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Case Series

Genetic epilepsy-digging in for gold: a case series on diagnostic genetic testing in epilepsy

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ABSTRACT

Developmental epileptic encephalopathy (DEE) is a group of ictal and interictal epileptiform disorders (clinical and encephalographic) associated with severe cognitive and behavioural impairments according to the classification and terminology criteria of the international league against epilepsy (ILAE). Less than half of the genetic etiologies have been identified, even though DEEs are genetically heterogenous. Hence, genetic diagnoses of childhood neurological disorders are important as well as challenging. This research aims at determining the diagnostic utility of genetic testing (whole exome sequencing) in heterogeneous group of childhood DEEs. Here, we present the case series of 5 children who have had at least 1 episode of seizure during their lifetime associated with developmental delay and a definite genetic etiology. In view of an unrecognised aetiology, parents were counselled for a genetic evaluation. Genetic test reports showed pathogenic gene variation for epilepsy. Even though intervention would be mostly be the same, genetic aetiology helped us in prognosticating and improving the family's outlook towards the disease condition. Hence it is desirable to identify genetic variations in all possible childhood epilepsy cases as it has the potential to improve family planning, aid the prognosis, and start specific interventions and also helps to save time in selecting appropriate anti-epileptic drugs.

Keywords: Genetics, Epilepsy, Developmental and epileptic encephalopathy

INTRODUCTION

Latest researches and evidence suggest that genetics play a pivotal role in paediatric DEEs and severe neurological disorders.[1] The diverse aetiologies which result in epilepsies, include monogenic as well as polygenic variations in structural brain lesions. Recent advances in both genetic testing and neuroimaging has resulted in identification of a significant number of early childhood epilepsies, that can be resolved aetiologically.[2]

The genetic causes of only approximately 50% of patients have been identified, despite the recent advances in molecular diagnostics.[3,4] Genetic etiology identification of DEE has improved our knowledge about the pathophysiology of the disease at the molecular level. But, the challenge of understanding the genotype-phenotype correlation still remains.

The identified genetic etiologies are rare. The case series and diagnostic yield are discussed below.

CASE SERIES

Case 1

A 7-year-old girl, first born of consanguineous marriage (Second degree) with global developmental delay and recurrent seizures from day 5 of life and is on multiple antiepileptic drugs. History of male sibling death on day

5 of life with neonatal seizures (Not evaluated). Examination revealed microcephaly, dolichocephaly, facial dysmorphism (Hypertelorism, depressed nasal bridge), flat foot, lordosis and hypotonia. EEG done showed focal epileptiform activity (Figure 1) and CT brain showed mild prominence of left lateral ventricle. Her karyotype, fundus examinations and metabolic screening were normal. Whole exome sequencing done revealed a homozygous missense variation in exon 16 of the ALDH7A1 gene, suggestive of pyridoxine dependent epilepsy (Figure 2). She was started on pyridoxine along with anti-epileptic drugs. Her seizure frequency decreased and anti-convulsant were tapered. She has been seizure-free for past two years, and is currently on sodium valproate and pyridoxine.

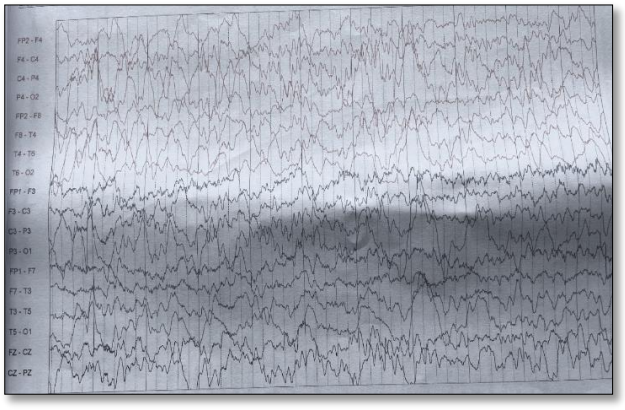
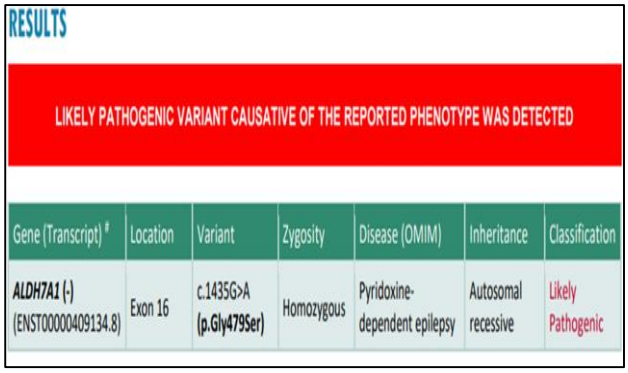


Figure 1: EEG of case 1.



