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ORIGINAL ARTICLE

Landscape of genetic infantile epileptic spasms syndrome—A multicenter cohort of 124 children from India

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Abstract

Objective: Literature on the genotypic spectrum of Infantile Epileptic Spasms Syndrome (IESS) in children is scarce in developing countries. This multicentre collaboration evaluated the genotypic and phenotypic landscape of genetic IESS in Indian children.

Methods: Between January 2021 and June 2022, this cross-sectional study was conducted at six centers in India. Children with genetically confirmed IESS, without definite structural-genetic and structural-metabolic etiology, were recruited and underwent detailed in-person assessment for phenotypic characterization. The multicentric data on the genotypic and phenotypic characteristics of genetic IESS were collated and analyzed.

Results: Of 124 probands (60% boys, history of consanguinity in 15%) with genetic IESS, 105 had single gene disorders (104 nuclear and one mitochondrial), including one with concurrent triple repeat disorder (fragile X syndrome), and 19 had chromosomal disorders. Of 105 single gene disorders, 51 individual genes (92 variants including 25 novel) were identified. Nearly 85% of children with monogenic nuclear disorders had autosomal inheritance (dominant-55.2%, recessive-14.2%), while the rest had X-linked inheritance. Underlying chromosomal disorders included trisomy 21 (n = 14), Xq28 duplication (n = 2), and others (n = 3). Trisomy 21 (n = 14), *ALDH7A1* (n = 10), *SCN2A* (n = 7), *CDKL5* (n = 6), *ALG13* (n = 5), *KCNQ2* (n = 4), *STXBP1* (n = 4), *SCN1A* (n = 4), *NTRK2* (n = 4), and *WWOX* (n = 4) were the dominant single gene causes of genetic IESS. The median age at the onset of epileptic spasms (ES) and establishment of genetic diagnosis was 5 and 12 months, respectively. Pre-existing developmental delay

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(94.3%), early age at onset of ES (<6 months; 86.2%), central hypotonia (81.4%), facial dysmorphism (70.1%), microcephaly (77.4%), movement disorders (45.9%) and autistic features (42.7%) were remarkable clinical findings. Seizures other than epileptic spasms were observed in 83 children (66.9%). Pre-existing epilepsy syndrome was identified in 21 (16.9%). Nearly 60% had an initial response to hormonal therapy.

Significance: Our study highlights a heterogenous genetic landscape and phenotypic pleiotropy in children with genetic IESS.

KEYWORDS

developmental and epileptic encephalopathy, genetic epileptic spasms, genetic infantile spasms, genetic West

1 | INTRODUCTION

Infantile epileptic spasms syndrome (IESS) is characterized by the onset of epileptic spasms (ES) in the 1-24 months age group along with abnormal interictal electroencephalogram (classically hypsarrhythmia or other epileptiform abnormalities) and temporally associated developmental slowing.[1] Although the incidence of IESS is estimated to be 6.7 cases per 10 000 live births, it is one of the commonest causes of developmental and epileptic encephalopathy in infancy.[2–4] The etiologies of IESS are diverse and include genetic, structural, metabolic, infectious, immune, unknown, or a combination of the above.[5–7]

With the advent of genetic testing, the proportion of children with defined genetic causes for IESS is increasing. It is well understood now that within the genetic subgroup, implicated genes are widely heterogeneous.[5,8–17] However, the literature on the novel genetic variations underlying IESS is mostly available from the developed Western countries through funded multinational consortia, such as the Epi4K consortium,[8] which is skewed toward these countries and does not represent the global genetic landscape of IESS.

Overall, there is a paucity of literature on genotype–phenotype correlates of 'unknown-etiology' IESS from developing countries, as many children remain incompletely investigated.[18,19] Therefore, exploring the same in developing countries is the need of the hour, especially in the era of precision-based medicine. Hence, scrutinizing the genetic determinants of IESS to better understand its pathogenesis, epidemiological aspects in a specific geographical region, any genotype–phenotype correlations, and any therapeutic or prognostic implications is of utmost importance. Therefore, our study aimed to address this knowledge gap by exploring the genetic profile of IESS, focused exclusively on unexplained IESS without known definite structural etiology, with objectives of genotypic and phenotypic characterization and determination of any detectable genotype–phenotype association.

Key points

- Of 124 with genetic IESS, 105 had single gene disorders (104 nuclear and one mitochondrial), including one with concurrent triple repeat disorder (fragile X syndrome), and 19 had chromosomal disorders.
- *Trisomy 21, ALDH7A1, SCN2A, CDKL5*, and *ALG13 were the common causes of genetic IESS in this study*.
- Pre-existing developmental delay, early age at onset of ES (<6mo), central hypotonia, facial dysmorphism, microcephaly, movement disorders, and autistic features were remarkable clinical findings.

2 | METHODS

This cross-sectional, multicentre study was conducted at a tertiary-care center in North India in collaboration with five other pediatric centers across India over 18 months (Jan 2021-June 2022).

2.1 | Standard protocol approvals, registrations, and patients consent

The study was initiated after approval from the Institutional Ethical Committee and Institute Collaborative Research Committee. Written informed consent was

obtained from the parents of the children who participated in the study. The Department Review Board also approved the manuscript.

2.2 | Study subjects

IESS, for the purpose of the study, was defined as a constellation of infantile-onset (2 months-2 years) epileptic spasms and classical or modified hypsarrhythmia on EEG with or without developmental delay or regression.

Recently diagnosed or under follow-up children with a prior diagnosis of genetic IESS, tested between January 2018 and June 2022, attending pediatric neurology services of any of the participating centers were included. For the purpose of the current study, genetic IESS was defined as "children with IESS who had a genetic etiology confirmed by genetic tests like next-generation sequencing, Sanger sequencing, karyotyping, chromosomal microarray, triplet repeat polymerase chain reaction, or methylation-specific MLPA". The variant classification was done as per the American College of Medical Genetics and Genomics (ACMG) 2015 recommendations, and only children with confirmed pathogenic and likely pathogenic variants were included.[20] Children with known structural-genetic (like neurofibromatosis-1, tuberous sclerosis complex, structural malformations such as Miller-Dieker syndrome, *ARX, TUBA1A, TUB4A*, etc.) and structural neurometabolic etiologies (like glutaric aciduria type 1, Leigh syndrome, sulfite oxidase deficiency, etc.) were excluded.

2.3 | Methodology

All the included children underwent detailed in-person assessment at the respective center they followed up with, except those who could not come for follow-up or had expired. These exceptions underwent telephonic assessment and retrospective chart review. A predesigned structured proforma was used to capture the clinical details, details of investigations (including neuroimaging and genetic analysis), and management at each center. The completed study proforma and genetic report details were shared with the principal investigator in Microsoft Excel by electronic mail after anonymization.

2.4 | Outcome measures

The primary outcome measure was genotypic particulars of children with genetic IESS, and secondary outcome measures included phenotypic characterization of these children as assessed by age at onset of ES, the severity of ES, pre-existing developmental delay, comorbid movement disorder and autistic features, neuroimaging findings, electroencephalogram findings, treatment response, cessation of spasms, relapse, etc. Response to treatment was defined by a complete clinical cessation of epileptic spasms lasting for at least 4-week duration during the course of therapy.

2.5 | Statistical analysis

The multicentric data were collated and analyzed using Microsoft spreadsheet and SPSS. Descriptive statistics were performed as applicable. The categorical variables were presented as the frequency with percentages, while the median (IQR) /mean (SD) were used to present summary figures for continuous variables.

3 | RESULTS

3.1 | Cohort recruitment

A total of 124 children with genetic IESS were recruited from six tertiary-care pediatric neurology centers in India, including the Postgraduate Institute of Medical Education and Research, Chandigarh (n = 45), Indira Gandhi Institute of Child Health, Bengaluru (n = 35), Christian Medical College, Vellore (n = 23), All India Institute of Medical Sciences, Rishikesh (n = 15), Bharati Vidyapeeth Deemed University Medical College, Pune (n = 3), and Royal Institute of Child Neuroscience, Ahmedabad (n = 3). All children [67 boys; median age at enrolment (Q1, Q3): 18 (8, 39) months] were evaluated by a pediatric neurologist for phenotypic characterization and data acquisition. The median age (Q1, Q3) at confirmation of genetic diagnosis was 12 (8, 27) months.

3.2 | Genotypic landscape

Of 124 included children, 19 had underlying chromosomal disorders (14/19 are Trisomy 21), 105 had single gene disorders (104 nuclear DNA, one mitochondrial DNA), and one had a triple repeat disorder (fragile X syndrome) along with a likely pathogenic nuclear gene (Figure 1). The commonest chromosomal disorder was trisomy 21 (Down syndrome; 14/19), followed by Xq28 duplication (2/19). Other chromosomal disorders were Cri-du-Chat syndrome, 15q duplication, and unbalanced translocation (1p36 deletion and 18q terminal duplication). Fifty-one pathogenic/likely pathogenic monogenic disorders with 92 variations

