REVIEW

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Autism spectrum disorder and epileptic encephalopathy: common causes, many questions

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Abstract

Epileptic encephalopathies represent a particularly severe form of epilepsy, associated with cognitive and behavioral deficits, including impaired social-communication and restricted, repetitive behaviors that are the hallmarks of autism spectrum disorder (ASD). With the advent of next-generation sequencing, the genetic landscape of epileptic encephalopathies is growing and demonstrates overlap with genes separately implicated in ASD. However, many questions remain about this connection, including whether epileptiform activity itself contributes to the development of ASD symptomatology. In this review, we compiled a database of genes associated with both epileptic encephalopathy and ASD, limiting our purview to Mendelian disorders not including inborn errors of metabolism, and we focused on the connection between ASD and epileptic encephalopathy rather than epilepsy broadly. Our review has four goals: to (1) discuss the overlapping presentations of ASD and monogenic epileptic encephalopathies; (2) examine the impact of the epilepsy itself on neurocognitive features, including ASD, in monogenic epileptic encephalopathies; (3) outline many of the genetic causes responsible for both ASD and epileptic encephalopathy; (4) provide an illustrative example of a final common pathway that may be implicated in both ASD and epileptic encephalopathy. We demonstrate that autistic features are a common association with monogenic epileptic encephalopathies. Certain epileptic encephalopathy syndromes, like infantile spasms, are especially linked to the development of ASD. The connection between seizures themselves and neurobehavioral deficits in these monogenic encephalopathies remains open to debate. Finally, advances in genetics have revealed many genes that overlap in ties to both ASD and epileptic encephalopathy and that play a role in diverse central nervous system processes. Increased attention to the autistic features of monogenic epileptic encephalopathies is warranted for both researchers and clinicians alike.

Keywords: Autism spectrum disorder, Epileptic encephalopathy, Mendelian disorders

Background

Though there is a well-known and interesting connection between autism spectrum disorder (ASD) and epilepsy, the association between ASD and epileptic encephalopathy is particularly intriguing. ASD is a disorder of neurodevelopment characterized by impaired social communication (abnormalities in social-emotional reciprocity, nonverbal communication used for social interaction, and social relationships) as well as restricted, repetitive interests and behaviors [1]. A significant percentage of children with ASD have co-morbid epilepsy, ranging from 9–22% in some studies [2, 3], encompassing a wide range of clinical severity. One of the most severe forms is epileptic encephalopathy, which is characterized by intractable seizures as well as frequent ictal or interictal epileptiform activity that contributes to the cognitive and behavioral phenotype including ASD [4]. This definition is based on evidence that epileptiform itself activity can disrupt brain development through multiple mechanisms such as alteration of neurotransmitter systems and neuronal properties [5]. In some cases, the epilepsy does not have an identified cause, while in others, it is due to an underlying structural/metabolic/genetic etiology (i.e., symptomatic).

When the cause of an epileptic encephalopathy is genetic, it raises the question, what is the nature and extent

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of the contribution of the gene defect, versus the epilepsy itself, towards the neurobehavioral phenotype? In other words, for different genetic epileptic encephalopathies, what is the autism profile, and how does this profile differ from the core deficits seen in individuals with the same genetic defect who have ASD but not epileptic encephalopathy? One approach to understanding the answers to some of these questions is by first examining the set of genetic causes common to both as well as the associated ASD phenotypes.

Indeed, a growing body of evidence suggests that ASD stems from genetic causes [6–8], such as complex inheritance, chromosomal copy number variation, single gene mutations, or epigenetic changes. Autism twin studies reveal significantly higher concordance rates for monozygotic twins (70–90%) compared to corresponding rates for dizygotic twins (0–10%) [9, 10], while family studies indicate that a child has a much higher risk of developing ASD, compared to the population prevalence, if there is a sibling in the family who is already affected [11]. Moreover, siblings and parents of affected probands have a greater likelihood of exhibiting autistic features strikingly similar to, but milder than, the social and communicative deficits seen in children with ASD [12, 13]. A subset of individuals with ASD have copy number variations (CNVs) affecting gene clusters implicated in neurodevelopment, such as 16p11 microdeletion/microduplication [14], 15q11 duplication [15], and many others [16]. Finally, there is evidence arguing that de novo mutations play a much greater role in ASD than previously expected. Statistical analysis of ASD family data suggests that sporadic autism may stem in part from parental germline mutations targeting any of a number of important loci [17]. These genes are responsible for many fundamental central nervous system (CNS) processes, including synaptic transmission and neuronal plasticity [18].

