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Febrile seizures, not so benign

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Abstract
Genetic Epilepsy (previously known as idiopathic epilepsy) is a result of a known or presumed genetic defect(s) that is not causative of a brain structural or metabolic disorder.
Objectives: Genetic epilepsy with febrile seizures plus is characterized by multiple febrile seizures and by several subsequent types of afebrile generalized seizures with variable degrees of severity. It has a complex and heterogeneous clinical presentation. Dravet Syndrome (DS) is a catastrophic early-life epilepsy disorder of the GEFS plus spectrum in which the seizures are usually refractory to treatment and are associated with intellectual disability. The detection rate of gene variants has gradually increased, and in addition to providing an accurate diagnosis, elucidating the genetic cause of paediatric-onset drug-resistant epilepsy can also help guide clinical management.
Method: Here, we selected cases with febrile seizures on presentation who later developed epilepsy, and evaluated those using genetic studies.
Results: The genes SCN1A, ADGRV2, GABBR2, and GPR98 as potential causes of GEFS (+) and Dravet syndrome have been highlighted in our report.
Conclusion: An improved understanding of the true physiopathology of genetic epilepsy and the identification of factors that are involved in phenotypic variations, will make it easier to understand genotype-phenotype correlations in the future and help implement individualized precision medical treatment regimens.

Keywords: febrile seizure, GEFS, paediatrics, genetic, dravet syndrome

Introduction
Epilepsy is a common disorder that affects nearly 4% of the population at some point in their life [1]. Incidence is age-dependent, with the highest (> 60 per 100,000) found in those under the age of 5 years [2]. Approximately 20–30% of cases are caused by acquired conditions such as stroke, tumor or head injury, but the remaining 70–80% of cases are believed to be due to one or more genetic factors [3]. Genetic Epilepsy (previously known as idiopathic epilepsy) implies that the epilepsy syndrome is a direct result of a known or presumed genetic defect(s) that is not causative of a brain structural or metabolic disorder [1]. Multiple causative gene mutations have been reported including those coding for ion channel subunits, mostly involving sodium, potassium, and calcium channels, and some others involved in synaptic function and brain development [1]. These channelopathies are a group of genetically and phenotypically heterogeneous neurologic disorders with mutations in the same gene causing different diseases and mutations in different genes resulting in the same disease phenotype [2].
Genetic epilepsy with febrile seizures plus (GEFS +) is characterized by multiple febrile seizures and by several subsequent types of afebrile generalized seizures, including generalized tonic–clonic, absence, myoclonic, atonic, or myoclonic astatic seizures with variable degrees of severity [4]. Dravet syndrome is the most severe of the phenotypic spectrum of febrile seizure-associated epilepsies. These early seizures are typically induced by fever, but they differ from the usual febrile convulsions as they are more prolonged, more frequent, focal and come in clusters leading to development delay [1].
Here, we review six patients with febrile seizures plus and Dravet syndrome and their phenotypic association with their genetic backgrounds. We also discuss the biological impact of genetic variants on generalised epilepsy with febrile seizure plus and the possibility of its application to therapy.

Method
This study was done at a tertiary care hospital in Navi Mumbai, Maharashtra.

A retrospective cohort from January 2018 to January 2021 was formed. Here, we selected cases with febrile seizures on presentation who later developed epilepsy, and evaluated those using genetic studies. We included six independent patients from six families who had undergone whole exome gene sequencing (WES). A descriptive and observational study was performed. Typical febrile seizures worsening in frequency and presentation with significant developmental delay led us to believe GEFS plus and Dravet Syndrome as possibilities which were confirmed with WES.

