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Mini-Review

High-altitude adaptation: Role of genetic and epigenetic factors

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After the completion of the Human Genome Project in 2003, the field of genetics has witnessed massive progress that spanned research in high-altitude biology also. Especially the decade of 2010s witnessed the most of it and revealed various genetic signatures of high-altitude adaptation in Tibetans, Andeans and Ethiopians. High-altitude area, with its extreme environment, harbors a tremendous potential for gene-environment interaction, an aspect that could be explored by epigenetic studies. There are only four original articles till now which explore the epigenetic aspect of high-altitude adaptation or acclimatization. However, there is no comprehensive review to provide complete information on the genetic and epigenetic aspects of high-altitude adaptations. Hence, we have prepared this mini-review to summarize the genetic and epigenetic studies that have correlated the high-altitude adaptation or acclimatization, until recently.

Keywords. High-altitude; adaptation; acclimatization; natural selection

1. High-altitude regions and human inhabitation

Across the world, there are three high-altitude regions – the Tibetan, Andean, and Ethiopian plateaus – with average elevation in the range of 2500 to 5000 meters, known to be inhabited by humans for ages and remained the major focus of interest towards high-altitude researchers. Among these, the earliest occupation of humans to high-altitude has been revealed to be in the Tibetan plateau. The largest inhabited high-altitude region of the world, the Tibetan plateau is situated in Central and East Asia and spans a vast area of Tibetan autonomous region, parts of China, including an enormous area of Qinghai province, extended up to Sichuan and Xinjiang provinces, parts of Nepal, Bhutan, Indian union territory Ladakh, Lahul and Spiti of Himachal Pradesh. Studies suggest that the Tibetan plateau was inhabited by humans as early as 30000–40000 years ago (Zhang *et al.* 2018). Other studies also estimate the initial colonization of the Tibetan plateau 25000–30000 years before present (YBP) and a second migration during 7000–10000 YBP (Aldenderfer 2011, 2003; Beall 2007; Qi *et al.* 2013). These migrations primarily stemmed from low-altitude East-Asians including the Han Chinese population (Jeong *et al.* 2014; Qi *et al.* 2013).

Andean altiplano is a part of the central Andes in west-central South America and spans parts of Chile, Ecuador, Peru, Bolivia and Argentina (Simonson 2015). The Andean altiplano with an average elevation of 3,750 meters, was colonized by humans as early as 12000–13000 YBP (Aldenderfer 2003; Chala-Aldana *et al.* 2018; Rademaker *et al.* 2014). According to some other researchers, permanent settlement began there during 8200–9200 YBP (Rademaker *et al.* 2014). The time of the split between high-altitude and low-altitude populations dates back to 8750 YBP (Lindo *et al.* 2018).

The Semien plateau is situated in Ethiopia, in the North-East part of Africa. The northernmost parts of Ethiopian highlands reach up to Eritrea. Two major populations inhabited in the Ethiopian Semien plateau are Amhara and Oromo. The Amhara are known to inhabit above 2500 meters at least for the last 5000 years, however, the Oromo are more recent migrants to high-altitude since the sixteenth century. The Amhara

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inhabited 2300–2400 meters altitude of Ethiopia for more than 70000 years (Alkorta-Aranburu *et al.* 2012; Lewis 1966; Marcus 1992).

2. High-altitude adaptation in the world populations

All the above-mentioned high-altitude regions have witnessed human inhabitation for hundreds of generations in the hypobaric hypoxic condition that led to various physiological and genetic adaptation – fields of enormous studies to high-altitude researchers. In the following sections, we would like to shed light on the genetic aspect as well as the epigenetic aspect that was hugely ignored till date.

3. Genetic aspects of high-altitude adaptation

Genetic aspects of high-altitude have been studied vastly, especially with the advent of high throughput sequencing technologies. The last decade (the 2010s) has witnessed huge growth in this field. While the Tibetans have been studied the most, with time, the pace was picked up gradually for the Andeans and then Ethiopians. A few reviews give pretty good coverage of the advancements of the field (Bigham 2016; Simonson 2015), however, in this mini-review, we discuss various studies in this field including the most recent ones, for ease of accessibility and quick grasp. The signatures of selection, identified in the above-mentioned 3 populations are being presented in table 1.

