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Congenital Immunodeficiencies in Infants: Mechanisms, Diagnosis, and Emerging Therapies

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ABSTRACT

Congenital immunodeficiencies, also known as primary immunodeficiency disorders (PIDs), are a heterogeneous group of genetic disorders that impair immune function, resulting in increased susceptibility to infections, autoimmune diseases, and malignancies. These conditions arise from mutations affecting immune cell development, differentiation, or signaling pathways, leading to deficiencies in innate and adaptive immunity. This review explores the genetic and molecular mechanisms underlying congenital immunodeficiencies, emphasizing key mutations and their impact on immune system functionality. We discuss current diagnostic strategies, including newborn screening for severe combined immunodeficiency (SCID), immunophenotyping, functional immune assays, and genetic testing, all of which are crucial for early identification and tailored management. Additionally, we examine emerging therapeutic options, such as hematopoietic stem cell transplantation (HSCT), gene therapy using viral vectors or CRISPR-Cas9, and immunomodulatory approaches, highlighting their efficacy, limitations, and ongoing research efforts. While significant advancements in molecular diagnostics and targeted treatments have improved prognosis and survival rates, challenges remain in accessibility, cost, and potential treatment toxicities. Continued research and expanded newborn screening programs will be essential in optimizing outcomes for infants affected by these life-threatening disorders.

Keywords: Congenital immunodeficiency, genetic mutations, immune dysfunction, gene therapy, hematopoietic stem cell transplantation, immunomodulation.

INTRODUCTION

Congenital immunodeficiencies, also known as primary immunodeficiency disorders, are a group of genetic conditions that impair the normal function of the immune system [1]. These disorders can affect various immune components, including T cells, B cells, phagocytes, and the complement system, leading to increased susceptibility to infections, autoimmune diseases, and even malignancies [2]. Infants with these conditions often experience recurrent, severe, or opportunistic infections that can be life-threatening if left untreated [3]. The classification of primary immunodeficiencies has expanded significantly with advances in immunogenetics [4]. The discovery of novel genetic mutations and their impact on immune function has provided a deeper understanding of disease mechanisms [5]. Next-generation sequencing and other molecular diagnostic tools have revolutionized the identification of these disorders, allowing for earlier and more precise diagnoses [6]. Early detection is crucial for implementing appropriate management strategies, which may include antimicrobial prophylaxis, immunoglobulin replacement therapy, hematopoietic stem cell transplantation, or emerging gene therapy approaches [7]. This review aims to explore the mechanisms underlying congenital immunodeficiencies, focusing on the genetic and molecular basis of these disorders. It discusses contemporary diagnostic strategies that enhance early identification and classification. Additionally, emerging therapeutic approaches, including gene editing technologies and novel biologic treatments, were examined as potential advancements in the management of primary immunodeficiency disorders. By integrating recent research findings, this

discussion seeks to provide a comprehensive overview of current challenges and future directions in the field of congenital immunodeficiencies.

Mechanisms of Congenital Immunodeficiencies

Primary immunodeficiencies (PIDs) arise due to mutations affecting genes responsible for the development, differentiation, and function of immune cells [8]. These mutations impact different components of the immune system, leading to various clinical manifestations and increased susceptibility to infections. Congenital immunodeficiencies can be broadly categorized based on the specific part of the immune system that is affected [9].

Defects in Innate Immunity

Innate immunity serves as the body's first line of defense against pathogens. Defects in this system arise from mutations affecting genes that encode critical proteins involved in pathogen recognition, phagocytosis, and inflammatory signaling [10]. Pathogen Recognition Defects: Toll-like receptors (TLRs) and other pattern recognition receptors (PRRs) play a crucial role in detecting microbial components [11]. Mutations in TLRs or associated signaling molecules (e.g., MYD88 or IRAK4) lead to impaired responses to bacterial and viral infections [12] Phagocytic Defects: Proper function of phagocytes, such as neutrophils and macrophages, is essential for clearing infections [13]. In chronic granulomatous disease (CGD), mutations in the NADPH oxidase complex impair the ability of phagocytes to produce reactive oxygen species, leading to recurrent bacterial and fungal infections [14]. Similarly, leukocyte adhesion deficiencies (LADs) result from defects in adhesion molecules required for leukocyte migration, causing recurrent infections and impaired wound healing.

