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The Spectrum of Inherited Neurological Disorders: Experience from Paediatric Neurology Department of A Tertiary Care Hospital

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ABSTRACT

Objective: To assess the spectrum of inherited neurological disorders presenting in a tertiary care hospital of Pakistan using Whole Exome Sequence (WES) analysis.

Study Design: Observational cross-sectional study.

Place and Duration of the Study: Department of Pediatric Neurology, University of Child Health Sciences and the Children's Hospital, Lahore, Pakistan, from July 2021 to March 2023.

Methodology: This study included 423 pediatric patients, from both genders, between the ages of 1 month to 18 years, with clinical suspicion of inherited neurological disorders. Samples were taken from the patients for WES examination to reach a genetic diagnosis.

Results: Among the 423 patients, 251 (59.34%) were males and 172(40.66%) were female. Ages were distributed in the following categories: 271 (64.10%) were found to be 0-5 years old, 85 (22.50%) were 6-10 years old, 45(10.60%) were 11-15 years old and 12 (2.80%) were 16-20 years old. Consanguinity was noted among parents of 376(88.89%) patients. Occurrence of developmental disorders was noted in 229 (110 WES positive/119 WES negative, DY 48.00%) patients, 66 (31 WES negative/35 WES positive, DY 53.00%) patients had neurometabolic disorders, 54 (21 WES negative/33 WES positive, DY 61.10%) patients had hereditary movement disorders, 45 (15 WES negative/30 WES positive, DY 66.70%) patients had epilepsy while 29 (15 WES negative/14 WES positive, DY 48.30%) patients had neuromuscular disorders. The overall diagnostic yield of WES was 52.50% for diagnosing hereditary neurological disorders.

Conclusion: The most common group of inherited neurological disorders was degenerative brain disorders with WES having high diagnostic yield as it not only ends diagnostic difficulty, helps better understand the disease and its outcome, it also redirects care to perinatal testing.

Keywords: Inherited neurological disorders, Whole Exome Sequence

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INTRODUCTION

Inherited neurological disorders are a devastating group of diseases,[1] with incidence among pediatric age group being as high as 2.50%, [2] making the diagnosis challenging, especially in resource-limited countries, like Pakistan, as diagnostic facilities are limited and genetic tests are not easily available. To diagnose a neurogenetic disorder, clinicians perform a detailed clinical evaluation, along with neuroimaging and various other laboratory tests, but often definitive diagnoses cannot be made even after exhaustive and costly work-up.[3] Initially, genetic diagnoses were made by finding a particular gene in patients with typical neurological phenotypes, where single gene testing tests include Sanger sequencing, deletion/duplication testing using Multiplex Ligation-dependent Probe Amplification (MLPA), Quantitative Polymerase Chain Reaction (qPCR) and Fragment Length Analysis (FLA) as this type of testing is useful for single-gene disorders with peculiar clinical phenotypes, known family history of a disorder and carrier testing, but single-gene testing may not be helpful in complex and overlapping presentations. Thus, WES, which is the sequencing of all the protein-forming portions of human DNA, provides testing of whole genetic material and results can be compared with the available online database of genes causing neurological disease.[5] The use of WES leads to more chances of finding a causative gene in a patient than single gene testing, making it a diagnostic breakthrough in neurogenetic disorders [6,7] with one study reporting a diagnostic value of 26.00% in suspected neurogenetic disorders, [8] while another study from Saudia Arabia, where most marriages are

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consanguineous, similar to Pakistan, reported a diagnostic value as high as 73.00%.[9] As the true burden of neurogenetic disorders is unknown,[10] especially in Pakistan, this study was carried out, in collaboration with University College London, United Kingdom, to determine the spectrum of genetic neurological disorders presenting to our set-up, using the WES.

METHODOLOGY

This observational cross-sectional study was conducted in the Department of Pediatric Neurology at The Children's Hospital, Lahore, Pakistan, from July 2021 to March 2023, after obtaining ERC letter number, issued on. A sample size of 423 was calculated, using the WHO sample size calculator, with an anticipated frequency of 30-50% for inherited neurological disorders among children.[11] Non-randomized consecutive sampling was used to enroll the required sample.

