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Species composition and environmental adaptation of indigenous Chinese cattle

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Indigenous Chinese cattle combine taurine and indicine origins and occupy a broad range of different environments. By 50 K SNP genotyping we found a discontinuous distribution of taurine and indicine cattle ancestries with extremes of less than 10% indicine cattle in the north and more than 90% in the far south and southwest China. Model-based clustering and f_4 -statistics indicate introgression of both banteng and gayal into southern Chinese cattle while the sporadic yak influence in cattle in or near Tibetan area validate earlier findings of mitochondrial DNA analysis. Geographic patterns of taurine and indicine mitochondrial and Y-chromosomal DNA diversity largely agree with the autosomal cline. The geographic distribution of the genomic admixture of different bovine species is proposed to be the combined effect of prehistoric immigrations, gene flow, major rivers acting as genetic barriers, local breeding objectives and environmental adaptation. Whole-genome scan for genetic differentiation and association analyses with both environmental and morphological covariables are remarkably consistent with previous studies and identify a number of genes implicated in adaptation, which include *TNFRSF19*, *RFX4*, *SP4* and several coat color genes. We propose indigenous Chinese cattle as a unique and informative resource for gene-level studies of climate adaptation in mammals.

China harbors around 10 million of indigenous cattle¹. It is commonly referred as yellow cattle and divided into 53 indigenous breeds raised in various agro-ecological environments^{2,3}. Their diversity and unique species composition emerged from a complex history. Domestic cattle spread to East Asia by at least two routes. Taurine cattle migrated from north Eurasia to northern China and northeast Asia between 5000 and 4000 BP⁴. This is supported by the evidence that ancient cattle from northern China, dated 4500 to 2300 BP, carried only taurine mtDNA haplotypes⁵. A unique mtDNA haplotype, T4, observed in East Asian cattle breeds^{6–9} is a subtype of the common haplogroup T3¹⁰, suggesting a founder effect in Chinese taurine cattle¹¹.

Indicine cattle (zebu) migrated eastward from their domestication center in the Indus valley and entered China from the south since 3000 BP^{4,12}. Southeast Asian and southern Chinese cattle are morphologically and genetically recognized as zebu^{13,14}. Yue *et al.* provided evidence for an additional southwestern immigration route of zebu from India into northwest China¹⁵.

The taurine and indicine cattle migrations resulted in a morphological gradient from humpless taurine cattle in the north to humped indicine cattle in southern and southwestern China³. This has been confirmed by genetic

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studies using mtDNA^{7,8,16,17} and Y-linked markers¹⁸. A genetic diversity study using microsatellite markers clustered Chinese indigenous cattle breeds into one taurine and four indicine groups¹⁹.

In addition to taurine and indicine cattle, several other bovine species have been living in southern China and Southeast Asia, including banteng (*Bos javanicus*), gaur (*Bos gaurus*) or gayal (*Bos frontalis*), which may have been the dominant cattle species until 4500 BP^{4,12}. Gayal in Yunnan province of China carried indicine or taurine mtDNA but gaur Y chromosome, indicating its hybrid origin²⁰. Meanwhile, in Tibetan Autonomous Region (TAR) of China, bidirectional introgression between yak and cattle has also been reported^{21–24}. Genetic admixture has been identified between zebu and Bali cattle (domestic banteng) in Indonesia^{22,25}. A previous study on hair color and blood protein polymorphism provided evidence of banteng introgression into Hainan cattle in southeastern China²⁶, which was confirmed by genomic SNP array data²⁵.

Genomic SNP array has become a powerful tool for population genomics studies in animals. A recent genomic variation study revealed a worldwide pattern of genetic admixture in domestic cattle²⁵. Other studies focused on Creole²⁷, American²⁸, East African zebu²⁹ and Korean cattle³⁰. These advanced approaches also allow the genomic localization of genes involved in the adaptation to natural or artificial selective constraints^{27,31–38}. In the current study, we generated 50 K SNP genotypes to infer the fine-scale characterization of unique species composition of highly diverse Chinese cattle. In addition, we performed a whole genome-scan for adaptive differentiation and association analyses with environmental and morphological population-specific covariables to detect genes that responded to adaptive constraints.

Results

Genomic variation. Observed heterozygosity (Table 1) ranged from 0.145 to 0.327 in Chinese cattle populations (Fig. 1). Mongolian cattle (MG, NM) and Kazakh cattle had the highest values but southern and southwestern Chinese cattle populations were the lowest. This is most likely explained by the ascertainment bias, by which the heterozygosity of indicine cattle is underestimated. Indeed, the observed heterozygosity correlates negatively ($r^2 = 0.96$) with the zebu ancestry. A similar trend has previously been observed in West-African cattle³⁹. Bali cattle (0.026), gayal (0.059) and yak (0.029) also have relatively low levels of heterozygosity as normally observed with SNP panels designed for a different species⁴⁰.

Population structure. Five methods were implemented in this part to explore the population structure.

PCA. Figure 2a shows a scatter plot of the first two principal components (PCs), allowing to assess the structuring of genetic diversity across all the 45 sampled populations, including outgroup species (Bali cattle, yak, gaur and gayal). The first PC accounting for 17.1% of total variation separates taurine and indicine cattle as well as other bovine species. The predominant taurine breeds from northern China and Tibet Autonomous Region of China (TAR) cluster with European breeds while populations from southeastern and far-southwestern China are closer to Indian zebu. The second component accounting for 3.1% of all variation displays the contrast of Chinese cattle to other bovine species (Bali, gayal and yak) and also differentiates European cattle breeds. The intermediate positions of LZ, MAD, BRE, Bali and gayal populations indicate gene flow between species.

In an analysis of only Asian cattle (Fig. 2b), the first PC that explains 14.5% of the genetic variation again corresponds to the taurine-indicine separation, but the second PC that explains 1.45% of the genetic variation represents a gradient from India via Southeast Asia to Southeastern China.

Model-based clustering. Figure 3a shows an unsupervised hierarchical clustering performed on the whole data set (i.e., including outgroup species) with different values of K, the number of clusters. $K = 2$ reproduces the first PCA coordinate with taurine and indicine clusters and a taurine-indicine gradient from north to south. Higher values of K differentiate European from Asian taurine breeds ($K = 3$), zebu from other bovine species ($K = 4$), and southern Chinese from Asian indicine cattle ($K = 5$). Increasing K further generates separate clusters for European cattle breeds whereas Chinese cattle populations tend to show admixed ancestries. The cross-validation error gave the lowest value at $K = 17$ (Supplementary Fig. S1), which differentiates Bali cattle, gayal, yak, the European taurine breeds and indicine cattle from India/Pakistan, Southeast Asia and southeastern China, respectively.

Figure 3b shows a supervised clustering with prior population information for taurine breeds (SH, HOL, BSW, SIM), indicine breeds (GIR, SAHW) and other bovine species. In this analysis, Bali cattle represents the banteng and the domestic gayal replaces the wild gaur since the latter was too inbred for this analysis. This analysis reproduces the zebu-banteng hybridization in Indonesia⁴¹ and yak introgression into Tibetan cattle, but also suggests minor banteng and gayal into southeastern China (Supplementary Fig. S2). Supplementary Figure S3 shows the geographic distribution of the inferred species components.