Defects in Humoral Immunity

Humoral immunity, mediated by B cells and antibodies, is essential for neutralizing pathogens and facilitating opsonization [15]. Deficiencies in this arm of immunity lead to recurrent bacterial infections, especially those caused by encapsulated organisms. X-linked Agammaglobulinemia (XLA): This condition results from mutations in the BTK gene, which is essential for B-cell maturation [16]. Affected individuals have an absence of mature B cells and a lack of immunoglobulin production, leading to severe bacterial infections early in life. Common Variable Immunodeficiency (CVID): A heterogeneous disorder characterized by impaired B-cell differentiation and defective antibody production. Patients suffer from recurrent respiratory and gastrointestinal infections, along with an increased risk of autoimmune diseases and malignancies [17].

Defects in Cellular Immunity

Cellular immunity, primarily mediated by T cells, is critical for adaptive immune responses. Deficiencies in this pathway often result in profound immune dysfunction, affecting both humoral and cell-mediated responses [18]. Severe Combined Immunodeficiency (SCID): A group of disorders caused by mutations affecting T-cell development and function. The most common form, X-linked SCID, results from mutations in the IL2RG gene, impairing interleukin receptor signaling and leading to severe opportunistic infections [19] DiGeorge Syndrome: A developmental disorder caused by 22q11.2 deletion, leading to thymic hypoplasia and T-cell deficiency. Affected individuals exhibit increased susceptibility to viral, fungal, and bacterial infections [20].

Complement System Deficiencies

The complement system enhances pathogen clearance through opsonization, lysis, and inflammation. Defects in complement proteins lead to increased infection risk and immune dysregulation [21]. C3 Deficiency: Affects all complement pathways, resulting in severe bacterial infections, particularly with encapsulated bacteria. Hereditary Angioedema (HAE): Caused by mutations in the C1 inhibitor (C1-INH) gene, leading to excessive complement activation and recurrent episodes of angioedema [22]. Understanding these mechanisms helps in diagnosing, managing, and developing targeted therapies for congenital immunodeficiencies.

Genetic Testing

Genetic testing plays a crucial role in diagnosing primary immunodeficiencies (PIDs) by identifying pathogenic variants responsible for immune dysfunction. Advanced sequencing technologies such as whole-exome sequencing (WES) and whole-genome sequencing (WGS) enable the detection of mutations in genes associated with immune system development and function [23]. WES focuses on sequencing protein-coding regions of the genome, which contain the majority of disease-causing mutations. It is particularly useful for identifying known and novel genetic defects in patients with suspected PIDs. WGS, on the other hand, provides a comprehensive analysis of the entire genome,

allowing for the detection of non-coding variants, structural variations, and copy number changes that may contribute to immune deficiencies [24] In addition to these high-throughput sequencing approaches, targeted gene panels are used for cost-effective and rapid diagnosis of specific PIDs. These panels include genes known to be associated with various immunodeficiency disorders, offering a focused and efficient diagnostic tool [25]. Early genetic diagnosis through these methods enables precise classification of PIDs, facilitates personalized treatment strategies, and aids in genetic counseling for affected families. The integration of genetic testing in clinical practice continues to improve patient outcomes by guiding therapeutic interventions such as hematopoietic stem cell transplantation and gene therapy.

Emerging Therapies

Recent advancements in therapeutic interventions have significantly improved outcomes for infants with congenital immunodeficiencies. These innovative approaches aim to restore immune function, reduce infection risks, and enhance quality of life.

Hematopoietic Stem Cell Transplantation (HSCT)

Hematopoietic stem cell transplantation (HSCT) remains the gold standard for treating severe primary immunodeficiencies, particularly severe combined immunodeficiency (SCID) [26]. It provides long-term immune reconstitution by replacing defective hematopoietic stem cells with healthy donor cells. Matched sibling donors offer the best outcomes; however, alternative donor sources, such as haploidentical transplantation and umbilical cord blood transplantation, have expanded treatment options. Advances in conditioning regimens have improved engraftment rates while reducing transplant-related complications [27].

