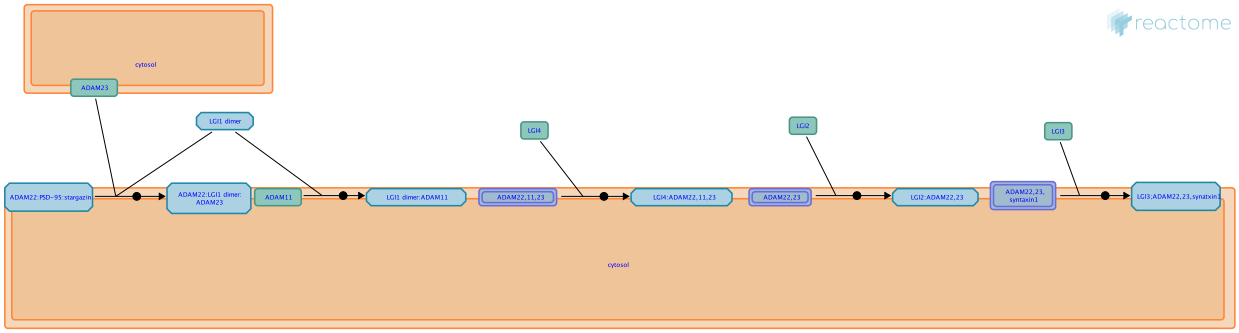
LGI-ADAM interactions



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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

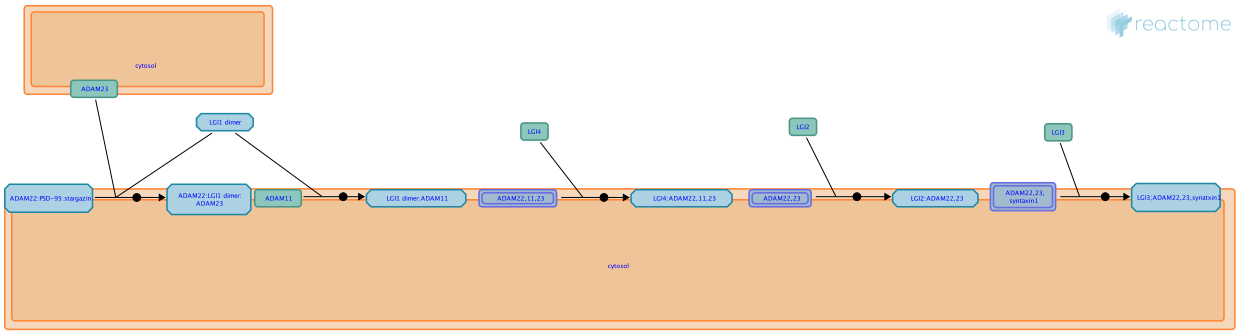
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

LGI-ADAM interactions ↗

Stable identifier: R-HSA-5682910

Compartments: extracellular region



Synapse formation and maturation require multiple interactions between presynaptic and postsynaptic neurons. These interactions are mediated by a diverse set of synaptogenic proteins (Kegel et al. 2013, Siddiqui & Craig 2011). Initial synapse formation needs both the binding of secreted proteins to presynaptic and postsynaptic receptors, and the direct binding between presynaptic and postsynaptic transmembrane proteins. One class of molecules that plays an important role in cellular interactions in nervous system development and function is the leucine-rich glioma inactivated (LGI) protein family. These are secreted synaptogenic proteins consisting of an LRR (leucine-rich repeat) domain and a epilepsy-associated or EPTP (epitempin) domain (Gu et al. 2002). Both protein domains are generally involved in protein-protein interactions. Genetic and biochemical evidence suggests that the mechanism of action of LGI proteins involves binding to a subset of cell surface receptors belonging to the ADAM (a disintegrin and metalloproteinase) family, i.e. ADAM11, ADAM22 and ADAM23. These interactions play crucial role in the development and function of the vertebrate nervous system mainly mediating synaptic transmission and myelination (Kegel et al. 2013, Novak 2004, Seals & Courtneidge 2003).

