease risk in specific populations. These mutations can disrupt host–microbe interactions and alter microbial diversity in the gut (Barnet et al., 2025). Such changes contribute to inflammation and increase susceptibility to intestinal disorders.

3.2.3. Regulatory variants

Noncoding variants can affect transcription factor binding sites, splicing, or chromatin structure, leading to differences in gene expression levels. Regulatory variation in innate signaling components (e.g., promoter polymorphisms in TLRs or cytokine genes) influences the magnitude of immune responses and may indirectly shape microbial ecology (Häder et al., 2023; Yeyeodu et al., 2024).

3.2.4 Population differences

Different ancestral populations show variable frequencies of innate immune gene variants. For instance, the common NOD2 risk alleles in European Crohn's disease patients are rare or absent in Asian cohorts, illustrating how evolutionary history and selection pressures influence genotype distribution and potentially host-microbial interactions (S. Nakagome et al., 2012).

These genetic factors interact with environmental exposures to generate diverse innate immune landscapes, which in turn influence the host's ability to sense and respond to microbial cues. Understanding this variation is foundational to linking host genetics, immune function, and microbiota composition.

4. Effects of genetic variations in PRRs

Pattern recognition receptors, particularly TLRs and NLRs, orchestrate initial host recognition of microbes and set the tone for downstream immune responses (Qing et al., 2022). Genetic variants in these sensors can alter the thresholds and quality of microbial detection, with consequences for microbial composition, community diversity, and host-microbe dynamics (Ayoub et al., 2025). Key innate immune genes influencing gut microbiota composition are summarized in Table 1.

Table 1. Key innate immune genes influencing gut microbiota composition

Gene	Immune function	Genetic variation	Microbiota effect	Reference
TLR2	Recognition of Gram-positive bacterial lipoproteins; immune tolerance	SNPs affecting signaling efficiency	Altered Firmicutes/Bacteroidetes ratio	(Abreu, 2010; Cheng et al., 2015; Choteau et al., 2017)

TLR4	LPS recognition; inflammatory regulation	Hypomorphic SNPs	Expansion of Proteobacteria	(Cheng et al., 2015; Loh et al., 2008; Routsias et al., 2025)
TLR5	Flagellin recognition	Loss-of-function mutation	Dysbiosis; metabolic syndrome	(Ayoub et al., 2025; Kawai & Akira, 2006)
TLR9	Bacterial DNA sensing	Regulatory SNPs	Altered immune tolerance	(Bauer et al., 2001)
NOD2	Peptidoglycan sensing; Paneth cell function	Loss-of-function variants	Reduced diversity; pathobiont expansion	(Barnet et al., 2025; Frank et al., 2007)
NLRP6	Inflammasome activation; mucus regulation	Functional polymorphisms	Prevotellaceae expansion	(Chen, 2014; Elinav et al., 2011; Wlodarska et al., 2014)
NLRP3	Inflammasome activation	SNPs affecting IL-1β production	Pro-inflammatory microbiota	(Biswas & Kobayashi, 2013; Guo et al., 2020)
DEFA5/6	Antimicrobial peptides (α-defensins)	Copy number variation	Loss of microbial containment	(Fu et al., 2023; Salzman et al., 2009; Wehkamp et al., 2005)
CAMP (LL-37)	Broad-spectrum antimicrobial activity	Reduced expression variants	Increased epithelial colonization	(Hooper et al., 2012)
IL10	Immune tolerance	Loss-of-function variants	Severe dysbiosis	(Sharifinejad et al., 2022)

4.1. Toll-Like Receptors (TLRs)

4.1.1. Biological role of TLRs in the gut

Toll-like receptors are transmembrane sensors distributed across epithelial and immune cells throughout the gastrointestinal tract (Chen et al., 2024; Kawai et al., 2024). Specific TLRs recognize distinct microbial components, including TLR2 that binds lipoproteins from Gram-positive bacteria and forms heterodimers with TLR1 or TLR6 for ligand discrimination (Choteau et al., 2017), TLR4 detects lipopolysaccharide (LPS), a signature of Gram-negative bacteria (Wan et al., 2023), TLR5 senses bacterial flagellin, abundant in motile species (Hug et al., 2018), and TLR9 recognizes unmethylated CpG DNA, common in bacterial genomes.

Upon ligand engagement, TLRs activate downstream signaling cascades (e.g., MyD88-dependent pathways), inducing transcription of cytokines, chemokines, and antimicrobial genes that balance immune tolerance with defence. TLR signaling is crucial for maintaining epithelial homeostasis, controlling microbial access, and shaping the immune milieu of the gut (Hug et al., 2018).

4.1.2. Genetic polymorphisms in TLR genes

Functional polymorphisms in TLR genes modulate receptor signaling and immune output. The TLR4 Asp299Gly and Thr399Ile variants alter the extracellular domain of TLR4, reducing responsiveness to LPS and associating with hyporesponsive signaling in vitro and altered disease risks clinically. TLR2 Arg753Gln decreases NF-κB activation in response to its ligands, influencing inflammatory responses (Routsias et al., 2025). Such polymorphisms influence receptor sensitivity and downstream gene expression profiles, potentially altering host recognition of microbial ligands and the baseline immune tone toward commensals and pathogens.

4.1.3. Impact on gut microbiota composition

Variants in TLR genes have been linked to shifts in microbiota features. Firstly, in human cohorts, TLR4 variants correlate with differences in abundance of major taxa such as Firmicutes and modulate disease risk in immune-related conditions like food allergy, potentially via altered microbial cues (Mehmet Kılıç et al., 2023). Secondly, mouse models deficient in specific TLRs show inconsistent but instructive results; while some studies report negligible effects of TLR2/TLR4 deficiency on overall bacterial community structure, others demonstrate that TLR5 deficiency leads to altered microbiota composition and predisposition to metabolic syndrome, highlighting context-dependent outcomes (Loh et al., 2008). These observations indicate that TLR variants can shift microbial diversity and community patterns, though the magnitude and consistency of these effects are influenced by the genetic background, environment, and study design.

4.2. NOD-Like Receptors (NLRs)

4.2.1. NOD2 and intestinal immunity

NOD2 (nucleotide-binding oligomerization domain containing 2) is a cytosolic PRR that senses muramyl dipeptide (MDP), a conserved peptidoglycan fragment from bacterial cell walls. NOD2 is abundantly expressed in Paneth cells and mononuclear phagocytes within the gut mucosa, where it regulates antimicrobial peptide secretion and epithelial defence, contributing to microbial containment and homeostatic signaling (Guo et al., 2020).

4.2.2. NOD2 genetic variants

Certain NOD2 variants (R702W, G908R, L1007fsinsC) compromise sensing of bacterial MDP and are among the strongest genetic risk factors for Crohn's disease in European populations. These mutations impair NF-κb activation and antimicrobial responses, leading to aberrant host–microbe interactions (Biswas & Kobayashi, 2013).