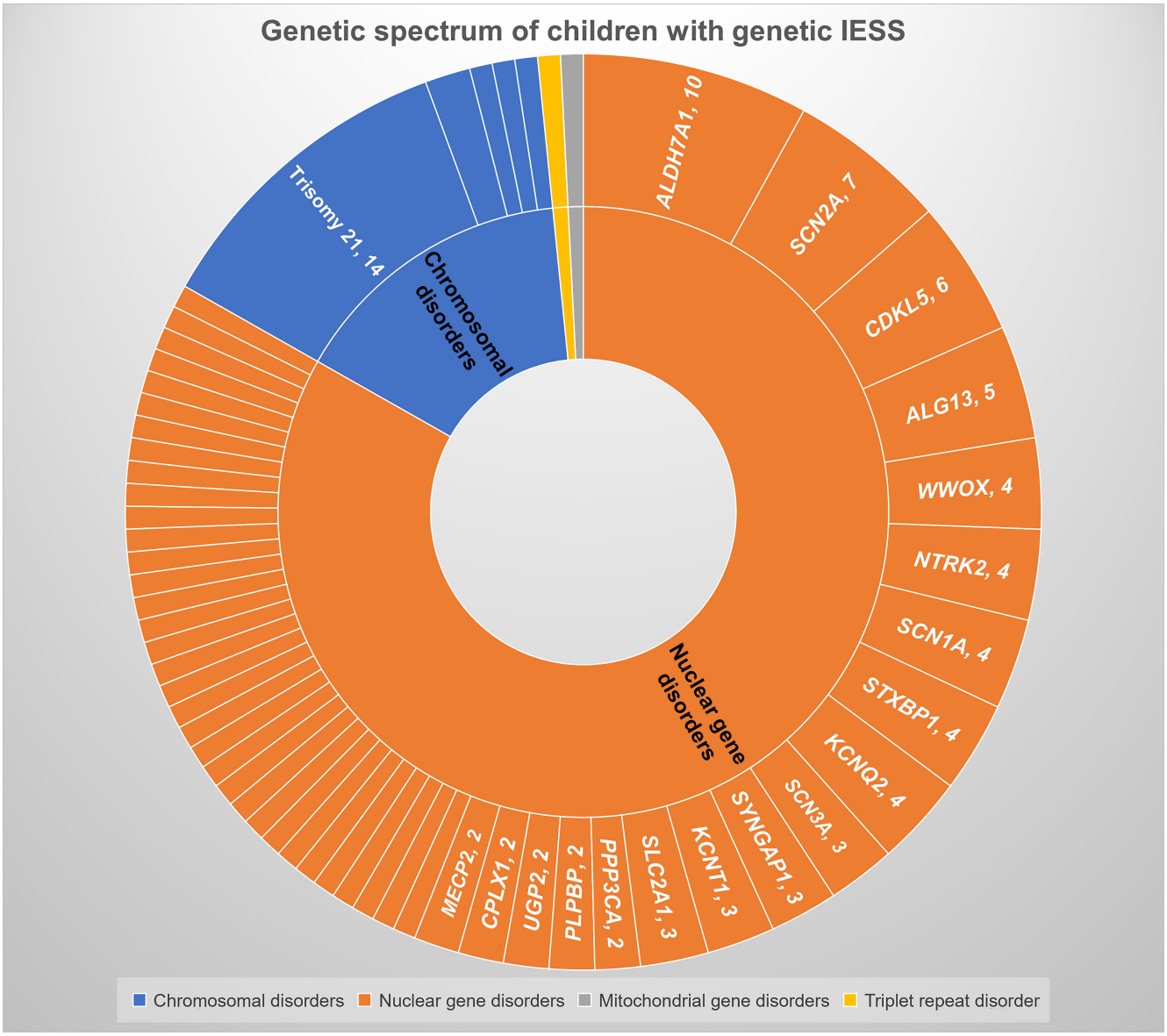

FIGURE 1 Genetic spectrum of children with genetic IESS.

(Table 1) were identified, with the most frequent ones being *ALDH7A1* (10/104), *SCN2A* (7/104), *CDKL5* (6/104), *and ALG13* (5/104) (Figure 2). Other common genes with pathogenic variations included *KCNQ2* n = 4, *NTRK2* n = 4, *STXBP1* n = 4, *SCN1A* n = 4, *and WWOX* n = 4. Twenty-five of the 92 identified variants were novel (Table 1). Few of the included cases in the study were reported previously, either as case reports or part of the case series, and are indicated in Table 1.[11,21–24] Among the single gene disorders, 58 (55.2%) were autosomal dominant, 31 (29.5%) were autosomal recessive, 15 (14.2%) were X-linked, and one had a mitochondrial inheritance.

The functional significance and relationship of the various genes were explored using STRING bioinformatics database version 11.5 (Figure 3 and Figure S1).[25] Among the various functional categories, the majority of genes had a role in regulating cell communication, signaling, nervous system development, and cellular component organization.

3.3 | Phenotypic characteristics

The median age at the onset of ES was 5 months (Q1-Q3: 3 to 10) (Figure S2). Onset after the first year of life was seen in 22 children [Trisomy 21 (n = 3), Xq28 duplication syndrome (n = 2), *ALG13* (n = 2), *SYNGAP1* (n = 2), *SLC2A1* (n = 2), 15q duplication syndrome (n = 1), *SCN1A* (n = 1), *SCN2A* (n = 1), *ADSL* (n = 1), *SATB1* (n = 1), *NRROS* (n = 1), *MECP2* (n = 1), *SCN3A* (n = 1), *IQSEC2* (n = 1), *FOXG1* (n = 1) *and GABBR2* with Fragile X syndrome (n = 1)]. Developmental delay before the onset

TABLE 1 Genotypic description of the children with genetic IESS due to monogenic causes.

Serial no.	Gene	Exon/intron location	Chromosomal location	Type of variation	Specify gene variation	Variant amino acid change	Zygosity	Inheritance pattern	Variant classification as per ACMG	Novelty
1	*ALDH7A1*	Exon 12	Chromosome 5	Nonsense	c.1048C>T	p.Arg350Ter	Homozygous	AR	Pathogenic	rs1015686016
2	*ALDH7A1*	Intron 12 and Exon 11	Chromosome 5	Splice site and nonsense	c.1093+1G>A and c.1003C>T	5′ splice site and p.Arg335Ter	Compound heterozygous	AR	Pathogenic	rs794727058; rs1015686016
3	*ALDH7A1* (ENST00000636879.1)	Exon 16 and Exon 15	Chromosome 5	Insertion and nonsense	c.1456_1457insG and c.1269T>G	p.Leu486ArgfsTer4; p.Tyr423Ter	Compound heterozygous	AR	Pathogenic	rs772766995, rs121912710
4	*ALDH7A1*	Exon 14	Chromosome 5	Missense	c.1279G>C	p.Glu427Gln	Homozygous	AR	Pathogenic	rs121912707
5	*ALDH7A1*	Exon 1	Chromosome 5	Nonsense	c.187G>T	p.Gly63Ter	Homozygous	AR	Pathogenic	rs760636660
6	*ALDH7A1*	Exon 17	Chromosome 5	Missense	c.1556G>A	p.Arg519Lys	Homozygous	AR	Likely pathogenic	rs561343926
7	*ALDH7A1* (ENST00000636879.1)	Exon 7	Chromosome 5	Missense	c.575C>A	p.Ala192Glu	Homozygous	AR	Likely pathogenic	rs764417585
8	*ALDH7A1*	Exon 9	Chromosome 5	Nonsense	c.841C>T	p.Gln281Ter	Homozygous	AR	Pathogenic	rs1170817007
9	*ALDH7A1*	Exon 1	Chromosome 5	Nonsense	c.187G>T	p.Gly63Ter	Homozygous	AR	Pathogenic	rs760636660
10	*ALDH7A1*	Exon 1	Chromosome 5	Nonsense	c.187G>T	p.Gly63Ter	Homozygous	AR	Pathogenic	rs760636660
11	*SCN2A* (NM_001040142.2)	Exon 23	Chromosome 2	Insertion	c.4004_4005insGGAAT	p.Ser1336GlufsTer5	Heterozygous	AD	Pathogenic	Novel
12	*SCN2A*	Exon 7	Chromosome 2	Missense	c.788C>T	p.Ala263Val	Heterozygous	AD	Pathogenic	rs387906686
13	*SCN2A*	Exon 3	Chromosome 2	Nonsense	c.330C>A	p.Tyr110Ter	Heterozygous	AD	Pathogenic	Reported without RS id
14	*SCN2A*	Exon 27	Chromosome 2	Missense	c.5645G>A	p.Arg1882Gln	Heterozygous	AD	Pathogenic	rs794727444
15	*SCN2A*	Exon 23	Chromosome 2	Nonsense	c.4303C>T	p.Arg1435Ter	Heterozygous	AD	Pathogenic	rs796053138
16	*SCN2A*	Exon 19	Chromosome 2	Missense	c.3631G>A	p.Glu1211Lys	Heterozygous	AD	Pathogenic	rs387906684
17	*SCN2A*	Exon 17	Chromosome 2	Missense	c.2995G>A	p.Glu999Lys	Heterozygous	AD	Likely pathogenic	rs796053126
18	*CDKL5*	Exon 6	Chromosome X	Missense	c.211A>G	p.Asn71Asp	Heterozygous	XL	Pathogenic	rs587783072
19	*CDKL5*	Exon 10	Chromosome X	Missense	c.587C>T	p.Ser196Leu	Heterozygous	XL	Pathogenic	rs267608501
20	*CDKL5*	Exon 6	Chromosome X	Missense	c.248G>T	p.Gly83Val	Heterozygous	XL	Pathogenic	rs587783402
21	*CDKL5* (NM_001323289.2)	Exon 18	Chromosome X	Deletion	c.2486delT	p.Leu829Argfs*8	Heterozygous	XL	Pathogenic	Novel
22	*CDKL5*	Intron 9	Chromosome X	Splice site	c.554+5G>A	5′ Splice site	Heterozygous	XL	Pathogenic	rs1925577525
23	*CDKL5* (ENST000 00379989)	Exon 10	Chromosome X	Deletion	c.633delT	p.Pro212LeufsTer16	Heterozygous	XL	Pathogenic	Novel
24	*ALG13*	Exon 3	Chromosome X	Missense	c.320A>G	p.Asn107Ser	Hemizygous	XL	Pathogenic	rs398122394
25	*ALG13*	EXON -3	Chromosome X	Missense	c.320A>G	p.Asn107Ser	Hemizygous	XL	Pathogenic	rs398122394
26	*ALG13*	Exon 17	Chromosome X	Missense	c.2057G>A	p.Cys686Tyr	Hemizygous	XL	Likely pathogenic	rs767698446
27	*ALG13*	Exon 3	Chromosome X	Missense	c.320A>G	P.Asn107Ser	Hemizygous	XL	Likely pathogenic	rs398122394
28[a]	*ALG13*	Exon 3	Chromosome X	Missense	c.320A>G	p.Asn107Ser	Hemizygous	XL	Likely pathogenic	rs398122394
29	*KCNQ2*	Exon 5	Chromosome 20	Missense	c.793G>A	p.Ala265Thr	Heterozygous	AD	Pathogenic	rs794727740
30	*KCNQ2*	Exon 6	Chromosome 20	Missense	c.917C>T	p.Ala306Val	Heterozygous	AD	Pathogenic	rs864321707

(Continues)

TABLE 1 (Continued)

