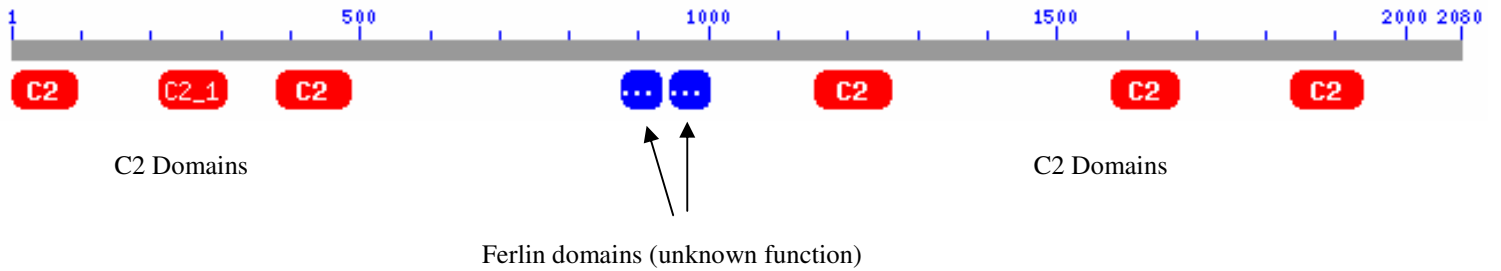
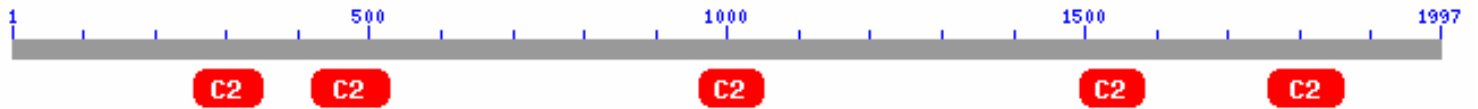


**Comparison of Conserved Domains (according to NCBI search)
Among Ferlin Family Members**

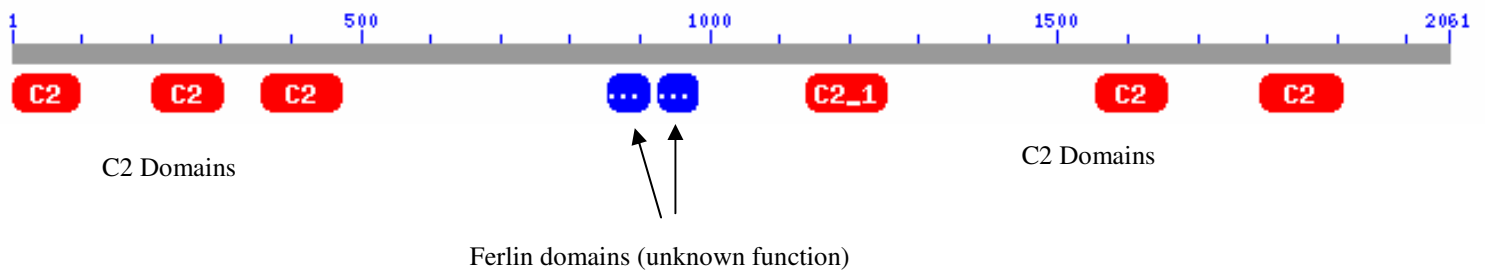
Dysferlin=Fer1L1
(protein sequence NP_003485)



Otoferlin=Fer1L2
(protein sequence Q9HC10)

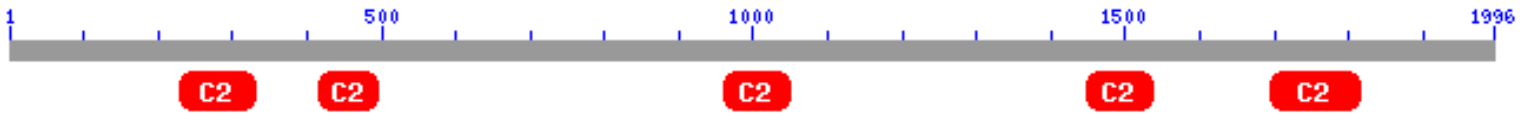


Myoferlin=Fer1L3
(protein sequence Q9NZM1)



