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Autism Spectrum Disorder and Epilepsy: disorders with a shared biology

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Abstract

There is an increasing recognition of clinical overlap in patients presenting with epilepsy and autism spectrum disorder (ASD), and a great deal of new information is available regarding the genetic causes of both disorders. Several biological pathways appear to be involved in both disease processes, including gene transcription regulation, cellular growth, synaptic channel function, and maintenance of synaptic structure. We review several genetic disorders where ASD and epilepsy frequently co-occur, and we discuss the screening tools available to practicing neurologists and epileptologists to help determine which patients should be referred for formal ASD diagnostic evaluation. Finally, we make recommendations regarding the workflow of genetic diagnostic testing available for children with both ASD and epilepsy.

Keywords

ASD; autism; epilepsy

Introduction

Autism spectrum disorders (ASDs) and epilepsies are both heterogeneous conditions that frequently coexist with other developmental disabilities including developmental delay, intellectual disability and behavioral impairments [1]. The co-occurrence of ASDs and epilepsies has long been recognized [2–5]. With the discovery of overlapping molecular

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causes of both disorders, some have proposed shared etiologic mechanisms [6]. We are just beginning to understand how the two conditions are interconnected.

Identifying these relationships is complicated by the complexity of ASDs and epilepsies, evolving diagnostic criteria, [7] changing classification schemas, [8,9] and a culture among researchers within each disorder that may discourage investigation of shared mechanisms. This separation of inquiry of ASDs from epilepsies is seen at the level of National Institutes of Health, where proposals addressing ASD are traditionally reviewed by the National Institute of Mental Health or Child Health and Development while those addressing epilepsy are reviewed by the National Institute of Neurological Disorders and Stroke, and proposals addressing both may struggle to find a receptive study section. Still, a number of recent advances in our biological knowledge underline the value of screening for the coexistence of these common developmental disorders [10].

Biology

Knowledge of genomic copy number and single gene causes of both ASDs and epilepsy [11,12,13] allows us to identify the biologic processes perturbed in these developmental disorders. As will be explored here, processes with shared involvement in ASDs and epilepsies include gene transcriptional regulation, cellular growth and proliferation, and synapse development, stability, and function (Figure 1).

Case definitions of ASD

Autism spectrum disorders (ASDs) are characterized by two core features: (1) deficits in social behaviors and communication and (2) restricted interests and repetitive patterns of behavior [7]. The overall prevalence of ASD is estimated to be 14.7 per 1,000 (1 in 68) children, varying from 5.7 to 21.9 per 1,000 among the CDC-established Autism and Developmental Disabilities Monitoring (ADDM) network sites [14]. ASDs typically manifest before the age of 3 years and are persistent. The heterogeneous phenotypic profile of ASDs has made categorization difficult. The Diagnostic and Statistical Manual of Mental Disorders, 5th edition [7] substantially revised previous classification systems by merging formerly separate diagnostic entities (autistic disorder, Asperger's disorder, pervasive developmental disorder not otherwise specified) into a single dimension, ASD. This approach may help identify subgroups based on quantity or quality of symptoms or patterns of abnormalities [15]. Additionally, Social Communication Disorder has been added as a new diagnostic category that describes patients with deficits in social communication without demonstrating repetitive behaviors or restricted interests [7].

Numerous primary genetic causes for ASD have been identified [16]. However, historical environmental associations such as fetal valproate and thalidomide exposure suggest multifactorial etiologies may play a role [17,18,19]. The prevalence of epilepsy among children with ASD and vice versa remains unclear. An approximate 16% co-occurrence of epilepsy and ASD was reported based on ADDM network data from 2002 [20]. Other reports estimate that approximately 20–25% children with ASD have epilepsy [21]. A recent population-based study found 44% of children with ASD received a subsequent diagnosis of epilepsy, and 54% of children with epilepsy received a subsequent diagnosis of ASD [22].

Age of onset for epilepsy in ASD is bimodally distributed, with a peak in early childhood (age 2–5 years) and a larger peak in adolescence [23]. Intellectual disability (ID) is a risk factor for epilepsy in ASD: the rate of epilepsy is approximately three times greater in people who have both ASD and ID than in people who have ASD but not ID [24]. Older age, female sex, poor language abilities, and history of regression are most commonly reported as other possible risk factors but are not clinically predictive once adjusted for IQ [25].

Case definition of epilepsy and epilepsy classifications

Epilepsy is defined as the occurrence of more than two unprovoked seizures due to sudden, disorderly, and excessive neuronal discharge [26]. The classification of epilepsies has undergone a change in recent years, moving away from broad schema unrelated to underlying biology (the classical *idiopathic*, *cryptogenic*, *symptomatic* terms) [8, 27], with the recognition that all epilepsy is likely *symptomatic* of something. More recent efforts have focused on linking classification to the underlying genetic neurobiology, as these mechanisms are discovered [28]. It is likely that the classifications of epilepsy will undergo further revision as these mechanisms are further discerned.

Genetic syndromes in which ASD and epilepsy co-occur

Several conditions caused by genomic copy number variation or mutations in single genes have been associated with both ASD and epilepsy, many of which are summarized in Table 1 and reviewed briefly below.

