

## Review

# Evolutionary Signatures and Functional Genomics of Stature Associated Loci in Domestic Cattle

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## ABSTRACT

The present review highlights current knowledge on the genetic architecture underlying bovine stature, with a particular focus on major Quantitative Trait Loci (QTL) and candidate genes identified through Genome-Wide Association Studies (GWAS) and fine-mapping efforts. Among these, the pleiomorphic adenoma gene 1 (*PLAG1*) locus on bovine chromosome 14 (*BTA14*) consistently emerges as a principal determinant of stature across diverse breeds, influencing growth through regulatory effects on insulin-like growth factor pathways. Other significant loci, including *MEF2C*, *HMGA2*, and genes within growth hormone signaling pathways, also contribute to body size variation. Evolutionary perspectives reveal the impact of domestication, historical stature reduction, recovery, and the introgression of advantageous alleles between *Bos taurus* and *Bos indicus*. Breed-specific adaptations, particularly in indigenous cattle, highlight genetic diversity linked to environmental resilience, disease resistance, and morphological variation. Despite major advances, challenges remain in addressing missing heritability, limited high-resolution data for local breeds, and the functional validation of noncoding variants. Future directions emphasize the integration of whole-genome sequencing, multi-omics approaches, and targeted functional genomics to elucidate causal mechanisms. Understanding the complex genomic basis of stature not only enhances selection strategies in commercial cattle but also underscores the importance of conserving genetic resources in indigenous breeds, ensuring sustainable improvement and adaptability in the face of changing production and environmental demands.

**Keywords:** Bovine stature, Genome-wide association studies (GWAS), Indigenous cattle, *PLAG1* gene, Polygenic traits

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## INTRODUCTION

Body size is a fundamental quantitative trait that exhibits continuous variation and has significant implications for ecological adaptation, production efficiency, and animal health. In cattle production systems, optimal stature varies according to production goals: in beef cattle, body size and weight are directly linked to meat yield and feed conversion efficiency, whereas in dairy cattle, desired body dimensions depend on management practices and breeding strategies. Stature is a moderately to highly heritable trait with strong correlations to economically important production traits, making it a valuable model for dissecting the genetics of complex traits (Visscher *et al.*, 2007; Kumar *et al.*, 2024). Comparative studies reveal that the genetic architecture of stature differs markedly among species. In humans, height is influenced by numerous small-effect variants under a quasi-infinitesimal model (Lango *et al.*, 2010; Yang *et al.*, 2010), while in dogs, a few large-effect genes, such as IGF1, account for most of

the variation among breeds (Sutter *et al.*, 2007; Boyko *et al.*, 2010; Hayward *et al.*, 2016). In cattle, domestication, historical selection, and breed improvement programs have shaped body size, with the ancestral auroch (*Bos primigenius*) standing about two meters tall compared to modern breeds, which range between 1.1 and 1.5 meters (Karim *et al.*, 2011).

Advances in Genome-Wide Association Studies (GWAS) and high-density Single Nucleotide Polymorphism (SNP) genotyping have identified multiple genomic regions influencing stature, with major Quantitative Trait Loci (QTL) reported on bovine chromosomes 5, 6, 14, and 18. The *PLAG1* gene on *BTA14* consistently shows strong associations with body height across diverse cattle populations (Littlejohn *et al.*, 2012; Karim *et al.*, 2011), while other important loci include *NCAPG-LCORL*, *MEF2C*, *HMGA2*, *FANCI*, and genes involved in hormonal and skeletal growth pathways. Notably, the *PLAG1* QTL is present in both *Bos taurus* and *Bos indicus* cattle despite their deep evolutionary

divergence (Murray *et al.*, 2010), suggesting ancient origins, recurrent selection, or introgression events. Although genomic insights have largely been derived from commercial breeds under intensive selection, indigenous cattle, often characterized by smaller stature and environmental resilience, harbor unique alleles of adaptive and economic importance (Zinovieva *et al.*, 2019). Understanding the interplay between major genes, polygenic background, and environmental adaptation will be crucial for designing sustainable breeding programs that optimize productivity while conserving genetic diversity. This review synthesizes current knowledge on the genetic basis of stature in cattle, emphasizing key genomic regions, evolutionary history, and implications for future breeding strategies.

