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Expression of the *Lingo/LERN* gene family during mouse embryogenesis

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Abstract

We have analysed the expression during mouse development of the four member *Lingo/LERN* gene family which encodes type 1 transmembrane proteins containing 12 extracellular leucine rich repeats, an immunoglobulin C2 domain and a short intracellular tail. Each family member has a distinct pattern of expression in the mouse embryo as is the case for the related *NLRR*, *FLRT* and *LRRTM* gene families. *Lingo1/LERN1* is expressed in the developing trigeminal, facio-acoustic and dorsal root ganglia. An interesting expression pattern is also observed in the somites with expression localising to the inner surface of the dermomyotome in the ventro-caudal lip. Further expression is seen in lateral cells of the hindbrain and midbrain, lateral cells in the motor horn of the neural tube, the otic vesicle epithelium and epithelium associated with the developing gut. *Lingo3/LERN2* is expressed in a broad but specific pattern in many tissues across the embryo. *Lingo2/LERN3* is seen in a population of cells lying adjacent to the epithelial lining of the olfactory pit while *Lingo4/LERN4* is expressed in the neural tube in a subset of progenitors adjacent to the motor neurons. Expression of all *Lingo/LERN* genes increases as the embryo develops but is low in the adult with only *Lingo1/LERN1* and *Lingo2/LERN3* being detectable in adult brain.

Keywords: Mouse; Lingo; LERN; Expression; Leucine rich repeat transmembrane; Somite; Neural tube; Ganglia

1. Results and discussion

Four similar multi-member gene families (*NLRR*, *FLRT*, *Lingo/LERN* and *LRRTM*) in mammals encode type I transmembrane proteins containing 10–12 extracellular leucine rich repeats and short intracellular tails (Lacy et al., 1999; Carim-Todd et al., 2003; Lauren et al., 2003; Hamano et al., 2004; Haines et al., 2005) that differ in the presence of immunoglobulin and fibronectin domains adjacent to the external cell membrane. They are often expressed in the nervous system (Carim-Todd et al., 2003; Lauren et al., 2003) and have been associated with neural regeneration (Ishii et al., 1996; Bormann et al., 1999; Robinson et al., 2004). FLRT3 has been shown to increase neurite outgrowth in cultured cells (Robinson et al., 2004; Tsuji et al., 2004). *Xenopus FLRT3* (*XFLRT3*) was identified as a gene with a similar expression pattern to FGF signalling molecules, particularly at the midbrain hindbrain boundary (Bottcher et al., 2004). It was shown to be regulated by FGF signalling, be able to modulate FGF signalling and to interact with the FGF receptor. All three mouse FLRTs can interact with FGFR1 and can be regulated by FGF signalling (Haines et al., 2006). Rat NLRR-3 may be involved in the regulation of EGF receptor signalling through an intracellular clathrin adapter interaction motif (Fukamachi et al., 2002) and the structurally similar vasorin protein has been shown to interact with the TGF-β ligand and regulate the cellular response to TGF-β (Ikeda et al., 2004). These data suggest that leucine rich repeat transmembrane proteins may function in the regulation of cell signalling.

The *Lingo/LERN* gene family was initially identified by Carim-Todd et al. (2003) as containing three members in human designated LERN1/Lrrn6A, LERN2/Lrrn6B and LERN3/Lrrn6C, which is identical to the gene described

