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The next generation sequencing among epileptic children in Erbil city, Kurdistan region, Iraq

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Talib Adil Abdulqadir [1]* Azad Anwar Hamad [2]

Abstract

Background and objective: Causes of epilepsy are different and the genetic component is hidden and provides an essential role in emergence of drug resist epilepsy. The aim of this study is to know the diagnostic yield of Whole exome sequence in pediatric epilepsy and its contribution in giving information about diagnosis of the epilepsy syndrome, possible preventive actions or treatment.

Methods: 60 children (6 weeks - 14 year) with drug resistant epilepsy, family history of epilepsy or child with diagnosis of epilepsy syndrome were enrolled in this cross sectional study. The study was done in Raparin pediatric teaching hospital in Erbil city from beginning of May 2021 to the end of April 2022. Demographic, clinical, MRI finding and genetic background using whole exome sequence were checked and analyzed.

Results: 33/60 (55%) of participants were male. The NGS (Next Generation sequence) study revealed: 13 (21%) pathogenic, 10 (17%) likely pathogenic, 21 (35%) variance of unknown significance and 16 (27%) negative result. The diagnostic yield by NGS for pathogenic or likely pathogenic is 38%. The positive findings were more relevant among female (*P* value = 0.04), children with age onset of seizure≤ 1 year of (*P* value = 001) and history of lack of sleep (*P* value = 0.02). Genetic diagnosis lead to change of treatment in 11/60 (18.3%) candidates.

Conclusion: The diagnostic genetic test by NGS is relevant in epileptic child especially among children with age of onset of seizure ≤ 1 year, female sex and lack of sleep. It is recommended to test the negative result periodically and more research to investigate impact of NGS on seizure freedom.

Keywords: Pathogenic; Likely pathogenic; Diagnostic yield.

Introduction

Epilepsy is a common neurological disease, affecting 65 million people worldwide (1-2 % of general population) with the highest incidence in infancy and elderly and slight higher rate in boys than in girls.[1, 2, 3]

Causes of epilepsy are wide and include: structural, genetic, infectious, and metabolic and unknown. Genetic cause contributed to 30% of epilepsy etiology.[3,4]

Genetic causes can be either related to chromosomal or gene abnormalities. The term genetic is not synonymous to inherited e.g. the child with epilepsy might have genetic predisposition to the seizure due to a new mutation in spite of negative family history, but this child can be regarded inheritable if the new mutation is dominant and the offspring will have 50% chance of transmission. A genetic cause dose not exclude an environmental role like lack of sleep and stress in seizure disorders.[4]

More than 500 epilepsy-associated genes have been described in the literature. According to the interaction of genetic and environmental factors, epilepsy divided into monogenic and complex. The monogenic

[1] Department of Pediatrics, College of Medicine, Hawler Medical University, Erbil, Iraq.
[2] Department of Medicine, College of Medicine, Hawler Medical University, Erbil, Iraq.
Correspondence: tabeeb2@gmail.com

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(Mendelian) which is regulated by one gene, it is simple and rare contributing to 1-2% of all epilepsy cases. The complex type is polygenic and common. Monogenic epilepsy is further classified into: channel opathies, regulation of synaptic process, mTorpathies and others. Sodium channelopathies are among the most common single –gene cause of epilepsy.[5,6,7,8,9]

The Whole Exome Sequencing (WES) refers to the sequencing of protein-encoding portions of the genome, called exomes. Overall, approximately 20,000 genes are found in the human exome, which is associated with most human diseases. The phenotype of the identified gene variants is calculated by the WES study and then a comparison is made with the polymorphic (non-pathogenic) variants distributed in the general population to classify the potential pathogenic variants.[10,11,12]

The diagnostic yield of NGS in epilepsy is variable (28-70%) depending on sample investigated and phenotype like epilepsy type, neurodevelopmental delay, etiology and autism.[13,14]

Genetic epilepsy is a rapidly developing area. Medical experts trained in theses filed are needed for genetic testing and test interpretation. Interpretation of a genetic tests is a formidable task and every report needs to be re-evaluated by an expert.[15]

This study was carried out to know the diagnostic yield of NGS in epileptic children and reveal any statistical association between genetic and structural cause of epilepsy.