RESULTS

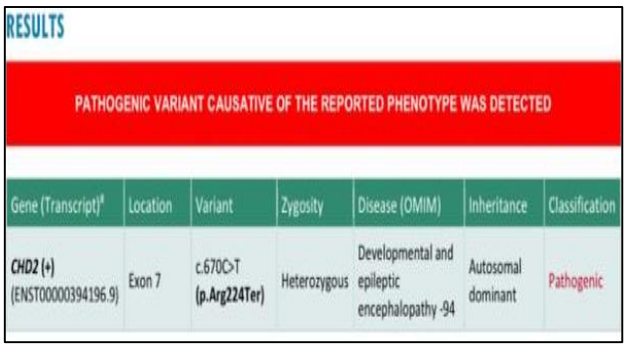
LIKELY PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

Gene (Transcript) #	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
ALDH7A1 (-) (ENST00000409134.8)	Exon 16	c.1435G>A (p.Gly479Ser)	Homozygous	Pyridoxine-dependent epilepsy	Autosomal recessive	Likely Pathogenic

Figure 2: Genetic test report of case 1.

Case 2

A 9 year old girl child, first child of a non-consanguineous marriage with uneventful antenatal and postnatal period presented with multiple episodes of generalized tonic clonic seizure from 7 months of age (GTCS) and is on multiple anti-convulsant. Family history of seizure in paternal cousin (+). Child was found to have microcephaly with mild development delay. EEG showed abnormal epileptiform activity in left hemisphere. MRI brain was normal. Genetic study revealed CHD 2 (+) gene in exon 7 suggestive of developmental and epileptic encephalopathy (Figure 3). Child was started on carnisure and is currently on only one anti-convulsant with no further seizure episodes.



RESULTS

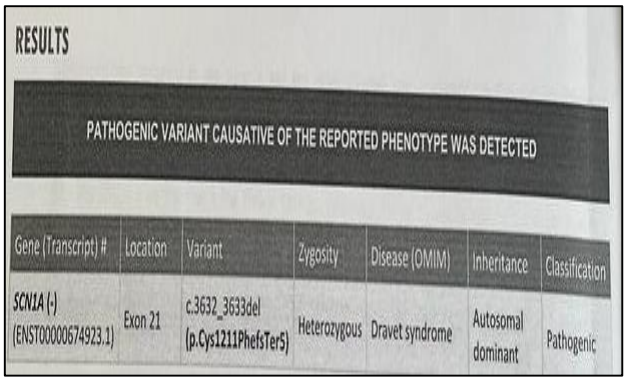
PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

Gene (Transcript)#	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
CHD2 (+) (ENST00000394196.9)	Exon 7	c.670C>T (p.Arg224Ter)	Heterozygous	Developmental and epileptic encephalopathy -94	Autosomal dominant	Pathogenic

Figure 3: Genetic test report of case 2.

Case 3

A 6-year-old girl, first child of a non-consanguineous marriage, born after 10 years of fertility treatment with normal birth history, presented with multiple episodes of seizures. The 1st episode was after 1st dose of DPT in the form of myoclonic movements of upper limb associated with head drop. She found to have hypotonia with mild developmental delay. EEG and MRI was normal. She continues to have breakthrough seizures despite multiple anti-convulsant. Genetic study revealed SCN1A gene (-) in exon 21 suggestive of Dravet syndrome. (Figure 4).



RESULTS

PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

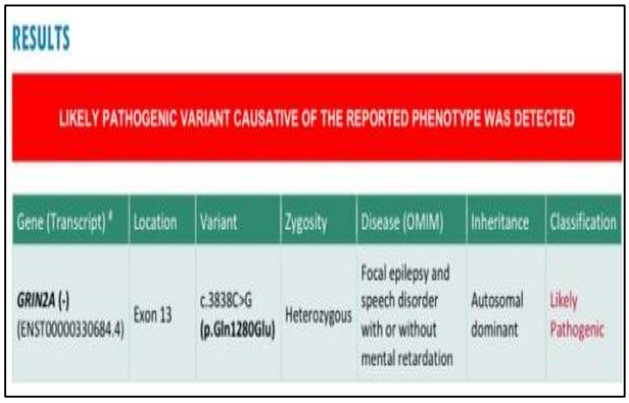
Gene (Transcript) #	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
SCN1A (-) (ENST00000674923.1)	Exon 21	c.3632_3633del (p.Cys1211PhefsTer5)	Heterozygous	Dravet syndrome	Autosomal dominant	Pathogenic

Figure 4: Genetic test report of case 3.

