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Unraveling genomic regions with transmission ratio distortion harboring putative lethal alleles and their biological implications in Nellore cattle from experimental selection lines

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Abstract

Transmission Ratio Distortion (**TRD**) refers to deviations from expected Mendelian inheritance patterns when alleles from heterozygous parents are transmitted at frequencies different from the expected 50%, influenced by biological mechanisms affecting reproduction. Therefore, this study aimed to 1) characterize genomic regions exhibiting TRD patterns in Nellore cattle (*Bos taurus indicus*), 2) detect TRD regions potentially harboring semilethal or lethal alleles, and 3) identify candidate genes and perform functional genomic enrichment analyses to reveal quantitative trait loci (**QTL**), biological processes, and metabolic pathways associated with TRD regions. TRD analyses were performed on a genomic dataset of 3,351 animals with 612,154 autosomal single nucleotide polymorphism (**SNP**) markers aligned to the ARS-UCD1.2 *Bos taurus* genome assembly. The software TRDscan v.2.0 was used to evaluate allelic (overall and parent-specific) and genotypic (additive and dominance) parametrizations of TRD effects using a Bayesian framework. Gene annotation, QTL identification, and functional genomic enrichment were conducted based on the locations of the identified TRD regions. A total of 37,783 SNPs and 174,190 haplotypes exhibiting TRD were identified, corresponding to 1,249 genomic regions distributed across all *Bos taurus* autosomes (802 overall TRD, 191 parent-specific TRD, and 256 genotypic TRD). Among these, 73 allelic TRD regions and 59 genotypic TRD regions were identified as potentially harboring semilethal or lethal alleles, with the highest number of underrepresented offspring reaching 1,501 individuals. We identified 2,265 candidate genes based on gene annotation, while functional enrichment analyses enabled the identification of 200 significant Gene Ontology (**GO**) terms, and 2 pathways involved in embryo development, morphogenesis, and growth regulation (P-value < 0.05). Additionally, significant enrichment of QTL associated with production and reproduction traits was observed within these TRD regions (P-value < 0.05). These findings underscore the critical importance of integrating TRD information into genomic selection strategies to enhance productive efficiency while mitigating the spread of deleterious alleles that adversely affect reproduction and embryo survival in Nellore cattle.

Lay Summary

This study investigated Transmission Ratio Distortion (**TRD**) in Nellore cattle, a genetic phenomenon when alleles are transmitted at frequencies differing from the expected 50% due to biological factors influencing reproduction. The primary objectives of this study were to characterize genomic regions with TRD patterns, detect lethal alleles, and identify biological mechanisms underlying TRD. Using genotypes from 3,351 individuals with 612,154 genetic markers, 1,249 genomic regions exhibiting TRD were identified, some of which are linked to genes involved in embryo development and reproductive processes. Some TRD regions were associated with a high number of underrepresented offspring, suggesting the presence of harmful alleles that could negatively impact cattle fertility and survival. A total of 2,265 candidate genes overlapped with TRD regions, and the functional genomic enrichment analyses revealed key biological processes, such as embryo development and growth regulation. These results highlight the importance of incorporating TRD information into breeding strategies to enhance productive efficiency while minimizing the transmission of deleterious alleles that could negatively affect reproduction and embryo survival in cattle.

Key words: beef cattle, embryo development, functional annotation, Mendelian inheritance, Quantitative Trait Loci, reproduction

Abbreviations: BF, Bayes factor; BP, biological processes; BTA, *Bos taurus* autosome; CC, cellular components; DIC, Deviance Information Criterion; EBVs, estimated breeding values; GO, Gene Ontology; GWAS, genome-wide association study; KEGG, Kyoto Encyclopedia of Genes and Genomes; LD, linkage disequilibrium; lncRNA, long noncoding RNA; MF, metabolic functions; miRNAs, microRNAs; misc_RNA, miscellaneous RNA; NeC, Nellore Control line; NeS, Nellore Selection line; NeT, Nellore Traditional line; QTL, quantitative trait loci; r^2, coefficient of determination for linkage disequilibrium; RFI, residual feed intake; rRNA, ribosomal RNA; SNP, single nucleotide polymorphism; snRNAs, small nuclear RNAs; *TR_V_gene*, T-cell receptor variable gene; TRD, transmission ratio distortion; WGS, whole-genome sequencing; YW, yearling weight; α, overall TRD effect; αd, dam TRD effect; αg, additive TRD effect; αs, sire TRD effect; δg, dominance TRD effect

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Introduction

Transmission Ratio Distortion (**TRD**) refers to deviations from expected Mendelian inheritance patterns, when specific alleles are disproportionately represented among offspring (Huang et al., 2013; Casellas et al., 2017; Fishman and Mcintosh, 2019). TRD can result from a variety of biological processes (**BP**), including meiotic drive, gametic selection, zygotic selection, and embryonic or fetal losses (Huang et al., 2013; Fishman and Mcintosh, 2019; Id-Lahoucine et al., 2023a). These mechanisms do not always involve deviations in allele transmission rates but may instead affect the viability of specific genotypes, ultimately altering the proportion of alleles observed among live individuals. In animal breeding, TRD has garnered increasing interest as it reveals non-Mendelian inheritance mechanisms that may influence reproductive success (Abdalla et al., 2020; Vázquez-Gómez et al., 2020; Id-Lahoucine et al., 2023a; Laseca et al., 2023). The investigation of TRD can provide valuable information about genomic regions associated with critical biological outcomes, such as fertility impairments, embryonic lethality, and the segregation of deleterious alleles (Abdalla et al., 2020; Id-Lahoucine et al., 2023a).

Genomic regions exhibiting TRD are particularly relevant due to their potential to harbor putative semilethal or lethal alleles. These alleles disrupt essential BP or metabolic pathways, often causing developmental disorders and non-Mendelian inheritance patterns (VanRaden et al., 2011; Amorim et al., 2017; Bosse et al., 2019). Genetic variants with harmful effects produce distinct TRD signals by impairing reproduction and newborn survival, frequently leading to embryonic lethality or reduced fitness in heterozygous or homozygous states (Fishman and Mcintosh, 2019; Abdalla et al., 2020). This issue poses significant challenges in livestock breeding, especially in populations under intense selection pressure, where inbreeding elevates the frequency and homozygosity of deleterious alleles (Wright, 1922; VanRaden et al., 2011; Bosse et al., 2019). Consequently, identifying TRD-associated genomic regions is critical for detecting and managing these alleles before their spread in the population.

In Holstein cattle (*Bos taurus taurus*), Id-Lahoucine et al. (2023b) identified 590 TRD regions, linking specific genomic regions to increased risks of nonpregnancy (27%) and stillbirth events (254%). Similarly, in Angus cattle (*Bos taurus taurus*), Id-Lahoucine et al. (2023c) uncovered 851 genomic regions with evidence of TRD, including 71 regions considered to harbor lethal or semilethal alleles. These findings highlight the substantial impact of TRD regions on reproductive performance, emphasizing the need for exploring this phenomenon in other breeds. However, despite the growing interest in TRD, its occurrence and biological implications in Zebu cattle populations (*Bos taurus indicus*) remain poorly understood. Nellore is the predominant Zebu breed raised for beef production in tropical regions due to its greater resilience to environmental challenges (Mota et al., 2020; Silva Neto et al., 2023; Rodrigues et al., 2024a), but to the best of our knowledge, no studies have explored TRD-associated genomic regions in this breed. Investigating TRD in Nellore cattle presents an opportunity to identify genomic regions harboring semilethal or lethal alleles and to elucidate their biological functions.

