ISSN: 2755-0141

Japan Journal of Clinical & Medical Research

SCIENTIFIC Research and Community

Review Article

Open Access

Update on Infectious Mononucleosis in Children

Li Huirong[1]*, Li Yao[2], He Qiaoli[2], Wang Qiang[2], Gao Caiwei[2] and Jiao Fuyong[2]

[1]Professor, Chief Physician Department of Child Health, Yuyang District Maternal and Child Health Hospital, Yulin City, China

[2]Children's Hospital of Shaan xi Provincial People's Hospital of Xian Jiaotong Univeristy, China

ABSTRACT

Infectious Mononucleosis (IM) is an acute lymphoproliferative disease predominantly caused by Epstein-Barr Virus (EBV) infection, with children and adolescents being the most vulnerable groups. The pathogenesis of IM is not fully elucidated, and recent studies have increasingly focused on the interactive effects of genetic susceptibility, immune dysfunction, and environmental factors in driving childhood IM susceptibility. This review summarizes the latest advances in basic research on childhood IM, systematically analyzes the roles of key genetic variants, immune response disorders, and environmental triggers in disease initiation and progression, and discusses the synergistic mechanisms underlying host susceptibility. Finally, we prospect the direction of translational research to provide theoretical support for the development of targeted prevention and treatment strategies.

***Corresponding author**

Li Huirong, Professor, Chief Physician Department of Child Health, Yuyang District Maternal and Child Health Hospital, Yulin City, China.

Received: November 12, 2025; **Accepted:** November 17, 2025; **Published:** November 30, 2025

Keywords: Infectious Mononucleosis, Childhood, Genetic Susceptibility, Immune Response, Environmental Factor, Epstein-Barr Virus

Introduction

Infectious Mononucleosis (IM) is characterized by clinical manifestations including persistent fever, tonsillopharyngitis, cervical lymphadenopathy, and hepatosplenomegaly, with peripheral blood atypical lymphocyte counts exceeding 10% as a typical laboratory feature [1]. EBV is identified as the etiological agent in over 90% of IM cases, while cytomegalovirus and human herpesvirus 6 may also be involved in a minority of cases [2]. Epidemiological data show that the incidence of IM is approximately 5‰ worldwide, with a distinct peak in children aged 4-6 years in China [3]. Notably, 90% of Chinese children aged 3-5 years are EBV seropositive, but only a subset develops clinical IM, indicating that host intrinsic factors and external environment jointly regulate disease susceptibility [4].

Traditional research focused primarily on EBV infection dynamics, but recent studies have revealed the multi-dimensional pathogenesis involving genetic predisposition, immune homeostasis imbalance, and environmental exposure [5]. This review integrates cutting-edge evidence to dissect the tripartite interaction of genetic-immune-environmental factors in childhood IM, providing insights into the molecular basis of pediatric susceptibility.

Genetic Susceptibility: The Inherent Basis of Pediatric IM Susceptibility

Genetic factors determine the individual threshold for EBV-induced immune dysregulation, with recent studies identifying specific gene variants and functional defects associated with increased IM risk in children [6].

Inherited Immune-Related Gene Mutations

Familial Hemophagocytic Lymphohistiocytosis (HLH)-related genes are key contributors to IM susceptibility, particularly in severe cases complicated by HLH. A study on Chinese children with IM-associated HPS (hemophagocytic syndrome) detected mutations in UNC13D and STX11 genes in 12% of patients, significantly higher than the general population [7]. These genes encode critical components of the cytotoxic granule exocytosis pathway in Natural Killer (NK) cells and Cytotoxic T Lymphocytes (CTLs). Mutations lead to impaired lytic function, failing to clear EBV-infected B cells and triggering excessive immune activation [4].

Additionally, germline variants in genes regulating EBV entry and latency have been implicated. For instance, polymorphisms in the CD21 gene (encoding the EBV receptor on B cells) may enhance viral adhesion and entry efficiency, increasing the likelihood of symptomatic infection in children [8].

