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ORIGINAL ARTICLE

WHOLE EXOME SEQUENCING IN THE DIAGNOSIS OF CHILDREN WITH SUSPECTED NEUROMETABOLIC DISEASES ATTENDING A TERTIARY CARE HOSPITAL OF BANGLADESH

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Abstract:

Background: *Neurometabolic disorders (NMD) encompass rare genetic errors affecting metabolism, often with neurological consequences. These disorders, characterized by genetic defects impacting enzyme function or vitamin deficiencies, can lead to severe neurological symptoms and lifelong disability. Whole exome sequencing (WES) is a vital diagnostic tool, offering a high yield in identifying genetic causes, especially in cases where traditional screenings fail to achieve diagnostic confirmation. Diagnostic confirmation is essential for providing precise treatment, genetic counseling, and prevention strategies for neurometabolic disorders. This study was conducted with the aim to observe the genetic profile of suspected neurometabolic diseases in children by whole exome sequencing.* ***Methods:*** *The cross sectional study was conducted at the department of pediatric neurology at the Institute of Pediatric Neurodisorder and Autism (IPNA) of Bangladesh Medical University (BMU) from April 2024 to March 2025, focused on infants and children suspected of neurometabolic diseases. Those aged over 1 month to less than 18 years with inconclusive initial metabolic screenings underwent whole exome sequencing for diagnosis. Real-world data were used, with subjects enrolled through convenience sampling with parental consent. The study adhered to the Ethical Committee's approval at Bangladesh Medical University. Detailed assessments included history taking, physical examinations, and investigations, with WES reports classified following ACMG guidelines.* ***Results:*** *In this study of 21 patients, with a gender distribution of 66.7% male and 33.3% female, consanguinity was present in 47.6% of cases. Common clinical features encompassed developmental delays, seizures, developmental regression. Basic metabolic screenings and neuroimaging unveiled specific abnormalities. Whole exome sequencing identified various gene mutations and neurometabolic diseases, including glycine encephalopathy, phenylketonuria and developmental and epileptic encephalopathies.* ***Conclusion:*** *This research demonstrated, whole exome sequencing (WES) provided valuable diagnostic information regarding different types of neurometabolic diseases in suspected children with neurometabolic diseases.*

Key words: *Whole exome sequencing, Neurometabolic disease, Genetic study, Children.*

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Introduction:

Neurometabolic disorders (NMD) are a group of inborn errors of metabolism with neurological manifestations. Although they are individually rare but as a group, neurometabolic disorders have a significant burden worldwide. These disorders are characterized by defects or mutations in a single gene that disrupt structure and function of corresponding enzyme or lack of vitamins necessary for a specific chemical reaction in the body.[1] Over one third of the inherited metabolic disorders are characterized by the central nervous system involvement.[2] Substrate accumulation occurs in these disorders result in minor to severe neurological and psychiatric manifestations and resulting in lifelong disability or death.

The incidence of IEM varies greatly, but collectively it is estimated to be 1 in 800 live births.[3] Progressive psycho motor regression, developmental delay, encephalopathy, seizures, hypotonia, persistent vomiting and peculiar body or urine odor, progressive gait dysfunction, progressive cerebellar ataxia, parental consanguinity, siblings or relatives with a similar type of illness or sib deaths of unexplained cause are the common manifestations.[3]

The most common neurometabolic disorders to be considered are amino acidapathies followed by neuronal ceroid lipofuscinoses, urea cycle disorders, congenital lactic acidosis, peroxisomal disorders, mucopolysaccharidoses and less frequently, sphingolipidoses, mucopolysaccharidoses, glycoprotein degradation disorders and fatty acid oxidation disorders.[4,5]

