

Feature Review

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Observing Human Evolution from High-Altitude Adaptation: Genetic Mechanisms Revealed by GWAS

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Abstract The study comprehensively explores the genetic mechanisms of human adaptation to high-altitude environments, with a focus on how genome-wide association studies (GWAS) reveal key genetic factors associated with high-altitude adaptation. The study introduces the challenges that high-altitude environments pose to human physiology and their impact on human evolution. It emphasizes the importance of studying high-altitude adaptive evolution in understanding human genetic diversity and evolutionary processes, and elaborates on the basic concepts and working principles of GWAS. Through specific case studies, such as the study of Xizang plateau residents, the achievements of GWAS in identifying key genes and biological pathways related to high-altitude adaptation are demonstrated. This study aims to enrich the understanding of human evolution and provide valuable genetic information for biomedical research, especially on how the human body responds to extreme environmental conditions such as hypoxia.

Keywords High-altitude adaptability; Genome-wide association studies (GWAS); Genetic mechanisms; Human evolution; Biological pathways

The environment in which humans live is extremely diverse, from hot deserts to cold polar regions, and then to high-altitude mountainous areas. Especially in high-altitude environments, human physiological functions are greatly challenged, including factors such as low oxygen, low pressure, and low temperature, which pose special requirements for the respiratory, circulatory, and metabolic systems of the human body (Jeong et al., 2014). For a long time, people living in these high-altitude areas have gradually developed a series of adaptive physiological characteristics to better cope with these extreme environments. This adaptive evolution process not only demonstrates the resilience and diversity of human biology, but also provides a unique perspective for studying human evolution.

The study of high-altitude adaptive evolution can not only help us understand how humans respond to extreme environmental challenges, but also reveal the formation and evolutionary process of human genetic diversity. With the development of genomics and molecular biology technologies, especially the application of genome-wide association studies (GWAS), researchers are now able to explore and identify genetic variations that affect high-altitude adaptation at the molecular level (Cirillo et al., 2018). These studies not only enhance our understanding of human genetics and evolutionary biology, but also provide new ideas and methods for related medical research, such as the prevention and treatment of hypoxia related diseases.

The aim of this study is to use GWAS technology to deeply analyze the genetic materials of populations living in high-altitude environments, identify genetic markers and pathways related to high-altitude adaptation. We will identify key genetic variations related to high-altitude adaptability through genetic comparison between high-altitude and low altitude populations, and reveal how these genetic variations affect physiological functions, especially the adaptation mechanisms to environmental factors such as hypoxia and low air pressure. Through this study, we hope to not only enrich our understanding of human evolution, but also provide valuable genetic information for biomedical research, especially on how the human body responds to extreme environmental conditions such as hypoxia.

1 Basic Concepts of GWAS Technology

1.1 Definition and principles of GWAS

Genome wide association studies (GWAS) are a research method used to search for associations between specific diseases or traits and genetic markers across the entire genome (Uffelmann et al., 2021). The core of GWAS lies in not relying on prior knowledge of candidate genes, but identifying genetic variations that affect specific diseases or traits by detecting statistical associations between thousands of single nucleotide polymorphisms (SNPs) in an individual's genome and specific phenotypes.

The working principle of GWAS is based on the theory of linkage disequilibrium (LD) in population genetics, which means that genetic markers closer to each other in the genome may be co inherited. By comparing the frequency differences of alleles at thousands of SNP loci between diseased individuals and healthy control groups, GWAS can reveal which genetic variations are associated with disease risk. This process requires a large number of samples to ensure the validity and accuracy of statistics.

1.2 Application of GWAS in human genetics

Since its introduction, GWAS technology has been widely applied in human genetic research, especially in the field of disease genetics, making significant progress. GWAS has successfully identified thousands of genetic markers associated with various diseases. For example, GWAS has revealed multiple SNPs associated with type 2 diabetes (T2DM). Cirillo et al. (2018) through network analysis, pathway information, and integration of different types of biological information (such as eQTLs and gene environment interactions) (Figure 1), this study revealed the T2D gene and its possible functions at the process level. These findings not only enhance our understanding of the genetic basis of the disease, but also provide clues for the development of new prevention and treatment strategies.

