

# Novel Findings for High Altitude Adaptation from the Yak Genome

An international consortium, led by Prof. Liu Jianquan Liu in Lanzhou University, comprising researchers from BGI, the world's largest genomics organization, Institute of Kunming Zoology, Chinese Academy of Sciences as well as the other 12 institutes, has completed evolutionary analyses of the genetic bases for yak to survive at high altitude based on the genomic sequence of a female yak. This important research was recently published by an article entitled "The yak genome and adaptation to life at high altitude" on *Nature Genetics* on July 1, 2012. This work was partly funded by National Natural Science Foundation of China (30725004 and 40972018 to Jianquan Liu).

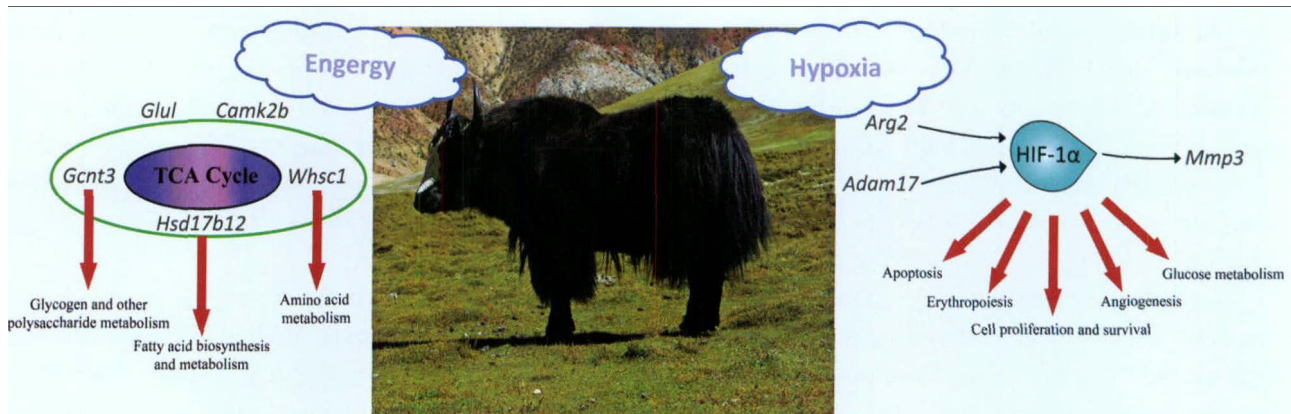
As a standard symbol of the Qinghai-Tibet Plateau (QTP) and high-altitude, yak (*Bos grunniens*) is the most important animal species for Tibetans and other nomadic pastoralists in the QTP and adjacent high-altitude regions. Yaks have provided them not only the basic food resources, i. e. , meats and milks, but also transportations, fuels (yak dung), and accommodation tents. 'No domestic yak, no conquest of the QTP by human beings' as suggested by a popular saying. In particular, yak has a very closely related relative, as we all know, cattle. Cattle could not survive at high altitude. Compared with cattle, yak has many anatomical and physiological traits that enable it to live at high altitude, including high energy metabolism, impressive foraging ability, enlarged hearts and lungs, and lack of hypoxic pulmonary vasoconstriction when faced with relatively low oxygen conditions. Therefore, the comparison between yak and cattle has become as a standard model for understanding high-altitude adaptation.

In order to understand genetic bases of the high-altitude adaptation in yak, researchers firstly sequenced the genome of a female domestic yak using whole-genome shotgun strategy based on Illumina HiSeq 2000 platform. The genomic data yielded a high-quality draft assembly, has contig and scaffold N50 size of 20.4 kilobases (Kb) and 1.4 megabases (Mb), respectively. The total length of the assembly is 2,657 Mb, close to 2,649 Mb previously reported for the cattle genome size. Based on the high coverage sequence data, researchers tracked down 2.2 million heterozygous SNPs within the sequenced individual. The researchers also performed whole transcriptome sequencing on RNA samples derived from fresh heart, liver, brain, stomach, and lung tissues collected from the same yak. Based on these RNA-sequence data, combined with homology alignment and gene prediction models, the researchers estimated that the yak genome contains 22,282 protein-coding genes. They also found that the heterozygosity rate is much higher in yak than in cattle. As they suggested that this may result from a longer and more systematic selection in cattle and/or introgression from wild yaks.

Then, researchers conducted the comparative genomic analyses between yak and cattle in order to understand genetic adaptation of yak to the high-altitude. Yak and cattle were estimated to diverge around 4.9 million years ago, around the same time when human and chimpanzee diverged. Therefore, many genes found in yak are similar to those in cattle and 99.5 percent proteins are similar. Despite this, they still found that yak developed its own (yak-endemic) 170 genes belonging to 100 gene families. In yak, genes also became more in the gene families related to sensory perception and energy metabolism. Similarly, in addition, domains also expanded in a few proteins related to the extracellular environment and hypoxic response. For example, the genes with Hig\_1\_n domain were found to be highly expressed under hypoxia stress. This domain significantly expanded in yak when compared to cattle and other mammals. The expansions of these gene families and domains in yak may be critical for its high-altitude survival.

Finally, researchers aligned and compared evolutions of the orthologous genes between yak and cattle. They found that those orthologous genes between yak and cattle related to hypoxia and energy metabolism

evolved much faster than others. Based on these findings, they further identified the most critical genes during such a high-altitude adaptation, which were assumed to have retained positively selected footprints. Three such genes were identified and these genes should have played important roles in helping yak to regulate hypoxia-response at high-altitudes. Five other such genes may have helped yak to optimize nutritional assimilation and energy production from the limited food resource at high-altitude (Fig. 1).



As pointed out by the researchers, the determination of the key genes in the natural high-altitude adaptation in yak will be highly useful to improve current understanding, treatment and prevention of altitude sickness and other hypoxia-related diseases in humans. In addition, the yak genome sequence together with the many SNPs recovered in this study will facilitate genetic dissection of agronomically important traits in the species and accelerate the genetic improvement of milk and meat production of this essential livestock to the Tibetan people and economy.

This research has aroused a widespread interest over the world. When the work was published online, *Science Now's* Science-Shot made a timely comment by the title “What gets yaks high” at its homepage ([scienceshot-what-gets-yaks-high.html](http://scienceshot-what-gets-yaks-high.html)). Since then, numerous institutes, news webs, newspapers and magazines reported this exciting work.