

LGI1 in Epilepsy: Genetic Synaptopathies and Autoimmune Mechanisms

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ABSTRACT: Epilepsy is a devastating neurological condition affecting an estimated 50 million individuals worldwide, arising from neuronal hyperexcitability due to disrupted excitatory-inhibitory balance. Mutations in the LGI1 (leucine-rich glioma inactivated 1) gene are the most common cause of Autosomal Dominant Lateral Temporal Lobe Epilepsy (ADLTE), a condition characterized by auditory and aphasic auras, often progressing into focal seizures. Moreover, the production of anti-LGI1 antibodies, inhibiting LGI1-ADAM22/23 interaction through blocked binding sites, causes anti-LGI1 Autoimmune Encephalitis, a distinct AE subtype. Patients with this condition suffer from memory disturbance, seizures, and may exhibit psychiatric symptoms (e.g., hallucinations, delirium). These pathophysiological mechanisms of LGI1 dysfunction (genetic and autoimmune) both give rise to epileptic conditions. Thus, it is a significant protein in understanding the molecular biology behind epilepsy and may have implications for the future of diagnosis and treatment of epilepsy. This literature review focuses on the structure, physiological function, and seizure-related disruption of LGI1, which regulates AMPA-R clustering through LGI1-ADAM22/23 and PSD95 interaction, linking presynaptic and postsynaptic proteins to stabilize excitatory synaptic transmission.

KEYWORDS: Medical and Health Sciences, Neurobiology, Epilepsy, Synaptic Transmission, LGI1.

■ Introduction

Epilepsy is one of the oldest and most common neurological conditions known to mankind, affecting individuals of both sexes and all ages.^{1,2} The World Health Organization estimates that 50 million individuals worldwide have a diagnosis of epilepsy at any given time.³ It is a chronic disorder characterized by recurrent, unprovoked seizures; seizures are alterations of neurologic function caused by the excessive, hypersynchronous discharge of neurons in the brain.^{4,5} Symptoms of epilepsy include loss of consciousness, anxiety, confusion, staring spells, muscle jerking/twitching, and muscle stiffness, as shown in Figure 1.⁶

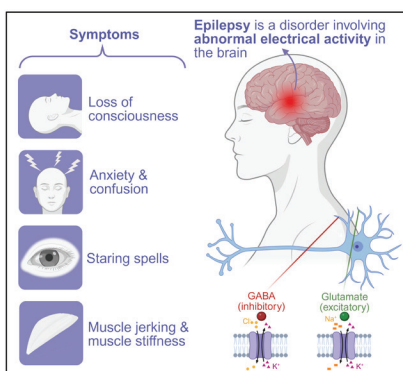


Figure 1: Epilepsy symptoms and neuronal role. Schematic illustration depicting a focal region of abnormal neuronal activity within the brain, with a simplified representation of a neuron highlighting disrupted excitatory-inhibitory signaling. Excessive glutamatergic excitation and reduced GABAergic inhibition increase neuronal firing through altered ion fluxes (e.g., K⁺, Cl⁻, Na⁺), leading to hyperexcitability and seizures. Symptoms include: loss of consciousness and confusion arising from disruption across many brain regions, staring spells indicating impairments of awareness, and involuntary muscle movement arising from abnormal neuronal activity. Created using biorender.com.

As depicted in Figure 1, normal neuronal function involves receiving a mix of transmitted signals. Glutamate (released at excitatory synapses) binds to receptors and increases the likelihood of the neuron firing an action potential, whereas GABA (released at inhibitory synapses) binds to receptors and decreases the likelihood of the neuron firing an action potential.^{7,8} The excitatory/inhibitory balance determines whether a neuron becomes active or remains silenced; in epilepsy, seizures are caused by hyperexcitability stemming from this imbalance, causing groups of neurons to become hyperexcitable and fire in a hypersynchronous manner, producing sustained abnormal discharges in the brain.^{9,10}

