GENOTYPE-PHENOTYPE SPECTRUM OF CHILDREN WITH EPILEPSY UNDERGOING WHOLE EXOME SEQUENCING

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INTRODUCTION

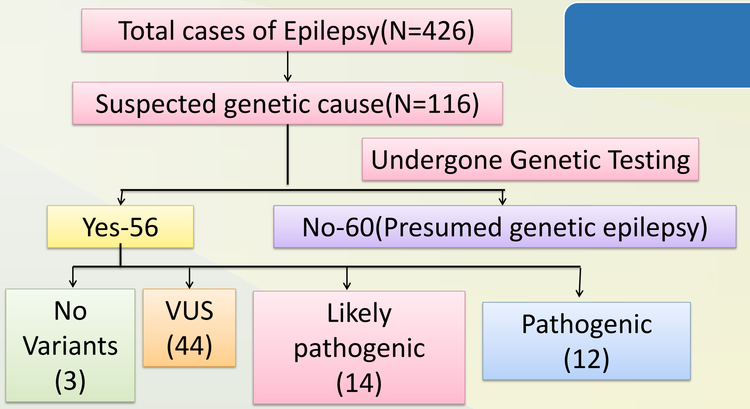
Epilepsy is one of the major neurological disorder with age dependent incidence; childhood(age<5years) having highest incidence[1]. Approximately 70-80% of epilepsies are related to genetic factors.[2] A genetic diagnosis of epilepsy may enable more accurate counselling regarding prognosis, precision therapy and recurrence risk.

OBJECTIVES

- To analyze the utility of Whole Exome Sequencing in children presenting with presumed Genetic Epilepsy.
- To analyze the different genetic variants causing epilepsy and their phenotypic correlation.

METHODS

TYPE OF STUDY: Prospective observational study
Duration-2 years(December 2021-November 2023
PLACE: Pediatric Neurology division, Dept. of Pediatrics, DYPMC, Pune
INCLUSION CRITERIA- Children aged ≤ 18 years. Presenting with Presumed Genetic Epilepsy who have underwent Whole Exome Sequencing.
EXCLUSION CRITERIA- Children with epilepsy due to acquired causes as a sequelae to HIE/NHBI/TBI /STROKE etc.
Approval was taken from institutional Ethics Committee.



RESULTS

Types of seizures	No.
Generalised	32
Focal	11
Infantile spasms	8
Myoclonic seizures	12
Atonic	4
Absence	3

DEE	22	Mentioned below
Non-DEE		
Genetic Focal Epilepsy	2	GRIN2A(2)
GEFS+	2	SCN1A(2)
Self-limiting epilepsy	2	PRRT2, SCN2A
Combined Generalised and focal epilepsy	1	BRAF
Other Neurological condition with epilepsy		
Neurodegenerative Disorders	10	LNPK, CLCN2, PPT1, NAXD, MECP2, FOXG1, DHDDS, RANBP2, NDUFS8, SPTAN1
Neurometabolic	8	FCSK, MTHFR(3), SLC2A1, BTD, SLC19A3, GFM2
Malformations of cortical development	5	COL4A1, CPA6, TUBA1A, RELN, ABCC8
Others	1	Chromosome 7 deletion

Developmental Epileptic Encephalopathy- 22 gene variants -KCNA2(2), KIF5A, SPTAN1(2), GABRB3, GABRA1. GNAO1, SCN2A(3), SCN4A, GABRD, PCDH19, SCN1A(2), SZT2, KCNQ2, GRIN2D, TBC1D24, ATP1A3, SYNJ1

- Of the 56 children, Mean age-3.6(+/-3.5) years.
- Infantile onset epilepsies-40(71%).
- Most common type of seizures-generalized onset tonic-clonic seizures (32,57%), Polymorphism-14.
- Family history of epilepsy was noted in 14(25%).
- Developmental Delay-31;55%,
- Neuroregression(19;34%), Behavioral issues(12,21.4%).
- Microcephaly(18;32%),Dysmorphic features(17;30.3%), Abnormal neurological examination(31,55.3%).
- 26 Children had abnormal Neuroimaging. Most common involvement was Dysplastic/thinning of Corpus Callosum.
- Abnormal interictal EEG was noted in 50 children with most common pattern being Epileptic encephalopathy(18).
- Of the VUS and likely pathogenic variants reverse phenotypic correlation matched with 38 gene variants.
- Total Yield-91%
- Sanger Sequencing of both parents was done for 3 patients which confirmed the diagnosis.
- Most used ASM was Levetiracetam;
- Drug refractoriness was noted in 25(44.6%) children. Ketogenic diet- 4 patients.
- Precision Therapy in SCN2A, GRIN2A, PRRT2, SLC2A1, ATP1a3 was found to be effective.

CONCLUSIONS

WES is an effective tool for diagnosing suspected genetic epilepsies which helps effectively managing the patients in all domains and understanding the natural history of the disease.

REFERENCES

1. ILAE classification and definition of epilepsy syndromes: Position statement by the ILAE Task Force on Nosology and Definitions. Zuberi SM et al.Epilepsia. 2022 Jun;63(6):1349-1397
2. Tian, Yuling MD et al. Trends and hotspots in gene research of epilepsy in children: A review and bibliometric analysis from 2010 to 2022. Medicine 102(30):p e34417, July 28, 2023. | DOI: 10.1097/MD.0000000000034417.