GRIN2A Gene

Subjects: Genetics & Heredity
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Glutamate ionotropic receptor NMDA type subunit 2A

Keywords: genes

1. Introduction

The *GRIN2A* gene provides instructions for making a protein called GluN2A (formerly known as NR2A). This protein is found in nerve cells (neurons) in the brain and spinal cord, including regions of the brain involved in speech and language. The GluN2A protein is one component (subunit) of a subset of NMDA receptors. There are several types of NMDA receptors, made up of different combinations of protein components. NMDA receptors are glutamate-gated ion channels; when brain chemicals called glutamate and glycine attach to the receptor, a channel opens, allowing positively charged particles (cations) to flow through. The flow of cations generates currents that activate (excite) neurons to send signals in the brain. NMDA receptors are involved in normal brain development, changes in the brain in response to experience (synaptic plasticity), learning, and memory. They also appear to play a role during deep (slow-wave) sleep.

The GluN2A subunit of NMDA receptors determines where in the brain the receptor is located and how it functions. It also provides the site to which glutamate binds.

2. Health Conditions Related to Genetic Changes

2.1. Epilepsy-aphasia spectrum

More than 50 mutations in the *GRIN2A* gene have been identified in some people with conditions that fall along the epilepsy-aphasia spectrum. This group of conditions is characterized by abnormal electrical activity in the brain, usually during slow-wave sleep; a loss of speech and language skills and sometimes other developmental skills; and in many cases, recurrent seizures (epilepsy). Landau-Kleffner syndrome (LKS) and epileptic encephalopathy with continuous spike-and-wave during sleep (ECSWS) are at the severe end of the spectrum, while childhood epilepsy with centrotemporal spikes (CECTS) is at the mild end. Several other conditions have signs and symptoms of intermediate severity.

Many *GRIN2A* gene mutations lead to production of a nonfunctional GluN2A protein or prevent the production of any protein at all. These mutations likely lead to a reduced number of NMDA receptors containing the GluN2A subunit. Researchers suspect that, as a result, signaling occurs through other types of NMDA receptors that more easily excite neurons, leading to excessive signaling in the brain. Other mutations lead to production of abnormal GluN2A proteins that likely alter how the NMDA receptors function, possibly increasing signaling. Excessive activity of neurons in the brain can lead to seizures and other abnormal brain activity and may result in death of the neurons. Changes in GluN2A appear to specifically affect signaling in regions of the brain involved in speech and language and disrupt brain activity during slow-wave sleep, leading to several of the signs and symptoms of this group of conditions. It is not clear why some *GRIN2A* gene mutations lead to a relatively mild condition and others cause more severe signs and symptoms.

2.2. Other disorders

GRIN2A gene mutations have been found in people with neurological disorders that have features similar to epilepsy-aphasia spectrum disorders (described above) but lacking consistent language problems. These shared features can include recurrent seizures (epilepsy), often of a type that originates from abnormal activity in the rolandic region of the brain (rolandic epilepsy); intellectual disability; and developmental delay. Some people with mutations in chromosome 16 that delete the *GRIN2A* gene as well as other nearby genes also have unusual facial features. The varying effects of different *GRIN2A* gene mutations and how they contribute to different neurological disorders are under study.

3. Other Names for This Gene

- EPND
- GluN2A
- glutamate receptor ionotropic, NMDA 2A isoform 1 precursor
- glutamate receptor ionotropic, NMDA 2A isoform 2 precursor
- glutamate receptor, ionotropic, N-methyl D-aspartate 2A
- LKS
- N-methyl D-aspartate receptor subtype 2A
- N-methyl-D-aspartate receptor channel, subunit epsilon-1
- N-methyl-D-aspartate receptor subunit 2A
- NMDAR2A
- NR2A

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