Review article

Epilepsy associated with autism and attention deficit hyperactivity disorder: Is there a genetic link?

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Abstract

Autism Spectrum Disorders (ASDs) and Attention Deficit and Hyperactivity Disorder (ADHD) are the most common comorbid conditions associated with childhood epilepsy. The co-occurrence of an epilepsy/autism phenotype or an epilepsy/ADHD phenotype has a complex and heterogeneous pathogenesis, resulting from several altered neurobiological mechanisms involved in early brain development, and influencing synaptic plasticity, neurotransmission and functional connectivity. Rare clinically relevant chromosomal aberrations, in addition to environmental factors, may confer an increased risk for ASDs/ADHD comorbid with epilepsy. The majority of the candidate genes are involved in synaptic formation/remodeling/maintenance (NRX1, CNTN4, DCLK2, CNTNAP2, TRIM32, ASTN2, CNTN5, SYN1), neurotransmission (SYNGAP1, GABRG1, CHRNA7), or DNA methylation/chromatin remodeling (MBD5). Two genetic disorders, such as Tuberous sclerosis and Fragile X syndrome may serve as models for understanding the common pathogenic pathways leading to ASDs and ADHD comorbidities in children with epilepsy, offering the potential for new biologically focused treatment options.

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Keywords: Epilepsy; Autism spectrum disorders; ADHD; Comorbidity; Genetics; CNVs; Tuberous sclerosis; Fragile X syndrome

1. Introduction

Epilepsy is one of the most common neurological disorders of childhood, occurring in 3.5–6.5 per 1000 children [1], and may be associated with several neurodevelopmental disorders, including intellectual disability (ID), attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASDs) [2].

ASDs symptoms may occur in 15–35% of children with epilepsy [3–5]. Epilepsy is estimated to affect 7–46% of patients with ASDs [6–8], occurring more frequently in those subjects presenting also an ID [9]. All seizure types have been reported in ASDs, but focal epilepsy seems to be prevalent [10]. Children and adolescents with epilepsy tend to show an increased risk of ADHD, which is present in 12–70% [11–13]. Overall, these findings suggest a strong interrelationship between the ASDs/ADHD phenotype and childhood epilepsy. Despite current classification systems (ICD-10, DSM-IV) [14] do not allow for a comorbid diagnosis of ASDs and ADHD, in the ASDs population 40–70% of individuals meet full ADHD diagnostic criteria [15,16]. Autistic-like communication and social deficits are evident in 28–62% of ADHD children [17]. These rates of co-occurrence are higher than expected for coincidental findings, making it unlikely that ASDs and ADHD are two independently occurring conditions.

The co-occurrence of an epilepsy/autism phenotype or an epilepsy/ADHD phenotype has a complex and heterogeneous pathogenesis, resulting from several...
altered neurobiological mechanisms involved in early brain development, and influencing synaptic plasticity, GABA transmission and functional connectivity [2]. It is likely that rare clinically relevant genetic aberrations, in addition to environmental factors, may confer an increased risk for ASDs/ADHD associated with epilepsy [2,18].

We reviewed the pathogenic mechanisms behind the high rate of comorbidity between epilepsy and ASDs/ADHD and provided an overview of new data from genetic models that have the potential to clarify this co-occurrence.

2. Search strategy and selection criteria

Information in this Review is mainly based on peer-reviewed medical publications from 1974 to 2012 (PubMed). The selection criteria utilized were the novelty and importance of studies, and their relevance to general medical doctors and child neurologists. Only articles published in English were reviewed. The filters included "epilepsy", "autism", "autism spectrum disorders", "attention deficit hyperactivity disorder", for the identification of studies reporting on a comparison of these neurodevelopmental conditions, and "molecular genetics", "CNV", "SNP" for the genetic data.

3. Genetic links

Different alterations of genes involved in neurodevelopment may result in common biological mechanisms that lead to complex neuropsychiatric phenotypes. Conceptually, during intrauterine brain development or at an early stage in life, common molecular pathways may disrupt developmental trajectories leading to abnormalities in neuronal migration, cortical organization and, finally, in synaptic and dendritic functions [19]. An example is represented by in the AUTS2 locus, involved in neurodevelopment, in which nucleotide changes could lead to several neurological diseases, including autism, ADHD, epilepsy, dyslexia, motor delay, language delay, visual impairment, microcephaly, and alcohol consumption [20].