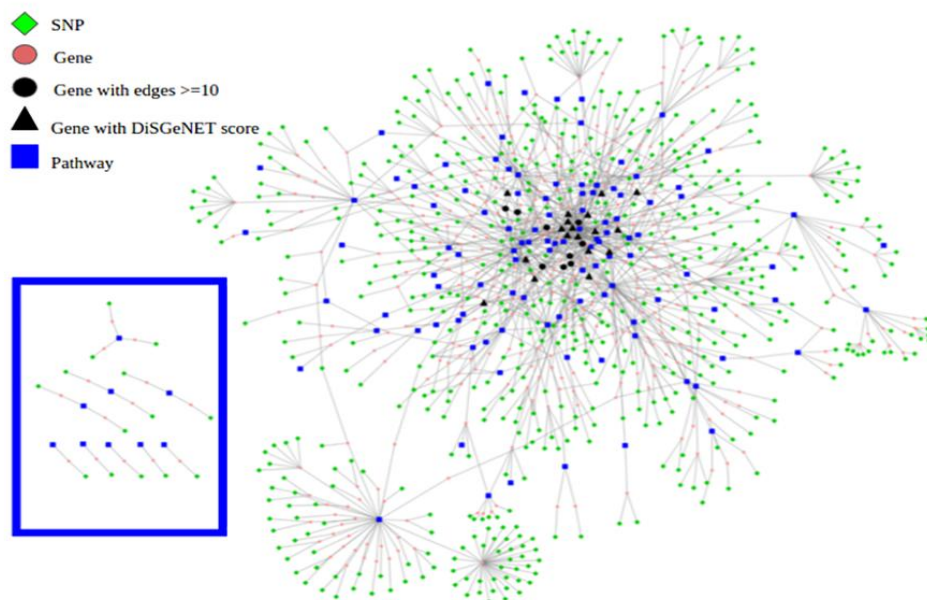


Figure 1 SNP-gene-pathway network (Cirillo et al., 2018)

Note: The network displays 580 SNPs (green diamonds), 365 genes (circles) and 117 pathway clusters (blue squares). Black symbols indicate genes with ten or more connections to pathway clusters, and triangles indicate genes with a positive DiSGeNET score

GWAS is also used to study genetic differences in individual responses to specific drugs, which is of great significance for personalized healthcare. For example, in patients in the Middle East and North Africa region (MENA), genetic variations associated with VKORC1 rs9934438 and CYP2C9 rs4086116 loci were discovered through GWAS, which can explain 39% and 27% of the variability in warfarin dosage requirements (Rouby et al., 2021). GWAS conducted in a sample from Brazil found that VKORC1 and CYP2C9 polymorphisms play an important role in warfarin dose variability (Parra et al., 2015). In a GWAS study involving 1053 Swedish subjects,

VKORC1, CYP2C9, and CYP4F2 were identified as the main genetic determinants of warfarin dosage (Takeuchi et al., 2009) (Figure 2). These studies indicate that individual differences in warfarin dosage requirements are largely determined by variations in the VKORC1 and CYP2C9 genes. By considering these genetic factors, doctors can more accurately predict the required dose of warfarin for patients, thereby optimizing treatment outcomes and reducing the risk of adverse reactions.