Gene Therapy

Gene therapy has emerged as a promising curative approach for certain PIDs. Ex vivo gene therapy utilizes viral vectors to introduce functional copies of defective genes into patient-derived hematopoietic stem cells before reinfusion. This strategy has demonstrated success in treating SCID-X1, Wiskott-Aldrich syndrome, and chronic granulomatous disease (CGD). Advancements in genome-editing technologies, such as CRISPR-Cas9, offer precise gene correction with minimal off-target effects, paving the way for safer and more effective treatments [28].

Immunomodulatory Therapies

Immunomodulatory therapies play a crucial role in managing congenital immunodeficiencies. Intravenous immunoglobulin (IVIG) therapy is widely used to supplement antibody deficiencies in B-cell disorders [29]. Additionally, cytokine-based therapies, including interleukin-2 (IL-2) and interferon-gamma (IFN-γ), are being investigated for their potential to modulate immune responses in specific PIDs [30]. These therapies aim to enhance immune function and reduce susceptibility to infections, providing a valuable adjunct to existing treatments. Continued research and advancements in these therapeutic strategies hold promise for improving long-term outcomes and quality of life for individuals with congenital immunodeficiencies.

Challenges and Future Directions

Despite remarkable progress in the diagnosis and treatment of congenital immunodeficiencies, several challenges persist that impact patient outcomes and healthcare accessibility. Delayed diagnosis remains a significant barrier, particularly in regions with limited access to newborn screening programs. Early detection is crucial for timely interventions, yet many infants with primary immunodeficiencies (PIDs) go undiagnosed until severe infections or complications arise. Treatment toxicity is another major concern. While hematopoietic stem cell transplantation (HSCT) is a life-saving procedure, it carries risks such as graft-versus-host disease (GVHD) and transplant-related complications [31]. Similarly, gene therapy, though promising, presents challenges such as insertional mutagenesis and immune responses against viral vectors. Refining conditioning regimens and improving gene-editing precision remain critical areas of research. Cost and accessibility continue to hinder widespread implementation of advanced therapies. Genetic treatments, including gene therapy and enzyme replacement therapies, remain prohibitively expensive and are not universally available [32]. This disparity limits equitable access to life-saving interventions, particularly in low-resource settings. Future research should prioritize optimizing gene-editing technologies, expanding newborn screening programs, and developing cost-effective therapeutic approaches. Efforts to improve global healthcare infrastructure and funding mechanisms will be essential in ensuring that all patients, regardless of geographic location or economic status, have access to timely and effective treatments. By addressing these challenges, the field can move toward more personalized, safe, and

accessible solutions for managing congenital immunodeficiencies.

CONCLUSION

Congenital immunodeficiencies pose a significant health challenge, requiring early diagnosis and precise treatment strategies to improve patient outcomes. Advances in molecular diagnostics have enhanced the identification of pathogenic variants, enabling earlier interventions. Innovative therapies, such as gene therapy and hematopoietic stem cell transplantation, have transformed the management of primary immunodeficiencies, offering the potential for long-term immune reconstitution. Despite these advancements, challenges remain in accessibility, affordability, and treatment-associated risks. Expanding newborn screening programs, refining gene-editing technologies, and improving healthcare infrastructure are essential for ensuring equitable access to life-saving therapies. Global collaborations and continued research efforts will be instrumental in overcoming these barriers and enhancing the prognosis for affected infants. By addressing these challenges, the medical community can move toward more effective, personalized, and widely available treatments, ultimately improving the quality of life for individuals with congenital immunodeficiencies.

