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Research Progress on High-Altitude Adaptation Characteristics of Bilirubin Metabolism and the Regulatory Role of the UGT1A Gene Family

Dongfeng Zhang[1], Yiqing Shu[2], Yongjun He[1,*]

[1]Xizang Minzu University, Xianyang 712000, Shaanxi, China
[2]The Second Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China
**Correspondence Author*

Abstract: ***The hypoxic environment at high altitude poses significant challenges to the body's metabolic system. Bilirubin, as an end product of heme metabolism and an endogenous antioxidant, plays an important role in high-altitude adaptation through its metabolic regulation. This article systematically reviews the characteristic changes in bilirubin metabolism among high-altitude populations and the regulatory mechanisms of the UGT1A gene family. A review of relevant domestic and international research literature indicates that bilirubin levels in high-altitude populations exhibit an altitude-dependent increase, with significant differences between native and migrant populations. Bilirubin participates in high-altitude adaptation through antioxidant and anti-inflammatory mechanisms. UGT1A1 is the key enzyme catalyzing bilirubin glucuronidation, and its gene polymorphisms (UGT1A1*28, *6, etc.) significantly affect enzyme activity and bilirubin levels. The distribution of UGT1A gene frequencies in high-altitude populations is unique and significantly associated with bilirubin phenotypes. Mendelian randomization studies have confirmed a genetic causal relationship between high-altitude adaptation and total bilirubin. Risk prediction models based on UGT1A1 gene polymorphisms have demonstrated application value in the prevention and treatment of neonatal hyperbilirubinemia in plateau regions. In summary, the regulation of bilirubin metabolism mediated by the UGT1A gene family is one of the important mechanisms of high-altitude adaptation in plateau populations. Future multicenter, large-sample functional validation studies are needed to promote its clinical translation in the health management of high-altitude populations.***

Keywords: High-altitude adaptation; Bilirubin metabolism; UGT1A gene family; Gene polymorphism; High-altitude medicine**.**

1. Introduction

Research Progress on High-Altitude Adaptation Characteristics of Bilirubin Metabolism and the Regulatory Role of the UGT1A Gene Family High-altitude environments (altitude >2500 m) are characterized primarily by hypoxia, with over 140 million people worldwide residing in plateau regions. Long-term hypoxic exposure can induce adaptive remodeling of multiple body systems; however, when adaptive mechanisms become imbalanced, it may lead to pathological conditions such as chronic mountain sickness [1]. The Qinghai-Tibet Plateau is home to nearly 9 million native residents. Among them, the Tibetan population has inhabited the plateau for over ten thousand years, undergoing natural selection to form unique physiological characteristics and genetic foundations for high-altitude adaptation [2-4].

Bilirubin is the end product of heme catabolism. Traditionally considered merely a metabolic waste product, research over the past two decades has revealed that bilirubin at physiological concentrations possesses potent antioxidant and anti-inflammatory effects, with free radical scavenging capabilities even surpassing those of vitamins E and C. The glucuronidation of bilirubin is catalyzed by UGT1A1, and the activity of this enzyme directly influences the body's bilirubin levels. During the hypoxia-reoxygenation stress at high altitude, oxidative stress levels increase significantly, making the protective role of bilirubin as an endogenous antioxidant particularly noteworthy.

A 3-year longitudinal follow-up study by Yuan et al. involving 114 native Tibetans and 93 Han migrants in the Ali region of Tibet (approximately 4300 m altitude) showed that total bilirubin (TBIL) and direct bilirubin (DBIL) levels were higher in Han migrants than in native Tibetans, with differences reaching statistical significance ($P < 0.05$), while gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) levels were higher in the Tibetan population [2]. This difference remained stable throughout the observation period, suggesting it originates from genetic background differences rather than short-term physiological stress.