Many of the genes that are associated with high-altitude adaptation are members of the Hypoxia-Inducible Factor (HIF) pathway or the focus has remained on them in a majority of the studies considering the hypoxic environment in the high-altitude area. Products of this pathway include vascular endothelial growth factors, erythropoietin and glycolytic enzymes, etc., that respond to lack of oxygen by increasing oxygen delivery orchestrating a plethora of cellular and systematic changes if required, or switching to metabolic pathways without the requirement of oxygen (Semenza 1996; Smith *et al.* 2008). HIF pathway genes like *EPAS1*, *EGLN1* have been found to be signatures of natural selection in multiple studies in Tibetans (table 1). While some of the genes are common in all three populations, some are unique to each population or common between two populations (Bigham 2016). This indicates, where few features could be common in all three populations, there are differences too in the mode of adaptation, which might be due to different genomic backgrounds or different duration of exposure to high-altitude environments, Tibetans being the most ancient.

4. Epigenetic aspects of high-altitude adaptation

While the genetic aspect of high-altitude adaptation has been studied substantially, the epigenetic aspect of it remained hugely ignored. Till date, a few review articles speculated that the epigenetic aspect could reveal an important facet of high-altitude adaptation, however, there were hardly any original research articles on this aspect except a few – Alkorta-Aranburu *et al.* (2012) touched upon it briefly and Childebayeva *et al.* published three articles in the recent past (Childebayeva *et al.* 2020, 2019b, 2019a). Speculations of the previous review articles were based on observations including the following: (1) perinatal exposure of hypoxia can influence vascular and pulmonary functions (Julian *et al.* 2015a), (2) offspring of women having hypertensive pregnancy showed unique DNA methylation profile; these offspring were residing in high-altitude area, (3) around 40% of the putative adaptive SNPs of *EPAS1* associated with high-altitude adaptation and hemoglobin concentration in the Tibetans, modify CpG content, which might have implication in DNA methylation change that majorly occurs at CpG context in mammals (Beall *et al.* 2010; Julian 2017; Julian *et al.* 2015b; Lister *et al.* 2009).

In their article, Alkorta-Aranburu *et al.* (2012) reported that a significant difference in DNA methylation too exists between high-altitude and low-altitude Ethiopian Oromo population, while studying genetic signatures of high-altitude adaptation in Ethiopians with major emphasis. The authors compared DNA methylation profiles obtained from; 1) blood samples from 17 high-altitude Amhara with 17 low-altitude Amhara people and 2) saliva samples from 17 high-altitude Oromo people with 17 low-altitude Oromo people. DNA methylation was measured at 27,578 CpG sites. There was no significant difference in DNA methylation in the Amhara population, however, after relevant corrections, 4 sites showed significantly differential methylation ($p<1.85\times10^{-6}$) in the Oromo population. Four sites were present in genes apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3G (*APOBEC3G*), paired-like homeodomain 2 (*PITX2*), metallothionein 1G (*MT1G*), and olfactory receptor family 2 subfamily K member 2 (*OR2K2*), none of which is a known candidate gene for

Table 1. Genetic signatures of selection, identified in Tibetans, Andeans and Ethiopians

Populations	No. of samples from high-altitude	Methods used	Genes associated with high-altitude	References
Tibetan	35	Illumina Veracode platform, Genome-Wide Allelic Differentiation Scan (502,722 SNPs)	*EPAS1*	Beall *et al.* 2010
	31	Affymetrix Genome-Wide Human SNP Array 6.0	*EPAS1*, *CYP2E1*, *EDNRA*, *ANGPTL4*, *CAMK2D*, *EGLN1*, *HMOX2*, *CYP17A1*, *PPARA*, *PTEN*	Simonson *et al.* 2010
	50	Illumina-Exome sequencing	*EPAS1*, *C1orf124* (nearby candidate *EGLN1*), *HBB*, *HBG2*, *FANCA*, *PKLR*	Yi *et al.* 2010
	50	Affymetrix Genome-wide Human SNP Array 6.0	*EPAS1*, *EGLN1*	Peng *et al.* 2010
	46	Affymetrix Genome-Wide Human SNP Array 6.0	*EPAS1*, *EGLN1*	Xu *et al.* 2011
	3008	Illumina-HumanCoreExome-12 BeadChip	*MTHFR*, *EPAS1*, *ADH7*, *HLA-DQB1*	Yang *et al.* 2017
Andean	50	Affymetrix, Gene Chip Human mapping 500 K array	*ENDRA*, *PRKAA1*, *NOS2A*	Bigham *et al.* 2009
	25	Illumina Human Omni Express Bead Chip (730,525 SNPs)	*VEGFB*, *ELTD1*	Eichstaedt *et al.* 2014
	35 (pooled)	Affymetrix Genome-Wide Human SNP Array 6.0	*FAM213A*, *SFTPD*	Valverde *et al.* 2015
	42	Illumina whole-genome sequencing	*BRINP3*, *NOS2*, *TBX5*, *TMEM38B*	Crawford *et al.* 2017
	63	Illumina 610 Quad SNP array	*SP100*, *DUOX2*, *CLC*	Jacovas *et al.* 2018
Ethiopian	28	Illumina 1M SNP array	*CBARA1*, *VAV3*, *ARNT2*, *THRB*, *UTRN*, *ADH1A*, *ADH1B*, *ADH6*, *SLC30A9*, *TMEM33*	Scheinfeldt *et al.* 2012
	165	Illumina genotyping arrays	*CUL3, ADRBK1, CORO1B, ASF1B, MAPKAPK2*	Alkorta-Aranburu *et al.* 2012
	68	Illumina Omni 1M SNP array	*BHLHE41* (also known as *DEC2* or *SHARP1*)	Huerta-Sánchez *et al.* 2013
	17	Whole Genome Sequencing-Illumina	*CIC*, *PAFAH1B3*, *LIPE*	Udpa *et al.* 2014

