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SHORT REPORTS

Genome-wide selective sweep analysis of the high-altitude adaptability of yaks by using the copy number variant

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Abstract

The domestic yak (*Bos grunniens*) from the Qinghai–Tibet Plateau is an important animal model in high-altitude adaptation studies. Here, we performed the genome-wide selective sweep analysis to identify the candidate copy number variation (CNV) for the high-altitude adaptation of yaks. A total of 531 autosomal CNVs were determined from 29 yak genome-wide resequencing data (15 high- and 14 low-altitude distributions) by using a CNV caller with a CNV identification interval > 5 kb, CNV silhouette score > 0.7, and minimum allele frequency > 0.05. Most high-frequency CNVs were located at the exonic (44.63%) and intergenic (46.52%) regions. In accordance with the results of the selective sweep analysis, 7 candidate CNVs were identified from the interaction of the top 20 CNVs with highest divergence from the F_{ST} and V_{ST} between the low (LA) and high (HA) altitudes. Five genes (i.e., *GRIK4*, *IFNLR1*, *LOC102275985*, *GRHL3*, and *LOC102275713*) were also annotated from the seven candidate CNVs and their upstream and downstream ranges at 300 kb. *GRIK4*, *IFNLR1*, and *LOC102275985* were enriched in five known signal pathways, namely, glutamatergic synapse, JAK–STAT signaling pathway, cytokine–cytokine receptor interaction, neuroactive ligand–receptor interaction, and olfactory transduction. These pathways are involved in the environmental adaptability and various physiological functions of animals, especially the physiological regulation under a hypoxic environment. The results of this study advanced the understanding of CNV as an important genomic structure variant type that contributes to HA adaptation and helped further explain the molecular mechanisms underlying the altitude adaptability of yaks.

Keywords High-altitude adaptability · Yak · Copy number variation · Selection signal analysis

Introduction

Yaks, which are important herbivores in the Qinghai–Tibet Plateau, provide protein food to local herders and are integrated into the local culture as carriers of culture and religion (Ma et al. 2013; Yue et al. 2016). Numerous local domestic breeds with outstanding plateau adaptability and diverse human production expectations have been successfully bred due to the natural selection and the human domestication of yaks (Zhang et al. 2016; Lan et al. 2018a, b). Numerous studies have used yak as an animal model to study the genetic mechanism of high-altitude (HA) adaptiveness (Qiu et al. 2012). Particularly, the widespread application of whole-genome next-generation sequencing technology has led to the identification of a series of related candidate genes (Guang-Xin et al. 2019; Lan et al. 2018a, b; Goshu et al. 2019).

As an important member of the genomic structure variation family, the copy number variation (CNV) has been paid

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increasing attention in recent years. Numerous studies have confirmed that CNV participates in several human tissue development processes and diseases (Signore et al. 2019; Dasouki et al. 2019). Domestic animal studies have confirmed that abundant CNV mutations are involved in the economic traits and development of many animals, such as litter size and egg production (Huang et al. 2018; Zhang et al. 2019), milk production performance (Di Gerlando et al. 2019), and growth traits (Wang et al. 2019a). An increasing number of studies have reported on the population phylogeny and special economic traits of yak by using CNVs (Jia et al. 2019; Goshu et al. 2019; Ge et al. 2019).

In the present study, the selective sweep analysis of CNVs was performed to further identify the genetic divergence between yaks habituated under extreme HA and low altitude (LA). Our findings may help in further understanding the molecular genetic mechanism of the HA adaptation of yaks.

Materials and methods

The unpublished CNV analytical results from our previously published sequencing data (SRA: SRX4605921–SRX4605949; Guang-Xin et al. 2019) were presented to survey the divergence in the CNV distribution among 15 yaks at extreme HA (4800–6100 m) in Tibet Naqu and 14 yaks at LA (2450–2966 m) regions in the Gansu Zhaxixiulong grassland.

The adapter and low-quality raw paired reads were filtered initially. Then, the adapter and read with N ratio greater than 10% were removed. In addition, data with the number of bases with a quality value (Q) ≤ 20 exceeding 50% of the entire reading were deleted to obtain high-quality reads.

