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Genetic Diagnosis in Primary Immunodeficiencies: From Clues to Confirmation

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Introduction

Primary ImmunoDeficiencies (PIDs), now more comprehensively termed Inborn Errors of Immunity (IEIs), are a diverse group of genetic disorders that impair the development and function of the immune system. These conditions range in severity from mild susceptibilities to infections to life-threatening immune dysregulation. With over 450 gene defects currently associated with PIDs, genetic diagnosis has become a cornerstone in identifying, managing and understanding the underlying mechanisms of these disorders. The journey from clinical suspicion to genetic confirmation begins with recognizing characteristic features, such as recurrent infections, failure to thrive, autoimmune manifestations, or a family history of immunodeficiency. Traditional diagnostic approaches rely on immunophenotyping and functional assays; however, these methods often lack specificity and can delay a definitive diagnosis. With the advent of Next-Generation Sequencing (NGS) technologies such as Whole-Exome Sequencing (WES) and targeted gene panels clinicians can now identify causative mutations with greater speed and accuracy. This has led to a paradigm shift in the diagnostic workflow, enabling earlier intervention and improved outcomes [1]. Genetic confirmation not only clarifies the diagnosis but also guides treatment decisions. For example, identifying mutations in genes such as IL2RG, RAG1, or ADA can direct patients toward curative therapies like hematopoietic stem cell transplantation or gene therapy. Furthermore, genetic insights can help avoid ineffective treatments and predict complications. Family members can also benefit from genetic testing through carrier detection, prenatal diagnosis, or preimplantation genetic screening. Importantly, molecular diagnosis expands the understanding of immune system biology and facilitates the discovery of novel gene defects. It also enhances classification of PIDs into mechanistic categories, such as those affecting immune regulation, phagocytic function, or complement pathways.

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This reclassification allows for more tailored therapeutic approaches and supports research into targeted therapies. The integration of genetic diagnosis into the clinical evaluation of primary immunodeficiencies has revolutionized the field of immunology. It bridges the gap between observable symptoms and molecular pathogenesis, offering patients precise diagnoses and access to personalized care. Continued advancements in sequencing technologies and bioinformatics promise to uncover even more genetic underpinnings of PIDs, ultimately transforming patient outcomes and deepening our grasp of immune function.

Description

Primary immunodeficiencies (PIDs), also known as inborn errors of immunity, represent a heterogeneous group of over 450 genetic disorders characterized by defects in the immune system. These conditions manifest clinically with recurrent or unusual infections, autoimmune features, lymphoproliferation, and, in some cases, malignancies. Diagnosing PIDs requires high clinical suspicion, especially in pediatric populations or individuals with a family history of immunological disorders. Traditional diagnostic tools such as immunoglobulin quantification, lymphocyte subset analysis and functional immune testing often provide initial insights but may not pinpoint the exact genetic cause [2]. Genetic diagnosis through advanced molecular techniques particularly Next-Generation Sequencing (NGS), including Whole-Exome Sequencing (WES) and targeted gene panels has revolutionized the identification of disease-causing mutations in patients with suspected PIDs. These tools allow for a more rapid and accurate diagnosis compared to conventional methods. In many cases, genetic diagnosis not only confirms clinical suspicions but also changes the management trajectory by enabling precision therapies such as gene therapy or hematopoietic stem cell transplantation. Additionally, genetic testing provides important information for family counseling, including carrier status, prenatal testing and potential gene-targeted interventions.

Conclusion

The role of genetic diagnosis in primary immunodeficiencies has transitioned from being a confirmatory step to a central component of early and accurate disease recognition. With the help of NGS and evolving molecular platforms, clinicians can uncover the underlying genetic etiology in many patients, leading to improved treatment strategies and prognostic clarity.

Genetic testing not only refines diagnostic accuracy but also opens the door to targeted therapies and preventative care for family members. As the field continues to advance, integrating genomic data with clinical immunology will be crucial for the optimal management of these complex disorders. Broader implementation of these technologies and continued research into novel gene mutations will further enhance our ability to diagnose, treat and ultimately prevent PIDs.

Acknowledgement

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Conflict of Interest

None.

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