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A genetic and biologic classification of infantile spasms

Alex R. Paciorkowski^{1,2}, Liu Lin Thio^{3,4}, and William B. Dobyns^{2,5}

¹Department of Neurology, University of Washington, Seattle, WA 98105

²Seattle Children's Research Institute, Seattle, WA 98101

³Departments of Neurology and Pediatrics, Washington University, St. Louis, MO 63110

⁴Pediatric Epilepsy Center, St. Louis Children's Hospital, St. Louis, MO 63110

⁵Division of Genetic Medicine, Department of Pediatrics, University of Washington, Seattle, WA 98105

Abstract

Infantile spasms are an age-dependent epilepsy that are highly associated with cognitive impairment, autism, and movement disorders. Previous classification systems have focused on a distinction between *symptomatic* and *cryptogenic* etiologies, and have not kept pace with the recent discoveries of mutations in genes in key pathways of central nervous system development in patients with infantile spasms. Children with certain genetic syndromes are much more likely to have infantile spasms, and we review the literature to propose a *genetic classification* of these disorders. Children with these genetic associations with infantile spasms also have phenotypes beyond epilepsy that may be explained by recent advances in the understanding of underlying biological mechanisms. We therefore also propose a *biologic classification* of the genes highly associated with infantile spasms, and articulate models for infantile spasms pathogenesis based on that data. The two best described pathways of pathogenesis are abnormalities in the gene regulatory network of GABAergic forebrain development, and abnormalities in molecules expressed at the synapse. We intend for these genetic and biologic classifications to be flexible, and hope that they will encourage much needed progress in syndrome recognition, clinical genetic testing, and ultimately the development of new therapies that target specific pathways of pathogenesis.

Keywords

Infantile spasms; developmental epilepsy; autism; movement disorders; gene regulatory networks

Introduction

Infantile spasms (ISS) are characterized by clusters of epileptic spasms with ictal electrodecrement, usually occurring before the age of 1 year [1]. The incidence of ISS is

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Correspondence to: Alex R. Paciorkowski, M.D., Seattle Children's Research Institute, Center for Integrative Brain Research, 1900 Ninth Avenue, MS C9S-10, Seattle, WA 98101, Phone: (206) 884-1084, arpac@u.washington.edu.

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0.25–0.4 per 1,000 live births [2], and they are important because of their frequent association with severe developmental outcome, including autism [3].

There have been many variations in terminology describing ISS over the years, with the eponym “West syndrome” generally referring to the triad of spasms, hypsarrhythmia, and mental retardation or regression – despite the difficulty of detecting the latter in a young infant presenting with ISS. Hypsarrhythmia is regarded by some as a key feature in the diagnosis of ISS, but can be so variable that it remains surprisingly troublesome to define, and evolves over time [4]. As a consequence, the literature contains references to “atypical” and “modified” hypsarrhythmia [5, 6], and there is little consensus on the meaning of these terms, or on how much of the electroencephalographic record should be abnormal [4, 7, 8]. In fact, the international West Delphi Group consensus statement did not regard the presence of hypsarrhythmia as essential for the diagnosis of ISS [1], and correctly refocused the core of the electroclinical disorder on the ictal event associated with an electrodecrement on EEG in an appropriately aged child. ISS without hypsarrhythmia are well documented [9]. We will continue to refer to the disorder as *infantile spasms*, while recognizing that in some children they may not occur during infancy, and may not manifest as classic flexor or extensor spasms, and hypsarrhythmia may only be an *associated* feature of the interictal EEG.

Infantile spasms and the genetics of brain development

In the past, the terms *symptomatic*, *cryptogenic*, and *idiopathic* were introduced to categorize ISS, and epilepsy in general [10]. The limitations of this approach to classification are well noted within the epilepsy community [11, 12], and these terms become even more untenable with growing evidence that ISS result from disturbances in key genetic pathways of brain development. Recent studies show that patients with ISS may have mutations in several genes including *ARX*, *CDKL5*, *FOXG1*, *GRIN1*, *GRIN2A*, *MAGI2*, *MEF2C*, *SLC25A22*, *SPTAN1*, and *STXBPI* [13–24]. While not all patients with mutations in these genes have ISS, the phenotype is consistent enough to speak of them as *ISS-associated genes*, modified by incomplete penetrance and variable expressivity. Taken together, these single genes, as well as other candidate genes identified from pathogenic copy number variants, suggest that abnormalities in ventral forebrain development and synaptic functional pathways play critical roles in ISS pathogenesis [25]. We caution that the pathogenesis of ISS may mirror autism in its genetic complexity, where each genetic abnormality probably accounts for about 1% of the disorder [26, 27]. Therefore, many more ISS-associated genes are likely to be discovered, and the evolving genetic data demand a reassessment of this disorder.

New molecular insights from the recent genetic data imply that all forms of ISS may be “symptomatic”, and that a diagnosis of “cryptogenic” ISS should no longer be accepted. For this reason, the International League Against Epilepsy (ILAE) recently recommended replacing the *symptomatic*, *cryptogenic*, and *idiopathic* classification system of epilepsy syndromes [12]. We strongly agree with their recommendation, but argue that it is also possible to take the first steps toward genetic and biologic classifications of ISS.

The biologic link between infantile spasms and autism

Many clinical studies of ISS have focused on the subsequent intractable epilepsy that develops in 40–60% of affected children [28, 29]. Although important, this approach has underemphasized the broader phenotypes to which ISS may belong. In contrast, classification systems based on the emerging genetic and biologic data would incorporate the historical connections between ISS and phenotypes other than intractable epilepsy. These observations are not new, and the spectrum of neurologic associations with ISS has

always been much broader than intractable epilepsy, as it was for William James West's son.

West syndrome is an unusual eponym because it is named after the father of the proband. The English physician, William James West, is credited with writing the first description of ISS in English by reporting the history of his son, James [30]. Most authors since have focused only on West's descriptions of the seizures. However, one report highlighted James' later history, which included lack of speech and "frequent fits of idiotic laughter, and rollings of the head... delighted by music and gay colours". This description leads "to the suspicion that James had features of autism" [31]. Langdon-Down, who cared for him in later life, reported that James and other children he observed with ISS had "a great tendency to automatism and rhythmical actions" including "salaams, horizontal swayings, and rotations of the head and body" [32]. These observations may be compatible with the stereotypies often seen with autism.