High-quality reads were mapped into the yak genome (BosGru_v2.0) through the BigBWA (Abuín et al. 2015) with 'mem 4 -*k* 32 -*M*', where -*k* is the minimum seed length. The -*M* option was used to mark shorter split alignment hits as auxiliary alignments. The SAM tools were used to convert the generated sequence alignment/graph format files into binary alignment/graph files. The Picard (V 1.129) (https://broadinstitute.github.io/picard/) was applied to sort, index, and delete duplicates.

The CNV was identified using the CNV caller (Wang et al. 2017) in accordance with CNV identification interval > 5 kb, CNV silhouette score > 0.7, and minimum allele frequency > 0.05. The selective sweep analysis was performed using the pairwise fixation indices, F_{ST} (Hudson et al. 1992) and V_{ST} (Sudmant et al. 2015). Here, V_{ST} was calculated using the equation: $V_{ST} = (V_{total} - [V_{pop1} \times N_{pop1} + V_{pop2} \times N_{pop2}]/N_{total})/V_{total}$, where V_{total} is the total variance, N_{pop} is the CN variance for each respective population, N_{pop} is the sample size for each respective population, and N_{total} is the total sample size. Statistical analysis and plot visualizations were achieved using the Perl and the R scripts. The gene-enriched signaling pathway was estimated using the KEGG database (https://www.genome.jp/kegg/pathway.html).

Results and discussion

A total of 531 CNVs were identified from 430 scaffolds and classified into six types (Supporting Material I, Fig. 1a). The majority of the high-frequency CNVs belonged to the exonic (44.63%) and intergenic (46.52%) types. The lowest count of CNVs was found at the intron region of the noncoding RNA (ncRNA_intronic, 0.19%). The relative variant data were published and uploaded in the genome variation map (GVM000055, https://bigd.big.ac.cn/gvm/getProjectDetail?project=GVM000055).

The results of the selective sweep analysis (Fig. 1b, c) showed that the F_{ST} of each CNV ranged from -0.0331 (CNV_492) to 0.2926 (CNV_199), whereas the V_{ST} of each CNV ranged from -0.0387 (CNV_353) to 0.3431 (CNV_200). Seven CNVs (i.e., CNV_199, CNV_201, CNV_231, CNV_202, CNV_265, CNV_200, and CNV_430) were identified from the intersection of the top 20 CNVs from the F_{ST} and the V_{ST} (Supporting Material I). The genes annotated with the location and their upstream–downstream 300 kb ranges in these seven CNVs were displayed, and five genes were found. These genes were glutamate ionotropic receptor kainate type subunit 4 (*GRIK4*), interferon lambda receptor 1 (*IFNLR1*), olfactory receptor 1052 (*LOC102275985*), grainyhead-like transcription factor 3 (*GRHL3*), and olfactory receptor 8H3-like (*LOC102275713*). *GRIK4*, *IFNLR1*, and *LOC102275985* were annotated in five known signaling pathways (i.e., glutamatergic synapse, JAK–STAT signaling pathway, cytokine–cytokine receptor interaction, neuroactive ligand–receptor interaction, and olfactory transduction; Supporting Material II).

Several studies have shown that the *GRIK4* gene, which is annotated in the glutamatergic synapse and neuroactive ligand–receptor interaction pathway, is involved in human autism, neurodepression, and nervous system development (Minelli et al. 2017; Ren et al. 2017; Arora et al. 2018; Sun et al. 2019). A large number of other genes from these two signaling pathways also participate in neural signal transmission and sensory learning (Rao et al. 2019; Quinn et al. 2019). Accumulating evidence confirms that the re-establishment of the behavioral and the emotional neural responses of an animal under HA hypoxic environment is critical to improve the adaptive evolution of animals and humans (Ustinova et al. 1989; Livanova et al. 1993). Specifically, according to thr recently published proteomics studies, *GRIK4* may be involved in the molecular mechanism of estrogen-mediated neuroprotection to reduce cerebral