Serial no.	Gene	Exon/intron location	Chromosomal location	Type of variation	Specify gene variation	Variant amino acid change	Zygosity	Inheritance pattern	Variant classification as per ACMG	Novelty
31	*KCNQ2* (NM_172107.4)	Exon 6	Chromosome 20	Missense	c.850T>C	p.Tyr284His	Heterozygous	AD	Likely pathogenic	Reported without RS id
32	*KCNQ2*	Exon 5	Chromosome 20	Missense	c.794C>T	p.Ala265Val	Heterozygous	AD	Likely pathogenic	rs587777219
33	*STXBP1*	Exon 18	Chromosome 9	Missense	c.1654T>C	p.Cys552Arg	Heterozygous	AD	Pathogenic	rs1842046459
34	*STXBP1*	Exon 9	Chromosome 9	Missense	c.704G>A	p.Arg235Gln	Heterozygous	AD	Pathogenic	rs794727970
35	*STXBP1*	Exon 14	Chromosome 9	Missense	c.1216C>T	p.Arg406Cys	Heterozygous	AD	Pathogenic	rs796053367
36	*STXBP1* (ENST00000637953.1)	Exon 10	Chromosome 9	Nonsense	c.863G>A	p.Trp288Ter	Heterozygous	AD	Pathogenic	Novel
37	*WWOX* (ENST00000566780.6)	Exons 6 and 9	Chromosome 16	Deletion and missense	c.553_566del and c.1193G>A	p.Ala185ArgfsTer6 and p.Trp398Ter	Compound heterozygous	AR	Likely pathogenic	rs759794876; Novel
38	*WWOX* (ENST00000566780.6)	Exons 2 and 7	Chromosome 16	Deletion and nonsense	c.155_156del and c.744C>A	p.Arg52Lyster16 and p.cys248Ter	Compound heterozygous	AR	Pathogenic	Novel; Novel
39	*WWOX* (ENST00000566780.6)	Exons 5 to 8; Intron 5	Chromosome 16	Deletion; splice site	(516+1_517–1)_ (1056+1_1057-1)del; c.517-3c>A	Exonic deletion and 3′ splice site	Compound heterozygous	AR	Likely pathogenic	Uncertain; Novel
40	*WWOX*	Exon 7	Chromosome 16	Nonsense	c.790C>T	p.Arg264Ter	Homozygous	AR	Pathogenic	rs756762196
41	*SCN1A*	Exon 16	Chromosome 2	Missense	c.2311G>A	p.Asp771Asn	Heterozygous	AD	Likely pathogenic	Reported without RS id
42	*SCN1A*	Intron 28	Chromosome 2	Splice site	c.4853-1G>C	3′ splice site	Heterozygous	AD	Pathogenic	rs1553520530
43[a]	*SCN1A* (ENST00000674923.1)	Exon 15	Chromosome 2	Duplication	c.2712dupT	p.Ala905CysfsTer10	Heterozygous	AD	Likely pathogenic	Novel
44	*SCN1A*	Exon 7	Chromosome 2	Missense	c.1007G>A	p.Cys336Tyr	Heterozygous	AD	Likely pathogenic	rs794726798
45	*NTRK2* (NM_006180.6) hg19	Exon 12	Chromosome 9	Missense	c.1301A>G	p.Tyr434Cys	Heterozygous	AD	Likely pathogenic	rs886041091
46[a]	*NTRK2* (NM_006180.6) hg19	Exon 12	Chromosome 9	Missense	c.1301A>G	p.TyrY434Cys	Heterozygous	AD	Likely pathogenic	rs886041091
47[a]	*NTRK2* (NM_006180.6) hg19	Exon 12	Chromosome 9	Missense	c.1301A>G	p.Tyr434Cys	Heterozygous	AD	Likely pathogenic	rs886041091
48[a]	*NTRK2* (NM_006180.6) hg19	Exon 12	Chromosome 9	Missense	c.1301A>G	p.Tyr434Cys	Heterozygous	AD	Likely pathogenic	rs886041091
49	*KCNT1* (ENST00000371757.7)	Intron 2	Chromosome 9	3′ splice site	c.255-2A>G	3′ splice site	Heterozygous	AD	Pathogenic	Novel
50	*KCNT1*	Exon 12	Chromosome 9	Missense	c.1038C>G	p.Phe346Leu	Heterozygous	AD	Pathogenic	rs767434859
51	*KCNT1*	Exon 11	Chromosome 9	Missense	c.862G>A	p.Gly288Ser	Heterozygous	AD	Pathogenic	rs587777264
52	*SYNGAP1*	Exon 5	Chromosome 6	Nonsense	c.490C>T	p.Arg164Ter	Heterozygous	AD	Pathogenic	rs1057518352
53	*SYNGAP1*	Exon 8	Chromosome 6	Non-sense	c.1081C>T	p.Gln361Ter	Heterozygous	AD	Pathogenic	rs1554121231
54	*SYNGAP1*	Exon 17	Chromosome 6	Non-sense	c.3718C>T	p.Arg1240Ter	Heterozygous	AD	Pathogenic	rs869312955
55	*SCN3A*	Exon 28	Chromosome 2	Missense	c.5576G>A	p.Arg1859His	Heterozygous	AD	Likely pathogenic	rs778995406
56	*SCN3A*	Exon 28	Chromosome 2	Missense	c.5576G>A	p.Arg1859His	Heterozygous	AD	Likely pathogenic	rs778995406
57	*SCN3A* (NM_006922.4)	Exon 21	Chromosome 2	Missense	c.3734A>C	p.Lys1245Thr	Heterozygous	AD	Likely pathogenic	Reported without RS id

TABLE 1 (Continued)

Serial no.	Gene	Exon/intron location	Chromosomal location	Type of variation	Specify gene variation	Variant amino acid change	Zygosity	Inheritance pattern	Variant classification as per ACMG	Novelty
58	*SLC2A1* (NM_006516.4)	Exon 9	Chromosome 1	Duplication	c.1119dup	p.Gly374TrpfsTer7	Heterozygous	AD	Pathogenic	Novel
59	*SLC2A1* (NM_006516.4)	Exon 6	Chromosome 1	Missense	c.691C>G	p.Leu231Val	Homozygous	AR	Pathogenic	Novel
60	*SLC2A1* (NM_006516.4)	Exon 6	Chromosome 1	Missense	c.691C>G	p.Leu231Val	Homozygous	AR	Pathogenic	Novel
61	*MECP2*	Exon 2	Chromosome X	Deletion	ChrX:g.(?_154019188_(154031459_?)del	Exonic deletion of 12.27 kb	Heterozygous	XL	Pathogenic	–
62	*MECP2*	Exon 3	Chromosome X	Nonsense	c.799C>T	p.Arg267Ter	Heterozygous	XL	Pathogenic	rs61749721
63	*CPLX1* (ENST00000304062.11)	Exon 3	Chromosome 4	Deletion	c.151_183del	p.Lys51_Ala61del	Homozygous	AR	Pathogenic	Novel
64	*CPLX1* (ENST00000304062.11)	Exon 4	Chromosome 4	Nonsense	c.210C>G	p.Tyr70Ter	Homozygous	AR	Likely pathogenic	Reported without RS id
65	*UGP2* (ENST00000445915.6)	Exon 2	Chromosome 2	Missense	c.61A>G	p.Met21Val	Homozygous	AR	Likely pathogenic	rs768305634
66	*UGP2*	Exon 2	Chromosome 2	Missense	c.34A>G	p.Met12Val	Heterozygous	AR	Likely pathogenic	rs768305634
67	*PPP3CA* (NM_000944.5)	Exon 12	Chromosome 4	Deletion	c.1255_1256del	p.Ser419CysfsTer31	Heterozygous	AD	Pathogenic	rs1553920383
68	*PPP3CA*	Exon 12	Chromosome 4	Duplication	c.1283dup	p.Thr429AsnfsTer22	Heterozygous	AD	Pathogenic	rs1727004803
69	*GRM7*	Exons 3–4	Chromosome 3	Deletion	c.(736+1_737–1)_(1033+1_1034-1)del	Exonic deletion of 7.99 kb	Homozygous	AR	Likely pathogenic	–
70	*TBCD*	Exon 18	Chromosome 17	Missense	c.1661C>T	p.Ala554Val	Homozygous	AR	Likely pathogenic	rs1555641324
71	*CHD2*	Exon 37	Chromosome 15	Missense	c.4763G>A	p.Arg1588Gln	Heterozygous	AD	Likely pathogenic	rs1164926261
72	*CDK19* (NM_015076.5)	Exon 12	Chromosome 6	18 base pair duplication	c.1113_1130dup	p.Gln373_Gln378dup	Heterozygous	AD	Likely pathogenic	Novel
73	*FOXG1* (NM_005249.5)	Exon 1	Chromosome 14	Single BP insertion	c.953_954insC	p.Arg320ProfsTer135	Heterozygous	AD	Pathogenic	Novel
74[a]	*NRROS*	Exon 2	Chromosome 3	Deletion	c.1359del	p.Ser454Alafs*11	Homozygous	AR	Likely pathogenic	rs1346764478
75[a]	*PURA* (NM_005859.5)	Exon 1	Chromosome 5	Duplication	c.479dup	p.Glu161GlyfsTer40	Heterozygous	AD	Pathogenic	Novel
76	*KANSL1*	Exon 6	Chromosome 17	Missense	c.1799A>G	p.Lys600Arg	Heterozygous	AD	Likely pathogenic	rs770594188
77	*GABBR2* (NM_005458.8)	Exon 15	Chromosome 9	Missense	c.2084G>A	p.Ser695Asn	Heterozygous	AD	Likely pathogenic	Reported without RS id
78	*GRIN1*	Exon 18	Chromosome 9	Missense	c.2452A>C	p.Met818Leu	Heterozygous	AD	Likely pathogenic	rs1554770628
79	*CSNK2A1* (NM_001895.4)	Exon 13	Chromosome 20	Missense	c.1012A>G	p.Ser338Gly	Heterozygous	AD	Likely pathogenic	Novel
80	*PNPO*	EXON 4	Chromosome 17	Missense	c.413G>A	p.Arg138His	Homozygous	AR	Likely pathogenic	rs764940495
81	*CACNA1A* (NM_001127222.2)	Exon 20	Chromosome 19	Deletion	c.3550delC	p.His1180ThrfsTer6	Heterozygous	AD	Likely pathogenic	Novel
82	*PLPBP* (NM_007198.4)	Exon 8	Chromosome 8	Missense	c.727G>A	p.Gly243Arg	Homozygous	AR	Likely pathogenic	Novel
83	*NPRL3*	Exon 5	Chromosome 16	Deletion	c.423_426del	p.Leu142IlefsTer27	Heterozygous	AD	Pathogenic	rs1567139896
84	*PLPBP* (NM_007198.4)	Exon 8	Chromosome 8	Missense	c.727G>A	p.Gly243Arg	Homozygous	AR	Likely pathogenic	Novel

(Continues)

TABLE 1 (Continued)