Later reports continued to show that autism could follow ISS [33–36]. This includes reports of tuberous sclerosis complex (TSC), ISS, and autism [37], with a similar correlation noted in patients with Down syndrome as well [38, 39]. Some argue that the subsequent autistic spectrum disorder is a *consequence* of severe epileptic encephalopathy [40, 41]. While this remains a compelling hypothesis, the most recent data suggest a primary biologic link between ISS and autism [25].

Infantile spasms and movement disorders

Several early reports of children with ISS described hyperkinesia, but the nature and significance of the finding remained unclear [36, 42]. The use of the term "cerebral palsy" as a putative "predisposing cause" may obscure recognition of a movement disorder as a specific feature associated with ISS [43, 44]. The discovery of *ARX* as the first gene clearly associated with (previously "cryptogenic") ISS led to a wider appreciation that involuntary movements may be a key clinical feature of certain syndromes that include ISS [45]. The description of *MEF2C* deletions and mutations in patients with ISS and dyskinesia strengthens this association [20, 21, 46]. The identification of *MEF2C* as another ISS-associated gene is interesting as *MEF2C* may be a transcriptional target of *ARX* during ventral forebrain development when GABAergic interneurons proliferate and migrate [47]. It is perhaps not surprising that children with mutations in *ARX* and *MEF2C* have similar phenotypes. Additionally, dyskinetic movements have been reported in children with *CDKL5* deletions [48] and *STXBPI* mutations as well [49].

A genetic classification of ISS

We agree with the spirit of the recent ILAE recommendation that epilepsies should be divided into genetic, structural/metabolic, and unknown categories [12]. However, the distinction between genetic and structural/metabolic is artificial and should be modified, as most epilepsies associated with structural brain malformations or inborn errors of metabolism are also genetic. Those that are not primarily genetic, such as epilepsy due to brain injury and infection, are distinct and deserve a place of their own.

A genetic classification has practical benefits. When ISS are recognized as a symptom found in many developmental disorders, rather than seen in isolation, the many disorders associated with ISS can be divided into two main groups: those with the predisposing genotype known and those with the predisposing genotype unknown. Of course, we recognize several important subdivisions, as listed in Table 1. We think that this approach will facilitate future progress in several areas including genetics, pathogenesis, and

treatment. Figure 1 illustrates the evaluation of ISS using the classification system presented in Table 1.

1. ISS with predisposing genotype known

1a. Prototypic developmental epilepsies

This group provides the core data supporting our emerging understanding of ISS pathogenesis, and from this group the later biologic classification of ISS can also be built. These are the newly described genes in which mutations, intragenic expansions, deletions and/or duplications frequently are associated with spasms. Some children with *ARX* and *STXBP1* mutations initially presented with early infantile epileptic encephalopathy (EIEE, Ohtahara syndrome) [17, 50–52] and illustrate a spectrum of infancy-onset epileptic encephalopathies. EIEE, early myoclonic encephalopathy (EME), and ISS remain enigmatic in their relationship to one another, and patient series of these infantile epilepsies overlap in genotype [49, 53–55], suggesting factors of incomplete penetrance and variable expressivity. The type of early-onset epilepsy may be related to severity of mutation, although more data are needed to show this relationship. Therefore, the term *prototypic developmental epilepsies* acknowledges the variability but likely biologic kinship of these phenotypes.

1b. Specific brain malformations

The two genes most commonly associated with classical lissencephaly, *PAFAH1B1/LIS1* and *DCX*, as well as the less common *TUBA1A* are strongly associated with ISS [56] with a prevalence as high as 80% in children with *PAFAH1B1/LIS1* deletions or mutations [57]. Severe mutations of *ARX* associated with X-linked lissencephaly with abnormal genitalia (XLAG) result in severe early-onset epilepsy that overlaps with EIEE. This pattern can evolve into ISS, but more commonly progresses to severe intractable epilepsy [58, 59]. *ARX*, *DCX*, and *PAFAH1B1/LIS1* are all expressed in GABAergic interneurons [60–62], and we hypothesize that spasms are linked to deficits in this neuronal cell type, rather than the obvious cortical malformation.

This category also includes TSC, as mutations in *TSC1* and *TSC2* are associated with cortical tubers, subependymal nodules and other TSC-related brain malformations. Around 40% of patients with TSC may have ISS [63], although the prevalence varies and precise phenotype-genotype data are not available. Recent molecular and pathology evidence suggests tuber formation may be the result of a combination of germline and somatic *TSC1/2* mutations [64]. The presence, location, and type of tubers correlate with ISS in some studies [65, 66]. A strong correlation has been established between TSC, ISS, and the subsequent development of autism [67–69], although the mechanism of this relationship remains unclear. Dysregulation of the mammalian target of rapamycin (mTOR) pathway in TSC is a key event leading to abnormal brain morphogenesis [70]. Given the phenotypic heterogeneity of TSC, ISS may occur when the mTOR pathway is perturbed in a specific neuronal population at a key neurodevelopmental stage.

1c. Inborn errors of metabolism

An association between ISS and certain inborn errors of metabolism has long been recognized. The best known examples include the aminoacidopathies phenylketonuria (PKU) and nonketotic hyperglycinemia (NKH); the organic acidemias methylmalonic acidemia (MMA), propionic acidemia (PA) and maple-syrup urine disease (MSUD); and a disorder of copper metabolism, Menkes disease [71–77]. Mutations of *KCNJ11* cause DEND syndrome (developmental delay, epilepsy, neonatal diabetes), which commonly features ISS and is a rare example of an ion channel gene associated with spasms [78–80]. The genetically-characterized mitochondrial disorders appear to be infrequently associated

with ISS, with very few clinical reports available [81]. Mutations in *SUCLA2* produce a specific mitochondrial encephalopathy, but only one reported patient had ISS [82].