Literature references

Kegel, L., Aunin, E., Meijer, D., Bermingham, JR. (2013). LGI proteins in the nervous system. *ASN Neuro, 5*, 167-81. ↗

Editions

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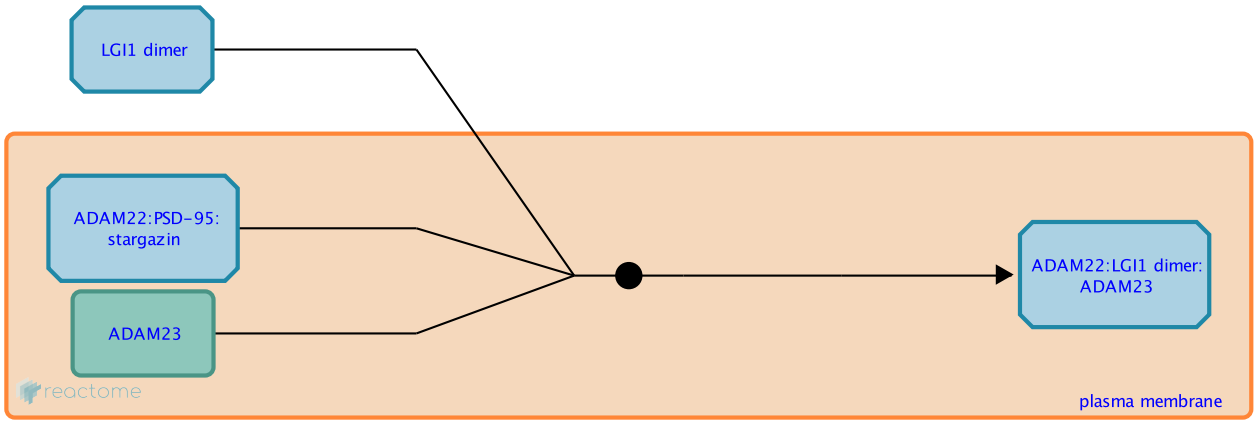
LGI1 binds ADAM22 and ADAM23 ↗

Location: LGI-ADAM interactions

Stable identifier: R-HSA-5682794

Type: binding

Compartments: plasma membrane, extracellular region



Leucine-rich glioma inactivated 1 (LGI1) is a secreted protein that interacts with ADAM (A Disintegrin And Metalloprotease) transmembrane proteins, and its mutations are linked to human epilepsy. Although LGI1 mutations can cause epilepsy, its precise functions in the CNS are still poorly understood. It has been suggested to be involved in controlling synaptic transmission at excitatory synapses and cerebellar development (Xie et al. 2015, Fukata et al. 2006). LGI1 binds simulatneously to the extracellular disintegrin domain of ADAM22 and ADAM23 with its EPTP (Epitempin) domain (Fukata et al. 2010) strengthening and stabilizing excitatory synapses. LGI1 interaction with ADAM23 modulates dendritic pruning and synapse elimination during development (Owuor et al. 2009, Zhou et al. 2009). LGI1 and ADAM22 are found to be part of a tripartite complex containing PSD95. PSD95 is expressed on the inner surface of postsynaptic neurons and with its third PDZ domain binds to ADAM22 cytoplasmic C-terminal ETSI-motif and with the first two PDZ domain in turn bind to stargazin. Stargazin is a transmembrane regulatory subunit of AMPA (alpha-amino-3- hydroxy-5-methylisoxazole-4-propionic acid)-receptors that is critical for AMPA-receptor trafficking and gating (Fukata et al. 2006). It has been suggested that LGI1 binds simultaneously ADAM23 and ADAM22, pulling pre and post-synaptic membranes together, physically stabilizing synapses containing these two proteins and strengthening neurotransmission in these synapses (Fukata et al. 2010). As mentioned earlier, LGI1 mutations result in ADPEAF (autosomal dominant partial epilepsy with auditory features) (OMIM 600512) (Kalachikov et al. 2002).

