reactome

Defective SLC17A8 causes autosomal dominant deafness 25 (DFNA25)

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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. ↗

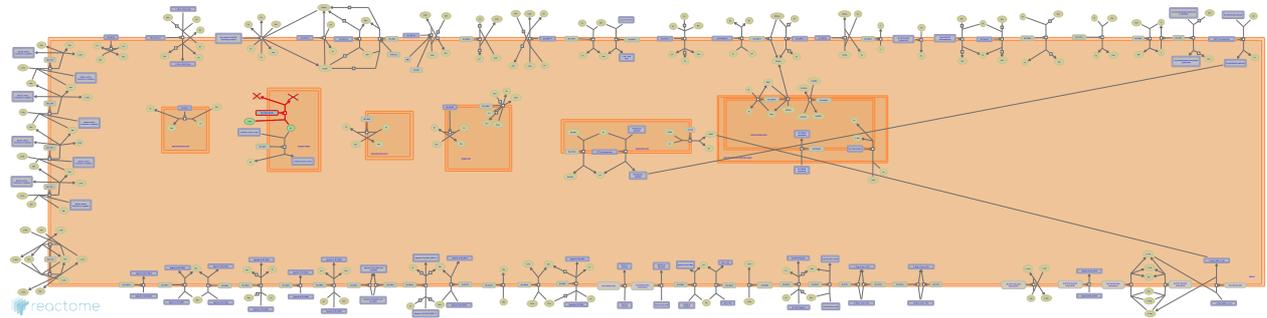Reactome database release: 74

This document contains 1 pathway and 1 reaction (see Table of Contents)

Defective SLC17A8 causes autosomal dominant deafness 25 (DFNA25) ↗

Stable identifier: R-HSA-5619076

Diseases: autosomal dominant nonsyndromic deafness

There are two classes of glutamate transporters; the excitatory amino acid transporters (EAATs) which depend on an electrochemical gradient of Na+ ions and vesicular glutamate transporters (VGLUTs) which are proton-dependent. Together, these transporters uptake and release glutamate to mediate this neurotransmitter's excitatory signal and are part of the glutamate-glutamine cycle. Three members of the SLC17A gene family (7, 6 and 8) encode VGLUTs 1-3 respectively. This uptake is thought to be coupled to the proton electrochemical gradient generated by the vacuolar type H+-ATPase. They are all expressed in the CNS in neuron-rich areas but SLC17A8 (VGLUT3) is also expressed on astrocytes and in the liver and kidney. Defects in SLC17A8 can cause autosomal dominant deafness 25 (DFNA25; MIM:605583), a form of non-syndromic sensorineural hearing loss. The cochlea expresses SLC17A8 and in mice which lack this transporter are congenitally deaf. Hearing loss is due to the lack of glutamate release by inner hair cells therefore a loss of synaptic transmission at the IHC-afferent nerve synapse. Successful restoration of hearing by gene replacement in mice could be a significant advance toward gene therapy of human deafness (Ruel et al. 2008, Akil et al. 2012).

Literature references

Akil, O., Seal, RP., Burke, K., Wang, C., Alemi, A., During, M. et al. (2012). Restoration of hearing in the VGLUT3 knockout mouse using virally mediated gene therapy. *Neuron, 75*, 283-93. ↗

Ruel, J., Emery, S., Nouvian, R., Bersot, T., Amilhon, B., Van Rybroek, JM. et al. (2008). Impairment of SLC17A8 encoding vesicular glutamate transporter-3, VGLUT3, underlies nonsyndromic deafness DFNA25 and inner hair cell dysfunction in null mice. *Am. J. Hum. Genet., 83*, 278-92. ↗

Editions

2014-08-22	Authored, Edited	Jassal, B.
2015-08-04	Reviewed	Broer, S.

