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BRAIN RESEARCH

Research Report

Regional distribution of the leucine-rich glioma inactivated (*LGI*) gene family transcripts in the adult mouse brain

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Abbreviations: ac, anterior commissure; Acb, accumbens nucleus; aci, anterior commissure, intrabulbar part; ACo, anterior cortical amygdaloid nucleus; AD, anterodorsal thalamic nucleus; AHA, anterior hypothalamic area; AOB, accesory olfactory bulb; AOD, anterior olfactory bulb, dorsal part; AOE, anterior olfactory bulb, external part; AOL, anterior olfactory bulb, lateral part; BA, basal amygdala; BLA, basolateral anterior amygdala; BMA, basomedial amygdaloid nucleus, anterior part; BST, bed nucleus of the stria terminalis; CA1, Ammon's horn 1; CA2, Ammon's horn 2; CA3, Ammon's horn 3; Ce, cerebellum; CeA, central amygdala; CIC, central nucleus of the inferior colliculus; CM, centromedial thalamic nucleus; CPu, caudate putamen; DC, dorsal cochlear nucleus; DCIC, dorsal cortex of the inferior colliculus; DD, deep dorsal nucleus; DeCe, dentate nucleus of the cerebellum; DeN, dentate nucleus; DEnd, dorsal endopiriform; DG, dentate gyrus; DGSC, deep gray layer of superior colliculus; Dk, Darkschewitsch nucleus; DpMe, deep mesencephalic nucleus; DR, dorsal raphe nucleus; DSub, dorsal subiculum; ec, external capsula; Ent, entorhinal cortex; EPL, external plexiform layer of the olfactory bulb; f, fornix; FC, fasciola cinereum; Gl, glomerular layer of the olfactory bulb; GrL, cerebellar granular layer; GrO, granular cell layer of the olfactory bulb; Hb, habenula; ic, inner capsula; icp, inferior cerebellar peduncle; IF, interfascicular nucleus; IGSC, inner gray layer of the superior colliculus; IO, inferior olive; IP, interpeduncular nucleus; IPl, internal plexiform layer of the olfactory bulb; La, lateral amygdala; LD, laterodorsal thalamic nucleus; LG, lateral geniculate nuclei; LH, lateral hypothalamic area; lHb, lateral habenula; LL, lateral lemniscus; LM, lateral mammillary nucleus; LP, lateral posterior thalamic nucleus; LPO, lateral preoptic area; LSd, lateral septal nucleus, dorsal part; LSi, lateral septal nucleus, intermediate part; LVe, lateral vestibular nucleus, dorsal part; MdR, medullary reticular nucleus; MeA, medial amygdala; mfb, medial forebrain bundle; MG, medial geniculate body; MGd, dorsal division of the medial geniculate body; MGv, ventral division of the medial geniculate body; mHb, medial habenula; Mi, mitral cell layer of the olfactory bulb; ML, lateral division of the medial mammillary nucleus; MM, medial division of the medial mammillary; MMn, median division of the medial mammillary nucleus; MnR, median raphe nucleus; MOB, main olfactory bulb; MoV, motor nucleus of the trigeminal nerve; MPO, medial preoptic area; MS, medial septal nucleus; MS/LS, transition area between medial and lateral septum; mta, mammillothalamic tract; mtg, mamillotegmental tract; NTS, nucleus of the solitary tract; Pa, pallidal nucleus; PAG, periaqueductal gray; PaV, paraventricular hypothalamic nucleus; pcvLGN, parvocellular division of the lateral geniculate nucleus; PIN, posterior intralaminar cortex; Pir, piriform cortex; Pn, pontine nuclei; PrV, principal nucleus of the trigeminus nerve; PTA, pretectal area; Pu, putamen; PVP, paraventricular thalamic nucleus, posterior division; pyx, pyramidal decussation; Re, reuniens thalamic nucleus; RF, reticular formation; RLi, rostral linear nucleus of the raphe; RN, red nucleus; RPC, red nucleus, parvicellular part; RPO, reticularis pontis oralis; Rt, reticular thalamic nucleus; SC, superior colliculus; SI, substantia innominata; sm, stria medullaris of the thalamus; SNc, substantia nigra, pars compacta; SNr, substantia nigra, pars reticulata; SpV, spinal trigeminal tract; st, stria terminalis; SuM, supramammillary nucleus; TT, taenia tecta; TS, triangular septal nucleus; VCA, ventral cochlear nucleus, anterior part; VCP, ventral cochlear nucleus, posterior part; vDB, nucleus of the vertical limb of the diagonal band; VL, ventrolateral thalamic nucleus; VP, ventral pallidum; VPL, ventral posterolateral thalamic nucleus; VPo, ventral posterior thalamic nucleus; VTA, ventral tegmental area; ZI, zona incerta