This study aims to identify genomic regions that exhibit TRD patterns in a Nellore cattle population subjected to 44 yr of artificial selection in a closed experimental breeding program design. Specifically, we aim to detect TRD regions that may harbor semilethal or lethal alleles, considering both allelic and genotypic parametrizations. Furthermore, candidate genes within these regions will be identified, and functional enrichment analyses will be performed to uncover BP and metabolic pathways underlying TRD regions. These findings are expected to contribute to the understanding of TRD in Nellore cattle, laying the foundation for future studies in Zebu breeds and informing strategies to enhance reproductive efficiency and sustainability in livestock production.

Materials and Methods

Ethical statement

Data was obtained from an existing database, and therefore, approval from the Ethics Committee was not required.

Population

All datasets used in this study come from a Nellore cattle population developed and maintained within an experimental breeding program at the Beef Cattle Research Center (Institute of Animal Science—IZ, Sertãozinho, SP, Brazil). This population includes three distinct selection lines subjected to 44 years of genetic selection (1980–2024), with varying criteria for yearling weight (**YW**) applied over the decades. The program began in 1980 with the objective of selecting animals based on YW, measured at 378 days of age for young bulls and 550 d of age for heifers.

Three selection lines were established: Line 1—Nellore Control (NeC), in which animals were selected based on YW close to the average of their contemporary group within the same birth year and herd; Line 2—Nellore Selection (NeS), where animals were selected for higher YW within their birth year and herd; and Line 3—Nellore Traditional (NeT), which involved selecting for higher YW and, since 2008, also selected considering lower estimated breeding values (**EBVs**) for residual feed intake (**RFI**) within the same birth year and herd. These selection lines are closed, meaning only bulls and dams born within the respective lines are used for breeding, with exception of NeT, which occasionally received animals from NeS. Inbreeding levels are carefully managed through planned matings based on co-ancestry coefficients (Bem et al., 2024).

The evaluated population holds significant relevance for the Nellore cattle population in Brazil, as the founding animals of the three selection lines were representative sires from the breed's national genetic foundation (Cyrillo et al., 2001; Mercadante et al., 2003). Furthermore, genetic material (semen and embryos) from elite animals (NeS and NeT herds) with superior EBVs for growth, feed efficiency, carcass, and reproductive traits have been commercialized and used for breeding across various Brazilian states and in other Latin American countries. Despite being closed herds under selection for 44 years, the evaluated selection lines remain highly relevant to the genetic improvement of the Nellore breed. Further details regarding the experimental breeding program and the selection lines can be found in Benfica et al. (2024) and Rodrigues et al. (2024a).

Genomic and pedigree data

The pedigree file used for the TRD analyses comprised 13,088 individuals, including 486 sires and 3,007 dams. The genomic dataset consisted of 3,351 animals, of which 1,766

were males and 1,581 were females, genotyped using three single nucleotide polymorphism (**SNP**) chip assays. Detailed information about the three SNP chips used, as well as the distribution of animals per chip, can be found in Rodrigues et al. (2024b) which utilized the same genotype database. Among these, 2,571 animals genotyped with medium-density SNP panels (50K and 75K SNP panels) were imputed to the Illumina BovineHD panel (770K) using FImpute v3 software (Sargolzaei et al., 2014), with a reference population of 6,862 animals genotyped on the HD SNP chip. Before imputation, genotype quality control was conducted, which involved the exclusion of markers that were 1) monomorphic, 2) had duplicated coordinates, 3) were located on nonautosomal chromosomes, and 4) had a GenCall score below 0.90. Genome coordinates for the imputation analyses were based on the ARS-UCD1.2 *Bos taurus* genome assembly (Rosen et al., 2020). The expected accuracy of genotype imputation exceeded 0.97 (Mota et al., 2024). After genotype imputation, the genomic dataset included 612,154 autosomal SNP markers and 3,351 animals that were considered for the TRD analyses. Descriptive statistics related to the pedigree and genomic datasets are presented in Table 1.

Identification of TRD regions

Specifically, the TRD analyses rely on the number of genotyped parent-offspring trios (individual–sire–dam), as the availability of trios can enhance the statistical power for estimating TRD parameters (Id-Lahoucine et al., 2019). Each trio enables the evaluation of whether the transmission of alleles from heterozygous parents deviates from the expected Mendelian ratio, a key aspect in identifying regions of the genome that exhibit TRD patterns. The number of informative offspring, defined as the number of progenies derived from one or both heterozygous parents, is the basis for detecting deviations, as they allow for the assessment of whether one allele is transmitted more or less frequently than expected. A larger number of trios increases the reliability and accuracy of TRD estimates by minimizing random TRD and enhancing the ability to detect distortions (Id-Lahoucine et al., 2019). In the present study, 1,891 trios were available for analyses (Table 1). Potential TRD regions were identified using two specific approaches: 1) allelic parametrization of TRD (Casellas et al., 2014) and 2) genotypic parametrization of TRD (Casellas et al., 2012, 2020), using both SNP-by-SNP and haplotype-based methods (Id-Lahoucine et al., 2019).

Table 1. Descriptive statistics of the pedigree and genomic datasets used for TRD analyses in experimental lines of Nellore cattle

Item	Value
SNPs[1] evaluated	612,154
Individuals in the pedigree	13,088
Individuals genotyped	3,351
Sires genotyped	264
Dams genotyped	1,295
Genotyped Individual–Sire pairs	2,476
Genotyped Individual–Dam pairs	2,212
Genotyped Individual–Sire–Dam trios	1,891

[1]Single nucleotide polymorphism.

The allelic parameterization of TRD describes the probability (P) of allele transmission from heterozygous parents (A/B) to their offspring. This model incorporates a single overall TRD effect (α) in a parent-unspecific framework or distinguishes between sire-specific (α_s) and dam-specific (α_d) TRD effects in a parent-specific model (Casellas et al., 2014, 2020). The probabilities for both the parent-unspecific and parent-specific models can be expressed as follows:

$$P(A) = 1 - P(B) = 0.5 + \alpha \text{ and}$$
$$P(B) = 1 - P(A) = 0.5 + \alpha$$

$$P_i(A) = 1 - P_i(B) = 0.5 + \alpha_i \text{ and } P_i(B) = 1 - P_i(A) = 0.5 + \alpha_i, \text{ with } i = [s, d]$$

where α, α_s, and α_d are TRD parameters assuming flat priors within a parametric space ranging from −0.5 to 0.5 (Id-Lahoucine et al., 2019). In a Bayesian inference framework, the conditional posterior probabilities of the TRD parameters can be defined as:

$$p(\alpha|\, y) \propto (p\,|\alpha)\, p(\alpha) \text{ and } p(\alpha_s,\ \alpha_d \mid y) \propto p(y \mid \alpha_s,\ \alpha_d)\, p(\alpha_s)\, p(\alpha_d)$$

where y is the vector of genotypes of the offspring generation.

The genotypic parameterization of TRD incorporates both additive (α_g) and dominance (δ_g) parameters without considering the origin of each allele (Casellas et al., 2012, 2020). The assumed probability of offspring (P_{off}) resulting from a heterozygous-by-heterozygous mating is as follows:

$$P_{off}(AA) = \frac{(1 + \alpha_g - \delta_g)}{4},$$
$$P_{off}(AB) = \frac{(1 + \delta_g)}{2} \text{ and}$$
$$P_{off}(BB) = \frac{(1 + \alpha_g - \delta_g)}{4}$$

where α_g and δ_g are additive- and dominance-TRD parameters, respectively. The frequencies in offspring from heterozygous-by-homozygous matings were also obtained to guarantee that $P_{off}(AA) + P_{off}(AB) + P_{off}(BB) = 1$. Under Bayesian implementation, the conditional posterior probabilities of the TRD parameters considering the genotypic parametrization were defined as:

$$P(\alpha_g, \delta_g \mid y) \propto P(y \mid \alpha_g, \delta_g)\, P(\alpha_g)\ p(p\alpha_g, \delta_g)$$

where y is the vector of genotypes of the offspring generation. Priors were assumed for α_g and δ_g considering a parametric space of −1 to 1 (Id-Lahoucine et al., 2019).