NeighborNet network. In a NeighborNet graph constructed from the matrix of Reynolds' distances between populations using Splitstree (Fig. 4), European and Indian cattle are at the extreme ends of the network, which is entirely in agreement with both the first PCA coordinate and the $K = 2$ clustering. Figure 4 also reproduces the intermediate positions of the predominantly taurine-indicine breeds from TAR or central China and also of the predominantly indicine breeds from central or southwestern China. In addition, the network confirms the affinity of Indonesian and southeastern Asian continental breeds with Bali cattle and gayal.

Population mixture. The taurine-indicine mixed composition of Chinese cattle was confirmed by the sensitive f_4 ratio test (Supplementary Table S1). The estimated taurine ancestry ranges from close to 0.0 in southeastern China to close to 1.0 in north, with intermediate values ranging from 0.282 to 0.760, from 0.240 to 0.320 and from

Population	Abbr.	Geographical Region	N	Ho ¹	Source ²
Yanbian	YB	Northern China	26	0.291	1
Mongolian_XilinGol	MG	Northern China	31	0.319	1
Mongolian_HulunBuir	NM	Northern China	24	0.317	1
Kazakh	KA	Northwestern China	21	0.327	1
Linzi	LZ	Tibet Autonomous Region of China (TAR), China	19	0.285	1
Lhasa	LS	Tibet Autonomous Region of China (TAR)	14	0.305	1
Qinchuan	QC	Central China	32	0.297	1,2
Jinnan	JN	Central China	14	0.299	1
Nanyang	NY	Central China	23	0.252	1
Luxi	LX	Central China	16	0.258	1,2
Wannan	WN	Southeastern China	31	0.199	1
Wenling	WL	Southeastern China	31	0.177	1
Hainan	HN	Southeastern China	8	0.145	1,2
Liping	LP	Southwestern China	5	0.179	1
Enshi	ES	Southwestern China	31	0.237	1
Guanling	GL	Southwestern China	4	0.232	1
Honghe	HH	Southwestern China	12	0.248	1
Dengchuan	DC	Southwestern China	31	0.243	1
Banna	BN	Far southwestern China	14	0.186	1
Dehong	DH	Far southwestern China	16	0.161	1
Bangladesh Zebu	BD	Bangladesh	16	0.169	1
Gayal (<i>Bos frontalis</i>)	GAY	Bangladesh	21	n.a.	1
Yak (<i>Bos grunniens</i>)	YAK	Tibet Autonomous Region of China (TAR)	12	n.a.	1
Simmental	SIM	Germany	20	0.297	1
Hanwoo	HAN	Korea	8	0.288	2
Mongolian	MGL	Mongolia	5	0.301	2
Wagyu	WAG	Japan	12	0.248	2
Aceh	ACE	Indonesia	12	0.149	2
Pesisir	PES	Indonesia	6	0.142	2
Brebes	BRE	Indonesia	9	0.158	2
Madura	MAD	Indonesia	7	0.150	2
Sahiwal	SAHW	Pakistan	17	0.159	2
Gir	GIR	India	20	0.157	2
Bali cattle (<i>Bos javanicus</i>)	BAL	Indonesia	20	n.a.	2
Gaur (<i>Bos gaurus</i>)	GAUR	India	10	n.a.	7
Shorthorn	SH	England	20	0.257	2
Holstein	HOL	Netherlands	20	0.314	3
Brown Swiss	BSW	Switzerland	20	0.281	6
Limousin	LMS	France	20	0.309	6
Central Thailand	THC	Thailand	5	0.165	4
Northeast Thailand	THNE	Thailand	8	0.157	4
North Thailand	THR	Thailand	10	0.166	4
South Thailand	THS	Thailand	5	0.142	4
Kalmyk	KAL	Kalmyk, Russian	20	0.319	5
Yakut	YKT	Siberian, Russian	20	0.256	5
Total			756		

Table 1. Sampling information of different cattle populations and their observed heterozygosity (Ho). ¹Ho was not analyzed for divergent bovine species (gayal, gaur, Bali, and yak) because the estimator is only informative for cattle. ²Source of data. 1) this study; 2) Decker *et al.*²⁵; 3) Gautier *et al.*⁸⁰; 4) Wangkunmhang *et al.* (2015); 5) Decker *et al.*⁸¹; 6) Matukumalli *et al.*⁶⁷; 7) Decker *et al.*⁶⁹.

0.656 to 0.770 in central China, southwestern China and TAR, respectively. This pattern was highly correlated with the average memberships estimated by model-based clustering ($r = 998$, Supplementary Table S1).

As shown in Fig. 5a, negative values of the four-population f_4 -statistics (GIR, X; BAL, YAK) suggests gene flow from Bali to indicine populations in southeastern China and Southeast Asia. This gene flow has clearly been more

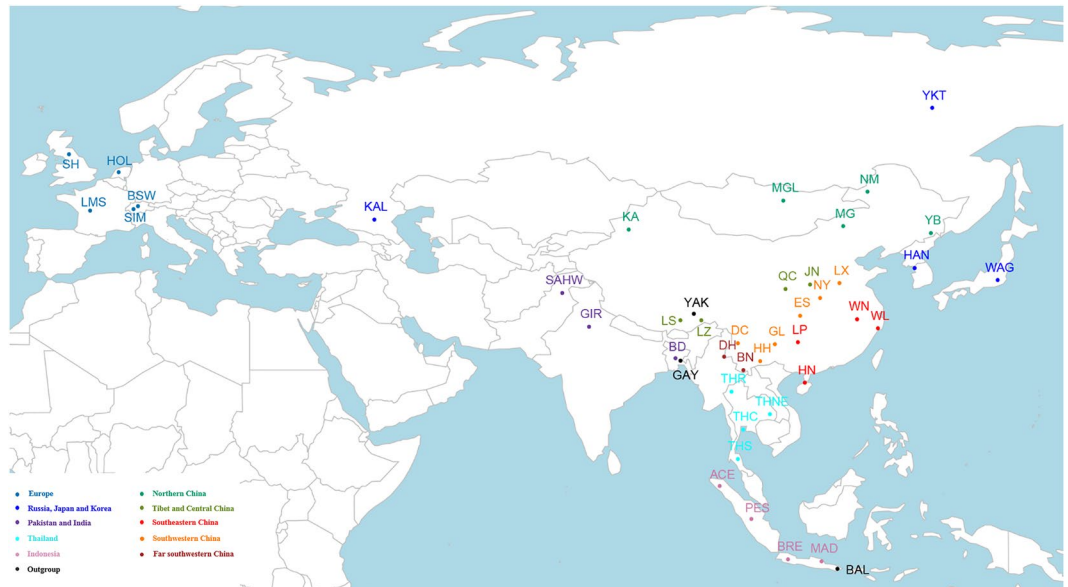


Figure 1. Geographical distribution of cattle populations. Detailed information is shown in Table 1. Map was created using R Project for Statistical Computing v. 3.3.1 (<https://www.R-project.org>) and packages *rworldmap* v. 1.3–6 (<https://cran.r-project.org/web/packages/rworldmap/index.html>), *maps* v. 3.2.0 (<https://cran.r-project.org/web/packages/maps/>) and *mapproj* v. 1.2–5 (<https://cran.r-project.org/web/packages/mapproj/index.html>). Package *rworldmap* v. 1.3–6 was used to generate outline and colorful dots while packages *maps* v. 3.2.0 and *mapproj* v. 1.2–5 were used to add texts. Different color indicates different geographical regions of population origins.

