Species composition and environmental adaptation of indigenous Chinese cattle

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Abstract

Indigenous Chinese cattle combine taurine and indicine origins and occupy a broad range of different environments. By 50K 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 *f4*-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.

Introduction

China harbors around 10 million of indigenous cattle[1]. 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 BP[4]. This is supported by the evidence that ancient cattle from northern China, dated 4500 to 2300 BP, carried only taurine mtDNA haplotypes[5]. A unique mtDNA haplotype, T4, observed in East Asian cattle breeds[6-9] is a subtype of the common haplogroup T3[10], suggesting a founder effect in Chinese taurine cattle[11].

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 China[15].

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 China[3]. This has been confirmed by genetic studies using mtDNA[7,8,16,17] and Y-linked markers[18]. A genetic diversity study using microsatellite markers clustered Chinese indigenous cattle breeds into one taurine and four indicine groups[19].

In addition to taurine and indicine cattle, several other bovine species have been living in southern China and Southeast Asia, including banteng, gaur or gayal, 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 origin[20]. 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 China[26], which was confirmed by genomic SNP array data[25].

Genomic SNP array has become a powerful tool for population genomics studies in animals. A recent genomic variation study by Decker *et al.* revealed a worldwide pattern of genetic admixture in domestic cattle[25]. Other studies focused on Creole[27], American[28], East African zebu[29] and Korean cattle[30]. These advanced approaches also allow the genomic localization of genes involved in the adaptation to natural or artificial selective constraints[27,31-33]. In the current study, we generated 50K 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 Hazak 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 cattle[34]. 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 species[35].

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

99 taurine breeds from northern China and TAR cluster with European breeds while populations from
100 southeastern and far-southwestern China are closer to Indian zebu. The second component
101 accounting for 3.1% of all variation displays the contrast of Chinese cattle to other bovine species
102 (Bali, gayal and yak) and also differentiates European cattle breeds. The intermediate positions of
103 LZ, MAD, BRE, Bali and gayal populations indicate gene flow between species.

104 In an analysis of only Asian cattle (Fig. 2b), the first PC that explains 14.5% of the genetic
105 variation again corresponds to the taurine-indicine separation, but the second PC that explains
106 1.45% of the genetic variation represents a gradient from India via Southeast Asia to Southeastern
107 China.

108

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

119 Figure 3b shows a supervised clustering with prior population information for taurine breeds
120 (SH, HOL, BSW, SIM), indicine breeds (GIR, SAHW) and other bovine species. In this analysis,
121 Bali cattle represents the banteng and the domestic gayal replaces the wild gaur since the latter
122 was too inbred for this analysis. This analysis reproduces the zebu-banteng hybridization in
123 Indonesia[36] and yak introgression into Tibetan cattle, but also suggests minor banteng and gayal
124 and southeastern China (Supplementary Fig. S2). Supplementary Figure S3 shows the geographic
125 distribution of the inferred species components.

126

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

134

135 *Population mixture.* The taurine-indicine mixed composition of Chinese cattle was confirmed by
136 the sensitive *f4* ratio test (Supplementary Table S1). The estimated taurine ancestry ranges from
137 close to 0.0 in southeastern China to close to 1.0 in north, with intermediate values ranging from
138 0.282 to 0.760, from 0.240 to 0.320 and from 0.656 to 0.770 in central China, southwestern China
139 and TAR, respectively. This pattern was highly correlated with the average memberships
140 estimated by model-based clustering (r=998, Supplementary Table S1).

141 As shown in Fig. 5a, negative values of the four-population *f4*-statistics (GIR, X; BAL,YAK)
142 suggests gene flow from Bali to indicine populations in southeastern China and Southeast Asia.
143 This gene flow has clearly been more consequential for the Indonesian cattle breeds, MAD, BRE
144 and PES as well as the southern Chinese breeds LP, HN, WN and WL. For the Indonesian breeds
145 this confirms previous results of Mohamad *et al.*[36] and Decker *et al.*[25]. Although Bali cattle are
146 relatively closely related to gaur, replacing Bali cattle by gaur as source of admixture generates
147 only a moderately negative value for the Indonesian breeds (Fig. 5b). This is even observed for
148 Bali cattle as a test breed and may reflect the inbreeding of the gaur samples. However, the same
149 plot shows relatively low (*i.e.*, negative, indicating gene flow) values for the southern Chinese
150 breeds. In combination with the supervised model-based clustering (Fig. 3b), this may suggest that
151 these breeds have been introgressed by gaur and/or gayal in addition to banteng, the wild ancestor
152 of Bali cattle.

153 A *f4*(SH,X;GAY,YAK) plot (Supplementary Fig. S4A) generated negative values for the
154 indicine GIR, SAHW and BD as test breeds. Since this is not observed with the wild gaur instead
155 of the domestic gayal (Supplementary Fig. S4B), this indicates indicine introgression into the
156 domestic gayal population. This is confirmed by two other observations:

157 • The statistic *f4*(GAU,GAY;X,YAK) is negative for all test breeds, but clearly more negative
158 for indicine than for taurine breeds (Supplementary Fig. S4C).

159 • *f4*(GIR,BAL;GAY,YAK) is positive but *f4*(GIR,BAL;GAU,YAK) is not (Supplementary Fig.
160 S4D; Fig. 5B). The same patterns are also observed if GIR is replaced by SH (Supplementary
161 Fig. S4A, B), which is phylogenetically close to the indicine GIR. Apparently the allele
162 sharing of GAY with GIR or SH outweighs the allele sharing expected because of the
163 phylogenetic relationship of gayal and Bali cattle, which most likely is an effect of the
164 ascertainment bias of the SNP panel towards taurine breeds[37].

165

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

173

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

178 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. 7). From 30 SNPs associated with morphological covariables (Supplementary Table S4), SNP ARS-BFGL-NGS-67505 on BTA25 was most significant (Fig. 7).

