

# Review of: "The CCN Family of Proteins: A Critical Approach to the Multi-Modular Structure of the CCN Domains"

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In his review entitled "The CCN Family of Proteins: A Critical Approach to the Multi-Modular Structure of the CCN Domains," Prof. Bernard Perbal discusses the modular structure of the members of the CCN protein family, the potential roles of their modules, and also considers peculiarities of the evolution of the tetramodular organization of these proteins. The article represents interesting reading and is informative. However, it seems that it is written for the CCN community, and as a result, several points require some additional clarifications to make this work more attractive to a broader audience.

1. It would be great to have a more general discussion of the CCN proteins, pointing out what they do and what the functional and structural differences are between the six human CCN proteins. Why are there six CCN proteins in humans? Do they have similar or different functions? I recognize that this information could be present in other articles, but I still think that a short introductory paragraph should be given.
2. What are the differences between "modules" and "domains"? How many domains are in the tetramodular CCN proteins?
3. Since AlphaFold has modeled the 3D structure for many proteins (including CCN proteins), I would strongly encourage the author to include a figure showing these structures for the six human CCN proteins.
4. It is stated that the CCN proteins are involved in a wide variety of interactions with regulatory factors. Is there a difference between their partners? Do CCN proteins interact with each other?
5. CCN proteins represent an interesting case of multifunctional proteins. Although this multifunctionality can be attributed to their tetramodular organization, it is likely that the intrinsic disorder and structural flexibility of some of their regions can also play a role. Probably, this option should be mentioned as well.