












Genomic responses to climatic challenges in beef cattle: A review

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Abstract

Climate change is a major concern for the near future and for livestock breeding. Cattle breeding, due to its greenhouse gas emissions, is one of the most implicated industries. Consequently, the main future goals are to breed animals resilient to climate change, with the aim of lowering the livestock impact on the environment and selecting animals that will be able to resist different, unsuitable, and changing climates. The aim of this literature review is to compare the most recent studies on the response and adaptation of beef cattle breeds to extreme environments, in terms of genes and pathways involved. Beef breeding is just starting to implement genomics in its selection plans, and shedding light on the genomic responses to extreme climates could speed up and simplify the adaptation of these breeds to climate change. This review discusses the genes involved in climatic stress responses, including those related to extremely cold climates, in beef and dual-purpose cattle breeds. Genes were associated with productive traits, coat and skin structure and development, thermotolerance, cellular physiology and DNA repair mechanisms, immune system, and fertility traits. The knowledge of genes and pathways involved in climate resilience should be taken into consideration for further selection in beef cattle breeding and could promote the valorization of local breeds adapted to extreme environmental conditions. The use of local or resilient breeds could enhance the environmental and social sustainability, animal welfare, and production, compared with the introduction of cosmopolitan breeds with uncertain adaptation in uncontrolled environmental areas.

KEYWORDS

environment, fitness, genes, heat stress, resilience

INTRODUCTION

The evidence of climate change is now undeniable. Global average temperatures have increased by almost

1°C in the last 2 centuries (Arora, 2019; Wheeler & Von Braun, 2013) and are expected to rise up to 1.5°C in the next decades (Hoegh-Guldberg et al., 2019; Kraaijenbrink et al., 2017). Nonetheless, climate change

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is also responsible for extreme weather events, such as heavy rains, floods, and drought (Ummenhofer & Meehl, 2017), which must also be addressed. According to the Food and Agriculture Organization (FAO), climate change is already affecting the food security in different ways, including food availability, physical and economic accessibility, and its use and distribution (Meybeck et al., 2018). One of the food supply chains most affected by climate change is livestock production (Hoffmann, 2010), in which ruminants, especially cattle, play a predominant role. This production system, which uses a significant portion of the Earth's surface, has an indisputable importance (Baumgard et al., 2012; Nardone et al., 2010).

As regards meat production, cattle are the third most important livestock species after poultry and pigs (FAOSTAT, 2023). Beef consumption, which represents approximately 25% of global meat consumption, is also expected to increase from 54 to 118 million tons by 2050 (Cooke et al., 2020). In addition to being significantly affected by climate change and severe climate stress (Lees et al., 2019; Ortiz-Colón et al., 2018), cattle also contribute to the emissions of greenhouse gases (GHG). Methane is a physiological residue of the digestion of ruminants, produced by the rumen microbiota as a product of CO_2 and H_2 metabolism and it is one of the most concerning GHG. Agriculture is responsible for 7%–18% of methane emission (Gerber et al., 2013), and 81% comes from livestock with the almost totality due, indeed, to ruminants (FAO, 2023; Gerber et al., 2013; McAllister et al., 2015; Tapio et al., 2017). Methane emission is not only a problem of environmental pollution, although it remains a predominant aspect, but it also implies a reduced energy intake for the ruminants of about 2%–12% (FAO, 2023; Johnson & Johnson, 1995; Martínez-Álvaro et al., 2022). Furthermore, a genetic component for methane emissions has been proven (Difford et al., 2018). Adaptation to extreme climatic conditions should be achieved through improving efficiency, which would result in lower GHG emissions, thus highlighting the strong double connection between the cattle livestock system and climate (Hoffmann, 2010; Kooverjee et al., 2022). Finally, it is well known that extreme temperatures impact animal productions, resulting in decreased feed intake, reduced growth, and lower yields (Finocchiaro et al., 2022; Nardone et al., 2006, 2010). However, those cattle breeds that have evolved under harsh environments have developed grazing patterns that allow them to be more nutritionally efficient especially with low-quality forages (Cooke et al., 2020; McIntosh et al., 2023; Russell et al., 2012), they are resistant to internal and external parasites (Ben-Jemaa et al., 2021), and are able to respond more quickly to environmental stimuli (Lees et al., 2018).

In recent years, due to the drastically decreasing cost of high-throughput genotyping and whole genome

sequencing, a remarkable amount of genomic data is constantly generated, giving animal scientists the opportunity to better understand the genomic architecture of different traits, as well as the implementation of genomic selection for the desired outcomes. Genome-wide association studies (GWAS) have become a suitable tool to study the genetic variants behind phenotypic differences by using a statistical unbiased approach with thousands of different molecular markers. These genomic approaches have been already implemented in dairy cattle breeds (Cheruiyot et al., 2022; Dikmen et al., 2013; Finocchiaro et al., 2022; Garner et al., 2016; Hayes, Bowman, Chamberlain, & Goddard, 2009; Hayes, Bowman, Chamberlain, Savin, et al., 2009; Macciotta et al., 2017; Silpa et al., 2021; Strandén et al., 2019). Moreover, several studies have addressed the relationships between climate change and environmental adaptation in livestock (Cheng et al., 2022; Passamonti et al., 2021; Rovelli et al., 2020; Xia et al., 2023). However, due to the polygenic adaptation, neither an individual gene, or supergene, nor a few gene families exclusively responsible for climatic adaptation have been proposed (Kambal et al., 2023), this phenomenon being rather due to the synergetic action of a multitude of genes. By contrast, the use of genomics in beef or dual-purpose cattle is less common, although already implemented for different traits (Piccoli et al., 2020). Genomic selection has not been adopted as widely in beef as in dairy cattle breeding. This is partly because the accuracy is lower, but also because the economic advantages are not as great. Genomic selection is most advantageous for traits that are difficult to select by using traditional selection tools. It is less advantageous in beef than dairy because progeny testing is not needed for traits that can be measured on selected candidates at a young age such as growth rate. However, several important traits in beef cattle are difficult to select for, such as feed conversion efficiency and beef quality. Because these traits are also expensive to record, it is costly to set up a large training population and there are no large companies that could justify this cost for their own breeding program. For these traits, a multibreed training population and non-linear analysis based on high-density SNPs or genome sequence data may be the best approach (Meuwissen et al., 2016); moreover, Pollak (2005) outlined the numerous tools that can be applied to beef cattle breeding, with molecular genetics showing the best promise for rapid genetic improvement.

In this review, we conducted a comprehensive search in the available literature on the genomic research contributions on the meat production and climate change, focusing on local and dual-purpose cattle breeds, to investigate and identify key genetic variants associated with adaptation to extreme environmental conditions (i.e., extremely high temperatures, altitudes, aridity). Furthermore, despite the fact that temperatures are generally rising, cold spells are not expected to vanish

entirely (Kodra et al., 2011), adaptations to extreme cold are also presented.

