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THE EFFECT OF BCMO1 (BCO1) GENE MUTATION ON EYE PHOTORECEPTORS – GAME EXCHANGER FOR VITAMIN A SUPPLEMENT - REVIEW STUDY

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ABSTRACT

Introduction: Photoreceptors located in the retina of the eye. These cells contain large amounts of a membranes that consist of photosynthetic pigment rhodopsin. Vitamin A is a fat-soluble compound that plays an important role in maintaining eye's organs. The most common clinical sign of vitamin A deficiency is xerophthalmia, which develops after a decrease in plasma retinol and depletion of ocular vitamin A reserves. The first sign of vitamin A deficiency is night blindness, or inability to see in dim light or darkness as a result of low levels of rhodopsin in the retina. Dry conjunctiva also affects the cornea and can eventually lead to permanent blindness. BCO1 gene is very important for the conversion of beta -carotene into provitamin. Genetic variant in the BCO1 gene cause varying amounts of the enzyme to be produced and cause a large difference in the amount of vitamin A produced from dietary beta- carotene. **Method:** Using NCBI databases, specifically GenBank to analyze DNA and genomic sequences of BCO1 gene codons. The GenBank file format was useful for extracting gene's accession number, amino acid numbers, numbers of introns and exons, and nucleotide length. The FASTA format also used in retrieving nucleotide sequences and obtaining protein function of that gene. At this stage four article were analyzed to conclude the effect of the BCO1 gene on eye integrity and vision. PubMed was helpful to get those articles. **Result:** NCBI analysis showed BCO1 gene is located on chromosome 16 and contains 11 exons. BCO1 is considered linear DNA and is responsible for the metabolism form vitamin A. **Conclusion:** Adequate supplementation of vitamin A may be recommended for increasing the activity of retinol dehydrogenase to make the eye function properly.

KEYWORDS: BCO1, Vitamin A, PubMed, Eye, GenBank, Rhodopsin, NCBI.

INTRODUCATION

Photoreceptors are cells found in the retina that respond to light. These cells contain large amounts of membrane that consists of photosynthetic pigment rhodopsin or a related molecule. To achieve a high optical density, a narrow packing is needed to allow for the absorption of a high amount of light photons that reach the photoreceptors. It is the absorption of photons that contributes to the photoreceptor output signal. (photoreception Process & Facts, 2022)

vitamin A is a component of rhodopsin, the protein found in rod photoreceptors. It is a fat-soluble compound that involves in many cellular and physiological functions. It plays a critical role in the maintenance and growth of different organs and tissues. On the other hand, it involves in the development and transmission of genes and support immune system. A deficiency of vitamin A occurs when the body's supply of this compound is insufficient to meet its physiological needs. It can be triggered by different factors, such as malnutrition. Most of the people who suffer from this condition are pregnant women and young children. (PWS BB Error, 2022)

The most common clinical sign of vitamin A deficiency is xerophthalmia, which develops after plasma retinol has been low and the eye's vitamin A reserves have become depleted. The first sign is night blindness, or the inability to see in low light or darkness because of low rhodopsin levels in the retina. Xerophthalmia also affects the cornea and can eventually lead to permanent blindness; vitamin A deficiency is one of the top causes of preventable blindness in children. (PWS BB Error, 2022)

The ability to see is dependent on the two main photoreceptors in the eye with the cones and rods. These two components are in the posterior portion of the eye and are responsible for controlling the light entering and leaving the eye. To be able to see, light must first enter and pass through the lens of the eye and then travel through the posterior segment (vitreous chamber). Next, the light must pass through ten layers of the neural retina to reach the rods and cones. The rods and cones consist of an inner segment, which contains the nucleus, and an outer segment, which consists of discs containing light-absorbing photopigments. When comparing the two photoreceptors, the rods are useful for night vision and the cones for day vision. Vitamin A is one of the necessary precursors for the formation of rhodopsin, the photopigment found in rods. Rhodopsin helps us to see at night. Without vitamin A, rhodopsin cannot be formed and "night blindness" occurs. (Photoreception - Structure and function of photoreceptors, 2022)