Patient 1

Patient 1 was a 4-year-old male child. At 2.5 years of age, he had presented with first episode of simple febrile generalised tonic - clonic convulsion. It started at the height of fever, associated with tonic clonic movements of all 4 limbs, aborted by itself, with no focal neurological deficit, bowel bladder incontinence or loss of consciousness. Patient continued to have repeated episodes of convulsions, initially associated with fever then later afebrile. The frequency and duration of episodes increased with them requiring sedative medication (like midazolam, lorazepam) injection to abort. Antenatal, natal and postnatal history were not significant. There were no similar complaints in parents or sibling but there was history of seizure disorder in maternal grandmother. Developmentally, Gross motor, Fine motor and social milestones were achieved but delay was seen in achievement of language milestones MRI Brain (plain + contrast) showed no underlying organic cause and EEG showed no abnormality. Patient was started on anti-epileptic medication (Valproic Acid). Due to refractory nature of seizures Levetiracetam was added after highest dose of Valproic acid was ineffective. The intensity of seizures was decreasing but their frequency was increasing gradually. Diagnosis of GEFS was considered. Repeat EEG showed generalised epileptic spikes and sharp waves without abnormal slowing suggestive of generalised Epilepsy. In correspondence with the above history of difficulty in seizure control even with highest dose of anti-epileptic medication, whole exome genetic testing was done. It revealed heterozygous variation in 2 independent autosomal dominant genes showing missense variations (c.18178G>A; p.Ala6060Thr) in the exon 86 of *ADGRV1* gene and (c.944T>C; p.Ile315Thr) in the exon 6 of *GABBR2* gene. After diagnosis, patient was started on Tab Topiramate. Valproic acid and Clobazam were continued and Levetiracetam tapered and omitted. Following Topiramate, seizure control was achieved and no further episodes were seen parents were screened and not found to have the same missense variations.

Patient 2

Patient 2 is a 4 year old male child. His first seizure was a febrile seizure at 4months of age for which symptomatic treatment was taken. He developed an afebrile seizure at 9 months of age, which started initially as a left focal convulsion then progressed to involve all 4 limbs associated with bladder incontinence and required sedative medication to abort. Patient had a third episode at 3 years of age also in the absence of fever which also started as a left focal convulsion and later progressed to generalised, associated with bladder bowel involvement and required medication to abort. In the last one year there is increased frequency of seizures with patient having one GTCS seizure every 15days requiring emergency care treatment to control. Multiple antiepileptics were prescribed and maximum doses given but control was not achieved. Antenatal, natal and postnatal history were not significant. There were no similar complaints in parents or sibling. Global developmental delay is present. Considering the above history and difficulty in seizure control using multi antiepileptic drugs like valproic acid and levetiracetam, a diagnosis of febrile seizure plus was suspected and genetic testing advised. WES revealed an a heterozygous one-base deletion in exon 15 of the *SCN1A* gene (c.2822delT) that resulted in a frameshift and premature truncation of the protein 2 amino acids downstream to codon 941 (p.Phe941SerfsTer2). Currently patient is controlled on Tablet Topiramate. Valproic acid and Clobazam. Parental genetic analysis could not be done due to personal monetary issues.

Patient 3

Patient 3 is an 8-year-old female child. Her first seizure was at 5 months of age (febrile), second at 9months (afebrile) then at 2years (afebrile), following which frequency of seizures increased. Seizures were short in the beginning, generalised tonic clonic, lasted for less than 5 minutes, and aborted by themselves. With time, they became afebrile, lasted for longer duration (between 10 and 20 minutes), thus requiring the need of acute treatment to stop the convulsions. Seizure type was generalized, with a frequency ranging from 1 to 4 seizures per month and were associated with tonic - clonic movements of the 4 extremities, perioral cyanosis, up rolling of the eyes, and a short post-ictal phase of less than 30 minutes, deviation of the mouth during the crisis to the right side. The crises were not cured or partially cured by anti-epileptic drugs with visible neurocognitive decline present. On genetic analysis a heterozygous missense variation in exon 26 of the SCN1A gene (chr2:166848539; C>C/T) that results in the amino acid substitution of Glutamic Acid for Glycine at codon 1749 (p.G1749E; ENST00000303395) was detected leading to a diagnosis of Dravet syndrome. A heterozygous 3' splice site variation in the DOCK7 gene was also detected. SCN1A mutation is pathogenic with variable significance and DOCK7 is also genetic mutation of variable significance, non-pathogenic. Currently patient is poorly controlled on Tablet Topiramate. Valproic acid and Clobazam. Parental genetic analysis was insignificant.