Genomic Disorders

Duplication of maternally inherited chromosome 15q11-q13 syndrome

Reciprocal duplications of the maternally inherited copy of chromosome 15q11-q13 region are the most frequently reported chromosomal aberration in individuals with ASDs (0.5 – 3%) [29]. Deletions spanning this region represent the most common mechanism for Prader–Willi and Angelman syndromes. Descriptions of the neurobehavioral phenotype associated with duplications of maternal 15q11q13 have emphasized the variability in presentation and frequent co-occurrence of intellectual disability [20].

Patients with duplications of maternal 15q11q13 had a high incidence of infantile spasms [31]. Lennox-Gastaut syndrome has been reported as well [32]. The location of several genes encoding GABA receptor subunits within the duplicated 15q11q13 region (*GABRA5, GABRB3, GABRG3*) has led to the hypothesis that dysregulation of inhibitory synapses mediates pathogenesis of the epilepsy and ASD phenotypes seen in this disorder [33].

Trisomy 21 (Down Syndrome)

Down Syndrome (DS) results from an extra copy of chromosome 21. DS is characterized by distinct facial dysmorphisms, intellectual disability and associated congenital anomalies. While individuals with DS were generally described as friendly and socially inclined [34], it has been estimated that 5–9% of people with DS meet criteria for ASD [35–38]. Diagnosing

ASD in children with DS remains a challenge due to comorbid intellectual disability. In a comparison between twenty children with trisomy 21 with and without ASD, those with ASD were found to have significantly more impaired language abilities, adaptive behavior and cognition [39]. Children with co-occurring DS and ASD may have an overall decrease in brain function as well as an increased risk for seizures [39].

The prevalence of epilepsy in patients with DS is approximately 8–13% [40,41]. Multiple seizure types have been reported in patients with DS, including progressive myoclonic epilepsy associated with dementia [42], infantile spasms [43], and Lennox-Gastaut syndrome with reflex seizures [44]. Reports of developmental outcome of children with a history of infantile spasms and DS has been mixed, with some reporting better than expected outcome [45] and others noting high prevalence of ASDs and less favorable outcome [46]. The reason for such variability in epilepsy and developmental outcome in children with trisomy 21 is unclear.

The effects of DS on brain development remain complicated and uncertain but there is an increased interest in the role of dual-specificity tyrosine phosphorylation-regulated kinase, *DYRK1A*, activity [47]. In mouse models, *Dyrk1A* has been shown to play important roles in cell cycle control [48] and synaptic plasticity [49]. Additionally, research whole exome sequencing has identified mutations in *DYRK1A* in several children with ASD and microcephaly [16].

Other copy number variants (CNV)

Certain pathogenic copy number variants are highly associated with ASD and epilepsy [12,13]. Most recent data support a model in which the severity of the neurodevelopmental disease increases with increasing genomic region affected [50]. Deletions of 15q11.2, 16p11.2 and duplication of 16p13.11 have been detected with high frequency in individuals with ASD [51]. However, the penetrance of these regions of genomic variation varies and the characterization of the pathogenicity of these events is, at times, a challenge [11]. It is not uncommon for a deletion in one of these regions to be inherited from normal parents or to be present in an unaffected or mildly affected sibling. A possible mechanism for ASD/epilepsy associated with these CNVs is a second mutation on the non-deleted allele [52].

Phelan-McDermid syndrome / SHANK3 deletion

Deletion of 22q13.3 containing the *SHANK3* gene has been associated with early hypotonia, developmental and speech delay, autism-like behaviors, lymphedema, and dysmorphic features [53,54]. Other complications include gastroesophageal reflux, kidney problems, and skin rashes [54]. The prevalence of epilepsy in patients with 22q13.3 deletion is not known. Some have reported a benign course of generalized tonic-clonic or myoclonic seizures with typical EEG features [55]. A larger series found seizures to be three times more common when the *de novo* deletion occurred on the maternally rather than paternally inherited chromosome 22 [54].

SHANK3 encodes a scaffolding protein found in the postsynaptic density, that regulates the expression of metabotropic glutamate receptor 5 (mGluR5) [56]. Shank3 also plays a role in

the regulation of AMPA receptors recycling and synaptic long-term potentiation [57], and interacts with the voltage-gated potassium channel Kvβ2 within the postsynaptic density [58]. Mice deficient in Shank3 display autistic behavior and have abnormalities in striatal synapses and corticostriatal circuits [59,60]. Deletions of *SHANK1* [61] and mutations in *SHANK2* have also been reported in patients with ASD [62].

Single gene disorders

Fragile X syndrome

Fragile X syndrome (FRX) is the most common inherited form of intellectual disability with an estimated prevalence of 1 in 4000 males [63]. FRX occurs when a triplet repeat (CGG) expansion leads to inactivation of the *FMR1* gene resulting in loss of FMRP expression. FMRP is an RNA-binding protein, localizing to dendritic ribosomes and likely plays a role in synaptic remodeling, required for normal learning and memory [64]. Physical features include prominent ears, long face, macrocephaly and macroorchidism. The cognitive profile includes hyperactivity, anxiety, tactile defensiveness, gaze avoidance and socialization difficulties [65]. FRX has been considered the principle monogenic disorder associated with ASD [63,65]. Reciprocal social interaction and adaptive socialization (as measured by ADI-R) were identified as the core autistic behaviors among a study cohort of FRX individuals, irrespective of intellectual disability [63].