Inclusion Criteria: All pediatric patients, from the ages of 1 month to 20 years, belonging to both genders, who underwent clinical examination by a pediatric neurologist suspected of having an inherited neurological disorder were enrolled.

Exclusion Criteria: Patients with any traumatic brain injury and or suspected infectious disease etiologies were excluded.

Parents were informed in detail about the nature of genetic testing and consent was taken from both parents after which a detailed history and examination was recorded by a pediatric neurologist with a record made of all performed investigations including imaging studies, metabolic blood tests such as arterial blood gases, serum ammonia lactate, serum amino acid and uric acid and electrophysiological studies.[12,13] Based on this information, samples for genetic testing were taken and sent to University College, London, United Kingdom, for WES with results received through email and parents informed about the results. All tests were done free of cost for patients. Gene card, an online Human Genome Database was used to look for the clinical presentation of each individual gene.[14] Using Statistical Package for the Social Sciences (SPSS) version 23.00, data analysis and interpretation of all collected data was done, percentages were calculated for gender, age categories (0-5, 6-10, 11-15 and 16-20 years) and consanguinity while percentage was also calculated for groups of neurological disorders along with the diagnostic yield of WES.

RESULTS

Out of 423 patients, 251(59.34%) were males and 172(40.66%) were female while age distribution of patients was as follows: 271(64.10%) children were between 0-5 years old, 85(22.50%) were between 6-10 years old, 45(10.60%) were between 11-15 years old and 12(2.80%) were between 16-20 years old. Frequency of consanguinity among parents of patients was 376(88.89%). Developmental disorders were noted in 229(54.10%) patients, 110 WES positive /119 WES negative. Diagnostic yield of 48.00% was noted with neurometabolic disorders being 66(15.60%), 35 WES Positive/31 WES negative while the diagnostic yield of Hereditary Movement Disorders was 53 % with 54(12.80%) being 33 WES Positive/21 WES negative. Diagnostic yield of 61.10% was noted for Epilepsy with 45(10.60%) being 30 WES Positive/15 WES negative and diagnostic yield of neuromuscular disorders was 30(66.00%) with 14 WES Positive/15 WES negative, resulting in diagnostic yield of 48.30% with a *p*-value of 0.049. Overall, the diagnostic yield of WES in our patients was 222(52.50%) as shown in Table-I. Genes identified using WES are listed in Table-II.

Table-I: Frequency of Inherited Neurological Disorders (n=423)

Clinical Diagnosis	WES Results		Total n (%)	Diagnostic Yield (%)
	Negative n (%)	Positive n (%)		
Developmental and Neuro-Psychiatric Disorders	119(51.96 %)	110 (48.03%)	229	48.00 %
Neurometabolic Disorders	31(46.96%)	35 (53.03%)	66	53.00%
Hereditary Movement Disorders	21 (38.89 %)	33 (61.11 %)	54	61.10 %
Epilepsy	15(33.35%)	30(66.70%)	45	66.70 %
Neuromuscular and Neurocutaneous disorders	15(51.70%)	14(48.30%)	29	48.30 %
Overall	201(47.51%)	222(52.48%)	423	52.50%

DISCUSSION

Inherited neurological disorders are groups of neurological disorders with Mendelian pattern of inheritance.14-16 There are certain genetic tests available in our country to diagnose more commonly

occurring neurological disorders, such as, Spinal Muscular Atrophy, and Duchenne Muscular Dystrophy, but for the majority of disorders, no genetic testing is available due to which when clinicians suspect an inherited neurological disorder, a diagnosis is made based on clinical features, using history and examination findings, but confirmation requires genetic testing 17. Similar clinical phenotypes can be caused by mutations at different alleles and there can be varied clinical presentations of a single mutation with new mutations identified every passing day,4 thus, use of WES to diagnose inherited neurological disorders showed high diagnostic yield with a variety of genetic diagnosis. The most common gene identified in this group were PLA2G6 (early onset dystonia, Parkinson's disease), NDUFA13,

Table-II: Identified Genetic Mutations (n=423)

