Review Article

Journal of Ophthalmology & Clinical Research

# Evolutionary Adaptation of Human Lens to Ultraviolet Radiation and Hypoxia

**Sarah I Y Ahmed*, Rayan S Ali and Eltahir AG Khalil**

*Institute of Endemic Diseases, University of Khartoum, Khartoum, Sudan.*

***Corresponding author**
Sarah IY Ahmed, Institute of Endemic Diseases, Medical campus, University of Khartoum, Qasser ST, P.O BOX 102, Khartoum, Sudan.

**Submitted**: 24 June 2017; **Accepted**: 01 July 2017; **Published**: 12 July 2017

## Abstract

*Genetic evolution of human lens and vision in extreme environments of high ultraviolet radiation (UVR) and low oxygen at high altitudes is an evidence of intense past of Natural Selection. This review is an attempt to explain how the adaptive genes associated with high altitudes adaptation to extreme environments can improve human vision and protect from many ocular disorders. We hypothesized that both EPAS1 and MTHFR genes that are known to be strongly associated with high altitudes adaptation are, in turn, also associated with adaptation of human lens epithelium to the conditions of high UVR and hypoxia, which are believed to be the main causes of lens opacities and cataracts. We suggested that the oxidative stress that may result from UVR and hypoxia are responsible for the down-regulation of high-fidelity DNA repair mechanisms in ocular tissues, skin, and other tissues. This probably leads to high genetic flexibility and variations that influence the process of Natural Selection on the basis of competition between the cells that bear different genetic signatures. This would result in more adaptive populations of cells that are better capable of surviving such extreme conditions, resulting in a better adaptive vision. Therefore, we adopt the concept of "Therapy by adaptation", to benefit from the human genetic heritage of ancient indigenous populations like Tibetans and their adaptive physiological response to extreme environments and how to explore these adaptive mechanisms for the prevention and cure of hypoxia-related and UVR-related disorders like cataracts.*

**Keywords:** Human lens/Vision, UVR/Hypoxia, oxidative stress, 1Adaptation, EPAS1/MTHFR genes.

## Introduction

The Tibetan Plateau in China has an average elevation of 4,000 meters above sea level, where the oxygen concentration is 40% lower and UV radiation is 30% stronger. The indigenous Tibetan people have developed a distinctive set of physiological characteristics to adapt to such extreme environmental conditions in the highlands [1]. This gives them the ability to be protected from the conditions of oxidative stress that follow hypoxia and high UVR, resulting in an increased generation of reactive oxygen species (ROS) and free radicals, which are believed to be the main causes of the progression of lens opacities and cataracts. This advantage is probably the reason for the variable proportions of age-related cataract in different ethnic populations, ranging from 82% in India to 53% in Tibet in the age group of 75-85 years old [2,3].

In a recent study, Yang and colleagues conducted a genome-wide study in Tibetans and non-Tibetan individuals of Eastern Asian ancestry. Using a large dataset, they detected strong signals of high-altitude adaptation at two loci, EPAS1 (Endothelial PAS Domain Protein 1) and MTHFR (methylenetetrahydrofolate reductase) genes that are strongly associated with blood-related phenotypes, such as hemoglobin, homocysteine, and folate in Tibetans [1]. Therefore, we suggest a direct role for EPAS1 gene in adaptation of human lens epithelium to oxidative stress, and we also take the folate-increasing allele of rs1801133 at the MTHFR locus as an example for the molecular basis of Natural Selection and evolutionary adaptation to high UV radiation.