Methods

This study was done in Raparin Pediatric Teaching Hospital in Erbil City/Iraq. This cross sectional study was conducted in a period of 12 months from the beginning of May 2021 to the end of April 2022. Sixty children aged from infancy to early adolescent conveniently with drug resistant epilepsy, epilepsy syndrome and family history of epilepsy were enrolled in the study. Exclusion criteria were neonatal age group, cerebral palsy, febrile seizure, post traumatic epilepsy, uncontrolled epilepsy due to poor compliance or inappropriate selection or dosing of anti-seizure medications and epileptic child without EGG and neuroimaging report. A thorough history was obtained from the mother or care taker about description of seizure, duration, type and age of seizure onset, epilepsy type, kind of treatment, compliance to treatment, post-ictal state, and sleep pattern.

Developmental milestones including gross motor, communication and language, and cognitive was asked. A detailed examination including neurological and systemic examination was applied. Growth parameters were plotted and compared on CDC growth chart. Epilepsy in children was defined and classified according to ILAE (International League Against Epilepsy) definition of epilepsy in 2014.[16] Drug resistant epilepsy was defined according to the ILAE in 2009.[17] Lack and quantity of sleep was analyzed by age according to the sleep foundation publication in 2015 into: recommended, may be appropriate and not recommended.[18]

All children had routine EEG during sleep and wakefulness and epilepsy protocol brain MRI. Positive MRI findings include malformation of cortical development, hippocampal sclerosis, cortical tuber, brain atrophy, destructive brain lesion in early life and others. A 3 ml of blood was drawn from each child and put in EDTA – test tube by trained medical staff and put on Centocard directly (CentoCard makes sending patient samples as easy as sending letter using Dried Blood spot technology), and Cento Card dried blood sample was sent by special team. Most of the samples were sent within 48-72 hours to United Kingdome (Department of Neuromuscular Disorders, UCL Institute of Neurology, 7th floor Queen Square, London, WC1N 3BG) and other samples were sent to Germany (CENTOGENE, THE REARE DISEASE COMPANY) using

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Next generation Sequence and Copy Number Variation to cover deletion and duplication. The result took around 30-45 days and it was sent back electronically in the form of PDF to our lab.

The result of genetic study was interpreted as: pathogenic, likely pathogenic, uncertain significant, likely begin and benign.[19]

Statistical analysis

The statistical analysis was performed with IBM SPSS 26 for windows 10. A *P* value of less than 0.05 was considered significant. Baseline characteristics was analyzed, Frequency of different symptoms and signs were calculated. Percentage and diagnostic yield of epileptic child with positive genetic result were calculated. Chi- square and Fisher's Exact Test were applied especially between genetic and structural abnormalities.

Problems anticipated

Was the sample size which is relatively small and might have impact on the result, the high cost of the investigation and difficulty of sending sample to the outside country and pending relatively long time result.

Results

60 Children conveniently with drug resistant epilepsy, epilepsy syndrome and family history of epilepsy were enrolled in the study. Fifty five percent of participants were male (33/60) and forty five percent were female (27/60) with male to female ratio 1.2:1. Age at enrollment was 6 weeks to 14 years with mean age 56.62±36.9 months. Forty nine children (81.7%) were from urban area while just eleven child (18.7%) belonged to rural area. (Table 1, Table 2)

Table 1 Sex and rural/urban distribution of epileptic children.

Patients	Number (%)
Gender	
Male	33 (55%)
Female	27 (45.0%)
Address	
Rural	11 (18.3)
Urban	49 (81.7%)
Total	60 (100%)

Table 2 Distribution of mean (SD) of age and growth parameters among epileptic child.

Parameters	Mean (SD)	CI (95%)
Age (month)	56.62 (36.99)	(47.47 - 66.21)
Weight (kg)	15.4383 (8.46)	(13.3806 -17.4643)
Height (cm)	96.7583 (21.86)	(91.3833 --- 102.0833)
Head circumference (cm)	46.1500 (4.68)	(44.9750 - 47.2833)

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The NGS study revealed: 13 (21%) pathogenic, 10 (17%) likely pathogenic, 21 (35 %) variance of unknown significance and 16 (27%) negative result. The diagnostic yield by NGS for pathogenic or likely pathogenic is 38%. We further analyzed negative results by CNV (Copy Number Variation), the diagnostic yield raised to 45% (Figure 1, Table 3).