4.2.3. Effects on gut microbial ecology

Functional loss of NOD2 signaling is associated with reduced bacterial diversity, expansion of pathobionts, and a dysbiotic microbial state that correlates with disease phenotypes. In experimental models, NOD2 deficiency alters Paneth cell function and antimicrobial peptide output, undermining ecological control of microbes and facilitating overgrowth of taxa that exploit weakened host defence niches (Chen, 2014).

4.3. Inflammasome-related genes

4.3.1. Role of Inflammasomes in Microbial Regulation

Inflammasomes are multi-protein complexes formed upon activation of certain NLR family members (e.g., NLRP3, NLRP6) that culminate in caspase-1 activation and processing of pro-inflammatory cytokines such as IL-1β and IL-18. These cytokines modulate epithelial repair, AMP secretion, and immune cell recruitment, thus influencing microbial community structure (Frühbeck et al., 2024).

4.3.2. Genetic variation and altered microbial sensing

Variants in inflammasome components affect their activation thresholds and cytokine outputs. For example, NLRP6 has been implicated in the regulation of mucosal IL-18 and antimicrobial peptide

release, with deficiency predisposing to altered microbiota and greater susceptibility to colitis. However, the extent and reproducibility of these effects remain areas of active investigation (Frühbeck et al., 2024; Michail Mamantopoulos et al., 2017).

4.3.3. Consequences for host-microbe interaction

Altered inflammasome function can disrupt the gut's ecological equilibrium, leading to microbial communities that either over-stimulate or evade host surveillance. Changes in inflammasome signaling have consequences for barrier integrity, inflammatory responses, and potentially systemic outcomes, linking innate genetic variation to microbial ecology and disease (Bevins & Salzman, 2011). Evidence from human cohort studies linking innate immune gene variants to gut microbiota alterations is summarized in Table 2.

Table 2. Human studies linking innate immune gene variants to gut microbiota composition

Population	Gene/Variant	Method	Main findings	Study
Crohn's disease patients	NOD2 variants	16S rRNA sequencing	Reduced microbial diversity; Proteobacteria expansion	(Frank et al., 2007)
Multi-cohort human study	NOD2, ATG16L1	Microbiome GWAS	Host genotype explains microbiota variation	(Knights et al., 2014)
Healthy adults	TLR5 SNP	Shotgun metagenomics	Altered microbial richness	(Leifer et al., 2014)
Twins (heritability)	Host genetic variation	16S rRNA profiling	Several host genetic loci linked to microbiome variation	(Goodrich et al., 2014)
Healthy adults	TLR5 SNP	16S & shotgun	Association between TLR5 variation and overall microbiome diversity	(Ayoub et al., 2025)
Healthy & IBD cohorts	IBD risk variants	MR analysis	Identified taxa (Akkermansia, Dorea) associated with IBD-linked host variants	(Mah et al., 2025)
Dutch cohorts	C-type lectin & innate immune genes	Meta-analysis	Innate immune gene variants associated with microbial taxa	(Kemis, 2018)

5. Effects of genetic variations in antimicrobial peptide pathways

5.1 Defensins and cathelicidins

AMPs constitute a fundamental effector arm of innate immunity in the gastrointestinal tract, acting at the interface between host defence and microbial ecology. Among these, defensins and cathelicidins are the most extensively studied and are central to microbial containment and community regulation.

Defensins are small, cysteine-rich peptides with broad-spectrum antimicrobial activity against bacteria, fungi, and viruses. In the human intestine, α-defensins (human defensin-5 and -6; HD5 and HD6) are predominantly produced by Paneth cells located at the base of intestinal crypts, while β-defensins are expressed by epithelial cells throughout the gut. These peptides exert microbicidal activity by disrupting microbial membranes and by shaping ecological niches through selective pressure on microbial taxa (Gallo & Hooper, 2012; GELFAND, 2004).

Cathelicidins, particularly LL-37 in humans, complement defensins by exerting antimicrobial, immunomodulatory, and wound-healing functions. LL-37 modulates epithelial responses,

neutralizes bacterial toxins, and influences microbial spatial organization in the gut mucosa (Wallaeys et al., 2022).

Paneth cell biology is central to AMP-mediated control of microbiota. Paneth cells integrate microbial sensing signals (e.g., via NOD2 and TLRs) and respond by releasing defensins into the crypt lumen, thereby regulating microbial proximity to the epithelium and protecting stem cell niches. Disruption of Paneth cell function is consistently linked to dysbiosis and intestinal inflammation (Pastalkova, 2006).

5.2. Genetic variation in defensin genes

Genetic variation in defensin genes significantly influences AMP availability and function, thereby altering host-microbe equilibrium.

One of the most prominent forms of variation is copy number variation (CNV), particularly affecting the β-defensin gene cluster (DEFB). CNVs in DEFB genes result in inter-individual differences in defensin dosage, with lower copy numbers associated with impaired antimicrobial defence and increased susceptibility to inflammatory diseases (Wehkamp et al., 2005).

Reduced expression of α-defensins has been repeatedly observed in individuals carrying NOD2 risk alleles, suggesting a gene–gene interaction between microbial sensing pathways and AMP production. Reduced HD5/HD6 expression compromises microbial containment and alters luminal microbial composition (Salzman et al., 2009).

Beyond coding regions, regulatory variants that affect the transcriptional control of defensin genes further contribute to variability in AMP expression across populations. Such variation likely reflects evolutionary pressures imposed by historical pathogen exposure and environmental factors.

5.3. Microbiota shifts due to impaired antimicrobial activity

Defective AMP pathways lead to reproducible alterations in gut microbial ecology. Reduced defensin activity permits the expansion of opportunistic bacteria and pathobionts that are otherwise suppressed under homeostatic conditions. Experimental models demonstrate that loss of Paneth cell defensins results in increased bacterial adherence to the epithelium and altered spatial segregation of microbes (Stolfi et al., 2022). In humans, impaired AMP function correlates with decreased microbial diversity and enrichment of inflammatory-associated taxa, contributing to barrier dysfunction and mucosal inflammation. This creates a permissive environment for chronic immune activation and disease progression (Shouval et al., 2014).

6. Effects of cytokine and immune regulatory gene variants

6.1 IL-10 and immune tolerance

IL-10 is a central anti-inflammatory cytokine essential for maintaining immune tolerance toward commensal microbiota. IL-10 signalling restrains excessive innate and adaptive immune activation, thereby preserving microbial diversity and mucosal integrity. IL-10 deficiency in mice results in spontaneous colitis driven by aberrant responses to commensal bacteria (Sharifinejad et al., 2022).

Human IL10 and IL10R variants are associated with early-onset IBD and severe intestinal inflammation, highlighting the importance of this pathway in host–microbe homeostasis (Pastras et al., 2025).

6.2. IL-23/Th17 axis

The IL-23/Th17 pathway plays a dual role in antimicrobial defence and inflammation. IL-23 promotes Th17 responses and production of IL-17 and IL-22, cytokines that enhance barrier function and AMP expression. Genetic variants in IL23R modulate susceptibility to IBD and influence microbial composition by altering mucosal immune tone (Sanchis-Artero et al., 2021).