BCO1 gene is naturally expressed in the eyes and other organs such as the liver, kidneys, reproductive tissues, skin, and the small intestine. The gene function is to convert beta-carotene into vitamin A in these tissues. (Gong, Marisiddaiah and Rubin, 2022)

In this review, four articles were analyzed to determine the relationship between BCO1 gene variation, plasma vitamin A levels, risk of low vitamin A in the eyes, and whether it is a major cause of night blindness. The question of this study is to find out the relationship between BCO1 gene variation and eye disorder like night blindness?

METHOD

Bioinformatics is a database used to collect, store, organize and analyze large amounts of biological, medical and health information. The information is used to conduct genetic and molecular research studies.

Using the PubMed database, four articles were selected using the keywords of our research such as BCO-1, vitamin A, eye, and blindness. Also, by using NCBI databases, specifically GenBank for DNA sequence and mRNA sequence analysis of the BCO-1 gene. The GenBank file format was useful for extracting a gene's accession number, amino acid number, number of introns and exons, and nucleotide length. The FASTA format was also useful in retrieving nucleotide sequences and obtaining protein function. BLAST is used to detect whether the protein product of the BCO-1 gene can be shared with one of the 'animals' to reveal its effect on vitamin A deficiency and night blindness.

The BCO-1 gene located in chromosome 16 (16q23.2) and contains'11 Exon. It is classified as liner DNA. The protein encoded by this gene is a key enzyme in beta-carotene metabolism form vitamin A. It catalyzes the oxidative cleavage of β, β-carotene into two retinal molecules.

Finally, the importance of BCO-1 gene is to convert beta-carotene into vitamin A (pro-vitamin A), in order to compensate for the lack of vitamin A in the body. Part of nucleotide sequence in FASTA format for liner DNA in figure (1)

>NC_000016.10:81238689-81291142 Homo sapiens chromosome 16, GRCh38.p14 Primary Assembly
GTGAATGTAAAGAGATCCAGGGCTCTTGGAGAG
GGACAAGTGAGAGCCAGCCAAAAAGGAAAAAG
CAAAGGCAGAAACGGCATCAGGAGAGACAGAG
ATGTGAAGGAGGGAAGGAGCAGGAGAGCAGGA
AGGAAACGCAGGAGGAGGGAGCAGCATCTCCT
GTGAACACAGAGGAGCACCTGTTTGCTGTTAAA
ATCGATCTCCCTCGGCACCCTGAGCAATGGATA
TAATATTTGGCAGGAATAGGAAAGAACAGCTGG
AGCCTGTGAGGGCCAAAGTGACAGGTGAGCATT
CTGATAAACACTGGGCTCTTTCTTCTATTTATTTT
ATTATTTTTTTTTTTTTTGAGGCGGAGTCTCGCTC
TGTCGCCCGGGCTGGAGTCCAGTGGCTTGATCTC
GGCCCACTGCAACCTCTGCCTCCTGGGTTCAAAC
GATCCTCCCACCACAGCCTCCCGAGTAGCTGAG
ATTACAGGCACCCACCACCAAGCCCGGCTAATC
TGTGTGTTTTTAGTAGAGACGGGGTTTCAGCATG
TTGGCCAGGCTGGTCTCGAACTCCTAGCCTCAA
GTGATCCACCCACCTCGGCCTCCGAAAGTGCTA
GGATTACAGGGGTGAGCCACTGCACCTGGCTTC
TTCCTTGTGTTTAGATGGACACTATTTTTTCCTG
ATGATATAAGTAATACTAATTGTAAATTACTTTT
GGAAAGTCTGGAAAACAGTACAGAGAGGGGAC
ACATTTTCTGTGAAAATCTAGGTATTCTTTTACA
CATTATAACTCCGTTTGCAAAGGGAGGAGAGTC
AGTCTCACTGTTCCCAGGAAAAAAGCATTGGAA
TGCCCCAGTGGGTACATAGACAATGGGATTAAT
CTGCAAACTGCTGCCTGTCTCAGATGCATGATGT
ATTTGTGCAAATGTATGCATTCTAAATTAGTTTC
AAAATGCTTAGAGGGGCGTGCATGAGCTCCCAC
GCATGCACATC