The scientific literature reviewed in this article was retrieved from the Scopus and Google Scholar databases using the keywords “beef cattle”, “genomic”, “environment”, “extreme climates”, “climate change”, “adaptation”. Only articles related to beef and dual-purposed breeds, and their genomic adaptation to harsh environments were retained, without any geographic restrictions. These breeds were classified as either beef breeds, which are recognized as such in scientific publications, or local, multi-purpose breeds for which no information about their suitability could be found. The scientific publications aiming to identify the genomic regions related to adaptation (Bernabucci et al., 2010) of the breeds to different extreme climates were finally divided according to the considered climate (i.e., hot–dry and humid, and cold). Cattle populations reported in this review, according to their agroecological zone, are depicted in Figure 1.

Findings from the literature reported some common metabolic pathways, biological functions, and genetic adaptations involved in extreme climates tolerance. Genes and pathways discussed in this review were mostly related to the following aspects: productive traits, feed intake, and energy metabolism, which are negatively affected by heat stress; coat features necessary to tolerate higher temperatures and UV light; thermotolerance and heat shock; cellular physiology and DNA repair; immune system; and fertility traits. These mechanisms and genes (i.e., *DNAJC8*, *STING1*) also overlap with a recent landscape genomic analysis on worldwide populations of indicine cattle, which are evolutionarily more prone

to adapt to tropical regions (Chen et al., 2023). Lastly, genomic adaptations to extreme cold environments and cold spells are also reported.

PRODUCTIVE TRAITS IN BEEF CATTLE

Growth and feed efficiency of livestock animals are known to be affected by high temperatures (Koooverjee et al., 2022), and selection efficacy strongly depends on the environment, which is very evident for growth performances (Santana et al., 2012, 2015). Genomic association analysis has been chosen as the most suitable tool to link genomic features to productive phenotypes (i.e., weights, daily live weight gains, carcass traits) (Colombi et al., 2024), and several association studies between these traits and climate conditions have been performed. Smith et al. (2019) conducted a genotype × environment analysis in Gelbvieh cattle, a beef breed originating from Germany, focusing on birth weight, weaning weight, and yearling weight. The results showed a high concordance between the considered traits and candidate genes previously associated with height, feed efficiency, and growth traits (i.e., *PLAG1*, *NCAPG*, *LCORL*, *ARRDC3*, *STC2*). Three genes were also found associated with birth weight: *GRB14* involved in insulin regulation; *FIGN* associated with plasma folate levels; and *UNG* involved in the removal of uracil residues from DNA and apoptosis. Another candidate gene is *TTN*, which is involved in myofibrillar assembly for skeletal and cardiac muscles, was found to be associated with weaning weight. Finally,

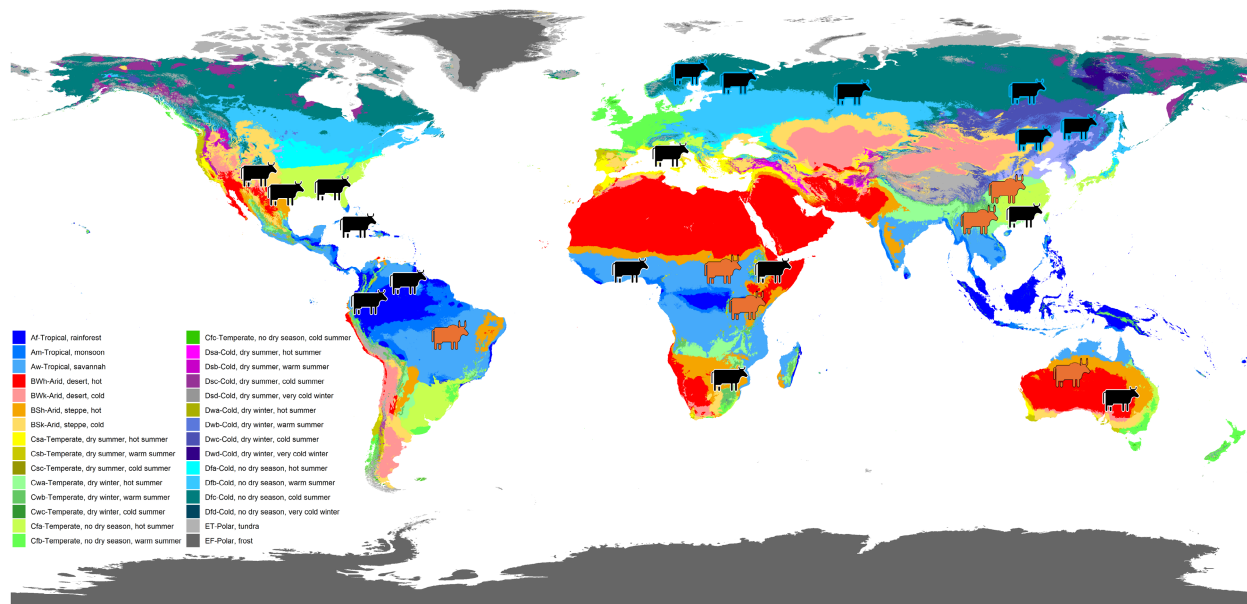


FIGURE 1 Distribution of taurine (black) and indicine (orange) cattle populations from scientific research reviewed in this paper. Cattle under cold stress are outlined in light blue. Populations are located on the Köppen–Geiger climate map related to 1991–2020 period; climatic data and mapping according to Beck et al. (2023).

LRAT, *FGG* and *LOC101904475* genes were associated with yearling weight. More recently, Smith et al. (2022) performed a genotype \times environment analysis in American Red Angus cattle on the same phenotypes, associated with different ecoregions, discrete climatic areas defined according to their mean temperatures, precipitations, and elevation (i.e., Upper Midwest and Northeast, Fescue Belt, Rainforest, Forested Mountains, High Plains, Foothills, Desert, Southeast, and Arid Prairie). The *PRKG1* gene, involved in feed efficiency and vasodilation, was found to be associated with birth weight in the Arid Prairie Ecoregion. Additionally, the genes *LOC531679*, *SEC61G*, and *NEK10*, all related to feed efficiency, were associated with the High Plains Ecoregion. In the case of weaning weight, the genes *LOC112447496* and *LOC112447497*, involved in carcass traits, were found to be associated with the Desert Ecoregion. *DNAJC12* and *SIRT1* genes, related to growth, development, and metabolism, were linked to the Upper Midwest and Northeast Ecoregion, while *LCLAT1* and *LOC782092* genes, related to feed efficiency and carcass traits, were associated with the Foothills Ecoregion. Regarding yearling weight, the genes *EDNRB* and *POU4F1*, involved in cellular proliferation and differentiation, as well as *PARD3B* and *NRP2*, associated with bovine growth and neural development, were found to be associated with the Foothills Ecoregion. The gene *ZHX3*, related to carcass traits, was associated with the Forested Mountains Ecoregion. Finally, *DNAJC12* and *SIRT1*, were also associated with the Upper Midwest and Northeast Ecoregion. Blackburn et al. (2017) compared different allelic frequencies in Hereford breed according to different American ecoregions and observed differences in ARS-BFGL-NGS-45806 and BTB-01271264 variants, involved in early embryonic survival, in populations in warm arid versus warm humid regions, and ARS-BFGL-NGS-39379 variant, associated with body weight, in cool arid versus cool humid regions. Barbato et al. (2020) exploited the genetic introgression of indicine origins in three Italian beef cattle breeds (Chianina, Marchigiana, and Romagnola) and reported several genomic regions shared between these breeds of partial indicine derivation; within those regions, the majority of genes were previously associated with beef and growth traits (Barbato et al., 2020). Finally, genomic approaches have made it possible to discriminate genes, related to productive traits, which are associated with adaptation to severe climatic conditions. The genes were involved in feed efficiency, feed intake, and energy metabolism (Li et al., 2020; Porto-Neto et al., 2014; Taye et al., 2017) and in body size, morphology, and muscle metabolism (Edea et al., 2018; Flori et al., 2019; Porto-Neto et al., 2014). *BMP2* gene was observed to be associated with mid- to high-altitude or dry and semi-arid environments in different Ethiopian cattle breeds by Edea et al. (2018). This gene is crucial