Metabolic diseases presumably cause epilepsy by disturbing neuronal energetics or by toxicity from the offending metabolite [83]. However, PKU may have secondary effects on synapse function [84], while NKH and a few other metabolic disorders are associated with agenesis of the corpus callosum and cortical malformations [85]. It is possible that abnormalities in neuronal energetics, synapse function, and brain morphogenesis may all be interrelated in metabolic patients with ISS, and their symptoms reflect the susceptibility of specific neuronal populations to the offending metabolite at a key point in neurodevelopment. Not surprisingly, ISS are usually not the only epilepsy type associated with these metabolic disorders, and overlap exists with other early infant-onset epilepsies, such as EME.

1d. Syndromes of genomic imbalance

At least five well-known syndromes of chromosomal copy number variation are predisposing genotypes for ISS. These are deletion 1p36.3, Pallister-Killian syndrome (tetrasomy 12p), duplication of maternal 15q11q13, Miller-Dieker syndrome (deletion 17p13.3), and Down syndrome (trisomy 21) [25, 86–95]. The biological mechanism(s) of ISS in these syndromes are not known, except for Miller-Dieker syndrome in which the deletion of *PAFAH1B1/LIS1* causes both abnormal primary glutamatergic and GABAergic interneuron migration [89, 96, 97]. Similarly, deletion of *MAGI2* at 7q11.2 may be associated with ISS in Williams syndrome [16], although there are also reports of ISS in Williams syndrome patients with deletions that do not include *MAGI2* [25, 98, 99]. Overall this suggests that copy number changes in key genes, in the right developmental context, influence the occurrence of ISS in these disorders. Further, “multiple hit” genomic events may account for some of the phenotypic variability seen in diseases mediated by copy number variants [100–102].

1e. Syndromes with putative association with ISS

ISS have occasionally been reported with several other well-characterized predisposing genotypes, often in reports predating molecular characterization of the disorder. For example, we found several reports of ISS in patients with Freeman-Sheldon, Schinzel-Giedeon, Smith-Lemli-Opitz, and Sotos syndrome [103–109]. There are also reports of ISS in patients with mutations in *FLNA* and *ARFGEF2*, genetic causes of periventricular nodular heterotopia [110, 111]. However, other seizure types are more common than ISS in most of these disorders, especially patients with heterotopia due to *FLNA* mutations, making it difficult to argue that these genes are reliably causative.

Several reports suggest an association between ISS and rasopathies (neurofibromatosis type I and cardio-facio-cutaneous syndrome), but not commonly enough to suggest a consistent link [112–114]. A single report each of ISS with Smith-Magenis and Pallister-Hall syndromes (the latter with hypothalamic hamartoma) suggest a rare association [115, 116].

2. ISS with predisposing genotype unknown

2a. Prototypic developmental epilepsies

This is a novel category introduced to refer to patients who present with ISS, but who lack features specific for any unifying diagnosis and accordingly have an unknown predisposing genotype. When reviewed at later ages, these children have features suggesting a global developmental disorder such as autistic features and dyskinesias that may not have been manifest at the time of presentation with ISS. Brain imaging studies may be normal, or may

have findings that do not define a specific syndrome – such as cortical gray or white matter volume loss, asymmetric ventricles, simplified gyral pattern, hypogenesis of the corpus callosum, polymicrogyria, and/or cerebellar malformations. The subsequent epilepsy course after ISS is variable, with some children developing intractable epilepsy and others few seizures. Due to the spectrum of imaging and neurobehavioral findings in this group, this is not a replacement for the previous “cryptogenic” designation. Rather, we think that all or most of these patients will ultimately be found to have predisposing genotypes, particularly in early CNS developmental genes.

2b. Recognizable unifying phenotype and clear association with ISS

This group contains well-described developmental disorders with unknown genotype but unifying phenotypes that have ISS as a core finding. The two best examples are Aicardi and progressive encephalopathy with edema, hypsarrhythmia and optic atrophy (PEHO) syndromes. Aicardi syndrome consists of agenesis of the corpus callosum, polymicrogyria, chorioretinal lacunes, other more variable anomalies, with ISS being a prominent feature [117]. It affects only females, suggesting a gene located on the X chromosome. PEHO syndrome is less common, appears to overlap with a PEHO-like phenotype, and most resembles a neurodegenerative disorder with marked brain and optic nerve atrophy [118–120].

Several more heterogeneous conditions have also been associated with a high incidence of ISS. Around 7% of patients with focal cortical dysplasia (FCD) may develop ISS [121], and the cortical abnormalities may be below the resolution of MRI [122]. Interestingly, persistence of immature GABAergic networks appear to play a role in focal cortical dysplasia [123], and dysfunction in the mTOR signaling pathway is a shared feature between FCD and tuberous sclerosis complex [124]. Finally, isolated hemimegalencephaly (HMEG) is included in this category because without cutaneous or systemic findings it is a clinical entity distinct from the many syndromes that also feature this malformation [125, 126].

2c. Biochemical/metabolic abnormalities putatively associated with ISS

As a clear relationship between ISS and inborn errors of metabolism has been established, we also recognize a category of diseases where a biochemical defect is demonstrable, but the genetic etiology remains unclear. Patients with pyridoxine-responsive ISS have been reported [127], but none with mutations in the one known pyridoxine-dependent epilepsy gene *ALDH7* [128, 129]. Several reports link mitochondrial respiratory chain dysfunction and ISS, but without a clear genetic mutation identified, making it unclear if the mitochondrial dysfunction is primary or secondary [130–133]. Finally, neonatal hypoglycemia has long been offered as a cause of ISS [44, 134], sometimes in the setting of hyperinsulinism [135]. The evaluations reported in these patients are often unclear or incomplete, so it is difficult to make a clear causal connection between the two.

2d. Extrinsic injury patterns

Extrinsic brain injuries such as hypoxic-ischemic encephalopathy (HIE), near-miss sudden infant death syndrome, stroke, and infection are commonly accepted as causes of ISS. These infants rarely undergo further evaluation. A closer survey of the patients reported, however, leads to some interesting observations. One is that brain imaging patterns such as atrophy, calcifications, and white matter hyperintensities previously interpreted as due to ischemic injury or infection can overlap with predisposing genotypes such as *CDKL5* and *SPTAN1* mutations [15, 22, 136, 137]. Clinicians should therefore be aware of the conditions that may present “HIE or infection look-alikes” on imaging.