Epilepsy is reported in approximately 10–20% of FRX individuals [64]. Seizure patterns in FRX typically resemble benign focal epilepsy of childhood (BFEC). In a review of 13 individuals with FRX and seizures, 10 were reported to have abnormal EEGs and 6 of these EEG studies showed centrotemporal spikes typical of BFEC [64]. Additionally, 23% individuals with FRX without clinical seizures demonstrated centrotemporal spikes on EEG [64]. It has been proposed that a voltage-gated inward current, $I_{mGluR(V)}$, mediates epileptogenesis by activation of the mGluR5 receptor [66]. The induction of $I_{mGluR(V)}$ may lead to global neuronal changes, rather than synapse-specific events [66]. The activation of mGluR5 across multiple synapses in the setting of poor FMRP translational control leads to heightened electrical excitability [66].

Pathogenic expansion and hypermethylation of a CGG triplet repeat in the 5’ untranslated region of *FMR1* results in transcriptional silencing [67,68]. The gene product, FMRP, is an RNA-binding protein [69], and its loss of function in several animal models is associated with a host of downstream effects on neurons. These include dysregulation of NeuroD1 expression in the rat [70], disrupted trans-synaptic signaling in Drosophila [71] and reduction of neuronal long-term potentiation and enhanced long-term depression in zebrafish [72]. In the FRX mouse model, dysregulation of excitatory synaptic formation [73], reduction in expression of specific GABA receptor subunits [74], and N-methyl-D-aspartate (NMDA) receptors [75] have been reported.

Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is a multisystem disorder characterized by hamartomas of the brain, heart, lungs, kidneys and skin and results from mutations in *TSC1* and *TSC2* [76]. Their protein products, hamartin and tuberin respectively, bind together and form a

protein complex involved in the regulation of the mammalian target of rapamycin (mTOR). The loss of TSC function results in increased Rheb activity and subsequent hyperactivity in mTOR, ultimately leading to disinhibition of protein synthesis and cell growth [77]. Neurologic manifestations of TSC include epilepsy [78], intellectual disability [79] and ASD [80], as well as the specific brain malformations and cortical tubers [81], subependymal nodules and subependymal giant cell astrocytomas [82], and increasing recognition for a role in focal cortical dysplasias [83–85].

Epilepsy occurs in more than 80–90% of patients with TSC [85,86]. Seizure type varies but is often progressive and refractory to pharmacologic treatment. Infantile spasms occur in approximately 20–38% of TSC patients [78] and are generally associated with a poorer prognosis [87]. Patients with intractable epilepsy are often treated with resection, especially if a single tuber is thought to be the epileptogenic focus [88]. There is increasing interest in the use of compounds to disrupt the mTOR pathway in epileptogenesis [89] and suggested mTOR inhibitors as antiepileptogenic therapy [90,91].

ASD is estimated to be present in 20–60% of individuals with TSC and is about equally common in males and females in this population [92]. Intellectual disability, infantile spasms and presence of temporal lobe lesions were initially reported as risk factors for ASD in individuals with TSC but have not been consistently supported [93, 94].

PTEN

PTEN is a tumor suppressor gene that encodes a phosphatase affecting G1 cell cycle arrest and inhibiting the PI3K/AKT/mTOR pathway [95]. Germline mutations of *PTEN* are associated with four known hamartoma syndromes: Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus syndrome and Proteus-like conditions [96]. Somatic mutations are reported in varying malignancies, most notably breast, thyroid, and endometrial cancers [96]. Macrocephaly and ASD have been reported in children with germline *PTEN* mutations [97,98]. *PTEN*-related ASD is therefore emerging as one of a group of megalencephaly disorders associated with dysregulation of the PI3K-AKT-mTOR pathway [99].

Seizures have been reported in patients with *PTEN* mutations [100,101], including a number with focal cortical dysplasia [102–104]. *Pten* knockout mice are known to have seizures [105] that can be suppressed with the mTOR pathway inhibitor rapamycin [106]. Epilepsy appears to be a part of the phentoype for many of the megalencephaly disorders associated with dysregulation of the PI3K-AKT-mTOR pathway [107,108], but the exact roles of mutations in specific genes in this pathway related to seizures and ASDs remains to be clarified.

MECP2-related disorder (formerly Rett syndrome)

MECP2-related disorder predominantly affects females and is characterized by intellectual disability, postnatal microcephaly, loss of spoken language and stereotypic hand movements. Onset of symptoms and regression typically occur at 6 to 18 months of age after a period of apparently normal development [109]. Individuals with *MECP2*-related disorder

demonstrate autistic symptoms [110,111] as well as distinct features that include respiratory rhythm abnormalities, gait impairment, and cardiac complications [112,113].

Among individuals with *MECP2* deficiency, 50–90% are reported to have seizures [114–116]. Seizure type is variable, age of onset is rarely before 2 years of age [116] and severity of seizures appears to decline after adolescence [115]. Specific *MECP2* mutations (p.T158M and p.R106W) were more highly associated with epilepsy [116].