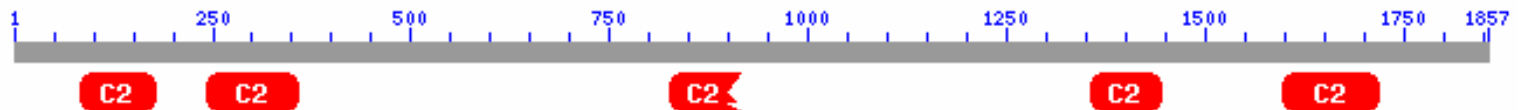
Fer1L4

(human draft sequence assembled from human ESTs, structure based on predicted chimpanzee sequence XP_525311 – [click here for assembled sequence](#))



Fer1L5

(protein sequence LOC654463)

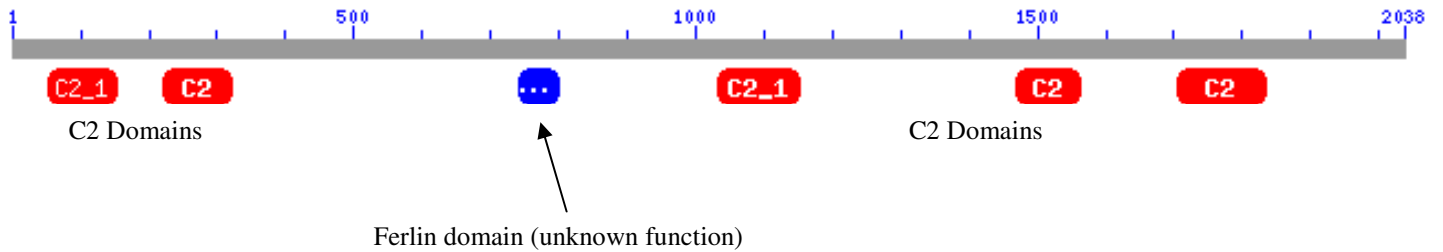


The sequence of Fer1L6 is at present somewhat uncertain. The amino acid sequence between the human draft based on the predicted chimpanzee sequence XP_515743, and the predicted human sequence hCG1810857 is virtually identical, but with a substantial number of gaps in both directions, indicating that the two predicted sequences have missed exons or include spurious exons. The chimp based draft does not include the first 131 amino acids of hCG1810857, which includes an N-terminal C2 domain. Conversely, hCG1810857 skips an exon comprising part of the second C2 domain, which is present in the chimp-based sequence.

Constructing a hybrid sequence by appending the first 131 amino acids of hCG1810857 to the chimp-based draft sequence (the two sequences overlap beginning at AA 132 of hCG1810857) yields a protein with six identified C2 domains, including one in the N-terminal region. This structure closely resembles that of dysferlin and myoferlin. Since these two proteins most closely resemble Fer1L6, this lends credence to this hybrid sequence.