6.3. TNF and inflammatory tone

TNF-α is a key pro-inflammatory cytokine with profound effects on epithelial integrity and microbial ecology. Variants influencing TNF expression can shift the inflammatory threshold of the gut environment, indirectly selecting for inflammation-tolerant microbial communities. Anti-TNF therapy in IBD patients has been shown to partially normalize dysbiotic microbiota, underscoring the bidirectional relationship between cytokine signalling and microbial composition (Medzhitov, 2007).

6.4 Consequences for microbial composition

Collectively, cytokine gene variants reshape microbial communities by modulating immune tolerance, barrier repair, and inflammatory pressure. Altered cytokine landscapes favour specific microbial assemblages that can either reinforce homeostasis or perpetuate chronic inflammation, depending on host genotype and environmental context.

7. Mechanistic pathways linking host genetics to microbiota changes

Genetic variation in innate immune genes influences gut microbiota composition through interconnected mechanistic pathways that govern microbial sensing, antimicrobial activity, inflammatory tone, and epithelial barrier integrity. These mechanisms operate simultaneously and dynamically, forming a multi-layered regulatory network that shapes host–microbe interactions (Abreu, 2010).

7.1. Altered microbial sensing

Innate immune receptors act as gatekeepers that detect microbial ligands and calibrate immune responsiveness. Genetic variants in PRRs can modify ligand recognition thresholds, downstream signal transduction, or receptor localization, resulting in altered discrimination between commensal and pathogenic microbes. Attenuated microbial sensing may permit overgrowth of normally controlled taxa, whereas hypersensitive signalling can promote inflammatory selection pressures that reduce microbial diversity. These genotype-dependent sensing differences represent one of the earliest determinants of microbiota composition (Vaishnava et al., 2011).

7.2 Changes in antimicrobial peptide secretion

Genetic variation affecting AMP pathways influences both the quantity and spatial distribution of antimicrobial peptides in the gut. Reduced defensin or cathelicidins secretion compromises microbial containment within the lumen and alters crypt-associated microbial niches. Studies demonstrate that AMP deficiencies enable bacteria to encroach upon epithelial surfaces, increasing

host-microbe contact and reshaping microbial communities toward inflammation-associated profiles (Parker et al., 2013).

7.3 Modulation of intestinal inflammation

Host genetic variants influence baseline inflammatory tone by regulating cytokine production and immune cell recruitment. Low-grade inflammation alters nutrient availability, oxygen gradients, and epithelial turnover, thereby selecting for microbial taxa adapted to inflammatory environments. This process, termed "inflammatory selection," promotes the expansion of facultative anaerobes and pathobionts that thrive under immune stress (Sonnenburg & Bäckhed, 2016).

7.4 Barrier integrity and mucus production

Genetic perturbations affecting epithelial integrity or mucus secretion modify physical separation between microbes and host tissues. Impaired mucus layers or tight junction dysfunction increase microbial access to the epithelium, intensifying immune activation and ecological instability. Genes regulating epithelial repair and mucus production indirectly influence microbial spatial organization and community resilience (Knights et al., 2014).

7.5 Feedback loops between microbiota and immunity

Microbiota-derived metabolites such as short-chain fatty acids (SCFAs), secondary bile acids, and tryptophan metabolites feed back onto host immune pathways, modulating PRR expression, cytokine production, and epithelial health. Genetic variation determines how effectively hosts respond to these microbial signals, reinforcing or destabilizing host–microbe equilibrium. These bidirectional feedback loops underscore the co-evolutionary nature of host genetics and the microbiome (Knights et al., 2014).

8. Clinical and biological implications

8.1. Inflammatory bowel disease

IBD represents the most compelling clinical model of gene-microbiota interactions. Variants in NOD2, IL10, IL23R, and defensin-related genes predispose individuals to dysbiosis and inappropriate immune activation. Longitudinal studies indicate that host genotype influences disease-associated microbial signatures, disease course, and therapeutic response (Hotamisligil, 2017).

8.2. Metabolic and autoimmune disorders

Host innate immune genetics also modulates susceptibility to metabolic and autoimmune diseases via microbiota-mediated mechanisms. Variants affecting microbial sensing and inflammation influence energy harvest, insulin sensitivity, and systemic immune activation. TLR and inflammasome pathways have been implicated in obesity, type 2 diabetes, and autoimmune disorders through microbiota-dependent effects (Khan et al., 2021).

8.3. Infection susceptibility

Innate immune genetic variation shapes colonization resistance against enteric pathogens. Defects in PRRs or AMP pathways compromise early microbial clearance, increasing susceptibility to

infection and altering post-infection microbiota recovery. Such effects have implications for both acute and chronic infectious diseases (Shahid, 2025).

8.4. Precision medicine and microbiome-based interventions

Understanding host genetic influences on microbiota composition opens avenues for precision medicine. Stratifying patients based on innate immune genotypes may improve prediction of probiotic efficacy, dietary interventions, faecal microbiota transplantation outcomes, and biologic therapy responses. Integrating host genetics with microbiome profiling represents a critical step toward personalized therapeutic strategies (Bauer et al., 2001; Tariq et al., 2025).

9. Limitations and future perspectives

Despite growing evidence linking innate immune genetic variation to gut microbiota composition, several critical gaps remain. Future studies must move beyond cross-sectional associations toward causal and temporally resolved analyses. Longitudinal cohort designs, particularly those initiated early in life, will be essential to capture how innate immune genotypes shape microbiota assembly, stability, and resilience across developmental and disease trajectories. Integrating causal inference approaches, such as Mendelian randomization and genetically informed intervention studies, will further help disentangle direct genetic effects from environmentally mediated influences.

Progress in this field will also depend on deeper integration of multi-omics and spatially resolved technologies. Coupling host genomics with transcriptomics, epigenomics, metabolomics, and metagenomics will enable the mechanistic dissection of how genetic variants alter immune signalling pathways and downstream microbial functions. Emerging single-cell and spatial profiling approaches offer unprecedented opportunities to resolve cell-type-specific host-microbe interactions at the mucosal interface, where innate immune regulation is most active.

Equally important is the systematic evaluation of gene–environment–microbiome interactions. Diet, medication exposure, infections, and lifestyle factors likely modulate the penetrance of innate immune variants, yet these interactions remain poorly characterized. Expanding studies to diverse ancestral populations will improve generalizability and provide evolutionary insight into how immune gene variation has co-adapted with microbial ecosystems. Finally, translating these insights into clinical applications represents a major frontier. Stratifying individuals by innate immune genotype may improve the prediction of responses to microbiome-based therapies, including dietary interventions, probiotics, and faecal microbiota transplantation. Ultimately, targeted modulation of innate immune pathways may enable precision manipulation of the gut microbiota to prevent and treat inflammatory, metabolic, and immune-mediated diseases.