### EPAS1, iron homeostasis, and adaptation of human lens

During normoxia, hypoxia-inducible factor -2 α (HIF-2α), the gene product of EPAS1, is inhibited by the binding of the iron regulatory protein 1 (IRP1) to an iron responsive element (IRE) in the 5'-untranslated region of the HIF-2α mRNA. Hypoxia causes repression of the IRP1-IRE binding, releasing HIF-2α to be translated and allowing HIF-2-mediated hypoxic responses [4]. HIF-2α promotes many physiological activities to adapt to hypoxia including high intestinal iron absorption and erythropoiesis to meet the increased iron demand in association with elevated red blood cells production like in high altitudes conditions. This renders iron homeostasis to be under the force of selective pressure [5,6]. In adaptation to hypoxia, the cells of lens epithelium lower iron uptake through changes in expression of iron handling proteins and increase the iron storage capacity of ferritin. This reserves excess free reactive iron into a metabolically inert form and prevents excessive ROS formation. These changes could represent protective mechanisms against iron-catalyzed damage by free radical formation which is increased in the low oxygen environment in which the lens resides. Interestingly, studies show a tenfold increase in the expression level of erythropoietin, the main hormone in erythropoiesis, in the hypoxia-treated cells of lens epithelium. Indeed, no erythropoietin protein expression was detected

in cells maintained in either hypoxia or atmospheric oxygen [7]. But it shows how human lens in response to hypoxia can be directly affected by the stabilization of the hypoxia-inducible factor activity.

On the other hand, increased production of ferritin light subunit (L-ferritin) over the heavy subunit (H-ferritin) is also likely to potentiate oxidative damage by limiting H-ferritin's ability to store iron. High levels of serum L-ferritin are known to be associated genetic cataract like in Hereditary hyperferritinemia cataract syndrome. However, Goralska et al. showed the formation of inclusion bodies of L-ferritin in older lenticular epithelial cells which raises the possibility of these ferritin aggregates participating in not only genetic cataract formation but also age-related cataractogenesis [8].

Long-term preservation of lens clarity is believed to highly depend on the maintenance of hypoxia in the lens nucleus. During aging, the lens loses its antioxidant potencies, this result in increased levels of oxidized and altered proteins, which probably lead to the formation of cataractous lens [9].

Tibetans indigenous populations, who have lived on the Tibetan Plateau for millennia, have acquired the ability for long-term physiological responses to high-altitude environments with a highly advanced antioxidant system. These adaptive physiological mechanisms give them the advantage to be protected against hypoxia-induced disorders like cataracts. Several studies show that the prevalence of hypoxia-related disorders in altitudes is affected considerably by the ethnic differences; Tibetans who are less fortunate and have less access to health facilities, thrive well on the ascent compared to other populations at the same altitude [10,11]. To our knowledge, many studies that suggest a high prevalence of age-related cataract and other lens opacities in high altitudes did not consider the ethnic differences among different populations [12,13]. This poses two important questions:

**a.** What are the molecular mechanisms of evolutionary adaptation that render Tibetans to become more adapted.

**b.** Can we explore these mechanisms for the benefit of other populations.

## Molecular basis for evolutionary adaptation

Two processes are hypothesized to be the basis for molecular mechanisms of adaptation to extreme environments. Firstly, genetic variability that gives the cells the chance to choose between different genetic variants. Secondly, Natural Selection for certain genetic variants that lead to better phenotypic characteristics.

## Genetic Variability

Genetic instability in human cells can be induced by hypoxia and UVR that result in oxidative stress. The stabilization of Hypoxia-inducible factors, the main transcriptional factors in hypoxia, down-regulates the major DNA repair mechanisms: mismatch repair and homologous recombination (HR). This leads to a switch from the high-fidelity repair mechanisms to the error-prone mutagenic non-homologous end joining mechanism (NHEJ). Ultimately, this results in various types of genetic alleles, holding different potentials [11,14,15].

