A Tibetan specific copy number deletion was identified that may account for high-altitude adaptation

With the support by the National Natural Science Foundation of China, the Strategic Priority Research Program of the Chinese Academy of Sciences, and the Science and Technology Commission of Shanghai Municipality, a research team led by Dr. Xu Shuhua from CAS-MPG Partner Institute for Computational Biology (PICB), Shanghai Institutes for Biological Sciences identified a Tibetan enriched copy number deletion near *EPAS1*, which was published in *The American Journal of Human Genetics* (*AJHG*) (2015, 97: 54—66).

High altitude adaptation (HAA) of Tibetan highlanders has been studied extensively and many candidate genes have been reported based on analysis of single nucleotide polymorphism (SNP) data. Among many reported HAA candidates, a hypoxia pathway gene, *EPAS1* is the top gene identified by most of previous studies as having the most extreme signature of positive selection in Tibetans. Subsequent efforts targeting to identify functional variants, however, so far have been not that successful.

With a newly developed method (WinXPCNVer) particularly for detecting population specific copy number variations, the research team identified a 3.4-kb copy number deletion near *EPAS1*, which is significantly enriched in high-altitude Tibetans, namely TED, as called by the team. About 90% of Tibetans carry this TED and 50% lose both copies, but only 3% of 2,792 worldwide samples are TED carriers and no homozygous deletion carriers were found in non-Tibetan samples. Interestingly, this TED is absent from Denisovan genome which was found to contribute their genetic component to Tibetans at *EPAS1*. The team further explored, by analyzing database and literature, functional potentials of the TED and found there is enhancer histone mark overlapping with this TED and the TED is associated with homoglobin concentration in Tibetans. The team also whole-genome deep sequenced seven Tibetans and verified the TED but failed to identify any other copy-number variations with comparable patterns, giving this TED top priority for further study.

Despite the function of the TED has not been fully characterized yet, many lines of evidence support that the TED is a promising candidate that might have played a critical role in high altitude adaptation of Tibetans. The team suggested additional experimental studies are still needed to verify the functional role of the TED in adaptation of Tibetan people to highland. The findings on this TED opened a new window to elucidate the functional mechanism of *EPAS1* which is expected to eventually understand the molecular basis of HAA in Tibetans.

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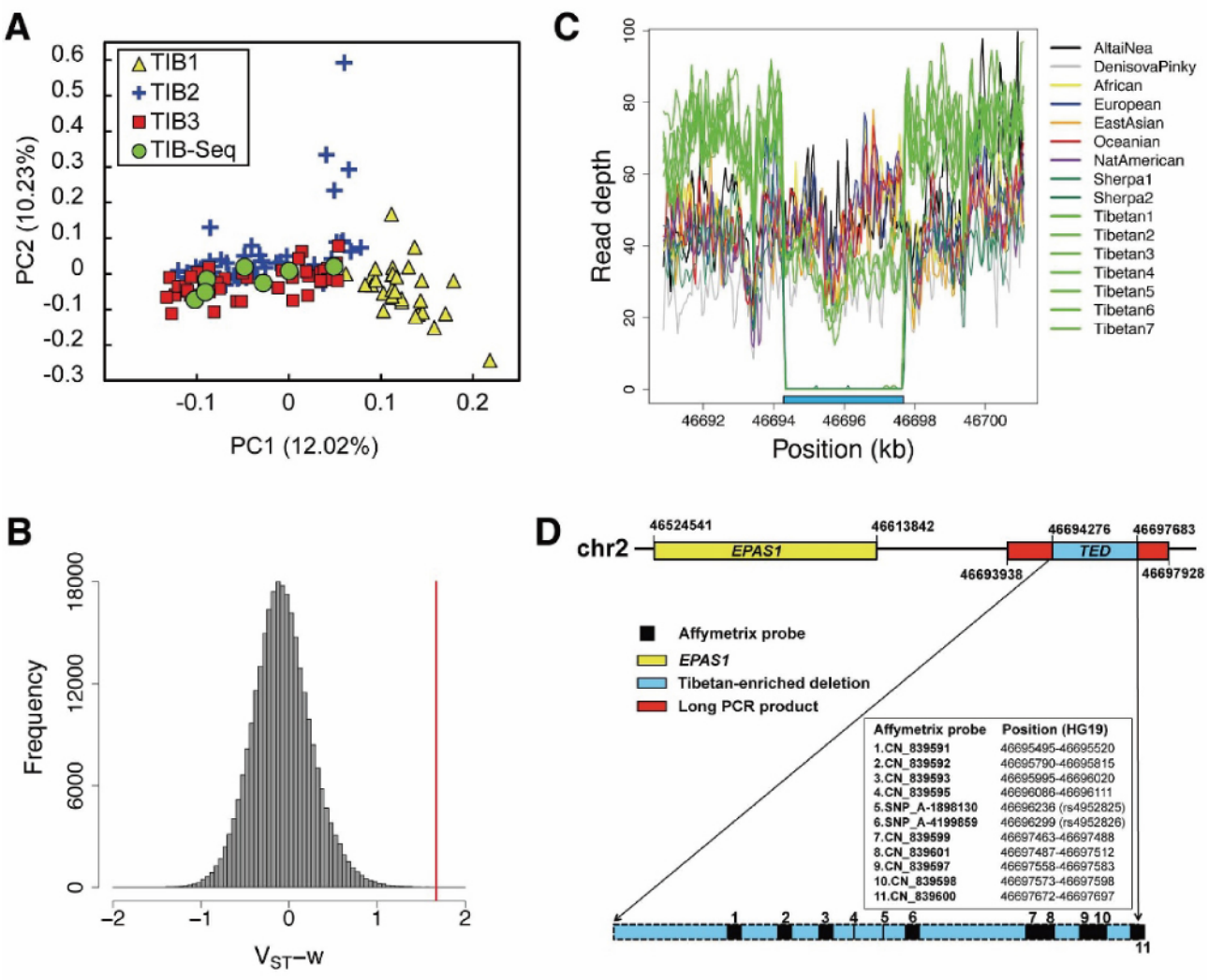

Figure Tibetan-enriched deletion downstream of *EPAS1*. (A) Population structure of Tibetan samples from different sources (Qinghai: TIB1; Tibet: TIB2, TIB3 and TIB-seq). The principal component analysis (PCA) plot was generated by 99,768 genome-wide random SNPs. Each dot represents one Tibetan individual. The *x*-axis and *y*-axis represent the first and the second principal component (PC), which explains 12.02% and 10.23% of the total variance, respectively. (B) Genome-wide distribution of V_{ST}-w calculated as the mean V_{ST} of the top three probes in each 3 kb-sliding window. The red vertical line represents the Tibetan-enriched deletion downstream of *EPAS1*. (C) Read depth (RD) of seven Tibetan, two Sherpa, one Neanderthal, one Denisovan and five modern human individuals. The deletion region is highlighted in the blue bar at the bottom. Samples with homozygous and heterozygous deletion showed a zero and half-level of the normal (flanking) RD, respectively. Four Tibetan and two Sherpa individuals carried homozygous deletion and the other three Tibetan individuals carried heterozygous deletion. No deletions were found in other individuals. (D) Diagram of locations of microarray probes, long PCR primers and *EPAS1* position.

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