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Gene Section
Short Communication

SLC45A2 (solute carrier family 45 member 2)

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Abstract

SLC45A2 gene, having a chromosomal location 5p13.2, encodes a membrane associated transporter protein (MATP). MATP is a transmembrane protein. It is present in the melanosomal membrane in the melanocytes. It maintains the osmotic potential by regulating the pH of the melanosomal lumen. Defects in the SLC45A2 gene causes oculocutaneous albinism type IV; OCA IV

Keywords
SLC45A2, MATP, albinism, OCA IV

Identity

Other names: AIM1, SHEP5; OCA4

HGNC (Hugo): SLC45A2

Location: 5p13.2

DNA/RNA

Description

In Chromosome 5, the 40,529 bases of DNA starts from 33,944,616 and ends at 33,985,144(GRCh38/hg38). Orientation: Minus strand. It contains 7 exons.

Transcription

The gene after transcription produces 7 different mRNAs, 6 alternatively spliced variants and 1 unspliced form. There are 4 non overlapping alternative last exons (https://www.ncbi.nlm.nih.gov/IEB/Research/Acembly/av.cgi?db=humanterm=slc45a2submit=Go).

Protein

Description

The human SLC45A2 protein is a 530-amino acid polypeptide that contains 12 putative trans-membrane domains, and is only expressed in the melanosomes in the melanocytes (Newton et al., 2001).

The SLC45A2 gene initially identified as AIM1 (absent in melanoma 1) by Newton et al, 2001 encodes a Membrane-Associated Transporter Protein (MATP). It acts as a transporter and regulates the melanosomal pH using a proton gradient.

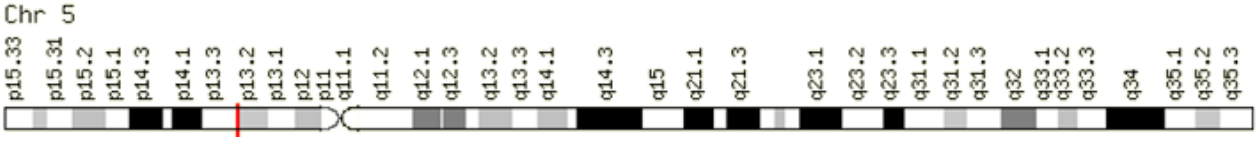

Figure 1. SLC45A2 Gene in genomic location: Cytogenetic band: 5p13.2 by Entrez Gene, 5p13.2 by HGNC, 5p13.2. The figure represents the cytogenetic banding of SLC45A2 locus (Ref https://www.genecards.org/cgi-bin/carddisp.pl?gene=SLC45A2)

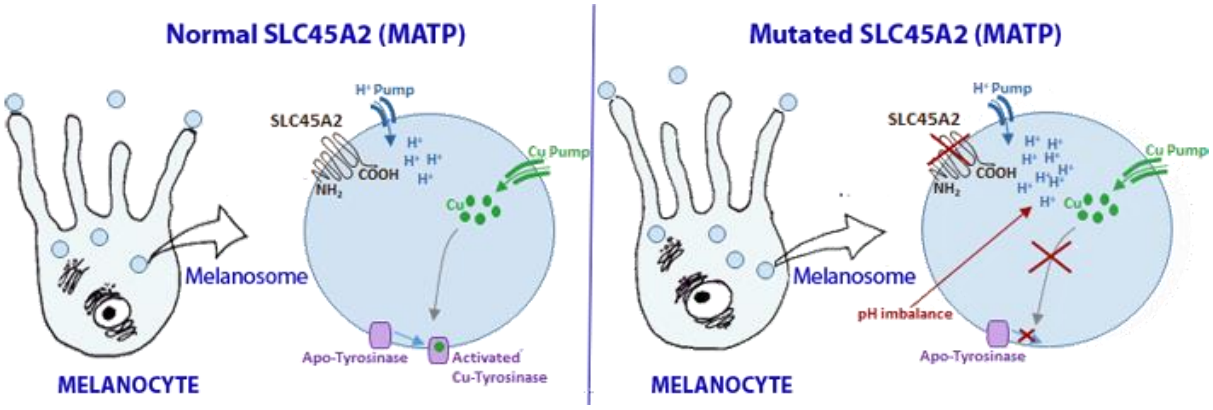

Figure 2. The SLC45A2 (MATP) acts as a transporter present on the melanosomal membrane. Under normal condition it controls the pH by using a proton gradient. Thus helps in Copper to bind to Apo-Tyrosinase and convert it to active Tyrosinase. In oculocutaneous albinism type IV (OCA4), any deleterious mutation in melanosomal MATP transporter protein makes the melanosomal lumen acidic. Under this condition, the Cu fails to bind to the Apo-Tyr and Tyrosinase activity is reduced. (Bin et al, 2015).