Literature references

Fukata, Y., Adesnik, H., Iwanaga, T., Bredt, DS., Nicoll, RA., Fukata, M. (2006). Epilepsy-related ligand/receptor complex LGI1 and ADAM22 regulate synaptic transmission. *Science, 313*, 1792-5. ↗

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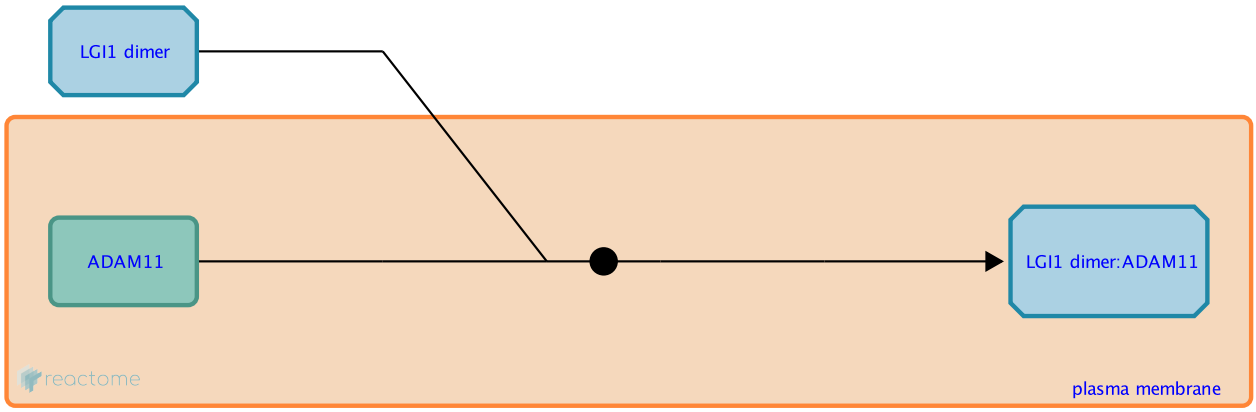
LGI1 binds ADAM11 ↗

Location: LGI-ADAM interactions

Stable identifier: R-HSA-5682826

Type: binding

Compartments: plasma membrane, extracellular region



In addition to ADAM22 and ADAM23, LGI1 also binds to ADAM11 (Sagane et al. 2008). ADAM11 is essential for a proper neuronal function because ADAM11-deficient mice showed deficits in special learning, motor coordination and nociceptive response (Takahashi et al 2006a,b).

Literature references

Sagane, K., Ishihama, Y., Sugimoto, H. (2008). LGI1 and LGI4 bind to ADAM22, ADAM23 and ADAM11. *Int. J. Biol. Sci.*, *4*, 387-96. ↗

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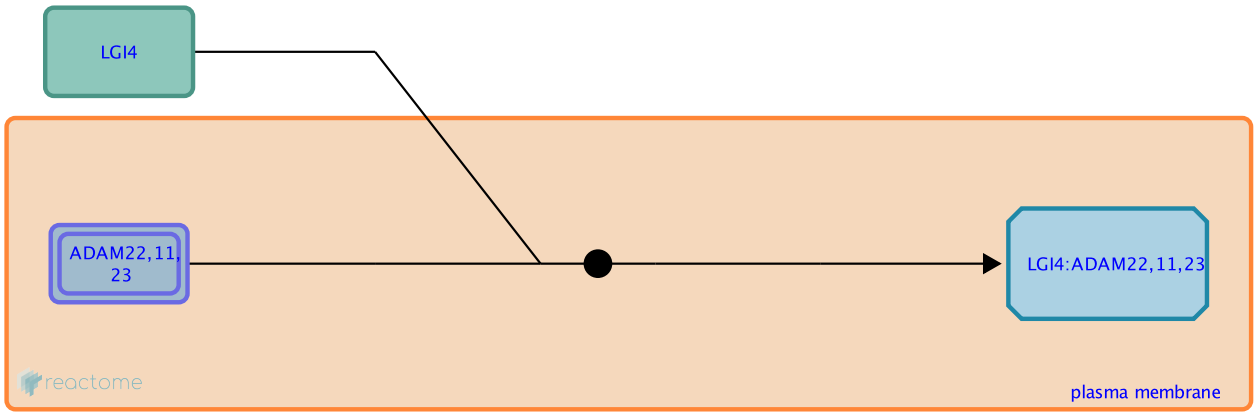
LGI4 binds ADAM22,23,11