10. Conclusion

Genetic variation in innate immune genes constitutes a critical determinant of gut microbiota composition and host-microbe interactions. Through effects on microbial sensing, antimicrobial effector pathways, inflammatory regulation, and barrier integrity, host genetics shapes the ecological landscape of the gut. These influences operate within a complex, dynamic network that integrates environmental exposures and microbial feedback signals. While individual genetic

effects are often modest, their cumulative impact is biologically meaningful and clinically relevant. Continued integration of host genetics, microbiome science, and functional validation will be essential for translating these insights into personalized interventions and improved disease management.

Acknowledgments: None

Conflicts of Interest: The authors declare no conflict of interest.

References

Abreu, M. T. (2010). Toll-like receptor signalling in the intestinal epithelium: how bacterial recognition shapes intestinal function. Nature Reviews Immunology, 10(2), 131–144. https://doi.org/10.1038/nri2707

Antonio Di Sabatino, Santacroce, G., Carlo Maria Rossi, Broglio, G., & Marco Vincenzo Lenti. (2023). Role of mucosal immunity and epithelial–vascular barrier in modulating gut homeostasis. Internal and Emergency Medicine, 18(6), 1635–1646. https://doi.org/10.1007/s11739-023-03329-1

Arumugam, P., Saha, K., & Nighot, P. (2025). Intestinal Epithelial Tight Junction Barrier Regulation by Novel Pathways. Inflammatory Bowel Diseases, 31(1), 259–271. https://doi.org/10.1093/ibd/izae232

Awany, D., Allali, I., Dalvie, S., Hemmings, S., Mwaikono, K. S., Thomford, N. E., Gomez, A., Mulder, N., & Chimusa, E. R. (2019). Host and Microbiome Genome-Wide Association Studies: Current State and Challenges. Frontiers in Genetics, 9. https://doi.org/10.3389/fgene.2018.00637

Ayoub, M., Chmouni, Y. A., Damaa, N., Eter, A., Medawar, H., Ghadieh, H. E., Bazzi, S., Khattar, Z. A., Azar, S., & Harb, F. (2025). Genetic and immunological regulation of gut Microbiota: The Roles of TLRs, CLRs, and key proteins in microbial homeostasis and disease. Gene, 149469. https://doi.org/10.1016/j.gene.2025.149469

Barnet, M. B., Jackson, K. J. L., Masle-Farquhar, E., Russell, A., Burnett, D. L., Chye, A., Jara, C. J., Faulks, M., Mawson, A., Peters, T. J., Brink, R., Wright, K., Allen, I., Junankar, S., Davis, I. D., Heller, G., Khan, Z., Bruce, J., Yang, C., & Prokopec, S. (2025). Common inherited loss-of-function mutations in the innate sensor NOD2 contribute to exceptional immune response to cancer immunotherapy. Proceedings of the National Academy of Sciences of the United States of America, 122(28), e2314258122. https://doi.org/10.1073/pnas.2314258122

Bauer, S., Kirschning, C. J., Hacker, H., Redecke, V., Hausmann, S., Akira, S., Wagner, H., & Lipford, G. B. (2001). Human TLR9 confers responsiveness to bacterial DNA via species-specific CpG motif recognition. Proceedings of the National Academy of Sciences, 98(16), 9237–9242. https://doi.org/10.1073/pnas.161293498

Belkaid, Y., & Hand, Timothy W. (2014). Role of the Microbiota in Immunity and Inflammation. Cell, 157(1), 121–141. https://doi.org/10.1016/j.cell.2014.03.011

Belkaid, Y., & Harrison, O. J. (2017). Homeostatic Immunity and the Microbiota. Immunity, 46(4), 562–576. https://doi.org/10.1016/j.immuni.2017.04.008

Bevins, C. L., & Salzman, N. H. (2011). Paneth cells, antimicrobial peptides and maintenance of intestinal homeostasis. Nature Reviews Microbiology, 9(5), 356–368. https://doi.org/10.1038/nrmicro2546

Biswas, A., & Kobayashi, K. S. (2013). Regulation of intestinal microbiota by the NLR protein family. International Immunology, 25(4), 207–214. https://doi.org/10.1093/intimm/dxs116

Blekhman, R., Goodrich, J. K., Huang, K., Sun, Q., Bukowski, R., Bell, J. T., Spector, T. D., Keinan, A., Ley, R. E., Gevers, D., & Clark, A. G. (2015). Host genetic variation impacts

microbiome composition across human body sites. Genome Biology, 16(1). https://doi.org/10.1186/s13059-015-0759-1

BURGNER, D., & LEVIN, M. (2003). Genetic susceptibility to infectious diseases. The Pediatric Infectious Disease Journal, 22(1), 1–6. https://doi.org/10.1097/00006454-200301000-00002

Chen, G. Y. (2014). Role of Nlrp6 and Nlrp12 in the maintenance of intestinal homeostasis. European Journal of Immunology, 44(2), 321–327. https://doi.org/10.1002/eji.201344135

Chen, L., Zhang, L., Hua, H., Liu, L., Mao, Y., & Wang, R. (2024). Interactions between toll-like receptors signaling pathway and gut microbiota in host homeostasis. Immunity, Inflammation and Disease, 12(7). https://doi.org/10.1002/iid3.1356

Chen, R., Zou, J., Chen, J., Zhong, X., Kang, R., & Tang, D. (2025). Pattern recognition receptors: function, regulation and therapeutic potential. Signal Transduction and Targeted Therapy, 10(1). https://doi.org/10.1038/s41392-025-02264-1

Cheng, Y., Zhu, Y., Huang, X., Zhang, W., Han, Z., & Liu, S. (2015). Association between TLR2 and TLR4 Gene Polymorphisms and the Susceptibility to Inflammatory Bowel Disease: A Meta-Analysis. PLOS ONE, 10(5), e0126803. https://doi.org/10.1371/journal.pone.0126803

Chigozie, V. U., Enyi, E. O., Akwari, A. A., & Esimone, C. O. (2025). Host-microbe interactions at barrier tissues and immunomodulation: a scoping review. Discover Bacteria, 2(1). https://doi.org/10.1007/s44351-025-00037-3

Choteau, L., Hélène Vancraeyneste, Roy, D. L., Laurent Dubuquoy, Romani, L., Thierry Jouault, Poulain, D., Boualem Sendid, Calandra, T., Roger, T., & Samir Jawhara. (2017). Role of TLR1, TLR2 and TLR6 in the modulation of intestinal inflammation and Candida albicans elimination. Gut Pathogens, 9(1). https://doi.org/10.1186/s13099-017-0158-0

Chu, H., & Mazmanian, S. K. (2013). Innate immune recognition of the microbiota promotes host-microbial symbiosis. Nature Immunology, 14(7), 668–675. https://doi.org/10.1038/ni.2635

Cui, C., Wang, F., Zheng, Y., Wei, H., & Peng, J. (2023). From birth to death: The hardworking life of Paneth cell in the small intestine. Frontiers in Immunology, 14. https://doi.org/10.3389/fimmu.2023.1122258