As a matter of expedience, we applied a sliding window approach to identify the main genomic regions of interest as described in Gautier[38]. Briefly, the UMD3.1 bovine genome assembly[39] 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. This yielded 27 significant regions detailed 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 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 adaption and morphological differentiation in Chinese cattle.

Previous genetic diversity studies using mtDNA and Y-linked markers have characterized a

206 north-south gradient of taurine and indicine admixture in Chinese cattle, which is consistent with
207 the transition from humpless to humped morphology[7,8,16-18]. A microsatellite study differentiated
208 five groups of Chinese indigenous cattle breeds[19].

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

213 • Cattle from Manchuria, Inner Mongolia and northwestern China with 4 to 8% indicine
214 admixture. This group corresponds to the taurine type 1[19] (this type also comprises Tibetan
215 cattle) and to Group 9B in the Felius classification[40].

216 • Taurindicine cattle in TAR and northern China above the Yellow or Wei River with 28 to 35%
217 indicine admixture, denoted as zebu type 2[19] and belonging to the Huanghuai group of central
218 Chinese cattle (Group 10A)[40].

219 • Taurindicine cattle below the Yellow River with 61 to 73% indicine genome, corresponding
220 to indicine types 1 and 4[19]. The northernmost LX, JX and NY breeds belong to the Huanghai
221 group (Group 10A)[40], but the other breeds to the Changzu group (Group 10B)[40].

222 • Predominant indicine cattle in southern China with an indicine genomic component of 79 to
223 87% (zebu type 3[19], Group 10B[40]).

224 • Indicine cattle with a >90% indicine genome (also indicine type 3[19], Group 10B[40]).

225 Cattle from Northeast Asia and northern China have typical taurine morphological features.
226 Its genetic distinctiveness and old origin evolved from the unique mtDNA haplogroup T4 found in
227 modern breeds from Japan, Korea, Mongolia[6,41], Siberia (Yakut cattle)[9], northern China[7,8]
228 (Supplementary Fig. S5A) and in ancient cattle in northern China from 2300-4500 BP[5]. In
229 addition, Decker *et al*. found a separate position of Japanese and Korean cattle[25]. In this study, we
230 found that northern Chinese, South Korean and Japanese cattle share genetic ancestry with the
231 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 Kazak, Holstein in LS, and Limousine in LX, JN and WL (Fig. 3).

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 breeds[11]. 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 zebus from the present Myanmar and Indochina to the north with a plausible contribution of an eastward gene flow in western China[15] 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 fitness[42]. 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 hump[2].

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 Wangkunmhang *et al.*[14]. The Mekong River acted also as a genetic barrier for swamp buffalo[43].

Another potential source of diversity in southern Chinese cattle are the introgressions from other bovine species living in China and Southeast Asia, including yak, gayal and its wild ancestor gaur, 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 polymorphism[26] suggested banteng ancestry in Hainan cattle. Using mtDNA and microsatellite genotyping, Mohamad *et al.*[44] characterized banteng admixture in Indonesian zebu breeds. This was confirmed by 50K SNP analysis[25], 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 gayal) with model based clustering (Fig. 3) and *f4*-statistics (Fig. 5) provided consistent evidence of both gayal 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 gayal, which has been confirmed in the gayal population from Yunnan carrying both indicine and taurine mitochondrial genomes[20]. Similarly, cattle introgression has been detected in yak populations[24].

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-taurine 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 adaption. 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) regions[45], while 20 and 23 regions overlap with breed-wise and breed group-wise hotspots of selective sweeps, respectively[46] (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 superfamily[47] is highly expressed during embryonic development[48].

In other studies, strong signals of selection in tropical cattle have been detected on BTA5[32,34,49,50]. Notably, Porto-Neto *et al.* identified a 20 Mb region on BTA5 with effects on parasite resistance, yearling weight, body condition score, coat color and penile sheath score[32]. We found a significant signature of selection for XtX and the environmenmtal PC1 and PC3 as well as the morphological PC1 in the region 69.5-71.0 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 expression[51] and play a critical role in brain development[19,52]. It was also found to affect heifer fertility in tropical composition breed Brangus[53].

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)[38,54], and *LEF1*[32,55] (here indicated by a peak in the XtX GWAS on BTA6). These genes and another candidate gene *MCM6* (near ARS-

315 BFGL-NGS-92772 on BTA2, also identified by Hudson *et al*.[50]) overlap with pigmentation QTL
316 regions underlying UV-protection[56]. The environmental PC1 signal near *IGFBP7* and the
317 combined XtX-morphological signal near *ADRA1D* (Table 2) are close to the coat color genes
318 *KIT*[56,57] and *ATRN*[56,58], respectively.

319 We further detected an environmental PC1 association signal near *SP4* (Sp4 transcription
320 factor) as novel candidate gene on BTA4. It is a member of the Sp1-family of zinc finger
321 transcription factors and is required for normal murine growth, viability, and male fertility[59]. In
322 cattle, *SP4* was suggested to have effect on body size and testicular growth from birth to yearling
323 age[60].

324 It is interesting to note that Chinese and African cattle have developed independently a
325 variable taurine-indicine ancestry following a gradient from tropical to temperate climates. An
326 attractive opportunity is a detailed comparison of gene variants involved in climate adaptation by
327 using whole genome sequence data[61]. It may be anticipated that in both regions adaptation to agro-
328 ecological constraints is mediated by recruiting and combining gene variants from taurine and
329 indicine origins with possible original contributions in Chinese indigenous cattle from the indicine
330 mtDNA, and the minor gayal, and banteng and yak genomic ancestry.