consequential for the Indonesian cattle breeds, MAD, BRE and PES as well as the southern Chinese breeds LP, HN, WN and WL. For the Indonesian breeds this confirms previous results^{25,41}. Although Bali cattle are relatively closely related to gaur, replacing Bali cattle by gaur as source of admixture generates only a moderately negative value for the Indonesian breeds (Fig. 5b). This is even observed for Bali cattle as a test breed and may reflect the inbreeding of the gaur samples. However, the same plot shows relatively low (*i.e.*, negative, indicating gene flow) values for the southern Chinese breeds. In combination with the supervised model-based clustering (Fig. 3b), this may suggest that these breeds have been introgressed by gaur and/or gayal in addition to banteng, the wild ancestor of Bali cattle.

A $f_4(\text{SH}, \text{X}; \text{GAY}, \text{YAK})$ plot (Supplementary Fig. S4A) generated negative values for the indicine GIR, SAHW and BD as test breeds. Since this is not observed with the wild gaur instead of the domestic gayal (Supplementary Fig. S4B), this indicates indicine introgression into the domestic gayal population. This is confirmed by two other observations:

- The statistic $f_4(\text{GAU}, \text{GAY}; \text{X}, \text{YAK})$ is negative for all test breeds, but clearly more negative for indicine than for taurine breeds (Supplementary Fig. S4C).
- $f_4(\text{GIR}, \text{BAL}; \text{GAY}, \text{YAK})$ is positive but $f_4(\text{GIR}, \text{BAL}; \text{GAU}, \text{YAK})$ is not (Supplementary Fig. S4D and Fig. 5B). The same patterns are also observed if GIR is replaced by SH (Supplementary Fig. S4A,B), which is phylogenetically close to the indicine GIR. Apparently the allele sharing of GAY with GIR or SH outweighs the allele sharing expected because of the phylogenetic relationship of gayal and Bali cattle, which most likely is an effect of the ascertainment bias of the SNP panel towards taurine breeds⁴².

Uniparental markers. Supplementary Tables S2 and S5 show mtDNA and Y-chromosomal haplotype distributions of Chinese cattle breeds, based on our data supplemented by literature data (Supplementary Table S3). These uniparental markers show a north-to-south taurine-indicine gradient that resembles closely the autosomal cline (Fig. 6). Haplotype diversity (Supplementary Table S2 and Fig. S5C) shows that the diversity of taurine mtDNA hardly decreased from north to south, while indicine mtDNA clearly decreases from southeastern and southwestern China to northern China.

Detection of genomic regions subjected to adaptive constraints. For a genome-wide scan for adaptive differentiation, the XtX differentiation statistics was estimated for each SNP under the so-called core model and visualized in a Manhattan plot (Fig. 7a). Among 84 significant SNPs, SNP Hapmap28985-BTA-73836 on BTA5 was the most significant.

The three synthetic environmental covariables are associated with 185 significant SNPs (Supplementary Table S4), from which SNP Hapmap44345-BTA-119580 on BTA11 was the most significant (Fig. 7b). From 30

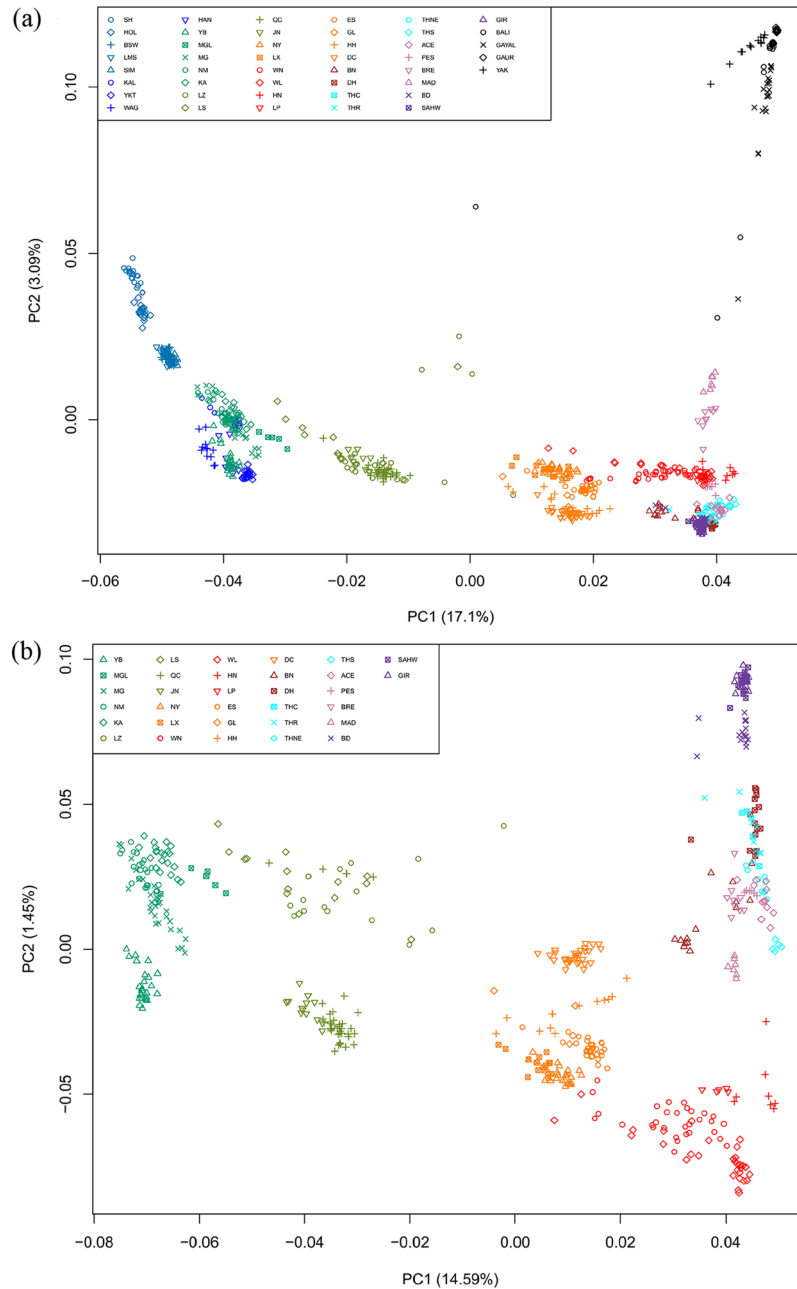


Figure 2. PCA plots describing the relationships among populations. (a) Whole data set of all the 45 sampled populations. (b) A subset of data including only Asian cattle. Different colors were used to indicate different regions as Fig. 1.