Serial no.	Gene	Exon/intron location	Chromosomal location	Type of variation	Specify gene variation	Variant amino acid change	Zygosity	Inheritance pattern	Variant classification as per ACMG	Novelty
85	*IQSEC2* (ENST000 00396435.3)	Exon 7	Chromosome X	Nonsense	chrX:g.53277315G>A	p.Arg855Ter	Homozygous	XL	Pathogenic	rs587777261
86	*CYFIP2*	Exon 4	Chromosome 5	Missense	c.259C>T	p.Arg87Cys	Heterozygous	AD	Likely pathogenic	rs1131692231
87	*MBOAT7* (NM_024298.5)	Exon 8	Chromosome 19	Deletion	c.1059del	p.Tyr354ThrfsTer11	Homozygous	AR	Likely pathogenic	Novel
88	*MBD5*	Exon 8	Chromosome 2	Insertion	c.539_540ins	p.Gln190TyrfsTer88	Heterozygous	AD	Pathogenic	–
89	*PPP2R1A* (NM_014225.6)	Intron 10	Chromosome 19	Splice site	c.1302+2T>G	5′ splice site	Heterozygous	AD	Pathogenic	Novel
90	*DNM1*	Exon 6	Chromosome 9	Missense	c.709C>T	p.Arg237Trp	Heterozygous	AD	Likely pathogenic	rs760270633
91	*NONO*	Intron 8	Chromosome X	Splice site	c.1028+3A>G	5′ splice site proximal	Hemizygous	XL	Likely pathogenic	rs1447518463
92	*EHMT1*	Exon 19	Chromosome 9	Missense	c.2842C>T	p.Arg948Trp	Heterozygous	AD	Likely pathogenic	rs368702408
93	*GNAO1*	Exon 8	Chromosome 16	Missense	c.935A>G	p.Asn312Ser	Heterozygous	AD	Pathogenic	rs758503575
94	*PRRT2*	Exon 2	Chromosome 16	Duplication	c.649dupC	p.Arg217Profs*8	Heterozygous	AD	Pathogenic	rs587778771
95	*AMT*	Exon 7 and Exon 1	Chromosome 3	Missense and others	c.794G>A and c.2T>C	p.Arg265His and p.Met1Thr	Compound Heterozygous	AR	Likely pathogenic	rs757918826; rs1266259634
96	*KMT2C*	Intron 37	Chromosome 7	4 (splice acceptor variant)	c.7443-2delA	Splice acceptor variant	Heterozygous	AD	Likely pathogenic	rs753425356
97	*ADSL* (ENST00000216194) hg19	Intron 6 and Exon 9	Chromosome 22	Missense	c.701+1G>A; and c.926G>A	5′ splice site and p.Arg309His	Compound Heterozygous	AR	Likely pathogenic	rs546878201; rs749817666
98	*SATB1* (NM_001131010.4)	Intron 10	Chromosome 3	Splice site	c.1780-2A>G	3′ splice site	Heterozygous	AD	Pathogenic	Novel
99	*PACS2* (ENST00000447393.6)	Exon 6	Chromosome 14	Missense	c.625G>A	p.Glu209Lys	Heterozygous	AD	Likely pathogenic	Novel
100	*HUWE1*	Exon 64	Chromosome X	Missense	c.9209G>A	p.Arg3070His	Hemizygous	XL	Pathogenic	rs2061745581
101	*ASNS*	Exon 10	Chromosome 7	Missense	c.1138G>T	p.Ala380Ser	Homozygous	AR	Likely pathogenic	rs758183057
102	*MIPEP* (NM_005932.4)	Exon 13	Chromosome 13	Missense	c.1409T>C	p.Leu470Pro	Homozygous	Ar	Likely pathogenic	Novel
103	*PLEKHG2*	Exons 18 and 19	Chromosome 19	Both missense	c.1855G>A and c.3953C>T	p.Glu619Lys and p.Ser1318Leu	Compound Heterozygous	AR	Likely pathogenic	rs750591987; rs755575206
104	*SCN8A*	Exon 27	Chromosome 12	Missense	c.5614C>T	p.Arg1872Trp	Heterozygous	AD	Likely pathogenic	rs796053228
105	*MT-ND5*	Mitochondrial DNA	Mitochondrial DNA	Missense	m.13513G>A	p.Asp393Asn	Heteroplasmic	Mito	Pathogenic	rs267606897

[a] Previously published cases.

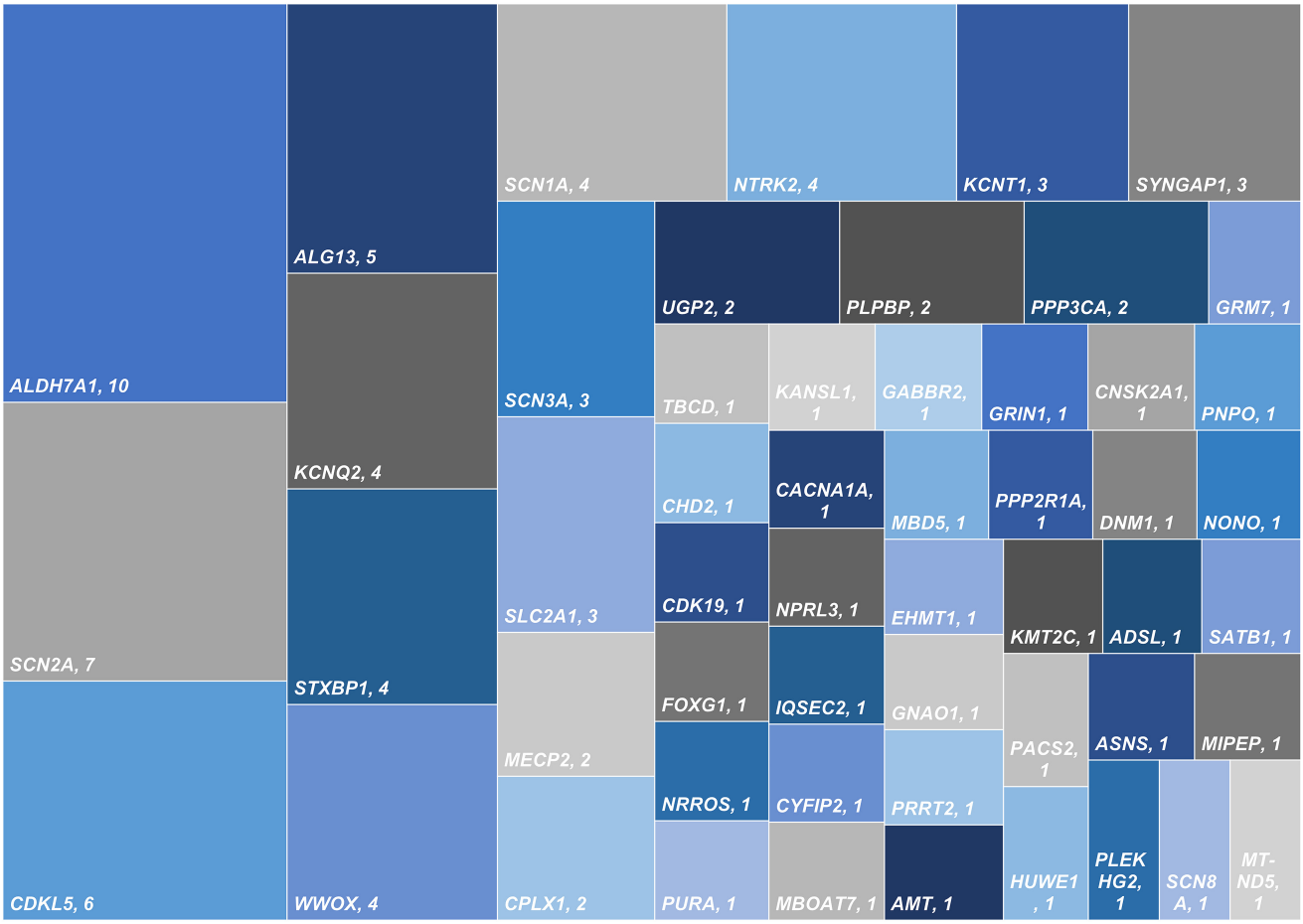

FIGURE 2 Distribution of single-gene disorders causing genetic IESS.

of ES was present in more than 90% of children, while seizures other than ES were observed in two-thirds of patients (Tables 2 and 3). Developmental delay before the onset of ES was present in all except seven children (*ALG13* n = 2, *NTRK2* n = 1, *KCNT1* n = 1, *GRIN1* n = 1, *SCN1A* n = 1, and *MECP2* n = 1) and they did not have any definite contrasting feature which delineated them from the rest of the cohort. Twenty-one (16.9%) children evolved from another epilepsy syndrome [Early infantile developmental and epileptic encephalopathy (n = 20) and Epilepsy of infancy with migrating focal seizures (n = 1)] to IESS (Table 2). Common clinical findings include central hypotonia (81%), facial dysmorphism (70.1%), microcephaly (77.4%), movement disorders (45.9%), and autistic features (42.7%). Normal neuroimaging in Magnetic Resonance imaging was observed in 67.7% and the remaining had non-specific neuroimaging findings without any neuroimaging clue (Table 2). Around 60% of children responded to initial hormonal therapy. Relapses after the initial therapeutic response were observed in one-third of children.

Eight of the included children (6.4%) had succumbed, with the median age at death being 42 months (Q1, Q3: 13, 60). Nearly 70% of children were seizure or spasms-free at the last follow-up, while one-fifth of included children required hospitalization for status epilepticus in the previous 2 years. Evolution to LGS was observed in 25% of the included children. All except one child had some developmental delay at the last follow-up. Around 40% of children were ambulatory, while 23% went to school. Significant behavioral issues were observed in two-thirds of surviving children (most common being autistic features), while sleep disturbances were observed in one-fourth of surviving children.

3.4 | Genotype–phenotype association

Phenotypic details of four common monogenic disorders seen in the cohort- *ALDH7A1* n = 10, *SCN2A* n = 7, *CDKL5* n = 6, and *ALG13* n = 5 have been compared (Table 4). Early onset of ES (<6 months) was remarkable and universal with *ALDH7A1* and *CDKL5*. Among these four disorders, all children except one child with *ALG13*-related DEE had pre-existing developmental delay; All these disorders except *ALG13* among these four monogenic DEE had

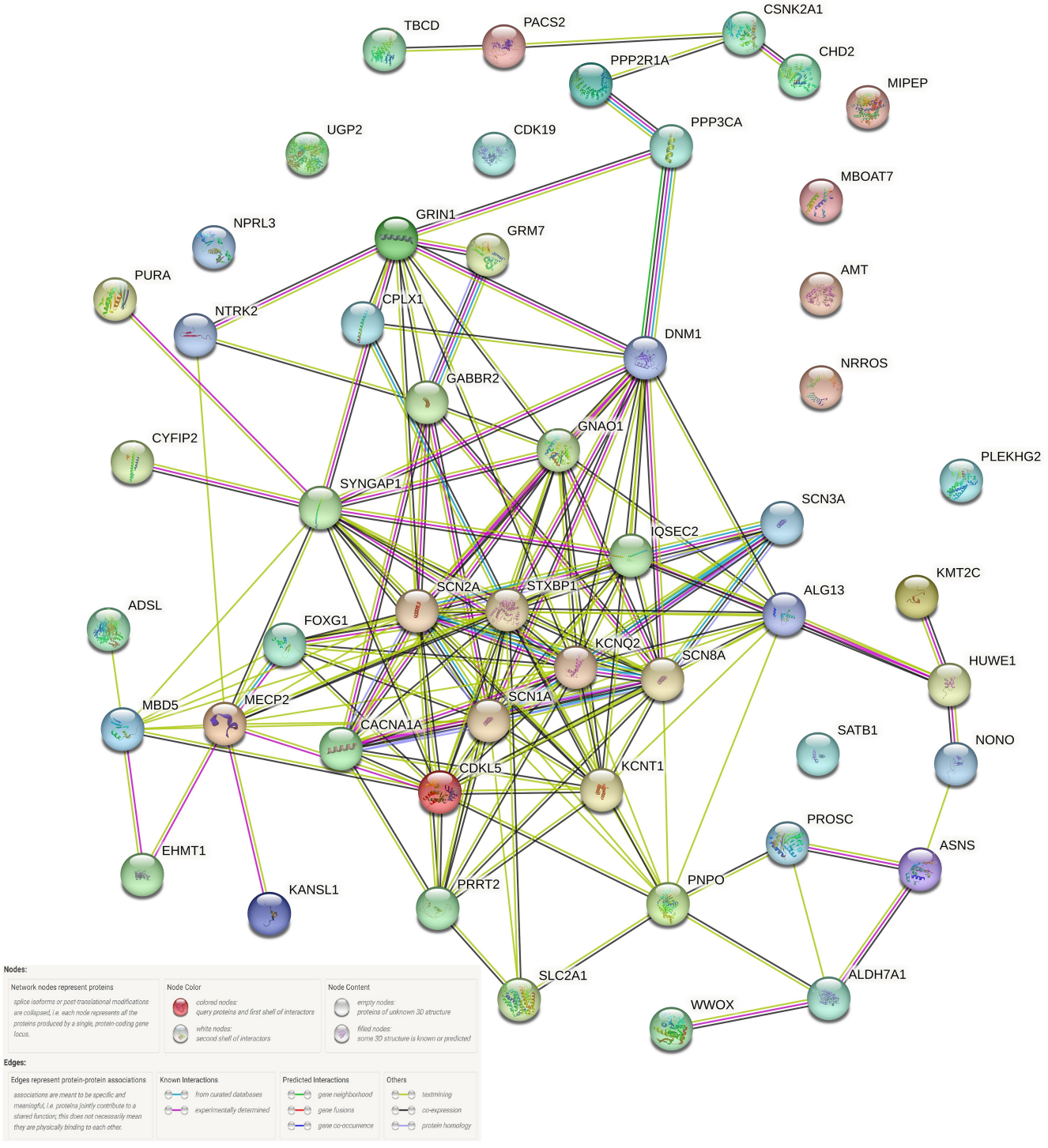

FIGURE 3 Gene network diagram and its interactions among the genes observed in the study.