There are many treatable neurometabolic diseases those cannot be diagnosed by traditional basic metabolic screening and even by TMS and GCMS. These tests might not reveal any clue to diagnosis of these diseases. For years, biochemical screening has been indicated as first-line etiological investigations for individuals with global developmental delay (DD) or ID with metabolic phenotype.[6,7] However, in isolated ID, the diagnostic yield of first-line biochemical screening is extremely low which around 1%. This percentage may be increased upto 5% in the presence of specific neurological features.[8] Exome sequencing now appears to be one of the most cost-effective and powerful tools for the diagnosis of specific etiology of GDD with a mean diagnostic yield of 68%. It has dramatically improved the diagnosis of nonspecific or atypical phenotypes and has led to the discovery of hundreds of unknown genes.[9]

The term "exome" denotes the complete set of exons within the human genome, encompassing around 180,000 genomic sequences that are transcribed and preserved in mature RNA. Despite representing only 3% of the human genome, the exome is associated with almost 85% of clinically significant genetic disorders.[10] As a result, whole exome sequencing (WES) has become a highly effective and efficient technique for uncovering the genetic underpinnings of diseases. WES is especially useful for identifying rare mutations in autosomal recessive disorders, notably within populations exhibiting high rates of consanguinity.[11] Recently, WES has become a crucial diagnostic tool for genetic and idiopathic neurometabolic disorders, offering cost-effectiveness and a quicker path to diagnosis. Precise diagnosis is essential for providing precision treatment for treatable conditions, appropriate genetic counseling to families and preventing the recurrence of similar conditions.[12]

Little knowledge exists about the pattern of genetic mutation in developing countries like Bangladesh. Limited studies have been published from these regions in this field. This study was conducted with the aim to observe the pattern of genetic abnormalities of children suspected as inherited neurometabolic diseases in children by whole exome sequencing. It will lead to a new era in this field of research that will help further large scale study and help to prevent death, improve prognosis and quality of life of these groups of children in these developing countries.

Methods

This cross sectional study was conducted among infants and children attending the departments of pediatric neurology, Institute of Pediatric Neurodisorder and Autism (IPNA) of Bangladesh Medical University (BMU) from April 2024 to March 2025. Aim of the study was to observe the diagnostic yield of whole exome sequencing in the diagnosis of neurometabolic diseases among children suspected as having neurometabolic diseases. All children of ages more than 1 month to less than 18 years were enrolled by convenience sampling after informed written consent were obtained from the parents, if they have developmental delay or developmental regression with metabolic phenotype, whose initial metabolic screening were inconclusive. A metabolic phenotype was defined as one or more of the following abnormalities on clinical features includes developmental or cognitive regression, seizure, abnormal hair or skin color or skin lesion, abnormal body or urine odor, features of encephalopathy, hypotonia, organomegaly. Subsequently whole exome sequencing was done to reach the diagnosis at a standard laboratory. Real-world data were used for this study. The study was conducted following approval of The Ethical Committee of Bangladesh medical university. The assessment protocols were followed for

all subjects. Complete history taking by face to face parent interview using structured questionnaire regarding demographic profile including age, sex, residence, socioeconomic status, clinical presentation including developmental delay or regression, seizure, visual or hearing impairment, lethargy or impaired consciousness, abnormal body or urine odor, focal neurologic deficit, detailed family history were taken and thorough physical examination including general examination for any facial dysmorphism, any skin or hair pigmentation abnormalities, eye abnormalities, abnormalities in size and shape of head, neurological examination for any tone abnormalities, any weakness, reflex abnormalities or any abnormal involuntary movement, gait abnormalities and developmental assessment were done to observe any developmental delay in different domains of development by trained assigned physicians. All available investigation reports were recorded. Reports of Whole exome sequencing were recorded and classified according to recent standards and guidelines of the American College of Medical Genetics and Genomics (ACMG). [13]

Results

Table I

Demographic characteristics of the studied subjects (n=21)

Demographic Features	n(%)
Age at diagnosis	4 months -9 years
Sex	
Male	14 (66.7%)
Female	7 (33.3%)
Consanguineous parents	10 (47.6%)

The study showed that total 21 patients were included. Among them 13(66.7%) were male and 7(33.3%) were female. Age at diagnosis ranged from 4 months to 9 years. Consanguinity was present in 10 (47.6%) patients (Table 1).

