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Review Article

# Role of GABAergic signaling and the $GABA_A$ receptor subunit gene cluster at 15q11-q13 in autism spectrum disorders, schizophrenia, and heroin addiction

Chia-Chun Huang [a,b], Chia-Hsiang Chen [a,c,d,*]

[a] Institute of Medical Sciences, Tzu Chi University, Hualien, Taiwan
[b] Department of Anesthesiology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan
[c] Division of Mental Health and Addiction Medicine, Institute of Population Health Sciences, National Health Research Institutes, Miaoli, Taiwan
[d] Department of Psychiatry, Chang Gung Memorial Hospital- Linkou Medical Center, Chang Gung University College of Medicine, Taoyuan, Taiwan

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ABSTRACT

Autism spectrum disorders, schizophrenia, and heroin addiction are all complex disorders with both genetic and environmental components to their etiology. The most common chromosomal abnormality in autism is a maternally derived duplication at 15q11-q13, which is where a cluster of gamma-aminobutyric acid ($GABA_A$) receptor subunit genes lies. In addition, copy number variations in this area have been implicated in the pathogenesis of schizophrenia. These findings suggest that GABAergic signaling might play a crucial role in contributing to susceptibility to the development of autism and schizophrenia. Furthermore, there is considerable evidence supporting a role for GABA neurotransmission in mediating the addictive properties of heroin. Hence, this review explores recent findings related to the involvement of GABAergic system in autism, schizophrenia, and heroin addiction. We also outline the implications that the presence of genetic variants in the $GABA_A$ receptor subunit cluster at 15q11-q13 may have on the risk of developing these psychiatric disorders. Finally, we make recommendations for future work that might help define the mechanisms underpinning the neuropathology that contributes to these psychiatric disorders.


## 1. Introduction

Segmental low copy repeats within chromosome 15q may mediate rearrangements during meiosis and these may contribute to the deletions or duplications in this region [1]. Paternal and maternal derived deletions of 15q11-q13 are known to result in the Prader-Willi and Angelman syndromes, respectively. Both conditions have some symptoms associated with autism [2]. Patients harboring a duplication overlapping the Prader-Willi/Angelman syndrome critical region may present with distinctive clinical manifestations, including hypotonia, developmental delay, intellectual disability, epilepsy, dysmorphic features, and autistic behavior [3]. In fact, the most common chromosomal abnormality in autism is a maternally derived 15q11-q13 duplication that accounts for 1%–3% of cases [4]. Nevertheless, chromosomal abnormalities within the interval 15q11-q13 are not restricted to childhood-onset neurodevelopmental disorders and several recent studies have implicated copy number variations (CNVs) within this region as risk factors for schizophrenia and other psychoses [5–7]. Thus, genes located within the 15q11-q13 chromosomal area might be considered as candidate genes for autism, schizophrenia, and other psychiatric disorders. These findings also provide evidence supporting the notion that an overlapping genetic etiology may exist among these psychiatric diseases.

A cluster of gamma-aminobutyric acid ($GABA_A$) receptor subunit genes lies within the chromosome 15q11-q13 area. These are GABRB3, GABRA5, and GABRG3, which encode subunits β3, α5, and γ3, respectively [2]. $GABA_A$ receptors are the major inhibitory ligand-gated chloride channels in the human brain. Typical synaptic $GABA_A$ receptors are heteropentamers comprising two α, two β, and a γ subunit [8]. Binding of GABA to $GABA_A$ receptors activates and opens the chloride channels. In the adult brain, this hyperpolarizes neurons and inhibits neuronal activity due to a chloride influx. However, in the developing brain, GABA acts as an excitatory neurotransmitter. In this circumstance, $GABA_A$ receptor activation results in a net chloride outflow and depolarization of the neurons because of the high intracellular chloride concentration [9]. Furthermore, it has been shown that GABAergic signaling

* Corresponding author. Division of Mental Health and Addiction Medicine, Institute of Population Health Sciences, National Health Research Institutes, 35, Keyan Road, Zhunan, Miaoli, Taiwan. Tel.: +886 37 246166x36713; fax: +886 37 586453.
*E-mail address:* cchen@nhri.org.tw (C.-H. Chen).

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system plays a crucial role during the whole period of neural tissue development, from the proliferation of neural progenitor cells, through migration and differentiation of neuronal precursor cells, to synaptogenesis and synapse refinement [10]. Together, these findings indicate that altered GABAergic signaling may contribute substantially to the pathogenesis of neurodevelopmental disorders such as autism in view of its important role during the entire period of neural genesis. Since there is strong evidence recognizing schizophrenia as having a neurodevelopmental origin [11–13], as well as the possibility that the disease might a shared biological pathway with autism [14], GABAergic signaling may be considered to potentially contribute to vulnerability to schizophrenia.