As with ASD, the genetic landscape of epileptic encephalopathy is expanding. Previous efforts have carefully characterized the phenotype of known genetic disorders that lead to epileptic encephalopathy, such as *CDKL5-*, *SCN1A-*, and *STXBP1*-related disorders. With next-generation sequencing approaches focusing on various epileptic encephalopathy syndromes, such as Lennox–Gastaut syndrome (LGS) and infantile spasms (IS), researchers have identified likely pathogenic variants in numerous other genes that are statistically associated with the underlying phenotype [19, 20]. Disruption to any one of these genes implicated in epileptic encephalopathy may have neurodevelopmental consequences that extend beyond epileptogenesis, influencing the realm of cognition and behavior.

In order to learn more about these causes, we compiled a database of genes associated with both epileptic encephalopathy and ASD. We limited our purview to Mendelian disorders not including inborn errors of metabolism, and

we focused on the connection between ASD and epileptic encephalopathy rather than epilepsy broadly, which is the subject of several existing reviews [21, 22].

Specifically, starting with a list of genes implicated in epileptic encephalopathy [23], we searched Pubmed and the Simons Foundation Autism Research Initiative (SFARI) gene (https://gene.sfari.org). For each gene of interest, when searching Pubmed, we used the query, "([gene symbol] AND autism) OR ([gene symbol] AND ASD)"; when searching SFARI Gene, we searched for the gene symbol. From the search results, we reviewed each article and extracted clinical information from it if it demonstrated pathogenic or likely pathogenic variant(s) affecting the gene of interest underlying clinical presentations of ASD and epileptic encephalopathy. Simultaneously, we collected information from studies that demonstrated the presence of pathogenic or likely pathogenic variants affecting the gene of interest underlying clinical presentations of ASD (regardless of other features such as epileptic encephalopathy). Regarding genetic variants, we included cases involving intragenic variants as well as those with CNVs that affected only the gene of interest. Regarding the description of ASD, we included studies that used the following terminology: "autistic features," "autistic-like features," "autism-like behavior," "autistic disorder," "autism," and "autism spectrum disorder". If we were unclear how the study authors defined the presence of ASD or autistic features, we surrounded their terminology in quotation marks; otherwise, we specified the basis for the diagnosis. Regarding the description of epileptic encephalopathy, we included studies that explicitly characterized patients having an "epileptic encephalopathy" or that delineated the presence of a known epileptic encephalopathy syndrome, such as LGS or IS. If the patient had "intractable epilepsy," then we reviewed the EEG description for features consistent with an epileptic encephalopathy.

Using this data, our review will cover four aims. The first aim is to discuss the overlapping presentations of ASD and monogenic epileptic encephalopathies. The second aim is to examine the impact of the epilepsy itself on neurocognitive features, including ASD, in monogenic epileptic encephalopathies. The third aim is to outline many of the genetic causes responsible for both ASD and epileptic encephalopathy. The final aim is to provide an illustrative example of a final common pathway that may be implicated in both ASD and epileptic encephalopathy.

Overview of monogenic epileptic encephalopathies

Monogenic epileptic encephalopathies encompass several known epilepsy syndromes characterized by generally severe presentations with varying ages of onset and typical electrographic findings. Some of these syndromes

present in the newborn period and respond poorly to treatments; examples include early-onset epileptic encephalopathy, early infantile epileptic encephalopathy, early myoclonic encephalopathy, and epilepsy of infancy with migrating focal seizures. Others, such as IS, Dravet syndrome (DS), and epilepsy with myoclonic-astatic seizures, lead to seizures later in infancy [23]. LGS is defined by the presence of multiple seizure types that emerge between 1–8 years of age [24]. Epilepsy-aphasia spectrum, which contains Landau-Kleffner syndrome (LKS) and continuous spike-wave discharges in slow wave sleep syndrome (CSWSS), has the notable feature of developmental regression [25]. A multitude of single gene defects are associated with different phenotypic classifications of epileptic encephalopathy, reflecting the heterogeneity of this group as a whole [23].

ASD profile across monogenic epileptic encephalopathies

ASD prevalence

Among the different genetic causes of epileptic encephalopathy, the prevalence of ASD features is not completely known, but it reaches high levels in some specific instances (Additional file 1: Table S1). Out of the disorders where we can calculate prevalence, the lowest prevalence (6%) occurs in *GRIN2A*-related disorders, which disrupt the N-methyl-D-aspartate (NMDA) receptor, critical for learning and memory (http://www.ncbi.nlm.nih.gov/gene/2903), resulting in epilepsy-aphasia spectrum. Out of 36 patients from 16 families with epileptic aphasia spectrum due to *GRIN2A* alterations, two non-related individuals had "autistic features" and CSWSS. One of the two had global developmental delay without regression; the other had a normal initial developmental period followed by global regression with predominant effects on language [26]. In contrast to *GRIN2A*-related disorders, epileptic encephalopathies associated with mutations in *CDKL5* (encoding cyclin-dependent kinase-like 5), *SCN1A* (encoding sodium voltage-gated channel alpha subunit 1), and *SLC6A1* (encoding GABA transporter 1, which enables GABA reuptake from the synaptic cleft) have a high co-occurrence of ASD features. In one case series of 10 patients with *CDKL5* mutations, all (100%) patients had "autistic features" in addition to epilepsy, though the cohort was enriched for patients with early-onset epileptic encephalopathy and/or a clinical diagnosis of Rett syndrome with negative *MECP2* sequencing [27]. Out of 15 patients with DS secondary to mutations in *SCN1A*, 11 (or 73%) had a diagnosis of ASD based on Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria, mild-severe intellectual disability (ID), and various seizure types [28]. In a cohort of 7 patients with *SLC6A1* variants underlying myoclonic-atonic epilepsy, 5 (71%) had "autistic features," mild-severe ID (along with regression in 2 individuals), and