Table II

Clinical features of the studied subjects (n =21)

Clinical features	n(%)
Developmental delay	16(76.1%)
Developmental regression	8 (38.0%)
Seizure	12(57.14%)
Involuntary movement	10(47.6%)
Abnormal body odor	0
Abnormal urine odor	0
Altered sensorium	5(23.8%)
Visual impairment	3(14.2%)
Hearing impairment	2(9.5%)
Failure to thrive	3(14.2%)
Abnormal skin change	3(14.2%)
organomegaly	2(9.5%)

Clinical features included developmental delay (76.1%), developmental regression (38.0%), seizures (57.14%), involuntary movements (47.6%), encephalopathy (23.8%), visual impairment (14.2%), hearing impairment (9.5%), abnormal skin lesions (14.2%), failure to thrive (14.2%), and organomegaly (9.5%) (Table 2).

Table III

Biochemical status of the studied patients (n-21)

Biochemical Profile	n(%)
S. Ammonia(increased)	6(28.4%)
S. Lactate (increased)	7(33.3%)
Hypoglycemia	1(4.7%)
Hyperglycemia	1(4.7%)
Urine ketone body(positive)	0
Acidosis	2(9.5%)

The basic metabolic screen showed that only 28.4% of patients had increased serum ammonia, and 33.3% had increased blood lactate. Hypoglycemia and hyperglycemia were found in only two patients. Acidosis was found only in two patients in the ABG (Table III).

Table IV

Neuroimaging and EEG profile of the studied subjects (n-21)

MRI of Brain	n(%)
Cortical atrophy	12(57.1%)
Basal ganglia hyperintensity	5(23.8%)
Corpus callosum hypoplasia	4(19.04%)
WM hyperintensity	4(19.04%)
Normal	2(9.5%)
EEG	
Normal	11(52.38%)
Epileptiform discharge	
Focal	2 (9.5%)
multifocal	3 (14.2%)
Burst suppression	3 (14.2%)
Diffuse slowing	2 (9.5%)

Neuroimaging was abnormal in most patients, with cortical atrophy being the most common (57.1%). Other findings included basal ganglia hyperintensity, white matter hyperintensity, and corpus callosum abnormality. Half of the patients had abnormal EEG results (Table 4).

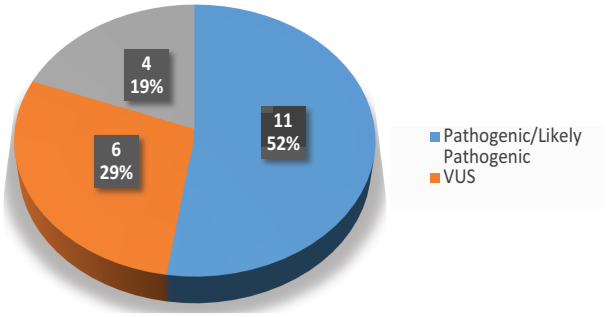

Figure 1: *Diagnostic rate of whole exome sequencing*

Whole exome sequencing (WES) revealed that 11 patients had pathogenic or likely pathogenic gene mutations, 6 patients had variants of uncertain significance (VUS), and 4 had normal reports (Figure 1).

Among 17 abnormal WES reports, 11 (64.7%) patients had various types of neurometabolic diseases, 3 had developmental and epileptic encephalopathy, 1 had metabolic disorder affecting kidney and 1 had coagulation disorders (Figure II).

