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ROLE OF MOLECULAR GENETICS IN THE DIAGNOSIS OF INBORN ERRORS OF METABOLISM: A REVIEW

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***Abstract*—**inborn errors of metabolism (IEMs) are a heterogeneous category of inherited genetic illnesses caused by abnormalities in genes coding for enzymes, transporters or cofactors involved in metabolic pathways. These errors affect normal biochemical processes resulting in accumulation of hazardous metabolites, deficiency of necessary products and a wide spectrum of clinical symptoms, from moderate metabolic disturbances to life-threatening diseases. Early and precise diagnosis is important for prompt treatment intervention, prevention of irreversible organ damage and better results in patients. Conventional biochemical assays remain necessary in the first examination of suspected IEMs. However, breakthroughs in molecular genetics have revolutionised the diagnostic method, allowing for more precise and sensitive detection of disease-causing genetic variations. Molecular genetic techniques such as polymerase chain reaction (PCR), Sanger sequencing, next generation sequencing (NGS), whole exome sequencing (WES), whole genome sequencing (WGS) and multiplex ligation-dependent probe amplification (MLPA) have greatly improved the detection and characterisation of inherited metabolic disorders. These technologies enable early diagnosis, genotype–phenotype correlation, carrier discovery, prenatal diagnosis, newborn screening, genetic counselling and application of precision medicine. The present review is an attempt to provide an overview of the role of molecular genetics in diagnosis of inborn errors of metabolism. Molecular diagnostic techniques, clinical applications, advantages, limitations and emerging innovations are highlighted. Furthermore, the review addresses future approaches such as multiomics integration, artificial intelligence-guided variant interpretation and gene-based treatment methods, which are anticipated to revolutionise the diagnosis and management of hereditary metabolic illnesses. The continuing integration of molecular genetics into everyday clinical practice is expected to increase diagnosis accuracy, optimise patient care and play a major role in the development of personalised medicine.

Keywords: Inborn errors of metabolism; molecular genetics; genetic diagnostics; polymerase chain reaction; next generation sequencing; whole exome sequencing; whole genome sequencing; newborn screening; precision medicine; metabolic diseases.

INTRODUCTION

Inborn errors of metabolism (IEMs), also known as inherited metabolic diseases (IMDs), are a heterogeneous set of monogenic disorders caused by pathogenic variations in genes producing enzymes, transport proteins, cofactors or other proteins involved in metabolic processes. These deficiencies affect normal biochemical reactions resulting to buildup of harmful metabolites, shortage of critical metabolic products or reduced energy production. Individual IEM are rare but combined they are a major source of morbidity and mortality in the neonatal and paediatric age groups. Because of the wide clinical range and phenotypic heterogeneity, many illnesses manifest in adolescence or adulthood [1].

The term inborn errors of metabolism was introduced in 1902 by Sir Archibald Garrod, based on his studies of alkaptonuria, thus demonstrating the link between inherited genetic variation and metabolic failure. Since that time, tremendous developments in biochemical genetics and molecular medicine have resulted in the discovery of more than one thousand hereditary metabolic diseases of amino acid, carbohydrate, lipid, mitochondrial, lysosomal and paroxysmal metabolism. This knowledge has considerably enhanced understanding of disease mechanisms and has contributed to the creation of more specific diagnostic and treatment techniques [1,2].

Traditional diagnosis of IEMs has been based on clinical assessment backed by biochemical investigations including plasma amino acid analysis, urine organic acid profile, tandem mass spectrometry, enzyme tests and metabolite quantification. These approaches are still essential for the detection of metabolic abnormalities, but they do not always identify the exact genetic flaw responsible for the disease,

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especially in patients with atypical clinical presentation or overlapping biochemical phenotypes [1,3].

Advances in molecular genetics have changed the diagnosis of hereditary metabolic diseases.

High sensitivity and specificity for quick identification of pathogenic variations are provided by technologies like polymerase chain reaction (PCR), Sanger sequencing, next-generation sequencing (NGS), whole-exome sequencing (WES), and whole-genome sequencing (WGS). These molecular technologies have greatly improved diagnostic yield, shortened the diagnostic odyssey endured by many patients, reinforced genotype–phenotype associations and allowed for personalised care regimens. Molecular diagnosis is also essential for carrier detection, prenatal diagnosis, confirmation of newborn screening, genetic counselling and selection of targeted medicines, thus enhancing patient outcomes and promoting precision medicine [3,4].