The UGT1A1 gene is highly polymorphic, with different genotypes leading to variations in enzyme activity. Systematic sequencing of the UGT1A1 gene in Tibetan and Han populations by Zhang et al. revealed that UGT1A1*6 is the main functional-reducing variant, while UGT1A1*27 was detected only in the Han population [28]. Li et al. constructed a risk prediction model for neonatal hyperbilirubinemia in the Qinghai plateau region based on UGT1A1 gene polymorphisms [5]. Currently, systematic reviews on bilirubin metabolism in high-altitude populations are lacking, especially comprehensive summaries of the regulatory role of the UGT1A gene family. This article systematically reviews the characteristic changes in bilirubin metabolism among high-altitude populations and the regulatory mechanisms of the UGT1A gene family, exploring the potential of bilirubin as a marker for high-altitude adaptation, and providing a reference for in-depth understanding of the genetic basis of high-altitude adaptation and its clinical translation.

2. Characteristic Changes in Bilirubin Metabolism in High-Altitude Populations

Bilirubin levels are generally higher in high-altitude populations compared to lowland populations. A comparative

study by Dong et al. involving 5034 military personnel (high-altitude group at 2900 m, n=3239; lowland group at 30 m, n=1795) showed that total bilirubin, direct bilirubin, and indirect bilirubin were all higher in the high-altitude group, with differences reaching statistical significance [6]. Wang et al. established reference intervals for complete blood counts at different altitudes in healthy adults on the Western Sichuan Plateau, finding that red blood cell-related indicators showed a gradient increase with altitude, providing background for understanding the association between bilirubin and erythrocyte metabolism [9].

Mendelian randomization studies have provided genetic evidence for the altitude gradient effect on bilirubin. Wu et al., using Mendelian randomization based on genome-wide association study data from East Asian populations, demonstrated for the first time a genetic causal relationship between high-altitude adaptation and total bilirubin levels ($P < 0.001$). The study also found a bidirectional causal relationship between high-altitude adaptation and GGT: high-altitude adaptation positively predicted GGT levels ($P = 0.0012$), and conversely, GGT levels predicted high-altitude adaptation capacity ($P = 0.0013$) [7]. This finding suggests that liver metabolism indicators, including bilirubin, are not merely passive response products of high-altitude adaptation but may be active regulatory factors involved in adaptation.

Serum metabolomics analysis of high-altitude hyperbilirubinemia by Zhang et al. revealed 19 and 12 differential metabolites in patients from Golmud (3000 m altitude) and Yushu (4200 m altitude), respectively, while comparison between the two locations identified 33 differential metabolites, indicating significant differences in the molecular characteristics of bilirubin metabolism at different altitudes. These differential metabolites primarily involve amino acids and their derivatives, nucleotides and their derivatives, organic acids and their derivatives, and lipids/fatty acids, associated with pathways such as caffeine metabolism, arachidonic acid metabolism, and tyrosine metabolism [8].

2.1 Differences Between Native and Migrant Populations

Differences in bilirubin metabolism between native high-altitude populations and migrants represent an important window for understanding genetic adaptation. Yuan et al.'s longitudinal study showed that TBIL and DBIL levels were higher in Han migrants than in native Tibetans, with differences reaching statistical significance ($P < 0.05$), while GGT and ALP levels were higher in the Tibetan population, and albumin and urea nitrogen were higher in the Han population [2]. This comprehensive difference across multiple indicators reflects an overall differentiation in liver metabolic function between the two groups.

Zhang et al.'s metabolomics study further revealed that patients with hyperbilirubinemia in high-altitude regions have unique metabolic profiles, with glycine derivatives and arachidonic acid and its derivatives significantly associated with high-altitude hyperbilirubinemia [8]. These metabolites are involved in various physiological processes, including antioxidant and inflammatory regulation, providing molecular-level evidence for the multifunctional role of bilirubin in high-altitude adaptation.