Table 3 Copy Number Variation result among epileptic child

CNV Coordinates	Interpretation	Patient Relevant Phenotype
chr1:1114595-4834582	Pathogenic	1p36 deletion syndrome
arr[GRCh37] 15q11.2q13.1(23290788_28560664)x1	Pathogenic	Angelman syndrome
arr[hg19] 7p22.3p22.2(43,377-3,241,619)x1	Likely pathogenic	Overlap with Distal monosomy 7p
arr[hg19] 6q25.1q27(151,494,860-170,914,297)x3	Likely pathogenic	Overlap with Distal trisomy 6q
chr16:97430-227410	Likely Pathogenic	Epilepsy, familial focal, with variable foci 3 - AD

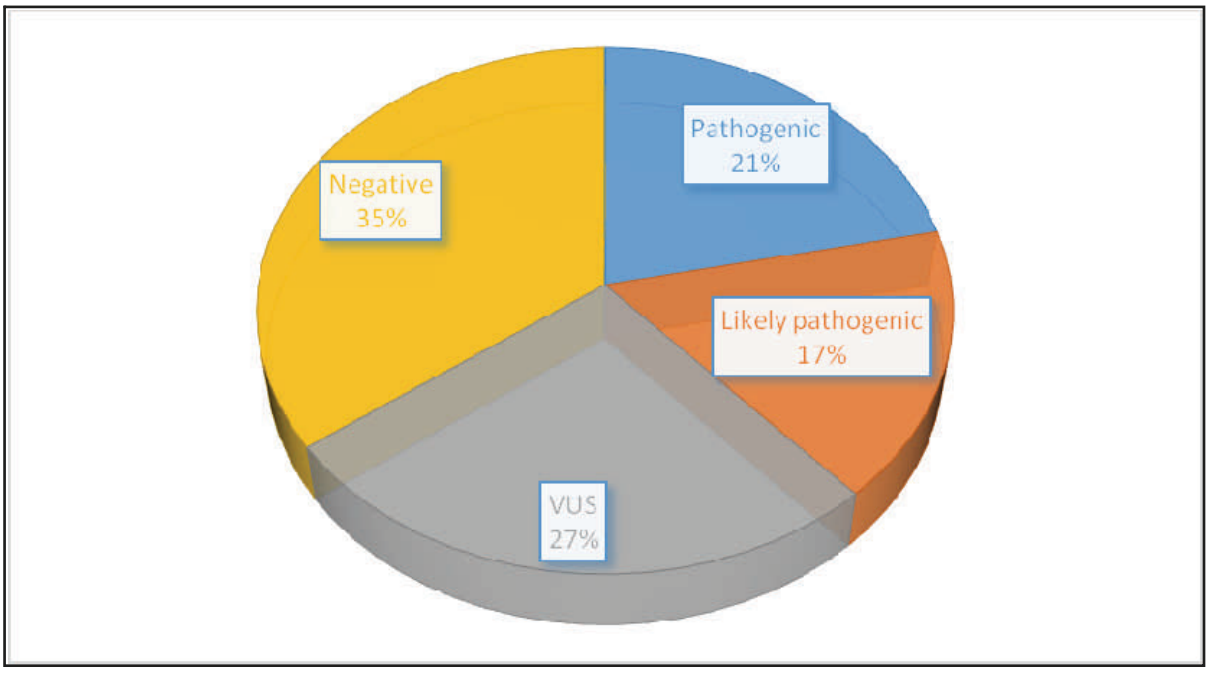

Figure 1 Diagnostic yield of Next Generation Sequence (Whole Exome Sequence) in Epileptic child.

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The pathogenic genes discovered by NGS were: BTD, POLG, UFSP2, PNPLA8, TREX1, PCH19, NCDN, NDUFS2, CASQ2, SLC16A2, COQ4, DLD and SNAP29 while the likely pathogenic genes were: SCN2A, WDR37, CDKL5, DOCK6, TRIT1, TSC2, NF1, CSTB, DYRK1A and PDHA1 (Table 4).

Monogenic epilepsy genes include: SCN1A, SCN2A, TSC2, CSTB, CDKL5, PCDH19, CACNA1A, GRIN2B and CHRNA4. Mutations in sodium channels were found in three subjects; two SCN1A (VUS) and one SCN2A (likely pathogenic) (Table 4).