Notwithstanding these developments, there are problems in the adoption of molecular genetic testing, including the interpretation of variations of unknown importance, high testing prices, limited accessibility in resource-constrained settings and the need for specialised bioinformatics skills. Therefore, the current best practice suggests integration of molecular genetic testing with biochemical, clinical and metabolomics investigations for an accurate and timely diagnosis. With the continuous development of sequencing technologies and their increased accessibility, molecular genetics is expected to play an even bigger role in the diagnosis and management of inborn errors of metabolism [1,3,4].

This review discusses the role of molecular genetics in the diagnosis of inborn errors of metabolism, highlighting the genetic basis of these disorders, current molecular diagnostic techniques, their clinical applications, limitations, and future perspectives in genomic medicine.

Inborn Errors of Metabolism (IEM)

Inborn errors of metabolism (IEMs), often called inherited metabolic disorders (IMDs), are a heterogeneous set of hereditary diseases caused by abnormalities in genes producing enzymes, transporters, cofactors or regulatory proteins of metabolic pathways. These deficiencies prevent normal biochemical reactions leading in accumulation of harmful metabolites, lack of necessary metabolic products or an inability to produce cellular energy. Each of these disorders is rare on its own, but IEMs are an important cause of newborn sickness, developmental delay, neurologic dysfunction, and multisystem disease worldwide, in aggregate [1].

The spectrum of IEMs has increased dramatically with developments in molecular genetics and biochemical medicine. 2 The International Classification of Inherited Metabolic Disorders enumerates over 1,400 disorders affecting various metabolic pathways including amino acid metabolism, organic acid metabolism, carbohydrate metabolism, fatty acid oxidation, lysosomal function, mitochondrial energy production, paroxysmal metabolism, and disorders of vitamins and cofactors [2].

IEMs have a broad range of clinical presentations and can develop at any age including neonatal period and adulthood. The usual presentation is with poor feeding, recurrent vomiting, seizures, metabolic acidosis, hypoglycaemia, developmental delay, intellectual disability, hepatomegaly, cardiomyopathy and progressive neurodegeneration. It is difficult to diagnose purely on clinical symptoms because these manifestations often overlap with other disorders. Therefore, early diagnosis necessitates an integration of clinical findings with biochemical and molecular investigations in order to avoid irreversible organ damage and improve long-term outcomes [1,3].

MOLECULAR BASIS OF INHERITED METABOLIC DISEASES

IEMs result from pathogenic mutations that disrupt genes encoding proteins necessary for normal metabolic activity. These variants include missense, nonsense, splice-site, frameshift, copy-number, and structural variants that may change protein production, stability, catalytic activity, or intracellular transport. The subsequent enzyme deficiency or dysfunction blocks metabolic pathways resulting in substrate accumulation, deficiency of products or activation of alternative metabolic pathways leading to production of toxic intermediates [1].

The mode of heredity of most IEMs is autosomal recessive, but autosomal dominant, X-linked and mitochondrial inheritance have been described. Residual enzyme activity, modifier genes, epigenetic impacts and environmental factors may all contribute to substantial clinical diversity for the same genetic disease. Hence, patients harbouring different pathogenic variants in the same gene may exhibit very different disease severity and age of onset [2,4].

Recent progress in genomic medicine has significantly increased our knowledge about the genetic architecture of inherited metabolic disorders. The advent of high-throughput sequencing technologies has led to the discovery of many new disease-causing genes and has improved our understanding of genotype-phenotype relationships. Furthermore, the integration of genomic data with transcriptomics, proteomics and metabolomics has revolutionised the interpretation of pathogenic variations and raised diagnostic yield in patients with previously unexplained metabolic diseases [4]

MOLECULAR GENETIC DIAGNOSTIC TECHNIQUES

The arrival of molecular genetic technologies has revolutionised diagnosis of inborn errors of metabolism (IEMs). These molecular methods identify directly the pathogenic variations causing metabolic dysfunction rather than aberrant amounts of metabolites as in conventional biochemical assays. Thus, molecular diagnosis not only

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validates the biochemical diagnosis but also enables carrier discovery, prenatal diagnosis, genotype–phenotype association, prognosis and tailored therapy planning [5].

PCR (polymerase chain reaction) is still one of the most commonly utilised molecular techniques in clinical laboratories. PCR can be used for fast amplification of certain DNA sequences to discover known harmful mutations associated with inherited metabolic diseases. It is widely used to confirm a mutation, screen for carriers and do targeted genetic testing in families where disease causative variations have been identified. However, PCR is selective for certain genomic areas and therefore less applicable to genetically diverse illnesses in which many genes may be involved [5].