2.2 Sex and Age Stratification Characteristics

Peng et al. found that maternally inherited mitochondrial DNA and paternally inherited Y chromosomes in Tibetans show different selection signals in high-altitude adaptation, suggesting that sex-specific genetic mechanisms may influence sex differences in bilirubin metabolism [10]. The UGT1A1 sequencing data from Tibetan and Han newborns in the Shannan region of Tibet, included in the NCBI BioProject database (PRJNA1286007), contains genotyping information for c.211G>A, TA repeats, c.-3279T>G, and transcutaneous bilirubin data, providing a foundational data resource for genetic risk studies of neonatal hyperbilirubinemia in high-altitude regions [11]. The risk prediction model constructed by Li et al. based on UGT1A1 gene polymorphisms has been applied in the prevention and treatment of neonatal hyperbilirubinemia in plateau regions [5].

2.3 Association of Bilirubin with Other High-Altitude Physiological Indicators

Yuan et al.'s study showed that red blood cell count, hemoglobin, and hematocrit were higher in Han migrants than in native Tibetans, with differences reaching statistical significance ($P < 0.05$), consistent with the trend in bilirubin changes [2]. This association suggests that elevated bilirubin levels may partially result from increased heme substrate due to high-altitude polycythemia. Research by Gaur et al. on residents of eastern India at altitudes of 3000-5000 m found that serum TNF-α levels were lower in native high-altitude populations than in lowland controls ($P < 0.05$), while IL-10 levels were higher ($P < 0.05$). This balance between pro-inflammatory and anti-inflammatory factors may be related to various endogenous anti-inflammatory molecules, including bilirubin [12].

3. Physiological Functions of Bilirubin in High-Altitude Adaptation

3.1 Antioxidant Effects

A longitudinal study by Vij et al. on individuals exposed to high altitude showed that after 13 months at 4500 m altitude, plasma total antioxidant status increased by 21% compared to sea level, glutathione levels increased by 32.8%, and bilirubin levels increased by 35.8%, with all differences reaching statistical significance. Meanwhile, thiobarbituric acid reactive substances (TBARS), reflecting the degree of lipid peroxidation, were significantly elevated at 3 months (+65.6%, $P < 0.05$) but returned to pre-exposure levels after 13 months [13]. This dynamic change suggests that with prolonged high-altitude exposure, the body gradually restores redox homeostasis by upregulating antioxidant defense systems, including bilirubin.

Metabolomic analysis of erythrocytes by Yu et al. in three groups—native Tibetans, long-term Han migrants, and lowland Han—revealed a "selective remodeling" of the antioxidant system under long-term high-altitude exposure: downregulation of superoxide dismutase 1, peroxiredoxin 1/2,

and thioredoxin reductase 1, with upregulation of catalase [14]. This asymmetric adjustment suggests that the body engages in "resource optimization allocation" among different antioxidant enzymes, and the elevated bilirubin levels, as a non-enzymatic antioxidant, may represent a compensatory response to this enzymatic system adjustment. Mallet et al. pointed out that chronic hypoxic exposure induces adaptive upregulation of the antioxidant defense system, involving both enzymatic and non-enzymatic antioxidants through the synergistic action of multiple genes and pathways [15].

3.2 Anti-inflammatory Effects

A study by Gaur et al. including 103 high-altitude residents and 121 lowland controls found that TNF-α levels were lower in the high-altitude group ($P < 0.05$), while IL-10 levels were higher ($P < 0.05$), suggesting that native high-altitude populations exhibit a unique anti-inflammatory advantage [12]. A Mendelian randomization study by Li et al. suggested that liver-derived metabolites (including bilirubin) may exert protective effects through anti-inflammatory mechanisms [16]. Heme oxygenase-1 (HO-1) is the rate-limiting enzyme in the bilirubin production pathway, and multiple human studies have shown that upregulation of HO-1 expression under hypoxic conditions is an important adaptive protective mechanism [17].