Reports remain in which ischemic events were well documented with no other predisposing condition identified, and it would appear that 5–10% of infants with ISS in these series have a presumed ischemic or infectious etiology [138–142]. Our concern is that this literature is retrospective, and may not accurately reflect the prevalence of ISS among children with acquired brain injuries. About 25% of children with perinatal hypoxia will have subsequent cerebral palsy, cognitive impairment, and epilepsy [143], but ISS do not appear to be a significant seizure type described in this population [144]. Despite the increased survival of very-low birth weight infants at risk for HIE, the rate of ISS has not increased [145], suggesting that other factors contribute to the development of spasms in this population. Perhaps hypoxia represents a “second hit” in a population made vulnerable to spasms by yet-undiscovered predisposing genotypes. While some may comment that there is no scientific data for such an assertion, we argue that the data are insufficient in either case. The study that prospectively follows a large cohort of patients with perinatal hypoxia and documents the prevalence of ISS has not yet been done.

Similar observations may be made about the many case series documenting infection as the cause of ISS [146–148]. While epilepsy can certainly be a long-term complication of CNS bacterial or viral infection during infancy, ISS as a specific consequence are not captured in outcome data [149–153]. If ISS are rare sequelae of CNS infection, predisposing genotype(s) may exist that lead to the expression of spasms in infants who have experienced CNS infection. It is also possible that ischemic or infectious events at a critical period in perinatal development may selectively damage specific neuronal populations – for example emerging GABAergic interneuron synaptic networks – and result in the later emergence of ISS. Therefore, children with extrinsic injury patterns are prime candidates for further study.

2e. Recognizable unifying phenotype and putative association with infantile spasms

This group of disorders contains syndromic phenotypes with unknown causative genotypes, in which ISS have been mentioned only in occasional clinical reports. In this category are frontal-perisylvian periventricular nodular heterotopia-polymicrogyria (PNH-PMG), hypomelanosis of Ito, macrocephaly polymicrogyria polydactyly hydrocephalus syndrome (MPPH) with the overlapping disorder macrocephaly capillary malformation syndrome (MCAP), and sebaceous nevus syndrome [154–157]. Also noted here are various nonsyndromic CNS neoplasms that have been reported with ISS, including choroid plexus papilloma, hypothalamic hamartoma (also described in Pallister-Killian syndrome), and ganglioglioma [158–160]. The association of these conditions and syndromes with ISS comes from a few patient reports, and requires further study to understand the exact relationship.

Interesting exceptions

Several developmental disorders with epilepsy are not associated with ISS, or a surprisingly small number of patients have been reported, suggesting some biological phenomena that may protect against the development of spasms. These disorders include Rett syndrome due to *MECP2* mutations [161], and given that *CDKL5* probably interacts with *MECP2* [162], it is not clear why the epilepsy phenotypes in these two developmental disorders are so different.

The 15q11q13 locus is also intriguing in this regard, as duplications of maternal 15q11q13 are a common cause of both epilepsy – including ISS – and autism, while deletion of maternal 15q11q13 causes Angelman syndrome and paternal deletion causes Prader-Willi syndrome. Very few examples of ISS have been reported in Angelman syndrome patients [163]. ISS has not been reported in Prader-Willi syndrome, though epilepsy is 16 times more prevalent than in the general population [164].

Dravet syndrome due to *SCN1A* mutations poses another interesting situation. Infants with Dravet syndrome typically present with fever-induced status epilepticus followed by intractable multifocal epilepsy [165]. Dravet syndrome has a severe behavioral phenotype, as well as an ataxia/movement disorder [166]. Despite the fact that GABAergic interneurons express *SCN1A* at high levels, and the mouse model of severe myoclonic epilepsy of infancy demonstrates abnormal interneuron excitability, there is only a single patient report of ISS in this population [167–169]. Further inquiry into these exceptions may yield important insights into the biology of ISS.

Single genes associated with ISS allow biologic classification

A biologic classification system for ISS begins with the recognition that this phenotype in many, if not most, disorders results from specific disturbances of gene regulation of brain development and function. The known ISS associated genes can be classified in a biologic model drawing from Gene Ontology (GO) [170], as well as gene expression data combined with CNS developmental stages. This biologic model can help formulate hypotheses to explain the varied phenotypes seen with ISS, and hopefully identify new treatment targets.

Single genes highly associated with ISS can be classified biologically if data exist regarding the gene expression pattern in specific cell types across the spectrum of CNS development. As these data are incomplete in humans, they must sometimes be extrapolated from animal models, usually the mouse. When these data are combined with the GO *molecular function* of the gene product, a role for the gene product in neurodevelopment can be described. This allows for classification systems built on biological relationships between genes and gene products.

A biologic classification of ISS

One of the benefits of a biologic classification system is that hypotheses to explain phenotype differences among patients with mutations in ISS associated genes can be made. It is hoped that grouping by biologic mechanism will also aid identification of future disease-specific therapies. Table 2 summarizes the ISS phenotype subgroups after this biologic classification. The molecular function of each gene highly associated with ISS was determined from the GO database (www.geneontology.org), and the primary literature is referenced for evidence of role(s) in or effect(s) on specific stages of brain development. Information from the mouse gene expression databases at BGEM (www.stjudebgem.org), GENSAT (www.gensat.org), and MGI (www.informatics.jax.org) was accessed as well.

The groups are organized so that Group A comprises transcription factors, Group B comprises genes important in proliferation and cell migration, and later groups reflect the terminal differentiation stages of synapse development. The two best characterized groups are the gene regulatory network of ventral forebrain development and the pre- and post-synaptic protein networks, illustrated in Figure 2.