MECP2 is primarily a transcriptional activator during brain development [117]. The consequences of mutations in *MECP2* include abnormal downstream regulation of multiple gene targets, and loss of *MECP2* function reduces GABAergic transmission [118] and impaired glutamatergic drive in specific populations of inhibitory interneurons [119]. There is evidence from mouse models that restoration of gene function reversed some of the neurodevelopmental deficits even after symptoms had emerged [120].

CDKL5-related disorder

CDKL5-related disorder is an X-linked condition characterized by early onset of epilepsy, usually infantile spasms, and severe neurodevelopmental outcome with postnatal microcephaly, absent spoken language, and hand stereotypies that are reminiscent of *MECP2*-related disorder [121]. Although girls with *CDKL5* mutations share some ASD features (abnormal social interactions, repetitive movements, and absent speech), the concomitant developmental disability and the epilepsy phenotype [122,123] are much greater than that typically seen in children with classical forms of ASD.

While *CDKL5*-related disorder was first described in 2004 [124], and its function as a serine-threonine kinase is well characterized, the developmental role of the protein was not known until recently. CDKL5 interacts with NGL-1 and PSD95 (key candidates in ASD pathogenesis in their own right), in glutamatergic post-synapses [125], during dendrite spine development [126], including an important role stabilizing the post-synaptic membrane [118].

FOXG1-related disorders

Children with duplications of *FOXG1* on chromosome 14q12 frequently present with infantile spasms [127–129]. Patients commonly respond to adrenocorticotropin therapy with remission of the epileptic spasms and normalization of the EEG [130,131], but have long-term developmental disability that includes autistic features [132]. In contrast, children with deletions of 14q12 that include *FOXG1* or intragenic loss-of-function mutations have a disorder of postnatal microcephaly, hypoplasia of the anterior corpus callosum, severe language and motor impairment, and a choreiform movement disorder [133–134]. The mean age of epilepsy onset for children with deletions/loss-of-function mutations of *FOXG1* is 22 months, compared to epilepsy onset at 7 months in children with duplications [132].

FOXG1 is a brain-specific transcriptional repressor protein that regulates dorsal-ventral patterning [135] and neurogenesis [136]. Overexpression of *FOXG1* in the developing forebrain is associated with thickening of the neuroepithelium [137], and more recent evidence supports a role for class switching in neuroprogenitor cells [138]. However, the

mechanisms by which changes in copy number in this gene leads to epilepsy and the associated developmental disabilities are not known.

MEF2C-related disorder

Patients with loss-of-function mutations and deletions of *MEF2C* on chromosome 5q14.3 were first described with severe intellectual disability, epilepsy, and stereotypic movements [139]. Further characterization of the phenotype includes children with autistic features [140,141] with some overlap noted with features found in *MECP2*-related disorder. In most patients head size and brain morphology are normal.

The epilepsy found in individuals with *MEF2C*-related disorder can be variable, with 20% presenting with infantile spasms, 33% with infant-onset myoclonic epilepsy, 24% with childhood-onset generalized epilepsy, and 23% having no epilepsy [142]. The reason for this observed clinical variability in epilepsy type and severity is unclear, but appears to be independent of mutational class, although subjects with partial *MEF2C* deletions were less likely to have epilepsy [142].

Mef2c plays several roles during brain development, and is a marker of cortical lamination driven by Tbr1 [143]. Mef2c expression is also diminished in *Arx* and *Dlx1/2* deficient mice [144] indicating a complex role during both dorsal glutamatergic and ventral GABAergic development [142]. Finally, Mef2c recognizes a binding site called the synaptic activity-response element (SARE) that activates a series of genes important for synaptic development and function [145].

CASK-related disorders

Mutations affecting *CASK* were first described in primarily female patients with severe microcephaly and pontocerebellar hypoplasia [146]. Males affected with intellectual disability and oculomotor abnormalities were later described [147]. Absent spoken language and autistic behaviors are described, particularly in girls on the milder spectrum of microcephaly [148].

CASK encodes a calcium/calmodulin-dependent serine protein kinase expressed in the brain [149]. CASK has a role in synapse formation, synapse function and cortical development. The core clinical features in females with CASK mutations includes a distinct malformation phenotype involving postnatal microcephaly and pontine and cerebellar hypoplasia, developmental delay, growth retardation, eye abnormalities and a pattern of facial dysmorphisms [148]. Hypomorphic CASK alleles in male patients appear to cause a milder phenotype, presumably due to a smaller disruption of protein structure and function [150]. However, CASK abnormalities have been reported in male patients with Ohtahara syndrome and severe phenotypic features consistent with previously reported CASK mutations [151]. Nearly all female patients have moderate or severe impairment in intellectual development. Language is generally impaired or absent as well. Behaviors such as hand stereotypies and self-biting are commonly seen. Data are unavailable on ASD prevalence in this population. ASD diagnosis is likely confounded by the severity of impairment and intellectual disability.

Epilepsy is reported in more than half of female patients with variable age of onset and seizure type [150].