The gold standard for mutation confirmation has been Sanger sequencing due to its great analytical accuracy . It is particularly beneficial for validation of variants identified by high-throughput sequencing technologies, and for analysis of single-gene illnesses with well-established molecular aetiologies. However, this approach is laborious and has mostly been replaced by next-generation sequencing (NGS) for illnesses with high genetic variability [5].

Next-generation sequencing (NGS) has revolutionised the field of molecular diagnostics by allowing the simultaneous examination of hundreds to thousands of genes in one experiment. Targeted gene panels, whole-exome sequencing (WES) and whole-genome sequencing (WGS) have boosted the diagnostic yield in patients with suspected IEMs, in particular those with atypical clinical presentation or ambiguous biochemical data. These strategies have also enabled the discovery of new disease-causing genes and broadened the phenotypic spectrum of many inherited metabolic illnesses [6,7].

Emerging multi-omics techniques further provide molecular diagnosis by integrating genomic, transcriptomic, proteomic and metabolomics data. This technique helps to understand variants of unknown significance, allows for functional validation of candidate variants and increases diagnostic accuracy in previously unresolved situations. As sequencing prices continue to decrease and bioinformatics tools improve, integrated multi-omics diagnostics are projected to constitute a significant part of precision medicine for hereditary metabolic illnesses [8].

CLINICAL APPLICATIONS OF MOLECULAR GENETICS

Molecular genetics has now become an integral part of the clinical work-up of patients with suspected IEMs. Identification of the underlying pathogenic variation offers a definitive diagnosis, particularly for illnesses with overlapping biochemical or clinical presentations. Furthermore, molecular confirmation aids doctors in choosing appropriate therapeutic strategies, forecasting illness development and tracking treatment response [6,8].

Genetic testing is a critical part of newborn screening follow-up, confirming positive biochemical screening results and differentiating true from false positives. Furthermore, molecular diagnosis allows for early treatment action before irreversible neurological or systemic problems arise. Carrier testing in family members, prenatal diagnosis and preimplantation genetic testing have greatly reduced the probability of recurrence in affected families through informed reproductive counselling [5,6].

Precision therapeutics for certain inherited metabolic illnesses have also been fast-tracked by recent advancements in genomic medicine. Molecular characterisation of disease-causing variations helps to identify patients who may benefit from enzyme replacement therapy, substrate reduction therapy, pharmacological chaperones or new gene-based therapeutics. Molecular genetics thus occupies a pivotal position in the field of precision medicine by enabling individualised treatment approaches based on the genetic defect of the patient [7,8].

ADVANTAGES OF MOLECULAR GENETIC DIAGNOSTICS

Molecular genetics has been incorporated into the diagnostic work-up of inborn errors of metabolism (IEMs) and has greatly enhanced the accuracy and efficiency of illness diagnosis. One of its key advantages is the possibility to identify the underlying pathogenic mutation, thereby providing a definitive diagnosis including in patients with equivocal biochemical data or uncommon clinical presentations. Early molecular diagnosis allows for the timely beginning of disease-specific treatment, lowers the diagnostic odyssey and minimises irreversible consequences associated with delayed intervention [9].

Molecular genetic testing is also useful for the correlation of genotype–phenotype, allowing clinicians to forecast severity of the disease, to monitor the disease progression and to choose appropriate therapy solutions. Moreover, identification of disease-causing variations allows accurate carrier detection, genetic counselling, prenatal diagnosis and preimplantation genetic testing, hence minimising recurrence risk in affected families. These developments have fortified precision medicine by enabling treatment options to be personalised to a person’s genetic makeup [10].

Whole-exome/genome sequencing and multi-omics technologies are more readily available, expanding the scope of detectable inherited metabolic diseases. These technologies have accelerated the discovery of new disease-causing genes and allowed the identification of individuals who may benefit from upcoming medicines such as enzyme replacement therapy, substrate reduction therapy, mRNA therapy and gene therapy. Thus molecular genetics has become an important component of modern metabolic medicine [11].

LIMITS OF MOLECULAR GENETIC DIAGNOSIS

Molecular genetic testing has some limitations, despite many advantages. The interpretation of Variants of Uncertain Significance (VUS) is a substantial difficulty, especially in the absence of functional confirmation. In addition, certain pathogenic variations are located in regulatory or non-coding areas of the genome, which may not be discovered by normal sequencing procedures. Further complicating the clinical interpretation are technical limitations, incomplete genotype–

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phenotype correlations, and incidental findings that may require further biochemical or functional investigation for confirmation [12].

