

Homology Modelling of Hypoxanthin–Guanine Phosphoribosyltransferase, Enzyme Involved in Salvage Pathway of Purine Metabolism

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Abstract

Hypoxanthin-guanine phosphoribosyltransferase (HPRT) is responsible for catalyzing a reaction which breaks down uric acid in the body. The lack of this enzyme creates a build-up of uric-acid, leading to a neurological problem, joint pain and kidney problem. The condition is called Lesch-Nyhan Syndrome. A comparative modelling of the protein Hypoxanthin-guanine phosphoribosyltransferase is performed using the modeling program modeller9v3. The following structure validation programs PROCHECK, PROSA, VERIFY3D and WHATIF are used. Descret Optimized Protein Energy (DOPE), is a statistical potential used to assess homology model in protein structure prediction. Predicted model can be useful to develop new inhibitor against Lesch-Nyhan Syndrome. CASTp can be used to study surface features and functional regions of proteins.

Keywords: Phosphoribosyltransferase; Catalysis; PROCHECK; Mmodeling; Validation; Lesch-Nyhan Syndrome

Introduction

HPRT catalyzes a reaction that is necessary to prevent the buildup of uric acid, a nitrogenous waste product that is ordinarily excreted from the body through the kidneys. A severe mutation in the HPRT gene leads to an absence of HPRT enzyme activity which causes Lesh-Nyhan Syndrome. The lack of HGPRT causes a build-up of uric acid in all body fluids, and leads to problems such as severe gout and kidney problems, poor muscle control, and moderate mental retardation, which appear in the first year of life. A striking feature of LNS is self-mutilating behaviors, characterized by lip and finger biting that begin in the second year of life. Neurological symptoms include facial grimacing, involuntary writhing, and repetitive movements of the arms and legs because a lack of HGPRT causes the body to poorly utilize vitamin B12, some boys may develop a disorder called megaloblastic anemia.

The symptoms caused by the buildup of uric acid (arthritis and renal symptoms) respond well to treatment with drugs such as allopurinol that reduce the levels of uric acid in the blood. The mental deficits and self-mutilating behavior do not respond to treatment. There is no cure, but many patients live to adulthood. LNS are rare, affecting about one in 380,000 live births. The disorder was first recognized and clinically characterized by medical student Michael Lesch and his pediatric mentor Bill

Nyhan who published their findings in 1964.

In this study, our aim is to derive a model of the tertiary structure of HPRT (Homo sapiens) by using a comparative modeling approach. It is 842 residue long mature peptide. Our strategy was to consider an extensive iterative procedure that combines the following steps, generation of models by comparative modelling, validation of a model by structure validation program.

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Materials and Methods

Selection of Templates and Input Preparation

Modeller is a computer program for comparative protein modeling (Fiser et al., 2000; Sali et al., 1993) comparative modeling consist of four steps – fold assignment that identifies overall similarities between the target and one known template structure, alignment of the target sequence and template, building a model based on the alignment with the template and predicting the accuracy of the model (Eswar et al., 2005).

Modelling Strategy

Five sets of models were generated by using the program MODELLER9V3. In this program, the models are generated by satisfaction of spatial restraint. The values of DOPE score for five models are -24749.36719, -24785.36328, -24730.32227, -24816.83398 and -25109.78125. Out of this five the 5th model show the lowest DOPE score value so that this model is selected as a final model.

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Result and Discussion

Comparative Modeling

The modelling approach can be summarized as follows. The derivation of sets of models by MODELLER9V3, lowest DOPE score value, the validation sets (PROCHECK (Laskowski, et al., 1993) Verify3d, PROSA (Sippl, 1993; Wiederstein, 2007) and WHATIF (Vried, 1990) made for model that is chosen from their relative objective function values.

The model that satisfied all the validation criteria as assessed by the following program WHATIF, Verify3d, PROSA and DOPE score is presented in Fig.1. Good overall stereochemistry is obtained for the model with 90.5% of the residue psi/phi angles falling in the most favoured regions and 7.9% in the al-



Figure 1: Best modeled structure of HPRT (Visualization in Rasmol).

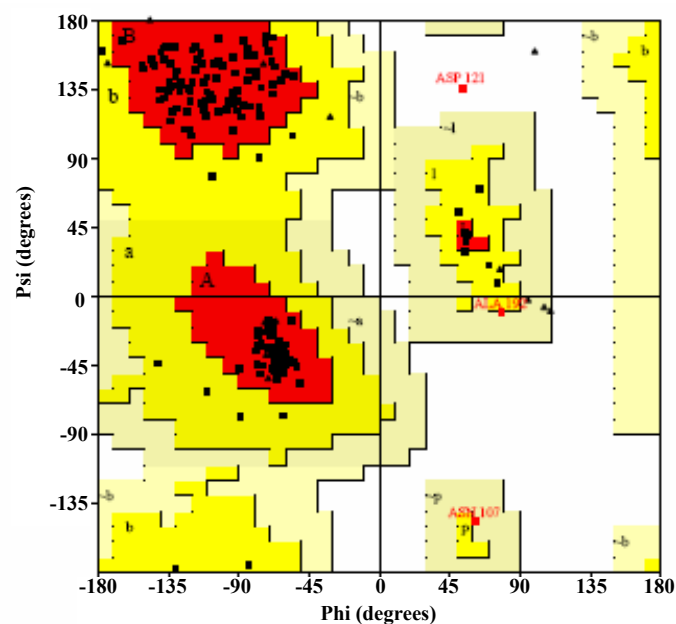


Figure 2: Ramachandran plot of the psi/phi distribution of the HPRT model as obtained by PROCHECK: 90.5% residues are in most favoured region and 7.9% are in additional allowed regions.