CASK is an example of a gene that plays multiple roles during brain development. Through interactions in the nucleus with the early cortical patterning proteins RELN and TBR1, CASK plays a role in neuronal migration [149]. CASK additionally plays an important role in post-synaptic structural support [149, 150].

SCN2A-related disorders

Deletion of chromosome 2q24.2q24.3 containing *SCN2A* was first reported in a child with autistic features and intellectual disability [152]. Then, nonsense mutations in *SCN2A* were discovered in two children with ASD using whole exome sequencing [153]. At the same time, several children were identified with a spectrum of severe early life epilepsies including Ohtahara syndrome [154–156] malignant migrating partial seizures of infancy [157], and infantile spasms [158–159] with mutations in *SCN2A*. Other children with *SCN2A* mutations have been reported with benign neonatal-infantile epilepsy [160] and generalized epilepsy with febrile seizures plus, and is an infrequent cause of Dravet syndrome [161]. While genotype phenotype correlations have been challenging in *SCN2A*-related epilepsies, there is emerging evidence that missense mutations resulting in more chemically dissimilar amino acid substitutions correlate with worse disease, and that truncating mutations are associated with the most severe phenotypes [162].

SCN2A encodes the voltage-gated sodium channel Na(v)1.2 predominantly expressed in excitatory neurons, and it is unclear how loss-of-function mutations can result in hyperexcitability [163–164]. Less clear is the mechanism by which ASD symptoms result.

Epilepsy syndromes with ASD as frequent neurodevelopmental sequelae

Evidence suggests children with ASD who have epilepsy may have seizures that do not fulfill criteria for specific named electroclinical syndromes [165]. However, several specific epilepsy syndromes appear to be risk factors for later diagnosis of ASD. These include infantile spasms and Lennox-Gastaut syndrome. More recently, overlap has been observed clinically with continuous slow waves during sleep (CSWS) and Landau-Kleffner syndrome and ASD [166].

Infantile spasms

Infantile spasms are a form of epilepsy associated with an EEG pattern of hypsarrythmia and characterized by epileptic spasms that occur before 2 years of age [167]. Infantile spasms are genetically heterogeneous and are associated with abnormalities in several brain developmental pathways [168]. The prevalence of ASD among children with a history of infantile spasms has not been reported consistently, but an association between the two is clearest in tuberous sclerosis [169] and duplications of *FOXG1* [132].

Lennox-Gastaut syndrome

Lennox-Gastaut syndrome (LGS) is a childhood-onset epilepsy phenotype characterized by electroclinical features of diffuse slow spike waves and generalized paroxysmal fast activity

in sleep. Little literature exists on the prevalence of ASD or the behavioral spectrum in LGS, although ASD has been reported [170–172] and LGS has occurred in patients with duplications of maternal 15q11q13 [32,173].

Landau-Kleffner syndrome / Continuous Spikes and Slow Waves during Slow Sleep

Landau-Kleffner syndrome (LKS) is an epilepsy-aphasia syndrome of unknown etiology characterized by language regression and characteristic continuous spike and waves during slow wave sleep on EEG [174–175]. As LKS became increasingly recognized, several children who had been diagnosed with ASD were noted to have a predominant language deficit [176]. Stereotypies and withdrawal are also common in LKS, but it is not clear that these children also have deficits in social reciprocity [177]. The association may be more related to severe receptive language deficit [175]. Studies have detected copy number variants in LKS patients that have also been associated with ASD [178], and most recently mutations in *GRIN2A* have been identified in patients with epilepsy-aphasia phenotypes [179–181].

ASD Screening and Diagnosis

Due to the association between seizures and ASD, it is important for epileptologists to recognize when and how to screen for ASD and appropriately refer for diagnostic evaluation. Although ASD persists across the lifespan, timely detection and intervention can alleviate symptoms [182]. We have described several syndromes in which epilepsy and ASD co-occur at a rate that warrants direct referral for an evaluation of ASD and other developmental disorders. Other situations warrant ASD screening in children with or without the genomic syndromes reviewed here. The American Academy of Pediatrics (AAP) recommends ASD screening for all 18- and 24-month old children who either have a sibling with ASD and a caregiver who expresses concerns about ASD symptoms, or who have concerns expressed by multiple caregivers and providers [183]. Screening also should occur if the child has no babbling at 12 months, no single words by 16 months, no spontaneous phrases by 24 months, or loss of social or language skills at any age [184]. Signs that may call for screening of older children and youth include disinterest in back-and-forth interactions with peers; problems with “reading” common social cues or interpreting nonliteral speech (e.g., sarcasm or metaphors); lack of understanding of the perspective of others; inability to engage in social chat or conversations, or highly rigid, perseverative, or repetitive patterns of behavior [183]. Screening usually involves administering a brief rating scale to the parent. For toddlers, the best-established screening instrument currently is the Modified Checklist for Autism in Toddlers – Revised with Follow-up (M-CHAT-R/F) [185–186]. The M-CHAT-R/F contains a 20-item, yes/no rating scale and a brief follow-up interview if three or more items on the rating scale indicate that the child is at risk for ASD. For children age 4 years and older, the most extensively validated screening instrument is the Social Communication Questionnaire, SCQ, which is a 40-item, yes/no rating scale [187]. If children at risk for ASD have a negative screen, the AAP recommends counseling parents on how to recognize ASD symptoms and scheduling a follow-up evaluation [183]. If children have a positive screen, they should be referred for a comprehensive diagnostic evaluation.