Accumulating evidence has linked GABAergic neurotransmission with heroin addiction, which is a highly relapsing disease [15]. There is considerable evidence indicating a significant genetic contribution to the development of substance abuse, and genetic studies have been successful at identifying genetic variants that act as risk factors for heroin addiction. Although research on the effect of the GABAergic signaling system on heroin addiction is still at an early stage, study in this area might serve as a basis for understanding the mechanism underlying this disease.

Here we review the evidence for the role of the GABAergic signaling in autism, schizophrenia, and heroin addiction. We also provide a brief overview of the genetic clues indicating that variants in the $GABA_A$ receptor subunit cluster at 15q11-q13 might influence the risk of developing these psychiatric disorders.

## 2. GABAergic signaling and the $GABA_A$ receptor subunit gene cluster at 15q11-q13 in relation to autism

Autism spectrum disorders (ASDs), encompassing autistic disorder, Asperger syndrome, and pervasive developmental disorder-not otherwise specified (PDD-NOS), are a constellation of neurodevelopmental disorders characterized by clinical hallmarks related to deficits in social interactions and language development, as well as the presence of restricted interests and/or repetitive behaviors. The prevalence of ASD is estimated to be approximately one per 110 children [16]. ASD affects males more than females, with a male-to-female ratio of approximately 4:1 [17]. The concordance rate for monozygotic twins is 70%–90% compared with that for dizygotic twins of 0%–10% [18,19]. In addition, the risk to siblings of being related to an affected individual is 2%–8%, which is 20–80 times higher than that in the general population [20]. These findings provide strong evidence for the contribution of genetic factors to the development of ASD.

A 48%–61% decrease in the glutamic acid decarboxylase 65 kDa and 67 kDa proteins (GAD65 and GAD67), which are isoforms of the rate-limiting enzymes in the synthesis of GABA, has been reported in the parietal and cerebellar brain areas of subjects with autism [21]. In addition, reductions in the protein levels of $GABA_A$ receptor subunits α1-5, β1, and β3 have been observed in the brain of subjects with autism [22,23]. In contrast, the mRNA levels of the α4, α5, and β1 subunits in various regions of the brain are not consistent [23]. In a postmortem study, Fatemi and colleagues detected significant reductions in the mRNA levels of the α4, α5, and β1 subunits in the BA9 area of patients with autism, while the mRNA levels for the α4, α5, and β1 subunits in cerebella of subjects with autism were significantly increased; this suggests discordant results between the proteins and mRNAs for some subunits. Moreover, aberrant GABAergic signaling has been shown to result in an autistic-like phenotype in mice [24]. Together, these results imply that an imbalance between the excitatory and inhibitory neurotransmission pathways within the central nervous system is involved in the pathogenesis of ASD [25].

It has long been recognized that a maternally derived 15q11-q13 duplication is responsible for 1%–3% of autism. Several studies have reported a genetic association between common variants in the $GABA_A$ receptor subunit cluster at 15q11-q13 and autism [26–28], supporting the existence of risk alleles for autism in this region. Among the three genes, *GABRB3* is the most extensively studied [29]. Furthermore, the rare mutation hypothesis has gained increasing appreciation recently [30] due to a study reporting that a maternally inherited rare mutation in the signal peptide of GABRB3 is associated with autism [31]. This mutant subunit has been proven to be unstable compared with the wild type subunit and may cause synaptic dysfunction that is relevant to autism. In addition, the authors have provided the first evidence of a rare coding variant of *GABRB3* that is associated with autism. These findings provide further support not only for the involvement of *GABRB3*, but also for impaired GABAergic signaling being associated with autism.

## 3. GABAergic signaling and $GABA_A$ receptor subunit gene cluster at 15q11-q13 in relation to schizophrenia

Schizophrenia is a neurodevelopmental disorder with a strong genetic component that affects approximately 1% of the worldwide population [32]. The clinical hallmarks are hallucinations, delusions, cognitive deficits, and affect disturbances. The heritability of schizophrenia is estimated to be approximately 80% [33]. Despite recent advances in genomic technology, the exact mechanism underlying schizophrenia remains largely unknown.

