A critical assessment of model building by homology:the test case of human GTP cyclohydrolase I

G.Tasco*, P.L.Martelli*, M.L.Agostoni-Carbone and R.Casadio*

Dipartimento di Genetica e Biologia dei Microorganismi, Tel.02-26605218; e-mail: pancar@mailserver.unimi.it, Universita' di Milano
* CIRB e Laboratorio di Biofisica, Dipartimento di Biologia Evoluzionistica e Sperimentale, Via Irnerio 42, 40126 Bologna. Tel. 051-2094005; Fax 051-242576. e-mail:casadio@alma.unibo.it, http://www.biocomp.unibo.it

It is well recognised that the 3D structure of a protein can be computed when its sequence is similar with a high level of identity to that of a template whose atomic structure is available. This procedure (building by homology) is however still questioned when the level of sequence identity is in the range of 30%. In this work we discuss a test case whose modelling was performed in spite of a low sequence identity with the target (32%) and compare the predicted model with its crystal structure.
The target protein is the human GTP cyclohydrolase I (hGTP-CH-I), that catalyzes the conversion of GTP to dihydroneopterin triphosphate. This activity in animals controls the level of tetrahydrobiopteridin. Mutations of GTP-CH-I are responsible for severe diseases including dopa-responsive dystonia and certain cases of atypical phenylketonuria. The structure of the Escherichia coli GTP-CH-I was available (determined by x-ray crystallography;1GTP, PDB code). This enzyme is homodecameric and is composed of two dimers of pentamers. Each monomer contains 221 amino acids and folds into an alfa+beta structure with a predominantly helical N-terminus. Modelling of the human target was performed on the E.coli template by homology building using a standard procedure: i) sequence alignment, based also on secondary structure prediction; ii) model building (with Modeller, Sali and Blundell, 1994); iii) model evaluation (with Procheck, Laskowski et al., 1993).
Recently a crystal structure of the recombinant hGTP-CH-I became available (Auerbach et al., 2000). This structure is partial and relative only to one of the two dimers of pentamers. Structure alignment of our predicted structure with the experimental one indicates an identity equal to 90% with a root mean square deviation of 0.119 nm.
These results indicate that our complete predicted model can be regarded as a good model of the protein structure and add to the availability of building by homology applied on the basis of function similarity.

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