The diagnostic evaluation for ASD ideally includes a clinical evaluation by a specialist (child neurologist, developmental behavioral pediatrician, child psychiatrist, clinical psychologist) who has expertise in ASD, a review of findings from developmental tests, a detailed medical and developmental history, referrals for additional testing as indicated by the assessment (e.g., genotyping for children with intellectual disability or dysmorphic features), and administration of a standardized diagnostic instrument. The most commonly used diagnostic instrument in clinical practice is the Autism Diagnostic Observation Schedule – Second Edition (ADOS-2) [188]. The ADOS-2 is a series of structured and semi-structured tasks, approximately 30–60 minutes in duration, involving social and communicative interaction between the examiner and the patient. Behaviors are assigned to predetermined observational categories that are subsequently used to produce a quantitative score [187]. The Autism Diagnostic Interview – Revised (ADI-R) is a companion standardized, 2–3 hour interview for caregivers of individuals with ASD that provides a diagnostic algorism for autism based on ICD-10 and DSM-IV [188,189]. The ADOS-2 and ADI-R are widely regarded as the best-established tools for diagnosing ASD [190]. Table 2 summarizes the commonly used screening and diagnostic tools for ASD.

The diagnosis of ASD is difficult in the context of intellectual disability. Although these standardized diagnostic tools are available to assist in making an ASD diagnosis, they need to be used as part of a broader evaluation by a clinician with expertise in ASD. The sensitivity of the ADOS-2 is high (.91-.97), but specificity is lower (.50–.94), particularly for children with ID or minimal verbal skills [191]. ID is common in many of the syndromes reviewed in this article, and there is considerable phenotypic overlap between ASD and ID, making differential diagnosis difficult [192]. In the absence of identified risk factors for ASD, it may be most efficient to begin by conducting a general developmental screen before administering a screen for ASD. Many children with epilepsy will not meet criteria for an ASD diagnosis but are likely to have other developmental concerns. For example, one study of children with epilepsy found a high percentage of positive screens for ASD using the SCQ (15%), M-CHAT (58%) and the ASQ (82%). Positive screening results were associated with ASD diagnosis in only 8% of patients with a positive M-CHAT and 57% of children with a positive SCQ, but a much higher percentage (20% of all children with positive screens) warranted referral for other services such as psychiatric, psychological, or educational services [193]. The frequency of referrals for services confirms the importance of developmental screening, but the high rate of false positive screens for ASD suggests that routine screening for ASD in all children with epilepsy may not be optimal [194].

Conclusion

The co-occurrence of ASD and epilepsy is well recognized but the mechanisms behind this association remain unclear [2–5]. Many of the reported series have small numbers of patients and have inconsistent and varying conclusions [25,195,196]. Low IQ is a well-established risk factor for ASD in children with epilepsy [25]. Developments in our ability to detect pathogenic genomic variations and single gene associations with ASDs and epilepsies have led to a better understanding of their shared biological processes and mechanisms. These pathways include, but are not limited to, gene transcriptional regulation, cellular growth, and synapse development, stability, and function.

ASD and epilepsies are often co-morbid with varying degrees of developmental delay, learning disability, intellectual disability and behavior problems that confound the diagnosis of ASD and will likely remain a persistent clinical challenge. It is important to recognize the key features of ASD (deficits in social behaviors and communication, restricted interests and repetitive patterns of behavior), when to screen and when to refer for more diagnostic evaluation. The evaluation of children with epilepsy who are at risk for ASD involves coordinated genetic and behavioral testing strategies, illustrated in Figure 2. The clinical genetic testing strategy for both epilepsies and ASD are similar and involve sequential use of chromosomal microarray (CMA), followed by targeted next-generation sequencing gene panels, and if those are normal, whole exome sequencing.

CMA has emerged as a powerful genetic tool in many patient populations, including individuals with ASDs with a reported overall diagnostic yield of 10% [197,198,199]. Certain selection factors such as dysmorphic features, intellectual disability and family history of ASD can increase diagnostic yield [200–203]. Children with ASD with abnormal features on physical exam are 10 times more likely to have a diagnosable genetic condition than those with normal phenotypic appearance [201]. Other clinical considerations include family history, micro- and macrocephaly, abnormal finger digit ratios and cognitive impairment [202]. CMA has demonstrated the highest diagnostic yield (66.7%) in patients with intellectual disability, ASD and dysmorphic features, supporting its use as the first-tier diagnostic genetic test in this subgroup [199,203].