other seizure types before the onset of ES (including neonatal onset seizures), and many of these had evolved from early infantile developmental and epileptic encephalopathy to IESS (Table 4). Central hypotonia was frequently associated with all these disorders, while microcephaly, autistic features, and movement disorders were associated with *SCN2A*, *CDKL5*, and *ALG13* (Table 4). The long-term outcome was good in *ALDH7A1*, with the attainment of seizure freedom with pyridoxine in all children. However, the long-term neurodevelopmental outcome was poor in most children with *SCN2A* (5/6 non-ambulatory, 4/7 autistic, one progressed to LGS); *CDKL5* (two succumbed, all had persistent daily seizures, three progressed to LGS), and *ALG13* (all except one had autistic features with stereotypies and prominent sleep disturbances).

TABLE 2 Phenotypic characteristics of the entire cohort of children with genetic IESS.

Phenotypic features (n = 124)	N (%)
Median age of onset of spasms in months with Q1, Q3	5 months (Q1, Q3: 3, 10)
Developmental delay before the onset of spasms	117 (94.3%) Global developmental delay (109), Only Language and Social adaptive delay (8)
Seizures other than epileptic spasms (n with %)	83 (66.9%)
Pre-existing epilepsy syndrome	21 (16.9%) Early infantile developmental and epileptic encephalopathy (20), Epilepsy of infancy with migrating focal seizures (1)
Other relevant history	
History of neonatal encephalopathy or seizures	15 (12.09%)
Consanguinity	19 (15.3%)
Family history of epileptic spasms/seizures/neurological illness	9 (7.2%)
Examination findings	
Facial dysmorphism	87 (70.1%)
Microcephaly	96 (77.4%)
Central hypotonia	101 (81.4%)
Autistic features	53 (42.7%)
Movement disorder	72 (58.0%)
With onset before the onset of epileptic spasms	17
Dystonia/choreoathetosis/both/stereotypies	24/10/7/38
Non-specific neuroimaging abnormalities without definite etiological clue	40 (32.3%)
Brain atrophy	16
Non-specific changes in cerebral cortex	2
Non-specific changes in white matter	2
Non-specific changes (morphology or signal intensity) in corpus callosum	15
Non-specific changes (morphology or signal intensity) in basal ganglia/thalamus/brainstem/cerebellum	2
Ventriculomegaly	3
Therapeutic response	
Clinical response to epileptic spasms attained anytime	97 (72.5%)
Response to initial hormonal therapy	74 (59.6%)
Response to vigabatrin	31
Response to nitrazepam	25
Response to zonisamide	4
Response to topiramate	None
Response to KD	5
Relapse observed	43 (34.6%)

4 | DISCUSSION

The current study provides a glance at the genotypic and phenotypic spectrum of genetic IESS in a multicentric Indian cohort of 124 children, diagnosed since January 2018 (over the last 4.5 years). The median diagnostic lag in genetic diagnosis was 7 months after the onset of ES, which might be multifactorial and contributed by due to the delay in the recognition of ES by parents and clinicians, the delay in other initial investigations, and the relatively huge cost of genetic investigations, which is usually out-of-pocket expenditure for Indian families and not covered by health insurance.[26] The structural genetic etiologies like tuberous sclerosis complex and malformations were

TABLE 3 Clinical outcomes of the cohort as observed at the last follow-up.

Characteristic (n = 124)	N (%)
Mortality	8 (6.4)
Median age at death with Q1, Q3 (n = 8)	42 (13, 60)
Median age at assessment for those surviving with Q1, Q3	18 months (8, 39)
Epilepsy outcomes	N = 116
Current spasms frequency per day	
Nil	84
1–5	20
5–10	4
More than 10 but <50	5
More than 50	3
Current seizure frequency per day (apart from spasms)	
Nil	81
1–3 episodes per day	27
3–5 episodes per day	4
More than 5 episodes per day	4
Admission for status epilepticus in last 2 y (n = 116)	24 (19.3%)
Evolution to Lennox Gastaut syndrome	31 (25%)
Developmental status at last visit (n = 124)	
Global developmental delay	109 (88%)
Only language delay	2 (1.6%)
Both language and socio-adaptive delay	12 (9.6%)
Normal development	1 (0.8%)
Ambulation at last follow-up (applicable for 101 children)	
Ambulatory	42 (33.8%)
Non-ambulatory	59 (47.5%)
School-going status at last follow-up (applicable for 59 children)	
School going	14 (11.2%)
Non-school going	45 (36.2%)
Behavioral issues at the last follow up	83 (67%)
Hyperactivity	11 (8.8%)
Autistic	43 (34.6%)
Autistic and hyperactivity	19 (15.3%)
Behavioral issues present but not fitting above	10 (8%)
No behavioral issues at the last follow up	41 (33%)
Sleep disturbances based on history at the last follow up	30 (24.1%)

excluded from the study as the point of interest in this study was exclusively unexplained and unknown etiology IESS. Hence, we did not include well-established structural genetic causes of IESS like tuberous sclerosis complex, lissencephaly, focal cortical dysplasia, and various structural malformations.

Nearly 90% and 67% of children had pre-existing developmental delay and epilepsy, which suggests the ongoing developmental epileptic encephalopathy associated with these genetic abnormalities since early infancy. Hence, most of the included children did not fit into the definition of "idiopathic IESS," which has normal prior development and a poor yield of genetic investigations. Many genetic abnormalities were associated with the late onset of ES (beyond 1 year of age). Some genes like *ALDH7A1, CDKL5, KCNQ2, KCNT1, NTRK2, STXBP1, UGP2*, and *WWOX* characteristically had an early infantile-onset in the current cohort similar to that described previously, while genetic variations in *NRROS* and *SYNGAP1* (2/3) had onset of ES beyond 1 year of life like that reported in most patients with these disorders.[10,12–15,21,27]

Microcephaly, facial dysmorphism, movement disorders, behavioral abnormalities, and non-specific neuroimaging findings were not uncommon in the current cohort, as reported previously with other developmental epileptic encephalopathies.[13–15] Therapeutic response to initial hormonal therapy was much higher than that reported in IESS from South Asia, suggesting a relatively better epilepsy outcome in genetic IESS.[28] However, the treatment response in this study was defined only clinically and it did not include electrographic resolution in the definition. Commenting on electrographic resolution was not possible as this was a multicentric study with slight variation in management practices and it included retrospectively enrolled cases as well. This was one of the challenges which we faced and this is one of the limitations of the study. Precision-based therapy was possible among identified genetic variants in *ALDH7A1, PLPBP, PNPO, SLC2A1, KCNQ2, KCNT1, SCN2A, and SCN8A* genes. However, response to precision-based therapy was documented only in children with identified genetic variants in *ALDH7A1, PLPBP, PNPO, and SLC2A1* genes. Ketogenic diet, a standard-of-care treatment modality for children with drug-resistant epilepsy was effective in five children and it highlights the need of its trial in resistant cases.[29] The mortality was much less than that reported in IESS, probably due to the lower median age at assessment (18 months).[28,30–34] Long-term epilepsy outcomes were much better than those reported in previous studies on IESS from India.[28,35] However, the long-term neurodevelopmental outcomes were broadly comparable. Trisomy 21 was the study's most typical cause of genetic IESS, followed by *ALDH7A1* (pyridoxine-dependent epilepsy), *SCN2A, and CDKL5*-related DEE. Overall, single-gene disorders were the most common genetic category, complementing the idea behind whole exome sequencing as the first-line genetic investigation for these children.[5,9,36] The commonest monogenic disorder observed was

TABLE 4 Master table of the phenotypic characteristics of the various genotypes among monogenic causes in descending order of frequency.

Serial no gene	Sex	Seizures (age in months); prior epilepsy syndrome if any	Movement disorder (onset: age in months)	Phenotypic characteristics	Treatment response	Outcome until the last follow-up (age in months)
1 *ALDH7A1*	M	FC (1), ES (3); prior EIDEE	Absent	MIC, C HYP	FIHT, responded with VGB & pyridoxine	ESC, SF, BC (8)
2 *ALDH7A1*	M	FC (2), ES (5)	Absent	NHC, C HYP	FIHT, response with VGB & pyridoxine	ESC, SF, AMB, BC (12)
3 *ALDH7A1*	M	MC (1), ES (5); prior EIDEE	Absent	NHC, C HYP	RIHT, relapse, response with pyridoxine	ESC, SF, Normal DEV (6)
4 *ALDH7A1*	F	GT (1), ES (4); prior EIDEE	Absent	NHC, C HYP	FIHT, response with pyridoxine	ESC, SF, AMB (22)
5 *ALDH7A1*	M	GT (1), ES (6)	Absent	NHC, C HYP	FIHT, response with pyridoxine	ESC, SF, AMB (48)
6 *ALDH7A1*	M	GT (1), ES (4); prior EIDEE	Absent	NHC, C HYP	FIHT, response with pyridoxine	ESC, SF, AMB (112)
7 *ALDH7A1*	M	GT (1), ES (3); prior EIDEE	Stereotypies (12)	NHC, C HYP	FIHT, response with pyridoxine	ESC, SF, AMB (15)
8 *ALDH7A1*	F	GT (1), ES (4); prior EIDEE	Absent	NHC, C HYP	FIHT, response with pyridoxine	ESC, SF, AMB (16)
9 *ALDH7A1*	F	FUA (1), ES (3); prior EIDEE	Stereotypies (10)	NHC, C HYP, CVI	FIHT, response with pyridoxine	ESC, SF, AMB (12)
10 *ALDH7A1*	M	GT (1), ES (5); prior EIDEE	Absent	NHC, C HYP	FIHT, response with pyridoxine	ESC, SF, AMB (15)
11 *SCN2A*	M	ES (18)	Absent	NHC, C HYP	FIHT, response with NZ, NRTP	ESC, SF, NAMB, AU (40)
12 *SCN2A*	F	FT, GT (1), ES (3); prior EIDEE	Absent	NHC, C HYP	FIHT, response with VGB, NRTP	ESC, SF, NAMB, BC (67)
13 *SCN2A*	F	ES (6)	Stereotypies (12)	MIC, C HYP	FIHT, relapse, response with VGB, NRTP	ESC, SF, NAMB, AU (60)
14 *SCN2A*	M	GT (1), ES (3); prior EIDEE	Absent	MIC, C HYP	FIHT, response with NZ	ESC, SF (8)
15 *SCN2A*	M	ES (10), GT (18)	Absent	MIC, C HYP	RIHT, relapse, response with VGB	ESC, SF, AMB (36)
16 *SCN2A*	F	GT (6), ES (7)	Stereotypies (14)	NHC, C HYP, CLDY	RIHT, relapse, response with VGB	ESC, SF, NAMB, AU (81)