Candidate genes associated with childhood epilepsy and ASDs/ADHD comorbidity are reported in Table 1. The majority of these genes are involved in synaptic formation/remodeling/maintenance (NRX1 [21–23], CNTN4 [24], DCLK2 [25,26], CNTNAP2 [27–29], TRIM32 [25], ASTN2 [25], CNTN5 [25,30], SYN1 [31,32]), neurotransmission (SYNAP1 [33], GABRG1 [34], CHRNA7 [29,34–36]) or DNA methylation/chromatin remodeling (MBD5 [37,38]).

GABAergic interneurons are involved in maturation and wiring of proper networks, in the regulation of critical period experience-dependent cortical plasticity, and in the control of minicolumns functions [39–41]. Alteration in neocortical experience-dependent maturation leads to an abnormal plasticity, and may significantly contribute to cognitive and behavioral impairments. This process is severely impaired in Ube3a deficient mice models of Angelman syndrome (OMIM #105830), a genetic entity characterized by ID, ASDs in one-half of cases, epilepsy, and ADHD [42,43]. Altered [GABA]/[glutamate] ratio has been evidenced in the frontal lobe of autistic patients, with respect to controls [44]. Moreover, SPECT studies showed a GABAergic system disturbance in the superior and medial frontal cortex, brain regions involved in several aspects of the Theory of Mind [45]. Hyperglutamatergia and other neurometabolic abnormalities have been demonstrated in pregenual anterior cingulate cortex of pediatric ASDs patients, with possible right-lateralization [46]. Moreover, Dopamine D(4) receptors seem to control the excitatory synaptic strength in local-circuit neurons and GABAergic inhibition in the prefrontal network, underlining the role of D(4) receptors cognitive processes associated with ADHD [47]. Abnormal excitability and disrupted synaptic plasticity in the developing brain may account both for epilepsy and its comorbidities [48,49].

Decreased cortical expression of the two isoforms of glutamic acid decarboxylase (GAD), GAD65 and GAD67, has been observed in autistic brain samples [49,50]. The importance of GAD65 for synthesis of GABA destined for extrasynaptic tonic inhibition, regulating epileptiform activity, was demonstrated in knock-out mice models [51].

Dlx homeobox genes, including Dlx1 and 2, encode for transcription factors important for specification, maintenance, and migration of interneurons in the adult brain. Dlx1/− mice shown a selective alteration in the dendritic morphology of interneurons and their progressive death, with onset of generalized electrographic seizures [52]. DLX1 and DLX2 genes are located in 2q32 band, a region associated with autism susceptibility; Single Nucleotide Polymorphisms (SNPs) of these genes have been documented in multiplex ASDs families [53].

ARX mutations, related to ID, epileptic encephalopathies and, rarely, autism [54] is essential for GABAergic interneurons migration, and is a direct downstream target of Dlx2 [55]. A decreased GABA receptor signaling has been documented in Fragile X syndrome, with a consequent imbalance between excitatory and inhibitory systems [56]. Finally, a selective ablation of MeCP2 from interneurons, causes many features of Rett syndrome and autistic behaviors in mice models [57].