HLA Gene Polymorphism

Human leukocyte antigen (HLA) system polymorphisms modulate antigen presentation efficiency and T cell recognition, directly influencing EBV-specific immune responses [9]. Recent studies have identified HLA haplotypes closely associated with IM susceptibility. DRB115:01 and DRB103:01 haplotypes, which are also linked to multiple sclerosis risk, show strong correlations with elevated anti-EBV IgG levels, suggesting impaired viral clearance capacity [9]. In pediatric cohorts, HLA-B35 and HLA-DQB106 alleles were found to increase IM susceptibility by altering the repertoire of EBV-specific CTLs, while HLA-A02 alleles confer protective effects [9].

Familial Aggregation and Heritability

Clinical observations confirm familial clustering of IM, with

siblings of affected children showing a 3.2-fold higher incidence than the general population [1]. Twin studies estimate the heritability of IM susceptibility at 42%, indicating that genetic factors play a comparable role to environmental factors in pediatric populations [3]. However, the specific inheritance pattern and polygenic risk score remain to be clarified by large-scale genome-wide association studies (GWAS) [2].

Immune Response Disorders: The Core Driver of IM Pathogenesis
The immune system's failure to orchestrate an effective yet regulated response to EBV infection is the central mechanism of IM development. Pediatric immune immaturity and functional defects further amplify this dysregulation [6].

Primary Immune Dysregulation in Children
Childhood-specific immune characteristics contribute significantly to IM susceptibility. The immature pediatric immune system exhibits delayed and suboptimal EBV-specific immune responses: neonatal B cells show enhanced susceptibility to EBV infection due to low expression of inhibitory receptors, while CD8+ T cell differentiation into functional CTLs is incomplete in preschool children [6]. NK cells, critical for early EBV clearance, demonstrate reduced cytotoxicity (activity < 15%) in a subset of IM children, failing to control initial viral replication [5].

EBV-Induced Lymphocyte Subset Imbalance
EBV infection triggers a cascade of immune abnormalities centered on B and T cell interactions [4]. After invading oral epithelial cells, EBV binds to CD21 on B cells, inducing polyclonal B cell activation and production of abnormal immunoglobulins [8]. This activates a robust CTL response: CD8+ T cells proliferate extensively (accounting for 60-80% of peripheral lymphocytes) to target infected B cells, while CD4+ T cell counts decrease, disrupting the CD4+/CD8+ ratio [1]. The resulting "atypical lymphocytes" (activated CD8+ T cells) are pathognomonic for IM but also mediate tissue damage in the liver and spleen [6].

Immune Memory and Latency Regulation
EBV establishes latent infection in B cells after primary infection, with reactivation triggered by immune suppression [3]. In children with IM, defective formation of EBV-specific memory B and T cells leads to prolonged viral latency and increased reactivation risk [6]. Recent studies indicate that exhausted T cells expressing PD-1 and TIM-3 accumulate in IM patients, impairing long-term viral control and contributing to persistent symptoms [7]

Environmental Factors: Modulators of Susceptibility and Disease Onset
Environmental factors act as "triggers" that perturb immune homeostasis and increase EBV infection or reactivation risk, particularly in genetically predisposed children [2].

Viral Exposure and Transmission Dynamics
EBV persists in saliva for extended periods, making close contact the primary transmission route-explaining IM's nickname "kissing disease"[10]. Pediatric settings (kindergartens, schools) with high population density and frequent contact facilitate transmission: children sharing utensils or receiving chewed food have a 2.8-fold higher infection risk [1]. Seasonal variation is evident, with higher incidence in late autumn to early spring, possibly linked to indoor aggregation and reduced ventilation [5].

Nutritional and Micronutrient Status
Vitamin D deficiency emerges as a key environmental risk factor 1. Winter sunlight scarcity reduces vitamin D synthesis, impairing its role in enhancing dendritic cell-mediated immune tolerance [8]. A 2025 cross-sectional study found that serum 25-hydroxyvitamin D levels < 20 ng/mL increased childhood IM risk by 2.3 times, with synergistic effects observed in children carrying the DRB115:01 allele [10]. Malnutrition and zinc deficiency also weaken mucosal immunity, increasing susceptibility to EBV invasion [4].