Most epilepsy pathophysiology mechanisms can be grouped into channelopathies, synaptopathies, structural abnormalities of the brain, and autoimmune mechanisms. Channelopathies, or ion channel dysfunction, are caused by mutations in voltage-gated or ligand-gated ion channels, which alter neuronal excitability, leading to repetitive firing.^{11,12} Synaptopathies, or synaptic protein dysfunction, involve abnormalities in proteins that govern synapse regulation, altering neuronal excitability and disrupting the excitatory/inhibitory balance.¹³ Structural abnormalities causing epilepsy include malformations of cortical development,¹⁴ or acquired causes such as brain tumors or trauma. Autoimmune mechanisms arise due to autoantibodies against synaptic proteins (e.g. anti- α -amino-3-hydroxy-5-methyl-4- isoxazolepropionic-acid receptor (anti-AMPA), anti-N-methyl-D-aspartate receptor (NMDAR)), which cause protein dysfunction, leading to hyperexcitability in autoimmune encephalitis.^{15,16}

Another way of categorizing epilepsy cases is by seizure type. There are three major categories of epileptic seizure types classified by the International League Against Epilepsy (ILAE),

most recently revised in 2017.¹⁷ The first category is epilepsy characterized by focal (partial) seizures, which have a specific origin in the brain; they can be further subdivided into focal aware seizures, in which consciousness is preserved, and focal impaired awareness seizures, in which consciousness is disrupted or lost.^{18,19} The second category is epilepsy, characterized by generalized seizures, which occur in both hemispheres of the brain simultaneously.²⁰ The third category involves seizures of unknown onset, if there is insufficient information to classify them.¹⁷

To understand the molecular biology of epilepsy, it is important to analyze different mechanistic categories of epilepsy pathophysiology, especially through the lens of proteins whose dysfunction gives rise to epileptic phenotypes. One such protein is LGI1, which is particularly relevant to epilepsy research due to its dual vulnerability to two mechanistic categories of epilepsy pathophysiology mentioned above: synaptopathies and autoimmune disorders. In Autosomal Dominant Lateral Temporal lobe Epilepsy (ADLTE), inherited mutations in the LGI1 gene impair excitatory-inhibitory balance and synaptic maturation.²¹ In anti-LGI1 Autoimmune Encephalitis (AE), antibodies disrupt LGI1's extracellular interactions.²² Despite their distinct origins (genetic versus autoimmune), the mechanisms causing ADLTE and anti-LGI1 AE affect the same proteins, and both produce epileptic phenotypes. Therefore, LGI1 is shown to have a central role in maintaining synaptic integrity and to be suitable as a model of synaptic vulnerability. This review analyzes the molecular mechanisms underlying ADLTE and anti-LGI1 AE through the LGI1 network, and discusses the implications of this analysis on our understanding, diagnosis, and treatment of epilepsy.

■ Discussion

LGI1 (leucine-rich, glioma inactivated 1) has emerged as a particularly suitable model of synaptic vulnerability in epilepsy. LGI1 is uniquely positioned at the excitatory synapse, where it forms trans-synaptic complexes to maintain the stability of synaptic transmission. Disruption of this role is linked to epileptic phenotypes exhibited in ADLTE and anti-LGI1 Autoimmune Encephalitis. Therefore, a thorough analysis of LGI1 provides an opportunity to examine the relationship between synaptic dysfunction and epilepsy.