With the advent of whole-genome association studies, several single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) have been associated to ID, ASDs, ADHD, epilepsy and a constellation of other neuropsychiatric disorders. A list of several syndromic conditions associated with chromosomal aberrations are summarized in Table 2. The co-occurrence of
<table>
<thead>
<tr>
<th>Genes and OMIM entries</th>
<th>Locus</th>
<th>Function(s)</th>
<th>Epilepsy</th>
<th>Autism spectrum</th>
<th>ADHD</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRXN1 (+600565)</td>
<td>2p16.3</td>
<td>Cell-surface receptor that binds neuroligins, forming a Ca(2+)-dependent transsynaptic complex required for efficient neurotransmission and involved in the formation of synaptic contacts</td>
<td>Severe early onset epilepsy</td>
<td>+</td>
<td>+</td>
<td>[21–23]</td>
</tr>
<tr>
<td>MBD5 (*611472)</td>
<td>2q23.1</td>
<td>Member of a family of genes involved in DNA methylation and/or chromatin remodeling</td>
<td>+</td>
<td>Autistic features</td>
<td>–</td>
<td>[37,38]</td>
</tr>
<tr>
<td>GABRG1 (*137166)</td>
<td>4p12</td>
<td>Member of the GABA-A receptor gene family involved in mediating responses to benzodiazepines</td>
<td>Neonatal seizures</td>
<td>+</td>
<td>+</td>
<td>[25,95]</td>
</tr>
<tr>
<td>DCLK2 (*613166)</td>
<td>4q31.3</td>
<td>In rat brain, DCX domain of Dck2 is required for microtubule binding</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>[25,26]</td>
</tr>
<tr>
<td>SYNGAP1 (*603384)</td>
<td>6p21.32</td>
<td>Encodes a RAS/RAP GTP-activating protein that is a part of N-methyl aspartate receptor (NMDAR) complex</td>
<td>CAE, GTCS, myoclonic seizures, drop attacks, partial complex seizures</td>
<td>+</td>
<td>+</td>
<td>[33]</td>
</tr>
<tr>
<td>CNTNAP2 (*604569)</td>
<td>7q35-q36</td>
<td>Member of the neurexin superfamily, a group of transmembrane proteins that mediate cell-cell interactions in CNS. Highly expressed in prefrontal and anterior temporal cortex, as well as in dorsal thalamus, caudate, putamen, and amygdale. Mutated in Pitt-Hopkins-like syndrome</td>
<td>CDFE generalized seizures</td>
<td>+</td>
<td>+</td>
<td>[27–29]</td>
</tr>
<tr>
<td>TRIM32 (*602290)</td>
<td>9q33.1</td>
<td>Encodes a tripartite motif containing E3 ubiquitin ligase protein, involved in deciding the fate of neuronal stem cell lineages. Mutated in Bardet–Biedl syndrome</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>[25]</td>
</tr>
<tr>
<td>ASTN2 (*612856)</td>
<td>9q33.1</td>
<td>Important in the developing mammalian brain by forming a complex with its paralog astrotactin 1 and regulating its expression on the surface of young cerebellar neuroblasts</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>[25]</td>
</tr>
<tr>
<td>CNTN5 (NB2) (*607219)</td>
<td>11q22.1</td>
<td>Neural adhesion molecule of the contactin subgroup of the Ig superfamily</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>[25,30]</td>
</tr>
<tr>
<td>CHRNA7 (*118511)</td>
<td>15q13.3</td>
<td>Nicotinic acetylcholine receptor, member of a superfamily of ligand-gated ion channels that mediate fast signal transmission at synapses</td>
<td>CAE, JAE, JME, GTCS, Rolandic epilepsy</td>
<td>Classic autism PDD-NOS</td>
<td>Asperger syndrome</td>
<td>[29,34–36]</td>
</tr>
<tr>
<td>MACROD2 (*611567)</td>
<td>20p12.1</td>
<td>It is expressed in fetal and adult human brain. In embryo and adult mice it is expressed in brain, especially in the ventricular zone. Its function is still unclear</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>[25,96]</td>
</tr>
<tr>
<td>SYN1 (*313440)</td>
<td>Xp11.23</td>
<td>It is associated with membranes of small synaptic vesicles, and may have a role in the regulation of neurotransmitter release in mature synapses and in neuronal development</td>
<td>Complex partial epilepsy, nocturnal epilepsy, GTCS</td>
<td>+</td>
<td>–</td>
<td>[31,32]</td>
</tr>
</tbody>
</table>