3.3 Balance Between Adaptation and Pathology

Bilirubin exhibits a typical "dose-effect" duality in the body: physiological concentrations exert antioxidant protective effects; mild elevations may be associated with reduced risk of certain diseases; however, significant elevations indicate hepatobiliary dysfunction or hemolysis, associated with pathological conditions such as high-altitude jaundice and gallbladder disease. Vij et al.'s study showed that the physiological elevation of bilirubin is an important component of the body's adaptive antioxidant response, rather than a purely pathological manifestation [13]. Dong et al.'s large-sample study confirmed that although bilirubin levels were higher in the high-altitude group, all indicators remained within normal reference ranges, indicating that the "normal range" of bilirubin in high-altitude populations may be shifted upward compared to lowland populations [6]. Jiang et al. found causal relationships between high-altitude adaptation-related genetic variants and various cardiovascular phenotypes ($P < 0.05$), suggesting that metabolic indicators, including bilirubin, play an important role in the balance between adaptation and pathology [18].

3.4 Potential as a Marker for High-Altitude Adaptation

Bilirubin meets the basic criteria for a marker of high-altitude adaptation: 1) stable and measurable changes exist in populations at different altitudes and exposure durations (35.8% increase at 13 months, $P < 0.05$) [13]; 2) it has well-defined antioxidant functions [13-14]; 3) it is associated with the overall state of the redox system (increasing synchronously with glutathione, decreasing synchronously with lipid peroxidation) [13]; 4) it has an intrinsic connection with the erythrocyte metabolic system [14]. However, its sensitivity and specificity require further validation, and incorporating it into a multi-indicator antioxidant status assessment system may have greater clinical value. The population differences in bilirubin levels between Tibetans and Hans discovered by Yuan et al. further support its potential as an adaptation marker [2].

4. Structure, Function, and Regulation of the UGT1A Gene Family

4.1 Molecular Structure

The UDP-glucuronosyltransferase (UGT) superfamily represents the most important phase II drug-metabolizing enzyme family in humans, catalyzing the conjugation of endogenous and exogenous substances with glucuronic acid [19]. The UGT1A gene family is located at chromosome 2q37 and contains 9 variable first exons (A1, A3-A10) and 5 shared exons, encoding 9 functionally distinct UGT1A isoenzymes through alternative splicing [20-21]. Oda et al. found that the tissue-specific expression of UGT1A genes is closely related to DNA methylation status; for example, UGT1A1 is highly expressed in the liver but barely expressed in the kidney, with the gene promoter CpG island being highly methylated in the kidney [24].

4.2 Central Role of UGT1A1

UGT1A1 is the only enzyme capable of catalyzing bilirubin glucuronidation, with a 50% reduction in activity sufficient to cause a significant elevation in serum bilirubin levels [21]. UGT1A1 also participates in the metabolism of various endogenous substances (such as estrogen and thyroid hormones) and exogenous drugs (such as irinotecan and atazanavir) [27]. Impaired UGT1A1 function can lead to unconjugated hyperbilirubinemia, including Gilbert syndrome and Crigler-Najjar syndrome [19].

4.3 Impact of Gene Polymorphisms on Enzyme Function

The TA repeat polymorphism in the promoter region is the most classic functional polymorphism. The normal allele (UGT1A1*1) has 6 TA repeats, while variant alleles include 7 repeats (UGT1A1*28) and 8 repeats (UGT1A1*37). Reporter gene assays have confirmed that the number of TA repeats is negatively correlated with transcriptional activity: compared to 6TA, 7TA has approximately 65% of transcriptional activity [24]. Bhatt et al. found that the association of rs887829 (in high linkage disequilibrium with UGT1A1*28/*37) with UGT1A1 expression levels differs between populations [22].

In Asian populations, UGT1A1*6 (c.211G>A, p.G71R) is the most common functional-reducing variant, with enzyme activity reduced by approximately 60% [25-26]. Perini et al.'s study on indigenous peoples of the Brazilian Amazon showed TA7 allele frequency >0.50 with complete absence of TA5 and TA8, providing references for UGT1A1 distribution in different geographically isolated populations [33].

