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Gene Section
Short Communication

TYR (tyrosinase (oculocutaneous albinism IA))

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Identity

Other names: CMM8, OCA1A, OCAIA, SHEP3

HGNC (Hugo): TYR

Location: 11q14.3

DNA/RNA

Description

Gene encompasses 80 kb of DNA, 5 exons.

Transcription

2082 bp.

Pseudogene

Tyrosinase Like Gene (TRYL 11p11.2) shares 98,55% sequence identity with the 3' region of Tyrosinase.
The sequence similarity lies in exons IV and V and lacks exons I, II, and III (Chaki et al., 2005).

Protein

Description

529 amino acids; nascent protein is 60 kDa; Posttranslationally modified by glycosylation giving an 80 kDa protein.
Contains an 18 amino acid long signal peptide, six N glycosylation sites, two copper binding sites (CuA and CuB) and a transmembrane domain (Mashima, 1994; Kosmadaki et al., 2010).

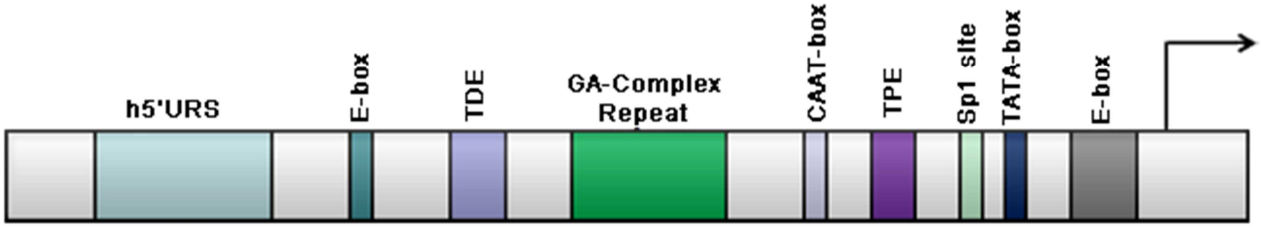
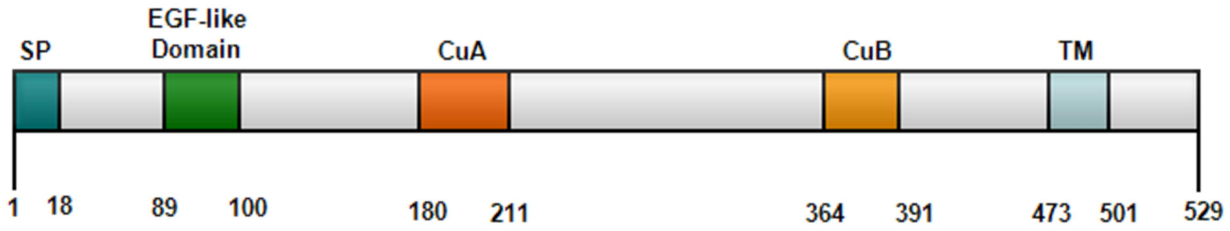


Diagram of Tyrosinase promoter region adapted from Ray et al. 2007. H5'URS(human 5' upstream regulatory sequence), TDE (Tyrosinase distal element), and TPE (Tyrosinase proximal element).



Schematic of Tyrosinase Polypeptide adapted from Mashima 1994. SP (signal peptide), EGF (Epidermal growth factor)-like domain, CuA and CuB (Copper binding domains) and TM (transmembrane domain).

Expression

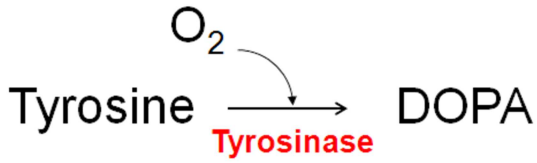
Expressed mainly in neural crest derived melanocytes and is sorted into the melanosomes within the melanocyte. Tyrosinase is also found in retinal pigment epithelium cells (Hearing, 2011).

Localisation

Transmembrane protein.