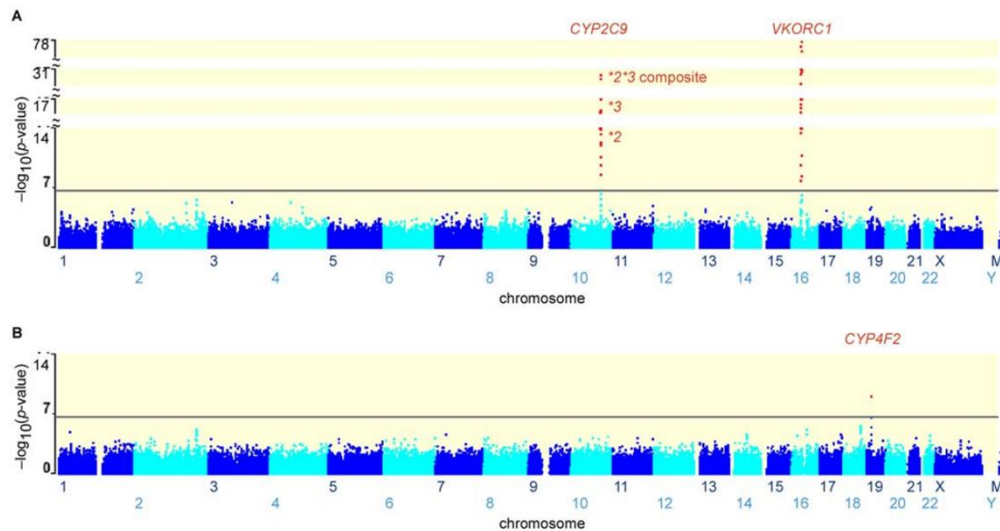


Figure 2 P-values for each GWAS SNP tested for association with warfarin dose (Takeuchi et al., 2009)

GWAS is not only applied to disease research, but also to explore the genetic basis of complex traits such as height, weight, and intelligence. Research has shown that multiple genetic loci identified by GWAS are associated with obesity related indices in children during adolescence. Especially, there is a significant correlation between variations in TMEM18 and FTO and obesity index during adolescence, while candidate SNPs such as NEGR1, GNPDA2, MTCH2, SH2B1, MC4R, and KCTD15 did not show significant effects (Wang et al., 2012). These studies have revealed a large number of genetic variations that affect complex traits, proving that the genetic basis of human traits typically involves the interaction of multiple genes.

GWAS is also used to study genetic differences between different populations and their evolutionary significance. For example, through GWAS, researchers have discovered some genetic variations related to high-altitude adaptation, which are more frequent in populations living in high-altitude areas for a long time. These findings not only reveal the genetic mechanisms by which humans adapt to extreme environments, but also provide important clues for understanding human evolution.

2 Genetic Mechanisms of High-altitude Adaptability

2.1 GWAS research case analysis

GWAS provides us with valuable insights in exploring the genetic basis of human high-altitude adaptability. The classic case is the GWAS study of Xizang plateau residents. The Xizang Plateau is one of the regions with the highest altitude in the world. Living in such a hypoxic environment for a long time, local residents have shown significant physiological adaptability, including low hemoglobin concentration and high oxygen saturation. Through GWAS analysis of Xizang plateau residents, researchers successfully identified multiple genetic variations related to high-altitude adaptability.

The studies of Simonson et al. (2010) and Xu et al. (2011) both indicate that *EPAS1* (also known as hypoxia inducible factor 2) α) Some genetic variations in the Tibetan population are closely related to low hemoglobin concentration (Figure 3), which is an important physiological characteristic for adapting to high-altitude and low oxygen environments. These variations in the *EPAS1* gene may help regulate the production of red blood cells.

Peng et al. (2011) found in their study that specific variations in the *EGLN1* gene are more frequent in the Tibetan population, and these variations are associated with physiological adaptability for survival in high-altitude environments, particularly with regulation of hemoglobin concentration.

From the above studies, it can be found that the frequency of specific mutations of *EPAS1* gene is significantly increased among the residents of Xizang Plateau. The *EPAS1* gene encodes hypoxia inducible factor 2 α (HIF-2 α). This protein is a key transcription factor in the hypoxia sensing pathway, involved in regulating various physiological processes such as red blood cell generation, energy metabolism, and angiogenesis. In addition, the variation of *EGLN1* is closely related to high-altitude adaptability. *EGLN1* encodes hydroxylase, which is responsible for labeling HIF for degradation under normoxic conditions, and its variation may affect the stability and activity of HIF.

In addition to *EPAS1* and *EGLN1*, other genes such as *GCHI* and *PAPPA2* have also been identified in high-altitude adaptability studies. The variation of these genes may participate in the complex process of adapting to high-altitude and low oxygen environments through different physiological pathways.

