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REVIEW ARTICLE

High-Throughout Techniques Assessing the Molecular Diagnosis for Neurometabolic Disorders: A Comprehensive Review

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ABSTRACT

Neurometabolic diseases associated with neurological manifestations are a group of heterogeneous genetic disorders that share the alteration in specific aspects of cellular metabolism, ultimately leading to the disease. Often first described by pediatricians, the more recently reported adult-onset forms have phenotypes considerably different, sometimes, from the pediatric ones and might mimic other more common adults neurological disorders. Adult-onset neurometabolic diseases are individually rare, heterogeneous and frequently show complex clinical presentations. These reasons, in addition to the myriad of specialized biochemical diagnostic tools available, account for a significant diagnostic delay and under-diagnosis. However, unlike many other neurogenetic diseases, a substantial part of neurometabolic diseases can be successfully treated, with both conservative and more recently approved innovative therapeutics. Early recognition and diagnosis of a treatable neurometabolic disease should have major impacts, supports the stabilization of the disease or even the regression of some signs and symptoms, halting unnecessary diagnostic investigations, and allowing for family screening and treatment of pre-symptomatic carriers. An overview of adult-onset neurometabolic diseases will be outlined, starting from important general considerations to phenotypical descriptions focusing on treatable diseases. A diagnostic approach for the adult neurologist will be developed to help decision making when suspecting a neurometabolic disease. Neurometabolic Syndromes (NMS) are rare, heterogeneous genetic disorders that primarily affect the central nervous system (CNS) due to defects in specific metabolic pathways. Accurate, early diagnosis is critically important for initiating disease-modifying therapies, such as enzyme replacement or gene therapy, before irreversible neurological damage occurs.

INTRODUCTION

Inborn errors of metabolism (IEMs) are also referred to as congenital metabolic diseases (CMDs) or inherited metabolic disorders (IMDs). They are a group of metabolic disorders caused by a genetic mutation that leads to deficiency of an enzyme required for the formation of a protein or for the catalysis of a biochemical reaction in the body. The problem arises usually from accumulation of substrate (toxic) or absence of an important product of the reaction. IEM can appear at birth or later in life such as phenylketonuria, albinism, lactose intolerance, Mucopolysaccharidosis (MPS), Gaucher disease, fabry disease ….etc [1].

Genetic mutations that affect the activity of the acid hydrolases causes what are known as lysosomal storage diseases (LSD). These mutations block the normal metabolism causing macromolecules accumulation inside the lysosomes that eventually lead to severe physiological damage. Lysosomal storage diseases have a rare incidence of 1 in 7000 live birth [2].

LSDs symptoms differ according to the affected enzyme, the type of accumulated substance and the type of cells that substance accumulates in. Also clinical picture can vary markedly within the same disorder [3, 4].

Lysosomal storage disorders (LSDs) constitute a group of >50 inherited disorders characterized by the accumulation of specific undegraded metabolites in the lysosomes. This over storage is commonly caused by a deficient or absent activity of one of the many lysosomal hydrolases or, in a few cases, by the deficiency of other non-enzymatic lysosomal proteins. Although singularly considered rare, the combined birth prevalence of LSD is estimated from 7.5 to 23.5 per 100,000 live births. Clinical signs and symptoms may occur from the prenatal period to adulthood, and may develop at different progression rate, according to the pathology, leading to a wide spectrum of disease forms, from mild to extremely severe, that in most cases affect the neurologic compartment, hence the neurometabolic disorders [4, 5].

Generally, the diagnostic approach includes an accurate clinical evaluation that leads to the formulation

of a suspicion for one or more of the neurometabolic disorders. This is followed by biochemical tests, aimed to detect the storage products in the body fluids, the biochemical results might be oriented by enzymatic analyses' aspects. Finally, if an enzyme deficiency is detected, genetic analysis is performed for the suspected gene [6]. However, this diagnostic route presents several limitations.