Expression

The MATP protein (58 kDa) is expressed in most melanoma cell lines and melanocytes and sorted into the melanosomal membrane. The highest expression level has been observed in the pigmented layer of retina (https://www.uniprot.org/uniprot/Q9UMX9).

Localisation

It is a transmembrane protein present in the melanosomal membrane in melanin producing melanocytes.

Function

SLC45A2 (MATP) allows the transport of sugar molecule across the membrane into the cytoplasm and maintains osmotic potential of the melanosomes (Rabea Bartolke, 2014, Reinders et al 2015). It maintains the pH of the melanosome which facilitates the binding of Copper to Tyrosinase resulting in the conversion of Apo-Tyrosinase to Tyrosinase. (Newton et al, 2011).

Homology

The human MATP shows syntenic homology with the proximal region of mouse chromosome 15. The human orthologue for the mouse underwhite gene locus (uw gene) is encoded by SLC45A2 gene. The predicted mouse MATP protein is 82% identical and 87% similar to the human MATP protein.

The highest degree of homology was found between MATP and sucrose/proton symporters found in plants. The homologous region of MATP includes the sucrose-transporter signature sequence: R-X-G-R-[K/R], found in between the transmembrane domains 2 and 3 (Meyer H et al, 2011, Newton et al, 2011).

The sucrose transporter Slc45-1 in Drosophila shows significant similarity to mammalian SLC45A2 and plays a role in melanin synthesis.

Mutations

Germinal

Homozygous mutation or Compound Heterozygote mutations in SLC45A2 gene has been found responsible for causing Oculocutaneous Albinism Type 4 (OCA4). To date around 80 mutations have been reported in SLC45A2 responsible for OCA4. (Kamaraj et al. 2014, Toth et al. 2017). OCA4 was first observed in Turkish population, it is rare among Caucasians and Africans and in Japan it is diagnosed in one of four persons affected with OCA.

There are several non-pathogenic polymorphisms which result into mild pigmentation.

The haplotypes at SLC45A2 is significantly associated in determination of dark or light pigmentation features in human population. (Fracasso et al.2017)

Epigenetics

In an attempt to identify genetic and epigenetic marks involved in population structure, a coding SNP: rs16891982 (p.L374F) of SLC45A2, known to play a role in normal pigmentation variation, was found to positively correlate with the methylation level of PM20D1 gene. The minor allele A was been found to be associated with lower methylation of the target gene. (https://www.ncbi.nlm.nih.gov/pubmed/20949057).

Implicated in

Oculocutaneous albinism type IV (OCA IV)

Disease

OCA IV is an autosomal recessive disorder of melanin biosynthesis that results in congenital hypopigmentation of ocular and cutaneous tissues.

Common developmental abnormalities of the eye like decreased visual acuity, macular hypoplasia, optic dysplasia, atypical choroidal vessels, and nystagmus are observed in patient suffering from OCA type IV.

The severity of hypopigmentation is correlated with melanosome size, shape, melanin content and maturity of the melanosomal structures demonstrating that the encoded protein is a major determinant of mammalian pigmentation.

Melanoma

In 2017, Park et al reported that a few variants present in SLC45A2 gene can be a promising immune therapeutic target for melanoma with high tumor selectivity and reduced potential for autoimmune toxicity.

It is associated with an increased risk for melanoma in light-skinned populations, and the encoded protein can elicit immune recognition.

The Cancer Genome Atlas Research Network (TCGA) database reported that it is expressed by approximately 80% of cutaneous melanomas.

In the same year Hafner et al showed that SLC45A2 (also called AIM1, absent in melanoma 1) function as a key suppressor of invasive phenotypes by working in association with the actin cytoskeleton. SLC45A2 becomes dysregulated and suppresses cytoskeletal remodelling in primary and metastatic prostate cancer and in non-malignant prostate epithelial cells.

In 2012, Fernandez et al reported in a family that adult siblings presented with congenital neutropenia which later developed into Crohn's Disease.

Molecular characterisation revealed homozygous mutations both in G6PC3 and SLC45A2 in the sister and mutation in single allele for both genes in the brother.

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