Case 4

A 8-year-old girl child, second born of a non-consanguineous marriage with normal antenatal period presented with developmental delay. History of poor sucking efforts and hypoglycemic seizures on day 8 of life requiring ventilator support. EEG and MRI were normal with low acylcarnitine level. Hence, fatty acid oxidation disorder suspected. Organic acid quantification done showed increased secretion of ethyl-malonate and methyl-succinate. She had global developmental delay with regression of milestone, squint and bilateral foot eversion. She walks with support and has difficulty in swallowing. Mitochondrial gene panel and CKMB came

out to be negative. Genetic study done revealed GRIN2A gene in EXON 13 suggestive of focal epilepsy, speech disorder with/without mental retardation (Figure 5). She started on carnisure, pacitane and physiotherapy. Currently, she walks and speaks few words.


RESULTS

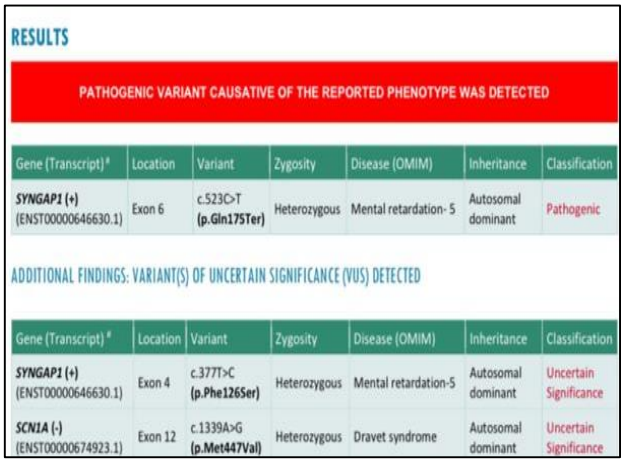
LIKELY PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

Gene (Transcript) #	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
GRIN2A (-) (ENST00000330684.4)	Exon 13	c.3838C>G (p.Gln1280Glu)	Heterozygous	Focal epilepsy and speech disorder with or without mental retardation	Autosomal dominant	Likely Pathogenic

Figure 5: Genetic test report of case 4.

Case 5

A 10-year-old girl, only child of non-consanguineous marriage, with complaints of delayed milestones and multiple episodes of fever associated seizures from one and half years of age was on intermittent frisium prophylaxis. Born as late preterm by vaginal delivery. Mother gives history of fall on day 2 of life and CT brain showed subdural hemorrhage. She also has precocious puberty and started on leuprolide. On examination, she has developmental delay. EEG showed generalized spike and wave discharge. MRI brain was normal. Child continued to have seizures and is managed with multiple antiepileptics. Genetic study done revealed SYNGAP 1 gene in exon 6, 4 suggestive of mental retardation and SCN1A gene in exon 12 suggestive of Dravet syndrome (Figure 6). She continues to have breakthrough seizures, but the frequency and duration has decreased.


RESULTS

PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

Gene (Transcript) #	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
SYNGAP1 (+) (ENST00000646630.1)	Exon 6	c.523C>T (p.Gln175Ter)	Heterozygous	Mental retardation- 5	Autosomal dominant	Pathogenic

ADDITIONAL FINDINGS: VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) DETECTED

Gene (Transcript) #	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
SYNGAP1 (+) (ENST00000646630.1)	Exon 4	c.377T>C (p.Phe126Ser)	Heterozygous	Mental retardation-5	Autosomal dominant	Uncertain Significance
SCN1A (-) (ENST00000674923.1)	Exon 12	c.1339A>G (p.Met447Val)	Heterozygous	Dravet syndrome	Autosomal dominant	Uncertain Significance

Figure 6: Genetic test report of case 5.

Table 1: Summary of the cases.

Cas eno.	Age/ gender (In years)	Consanguinity	Presenting complaints	Addl. neuro findings	Paraclinical findings	Genetic test	Diagnosis
1	7, girl	Yes	GDD + Seizures + recurrent seizures from d5 of life	Microcephaly, facial dysmorphism, hypotonia	EEG + focal epileptiform activity	Exon 16 of aldh7a1 gene	Pyridoxine dependent epilepsy
2	9, girl	No	Seizures + multiple episodes of GTCS Dd +	Microcephaly	EEG + abnormal epileptiform activity in left hemi-sphere	CHD 2 (+) gene in exon 7	CHD 2 related DEE
3	6, girl	No	Seizures + multiple episodes of seizures Dd +	Hypotonia	Eeg and MRI- normal	Scn1a gene in exon 21	Dravet syndrome
4	8, girl	No	Seizures + GDD+ developmental delay with regression	Yes Squint Bilateral foot eversion	EEG, MRI- normal	Grin2a gene in exon 13	Grin2a related epilepsy and speech disorder
5	10, girl	No	GDD + Seizures + Multiple episodes of fever associated seizures Precocious puberty	No	EEG + generalized spike and wave discharge MRI brain - normal	Syngap1 gene in exon 6,4 Scn1a gene in exon 12	Syngap1 related dee Dravet syndrome