Elinav, E., Strowig, T., Kau, A. L., Henao-Mejia, J., Thaiss, C. A., Booth, C. J., Peaper, D. R., Bertin, J., Eisenbarth, S. C., Gordon, J. I., & Flavell, R. A. (2011). NLRP6 inflammasome regulates colonic microbial ecology and risk for colitis. Cell, 145(5), 745–757. https://doi.org/10.1016/j.cell.2011.04.022

Europe PMC. (2016). Europe PMC. Europepmc.org. https://europepmc.org/article/med/33462485?utm_source=chatgpt.com

Frank, D. N., St. Amand, A. L., Feldman, R. A., Boedeker, E. C., Harpaz, N., & Pace, N. R. (2007). Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proceedings of the National Academy of Sciences, 104(34), 13780–13785. https://doi.org/10.1073/pnas.0706625104

Frühbeck, G., Gómez-Ambrosi, J., Ramírez, B., Becerril, S., Amaia Rodríguez, Amaia Mentxaka, Víctor Valentí, Moncada, R., Reina, G., Baixauli, J., Casado, M., Silva, C., Escalada, J., & Catalán, V. (2024). Decreased expression of the NLRP6 inflammasome is associated with increased

intestinal permeability and inflammation in obesity with type 2 diabetes. Cellular and Molecular Life Sciences, 81(1), 77–77. https://doi.org/10.1007/s00018-024-05124-3

Fu, J., Zong, X., Jin, M., Min, J., Wang, F., & Wang, Y. (2023). Mechanisms and regulation of defensins in host defense. Signal Transduction and Targeted Therapy, 8(1). https://doi.org/10.1038/s41392-023-01553-x

Fukata, M., & Arditi, M. (2013). The role of pattern recognition receptors in intestinal inflammation. Mucosal Immunology, 6(3), 451–463. https://doi.org/10.1038/mi.2013.13

Gallo, R. L., & Hooper, L. V. (2012). Epithelial antimicrobial defence of the skin and intestine. Nature Reviews Immunology, 12(7), 503–516. https://doi.org/10.1038/nri3228

Garlanda, C., Ceglie, I. D., & Sebastien Jaillon. (2025). IL-1 family cytokines in inflammation and immunity. Cellular and Molecular Immunology. https://doi.org/10.1038/s41423-025-01358-8

GELFAND, E. (2004). Inflammatory mediators in allergic rhinitis. Journal of Allergy and Clinical Immunology, 114, S135–S138. https://doi.org/10.1016/j.jaci.2004.08.043

Gensollen, T., Iyer, S. S., Kasper, D. L., & Blumberg, R. S. (2016). How colonization by microbiota in early life shapes the immune system. Science (New York, N.Y.), 352(6285), 539–544. https://doi.org/10.1126/science.aad9378

Giambra, V., Pagliari, D., Rio, P., Totti, B., Chiara Di Nunzio, Bosi, A., Giaroni, C., Gasbarrini, A., Gambassi, G., & Cianci, R. (2023). Gut Microbiota, Inflammatory Bowel Disease, and Cancer: The Role of Guardians of Innate Immunity. Cells, 12(22), 2654–2654. https://doi.org/10.3390/cells12222654

Gieryńska, M., Szulc-Dąbrowska, L., Struzik, J., Mielcarska, M. B., & Gregorczyk-Zboroch, K. P. (2022). Integrity of the Intestinal Barrier: The Involvement of Epithelial Cells and Microbiota—A Mutual Relationship. Animals, 12(2), 145. https://doi.org/10.3390/ani12020145

Goodrich, Julia K., Davenport, Emily R., Beaumont, M., Jackson, Matthew A., Knight, R., Ober, C., Spector, Tim D., Bell, Jordana T., Clark, Andrew G., & Ley, Ruth E. (2016). Genetic Determinants of the Gut Microbiome in UK Twins. Cell Host & Microbe, 19(5), 731–743. https://doi.org/10.1016/j.chom.2016.04.017

Goodrich, Julia K., Waters, Jillian L., Poole, Angela C., Sutter, Jessica L., Koren, O., Blekhman, R., Beaumont, M., Van Treuren, W., Knight, R., Bell, Jordana T., Spector, Timothy D., Clark, Andrew G., & Ley, Ruth E. (2014). Human Genetics Shape the Gut Microbiome. Cell, 159(4), 789–799. https://doi.org/10.1016/j.cell.2014.09.053

Guo, H., Gibson, S. A., & Ting, J. P. Y. (2020). Gut microbiota, NLR proteins, and intestinal homeostasis. Journal of Experimental Medicine, 217(10). https://doi.org/10.1084/jem.20181832

Häder, A., Schäuble, S., Gehlen, J., Thielemann, N., Buerfent, B. C., Schüller, V., Hess, T., Wolf, T., Schröder, J., Weber, M., Hünniger, K., Löffler, J., Vylkova, S., Panagiotou, G., Schumacher, J., & Kurzai, O. (2023). Pathogen-specific innate immune response patterns are distinctly affected by genetic diversity. Nature Communications, 14(1), 3239. https://doi.org/10.1038/s41467-023-38994-5

Hooper, L. V., Littman, D. R., & Macpherson, A. J. (2012). Interactions Between the Microbiota and the Immune System. Science, 336(6086), 1268–1273. https://doi.org/10.1126/science.1223490

Hotamisligil, G. S. (2017). Inflammation, metaflammation and immunometabolic disorders. Nature, 542(7640), 177–185. https://doi.org/10.1038/nature21363

Hou, K., Wu, Z.-X., Chen, X.-Y., Wang, J.-Q., Zhang, D., Xiao, C., Zhu, D., Koya, J. B., Wei, L., Li, J., & Chen, Z.-S. (2022). Microbiota in Health and Diseases. Signal Transduction and Targeted Therapy, 7(135). https://doi.org/10.1038/s41392-022-00974-4

Hug, H., Mohajeri, M., & La Fata, G. (2018). Toll-Like Receptors: Regulators of the Immune Response in the Human Gut. Nutrients, 10(2), 203. https://doi.org/10.3390/nu10020203

Iliev, I. D., Blander, J. M., Collins, N., Guo, C.-J., Longman, R. S., Sonnenberg, G. F., Zeng, M. Y., & Artis, D. (2025). Microbiota-mediated mechanisms of mucosal immunity across the lifespan. Nature Immunology, 26(10), 1645–1659. https://doi.org/10.1038/s41590-025-02281-w

Kawai, T., & Akira, S. (2006). TLR signaling. Cell Death and Differentiation, 13(5), 816–825. https://doi.org/10.1038/sj.cdd.4401850

Kawai, T., & Akira, S. (2010). The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nature Immunology, 11(5), 373–384. https://doi.org/10.1038/ni.1863

Kawai, T., Moe Ikegawa, Ori, D., & Shizuo Akira. (2024). Decoding Toll-like receptors: Recent insights and perspectives in innate immunity. Immunity, 57(4), 649–673. https://doi.org/10.1016/j.immuni.2024.03.004