331

332 Methods

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

337

338 **Samples collection and genotyping.** We collected samples of 437 animals from 24 breeds
339 (Table 1), twenty of which are indigenous cattle populations from northeastern China, central
340 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 gayal and yak. Samples were genotyped with Illumina BovineSNP50 BeadChip using standard procedures[62]. 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 PLINK[63], 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*)[64] 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 PLINK[63] 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 SNPRelate[65], 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 software[66]. The results were visualized using the program Distruct[67]. Third, a NeighbourNet network was constructed using Reynold's distances between populations using Splitstree 4.13[68].

To investigate species composition of Chinese cattle, we used the four-population test (*f4*-statistics) implemented in ADMIXTOOLS[69]. 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 populations[69]. 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 options[69].

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]. These 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 DnaSP[70]. Y-chromosomal genotyping was carried out with the protocol described by Bonfiglio *et al.* (2012)[71], which differentiates Y1 (dominant in north Europe) and Y2 (dominant in other taurine cattle) and Y3 (indicine cattle) type Y chromosome[72].

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 2.1[38]. The underlying models explicitly account for the covariance structure among the population allele frequencies, which make the approach particularly robust to complex demographic histories[38]. Identification of overly differentiated SNPs was based on the XtX statistics[38,73] 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 Gautier[38]. 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 0.28[38]. 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.

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 association[38].

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 Resources[3], but these data were not available for the breeds 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).

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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

Competing financial interests: The authors declare no competing financial interests.

Figure legends

Figure 1. Geographical distribution of cattle populations. Detailed information is showed in Table 1. Map was created using R 3.3.1 packages *rworldmap*, *maps* and *mapproj* (https://cran.r-project.org/web/packages/). Package *rworldmap* was used to generate outline and colorful dots while packages *maps* and *mapproj* were used to add texts.

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**.**

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.

Figure 5. Visualization of *f4*-statistics. (a) *f4*-statistics of the form D (GIR, X; BAL, YAK) identified gene flow from Bali to other breeds. (b) *f4*-statistics of the form D (GIR, X; GAU, YAK) identified gene flow from Gaur to other breeds. The whiskers represent the standard error.

Figure 6. Correlation of autosomal, mtDNA and Y-chromosomal indicine components. Uniparental markers were used to build the correlation graph which showed a north-to-south taurine-indicine gradient that resembles closely the autosomal cline.

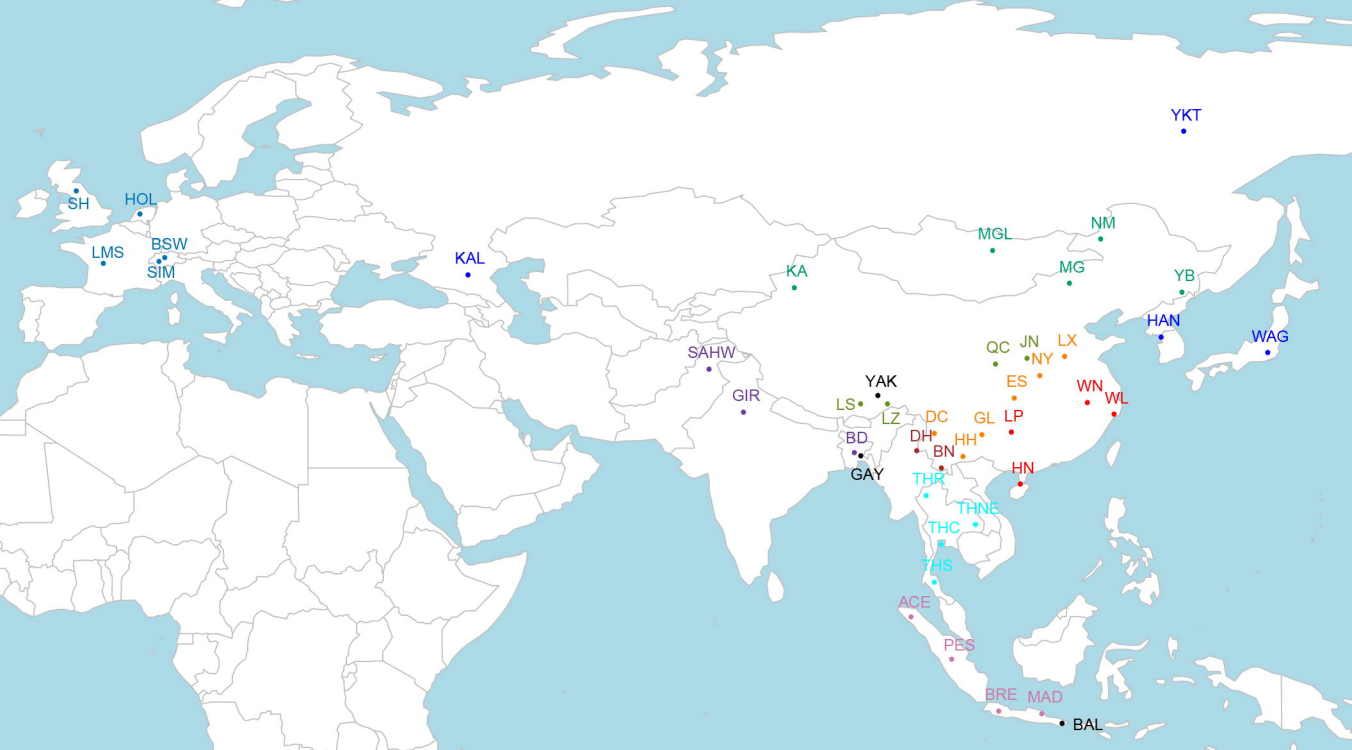
Figure 7. Whole genome scan for adaptive divergence and association analyses in 20 Chinese cattle breeds. (a) Manhattan plot of the XtX statistics. (b) Manhattan plot of the BFmc (association with environmental PC1). (c) Manhattan plot based on the BFmc (association with morphological PC1).