for body size and development as it affects osteoblast and adipocyte differentiation (Serranito et al., 2021) and fat deposition (Mastrangelo et al., 2019). Previous research has also connected this gene to dry conditions in Egyptian, Chinese, and Mediterranean sheep (Kim et al., 2016; Serranito et al., 2021; Yang et al., 2016). Nonetheless, selective pressure for high altitude was reported for this gene in Tibetan sheep and yaks (Qi et al., 2018; Wei et al., 2016). All genes involved, along with more detailed information about the analysis conducted, are reported in Table 1.

COAT TRAITS

Traits such as coat color have been promoted as selection options for improved heat tolerance (Dikmen et al., 2017). Coat characteristics, including skin color and structure, hair growth, and sweat glands development, have a predominant role in resilience to severe heat stress conditions. Genes affecting hair and skin color, and hair length and density have been identified in cattle (Collier et al., 2008). The role of coat color as a defense mechanism against heat stress and ultraviolet (UV) radiation has been widely recognized (Xia et al., 2023). Chen et al. (2023) reported indeed a selective sweep in *LEF1* and *ASIP* genes in light-coated South Asian indicine cattle that may have arisen as natural adaptation due to thermal stress, UV exposure, or by human selection. The same genes and mechanisms were also suggested for Brahman and Tropical Composite cattle (Porto-Neto et al., 2014) and Mediterranean breeds (Flori et al., 2019). Heat tolerance in beef cattle with the 'slick hair gene' is well established (Olson et al., 2003). Evidence was found that supports the existence of this major gene, dominant in mode of inheritance, which is responsible for producing a very short, sleek hair coat. Cattle with sleek hair were observed to maintain lower rectal temperatures. The gene was found in Senepol cattle and Criollo (Spanish origin) breeds in Central and South America (Olson et al., 2003). Selection signatures and genome wide association studies in different cattle adapted to tropical climates revealed genes under putative pressure involved in coat pigmentation, UV protection and light sensitivity (Ding et al., 2022; Edea et al., 2018; Flori et al., 2019; Kim et al., 2017; Li et al., 2020; Porto-Neto et al., 2014; Rowan et al., 2021). The physical structure of skin and hair has also been observed to be involved in tropical beef cattle breeds thermotolerance (Taye et al., 2017), with a specific mention of genes involved in sweating and sweat glands development (Pitt et al., 2019; Taye et al., 2017, 2018). For example, the homeobox genes *HOXC12* and *HOXC13* play a role in hair follicle differentiation, growth, and development by regulating keratin differentiation-specific genes, and are associated with adaptation to thermal stress in cattle (Taye et al., 2017). Involvement of keratin genes in response to the increase

TABLE 1 Candidate genes involved in different mechanisms in beef and local cattle breeds under hot climatic conditions.

Candidate genes	Productive traits	Coat traits	Thermotolerance	Cellular physiology	Immune system	Fertility traits	Breed	Total number of animals in the study	Type of analysis	Number of variants in the study	References
<i>GRB14</i> ; <i>FIGN</i> ; <i>UNG</i> ; <i>TTN</i> ; <i>LRAT</i> ; <i>FGG</i> ; <i>LOC101904475</i>							Gelbvieh	10837	GWAS	618 735	Smith et al. (2019)
<i>PRKGI</i> ; <i>LOC531679</i> ; <i>SEC61G</i> ; <i>NEK10</i> ; <i>LOC112447496</i> ; <i>LOC112447497</i> ; <i>DNAJC12</i> ; <i>SIRT1</i> ; <i>LCLATI</i> ; <i>LOC782092</i> ; <i>EDNRB</i> ; <i>POU4F1</i> ; <i>PAR3D3B</i> ; <i>NRP2</i> ; <i>ZHX3</i>							American Red Angus	12 388– 15 815	G × E	674 493– 675 115	Smith et al. (2022)
<i>CCDC14</i> ; <i>ROPNI</i> ; <i>CPNE4</i> ; <i>H2AFY</i> ; <i>CXCL14</i> ; <i>SBF2</i> ; <i>USP10</i> ; <i>CRISPLD2</i> ; <i>ZDHC7</i> ; <i>KIAA0513</i> ; <i>FAM92B</i> ; <i>SERPINB10</i>							Chianina, Marchigiana, Romagnola	59	Adaptive introgression	647 132	Barbato et al. (2020)
<i>ATP8A1</i> ; <i>SHC3</i>		<i>RAB31</i>	<i>HSF1</i>	<i>PLCBI</i> ; <i>PLCB4</i>	<i>LIPH</i> ; <i>TP63</i> ; <i>CBFA2T3</i>	<i>TP63</i> ; <i>MAP3K13</i> ; <i>PTPN4</i> ; <i>PPP3CC</i> ; <i>ADAMTSL1</i> ; <i>SSI8L1</i> ; <i>OSBPL2</i> ; <i>TOX</i> ; <i>RREB1</i> ; <i>GRK2</i>	Dehong humped	20	Fst, XP-CLR and XP-EHH	619 375	Li et al. (2020)
<i>LDHA</i> ; <i>IGFBP4</i> ; <i>ATP7A</i> ; <i>STEAP2</i> ; <i>MON2</i> ; <i>MYH2</i> ; <i>ASPH</i> ; <i>APOBEC2</i>		<i>ASIP</i>			<i>LYN</i> ; <i>CHD7</i> ; <i>ADORA2B</i> ; <i>IRAK3</i> ; <i>CORO2A</i> ; <i>TOX</i>		Brahman, Tropical Composite	4662	GWAS	729 068	Porto-Neto et al. (2014)
<i>ATRN</i> ; <i>NEATC</i> ; <i>FTO</i>	<i>CFTR</i> ; <i>ITPR2</i> ; <i>SGKI</i> ; <i>SLC9A4</i> ; <i>SCNN1D</i> ; <i>MLPH</i> ; <i>RABI7</i> ; <i>RAB37</i> ; <i>HOXC12</i> ; <i>HOXC13</i> ; <i>SLC45A2</i> ; <i>MC5R</i> ; <i>ATRN</i>		<i>HSF5</i> ; <i>IGF-1</i>	<i>SOD1</i> ; <i>GPX7</i> ; <i>SLC23A1</i> ; <i>SLC23A2</i> ; <i>PLCBI</i> ; <i>PRLH</i> ; <i>BHMT2</i>		<i>CSF1</i> ; <i>ESR2</i> ; <i>RXF3</i> ; <i>CIB1</i> ; <i>MC2R</i> ; <i>MC5R</i>	Ankole, Boran, Ogaden, N'Dama, Kenana	48	XP-CLR and XP-EHH	~37 million SNPs	Taye et al. (2017)