The allelic parameterization of TRD ranges from −0.5 to 0.5 as it models deviations from Mendelian expectations in allele transmission from heterozygous parents, reflecting biases in inheritance. In contrast, the genotypic parameterization, ranging from −1 to 1, does not account for parental origin but instead models genotype frequencies directly, incorporating additive and dominance effects to capture both transmission and segregation distortions.

The TRD was evaluated on an SNP-by-SNP basis and across different haplotype sizes (5, 10, 15, 20, and 25 SNPs) considering the sliding windows method (Li et al., 2007; Guo

et al., 2009) within the 612,514 autosomal SNPs available for this study. For the haplotype sliding windows analyses, the biallelic haplotypes and heterozygous pairwise combinations procedures were considered (Id-Lahoucine et al., 2019). All analyses were performed within a Bayesian framework using the TRDscan v.2.0 software (Id-Lahoucine et al., 2019), employing a single Monte Carlo Markov chain with 110,000 iterations, where the first 10,000 iterations were discarded as burn-in, and an interval of 10 iterations were sampled to estimate the TRD parameters. The overall (parent-unspecific), parent-specific, and genotypic parameterizations of TRD were compared using the Deviance Information Criterion to assess the adjustment of these models and inheritance patterns of SNPs and haplotypes.

TRD events were identified based on quality control criteria outlined by Id-Lahoucine et al. (2019; 2023a; 2023b; 2023c): 1) For each SNP or haplotype window, a minimum number of 20 heterozygous sires, 50 heterozygous dams, and 1,000 informative offspring were required to ensure greater statistical power in the inference regarding the TRD phenomena; 2) TRD regions that presented an approximate empirical null distribution of TRD > 0.001% margin error were discarded to minimize the likelihood of false positives due to random variation (gamete sampling). Details regarding the empirical null distribution parameters can be found in Id-Lahoucine et al. (2019); 3) TRD regions with a coefficient of variation greater than 20% for the TRD effects were excluded to ensure consistency, as regions with a narrower confidence interval are more reliable; and, 4) regions with fewer than four heterozygous sires exhibiting highly skewed transmission, which could be indicative of genotyping errors, were discarded.

Following these steps, the statistical significance of the TRD effect was evaluated using the Bayes factor (**BF**; Kass and Raftery, 1995). To be considered as statistically significant, SNPs were required to have a Log_{10} (BF) > 100, and haplotype windows (5, 10, 15, 20, and 25 SNPs) needed to have a Log_{10} BF > 50 for the TRD effect. These thresholds were defined to minimize the risk of false positives and to prioritize the most biologically meaningful TRD signals supported by both the data and statistical evidence. Specifically, the threshold applied corresponded approximately to the top 0.01% of all TRD signals detected, serving as a highly stringent filter to ensure robustness given the limitations of the dataset. A similar strategy has been previously employed in epistatic TRD analyses to focus on the most significant results (Id-Lahoucine et al., 2023d). The threshold values for the BF in SNP-by-SNP and haplotype window analyses differed due to the greater number of parameters and combinations that need to be estimated in the haplotypes analyses, which may result in a lower BF for this approach (Id-Lahoucine et al., 2019). Only TRD regions meeting all these criteria were considered for further analyses.

Since many SNPs or haplotypes could be observed with evidence of TRD events and located close to each other due to high linkage disequilibrium (**LD**), genomic regions were defined. The LD between the SNPs was calculated using the PLINK software (Purcell et al., 2007), and markers located within 100 Kb (upstream and downstream) of each other on the same chromosome, with an r^2 value greater than 0.80, were grouped and classified as part of the same genomic region. After defining the genomic regions, TRD regions were identified, and the genetic variant (SNP or haplotype window) with the highest BF within each genomic region exhibiting evidence of TRD was selected to represent the TRD event within that region.

Detection of TRD regions harboring potential lethal alleles

After identifying the genomic regions associated with allelic and genotypic TRD patterns, candidate regions potentially harboring lethal or semilethal alleles were identified based on the number of underrepresented offspring. In the context of TRD analyses, underrepresented offspring are those whose expected inheritance pattern is not observed, resulting in a lower frequency of a given allele or genotype than anticipated under Mendelian expectations (Abdalla et al., 2020). These offspring are indicative of a selective disadvantage for the under-transmitted allele, possibly due to lethal or semilethal effects that impact the viability of the offspring (Id-Lahoucine et al., 2023c).

For the allelic TRD model, the number of underrepresented offspring ($N_{alellic\ underrepresented}$) was calculated as:

$$N_{alellicunderrepresented} = N_{informative} \times 2 \times |\alpha|$$

where $N_{informative}$ is the number of informative offspring and α is the estimated allelic TRD effect (overall, sire-specific, or dam-specific TRD effect).

In the genotypic TRD model, underrepresented genotypes were identified by comparing observed genotype counts with those expected under Mendelian inheritance across specific mating types. For instance, the expected genotype proportions under the null hypothesis (no TRD) are:

$$AA \times AB = 50\%\ AA_1, 50\%\ AB_1;$$
$$AB \times BB = 50\%\ AB_2, 50\%\ BB_2;\ \text{and}$$
$$AB \times AB = 25\%\ AA_3, 50\%\ AB_3, 25\%\ BB_3$$

where AA_1 and AB_1 are the offspring genotypes from $AA \times AB$ matings; AB_2 and BB_2 are the offspring genotypes from $AB \times BB$ matings; and AA_3, AB_3, and BB_3 are the offspring genotypes from $AB \times AB$ matings.

Accordingly, the number of underrepresented offspring ($N_{genotypic\ underrepresented}$) in the genotypic model was calculated based on deviations from these expectations using the following expression:

$$N_{genotypic\ underrepresented} = (AA_1 - AB_1) + (AB_2 - BB_2) + (2 \times AA_3 - AB_3) + (AA_3 - BB_3)$$

To ensure comprehensive detection of TRD effects, reciprocal mating types (e.g., *AA* sire × *AB* dam and *AB* sire × *AA* dam) were both considered in the analyses. Genomic regions were prioritized as putative carriers of lethal or semilethal alleles based on model-specific thresholds established to capture biologically relevant deviations from Mendelian inheritance. In the allelic TRD model, regions were selected when the estimated TRD effect ($|\alpha|$, $|\alpha_s|$, or $|\alpha_d|$) was ≥ 0.20, and the number of underrepresented offspring exceeded 1,000. For the genotypic TRD model, candidate regions were identified when the additive effect ($|\alpha_g|$) exceeded 0.50, the dominance TRD effect ($|\delta_g|$) exceeded 0.10, and the total number of underrepresented offspring also surpassed 1,000. These thresholds were adopted to ensure the selection of regions with robust evidence of transmission distortion and potential impacts on embryonic or postnatal viability.