Population	Abbr.	Geographical Region	Type	N	Ho	Source[1]
Yanbian	YB	Northern China	taurine	26	0.291	1
Mongolian_XilinGol	MG	Northern China	taurine	31	0.319	1
Mongolian_HulunBuir	NM	Northern China	taurine	24	0.317	1
Kazakh	KA	Northwestern China	taurine	21	0.327	1
Linzhi	LZ	Tibet, China	taurine	19	0.285	1
Lhasa	LS	Tibet, China	taurine	14	0.305	1
Qinchuan	QC	Central China	mixed	32	0.297	1,2
Jinnan	JN	Central China	mixed	14	0.299	1
Nanyang	NY	Central China	mixed	23	0.252	1
Luxi	LX	Central China	mixed	16	0.258	1,2
Wannan	WN	Southeastern China	zebu	31	0.199	1
Wenling	WL	Southeastern China	zebu	31	0.177	1
Hainan	HN	Southeastern China	zebu	8	0.145	1,2
Liping	LP	Southwestern China	zebu	5	0.179	1
Enshi	ES	Southwestern China	mixed	31	0.237	1
Guanling	GL	Southwestern China	mixed	4	0.232	1
Honghe	HH	Southwestern China	mixed	12	0.248	1
Dengchuan	DC	Southwestern China	mixed	31	0.243	1
Banna	BN	Far southwestern China	zebu	14	0.186	1
Dehong	DH	Far southwestern China	zebu	16	0.161	1
Bangladesh Zebu	BD	Bangladesh	zebu	16	0.169	1
Gayal	GAY	Bangladesh	*Bos frontalis*	21	0.059	1
Yak	YAK	Tibet, China	*Bos grunniens*	12	0.029	1
Simmental	SIM	Germany	taurine	20	0.297	1
Hanwoo	HAN	Korea	taurine	8	0.288	2
Mongolian	MGL	Mongolia	taurine	5	0.301	2
Wagyu	WAG	Japan	taurine	12	0.248	2
Aceh	ACE	Indonesia	zebu	12	0.149	2
Pesisir	PES	Indonesia	zebu	6	0.142	2
Brebes	BRE	Indonesia	zebu	9	0.158	2
Madura	MAD	Indonesia	zebu	7	0.150	2
Sahiwal	SAHW	Pakistan	zebu	17	0.159	2
Gir	GIR	India	zebu	20	0.157	2
Bali cattle	BAL	Indonesia	*Bos javanicus*	20	0.026	2
Gaur	GAUR	India	*Bos gaurus*	10	0.000	7
Shorthorn	SH	England	taurine	20	0.257	2
Holstein	HOL	Netherlands	taurine	20	0.314	3
Brown Swiss	BSW	Switzerland	taurine	20	0.281	6
Limousin	LMS	France	taurine	20	0.309	6
Central Thailand	THC	Thailand	zebu	5	0.165	4
Northeast Thailand	THNE	Thailand	zebu	8	0.157	4
North Thailand	THR	Thailand	zebu	10	0.166	4
South Thailand	THS	Thailand	zebu	5	0.142	4
Kalmyk	KAL	Kalmyk, Russian	taurine	20	0.319	5
Yakut	YKT	Siberian, Russian	taurine	20	0.256	5
Total				756		

Table 1. Sampling information of different cattle populations and their observed heterozygosity (Ho). Source of data. 1) this study; 2) Decker *et al.* (2014); 3) Gautier *et al.* (2010); 4) Wangkunmhang *et al.* (2015); 5) Decker *et al.* (2016); 6) Matukumalli *et al.* (2009); 7) Decker *et al.* (2009).