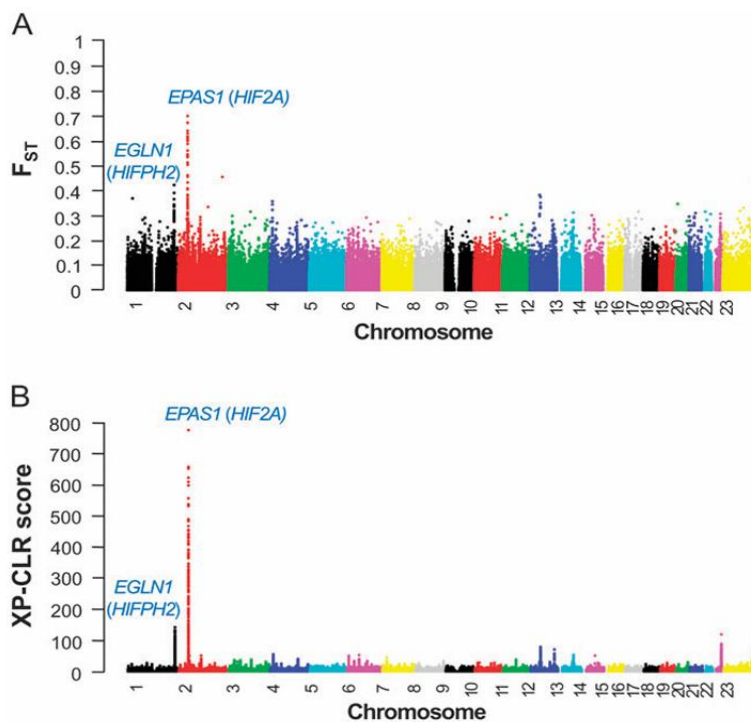


Figure 3 Genomic distribution of F_{ST} (A) and XP-CLR score (B) (SNP specific F_{ST} statistic between Tibetan and Han Chinese populations was calculated for every SNP that passes QC) (Xu et al., 2011)

2.2 Function of adaptive genetic variation

These genetic variations discovered through GWAS research reveal the complex genetic mechanisms underlying high-altitude adaptability. For example, mutations in the *EPAS1* gene affect HIF-2 α . It may reduce the production of red blood cells to avoid the increase of blood viscosity caused by excessive hemoglobin concentration, help Xizang plateau residents maintain high blood oxygen saturation and adapt to the hypoxic environment. The mutations in *EGLN1* and *PAPPA2* genes may help individuals optimize energy consumption and utilization to meet physiological needs in high-altitude environments by regulating metabolic and growth related pathways.

These adaptive genetic variations not only reveal how humans face extreme environmental challenges through genetic adaptation, but also provide new perspectives for understanding the regulation of human physiological functions. For example, studying the *EPAS1* gene not only helps to understand high-altitude adaptability, but may also provide potential therapeutic targets for studying medical conditions related to oxygenation, such as hypoxic diseases (Liu et al, 2019).

3 Genetic mechanisms revealed by GWAS

3.1 Key genes and pathways

GWAS has made significant progress in revealing the genetic basis of adaptability to high-altitude environments. Through large-scale population genetic analysis, researchers have identified multiple key genes and biological pathways associated with high-altitude adaptability. Here are some important findings:

EPAS1 gene: *EPAS1* gene encodes hypoxia inducible factor 2 α (HIF-2 α). It is one of the earliest genes discovered to be associated with high-altitude adaptability. In high-altitude residents, specific *EPAS1* gene mutations are associated with low hemoglobin levels and high blood oxygen saturation, indicating their crucial role in adapting to hypoxic environments. Research has shown that certain single nucleotide polymorphisms (SNPs) in the *EPAS1* gene exhibit significant frequency differences between Tibetan and Han samples (Simonson et al., 2010), representing the fastest observed allele frequency changes in any human gene to date. The association between this SNP and red blood cell abundance supports the role of *EPAS1* in high-altitude adaptation.