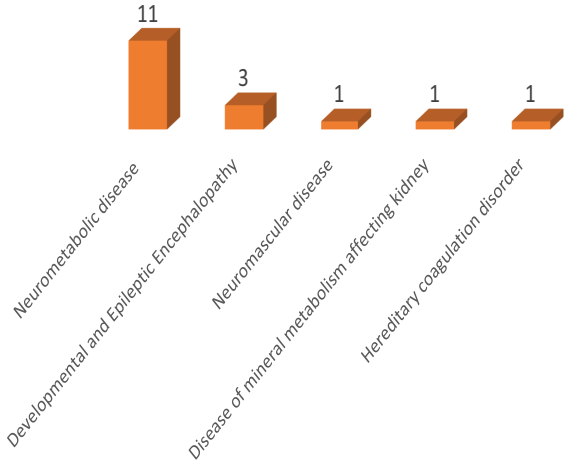

Figure 2: *Profile of the diseases diagnosed by WES*

Table V

Genetic profile of the studied subjects (n=21)

Cases		Location	Variance	Gene	Zygocity	Inheritance	Disease	Significance
1.6m, M	Neuroregression,sib death,lethergy,failure to thrive	Exon 3	Chr3.18070587 7G>C c.63 C>G p.Tyr21Ter	*DNAJC19*	Homozygous	ARD	3,methylglutaconic aciduria, type V	P
2.9 years, M	Behavioral abnormality,hyperactivity,autistic features	Exon 7	c.842C>T p.Pro281Leu	*PAH*	Homozygous	ARD	Phenylketonuria	P
3.2y, M	Neuroregression,organo,megaly,diarrohoea,abdominal pain	Exon 9	c.1417C>T p.Arg473	*SLC7A7*	Homozygous	ARD	Lysinuric protein intolerance	P
4.13m ,F	Neuroregression, seizure,dystonia	Exon 2	c.433C>T	*MMAA(+)*	Homozygous	ARD	Vitamin B12 Responsive cb1A Type Methlymalonic acidemia	P
5.4 months, F	Neuroregression,dystonia,epileptic spasm,oculgyric crisis	Exon 3	c.946A>T p.Asn316Tyr	*SLC19A3(-)*	Homozygous	ARD	Biotin/Thiamin responsive basal ganglia disease	VUS
6. 1 year, F	Neurogression,organomegaly,hypotonia	Exon 6	c.1624C>T (p.Arg542Tyr)	*SMPD1(+)*	Homozygous	ARD	Niemann-Pick disease Type A & B	P
7. 1 year, M	Neuroregression,dystonia,affected sib	Exon 9	c.877G>A(p.Ala293Thr)	*GCDH(+)*	Homozygous	ARD	Glutaric aciduria Type 1	P
8. 9 months, M	Seizure, Developmental delay and regression, hypotonia, choreo athetoid movement	Exon 23	Chr9:6536059 C>T c. 2838+5G>A	*GLDC*	Heterozygous	ARD	Glycine encephalopathy 1	VUS
9. 7 year,M	Walking difficulty , hypotonia,bilateral positive babniski sign,ID	Exon 2	Chr8.17933065 G>A c.110C>T p.Pro37Leu	*ASAH1*	Homozygous	ARD	Spinal Muscular Atrophy with progressive myoclonic epilepsy	VUS

Table V (Cont'd)

Genetic profile of the studied subjects (n=21)