Function

Tyrosinase catalyzes conversion of tyrosine to DOPA; the rate limiting step of melanin biosynthesis and subsequently DOPA to dopaquinone (Olivares et al., 2009).



Tyrosinase catalyzes the conversion of tyrosine to DOPA in the rate-limiting step of melanin biosynthesis.

Homology

The protein tyrosinase related protein 1 (TRP1) is a member of the tyrosinase protein family and utilizes copper as its cofactor. Its function in humans is not well elucidated but is thought to aid in maintaining tyrosinase catalytic activity and stability. It is also involved in maintaining melanosome structure as well as proliferation and cell death of melanocytes (Sarangarajan et al., 2000; Ghanem et al., 2011). Tyrosinase related protein 2 (TRP2), which is also known as DOPAchrome tautomerase catalyzes the conversion of DOPAchrome to 5,6-dihydroxy indole-2-carboxylic acid (DHICA). TRP2 binds 2 zinc ions as cofactors instead of copper (Olivares et al., 2001; Wan et al., 2011).

Mutations

Germinal

Partial or complete deletion of Tyrosinase leads to dysregulation of melanin synthesis within the melanosomes leading to oculocutaneous albinism (OCA1). The presence of non-pathologic polymorphisms results in variations in skin pigmentation. There are a total of 189 reported OCA1 mutations including 148 missense or nonsense, 23 small deletions, 8 small insertions, 2 insertion/deletion type 1, 1 complex rearrangement, and 7 splice site alterations (Ray et al., 2007; Ko et al., 2011).

Implicated in

Melanoma

Disease

Highly aggressive neoplasma arising from melanocytes. Melanoma is responsible for the majority of skin cancer related deaths with a very high probability of metastasis. This neoplasm is greatly resistant to most conventional therapies. Due to the longevity of melanocytes, these cells are considered to have a greater mutagenic burden. This burden is also greater due to the position of melanocytes within the skin and their exposure to UV light. Tyrosinase enzymatic activity has been found to be associated with a better prognosis due to its association with functional activity of the tumor supressor p53. Tyrosinase-mediated melanin production signaled by p53 activation is a key protective response to UV damage (Flaherty, 2012; Gilcrest, 2011).

Oncogenesis

Several environmental and genetic factors are involved in the complex process of melanocytic tumorigenesis. Melanin production involving tyrosinase as the rate-limiting step has been shown to protect keratinocytes from DNA damage and oxidative stress from ultra violet radiation; A low incidence of melanoma in darker skinned populations has been observed, indicating a photoprotective role of melanin (Kanavy, 2011).

Oculocutaneous albinism 1A

Disease

Autosomal recessive condition that results in partial or complete loss of tyrosinase activity. Complete loss of activity results in the absence of melanin in the skin and eyes and is classified as OCA1A and the presence of only reduced tyrosinase activity is classified as OCA1B. Complete loss of tyrosinase activity results in the total absence of melanin in the skin and hair. The iris in patients with OCA1A is light blue or gray and the retina lacks pigmentation as well. Tyrosinase null patients have greatly reduced visual acuity accompanied by nystagmus, strabismus, and usually photophobia (Ray et al., 2007). Patients with OCA1B present with varying levels of pigment. The hair in these patients is often yellow. The yellow color is a result of the pheomelanin synthesis.
Dopaquinone has a high affinity for sulfhydryl compounds and produces pheomelanin as a result, causing yellow pigmentation. Patients with OCA1B often develop pigmentation in the cooler regions of the body, like the extremities (Chiang et al., 2008).

Prognosis

Prognosis in patients is generally good with no system abnormalities other than the loss or reduction in pigmentation. Patients are advised to protect their skin from sun to prevent sunburn (Ray et al., 2007).

Oncogenesis

Transcription of tyrosinase has been shown to increase with activation of the tumor suppressor p53, linking both to the tanning response following exposure to UV damage (Khlgatian et al., 2002 and Cui et al., 2007).

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