Types of sequence and structural changes were reported among the P/LP (Pathogenic/Likely Pathogenic) cases 27/60 (45%), of them 20/60 (33.3%) had Single nucleotide variants (missense, nonsense, or splice site) and 3/27 (5%) had frameshift variants and 4/60 (6.6%) had 5 Copy number variants. Mode of inheritance was explained for 39 variants: 49% (19/39) was AR, 38% (15/39) was AD and 13% (5/39) was XL (Table 4).

Table 4 Identification of genotype, phenotype, inheritance, mutation type and classification.

Gene	Variant Coordinates	Amino Acid Change	Zygosity	Mutation Type	Mutation Classification	Diagnosis
BTD	NM_001281723.2:c.104_110delinsTCC	p.(Cys35Phefs*36)	homozygous	Frameshift	Pathogenic (class 1)	Biotidinase deficiency (AR)
POLG	NM_001126131.1:c.3286 C>T	p.(Arg1096Cy s)	homozygous	Missense	Pathogenic (class 1)	POLG- AR mitochondrial DNA depletion syndrome.
UFSP2	ENST00000264689.10:c.344T>A	p.Val115Glu	homozygous	Missense	Pathogenic (class 1)	Infantile spasm, refractory epilepsy (AD)
PNPLA8	NM_001256008:exon2:c.793dupA	p.T265fs	homozygous	frameshift	Pathogenic (class 1)	Mitochondrial myopathy with lactic acidosis (AR)
TREX1	ENST00000444177.1:c.213_216del	p.Ser72ArgfsTer5	heterozygous	frameshift	Pathogenic (class 1)	Infantile spasm (AD)
PCDH19	NM_001184880.1: c.695A>G	p.Asn232Ser	Heterozygote	Missense	Pathogenic (class 1)	Developmental and epileptic encephalopathy 9 (XL)
NCDN	NM_001014839.1: c.555C>G	p.Tyr185Ter	Heterozygote	Missense	Pathogenic (class 1)	Neurodevelopmental disorder with infantile epileptic spasms (AD)
NDUFS2	NM_004550.4: c.1324C>T	p.Arg442Ter	Homozygote	Missense	Pathogenic (class 1)	-Mitochondrial complex I deficiency, nuclear type 6 (AR)
CASQ2	NM_001232.4:c.320-2A>G	p.?	Homozygote	Splicing	Pathogenic (class 1)	Epilepsy and Ventricular Tachycardia, Catecholaminergic Polymorphic, 2 (AR)
SLC16A2	ENST00000587091.5:c.1171-1G>A	P.?	Homozygote	Splicing	Pathogenic (class 1)	Allan-Herndon-Dudley syndrome (XL)
COQ4	ENST00000300452.7:c.437T>G	p.Phe146Cys	Homozygote	Missense	Pathogenic (class 1)	Coenzyme Q10 deficiency, primary,7(AR)
DLD	ENST00000205402.9:c.197A>G	p.Lys66Arg	Homozygote	Missense	Pathogenic (class 1)	Dihydrolipoamide dehydrogenase deficiency (MSUD type III) -AR