a full spectrum of seizure types [29]. Other disorders with relatively high rates of ASD features alongside epileptic encephalopathy include *HCN1*-related epilepsy (67% [30]) and *SIK1*-related epilepsy (50% [31]). *HCN1* mutations affect hyperpolarization-activated, cyclic nucleotide-gated (HCN) channels which regulate pacemaker currents in neurons, resulting in an early infantile epileptic encephalopathy with characteristics of DS initially followed later by the emergence of atypical absences, ID, and ASD features [30]. Defects in salt-inducible kinase 1 (*SIK1*), encoding a serine/threonine protein kinase implicated in signal transduction, cause a spectrum of epileptic encephalopathies including early myoclonic encephalopathy, IS, and Ohtahara syndrome (OS) [31].

Of note, these ASD prevalence numbers are based on descriptive case series comprising at least five patients with variants in the gene of interest who have epileptic encephalopathy. As a result, there is insufficient data to calculate ASD prevalence rates for all the genes in Additional file 1: Table S1. For a number of genes implicated in epileptic encephalopathy, future studies may provide more detailed associations with ASD features. Moreover, these numbers represent estimates rather than true prevalence rates because the primary emphasis of the source studies is not necessarily to characterize the ASD phenotype, which leads to indirect terminology such as "autistic features" rather than detailed accounts of formal ASD evaluations. Methodological limitations notwithstanding, there is ample evidence to suggest that within monogenic epileptic encephalopathies, a substantial percentage of patients may be affected by ASD characteristics.

ASD features

Across monogenic epileptic encephalopathies, actual descriptions of core ASD features are sparse, but there are descriptions of various repetitive behaviors (see Additional file 1: Table S1). The spectrum of repetitive behaviors includes repetitive movements with a lower order cognitive component (such as motor stereotypies and self-injurious behavior [SIB]) as well as behaviors with a higher order cognitive component (such as obsessions and perseverations). In patients with epileptic encephalopathy and features of ASD, motor stereotypies are specifically noted in disorders involving the following genes: *CDKL5* (hand flapping) [32], *HCN1* [30], *IQSEC2* (hand flapping) [33], *MEF2C* (hand wringing) [34], *NRXN1* (body rocking) [35], *PCDH19* (hand flapping, hand mouthing, and spinning) [36], *SIK1* (hand flapping) [31], *SLC35A2* (head and hand stereotypies) [37], *SLC6A1* [29], and *STXBP1* (hand flapping and stereotyped hand washing) [38, 39]. Similarly, SIB occurs in *CDKL5*-related disorders (hand biting) [32], *IQSEC2*-related disorders [33], *PCDH19*-related disorders [36], and *SIK1*-related disorders (head banging and biting) [31], while obsessive/

perseverative behaviors are associated with *PCDH19*-related disorders [36] and *SCN8A*-related disorders [40]. Though generally speaking the data is too limited to define an overarching ASD profile across multiple monogenic epileptic encephalopathies, description of different types of repetitive behaviors is certainly noteworthy.

Related neurodevelopmental dysfunction

Defects in genes associated with epileptic encephalopathy and ASD can result in neurodevelopmental dysfunction beyond these two phenotypes. Attention-deficit hyperactivity disorder (ADHD)-like clinical characteristics can exist in individuals with ASD and epileptic encephalopathy who have alterations in *CHD2* [41], *GRIN2A* [26], *PCDH19* [36, 42], *SLC6A1* [29], and *STXBP1* [43]. Interestingly, some epileptic encephalopathy and ASD genes are separately implicated in psychiatric presentations: variants in *KCNQ2* [44, 45] and *KCNQ3* [46] may influence susceptibility to bipolar disorder (BPD), while alterations affecting *ERBB4* [47], *GRIN2A* [48], *GRIN2B* [49], *NRXN1* [49–54], *PCDH19* [55], *SCN2A* [56], *SLC12A5* [57], and *TCF4* [58, 59] may mediate risk for schizophrenia (SCZ). In addition, there is evidence to suggest that deletions involving *NRXN1* are implicated in Tourette syndrome [60], and variants in *GRIN2B* are associated with obsessive-compulsive disorder (OCD) [61]. ID is perhaps the most important factor to consider. Collectively, all of the genes underlying presentations of epileptic encephalopathy and ASD are associated with the full spectrum of ID.