Kemis, J. (2018). ELUCIDATION OF HOST GENETICS -GUT MICROBIOME INTERACTIONS, AND THE CONSEQUENCES ON METABOLIC DISEASE. https://asset.library.wisc.edu/1711.dl/EQHPFM5V74FP384/R/file-10c79.pdf?utm_source=chatgpt.com

Khan, I., Bai, Y., Zha, L., Ullah, N., Ullah, H., Shah, S. R. H., Sun, H., & Zhang, C. (2021). Mechanism of the Gut Microbiota Colonization Resistance and Enteric Pathogen Infection. Frontiers in Cellular and Infection Microbiology, 11. https://doi.org/10.3389/fcimb.2021.716299

Kim, J. M. (2014). Antimicrobial Proteins in Intestine and Inflammatory Bowel Diseases. Intestinal Research, 12(1), 20. https://doi.org/10.5217/ir.2014.12.1.20

Knights, D., Silverberg, M. S., Weersma, R. K., Gevers, D., Dijkstra, G., Huang, H., Tyler, A. D., van Sommeren, S., Imhann, F., Stempak, J. M., Huang, H., Vangay, P., Al-Ghalith, G. A., Russell, C., Sauk, J., Knight, J., Daly, M. J., Huttenhower, C., & Xavier, R. J. (2014). Complex host genetics influence the microbiome in inflammatory bowel disease. Genome Medicine, 6(12). https://doi.org/10.1186/s13073-014-0107-1

Koch, L. (2014). Shaping the gut microbiome. Nature Reviews Genetics, 16(1), 2–3. https://doi.org/10.1038/nrg3869

Kühn, R., Löhler, J., Rennick, D., Rajewsky, K., & Müller, W. (1993). Interleukin-10-deficient mice develop chronic enterocolitis. Cell, 75(2), 263–274. https://doi.org/10.1016/0092-8674(93)80068-p

Kurilshikov, A., Medina-Gomez, C., Bacigalupe, R., Radjabzadeh, D., Wang, J., Demirkan, A., Le Roy, C. I., Raygoza Garay, J. A., Finnicum, C. T., Liu, X., Zhernakova, D. V., Bonder, M. J., Hansen, T. H., Frost, F., Rühlemann, M. C., Turpin, W., Moon, J.-Y., Kim, H.-N., Lüll, K., & Barkan, E. (2021). Large-scale association analyses identify host factors influencing human gut microbiome composition. Nature Genetics, 53(2), 156–165. https://doi.org/10.1038/s41588-020-00763-1

Lee, H., Brott, B. K., Kirkby, L. A., Adelson, J. D., Cheng, S., Feller, M. B., Akash Datwani, & Shatz, C. J. (2014). Synapse elimination and learning rules co-regulated by MHC class I H2-Db. Nature, 509(7499), 195–200. https://doi.org/10.1038/nature13154

Leifer, C. A., McConkey, C., Li, S., Chassaing, B., Gewirtz, A. T., & Ley, R. E. (2014). Linking genetic variation in human Toll-like receptor 5 genes to the gut microbiome's potential to cause inflammation. Immunology Letters, 162(2), 3–9. https://doi.org/10.1016/j.imlet.2014.07.017

Ley, R. E., Turnbaugh, P. J., Klein, S., & Gordon, J. I. (2006). Human gut microbes associated with obesity. Nature, 444(7122), 1022–1023. https://doi.org/10.1038/4441022a

Loh, G., Brodziak, F., & Blaut, M. (2008). The Toll-like receptors TLR2 and TLR4 do not affect the intestinal microbiota composition in mice. Environmental Microbiology, 10(3), 709–715. https://doi.org/10.1111/j.1462-2920.2007.01493.x

Mah, C., Bessède, E., Benech, N., Hold, G., Sokol, H., Mah, C., Bessède, E., Equally, N., & Sokol, H. (n.d.). IMPACT OF DIET ON IBD AND THE GUT MICROBIOTA This work is licensed under a Creative Commons Attribution-Non-Commercial-Share Alike 4.0 International License. Retrieved January 3, 2026, from https://www.microbiotajournal.com/wp-content/uploads/sites/7/2021/09/e590.pdf?utm_source=chatgpt.com

Marek Vebr, Renáta Pomahačová, Sýkora, J., & Schwarz, J. (2023). A Narrative Review of Cytokine Networks: Pathophysiological and Therapeutic Implications for Inflammatory Bowel Disease Pathogenesis. Biomedicines, 11(12), 3229–3229. https://doi.org/10.3390/biomedicines11123229

Medzhitov, R. (2007). Recognition of microorganisms and activation of the immune response. Nature, 449(7164), 819–826. https://doi.org/10.1038/nature06246

Mehmet Kılıç, Elif Beyazıt, Ebru Etem Önalan, Tuğçe Kaymaz, & Erdal Taşkın. (2023). Evaluation of toll-like receptors 2 and 4 polymorphism and intestinal microbiota in children with food allergies. The Turkish Journal of Pediatrics, 65(5), 758–768. https://doi.org/10.24953/turkjped.2023.389

Michail Mamantopoulos, Ronchi, F., Filip Van Hauwermeiren, Vieira-Silva, S., Yilmaz, B., Martens, L., Yvan Saeys, Drexler, S. K., Yazdi, A. S., Raes, J., Lamkanfi, M., McCoy, K. F., & Wullaert, A. (2017). Nlrp6- and ASC-Dependent Inflammasomes Do Not Shape the Commensal Gut Microbiota Composition. 47(2), 339-348.e4. https://doi.org/10.1016/j.immuni.2017.07.011

Mota, J. F., Walter, J., & Prado, C. M. (2018). Insights Into the Relationship Between Gut Microbiota and Colorectal Cancer. Current Colorectal Cancer Reports, 14(6), 251–265. https://doi.org/10.1007/s11888-018-0419-4

Muniz, L. R., Knosp, C., & Yeretssian, G. (2012). Intestinal antimicrobial peptides during homeostasis, infection, and disease. Frontiers in Immunology, 3. https://doi.org/10.3389/fimmu.2012.00310

Nombulelo Mntambo, Arumugam, T., Ashiq Pramchand, Pillay, K., & Veron Ramsuran. (2025). A Review of Global Patterns in Gut Microbiota Composition, Health and Disease: Locating South Africa in the Conversation. Microorganisms, 13(12), 2831–2831. https://doi.org/10.3390/microorganisms13122831

Ohara, D., Takeuchi, Y., & Hirota, K. (2024). Type 17 immunity: novel insights into intestinal homeostasis and autoimmune pathogenesis driven by gut-primed T cells. Cellular and Molecular Immunology, 21(11), 1183–1200. https://doi.org/10.1038/s41423-024-01218-x

Okumura, R., & Takeda, K. (2017). Roles of intestinal epithelial cells in the maintenance of gut homeostasis. Experimental & Molecular Medicine, 49(5), e338–e338. https://doi.org/10.1038/emm.2017.20