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SNAP29	ENST00000215730.11:c.586C>T	p.Arg196Ter	Homozygote	stop_gained	Pathogenic (class 1)	Cerebral dysgenesis, neuropathy, icthyosis, and palmoplantar keratoderma syndrome (AR)
SCN2A	NM_001040142.1: c.4446+1A>G	p.?	heterozygous	Splicing	Likely Pathogenic (class 2)	AD- developmental and epileptic encephalopathy-11 (DEE11)
WDR37	NM_014023.3: c.356C>A	p.(Ser119Tyr)	heterozygous	Missense	Likely pathogenic (class 2)	Neurooculocardio-genitourinary syndrome (AD)
CDKL5	NM_001037343.1:c.403+1G>T	P.?	heterozygous	Splicing	Likely Pathogenic (class 2)	Early infantile epileptic encephalopathy type 2 (XLD)
DOCK6	NM_020812.3:c.4708G>T	p.(Glu1570*)	homozygous	Nonsense	Likely Pathogenic (class 2)	Adams-Oliver syndrome type 2 (AR)
TRIT1	NM_017646.5:c.1204C>T	p.(Arg402*)	homozygous	Nonsense	Likely Pathogenic (class 2)	Combined oxidative phosphorylation deficiency type 35 (AR)
TSC2	NM_000548.3:c.976-1G>T		heterozygous	Splicing	Likely Pathogenic (class 2)	Tuberous sclerosis type 2 (AD)
NF1	NM_001042492.2: c.4333-2A>T	p.?	heterozygous	Splicing	Likely Pathogenic (class 2)	Neurofibromatosis type 1 (AD)
CSTB	ENST00000291568.6:c.10G>T	p.Gly4Trp	Homozygote	Missense	Likely Pathogenic (class 2)	Progressive myoclonic epilepsy – 1A (AR)
DYRK1A	ENST00000338785.8:c.980A>T	p.Val115Glu	heterozygous	Missense	Likely Pathogenic (class 2)	Intellectual develop-mental disorder type 7 (AD)
PDHA1	NM_001173454.2	p.Gly268Arg	heterozygous	Missense	Likely Pathogenic (class 2)	Pyruvate dehydogenase E1-alpha deficiency (XLD)
SHROOM4	NM_020717.3:c.3997C>G	p.(Arg1333Gly)	hemizygous	Missense	Uncertain significance (class 3)	X-linked syndromic intellectual developmental disorder
CACNA1A	NM_023035.2:c.6681_6686del	p.(Pro2228_Pro2229del)	heterozygous	In-frame	Uncertain significance (class 3)	AD-Developmental and epileptic encephalopathy-42 (DEE42)
GRIN2B	NM_000834.3:c.3912C>A	p.(Tyr1304*)	heterozygous	Nonsense	Uncertain significance (class 3)	AD- Developmental and epileptic encephalopathy type 27 (DEE27)
MBD5	NM_018328.4:c.4450C>A	p.(Pro1484Thr)	heterozygous	Missense	Uncertain significance (class 3)	AD – Mental Retardation type1
PIGM	NM_145167.2:c.425G>T	p.(Ser142Ile)	homozygous	Missense	Uncertain significance (class 3)	AR - glycosylphosphatidy-linositol deficiency

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CHRNA4	NM_000744.6:c.1787T>G	p.(Met596Arg)	heterozygous	Missense	Uncertain significance (class 3)	AD- nocturnal frontal lobe epilepsy type 1
PNPLA8	NM_001256007.2: c.793dup	p.(Thr265Asnfs*13)	homozygous	Frameshift	Uncertain significance (class 3)	Mitochondrial myopathy with lactic acidosis (AR)
TRAPPC9	NM_031466.6: c.1598C>T	p.(Thr533Met)	homozygous	Missense	Uncertain significance (class 3)	Mental retardation type 13 (AR)
SCN1A	NM_001165963: c.2236T>t	p.Leu746Leu	Heterozy-gous	Missense	Uncertain significance (class 3)	Dravet syndrome (AD)
SCN1A	AB09354B.1:c.4412C>T	p.(Ser1471Phe)	Heterozygote	Missense	Uncertain significance (class 3)	Dravet syndrome (AD)
UBE4A	NM_004788.3:c.217C>T	p.(Arg73*)	homozygous	Nonsense	Uncertain significance (class 3)	Intellectual disability and global developmental delay (AR)
GRIA2	NM_000826.6: c.677T>C	p.Ile226Thr	Heterozygote	Missense	Uncertain Significance (class 3)	Neurodevelopmental disorder with language impairment and behavioral ab-normalities, AD
ALS2	ENST00000439495.5:c.1751_1753del	p.Leu585del	Homozygote	Inframe_ deletion & NMD _ transcript_ variant	Uncertain Significance (class 3)	Spastic paralysis, infantile onset ascending (AR)
MOGS	ENST00000233616.8:c.2123G>A	p.Arg708His	Homozygote	Missense	Uncertain Significance (class 3)	Congenital disorder of glycosylation type IIb (AR)
WDR37	ENST00000434634.6:c.354T>G	p.Asp118Glu	Homozygote	Missense	Uncertain Significance (class 3)	Galloway-Mowat syndrome 1(AR)
ALDH5A1	ENST00000348925.2:c.1144C>T	p.Arg382Cys	Homozygote	Missense	Uncertain Significance (class 3)	Succinate semial dehyde dehydegenase deficiency (AR)