Cases		Location	Variance	Gene	Zygocity	Inheritance	Disease	Significance
10. 5m,Male	Epileptic spasm,GDD,spasticity	Negative for disease causing or likely disease causing variants in the genes, no clinically significant CNVs, Negative for disease causing or likely disease causing variants in the mitochondrial genes tested in this sample						
11. 26 months, F	Developmental delay,dystonia,spasticity	Exon 8	c.695dup p.Asn233LysfsTer17	*ACTL6B(-)*	Homozygous	ARD	Developmental and epileptic encephalopathy 76	P
12,12 months, M	Seizure,GDD	Negative for disease causing or likely disease causing variants in the genes, no clinically significant CNVs, Negative for disease causing or likely disease causing variants in the mitochondrial genes tested in this sample						
13.,12 month, M	Dysmorphism,GDD,seizure,hypotonia	Exon 14		STT3B	Homozygous	ARD	Congenital disorder of glycosylation, type Ix	VUS
14. 12 months, M	Epileptic spasm,GDD	Negative for disease causing or likely disease causing variants in the genes, no clinically significant CNVs, Negative for disease causing or likely disease causing variants in the mitochondrial genes tested in this sample						
15. 2 yr,M	Epileptic spasm,GDD	Negative for disease causing or likely disease causing variants in the genes, no clinically significant CNVs, Negative for disease causing or likely disease causing variants in the mitochondrial genes tested in this sample						
16. 12 months, F	Developmental delay, feeding difficulty, failure to thrive	Exon 14	c.1298C>T (p.Thr433Ile)	*AAAS (-)*	Homozygous	ARD	Achalasia-addisoniasm-alacrima Syndrome	VUS
17.2 years,M	Seizure, poor feeding, lethargy, negative septic screening	Exon 28	c.4792_4793delins TA(p.Thr1598ter)	*TRPM6(-)*	Homozygous	ARD	Familial hypomagnesemia with secondary hypocalcemia	P
18. 2 years,F	Behavioral problem, seizure,neuroregression, stereiotipies	Exon 3	c.(259+1_260-1)_(327+1_328-1)del	*GABRG2*	Heterozygous	ADD	Developmental and epileptic encephalopathy 74	P
19. 2 month, M	Seizure, GDD, repeated diarrohrea, dyspepsia, hypotonia, dystonia	Exon5	c.344T>A p. Val115Glu	*UFSP2(-)*	Homozygous	ARD	Developmental and epileptic encephalopathy 106	P
20. 3 yr, M	Walking difficulty, hypertrichosis,polydactyly,hypotonia,ataxia..	Exon 8	C.792_793del (p.Arg264Serfster27)	*SURF1(-)*	Homozygous	ARD	Mitochondrial complex IV deficiency, Nuclear type 1	P
21. 4 yrs,M	Neuroregression,seizure,hemiparesis.		c.1405G>C p.Glu469Gln	*PROS199-)*	Heterozygous	ARD	Thrombophilia 5 due to protein S deficiency	VUS

Types of neurometabolic disease were Glycine encephalopathy, 3, methylglutaconic aciduria, type V, Phenylketonuria, Lysinuric protein intolerance, Vitamin B12 Responsive cb1A Type Methlymalonic acidemia, Biotin/Thiamin responsive basal ganglia disease type, Glutaric aciduria Type 1, Congenital disorder of glycosylation, type Ix, Mitochondrial complex IV deficiency, Nuclear type 1, Niemann-Pick Disease Type A & B, Achalasia-addisoniasm-alacriama Syndrome.

Developmental and epileptic encephalopathies were *ACTL6B (-), GABRG2* and *UFSP2(-).* One neuromuscular disease was spinal muscular atrophy with progressive myoclonic epilepsy, 1 had mineral metabolism affecting kidney named familial hypomagnesemia with secondary hypocalcemia and one patient had hereditary coagulation disorder, thrombophilia 5 due to protein S deficiency. No diseases causing mutation was found among 4 of them (Table 5).

Discussion

This study on whole-exome sequencing (WES) in the diagnosis of children with suspected neurometabolic diseases attending a tertiary care hospital in Bangladesh yielded crucial insights into the genetic underpinnings of various conditions. The study encompassed 21 patients, with a male predominance (66.7%) and a significant portion (47.6%) having consanguineous parents. The symptoms varied among patients. The most common were developmental delay (76.1%), seizures (57.4%), involuntary movements (47.6%), and developmental regression (38%). Other symptoms included encephalopathy, visual problems, and organomegaly. In a study by AI Khudari et al. (2025), similar patterns were observed, but seizures were the most frequent symptom in their study.[14]

In this study, WES provided valuable clinical insights for the majority of patients, especially when other diagnostic tests were inconclusive. WES identified pathogenic or likely pathogenic gene mutations in 11 patients, while 6 had variants of uncertain significance (VUS) and 4 had normal reports. Notably, whole-exome sequencing (WES) provided important clinical information in this study in 80.9% (17 out of 21) of patients and successfully diagnosed conditions in 52.3% (11 out of 21), aligning with rates seen in similar studies from Qatar, UAE, and Syria (ranging from 50% to 53%).[14-16] In contrast, a larger study in the United States, which examined 250 samples, reported a notably lower diagnostic rate of 25%17. This disparity may arise from differences in the prevalence of autosomal recessive disorders and the impact of consanguinity within these populations.