(Continues)

TABLE 1 (Continued)

Candidate genes	Productive traits	Coat traits	Thermotolerance	Cellular physiology	Immune system	Fertility traits	Breed	Total number of animals in the study	Type of analysis	Number of variants in the study	References
		<i>MAPK12</i> ; <i>SGPL1</i> ; <i>KRT33A</i> ; <i>KRTAP27-1</i> ; <i>KRTAP9-1</i> ; <i>COL12A1</i> ; <i>COL8A1</i> ; <i>PRG3</i> ; <i>VW42</i> ; <i>ATRn</i> ; <i>SLC45A2</i> ; <i>MLPH</i> ; <i>RAB17</i> ; <i>RAB37</i> ; <i>RAB42</i> ; <i>RAB7A</i>	<i>DNAJC11</i> ; <i>DNAJC8</i> ; <i>HSF5</i> ; <i>PPP2R3E</i>	<i>PLCB1</i>	<i>BoLA4</i> ; <i>TNFAIP8L3</i> ; <i>SLC25A48</i> ; <i>TNFAIP3</i> ; <i>DMBT1</i>	<i>IGF-1</i> ; <i>ESR2</i> ; <i>FGFR2</i>	Boran, Ogaden, Kenana	28	XP-CLR and XP-EHH	~37million SNPs	Taye et al. (2018)
	<i>TFEC</i> ; <i>AKIRIN2</i> ; <i>BMP2</i> ; <i>LYN</i> ; <i>NPM1</i>	<i>MYO1A</i> ; <i>ERBB3</i>	<i>HSP70</i> ; <i>HSF1</i>	<i>EIF2AK4</i> ; <i>MTOR</i> ; <i>NFATC1</i> ; <i>NPM1</i>	<i>WIF1</i> ; <i>HSP70</i> ; <i>AKIRIN2</i> ; <i>NMNATI</i>	<i>ID3</i> ; <i>HSP70</i> ; <i>UBE2D3</i> ; <i>PSPCI</i> ; <i>NCOA2</i> ; <i>NMNATI</i> ; <i>ARNTL</i> ; <i>PIK3CD</i> ; <i>RELE</i>	Raya-Azebo, Fogera, Arado, Begaït, Boran, Arsi, Guraghe, Ogaden, Deshi, Red Chittagong, Nellore	275	Fst	68 202	Edea et al. (2018)
	<i>NDUFB3</i> ; <i>FBN1</i>	<i>RAI14</i> ; <i>TIAMI</i> ; <i>GRIK1</i>	<i>GADL1</i> ; <i>GLDC</i> ; <i>NRG1</i> ; <i>SLC46A1</i> ; <i>ALDH1A</i> ; <i>AMER1</i> ; <i>CDH4</i> ; <i>EYAI</i> ; <i>FBN1</i> ; <i>LAMC1</i> ; <i>MST1</i> ; <i>MYC</i> ; <i>NOG</i> ; <i>PTGS2</i> ; <i>PTPRF</i> ; <i>SHH</i> ; <i>SLC19A1</i> ; <i>SMO</i> ; <i>SST</i> ; <i>TP53</i> ; <i>VEGFA</i> ; <i>VHL</i>	<i>METTL3</i>	<i>NTXR2</i> ; <i>MAP3K8</i> ; <i>MLST8</i> ; <i>SMYD3</i>		Senepol	153	EHH	47 365	Flori et al. (2012)
	<i>LEFI</i>		<i>GADL1</i> ; <i>GLDC</i> ; <i>NRG1</i> ; <i>SLC46A1</i> ; <i>ALDH1A</i> ; <i>AMER1</i> ; <i>CDH4</i> ; <i>EYAI</i> ; <i>FBN1</i> ; <i>LAMC1</i> ; <i>MST1</i> ; <i>MYC</i> ; <i>NOG</i> ; <i>PTGS2</i> ; <i>PTPRF</i> ; <i>SHH</i> ; <i>SLC19A1</i> ; <i>SMO</i> ; <i>SST</i> ; <i>TP53</i> ; <i>VEGFA</i> ; <i>VHL</i>	<i>METTL3</i>	<i>NTXR2</i> ; <i>MAP3K8</i> ; <i>MLST8</i> ; <i>SMYD3</i>		21 different Mediterranean breeds	640	GWAS	39 921	Flori et al. (2019)
	<i>SLC45A2</i>						28 Chinese indigenous cattle breeds, Angus	571	Allelic variance in a gene	–	Ding et al. (2022)

TABLE 1 (Continued)