## MTHFR as an example for Natural Selection

The functions of many organs under normal physiological conditions depend on the continuous destruction and renewal of their cells. In conditions of high UV radiation, the primary selective pressure is to protect folate from photolysis by dark pigmentation and by the selection of high MTHFR enzyme activity. MTHFR enzyme uses folate vitamin to convert amino acid homocysteine to participate in the production of DNA, RNA, and proteins. The lower enzyme activity results in high levels of homocysteine, which is found to be associated with age-related cataracts. This is probably because high homocysteine levels dramatically contribute to the generation of ROS and the down-regulation of antioxidant enzymes. Inside the cells, the genes shuffle their nucleotides and express different genetic variants. At rs1801133 MTHFR locus, there are two alleles, C and T, affecting the enzyme function. Allele T reduces the enzyme activity by almost 35%. The severe competition for folate for the needs of cell division, DNA repair and melanogenesis is the basis for Natural Selection between cells under such stressful conditions. The cells that retain competitive alleles like C allele are more active, divide more and eventually predominate over other cells populations. As a result, the folate-increasing allele of rs1801133 is more increased in Tibetans compared to other Eastern Asian ancestry populations, and this was suggested to be one of the genomic consequence of adaptation to high UV radiation. [1,16]. It is noteworthy to mention that combined alleles at different genetic loci can determine the competitive nature of a particular cell or groups of cells.

## Therapy by adaptation

In order to exploit the molecular mechanisms of evolutionary adaptation for the best use in clinical settings, we adopt the concept of "therapy by adaptation". Therapy by Adaptation can be either: ***Naturally*** by exposing individuals who are prone to oxidative stress disorders like cataracts or healthy individuals to a certain course of hypoxia before the onset of the disease. This can be done by healthy exercise accompanied by genetic follow-up to monitor e.g. acquired genetic variants and adaptive circulating miRNAs compared to the genetic profiles of highly adaptive individuals like Tibetans. Under physical exertion, individuals experience different degrees of hypoxia as a result of a significant increase in the need for oxygen. Gradually, the body adapts to the conditions of oxygen shortage by rising oxygen capacity of blood, increasing the number of mitochondria and accelerating the synthesis of respiratory proteins and enzymes , providing the body with an active antioxidant system to ensure a high resistance to hypoxia. It was revealed that the expression level of MTHFR enzyme increases significantly in response to the stimulatory and adaptive effects of training under conditions of hypoxia (Zhur et al, online unpublished data). Moreover, recent studies indicated that certain types of high total physical activity, especially in the long term, may be associated with decreased risk of age-related cataract and other ocular disorders by reducing the level of oxidative stress [17,18]. Therapy by adaptation can also be through ***Direct intervention*** by driving micro-evolutionary processes that are well known to the biological system, like inducing site-specific mutation using technologies like CRISPR- cas9, allowing for precise adaptive variants to be made, or by mimicking circulating adaptive miRNAs.

## Future perspectives

A need for a Database for Tibetans indigenous populations and other well adapted Highlanders to study the adaptive mechanisms they have gained through generations to stand the extreme environments of hypoxia and UV light. The database can be used as a standard for comparative studies; like healthy exercise and adaptation biomarkers, beneficial genetic variants and genetic susceptibility for protection from hypoxia-induced and UVR-

induced disorders. It can also be used in prognosis and follow-up e.g. levels of acquired adaptive circulating miRNAs in certain individuals in compare to the adaptive genetic profile and can give a clue for the role of adaptive genetic variants and circulating adaptive miRNAs as therapeutic targets.

## Conclusion

Understanding the basic molecular mechanisms of adaptation in ancient indigenous populations like Tibetans can provide a chance to share the torch with the marathonian mechanisms of evolution, so as to help our body in running fast on the track of evolutionary adaptation.


## Acknowledgments

The authors kindly thank the staff and students of the Institute of Endemic Diseases, University of Khartoum, Sudan. Special thanks are to my father Dr. I Y Ahmed for the interesting stories on his adventures in Marrah Mountains in West Sudan.


