

THE INTRIGUING STORY OF *EPAS1* IN HUMAN GROUPS LIVING AT EXTREME ALTITUDES

In 2014 Huerta-Sanchez et al. (1) reported a study on altitude adaptations in Tibetans. The study confirmed previous studies that the *EPAS1* gene variant was subjected to Darwinian selection. The authors noted, intriguingly, that this variant was present in Denisovans (cousins of Neanderthals), thus hypothesizing that the variant was an introgression event.

But how did Denisovans acquire this adaptation? Did they also dwell at high altitudes? The answer arrived in 2019 when Chen et al. (2) unearthed a Denisovan mandible in the Tibetan Plateau (3.280m). While standard DNA sequencing was unusable, cutting-edge proteomic technologies (liquid chromatography and tandem mass spectrometry) revealed that the same protein variant found in Tibetans was present in the mandible. This finding strongly supported the hypothesis of Denisovan inheritance.

A recent article published in *Science Advances* (3) reports that a different variant of this same *EPAS1* gene is present in Andean highlanders living up to above 4.000 m.

Science comment: "The mutation in the same gene allows two different groups of humans to thrive at extreme altitudes".

- (1) <https://link.springer.com/article/10.1007/s10577-007-1208-0>
- (2) <https://www.nature.com/articles/s41586-019-1139-x>
- (3) <https://genomebiology.biomedcentral.com/articles/10.1186/s13059-023-02912-1>