It is intriguing that the same gene implicated in severe, intractable epilepsy may have other (and sometimes concomitant) childhood presentations which are more cognitive/behavioral in nature, such as ASD and ID, as well as adult-onset presentations which are more psychiatric in nature. This spectrum may reflect variable expressivity, which is commonly seen in epilepsy genetics [62]. Another possibility is that the type of variant may influence the disease course. Some genetic changes may confer susceptibility to a certain condition (e.g., SCZ), requiring interaction with other genetic and environmental factors before leading to the condition, while other variants may have a more direct impact on CNS pathology.

Given that there is considerable overlap between ID and ASD [63], one may argue that the ASD features seen in epileptic encephalopathy are not necessarily related to epilepsy but rather reflect the presence of ID. It could be that a genetic defect leads to severe to profound ID, which may be a substantial contributor to the appearance of an ASD-like phenotype, more so than either the genetic defect or epilepsy alone. In fact, with increasing ID severity, it becomes progressively difficult to disentangle a diagnosis of ASD from the social-communication deficits commensurate with a patient's developmental age. Repetitive behaviors can occur with severe to profound ID,

without necessarily reflecting the presence of ASD. However, when ID is severe to profound, one can acknowledge the presence of autism features but be careful about labeling a diagnosis of ASD. Moreover, there are also cases of mild and moderate ID in some monogenic epileptic encephalopathies, so one cannot discount completely the development of ASD in monogenic epileptic encephalopathies. In the following section, we will discuss the contribution of epilepsy to the cognitive/behavioral phenotype above and beyond what one would expect from the genetic defect alone.

Impact of epilepsy on ASD in monogenic epileptic encephalopathies

Key questions in the debate

Among epileptic encephalopathies, a critical and controversial subject is whether the features of epilepsy independently *worsen* the development of ASD. In other words, in a child with a genetic disorder associated with the presentation of epileptic encephalopathy, it is not clear if the seizures/interictal epileptiform activity serve as a so-called second-hit against an already vulnerable brain predisposed to developing epilepsy and ASD as separate downstream effects of a single gene defect [64]. Relevant to this central debate are the following auxiliary questions:

- Since IS are one of the most catastrophic forms of epilepsy, does their presence herald the onset of ASD related to increasingly disrupted brain function?
- With respect to other seizures types among monogenic epileptic encephalopathies, is seizure severity related to neurocognitive severity?
- Within epileptic encephalopathies associated with ASD, does the age of seizure onset predict neurodevelopmental outcomes? After all, if epileptic activity does in fact exacerbate the neurobehavioral phenotype, then the emergence of seizures at an earlier age—especially during the period of rapid brain growth that takes place in the first 2 years of life [65]—could portend worse outcomes.

In theory, the answers to all of these questions are yes based on the definition of epileptic encephalopathy according to the International League Against Epilepsy (ILEA) [4]; however, in reality, the evidence from clinical studies is mixed.

Infantile spasms and ASD development

In cases of IS—one of the most common causes of epileptic encephalopathy—it is the underlying cause, more so than the spasms themselves, that helps predict the onset of ASD. IS are a distinct epilepsy syndrome with onset less than 1 year of age, appearing as clusters of flexion movements/extension movements/head drops, with a chaotic

high-voltage EEG pattern called hypsarrhythmia (though atypical forms can exist without this pattern) [66]. In a heterogeneous cohort of 95 children with unprovoked, infantile-onset seizures comprising the basis for a case–control study, the diagnosis of ASD (which defined the cases) was not contingent on a history of IS after adjusting for whether the seizures were symptomatic, but it was associated with symptomatic seizures after adjusting for whether the seizures were IS. In other words, it is the presence of an underlying metabolic/genetic/structural cause, rather than the occurrence of IS per se, that more likely predicts ASD. In this study, ASD evaluation took place at a mean age of 11 years and 2 months, based on (1) meeting a certain cutoff on the Social Communication Questionnaire (SCQ), (2) subsequent evaluation with the Autism Diagnostic Interview-Revised (ADI-R), Autism Diagnostic Observation Schedule (ADOS), and Childhood Autism Rating Scale (CARS) suggesting impairments in the domains of social interaction, communication, and stereotyped/repetitive behavior in accordance with International Classification of Diseases-Tenth Revision (ICD-10) criteria. Out of the 13 cases (those with ASD), 6 had IS and 4 had a mental age < 24 months; out of the 82 controls (those without ASD), 11 had IS and 8 had a mental age < 24 months. In this study, ID and ASD were closely linked, as there was only one subject with ASD who did not have ID. However, when the analysis was limited to patients with a mental age >24 months, the odds ratio for ASD risk due to symptomatic seizures (and for ASD risk due to IS) actually increased, suggesting that ID severity was not the major driving force for ASD risk [67]. Likewise, out of the nine patients with IS who underwent a prospective treatment study involving either ACTH or vigabatrin with crossover for non-responders, the three individuals who developed ASD (based on the ADOS) all had symptomatic epilepsy. Two of the three were severely delayed in cognitive development on follow-up evaluations based on the Bayley Scales of Infant Development (the cognitive status of the third is unclear from the data). The other six patients in the cohort who did not develop ASD had, upon follow up assessment, variable cognitive outcomes, ranging from normal to significantly delayed development [68]. In a retrospective cohort of individuals with tuberous sclerosis complex (TSC)—a disorder of mTOR signaling caused by mutations in *TSC1* and *TSC2* and associated with IS and high prevalence rates of ASD (36%) [69]—IS occurrence predicted ASD development as determined by ICD-10 criteria in conjunction with review of ADI-R and ADOS testing [70]. However, in this study in the TSC population, not all individuals with IS developed ASD, and not all individuals with ASD had preceding IS [70]. Finally, in 90 children with epilepsy and ID stratified by ASD diagnosis (based on DSM-III-R and DSM-IV criteria), the presence of IS was