REFERENCES

1. McCusker, C., Upton, J. & Warrington, R. Primary immunodeficiency. *Allergy Asthma Clin Immunol* **14** (Suppl 2), 61 (2018). https://doi.org/10.1186/s13223-018-0290-5
2. Redmond, M.T., Scherzer, R. & Prince, B.T. Novel Genetic Discoveries in Primary Immunodeficiency Disorders. *Clinic Rev Allerg Immunol* **63**, 55–74 (2022). https://doi.org/10.1007/s12016-021-08881-2
3. Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Childhood Illnesses. 2nd edition. Geneva: World Health Organization; 2013. 8, Children with HIV/AIDS. Available from: https://www.ncbi.nlm.nih.gov/books/NBK154455/
4. Heron, J.E., Bagnis, C.I. & Gracey, D.M. Contemporary issues and new challenges in chronic kidney disease amongst people living with HIV. *AIDS Res Ther* **17**, 11 (2020). https://doi.org/10.1186/s12981-020-00266-3
5. Davisson MT, Bergstrom DE, Reinholdt LG, Donahue LR. Discovery Genetics - The History and Future of Spontaneous Mutation Research. Curr Protoc Mouse Biol. 2012 Jun 1;2:103-118. doi: 10.1002/9780470942390.mo110200. PMID: 25364627; PMCID: PMC4215558.
6. Knight JC. Genomic modulators of the immune response. Trends Genet. 2013 Feb;29(2):74-83. doi: 10.1016/j.tig.2012.10.006. Epub 2012 Nov 1. PMID: 23122694; PMCID: PMC3605582.
7. Carrie L. Lucas, Human genetic errors of immunity illuminate an adaptive arsenal model of rapid defenses, Trends in Immunology, 2024; 45 (2); 113-126. https://doi.org/10.1016/j.it.2023.12.006.
8. Benton, M.L., Abraham, A., LaBella, A.L. *et al.* The influence of evolutionary history on human health and disease. *Nat Rev Genet* **22**, 269–283 (2021). https://doi.org/10.1038/s41576-020-00305-9
9. Quan, M., Cao, S., Wang, Q. *et al.* Genetic Phenotypes of Alzheimer's Disease: Mechanisms and Potential Therapy. *Phenomics* **3**, 333–349 (2023). https://doi.org/10.1007/s43657-023-00098-x
10. Chehelgerdi, M., Chehelgerdi, M., Khorramian-Ghahfarokhi, M. *et al.* Comprehensive review of CRISPR-based gene editing: mechanisms, challenges, and applications in cancer therapy. *Mol Cancer* **23**, 9 (2024). https://doi.org/10.1186/s12943-023-01925-5
11. Wicherska-Pawłowska K, Wróbel T, Rybka J. Toll-Like Receptors (TLRs), NOD-Like Receptors (NLRs), and RIG-I-Like Receptors (RLRs) in Innate Immunity. TLRs, NLRs, and RLRs Ligands as Immunotherapeutic Agents for Hematopoietic Diseases. Int J Mol Sci. 2021 Dec 13;22(24):13397. doi: 10.3390/ijms222413397. PMID: 34948194; PMCID: PMC8704656.
12. Luqman M, Nawazash Ali S, Khalid Z, Anwar I, M. Goyal S, Shahid Mahmood M. Toll-Like Receptors and Emerging Viral Infections [Internet]. Thirty Years since the Discovery of Toll-Like Receptors. IntechOpen; 2024. Available from: http://dx.doi.org/10.5772/intechopen.1003725

