

## **S2 Text.** No genetic association between the nonsynonymous *EGLN1* SNPs and Hb phenotypes

Two nonsynonymous variants in the *EGLN1* gene, rs12097901 and rs186996510, were previously shown to harbor strong signatures of selective sweep [1, 2]. An early study reported an association of the *EGLN1* haplotype (defined by a combination of three SNPs; rs2275279, rs2790859 and rs961154) with lower Hb in a sample of mixed gender with large effect size estimate 1.676 g/dL per allele [3]. However, two more recent studies, each with more than 500 Tibetan participants, reported that the derived allele of rs186996510 was associated with lower Hb only in males [1, 4]. Similarly, an analysis of *EGLN1* SNPs in 3,008 Tibetans did not detect a significant association with Hb, and reported a larger effect size for males compared to females [5]. Consistent with the more recent evidence, we did not detect a significant association at either of the two nonsynonymous SNPs with Hb ( $p \geq 0.224$ ) or with oxyHb ( $p \geq 0.268$ ) in our Tibetan sample, which includes only females. No association was detected when we either added menopause status, a female-specific covariate of Hb, as an additional covariate or confined our analysis to post-menopausal women ( $p \geq 0.641$ ), thus excluding it as an explanation for the lack of association in females. We calculated that our power to detect an association with a single test ( $\alpha = 0.05$ ) for the observed allele frequency of rs186996510 (0.336) and our sample size ( $N = 649$ ) was  $\geq 99\%$  for an effect size as low as 0.332 g/dL per allele, which is well below previous estimates (S11 Table). The reasons for the inconsistent findings regarding an association of *EGLN1*, an oxygen sensor in the oxygen homeostasis pathway, and hemoglobin concentration are unknown.

A recent study suggested an interaction between the effects of *EGLN1* and *EPAS1* SNPs on Hb levels [6]. However, our data showed no significant interaction between the *EPAS1* and *EGLN1* SNPs (rs372272284 and rs186996510, respectively) in the association with Hb ( $p = 0.613$ ).

## **References**

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