**Abbreviations:** CAE = childhood absence epilepsy; CDFE = cortical dysplasia-focal epilepsy syndrome (reported in homozygous mutation of CNTNAP2 in Old Order Amish children); CNS = central nervous system; GTCS = generalized tonic-clonic seizures; GABA = gamma-aminobutyric acid; JAE = juvenile absence epilepsy; JME = juvenile myoclonic epilepsy; PDD-NOS = pervasive developmental disorder – not otherwise specified.
<table>
<thead>
<tr>
<th>Chromosomal segment</th>
<th>Genes potentially involved</th>
<th>Autism</th>
<th>Epilepsy</th>
<th>ADHD</th>
<th>Dismorphisms and other features</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del 1q21.1</td>
<td>PRKAB2, FMO5, CHD11L, BLC9, ACP6, GJA5, GJA8, GPR89B, HYDIN2</td>
<td>ASDs autistic features</td>
<td>GTCS, typical and atypical absence seizures, head drops, drop attacks</td>
<td>+</td>
<td>Variable/subtle dysmorphisms. Microcephaly, mild-moderate ID, MCA, eye abnormalities, short stature. Behavioral problems</td>
<td>[29,97,98]</td>
</tr>
<tr>
<td>Dup 1q21.1</td>
<td>ASDs autistic features</td>
<td>+</td>
<td>+</td>
<td>Variable/subtle dysmorphisms. Microcephaly, eye abnormalities. Behavioral problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Del 2q23.1</td>
<td>MBDS&lt;sup&gt;5&lt;/sup&gt;, EPC2</td>
<td>ASDs autistic features</td>
<td>FS, absence seizures, atonic seizures, tonic seizures, GTCS</td>
<td>ADHD short attention span hyperactivity impulsiveness</td>
<td>Microcephaly/brachicephaly, craniofacial abnormalities, broad forehead, thick/arched eyebrows, eye, nasal and ear abnormalities, macrostomia. Motor and language impairments, ataxia, behavioral problems</td>
<td></td>
</tr>
<tr>
<td>Del 15q13.3</td>
<td>CHRNA7&lt;sup&gt;*&lt;/sup&gt;, OTUD7A, KLLF13, TRPM1, -MTMR10, MTMR5</td>
<td>Classic autism PDD-NOS Asperger syndrome autistic features</td>
<td>CAE, JAE, JME, Rolandic epilepsy</td>
<td>ADHD short attention span impulsiveness</td>
<td>Subtle dysmorphic features DD, Normal IQ-moderate ID, language impairment, behavioral problems</td>
<td></td>
</tr>
<tr>
<td>Dup 15q13.3</td>
<td>+</td>
<td>Not significant association</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Del 16p11.2</td>
<td>QPRT, DOC2A, SEZ6L2, KCTD13, MAPK3</td>
<td>ASDs autistic features (more common than in dup)</td>
<td>GTCS, MMPSI (more common than in dup)</td>
<td>+</td>
<td>MCA, MRI abnormalities. Macrocephaly, broad forehead, flat midface, micrognatia, hypertelorism</td>
<td></td>
</tr>
<tr>
<td>Dup 16p11.2</td>
<td>+</td>
<td>+</td>
<td>+ (more common than in del)</td>
<td>More severe language impairment, ID and dysmorphic features (but not recognizable) than deletion, microcephaly. Common behavioral problems. MCA, MRI abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Del 16p13.11</td>
<td>MYH11, NDE1, ABCC1, ABCC6</td>
<td>+</td>
<td>CAE, GTCS, JAE, JME</td>
<td>Generalized epilepsy</td>
<td>Subtle-severe dysmorphic features ID, brain MRI abnormalities, micro-macrocephaly, congenital heart defects, bone and kidney abnormalities</td>
<td>[59,63]</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADHD = Attention Deficit and Hyperactivity Disorder; ASD = Autism Spectrum Disorders; CAE = childhood absence epilepsy; DD = developmental delay; Del = deletion; Dup = duplication; FS = febrile seizures; GTCS = generalized tonic-clonic seizures; ID = intellectual disability; IQ = intelligent quotient; MCA = multiple congenital anomalies; MMPSI = malignant migrating partial seizures of infancy; TC = tonic-clonic seizures; JAE = juvenile absence epilepsy; JME = juvenile myoclonic epilepsy.

* See also Table 1 for more information about MBDS<sup>5</sup> and CHRNA7 genes.
epilepsy/ASDs/ADHD varies among different conditions, but ID is present in the majority of aberrations.

Interestingly, de novo CNVs occur in about 7.5% of boys and in about 12% of girls with non-syndromic forms of ASDs. In syndromic patients, the detection of a causal CNV can reach up to 25% [58]. In patients with focal and generalized epilepsies without ID or ASDs comorbidities, CNVs have been found in about 3–9% of cases, with recurrent structural variations at 15q11.2, 15q13.3, 16p13.11 and 16p13.3 [29,35,58,59]. However, these genomic hotspots have been also associated with ID, autism, and other neuropsychiatric phenotypes [60–63]. Patients with epilepsy have a significantly increased burden of larger, gene-rich CNVs respect to controls, in particular when ID of mild-moderate degree or other neuropsychiatric conditions are associated to the epileptic phenotype. However, no significant association between the CNVs frequency or size and the type of epilepsy was found [64]. Also in this case, the only significant difference was represented by the cognitive level of patients [64].