Parker, J., Tsagkogeorga, G., Cotton, J. A., Liu, Y., Provero, P., Stupka, E., & Rossiter, S. J. (2013). Genome-wide signatures of convergent evolution in echolocating mammals. Nature, 502(7470), 228–231. https://doi.org/10.1038/nature12511

Pastalkova, E. (2006). Storage of Spatial Information by the Maintenance Mechanism of LTP. Science, 313(5790), 1141–1144. https://doi.org/10.1126/science.1128657

Pastras, P., Aggeletopoulou, I., Papantoniou, K., & Triantos, C. (2025). Targeting the IL-23 Receptor Gene: A Promising Approach in Inflammatory Bowel Disease Treatment. International Journal of Molecular Sciences, 26(10), 4775. https://doi.org/10.3390/ijms26104775

Qin, J., Li, R., Raes, J., Arumugam, M., Burgdorf, K. S., Manichanh, C., Nielsen, T., Pons, N., Levenez, F., Yamada, T., Mende, D. R., Li, J., Xu, J., Li, S., Li, D., Cao, J., Wang, B., Liang, H., Zheng, H., & Xie, Y. (2010). A human gut microbial gene catalogue established by metagenomic sequencing. Nature, 464(7285), 59–65. https://doi.org/10.1038/nature08821

Qing, F., Xie, T., Xie, L., Guo, T., & Liu, Z. (2022). How Gut Microbiota Are Shaped by Pattern Recognition Receptors in Colitis and Colorectal Cancer. Cancers, 14(15), 3821. https://doi.org/10.3390/cancers14153821

Ra, Y. E., & Bang, Y.-J. (2024). Balancing Act of the Intestinal Antimicrobial Proteins on Gut Microbiota and Health. Journal of Microbiology, 62(3), 167–179. https://doi.org/10.1007/s12275-024-00122-3

Rakoff-Nahoum, S., Paglino, J., Eslami-Varzaneh, F., Edberg, S., & Medzhitov, R. (2004). Recognition of Commensal Microflora by Toll-Like Receptors Is Required for Intestinal Homeostasis. Cell, 118(2), 229–241. https://doi.org/10.1016/j.cell.2004.07.002

Rolland, A., Véronique Douard, & Lapaque, N. (2024). Role of pattern recognition receptors and microbiota-derived ligands in obesity. Frontiers in Microbiomes, 3. https://doi.org/10.3389/frmbi.2024.1324476

Routsias, J., Verra, C., Tsiakalos, A., Tsakris, A., & Mavrouli, M. (2025). The Role of TLR2/TLR4 Receptors in Host Genetic Susceptibility to Recurrent Vulvovaginitis. Journal of Fungi, 11(11), 804. https://doi.org/10.3390/jof11110804

Rowland, I., Gibson, G., Heinken, A., Scott, K., Swann, J., Thiele, I., & Tuohy, K. (2017). Gut microbiota functions: metabolism of nutrients and other food components. European Journal of Nutrition, 57(1), 1–24. https://doi.org/10.1007/s00394-017-1445-8

S. Nakagome, Mano, S., Kozlowski, L., Bujnicki, J. M., Shibata, H., Y. Fukumaki, Kidd, J. R., Kidd, K. K., Kawamura, S., & H. Oota. (2012). Crohn's Disease Risk Alleles on the NOD2 Locus Have Been Maintained by Natural Selection on Standing Variation. Molecular Biology and Evolution, 29(6), 1569–1585. https://doi.org/10.1093/molbev/mss006

Salzman, N. H., Hung, K., Haribhai, D., Chu, H., Karlsson-Sjöberg, J., Amir, E., Teggatz, P., Barman, M., Hayward, M., Eastwood, D., Stoel, M., Zhou, Y., Sodergren, E., Weinstock, G. M., Bevins, C. L., Williams, C. B., & Bos, N. A. (2009). Enteric defensins are essential regulators of intestinal microbial ecology. Nature Immunology, 11(1), 76–82. https://doi.org/10.1038/ni.1825

Sanchis-Artero, L., Juan Francisco Martínez-Blanch, Manresa-Vera, S., Cortés-Castell, E., Valls-Gandia, M., Iborra, M., Jose Maria Paredes-Arquiola, Boscá-Watts, M., Jose Maria Huguet, Gil-Borrás, R., Rodríguez-Morales, J., & Cortés-Rizo, X. (2021). Evaluation of changes in intestinal microbiota in Crohn's disease patients after anti-TNF alpha treatment. Scientific Reports, 11(1). https://doi.org/10.1038/s41598-021-88823-2

Scepanovic, P., Hodel, F., Mondot, S., Partula, V., Byrd, A., Hammer, C., Alanio, C., Bergstedt, J., Patin, E., Touvier, M., Lantz, O., Albert, M. L., Duffy, D., Quintana-Murci, L., & Fellay, J. (2019). A comprehensive assessment of demographic, environmental, and host genetic associations with gut microbiome diversity in healthy individuals. Microbiome, 7(1). https://doi.org/10.1186/s40168-019-0747-x

Shahid, U. (2025). Microbiome-guided precision medicine: Mechanistic insights, multi-omics integration, and translational horizons. The Journal of Precision Medicine: Health and Disease, 3, 100018. https://doi.org/10.1016/j.premed.2025.100018

Shang, L., Fukata, M., Thirunarayanan, N., Martin, A. P., Arnaboldi, P., Maussang, D., Berin, C., Unkeless, J. C., Mayer, L., Abreu, M. T., & Lira, S. A. (2008). Toll-Like Receptor Signaling in Small Intestinal Epithelium Promotes B-Cell Recruitment and IgA Production in Lamina Propria. Gastroenterology, 135(2), 529-538.e1. https://doi.org/10.1053/j.gastro.2008.04.020

Sharifinejad, N., Zaki-Dizaji, M., Sepahvandi, R., Fayyaz, F., dos Santos Vilela, M. M., ElGhazali, G., Abolhassani, H., Ochs, H. D., & Azizi, G. (2022). The clinical, molecular, and therapeutic features of patients with IL10/IL10R deficiency: a systematic review. Clinical and Experimental Immunology, 208(3), 281–291. https://doi.org/10.1093/cei/uxac040

Shirin Manshouri, Seif, F., Kamali, M., Mohammad Ali Bahar, Arshideh Mashayekh, & Rasol Molatefi. (2024). The interaction of inflammasomes and gut microbiota: novel therapeutic insights. Cell Communication and Signaling, 22(1). https://doi.org/10.1186/s12964-024-01504-1

Shouval, D. S., Ouahed, J., Biswas, A., Goettel, J. A., Horwitz, B. H., Klein, C., Muise, A. M., & Snapper, S. B. (2014). Interleukin 10 Receptor Signaling: Master Regulator of Intestinal Mucosal Homeostasis in Mice and Humans. Advances in Immunology, 122, 177–210. https://doi.org/10.1016/B978-0-12-800267-4.00005-5