LGI1-mediated protein interaction at the synapse:

LGI1 (leucine-rich, glioma inactivated 1) is a secreted neuronal synaptic protein that plays key roles in excitatory neurotransmission, synaptic maturation, and maintaining network stability.²³ In a study, purification of neuronal LGI1 led to the isolation of abundant components of the LGI1-mediated protein complex. The relevant proteins in understanding LGI1 protein network function include ADAM22 and other ADAM family members (ADAM23, 11) and Post Synaptic Density Proteins (PSD95, PSD93).²⁴

ADAM22 is associated with the PSD95 complex found in excitatory postsynaptic densities; ADAM22 has a short C-terminal intracellular sequence that anchors it to PSD95 through its PDZ domain.²⁵ PSD95 anchors AMPA recep-

tors by interacting with Stargazin, a TARP (transmembrane AMPA-R regulatory protein).^{22,26} The LGI1-ADAM22 complex stabilizes AMPA receptors by reinforcing their connection to PSD95, making it essential for efficient regulation of excitatory neurotransmission. It has been shown that the LGI1-ADAM22 complex forms a tether that aligns presynaptic glutamate release sites with postsynaptic AMPA receptors, proving it is fundamental for transsynaptic nanoalignment, as shown in Figure 2.²⁷ Although LGI1 has been proven to bind ADAM23 through ELISA tests and transfected HEK cells, there is still uncertainty surrounding their direct interaction and physiological function.^{28,29} However, ADAM23 is a major receptor of LGI1 and is likely to play an important role, presumably in regulating neurotransmission.³⁰

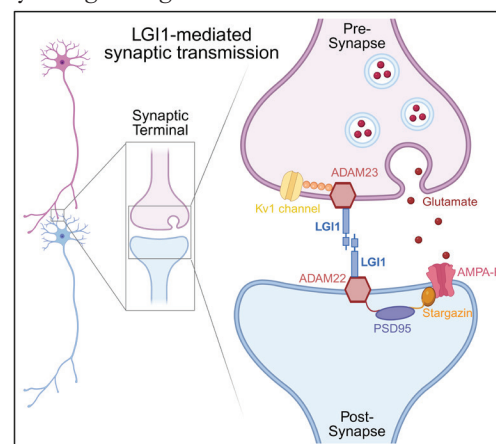


Figure 2: LGI1 in the trans-synaptic space. Schematic depicting transmission between excitatory neurons (from nerve endings of one neuron to dendrites of another) at the synaptic terminal. Calcium ions flood into the presynaptic terminal, causing vesicles to fuse with the membrane and release glutamate neurotransmitters into the synaptic cleft. Glutamate diffuses across the cleft and binds to AMPA receptors, which in turn causes an action potential in the postsynaptic neuron. LGI1 mediates this process by binding ADAM22 (postsynaptic) and ADAM23 (presynaptic), forming a transsynaptic tether. As ADAM22 interacts with the PSD95 scaffolding protein, the LGI1-ADAM22 complex stabilizes and clusters AMPA receptors by reinforcing their connection to PSD95 (which indirectly interacts with AMPA receptors through stargazin, a TARP). For the sake of simplicity, this diagram does not depict the complex 3:3 heterohexameric LGI1-ADAM22 assembly, showing only the interaction of LGI1 molecules with ADAM22/23. Created using biorender.com.

LGI1 protein structure:

LGI1 is a glycoprotein with a molecular mass of approximately 60-64 kDa.^{27,29} LGI1 is a member of the leucine-rich glioma inactivated family, which consists of secreted glycoproteins with a leucine-rich repeat domain, or LRR, and an epitempin domain, or EPTP, also known as the epilepsy-associated repeat domain (EAR).³¹ A computational rendering of the structure described below is depicted in Figure 3. The LRR domain contains four LRR repeats, flanked by LR-RNT (leucine-rich repeat N-terminal, the start of the chain) and LRRCT (leucine-rich repeat C-terminal, the end of the chain).³² Both the N-terminal and C-terminal are cysteine-rich and form intramolecular disulfide bonds that 'cap' the ends of the LRR solenoid, reinforcing its structural integrity, which is crucial to LGI1's role as a secreted protein.³³ The EPTP (epitempin) domain has seven EPTP repeats,

which fold into a structure that resembles a conical doughnut, known as a seven-bladed β -propeller; each blade is composed of a four-stranded antiparallel β -sheet.³⁴ Notable features of LGI1 EPTP are the disulfide bond inside the β -propeller and a Ca^{2+} ion bound inside the central channel, which stabilize the whole β -propeller structure and ensure correct orientation.³⁵ The name epitempin comes from the observation that this domain is found in LGI1 and another epilepsy-associated protein, GPR98 (a G-protein-coupled receptor).³⁶ Mutations in epitempin-encoding genes LGI1 and GPR98 both produce auditory symptoms such as noise-induced seizures or deafness.³⁷