hypoxia. A few CpG sites showing a nominally significant difference ($p<6.7\times10^{-5}$) were close to genes showing significant differential expression in hypoxia. These include toll-like receptor 6 (*TLR6),* mif two 3 homolog 1 (*SUMO1*), phosphodiesterase 4A (*PDE4A),* human immunodeficiency virus type I enhancer binding protein 2 (*HIVEP2*) (Alkorta-Aranburu *et al.* 2012).

Childebayeva *et al.* (2019a) showed that a significant difference in DNA methylation exists in the Andean Quechua population from high and low altitudes respectively. Using quantitative pyrosequencing in blood samples from 572 Andean Quechua (282 individuals born and raised at high-altitude, 147 individuals born in high altitude but migrated to low altitude and 143 born and raised in low altitude), they show that individuals born and raised at high-altitude had higher DNA methylation in Long Interspersed Nuclear Element-1 (LINE-1) repetitive DNA element, methylation of which has been shown to influence the expression of genes nearby. While LINE-1 promoter showed higher methylation in highlanders, lower DNA methylation was observed in *EPAS1* promoters. *EPAS1* is a hypoxia-responsive transcription factor and has been involved in high-altitude adaptation in Tibetans (Beall *et al.* 2010; Simonson *et al.* 2010; Xu *et al.* 2011). DNA methylation of LINE-1 increased significantly with higher residence in high-altitude and average LINE-1 methylation was shown to be associated

significantly (p-value <0.05) with four SNPs of one-carbon (1C) metabolism pathway, rs2236225, rs502396, rs202676 and rs10975681 of *MTHFD1, TYMS, FOLH1, GLDC* genes. *EPAS1* methylation was shown to be negatively associated with years spent high at altitude. Overall, this study revealed the epigenetic component of high-altitude exposure in the Andeans (Childebayeva *et al.* 2019a).

In another article, Childebayeva *et al.* (2019b) showed that changes in DNA methylation are associated with incremental upward movement in people with European ancestry (n=21) during trekking. Using quantitative pyrosequencing from saliva samples, they measured DNA methylation in LINE-1, *EPAS1*, *EPO, PPARa,* and *RXRa* and explored that, DNA methylation is significantly lower in LINE-1, *EPO*, and *RXRa* at low altitude compared to higher altitude(s) whereas, *PPARa* and *EPAS1* showed an increasing trend. This study shows that epigenetic profile gets affected during high-altitude acclimatization (Childebayeva *et al.* 2019b).

In their most recent study, using microarray for ~850,000 CpG sites in 113 Andean Quechua individuals, Childebayeva *et al.* (2020) reported differentially methylated positions and differentially methylated regions associated with high-altitude exposure (Childebayeva *et al.* 2020).

Unpublished data from our lab (Basak *et al.*) explored that a significant difference in methylation exists between Tibetans from high-altitude and low altitude respectively. Several regions harboring significant differences in methylation map to the genes associated with erythrocyte count, hemoglobin measurement, hematocrit, basophil count, eosinophil count, which could be interesting considering the hematological perturbation observed between these two groups (Basak *et al.* 2021).