Table 2. SNPs, haplotypes, and genomic regions associated with TRD in Nellore cattle

Parameter	Number
SNPs exhibiting TRD	37,783
Haplotypes exhibiting TRD	174,190
Genomic regions exhibiting TRD	1,249
Overall-TRD	802
Parent-specific TRD	191
Genotypic-TRD	256

Gene annotation, QTL identification, and functional enrichment analyses

The genomic regions identified as being associated with allelic or genotypic TRD patterns were used for gene annotation and subsequent functional enrichment analyses. Gene annotation and identification of Quantitative Trait Loci (**QTL**) overlapping with TRD regions were performed using the GALLO R package (Fonseca et al., 2020). For gene annotation, data from the Ensembl database for *Bos taurus* and the ARS-UCD1.2 genome assembly (Rosen et al., 2020) were utilized. The annotation of QTL was performed using data from the Cattle QTL Database (Hu et al., 2022), with a focus on QTL associated with production, fertility, and reproduction traits. This approach contributes to identifying specific TRD regions overlapping with QTLs associated with production efficiency traits under direct selection in the evaluated population (YW and RFI). Such findings could provide evidence for the presence of TRD in genomic regions influencing the phenotypic expression of target traits. Furthermore, QTLs associated with reproductive traits were emphasized due to the critical role of reproduction in shaping non-Mendelian patterns of inheritance and its well-documented potential to drive TRD events (Huang et al., 2013; Fishman and Mcintosh, 2019).

Positional candidate genes were further investigated for their functional profiles through genomic enrichment analyses of Gene Ontology (**GO**) terms related to BP, metabolic functions (**MF**), and cellular components (**CC**), as well as the Kyoto Encyclopedia of Genes and Genomes (**KEGG**) pathways. Functional enrichment analyses were conducted using the gprofiler2 R package (Kolberg et al., 2023). The Bonferroni correction for multiple testing was applied to calculate *P*-values for gene and QTL enrichment analyses, with a significance threshold set at 0.05.

Results

Identification of TRD regions

Table 2 summarizes the number of SNPs, haplotypes, and genomic regions associated with TRD based on the established criteria for identifying potential TRD events. A total of 37,783 SNPs exhibited evidence of TRD with a Log_{10} BF > 100, and 174,190 haplotypes had a Log_{10} BF > 50 with different window sizes (comprising 5, 10, 15, 20, or 25 SNPs). The highest Log_{10} BF observed for the overall, parent-specific, and genotypic TRD were 252.43, 160.71, and 145.66, respectively. Manhattan plots depicting the BF values for the overall TRD effect considering SNP-by-SNP and the different haplotype window sizes are presented in Figure 1.

Considering the SNPs (n = 35,500) and haplotypes (n = 160,231) associated with the overall TRD event, the mean α (± standard deviation) was 0.058 ± 0.001, with the most extreme value observed on BTA10 (100.20 Mb) with 0.431 ± 0.007. For SNPs (n = 1,688) and haplotypes (n = 9,784) associated with parent-specific TRD effects, it was observed that in certain genomic regions, sires and dams exhibited opposite directions of TRD effects. This suggests that certain alleles were transmitted preferentially by sires but less so by dams, while others were transmitted preferentially by dams but to a lesser extent by sires. Nevertheless, the largest α_s observed was 0.445 ± 0.010 (BTA9, 95.15 Mb), with an average of 0.086 ± 0.001. For α_d, the largest observed effect was 0.443 ± 0.010 (BTA18, 64.66 Mb), with an average of 0.099 ± 0.012. Regarding the genotypic model of TRD, it was observed that additive effects exhibited a higher Log_{10} BF compared to dominance effects, indicating stronger and more decisive evidence for additive effects over dominance effects. For the SNPs (n = 595) and haplotypes (n = 4,175) where the genotypic parameterization of TRD effects provided a more accurate description of the transmission pattern in the respective regions, the mean α_g was −0.129 ± 0.001, with a minimum value of −0.994 ± 0.001 (BTA24, 43.42 Mb) and a maximum value of 0.992 ± 0.001 (BTA24, 43.41), while the δ_g ranged from −0.196 ± 0.024 (BTA4, 101.76 Mb) to 0.022 ± 0.023 (BTA19, 16.41 Mb) with an average value of −0.110 ± 0.023.

It is important to note that many of the SNPs and haplotype windows showing evidence of TRD were mapped to the same genomic regions. For instance, some regions exhibited consistent TRD patterns where a single SNP, along with all haplotype windows containing that SNP were associated with the same TRD effect. Furthermore, these SNPs and haplotypes were grouped into genomic regions based on LD between adjacent SNPs in the same chromosome. As a result, 1,249 genomic regions were associated with TRD, categorized into three types: overall TRD (802 regions), parent-specific TRD (191 regions), and genotypic TRD (256 regions) (Table 2). None of the TRD regions identified in this study overlapped with those previously reported in *Bos taurus taurus* populations. The genomic regions exhibiting TRD signals covered approximately 9.22% of the bovine genome, corresponding to a total of ~249.8 Mb. Among the parent-specific TRD regions, seven genomic regions exhibited evidence of TRD effects originating from the dam, while 183 regions showed TRD effects associated with the sire. Notably, one region displayed distorted allele transmission from both the sire and dam simultaneously (BTA2, 32.45 to 32.65 Mb). The distribution of the TRD regions across the *Bos taurus* autosomes (**BTAs**) can be visualized in Figure 2. In general, all BTAs contained at least one genomic region with a TRD effect, with nearly all chromosomes exhibiting all three types of patterns. BTA25 was the only exception, showing evidence exclusively for overall and genotypic TRD events without any parent-specific TRD. The comprehensive list detailing the genomic regions associated with TRD and their specific parameters is available in Supplementary File 1, Supplementary Table S1.

Genomic regions with TRD harboring semilethal or lethal alleles

The number of underrepresented offspring in genomic regions exhibiting evidence of TRD ranged from 323 to 1,501, with an average of 881 ± 145 individuals. After establishing a threshold of 1,000 underrepresented offspring and

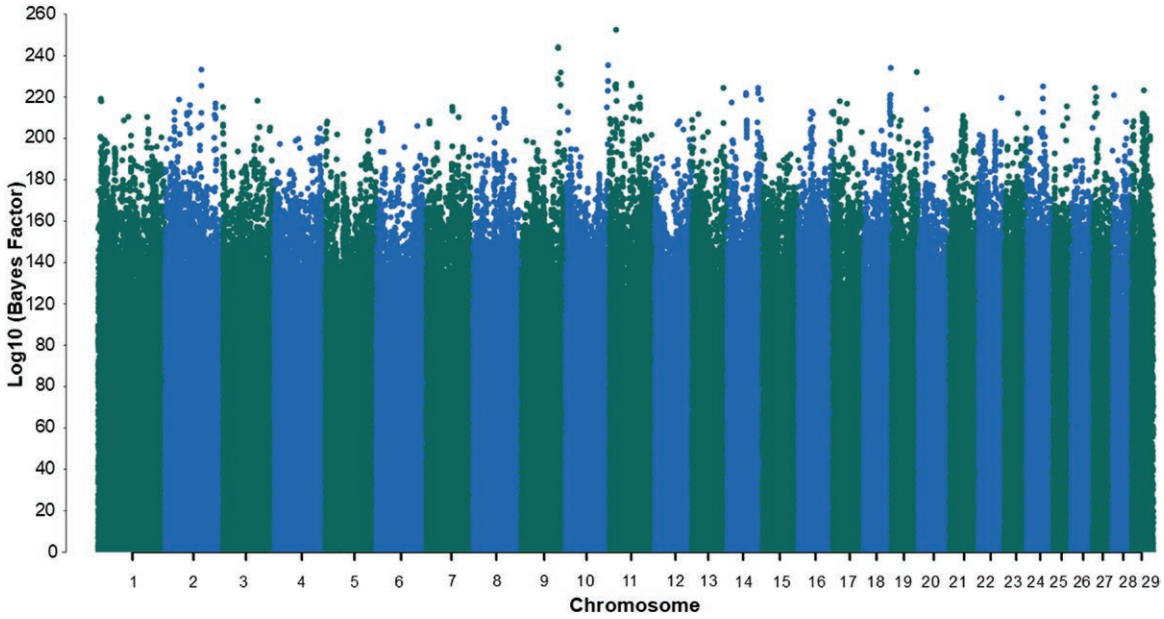

Figure 1. Manhattan plot of the Log_{10} BF for the overall TRD effect, considering SNP-by-SNP and moving haplotype windows of 5, 10, 15, 20, and 25 SNPs in Nellore cattle.

