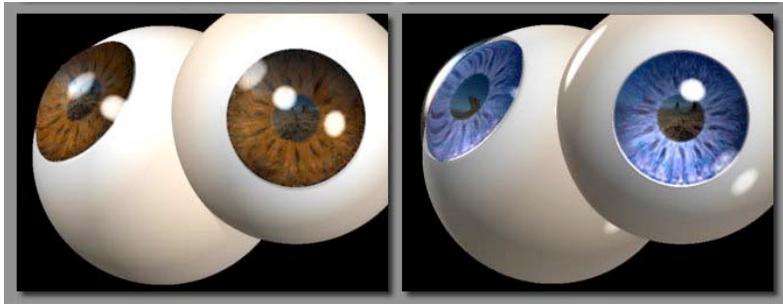




Center of the University & School of Milan for Bioscience  
education

[www.cusmibio.unimi.it](http://www.cusmibio.unimi.it)

## **Brown eyes, blue eyes. From a gene to its protein**



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## Brown eyes, blue eyes. From a gene to its protein

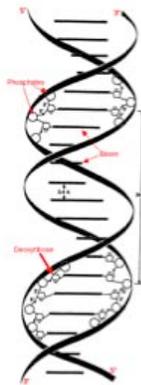
There is a famous sequence in *Quai des Brumes* – a very popular French film shot in the 1930s – in which Jean Gabin, subdued by the sky blue of his interlocutor’s gaze, leans over and breathes into Michèle Morgan’s ear, “T’as d’beaux yeux tu sais” – meaning literally: “You’ve got beautiful eyes you know” ... though it means far more. The blue of an eye is both fascinating and mysterious, and we are getting closer to an explanation for it. It is common knowledge that the colour of our eyes is due to the accumulation of a pigment in the iris – melanin – whose synthesis depends on the activity of a protein known as P protein. Despite years of research, scientists had not been able to pin down a modification in P protein, which could explain the azure of a look, until recently when after a long sought a mutation was discovered – only not at all where they were expecting it!

P protein is essential to pigmentation. Although its precise function is unknown, it is a key factor in the synthesis of melanin – the pigment which gives our skin, our hair and our eyes their colour. The motto goes: the more the melanin, the darker the eyes. Albinism, on the other hand, which results from the discolouration of our skin, eyes and

hair occurs following a serious defect in melanin synthesis. To date, approximately 40 mutations have been identified on the P protein gene, which are all involved in one of the major forms of albinism.

## Genes Associated with Albinism & Pigmentation:

- Tyrosinase: major enzyme involved in melanin formation. Ocular Albinism Gene 1 (OCA1)
  - Location: Chromosome 11
- P Gene: OCA2 involved in the transport of tyrosine, the precursor to melanin synthesis, within the melanocyte
  - Location: Chromosome 15
- TYRP1: loss of function of this enzyme involved in melanin biosynthesis leads to a form of albinism OCA3
  - Location: Chromosome 9
- Phenyl-alanine hydroxylase, tyrosine synthesis
  - Location: Chromosome 12



Note that there are several other genes (and proteins) whose loss of function is the cause of different forms of albinism. All of them are involved in pigment biosynthesis and/or metabolism.

To find more info about the P protein, visit

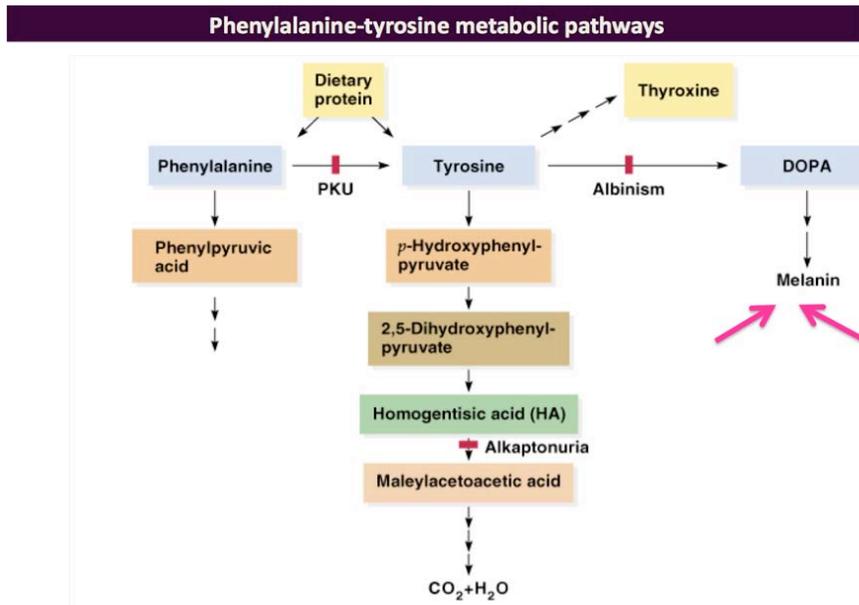
<http://www.ncbi.nlm.nih.gov/>

From the database pull down menu on the left select the protein database and type “P protein homo sapiens” in the search box.