5. Physiological relevance

Investigation of genetic and epigenetic aspects of high-altitude adaptation is important. However, without physiological relevance or functional studies, it remains incomplete. Due to the hypoxic condition in high-altitude areas, one of the most studied phenotypes in highlanders is hemoglobin concentration, an important component of the oxygen transport system in mammals. An increase in hemoglobin concentration has remained an important hallmark of response towards hypoxia for the sojourners to high-altitudes. Though it may seem that higher hemoglobin could be beneficial in hypoxic conditions to increase oxygen delivery, however, higher hemoglobin concentration increases the viscosity of blood leading to clinical conditions such as myocardial infarction and stroke (Mejía *et al.* 2005; Monge *et al.* 1992). Among the Tibetans, Andeans and Ethiopians, the Andeans have the highest hemoglobin concentration, followed by the Tibetans and the Ethiopians. The hemoglobin concentration of the Ethiopians is comparable to that of sea-level residents (Beall 2006). The Andeans are the most prone to chronic mountain sickness (CMS), a clinical condition, generally believed to have resulted from maladaptation towards the hypoxic environment at high-altitude areas and is characterized by polycythemia i.e. increase in the number of red blood cells (which results in elevated hematocrit and hemoglobin as well) and hypoxemia, which are accompanied by pulmonary hypertension, leading to congestive heart failure in many cases (León-Velarde *et al.* 2005; Ronen *et al.* 2014; Sahota *et al.* 2013). In the CMS subjects, tissue hypoxia and increased blood viscosity lead to myocardial infarction and stroke often (Ronen *et al.* 2014). The prevalence of CMS is high among the Andeans but low among the Tibetans. Beall *et al.* have shown that the adaptive variants in *EPAS1* are associated with lower hemoglobin concentration in the Tibetans, which is believed to give them protection against chronic mountain sickness apparently (Beall *et al.* 2010). Similarly, variants in *EGLN1* are associated with lower hemoglobin as well in the Tibetans (Tashi *et al.* 2017). Difference of severity of chronic mountain sickness among the Tibetans and Andeans possibly indicates that the adaptation of the Andeans to altitude is still going on. The Tibetans apparently adapted to different mechanisms to maintain oxygen delivery to the tissues. For example, their hypoxic ventilatory response (HVR) and resting ventilation are higher compared to the Andeans but oxygen saturation is lower. Capillary density is higher in the high-altitude Tibetans compared to their Andean counterpart which probably ensures better oxygen delivery. While blood flow is increased in the uterine arteries in pregnant Tibetan women to ensure efficient oxygen delivery to the uterus and placenta, the Andeans achieve the same by increasing ventilation and oxygen saturation (Beall 2007). The difference in the genetic makeup and extent of high-altitude adaptation might be the driving forces behind these differences in mechanisms among the Tibetans, Andeans and Ethiopians to achieve same the goal-offsetting hypoxia (figure 1).

As discussed earlier, only a few studies explored epigenetic aspects of high-altitude adaptation till now