Neurometabolic disorders are largely overlapping in their phenotypic manifestations, hence their identification requires deep clinical phenotyping. Moreover, the biochemical methods are laborious, and they are often subject to high variability, taking into consideration that multiple enzymatic assays should be expensive. Also, not all of these disorders present with elevated levels of storage products. This may delay the diagnosis that could be even difficult to reach [7].

The diagnosis of neurometabolic disorders is a demanding task for clinicians due to the phenotype and penetrance variability, the shared signs and symptoms, and the uncertainties related to biochemical enzymatic assay results [6].

Advanced gene sequencing and analysis techniques constitute the most reliable current approach for diagnosing, preventing, and treating this complex group of disorders. High-Throughput Technologies, such as Next-generation sequencing (NGS)[8,9]; including whole-exome sequencing (WES) and targeted gene panels have revolutionized this field.

Table 1: Examples of Genes that will be Included in the Panel and Their Associated Neurometabolic disorders[7]

Gene	Syndrome	Enzyme/substrate
SGSH	MPS IIIA, Sanfilippo syndrome A	N-Sulfoglucosamine Sulfohydrolase (Heparan sulfate)
NAGLU	MPS IIIB, Sanfilippo syndrome B	e N-Acetyl-α-glucosaminidase (Heparan sulfate)
HGSNAT	MPS IIIC, Sanfilippo syndrome C	Heparan-α-glucosaminideN-acetyltransferase (Heparan sulfate)
GNS	MPS IIID, Sanfilippo syndrome D	N-acetylglucosamine-6-Sulfatase (Heparan sulfate)
GLA	Fabry disease	α-Galactosidase A (Globotriaosylceramide)
GLB1	GM1 gangliosidosis: type I, II, III	β-Galactosidase (GM1 ganglioside, keratan sulfate & oligosaccharides)
HEXA	GM2 gangliosidosis, Tay–Sachs disease	β-Hexosaminidase (GM2 ganglioside, Glycosphingolipids& oligosaccharides)
HEXB	GM2 gangliosidosis, Sandhoff disease	β-Hexosaminidase (GM2 ganglioside, GA2 glycolipid & oligosaccharides)
GALC	Krabbe disease (KD)	galactocerebrosidase

Neurometabolic disordersis a clinically heterogeneous group in which the neurological manifestations are prominent clinical findings. Lysosome facilitates the degradation of various products of the cellular turn-over that are mainly derived from lysosomes through endocytosis. Alternative pathways for substrate entry into lysosomes are phagocytosis. Mucopolysaccharidoses comes from abnormalities in the turnover of keratin sulfate, heparin, and dermatan sulfate and Fabry disease results from alpha-galactosyl sphingolipids oligosaccharides. GM1 gangliosidosis is the results of a beta-galactosidase deficiency and the accumulation of ceramides caused by an acid ceramidase deficiency that causes Farber disease. GM2 gangliosidosis as Tay-Sachs disease (an alpha subunit of beta hexosaminidase deficiency); Sandhoff disease (a beta subunit of beta-hexosaminidase deficiency); and the GM2 AB variant are other types of lysosomal storage diseases. The complex lipid of gangliosides is found predominantly in gray matter in the brain. Classic forms of gangliosidoses present in early and late infancy and are usually fatal during these periods. In the early infantile form of GM1, gangliosidoses dysmorphic features may present at birth and often hepatosplenomegaly is noted [10].

Fabry disease is transmitted as X-linked traits however most neurometabolic disorders are transmitted in autosomal recessive inheritance. Fortunately, enzyme replacement therapy (ERT) for Fabry disease is available. The early timing of therapeutic interventions is of utmost importance because of the limited regenerative capacity of the brain [11].