(Continues)

TABLE 4 (Continued)

Serial no gene	Sex	Seizures (age in months); prior epilepsy syndrome if any	Movement disorder (onset: age in months)	Phenotypic characteristics	Treatment response	Outcome until the last follow-up (age in months)
17 *SCN2A*	F	GT (2), ES (2); prior EIDEE	Absent	NHC, MS, HTL, HAP, spasticity, CVI, HI	RIHT, relapse, poor responder	PES, DRE, NAMB, LGS, AU (18)
18 *CDKL5*	F	FC, MC (3), ES (5)	Stereotypies (12)	MIC, C HYP, CVI bruxism	FIHT, response with NZ	ESC, DRE, NAMB, AU (72)
19 *CDKL5*	F	ES (4), GT (12)	Stereotypies (84)	MIC, C HYP prominent ears	FIHT, response with NZ	ESC, DRE, NAMB, AU (120)
20 *CDKL5*	F	GT (1), ES (5); prior EIDEE	Absent	MIC, C HYP	FIHT, response with NZ	ESC, DRE, non-ambulatory, AUHA (60)
21 *CDKL5*	F	GT, MC (1), ES (4)	Stereotypies (24)	NHC, C HYP	FIHT, relapse, response with VGB	ESC, DRE, NAMB, AU (44)
22 *CDKL5*	F	FC (2), ES (4)	Stereotypies (12)	MIC, C HYP	FIHT, response with ZON	ESC, DRE, NAMB, AU (36); EXP due to SUDEP
23 *CDKL5*	M	ES (2)	Choreathetosis and Dystonia (2)	NHC, C HYP, CVI	RIHT, relapse, response with VGB	DRE, LGS, NAMB, AU (46); EXP at 48 m due to AP
24 *ALG13*	F	ES (5)	Stereotypies (12)	MIC, C HYP	RIHT, relapse, response with NZ	ESC, SF, AMB, AU (50)
25 *ALG13*	F	ES (6)	Dystonia (6)	MIC, C HYP, LSE, HTL	RIHT, relapse, response with VGB	ESC, SF, NAMB (12)
26 *ALG13*	M	ES (14), FUBA (14)	Stereotypies (5)	MIC, C HYP	RIHT, relapse, response with VGB	ESC, SF, AMB, AU (47)
27 *ALG13*	F	ES (13)	Stereotypies (5)	MIC, C HYP	RIHT, relapse, response with VGB	ESC, SF, AMB, AU (19)
28 *ALG13*	F	ES (5)	Stereotypies (12)	MIC, C HYP	RIHT, relapse, response with VGB	ESC, SF, NAMB, AU (27)
29 *KCNQ2*	M	FC (2), ES (4)	Absent	NHC, C HYP	FIHT, response with NZ	ESC, SF, NAMB (22)
30 *KCNQ2*	M	MC (1), ES (2)	Absent	MIC, C HYP	RIHT, relapse, response with NZ	ESC, SF, NAMB (26)
31 *KCNQ2*	F	FT (1), GT (1), ES (6); prior EIDEE	Absent	MIC, C HYP	FIHT, response with NZ	PES, DRE, LGS, AUHA (47)
32 *KCNQ2*	F	GT (1), ES (6); prior EIDEE	Dystonia and Choreoathetosis (24)	MIC, C HYP	RIHT, relapse, response with NZ	ESC, DRE, NAMB, AU (36)

TABLE 4 (Continued)

Serial no gene	Sex	Seizures (age in months); prior epilepsy syndrome if any	Movement disorder (onset: age in months)	Phenotypic characteristics	Treatment response	Outcome until the last follow-up (age in months)
33 *STXBP1*	F	ES (2)	Absent	MIC	FIHT, poor responder	PES, SF, NAMB (50)
34 *STXBP1*	M	ES (3)	Dystonia (5)	NHC, C HYP	RIHT, no requirement of second-line therapy	ESC, SF, AMB, BC (24)
35 *STXBP1*	F	FUA (2), ES (3)	Dystonia (5)	NHC	FIHT, response with VGB	PES, SF, NAMB (7)
36 *STXBP1*	F	FUBA (1), ES (3)	Dystonia (6)	NHC, C HYP	FIHT, response with VGB	ESC, SF, AMB, (18)
37 *WWOX*	M	FUA (2), ES (4)	Absent	MIC, C HYP	FIHT, response with VGB	ESC, SF (12)
38 *WWOX*	F	ES (3)	Absent	MIC, C HYP	RIHT, relapse, response with NZ	ESC, SF, NAMB (12)
39 *WWOX*	F	GTC (2), ES (3)	Absent	MIC, C HYP, UTN, SP	FIHT, response with ZON	PES, SF (6)
40 *WWOX*	F	ES (2)	Dystonia (8)	MIC, C HYP, LSE UTN, SP, HYTR	FIHT, poor responder, Failed KD	PES, DRE, NAMB (30)
41 *SCN1A*	F	ES (10)	Stereotypies (9)	MIC	FIHT, response with VGB	ESC, SF, NAMB, LGS, AUHA (25)
42 *SCN1A*	M	ES (5)	Absent	NHC	RIHT, relapse, response with NZ	ESC, DRE, ASE, NAMB, AUHA (40)
43 *SCN1A*	F	ES (2), GTC (3)	Absent	MIC	RIHT, relapse, response with VGB	PES, DRE, ASE, AMB, BC (48)
44 *SCN1A*	M	ES (24), GTC (6)	Absent	NHC, C HYP	RIHT, relapse, response with NZ	ESC, SF, AMB, HA (92)
45 *NTRK2*	M	ES (6)	Stereotypies and choreoathetosis (6)	NHC, C HYP	RIHT, no requirement of second-line therapy	ESC, SF, NAMB (24)
46 *NTRK2*	M	ES (3), FC (11), GT (11)	Stereotypies and choreoathetosis (9)	NHC, C HYP, CVI	FIHT, response with KD, relapse	PES, DRE, ASE, NAMB, HA (74)
47 *NTRK2*	F	ES (6)	Dystonia and choreoathetosis	NHC	FIHT, response to valproate and clobazam, relapse	PES, SF, NAMB (55)

(Continues)

TABLE 4 (Continued)

Serial no gene	Sex	Seizures (age in months); prior epilepsy syndrome if any	Movement disorder (onset: age in months)	Phenotypic characteristics	Treatment response	Outcome until the last follow-up (age in months)
48 *NTRK2*	M	ES (6), FT (6)	Absent	MC, C HYP	RIHT, relapse, poor responder	ESC, DRE, LGS, NAMB (58)
49 *KCNT1*	M	ES (7)	Absent	NHC, C HYP	RIHT, no requirement of second-line therapy	ESC, SF, AMB (23)
50 *KCNT1*	F	GT (2), FT (2), ES (4)	Absent	MIC, C HYP, CVI	FIHT, relapse, response with VGB	ESC, SF, AMB (24)
51 *KCNT1*	M	FT (2), FTBTC (3),ES (3); Prior EIMFS	Stereotypies (8)	MIC, C HYP	FIHT, poor responder	ESC, DRE, LGS, NAMB, AU (43)
52 *SYNGAP1*	M	ES (11), MA with EM (13)	Stereotypies (18)	NHC, C HYP long face, large ears	RIHT, no requirement of second-line therapy	ESC, SF, AMB, AU (48)
53 *SYNGAP1*	F	ES (24)	Stereotypies (12)	NHC, C HYP	RIHT, relapse, response with clobazam	ESC, SF, AMB, AU (123)
54 *SYNGAP1*	M	ES (15), MA with EM (18)	Stereotypies (18)	NHC, C HYP	RIHT, relapse, poor responder	ESC, SF, AMB, AUHA (92)
55 *SCN3A*	M	ES (18), GTC (20)	Dystonia (6)	MIC, C HYP	RIHT, relapse, Responded with VGB	ESC, DRE, LGS, NAMB, AU (32)
56 *SCN3A*	M	ES (12), GTC (18)	Dystonia (9)	MIC	RIHT, No requirement of second-line therapy	ESC, DRE, AMB, HA (44)
57 *SCN3A*	M	ES (2)	Absent	NHC	RIHT, relapse, response with VGB	ESC, SF, AMB (31)
58 *SLC2A1*	M	GTC (2), ES (5)	Absent	MIC, C HYP	FIHT, response with KD	ESC, SF, AMB, AUHA (40)
59 *SLC2A1*	M	ES (14), GTC (10)	Dystonia and choreoathetosis (24)	MIC, C HYP	FIHT, response with KD	ESC, SF, AMB, AU (38)
60 *SLC2A1*	M	ES (13), GTC (11)	Dystonia and choreoathetosis (20)	MIC	FIHT, response with KD	ESC, SF, AMB, AU (24)
61 *MECP2*	F	GT (5), MC (5), ES (10)	Stereotypies (8) and choreoathetosis (12)	MIC, C HYP	RIHT, no requirement of second-line therapy	ESC, SF, AMB, AU, prominent sleep disturbance (39)
62 *MECP2*	F	ES (18)	Stereotypies (8) and ataxia (12)	MIC, C HYP	RIHT, no requirement of second-line therapy	ESC, SF, AMB, AU (27)
63 *CPLX1*	F	ES (3), MC (3)	Absent	MIC, C HYP	FIHT, poor responder	PES, DRE, ASE, NAMB (48)

TABLE 4 (Continued)