Candidate genes	Productive traits	Coat traits	Thermotolerance	Cellular physiology	Immune system	Fertility traits	Breed	Total number of animals in the study	Type of analysis	Number of variants in the study	References
		<i>CUX1</i>					Red Angus, Simmental, Gelbvieh	42 676	envGWAS	836 118	Rowan et al. (2021)
		<i>GDNF</i> ^(1,2,3)	<i>ENO</i> ; <i>SHTNI</i> ; <i>VAX1</i> ; <i>KCNK18</i> ; <i>PDZD8</i> ⁽⁴⁾	<i>WDR70</i> ; <i>NIPBL</i> ; <i>FBXL5</i> ^(1,2,3)	<i>CIQTNF7</i> ; <i>BST1</i> ; <i>CD38</i> ^(1,2,5)	<i>CFAP6</i> ^(1,2,5)	Romosinuano ¹ , San Martinero ² , Senepol ³ , Florida Cracker ⁴ , Texas Longhorn ⁵	412 ^a	Fst and XP-EHH	33 342	Pitt et al. (2019)
		<i>KRT15</i> ; <i>KRT31</i> ; <i>KRT32</i> ; <i>KRT33A</i> ; <i>KRT34</i> ; <i>KRT36</i>		<i>PLA2G4B</i> ; <i>PLA2G4E</i> ; <i>GRIN2D</i> ; <i>GRIK2</i>			Simmental	8546– 13 427	G × E	706 771– 710 202	Braz et al. (2021)
		<i>KRT1</i> ; <i>KRT3</i> ; <i>KRT4</i> ; <i>KRT76</i> ; <i>KRT77</i> ; <i>KRT78</i> ; <i>KRT79</i> ; <i>CEP290</i>					American Angus	8619	GWAS	174 194	Durbin et al. (2020)
		<i>CCHCR1</i> ; <i>CDSN</i>	<i>ATP9A</i> ; <i>GABBR1</i> ; <i>PGR</i> ; <i>PTPN1</i> ; <i>UCPI</i>				Chacuba	12	EHH	Whole-genome sequencing	Ramirez-Ayala et al. (2021)
				<i>HAS2</i> ; <i>REG3A</i> ; <i>REG3G</i> ; <i>FZD1</i> ; <i>SH3BP4</i> ; <i>ASTN2</i> ; <i>DMRTA2</i> ; <i>FAFI</i> ; <i>GLUL</i> ; <i>IQGAP2</i> ; <i>MKNK2</i> ; <i>PAPP4</i> ; <i>PRCF</i> ; <i>SV2C</i> ; <i>TRIM32</i> ; <i>ZNF703</i>	<i>IL13</i> ; <i>IL4</i> ; <i>AP3D1</i> ; <i>KIF3A</i> ; <i>RAD50</i>		Nellore	13 806	GWAS based on RNM	412 456	Carvalho et al. (2019)
				<i>STAC</i> ; <i>WRNIP1</i> ; <i>MLHI</i> ; <i>RIPK1</i> ; <i>SMC6</i> ; <i>GEN1</i> ; <i>SERPINB9</i> ; <i>KCNS3</i> ; <i>SLC22A23</i> ; <i>TRPC4</i>			Crossbred of Angus, Simmental and Piedmontese	239	GWAS	50 000	Howard et al. (2014)

Abbreviations: EHH, extended haplotype homozygosity; envGWAS, environmental genome-wide association studies; Fst, differentiation index; G × E, genotype-by-environment interactions; GWAS, genome-wide association studies; RNM, reaction norm models.; XP-CLR, cross-population composite likelihood ratio; XP-EHH, cross-population extended haplotype homozygosity.

^aThe number considers all breeds involved in the study.

in environmental temperature has also been observed through selection signatures analysis in Ethiopian cattle breeds (Taye et al., 2018), genotype \times environment analysis in Simmental cattle (Braz et al., 2021), and genome-wide analysis in American Angus (Durbin et al., 2020). Lastly, genes associated with hair development in the Chacuba breed (Ramírez-Ayala et al., 2021), and the slick hair phenotype (Flori et al., 2012) in the Senepol breed have been associated with heat stress resistance. All genes involved, along with more detailed information about the analysis conducted, are reported in Table 1.

THERMOTOLERANCE

Genetic selection for development of thermotolerant breeds, modification of the environment, and nutritional intervention are key strategies to consider for livestock production under hot environments (Johnson, 2018). In cattle, several SNPs within different genes (e.g., *HSP70*, *HSP90*, *HSF1*, *EIF2AK4*, *HSBP1*, *HSPB8*, *HSPB7*, *SOD1*, *PRLH*, *MTOR*, *MYO1A*, and *ATPIA1*) have been reported to be associated with thermotolerance traits (Hariyono & Prihandini, 2022; Zeng et al., 2023). Moreover, all the aforementioned genes have critical roles in many cellular activities during thermal stress, protecting cells against stress. Furthermore, stress-induced gene expression and activation of heat shock proteins (HSPs) are key indicators of the animal's response to thermal stress in cellular and molecular activities (Garbuz, 2017). In fact, HSPs are the first active responses to heat stress (Archana et al., 2017). At the same time, an association of HSPs with meat tenderness and quality has been reported (Carvalho et al., 2014; Lomiwes et al., 2014; Reis et al., 2023). Hooper et al. (2019) observed in Nellore cattle a decrease in HSP transcripts during heat stroke (42°C), with *HSP60* resulting as the most highly expressed one. In different months, Pires et al. (2019) evaluated the relative expression of HSPs in Caracu taurine breed and Nellore indicine breed maintained in a pen with some trees in the morning and in a shaded or in a sun pen during the afternoon. Those authors reported the highest gene expression of *HSP60* in Caracu breed compared with Nellore breed, and this gene was more expressed than *HSPA1A* and *HSP90AA1*. However, *HSP60* did not show any difference between the three treatments of morning, shade, and sun, but its relative expression changed according to the month, with the highest expression observed in Nellore cattle in October. The highest expression of *HSPA1A* was observed in December, during the highest relative humidity, and no difference was found between breeds (Pires et al., 2019). *HSP90AA1* was more expressed in Nellore than Caracu and the highest levels were observed in October and December, corresponding to the most severe heat stress conditions. Genes associated with

heat shock response and thermotolerance during heat stress, or adaptation to harsh and drought conditions were also observed using genome-wide approaches (Edea et al., 2018; Flori et al., 2019; Li et al., 2020; Pitt et al., 2019; Ramírez-Ayala et al., 2021; Taye et al., 2017, 2018). Blackburn et al. (2017) found different allelic frequencies in Hereford breed raised in different American ecoregions (i.e., cold, warm, arid, humid). These authors reported differences in the distribution of four environmental stressors-associated markers in warm-arid versus warm-humid ecoregions and six in cool-arid versus cool-humid ecoregions. Temporal *HSP70* gene expression is a biomarker for adaptive gene discovery in cattle and has significant implications in the development of heat- and cold-tolerant genotypes in the context of climate change (Kumar et al., 2015). All genes involved, along with more detailed information about the analysis conducted, are reported in Table 1.

CELLULAR PHYSIOLOGY

As a consequence of exposure to extreme climatic conditions, the cell has to face different forms of metabolic stress, such as oxidative and osmotic stress and UV irradiation. Several genes associated with oxidative and osmotic stress response have been observed (Edea et al., 2018; Li et al., 2020; Pitt et al., 2019; Taye et al., 2017). Moreover, genes involved in DNA damage repair after UV exposure have been reported in a composite population of local Ethiopian and indicine (Edea et al., 2018), Creole (Pitt et al., 2019), and Mediterranean breeds (Flori et al., 2019), where the impact of sunlight is stronger. Hypoxia, often associated with high-altitude grazing, is also a stressor of great significance as reported in African indigenous cattle (Kambal et al., 2023). Lastly, genes relevant for apoptosis as an outcome of cellular damages due to environmental stress have been observed (Carvalho et al., 2019; Edea et al., 2018; Howard et al., 2014). Braz et al. (2021) reported the implication of glutamatergic neurotransmission genes involved in the response to hypoxia in Simmental cattle. Furthermore, Rowan et al. (2021) observed an association between the response to heat, cold and altitude stress with neural development and signaling pathways, alongside with vasoconstriction and vasodilatation on Red Angus, Simmental, and Gelbvieh breeds. Genes associated with body temperatures during summer, involved in stress response and ion transport were observed in a crossed population of Angus, Simmental and Piedmontese breeds by Howard et al. (2014); in particular, the *TRPC4* gene has been observed as a major adaptive selection signature in goats (Serranito et al., 2021), implicated in mediating thermic sensation and consequently regulating blood vessel tone (Duan et al., 2018; Freichel et al., 2004). All genes involved, along with more detailed information about the analysis conducted, are reported in Table 1.