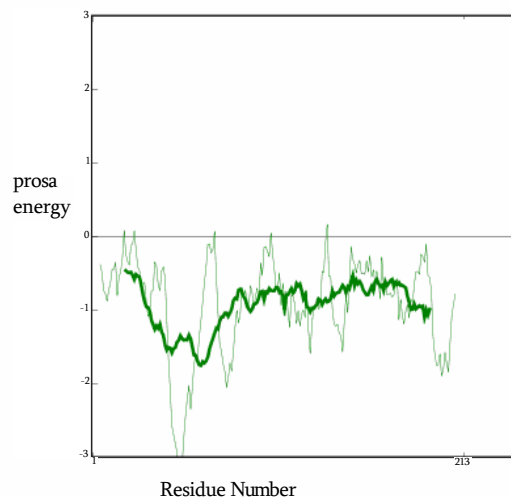


Figure 3: Prosa energy plot for the HPRT.

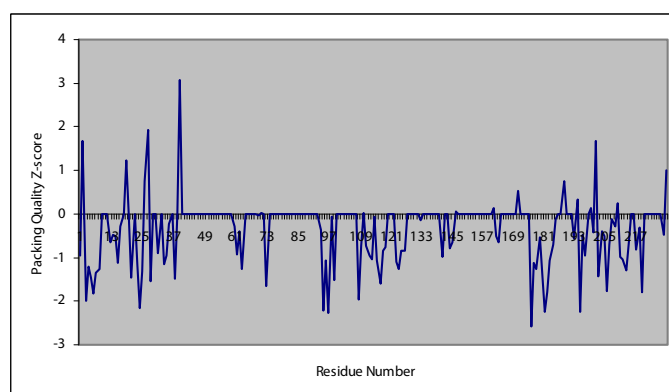


Figure 4: WHATIF quality control values calculated for the HPRT.

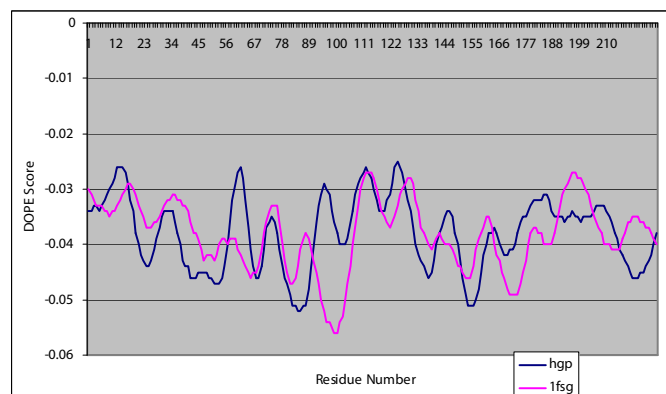


Figure 5: Analysis of DOPE Score profile of HPRT and 1fsg (template).

lowed region. The Ramachandran plot is shown in Fig.2. The interaction energy per residue is also calculated by program PROSA and Verify3D Fig.3. displays the PROSA profile calculated for the HPRT model. Fig.4. display the Verify3D profile calculated for the HPRT model along with the template. A final test is the packing quality of each residue as assessed by the WHATIF program.Fig.4. present the profile obtained with respect to the residues.As the evaluation criterion corresponds in this case to a threshold of-5; one can see that all residues show satisfactory packing values.

Analysis of Model

The DOPE (Discrete Optimized Protein Energy, is a statistical potential used to assess homology models in protein structure prediction. DOPE is based on an improved reference state that corresponds to non-interacting atoms in a homogeneous sphere with the radius dependent on a sample native structure; it thus accounts for the finite and spherical shape of the native structures) method is generally used to assess the quality of a structure model as a whole. It is implemented in the popular homology modeling program MODELLER and used to assess the energy of the protein model generated through many iterations by MODELLER, which produces homology models by the satisfaction of spatial restraints. , DOPE is implemented in Python and is run within the MODELLER environment (Sali et al., 1993; Eramian et al., 2006; John et al., 2003; Melo et al., 2002; Marti-Renom et al., 2000).

Discussions

In the process of modeling HPRT, we identify useful templates that shares good similarity with HPRT. Interestingly, one of the models derived from comparative modeling in MODELLER (minimum energy) was validated and displayed several meaningful features: secondary structure, charge distribution, conserved residues engaged in non-bonded interaction. Since the above work is an in-silico work, the predicted model can be useful to develop new inhibitor against Lesch-Nyhan Syndrome. The above work aims to serve all those researcher and patient who are currently experiencing this incurable disease. The in-silico approach helps researchers by giving them an in-hand idea so that they can happily advance towards the treatment of the disease. This work also aims to prove that no disease is incurable but the cure may be hidden in some other form.

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