Position	XtX	Bfmc				Closest RefSeq gene
		env. PC1	env. PC2	env. PC3	morpho. PC1	
BTA02 : 61.5 - 62.5	-	61.89 (25.50 ; 2)	-	-	-	*LCT* (61.87-61.92)
BTA03 : 33.0 - 34.5	-	33.98 (15.14 ; 2)	-	-	-	*AMPD2* (33.93-3394)
BTA03 : 46.5 - 48.0	-	47.34 (24.04 ; 2)	-	-	-	*PAPSS1* (47.27-47.67)
BTA03 : 90.0 - 91.5	-	90.55 (22.17 ; 3)	-	-	-	*PLPP3* (90.19-90.27)
BTA04 : 30.0 - 31.0	-	30.04 (22.70 ; 2)	-	-	-	*SP4* (30.32-30.41)
BTA05 : 17.5 - 19.0	-	18.02 (35.87 ; 2)	-	-	-	*TMTC3* (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)	*RFX4* (70.22-70.39)
BTA06 : 17.5 - 19.0	18.29 (44.13 ; 2)	-	-	-	-	*LEF1* (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)	*SLIT2* (41.24-41.64)
BTA06 : 46.0 - 47.5	-	46.79 (26.40 ; 2)	-	-	-	*SELL1L3* (46.79-46.88)
BTA06 : 73.5 - 75.0	-	74.35 (22.14 ; 2)	-	-	-	*IGFBP7* (74.07-74.15)