IMMUNE SYSTEM

Another function that is sensitive to extreme climates is the immune defense. It has been established that heat stress has a negative impact on the immune system via both cell mediated and humoral immune responses (Bagath et al., 2019; Kambal et al., 2023; Lacetera et al., 2005). Additionally, heat stress in cattle is responsible for immunosuppression due to cortisol production and for proinflammatory cytokines synthesis (Lemal et al., 2023). More specifically, cattle adapted to tropical environments must face an increased number of different parasites, typical of the regions, and a highest prevalence of ticks, for which genetic resistance is the first form of animal defense (Cardoso et al., 2021; Mota et al., 2016). For instance, African indigenous cattle have been reported to highly express genes associated with trypanosomiasis and tick resistance (Kambal et al., 2023). In this context, Ben-Jemaa et al. (2021) propose a possible strong involvement of chemokine ligand genes, genes associated with natural and adaptative immunity, and immunity-related mechanisms in local adaptation to the malarial environment of rustic Maremmana cattle. Similarly, enhanced involvement of genes related to these events has been observed by Taye et al. (2018) in local African indicine cattle. Genes involved in immunity have also been observed to be associated with adaptation to tropical and

hot climates by several authors (Carvalho et al., 2019; Edea et al., 2018; Flori et al., 2019; Li et al., 2020; Pitt et al., 2019; Porto-Neto et al., 2014). Using whole-genome re-sequenced data, Weldenegodguad et al. (2019) identified positively selected candidate genes underlying disease resistance in northern Eurasian native cattle breeds. All genes involved in immunity, along with more detailed information about the analysis conducted, are reported in Table 1.

REPRODUCTION AND FERTILITY

Animals exposed to high ambient temperatures may also show a decreased fertility, which is responsive to environmental variations (Ambrosini et al., 2016), and this significantly impacts on cattle in terms of both wellness and productive features. Such impact has been observed to be correlated with different traits such as female fertility, conception rates, and calving interval (i.e., *NMNAT1*, *NCOA2*); gonadal development and functionality (i.e., *IGF-1*, *MC2R*, *MC5R*); gametogenesis (i.e., *ESR2*, *RXFP3*, *PSPCI*); and embryonic development and survival (i.e., *FGFR2*, *ID3*, *RERE*) (Hansen, 2009). Genes involved in reproductive functions are reported (Edea et al., 2018; Li et al., 2020; Pitt et al., 2019; Porto-Neto et al., 2014; Taye et al., 2017, 2018), along with more

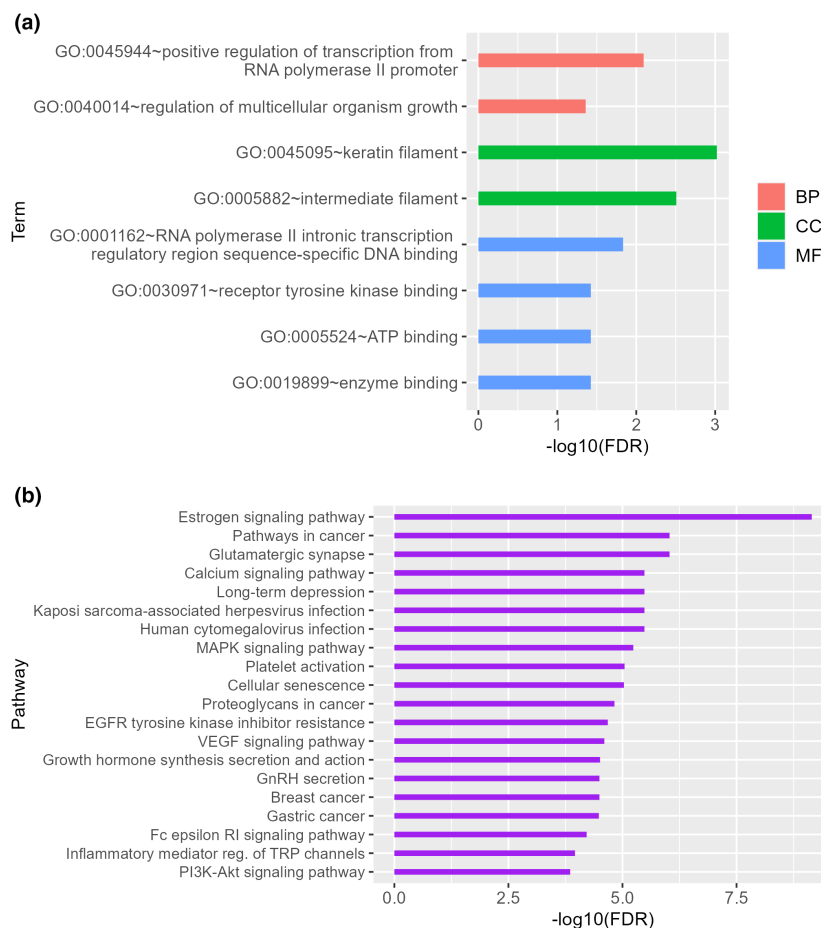


FIGURE 2 Meta gene-enrichment analysis. (a) Gene ontology; (b) Kyoto Encyclopedia of Genes and Genomes pathways. BP, biological process; CC, cellular component; FDR, false discovery rate; MF, molecular function.

detailed information about the analysis conducted, in [Table 1](#).

