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Gene Section
Mini Review

GPHN (Gephyrin)

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Identity

Other names: KIAA1385; GPHRYN

HGNC (Hugo): GPHN

Location: 14q23.3

Local order: The markers associated with the gephyrin sequence correspond to the D14S63-D14S1069 interval.

DNA/RNA

Description

29 exons (30 exons with the putative C1 exon), spanning over 800 kb.

Transcription

In a telomeric to centromeric direction. The alternative use of different exons, particularly of the exons termed C1 to C7, produces splice variants which are differentially expressed in the central nervous system and other tissues.

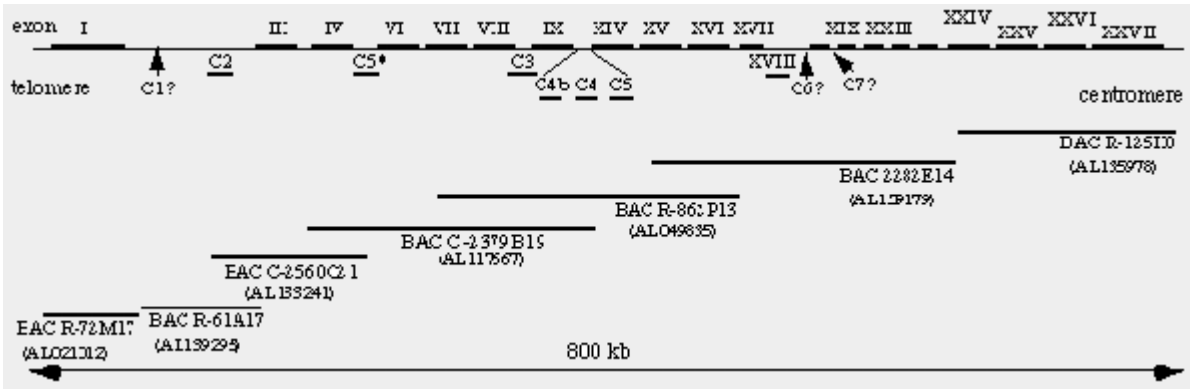
Protein

Note

Gephyrin is a cytoplasmic, peripheral membrane protein that anchors the GlyR as well as a subset of GABAA receptors to the subsynaptic cytoskeleton in neurons.

Description

736-770 amino acids; sizes varying from 93-105 kDa to smaller products 52-60 kDa. The N-terminal domain of gephyrin is homologous to the bacterial protein MogA, and the C-terminal domain is homologous to bacterial MoeA, both proteins being involved in the biosynthesis of Moco.



Exon-intron organization of the human gephyrin gene. Exons coding for the geghyrin are depicted by large traits and roman numerals with the alternative cassettes C1-C7 and exon VIII represented beneath the constant exons (exon VIII is putatively another cassette because one cDNA lacking this exon has been isolated). C1, C6 and C7 were not localized but their site of insertion is indicated by a ? as described . Exons and introns sizes are not drawn to scale. Exon I is telomeric to exon XXVII.

Expression

Wide if not ubiquitous, especially in brain, spinal cord, lung, liver and kidney. Precise distribution of expression of the different variants is not known.

Localisation

Gephyrin is a cytoplasmic, peripheral membrane protein.

Function

Anchor inhibitory neuronal receptors (glycine, GABA) to the sub-synaptic cytoskeleton; plays a role in Moco biosynthesis.

Homology

Bacterial MogA et MoeA, drosophila Cinnamon and Arabidopsis thaliana Cnx1.

Mutations

Note

Deletion of the exons 2 and 3 resulting into a frameshift after 21 codons of the normal coding sequence. No gephyrin detected in the patient's fibroblats.

Implicated in

Molybdenum cofactor (Moco) hereditary deficiency syndrome

Note

Disruption of the gephyrin gene is lethal at birth in the mouse. The mutant phenotype resembles that of humans with hereditary deficiency of molybdenum cofactor and hyperhekplexia, a disease which is associated with defects in glycinergic inhibition in many patients suggesting that gephyrin function may be impaired in patients affected by either of these two diseases.

Prognosis

Lethal in the three cases described.

t(11;14)(q23;q23) in ANLL --> MLL - GPHN

Abnormal protein

The fusion protein contains the MLL AT hook motifs and a DNA methyl transferase homology domain fused to the C-terminal part of Gephyrin, including a presumed tubulin binding site and a domain homologous to the Escherichia coli molybdenum cofactor biosynthesis protein MoeA.

To be noted

Note

High-titer antibodies against gephyrin have been identified in a patient with a mediastinal cancer and clinical features of stiff-man syndrome. These findings provided evidence for a link between autoimmunity directed against components of inhibitory synapses and neurologic conditions characterized by chronic rigidity and spams.

References

Prior P, Schmitt B, Grenningloh G, Pribilla I, Multhaup G, Beyreuther K, Maulet Y, Werner P, Langosch D, Kirsch J. Primary structure and alternative splice variants of gephyrin, a putative glycine receptor-tubulin linker protein. Neuron. 1992 Jun;8(6):1161-70

Feng G, Tintrup H, Kirsch J, Nichol MC, Kuhse J, Betz H, Sanes JR. Dual requirement for gephyrin in glycine receptor clustering and molybdoenzyme activity. Science. 1998 Nov 13;282(5392):1321-4

David-Watine B. The human gephyrin (GPHN) gene: structure, chromosome localization and expression in non-neuronal cells. Gene. 2001 Jun 27;271(2):239-45

Eguchi M, Eguchi-Ishimae M, Seto M, Morishita K, Suzuki K, Ueda R, Ueda K, Kamada N, Greaves M. GPHN, a novel partner gene fused to MLL in a leukemia with t(11;14)(q23;q24). Genes Chromosomes Cancer. 2001 Nov;32(3):212-21

Reiss J, Gross-Hardt S, Christensen E, Schmidt P, Mendel RR, Schwarz G. A mutation in the gene for the neurotransmitter receptor-clustering protein gephyrin causes a novel form of molybdenum cofactor deficiency. Am J Hum Genet. 2001 Jan;68(1):208-13

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