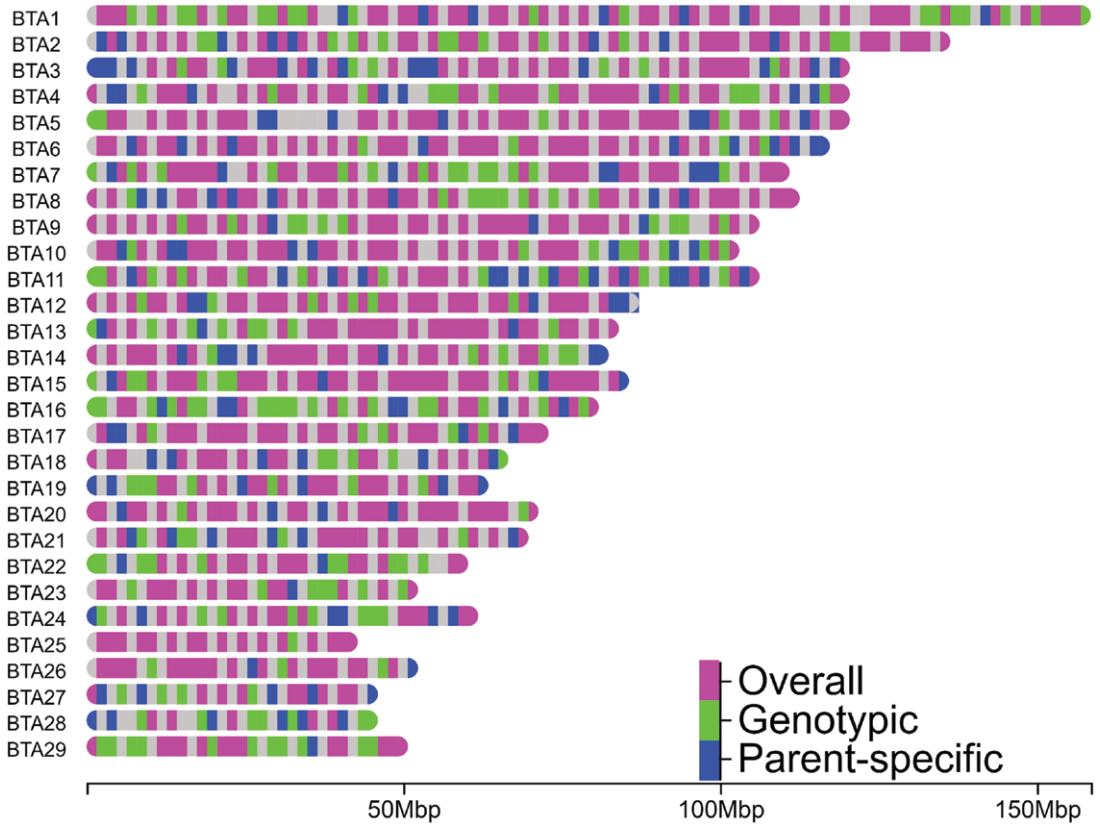

Figure 2. Distribution of TRD regions (overall, parent-specific, and genotypic) by BTA.

a minimum TRD effect of |0.20| to identify potential allelic TRD genomic regions harboring semilethal or lethal alleles, 73 regions were identified. Table 3 presents the 30 genomic regions with the highest number of underrepresented offspring, while the complete list containing the 73 candidates is provided in Supplementary File 2, Supplementary Table S2. Among the 73 regions with allelic TRD patterns, 45 were associated with overall TRD, and 28 with parent-specific TRD (27 sire TRD and 1 dam TRD). The α in these regions ranged from -0.402 ± 0.008 (BTA17, 16.80 to 17.00 Mb) to 0.390 ± 0.008 (BTA14, 10.79 to 10.99 Mb). The α_s ranged from -0.428 ± 0.009 (BTA14, 79.58 to 79.78 Mb)

Table 3. Genomic regions potentially associated with semilethal or lethal alleles based on the allelic parametrization of TRD in Nellore cattle

Chr[1]	Region[2]	Freq[3]	SireH[4]	DamH[5]	Informative Offspring[6]	TRD type[7]	TRD effects[8]	Log_{10} (BF)[9]	Underrepresented offspring[10]
BTA29	35.28–35.48	0.046	45	232	1,572	Parent-Specific (Dam)	$\alpha_d = -0.43$	103.51	1,374
BTA9	92.70–92.90	0.080	82	302	1,720	Parent-Specific (Sire)	$\alpha_s = 0.36$	144.61	1,249
BTA10	20.55–20.75	0.878	100	448	2,096	Overall	$\alpha = 0.27$	175.89	1,146
BTA11	16.55–16.75	0.094	77	338	1,690	Overall	$\alpha = -0.34$	218.05	1,134
BTA28	3.90–4.10	0.929	87	264	1,609	Overall	$\alpha = 0.35$	220.82	1,132
BTA11	38.48–38.68	0.062	48	246	1,408	Parent-Specific (Sire)	$\alpha_s = -0.40$	138.65	1,128
BTA3	35.19–35.39	0.934	73	250	1,448	Parent-Specific (Sire)	$\alpha_s = 0.39$	141.91	1,119
BTA6	116.48–116.68	0.082	61	260	1,503	Parent-Specific (Sire)	$\alpha_s = -0.37$	132.51	1,118
BTA19	59.76–59.96	0.942	64	247	1,493	Overall	$\alpha = 0.37$	231.96	1,114
BTA17	59.49–59.69	0.924	64	291	1,492	Parent-Specific (Sire)	$\alpha_s = 0.37$	114.66	1,104
BTA18	61.88–62.08	0.888	87	403	1,874	Overall	$\alpha = 0.29$	178.58	1,100
BTA2	21.94–22.14	0.068	71	271	1,541	Overall	$\alpha = -0.36$	212.50	1,097
BTA23	32.46–32.66	0.055	62	211	1,442	Parent-Specific (Sire)	$\alpha_s = -0.38$	149.23	1,092
BTA6	11.49–11.69	0.078	73	286	1,588	Overall	$\alpha = -0.34$	207.29	1,090
BTA1	61.38–61.58	0.068	69	250	1,446	Parent-Specific (Sire)	$\alpha_s = -0.38$	114.48	1,081
BTA1	5.88–6.08	0.075	79	294	1,562	Overall	$\alpha = -0.34$	200.64	1,076
BTA2	44.09–44.29	0.887	83	382	1,752	Overall	$\alpha = 0.31$	183.51	1,074
BTA9	87.33–87.53	0.041	51	202	1,261	Parent-Specific (Sire)	$\alpha_s = -0.42$	157.28	1,069
BTA5	4.57–4.77	0.070	76	303	1,524	Overall	$\alpha = -0.35$	208.04	1,069
BTA3	50.90–51.10	0.079	72	314	1,404	Parent-Specific (Sire)	$\alpha_s = -0.38$	116.54	1,068
BTA8	28.93–29.13	0.928	63	257	1,382	Parent-Specific (Sire)	$\alpha_s = 0.39$	126.89	1,067
BTA11	87.07–87.27	0.075	70	302	1,561	Overall	$\alpha = -0.34$	199.51	1,065
BTA2	34.37–34.57	0.077	83	319	1,562	Overall	$\alpha = -0.34$	202.03	1,062
BTA17	68.60–68.80	0.922	71	261	1,518	Overall	$\alpha = 0.35$	203.03	1,060
BTA23	28.71–28.91	0.075	83	273	1,548	Overall	$\alpha = -0.34$	199.61	1,058
BTA14	44.53–44.73	0.943	75	241	1,405	Overall	$\alpha = 0.38$	220.95	1,058
BTA2	42.38–42.58	0.065	67	260	1,373	Parent-Specific (Sire)	$\alpha_s = -0.38$	130,21	1,055
BTA18	4.44–4.64	0.085	84	293	1,624	Overall	$\alpha = -0.32$	185.46	1,054
BTA1	18.71–18.91	0.101	80	347	1,683	Overall	$\alpha = -0.31$	181.05	1,053
BTA14	79.58–79.78	0.038	58	166	1,229	Parent-Specific (Sire)	$\alpha_s = -0.43$	157.89	1,053

