Current Understanding of Neurodevelopmental Diseases Linked to *SLC6A1*

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Abstract

monogenic cause of neurodevelopmental diseases such as epilepsy with myoclonic atonic seizures, autism spectrum disorder, and intellectual impairment thanks to advances in gene identification. The principal inhibitory neurotransmitter in the central nervous system, GABA, is reabsorbed from the extracellular space by the GABA transporter protein type 1 that is encoded by the solute carrier family 6 member 1 gene. In order to balance neuronal excitement, GABAergic inhibition is crucial, and when it is considerably disturbed, seizures and developmental abnormalities result. Understanding of the genotypic and phenotypic range of this condition is expanded by the collection of patient variations and documented clinical symptoms. We evaluate genetics here. & behavioral traits in 116 people who have solute carrier family 6 members 1 mutation; the great majority of these polymorphisms are predicted to cause loss-of-function of GABA transporter protein type 1. The gathered knowledge will direct therapy choices and the creation of focused therapies that specifically improve transporter function and may alleviate symptoms. We examined the location of the patient and control missense variations in a unique GABA transporter protein type 1 protein structure model, as well as the longitudinal and cell type-specific expression of solute carrier family 6 members 1 in humans. Here, we provide an update on the knowledge and treatment of illnesses associated with the solute carrier family 6 members 1 that has resulted from the combined efforts of doctors, researchers, and family support organizations.

Introduction

Since the first reports of SLC6A1-related illnesses in 2015, developmental and epileptic encephalopathies are increasingly being linked to these conditions. GABA is reuptake into presynaptic neurons and glia by the GABA transporter protein type 1 (GAT1), which is encoded by the gene *SLC6A1*. Neurodevelopmental problems, such as intellectual impairment, autism spectrum disorder, and seizures of various forms and intensities, are frequently caused by the disruption of *SLC6A1*. *SLC6A1* was identified among the top 10-20 genes with the highest number of harmful mutations in the current three biggest genomic screenings of people with epilepsy Collaborative. *SLC6A1* was among the top 10 genes in the largest variation enrichment in autistic patients compared to 23,598 controls in the current investigation. Recently, uncommon de novo missense mutations in SLC6A1 were shown to be related to schizophrenia in three patients after exome sequencing of people with schizophrenia, broadening the phenotypic range beyond epilepsy, the overall incidence of SLC6A1-related diseases is expected to be per 100,000 newborns. We summarise the current state of research and future directions following the second SLC6A1 Symposium hosted by the SLC6A1 Connect Foundation 1 October 2020, date last accessed. The symposium brought together academic scientists, medical professionals, and family advocacy organizations. With associated clinical phenotyping, we gathered and curated the largest collection of SLC6A1 variations to date. Our research marks a substantial advance in the definition of the clinical and genotypic range of SLC6A1-related illnesses and will eventually aid in clinical treatment. In transmembrane domains, which are required for the conformational shifts throughout the transport process, key residues for sodium and substrate binding have been identified using homology models based on a 20%–25% sequence similarity to GAT1. The SLC6A1 gene is one of 20 paralogues in a gene family. Six of these proteins, which are expressed by 13 of these genes, can transport GABA to varying degrees and show greater than 80% sequence similarity. Abnormalities of neurodevelopment Broer and Gether, In compared to variations from the general population, disease-associated variants identified in various family members significantly cluster together in two amino acid regions after linear protein sequence alignment of the 13 most paralogue-conserved gene family members. Any missense variant detected in these areas is 106 times more likely to be labeled as pathogenic than benign. These areas are known as pathogenic variant enriched regions. However, disease-causing mutations in SLC6A1 among afflicted people are widely dispersed along its sequence, as in the case of many other genetic etiologies connected to neurodevelopmental disorders.

Conclusion

The mammalian central nervous system expresses the SLC6A1 gene, mostly in the adult frontal cortex. While GAT1 may be found in astrocytes, *oligodendrocytes*, and *microglia*, it is almost exclusively expressed in *GABAergic* axon terminals, unlike other GABA transporters. Although the *GABAergic* system continues to fully develop until puberty, GAT1 is produced inside fully functioning *GABAergic* neurons throughout embryonic development even before glutamatergic excitatory activity. GABA transporters link the elimination of the electrochemical gradient for sodium and chloride with the translocation of GABA. By diffusing these ions in a predetermined ratio across the membrane. In the absence of GABA, GABA binds to GAT1 and causes a leak current mediated by alkali ions. Last but not least, GAT1 produces a sodium-dependent capacitive current in the absence of GABA. GAT1 activation can result in a shunt for membrane resistance or local changes in membrane potential via these currents. The frequency, amplitude, and kinetics of spontaneous GABA postsynaptic currents are unaffected, but tonic inhibition is enhanced and the decay time of evoked phasic currents mediated by GABA receptors is extended in GAT1 defective animals. It's interesting to note that other studies using GAT1-deficient animals demonstrate a decrease in the frequency of little inhibitory postsynaptic currents. This impact is linked to an uptick in the production of enzymes that help produce GABA in inhibitory neurons' presynaptic terminals.

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