Developmental Disorders	Neurometabolic Disorders	Hereditary Movement Disorder	Epilepsy and Epileptic Encephalopathy	Neurometabolic Disorder
GAD1,GAD1,AP5Z1,KMT5B,SIN3A,SIN3A				
ASPA,ASPA,ARSA,PCNT,SLC13A5,LAMA2,SURF1				
HEXB,EPRS1,CSMD1,CSMD1,CSMD1				
PIGS,PIGQ				
p.Arg538AlafsTer24,SIL1,SIL1,GNB5				
EPS15L1,PIGG,SEC14L5,				
DOK7,SNAPC1, PDE2A				
SNAPC1,				
PDE2A,DGKG,ADGRG1		ADGRB2		
ADGRG1,MED8,	PAH	BET1		
GALNT11,PLA2G6,PLA2G6	PAH	SH3TC2	PSPC1,OPN3, SPRR1A	
NDUFB11,COL6A6,COL6A6,P	PACS1	SH3TC2	COG4	
OLG, SCAF8, AKAP9,	SRD5A3	ATM	ALDH7A1	
ETFB?,POLG, SCAF8, AKAP9,	GNB5	MRPS22	ADGRB2	
ETFB?	AGTPBP1	TAB1, BLZF1,	VPS13D, SLC13A5	
TPP1 KIF6 (p.Asp250His)	MMACHC	TAB1,	SLC13A5	
segregationRAB3B	NAGLU	TAB1,	MFSD7, TMEM129, GZMH?	
SCN1B,SCN1B,SCN1B,PIGG,P	BHLHE22, CACNA1H	ALPK3	CARS2	
IGS,C12orf66?	NDUFS1, MAP2?	ATP8A2, GFM2	MFSD7, TMEM129, GZMH	
CLN6,ANKRD1,PARS2,PLA2	SGCG	GFM2	CARS2	
G6,PLA2G6,ALDH1A2	SGCG	SETX	SCN1B	ABHD12
NDUFV1,ASAH1,ASAH1,AS	ATP8A2	KATNAL1	SCN1B	ABHD12
AH1,CIC,CIC,AP5B1	DSCC1	LAMA2	TBC1D24	SH3TC2, MBOAT7
KIF4A? ,ALMS1,ITGAX,	DSCC1	LAMA2	EPHA8	GAN, ASCC1, AIMP2
TMEM184A	BRWD3	MRPS22	CDC42EP1	MTMR2
CEP290 ,FAM63A, GNA12,	DNHD1	MRPS22	CBS	WNK1 (stop gain)
FAM63A,AP3B2 (stop	DNHD1	MRPS22	CBS	WNK1 (stop gain)
gain),NALCN	DNHD1	GDAP2 segregation?	PIGS c.174G>C	ATP13A2
NALCN,NALCN,SUN2 ,	ALDH18A1	SEC16A	SPG15	KIF4A,ALMS1
PIK3CG, TRAPPC8, NPTXR,	ALDH18A1	SEC16A	SPG15	ARHGAP19
SZT2,SUN2 , PIK3CG,	ALDH18A1	TOE1	SLC13A5	SPEG
TRAPPC8, NPTXR,	TSEN2	TOE1	SLC13A5	MTMR2
SZT2,SUN2 , PIK3CG,	COMMD1	TOE1	SLC13A5	MTMR2
TRAPPC8, NPTXR, SZT2	GPAA1 known mutation	CRYAB	ASB11, WNK1	MTMR2
CELSR1, CDH24,CELSR1,	GBP7, VAV3, ATG9A	CRYAB	CNDP2, APBB3	
CDH24,CLN7 (MFSD8)	FRRSIL	CRYAB	CNDP2, APBB3	
C9ORF3,C9ORF3,NDUFA13,S	FA2H	PANK2	CNPY3	
LC22A11	FA2H	HIVEP3, RAD54L, KCNK15,	TRPC3	
HEXB,HEXB,rs1164412354,TR	DIAPH1	MYOM2	TRPC3	
MT1	VPS13D	NDUFS1	CNPY3	
TRMT1,GNB5,TBCD,arsa	VPS13D	VAV1, LRCH2, LAMP2,	CNPY3	
Arsa,arsa,CAMLG,CAMLG	GRN	ARHGAP4	LGI1	
FUCA1,rs281875316&CM0207	GRN	NDUFS4		
83,CSPG5	CNPY3	SLC39A14		
NDUFV1				
NDUFV1				
CLN5				
CLN5				
PRUNE1				
PRUNE1				
UFSP2				
TOR1A				
TOR1A				
NDUFA13				
NDUFA13,UFSP2,PLA2G6,AR				
SA /				
EPRS,IFT57,PLA2G6,PLA2G6				