SNPs associated with morphological covariables (Supplementary Table S4), SNP ARS-BFGL-NGS-67505 on BTA25 was most significant (Fig. 7c).

By applying the sliding window approach, 27 significant genomic regions were obtained (in Table 2), of which eight showed significantly differentiated SNPs; 22, 0 and 4 displayed SNPs associated with the first, the second and the third environmental co-variable, respectively; and 4 displayed SNPs associated with the morphological covariable. Note that only 3 regions (out of the 8) containing significantly differentiated SNPs did not contain any SNPs associated with the population-specific covariables studied. Finally, a total of 28 candidate genes were annotated in the significant regions using UCSC (<https://genome.ucsc.edu/>) (Table 2).

Discussion

We have investigated the species composition and genomic, mitochondrial as well as Y-chromosomal variation in Chinese cattle populations. A clear north-south gradient of taurine and indicine cattle ancestries combined with banteng, gayal and yak introgressions into southern and southwestern Chinese cattle populations defines the pattern of admixture among Chinese indigenous cattle, which are supposed to underlie local breeding objectives and

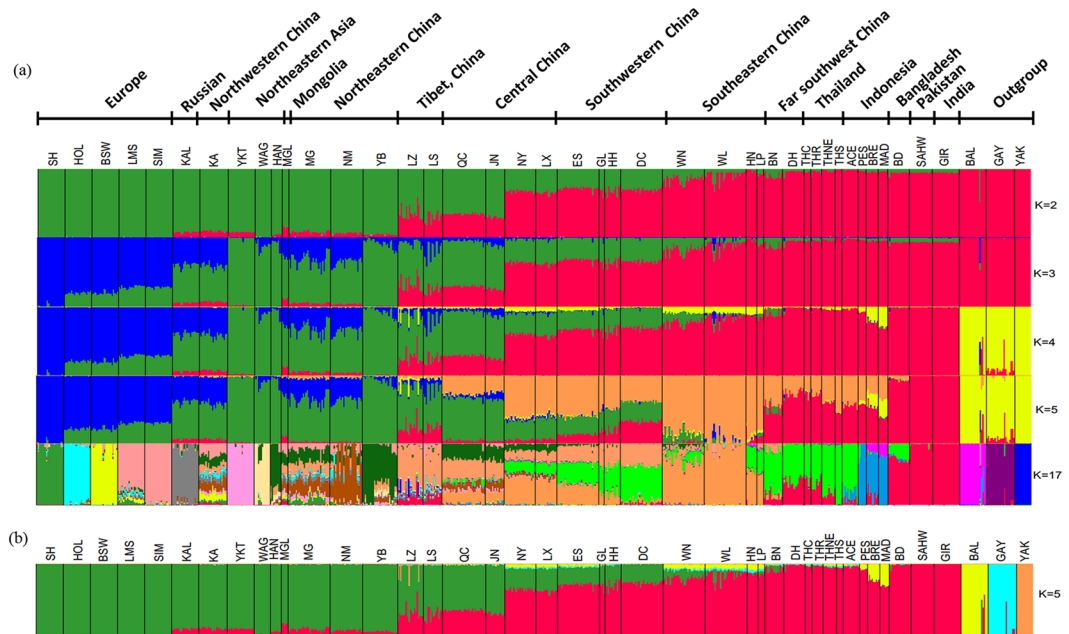


Figure 3. Ancestries and population structuring of Chinese cattle revealed by (a) unsupervised Admixture analysis (K = 2, 3, 4, 5, 17) and (b) supervised Admixture analysis (K = 5). For supervised admixture analysis, five European cattle breeds (SH, HOL, LMS, SIM) were set to represent taurine ancestry whereas GIR and SAHW represented indicine ancestry. BAL, GAY and YAK were three outgroup bovine species. The putative hybrid animals in Bali and Gayal detected by unsupervised admixture analysis were excluded from the pure ancestry.

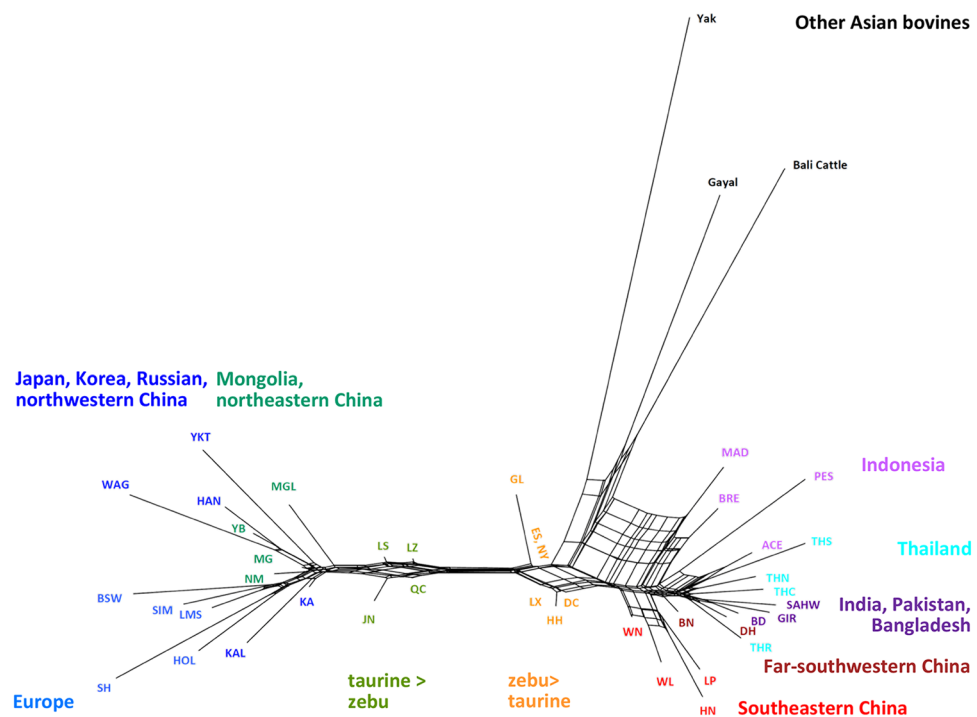


Figure 4. NeighborNet graph of 44 cattle populations. An allele frequency-dependent distance metric (Reynolds) was used to construct the NeighborNet. Different colors were used to indicate different regions as Fig. 1.