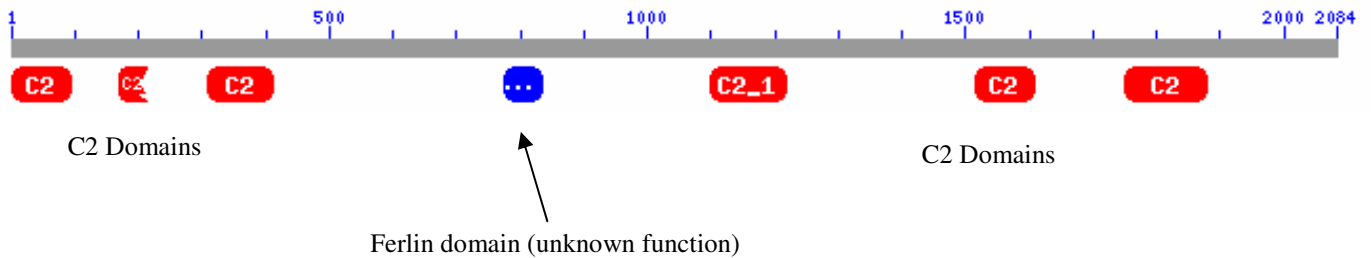
Fer1L6:human-chimp homology

(human draft sequence assembled from human ESTs/reference DNA sequences, structure based on predicted chimpanzee sequence XP_515743 – [click here for assembled sequence](#))



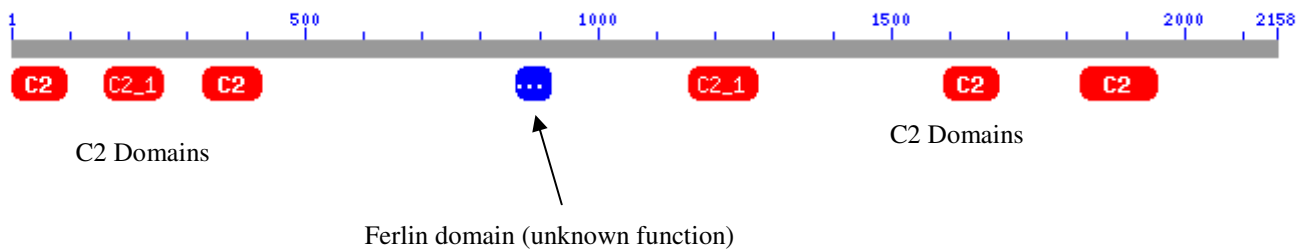
Fer1L6:Celera

(hCG1810857, isoform CRA_b)



“Composite” Fer1L6

(AA 1-131 of hCG1810857, isoform CRA_b + AA 26-2038 of human draft sequence based on predicted chimpanzee sequence XP_515743)



Transmembrane domains of ferlins:

`waiilfiilfilllflaifiyaf` dysferlin—ends 13 AA from C-terminus

`lllllllllllalfly` otoferlin—ends 13 AA from C-terminus

`wviigllflllllflvavllly` myoferlin—ends 15 AA from C-terminus

`tlvllllvlltvflllvfyti` Fer1L4—ends 14 AA from C-terminus

`yiiiafiliiliiflflvlfy` Fer1L5—ends 14 AA from C-terminus

`liafmvisiialmlf` Fer1L6 (?) —ends 81 AA from C-terminus

Comments:

None of the Fer1L6 draft sequences appear to contain an obvious transmembrane hydrophobic domain in the C-terminal region. The most likely candidate is smaller in size, of different composition (contains less leucine/isoleucine) and is located farther from the C-terminus than the transmembrane domains of the other ferlins.

If the Fer1L6 protein truly lacks a transmembrane domain, this would be unexpected, and imply a very different biological function for Fer1L6 than for the other ferlins. It remains to be seen if Fer1L6 lacks a transmembrane domain, or if the predicted sequences simply are missing the relevant exons.

The full-length transcripts of ferlin family members (members often have multiple transcripts of varying sizes) contain approximately 2000 amino acids. The family members all have multiple C2 domains, and (except perhaps in the case of Fer1L6) a transmembrane domain near the C-terminus consisting of 15-20 consecutive hydrophobic amino acids (predominantly leucine and/or isoleucine).

Some differences are apparent between the dysferlin and otoferlin subfamilies. The members of the dysferlin subfamily all have six C2 domains in the full length isoform (according to the NCBI identification algorithm—the number of identified C2 domains is known to vary between algorithms), including one in the N-terminal region. The otoferlin subfamily members all have five C2 domains per the NCBI algorithm, and do *not* have a C2 domain in the N-terminal region.

The dysferlin subfamily members also have a ferlin domain or domains near the middle of the protein (in the region of AAs 800-1000). The otoferlin subfamily members apparently lack these.