EGLN1 gene: The *EGLN1* gene encodes proline hydroxylase, which is involved in the degradation process of HIF. Research has shown that certain mutations in *EGLN1* may enhance the ability to stabilize HIF under low oxygen conditions and promote high-altitude adaptability (Peng et al., 2011). *EGLN1* and *EPAS1* genes exhibit strong selective scanning signals in the Tibetan population, indicating that these genes may be crucial for long-term biological adaptation in high-altitude areas.

PAPPA2 gene: The *PAPPA2* gene is associated with regulating insulin-like growth factor activity. Research has found that mutations in the *PAPPA2* gene are associated with higher physical adaptability, such as improved energy utilization efficiency and growth rate, in populations in certain high-altitude areas.

Through the discovery of these genes, GWAS has revealed the complex genetic mechanisms by which humans adapt to high-altitude environments, which mainly involve aspects such as blood oxygen transport, energy metabolism, and cell growth.

3.2 The evolutionary significance of genetic variation

These genetic variations related to high-altitude adaptability not only demonstrate the physiological adaptation mechanisms of humans in specific environments, but also reflect the ability of humans to cope with environmental stress through genetic variations during the evolutionary process. For example:

Buroker et al. (2012) found that three SNPs found in the *EPAS1* and *EGLN1* genes were evaluated in Han Chinese patients with acute mountain disease (AMS) and Tibetan patients with chronic mountain disease (CMS). The study found a significant correlation between *EPAS1* and *EGLN1* SNPs and AMS and CMS, indicating that these nucleotide changes have physiological effects on the development of high-altitude diseases.

Jeong et al. (2014) found that Tibetans are a mixture of ancestral populations related to Mount Everest and Han Chinese. The *EGLN1* and *EPAS1* genes show significant enrichment in the Tibetan genome of high-altitude ancestors, indicating that immigrants from low altitudes obtained adaptive alleles from highland residents.

Peng et al. (2011) conducted a genome-wide sequence variation analysis on the Tibetan population and found that the *EPAS1* and *EGLN1* genes exhibited strong selection signals. These gene mutations have a higher frequency among Tibetans, but a lower frequency among Han and Japanese populations, indicating that these genes play an important role in obtaining biological adaptation to high-altitude hypoxia for long-term survival in high-altitude environments.

These studies indicate that mutations in the *EPAS1* and *EGLN1* genes undergo positive selection in Tibetan populations in high-altitude environments, providing survival advantages and gradually accumulating in gene pools. This provides important biological insights for understanding human genetic adaptation in high-altitude environments.

At the same time, the discovery of these genetic variations proves that humans improve their ability to survive and reproduce through genetic adaptive evolution when facing extreme environmental pressures. The revelation of these genetic mechanisms provides important clues for understanding human evolution. In addition, research on high-altitude adaptability also indicates that human genetic diversity is an important resource for responding to environmental changes. The adaptation of different populations to the same environmental pressure demonstrates the diversity of genetic strategies, which is an important driving force for human evolution.

4 Adaptation to High Altitude and Human Evolution

4.1 Models of adaptive evolution

The adaptation of humans to high-altitude environments is an important case in adaptive evolution research. Based on the results of GWAS, we can gain a deeper understanding of how humans adapt to extreme environmental challenges through genetic variation. In high-altitude environments, low oxygen is the most direct and significant survival challenge, and humans have shown various adaptive evolutionary patterns.

The key genetic variations related to high-altitude adaptability, such as *EPAS1* and *EGLN1*, reveal the key genetic mechanisms for human survival in low oxygen environments. The variation of these genes affects the stability and activity of hypoxia inducible factor (HIF), which in turn regulates hemoglobin production, energy metabolism, and other physiological adaptation processes. This genetic adaptation not only reflects the physiological adaptation of humans to specific environments, but also reflects the plasticity and evolutionary potential of the human genome.

These evolutionary patterns of genetic adaptation are also reflected in the geographical distribution of genetic variations. Although people living in different high-altitude areas face similar challenges of hypoxia, there may be differences in specific adaptive genetic variations, indicating the diversity and complexity of human adaptive evolution. For example, Heinrich et al. (2019) found that the protein coding variation of the *EGLN1* gene related to the adaptation of the Xizang plateau population either does not exist in the Andean highland residents or has a very low frequency, indicating that the high-altitude adaptation of the Andean population may involve a different mechanism from that of the Xizang population, indicating that different populations may have different mechanisms for adapting to high-altitude.