Location: LGI-ADAM interactions

Stable identifier: R-HSA-5682709

Type: binding

Compartments: plasma membrane, extracellular region



Leucine-rich glioma inactivated 4 (LGI4) protein is another candidate ligand for ADAM22 receptor. Schwann cells secrete LGI4, which through binding to the axonal receptor ADAM22 drives axonal ensheathment and myelination in the peripheral nervous system (PNS) but not central nervous system. LGI4 secretion defect results in inability of Schwann cells to correctly myelinate peripheral nerves, resulting in peripheral nervous system hypomyelination and the murine claw-paw phenotype (Birmingham et al. 2006). LGI4 interacts with not only ADAM22 but also interacts moderately with ADAM11 and ADAM23 (Ozkaynak et al. 2010, Sagane et al. 2008, Nishino et al. 2010).

Literature references

Sagane, K., Ishihama, Y., Sugimoto, H. (2008). LGI1 and LGI4 bind to ADAM22, ADAM23 and ADAM11. *Int. J. Biol. Sci., 4*, 387-96.

Ozkaynak, E., Abello, G., Jaegle, M., van Berge, L., Hamer, D., Kegel, L. et al. (2010). Adam22 is a major neuronal receptor for Lgi4-mediated Schwann cell signaling. *J. Neurosci., 30*, 3857-64.

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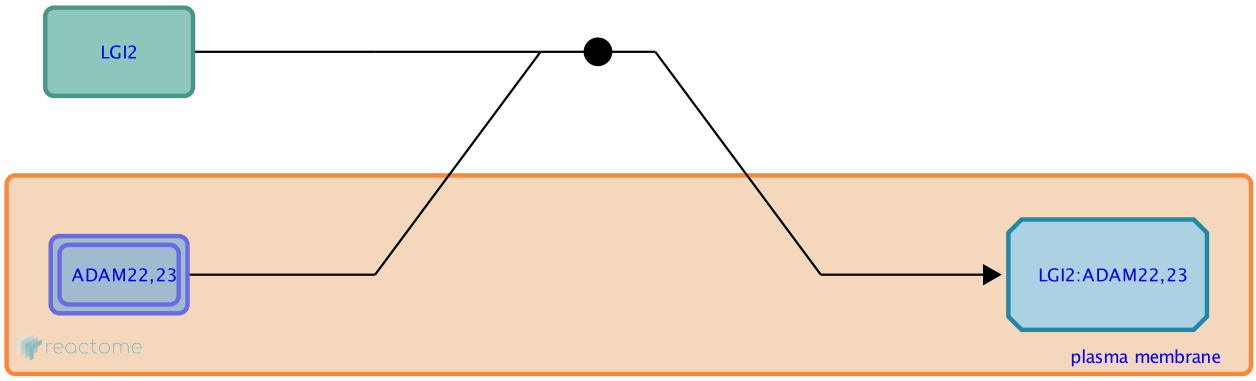
LGI2 binds ADAM22,23 ↗

Location: LGI-ADAM interactions

Stable identifier: R-HSA-5682769

Type: binding

Compartments: extracellular region, plasma membrane



Leucine-rich glioma inactivated 2 (LGI2) like LIG1, is neuronally secreted and acts on ADAM (a-disintegrin-and-metalloproteinase) family of neuronal membrane proteins, which function in synapse remodelling. Based on the experiments performed in canine and rat brain it proves that LGI2 interacts with ADAM22 and ADAM23 following secretion. Truncation of Lgi2 prevents its secretion and ADAM interactions causing remitting focal-onset epilepsy in dogs between ages one and four months, which is equivalent to human two to eight years. It has been suggested that LGI2 participates in protecting the brain against seizures during the pruning phase of neurodevelopment (Seppala et al. 2011).