In our patient group, 71.4% (15 out of 21) had autosomal recessive conditions, contrasting with the 29% observed in the U.S. study.[21] Moreover, 47.6% (10 out of 21) of our patients had a family history of consanguinity; similar findings were noted in a Saudi Arabian study.[12] Consanguinity emerges as a crucial factor influencing the diagnostic effectiveness of WES, as indicated by various research findings. Turkdogan et al. highlighted a diagnostic yield of 39% for pathogenic or likely pathogenic variants, a figure that rose to 61% when incorporating de novo variants associated with compatible clinical features.[18] In our investigation, four cases revealed variants of uncertain significance (VUS), all correlating with recognized phenotypes. Consequently, the diagnostic yield surged from 55% to 80% when these variants were linked to compatible clinical features.

In this study, a total of 17 patients had abnormal findings in WES, among them 11 out of 17 were diagnosed with neurometabolic diseases. Various neurometabolic diseases were detected, including phenylketonuria, glycine encephalopathy, methylglutaconic aciduria, lysinuric protein intolerance, and more. These findings were comparable to findings revealed by Kundu et al (2021).[19] In this study, most diagnosed neurometabolic diseases were treatable even though their initial investigation reports were inconclusive. Similar findings were found by AI Khudari et al. (2025), where WES led to a diagnostic change in 83% of cases and change of treatment of 73% of cases.[14] In developing countries, due to financial constraints, the majority of cases of suspected neurometabolic diseases remain undiagnosed, despite having specific treatment. The identification of specific genetic mutations through WES can significantly aid in the diagnosis and management of complex neurometabolic disorders.[20]

Understanding the genetic basis of these conditions can guide personalized treatment strategies and genetic counseling for affected families. The study highlights the importance of advanced genetic testing techniques in unraveling the underlying causes of rare and complex diseases, especially in a resource-limited setting like Bangladesh.

In a nut shell, the study emphasizes the utility of WES in diagnosing neurometabolic diseases in children, shedding light on the genetic landscape of these conditions and paving the way for improved patient care and management strategies.

The study encompassed a relatively small sample size of 21 patients, which may limit the generalizability of the findings. Another limitation is that, it was conducted at a single tertiary care hospital in Bangladesh; the study's findings may not represent the broader population or different healthcare settings. Improving sample size, conducting multi-center studies, expanding the scope of diseases studied could enhance the study's impact and applicability in diverse healthcare settings.

Conclusion

This research demonstrated, whole exome sequencing (WES) in providing valuable diagnostic information regarding different types of neurometabolic diseases.

WES has led to the confirmation of diagnoses, modifications in treatment strategies, adjustments in prognoses, and the adoption of preventive measures in cases of neurometabolic diseases.

Author contributions

Conception and design of the work: SA, SA, FND, ST, KF, Acquisition, analysis, or interpretation of data for the work: SA, SA, FND, STA, KF, KAI, BCP, Drafting the work or reviewing it critically for important intellectual content: SA, SA, STA, KF, Final approval of the version to be published: SA, SA, STA, KF, KA, BCP, FND

Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: SA.

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Ethical approval

The study was approved by the Institutional Review Board (IRB) of Bangladesh Medical University (Ref No: BSMMU/2024/203, Date: 06-01-2024). Informed written consent was obtained before data collection.

Conflicts of interest

We do not have any conflict of interest.

Data availability statement

We confirm that the data supporting the findings of this study will be shared upon reasonable request.

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