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There were 4 positive results by CNV: 2 pathogenic and 2 likely pathogenic. In case number 36, there were 2 CNVs: a one-copy loss within the 7p22.3p22.2 chromosomal region encompassing the entire of 57 genes, this CNV has overlap with Distal monosomy 7p region and another one-copy gain within the 6q25.1q27 chromosomal region encompassing the entire of 151 genes. This CNV has overlap with Distal trisomy 6q region. In case number 5,Angelman syndrome was reported by CNVs and a 5270 kb large 1 copy loss on the long arm of chromosome 15 including 119 genes was detected and confirmed by chromosomal microarray analysis. Furthermore, by MS-MLPA analysis, this deletion was associated with an aberrant methylation profile (hypomethylation) (Table 3)

The pathogenic or likely pathogenic findings were more common among children with onset of seizure ≤ 1 yr. of age (22/33) in comparison to a children with onset of seizure above 1 yr. (5/27), and there was a significant statistical association (*P* value <0.001). The positive genetic findings (P/LP) among boy and girl were analyzed and found that the parent-age of female was greater than male, 59.3% vs 40.7% respectively and this was associated with significant statistical association (*P* value = 0.045). Sleep patterns were identified and revealed that not recommended sleep pattern was more prevalent among P/LP group (16/27) in relation to VUS or negative group (9/33), and it found that there was a significant statistical association (*P* value = 0.02) (Table 5).

Epileptic child with positive MRI finding in P/LP group was comparable to candidates in VUS/negative group, 16/60 vs 17/60 respectively while normal findings were recorded more among VUS/Negative group in comparison to P/LP group, 16/60 vs 11/60 respectively, and it found that these results had no significant statistical association (*P* value = 0.549) (Table 5).

Other parameters were included in the study like family history of epilepsy, history of febrile seizure, craniofacial features (microcephaly, macrocephaly or facial features) and cognition abnormalities in P/LP and VUS/Negative groups and found that there were no any significant statistical association between them. (Table 5).

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Table 5 Distribution of different parameters in P/LP vs VUS/Negative group.

Parameters	P/LP (n= 27)	Negative or VUS (n=33)	Total**	*P* value
Age at seizure onset				
Age ≤ 1yr.	22 (81.5%)	11 (33.3%)	33 (55.0%)	<0.001
Age > 1 yr.	5 (18.5%)	22 (66.7%)	27 (45%)	
Gender				
Male	11(40.7%)	22 (66.7%)	33 (55.0%)	0.045
Female	16 (59.3%)	11(33.3%)	27 (45.0%)	
Epilepsy type				
Focal	8 (29.6%)	17 (51.5%)	25 (41.7%)	
Generalized	18 (66.7%)	15 (45.5%)	33 (55%)	0.172 *
Combined	1 (3.7%)	1(3%)	2 (3.3%)	
Family History of epilepsy				
Positive	12 (44.4%)	20 (60.6%)	32 (53.3%)	0.212
Negative	15 (55.6%)	13 (39.4%)	28 (46.7%)	
History of Febrile seizure				
Positive	7 (25.9%)	7 (21.2%)	14 (23.3%)	0.668
Negative	20 (74.1%)	26 (78.8%)	46 (76.7%)	
Sleep pattern				
Recommended	1 (3.7%)	1 (3%)	2 (3.3%)	
Appropriate	10 (37%)	23 (69.7%)	33 (55%)	0.02 *
Not recommended	16 (59.3%)	9 (27.3%)	25 (41.7%)	
Craniofacial features				
Dysmorphic	19 (70.4%)	18 (54.5%)	37 (61.7%)	0.210
Normal	8 (29.6%)	15 (29.6%)	23 (38.3%)	
Cognition				
Abnormal	6 (22.2%)	12 (36.4%)	18 (61.7%)	0.234
Normal	21 (77.8%)	21 (63.6%)	23 (38.3%)	
Brain MRI findings				
Normal	11 (40.7%)	16 (48.5%)	27 (45.0%)	0.549
Abnormal	16 (59.3%)	17 (51.5%)	33 (55%)	

*this indicate Fisher exact test used instead of person Chi square
**Column % was calculated