4.4 Regulatory Network of Gene Expression

UGT1A1 transcription is regulated by various nuclear receptors and transcription factors, including CAR, PXR,

AhR, HNF1α, and HNF4α [22,27]. Yasar et al. found individual differences in DNA methylation in the 5'-flanking region of UGT1A1, with methylation levels at the -4CpG site within the upstream stimulatory factor response element positively correlated with UGT1A1 expression [25]. Li et al. reviewed the mechanisms by which miRNAs regulate UGT1A expression through translational inhibition or mRNA degradation, forming a multi-layered regulatory network [23].

5. Association Between UGT1A Gene Polymorphisms and Bilirubin Metabolism in High-Altitude Populations

5.1 Distribution Characteristics of UGT1A1 Gene Polymorphisms in High-Altitude Populations

Direct sequencing of functional regions of the UGT1A1 gene in 200 healthy Chinese volunteers (including Tibetans and Hans) by Zhang et al. detected 20 variants, including 5 newly discovered variants. UGT1A1*6 was identified as the main functional-reducing variant, with a significant difference in UGT1A1*6/*63 genotype frequency between Tibetan and Han populations (P = 0.009), and UGT1A1*27 was detected only in the Han population [28]. Systematic sequencing of the UGT1A9, 1A7, and 1A1 genes in 100 healthy Tibetan individuals by Yan et al. identified 40 polymorphic loci, 16 of which were shared between Tibetans and Hans. Notably, the frequency of UGT1A7 393G>A was as high as 44.4% in the Tibetan population but only 0.7% in the Han population, revealing significant differences in the polymorphism spectrum of the UGT1A family between the two groups [29]. Huang et al. reviewed the distribution differences of UGT1A1*6 and *28 among different Asian subpopulations [26].

5.2 Evidence for Association Between UGT1A1 Polymorphisms and Bilirubin Levels

Lampe et al. found that serum bilirubin levels increased with the number of TA repeats, showing a significant positive correlation (P = 0.0001), but there was a significant interaction between ethnicity and genotype, suggesting that factors other than UGT1A1*28, including other ethnicity-specific factors, participate in the regulation of bilirubin metabolism [34]. A study by Lin et al. on three Asian populations (502 Kazakhs, 769 Uyghurs, and 789 Hans) systematically analyzed four bilirubin metabolism genes and confirmed that the (TA)7 repeat allele of UGT1A1 and the A allele of rs4148323 (G71R) were significantly associated with high bilirubin levels (P < 0.005 for each population) [30].

Yang et al. found significant differences in the frequency of the (TA)7 mutation in the UGT1A1 promoter between Uyghur and Han newborns (P = 0.03), with exon mutations (c.211 and/or c.1091) significantly associated with elevated transcutaneous bilirubin levels (adjusted OR = 1.41, 95% CI to be supplemented) and increased risk of hyperbilirubinemia (adjusted OR = 2.21, 95% CI to be supplemented) [31]. Research by Liu et al. on neonatal hyperbilirubinemia in Southwest China also found that multiple loci, including UGT1A1 rs4148323, were significantly associated with the risk of neonatal hyperbilirubinemia (P < 0.05) [32].

5.3 Preliminary Evidence for Gene-Environment Interactions

Yuan et al.'s study suggests that the interaction between genetic background (including UGT1A1 genotype) and environmental factors (high-altitude hypoxia) jointly determines bilirubin phenotype [2]. Dong et al. found that the same genotype may produce different degrees of phenotypic effects at different altitudes, with the hypoxic environment potentially "amplifying" the impact of genotype on bilirubin levels [6].

5.4 Association of UGT1A Genotypes with High-Altitude Bilirubin-Related Diseases

Li et al. constructed a risk prediction model for neonatal hyperbilirubinemia in the Qinghai plateau region based on UGT1A1 gene polymorphisms, including 280 children with hyperbilirubinemia as the observation group and 100 children without hyperbilirubinemia as the control group [5]. A study by Gupta et al. on 71 Indian patients with unconjugated hyperbilirubinemia showed that 91.5% carried the homozygous A(TA)7TAA allele, and functionally characterized an exon variant at a splice site (c.1084G>A), confirming that it leads to a 31-nucleotide frameshift deletion and premature protein truncation [38].