not a distinguishing factor [71]. Taken together, these findings suggest that, from a mechanistic standpoint, ASD and IS may be two separate end-results of a common CNS defect.

Timely treatment of spasms does not necessarily impact the development of ASD. Among infants with new-onset IS treated rapidly with a standardized protocol and followed longitudinally, the incidence of ASD based on ADOS testing at >30 months was 23% [72]. The prevalence of ASD is 1.5% in the general population [73] and 9–35% in IS [67, 74–77], so this incidence of 23% falls within expected range, suggesting that early treatment of the spasms does not diminish ASD risk.

Children with IS who develop ASD may have persistent epileptiform abnormalities despite treatment of spasms. Such abnormalities can occur in the frontal [72] and temporal regions [72, 75]. Likewise, positron emission tomography (PET) studies show hypometabolism in these areas, in addition to the parietal lobe, in patients with IS who developed ASD [74, 78]. In some cases, epileptiform activity may precede onset of IS or epilepsy, such as with TSC [79, 80]. The time gap between detection of EEG abnormalities and onset of seizures or spasms in infants with TSC creates a window of opportunity for possible intervention. Indeed, there is an ongoing randomized, placebo-controlled clinical trial (Preventing Epilepsy Using Vigabatrin In Infants With Tuberous Sclerosis Complex; https://clinicaltrials.gov/ct2/show/NCT02849457) that will enroll infants with TSC in order to determine whether administration of vigabatrin before clinical seizure onset prevents epilepsy and improves neurobehavioral outcomes including ADOS scores. This treatment strategy may serve as a model for monogenic epileptic encephalopathies where ASD can be a downstream feature. Hence, in IS, while treatment of the spasms themselves may not prevent the development of ASD, treatment directed toward the preceding epileptic activity holds promise for altering this trajectory.

Seizure severity versus neurocognitive severity

In cases of epileptic encephalopathy besides IS, epilepsy severity does not necessarily impact neurobehavioral outcomes. *STXBP1*-related encephalopathy is one example. *STXBP1* encodes syntaxin-binding protein 1, which helps regulate synaptic vesicle release [81]. Defects in this gene result in an epileptic encephalopathy [82] accompanied by ID, motor abnormalities (hypotonia, ataxia, tremor, spasticity, dyskinesia, dystonia), and ASD features [43]. Stamberger et al. [43] analyzed the relationship between cognitive outcomes and epilepsy severity in 147 patients with *STXBP1* encephalopathy, 95% of whom had epilepsy (including 21% who

presented with OS, 9.5% who presented with West syndrome (WS), and 53% who presented as early-onset epilepsy and encephalopathy). The authors did not find a statistically significant relationship between level of cognitive impairment and either age at seizure onset or length of time from seizure onset to seizure freedom (ASD severity was not a reported outcome), though they did acknowledge that the study was underpowered. Furthermore, in this analysis, as noted above, about half the cases were early-onset epilepsy and encephalopathy, which is a different entity from epileptic encephalopathy [43].

DS is another example where cognitive outcomes do not necessarily reflect seizure severity. DS is characterized by myoclonic seizures in infancy, often associated with fever, that evolve into other seizure types [83]. Mutations in *SCN1A* (sodium voltage-gated channel alpha subunit 1)—which are implicated in sporadic cases of ASD [84]—are a common cause of DS [85]. In a prospective cohort of 67 patients with DS, developmental/intelligence quotient (DQ/IQ) did not correlate with measures of epilepsy severity [86]. Similar findings were present in a retrospective study of 21 patients with DS, ages 6–10 years [87]. These findings as a whole suggest that among epileptic encephalopathies, the underlying genetic defect may be the predominant contribution to the clinical presentation, overshadowing the possible impact of epilepsy severity on the cognitive phenotype. Of note, among monogenic epileptic encephalopathies, there has been a scarcity of studies that have contrasted the ASD phenotype to idiopathic ASD, especially in relation to epilepsy severity. Such studies will be essential to help delineate whether epilepsy severity impacts the ASD profile.

