Codon 104 of p53 is not an adaptively selected site for extreme environments in mammals of the Tibet plateau

The theories of molecular evolution are very helpful to yield insights into the genetic mechanisms for phenotypes or physiological roles that are difficult to discern in the laboratory. Mutations of functional genes that benefit fitness may experience fixation, especially when they originate in species living in challenging environments where selection may be extreme. Based on comparison of p53 sequence data and functional studies, Zhao et al. (1) conclude that asparagine-104 (104N) in the wild zokor (*Myospalax baileyi*) and glutamic acid-104 (104E) in root vole (*Microtus oeconomus*) are "adaptively variable, meeting the environment stresses of the Tibetan plateau." I believe that this conclusion is unwarranted.

Zhao et al. (1) contend that the amino acids of 104N and 104E in p53 are an outcome of environmental adaptation and evolutionary selection to high elevation living for *M. baileyi* and *M. oeconomus*, respectively. If the independent mutations yielded advantages to stressful environments, then selection should have exclusively fixed them in taxa high elevation species. However, searching in National Center for Biotechnology Information and Ensembl databases reveals that 104N also occurs in many lowland rodents, including mouse, rat, gerbil, naked mole-rat, lesser Egyptian jerboa, degu, and chinchilla, which suggests that the mutation has already occurred in the ancestors of rodents. In addition, this mutation also occurs in more diverse lowland taxa, such as mouse lemur, hedgehog, cow, sheep, rabbit, and horseshoe bat. Similarly, 104E of p53 is not unique to *M. oeconomus*. This amino acid also occurs in the closely related prairie vole (*Microtus ochrogaster*), which lives in lowland areas (2). Its origin appears to have occurred in ancestral *Microtus*, if not earlier. Thus, there is no indication at the sequence level that the mutational variation of S104N/E of p53 in *M. baileyi* and *M. oeconomus* is fixed adaptively for facing the environmental stresses of the Tibetan plateau.

Zhao et al. further contend that 104N/E contributed functionally to adaptive resistance to extreme environments of the Tibet plateau. However, their data do not support that assertion. Considering phylogenetic relationships, the human control in their functional studies may have yielded misleading results caused by lineage-specific history due to long divergence times (3). Compared with the lowland relative of Gansu zokor (*Myospalax cansus*), *M. baileyi* exhibited that three (*Apaf1*, *Bax*, and *Puma*) of six p53 target genes were differentially expressed (figure S4 from ref. 1). However, 104N of p53 in *M. baileyi* does not result in their expression difference. Upon mutating 104N into 104S in *M. baileyi*, the expression level of *Apaf1* did not increase, as it did in *M. cansus*, but rather it decreased; the expression levels of *Bax* and *Puma* did not change significantly (figure 2 from ref. 1). The functional experiments of Zhao et al. do not determine whether site 104 was under positive selection or not, even if this site appears to play an important role in p53 function, because most of important functional sites of genes typically tend to be under purifying and not adaptive selection (4, 5).

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