You will find the record Q04671, Melanocyte-specific transporter protein.

From this site collect info about the P protein. It has 838aa.

FUNCTION: Could be involved in the transport of tyrosine, the precursor to melanin synthesis, within the melanocyte. Regulates the pH of melanosome and the melanosome maturation. One of the components of the mammalian pigmentary system. Seems to regulate the post-translational processing of tyrosinase, which catalyzes the limiting reaction in melanin synthesis. May serve as a key control point at which ethnic skin color variation is determined. Major determinant of brown and/or blue eye color.



In the FEATURES section you will find the name of the corresponding gene OCA2 (ocular cutaneous albinism, form 2).

In the list of references (articles) you'll find a recent paper by a group of Danish scientists which cast a new light on the function of P protein in determining eye color.

Authors: Eiberg,H., Troelsen,J., Nielsen,M., Mikkelsen,A., Mengel-From,J., Kjaer,K.W. and Hansen,L.

TITLE: Blue eye color in humans may be caused by a perfectly associated founder mutation in a regulatory element located within the HERC2 gene inhibiting OCA2 expression

JOURNAL: Hum. Genet. 123 (2), 177-187 (2008)

Blue eyes have poor melanin content. Convinced that this might have something to do with P protein, researchers carried out a major study in the hope of discovering what it is that makes the difference between brown eyes and blue eyes. To their surprise, they found only one mutation and, what's more, not on the P protein gene but on an adjacent gene: HERC2. This particular mutation has the same effect as a switch and slows down protein P synthesis, thus reducing its production. Without it, P protein is produced normally and eyes are brown. In individuals carrying this mutation, P protein is produced in smaller quantities and eyes turn out to be blue.

Check the chromosomal location of the two genes OCA2 and HERC2.

Return to NCBI home page and from the database pull down menu on the left select the Gene database and type separately "OCA2" and "HERC2" in the search box.

OCA2: Chromosome: 15; Location: 15q11.2-q12

HERC2: Chromosome: 15; Location: 15q13

In conclusions, HERC2 is adjacent to OCA2. The terminal part of the HERC2 gene contains a switch which regulates OCA2 expression!

The authors have found that “One single haplotype, represented by six polymorphic SNPs covering half of the 3' end of the HERC2 gene, was found in 155 blue-eyed individuals from Denmark, and in 5 and 2 blue-eyed individuals from Turkey and Jordan, respectively”.

What this implies, is that this mutation is a “founder mutation” i.e. it is shared by both North European individuals and subjects from Turkey and Jordan. All blue-eyed individuals indeed carry the same mutation which seems to have appeared about ten thousand years ago. Before that, everyone had dark eyes. The first blue look appeared on earth during the Neolithic period (about 6-10,000 years ago) when our ancestors left the region of the Black Sea for a better future, and built settlements in Northern Europe. Ever since, blue eyes have cleared millennia, gliding successfully through time.

### **Why are blue eyes still around? Why has evolution kept them?**

The high frequency of blue eyed individuals in Scandinavia and Baltic regions indicates a positive selection for this trait.

Several theories have been suggested to explain the evolutionary selection for pigmentation traits which include UV radiations causing skin cancer, vitamin D synthesis from precursors in diet food requiring UV radiations reaching the deep layers of derma, and also sexual selection .

White skin – which is a phenotype so typical to our Northern hemisphere – is explained as an adaptation to poor sunlight, thus favouring the synthesis of vitamin D. But blue eyes? What are they for? A number of researchers suggest that it may simply have something to do with sexual selection. Why not? How many of us have got hopelessly lost in an ocean blue gawp? Jean Gabin seemed to know better.....

### **Structural features of the protein**

For a complete card of the P protein go to

<http://uniprot.org/uniprot/Q04671>.

This protein is a transporter protein with at least one transmembrane domain

To view its main structural features copy it in FASTA format (click the yellow button on the top right of the page).