Defective SLC17A8 does not exchange cytosolic L-Glu for synaptic vesicle H+ ↗
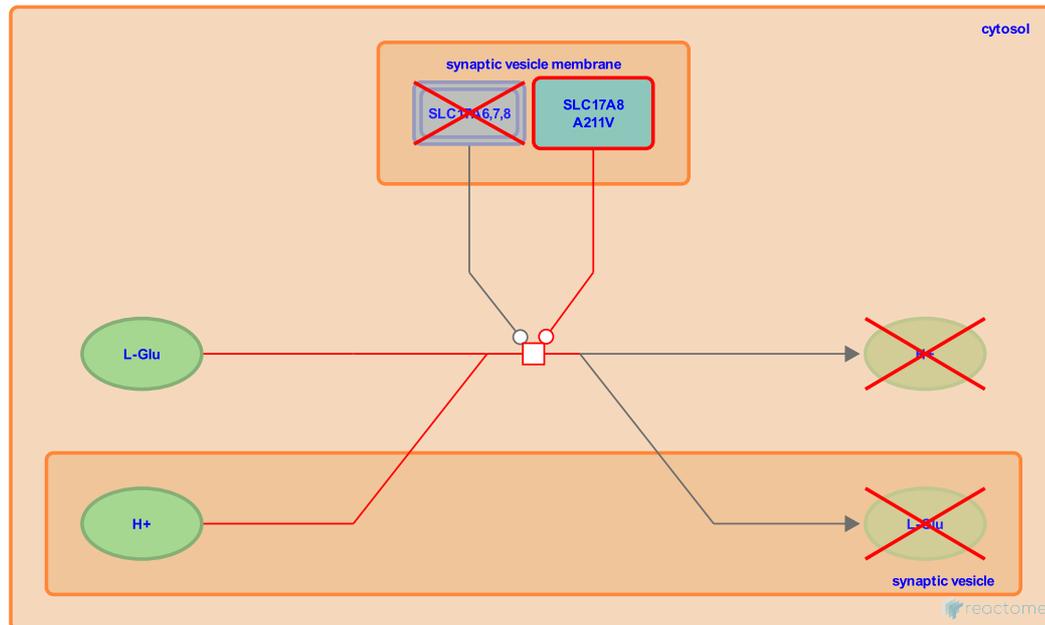
Location: Defective SLC17A8 causes autosomal dominant deafness 25 (DFNA25)

Stable identifier: R-HSA-5624256

Type: transition

Compartments: cytosol, synaptic vesicle, synaptic vesicle membrane

Diseases: autosomal dominant nonsyndromic deafness

There are two classes of glutamate transporters; the excitatory amino acid transporters (EAATs) which depend on an electrochemical gradient of Na+ ions and vesicular glutamate transporters (VGLUTs) which don't. Together, these transporters uptake and release glutamate to mediate this neurotransmitter's excitatory signal and are part of the glutamate-gluatamine cycle. Three members of the SLC17A gene family (7, 6 and 8) encode VGLUTs 1-3 respectively. This uptake is thought to be coupled to the proton electrochemical gradient generated by the vacuolar type H+-ATPase. They are all expressed in the CNS in neuron-rich areas but SLC17A8 (VGLUT3) is also expressed on astrocytes and in the liver and kidney. Defects in SLC17A8 can cause autosomal dominant deafness 25 (DFNA25; MIM:605583), a form of non-syndromic sensorineural hearing loss. The cochlea expresses SLC17A8 and in mice which lack this transporter are congenitally deaf. Hearing loss is due to the lack of glutamate release by inner hair cells therefore a loss of synaptic transmission at the IHC-afferent nerve synapse.

In two unrelated families, a heterozygous missense mutation, c.632C->T (p.A211V), was found to cause DFNA25. The A211 residue is conserved in VGLUT3 across species and in all human subtypes, suggesting an important functional role (Ruel et al. 2008).

Literature references

Ruel, J., Emery, S., Nouvian, R., Bersot, T., Amilhon, B., Van Rybroek, JM. et al. (2008). Impairment of SLC17A8 encoding vesicular glutamate transporter-3, VGLUT3, underlies nonsyndromic deafness DFNA25 and inner hair cell dysfunction in null mice. *Am. J. Hum. Genet., 83*, 278-92. ↗

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