### Major Genomic Regions and Candidate Genes Influencing Bovine Stature

The genetic control of body size in cattle is polygenic and has been explored extensively through QTL mapping and GWAS. Numerous genomic regions influencing stature have been identified (Bouwman *et al.*, 2018; Purfield *et al.*, 2019; Zepeda-Batista *et al.*, 2021). Among these, bovine chromosome 14 (*BTA14*) is the most consistently reported determinant of stature and body weight in diverse cattle populations (Hoshiba *et al.*, 2013; Fortes *et al.*, 2013; Naserkheil *et al.*, 2020). Fine mapping by Randhawa *et al.*, (2015) identified a selection signal within the 24.79 to 28.25 Mb region on *BTA14* (Ziminet *et al.*, 2009), later refined to 24.80 to 25.08 Mb in *Bostaurus* breeds using whole genome sequencing (Boitard *et al.*, 2016). Abdelmanova *et al.*, (2022) also reported strong associations between SNPs in the 24.5 to 25.2 Mb interval and stature, clearly differentiating high and low stature groups.

Within this key *BTA14* segment, *pleiomorphic adenoma gene 1* (*PLAG1*) has been identified as a major candidate for stature variation. Functional evidence shows that *PLAG1* knockout mice display dwarfism and growth retardation (Hensen *et al.*, 2004). *PLAG1* encodes a transcription factor regulating multiple growth factors, notably *insulin-like growth factor II* (*IGF2*), which is crucial for growth across species (Juma *et al.*, 2016; Fortes *et al.*, 2013). Quantitative trait nucleotides located between *PLAG1* and *CHCHD7* alter promoter activity and nuclear factor binding, affecting the expression of a group of seven genes within the region. The *BTA14* region is also a pleiotropic QTL influencing reproduction traits alongside stature (Saatchi *et al.*, 2014; Hartati *et al.*, 2015; Pereira *et al.*, 2016). Utsunomiya *et al.*, (2017) reported that a derived haplotype within *PLAG1* played a major role in stature recovery in modern cattle. Beyond *BTA14*, other chromosomes also harbor important loci. Bolormaa *et*

*al.*, (2011) detected significant regions on *BTA2*, 3, 5, and 6 associated with stature in dairy and beef breeds. Comparative analysis by Pryce *et al.*, (2011) found orthologous genes influencing stature in both humans and cattle, including *NCAPG*, the *PLAG1-CHCHD7-RDHE2* cluster, and *HMGA2*, all of which are linked to cell cycle regulation. Guo *et al.*, (2012) identified a pleiotropic region on *BTA25* affecting stature, milk yield, and other traits in Brown Swiss cattle, with candidate genes such as *IGFAL* and *IL8*. Abdelmanova *et al.*, (2022) also highlighted SNPs on *BTA4* (77.3 to 77.8 Mb) and other growth-related genes in different cattle populations.

*Myocyte Enhancer Factor 2C* (*MEF2C*), located at 90.5 Mb on *BTA7*, is another promising candidate gene. It is associated with QTL for body and carcass weight (Cole *et al.*, 2011) and plays essential roles in muscle, bone, and neural development (Panda *et al.*, 2014; Rashid *et al.*, 2014). *MEF2C* also affects reproduction and meat quality traits (Oteru *et al.*, 2012; Sevane *et al.*, 2013). In Chinese native cattle, variants within *MEF2C* were linked to body weight, hucklebone width, and withers height (Cao *et al.*, 2016). Additional genes, such as *Short Stature Homeobox* (*SHOX*) on *BTA2*, detected via copy number variations, and *NPR2* on *BTA8* are associated with skeletal growth and have human orthologs involved in short stature syndromes (da Silva *et al.*, 2016). Chen *et al.*, (2020) identified an SNP near *LCORL* associated with ischium width in Brahman and Yunling cattle, while *CNTNAP5* was associated with hip cross height. In Beninese indigenous cattle, significant SNPs for withers and sacrum height were found near genes including *VEPH1*, *PIK3R6*, *PIK3R1*, *SSH2*, *CCDC117*, and *LYPD8* (Vanvanhossou *et al.*, 2020).

Studies on *Bos indicus* breeds have added further insight. Dixit *et al.*, (2020, 2021) reported differences in runs of homozygosity on *BTA3* and *BTA5* between large and small statured breeds, with genes such as *PTGFR* and *HMGA2* located within these regions. *HMGA2* polymorphisms were specifically linked to short stature in Vechur cattle and have been associated with size variation across multiple species (Pryce *et al.*, 2011). Tijjani *et al.*, (2019) found positive selection signatures in the endangered West African Muturu breed in genes such as *GHR* and *GHRHR*, which influence growth and reflect adaptation to small body size. Meta-analysis of data from over 58,000 cattle identified lead variants across 163 genomic regions explaining a large proportion of phenotypic variance, with the strongest association at *PLAG1* (Bouwman *et al.*, 2018). Many lead variants were located in noncoding regulatory regions, highlighting the importance of gene expression control in stature variation. Comparative evidence

**Table 1:** Genomic regions, QTLs, and candidate genes associated with stature and their biological functions in cattle.