Age of seizure onset related to ASD development

In contrast, the timing of ASD development—commonly after seizure onset in monogenic epileptic encephalopathies, most strikingly when regression is involved—argues *for* the notion that seizure activity may influence ASD emergence. One example is LKS, which results in language regression, characteristically in conjunction with temporal lobe epileptiform activity [25], and is linked to defects in *GRIN2A* [26, 88]. Along with regression and epileptic encephalopathy, features of ASD can occur in LKS [89]. Because the areas affected by epileptiform activity play a role in language, a prevailing thought is that the cognitive difficulties seen in this disorder are a direct consequence of electrographic changes. However, this hypothesis remains the subject of debate. It should be noted that the language regression associated with LKS is different from that of autistic regression. The former is characterized by relatively typical early development followed by language regression usually between 3–9 years of age [89]. In contrast, the latter is characterized by loss of language and social skills usually before 3 years of

age, and early development may be typical or show subtle abnormalities [90].

Disruptions in other ion channel genes, including *SCN2A* and *SCN8A*, may also result in epileptic encephalopathy and developmental regression before emergence of ASD symptoms. One report describes a 29-year-old woman with a de novo nonsense variant in *SCN2A* who developed intractable epilepsy and cognitive decline starting with seizures at 1 year and 7 months of age as well as "autistic" and hyperkinetic features at 2 years of age [91]. *SCN2A* encodes one of the alpha subunits of the voltage-gated sodium channel and plays an important role in action potential generation and propagation (http://www.ncbi.nlm.nih.gov/gene/6326). Another report characterizes a female with a de novo *SCN8A* missense variant who developed generalized seizures at 6 months of age, followed by epileptic spasms at 4 years of age. Over the following 1–2 years, her language and socialization skills deteriorated while obsessive-compulsive and repetitive behaviors emerged, culminating in a diagnosis of ASD at 5 years of age [40].

Even without regression, other monogenic causes of epileptic encephalopathy also lead to ASD symptoms around the same time as, or after, seizure onset. *SCN2A* is not always associated with regression. A 10-year-old boy with a de novo splice site *SCN2A* variant had a presentation of ID, intractable epilepsy, hypotonia, intermittent ataxia, and cerebral/cerebellar brain atrophy. He developed seizures at 3 years of age, around the same time as his diagnosis of "autism" [92]. Out of six individuals with epileptic encephalopathies (early myoclonic encephalopathy, OS, and IS) due to *SIK1* variants, three developed features of ASD in the context of experiencing IS between 2–4 months of age [31]. In some instances, autism features can emerge in the wake of plateaued development and seizure onset, as is the case with *SCL35A2*-related disorders [37]. Overall, the data suggests that among these disorders, there could be a temporal relationship between seizure onset and ASD symptoms. However, the causative nature of this relationship is not fully clear, and larger, carefully phenotyped cohorts are necessary for further investigation. An alternative possibility is that in some cases, epileptic encephalopathy may indeed be contributing to emergence of ASD symptoms, while in others, epileptic encephalopathy and ASD may be two separate outcomes resulting from final common disrupted pathways due to the underlying gene defect. This mechanistic heterogeneity might reflect the vast range of cellular pathways implicated in different monogenic epileptic encephalopathies.

Furthermore, as discussed previously, it can be difficult to separate a diagnosis of ASD from severe ID as was the case for some of these examples that described level of cognitive impairment. Hence, one must be careful to

characterize these as autistic features in the absence of careful evaluations of social-communication that take into account cognitive status.

Genetic overlap between ASD and epileptic encephalopathy

Studies linking epileptic encephalopathy genes to ASD

Despite uncertainty surrounding whether epileptic encephalopathy in and of itself drives ASD development, what is clear is that there is a rich genetic overlap between the two entities. Out of the 62 genes implicated in the development of epileptic encephalopathy (selected from [23]), 34 also serve as risk factors in the pathogenesis of ASD. This gene set includes causes of both idiopathic ASD (where ASD is the primary diagnosis) and syndromic ASD (where ASD exists alongside other clinical features that help define a recognized syndrome). The strongest evidence for ASD association, based on the Simons Foundation Autism Research Initiative Gene Scoring Criteria (https://gene.sfari.org/autdb/GS_Classification.do), comes in the form of full sequencing studies of phenotypically well-defined cohorts of individuals/families with ASD and unrelated controls. Such studies should demonstrate that recurrent pathogenic variants in certain genes occur at a statistically higher frequency in cases compared to controls and segregate with the ASD phenotype in families, if applicable; moreover, findings must be replicable.