NDUFV1, NDUFB11 (mitochondrial deficiency disorders), PIGs gene (Developmental and Epileptic Encephalopathy and Multiple Congenital Anomalies-Hypotonia-Seizures Syndrome), CSMD1 (Schizophrenia and autism), ASAH1 (Farber Lipogranulomatosis, Spinal Muscular Atrophy, Progressive Myoclonic Epilepsy) while the second largest group of patients had neurometabolic disorder with common genes identified being NAGLU (Sanfillipo MPS), GPAA1 (Glycosylphosphatidylinositol Biosynthesis Defect and Multiple Congenital Anomalies-Hypotonia-Seizures Syndrome), GRN (Ceroid Lipofuscinosis, Neuronal, and Frontotemporal Lobar Degeneration),PAH (Phenylketonuria)[11-15]. The highest yield of WES was in epilepsies and epileptic encephalopathy, highlighting the high prevalence of genetic cause in our country while the common genes identified included SCN1B (Febrile Seizures Plus, Epileptic Encephalopathy), SLC13A5 (Developmental delay, Epileptic Encephalopathy), CNPY3 (Developmental and Epileptic Encephalopathy, and West Syndrome). WES showed high diagnostic yield in our study as compared to other studies [11,18]. A similar study using WES in Pakistan showed a diagnostic yield of 61.30% which is comparable to our study4 as this study not only identified different genes causing neurological disorders in our population but also identified a few novel genes ,which can be further evaluated for disease association, while various other genes like oncogenes were also identified such as KCNK[15] (Adrenal Cortical Adenocarcinoma and Brain Glioblastoma Multiforme), MYOM 2, (Rheumatic Fever and Blood Protein Disease), AKAP 9 (Long QT syndrome), GNA 12 (Familial Hyperaldosteronism), which, although they had no direct neurological manifestation, but these results were also explained to parents. This information is critical in understating the burden of neurological disorders in our population and proves the utility of WES as an initial diagnostic tool for inherited neurological disorders in our country, but the prohibitive cost must be reduced significantly for its adaption at the local level.

LIMITATIONS OF STUDY

The main limitation of this study was that samples needed to be sent abroad, which was time-consuming. The substantial time required to complete whole exome sequencing (WES) and the lack of local availability of this technology likely contributed to delays in diagnosis and may limit the generalizability or feasibility of implementing WES on a broader scale within resource-constrained settings. Additionally, the single-center, cross-sectional design and the absence of longitudinal follow-up data to assess clinical outcomes represent further inherent constraints of the study.

CONCLUSION

The diagnostic yield of WES is high in all groups of inherited neurological disorders in our population. It provides an accurate diagnosis, reassuring parents and guiding direction of care to surveillance and prevention of disease in future generations which warrant its adoption at the local level.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SZS & TS: Data acquisition, data analysis, critical review, approval of the final version to be published.

SI & SYS: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

SR & JRA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be 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.

REFERENCES

1. Huang Y, Yu S, Wu Z, Tang B. Genetics of hereditary neurological disorders in children. Transl Pediatr. 2014; 3(2): 108-119. https://doi.org/10.3978/j.issn.2224-4336.2014.03.04
2. Virk AO, Zafar F, Sultan T. Clinico-radiological findings and genetic analysis of children with hereditary neurological disorders. Pak Armed Forces Med J. 2019; 69(2): 326-331
3. Riazuddin S, Hussain M, Razzaq A, Iqbal Z, Shahzad M, Polla DL, et al. Exome sequencing of Pakistani consanguineous families identifies 30 novel candidate genes for recessive intellectual disability. Mol Psychiatry. 2017; 22(11): 1604-1614. https://doi.org/10.1038/mp.2016.109
4. Aslamkhan M. Clinical genetics and genetic counselling in Pakistan. J Genes Cells. 2015; 1(2): 31-33. https://doi.org/10.15562/gnc.17
5. Córdoba M, Rodriguez-Quiroga SA, Vega PA, Salinas V, Perez-Maturo J, Amartino H, et al. Whole exome sequencing in neurogenetic odysseys: an effective, cost- and time-saving diagnostic approach. PLoS One. 2018; 13(2): e0191228. https://doi.org/10.1371/journal.pone.0191228
6. Carmichael N, Tsipis J, Windmueller G, Mandel L, Estrella E. "Is it going to hurt?": the impact of the diagnostic odyssey on children and their families. J Genet Couns. 2015; 24(2): 325-335. https://doi.org/10.1007/s10897-014-9773-9

