

SMART Teams 2014-2015

Research and Design Phase

Brookfield Academy Upper School SMART Team

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Modeling the N-Terminal Domain of Cystathionine β -Synthase to Identify Mutations Correlated with Homocystinuria

PDB: 1JBQ

Primary Citation: Markus Meier, Miroslav Janosik, Vladimir Kery, Jan P. Kraus, and Peter Burkhard. (2001) Structure of human cystathionine beta-synthase: a unique dependent heme protein. *EMBO J.* **20:** 3910-3916

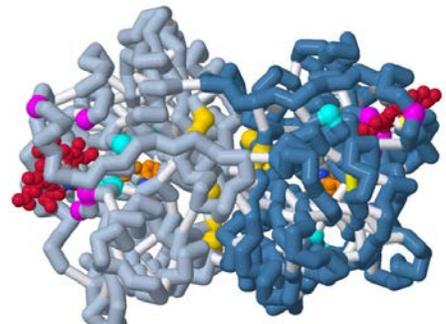
Format: Alpha carbon backbone

RP: Zcorp with plaster

Description:

Homocystinuria is an autosomal recessive disorder affecting approximately 1 in 350,000 people worldwide and is characterized by skeletal, nervous system, and vascular, abnormalities, such as delayed developmental milestones, myopia, dislocation of the eye lens, osteoporosis, mental retardation, and increased risk of blood clotting.

Major causes of homocystinuria are mutations in the enzyme cystathionine β -synthase (CBS), which catalyzes the condensation of serine and homocysteine to cystathionine, an intermediate in cysteine synthesis. CBS is a pyridoxal 5'-phosphate (PLP) and heme dependent enzyme regulated by S-adenosylmethionine (SAM). CBS is a homotetramer, each subunit consisting of distinct N and C-terminal domains. The N-terminal domain is the catalytic region, containing both the PLP and the heme cofactor, while the C-terminal domain is the regulatory region, binding SAM. Upon binding with SAM, the C-terminal domain is removed, and the enzyme functions as a homodimer. The PLP is covalently attached to CBS by lysine 119, while the heme is reversibly bound to CBS by coordination with cysteine 52 and histidine 65. Over 150 mutations have been identified affecting the enzyme. These mutations primarily cluster around three areas of the enzyme: the heme binding site, the PLP and substrate binding active site, and the dimer interface. Homocystinuria can lead to several cardiovascular defects such as increased carotid plaque thickness, known as atheroma, in artery walls and intravascular thrombosis, the formation of a blood clot that obstructs blood flow through the circulatory system. A primary research goal is to understand how mutations in CBS, an enzyme found in muscle tissue, may lead to vascular abnormalities by identifying changes in embryonic vascular development in zebrafish (*Danio rerio*) lacking expression of the CBS-B isoform. Using 3D printing techniques, the Brookfield Academy SMART (Students Modeling A Research Topic) Team modeled the N-Terminal domain of the CBS enzyme, highlighting the heme and PLP coenzymes, along with various mutations associated with homocystinuria.



Specific Model Information:

- Chain A subunit backbone is colored lightsteelblue.
- Chain B subunit backbone is colored steelblue
- Heme cofactor is displayed as ball and stick and is colored crimson
- Heme iron is displayed as spacefill and colored coral.
- Amino acids Histidine-65 and Cysteine-52, which coordinate heme cofactor are displayed as ball and stick in CPK coloration.
- Lysine119, which makes Schiff base covalent bond to the cofactor PLP, is displayed as ball and stick in CPK coloration.
- The PLP cofactor is displayed as ball and stick and colored darkorange
- Disulfide bridge is displayed in yellow.
- Mutations associated with homocysteinuria are displayed with alpha-carbons in spacefill and the following color scheme:
 - Mutations around the heme binding pocket are colored magenta.
 - Mutations located at the dimer interface between subunits A and B are gold.
 - Mutations located within the PLP and substrate binding sites are colored cyan.
- Structural supports and H-bonds are colored ghostwhite.

<http://cbm.msoe.edu/smartTeams/>

The SMART Team Program is supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Number 8UL1TR000055. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.