## References


1. Yang J, Jin Z, Chen J, Huang X, Li X, et al. (2017) Genetic signatures of high-altitude adaptation in Tibetans. PNAS 114: 4189-4194.
2. Genetics O, Era SA, Era SR, Era AE (2014) Polymorphism of GST and FTO Genes in Risk Prediction of Cataract among a North Indian Population. Ophthalmic Genet 37: 19-24.
3. Asbell PA, Dualan I, Mindel J, Brocks D, Ahmad M, et al. (2005) Age-related cataract. Lancet 365: 599-609.
4. Zimmer M, Ebert BL, Neil C, Brenner K, Melas A, et al. (2008) Small molecule inhibitors of HIF-2a translation link its 5'-UTR Iron-Responsive Element (IRE) to oxygen sensing. Mol Cell 32: 838-848.
5. Patot MCT Van, Gassmann M (2011) Hypoxia: Adapting to High Altitude by Mutating EPAS-1, the Gene Encoding HIF-2 a. High Alt Med Biol 12: 157-167.
6. Rankin EB, Biju MP, Liu Q, Unger TL, Rha J, et al. (2007) Hypoxia-inducible factor-2 (HIF-2) regulates hepatic erythropoietin in vivo. J Clin Invest 117: 1068-1077.
7. Neelam S, Brooks MM, Cammarata PR (2013) Lenticular cytoprotection. Part 1: The role of hypoxia inducible factors-1α and -2α and vascular endothelial growth factor in lens epithelial cell survival in hypoxia. Mol Vis 19: 1-15.
8. Loh A, Hadziahmetovic M, Dunaief JL (2009) Iron homeostasis and eye disease. Biochim Biophys Acta 1790: 637-649.
9. Goralska M, Nagar S, Colitz CMH, Fleisher LN, Mcgahan MC (2009) Changes in Ferritin H- and L-Chains in Canine Lenses with Age-Related Nuclear Cataract. Invest Ophthalmol Vis Sci 50: 305-310.
10. Moore LG, Young D, Mccullough RE, Droma T, Zamudio S (2001)Tibetan Protection From Intrauterine Growth Restriction (IUGR) and Reproductive Loss at High Altitude. Am J Hum Biol 13: 635-644.
11. Ahmed SIY, Ibrahim ME, Khalil EAG (2017) High altitude and pre-eclampsia: Adaptation or protection. Med Hypotheses 104: 128-132.
12. Yu JM, Yang DQ, Wang H, XU J, Gao Q, et al. (2016) Prevalence and risk factors of lens opacities in rural populations living at two different altitudes in China. Int J Ophthalmol 9: 610-616.
13. Shrestha S, Shrestha SM, Gurung A (2016) Comparative Study of Prevalence of Cataract at High Altitude and Kathmandu Valley. J Nepal Health Res Counc14: 81-84.
14. Rapp A, Greulich KO (2004) After double-strand break induction by UV-A, homologous recombination and nonhomologous end joining cooperate at the same DSB if both systems are available. J Cell Sci117: 4935-4945.
15. Galhardo RS, Hastings PJ, Rosenberg SM (2007) Mutation as a Stress Response and the Regulation of Evolvability. Crit Rev Biochem Mol Biol 42: 399-435.
16. Romero-Sánchez C, Gómez-Gutierrez A, Gómez PE, Maria Consuelo Casas-Gomez, Ignacio Briceño (2015) C677T (rs1801133) MTFHR gene polymorphism frequency in a colombian population. Colomb Med (Cali) 46: 75-79.
17. Selin JZ, Orsini N, Lindblad BE, Wolk A (2015) Long-Term Physical Activity and Risk of Age-Related Cataract A Population-Based Prospective Study of Male and Female Cohorts. Ophthalmology 122: 274-280.
18. Menshikova E V, Ritov VB, Fairfull L, Ferrell RE, David E, et al. (2006) Effects of Exercise on Mitochondrial Content and Function in Aging Human Skeletal Muscle. J Gerontol A Biol Sci Med Sci 61: 534-540.