Organism/ Official Symbol	Homo sapiens/BCO1	Mus musculus/ BCO1
Enzyme	beta-carotene oxygenase 1	
Also Known as	BCO; BCDO; BCMO; BCDO1; BCMO1	Bcdo; CMO1; Cmoi; Bcdo1; Bcmo1; beta-CD; betaCMOOX
Source	Homo sapiens (human)	Mus musculus (house mouse)
Accession	NC_000016 REGION: 81238689..81291142	NC_000074 REGION: 117822590..117860459
Chromosome	16	8

Figure (1) Part of nucleotide sequence in FASTA format for liner DNA.

DISCUSSION

Vitamin A is a type of fat-soluble vitamin such as retinol, and its deficiency in the human body causes epithelial tissues to become keratinous as in the eye with resulting visual defects. (Merriam dictionary, 2022)

Vitamin A deficiency is common, especially with children under the age of 5 years, which directly affects the eye. It may cause night blindness, corneal dryness, corneal softening, and corneal iridescence. It is a mixture of retinol, retinal and retinoic acid with other ingredients such as beta-carotene. Furthermore, vitamin A combines with the retina and opsin to produce rhodopsin in the retina, which is important for both color vision and reverse vision in low light. (Alanazi et al., 2019)

Beta-carotene is the predominant form of vitamin A in the human diet. Once beta-carotene is digested, mixed with fats, and absorbed, it converts it into retinol. This conversion uses the enzyme β-carotene 15,15′-monooxygenase (BCMO1 or BCO1 gene), which converts beta-carotene into the retina. The retina turns into retinol. Genetic variants in the BCO1 gene cause varying amounts of the enzyme to be produced and cause a large difference in the amount of vitamin A produced from dietary beta-carotene.

Many structures exposed to light such as the human retina contain much xanthophyll (oxygen-containing) carotenoids, namely lutein (L), a structural isomer of zeaxanthin (Z), and mesozeaxanthin (miso-Z), the metabolite of lutein and zeaxanthin. stereoisomer Diet L and its isomers are selectively concentrated in the visual system (eyes and brain) with 80% to 90% of the carotenoids present in human eyes and the rest in the brain.

All human ocular structures contain lutein except for the vitreous, cornea, and sclera on L and Z receptors. The highest concentrations of L and Z are in the retina and the highest concentrations are in the central fovea of the retina. This cone-rich region gives the highest visual acuity and has the highest exposure to light in the retina, and the further we go from this point, the lower the l and Z focus.

In the lens of the eye, three types of carotenoids are concentrated, namely L, Z and oxidative receptors, and 75% of L, Z are in the lens tissues that are most exposed to light and are most metabolically active in the cortical lens layers, on the other side (the central region of the lens of the eye (nuclear)) It has less concentration.

The function of the carotenoids lies in absorbing the amount of light falling on the eye directly, and the absorption ratio is from 40 to 90% of the light, in order to protect the retina from damage caused by light and also reduce the scattering of light, so we find the highest concentration of the macular carotenoids in the fovea in the outer plexiform layer It is a layer of synapses in the retina located between the rod and cone photoreceptors, their axons, and other retinal cells. The function of L AND Z is to protect against oxidative stress indirectly by absorbing light. (Mares, 2016)

In all animals there are two types of carotenoid cleavage enzymes, BCO1 and BCO2 (carotene oxygenase enzymes 1 and 2) also known as β, β-carotene monooxygenase, which primarily cleave protamine A-carotenes such as β-carotene or β-cryptoxanthin at the carbon double bond and carbon to produce all-trans retinal, all-trans 3-hydroxyretinal (in the case of β-cryptoxanthin), or acyloretinal (in the case of lycopene). All can be converted via the retina into fully retinol which is involved in the visual cycle and can also be oxidized to retinoic acid which is of great importance for determining the regulation of different gene pathways.