Group A comprises patients who have abnormalities in transcription factors that are essential for ventral CNS development. These include duplications of *FOXP1*, mutations of *ARX*, and deletions of *MEF2C*. Abnormalities in *FOXP1* affect development of major telencephalic structures, including the neocortex, hippocampus, and the lateral and medial ganglionic eminences [171]. Patients have mental retardation with an autistic phenotype and stereotypic movements [18, 172]. *ARX* is an important regulator of GABAergic interneuron differentiation and migration [173]. More severe mutations in *ARX* lead to lissencephaly, intractable epilepsy, and a phenotype overlap with Group B1. While *MEF2C* expression is altered in the absence of *ARX* [47], its exact position in the gene regulatory network of

forebrain development remains unclear. Both *ARX* and *MEF2C* patients can have ISS associated with prominent movement disorders.

Group B1 comprises patients with mutations in *DCX*, *PAFAH1B1/LISI*, and *TUBA1A*, which encode binding proteins that are expressed throughout much of forebrain development, in both glutamatergic and GABAergic cell types. Synaptogenesis appears to be disrupted by a secondary effect of abnormal neuronogenesis and migration. These genes also play direct roles in axonogenesis and synapse formation. Group B1 patients have severe brain malformations that include lissencephaly and variable cerebellar hypoplasia. Group B2 is related conceptually to Group B1 because genes in both groups are involved in neuronal proliferation and migration. Similar to Group B1 patients, TSC patients also have characteristic brain malformations, and can have severe cognitive impairment, and intractable epilepsy, but the neurobehavioral phenotype in TSC often distinctly involves autism.

Group C1 patients have mutations in genes such as *GLDC* and *PAH* that play roles in neuronal and non-neuronal cell metabolism but not directly in brain morphogenesis. Mutations in these genes appear to have secondary effects on synapse function, best documented in PKU. These patients have metabolic diseases that, if controlled, as a general rule (but not always) have less severe cognitive impairment and less epilepsy. Group C2 comprises patients with metabolic disorders such as DEND and Menkes disease where the causative gene also has a role in neurodevelopment and the phenotype is characterized by a severe encephalopathy. The genes that cause these disorders have ion transport and/or catalytic activity and play primary roles in synapse development.

Group D comprises patients with abnormalities of *MAGI2*, *SPTAN1*, and *STXBP1*, which encode proteins with direct roles in synaptic development and function. Group D patients tend to have intractable epilepsy, with the *MAGI2* deletion patients so far reported also having Williams syndrome. The recent description of patients with mutations of *GRIN1* [19] and *GRIN2A* [24] associated with ISS illustrates that further discoveries in synapse development and function likely lay ahead.

Future directions

ISS have long posed classification difficulties, and may be most accurately conceptualized as a phenotype “at the tip of the iceberg” of a broader group of developmental disorders that overlap with autism, intractable epilepsy, and movement disorders. This review does not claim to resolve all of these issues, but seeks to open a discussion in new directions. Knowledge is accumulating rapidly about the genetic associations of ISS, and ISS appear to be a genetically heterogeneous condition that can result from abnormalities in key brain development pathways. Like autism, each associated gene may account for only 1% of the condition. Taken together, however, these are not “rare causes”, as is currently commonly perceived. Instead, animal models of the genetic syndromes highly associated with ISS will likely prove helpful in improving our understanding of pathogenesis of ISS, and hopefully will lead to new therapies.

We propose the first genetic and biologic classifications of ISS. These classifications are designed to be flexible, and will allow the incorporation of new causes as they are discovered. They will help the clinician better direct diagnostic testing, and provide more accurate prognostic information and genetic counseling. Of equal importance, a biologic classification system for ISS is essential for the development of new disease-specific therapies, and helps to explain the phenotypes of various ISS syndromes.

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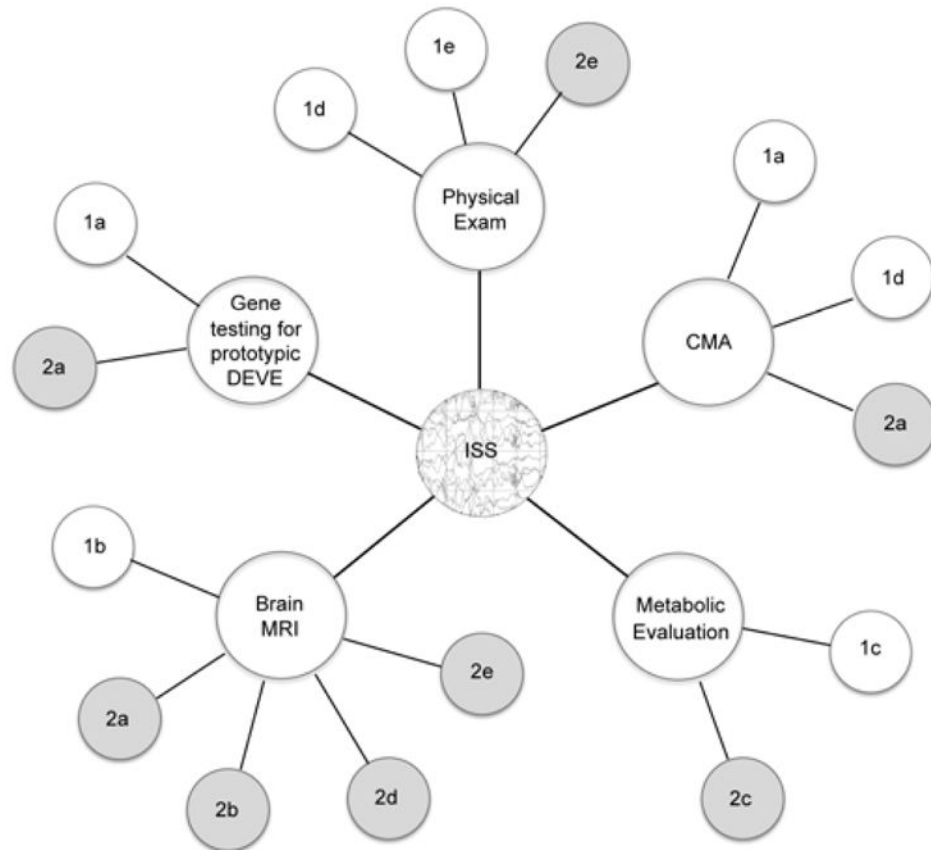


Figure 1.