[1]Chr, Chromosome; BTA, *Bos taurus* autosome.
[2]The region reported is in megabase unit (Mb) and corresponds to the location considering the ARS-UCD1.2 *Bos taurus* genome assembly (Rosen et al., 2020).
[3]Frequency of the allele in the population.
[4]Number of heterozygous sires.
[5]Number of heterozygous dams.
[6]Informative offspring were defined as the number of progenies derived from one or both heterozygous parents.
[7]Indicate the type of TRD that better describes the inheritance pattern observed.
[8]α, α_s, and α_d represent the overall, sire, and dam allelic TRD effect, respectively.
[9]The Log_{10} (BF) indicates the BF for the TRD effect.
[10]The number of underrepresented offspring refers to the total expected offspring that were not observed for a given allele. This value is equivalent to the number of informative offspring multiplied by twice the magnitude of the TRD effect (Id-Lahoucine et al., 2019, 2023a). Full list containing the 73 genomic regions harboring potential semilethal or lethal alleles showing TRD allelic patterns can be found in Supplementary File S2, Supplementary Table S2.

to 0.427 ± 0.009 (BTA24, 38.84 to 39.04 Mb), and the α_d observed was −0.430 ± 0.012 (BTA29, 35.28 to 35.48 Mb). It is noteworthy that BTA15, BTA16, BTA20, and BTA25 did not exhibit any potential allelic TRD.

Considering the genotypic parametrization of TRD models, 59 genomic regions containing potential candidates for semilethal or lethal alleles were identified. Table 4 presents the 30 genomic regions with the highest number of underrepresented offspring, while the complete list containing the 59 candidates is provided in Supplementary File 3, Supplementary Table S3. Within these regions, the higher estimated $|\alpha_g|$ was 0.993 ± 0.006 on BTA24 (43.31 to 43.51 Mb), with strong statistical support for additive TRD events ($\log_{10}$ BF > 100). The highest $|\delta_g|$ was 0.196 ± 0.024 on BTA4 (101.66 to 101.86 Mb), with the strongest evidence for a dominance TRD signal reflected by a $\log_{10}$ BF of 24.64. In some genotypic TRD regions, no *AA* or *BB* individuals were observed among the offspring of heterozygous-by-heterozygous (*AB* × *AB*) matings. Specifically, the TRD region in which no AA individuals were detected was located on BTA1 (9.54 to 9.74 Mb). Likewise, regions with complete absence of BB individuals from *AB* × *AB* matings were identified on four chromosomes: BTA1 (40.84 to 41.04 Mb), BTA13 (1.24 to 1.44 Mb), BTA24 (43.31 to 43.51 Mb), and BTA27 (26.17 to 26.37 Mb).

Forty-four TRD genomic regions identified in the present study (Table 5) overlapped lethal haplotype regions in Nellore cattle previously reported by Schmidt et al. (2023) and

Table 4. Genomic windows potentially associated with semilethal or lethal alleles based on the genotypic parametrization of TRD in Nellore cattle

Chr[1]	Region[2]	Freq[3]	SireH[4]	DamH[5]	Informative Offspring[6]	TRD effects[7]				Number of underrepresented offspring[8]
						α_g	$\text{Log}_{10}(BF_{\alpha_g})$	δ_g	$\text{Log}_{10}(BF_{\delta_g})$	
24	43.31–43.51	0.8435	116	459	2,145	0.993	145.66	−0.125	12.26	1,501
4	101.66–101.86	0.8625	113	396	2,054	0.991	105.19	−0.196	24.64	1,368
19	41.63–41.83	0.8349	120	449	2,079	0.990	131.48	−0.111	12.65	1,361
1	40.84–41.04	0.8470	104	451	2,074	0.991	120.50	−0.129	11.42	1,344
13	1.24–1.44	0.8544	111	428	2,023	0.989	110.57	−0.162	18.76	1,340
7	61.87–62.07	0.8344	104	452	2,005	0.989	116.84	−0.158	23.82	1,327
18	64.52–64.72	0.8463	97	462	2,041	0.986	108.18	−0.148	16.36	1,301
17	46.99–47.19	0.8381	108	459	2,068	0.974	100.21	−0.161	21.26	1,300
7	101.06–101.26	0.8554	107	406	2,010	0.988	107.13	−0.157	15.85	1,297
11	71.87–72.07	0.8593	108	403	1,975	0.990	105.71	−0.171	16.12	1,296
24	17.85–18.05	0.8379	118	424	1,999	0.984	104.83	−0.162	21.07	1,288
3	44.53–44.73	0.8621	98	425	1,936	0.991	111.24	−0.154	11.04	1,284
8	64.16–64.36	0.8561	97	435	1,991	0.993	125.26	−0.104	5.17	1,279
13	73.89–74.09	0.8133	113	461	2,123	0.958	107.26	−0.115	10.70	1,279
9	99.22–99.42	0.8452	97	418	1,979	0.990	118.26	−0.122	11.20	1,276
27	26.17–26.37	0.8482	107	439	2,065	0.986	112.71	−0.111	10.24	1,274
1	84.50–84.70	0.8308	104	440	1,904	0.987	106.00	−0.170	22.61	1,269
11	0.16–0.36	0.8432	103	416	1,939	0.992	119.57	−0.125	10.28	1,265
24	20.98–21.18	0.8512	107	435	1,957	0.987	100.10	−0.171	19.41	1,263
15	69.69–69.89	0.8244	112	470	1,976	0.985	112.43	−0.123	13.27	1,250
16	30.86–31.06	0.8017	111	508	2,148	0.958	114.04	−0.079	4.75	1,249
7	58.48–58.68	0.8522	95	430	1,871	0.991	107.81	−0.159	13.05	1,245
23	27.37–27.57	0.8589	97	405	1,925	0.990	104.02	−0.162	15.04	1,241
7	11.66–11.86	0.8317	104	466	1,982	0.980	103.78	−0.143	18.01	1,239
4	8.44–8.64	0.8438	108	435	1,945	0.986	101.16	−0.161	17.29	1,237
10	97.31–97.51	0.8495	95	422	1,824	0.992	113.70	−0.143	8.38	1,236
22	0.29–0.49	0.8380	102	448	2,017	0.988	115.86	−0.106	10.30	1,235
22	40.73–40.93	0.8630	101	402	1,952	0.989	102.10	−0.154	14.18	1,234
16	27.43–27.63	0.8024	120	505	2,134	0.915	102.31	−0.094	5.12	1,230
3	21.65–21.85	0.7961	109	486	2,126	0.912	102.74	−0.084	3.69	1,227