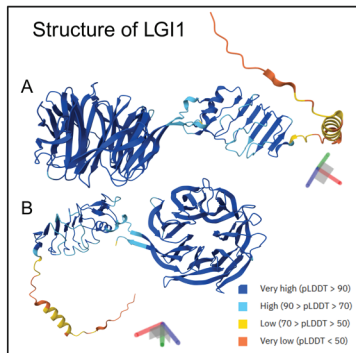


Figure 3: LGI1 protein structure. (A) Computational rendering of the LGI1 structure shows a sideways view of the EPTP domain β -propeller structure; β -pleated sheets are visible. LGI1 predominantly features β -pleated sheets in both its EPTP and LRR domains; it features minimal to no α -helices. (B) Another orientation of the LGI1 protein is shown, including a front view of the β -propeller structure consisting of seven four-stranded antiparallel β -sheets folded into a doughnut-like shape, as well as the LRR domain and its β -pleated sheet composition. Source: alphafold.com.

The LGI1-ADAM22 complex:

ADAM family proteins consist of multiple domains, including a metalloproteinase domain, a disintegrin domain, a transmembrane domain, a cytoplasmic carboxy (C)-terminal tail, and an epidermal growth factor (EGF)-like domain.^{29,38} Eight of twenty-one ADAMs lack functional zinc metalloproteinase domains and are instead associated with protein-protein interactions instead of membrane protein ectodomain shedding (a type of post-translational modification).³⁹ Three ADAM proteins (ADAM22, ADAM23, ADAM11) bind to LGI1 and are solely expressed in the central nervous system.⁴⁰ ADAM22, the first major receptor of LGI1, has an intracellular domain that interacts with PSD-95 and AMPA receptors in the postsynaptic density, and an extracellular domain, or ECD, which interacts with LGI1 to govern transsynaptic nanoalignment.^{41,42} The seven-bladed β -propeller of LGI1 forms a hydrophobic pocket, and the metalloprotease-like domain of ADAM22 inserts into the hydrophobic pocket, forming a tight link, but without covalent bonding, as shown in Figure 4A.^{35,44}

Structural analysis through crystallization of the LGI1-ADAM22 complex revealed a 2:2 heterotetrameric assembly, meaning two LGI1 molecules and two ADAM22 molecules form a four-part complex, where each LGI1 binds to one ADAM22, and LGI1 molecules interact with each other.²⁷ In this way, it was proposed that LGI1 bridges two ADAM22

molecules through LRR-EPTP interaction of adjacent LGI1 molecules.³⁵ This 2:2 tetrameric configuration was further supported using cryo-electron microscopy analysis.⁴³ However, recent cryo-electron microscopy analyses have suggested the existence of a 3:3 heterohexameric higher-order complex, which forms a ring-like structure (where each LGI1 bridges two ADAM22 molecules), depicted in Figure 4B.^{27,44,45} This evolution in structural understanding suggests a more stable and functionally relevant synaptic architecture.