Evaluation of infantile spasms (ISS) using the classification system in Table 1. Diagnosis of ISS centers upon epileptic spasms associated with ictal electrodecrement. Evaluations may be carried out concurrently, depending upon the clinical scenario. Physical exam findings may lead to recognition of syndromes of genomic imbalance (Group 1d) such as Down syndrome, Williams syndrome, or Miller-Dieker syndrome; or may suggest other syndromes putatively associated with ISS (Group 1e); or recognizable genotype-unknown syndromes (Group 2e). Gene testing for the prototypic developmental epilepsies (DEVE) may find mutations in known associated genes (Group 1a); or if negative may suggest a genotype-unknown prototypic DEVE (Group 2a). Brain MRI may find specific structural brain malformations (Group 1b) and lead to specific follow-up genetic testing; or may reveal non-specific abnormalities associated with genotype-unknown prototypic DEVE (Group 2a), findings associated with genotype-unknown syndromes (Group 2b), extrinsic injury patterns (Group 2d), or recognizable abnormalities putatively associated with ISS (Group 2e). Metabolic evaluation may lead to identification of specific inborn errors of metabolism associated with ISS, leading to genetic testing for those disorders (Group 1c); or may reveal metabolic abnormalities associated with genotype-unknown conditions (Group 2c). Chromosomal microarray (CMA) may identify prototypic DEVE such as duplication of *FOXG1* or deletion of *CDKL5* or *MEF2C* (Group 1a); diagnose known syndromes of genomic imbalance associated with ISS (Group 1d); or may be negative suggesting a genotype-unknown prototypic DEVE (Group 2a).

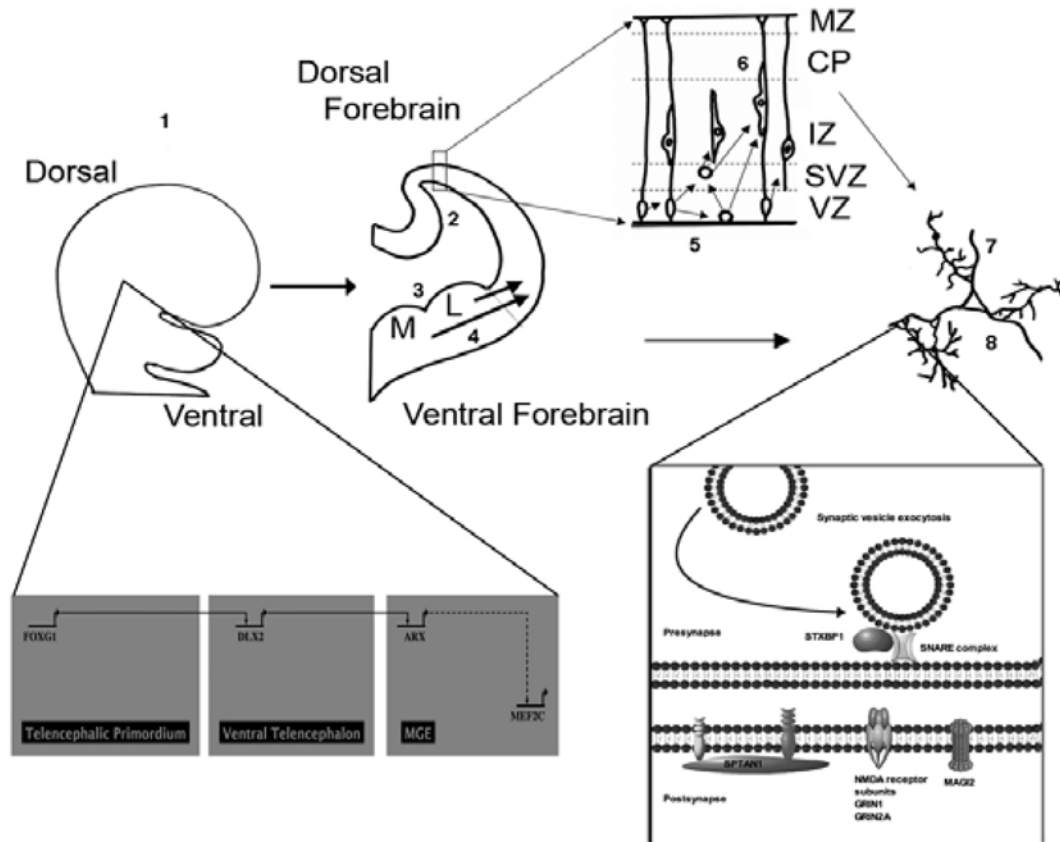


Figure 2.

The two best characterized subgroups of ISS-associated genes illustrated with the stages of central nervous system (CNS) development. Group A includes transcription factors essential to CNS dorsal-ventral differentiation (*FOXG1*), affecting neuroprogenitor cells broadly, with downstream effects on synapse function, as well as *ARX*, which is involved in ventral GABAergic interneuron differentiation, migration, and synaptogenesis. *MEF2C* is probably involved in this process as well. Group D genes (*GRIN1*, *GRIN2A*, *MAGI2*, *SPTAN1*, *STXBP1*) encode binding proteins or receptors with direct roles in presynaptic and/or postsynaptic development and function. 1 = Dorsal-ventral differentiation; 2 = Dorsal neuroprogenitor cell proliferation; 3 = Ventral neuroprogenitor cell proliferation; 4 = GABAergic interneuron migration; 5 = Intermediate progenitor cell proliferation; 6 = Glutamatergic neuron migration; 7 = Axonogenesis; 8 = Synaptogenesis; Red = primary role in developmental stage; Pink = Secondary effect on developmental stage; L = lateral ganglionic eminence; M/MGE = medial ganglionic eminence; MZ = marginal zone; CP = cortical plate; IZ = intermediate zone; SVZ = subventricular zone; VZ = ventricular zone

Table 1a
Genetic classification of infantile spasms with known genotype and key phenotypes