Targeted sequencing is an appealing approach to implement in routine diagnostic strategy, given its low sequencing costs and short sequencing time [9,12–14]. However, a good coverage must be ensured and, when this is not reached, validation by Direct sequencing needs to be performed on the proband and on the

parents as final step [15.] Moreover, the possibility to fill the gaps in the panel design must be guaranteed, especially in case of strong suspicion for a specific disease [16]. Sanger sequencing still remains a reliable sequencing technique, and it should be considered an important support to NGS approaches, especially for confirmation of variants with a coverage below the good coverage threshold[14]. Therefore, each laboratory should have a diagnostic flow chart, providing appropriate molecular genetic tools to address the clinical suspicion [17]. We believe that the application of the panel or, in a near future, of a WES or WGS analysis will be the first or one of the first steps in diagnostic route, supported by a thorough phenotyping of the patients [16]. A tight collaboration between clinics and laboratory could increase the yield of the diagnostic process of neurometabolic disorders.

Genomics takes a comprehensive view that implicates all the genes within an organism, including protein-coding genes, RNA genes, cis- and trans-elements, etc. It is a data-driven science involving the high-throughput technological development of next-generation sequencing (NGS) that generates the entire DNA data of an organism. These techniques include whole genome sequencing (WGS), whole exome sequencing (WES), and transcriptomic and proteomic profiling [18–23]. With the recent rapid accumulation of these omics data, increased attention has been paid to bioinformatics and machine learning (ML) tools with established superior performance in several genomics implementations [24].

1. The Power of High-Throughput Omics

High-throughput technologies, collectively known as '**omics**', allow for the simultaneous measurement of thousands of molecules in a single biological sample (blood, urine, CSF, or tissue). This shifts diagnosis from searching for a single missing enzyme to identifying an entire **molecular signature** of the disease.

1.1 Genomics and Transcriptomics

Whole Exome Sequencing (WES) & Whole Genome Sequencing (WGS) rapidly identify mutations in all known disease-causing genes and can uncover novel genetic variants. WES/WGS drastically reduces the diagnostic odyssey for NMS patients, whose clinical symptoms often overlap with common neurodevelopmental disorders.

Transcriptomics (RNA-Seq) meeasures the expression levels of all RNA molecules. This helps in understanding the functional consequence of a mutation—for example, if a variant causes abnormal splicing or reduced expression of a critical enzyme.

1.2 Metabolomics and Proteomics

Metabolomics technique [25] measures small molecule metabolites (e.g., amino acids, organic acids, lipids, GAGs). This is arguably the most critical high-throughput technology for NMS, as the accumulation of specific, undegraded metabolites (like heparan sulfate in Sanfilippo syndrome) is the direct cause of the pathology. High-resolution mass spectrometry (HRMS) enables the simultaneous detection and quantification of hundreds of these molecules.

Proteomics approach [26] **m**easures the quantity and modification of all proteins. For NMS, this can reveal downstream effects, such as elevated inflammatory proteins (cytokines) or changes in lysosomal proteins due to storage stress.

2. ML/AI in the Diagnostic Pipeline

The immense volume and complexity of high-throughput data generated by 'omics (terabytes of genomic data, hundreds of metabolites per sample) require sophisticated computational tools. AI and ML algorithms are essential for extracting meaningful, actionable insights from this noise [27,28].

2.1 Pattern Recognition and Classification

ML models, such as **Support Vector Machines (SVM)** and **Random Forests**, excel at binary classification (Disease vs. Healthy) or multi-class classification (Subtype A vs. Subtype B). AI automatically identifies the most important 'features' (e.g., a specific ratio of three metabolites plus two gene expression values) that distinguish a disease state, effectively simplifying complex biological reality into a diagnostic signature [29].

ML models can be trained on i**mproving newborn screening** data (dried blood spots) to differentiate between true positive cases and common false positives, thus reducing unnecessary follow-up tests and anxiety for families.