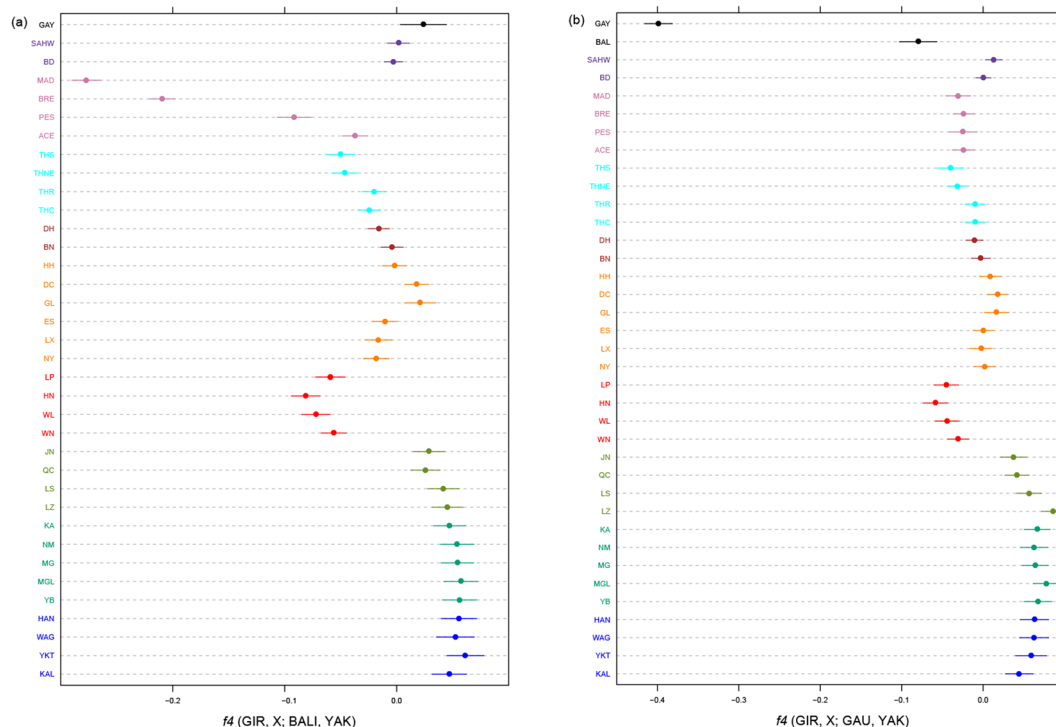


Figure 5. Visualization of f_4 -statistics. (a) f_4 -statistics of the form $D(GIR, X; BALI, YAK)$ identified gene flow from Bali to other breeds. (b) f_4 -statistics of the form $D(GIR, X; GAU, YAK)$ identified gene flow from Gaur to other breeds. The whiskers represent the standard error. Different colors were used to indicate different regions as Fig. 1.

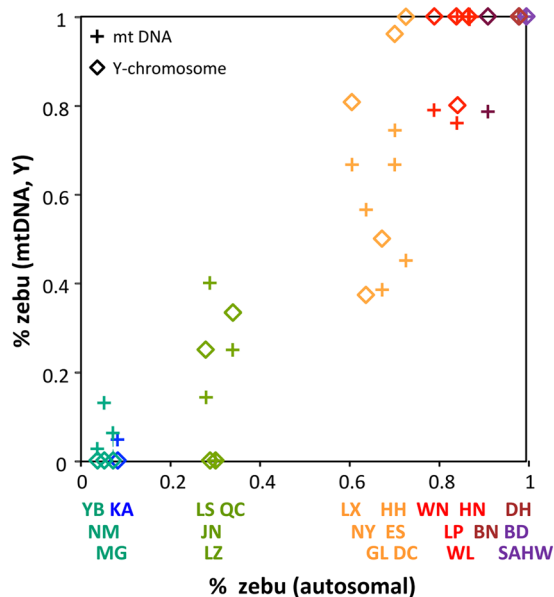


Figure 6. Percentages of indicine mtDNA and Y-chromosomes per breed plotted against the breed average of the autosomal indicine component as derived from the Admixture analysis.

adaptation to different agro-ecological environments. Genome scan for adaptive differentiation and association with population-specific covariable identify regions and candidate genes relevant for environmental adaptation and morphological differentiation in Chinese cattle.

Previous genetic diversity studies using mtDNA and Y-linked markers have characterized a north-south gradient of taurine and indicine admixture in Chinese cattle, which is consistent with the transition from humpl

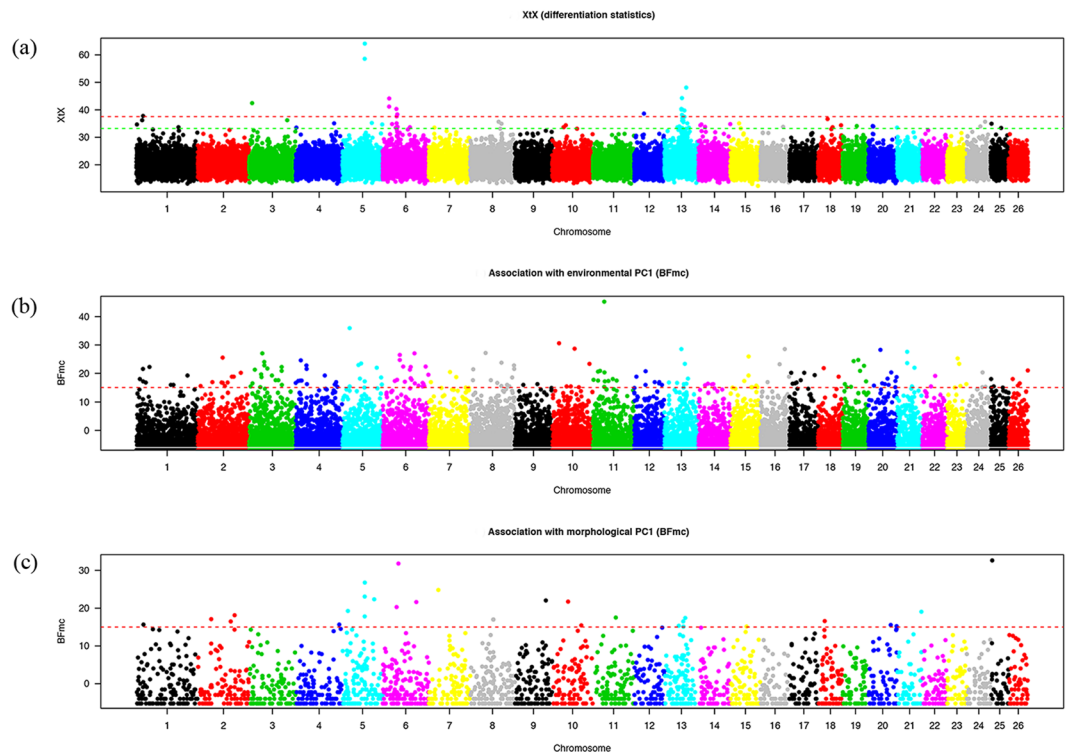


Figure 7. Whole genome scan for adaptive divergence and association analyses in 20 Chinese cattle breeds. **(a)** Manhattan plot of the XtX statistics. **(b)** Manhattan plot of the BFmc (association with environmental PC1). **(c)** Manhattan plot based on the BFmc (association with morphological PC1).

to humped morphology^{7,8,16–18}. A microsatellite study differentiated five groups of Chinese indigenous cattle breeds¹⁹.