Serial no gene	Sex	Seizures (age in months); prior epilepsy syndrome if any	Movement disorder (onset: age in months)	Phenotypic characteristics	Treatment response	Outcome until the last follow-up (age in months)
64 *CPLX1*	M	ES (3)	Absent	NHC, C HYP	FIHT, poor responder	PES, DRE (6)
65 *UGP2*	M	ES (3)	Absent	MIC, C HYP	RIHT, relapse, response with VGB	EXP at 13 months
66 *UGP2*	F	GT (3), ES (4)	Dystonia (4)	MIC, C HYP	FIHT, relapse, response with VGB and ZON	PES, SF, prominently delayed onset and fragmented sleep (8)
67 *PPP3CA*	F	ES (3)	Absent	MIC, C HYP, CVI	FIHT, response with ZON	PES, CVI (9)
68 *PPP3CA*	F	ES (4), FC (15)	Stereotypies (10)	MIC, C HYP, CVI, HI	FIHT, poor responder	DRE, NAMB, LGS, AU (26)
69 *GRM7*	F	GT (1), ES (11)	Absent	NHC, C HYP	FIHT, poor responder, sedation with ZON	PES, NAMB, AU (17)
70 *TBCD*	M	ES (12), FUBA (20), FTBTC (22), GT (24)	Stereotypies (18), dystonia (30)	MIC, C HYP	RIHT, transaminitis with valproate	ESC, DRE, ASE, LGS, AU (52)
71 *CHD2*	M	ES (7)	Absent	NHC, C HYP	RIHT	ESC, SF (12)
72 *CDK19*	M	ES (8)	Absent	MIC, C HYP, CVI, HI, hypotelorism, bulbous nose	FIHT, response with VGB	PES, BC (13)
73 *FOXG1*	F	GT (8), GTC (8), ES (14)	Stereotypies (6), dystonia, and choreo-athetosis (6)	MIC, C HYP, AUHA	RIHT, relapse, response with VGB	ESC, DRE, ASE, AUHA, prominently decreased sleep (42)
74 *NRROS*	M	FUBA (9), ES (18)	Dystonia (30)	MIC, HI	FIHT, poor responder, neuroregression	PES, DRE, NAMB; EXP at 36 months
75 *PURA*	F	ES (5)	Stereotypies, dystonia	NHC, HTL, CVI, AU, plagiocephaly	FIHT, response with VGB	ESC, SF, NAMB, AU (51)
76 *KANSL1*	M	ES (12)	Absent	NHC, C HYP, Obesity	Initially started on VGB, response with VGB, relapse, response with NZ	PES, DRE, LGS, NAMB, BC (27)
77 *GABBR2*	M	ES (18)	Stereotypies (12)	NHC, C HYP, AU, BF	FIHT, response with VGB, relapse, response with NZ	ESC, SF, NAMB, AU (36)

(Continues)

TABLE 4 (Continued)

Serial no gene	Sex	Seizures (age in months); prior epilepsy syndrome if any	Movement disorder (onset: age in months)	Phenotypic characteristics	Treatment response	Outcome until the last follow-up (age in months)
78 *GRIN1*	F	GT (2), ES (2); prior EIDEE	Stereotypies (8)	MIC, C HYP	RIHT, relapse, poor responder	PES, AMB, LGS, delayed onset sleep prominently (13)
79 *CSNK2A1*	F	ES (3)	Absent	MIC, C HYP, LSE, MS, MG	RIHT, no requirement of second-line therapy	ESC, SF (9)
80 *PNPO*	F	GT (1), ES (2)	Dystonia (3)	MIC, C HYP	RIHT, relapse, response with VGB, good response to pyridoxine and P-5P	ESC, SF, AMB (26)
81 *CACNA1A*	F	ES (2), GTC (3)	Absent	MIC, C HYP	RIHT, no requirement of second-line therapy	ESC, SF (30)
82 *PLPBP*	M	FUBA (2), ES (5)	Absent	NHC	RIHT, relapse, response with NZ	ESC, SF, AMB, AUHA (120)
83 *NPRL3*	F	FT (1), GT (1), ES (3); prior EIDEE	Absent	NHC	RIHT, no requirement of second-line therapy	ESC, SF (6)
84 *PROSC*	M	GT (1), ES (6); Prior EIDEE	Stereotypies (6)	MIC, C HYP	FIHT, response with NZ	ESC, DRE, ASE, LGS, AMB, HA (120)
85 *IQSEC2*	M	FT (6), ES (19), GT (50)	Stereotypies (24)	MIC, C HYP	FIHT, poor responder	ESC, DRE, LGS, AMB, HA (90)
86 *CYFIP2*	M	FC (2), ES (11)	Absent	MIC, C HYP	RIHT, relapse, response with KD	NAMB before death; EXP at 2 y 7 mo of age
87 *MBOAT7*	M	ES (6)	Absent	NHC, C HYP	RIHT, no requirement of second-line therapy	ESC, SF, NAMB (22)
88 *MBD5*	M	GTC (6), ES (6)	Absent	NHC, C HYP	RIHT, poor responder	ESC, DRE, AMB (30)
89 *PPP2R1A*	F	E (4), MC (11)	Stereotypies (9)	NHC, C HYP	FIHT, poor responder	DRE, LGS, AMB, AUHA (132)
90 *DNM1*	M	ES (3)	Absent	MIC, C HYP, CVI, HI	FIHT, poor responder	PES, NAMB (40)
91 *NONO*	M	ES (6), GTC (84)	Stereotypies (12)	NHC, C HYP	FIHT, poor responder	PES, AMB, AU (199)
92 *EHMT1*	F	ES (5)	Stereotypies (12)	MIC, C HYP, synophrys, LSE, brachycephaly	RIHT, no requirement of second-line therapy	ESC, SF, NAMB, AU (20)
93 *GNAO1*	F	GT (2), ES (3)	Dystonia (3)	NHC, C HYP	FIHT, response with NZ	ESC, SF, NAMB (48)

TABLE 4 (Continued)

Serial no gene	Sex	Seizures (age in months); prior epilepsy syndrome if any	Movement disorder (onset: age in months)	Phenotypic characteristics	Treatment response	Outcome until the last follow-up (age in months)
94 *PRRT2*	F	GT (4), ES (7)	Dystonia (5)	NHC	FIHT, response with VGB	ESC, SF (9)
95 *AMT*	M	FC (2), ES (3)	Absent	MIC	FIHT, response with NZ	ESC, DRE (10)
96 *KMT2C*	M	FC (3), ES (5)	Stereotypies (18)	MIC, C HYP, AU	FIHT, response with NZ	PES, DRE, AMB, AU (108)
97 *ADSL*	F	FC (2), ES (15)	Stereotypies	MIC, Long eyebrows	FIHT, response with NZ	ESC, DRE, LGS, NAMB, AU (84)
98 *SATB1*	M	ES (18), FUBA (130), GT (132)	Stereotypies	MIC, LSE	FIHT, response with VGB	ESC, AMB, AUHA (144)
99 *PACS2*	M	ES (5)		MIC, C HYP	FIHT, response with NZ	ESC, NAMB, AUHA (44)
100 *HUWE1*	M	ES (10), GT (13)	Dystonia and choreoathetosis (12)	MIC, C HYP, BF, flat occiput, LSE, brachydactyly, NPF, deep eyes	RIHT, relapse, response with NZ	ESC, NAMB (20)
101 *ASNS*	M	FC (2), MC (2), ES (6)	Stereotypies	MIC	RIHT, relapse, response with ZON	ESC, DRE, AU, EXP at 8 months
102 *MIPEP*	M	ES (6), GTC (6)	Severe dystonia (8)	MIC, C HYP	RIHT, relapse, response with VGB	ESC, SF, NAMB (22)
103 *PLEKHG2*	F	GTC (4), MC (4), ES (9)	Stereotypies Dystonia (6)	MIC, C HYP, AU	RIHT, no requirement of second-line therapy	ESC, SF, AMB, AU (132)
104 *SCN8A*	M	GT (5), FUBA (6), ES (8)	Stereotypies	NHC, C HYP, HTL, LSE, deep eyes	FIHT, responded with NZ, No response to phenytoin	ESC, SF, AU (10)
105 *MT-ND5*	F	ES (6)	Dystonia (10)	NHC, C HYP, BF, large ears	RIHT, no requirement of second-line therapy	ESC, SF, NAMB, neuroregression following varicella around 2 y of age (30)

Abbreviations: AMB, ambulatory; AP, aspiration pneumonia; ASE, admission for status epilepticus in the preceding 2 y at last visit; AU, autistic; AUHA, autistic and hyperactive; BC, behavioral concerns like excessive anger, disobedient, self-injurious behavior, etc.; BF, broad forehead; C HYP, central hypotonia; CLDY, clinodactyly; CVI, cortico visual impairment; DEV, development; DRE, drug refractory epilepsy; EIDEE, early infantile developmental and epileptic encephalopathy; EIMFS, epilepsy of infancy with migrating focal seizures; ESC, epileptic spasms under control; ES, epileptic spasms; EXP, expired; FC, focal clonic; F, female; FIHT, failed initial hormonal therapy; FTBTC, focal tonic to bilateral tonic clonic; FT, focal tonic; FUA, focal unaware seizure with automatisms; FUBA, focal unaware seizure with behavioral arrest; GT, generalized tonic; HA, hyperactive; HAP, high arched palate; H, hormonal therapy; HI, hearing impairment; HTL, hypertelorism; IESS, infantile epileptic spasms syndrome; LSE, low set ears; MC, myoclonic; MIC, microcephaly; M, male; MS, mongoloid slant; NAMB, non-ambulatory; NHC, normal head circumference; NPF, narrow palpebral fissure; NRTP, no response to phenytoin; PES, persistent epileptic spasms; RIHT, responded to initial hormonal therapy; SF, seizure free.

PDE, contrasting the findings of large genetic IESS cohorts.[8,10,12–15] This might be because seven children with PDE (three unrelated cases had the same variant; possible founder variation) were contributed by a single center catering to a population with a high prevalence of consanguinity. The frequencies of the other monogenic disorders, such as *SCN2A, CDKL5, STXBP1, WWOX*, etc., were comparable to that reported in previous cohorts.[8,10,12–15] The other common genes reported in previous cohorts, such as *ARX, TSC, TUBA1A*, Miller Dieker syndrome, and other structural neurometabolic disorders at initial presentation, were not observed in the current study since these were systematically excluded at the outset due to the associated characteristic neuroimaging abnormalities.[8,10,12–14] Furthermore, one child had a mitochondrially inherited disorder. Hence, the mitochondrial genome needs to be considered during evaluation once other genetic investigations are unyielding. The metabolic causes of genetic IESS in the current cohort with no definite neuroimaging clues include pyridoxine-dependent epilepsy, adenylosuccinate lyase deficiency, arginosuccinate synthetase deficiency, mitochondrial disease, and glycine encephalopathy/nonketotic hyperglycinemia. This highlights the importance of genetic testing in unknown etiology IESS to identify potentially treatable metabolic conditions like pyridoxine-dependent epilepsy.

The current study represents the largest cohort of genetic IESS from South Asia and provides the spectrum and the distribution of the various genetic causes and their phenotypic characteristics which exist in a resource-limited setting. Unlike the large funded multinational consortia on epilepsy genetics, such as the Epi4K consortium, this study gives an insight into the impediments faced by epilepsy researchers working in low-middle income settings. The genetic testing in resource-limited settings is primarily done through out-of-pocket expenditure, and many families might not be affording. Hence, the yield and the landscape represented in the current cohort may not represent the actual figures. Unless robust funding mechanisms are available to pursue epilepsy genetic research in these countries with a huge burden, this seems the most feasible way to study the genotypic landscape (although with its shortcomings). Efforts were made to overcome these concerns associated with the retrospective study design, such as recall and case ascertainment biases in old cases, etc., through prospective assessment and case record review of all patients by a pediatric neurologist. Besides, it would have been useful and interesting to know the genetic yield of each diagnostic test and the distribution of the various etiologies of IESS including non-genetic ones identified from all the centres in the study period. However, these details were not available as this was a non-funded multicentre study and the objective of the study was focussed on understanding the genetic landscape of unexplained cases of IESS. Hence, the denominator of total number of IESS cases managed at all centers was not particularly looked at.