[1]Chr, Chromosome; BTA, *Bos taurus* autosome.
[2]The region reported is in megabases (Mb) and corresponds to the ARS-UCD1.2 *Bos taurus* genome assembly (Rosen et al., 2020).
[3]Frequency of the haplotype allele in the population.
[4]Number of heterozygous sires. [5]Number of heterozygous dams.
[6]Informative offspring were defined as the number of progenies derived from one or both heterozygous parents.
[7]α_g, and δ_g represent the additive and dominance TRD effect, respectively. The Log_{10} (BF) indicates the BF for the TRD effect.
[8]The number of underrepresented offspring refers to the total expected offspring that were not observed for a given allele. Full list containing the 59 genomic regions harboring potential semilethal or lethal alleles showing TRD allelic patterns can be found in Supplementary File S3, Supplementary Table S3.

Table 5. Genomic regions with TRD that have previously been reported as potential carriers of recessive lethal haplotypes in Nellore cattle

Chr[1]	Region[2]	Freq[3]	TRD type	TRD effects[4]	Number of underrepresented offspring[5]	Previously reported by
BTA1	21.63–21.83	0.171	Genotypic	$\alpha_g = -0.98$; $\delta_g = -0.12$	920	Schmidt et al. (2023)
BTA1	36.34–36.54	0.945	Overall	$\alpha = 0.37$	872	Rodrigues et al. (2025)
BTA1	40.84–41.04	0.847	Genotypic	$\alpha_g = 0.99$; $\delta_g = -0.13$	1,344	Rodrigues et al. (2025)
BTA1	81.66–81.89	0.949	Parent-specific	$\alpha_s = 0.36$; $\alpha_d = 0.32$	511	Rodrigues et al. (2025)
BTA1	92.14–92.34	0.094	Overall	$\alpha = -0.31$	966	Schmidt et al. (2023)
BTA2	27.51–27.71	0.028	Overall	$\alpha = -0.41$	828	Rodrigues et al. (2025)
BTA2	126.03–126.23	0.048	Overall	$\alpha = -0.37$	754	Schmidt et al. (2023)
BTA3	84.42–84.62	0.944	Overall	$\alpha = 0.37$	889	Schmidt et al. (2023)
BTA7	20.27–20.47	0.055	Overall	$\alpha = -0.37$	733	Schmidt et al. (2023)
BTA7	36.96–37.16	0.910	Overall	$\alpha = 0.31$	893	Schmidt et al. (2023) and Rodrigues et al. (2025)
BTA7	52.99–53.19	0.153	Genotypic	$\alpha_g = -0.99$; $\delta_g = -0.13$	835	Rodrigues et al. (2025)
BTA7	81.35–81.55	0.949	Parent-specific	$\alpha_s = 0.38$; $\alpha_d = 0.35$	871	Schmidt et al. (2023)
BTA7	106.9–107.1	0.061	Overall	$\alpha = -0.34$	719	Schmidt et al. (2023)
BTA8	22.54–22.74	0.044	Parent-specific	$\alpha_s = -0.39$; $\alpha_d = -0.36$	818	Rodrigues et al. (2025)
BTA9	48.54–48.74	0.060	Overall	$\alpha = -0.36$	796	Schmidt et al. (2023)
BTA9	72.77–72.97	0.091	Overall	$\alpha = -0.30$	827	Schmidt et al. (2023)
BTA10	22.36–22.56	0.949	Overall	$\alpha = 0.38$	831	Rodrigues et al. (2025)
BTA10	24.7–24.9	0.043	Overall	$\alpha = -0.40$	914	Rodrigues et al. (2025)
BTA10	86.13–86.38	0.195	Genotypic	$\alpha_g = -0.88$; $\delta_g = 0.01$	421	Schmidt et al. (2023)
BTA12	16.33–16.53	0.052	Parent-specific	$\alpha_s = -0.39$; $\alpha_d = -0.34$	989	Rodrigues et al. (2025)
BTA13	13.33–13.53	0.933	Overall	$\alpha = 0.36$	835	Rodrigues et al. (2025)
BTA13	15.89–16.09	0.190	Genotypic	$\alpha_g = -0.94$; $\delta_g = -0.07$	771	Rodrigues et al. (2025)
BTA13	16.09–16.29	0.960	Overall	$\alpha = 0.40$	809	Rodrigues et al. (2025)
BTA14	56.98–57.18	0.928	Overall	$\alpha = 0.33$	855	Rodrigues et al. (2025)
BTA15	21.13–21.33	0.189	Genotypic	$\alpha_g = -0.92$; $\delta_g = -0.05$	740	Rodrigues et al. (2025)
BTA15	22.96–23.16	0.209	Genotypic	$\alpha_g = -0.89$; $\delta_g = -0.06$	719	Rodrigues et al. (2025)
BTA16	1.09–1.29	0.810	Genotypic	$\alpha_g = 0.93$; $\delta_g = -0.09$	1,193	Rodrigues et al. (2025)
BTA17	67.04–67.24	0.056	Parent-specific	$\alpha_s = -0.39$; $\alpha_d = -0.33$	961	Rodrigues et al. (2025)
BTA17	70.36–70.56	0.878	Overall	$\alpha = 0.28$	913	Rodrigues et al. (2025)
BTA18	9.91–10.11	0.946	Parent-specific	$\alpha_s = 0.38$; $\alpha_d = 0.34$	867	Schmidt et al. (2023)
BTA18	28.3–28.5	0.047	Overall	$\alpha = -0.38$	791	Rodrigues et al. (2025)
BTA18	36.88–37.08	0.146	Genotypic	$\alpha_g = -0.99$; $\delta_g = -0.10$	828	Schmidt et al. (2023)
BTA18	54.94–55.14	0.882	Overall	$\alpha = 0.31$	943	Rodrigues et al. (2025)
BTA18	63.8–64	0.968	Parent-specific	$\alpha_s = 0.41$; $\alpha_d = 0.44$	906	Rodrigues et al. (2025)
BTA22	19.4–19.6	0.069	Overall	$\alpha = -0.34$	897	Schmidt et al. (2023)

Table 5. Continued

Chr[1]	Region[2]	Freq[3]	TRD type	TRD effects[4]	Number of underrepresented offspring[5]	Previously reported by
BTA22	46.6–46.8	0.121	Overall	$\alpha = -0.29$	1,051	Schmidt et al. (2023) and Rodrigues et al. (2025)
BTA24	18.6–18.8	0.060	Overall	$\alpha = -0.35$	849	Schmidt et al. (2023)
BTA25	4.21–4.41	0.949	Overall	$\alpha = 0.38$	924	Rodrigues et al. (2025)
BTA25	12.73–12.93	0.095	Overall	$\alpha = -0.32$	959	Rodrigues et al. (2025)
BTA26	12.86–13.06	0.074	Overall	$\alpha = -0.33$	890	Rodrigues et al. (2025)
BTA26	14.89–15.09	0.057	Overall	$\alpha = -0.39$	882	Rodrigues et al. (2025)
BTA27	17.58–17.78	0.059	Overall	$\alpha = -0.35$	887	Rodrigues et al. (2025)
BTA29	40.66–40.86	0.058	Overall	$\alpha = -0.36$	853	Schmidt et al. (2023)
BTA29	48.41–48.61	0.938	Overall	$\alpha = 0.36$	849	Rodrigues et al. (2025)

[1]Chr: chromosome; BTA: *Bos taurus* autosome.
[2]The region reported is in megabases (Mb) and corresponds to the ARS-UCD1.2 *Bos taurus* genome assembly (Rosen et al., 2020).
[3]Frequency of the haplotype allele in the population that is under-transmitted.
[4]α, α_s, α_d, α_g, and δ_g represent the overall, sire, dam, additive, and dominance TRD effect, respectively.
[5]The number of underrepresented offspring refers to the total expected offspring that were not observed for a given allele (Id-Lahoucine et al., 2019, 2023a).