BTA06 : 105.0 - 106.5	-	105.63 (16.52 ; 2)	-	-	-	*STK32B* (105.52-105.89)
BTA08 : 59.5 - 60.5	-	-	-	-	60.00 (16.98 ; 2)	*UNC13B* (59.79-60.01)
BTA08 : 81.0 - 82.0	81.57 (34.93 ; 1)	81.57 (23.66 ; 2)	-	-	-	*GAS1* (81.50-81.51)
BTA08 : 111.5 - 113.0	-	112.13 (22.78 ; 2)	-	-	-	*PHF19* (112.14-112.16)
BTA10 : 31.0 - 32.5	31.66 (33.71 ; 2)	-	-	-	-	*COPS5* (31.70-31.70)
BTA11 : 9.00 - 10.5	-	9.91 (20.55 ; 2)	-	-	-	*SEMA4F* (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)	-	-	-	*TNFRSF19* (34.67-34.76)
BTA12 : 78.0 - 79.0	-	78.61 (16.86 ; 2)	-	-	-	*RAP2A* (78.51-78.55)
BTA13 : 45.5 - 48.5	47.02 (44.22 ; 10)	46.08 (28.49 ; 1)	-	48.09 (45.17 ; 1)	-	*DIP2C* (46.89-47.18) ; *PROKR2* (47.91-4792)
BTA13 : 50.5 - 52.0	51.42 (36.09 ; 2)	-	-	-	50.7 (16.42 ; 2)	*ADRA1D* (51.37-51.39) ; *UBE2E3* (50.38-50.65)