2.2 Biomarker Discovery and Validation

Many NMS lack effective, non-invasive biomarkers, especially those reflecting CNS involvement. ML is transforming this search, **multi-Omics integration by using the** AI models use techniques like **Factor Analysis** or **Deep Neural Networks** to integrate different 'omics layers (e.g., genomic variants, plasma metabolites, and clinical symptoms) to discover novel **panels of biomarkers** that are more sensitive and specific than single-molecule markers. For e*xample;* identifying a panel of neuro-inflammatory cytokines (from proteomics) combined with a specific urine GAG profile (from metabolomics) that together indicate advanced stages of neurodegeneration in MPS III [30].

ML analyzes sensor data (wearable devices, sleep monitors) to quantify clinical features like gait, hyperactivity, or sleep disruption, generating **digital biomarkers** that correlate with disease progression and therapeutic response.

Analysis of Neurometabolic Disorder Gene Interactions Using GeneMANIA

The GeneMANIA database [31] was utilized as a key bioinformatic tool to systematically explore and visualize the functional associations and interaction networks among the genes and proteins implicated in

the ten Neurometabolic Disorders (NMDs) detailed in Table 1.

This approach provides a contextual framework for understanding the molecular complexity underlying these heterogeneous syndromes. The resulting comprehensive network, presented in Figure 1, illustrates various modes of interaction, including; physical interactions, co-expression, co-localization, genetic interactions, and pathway membership.