5 | CONCLUSIONS

The spectrum of genetic IESS is heterogenous. Collectively, monogenic disorders are the most common cause of genetic IESS. Trisomy 21, *ALDH7A1, SCN2A, CDKL5*, and *ALG13* are the common causes of genetic IESS. Strikingly, the cohort shows clinicians' efforts in identifying the treatable causes, such as pyridoxine-dependent epilepsy in resource-limited settings (*ALDH7A1* was the commonest monogenic disorder). The mitochondrial inherited disorder can cause IESS. Central hypotonia, developmental delay before the onset of spasms, early onset of spasms (<6 months of age), autistic features, and facial dysmorphism were notable findings observed in children with genetic IESS.

6 | FUTURE PERSPECTIVE

In the future, more genotypic-specific multicentric studies exploring phenotypes and phenotype–genotype association are needed to broaden our understanding and knowledge in this area. This vital information on the neurobiology of these genes and genetic causes could have future prognostic and therapeutic implications. This is only the initial step in the right direction in the field of epilepsy genetics, with an ongoing quest for precision medicine in IESS.

AUTHOR CONTRIBUTIONS

BN: study design, drafting the work, data collection, data analysis, data interpretation, manuscript writing and approval of the manuscript; AK, AGS, LS, RS, and NS: study design, data analysis, data interpretation, drafting the work, and approval of the manuscript; PM: data collection, data interpretation, revising work critically, and approval of the manuscript; VKG, SY, IS, KS, NV, and others: study design, data interpretation, revising work critically and approval of manuscript JKS: conceptualization of study and design, drafting the work, data collection, data interpretation, manuscript writing, and approval of the manuscript.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

All-important data generated or analyzed during this study are included in this published article and uploaded as supplementary information.

ETHICAL APPROVAL

The study was approved by the Institute Ethics Committee and Institute Collaborative Research Committee.

ADDITIONAL FINANCIAL INFORMATION UNRELATED TO THE CURRENT RESEARCH COVERING THE PAST YEAR

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POLICY ON ETHICAL PUBLICATION

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

CONSENT TO PARTICIPATE

Informed consent was obtained from the parents.

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REFERENCES

1. Zuberi SM, Wirrell E, Yozawitz E, Wilmshurst JM, Specchio N, Riney K, et al. ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: position statement by the ILAE task force on nosology and definitions. Epilepsia. 2022;63(6):1349–97.
2. Lux AL, Osborne JP. A proposal for case definitions and outcome measures in studies of infantile spasms and West syndrome: consensus statement of the West Delphi group. Epilepsia. 2004;45(11):1416–28.
3. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the international league against epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):522–30.
4. Hunter MB, Yoong M, Sumpter RE, Verity K, Shetty J, McLellan A, et al. Incidence of early-onset epilepsy: a prospective population-based study. Seizure. 2020;75:49–54.
5. Wirrell EC, Shellhaas RA, Joshi C, Keator C, Kumar S, Mitchell WG. How should children with West syndrome be efficiently and accurately investigated? Results from the National Infantile Spasms Consortium. Epilepsia. 2015;56:617–25.
6. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512–21.
7. Osborne JP, Lux AL, Edwards SW, Hancock E, Johnson AL, Kennedy CR, et al. The underlying etiology of infantile spasms (West syndrome): information from the United Kingdom infantile spasms study (UKISS) on contemporary causes and their classification. Epilepsia. 2010;51:2168–74.
8. Epi4K Consortium, Epilepsy Phenome/Genome Project, Allen AS, Berkovic SF, Cossette P, Delanty N, Dlugos D, et al. De novo mutations in epileptic encephalopathies. Nature. 2013;501(7466):217–21. https://doi.org/10.1038/nature12439
9. Lemke JR, Riesch E, Scheurenbrand T, Schubach M, Wilhelm C, Steiner I, et al. Targeted next generation sequencing as a diagnostic tool in epileptic disorders. Epilepsia. 2012;53:1387–98.
10. McTague A, Howell KB, Cross JH, Kurian M, Scheffer I. The genetic landscape of the epileptic encephalopathies of infancy and childhood. Lancet Neurol. 2016;15:304–16. https://doi.org/10.1016/S1474-4422(15)00250-1
11. Madaan P, Negi S, Sharma R, Kaur A, Sahu JK. X-linked ALG13 gene variant as a cause of epileptic encephalopathy in girls. Indian J Pediatr. 2019;86(11):1072–3. https://doi.org/10.1007/s12098-019-03059-3
12. Michaud JL, Lachance M, Hamdan FF, Carmant L, Lortie A, Diadori P, et al. The genetic landscape of infantile spasms. Hum Mol Genet. 2014;23(18):4846–58.
13. Krey I, Krois-Neudenberger J, Hentschel J, Syrbe S, Polster T, Hanker B, et al. Genotype-phenotype correlation on 45 individuals with West syndrome. Eur J Paediatr Neurol. 2020;25:134–8.
14. Yuskaitis CJ, Ruzhnikov MRZ, Howell KB, Allen IE, Kapur K, Dlugos DJ, et al. Infantile spasms of unknown cause: predictors of outcome and genotype-phenotype correlation. Pediatr Neurol. 2018;87:48–56.

15. Mitta N, Menon RN, McTague A, Radhakrishnan A, Sundaram S, Cherian A, et al. Genotype-phenotype correlates of infantile-onset developmental & epileptic encephalopathy syndromes in South India: a single Centre experience. Epilepsy Res. 2020;166:106398.
16. Surana P, Symonds JD, Srivastava P, Geetha TS, Jain R, Vedant R, et al. Infantile spasms: etiology, lead time and treatment response in a resource limited setting. Epilepsy Behav Rep. 2020;14:100397.
17. Heyne HO, Singh T, Stamberger H, Abou Jamra R, Caglayan H, Craiu D, et al. De novo variants in neurodevelopmental disorders with epilepsy. Nat Genet. 2018;50(7):1048–53.
18. Wanigasinghe J, Sahu JK, Madaan P, Fatema K, Linn K, Chand P, et al. Classifying etiology of infantile spasms syndrome in resource-limited settings: a study from the south Asian region. Epilepsia Open. 2021;6(4):736–47. https://doi.org/10.1002/epi4.12548
19. Madaan P, Chand P, Linn K, Wanigasinghe J, Lhamu Mynak M, Poudel P, et al. Management practices for West syndrome in South Asia: a survey study and meta-analysis. Epilepsia Open. 2020;5(3):461–74. https://doi.org/10.1002/epi4.12419
20. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405–24. https://doi.org/10.1038/gim.2015.30
21. Yoganathan S, Arunachal G, Gowda VK, Vinayan KP, Thomas M, Whitney R, et al. NTRK2-related developmental and epileptic encephalopathy: report of 5 new cases. Seizure. 2021;92:52–5.
22. Gowda VK, Amoghimath R, Battina M, Shivappa SK, Benakappa N. Case series of early SCN1A-related developmental and epileptic encephalopathies. J Pediatr Neurosci. 2021;16:212–7.
23. Madaan P, Kaushal Y, Srivastava P, Crow YJ, Livingston JH, Ahuja C, et al. Delineating the epilepsy phenotype of NRROS-related microgliopathy: a case report and literature review. Seizure. 2022;100:15–20.
24. Johannesen KM, Gardella E, Gjerulfsen CE, Bayat A, Rouhl RPW, Reijnders M, et al. *PURA*-related developmental and epileptic encephalopathy: phenotypic and genotypic spectrum. Neurol Genet. 2021;7(6):e613.
25. Szklarczyk D, Gable AL, Nastou KC, Lyon D, Kirsch R, Pyysalo S, et al. The STRING database in 2021: customizable protein–protein networks, and functional characterization of user-uploaded gene/measurement sets. Nucleic Acids Res. 2021;49(D1):D605–12.
26. Anbarasu A, Sahu JK, Sankhyan N, Singhi P. Magnitude, determinants and impact of treatment lag in West syndrome: a prospective observational study. J Pediatr Neurosci. 2023. https://doi.org/10.4103/jpn.JPN_101_21
27. Bartolini E. Inherited developmental and epileptic encephalopathies. Neurol Int. 2021;13(4):555–68. https://doi.org/10.3390/neurolint13040055
28. Aramanadka R, Sahu JK, Madaan P, Sankhyan N, Malhi P, Singhi P. Epilepsy and neurodevelopmental outcomes in a cohort of West syndrome beyond two years of age. Indian J Pediatr. 2022;89(8):765–70. https://doi.org/10.1007/s12098-021-03918-y
29. Devi N, Madaan P, Kandoth N, Bansal D, Sahu JK. Efficacy and safety of dietary therapies for childhood drug-resistant epilepsy: a systematic review and network meta-analysis. JAMA Pediatr. 2023;177(3):258–66. https://doi.org/10.1001/jamapediatrics.2022.5648
30. Vendrame M, Guilhoto LMFF, Loddenkemper T, Gregas M, Bourgeois BF, Kothare SV. Outcomes of epileptic spasms in patients aged less than 3 years: single-center United States experience. Pediatr Neurol. 2012;46:276–80. https://doi.org/10.1016/j.pediatrneurol.2012.02.022
31. Widjaja E, Go C, McCoy B, Snead OC. Neurodevelopmental outcome of infantile spasms: a systematic review and meta-analysis. Epilepsy Res. 2015;109:155–62. https://doi.org/10.1016/j.eplepsyres.2014.11.012
32. Riikonen R. Infantile Spasms: Outcome in clinical studies. Pediatr Neurol. 2020;108:54–64. https://doi.org/10.1016/j.pediatrneurol.2020.01.015
33. Harini C, Nagarajan E, Bergin AM, Pearl P, Loddenkemper T, Takeoka M, et al. Mortality in infantile spasms: a hospital-based study. Epilepsia. 2020;61:702–13. https://doi.org/10.1111/epi.16468
34. Sillanpää M, Riikonen R, Saarinen MM, Schmidt D. Long-term mortality of patients with West syndrome. Epilepsia Open. 2016;1:61–6. https://doi.org/10.1002/epi4.12008
35. Bhanudeep S, Madaan P, Sankhyan N, Saini L, Malhi P, Suthar R, et al. Long-term epilepsy control, motor function, cognition, sleep and quality of life in children with West syndrome. Epilepsy Res. 2021;173:106629. https://doi.org/10.1016/j.eplepsyres.2021.106629
36. Symonds J, McTague A. Epilepsy and developmental disorders: next generation sequencing in the clinic. Eur J Paediatr Neurol. 2020;24:15–23. https://doi.org/10.1016/j.ejpn.2019.12.008

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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