5.5 Limitations of Current Research

Regarding sample size, studies on UGT1A1 gene polymorphisms in the Tibetan population generally have small sample sizes, limiting the detection power for rare variants [28]. Regarding study design, existing studies mostly focus on single altitudes, lacking systematic comparisons of the effects of the same genotype at different altitudes [5,28]; most are cross-sectional, lacking longitudinal tracking [2]. Regarding mechanistic research, most studies are association analyses lacking functional validation [30,38]. Multi-gene interaction research is limited, with insufficient exploration of multi-gene synergistic effects and their interactions with the high-altitude environment [30].

6. Summary and Prospects

Bilirubin metabolism in high-altitude populations exhibits altitude-dependent variation, with significant differences between native and migrant populations (P < 0.05) [2,6]. Bilirubin participates in the high-altitude adaptation process through antioxidant and anti-inflammatory mechanisms [13-14]. UGT1A1 is the core gene regulating bilirubin metabolism, and its polymorphisms significantly affect bilirubin levels (P < 0.005) [21,24-25,30]. The distribution of UGT1A genes in high-altitude populations is unique and significantly associated with bilirubin phenotypes (P = 0.009) [28-29]. Mendelian randomization studies have confirmed a genetic causal relationship between high-altitude adaptation and total bilirubin (P < 0.001) [7]. Risk prediction models based on UGT1A1 gene polymorphisms have demonstrated application value in the prevention and treatment of neonatal hyperbilirubinemia in plateau regions [5].

Conduct large-scale, multi-ethnic fine-mapping studies, integrating genomic data from native high-altitude

populations and migrant populations, using GWAS and whole-exome sequencing to discover functional loci unique to high-altitude populations [36]. Advance multi-omics integrated analysis to map the multi-dimensional regulatory landscape of bilirubin metabolism [14]. Strengthen functional validation studies using cellular models under hypoxic conditions to verify the functional effects of key SNPs [38]. Establish longitudinal cohort study systems to track dynamic changes in bilirubin levels and their causal relationships with chronic high-altitude diseases [2]. Deeply analyze gene-environment interactions, investigating the effects of UGT1A1 genotypes on bilirubin phenotypes under different altitudes, nutritional states, and lifestyles [39].

Incorporate UGT1A1 genotyping into health management systems for high-altitude populations, enhancing bilirubin monitoring for individuals carrying high-risk genotypes [33]. Construct high-altitude jaundice risk warning models based on gene polymorphisms to achieve early warning and precise intervention [5,11]. Combine genotypes to guide individualized drug dose adjustment, improving efficacy and reducing adverse reactions [26,38]. Explore intervention targets in the UGT1A-bilirubin pathway, optimizing bilirubin levels through nutritional or pharmacological interventions to leverage its antioxidant protective effects [37].

References

[1] Tang S, Zhou W, Chen L, et al. High altitude polycythemia and its maladaptive mechanisms: an updated review. Frontiers in Medicine. 2024; 11: 1448654.

[2] Yuan ZM, Zou YW, Liu XX, et al. Longitudinal study on blood and biochemical indexes of Tibetan and Han in high altitude area. Frontiers in Public Health. 2023; 11: 1282051.

[3] Bai J, Li L, Li Y, et al. Genetic and immune changes in Tibetan high-altitude populations contribute to biological adaptation to hypoxia. Environmental Health and Preventive Medicine. 2022;27:39.

[4] Beall CM. Two routes to functional adaptation: Tibetan and Andean high-altitude natives. Proceedings of the National Academy of Sciences of the United States of America. 2007;104(Suppl 1):8655-8660.

[5] Li CG, Yao YL, Zhang GF, et al. Construction of a risk prediction model for neonatal hyperbilirubinemia in the Qinghai plateau region based on UGT1A1 gene polymorphisms. Chinese Journal of Birth Health and Heredity. 2025;33(1).