Just as for autism, an imbalance between excitatory and inhibitory neurotransmission pathways has also been implicated in the pathogenesis of schizophrenia [34]. The involvement of the GABA neurotransmission pathway in schizophrenia has been indicated by multiple lines of evidence. For example, in postmortem studies, reduced mRNA expression of the presynaptic GABA neurotransmission component, glutamic acid decarboxylase 67 kDa protein (GAD67), has been noted in the GABAergic interneurons in the dorsolateral prefrontal cortex (DLPFC) of subjects with schizophrenia [35,36]. The altered GABAergic signaling found in schizophrenia is not restricted to the DLPFC; in the lateral cerebellar hemisphere, a decrease in mRNA expression of the GAD65 and GAD67 together with an increase in mRNA expression of the $GABA_A$ receptor α6 and δ subunits has also been found [37]. Similar reductions in mRNA expression of the GAD65 and GAD67 have also been revealed in the hippocampus of patients with schizophrenia [38].

Further evidence for the importance of the 15q11-q13 region has emerged from genetic studies of this region. Microdeletions at 15q11.2 and 15q13.3 are now considered to be susceptibility factors for schizophrenia [5,6,39]. Furthermore, it has been documented that the frequency of a 6-Mb maternally derived duplication of chromosome 15q11.2-q13.1 among patients with schizophrenia is significantly higher than that among control subjects [7]. The possible mechanism of action by which CNVs predispose individuals to schizophrenia has been hypothesized to include gene dosage effects, position effects, and disruption of genes [40]. Thus, genes located within this region might be considered as candidates for investigating their potential involvement in schizophrenia. A previous genetic association study demonstrated that a microsatellite marker of *GABRB3* is associated with manifestation of hallucinations in subjects with schizophrenia [41]. To date, although no rare mutation has been identified for schizophrenia in the $GABA_A$ receptor gene cluster located in this region, identifying disease-causing or disease-modifying mutations in this gene cluster or genes located within 15q11-q13 remains a hypothetical

possibility for schizophrenia on the basis of the prior knowledge of the biological functions of the products of these genes.

## 4. GABAergic signaling and $GABA_A$ receptor subunit gene cluster at 15q11-q13 in relation to heroin addiction

Heroin, which is a semisynthetic form of morphine, has been considered to be one of the most addictive substances in the world. Heroin addiction is a chronic highly relapsing disease characterized by obsession, compulsion, or physical/psychological dependence. The heritability of heroin addiction is estimated to be approximately 40%–60% [42], implying that genetic factors may play a crucial role in predisposing individuals to this disorder. Since this complex disorder can cause a huge economic burden on the community [43], genetic studies identifying these variants are needed to explore its possible pathogenesis. However, little is known about the precise mechanism underlying heroin addiction.

It has been proposed that the binding of opioids to the opioid receptors hyperpolarizes GABA-containing interneurons in the ventral tegmental area and inhibits GABA release, which in turn may disinhibit dopaminergic neurons [44]. This enhances dopamine release and increases the firing rate of dopamine-containing neurons in the nucleus accumbens, which has a critical role in the reinforcing effects of opioids abuse [45]. Furthermore, it has been shown that an elevation of the mesolimbic GABA concentration is able to block heroin self-administration in rats [15]. Taken together, these results support a role for the GABAergic system in opioid addiction. Given that heroin binds to the opioid receptors present on GABA interneurons and that the GABA concentration might play a role in heroin self-administration, GABA receptor subunit genes need to be considered as candidates for potential involvement in developing heroin addiction and need to be investigated.

A recent genetic study showed that a single nucleotide polymorphism (SNP) (rs7165224) located close to the *GABRB3* gene, which encodes the $GABA_A$ receptor β3 subunit, is associated with heroin addiction in African Americans [46]. Although this association was not significant after correction for multiple testing, the contribution of *GABRB3* to vulnerability to heroin addiction cannot be completely excluded.

## 5. Conclusions and future directions

Autism, schizophrenia, and heroin addiction are all complex diseases with complex genetic etiologies. Significant progress has been made in searching for genes and susceptibility alleles that increase the risk of these diseases. Despite the progress in these genetic studies, a comprehensive understanding of the molecular mechanisms of these diseases is still lacking. Furthermore, pathway-based investigations have only recently been utilized to unravel the mystery of such complex diseases [47]. Thus, further exploration of various neurotransmission pathways, such as glutamatergic signaling and cholinergic signaling, is warranted.

The last decade has seen a revolution in genetic technologies, and now identifying numerous genetic variants can be achieved in a significant number of individuals within a limited time. For example, exome sequencing has been developed and used to search for protein-altering mutations that are responsible for complex disorders [48,49]. This approach effectively allows the identification, analysis and study of functional variants in known and unknown genes. In addition, much work is still required that focuses on the relationship between genes and other biologic variables, including the environment, in order to broad our understanding of the neurobiology of these type of disorders. These approaches will be crucial to the development of better diagnosis of diseases like autism, schizophrenia, and heroin addiction as well as improved treatment strategy of these diseases.

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