Patient 4

Patient 4 is a 4 year old male child born of non-consanguineous marriage. First seizure was at the height of fever at 8 months of age, which was generalised tonic - clonic in nature not associated with bowel bladder involvement or loss of consciousness or any focal neurological deficits following which patient developed paroxysmal events where he suddenly, without warning, collapsed onto the floor as if his legs had been pulled from under him. No loss of consciousness was apparent. Myoclonic astatic epilepsy was considered. There was gradual increase in seizure frequency and intensity from once in 6 months to once in a month to weekly episodes. Intensity also increased with recent episodes associated with loss of consciousness Investigations revealed a high plasma lactate level. Antenatal, natal and postnatal history were not significant. There were no similar complaints in parents or sibling. MRI was normal but EEG was abnormal. Patient

was developmentally normal prior to the seizures but there is significant developmental delay present now in all 4 domains i.e., motor, language and socio-adaptive skills with developmental age being 2 years in contrast to the chronological age of 4 years. Due to the refractory nature of the seizures and poor control achieved with anti-epileptics a genetic whole exome sequencing was done which revealed a heterozygous nonsynonymous variation at position Chr5:89925082 (c.1565C>G) in the exon 9 of ADGRV1 gene. This variation causes a change of amino acid proline to arginine at position 522 (p.Pro522Arg; ENST00000405460.9) in the ADGRV1 protein sequence. Secondly, a heterozygous nonsynonymous variation at position Chr5:89924495 (c.1355G>A) in the exon 8 of ADGRV1 gene was also detected in this sample. This variation causes a change of amino acid serine to asparagine at position 452 (p.Ser452Asn; ENST00000405460.9) in the ADGRV1 protein sequence. ADGRV1 gene mutation is a mutation of variable significance requiring further testing for confirmation. Currently patient is on Tablet Topiramate. Valproic acid and Clobazam. Parental Analysis could not be done.

Patient 5

Patient 5 is 21 month old male child born of non-consanguineous marriage. First seizure was at 6 months of age (febrile), generalised tonic – clonic movements, and associated with deviation of angle of mouth, frothing from lips, bladder and bowel incontinence present, with no loss of consciousness or focal neurological deficit. Following which patient had both febrile and afebrile seizures with increasing duration and frequency requiring multiple hospital admissions with subsequent stepping up of anti-convulsant medication. Patient also exhibited increased hyperactivity with reduced concentration and response. There was no significant antenatal, natal or postnatal history. There were no similar complaints in parents or sibling. EEG was abnormal and MRI was normal. Patient had global developmental delay with 16month gross-motor, fine motor, social and language milestones achieved. There was worsening of seizure intensity and increased frequency over the next 12 months with little response seen to antiepileptics. Genetic whole exome sequencing revealed a heterozygous missense variation in the SCN1A gene (chr.4126T; T >C) was detected leading to a diagnosis of Dravet syndrome. A pathological variant is noticed in sequencing. Currently patient is on Tablet Topiramate. Valproic acid, Clobazam and Aripiprazole. Parental genomic screening has been advised.