4.2 Comparison with other adaptive studies

Comparing high-altitude adaptability research with other environmental adaptability studies can reveal the commonalities and specificities of human adaptive evolution. For example, research on tropical disease resistance has found that adaptive genetic variations targeting diseases such as malaria, such as sickle cell disease and G6PD deficiency, also reflect human adaptive evolution to specific environmental challenges.

G6PD deficiency is an X-linked enzyme deficiency disorder that affects intracellular reduction processes by altering NADPH levels in red blood cells, and is associated with human adaptive resistance to diseases such as malaria. Kawamoto et al. (2017) found significant differences in the distribution and variation types of G6PD deficiency in different geographical locations and populations, reflecting human adaptation to environmental challenges, particularly malaria. For example, in Southeast Asia, including Vietnam and China, studies have found multiple variants of G6PD deficiency.

Howes et al. (2013) found that certain variants of G6PD deficiency may be associated with malaria resistance. This is of great significance in human evolution, as these variants have been particularly common in malaria endemic areas throughout history, indicating that they may have provided carriers with some survival advantage.

The commonality of these adaptive evolutions is that humans are able to cope with environmental challenges through genetic variations, which provide advantages for survival or reproduction in specific environments and are therefore preserved by natural selection. Meanwhile, these studies also reveal the specificity of adaptive evolution, that is, humans adopt different adaptive genetic strategies under different environmental pressures, which may involve different genes, biological pathways, and molecular mechanisms.

These comparative studies emphasize the complexity of human adaptive evolution. In some cases, adaptive genetic variations may bring other health risks, such as sickle cell disease, which enhances resistance to malaria but also leads to sickle cell anemia. This phenomenon is called evolutionary trade offs and is an important concept in adaptive evolutionary research.

5 Discussion and Outlook

Although GWAS has revealed many key genetic markers related to high-altitude adaptability, current research still has some limitations. Due to the limited sample size of the study, it may affect the broad applicability and statistical significance of the research results. Especially in some high-altitude populations, the remote geographical location and difficulty in obtaining samples limit the possibility of large-scale sample collection. Moreover, current research mainly focuses on specific genes and loci, with insufficient consideration given to the complexity of gene environment interactions and phenotypes. High altitude adaptability is a complex multi gene trait that involves the interaction of multiple genes and environmental factors, and current research methods may not be able to fully capture this complexity.

Faced with these challenges, future research directions can focus on increasing sample size and diversity, adopting multi omics methods, and exploring gene environment interactions in depth. Through international cooperation, collecting samples from a wider range of regions and diverse populations, especially high-altitude populations that have not been extensively studied, is expected to improve the representativeness and statistical power of research, as the genetic information of these populations is crucial for understanding human adaptive evolution. At the same time, combining genomics, transcriptomics, proteomics, and metabolomics data can more comprehensively reveal the biological mechanisms of high-altitude adaptability, helping us to deeply understand how genes affect physiological adaptability through different pathways and networks. In addition, developing new statistical models and experimental designs to explore the interaction between genes and environmental factors, studying changes in gene expression under specific environmental conditions, and how environmental stress affects the selection of genetic variation are also key directions for future research.

The study of high-altitude adaptability is of great significance for understanding human evolution. These studies not only reveal how humans adapt to extreme environments through genetic variation, but also demonstrate the richness and complexity of human genetic diversity. From a broader perspective, these studies provide important insights into understanding human survival and reproduction strategies in various global environments. Meanwhile, research on high-altitude adaptability also has potential application value. For example, in-depth research on high-altitude adaptability related genes can help develop new treatment methods to address health issues in high-altitude environments such as altitude sickness. Meanwhile, these studies also provide valuable information for predicting and addressing environmental pressures caused by global climate change.

Authors' Contributions

HYP was the designer and executor of this study, responsible for writing and revising the paper; LW participated in literature analysis, paper revision, and English translation. Both authors read and approved the final manuscript.

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