Our PCA (Fig. 2) and model-based clustering (Fig. 3, Supplementary Fig. S3) patterns as well as the NeighborNet graph (Fig. 4) reveal a clear transition from taurine cattle in the north to zebu in the south with consistent admixture levels within the breeds and a clear demarcation:

- Cattle from Manchuria, Inner Mongolia and northwestern China with 4 to 8% indicine admixture. This group corresponds to the taurine type 1¹⁹ (this type also comprises Tibetan cattle) and to Group 9B in the Felius classification⁴³.
- Taurindicine cattle in TAR and northern China above the Yellow or Wei River with 28 to 35% indicine admixture, denoted as zebu type 2¹⁹ and belonging to the Huanghuai group of central Chinese cattle (Group 10A)⁴³.
- Taurindicine cattle below the Yellow River with 61 to 73% indicine genome, corresponding to indicine types 1 and 4¹⁹. The northernmost LX, JX and NY breeds belong to the Huanghai group (Group 10A)⁴⁰, but the other breeds to the Changzu group (Group 10B)⁴³.
- Predominant indicine cattle in southern China with an indicine genomic component of 79 to 87% (zebu type 3¹⁹, Group 10B⁴³).
- Indicine cattle with a >90% indicine genome (also indicine type 3¹⁹, Group 10B⁴³).

Cattle from Northeast Asia and northern China have typical taurine morphological features. Its genetic distinctiveness and old origin evolved from the unique mtDNA haplogroup T4 found in modern breeds from Japan, Korea, Mongolia^{6,44}, Siberia (Yakut cattle)⁹, northern China^{7,8} (Supplementary Fig. S5A) and in ancient cattle in northern China from 2300–4500 BP⁵. In addition, a separate position of Japanese and Korean cattle was found in previous study²⁵. In this study, we found that northern Chinese, South Korean and Japanese cattle share genetic ancestry with the Siberian Yakut and the indigenous northeastern China close to Korea. These breeds represent the eastern range of Turano-Mongolian cattle, which have retained their original dark-brown coat color pattern in Mongolian and Korean cattle.

The admixture pattern, however, suggests European cattle influence to northern Chinese cattle diversity. Possibly migrations of nomads in the steppes of Central Asia and Mongolia, which in the Middle Ages led to the establishment of the Mongolian empire, facilitated eastward as well as westward gene flow across Eurasia. Additionally, in the past few decades programs have been implemented in China to upgrade productivity by crossing local breeds with European breeds^{3,12}. Influence of European cattle was captured by model-based clustering analysis, e.g. Brown Swiss and Simmental in Kazakh, Holstein in LS, and Limousine in LX, JN and WL (Fig. 3).

Position	XtX	Bfmc				Closest RefSeq gene
		env. PC1	env. PC2	env. PC3	morpho. PC1	
BTA02: 61.5–62.5	—	61.89 (25.50; 2)	—	—	—	<i>LCT</i> (61.87–61.92)
BTA03: 33.0–34.5	—	33.98 (15.14; 2)	—	—	—	<i>AMPD2</i> (33.93–33.94)
BTA03: 46.5–48.0	—	47.34 (24.04; 2)	—	—	—	<i>PAPSS1</i> (47.27–47.67)
BTA03: 90.0–91.5	—	90.55 (22.17; 3)	—	—	—	<i>PLPP3</i> (90.19–90.27)
BTA04: 30.0–31.0	—	30.04 (22.70; 2)	—	—	—	<i>SP4</i> (30.32–30.41)
BTA05: 17.5–19.0	—	18.02 (35.87; 2)	—	—	—	<i>TMTC3</i> (17.99–18.05)
BTA05: 69.5–71.0	70.34 (64.00; 2)	70.31 (17.19; 1)	—	70.34 (18.64; 1)	70.34 (26.72; 3)	<i>RFX4</i> (70.22–70.39)
BTA06: 17.5–19.0	18.29 (44.13; 2)	—	—	—	—	<i>LEF1</i> (18.33–18.45)
BTA06: 39.5–41.5	39.84 (40.33; 3)	41.25 (17.72; 1)	—	39.84 (25.61; 1)	40.33 (20.22; 1)	<i>SLIT2</i> (41.24–41.64)
BTA06: 46.0–47.5	—	46.79 (26.40; 2)	—	—	—	<i>SELLL3</i> (46.79–46.88)
BTA06: 73.5–75.0	—	74.35 (22.14; 2)	—	—	—	<i>IGFBP7</i> (74.07–74.15)
BTA06: 105.0–106.5	—	105.63 (16.52; 2)	—	—	—	<i>STK32B</i> (105.52–105.89)
BTA08: 59.5–60.5	—	—	—	—	60.00 (16.98; 2)	<i>UNC13B</i> (59.79–60.01)
BTA08: 81.0–82.0	81.57 (34.93; 1)	81.57 (23.66; 2)	—	—	—	<i>GAS1</i> (81.50–81.51)
BTA08: 111.5–113.0	—	112.13 (22.78; 2)	—	—	—	<i>PHF19</i> (112.14–112.16)
BTA10: 31.0–32.5	31.66 (33.71; 2)	—	—	—	—	<i>COP55</i> (31.70–31.70)
BTA11: 9.00–10.5	—	9.91 (20.55; 2)	—	—	—	<i>SEMA4F</i> (9.94–9.97)
BTA11: 22.5–24.5	—	23.09 (45.17; 3)	—	23.80 (16.19; 1)	—	NA
BTA12: 34.0–35.5	—	34.68 (20.72; 2)	—	—	—	<i>TNFRSF19</i> (34.67–34.76)
BTA12: 78.0–79.0	—	78.61 (16.86; 2)	—	—	—	<i>RAP2A</i> (78.51–78.55)
BTA13: 45.5–48.5	47.02 (44.22; 10)	46.08 (28.49; 1)	—	48.09 (45.17; 1)	—	<i>DIP2C</i> (46.89–47.18); <i>PROKR2</i> (47.91–47.92)
BTA13: 50.5–52.0	51.42 (36.09; 2)	—	—	—	50.7 (16.42; 2)	<i>ADRA1D</i> (51.37–51.39); <i>UBE2E3</i> (50.38–50.65)
BTA13: 53.0–54.5	53.81 (39.73; 2)	—	—	—	—	<i>SIRPB1</i> (53.90–53.94)
BTA15: 52.0–53.5	—	52.80 (25.87; 2)	—	—	—	<i>CLPB</i> (52.66–52.80)
BTA20: 67.5–69.0	—	68.40 (17.23; 2)	—	—	—	<i>ADAMTS16</i> (67.94–68.14)
BTA21: 27.5–29.0	—	28.20 (27.59; 2)	—	—	—	<i>KLF13</i> (28.22–28.22)
BTA24: 39.5–40.5	—	40.49 (20.22; 2)	—	—	—	<i>LAMA1</i> (40.35–40.51)

Table 2. Regions consisting of overlapping windows each containing at least one SNP with XtX score >32.2 or at least one Bfmc score >15 identified by BayPass whole genome scan. For each XtX or Bfmc test, the table gives the peak position in Mb as well as the peak statistics value and the number of SNPs in parentheses with a test value above the corresponding threshold. Dash (—) indicates non-significant results.