ADAM23, the second major receptor of LGI1, has an intracellular domain in the presynaptic density and an extracellular domain that interacts with LGI1. It likely interacts with LGI1 in a manner similar to ADAM22, since the amino acid sequence similarity between ADAM22 and ADAM23 is relatively high in humans (approx. 50%).^{27,46}

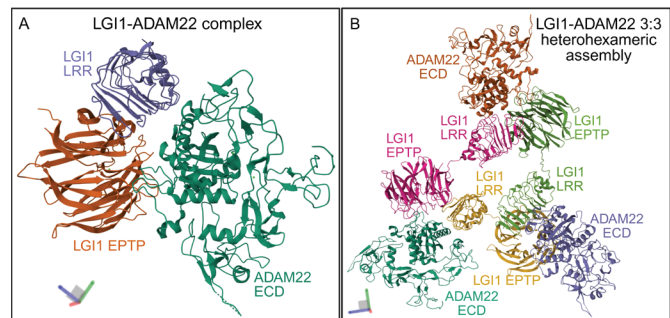


Figure 4: LGI1-ADAM22 complex and 3:3 heterohexameric assembly. (A) The metalloprotease-like domain (ECD) of ADAM22 interacts directly with LGI1 EPTP by inserting into the hydrophobic pocket created by the seven-bladed β -propeller. LGI1 LRR interacts weakly/indirectly with ADAM22 ECD, providing structural support. (B) Three LGI1 molecules associated with three ADAM22 molecules in a symmetrical ring-like arrangement, forming a 3:3 heterohexameric higher-order assembly. The assembly stabilizes the LGI1-ADAM22 complex and allows it to perform its functions (organizing AMPA receptors via ADAM22-PSD95 interactions, etc.). Structure determined experimentally by cryo-electron microscopy (cryo-EM). Source: RCSB Protein Data Bank.

LGI1 pathogenic mutations in ADLTE:

Autosomal dominant lateral temporal lobe epilepsy (ADLTE), also known as autosomal dominant partial epilepsy with auditory features (ADPEAF), is a genetic focal epilepsy syndrome characterized by recurrent seizures with aura suggestive of a lateral temporal lobe onset.^{35,47,48} The lateral temporal lobe (especially the superior temporal gyrus and middle temporal gyrus) houses primary and association auditory cortex and the language comprehension area. Therefore, ADLTE symptoms include auditory auras and aphasic auras, often progressing to focal seizures. Visual and olfactory symptoms have also been reported.^{49,50}

Interestingly, déjà vu, defined by V.M. Neppe in 1983 as “any subjectively inappropriate impression of familiarity of a present experience with an undefined past”, has been reported as a predominant feature of seizures in ADLTE patients in several cases.^{51,52} The explanation can be inferred by an experiment done by Halgren in 1978, who proved that a ‘dreamy state’, consisting of vivid memory-like hallucinations and déjà vu, can be evoked by electrical stimulation of the lateral temporal neocortex, as a result of spontaneous seizures.⁵³

ADLTE is associated with inherited mutations in the LGI1, RELN, and MICAL1 genes.⁵⁴ This literature review focuses on the primary, most common cause of ADLTE, which is LGI1 and its pathogenic mutations. Several secretion-positive mutations, including R474Q and R407C, impair LGI1's ability to bind to neuronal receptors ADAM22/23 by altering its EPTP domain, which is crucial for receptor binding.⁵⁵ The R474Q mutation disables the tripartite complex assembly of ADAM22, ADAM23 and LGI1 by disrupting LGI1-LGI1 interaction. Many secretion-defective mutations cause protein misfolding, including A110D, I122K, and R136W. Other secretion-defective mutations cause disruption of disulfide bonds, including C46R (disruption of the disulfide bond with C55) and C200R (disruption of the disulfide bond with C177).^{24,27,35} These mutations, among others, are named and organized by location in Figure 5.