BCO2 that acts directly on the carotenoids section and in particular the xanthophyll carotenoids which results in apo-10′-carotenoid and ionone, or rosafluene. Unreasonable mutations such as polynucleotide polymorphisms in the BCO2-stimulated region may cause the accumulation of lutein or zeaxanthin, which leads to yellowing of their color.

Although BCO1 does not cleave zeaxanthin and lutein in humans, it can still indirectly affect their tissue levels by regulating the activity of a protein known as the scavenger receptor BI. The presence of multiple genetic variants associated with the BCO1 gene has been shown to influence the levels of serum and macular pigment optical density.

In the first article, analyze around 46 samples (22 males and 24 females) with an average age of youth in order to determine the effect of BCO1 Single Nucleotide Polymorphisms (SNPs) rs11645428, rs6420424 and rs6564851 on the Macular Pigment Optical Density (MPOD) in a group of healthy young participants of Caucasian origin with normal visual health.

The analysis of the study showed that the MPOD decreases over life. The macular pigment concentration was higher in the younger group and therefore any competition for uptake would be irrational as the older group with a lower mean MPOD affected the rate of competition for deposition of macular pigment within the central retina. It may be that bco1 is not the determining factor for macular pigment density in the younger group.

This study concluded that the genotypes in BCO1 do not affect MPOD; the researchers noted that MPOD is affect by age and this may be due to genetic reasons and may be the absorption of BCO1 effect in the elderly, which can be determined by measuring transport proteins. The limitation of this study is the age group chosen, as it was only the youth group.

In the second Article, the number of samples was 1663 samples from women only, and those samples were from different regions, in order to study the carotenoids and their effect on eye diseases at different ages. The relationship between single nucleotide polymorphisms (SNPs) of candidate genes for lutein and zeaxanthin related to macular pigment optical density (MPOD) has been described. The genes associated with MPOD and serum levels of these carotenoids include β-carotene 15, 15′-monooxygenase 1 (BCMO1); ATP-binding cassette, subfamily A, member 1 (ABCA1) and subfamily G member 5 (ABCG5); scavenger receptor class B member 1 (SCARB1); The pigment epithelium-specific protein is 65 kDa (RPE65). In this study, two variants of the carotenoids BCO1 and BCO2, both of which are carotenoid enzymes, were linked with age-related macular degeneration (AMD). The β,β-carotene 15,15′-monooxygenase 1 is a cytosolic enzyme that cleaves symmetrically and β,β-carotene 9′,10′-dioxygenase 2 is a mitochondrial enzyme that cleaves asymmetrically. The presence of one or two of the A-alleles at rs11645428 (BCO1) was associated with higher levels of lutein and zeaxanthin in the serum and the macula and a 20% lower probability of AMD. In contrast, women with the rs6564851 variant related to higher serum and macular levels also were less likely to have AMD.

In other samples, this genetic change was associated with higher levels of lutein and zeaxanthin and a higher catalytic activity of BCO1 enzyme in women, which means a higher transfer of beta-carotene to the retina, which results in a decrease in the circulation cycle of beta-carotene.

In the third article, in the third article, the study focused on the work of all samples from mice to follow the effect of BCO1 in mice. It has been observed that the cleavage of beta-carotene by BCO1 produces retinaldehyde, which can be converted to retinol, a retinyl ester for storage, and to retinoic acid. Retinoids such as retinoic acid and retinaldehyde are ligands of nuclear receptors including retinoic acid receptors and peroxisome proliferator-activated receptors that help control lipogenesis. In turn, retinoic acid also plays an important role in determining the different genetic pathways of BCO1.

