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FUNCTIONAL CHARACTERISTICS OF THE CALCIUM MODULATED PROTEINS SEEN FROM AN EVOLUTIONARY PERSPECTIVE

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We have constructed dendrograms relating 173 EF-hand proteins of known amino acid sequence. The EF-hand, or calmodulin fold, consists of 29 amino acids -- 1-10 in helix E; calcium coordinating side chains 10 X, 12 Y, 14 Z, 18 -X, 21 -Z; and 21-29 in helix F. This homolog domain is present in from two to eight random repeats in (nearly) all calcium-modulated proteins in the cytosol. The intradomain regions are much more highly conserved than the interdomain regions. We aligned all of these proteins by their EF-hand domains, omitting interdomain regions. Initial dendrograms were computed by minimum mutation distance methods. Using these as starting points we determined the best dendrogram by the method of maximum parsimony, scored by minimum mutation distance.

We identified fourteen distinct subfamilies as well as six unique proteins (indented), perhaps the sole representatives of other subfamilies:

Name	Ca-binding in Domains	1	2	3	4	5	6
Calmodulin		+	+	+/?	+/?		
Troponin C		+/-	+	+/-	+		
Troponin C (Astacus)		-	+	-	+		
Parvalbumin			-	+	+		
Calbindin		+	-	+	+	+	-
Calcineurin B		+	+	+	+		
S100		+/-	+/-				
Essential Light Chain of Myosin		+/-	-	+/-	+/-		
Calcium Vector Protein		-	-	+	+		
Regulatory Light Chain of Myosin		+	-	-	-		
Caltractin & CDC31		+	+/-	+/-	+		
Stronglyocentrotus ectodermal prot.		+	+/?	+/?	+		
α- Actinin		+/-	+/-				
25 kDa Protein (Tetrahymena)		+	+	?	+		
Ca-binding protein (Lytechinus)		+	+	+	+		
Sarcoplasm Ca-binding Protein		+	+/-	+/-	+/-		
Ca-binding Protein (Streptomyces)		+	?	+	+		
Aequorin		+	-	+	+		
Calpain		+	+	-	-		
Ca-binding Protein (Canis thyroid)		+	+	+	?		

Within subfamilies, one can easily align interdomain regions. The resulting dendrograms are very similar to those computed using domains only. Dendrograms constructed using pairs of domains show general congruence. However, there are enough exceptions to caution against an overly simple scheme in which a pair of gene duplications leads from a one domain precursor to a four domain prototype from which all other forms evolved. The ability to bind calcium was lost and acquired multiple times during evolution.

The distribution of introns does not conform to the dendrogram based on amino acid sequences.

The rates of evolution appear to be much slower within subfamilies, especially within calmodulin, than those prior to the definition of subfamily.