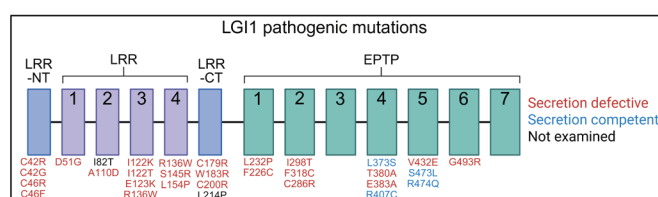


Figure 5: Pathogenic LGI1 mutations. Diagram showing known pathogenic LGI1 mutations, separated into secretion-defective (causing misfolding or disruption of disulfide bonds), secretion-competent (LGI1 is secreted, but there is disruption of binding to ADAM22 or other LGI1 molecules), and not experimentally examined. The mutations are organized by the location on LGI1 they affect; the LRR domain is split into the N-terminal, C-terminal, and 4 LRR repeats, & the EPTP domain is split into the 7 EPTP repeats. As shown, all secretion-competent mutations known affect the EPTP domain. Created using biorender.com.

Pathogenic LGI1 mutations, regardless of secretion status, disrupt LGI1's physiological function, which is to bind ADAM22/23, forming a transsynaptic tether.²⁹ Secretion-defective mutations cause LGI1 to misfold and be trapped in the endoplasmic reticulum, unable to be secreted into the synaptic cleft to bind ADAM22/23. Secretion-competent mutations prevent LGI1 from properly binding to ADAM22/23, breaking the transsynaptic complex.⁵⁶ This causes AMPA-R clustering to be disturbed, and the excitatory/inhibitory balance is not fully maintained, leaning towards hyperexcitability (especially in the lateral temporal cortex, a region where auditory and association processing is abundant).^{57,58}

Beyond its central role in maintaining AMPA receptor clustering in mature synapses, LGI1 is also a regulator of synaptic maturation and participates in broader developmental processes.⁵⁹ In murine models, LGI1 mRNA and protein are expressed during embryonic brain development, and expression persists and often increases postnatally. Studies emphasize its functional importance during the postnatal period, suggesting its role in synaptic maturation.^{60,61} Expression of LGI1 during development follows an orchestrated pattern and is regionally specific, particularly in cortical and temporal regions (which show seizure susceptibility).⁶² This implies that LGI1 may be involved in shaping brain architecture and neuronal function during brain development. Therefore, in ADLTE, pathogenic LGI1 mutations are likely to disrupt not only synaptic

stabilization at mature excitatory synapses but also synaptic maturation, leading to hyperexcitability in regions susceptible to epilepsy, such as the lateral temporal cortex.

Anti-LGI1 autoimmune encephalitis:

Autoimmune encephalitis (AE) comprises a group of inflammatory brain disorders characterized by acute or subacute onset of symptoms, including seizures, memory impairment, altered consciousness, and behavioral change.^{63,64} They are caused by immune responses against neuronal antigens, often autoantibodies against antigens localized on the neuronal cell surface or at synapses, leading primarily to functional neuronal disruption (as opposed to structural disruption).⁶⁵

Anti-LGI1 antibody-associated autoimmune encephalitis, an AE subtype, is the second most prevalent autoimmune encephalitis after anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, accounting for 20-35% of seropositive cases.⁶⁶ Other AE subtypes include anti-NMDAR, anti-CASPR2, anti-GABAR, and anti-AMPA.⁶⁷ Patients with anti-LGI1 antibodies develop symptoms of limbic encephalitis, manifesting in memory disturbance, distinct seizure types, confusion, etc. Patients may also show psychiatric symptoms such as hallucinations, delusions, and delirium with disorganized speech.⁶⁷

At the molecular level, LGI1 antibodies associated with limbic encephalitis inhibit LGI1-ADAM22/23 interaction by targeting the EPTP domain of LGI1, greatly reducing synaptic AMPA receptor clusters.⁶⁸ Reduced LGI1-ADAM22/23 interaction is the most reasonable pathogenic mechanism for limbic encephalitis. This is supported by the fact that genetic deletion of LGI1 or ADAM22/23 causes lethal epilepsy in murine models and is further backed up by the presence of secretion-defective LGI1 mutations in ADLTE.³⁰ Although knowledge on the precise mode of action of LGI1 antibodies remains incomplete, synaptic autoimmune disorders are thought to involve antibody-mediated dysfunction of target ion channels and key synaptic proteins, such as NMDAR and AMPAR, leading to network hyperexcitability, causing seizures.⁶⁹