Patient 6

Patient 6 is a 2.5year old male child born of non-consanguineous marriage. First seizure was at 9 months of age (febrile), following which patient had multiple episodes of febrile and afebrile seizures. Patient had multiple seizures with increasing frequency atleast 1 to 2 per month (afebrile).Progressive episodes were focal going into tonic-clonic with bowel bladder incontinence with advanced worsening requiring hospitalization for abortion. Birth history was insignificant. There were no similar complaints in parents or siblings. EEG and MRI were normal initially but repeat EEG at 2 years was suggestive of generalised epilepsy. Patient had global developmental delay. Due to poor control on highest doses of Valproic Acid and Clobazam, genetic whole exome sequencing was advised. A heterozygous missense variation in exon 6 of the SCN1A gene (chr2:166908352; G > G/T) that results in the amino acid substitution of Threonine for Proline at codon 281 (p.Pro281Thr; ENST00000303395) was detected leading to a diagnosis of early infantile epileptic encephalopathy-6, also known as Dravet syndrome. There was a heterozygous variation in another autosomal dominant exon 85 of GPR98 (c.17987 G > G/T) gene. Currently patient is on Valproic acid, Clobazam and CBD (cannabidiol) oil. The use of cannabidiol oil as a treatment modality though rare is being widely accepted in cases of Dravet syndrome and proven to be effective. Parental screening was negative.

Discussion

The ILAE Commission on Classification and Terminology (2005–2010) defined genetic epilepsies as in which seizures occur as a result of a known or presumed genetic defect (s) [5]. Achieving a genetic diagnosis is important for understanding the biological basis of a disease and has implications for appropriate treatment and family planning.

GEFS+ is an autosomal dominant disorder with a complex and heterogeneous clinical presentation. Febrile seizures occur in approximately 5% of all children under the age of six years and typically are not associated with increased risk of epilepsy in adolescence and adulthood. In contrast, patients with GEFS+ demonstrate febrile seizures that persist beyond six years of age and are associated with generalized or partial epilepsies, such as absence epilepsy, myoclonic seizures, atonic seizures, and myoclonic-astatic epilepsy [6]. Affected individuals within GEFS+ families often display a wide variety of epilepsy subtypes with markedly different ages of onset and severity, suggesting the action of genetic and/or environmental modifiers [7].

Dravet Syndrome (DS) is a catastrophic early-life epilepsy disorder in which the seizures are usually refractory to treatment and are associated with intellectual disability. This syndrome includes classical DS (severe myoclonic epilepsy of infancy) and borderline DS (severe myoclonic epilepsy of infancy borderline), in which patients show only a subset of clinical features. DS is characterized by febrile hemi-clonic seizures or generalized status epilepticus starting at approximately six months of age, with other seizure types including partial, absence, atonic, and myoclonic seizures occurring after one year. In classical DS, development is delayed and patients often experience motor impairment, including spasticity and ataxia [7].

Dravet syndrome has a prevalence of about 1/400,000 and is responsible for approximately 7% of severe epilepsies with seizure onset before age 3 years. Criteria for diagnosis of Dravet syndrome obtained from international league against epilepsy (ILAE) are as follows: 1- normal development before seizure, 2- seizure onset before one year of age, 3-multiple seizure type, 4-family history of epilepsy or febrile convulsion, 5- abnormal EEG findings, 6- psychomotor retardation after age 2 years, 7- ataxia and pyramidal signs, 8- anticonvulsant resistance, and 9-exacerbation of seizure with fever [6].

Epilepsy genes have been shown to carry all types of mutations, from missense to frameshift mutations to chromosomal aberrations and copy number variations, which account for phenotypic heterogeneity seen in epilepsy. Normal development before seizure onset, seizures beginning before age one year, and psychomotor retardation

after age two years are the most significant criteria in SCN1A mutation positive patients. Generalized epilepsy with febrile seizures plus, type 2, familial febrile seizures-3A (OMIM#604403) and Dravet syndrome (OMIM#607208) are caused by heterozygous mutations in the SCN1A gene (OMIM*182389). Mutations occurring in SCN1A are all dominant, and they can result in either loss of function (most commonly observed in DS) or altered function (most commonly observed in GEFS (+) [8]. The G1749E variant has previously been reported in a patient affected with severe myoclonic epilepsy of infancy [8].