Genomic Region/QTL/ Candidate Genes	Biological Function	References
BTA14 (24.5-25.2 Mb)	A major pleiotropic QTL that significantly influences stature and body size, as well as various reproduction traits in cattle. It's a key determinant of stature and body weight across diverse cattle populations.	Pereira <i>et al.</i> , (2016) Bouwman <i>et al.</i> , (2018) Naserkheil <i>et al.</i> , (2020) Abdelmanova <i>et al.</i> , (2022)
PLAG1	A transcription factor within the BTA14 region that regulates the expression of growth factors like IGF2. Its role in growth is confirmed by studies showing that knockout mice exhibit dwarfism.	Fortes <i>et al.</i> , (2013) Juma <i>et al.</i> , (2016) Utsunomiya <i>et al.</i> , (2017)
BTA2, 3, 5, 6	These genomic regions contain shared genetic factors that influence body size in both dairy and beef cattle.	Bolormaa <i>et al.</i> , (2011)
NCAPG	Associated with fetal growth and carcass size, showing a conserved role in regulating growth physiology.	
PLAG1-CHCHD7-RDHE2 Cluster	This gene cluster on BTA14 shows a conserved role in regulating growth, primarily through cell division and cell cycle regulation.	Pryce <i>et al.</i> , (2011)
HMGA2	A gene consistently implicated in human stature and body size variation, showing a conserved role in regulating growth physiology in cattle. It has been specifically linked to short stature in certain <i>Bos indicus</i> breeds.	Pryce <i>et al.</i> , (2011) Dixit <i>et al.</i> , (2020) Dixit <i>et al.</i> , (2021)
BTA25 (including IGFAL & IL8)	A pleiotropic signal influencing stature, milk yield, and other production traits in Brown Swiss cattle.	Guo <i>et al.</i> , (2012)
BTA4 (77.3-77.8 Mb)	Contains key SNPs associated with stature and genes involved in metabolism and growth.	Abdelmanova <i>et al.</i> , (2022)
MEF2C	A transcription factor on BTA7 (90.5 Mb) that plays essential roles in muscle, bone, and neural development, with variants and haplotypes linked to body weight, hucklebone width, and withers height.	Sevane <i>et al.</i> , (2013) Panda <i>et al.</i> , (2014) Rashid <i>et al.</i> , (2014) Cao <i>et al.</i> , (2016)
SHOX	Located on BTA2, this gene is associated with stature and skeletal growth. Mutations in its human ortholog are linked to various short stature syndromes.	da Silva <i>et al.</i> , (2016)
NPR2	Found on BTA8 and associated with stature and skeletal growth.	
LCORL & CNTNAP5	A highly significant SNP downstream of LCORL is associated with ischium width, while CNTNAP5 is associated with hip cross height.	Chen <i>et al.</i> , (2020)
VEPH1, PIK3R6, PIK3R1, SSH2, CCDC117 & LYPD8	These genes are associated with height at withers and sacrum height in Beninese indigenous cattle, with some overlapping with adaptive traits.	Vanvanhossou <i>et al.</i> , (2020)
PTGFR	Located on chromosome 3 within an ROH island, it is associated with milk production.	Dixit <i>et al.</i> , (2020) Dixit <i>et al.</i> , (2021)
GHR & GHRHR	These genes showed signatures of positive selection in Muturu cattle, reflecting adaptation to their local environment and small body size.	Tijjani <i>et al.</i> , (2019)

from multiple mammals points to conserved growth regulators such as those in the *IGF2* pathway.

The collective findings reveal that bovine stature results from the combined effect of major loci like *PLAG1*, *NCAPG*, *MEF2C*, *HMGA2*, and numerous small-effect

variants, forming a complex genetic architecture. These discoveries not only deepen the understanding of growth biology but also provide potential targets for genomic selection strategies aimed at improving cattle body size while considering breed-specific needs and environmental adaptation.