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ABSTRACT

The leucine-rich glioma inactivated (*LGI*) gene subfamily contains four highly conserved members (*LGI1*, *2*, *3* and *4*), which have been described in human, mouse and other mammalians. Although their main roles remain unknown, *LGI1* gene mutations have been found in human partial temporal lobe epilepsy. Moreover, previous studies showed that the products of these genes exert their function in the nervous system. The anatomical distribution of these gene transcripts in the brain might give some insight to elucidate their possible function. In this study, the pattern of expression of the four *LGI* genes was assessed in the brain of C57BL/*6J* adult mice by in situ hybridization. We found that the *LGI1* transcript is mainly expressed in the dentate gyrus and CA3 field of the hippocampus. *LGI2* and *LGI4* genes, which showed a similar pattern of distribution with minor differences, were mostly expressed in the medial septal area, thalamic reticular nucleus and substantia nigra pars compacta. *LGI3*-expressing cells were distributed widespread, but were more consistently observed in the hippocampal formation, thalamic and hypothalamic nuclei, substantia nigra and reticular formation. In summary, *LGI1* gene expression is very restricted to intrahippocampal circuitry, which might be related to its involvement in temporal lobe epilepsy. The patterns of expression of *LGI2* and *LGI4* genes are very similar and their distribution in the vertical limb of the diagonal band and in putative hippocampal interneurons suggests that the function of these genes might be related to the generation of hippocampal theta rhythm. Finally, *LGI3* gene widespread expression in the brain suggests that its transcripts might be involved in a common cellular process present in different neuronal types.

1. Introduction

The leucine-rich glioma inactivated (*LGI/Epitempin*) gene subfamily belongs to the large leucine-rich repeat protein family. Searching for homology sequences in public databases, based on the previously known LGI1 protein sequence, revealed the existence of a highly homologous group of proteins that contain the so-called EPTP repeats (Pfam *PF03736*): LGI1, LGI2, LGI3, LGI4, VLGR1 and TNEP1 (Staub et al., 2002). The EPTP repeats were first identified in the LGI1 sequence and are thought to generate a beta-propeller structure, a potential protein–protein interaction domain (Kobe and Kajava, 2001). Moreover, the four LGI proteins also contain cysteine-flanked leucine-rich repeats, which confer them a highly similar domain structure (Staub et al., 2002). Another common feature of this group of proteins is that overexpression in several cell lines of either *LGI* shows that the products of these genes are glycosylated secreted proteins (Senechal et al., 2005). In addition, defective *LGI1* gene gives rise to a mutant protein that is neither secreted nor unstable (Senechal et al., 2005).

Information about the *LGI1* gene and protein is more abundant than for the rest of the family members. *LGI1* gene was discovered in the T98G glioblastoma cell line, where it was rearranged as a result of a t(10;19)(q24;q13) balanced translocation (Chernova et al., 1998). Thus, it was proposed to be a tumor suppressor gene based on its lower expression in human glial tumor and glioblastoma cell lines when compared to normal brain samples (Chernova et al., 1998). Further investigation led to the discovery that *LGI1* gene mutations caused autosomal dominant lateral temporal epilepsy (ADLTE) (Gu et al., 2002a; Kalachikov et al., 2002; Morante-Redolat et al., 2002). Analysis of *LGI1* gene expression revealed that it is strongly transcribed in neurons, but not in glial cells (Kalachikov et al., 2002; Senechal et al., 2005); nevertheless, *LGI1* gene is also expressed in other tissues (Head et al., 2007). It has been hypothesized that LGI1 protein might be involved in cell motility and invasiveness (Kunapuli et al., 2003, 2004). Furthermore, Schulte et al. (2006) reported that the LGI1 protein binds to the presynaptic voltage-gated K^+ channel (Kv) which, as part of the Kv complex, prevents the N-type inactivation mediated by the Kvβ1 subunit. Mutant LGI1 proteins may fail in inactivating Kvβ1, which would result in channels closing faster. Thus, slowly repolarized terminals of LGI1 defective neurons may induce focal seizures (Schulte et al., 2006). Additional information on putative LGI1 function arises from the observation that LGI1 oligomers interact with post-synaptic ADAM22 receptors (Fukata et al., 2006), which suggests that secreted LGI1 protein enhances AMPA receptor-mediated excitatory transmission (Fukata et al., 2006). But the most relevant proof about the function of LGI1 lies on the discovery by Zhou and co-workers, that this protein mediates postnatal structural pruning and functional maturation of glutamatergic synapses in hippocampus, while mutant LGI1 prevents this process in transgenic mice. Moreover, they suggest that LGI1 acts at the presynaptic terminus to reduce Kvβ1-mediated inhibition over the Kv1.1 channel (Zhou et al., 2009).

Conversely, there are scarce data on the function of *LGI3* and *LGI4* and no data about *LGI2*. Several studies have shown that the beta amyloid peptide (Abeta) upregulates and colocalizes with LGI3 protein in the cell membrane and with internalized Abeta in astrocytes (Kimura et al., 2007; Okabayashi and Kimura, 2007, 2008). Western blot analyses