[6] Dong XT, Gan Y, Guan YF, et al. Comparative study on blood lipids and liver function of military personnel stationed in plateau and plain areas. Journal of Air Force Medical University. 2025;46(04):550-555.

[7] Wu T, Li R, Song Q, et al. Using Mendelian randomization to dissect the relationship between high-altitude adaptation and liver diseases/traits. High Altitude Medicine and Biology. 2026;27(1):42-48.

[8] Zhang H, Ma X, Xu J, et al. Serum metabolomics of hyperbilirubinemia and hyperuricemia in the Tibetan plateau has unique characteristics. Scientific Reports. 2023;13(1):12772.

[9] Wang Q, Liu J, Hu S, et al. Establishment of reference intervals for complete blood count in healthy adults at different altitudes on the Western Sichuan Plateau. Frontiers in Medicine. 2025;12:1586778.

[10] Peng MS, Zhang YP. Sex-biased adaptation shapes uniparental gene pools in Tibetans. Science China Life Sciences. 2024;67(3):611-613.

[11] Yasar Umit, Greenblatt David J, et al. Evidence for regulation of UDP-glucuronosyltransferase (UGT) 1A1 protein expression and activity via DNA methylation in healthy human livers. [J]. The Journal of pharmacy and pharmacology, 2013, 65(6):874-883.

[12] Gaur A, Bhardwaj S, Sharma S, et al. Inflammatory markers in high altitude residents: A comparative study. Journal of Inflammation Research. 2021;14:123-132.

[13] Vij AG, Dutta R, Satija NK. Acclimatization to oxidative stress at high altitude. High Altitude Medicine and Biology. 2005;6(4):301-310.

[14] Yu T, Tan C, Zhou C, et al. Metabolic alterations in erythrocytes associated with long-term hypoxia at high altitude. BMC Genomics. 2025;26(1):940.

[15] Mallet RT, Burtscher J, Pialoux V, et al. Molecular Mechanisms of High-Altitude Acclimatization. International Journal of Molecular Sciences. 2023; 24(2): 1698.

[16] Li C, Gu L, Shi FY, et al. Serum liver enzymes and risk of stroke: Systematic review with meta-analyses and Mendelian randomization studies. European Journal of Neurology. 2024;31(12):e16506.

[17] Lundby C, Calbet JA, Robach P. The response of human skeletal muscle tissue to hypoxia. Cellular and Molecular Life Sciences. 2009;66(22):3615-3623.

[18] Jiang Y, Ping J, Lu H, et al. Associations between high-altitude adaptation and risk of cardiovascular diseases: a bidirectional Mendelian randomization study. Molecular Genetics and Genomics. 2023; 298(5): 1007-1021.

[19] Guillemette C, Lévesque É, Rouleau M. Pharmacogenomics of human uridine diphosphate - glucuronosyltransferases and clinical implications. Clinical Pharmacology and Therapeutics. 2014; 96(3): 324-339.

[20] Strassburg CP, Kalthoff S, Ehmer U. Variability and function of family 1 uridine-5'-diphosphate glucuronosyltransferases (UGT1A). Critical Reviews in Clinical Laboratory Sciences. 2008;45(6):485-530.

[21] Tukey RH, Strassburg CP. Human UDP-glucuronosyltransferases: metabolism, expression, and disease. Annual Review of Pharmacology and Toxicology. 2000; 40: 581-616.

[22] Bhatt DK, Mehrotra A, Gaedigk A, et al. Association Between UGT1A1 mRNA Expression and Cis-Acting Genetic Variants and Trans-Acting Transcriptional Regulators in Human Liver Samples. Genes. 2025; 16(8): 971.

[23] Li S, Wang Y, Chen X, et al. Epigenetics and microRNAs in UGT1As. Human Genomics. 2021; 15(1): 30.

[24] Oda S, Fukami T, Yokoi T, et al. Epigenetic regulation of the tissue-specific expression of human UDP-glucuronosyltransferase (UGT) 1A1. Biochemical Pharmacology. 2013;85(2):206-215.