Clinical Syndrome	Gene or Locus	% with ISS	Brain imaging	Other neurodevelopmental phenotype	Reference(s)
I. Infantile spasms as part of developmental disorder with predisposing genotype known					
1a. Prototypic developmental epilepsies					
ISSX	ARX (less severe mutations)	High	Cortical atrophy, reduced WM, abnormal BG	EIEE, variable LGS, dystonia/hyperkinesia common	[45, 50, 51]
	CDKL5	High	Cortical atrophy, abnormal WM, calcifications	LGS, autistic features common	[15, 136]
	FOXG1 duplications	50%	Variable dysgenesis of CC	Autistic features common	[18, 172]
	MEF2C	High	Atrophy, reduced WM	Variable subsequent epilepsy, severe cognitive impairment, hyperkinesia common	[20, 21]
	SLC25A22	High	Atrophy, dysgenesis of CC, CBLH	EIEE, severe cognitive impairment, abnormal electroretinogram	[23, 174]
	SPTAN1	High	Cortical atrophy and CBLA, hypomyelination, reduced WM, thin CC	EIEE	[22]
	STXBP1	High	Atrophy, abnormal WM	EIEE, severe cognitive impairment	[17]
1b. Specific structural brain malformations					
XLAG	ARX (more severe mutations)	High	LIS	Neonatal seizures, LGS, severe cognitive impairment, genital hypoplasia	[58, 59]
ILS	DCX	Presumed high	LIS	LGS, severe cognitive impairment	[57]
ILS	PAFAH1B1/LIS1	High	LIS	LGS, severe cognitive impairment, choreiform movements	[57]
Tuberous sclerosis complex	TSC1 TSC2	40%	Tubers	Variable LGS, cognitive impairment variable, autistic features common	[63]
	TUBA1A	Presumed high	LIS, CBLH	LGS, severe cognitive impairment	[56]
1c. Inborn errors of metabolism					
Amino acidopathies (NKH, PKU)	GLDC, GCST, GCSH (NKH); PAH (PKU)	High	NKH: Variable agenesis of CC PKU: Abnormal WM	EME, subsequent epilepsy may be severe in NKH; cognitive impairment may be severe if metabolic disease uncontrolled	[72, 73, 77]
DEND	KCNJ11	Several patient reports		Diabetes mellitus onset in infancy, severe cognitive impairment, ataxia	[78-80]
Organic acidemias (MMA, MSUD, PA)	MUT (MMA); BCKDHA, BCKDHB, DBT, DLD (MSUD); PCCA, PCCB (PA)	Several patient reports		Subsequent epilepsy, cognitive impairment, and autistic features variable	[76, 175]

Clinical Syndrome	Gene or Locus	% with ISS	Brain imaging	Other neurodevelopmental phenotype	Reference(s)
Menkes disease	ATP7A	High	Cortical atrophy, abnormal WM, "ischemic changes"	Intractable epilepsy, severe cognitive impairment	[71, 74, 75]
Id. Syndromes of genomic imbalance					
Deletion 1p36 syndrome	Deletion 1p36	20%	Cortical atrophy, abnormal WM, thin CC	EIEE; 35% develop LGS; moderate to severe cognitive impairment	[25, 176]
Williams syndrome plus	Deletion 7q11.23 (deletion of MAGI2, and/or other genes)	Several patient reports		Mild-moderate cognitive impairment, characteristic neurobehavioral profile	[16, 25, 98, 99, 177]
Pallister-Killian syndrome	Tetrasomy 12p	Multiple patient reports	Cortical atrophy, delayed myelination	Severe cognitive impairment	[91, 94, 95]
Duplication 15q syndrome	Maternal duplication 15q11q13	~20%		Variable LGS; autistic features	[25, 93, 178]
Miller-Dieker syndrome	Deletion 17p13 (deletion of LIS1)	High	LIS, mild CBVH	LGS common, severe cognitive impairment	[57, 89]
Down syndrome	Trisomy 21	~5%	CBLH reported	Variable subsequent epilepsy, LGS; cognitive impairment, autistic features common	[87, 88, 90, 92]
Ie. Syndromes with putative association with infantile spasms					
Autosomal recessive severe microcephaly with PNH	ARFGEF2	Single patient report	PNH	Severe cognitive impairment, intractable epilepsy	[110]
Freeman-Sheldon syndrome	MYH3	Patient report preceded genotyping		Distal arthrogyposis	[104]
Mitochondrial encephalomyopathy with elevated methylmalonic acid	SUCLA2	Single patient report	Variable cortical atrophy, delayed myelination	Severe hypotonia, choreoathetosis	[82]
Neurogenic muscle weakness, ataxia, retinitis pigmentosa (NARP)	MT-ATP6	Single pedigree			[81]
Neurofibromatosis type I	NFI	Several patient reports		Variable cognitive impairment	[112, 113]
Schinzel-Giedion syndrome	SETBP1	Multiple patient reports	Cortical atrophy, abnormal WM		[105, 107, 108]
Smith-Lemli-Opitz syndrome	DHCR7	Patient reports preceded genotyping		Severe cognitive impairment	[103, 106]
Smith-Magenis syndrome	Deletion 17p11.2	Single patient report		Moderate-severe cognitive impairment, characteristic neurobehavioral profile	[115]
Sotos syndrome	NSD1	Patient reports preceded genotyping			[109]
X-linked PNH	FLNA	Patient reports	PNH	Intractable epilepsy common, variable cognitive impairment	[111]

Table 1b

Genetic classification of infantile spasms with unknown genotype status with key phenotypes.