■ Conclusion

Epilepsy is a common neurological condition caused by the disruption of excitatory-inhibitory neuronal balance (hyperexcitability), leading to seizures. As previously discussed, LGI1 is a fundamental regulator of synaptic transmission, as LGI1-mediated interactions with ADAM22/23 and PSD95 are essential in AMPA-R clustering; it is uniquely positioned to act as a transsynaptic 'tether', linking presynaptic and postsynaptic proteins. ADLTE and anti-LGI AE represent two distinct mechanisms causing epilepsy (one genetic and one autoimmune) that converge on the same molecular pathway involving dysfunction of LGI1-mediated synaptic stabilization. In ADLTE, pathogenic mutations impair the secretion of LGI1 or its ability to form a functional complex with ADAM22/23, whereas in anti-LGI AE, autoantibodies block this interaction at the synapse. Another significant difference is that ADLTE is a developmental disorder arising from abnormalities during brain development, while anti-LGI AE is an

acquired disorder that develops after normal brain development (as a result of autoantibodies). However, both conditions destabilize AMPAR clustering and disrupt excitatory neurotransmission, leading to hyperexcitability in the network. This similarity highlights LGI1 as a critical player in seizure susceptibility.

One diagnostic implication involves genetic testing for LGI1 mutations in ADLTE; however, in practice, genetic testing for LGI1 may not be widely performed. This may be due to the presence of other possible gene mutations causing ADLTE (such as RELN), although LGI1 mutations make up most cases. It may also be due to a diagnosis based on EEG findings and symptoms alone. Nevertheless, earlier identification of LGI1-related ADLTE may prevent misdiagnosis from finding no structural abnormalities; clinicians must understand the genetic component of ADLTE. A second diagnostic implication involves early testing for anti-LGI1 antibodies in patients with seizures, limbic symptoms, or other symptoms relevant to autoimmune encephalitis. Consideration of anti-LGI1 antibodies could prevent delayed diagnosis. Even so, anti-LGI1 antibody testing sensitivity and specificity may not be optimal.

Understanding LGI1 and its pathophysiology is highly relevant to future implications on the treatment of ADLTE and anti-LGI1 AE. Current treatments mostly suppress seizures and treat symptoms rather than correcting the underlying molecular dysfunction. For example, current treatment of ADLTE remains symptomatic, but gene editing may be a plausible treatment in the future. Another future direction could be administering drugs to stabilize synaptic transmission or moderate network excitability in ADLTE, compensating for LGI1 dysfunction. In contrast, anti-LGI1 autoimmune encephalitis is already treated, often effectively, through immunotherapy. However, it may be useful to understand anti-LGI1 autoantibody mechanisms to optimize immunotherapy in the future. Of note, because this literature review primarily focuses on LGI1 as a model of synaptic transmission in epilepsy, it focuses on excitatory synaptic dysfunction, particularly AMPA-R clustering, whereas epilepsy arises from an excitatory-inhibitory imbalance in a wider neuronal network. Alterations in inhibitory GABAergic transmission were not investigated in depth. In addition, zooming in on a single molecular pathway risks oversimplifying the complexity of the pathophysiology of epilepsy; further exploration into other mechanistic categories is needed.

In conclusion, LGI1 and its associated epilepsies illustrate how disruption of a single synaptic protein can give rise to diverse epileptic phenotypes, underscoring the significance of molecular mechanisms in understanding, diagnosis, and treatment of epilepsy. As our understanding of synaptic protein networks deepens, LGI1 may serve as a reference point for analyzing other epilepsy-associated synaptic proteins, paving the way for molecular mechanism-based diagnosis and therapies.

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