13. Brown GD. Innate antifungal immunity: the key role of phagocytes. Annu Rev Immunol. 2011;29:1-21. doi: 10.1146/annurev-immunol-030409-101229. PMID: 20936972; PMCID: PMC3434799.
14. Andrews T, Sullivan KE. Infections in patients with inherited defects in phagocytic function. Clin Microbiol Rev. 2003 Oct;16(4):597-621. doi: 10.1128/CMR.16.4.597-621.2003. PMID: 14557288; PMCID: PMC207096.
15. Janeway CA Jr, Travers P, Walport M, et al. Immunobiology: The Immune System in Health and Disease. 5th edition. New York: Garland Science; 2001. Chapter 9, The Humoral Immune Response. Available from: https://www.ncbi.nlm.nih.gov/books/NBK10752/
16. Sebina I, Pepper M. Humoral immune responses to infection: common mechanisms and unique strategies to combat pathogen immune evasion tactics. Curr Opin Immunol. 2018 Apr;51:46-54. doi: 10.1016/j.coi.2018.02.001. Epub 2018 Feb 23. PMID: 29477969; PMCID: PMC6197480.
17. Dunkelberger, J., Song, WC. Complement and its role in innate and adaptive immune responses. *Cell Res* **20**, 34–50 (2010). https://doi.org/10.1038/cr.2009.139
18. Sun, L., Su, Y., Jiao, A. *et al.* T cells in health and disease. *Sig Transduct Target Ther* **8**, 235 (2023). https://doi.org/10.1038/s41392-023-01471-y
19. Mahdavi FS, Keramatipour M, Ansari S, Sharafian S, Karamzade A, Tavakol M. X-linked SCID with a rare mutation. Allergy Asthma Clin Immunol. 2021 Oct 11;17(1):107. doi: 10.1186/s13223-021-00605-7. PMID: 34635152; PMCID: PMC8507167.
20. Allenspach EJ, Rawlings DJ, Petrovic A, et al. X-Linked Severe Combined Immunodeficiency. 2003 Aug 26 [Updated 2021 Aug 5]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1410/
21. Lim, C.K., Abolhassani, H., Appelberg, S.K. *et al. IL2RG* hypomorphic mutation: identification of a novel pathogenic mutation in exon 8 and a review of the literature. *Allergy Asthma Clin Immunol* **15**, 2 (2019). https://doi.org/10.1186/s13223-018-0317-y
22. Ostrycharz E, Hukowska-Szematowicz B. New Insights into the Role of the Complement System in Human Viral Diseases. Biomolecules. 2022 Jan 28;12(2):226. doi: 10.3390/biom12020226. PMID: 35204727; PMCID: PMC8961555.
23. Cedzyński M, Thielens NM, Mollnes TE, Vorup-Jensen T. Editorial: The Role of Complement in Health and Disease. Front Immunol. 2019 Aug 7;10:1869. doi: 10.3389/fimmu.2019.01869. PMID: 31440250; PMCID: PMC6693436.
24. Mondana H. Ghias, Michael J. Hyde, Lewis E. Tomalin, B. Paul Morgan, Afsaneh Alavi, Michelle A. Lowes, Vincent Piguet, Role of the Complement Pathway in Inflammatory Skin Diseases: A Focus on Hidradenitis Suppurativa, Journal of Investigative Dermatology, 2020; 140(3):531-536.e1. https://doi.org/10.1016/j.jid.2019.09.009.
25. Łukawska, E., Polcyn-Adamczak, M. & Niemir, Z.I. The role of the alternative pathway of complement activation in glomerular diseases. *Clin Exp Med* **18**, 297–318(2018). https://doi.org/10.1007/s10238-018-0491-8
26. Wahlstrom JT, Dvorak CC, Cowan MJ. Hematopoietic Stem Cell Transplantation for Severe Combined Immunodeficiency. Curr Pediatr Rep. 2015 Mar 1;3(1):1-10. doi: 10.1007/s40124-014-0071-7. PMID: 25821657; PMCID: PMC4371740.
27. Castagnoli R, Delmonte OM, Calzoni E, Notarangelo LD. Hematopoietic Stem Cell Transplantation in Primary Immunodeficiency Diseases: Current Status and Future Perspectives. Front Pediatr. 2019 Aug 8;7:295. doi: 10.3389/fped.2019.00295. PMID: 31440487; PMCID: PMC6694735.
28. Galgano, L., Hutt, D., Mekelenkamp, H. (2023). HSCT: How Does It Work?. In: Kenyon, M., Babic, A. (eds) The European Blood and Marrow Transplantation Textbook for Nurses. Springer, Cham. https://doi.org/10.1007/978-3-031-23394-4_2
29. Mitrevski M, Marrapodi R, Camponeschi A, Cavaliere FM, Lazzeri C, Todi L, Visentini M. Intravenous Immunoglobulin and Immunomodulation of B-Cell - in vitro and in vivo Effects. Front Immunol. 2015 Jan

22;6:4. doi: 10.3389/fimmu.2015.00004. PMID: 25657650; PMCID: PMC4302981.

30. Velikova T, Sekulovski M, Bogdanova S, Vasilev G, Peshevska-Sekulovska M, Miteva D, Georgiev T. Intravenous Immunoglobulins as Immunomodulators in Autoimmune Diseases and Reproductive Medicine. Antibodies (Basel). 2023 Mar 2;12(1):20. doi: 10.3390/antib12010020. PMID: 36975367; PMCID: PMC10045256.
31. Khaddour K, Hana CK, Mewawalla P. Hematopoietic Stem Cell Transplantation. [Updated 2023 May 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK536951/
32. Juric MK, Ghimire S, Ogonek J, Weissinger EM, Holler E, van Rood JJ, Oudshoorn M, Dickinson A, Greinix HT. Milestones of Hematopoietic Stem Cell Transplantation - From First Human Studies to Current Developments. Front Immunol. 2016 Nov 9;7:470. doi: 10.3389/fimmu.2016.00470. PMID: 27881982; PMCID: PMC5101209.

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