Genetic testing for single gene disorders such as Fragile X should be routinely performed for males with ASD. *MECP2* sequencing should be performed for all females with ASD and *MECP2* duplication testing should be performed in males with a suggestive phenotype. *PTEN* testing is recommended in individuals with significant macrocephaly (> 2.5 SD above mean). More recently, the availability of next-generation sequencing panels means that in many cases multiple genes can be evaluated simultaneously with one test, at reduced cost overall. The estimated yield of diagnostic whole exome sequencing in the clinical setting is at least 25% [204], and should be considered if CMA and more targeted gene panel sequencing are normal. Advances in this area have led to identification and discovery of many new *de novo* mutations in ASD [16,153,205]. Continued research focused on children with epilepsy and ASD will likely yield further knowledge with insight into new therapies.

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Highlights

- ASD and epilepsies commonly co-occur.
- A number of new genetic discoveries suggest shared biology for both disorders.
- Several screening and diagnostic tools are available to clinicians.

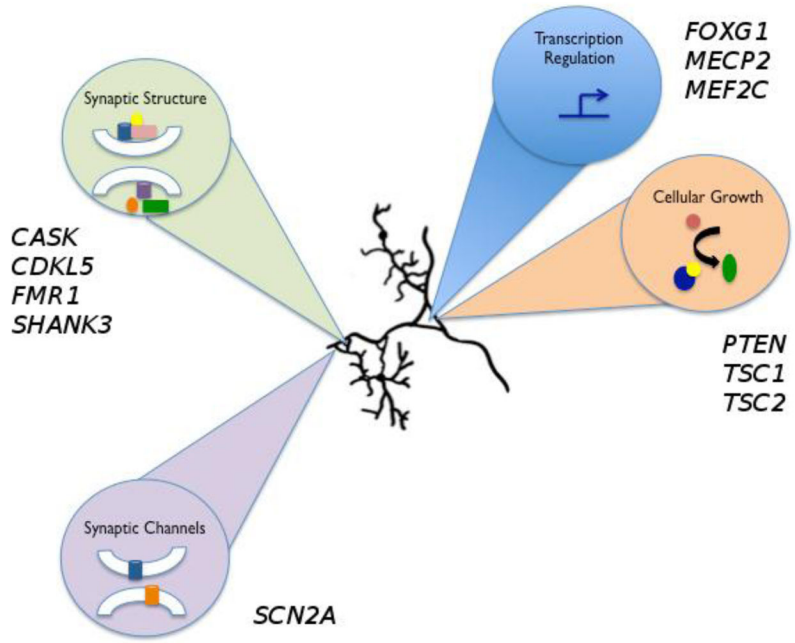

Figure 1.

Overview of biological pathways common to autism and epilepsy. At least four biological pathways important in neuronal development and function are implicated by involvement of several genes in autism and epilepsy pathogenesis. These pathways include transcriptional regulation (FOXG1, MECP2, MEF2C), cellular growth (PTEN, TSC1, TSC2), synaptic channels (SCN2A), and synaptic structure (CASK, CDKL5, FMR1, SHANK3).

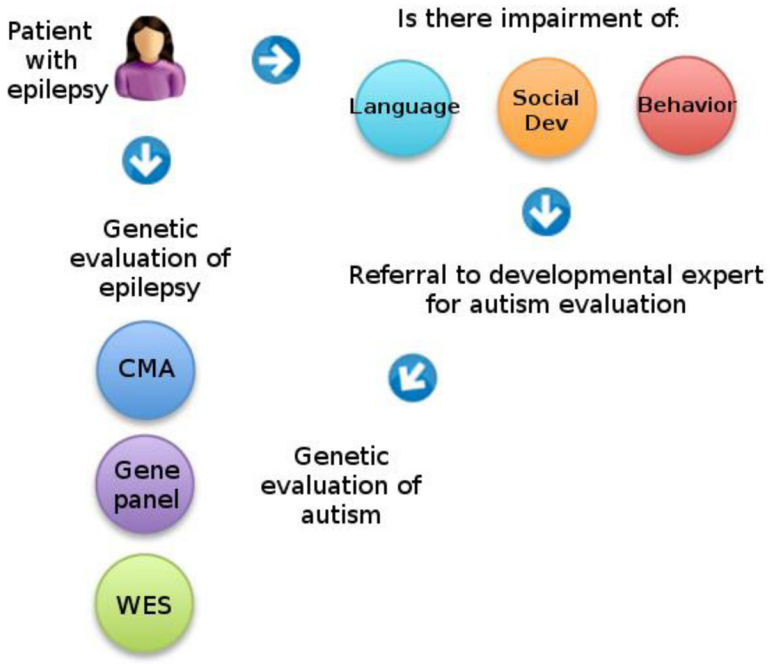

Figure 2.

Suggested workflow for evaluation of epilepsy patients who may be at risk for autism. A patient with epilepsy should be screened for impairment in language, social development, and/or behavior. If warranted, the patient should be referred to a trained expert in autism diagnosis. If a diagnosis of autism is confirmed, or if significant other developmental concerns exist (i.e. intellectual disability), genetic evaluation is appropriate. The clinical genetic evaluation for autism and epilepsy may have overlap, and may be tailored by recognition of conditions detailed in this paper where autism and epilepsy overlap. Current clinical genetic evaluation includes sequentially chromosomal microarray (CMA), autism and epilepsy next-generation sequencing gene panels, and if necessary, whole exome sequencing (WES).