Familial febrile seizures-4 (FEB4) (OMIM# 604352) is caused by heterozygous mutations in the ADGRV1 gene on chromosome 5q14 (OMIM# 602851). This syndrome is transmitted in an autosomal dominant pattern. Familial febrile seizures-4 (FEB4) is characterised by multiple features including generalised seizures, tonic-clonic seizures, hypertonic seizures and hypotonic seizures [8]. Since these variations have not been reported in literature or any affected individuals, therefore, based on the above evidence and considering ACMG classification guidelines, these ADGRV1 gene variations have currently been classified as a variant of uncertain significance. Our case series helps prove ADGRV1 as a cause of familial febrile seizure and supports its association with the reported symptoms and clinical features.

GABBR2 is a genetic factor that determines RTT- or EE-like phenotype expression depending on the variant positions. GABBR2-mediated γ-aminobutyric acid signalling is a crucial factor in determining the severity and nature of neurodevelopmental phenotypes [9]. Detailed correlation with genetic epilepsy could not be found in literature.

In our study we found 3 genes ADGRV1, GABBR2 and SCN1A all having autosomal dominant pattern of inheritance. SCN1A variant was likely pathogenic due to previous studies showing considerable genotypic-phenotypic correlation. SCN1A as a cause of Dravet syndrome has been previously established and reconfirmed in our study with patients having severe deterioration and delay. In contrast the ADGRV1, GABBR2 and GPR98 variant though found were given uncertain significance due to lack of proper data available. [Table 1] Also, we would like to suggest the use of Topiramate, Valproic Acid and Clobazam as combined treatment for GEFS (+) and Dravet syndrome [Table 1].

The detection rate of gene variants has gradually increased, and in addition to providing an accurate diagnosis, elucidating the genetic cause of paediatric-onset drug-resistant epilepsy can also help guide clinical management. As we continue to gain an improved understanding of the true complexity underlying the physiopathology of genetic epilepsy and the identification of factors that are involved in phenotypic variations, it will be easier to understand genotype-phenotype correlations and implement individualized precision medical treatment regimens. The phenotypic heterogeneity that is characteristic of GEFS+ families is likely to be due to modifier genes like ADGRV1 mutation. Interpretation of the significance of a SCN1A missense mutation requires a thorough understanding of the severe phenotypes in the GEFS+ spectrum especially associated with Dravet syndrome.

The case number in our case series was limited, and thus, further studies with larger patient populations are needed.

Table 1: Correlation of Age and Sex with developmental delay, antiepileptic use and control achieved with genes identified

Patient	Age / Sex	First seizure type and age	Antiepileptic given	Developmental status	Controlled / Refractory Seizures	Genes identified	Pattern of inheritance
1	4 years / Male	Febrile / 2.5 years	Topiramate Valproic acid Clobazam	Language delay only	Controlled	ADGRV1 GABBR2	Autosomal Dominant
2	4 years / Male	Febrile / 2.5 months	Topiramate Valproic acid Clobazam	GDD	Controlled	SCN1A	Autosomal Dominant
3	8 years / Female	Febrile / 5 months	Topiramate Valproic acid Clobazam	GDD	Refractory	SCN1A DOCK7	Autosomal Dominant
4	4 years / Male	Febrile / 8 months	Topiramate Valproic acid Clobazam	GDD	Refractory	ADGRV1	Autosomal Dominant
5	21 months / Male	Febrile / 6 months	Topiramate Valproic acid Clobazam Aripiprazole	GDD with hyperactivity	Refractory	SCN1A	Autosomal Dominant
6	2.5 years / male	Febrile / 9 months	Valproic Acid Clobazam CBD Oil	GDD	Refractory	SCN1A GPR98	Autosomal Dominant

Conclusion

Whole exome sequencing is an effective diagnostic tool for patients with drug-resistant epilepsy. Genetic diagnosis can also help in focused epilepsy patient management, leading to significant prognostic implications. With this study we would like to highlight the genes SCN1A, ADGRV2, GABBR2 and GPR98 as potential causes of GEFS (+) and Dravet syndrome. Early recognition of Dravet syndrome is important as aggressive control of seizures may improve developmental outcome.

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