

Ancestral reconstruction of transthyretin / 5-hydroxy isourate hydrolase sequences

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Abstract

Transthyretin (TTR) is a tetrameric protein – each of the four identical chains having about 130 amino acids (14 kDa) – that transport thyroid hormones in blood and brain. It also participates indirectly in transport of retinoic acid by coupling to retinol binding proteins. It was firstly described in eutherian mammals as a carrier of thyroxine (T₄), however in most vertebrates it has more affinity to the active form of this hormone, triiodothyronine (T₃). Mutations in this protein can lead to several diseases, like high concentrations of thyroid hormones in blood, or even formation of amyloid fibrils, associated to neurodegenerative diseases. Some evidence suggest that the gene for TTR has arisen during the emergence of vertebrates, from a putative gene duplication of an enzyme found since bacteria to vertebrates, involved in uric acid metabolism: the 5-hydroxy isourate hydrolase (HIUase). Since they are present in all kingdoms of life, have a stable and conserved structure, don't suffer post-translational modifications and are able to have their activity modified from enzyme to hormone carrier by changing just a few amino acids in the active site, they are considered an excellent model for studies of molecular evolution, specifically function divergence, in homologous protein families. One common way to assess protein evolution is to look at a multiple sequence alignment. More specifically, some methods are capable of predicting putative ancestral sequences starting from nowadays sequences. In the present work, a bayesian phylogenetic analysis of sequences belonging to TTR/HIUase family was proceeded and, for some key nodes of the phylogenetic tree, ancestral sequences were reconstructed by maximum likelihood methods. Their 3D structure were predicted by similarity and their corresponding genes were submitted to synthesis for further experimental characterization. Some conservational patterns in active sites could be verified according to information available in literature, corroborating some hypothesis concerning specificity determining positions.

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