BTA13 : 53.0 - 54.5	53.81 (39.73 ; 2)	-	-	-	-	*SIRPB1* (53.90-53.94)
BTA15 : 52.0 - 53.5	-	52.80 (25.87 ; 2)	-	-	-	*CLPB* (52.66-52.80)
BTA20 : 67.5 - 69.0	-	68.40 (17.23 ; 2)	-	-	-	*ADAMTS16* (67.94-68.14)
BTA21 : 27.5 - 29.0	-	28.20 (27.59 ; 2)	-	-	-	*KLF13* (28.22-28.22)
BTA24 : 39.5 - 40.5	-	40.49 (20.22 ; 2)	-	-	-	*LAMA1* (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.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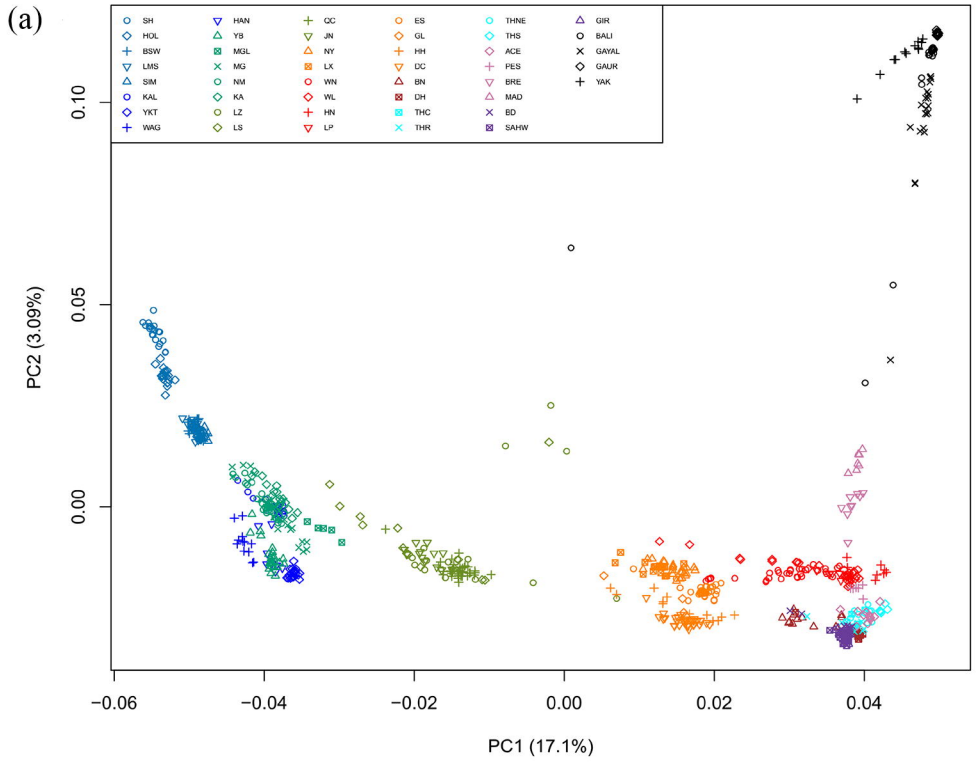
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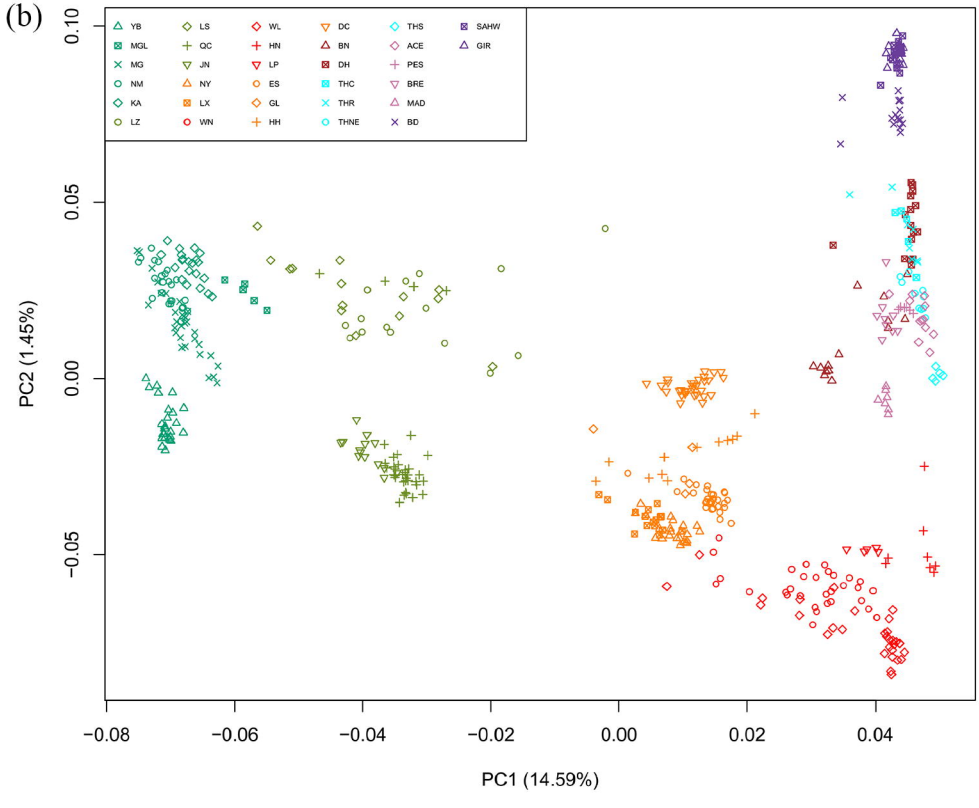
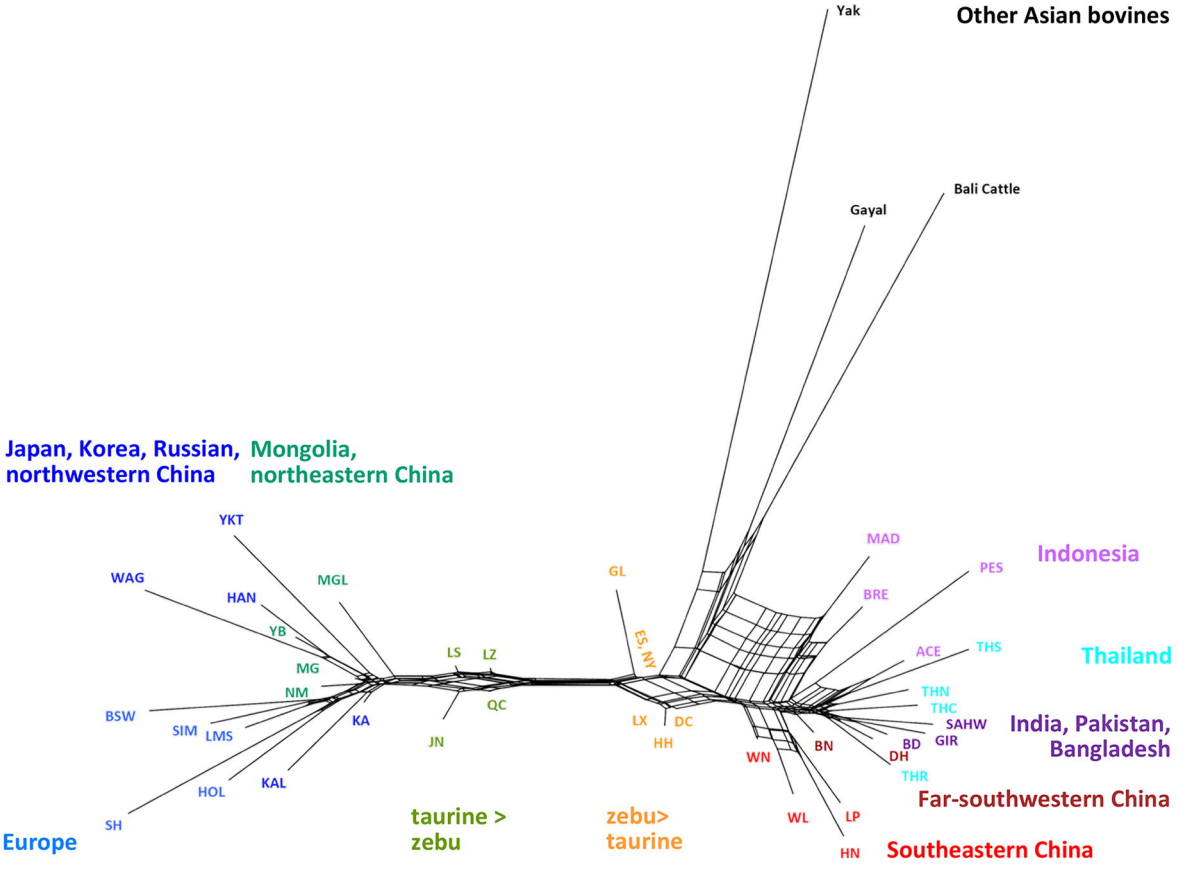
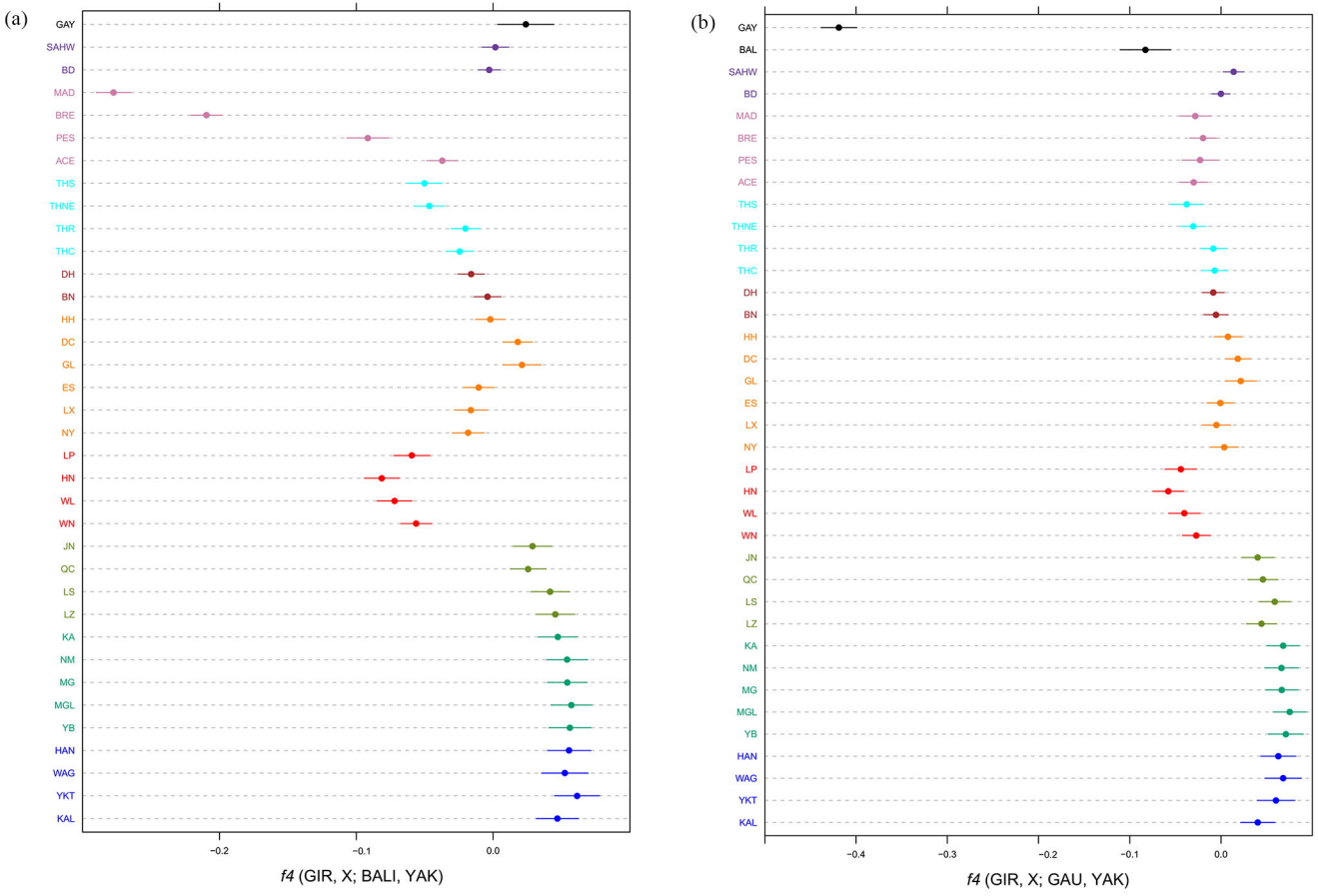
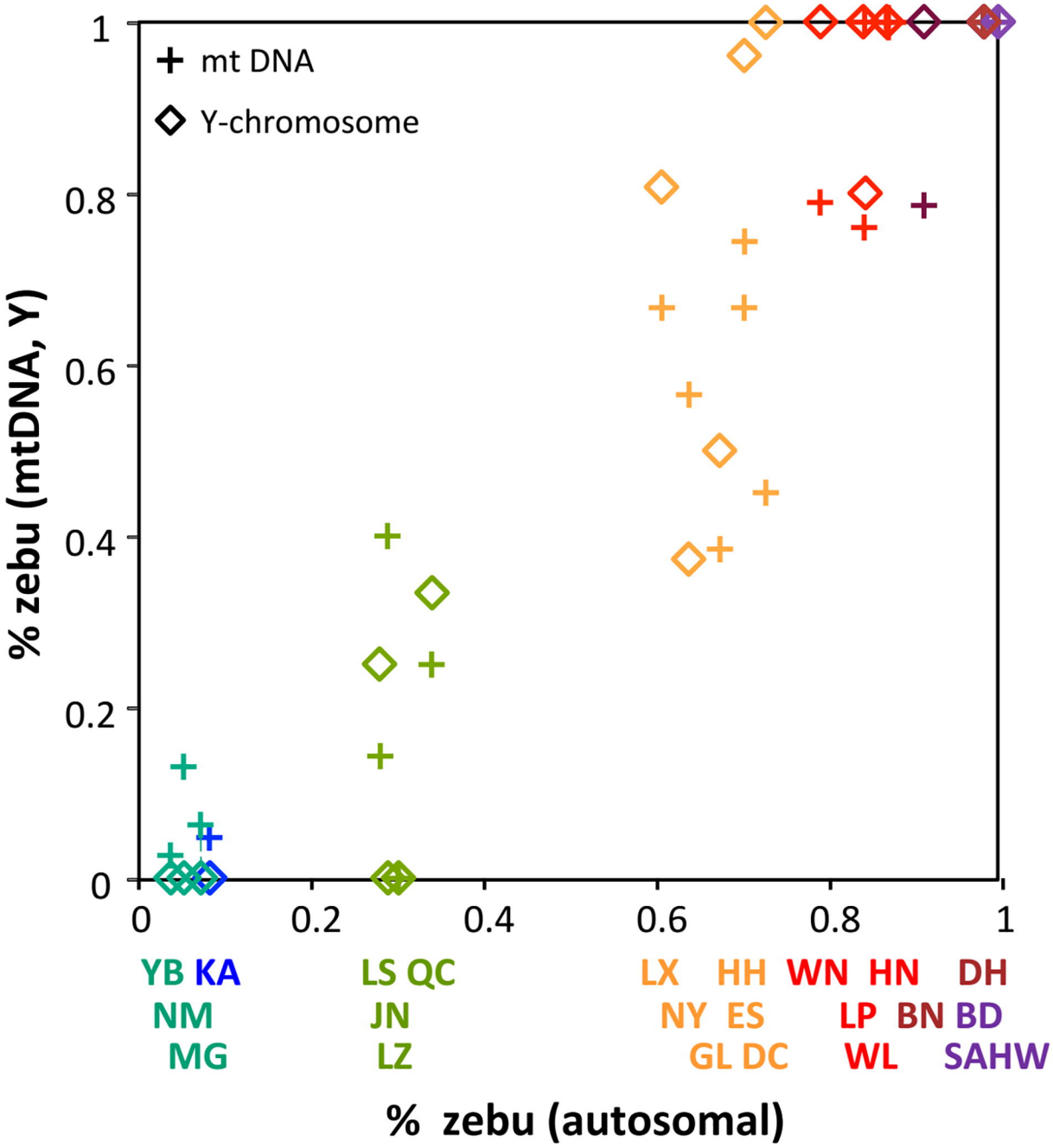
PC2 (3.09%)
−0.06
−0.04
−0.02
0.00
0.02
0.04
PC1 (17.1%)

