

## Short Communication

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## Decreased GAD2 in Schizophrenia

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**Received:** May 06, 2024; **Accepted:** May 14, 2024; **Published:** May 20, 2024**Introduction**

Schizophrenia is a complex psychiatric disorder characterized by a range of symptoms, including hallucinations, delusions, cognitive impairments, and changes in emotional expression. The etiology of schizophrenia is multifactorial, involving genetic, environmental, and neurobiological factors. Among the various hypotheses proposed to explain the pathophysiology of schizophrenia, the role of the glutamate neurotransmitter system, and specifically the glutamic acid decarboxylase 2 (GAD2) gene, has been a subject of research interest.

GABA, the major inhibitory neurotransmitter in mammalian brain, has been implicated in both brain development and schizophrenia. Two genes, GAD1 and GAD2, control GABA synthesis [1, 2].

Although viable, GAD2 deficient mice are susceptible to seizures, show a reduction in GABA release during prolonged activation of inhibitory neurons, and decreased GABA release in the visual cortex with potassium stimulation [3,4].

GAD2 plays a role in the synthesis of GABA for synaptic release [5].

Located predominantly in synapses, GAD2 full length protein is associated with synaptic vesicles and produces synaptic GABA during intense neuronal activity [6].

Glutamate decarboxylase 2 (GAD2) is an enzyme that in humans is encoded by the GAD2 gene and is likely to be important for GABA synthesis during sustained periods of neuronal activity [7-9].

The GAD2 gene is involved in the synthesis of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the brain. It has been hypothesized that genes involved in the glutamate neurotransmitter system, including GAD2, could be candidates for schizophrenia susceptibility [10].

Reductions in GABAergic and dopamine neuron markers have been linked in schizophrenia, with evidence of reductions across multiple brain regions [10]. Specifically, reductions in gene and protein expression of GABAergic inhibitory interneuron markers and other GABA-related molecules have been demonstrated [10].

This includes a reduction in GAD gene and protein expression in the midbrain of individuals with schizophrenia [10].

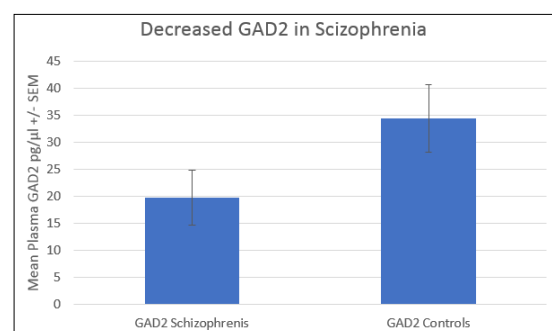
Genetic and environmental risk factors that predispose individuals to schizophrenia are believed to disrupt the development and normal functioning of the GABAergic system [11]. The development of the GABA system is a convergence point for these susceptibility factors [11]. Deficits in GAD1, a gene related to GAD2, and its relationships with other genes such as RELN, BDNF, NRG1, and DISC1, have been implicated in the neurodevelopmental aspects of schizophrenia [11].

Schizophrenia has also been hypothesized to involve autonomic nervous system dysfunction, leading to dysregulation of immune tolerance mechanisms in brain-resident and peripheral immune cells [12]. This dysregulation could lead to excessive production of pro-inflammatory cytokines and impaired fetal immune tolerance mechanisms, contributing to neurodevelopmental abnormalities [12].

In this study we used an ELISA to measure GAD2 levels in individuals with schizophrenia and neurotypical controls.

**Results**

We measured GAD2 levels in 22 schizophrenia patients and 19 age and gender similar neurotypical controls. We found that GAD2 levels were significantly lower in Schizophrenia patients compared to neurotypical controls ( $p=0.03$ ) (Figure 1).



**Figure 1:** GAD2 Levels are Significantly Lower in Schizophrenia Patients Compared to Neurotypical Controls ( $p=0.03$ )

## Discussion

In the four brain regions of the epigenetic animal model of schizophrenia, the expression of GABBR1, GAD1, and GAD2 genes increased significantly. Following administration of HDACI VPA, the mRNA expression of this gene in the four swbrain regions decreased or approached normal levels. GABBR1, GAD1 and GAD2 are likely to be the target genes affected by the HDACI VPA [12]. This supports the use of Valproate Acid therapy in schizophrenia.

Prenatal immune activation increased prefrontal levels of 5-methylated cytosines (5mC) and 5-hydroxymethylated cytosines (5hmC) in the promoter region of GAD1, which encodes the 67-kDa isoform of the GABA-synthesizing enzyme glutamic acid decarboxylase (GAD67). The early-life challenge also increased 5mC levels at the promoter region of GAD2, which encodes the 65-kDa GAD isoform (GAD65). These effects were accompanied by elevated GAD1 and GAD2 promoter binding of methyl CpG-binding protein 2 (MeCP2) and by reduced GAD67 and GAD65 mRNA expression [13]. This suggests that prenatal infection(s) may result in increased GAD2 and may be a precursor to the development of schizophrenia in offspring.

A study examining single nucleotide polymorphisms (SNPs) in the GAD2 gene found no significant associations with schizophrenia after correcting for multiple testing [14]. This suggests that GAD2 may not play a major role in the pathogenesis of schizophrenia [14].

Research has shown that the expression of the full-length GAD2 transcript is decreased in the dorsolateral prefrontal cortex (DLPFC) of patients with schizophrenia and bipolar disorder [15]. Conversely, a truncated transcript of GAD2 is increased in bipolar disorder patients but decreased in schizophrenia patients [15].

These findings indicate that alternative transcripts of GAD2 could be important in the development of GABA-synthesizing neurons and in the abnormal GABA signaling observed in these disorders [15].

Recent studies have focused on abnormalities in the GABA system in the postmortem brains of individuals with schizophrenia [16]. The reduction of GAD67, another isoform of glutamate decarboxylase, has been of particular interest due to its role in  $\gamma$ -oscillations and potential involvement in cognitive dysfunction in schizophrenia [16]. GAD67 knockout rats exhibit impairments in spatial working memory, suggesting a link between GAD67 reduction and cognitive impairment [16].

The expression of GAD2 full length transcript is decreased in the human dorsolateral prefrontal cortex of schizophrenia and bipolar disorder patients, while GAD2 truncated transcript is increased in bipolar disorder patients but decreased in schizophrenia patients [14].

This supports our finding that GAD2 levels are lower in individuals with schizophrenia and suggests that GAD2 may be associated with the etiology of the disorder.

The research on GAD2 in schizophrenia presents a complex picture. While initial studies did not find a significant association between GAD2 gene polymorphisms and schizophrenia, subsequent research has highlighted the importance of GAD2 expression and alternative transcripts in the disorder. The GABAergic system's involvement in schizophrenia, particularly

the role of GAD67, remains a promising area for understanding the neurobiological underpinnings of the disorder and for developing potential therapeutic targets [17].

Further research is needed to elucidate the precise role of GAD2 and the GABAergic system in schizophrenia, as well as the interplay between genetic, neurodevelopmental, and immune factors in the etiology of this complex disorder.

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