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Discussion

Our study revealed that the diagnostic yield of WES for pathogenic or likely pathogenic variant is 38% which is harmony to a study done in Boston Children Hospital in USA from 2010-2017 that the diagnostic yield for epilepsy is 40%,[13] while through systematic literature review, it found that the overall diagnostic yield was 24 % for epilepsy.[20]

The diagnostic yield of P/LP for CNV in our study was ~ 7 % which is comparable to a study done by Lindy et al. and they found CNV account for ~ 9% of positive results.[21]

The positive finding (P/LP) was more observed among children with age of onset of seizure ≤ 1 year in comparison to a children above 1 year. (*P* value <0.001), This result is in agreement other study done in Qilu Hospital in China and demonstrated that the deleterious variants is more common in pediatric refractory epilepsy with age of onset of seizure ≤ 1 year (*P* value 0.006).[22] This is might be attributed to expression of some epilepsy associated genes in early age.

The female epileptic child had significant statistical association with genetic result, this was in disagreement with study done in Shenzhen children hospital in China from 2016-2017 and it found that the gender had no any statistical association among children with pathogenic or likely pathogenic variants in regard to children without causative variants.[23] This is might be attributed to relatively small sample size.

Lack of sleep or not recommend sleep was more prevalent among epileptic children with positive genetic result (*P* value = 0.02). Planas-Ballvé et al found that poor sleep quality was associated with poor seizure control among epileptic patients.[24] Sleep and epilepsy had a bidirectional relationship and lack of sleep had impact on genetic cause through changing epigenetic status. Recently, it found that dysregulated micro RNA had role in sleep problems in patients with epilepsy.[4,25,26]

Candidates with P/LP variants had no any significant statistical association with family history (*P* value = 0.212). This study in accordance with study done by Horak et al (*P* value = 0.072).[27] History of febrile seizure had no any significant statistical association (*P* value = 0.668). This result in disagreement with study done by Bayat et al. (*P* value = 0.002),[28] and this might be attributed to the sample size.

It found that in our study epilepsy type, craniofacial features and cognition abnormality had no impact in both positive and negative groups and there were no any significant statistical association, this is in disagreement with study done Chen et al. they found that these three features had significant statistical association between children with positive and negative genetic result.[29] This might be attributed to relatively small sample size.

Epileptic child with positive MRI finding in both groups were comparable and it found that these results has no any significant statistical value (*P* value = 0.549). This result in parallel with study done by Horak et al they found brain MRI pathology had no any significant statistical association between children with positive and negative genetic result (*P* value = 0.7209).[27]

Among the P/LP (27/60) cases, of whom 19/60 (33.3%) had Single nucleotide variants (missense, nonsense, or splice site) and 3/27 (5%) had frame shift variants and 4/60 (6.6%) had 5 Copy number variants. Our study is comparable to a study done by Zou et al. they found P/LP in 117/320 children (36.6%), of Whom 93 (29.1%) had SNV and 22 (6.9%) had CNVs.[23]

In present study, genetic testing led to a change of treatment in 11/60 (18.3%) candidates (one BTD, one PCDH19, five mitochondrial gene disorders, one TSC2, one CDKL5, one PDHA1, and one SCN1A). In a study done by Hoelz et al. revealed that genetic testing by NGS lead to change of medication in 7/91 patients [14] while the study done by Bayat et al. they found genetic diagnosis led to treatment change in 32/53 children (17 SCN1A,

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5TSC, 4 SCN8A) [28]

Conclusion

The diagnostic yield of pathogenic or likely pathogen variant is more relevant and statically significant in female epileptic child who seizure started at an earlier age (≤ 1yr of age) and history of lack of sleep. Although some epilepsy syndrome had dual structural and genetic component, there is no significant statistical association between structural (revealed by brain MRI) and genetic abnormality.

We recommended periodic re-analysis for negative result, more research to study impact of NGS result on seizure freedom and genetic counseling including parents to reveal carrier state and de novo mutation.

Funding

Not applicable.

Competing interests

The author declares that he has no competing interests.

Ethical Consideration

The study was approved by the ethical committee of college of medicine, Hawler medical university, and it followed the Helsinki declaration of medical ethics in human research conduction. A written informed consent was taken from the caregivers. The personal information will be stored for at least 2 years from date of completion of the study.

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