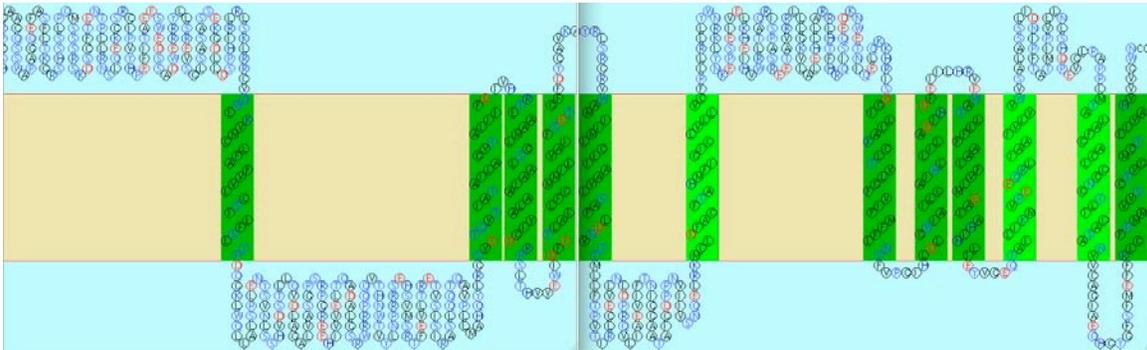
Go to:

[http://bp.nuap.nagoya-u.ac.jp/sosui/sosui\\_submit.html](http://bp.nuap.nagoya-u.ac.jp/sosui/sosui_submit.html)

and Paste the FASTA sequence in the search box. Click execute.

This software is dedicated to the prediction of transmembrane protein domains based on R groups of aminoacid residues and gives a graphic representation of the disposition of transmembrane domains in the membrane.

Look at the predicted transmembrane domains.



How many are they?

Which R groups are the most frequent in the aa predicted to be part of transmembrane domains?

To answer this question visit also this listing of the different side groups for the various amino acids: <http://www.elmhurst.edu/~chm/vchembook/562review.html>

### 3D structure of the protein

Return to <http://uniprot.org/uniprot/Q04671>

Scroll down the page to the section “3D structure databases” and click search.

Sequence Model Coverage	
Sequence Identity	13.00%
E-Value	3.2e-07
Model Score	0.15
Target Region	420-636
Protein Length	838
Template PDB Code	2a65A
Template Region	9-428
MPOG	0.57
z-Dope	-1.44
Dataset	H.sapiens
ModPipe Version	ModPipe2.0

Crystal structure of leuTaa, a bacterial homolog of na+Cl- dependent neurotransmitter transporters

Your search hasn't found any record for 3D structure of the human P protein; the first in the list is

You can download the file with the blue arrow icon (PDB code 2a65A )and open it with DeepView.

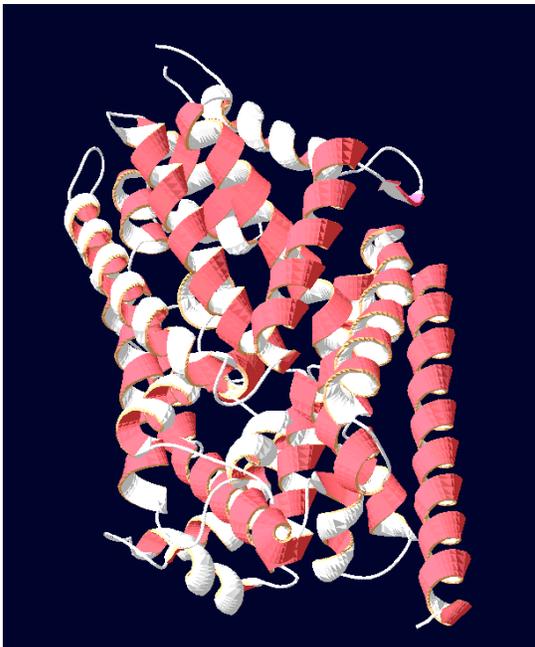
### **Deep View**

Deep View (formerly called Swiss-PdbViewer) is a powerful molecular graphics program available from the **Expert Protein Analysis System (ExPASy)** Molecular Biology Server in Geneva, Switzerland.

Deep View is downloadable from <http://www.expasy.org/spdbv/>.

Deep View is an application that provides a user friendly interface allowing to view protein 3D structures, create models and also analyse several proteins at the same time. The proteins can be superimposed in order to deduce structural alignments and compare their active sites or any other relevant parts. Amino acid mutations, H-bonds, angles and distances between atoms are easy to obtain thanks to the intuitive graphic and menu interface.

For proteins of known sequence but unknown structure, DeepView submits amino acid sequences to ExPASy to find homologous proteins, onto which you can subsequently align your sequence to build a preliminary three-dimensional model. Then DeepView submits your alignment to ExPASy, where the SWISS-MODEL server builds a final model, called a homology model, and returns it directly to DeepView.



With the Deep View software, you will learn to:

- observe tertiary structures of proteins, identify domains and secondary structures
- get familiar with the different types of visualizations: ribbon diagrams, backbone and sidechains
- Superimpose and compare two, or many, models simultaneously