Based on these criteria, *SCN2A*—commonly linked to epileptic encephalopathy—has the highest level of evidence supporting its role in ASD. It is one of the causes of a number of epileptic encephalopathy syndromes (early-onset epileptic encephalopathy, early infantile epileptic encephalopathy, IS, epilepsy of infancy with migrating focal seizures, and LGS) [23], and affected children can present with severe to profound ID, hypotonia, spasticity, movement disorders, and gastrointestinal symptoms [93]. Moreover, several studies have identified rare, likely pathogenic *SCN2A* variants in idiopathic ASD. Out of 117 multiplex ASD families who underwent *SCN1A*, *SCN2A*, and *SCN3A* sequencing, there was one affected individual with an *SCN2A* variant, which was absent in controls. Based on functional studies demonstrating disrupted calcium-calmodulin binding, this missense variant was characterized as a potential disease causing mutation [94]. In a whole-exome sequencing study of 238 simplex ASD families comparing probands to unaffected controls, de novo nonsense variants in *SCN2A* occurred in two of the probands, neither of whom had a history of seizures [95]. In a large-scale sequencing analysis of coding variants in ASD subjects versus controls involving a TADA (Transmission and De novo Association)-based statistical model, *SCN2A* had a false discovery rate of ≤0.01, suggesting a high likelihood for true association with ASD [96]. Overall, the data is convincing that *SCN2A* leads to neurodevelopmental dysfunction other than epileptic encephalopathy.

Multiple lines of evidence have highlighted the involvement of other epileptic encephalopathy genes, with diverse functions, in ASD (see Additional file 2: Table S2 and Additional file 3: Table S3). We have organized evidence connecting each of these genes to ASD into the following three categories: (1) variant discovery (next-generation sequencing, single nucleotide polymorphism (SNP) association study, and copy number variant analysis) in cohorts where ASD is the primary phenotype; (2) variant discovery (next-generation sequencing) in cohorts with ASD-related neurodevelopmental phenotypes (e.g., epilepsy and ID), revealing genetic findings in a subset of patients who also have ASD; and (3) clinical characterization (case reports/series) of known genetic disorders in patients, some of whom may have ASD as a manifestation of the disease. Focusing on well-defined ASD cohorts, whole-exome or targeted sequencing studies have implicated genes involved in ion channel function (*GABRA1*, *GABRB1*, *GRIN2A*, *KCNQ2*, *KCNQ3*), ion transporter function (*SLC6A1*, *SLC12A5*), transcriptional regulation (*ARX*, *TCF4*), signal transduction (*SIK1*), cell adhesion (*PCDH19*), and DNA replication (*SETBP1*). A small number of SNP and CNV studies have additionally connected ASD to variants in *ERBB4*, *FLNA*, *GABRG2*, and *PLCB1*, while descriptive case series on patients with variants in a specific gene of interest have revealed ASD associations with *CACNA1A*, *GRIN1*, *HCN1*, *IQSEC2*, *SCN8A*, and *SLC35A2*.

An important caveat is that many of the case reports/case series in Additional file 2: Table S2 which referenced ASD defined it poorly or nonspecifically. In these instances, affected individuals did not have a formal diagnosis of ASD based on, for example, DSM criteria. Rather, they had "autistic features" or a label of ASD without a clear indication of diagnostic methodology or further delineation of the behavioral phenotype. Nonetheless, given the relatively rare occurrence of genetic epileptic encephalopathies, these studies are worth noting until larger cohorts of affected patients become available for rigorous neurodevelopmental phenotyping.

Common final pathways shared between ASD and epileptic encephalopathy

Overview

The genetic diversity surrounding monogenic epileptic encephalopathies associated with ASD suggests multiple possible mechanisms for epileptogenesis and cognitive/behavioral disturbance. Collectively, these genes play fundamental roles in human neurobiology, including synapse formation, action potential generation, and neurotransmitter release. It is easy to imagine how disruption to any one of these processes can lead to CNS

dysfunction through independent mechanisms related to the specific gene function. However, in order to explain clinical entities like ASD and epileptic encephalopathy in the context of multiple single-gene etiologies, it may be reasonable to consider that these phenotypes represent the end-product of final common disrupted pathways. Below, we will discuss one such pathway that serves as possible explanations for both ASD and epileptic encephalopathy in the setting of shared monogenic etiologies. This constitutes a salient example rather than an exhaustive list.

Disrupted excitatory inhibitory balance

Features of ASD and epileptic encephalopathy may result from an imbalance between excitatory and inhibitory signaling in the CNS. The list of genes implicated in ASD and epileptic encephalopathy includes several that are involved in the function of ion channels that play important roles in the brain, like voltage-gated sodium channels or γ-aminobutyric acid (GABA) type A (GABA$_A$) receptors. Increased excitatory neurotransmission (especially from sodium channel alterations) and decreased inhibitory neurotransmission (especially from GABA$_A$ receptor alterations) both result in neuronal hyperexcitability, one of the hallmarks of epilepsy [97]. Furthermore, GABAergic interneurons are instrumental in shaping neuronal circuits through various mechanisms, with implications for brain development and neuronal plasticity [98, 99]. Therefore, defects in GABAergic signaling—specifically tilting the excitatory/inhibitory balance towards excitatory signaling—may explain some of the features of ASD [100].