Sonnenburg, J. L., & Bäckhed, F. (2016). Diet–microbiota interactions as moderators of human metabolism. Nature, 535(7610), 56–64. https://doi.org/10.1038/nature18846

Stolfi, C., Maresca, C., Monteleone, G., & Laudisi, F. (2022). Implication of Intestinal Barrier Dysfunction in Gut Dysbiosis and Diseases. Biomedicines, 10(2), 289. https://doi.org/10.3390/biomedicines10020289

Takeuchi, O., & Akira, S. (2010). Pattern Recognition Receptors and Inflammation. Cell, 140(6), 805–820. https://doi.org/10.1016/j.cell.2010.01.022

Takiishi, T., Fenero, C. I. M., & Câmara, N. O. S. (2017). Intestinal barrier and gut microbiota: Shaping our immune responses throughout life. Tissue Barriers, 5(4), e1373208. https://doi.org/10.1080/21688370.2017.1373208

The Human Microbiome Project Consortium. (2012). Structure, Function and Diversity of the Healthy Human Microbiome. Nature, 486(7402), 207–214. https://doi.org/10.1038/nature11234

Thursby, E., & Juge, N. (2017). Introduction to the Human Gut Microbiota. Biochemical Journal, 474(11), 1823–1836. https://doi.org/10.1042/bcj20160510

Troisi, J. (2022). Metabolomics Perspectives. Elsevier.

Turnbaugh, P. J., Ley, R. E., Mahowald, M. A., Magrini, V., Mardis, E. R., & Gordon, J. I. (2006). An obesity-associated Gut Microbiome with Increased Capacity for Energy Harvest. Nature, 444(7122), 1027–1031. https://doi.org/10.1038/nature05414

Vaishnava, S., Yamamoto, M., Severson, K. M., Ruhn, K. A., Yu, X., Koren, O., Ley, R., Wakeland, E. K., & Hooper, L. V. (2011). The Antibacterial Lectin RegIII Promotes the Spatial Segregation of Microbiota and Host in the Intestine. Science, 334(6053), 255–258. https://doi.org/10.1126/science.1209791

Wallaeys, C., Garcia-Gonzalez, N., & Libert, C. (2022). Paneth cells as the cornerstones of intestinal and organismal health: a primer. EMBO Molecular Medicine, 15(2). https://doi.org/10.15252/emmm.202216427

Wan, T., Wang, Y., He, K., & Zhu, S. (2023). Microbial sensing in the intestine. Protein & Cell, 14(11), 824–860. https://doi.org/10.1093/procel/pwad028

Wang, J., Kurilshikov, A., Radjabzadeh, D., Turpin, W., Croitoru, K., Bonder, M. J., Jackson, M. A., Medina-Gomez, C., Frost, F., Homuth, G., Rühlemann, M., Hughes, D., Kim, H., Spector, T. D., Bell, J. T., Steves, C. J., Timpson, N., Franke, A., Wijmenga, C., & Meyer, K. (2018). Meta-analysis of human genome-microbiome association studies: the MiBioGen consortium initiative. Microbiome, 6(1). https://doi.org/10.1186/s40168-018-0479-3

Wang, Q., Wang, Q., Meng, Q., Meng, Q., Chen, Y., Chen, Y., Liu, Y., Liu, Y., Li, X., Li, X., Zhou, J., Zhou, J., Ma, Y., Ma, Y., Yu, Z., Yu, Z., Chen, X., & Chen, X. (2025). Interaction between gut microbiota and immunity in health and intestinal disease. Frontiers in Immunology, 16. https://doi.org/10.3389/fimmu.2025.1673852

Wang, S., Gong, J., Wang, J., Wang, W.-L., & Huang, L.-H. (2025). Interleukin-22: the hub bridging gut homeostasis and metabolism. Trends in Immunology, S1471-4906(25)002534. https://doi.org/10.1016/j.it.2025.10.009

Wehkamp, J., Salzman, N. H., Porter, E., Nuding, S., Weichenthal, M., Petras, R. E., Shen, B., Schaeffeler, E., Schwab, M., Linzmeier, R., Feathers, R. W., Chu, H., Lima, H., Fellermann, K., Ganz, T., Stange, E. F., & Bevins, C. L. (2005). Reduced Paneth cell -defensins in ileal Crohn's disease. Proceedings of the National Academy of Sciences, 102(50), 18129–18134. https://doi.org/10.1073/pnas.0505256102

Wlodarska, M., Thaiss, Christoph A., Nowarski, R., Henao-Mejia, J., Zhang, J.-P., Brown, Eric M., Frankel, G., Levy, M., Katz, Meirav N., Philbrick, William M., Elinav, E., Finlay, B. Brett, & Flavell, Richard A. (2014). NLRP6 Inflammasome Orchestrates the Colonic Host-Microbial Interface by Regulating Goblet Cell Mucus Secretion. Cell, 156(5), 1045–1059. https://doi.org/10.1016/j.cell.2014.01.026

Xiao, H., & Kang, S. (2020). The Role of the Gut Microbiome in Energy Balance with a Focus on the Gut-Adipose Tissue Axis. Frontiers in Genetics, 11. https://doi.org/10.3389/fgene.2020.00297

Yamaguchi, N., Suzuki, Y., Mahbub, M. H., Takahashi, H., Hase, R., Ishimaru, Y., Hiroshi Sunagawa, Watanabe, R., Yoshinobu Eishi, & Tanabe, T. (2017). The different roles of innate immune receptors in inflammation and carcinogenesis between races. Environmental Health and Preventive Medicine, 22(1), 70–70. https://doi.org/10.1186/s12199-017-0678-8

Yao, Y., Shang, W., Bao, L., Peng, Z., & Wu, C. (2024). Epithelial-immune cell crosstalk for intestinal barrier homeostasis. European Journal of Immunology, 54(6). https://doi.org/10.1002/eji.202350631

Yatsunenko, T., Rey, F. E., Manary, M. J., Trehan, I., Dominguez-Bello, M. G., Contreras, M., Magris, M., Hidalgo, G., Baldassano, R. N., Anokhin, A. P., Heath, A. C., Warner, B., Reeder, J., Kuczynski, J., Caporaso, J. G., Lozupone, C. A., Lauber, C., Clemente, J. C., Knights, D., & Knight, R. (2012). Human gut microbiome viewed across age and geography. Nature, 486(7402), 222–227. https://doi.org/10.1038/nature11053

Yeyeodu, S., Hanafi, D., Webb, K., Laurie, N. A., & K. Sean Kimbro. (2024). Population-enriched innate immune variants may identify candidate gene targets at the intersection of cancer and cardio-metabolic disease. Frontiers in Endocrinology, 14. https://doi.org/10.3389/fendo.2023.1286979

Zurgham, A. M., & Mehwish, M. (2025). Optimization of Deep Learning Convolutional Neural Network for Genomic Sequence Classification. International Journal of Advanced Multidisciplinary Research and Studies, 5(4), 1159–1162. https://doi.org/10.62225/2583049x.2025.5.4.4740