Functional and evolutionary study of the LGI family related to epilepsy and glioblastoma

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Background and Objective: Autosomal dominant lateral temporal lobe epilepsy (ADLTE) was the first human idiopathic epilepsy known to be caused by mutations in a gene (*LGI1*, leucine-rich glioma associated gene 1) which does not code for an ion channel subunit.[1-2] Additionally, *LGI1* was also shown to be a putative metastasis suppressor gene involved in the malignancy of glioblastoma. Human *LGI1* belongs to a gene subfamily with three other paralogues genes, *LGI2-LGI4*. High sequence homology among the paralogues, their chromosomal localisations and their expression patterns enable all *LGI* genes to be considered as candidates for epilepsy genes and possible tumor suppressor genes. It's thus of great interest to study the emerging and development of this gene family in an evolutionary context. Also, to study the function of *LGI1*, which is yet fully unknown, and thus to understand the etiology of ADLTE, we searched for interaction partners of LGI1 proteins.

Methods: Yeast two-hybrid experiments were carried out for *LGI1* gene to look for proteins interacting with LGI1. We systematically searched for *LGI* homologues in genomes of Drosophila, Ciona intestinalis, fugufish, zebrafish, xenopus, chick, mouse and chimanzee. In zebrafish and xenopus, we used RT-PCR and RACE PCR to determine the gene sequences experimentally. In-situ hybridization of the zebrafish *lgi* homologues were carried out with zebrafish embryos.

Results: Two-hybrid experiments successfully identified two possible interaction partners of LGI1 protein: a putative protein phosphatase and a protein associated with the cellular mitosis apparatus. The *LGI* family emerged around the emerging of vertebrates. *LGI4* is the youngest one, probably existing only in mammals. The fish orthologues of human *LGI1*, *lgi1a* and *lgi1b* are expressed in nervous system and show subfunctionalization. *lgi2a* and *lgi2b*, the fish orthologues of human *LGI2*, are expressed in a few cells of putative ectodermal origin during embryogenesis. They have very similar expression pattern. *lgi3* is the only zebrafish *lgi* family member with mesodermal expression.

Conclusion: The confirmation of the two interaction partners of LGI1 will contribute greatly to the understanding of LGI function and the etiology of ADLTE. The analysis of the homologue gene sequences and expressions enabled us to draw a rough scheme of the evolutionary history of this interesting gene family.

References

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