Expensive expenses, poor laboratory equipment, and poor bioinformatics resources, and lack of skilled workers, especially in low- and middle-income countries, also hinder the implementation of modern molecular diagnostic technologies. Ethical considerations such as informed permission, data privacy and secondary discoveries need to be carefully considered when genetic testing is integrated into ordinary clinical practice [9,12].

FUTURE PERSPECTIVES

Rapid breakthroughs in genomic technology are likely to further change the diagnosis and therapy of hereditary metabolic diseases. Conventional genomic methodologies have limited capacity to detect and functionally characterise undiagnosed disease-causing variants, but novel methodologies (e.g. long-read sequencing, RNA sequencing, epigenomic profiling, artificial intelligence-assisted variant interpretation and integrated multi-omics analyses) are improving the detection and functional characterisation of such variants. These advances are likely to improve the diagnostic yield and provide further insights into illness pathophysiology [10,11].

At the same time, precision medicine is changing the therapeutic approach for IEMs, offering the possibility of individualised therapy based on the specific molecular flaw of the patient. New advances in gene therapy, genome editing, messenger RNA treatments and targeted pharmaceutical therapies offer intriguing prospects to cure the underlying genetic defects rather than simply manage signs of disease. Ongoing collaboration among physicians, molecular geneticists, bioinformaticians, and academics will be crucial to convert these improvements into routine clinical practice and improve long-term outcomes for persons with hereditary metabolic disorders [12].

CONCLUSION

The advent of advanced genomic technologies has transformed the diagnosis and management of inborn errors of metabolism (IEMs) by the ability to accurately identify pathogenic variants, improve diagnostic accuracy, shorten diagnostic delay and facilitate early therapeutic intervention. Molecular testing, which enables genotype-phenotype correlation, carrier discovery, prenatal diagnosis and personalised patient care, also advances precision medicine with targeted medicines. However, these achievements are still challenged by issues such as variations of unknown significance, high costs and limited access to genomic technology, particularly in low- and middle-income nations. Ongoing investment in genetic research, bioinformatics, multidisciplinary collaboration and clinical integration will further improve diagnostic and patient outcomes.

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REFERENCES

[1.]Ferreira CR, van Karnebeek CDM. Inborn errors of metabolism. Handb Clin Neurol. 2019;162:449–481

[2.]Ferreira CR, van Karnebeek CDM, Vockley J, Blau N. A proposed nosology of inborn errors of metabolism. Genet Med. 2019;21(1):102–106.

[3.]Ferreira CR, Rahman S, Keller M, Zschocke J; ICIMD Advisory Group. An international classification of inherited metabolic disorders (ICIMD). Journal of Inherited Metabolic Disease. 2021;44(1):164–177.

[4.]Stenton SL, Kremer LS, Kopajtich R, Ludwig C, Prokisch H. The diagnosis of inborn errors of metabolism by an integrative multi-omics approach: A perspective encompassing genomics, transcriptomics, and proteomics. J Inherit Metab Dis. 2020;43(1):25–35.

[5.]StatPearls Publishing. Inborn Errors of Metabolism. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.

[6.]Rehm HL. Molecular genetic testing and the future of clinical diagnostics. N Engl J Med. 2017;376(8):756–765.

[7.]Ferreira CR, Rahman S, Keller M, Zschocke J; ICIMD Advisory Group. An international classification of inherited metabolic disorders (ICIMD). J Inherit Metab Dis. 2021;44(1):164–177..

[8.]Wojcik MH, Reuter CM, Marwaha S, et al. Beyond the exome: What's next in diagnostic testing for Mendelian conditions? Am J Hum Genet. 2024;111(1):1–22.

[9.]Mansoor S, Qamar R, Azam M. inborn errors of metabolism: Historical perspectives to Contemporary management. Clin Chim Acta. 2024;562:119883.

[10.]Didiasova M, Banning A, Tikkanen R. Development of precision therapies for rare inborn errors of metabolism: Functional investigations in cell culture models. J Inherit Metab Dis. 2024;47(3):509–516.

[11.]Baruteau J, Keshavan N, Venditti CP. Mission possible: Gene therapy for inherited metabolic diseases. J Inherit Metab Dis. 2024;47(1):5–6.

[12.]Smirnov D, Konstantinovskiy N, Prokisch H. Integrative omics approaches to advance rare disease diagnostics. J Inherit Metab Dis. 2023;46(5):824–838.

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