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Genomic Analysis of High Altitude Adaptation: Innovations and Implications

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Introduction

Endurance exercise and high altitude exposure share the physiological challenge of reduced oxygen supply relative to metabolic demand (*e.g.*, 8). This similarity suggests that biological features considered to be adaptive for life at high altitude are likely also relevant for endurance exercise. The recent application of genomics to examine adaptations to chronic hypoxia is important for exercise scientists because it provokes new questions about what constitutes an advantageous phenotype for exercise performance.

Evolution at High Altitude

Four recent studies have explored genetic adaptations to hypoxia by searching for signals of evolution in the genomes of the high-altitude adapted populations of the Tibetan Plateau. Populations of high-altitude origin such as Tibetans and Andeans exhibit adaptive phenotypes that increase their evolutionary fitness (ability to survive, thrive, and reproduce) over populations new to high altitude [*e.g.*, Han Chinese (Tibetan Plateau), Europeans (Colorado, Andes)], suggesting that they have undergone natural selection for high-altitude life. Specifically, high-altitude natives are less prone to altitude-related disease (11,15,17), and have a smaller maximal oxygen consumption decrement (5) with hypoxia compared to recent high-altitude migrants.

Genomic evidence of natural selection should be detectable in high-altitude natives because hypobaric hypoxia 1) has a negative effect on evolutionary fitness, 2) is not easily mitigated through behavioral means and 3) has a differential effect on populations of high vs low altitude origin, suggesting genetic adaptation has occurred. Recent advances in genomics led to identification of an important role for genes associated with oxygen sensing pathways for human adaptation to high altitude.

Genomic Studies

In the first genome-wide search for genetic adaptations to high altitude, Beall et al. (2) used a genome-wide allelic differentiation scan (GWADS) to identify whether allelic frequencies at individual loci differ between Tibetans living at high altitude (investigator collected) and Han Chinese (CHB from HapMap database, Phase III). Han Chinese are often used as a control population since they are of lowland origin, seem to have no high altitude adaptations, and have a close genetic relationship to Tibetans. Eight single nucleotide

polymorphisms (SNPs) downstream of endothelial PAS domain protein 1 [EPAS1; or hypoxia inducible factor 2A (HIF2A)] had different allelic frequencies in Tibetans versus Han Chinese. Notably, Tibetan genotypes at different SNPs within the EPAS1 gene region correlated with lower [Hb], considered to be a hallmark of Tibetan high-altitude adaptation.

While Beall et al.'s study engenders excitement, it also warrants a bit of caution in assigning EPAS1 as the target of natural selection. For example, five other transcripts that were identified by GWADS within genes nearby the EPAS1 region also could play a role in determining lower [Hb] in Tibetans. With no functional analysis, the effects of lesser-known nearby genes cannot be ruled out. Secondly, Beall et al. used only one of many analytical approaches available to search for genomic signs of natural selection, instead of using complementary methods that would strengthen their findings by providing internal validation.

Three other reports provide additional evidence in support of a role for EPAS1 in human adaptation to high altitude. Simonson et al.'s study (14), using two haplotype-based approaches to examine genetic adaptation in high altitude populations in Tibet, validates Beall et al.'s results (2) and addresses Beall et al.'s use of a single analytic strategy. The use of haplotypes to detect natural selection is based on the assumption that if an allele is selectively advantageous, then it and its neighboring alleles will be differentially inherited as a unit due to genetic linkage. If selection is strong enough, diversity of the surrounding alleles is reduced and the haplotype that includes the evolutionarily-advantageous allele is favored. iHS (16), the method used by Simonson et al., detects recent selective sweeps (advantageous alleles being selected for in recent migrants), but is limited by the inability to detect advantageous alleles that have become fixed in a population. To resolve this limitation, Simonson et al. (14) used an additional approach, XP-EHH (13), to identify haplotypes with decreased diversity (indicating increased linkage disequilibrium) in adapted versus unadapted populations to identify alleles at or nearing fixation. XP-EHH, measuring loci near fixation similar to Beall et al.'s GWADS (2), identified EPAS1 as showing evidence of natural selection (14). However, since the EPAS1 genotype was not tested against phenotype, Simonson's report may not be used to confirm the relationship between EPAS1 and [Hb].