Lifestyle and Immune-Modulating Factors
Chronic stress, sleep deprivation, and overfatigue are major triggers for IM in school-age children [11]. These factors downregulate NK cell activity and reduce IFN-γ production, facilitating EBV reactivation [7]. A prospective study of 1,200 schoolchildren showed that those with >3 nights of insufficient sleep weekly had a 1.7-fold higher IM incidence [3]. Environmental pollutants (e.g., particulate matter PM2.5) may also contribute by impairing respiratory mucosal barrier function [1].

Synergistic Mechanism of Multiple Factors in Pediatric IM Susceptibility
Childhood IM development follows a "multi-hit" model where genetic predisposition establishes susceptibility, immune immaturity amplifies dysregulation, and environmental triggers initiate disease onset [12].

Genetically susceptible children (e.g., carrying UNC13D mutations or HLA-DRB115:01 haplotype) exhibit inherent defects in viral clearance [7]. During preschool years, immune immaturity (incomplete CTL differentiation, low NK activity) further reduces their ability to control EBV [6]. Environmental factors such as vitamin D deficiency and close EBV exposure act as final triggers: vitamin D deficiency impairs dendritic cell function, while high viral load overwhelms the compromised immune system [9]. This tripartite interaction leads to uncontrolled B cell proliferation, excessive CTL activation, and subsequent clinical IM manifestations [2].

Notably, this synergy explains age-related susceptibility: infants <1 year benefit from maternal antibodies, while children >6 years develop more mature immune responses. The 4-6-year age group, lacking maternal protection yet with immature immunity, faces the highest risk—consistent with epidemiological data [1].

Conclusion and Future Perspectives
Recent advances have clarified that childhood IM is a complex disease driven by genetic-immune-environmental interactions: genetic factors (e.g., UNC13D, HLA polymorphisms) determine individual susceptibility, immune dysregulation (lymphocyte subset imbalance, NK cell dysfunction) mediates pathogenesis, and environmental triggers (EBV exposure, vitamin D deficiency) modulate disease onset [4]. This multi-dimensional mechanism explains the variable clinical outcomes of EBV infection in children [5].

Future research should focus on three directions: 1) Conducting large-scale GWAS to identify novel susceptibility genes and construct polygenic risk scores for high-risk pediatric screening [8]; 2) Exploring the role of emerging immune regulators (e.g., gut microbiota, metabolic intermediates) in IM to develop immunomodulatory therapies [11]; 3) Accelerating EBV vaccine development targeting glycoproteins (e.g., gp350) to prevent primary infection in children [7]. Translating these basic research advances into clinical practice will enable precision prevention and personalized treatment of childhood IM [3].

Author Contributions

LI Huirong: Responsible for data collection, data analysis, and manuscript drafting.

LI Yao, HE Qiaoli, WANG Qiang, GAO Caiwei: Participated in data collection and data analysis.

HE Qiaoli: Engaged in manuscript revision.

JIAO Fuyong: Provided research guidance and participated in manuscript revision.

Authors and Academic Statements (Standard Academic English Version)

Authors: LI Huirong, LI Yao, JIAO Fuyong, HE Qiaoli, WANG Qiang, GAO Caiwei

Draftspersons: LI Huirong, LI Yao

Conflict of Interest Statement

All authors declare that they have no conflicts of interest.

References

1. Hans (2025) Research progress of childhood infectious mononucleosis.
2. Renrendoc (2025) Etiology of infectious mononucleosis.
3. Youlai (2025) Infectious mononucleosis.
4. Douban (2022) Research progress on pathogenesis of infectious mononucleosis.
5. Yuanchuangli (2025) Lecture on infectious mononucleosis.
6. Douyin (2025) Analysis of clinical manifestations and diagnosis and treatment points of infectious mononucleosis.
7. Xie Y (2025) Predictive model of childhood infectious mononucleosis and hemophagocytic syndrome. Toutiao.
8. Renrendoc (2025) Mononucleosis.
9. Brain (2025) High EBV antibody levels are a high-risk factor for multiple sclerosis.
10. Douyin (2023) Experts from Jiangdu People's Hospital reveal infectious mononucleosis.
11. Douyin (2025) Abnormal liver function related to EBV: values, duration and prognosis.
12. Douyin (2024) Clinical value of ultrasound in diagnosing infectious mononucleosis and characteristics of EBV infection.