A META-GENE ENRICHMENT ANALYSIS ON REPORTED GENES

To better highlight the metabolic pathways and mechanisms involved in environmental adaptation in beef cattle, a gene ontology (GO) analysis was performed using DAVID (Database for Annotation, Visualization and Integrated Discovery) approach (Huang et al., 2009; Sherman et al., 2022), and the resulting GO terms (false discovery rate-adjusted p -value < 0.05) are reported in [Figure 2a](#). About the biological processes, two GO terms resulted enriched: positive regulation of transcription from RNA polymerase II promoter (GO:0045944), as previously observed by Fang et al. (2021), and regulation of multicellular organism growth (GO:0040014). These pathways suggest and confirm what has been previously stated: animal growth (GO:0040014) and its productions are primarily affected by environmental stress. Interestingly, the most enriched cellular component was keratin filament (GO:0045095), which resulted also the most enriched GO term, followed by intermediate filament (GO:0005882). Keratin is the primary component of cattle hair (Zhang et al., 2023), enrichment of this pathway could indicate an improved barrier against parasites and ticks, UV light, and other stressors (Braz et al., 2021). Moreover, keratin and keratin-associated proteins are central in the cyclic process of hair development and shedding, which results in animal adaptation to different climates (Khan et al., 2014; Stenn & Paus, 2001). Durbin et al. (2020), in a functional enrichment analysis using candidate genes from a GWAS for thermotolerances in Angus beef cattle, identified pathways involved in keratin formation, prolactin signaling, host–virus interaction, and other biological processes. The enriched molecular function GO terms included RNA polymerase II intronic transcription regulatory region sequence–specific DNA binding (GO:0001162); receptor tyrosine kinase binding (GO:0030971); ATP binding (GO:0005524); enzyme binding (GO:0019899). Kyoto Encyclopedia of Genes and Genomes pathways (top 20; false discovery rate-adjusted p -value < 0.05), resulted using ShinyGO (Ge et al., 2020), are reported in [Figure 2b](#). The most enriched Kyoto Encyclopedia of Genes and Genomes pathways included the estrogen signaling pathway and pathways in cancer, which also resulted enriched for heat stress in dairy cattle (Fang et al., 2021). The following most significant pathways resulted glutamatergic synapse, which has also been observed in heat tolerant dairy cows (Cheruiyot et al., 2021), and calcium signaling pathway, also observed as the most enriched in Holstein Friesian cows under heat stress (Kim et al., 2020).

ADAPTATION TO COLD CLIMATES

Similarly to heat resistance, another extreme climate that cattle must eventually adapt to is the extremely cold environments, often associated with high altitude and hypoxia. Weldenegodguad et al. (2019) sequenced Eastern and Western Finncattle and Yakut cattle and northern native breeds well adapted to cold climates, and identified selection signatures related to the northern and subarctic environments and respective genes associated with cold resistance in these breeds. Buggiotti et al. (2021) observed, by sequencing Yakut breed, an allelic variant in the *NRAP* gene, which has been only observed in hibernating mammals and it was associated with cold adaptation and ability to enter torpor, and other genes as positively selected, associated with energy metabolism and thermogenesis, lipid metabolism, and cold resistance in different biological processes. Yang et al. (2017) performed GWAS based on copy number variation in several Chinese cattle breeds, identifying a candidate gene for cold tolerance named *COL27A1*, involved in average daily gain, cartilage calcification and bone and muscle development in the Northern Menggu and Yanhuang breeds. Xu et al. (2017) studied the differential gene expression of peripheral blood mononuclear cells in Chinese Sanhe cattle after exposure to severe cold stress. The top involved signaling pathways were *IL10*, *EIF2*, *Gαi*, *GDNF* family ligand–receptor interactions, *IL17A*, *LXR/RXR* Activation and *VEGF* family ligand–receptor interactions, whose differential expressed genes are reported in [Table 2](#). Ghoreishifar et al. (2020) detected selection signatures in different Swedish cattle breeds. Among the breeds, those authors found two genes in the Swedish Red Cattle, historically used for meat production (Eriksson et al., 2020), related to cold adaptation and high altitude and hypoxia adaptation. Yurchenko et al. (2018) performed a genome scan for signatures of selection in several breeds adapted to cold environments. The Russian beef cattle breed genomes contained regions under putative selection with different genes related to adaptations to harsh environments. Pokharel et al. (2019), by transcriptome analyses, proposed candidate genes for adaptation to sub-arctic climates in Yakut cattle and Northern Finncattle. Igoshin et al. (2019) combined results from GWAS and signatures of selection for body temperatures in Hereford and Kazakh Whiteheaded breeds exposed to severe cold stress and genes involved in body thermoregulation and cold shock responses were observed in both analyses. In addition, selection signature analyses revealed genes involved in adaptation, pigmentation, growth traits, reproduction and cell division. In a more recent study, Igoshin et al. (2021) observed genes under selective pressure related to thermotolerance and cold adaptation by resequencing Hereford and Kazakh Whiteheaded cattle breeds. Recently, Tian et al. (2023)

TABLE 2 Candidate genes in beef and local cattle breeds under extreme cold climatic conditions.

Candidate genes	Breed	References
<i>DNAJC23; HSP90BI; AGTRAP; TAF7; TRIP13; NPPA; NPPB; CD14; COBL; JMJDIC; KCNMA1; PLA2G4; SERPINF2; SRA1; TAF7; DNAJC9; SOCS3; TRPC7; SLC8A1; GLPIR; PKLR; TCF7LD</i>	Eastern Finncattle, Western Finncattle, Yakut	Weldenegodguad et al. (2019)
<i>NRAP; PTN; PLA2G2A; ANGPTL8; SPTBN5; MYO10</i>	Yakut	Buggiotti et al. (2021)
<i>COL27A1</i>	Menggu, Yanhuang	Yang et al. (2017)
<i>FOS; MAPK1; IL1R1; FCGR2B; RPS18; EIF2B1; RPLP2; RPL7L1; EIF2S3; P2RY13; CNR2; SIPR1; DOK1; LYZ; MSR1; LPL; NPR2</i>	Sanhe	Xu et al. (2017)
<i>HSPB8; DCAF8</i>	Swedish Red Cattle	Ghoreishifar et al. (2020)
<i>TNKS; RETREG1; RPL7; RGS7; HDAC3; ARRC3; CERKL; RAD50; IL4; IRF1</i>	Several Russian breeds	Yurchenko et al. (2018)
<i>CCL4; CCL5; CHST1; CHST2; CX3CR1; CXCR6; GAS6; GAS7; GZMB; GZMM; GZMH; IGFBP4; IGFBP7; NCR1; NCR3; BHLHE40; PRKCG; PRF1; KRT72; TMEM8A</i>	Yakut, Northern Finncattle	Pokharel et al. (2019)
<i>GRIA4; MSANTD4; MEF2A; NBEA; EDN3; FAM110B; TOX; FGF6; LCORL; XKR4; PKP2; OPRK1; WIF1</i>	Hereford, Kazakh Whiteheaded	Igoshin et al. (2019)
<i>DDX23; MAATS1; GRIA4; COX17; THBS1; CCL5; UPK1B; PLA1A; NR1I2; ATF1; PRKAG1; IFNGR1; PPT1</i>	Hereford, Kazakh Whiteheaded	Igoshin et al. (2021)
<i>NOS; EGLN1; EPAS1</i>	Zhangmu	Liu et al. (2021)
<i>TRPM8; NMUR1; OXR1; PRKAA2; SMTNL2; PLCB4; SIN3A</i>	Mongolian and Red Angus crossbred	Tian et al. (2023)
<i>UQCR1; DNAJC18; EGRI; STING1</i>	Several Chinese native cattle	Huang et al. (2023)