## Evolutionary Dynamics and Breed-Specific Adaptations of Stature

The genetic architecture of stature in cattle reflects complex evolutionary dynamics shaped by both natural and artificial selection, from the large ancestral auroch to modern domesticated breeds. A striking example is the persistence of the *PLAG1* QTL in both *Bos taurus* and *Bos indicus* despite their deep evolutionary divergence (Murray *et al.*, 2010). This could result from ancient variants in the common ancestral *Bos primigenius* population, independent mutations in each lineage, or introgression of advantageous alleles between subspecies. Utsunomiya *et al.*, (2017) reported that a derived *PLAG1* haplotype, likely originating in Northwestern Europe between the sixteenth and eighteenth centuries, contributed to the recovery of stature in modern-day cattle and subsequently spread worldwide, including into *B. indicus* breeds such as Nellore and Brahman via crossbreeding (Fortes *et al.*, 2013; Decker *et al.*, 2014; O'Brien *et al.*, 2015; Utsunomiya *et al.*, 2014). Beyond *PLAG1*, breed-specific adaptations reveal diverse genetic trajectories. For instance, the endangered West African Muturu breed, known for trypanotolerance and short stature, shows selection signals in genes such as *GHR* and *GHRHR* linked to growth regulation (Tijjani *et al.*, 2019). Similarly, the short-statured Indian Vechur breed exhibits runs of homozygosity (ROH) islands containing *PTGFR* and *HMGA2*, with *HMGA2* polymorphisms associated with differences in stature (Dixit *et al.*, 2020; Dixit *et al.*, 2021). Stature-associated SNPs also differentiate high- and low-stature cattle, reflecting distinct breeding histories where primitive breeds were selected for environmental adaptation and beef production, while dairy breeds underwent intensive selection for increased height and milk yield (Abdelmanova *et al.*, 2022). In Beninese indigenous cattle, morphometric trait-associated genomic regions overlap with adaptive traits such as disease resistance and feed efficiency, suggesting pleiotropy or strong genetic correlations shaped by natural selection and farmer preferences (Vanvanhossou *et al.*, 2020). Such findings highlight the need to consider environmental context and breed history when interpreting stature genetics and underscore the conservation value of indigenous cattle as reservoirs of unique genetic diversity (Zinovieva *et al.*, 2019).

## Challenges and Future Directions

Despite significant advancements in unraveling the genomic signatures of bovine stature, several challenges remain. A significant issue is the “missing heritability” of highly polygenic traits, as detected variants explain only part of the observed variation.

Large-scale studies, such as Bouwman *et al.*, (2018), have mapped multiple loci, yet many gene-gene and gene-environment interactions remain unresolved. Although candidate genes like *PLAG1* and *MEF2C* have been implicated in growth regulation, the functional mechanisms by which many noncoding regulatory variants affect gene expression and phenotype require deeper investigation (Fink *et al.*, 2017). Functional genomics approaches, including CRISPR-based gene editing and regulatory element analysis, will be vital to establish causality. Data limitations also hinder progress; many local and indigenous breeds lack high-resolution genomic data and detailed phenotypic records, restricting the discovery of novel alleles for resilience and productivity. Prioritizing whole-genome sequencing and generating comprehensive datasets for underrepresented breeds would capture rare and structural variants missed by SNP arrays. Integrating multi-omics data, such as transcriptomics and proteomics, with genomic analyses could yield a more complete understanding of biological pathways underlying stature variation. Translating these findings into accessible, cost-effective breeding tools remains a pressing challenge, requiring collaboration between researchers, breeders, and policymakers to ensure that advances benefit both commercial and smallholder production systems worldwide.

## CONCLUSION

The comprehensive genomic studies over the past decades have significantly advanced our understanding of bovine stature, revealing it as a highly polygenic trait influenced by numerous genomic regions and candidate genes. The consistent identification of the *PLAG1* locus on *BTA14* as a major determinant, alongside other key genes like *MEF2C*, *HMGA2*, and those involved in the growth hormone pathway, underscores the intricate genetic landscape governing cattle body size. This review has not only shed light on the conserved genetic mechanisms across mammals but also illuminated the profound impact of evolutionary forces, including historical domestication and breed-specific selection pressures, in shaping stature phenotypes. The findings hold immense potential for modern breeding strategies, particularly in facilitating marker-assisted selection for desired stature traits in commercial cattle. Crucially, these studies also highlight the importance of recognizing and leveraging the unique genetic diversity and adaptive traits present in indigenous cattle populations. Moving forward, addressing challenges such as missing heritability, ensuring greater data diversity and resolution for understudied breeds, and integrating multi-omics approaches will be essential. Ultimately, the successful translation of these complex genomic insights into practical breeding tools will be

paramount for sustainable livestock development, enabling both enhanced productivity and the crucial preservation of genetic resources.

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