From north to south, levels of taurine autosomal, mitochondrial and Y-chromosomal DNA decrease, but are still appreciable in southwestern China (Supplementary Figs S3 and S5). The occurrence of indicine mtDNA in mixed taurine-indicine cattle is a unique feature of Chinese breeds¹¹. The high taurine mtDNA diversity in southern China (Supplementary Fig. S5C) indicates an absence of a major founder effect. This is more compatible with immigration before the arrival of indicine cattle around 3000 BP than with a later introgression into an existing indicine population. The immigration of zebu from the present Myanmar and Indochina to the north with a plausible contribution of an eastward gene flow in western China¹⁵ resulted in significant indicine components in northern Chinese and Mongolian cattle (Supplementary Figs S3 and S5). The pattern of indicine mtDNA diversity (Supplementary Fig. S5C) suggests a population bottleneck when they crossed the Pearl River in southeastern China.

Y-chromosomal and autosomal indicine components correlate well (Fig. 6). Exceptions are the Guanlin (GL) and Nanyang (NY) breeds with relatively low indicine Y-chromosomal frequencies. Remarkably, the indicine autosomal component has a discontinuous distribution (Figs 2–4; Supplementary Fig. S3) with the largest gap across the Yellow River separating JN (29% zebu) from ES (61%) and NY (64%). This river might be a physical barrier of gene flow, but this cannot explain the absence in our panel of cattle with an indicine component between 35% and 61%. It might be hypothesized that in cattle with equal taurine and indicine components, outbreeding depression outweighs heterosis, for instance by incompatibility of genes from different origins conferring fitness⁴⁵. It is again remarkable that cattle at both sides of the river are categorized as belonging to the Huanghuai group and resemble western Asian and African cattle because of their similar cervico-thoracic hump².

The NeighborNet shows that indicine cattle from far southwestern China (DH, BN), which are found in the west of the Mekong River, are more closely related to Thai cattle than to southeastern Chinese cattle. This is also supported by the PCA and admixture patterns (Figs 2 and 3). The separate position of Thai cattle confirms the results of previous study¹⁴. The Mekong River acted also as a genetic barrier for swamp buffalo⁴⁶.

Another potential source of diversity in southern Chinese cattle are the introgressions from other bovine species living in China and Southeast Asia, including yak, gaur and its wild ancestor gaur⁴³, and banteng, represented by its domestic relative Bali cattle. (Fig. 3; Supplementary Fig. S2). There are several examples of hybridization of different bovine species. Yak mtDNA has been detected in indigenous cattle distributed on the Qinghai-Tibetan plateau and in Diqing cattle (DQ) of Yunnan province^{21,23}. We did not detect yak mtDNA in our cattle panel, but we detected influence of yak in the Tibetan LZ population based on the model-based clustering analysis.

A study of blood protein polymorphism²⁶ suggested banteng ancestry in Hainan cattle. Using mtDNA and microsatellite genotyping, Mohamad *et al.*⁴⁷ characterized banteng admixture in Indonesian zebu breeds. This was confirmed by 50 K SNP analysis²⁵, which also detected a low level of banteng introgression in southern Chinese breeds. However, analyzing Chinese cattle together with both banteng (represented by its domestic derivative Bali cattle) and gaur (the wild ancestor of gaur) with model based clustering (Fig. 3) and *f₄*-statistics (Fig. 5) provided consistent evidence of both gaur and banteng introgression into WL, WN and HN breeds from southeastern China and also into Thai zebu at a relatively low proportion.

Conversely, similar *f₄*-statistics (Supplementary Fig. S4) suggested introgression of zebu into gaur, which has been confirmed in the gaur population from Yunnan carrying both indicine and taurine mitochondrial genomes²⁰. Similarly, cattle introgression has been detected in yak populations²⁴.

The genetic variation described above reflects the combined effect of prehistoric immigrations of taurine and indicine cattle, subsequent gene flow between populations, local selection objectives and environmental adaptation. Indigenous Chinese cattle with indicine-aurine ratios varying between zero and one and subject to a broad range of climates is a valuable resource to identify potential genomic regions and functional genes underlying the environmental adaptation. By combining signals of population differentiation (XtX) and association with three synthetic environmental covariables and one synthetic morphological covariable (Supplementary Fig. S6), we identified 27 genomic regions and 28 candidate genes targeted by natural or artificial selection (Table 2).

Interestingly, 12 out of the 27 regions overlap with core selective sweep (CSS) regions⁴⁸, while 20 and 23 regions overlap with breed-wise and breed group-wise hotspots of selective sweeps, respectively⁴⁹ (Supplementary Table S5). However, we report for the first time the region BTA12: 34.0–35.5 Mb, which harbors *TNFRSF19*. This member of the TNF-receptor superfamily⁵⁰ is highly expressed during embryonic development⁵¹.

In other studies, strong signals of selection in tropical cattle have been detected on BTA5^{32,39,52,53}. Notably, Porto-Neto *et al.*³² identified a 20 Mb region on BTA5 with effects on parasite resistance, yearling weight, body condition score, coat color and penile sheath score. We found a significant signature of selection for XtX and the environmental PC1 and PC3 as well as the morphological PC1 on BTA5 region 69.5–71.0 (Table 2), which contains the candidate gene *RFX4*. This gene is a member of Regulatory Factor X (RFX) family of transcriptional regulators that influence MHC class II expression⁵⁴ and play a critical role in brain development^{19,55}. It was also found to affect heifer fertility in tropical composition breed Brangus⁵⁶.

Coat color is an important target of selection in many domestic animals. The common denotation of yellow cattle for the indigenous Chinese cattle refers to its predominant light to dark brown color. In current study, selection signatures were identified near several known color genes, including *KITLG* (near SNP BTA-74300-no-rs on BTA5)^{57,58}, and *LEF1*^{32,59} (here indicated by a peak in the XtX GWAS on BTA6). These genes and another candidate gene *MCM6* (near ARS-BFGL-NGS-92772 on BTA2, also identified by Hudson *et al.*⁵³) overlap with pigmentation QTL regions underlying UV-protection⁶⁰. The environmental PC1 signal near *IGFBP7* and the combined XtX-morphological signal near *ADRAID* (Table 2) are close to the coat color genes *KIT*^{60,61} and *ATRN*^{60,62}, respectively.

We further detected an environmental PC1 association signal near *SP4* (Sp4 transcription factor) as novel candidate gene on BTA4. Interestingly, this signal is overlapped with a selection signature region in African cattle³⁴. *SP4* is a member of the Sp1-family of zinc finger transcription factors and is required for normal murine growth, viability, and male fertility⁶³. In cattle, *SP4* was suggested to have effect on body size and testicular growth from birth to yearling age⁶⁴. In human, diseases associated with *SP4* include bipolar disorder⁶⁵ and schizophrenia⁶⁶.

It is interesting to note that Chinese and African cattle have developed independently a variable taurine-indicine ancestry following a gradient from tropical to temperate climates. An attractive opportunity is a detailed comparison of gene variants involved in climate adaptation by using whole genome sequence data³⁴. It may be anticipated that in both regions adaptation to agro-ecological constraints is mediated by recruiting and combining gene variants from taurine and indicine origins with possible original contributions in Chinese indigenous cattle from the indicine mtDNA, and the minor gaur, and banteng and yak genomic ancestry.