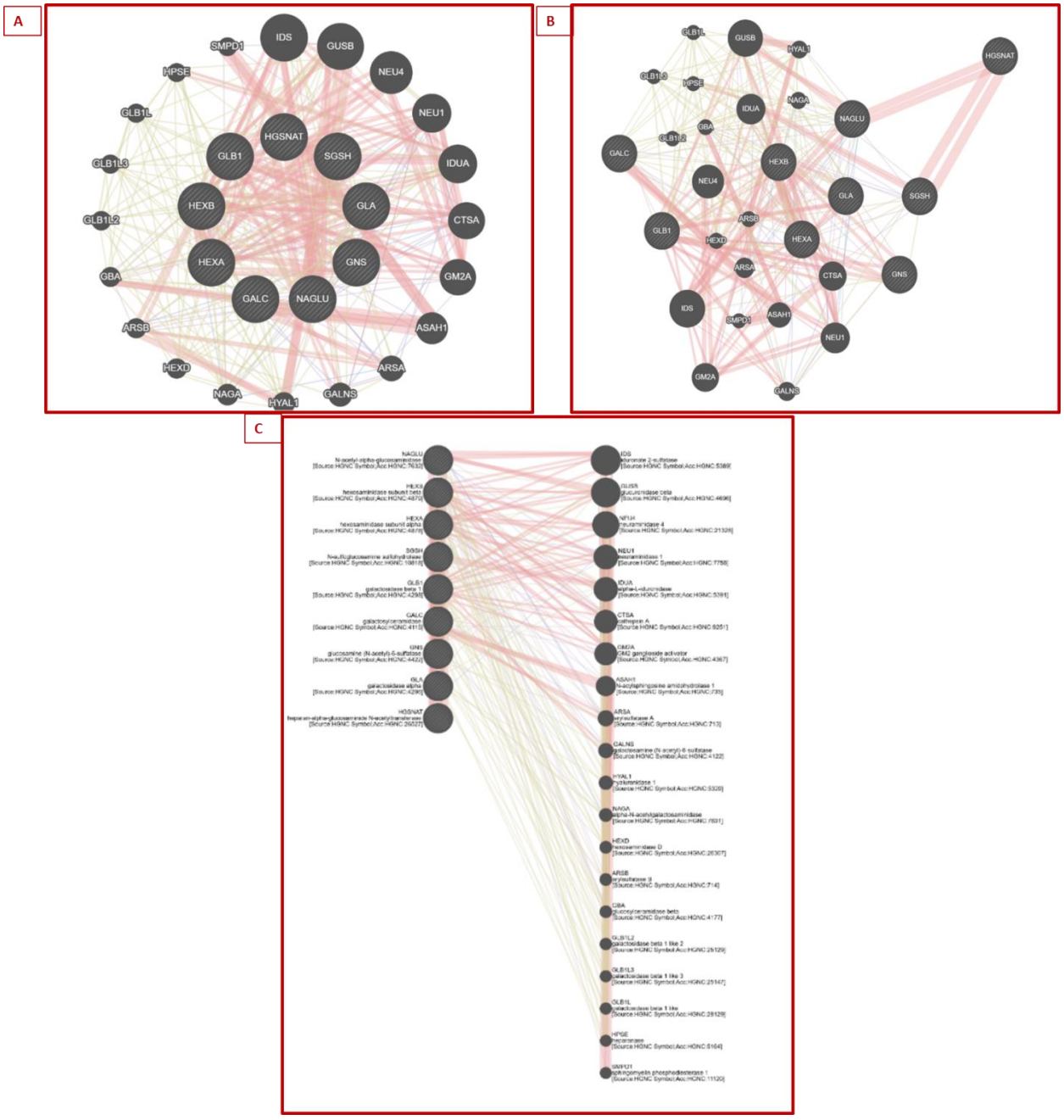

Fig. 1: GeneMANIA analysis showing the functional associations among the genes and proteins related to the ten Neurometabolic disorders (NMDs) in Table 1. Represent integrated network evidence derived from physical interactions, co-expression, co-localization, genetic interactions, and pathway membership.

The construction of this network serves to identify key hub genes that share interaction partners across multiple NMDs. This insight is crucial for revealing shared molecular mechanisms and identifying potential convergence points in the disease pathology, which may suggest common diagnostic markers or therapeutic targets across seemingly distinct disorders.

The data derived from the GeneMANIA analysis, visually represented in Figure 1, provides a powerful, evidence-based foundation for interpreting the functional relationships of the proteins associated with the NMDs listed in Table 1, thereby enriching our understanding of their underlying etiology.

Egyptian Experiences

Our team's research has centered on leveraging advanced computational and molecular methodologies to enhance the diagnosis and therapeutic understanding of rare genetic disorders, with a specific focus on lysosomal storage diseases. Our core contribution to Sanfilippo syndrome research [32–34] lies in the development and validation of a novel gene-specific Bayesian Gaussian mixture achine learning (ML) model to predict the missense variant pathogenicity of Sanfilippo syndrome [35]. This hybrid computational tool is specifically designed to accurately predict the pathogenicity of novel missense variants across all known subtypes of the syndrome. This predictive capability is critical for accelerating molecular diagnosis and clarifying the clinical significance of variants of uncertain significance (VUSs) identified during high-throughput genetic screening.

We have conducted comprehensive studies providing genetic insights into Fabry disease [36]. Furthermore, our team has successfully secured approval and executed therapeutic experiments aimed at evaluating and validating potential treatment strategies for this X-linked lysosomal storage disorder.

Our work extends beyond these specific disorders, encompassing several other genetic conditions [37–42]. A primary strategic focus moving forward is the expanded application of Artificial Intelligence (AI) and Machine Learning (ML) techniques. This integration will be instrumental in Improving Diagnostic Accuracy by utilizing AI/ML for the analysis of complex genetic and clinical data to significantly increase the precision and speed of molecular diagnosis across a broader spectrum of rare diseases.

CONCLUSION

The convergence of high-throughput 'omics and AI/ML is transforming the diagnosis of neurometabolic syndromes. By moving beyond single-gene or single-enzyme defects to interpret holistic, multi-layered molecular signatures, these technologies are paving the way for faster, more accurate diagnoses, better patient stratification, and the discovery of novel therapeutic targets. This ensures that life-saving interventions can be delivered at the earliest possible stage, significantly improving outcomes for children affected by these rare disorders.

Applying computational models to screen, prioritize, and predict the efficacy of novel compounds, thereby streamlining the development and personalization of future therapeutic interventions. This ongoing research portfolio demonstrates our commitment to transforming the field of rare disease diagnostics and treatment through the strategic convergence of genomics, bioinformatics, and artificial intelligence.

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