Of nine other gene regions involved in the biological response to hypoxia identified as naturally-selected in Simonson et al. (14), two (EGLN1 and PPARA) were associated with [Hb] and two (EGLN1 and CYP17A1) were associated with arterial oxygen saturation, another hallmark of human adaptation to high altitude. These results suggest that EPAS1 is likely not the only naturally-selected gene region responsible for determining [Hb] and arterial oxygen saturation at high altitude.

Yi et al. (18) further confirmed the selective signature near EPAS1 by comparing the differentiation of exomic (the transcribed and translated portion of the genome) sequences of Tibetan populations and HapMap Han Chinese, with a European control group (outgroup). Exomic sequencing is unique in that, if the adaptive allele is in an exon, it is measured directly rather than relying on linkage. Exons identified through this method provide a clear target to determine mechanistic effects. Yi et al. (18) found signatures near EPAS1, EGLN1 and hemoglobin beta, as well as other oxygen-related genes, and also found a strong association between EPAS1 and [Hb].

Finally, Bigham et al. (3) searched for genomic evidence of natural selection in Tibetans and Andeans using four analytical tests; three of these identified EPAS1 as a target of natural selection in Tibetans. Interestingly, EPAS1 and EGLN1 gene regions showed evidence of natural selection in Andeans, but these gene regions did not overlap those detected in

Tibetans, suggesting Tibetans and Andeans may achieve their respective high altitude adaptations through separate mutations in the same gene, a process known as convergent evolution. Bigham et al. (3) did not report whether the EPAS1 genotype was associated with [Hb] in Andeans.

Taken together, these four studies create strong case for natural selection of the EPAS1 gene region in Tibetans by 1) using a diverse set of analytical tools, 2) validation by independent investigators, and 3) the association of apparent naturally-selected genotypes with [Hb].

[Hb]: The Key to High Altitude Adaptation?

Three of these studies used [Hb] (2,14,18) and oxygen saturation (14,18) as the adaptive high-altitude phenotype. While [Hb] is a key component of oxygen transport, its utility as a marker of high altitude adaptation is unclear. Strong natural selection for low [Hb] at high altitude seems contradictory in the context of exercise performance and oxygen delivery. Optimal [Hb] for endurance performance at low or high altitude is a largely unexplored topic (11). Raising [Hb] generally leads to greater endurance performance at low altitude (5), however the same may not be true at higher elevations (4,17). Furthermore, beyond a certain threshold, increasing [Hb] can become deleterious (6,10,15) as in chronic mountain sickness (CMS or excessive erythrocytosis) (9).

Tibetans have lower average [Hb] compared to Andeans and a very low rate of CMS (11,17). The latter likely affords a greater relative likelihood of surviving through the reproductive period (i.e., improved evolutionary fitness) for Tibetans. Because the effect of EPAS1 on low [Hb] is not yet known, future studies are required to investigate the effect on Tibetans' ability to thrive and reproduce. It should also be recognized that EPAS1 could influence numerous phenotypes; therefore, [Hb] may only be a byproduct of the naturally-selected phenotype.

Conclusion

Future studies need to address 1) appropriate control populations with identical selection criteria for both control (*e.g.*, lowlander) and experimental (*e.g.*, highlander) groups, 2) the polygenic, multifactorial nature of most human phenotypes likely requires models allowing for multiple gene effects and/or environmental interactions, and 3) whether [Hb] is the optimal phenotype for high-altitude adaptation. The latter point highlights the fact that the adaptive value of characteristics considered to be advantageous at high altitude is largely unknown. Linking comprehensive and comparable phenotypic and genomic findings would provide the opportunity to identify the mechanisms by which natural selection has functioned at high altitude. In addition to giving an interesting view of human evolution and natural adaptive responses to hypoxia, such studies could be informative for understanding genetic effects on oxygen utilization and conservation and, thus, on endurance exercise performance.

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