The fat is necessary for the integrity of vision, as it is responsible for the integrity of the eye completely. Since the lipid layer is an essential component of the tear film in the eye, it is responsible for providing a smooth optical surface to the cornea and delaying evaporation from the eye. The thickness of the fatty layer affects the integrity of the eye organs, such as the retina. (Bron et al., 2004).

In the fourth article, the importance of carotenoids is discussed. It is a series of polyenes that play an important role in absorbing light from the maximum UV rays between 450 and 570 nm. In this review, it is revealed that the activity of BCO1 protein in the tear film can stimulate the luminal cleavage of some xanthophylls such as lutein and zeaxanthin. The two enzymes differ in their cellular localization. The centrosome cleavage enzyme, known as BCMO1, is located in the cytosol region of the cell, while the eccentric division enzyme, known as BCDO2, is located in the mitochondria.

It was initially thought that central cleavage of beta-carotene could be an alternative pathway for the production of vitamin A and retinoid. However, when animals feeding on beta-carotene, they become deficient in vitamin A. This indicates that BCO1 is the primary component of the enzyme responsible for the production of these two nutrients.

The study showed that BCO1 and BCO2 are expressed in renal tubules, external pancreas, Leydig and Sertoli cells in the testis, intestinal mucosa, stomach, adrenal gland and eye epithelium, and in contrast BCO2 is expressed only in the heart, skeletal muscle, prostate, connective tissue, endometrium and pancreas, which can be expected that BCO2 has a function independent of vitamin A production.

Retinoids, called any of the various synthetic or natural analogues of vitamin A, are chemical compounds related to vitamin A that have many mechanisms to normalize carotenoids and aid their maturation, have immunomodulatory effects and act as anti-inflammatory (Merriam dictionary, 2022). The cloning of these retinoids for the treatment of dry eye syndrome and blepharitis and conjunctivitis are the most common positive side effects, as 20% to 50% of those treated with retinoids showed improvement in vision. (Bergler-Czop, Bilewicz-Stebel, Stańkowska and Bilewicz-Wyrozumska, 2016)

Finally, all the reports discussed show that the BCO1 gene responsible for converting beta-carotene into pro-vitamin A has a direct effect on eye safety and vision and may affect night blindness. The BCO1 genetic defect affects the maintenance of vitamin A levels. Summary of findings for all articles in figure (2).

Number of article	Name of article	Author	Finding
1	The Effect of BCMO1 Gene Variants on Macular Pigment Optical Density in Young Healthy	Zachary Kyle-Little 1, Andrew J Zele 2, C Phillip Morris 1, Beatrix Feigl 3	Analyze around 46 samples (22 males and 24 females. The results of the analysis showed that neither macular pigment optical density varied significantly with BCMO1 rs11645428 (F2,41 = 0.70, p = 0.503), rs6420424 (F 2,41 = 0.21, p = 0.801) nor rs6464851 homozygous or heterozygous genotypes. (F 2,41 = 0,

	Caucasians		13, p = 0.88). There was a significant negative correlation with MPOD and central retinal thickness
2	Genetic evidence for role of carotenoids in age-related macular degeneration in the Carotenoids in Age-Related Eye Disease Study (CAREDS)	Kristin J Meyers et al	1663 samples from women only A total of 24 variants from five genes (BCMO1, BCO2, NPCL1L1, ABCG8, and FADS2) not previously related to AMD and four genes related to AMD in previous studies (SCARB1, ABCA1, APOE, and ALDH3A2) were associated independently with AMD, after adjusting for age and ancestry. Variants in all genes (not always the identical SNPs) were associated with lutein and zeaxanthin in serum and/or macula, in this or other samples, except for BCO2 and FADS2
3	Beta-carotene reduces body adiposity of mice via BCMO1	Jaume Amengual et al	All samples used are from mice Evidence from cell culture studies indicates that β-carotene-(BC)-derived apocarotenoid signaling molecules can modulate the activities of nuclear receptors that regulate many aspects of adipocyte physiology It has been observed that BCO1 affects the production of retinoblasts
4	Carotenoid metabolism in mammals, including man: formation, occurrence, and function of apocarotenoids	Abdulkerim Eroglu, Earl H Harrison	Beta-carotene is cleaved into its double vitamin A production center (retinal or beta-apo-15 beta-carotene) provitamin A carotenoids are responsible for the formation of vitamin A (retinoids)

Figure (2): Summary of findings for four articles.