Methods

Ethics statement. The protocols for collection of the blood and hair samples of experimental individuals were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) at China Agricultural University. All experiments were performed in accordance with approved relevant guidelines and regulations.

Samples collection and genotyping. We collected samples of 437 animals from 24 populations (Table 1), twenty of which are indigenous cattle populations from northeastern China, central China, southeastern China, southwestern China, far southwestern China and or TAR (Fig. 1). We also examined Bangladeshi cattle and German Simmental, and two related bovine species, the gaur and yak. Samples were genotyped with Illumina BovineSNP50 BeadChip using standard procedures⁶⁷. Genotypes are accessible via the WIDDE repository (<http://widde.toulouse.inra.fr/widde/>).

We compared these newly generated data with published genotypes of some European and Asian cattle breeds, Bali cattle and gaur (Table 1). The combined data set comprises 37,429 SNPs. Using PLINK⁶⁸, we removed SNPs with call rates <90% or with minor allele frequencies <0.001 and discarded individuals with 10% missing genotypes. The resulting data set contained 36,872 SNPs and 736 animals from 44 populations representing taurine

cattle, zebu, and three species related to cattle (*Bos javanicus* - banteng, *Bos gruniens* - yak and, *Bos frontalis* - gayal). Gaur (*Bos gaurus*)⁶⁹ was used instead of gayal in *f4* analysis (see below) of the species composition of Chinese cattle because of the indicine zebu introgression into gayal.

Population genetic analysis. We used PLINK⁶⁸ to calculate the observed homozygosity for each population. Three complementary methods were used to analyze the genetic diversity among populations. First, a Principal Component Analysis (PCA) was carried out to investigate the pattern of genetic differentiation among populations and individuals using the R package SNPRelate⁷⁰, which performs eigen-decomposition of the genetic covariance matrix to compute the eigenvalues and eigenvectors. Second, population structure was evaluated by unsupervised and supervised model-based hierarchical clustering implemented in the Admixture software⁷¹. The results were visualized using the program Distruct⁷². Third, a NeighbourNet network was constructed using Reynold's distances between populations using Splitstree 4.13⁷³.

To investigate species composition of Chinese cattle, we used the four-population test (*f4*-statistics) implemented in ADMIXTOOLS⁷⁴. Additionally, taurine and indicine ancestries in Chinese cattle populations were quantified via the *f4* ratio estimation in ADMIXTOOLS, which allows inference of the admixture proportions without access to accurate surrogates for the ancestral populations⁷⁴. The proportion of taurine ancestry was then computed as

$$\alpha = \frac{f4(A, O; X, C)}{f4(A, O; B, C)}$$

in which O is an outgroup (BAL), B a reference taurine cattle (YKT), C an Indian zebu cattle (GIR), A a population related to B (SH), and X the Chinese target population. Standard errors were computed with the Block Jackknife procedure in ADMIXTOOLS using default options⁷⁴.

Mitochondrial DNA and Y-chromosomal markers. A 445-bp mtDNA control region was amplified and sequenced as described previously (GenBank accession codes KY682307-KY682687)²⁰. A total of 381 newly generated sequences were analyzed together with published sequences (Supplementary Tables S2 and S3). Haplotype diversity of the segment 16,023–16,262 (numbering according to GenBank accession no. V00654) was computed using the software DnaSP⁷⁵. Y-chromosomal genotyping was carried out for 140 samples (Table S2) with the protocol described by Bonfiglio *et al.* (2012)⁷⁶, which differentiates Y1 (dominant in north Europe) and Y2 (dominant in other taurine cattle) and Y3 (indicine cattle) type Y chromosome⁷⁷.

Genome-scan for adaptive differentiation and association with environmental and morphological covariables. Whole genome-scans for adaptive differentiation and association with population-specific co-variables were performed with BayPass 2.1⁵⁷. The underlying models explicitly account for the covariance structure among the population allele frequencies, which make the approach particularly robust to complex demographic histories⁵⁷. Identification of overly differentiated SNPs was based on the XtX statistics^{57,78} estimated under the core model of BayPass. To calibrate the XtX's, a pseudo-observed data set (POD) containing 250,000 SNPs simulated under the inference model with hyperparameters equal to those estimated on the real data set was generated and further analyzed under the same conditions following the procedure described in Gautier⁵⁷. In particular, we ensured that the posterior estimate of the scaled covariance matrix of population allele frequencies (Omega) obtained with the POD was similar to that obtained on the real data since the FMD distance between the two matrices was found equal to 0.28⁵⁷. Similarly, the posterior means of the two hyperparameters *a* and *b* for the Beta distribution of across population allele frequencies obtained on the POD (*a* = *b* = 1.02) were almost equal to the ones obtained in the original data (*a* = *b* = 1.00). Taken together, these sanity checks indicated that the POD faithfully mimics the real data set, allowing us to define a 0.1% significance threshold on the XtX statistics (XtX = 32.3) to identify genomic regions harboring footprints of selection.

We collected values for six environmental covariables, i.e. average temperature, average relative humidity, sunshine, average air pressure, wind speed, and precipitation from China Meteorological Administration (<http://data.cma.cn/>). Values for 10 morphological covariables, i.e. male body weight, female body weight, male height, female height, male body length, female body length, male heart girth, female heart girth, male fore-shank circumference, and female fore-shank circumference were provided for 17 out of the 20 studied indigenous breeds in National Commission of Animal Genetics Resources³, but these data were not available for the populations LZ, BN and HH. We carried out a PCA on scaled variables for environmental and morphological co-variables separately. The first three environmental PCs and the first morphological PC were retained as uncorrelated co-variables for association studies (Supplementary Tables S6 and S7).

Genome-wide analysis of association with population specific co-variables was carried out using the default options of the AUX model parameterized with the scaled covariance matrix (Omega) obtained on the real data set as described above. This model allows to account explicitly for multiple testing issue by integrating over (and estimating) the unknown proportion of SNPs actually associated with a given covariable. The support for association of each SNP with each co-variable was evaluated by computing Bayes Factor (BF) and a BF > 15 is considered as decisive evidence for association⁵⁷.

As a matter of expedience, we applied a sliding window approach to identify the main genomic regions of interest as described in previous study⁵⁷. Briefly, the UMD3.1 bovine genome assembly⁷⁹ on which all the SNPs were mapped was first split into 4718 consecutive 1-Mb windows (with a 500-kb overlap). For each window, we counted the number *n_s* of SNPs that were either significantly differentiated at the 0.1% threshold (i.e., with XtX > 32.3) or associated (BF > 15) with at least one of the four population-specific covariables. Windows with *n_s* >= 2 were deemed significant and overlapping windows were further merged.

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Author Contributions

Y.Z., J.A.L. and M.G. conceived the experiments. Y.G., M.G., X.D., H.Z., Y.W., X.W., M.O.F., J.L., S.Y., X.G., J.H., J.A.L. and Y.Z. contributed samples. Y.G., M.G., J.A.L. and Y.Z. analysed the data. Y.G., M.G., J.A.L. and Y.Z. prepared the original draft. J.H., J.A.L. and Y.Z. reviewed and edited the paper.

Additional Information

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