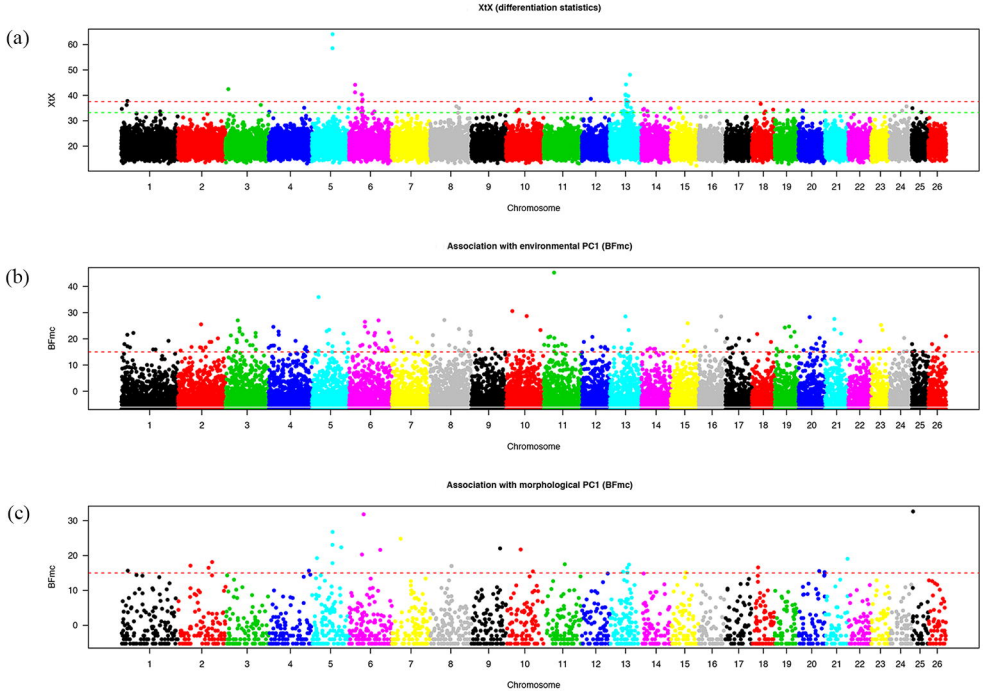

(b)
YB
MGL
MG
NM
KA
LZ
LS
QC
JN
NY
LX
WN
WL
HN
LP
ES
GL
HH
DC
BN
DH
THC
THR
THNE
THS
ACE
PES
BRE
MAD
BD
SAHW
GIR
0.10
0.05
0.00
−0.05
PC2 (1.45%)
−0.08
−0.06
−0.04
−0.02
0.00
0.02
0.04
PC1 (14.59%)

(a)
Europe
Russian
Northwestern China
Northeastern Asia
Mongolia
Northeastern China
Tibet, China
Central China
Southwestern China
Southeastern China
Far southwest China
Thailand
Indonesia
Bangladesh
Pakistan
India
Outgroup
SH HOL BSW LMS SIM KAL KA YKT WAG HAN MGL MG NM YB LZ LS QC JN NY LX ES GL HH DC WN WL HN LP BN DH THC THR THNE THS ACE PES BRE MAD BD SAHW GIR BAL GAY YAK
K=2
K=3
K=4
K=5
K=17
(b)
SH HOL BSW LMS SIM KAL KA YKT WAG HAN MGL MG NM YB LZ LS QC JN NY LX ES GL HH DC WN WL HN LP BN DH THC THR THNE THS ACE PES BRE MAD BD SAHW GIR BAL GAY YAK
K=5


Yak
Other Asian bovines
Gayal
Bali Cattle
Japan, Korea, Russian, northwestern China
Mongolia, northeastern China
YKT
WAG
MGL
HAN
YB
MG
NM
BSW
SIM
LMS
KA
HOL
KAL
SH
LS
LZ
QC
JN
GL
ES, NY
LX
DC
HH
MAD
PES
Indonesia
BRE
ACE
THS
Thailand
THN
THC
SAHW
GIR
India, Pakistan, Bangladesh
BD
DH
THR
BN
WN
WL
LP
HN
Far-southwestern China
Southeastern China
Europe
taurine > zebu
zebu> taurine


(a)
GAY
SAHW
BD
MAD
BRE
PES
ACE
THS
THNE
THR
THC
DH
BN
HH
DC
GL
ES
LX
NY
LP
HN
WL
WN
JN
QC
LS
LZ
KA
NM
MG
MGL
YB
HAN
WAG
YKT
KAL
−0.2
−0.1
0.0
f4 (GIR, X; BALI, YAK)
(b)
GAY
BAL
SAHW
BD
MAD
BRE
PES
ACE
THS
THNE
THR
THC
DH
BN
HH
DC
GL
ES
LX
NY
LP
HN
WL
WN
JN
QC
LS
LZ
KA
NM
MG
MGL
YB
HAN
WAG
YKT
KAL
−0.4
−0.3
−0.2
−0.1
0.0
f4 (GIR, X; GAU, YAK)


mt DNA
Y-chromosome
% zebu (mtDNA, Y)
1
0.8
0.6
0.4
0.2
0
0
0.2
0.4
0.6
0.8
1
YB KA
NM
MG
LS QC
JN
LZ
LX HH WN HN DH
NY ES LP BN BD
GL DC WL SAHW
% zebu (autosomal)


(a)
XtX (differentiation statistics)
XtX
60
50
40
30
20
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
Chromosome
(b)
Association with environmental PC1 (BFmc)
BFmc
40
30
20
10
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
Chromosome
(c)
Association with morphological PC1 (BFmc)
BFmc
30
20
10
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
Chromosome