CONCLUSION

The BCO1 gene plays an essential role in maintaining the eye vision. This gene converts beta-carotene into provitamin A. All research shows that one of the main sources of vitamin A for the human body is BCO1 gene. All reports prove that any genetic defects in BCO1 will negatively affects the safety of the individuals with certain variants of the gene are associated with nearly 60% reduction in enzyme activity. Individuals with variations in the BCMO1 gene may require more vitamin A.

As low levels of vitamin A are associated with a variety of poor health outcomes, dietary consumption of adequate amount of vitamin A will increasing the activity of retinol dehydrogenase to make the eye function properly.

REFERENCE

1. Encyclopedia Britannica. 2022. *photoreception | Process & Facts*. [online] Available at: <https://www.britannica.com/science/photoreception > [Accessed 8 May 2022].
2. Ods.od.nih.gov. 2022. *Office of Dietary Supplements - Vitamin A and Carotenoids*. [online] Available at: <https://ods.od.nih.gov/factsheets/VitaminA-HealthProfessional/> [Accessed 10 May 2022].
3. Encyclopedia Britannica. 2022. *photoreception - Structure and function of photoreceptors*. [online] Available at: <https://www.britannica.com/science/photoreception /Structure-and-function-of-photoreceptors> [Accessed 15 May 2022].
4. PubMed. 2022. *Beta-Carotene*. [online] Available at: <https://pubmed.ncbi.nlm.nih.gov/30000966/> [Accessed 17 May 2022].
5. Chen, Q., Wu, B., Pan, D., Sang, L. and Chang, B., 2021. Beta-carotene and its protective effect on gastric cancer. *World Journal of Clinical Cases*, 9(23): 6591-6607.
6. Mount Sinai Health System. 2022. *Beta-carotene Information | Mount Sinai - New York*. [online] Available at: <https://www.mountsinai.org/health-library/supplement/beta-carotene> [Accessed 23 May 2022].
7. Cheng, J., Balbuena, E., Miller, B. and Eroglu, A., 2022. *The Role of β-Carotene in Colonic Inflammation and Intestinal Barrier Integrity*.
8. Gong, X., Marisiddaiah, R. and Rubin, L., 2017. Inhibition of pulmonary β-carotene 15, 15'-oxygenase expression by glucocorticoid involves PPARα. *PLOS ONE*, 12(7): e0181466.
9. Mares, J., 2016. Lutein and Zeaxanthin Isomers in Eye Health and Disease. *Annual Review of Nutrition*, 36(1): 571-602.

10. Bron, A., Tiffany, J., Gouveia, S., Yokoi, N. and Voon, L., 2004. Functional aspects of the tear film lipid layer. *Experimental Eye Research*, 78(3): 347-360.
11. 2022. [online] Available at: <https://www.merriam-webster.com/dictionary/retinoid> [Accessed 13 June 2022].
12. Bergler-Czop, B., Bilewicz-Stebel, M., Stańkowska, A. and Bilewicz-Wyrozumska, T., 2016. Side effects of retinoid therapy on the quality of vision. *Acta Pharmaceutica*, 66(4): 471-478.
13. 2022. [online] Available at: <https://www.merriam-webster.com/dictionary/vitamin%20A> [Accessed 14 June 2022].
14. Alanazi, S., El-Hiti, G., Al-Baloud, A., Alfarhan, M., Al-Shahrani, A., Albakri, A., Alqahtani, S. and Masmali, A., 2019. <p>Effects of short-term oral vitamin A supplementation on the ocular tear film in patients with dry eye</p>. *Clinical Ophthalmology*, 13: 599-604.