7. Retterer K, Juusola J, Cho MT, Vitazka P, Millan F, Gibellini F, et al. Clinical application of whole-exome sequencing across clinical indications. Genet Med. 2016; 18(7): 696-704. https://doi.org/10.1038/gim.2015.148
8. Tsang MHY, Chiu ATG, Kwong BMH, Liang R, Yu MHC, Yeung KS, et al. Diagnostic value of whole-exome sequencing in Chinese pediatric-onset neuromuscular patients. Mol Genet Genomic Med. 2020; 8(5): e1205. https://doi.org/10.1002/mgg3.1205
9. Dragojlovic N, Elliott AM, Adam S, van Karnebeek C, Lehman A, Mwenifumbo JC, et al. The cost and diagnostic yield of exome sequencing for children with suspected genetic disorders: a benchmarking study. Genet Med. 2018; 20(9): 1013-1021. https://doi.org/10.1038/gim.2017.226
10. Fogel BL, Lee H, Strom SP, Deignan JL, Nelson SF. Clinical exome sequencing in neurogenetic and neuropsychiatric disorders. Ann N Y Acad Sci. 2016; 1366(1): 49-60. https://doi.org/10.1111/nyas.12873
11. Muthaffar OY. The utility of whole exome sequencing in diagnosing pediatric neurological disorders. Balkan J Med Genet. 2021; 23(2): 17-24. https://doi.org/10.2478/bjmg-2020-0028
12. Hong S-Y, Yang J-J, Li S-Y, Lee I-C. A wide spectrum of genetic disorders causing severe childhood epilepsy in Taiwan: a case series of ultrarare genetic cause and novel mutation analysis in a pilot study. J Pers Med. 2020; 10(4): 281. https://doi.org/10.3390/jpm10040281
13. Akbar F, Saleh R, Kirmani S, Chand P, Mukhtiar K, Jan F, et al. Utility of genetic testing in pediatric epilepsy: experience from a low to middle-income country. Epilepsy Behav Rep. 2022; 20: 100575. https://doi.org/10.1016/j.ebr.2022.100575
14. GeneCards [Internet]. Tel Aviv: Weizmann Institute of Science. Available from: https://www.genecards.org
15. Ross JP, Dion PA, Rouleau GA. Exome sequencing in genetic disease: recent advances and considerations. F1000Res. 2020; 9: F1000 Faculty Rev-336. https://doi.org/10.12688/f1000research.19444.1
16. Skrahin A, Cheema HA, Hussain M, Rana NN, Rehman KU, Kumar R, et al. Secondary findings in a large Pakistani cohort tested with whole genome sequencing. Life Sci Alliance. 2023; 6(3): e202201673. https://doi.org/10.26508/lsa.202201673
17. Rehman AU, Peter VG, Quinodoz M, Dawood M, Rivolta C. Whole-exome sequencing in a consanguineous Pakistani family identifies a mutational hotspot in the COL7A1 gene, causing recessive dystrophic epidermolysis bullosa. Clin Dysmorphol. 2020; 29(2): 86-89. https://doi.org/10.1097/MCD.0000000000000299
18. Scocchia A, Wigby KM, Masser-Frye D, Del Campo M, Galarreta CI, Thorpe E, et al. Clinical whole genome sequencing as a first-tier test at a resource-limited dysmorphology clinic in Mexico. NPJ Genom Med. 2019; 4: 5. https://doi.org/10.1038/s41525-018-0076-1