**Title: Genome-to-Network Evidence for Convergent Evolution in Tibetans and Andeans Under High-Altitude Stress**

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**Introduction**

High-altitude adaptation is a striking example of natural selection in humans. Tibetans have inhabited the Tibetan Plateau for tens of thousands of years, whereas Andean populations, despite their distinct ancestry and demographic history, have also lived at high altitude for millennia. Although these groups differ substantially, both are exposed to comparable hypoxic stressors, suggesting the possibility of convergent evolution. Previous studies have identified individual genes such as *EPAS1* as candidates for convergent adaptation, but systematic genome-wide evidence remains limited. Here, we sought to characterize convergent signatures of adaptation between Tibetans and Andeans using an integrated population genetics and network-based framework.

**Methods**

We conducted population genetic selection scans in 27 Tibetan and 40 Andean individuals using the Composite of Multiple Signals (CMS) test. Variants exceeding a CMS score threshold of six were retained as strong candidates for positive selection. We then applied the Open Targets Genetics variant-to-gene framework, incorporating pathogenicity, genomic proximity, and GTEx expression data, to assign variants to likely effector genes (attribution score ≥ 0.2). Gene sets were propagated through a heterogeneous biological knowledge graph (~1 million nodes, 13 million edges, 18 entity types), and enrichment significance was evaluated against null simulations. Results were contextualized through literature review and automated retrieval with a large-language model agent connected to the same knowledge graph.

**Results**

We identified 16 convergent genes with strong attribution in both populations, including EP300 and *ACO2* (metabolic efficiency), *TBC1D7* (mTOR regulation), *VNN2* (oxidative stress defense), *COL18A1* (angiogenesis), *CD86* (immune regulation), and *TEF* (circadian control). These genes converge on pathways supporting oxygen utilization, vascular remodeling, metabolic timing, and stress resilience. Anatomical analysis revealed 211 convergent structures, dominated by respiratory (29%), lymphatic (21%), digestive (15%), and cerebellar nervous system (12%) adaptations, reflecting enhanced oxygen extraction, immune surveillance, nutrient absorption, and motor coordination. At the cellular level, 26 convergent cell types were detected, with enrichment in immune populations (57.7%), vascular-associated cells (15.4%), and cerebellar neurons, alongside colonocytes, mesenchymal stem cells, and melanophages. Analyses of additional modalities, including biological pathways, proteins, and regulatory elements, also demonstrated convergent signatures.

**Conclusion**

Our findings provide genome-wide evidence of convergent adaptation between Tibetans and Andeans across multiple biological layers. By integrating population genetics with gene attribution and network-based propagation, this study reveals coordinated selection on metabolic, vascular, immune, and neural systems, highlighting the multi-systemic nature of human adaptation to high altitude.