observed genes involved in cold climate adaptation and energy metabolism, and in the immune system, to be associated with cold climate adaptation of Mongolian and Red Angus crossbred, whereas Huang et al. (2023) revealed different genes related to thermogenesis and energy metabolism in native Chinese breeds, providing new insights into adaptations to cold climates in cattle. Regarding adaptation to hypoxia related to high altitudes, which is possibly the most stringent climatic condition causing a decrease in oxygen availability in tissues (Xia et al., 2023), Liu et al. (2021) identified pervasive introgression from the yak to Zhangmu cattle that cover several genes involved in the hypoxia response and previously identified as positive selection genes in other species, which suggested that the adaptive introgression from yak may have contributed to the adaptation of Zhangmu to high-altitude environments. The *JMJDIC* gene, which has a role in response to hypoxia (Melvin & Rocha, 2012), was reported by Weldenegodguad et al. (2019). The *EDN3* and *NBEA* genes may also present a role in hypoxia tolerance, since they have been reported by Igoshin et al. (2019) to be involved in pigmentation and body temperature support and body weight, respectively. *EDN3* has been also identified to be involved in hypoxia tolerance in cetaceans (Tian et al., 2016) while *NBEA* was previously associated with high-altitude acclimation in cattle (Zeng, 2016), yaks (Qi et al., 2018), and sheep (Edea et al., 2019; Yang et al., 2016). Stronen et al. (2019) highlighted different genes under selection in northern European cattle; of them, *DPH6* was observed in yaks (Lan et al., 2018) and Chinese sheep (Yang et al., 2016)

in high-altitude conditions. Finally, these genes were linked to high altitudes and temperatures gradient in Mediterranean sheep and goats (Serranito et al., 2021). All genes involved in adaptation to extreme cold are reported in Table 2.

CONCLUSIONS AND FUTURE PERSPECTIVES

The adaptation to changing climates and extreme environments is a major concern for beef cattle breeding, and its relevance will exponentially increase in the near future. This paper has reviewed the most recent findings about beef and dual-purpose cattle adaptations and responses to different climates from a genomic point of view. The literature analysis highlights pathways and biological functions that are mostly related to heat stress. Heat-stressed animals show reduced feed intake and metabolic alterations, alongside lower growth rates and weight gains. These effects are partially mitigated in local and adapted breeds, which exhibit enhanced ease of growth in harsh and hot conditions. This allows the exploitation of environments that would otherwise not permit the introduction and correct development of commercial breeds. The coat structure represents an exceptional tool for physical thermoregulation and a first defense against UV light exposure in hot climates. Adaptation involves the predominant role of structural modifications of coat characteristics, both in the skin and in the hair of the animal, with the keratin gene family playing an important role in this aspect. Additionally,

HSPs and heat shock factors have also a major role in this aspect, as well as mechanisms of DNA repair after UV, oxidative, or osmotic cellular stress and DNA damages. Moreover, animals less resistant to heat stress conditions, or tropical environments, are more susceptible to tropical diseases, parasitosis, and ticks, common in such regions, as highlighted by the numerous genes associated with immunity. By contrast, adapted breeds show genes related to genetic resistance to parasitosis and ticks. Finally, several genes and pathways related to fertility traits were reported to be affected as well, and analogously to productive traits, local and adapted breeds may also be preferred due to their discrete performances during harsh conditions, which do not impact as debilitatingly as on other breeds.

As a secondary aspect regarding extreme temperature adaptations in beef cattle, scientific publications about genomic adaptation to extreme cold climates were reviewed, since extreme cold spells and extreme climatic events are not disappearing, and they are also becoming more unpredictable. Similar to what was previously stated, the pathways involved in extremely cold climates adaptation were related to those observed during heat stress, with particular regard to response to hypoxia, energy metabolism, and growth traits, but from the perspective of thermogenesis rather than thermoregulation, productivity, immune functions, and coat characteristics.

Interestingly, the scientific publications here reviewed did not show a high concordance or overlap in terms of single genes reported. This may be mainly attributable to the extreme polygenicity of these traits, the heterogeneity of breeds, environments, analysis, models applied, and the use of very wide-ranging statistical surveys of the genome. Overlap was, indeed, observed in studies targeting specific and well-known genes and pathways (i.e., HSPs, heat shock factors, keratins).

Genomics is indeed an excellent tool to faster address selection to increase animal resilience to challenging environments. The knowledge about the genes involved in adaptation to changing climate conditions will help to increase animal resilience versus high ambient temperature, arid and unfertile pastures, or any eventual acclimatation to nonoptimal conditions. There are opportunities to reduce the impact of heat stress on cattle production by identifying the causative mutations responsible for genetic variation in thermotolerance and transferring specific alleles that confer thermotolerance to breeds not adapted to hot climates. Genomic selection is proposed as a promising approach to accelerate genetic gains for thermotolerance since young bulls and heifers can be selected based on their genomic estimated breeding value. Genomic selection considering the reported genes and pathways, along with a preference in using well-adapted local breeds, will significantly contribute to increase

production and sustainability in a constantly changing world. Furthermore, this scientific knowledge might be taken into consideration for emerging technologies in molecular genetic techniques and genome editing (e.g. CRISP-CAS9) and may pave the way for potential novel approaches in the next decades, allowing introduction of site-specific gene modifications.

The use of local breeds has been getting a lot of interest recently; although such breeds are evidently minor in terms of growth and production, they have been naturally selected over centuries to resist their specific and frequently prohibitive environments. Nonetheless, local breeds play a crucial role in soil and land management, and have a huge relevance in the social, cultural, and historical background of a region. The use of local or resilient breeds could enhance the environmental and social sustainability, animal welfare, and production, in several areas of the world using free range systems, compared with the introduction of cosmopolitan breeds with uncertain adaptation in uncontrolled environment areas.

The scientific results reported in this review confirm that most local breeds are genetically prone to face extreme climatic conditions; thus, breeding of such animals should be increased, or even preferred in difficult areas that are mostly subjected to climate change.

AUTHOR CONTRIBUTIONS

Daniele Colombi: Conceptualization; data curation; formal analysis; investigation; methodology; software; validation; visualization; writing – original draft. **Francesco Perini:** Conceptualization; investigation; methodology; supervision; writing – review & editing. **Stefano Bettini:** Writing – review & editing. **Salvatore Mastrangelo:** Writing – review & editing. **Fabio Abeni:** Writing – review & editing. **Giuseppe Conte:** Writing – review & editing. **Donata Marletta:** Writing – review & editing. **Martino Cassandro:** Writing – review & editing. **Umberto Bernabucci:** Writing – review & editing. **Roberta Ciampolini:** Writing – review & editing. **Emiliano Lasagna:** Conceptualization; funding acquisition; project administration; supervision; writing – review & editing.

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CONFLICT OF INTEREST STATEMENT

No potential conflict of interest was reported by the authors.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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