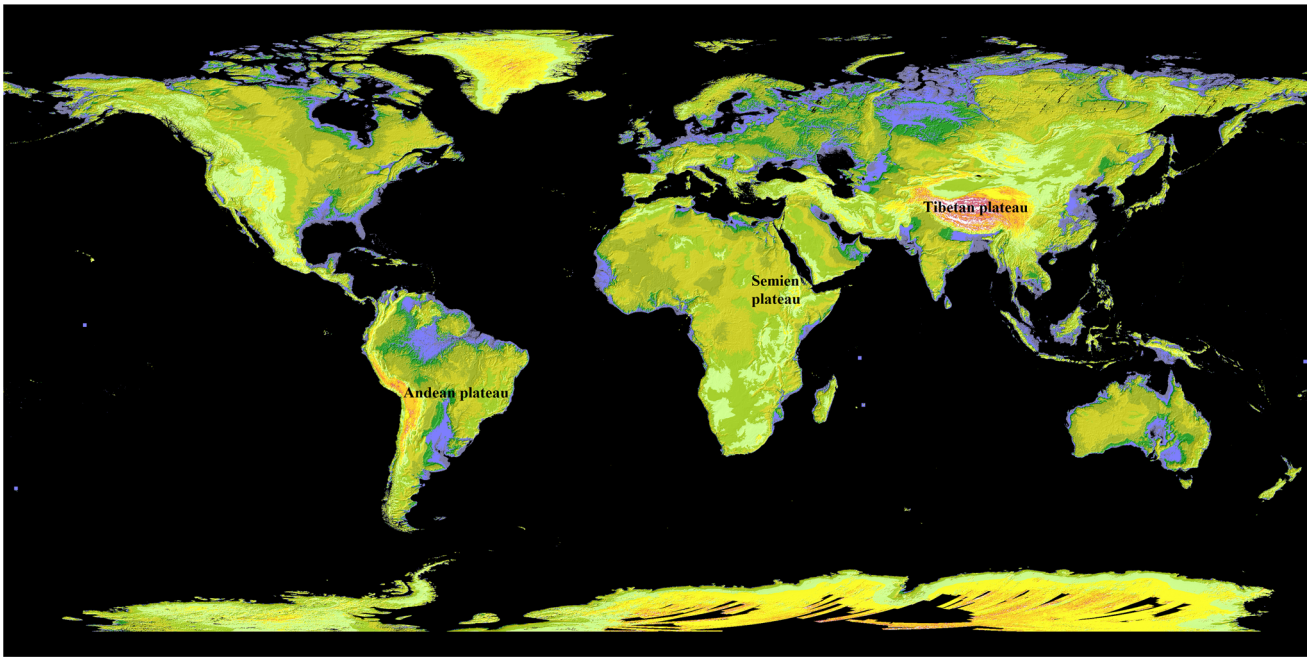

Figure 1. Three mostly studied high-altitude regions in the world, i.e. Tibetan plateau, Andean plateau and Semien plateau, in the world map [Image adapted and modified from *https://www.nasa.gov/topics/earth/features/20090629.html*]. In the image, low elevations are purple, medium elevations are greens and yellows, and high elevations are orange, red and white.

and that is also limited to the Andean highlanders only. Therefore more studies are required to explicitly understand the role of epigenetic hallmarks on physiological changes. Childebayeva *et al.* (2020), performed association studies between differentially methylated positions (between Andean Quechua from high and low altitudes) with the fractional exhaled nitric oxide (FeNO), hemoglobin concentration, body mass index (BMI), forced vital capacity (FVC) and oxygen saturation at rest, which were earlier shown to be associated with high-altitude adaptation (Beall *et al.* 2001; Brutsaert *et al.* 1999). However, a significant association of differentially methylated positions was noticed only with FeNO among these parameters. Nitric oxide is a vasodilator and seems to play an important role to offset hypoxia by increasing oxygen uptake from the lungs and improving oxygen delivery to the peripheral tissues presumably (Beall *et al.* 2001). Interestingly, a significant association was observed between local genetic variations and DNA methylation levels for *EPAS1* as well, where the minor alleles in the intronic SNPs of *EPAS1* (rs7579899(A<G) and rs2044456(G<A)) were shown to be associated with lower *EPAS1* methylation (Childebayeva *et al.* 2020).

A few studies have investigated the functional aspects of a few putative adaptive variants, for example, Udpa *et al.* identified regions undergoing selective sweep in the Ethiopians in genes including *CIC*, *LIPE*, *PAFAH1B3*. The study shows that the orthologs of these genes in *Drosophila* significantly affect hypoxia tolerance and impact the rate of survival in hypoxic conditions (Udpa *et al.* 2014). Stobdan *et al.* studied *EdnrB*, an ortholog of *EDNRB* (Endothelin receptor type B), a candidate gene involved in high-altitude adaptation, identified by Udpa *et al.* (2014) in their study of Ethiopian highlanders. They showed that decreased Endothelin receptor type B improves cardiac tolerance to hypoxia in mice (Stobdan *et al.* 2015). Peng *et al.* explored that the *EPAS1* variants enriched in the Tibetans, down-regulate the expression of the gene in human umbilical endothelial cells and placentas under hypoxic conditions. Heterozygous *EPAS1* knockout mice exhibited blunted hypoxic responses (Peng *et al.* 2017). With the advancement of technology, it has been now possible to edit epigenome as well. CRISPR-Cas9-based tools or optogenetic tools are being used to edit epigenome (Choudhury *et al.* 2016a, 2016b; Lo *et al.* 2017). Application of such techniques could be fruitful to elucidate the role of epigenetic signatures of high-altitude adaption as well, using appropriate model systems.

6. Conclusion

Genetic and physiological aspects of high-altitude adaptation have been studied extensively in multiple populations; however, investigation of epigenetic aspects remained hugely neglected. High-altitude areas, with their associated hypoxia, cold, aridity, higher solar radiation, etc. represent extremely different environments altogether. Gene–environment interactions that could be revealed by epigenetic studies could be hence a very important aspect to look into in high-altitude populations. Physiological features also vary between populations at high-altitude at the same altitude, oxygen saturation and hemoglobin concentration are higher in Andean highlanders compared to the Tibetans, however, Ethiopian highlanders do not show a significant difference in these traits with sea-level residents (Beall 2006). Chronic mountain sickness is higher in Andeans than in Tibetans (Villafuerte *et al.* 2016). Gene–environment interaction studies would probably shed light on variations of physiological aspects as well. Altogether, if the vast knowledge obtained from genetic and physiological studies can be complemented with epigenetic studies, many aspects which are beyond explanation till now would probably be decipherable.

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