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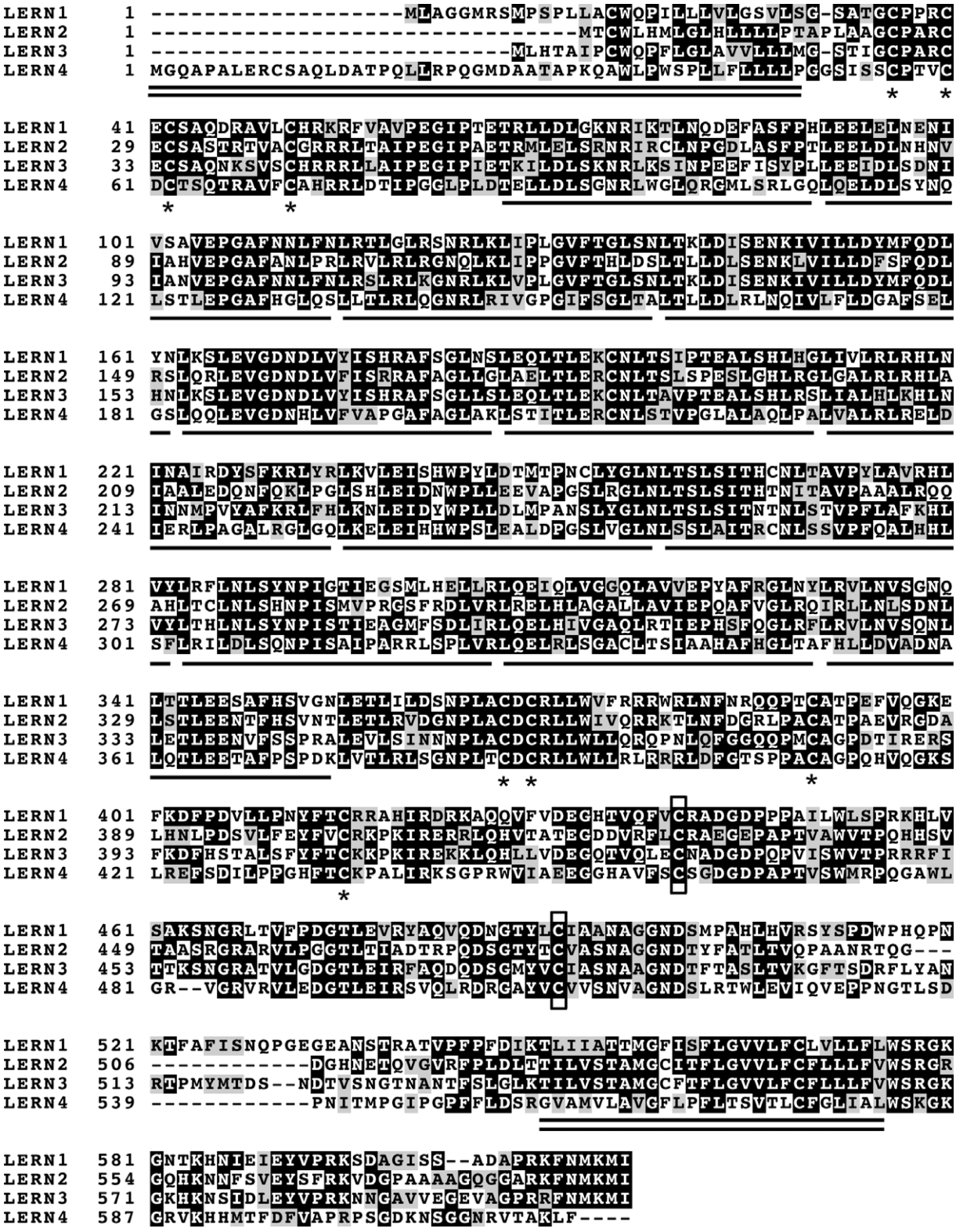

Fig. 1. Comparison of the amino acid sequences of the mouse Lingo/LERN protein family. The alignment shows the conserved secondary structure of the Lingo/LERN proteins. Leucine rich repeats are underlined. Cysteine residues of the C- and N-terminal flanking sequences are highlighted by asterisks. Conserved cysteine residues of the immunoglobulin C2 domain are boxed. Hydrophobic signal and transmembrane sequences are double underlined.

as NLRR5 (Hamano et al., 2004). The mouse homologues of these genes have been named the *Lingo* gene family (Mi et al., 2004). Lingo1 (Genbank Accession No. NP_851419) is a homologue of LERN1 and Lingo2 (Genbank Accession No. NP_780725) is a homologue of LERN3. Lingo3 (Genbank Accession No. NP_001013780) is homologous