The detection-rates of genome wide techniques in “pure” ADHD varies from 7% to 17% [27,65–67]. The presence of CNVs is not related to an atypical form of the disorder, and no difference has been observed in terms of severity, comorbidity, developmental features, family history or pre-/perinatal markers between patients with ADHD and CNVs and patients with ADHD only. The only significant difference was represented by the cognitive level of patients [27,65–67].

Several large studies have assessed the validity of copy-number changes (CNVs) analysis in the diagnostic workup for intellectual disability and autism, [42,68–71] and, more recently, array CGH has also been proposed in the diagnostic evaluation of patients with complicated epilepsy [72]. Therefore, there is a significant contribution of de novo CNVs recurrence in sporadic ASDs, ADHD, and epilepsy cases, however, the same alterations have also been detected in unaffected individuals and in complex phenotypes, suggesting that rare CNVs predispose to diseases, acting in an additive manner with other genetic or environmental factors [58]. In a recent array CGH study conducted on children known to carry a CNV associated with ID and congenital abnormalities, a second large CNV in addition to the primary genetic lesion has been detected in about 10% of cases [73]. Moreover, syndromic children could be distinguished from children with extreme phenotypic heterogeneity on the basis of the total number of CNVs, and whether the variants are inherited or de novo [73]. These findings support a “two-hit model”, in which a single CNV both increases the risk to have a neuropsychiatric phenotype as a single event, and exacerbates this phenotype in association with other additive large deletions or duplications. [74,75]. However, clinicians should be aware that array-based analysis may not lead to improved health outcomes of children with developmental disorders [76,77].

4. Animal models

Some genetic disorders, such as TSC and FXS, may serve as a model for understanding the common pathogenic pathways leading to epilepsy-associated ASDs and ADHD comorbidities, and offering the potential for new biologically focused treatment possibilities.

TSC is one of the largest identifiable causes of epilepsy, the second major cause of autism [78] and is frequently associated with ADHD-like symptoms, which affect about 30–60% of TSC children [79]. Exact mechanisms of epilepsy and ASDs in TSC are not totally understood, even if it seems clear that alterations in AMPARs and in expression of specific subunits of glutamate and GABA receptors, as well as a decreased expression of AMPARs and GABA receptor pathways [87,88]. In FXS, the uncon-
metabolism, release, and receptor expression of the GABAergic pathway may alter specific brain regions, such as basolateral amygdala, cerebral cortex, striatum, and hippocampus/subiculum, justifying the neurocognitive and psychiatric phenotypes observed in FXS [89].

In FXS patients, the treatment implications of excessive mGluR activation have been tested using different mGluR antagonists. Treatments with fenobam and acamprose resulted in reduction of ADHD core symptoms and improved communication skills, respectively [90,91]. In patients with a full methylation at FMR1 promoter, AFQ056 administration showed a significant improvement on stereotypes, hyperactivity, and inappropriate speech versus placebo [92]. A novel potential therapeutic target is represented by Striatal-Enriched protein tyrosine Phosphatase (STEP), involved in the inappropriate AMPA and NMDA receptors internalization, and ERK1/2 pathway dysregulation observed in FXS animal models. STEP levels are elevated in Fmr1 KO mice and probably mediate the exaggerated mGluR-dependent LTD, thus contributing to synaptic weakening, consequent cognitive deficits and predisposition to seizures [93].

5. Future directions

Both ASDs and ADHD are common disorders in childhood epilepsy, and this co-occurrence may share a strong genetic basis. Future studies are required to assess the bidirectional relationship between these conditions. Functional genetic studies will shed further light on the biological mechanisms by which genetic variants predispose to ASDs/ADHD comorbidity associated with childhood epilepsy and hopefully may provide new insights for developing biologically tailored treatment options. However, a better knowledge can only be achieved by considering homogeneous populations of patients. Recently, dietary supplementation in Branched Chain Ketoacid Dehydrogenase Kinase (Bckdck) knock-out mice showed a significant improvement of neurobehavioral phenotype, providing hope that this form of Mendelian autism associated with ID and epilepsy, may represent a potentially treatable syndrome [94].

While a developmental framework offers a way of understanding the pathogenic complexity of epilepsy and associated comorbidities, the current lack of longitudinal data does not allow to disentangle how different combinations of genetic-environmental risk factors may disrupt developmental trajectories in the brain leading to distinguished neurobiological deficits, and to different clinical endophenotypes.

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