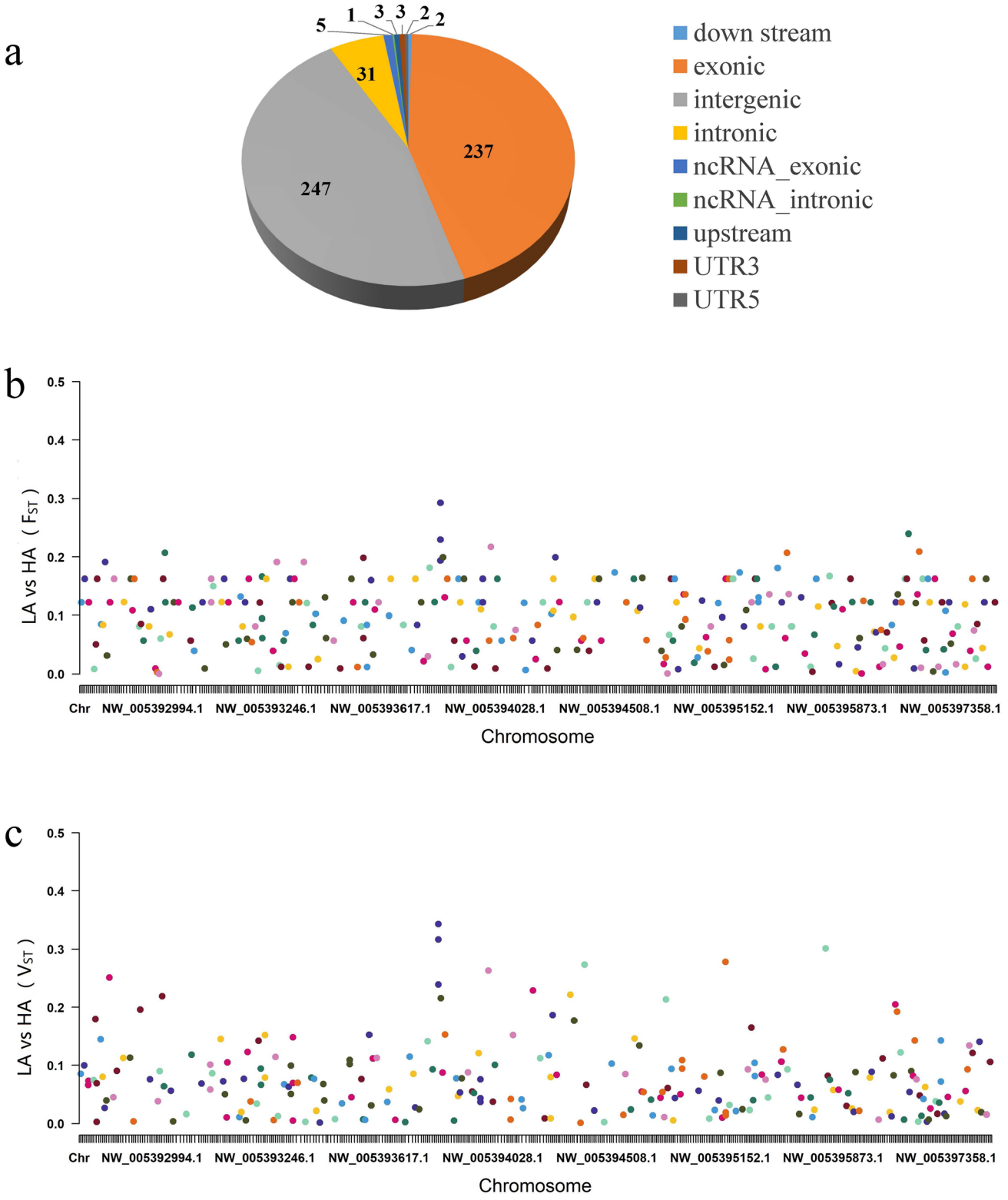

Fig. 1 Copy number variation (CNV) type description and genome-wide selection scan for CNV in high- and low-altitude yaks by using F_{ST} and V_{ST}. **a** CNV frequency and karyotypic location type. Manhattan plots show the selection signal of the CNV of the high- and low-altitude yaks by using **b** F_{ST} and **c** V_{ST}

ischemic injury (He et al. 2018). Studies have confirmed that the cooperative expression pattern of genes directly or indirectly interacting with *GRIK4* and NMDA receptors is involved in regulating the response of the retina to hypoxia (Crosson et al. 2009).