Table 1

Single gene and genomic copy number regions commonly associated with autism and epilepsy

Gene or genomic region	Associated syndrome	Key features
15q11-q13	Chromosome 15q11–13 duplication syndrome	Autism, intellectual disability, ataxia, seizures, developmental delays, and behavioral problems *Deletion of this region is associated with Angelman/Prader- Willi Syndromes
Chromosome 21	Down Syndrome	Distinct facial dysmorphisms, intellectual disability, congenital anomalies and medical comorbidities.
22q13.3 SHANK3	Phelan-McDermid syndrome	Neonatal hypotonia, global developmental delay, absent to severely delayed speech and autistic behavior and minor dysmorphic features
FMR1	Fragile X Syndrome	Moderate to severe intellectual disability, macroorchidism, and distinct facial features (long face, large ears, and prominent jaw).
TSC1/2	Tuberous sclerosis	Multisystem disorder characterized by hamartomas (brain, heart, lungs, kidneys and skin).
PTEN	PTEN-related disorders	Hamartoma syndromes and malignancies (breast, thyroid, endometrial). Macrocephaly and ASD has been reported in children with PTEN mutations.
MECP2	MECP2-related disorder	Severe neurodevelopmental disorder characterized by arrest of development between 6 and 18 months of age, regression of skills, loss of speech, stereotypic hand movements, microcephaly, seizures, and intellectual disability.
CDKL5	CDKL5-related disorder	X-linked dominant condition characterized by early onset of seizures, severe global developmental delay and postnatal microcephaly. Other features include subtle dysmorphic facial features, sleep disturbances, gastrointestinal problems, stereotypic hand movements and intellectual disability.
FOXG1	FOXGI-related disorders	Severe neurodevelopmental disorder with features of classic Rett syndrome but earlier onset in the first months of life
MEF2C	MEF2C-related disorder	Severe neurodevelopmental disorder characterized by intellectual disability, epilepsy and stereotypic movements.
CASK	CASK-related disorders	Characterized by a distinct malformation phenotype in females involving postnatal microcephaly and pontine and cerebellar hypoplasia, developmental delay, growth retardation and eye abnormalities.
SCN2A	SCN2A-related disorders	Autosomal dominant seizure disorder characterized by infantile onset of refractory seizures.

Table 2

Features of available autism diagnostic and screening tools.

Name	Purpose	Completed by	Description	Time (minutes)	Strengths/Weaknesses
Autism Diagnostic Observation Scale (ADOS)	Diagnostic	Clinician	Series of structured and semi- structured tasks involving social and communicative interaction.	60	Requires training Time for administration Widely used in research and clinical settings
ADI-R	Diagnostic	Clinician	Clinical interview that probes for autism symptoms and behaviors.	120–180	Standard tool used clinically and in research Time constraint limits clinical use
Childhood Autism Rating Scale (CARS)	Diagnostic	Clinician	15-item direct- observation tool for children over 2 years old that includes items drawn from five prominent systems for diagnosis.	20–30	Not appropriate for infants or toddlers Requires training
Gilliam Autism Rating Scale (GARS-3)	Diagnostic	Clinician	56-item assessment for use in 3 to 22 years old grouped into 6 subscales including restrictive and repetitive behaviors, social interaction and communication, emotional responses, cognitive style, and maladaptive speech.	5–10	Gives severity estimation 44 new items recently added to GARS-3; requires training for administration and interpretation Demonstrated good reliability and validity
Ages and Stages Questionnaires (ASQ)	Screening	Caregiver	19 age-specific questionnaires (4 – 60 months) for use as developmental and social- emotional screening tool.	10–15	Requires little training Fast administration Available in several languages Only tool that links to developmental milestones
Communication and Symbolic Behavior Developmental Profile (CSBS DP) Infant Toddler Checklist (ITC)	Screening	Caregiver	24-item questionnaire designed to identify at-risk children between 6 and 24 months of age based on communication and symbolic abilities.	5–10	Fast administration High sensitivity and specific to identify infants and toddlers with developmental delay Does not discriminate between ASD and other communication disorders
Parents' Evaluation of Developmental Status (PEDS)	Screening	Caregiver	10 single-response form for all ages designed to elicit and address parents' concerns about their child's development and health.	2–10	Quick administration Available in multiple languages Low Readability
Modified Checklist for Autism in Toddlers (MCHAT-R/F)	Screening	Caregiver	20-item yes/no questions appropriate for ages 16 to 30 months assesses risk of ASD. Includes structured follow-up questions for children at medium risk prior to referral for diagnostic evaluation.	5–10	Validated first-tier screen Available in multiple languages Ease of administration and scoring
Screening Tool for Autism in Toddlers and Young Children (STAT)	Screening	Clinician	Interactive tool designed as second-level screen for children with suspected developmental concern. 12 observed activities that assess behaviors in 4 social-communicative domains.	20	Requires training Restricted to ages 24–35 months Not validated as a first-tier screen Language comprehension is not required
Social Communication Question ;formerly Autism Screening Questionnaire (SCQ)	Screening	Caregiver	Parent-report screen consisting of 40 yes-no questions designed to identify children at risk for ASD from general population.	5–10	Fast administration Well-validated Less valid in young children with limited language