DISCUSSION

Case 1: Pyridoxine dependent epilepsy[5]

Pyridoxine-dependent epilepsy-ALDH7A1 (PDE-ALDH7A1) is characterized by refractory seizures, not well controlled with anti-seizure medication, but responds to daily supplements of pyridoxine (vitamin B6), both clinically and electrographically. In classic PDE-ALDH7A1, intellectual disability is common. Early onset seizures (classical), usually begin within the first weeks to months of life. Late-onset seizures (atypical) begins between late infancy and three years.

Molecular genetic testing and lifelong pharmacologic supplements of pyridoxine and dietary modifications targeted at reducing lysine intake.

Case 2: CHD 2 related neurodevelopmental disorders[6]

It is characterized by early-onset epileptic encephalopathy (i.e., refractory seizures and cognitive slowing or regression associated with frequent ongoing epileptiform activity). Seizure onset is typically between six months to four years. Seizure variations include myoclonus, drop attacks and rapid onset of multiple seizure types associated with generalized spike-wave on EEG. Autism spectrum disorders and/or intellectual disability are also commonly seen.

Case 3: Dravet syndrome[6]

SCN1A seizure disorders consists of a spectrum that ranges from Dravet syndrome and intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC) at the severe end to simple febrile seizures and generalized epilepsy with febrile seizures plus (GEFS+) at the mild end. Dravet syndrome is often associated with cognitive decline. Even within the same family, the phenotype of SCN1A seizure disorders can vary.

Case 4: GRIN2A related disorders[6]

GRIN2A-related speech disorders and epilepsy are characterized by a range of epilepsy syndromes in about 90% and speech disorders in all affected individuals. Severe speech disorders can include both receptive and expressive language delay/regression, dysarthria and speech dyspraxia. Onset of seizure is usually between three to six years, and they usually present as focal epilepsy with language and/or global developmental regression, showing continuous spike-and-wave discharges in sleep or very active centrotemporal discharges on electroencephalogram (EEG).

Case 5: SYNGAP 1 related neurodevelopmental disorders[6]

It is characterized by intellectual disability (ID) or developmental delay (DD) in 100% of the affected cases, generalized epilepsy in approximately 84%, and autism spectrum disorder (ASD) and other behavioural abnormalities in less than 50%. The epilepsy is generalized. Behavioural abnormalities can include stereotypic as well as poor social development. Molecular genetic testing and appropriate anti- seizure medications to be given DEE is suspected when a child has at least 1 episode of seizure and developmental delay, where the etiology is not obvious. Other clinical findings like dysmorphism or neurological deficits may/may not be present making a genetic diagnosis more relevant.

In general, between 30% and 50% of the DEEs can now be attributed to a pathogenic variant, the majority of which arise de novo.[7-9] The earliest gene variant discoveries in DEE including CHD2 and SYNGAP1 are the new causes of epileptic encephalopathies, accounting for 1.2% and 1% of cases, respectively.[10,11] GRIN2A should now be considered a crucial genetic link between different epileptic and speech disorders of the same continuum, from atypical rolandic epilepsy with speech impairment to the more severe LKS and CSWSS.[12]

Among the genes known to be involved in epilepsy, the SCN1A gene represents one of the most commonly mutated human epilepsy genes, referred to be as super culprit gene.[13]

Pyridoxine dependent epilepsy is a treatable epileptic encephalopathy characterized by a positive response to pharmacologic doses of pyridoxine.[14]

In most cases, the developmental delay and seizures will lead to severe cognitive and behavioral abnormalities. Hence early diagnosis helps the child and family in effective treatment and early intervention.

CONCLUSION

Genetic testing has improved our understanding of epileptic pathophysiology at the molecular level that can be aetiologically resolved. Genetic aetiology helped us in prognosticating and improving the family's outlook towards the disease, even though the intervention would mostly be the same. Hence it is desirable to identify genetic variations in all possible childhood epilepsy cases as it has the potential to improve family planning, aid the prognosis, and start specific interventions and also helps to save time in selecting appropriate anti-seizure medication.

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