The present study suggested that the CNV_202 in the intron region of the *GRIK4* gene may change the splicing and expression of the *GRIK4* gene. This process assists the behavioral cognition and the nervous system of yak at different altitudes to adapt to the pressure of natural selection.

Furthermore, *IFNLR1* belongs to the class II cytokine receptor family. *IFNLR1* was annotated in the JAK–STAT signaling pathway and the cytokine–cytokine receptor interaction. An interferon lambda (IFN) is a cytokine induced by viral infection and has antiviral and antitumor effects (Peterson et al. 2019). *IFN* can activate the signal transduction pathway and exert antiviral and antitumor effects after binding to the receptor (Fragale et al. 2017; Hemann et al. 2019). Studies have shown that mutations in *IFNLR1* are associated with autosomal dominant nonsyndrome hearing loss (Gao et al. 2018).

The signal pathway of JAK–STAT is divided into three parts, namely, cell surface receptors, a kinase (Janus kinase, *JAK*), and a signal transduction and transcription activation factor (signal transducer and activator of transcription [*STAT*]). This system transmits extracellular signals into the nucleus and activates the transcription of downstream target genes, including a series of genes related to immunity, proliferation, differentiation, apoptosis, and oncogenes (Morris et al. 2018; Hashimoto et al. 2020). Thus, the JAK–STAT pathway may be involved in the multiple adaptive evolutions of yak caused by differences in the habitat altitude.

Another outstanding highly selective CNV (CNV_199) from NW_005393834.1 (126,001–144,000 bp) was observed and located downstream of *LOC102275985* (olfactory receptor [*OR*] 1052) at 10, 287 bp, which was enriched in the olfactory transduction signal pathway. The *OR* belongs to the G protein-coupled receptor family and identifies thousands of odor molecules in the olfactory sensory system (Antunes and Simoes de Souza 2016; Zhang et al. 2020; Krolewski et al. 2020). To date, *OR* genes have been found to belong to a multi-gene family distributed in various species, such as fish and mammals (Liu et al. 2019; Wakisaka et al. 2017). Several studies have reported the expression pattern and the genomic structure of *OR* genes under adaptive evolution with different ecological habitats (Madsen et al. 2019; C Silva et al. 2020). Thus, the *OR* genes of yak have evolved adaptively due to the diversity in the distribution of vegetation species at different altitudes. Specifically, yaks in LA habitats are more likely to benefit from the rich byproducts of agricultural areas than those in HA regions. As a result, the *OR* genes of local yaks have possibly adapted with the agricultural crops provided by humans.

The annual average temperature gradually decreases, whereas precipitation and wind speed increase with increasing altitude in the Qinghai–Tibet Plateau. These harsh ecological climatic conditions on the Tibetan Plateau limit the expansion of biological genetic diversity. However, animals that have undergone long-term natural selection and have adapted to HA climates have already exhibited a corresponding adaptive phenotype physiologically. Several studies have suggested that certain *OR* genes are involved in the growth and development of animal hair. For example, the *OR2AT4* stimulates the proliferation of skin keratinocytes, and its silencing can inhibit hair growth, indicating that *OR*-dependent chemosensation is involved in human hair follicle growth (Chéret et al. 2018; Busse et al. 2014). The JAK–STAT pathway is also widely recognized as an important signal regulating pathway for determining skin and hair follicle development (Wang et al. 2019b; Samadi et al. 2017; Kim et al. 2016). Thus, results indicated that yak populations under different altitude distributions can undergo natural selection from specific ecological conditions in the neurosensing system and exhibit various types of growth.

Conclusion

HA adaptability is an important physiological characteristic of Tibetan plateau animals, such as yaks. In this study, the genome-wide selection signature analysis of CNV among 15 yaks at extreme HA and 14 yaks at LA were compared. Candidate CNV and genes (i.e., *GRIK4*, *IFNLR1*, *LOC102275985*, *GRHL3*, and *LOC102275713*) were identified.

Therefore, this study may contribute to the in-depth understanding of the molecular regulation of the HA adaptability of yaks. However, the authenticity and the positive rate of the identified CNVs confirmed by a large sample size and their molecular mechanism for HA adaptability still need further study.

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Compliance with ethical standards

Conflict of interest Authors declare no conflict of interest.

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