Further evidence for the role of GABAergic signaling in cognition, behavior, and epileptogenesis comes from study of two neurodevelopmental disorders, Prader-Willi syndrome (PWS) and Angelman syndrome (AS). These are disorders that both involve inactivation or deletion of one parent's contribution to chromosome 15q11.2-q13, but they result in different phenotypes because of parent-specific imprinting patterns leaving certain genes epigenetically silenced. AS is characterized by severe to profound ID, epilepsy, and ataxia, while PWS is characterized by mild intellectual disability, behavioral problems, and endocrine abnormalities, among other features. Both feature a relatively high prevalence of ASD [101]. About 5% of cases of AS and 25% of cases of PWS result from uniparental disomy (UPD), while a significantly larger fraction (70%) stem from chromosomal deletions in 15q11.2-q13 [102]. This chromosomal segment contains both imprinted and non-imprinted genes, and among the non-imprinted genes are *GABRA5*, *GABRB3*, and *GABRG3* [103]. PWS and AS patients with chromosome 15q deletions have fewer working copies of these non-imprinted genes compared to PWS

and AS patients with UPD. Interestingly, patients in the former category are also more affected than those in the latter category, with poorer physical growth, more frequent seizures, higher incidence of microcephaly, more ataxia, and lower cognitive skills in the case of AS [104] and more frequent seizures in the case of PWS [105]. Taken together, these findings underscore the crucial role of GABAergic signaling and excitatory-inhibitory balance in neurodevelopmental functioning ranging from seizure threshold to behavior and cognition, which serves as but one illustrative example of final common pathways shared between epilepsy and ASD development.

Conclusions

In summary, there is phenotypic overlap in the presentations of epileptic encephalopathy and ASD. Certain types of epileptic encephalopathy are more commonly associated with development of ASD, including IS. However, the precise relationship between epileptic encephalopathy and ASD remains the subject of continued discovery. Finally, advances in genetics have revealed genes that overlap in ties to both ASD and epileptic encephalopathy. Overall, many unanswered questions remain about the connection between ASD and monogenic epileptic encephalopathies, including how to differentiate severe to profound ID from ASD—a common and well-known challenge across many genetic and non-genetic conditions. Nonetheless, clinicians caring for children with epileptic encephalopathies should be aware of at least the possibility of the emergence of ASD in conjunction with other developmental delays. Given the strong likelihood of developmental impairment associated with monogenic epileptic encephalopathies, developmental surveillance is crucial starting from infancy. In fact, statewide programs providing early intervention services often allow eligibility not only for infants and toddlers with established developmental diagnoses but also for those who have medical and genetic conditions associated with a high risk of future developmental disabilities (though exact statutes may vary from state to state). Epileptologists and other clinicians taking care of patients with epileptic encephalopathies can facilitate referrals to these kinds of services or to developmental pediatricians. If a diagnosis of ASD is made, then early intervention with applied behavioral analysis therapy may be helpful [105].

Additional files

Additional file 1: Table S1. ASD and epilepsy features associated with monogenic epileptic encephalopathies. (DOCX 93 kb)

Additional file 2: Table S2. Evidence linking epileptic encephalopathy genes to ASD. (DOCX 218 kb)

Abbreviations

ADI-R: Autism Diagnostic Interview-Revised; ADOS: Autism Diagnostic Observation Schedule; AS: Angelman syndrome; ASD: Autism spectrum disorder; BPD: Bipolar disorder; CARS: Childhood Autism Rating Scale; CNS: Central nervous system; CNV: Copy number variation; CSWSS: Continuous spike-wave discharges in slow wave sleep syndrome; DQ/IQ: Developmental/intelligence quotient; DS: Dravet syndrome; DSM: Diagnostic and Statistical Manual of Mental Disorders; GABA: γ-Aminobutyric acid; ICD: International Classification of Diseases; ID: Intellectual disability; ILEA: International League Against Epilepsy; IS: Infantile spasms; LGS: Lennox–Gastaut syndrome; LKS: Landau-Kleffner syndrome; OCD: Obsessive-compulsive disorder; OS: Ohtahara syndrome; PET: Positron emission tomography; PWS: Prader-Willi syndrome; SCQ: Social Communication Questionnaire; SCZ: Schizophrenia; SIB: Self-injurious behavior; SNP: Single nucleotide polymorphism; TSC: Tuberous sclerosis complex; WS: West syndrome

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SS wrote the manuscript. MS helped conceptualize and edited the manuscript. Both authors read and approved the final manuscript.

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