Clinical Syndrome	Gene or Locus	% with ISS	Brain imaging	Other neurodevelopmental phenotype	Reference(s)
2. Infantile spasms as part of developmental disorder with predisposing genotype unknown					
2a. Prototypic developmental epilepsies					
Developmental disorder with ISS	Unknown	All, by definition	Normal, or non-specific (WM changes, asymmetric LV, atrophy, ACC, CBLH, CBVH)	Developmental disorder that can have subsequent epilepsy, cognitive impairment, autistic features, and/or movement disorder – presumably depending on underlying genotype not yet discovered	Novel category
2b. Recognizable unifying phenotype and clear association with infantile spasms					
Aicardi syndrome	Unknown	High	ACC, HET, PMG-like, CBLH, CBVH	Variable subsequent epilepsy, moderate to severe cognitive impairment, can have autistic features	[117]
Focal cortical dysplasia	Unknown	~7%	Cortical dysplasia	Focal epilepsy common	[121]
Isolated HMEG	Unknown	High	HMEG	Focal epilepsy common	[125, 126]
PEHO and PEHO-like	Unknown	High	Microcephaly, CBLA	Severe cognitive impairment with regression	[119, 120]
2c. Metabolic abnormalities					
Mitochondrial dysfunction	Unknown	10–20%	Cortical atrophy, infarct, CBLA, BGTH increased signal		[130–133]
Neonatal hypoglycemia	Unknown	Multiple patient reports			[134]
Pyridoxine-dependent/responsive epilepsies	Unknown (not ALDH7A1)	~10%	Cortical atrophy, CBLA		[128, 129]
2d. Extrinsic injury pattern					
Perinatal stroke or other CNS hypoxic event	Unknown	Unknown	Porencephaly, some PMG, abnormal WM, ischemic changes	Variable rate of intractable epilepsy, dystonia may be present	[139–142]
Post-infectious (TORCH, other viruses, bacterial meningitis)	Unknown	Unknown	Microcephaly, calcifications		[146–148]
Schizencephaly	Unknown (not EMX2)	Unknown	SCH, PMG, ASP-SOD	Variable subsequent epilepsy, often focal	[179]
2e. Recognizable unifying phenotype and putative association with infantile spasms					
Frontal-perisylvian PNH-PMG	Unknown	60%	PNH, PMG		[180]
Hypomelanosis of Ito	Unknown	<10%			[155]

Clinical Syndrome	Gene or Locus	% with ISS	Brain imaging	Other neurodevelopmental phenotype	Reference(s)
MPPH/MCAP	Unknown	30%	MEG, PMG, hydrocephalus, CBTH		[156]
Sebaceous nevus syndrome	Unknown	High	HMEG, ACC, CBVH		[154, 157]

Abbreviations: ACC = agenesis of corpus callosum; ASP-SOD = absent septum pellucidum-septo-optic-dysplasia; BG = basal ganglia; BGTH = basal ganglia-thalami; CBLA = cerebellar atrophy; CBLH = diffuse (proportionate vermis and hemispheres) cerebellar hypoplasia; CBTH = cerebellar tonsillar herniation; CBVH = cerebellar vermis hypoplasia; CC = corpus callosum; DEND = developmental delay, epilepsy, and neonatal diabetes; EIEE = early infantile epileptic encephalopathy (aka Ohatahara syndrome); EME = early myoclonic encephalopathy; HET = heterotopia; HMEG = hemimegalencephaly; LGS = Lennox-Gastaut syndrome; LIS = lissencephaly; LV = lateral ventricles; MEG = megalencephaly; MMA = methylmalonic aciduria; MSUD = maple syrup urine disease; MPPH/MCAP = megalencephaly perisylvian polymicrogyria with postaxial polydactyly and hydrocephalus/macrocephaly capillary malformation syndrome; NKH = nonketotic hyperglycinemia; PA = propionic aciduria; PKU = phenylketonuria; PMG = polymicrogyria; PNH = periventricular nodular heterotopia; SCH = schizencephaly; WM = white matter

Table 2

Biologic classification of infantile spasms. Genes are organized into groups by Gene Ontology molecular function and roles in or effect on central nervous system development.

Group	Neurodevelopmental phenotype besides ISS	Gene(s)	GO Molecular Function	Role in/Effect on CNS development	References
A	<ol style="list-style-type: none"> 1 Autistic features 2 Movement disorder 3 Severe cognitive impairment 	ARX FOXG1 MEF2C	Transcription factors	<ol style="list-style-type: none"> 1 Dorsal-ventral differentiation (FOXG1) 2 Ventral NPC proliferation 3 GABAergic iN differentiation (ARX) 4 GABAergic iN migration (ARX) 5 Synapse function (secondary effect) 	[181–184]
B1	<ol style="list-style-type: none"> 1 Severe brain malformation 2 Severe cognitive impairment 3 Intractable epilepsy 	DCX PAFAH1B1/LISI TUBA1A	Binding	<ol style="list-style-type: none"> 1 Dorsal NPC proliferation 2 GABAergic iN migration 3 IPC proliferation 4 Glutaminergic N migration 5 Axonogenesis 6 Synaptogenesis (secondary effect) 	[61, 185–189]
B2	<ol style="list-style-type: none"> 1 Brain malformations of TSC 2 Severe cognitive impairment 3 Autism 4 Intractable epilepsy 	TSC1 TSC2	Signal transduction	<ol style="list-style-type: none"> 1 Dorsal NPC proliferation 2 IPC proliferation 3 Glutaminergic N migration 4 Axonogenesis 5 Synaptogenesis 	[190, 191]
C1	<ol style="list-style-type: none"> 1 Metabolic disease 2 Variable cognitive impairment 3 Variable subsequent epilepsy 	GLDC PAH	Binding, catalytic activity	<ol style="list-style-type: none"> 1 Neuronal and non-neuronal cell metabolism 2 Synapse function (secondary effect) 	[192, 193]
C2	<ol style="list-style-type: none"> 1 Metabolic disease 2 Intractable epilepsy 	ATP7A KCNJ11	Transporter, catalytic activity	<ol style="list-style-type: none"> 1 Synaptogenesis 	[194–196]
D	<ol style="list-style-type: none"> 1 Intractable epilepsy 2 Severe cognitive impairment 	GRIN1 GRIN2A MAGI2 SPTAN1 STXBPI	Binding	<ol style="list-style-type: none"> 1 Synaptogenesis 	[19, 22, 24, 55, 197, 198]

Group	Neurodevelopmental phenotype besides ISS	Gene(s)	GO Molecular Function	Role in/Effect on CNS development	References
E	<ol style="list-style-type: none"> 1 Intractable epilepsy 2 Retinitis 	SLC25A22	Transporter	<ol style="list-style-type: none"> 1 Synapse function (secondary effect) 	[23]

Abbreviations: iN = interneurons; IPC = intermediate progenitor cells; N = neurons; NPC = neuronal progenitor cells