Literature references

Seppälä, EH., Jokinen, TS., Fukata, M., Fukata, Y., Webster, MT., Karlsson, EK. et al. (2011). LGI2 truncation causes a remitting focal epilepsy in dogs. *PLoS Genet., 7*, e1002194. ↗

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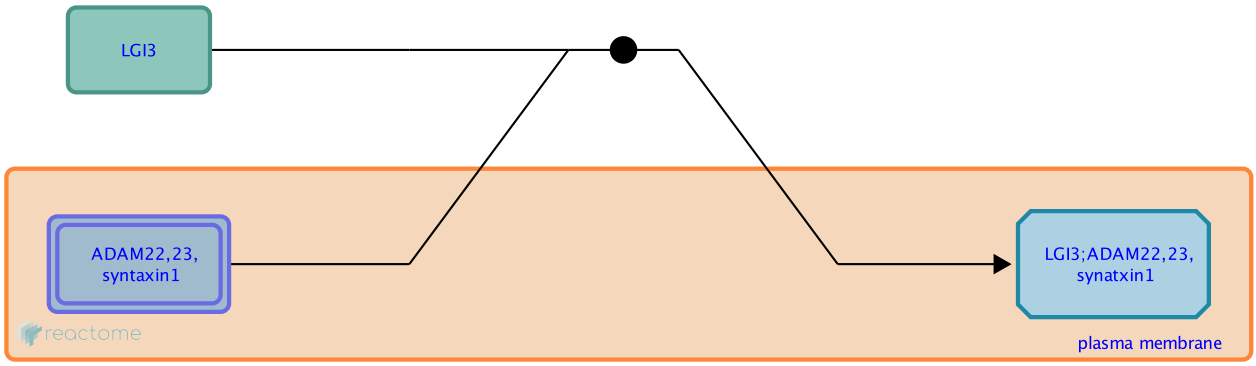
LGI3 binds ADAM22,23,synatxin1 ↗

Location: LGI-ADAM interactions

Stable identifier: R-HSA-5682802

Type: binding

Compartments: extracellular region, plasma membrane



Leucine-rich glioma inactivated 3 (LGI3) is a secreted protein and a member of LGI/epitempin family expressed in the peripheral nerve and interacts with ADAM22 and ADAM23 as well as syntaxin1 in the presynaptic SNARE complex. LGI3 is suggested to be involved in multiple functions. It induces neurite outgrowth and increases phosphorylation of the signal transduction proteins AKT and FAK (focal adhesion kinase) (Park et al. 2010). It appears to promote amyloid beta and synataxin1 endocytosis (Kimura et al. 2007, Okabayashi & Kimura 2008,2010).

Literature references

Kimura, N., Ishii, Y., Suzaki, S., Negishi, T., Kyuwa, S., Yoshikawa, Y. (2007). Abeta upregulates and colocalizes with LGI3 in cultured rat astrocytes. *Cell. Mol. Neurobiol., 27*, 335-50. ↗

Okabayashi, S., Kimura, N. (2010). LGI3 interacts with flotillin-1 to mediate APP trafficking and exosome formation. *Neuroreport, 21*, 606-10. ↗

Park, WJ., Lim, YY., Kwon, NS., Baek, KJ., Kim, DS., Yun, HY. (2010). Leucine-rich glioma inactivated 3 induces neurite outgrowth through Akt and focal adhesion kinase. *Neurochem. Res., 35*, 789-96. ↗

Okabayashi, S., Kimura, N. (2008). Leucine-rich glioma inactivated 3 is involved in amyloid beta peptide uptake by astrocytes and endocytosis itself. *Neuroreport, 19*, 1175-9. ↗

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