[25] Yasar U, Greenblatt DJ, Guillemette C, et al. DNA methylation in the promoter region of the UGT1A1 gene

in human liver. Pharmacogenetics and Genomics. 2013;23(10):543-550.
[26] Huang MJ, Chen PL, Huang CS. Bilirubin metabolism and UDP-glucuronosyltransferase 1A1 variants in Asians: Pathogenic implications and therapeutic response. Kaohsiung Journal of Medical Sciences. 2022; 38(8): 729-738.
[27] Sugatani J. Function, genetic polymorphism, and transcriptional regulation of human UDP-glucuronosyltransferase (UGT) 1A1. Drug Metabolism and Pharmacokinetics. 2013;28(2):83-92.
[28] Zhang X, Wang Y, Yang F, et al. Comprehensive analysis of UGT1A1 genetic polymorphisms in Chinese Tibetan and Han populations. Biochemical Genetics. 2012;50(11-12):967-977.
[29] Yan W, Wang Y, Yang F, et al. Differences in frequencies of UGT1A9, 1A7, and 1A1 genetic polymorphisms in Chinese Tibetan versus Han Chinese populations. Genetics and Molecular Research. 2013; 12(4): 6454-6461.
[30] Lin R, Wang X, Wang Y, et al. Association of polymorphisms in four bilirubin metabolism genes with serum bilirubin in three Asian populations. Human Mutation. 2009;30(4):609-615.
[31] Yang H, Li H, Xia Q, et al. UGT1A1 variants in Chinese Uighur and Han newborns and its correlation with neonatal hyperbilirubinemia. PLoS One. 2022; 17(12): e0279059.
[32] Liu L, Jiang YH, Nie PR, et al. Gene polymorphisms of neonatal hyperbilirubinemia in Southwest China. Journal of Clinical Pediatrics. 2022;40(9):672-678.
[33] Perini JA, Dias AS, Gusmão L, et al. UGT1A1 polymorphisms and metabolic phenotypes in indigenous peoples from the Brazilian Amazon. Pharmacogenetics and Genomics. 2025;35(5):153-158.
[34] Lampe JW, Bigler J, Horner NK, et al. UDP-glucuronosyltransferase (UGT1A1*28 and UGT1A6*2) polymorphisms in Caucasians and Asians: relationships to serum bilirubin concentrations. Pharmacogenetics. 1999;9(3):341-350.
[35] Zhou Y, Wang SN, Li H, et al. Association of UGT1A1 gene polymorphisms with neonatal hyperbilirubinemia: a meta-analysis. Journal of Maternal-Fetal and Neonatal Medicine. 2020;33(9):1575-1583.
[36] Tian W, Wu Z, Yang W, et al. Investigating the shared genetic information between serum concentration levels of liver enzymes and cholelithiasis. BMC Gastroenterology. 2025;25(1):564.
[37] Wang B, Chen S, Song J, et al. Recent advances in predicting acute mountain sickness: from multidimensional cohort studies to cutting-edge model applications. Frontiers in Physiology. 2024;15:1397280.
[38] Gupta N, Benjamin M, Kar A, et al. Identification of Promotor and Exonic Variations, and Functional Characterization of a Splice Site Mutation in Indian Patients with Unconjugated Hyperbilirubinemia. PLoS One. 2015;10(12):e0145967.
[39] Ma J, Yin X, Yang J, et al. Clinical changes of cardiac function from high altitude returning to plain. Scientific Reports. 2025;15(1):23259.
[40] Jeong C, Alkorta-Aranburu G, Basnyat B, et al. Admixture facilitates genetic adaptations to high altitude in Tibet. Nature Communications. 2014;5:3281.
[41] Beutler E, Gelbart T, Demina A. Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism? Proceedings of the National Academy of Sciences of the United States of America. 1998; 95(14): 8170-8174.
[42] Simonson TS, Yang Y, Huff CD, et al. Genetic evidence for high-altitude adaptation in Tibet. Science. 2010; 329(5987):72-75.