Rodrigues et al. (2025). These regions were distributed across BTA1, BTA2, BTA3, BTA7, BTA8, BTA9, BTA10, BTA12, BTA13, BTA14, BTA15, BTA16, BTA17, BTA18, BTA22, BTA24, BTA25, BTA26, BTA27, and BTA29. Among the identified regions, 28 were classified as overall TRD, seven as parent-specific TRD (sire TRD), and nine as genotypic TRD. The number of underrepresented offspring in these regions ranged from 421 to 1,344. Notably, the TRD regions on BTA1 (40.84 to 41.04 Mb), BTA16 (1.09 to 1.29 Mb), and BTA22 (46.60 to 46.80 Mb) were also identified in this study as potential loci harboring semilethal or lethal alleles due to the presence of over 1,000 underrepresented offspring.

Genes, QTLs, and functional enrichment for the TRD regions

Considering all genomic regions (1,249) associated with TRD events, 2,265 genes were annotated. These included one long noncoding RNA (lncRNA), 90 microRNAs (miRNAs), one miscellaneous RNA (misc_RNA), 2,140 protein-coding genes, five pseudogenes, one ribosomal RNA (rRNA), 18 small nucleolar RNAs (snoRNAs), seven small nuclear RNAs (snRNAs), one T-cell receptor variable gene (*TR_V_gene*), and one Y RNA. A comprehensive list detailing the genes identified, their genome locations, and biotypes is provided in Supplementary File S4, Supplementary Table S4.

Table 6 provides an overview of the QTL identified within genomic regions exhibiting TRD events. Twenty distinct enriched QTL (P-value < 0.05), associated with production (12) and reproduction (8) traits, were observed. Among the production-related QTL, traits related to growth (average daily gain, body circumference, body height, body length, metabolic body weight, maturity rate, and rump width) and feed efficiency (RFI and dry matter intake) significantly overlapped with TRD regions. Reproductive traits included QTL associated with female reproductive performance (age at first calving, calving ease, gestation length, inhibin level, and interval from first to last insemination), male reproductive traits (inhibin level and scrotal circumference), and calf survival (stillbirth). Notably, a genotypic TRD region on BTA10 (86.13 to 86.33 Mb) was significantly associated with calving ease (P-value < 0.0001) and overlapped with 366 QTL for this trait.

In the functional enrichment analyses of genes within TRD regions, 200 GO terms (including 129 BP, 29 CC, and 42 MF) and two KEGG pathways were significatively found after applying the Bonferroni correction for multiple testing (P-value < 0.05). The full list including all the BP, their significance level, and associated genes can be found in Supplementary File S5, Supplementary Table S5. The results revealed expressive overrepresentation of terms related to reproductive and developmental processes. Key BP identified included embryo development (GO:0009790), embryonic morphogenesis (GO:0048598), animal organ morphogenesis (GO:0009887), and development of primary female sexual characteristics (GO:0046545). Processes linked to cellular and molecular dynamics, such as G2/M transition of the mitotic cell cycle (GO:0000086), cell differentiation (GO:0030154), and cell morphogenesis (GO:0000902), were also identified. Functional enrichment of terms associated with signaling and growth regulation, including response to growth factor (GO:0070848) and cell–cell signaling (GO:0007267), further highlights the importance of these genomic regions in key developmental functions. Molecular functions such as

Table 6. QTL enrichment in genomic regions showing TRD in Nellore cattle

QTL name	Number of QTLs	Chr[1]	TRD region (Mb)	TRD type	*P*-value	QTL type
Average daily gain	8	BTA29	40.66–40.86	Overall	0.0028	Production
Body circumference	4	BTA13	43.84–44.04	Overall	0.0232	Production
Body height	14	BTA8	3.33–3.53	Overall	<0.0001	Production
Body length	6	BTA10	91.22–91.42	Genotypic	0.0008	Production
Cannon bone circumference	3	BTA10	52.13–52.33	Overall	0.0339	Production
Dry matter intake	10	BTA2	107.55–107.75	Overall	0.0453	Production
Dry matter intake	5	BTA11	6.69–6.89	Parent-Specific (Sire)	0.0424	Production
Dry matter intake	25	BTA20	4.74–4.94	Parent-Specific (Sire)	<0.0001	Production
Length of productive life	13	BTA29	47.80–48.00	Overall	0.0002	Production
Maturity rate	9	BTA21	5.36–5.56	Overall	0.0008	Production
Metabolic body weight	9	BTA1	63.63–63.83	Overall	0.0156	Production
Residual feed intake	23	BTA14	44.53–44.73	Overall	<0.0001	Production
Rump width	14	BTA8	3.33–3.53	Overall	<0.0001	Production
Age at first calving	18	BTA2	117.36–117.56	Genotypic	<0.0001	Reproduction
Calving ease	17	BTA10	86.13–86.33	Genotypic	0.0075	Reproduction
Calving ease	349	BTA21	2.68–2.88	Overall	<0.0001	Reproduction
Gestation length	8	BTA29	48.41–48.61	Overall	0.0015	Reproduction
Inhibin level	47	BTA5	42.69–42.89	Overall	<0.0001	Reproduction
Interval from first to last insemination	60	BTA17	68.60–68.80	Overall	<0.0001	Reproduction
Scrotal circumference	40	BTA5	53.96–53.16	Parent-Specific (Sire)	<0.0001	Reproduction
Stillbirth	13	BTA10	86.13–86.33	Genotypic	0.0396	Reproduction

[1]Chr, Chromosome; BTA, *Bos taurus* autosome.

voltage-gated ion channel activity (GO:0005244) and hormone receptor activity and CC, including synaptic membrane (GO:0097060) and plasma membrane-bounded cell projections (GO:0120039 and GO:0120036), were also observed.

Discussion

The identification of genomic regions associated with TRD events in Zebu breeds can provide new perceptions into the genetic mechanisms driving deviations from Mendelian inheritance in cattle. Despite growing interest in TRD phenomena across various livestock species, research specifically focusing on Nellore cattle remains limited. The growing availability of genotyped animals and advancements in genotyping technologies, particularly high-density SNP chips and whole-genome sequencing (**WGS**), have enabled the comprehensive study of TRD regions across the genome of livestock species. SNP chips allow the simultaneous genotyping of thousands of loci across the genome, being an effective tool for detecting subtle deviations in allelic transmission patterns that may indicate the presence of TRD events. Thus, this study represents an important advancement in the detection and characterization of allelic and genotypic TRD regions in Nellore cattle. By addressing this gap, our study offers valuable perceptions into the biological basis of TRD in Nellore cattle, providing opportunities to improve reproductive outcomes and enhance the sustainability of tropical beef cattle production. The findings also have the potential to highlight novel genomic regions that may harbor semilethal or lethal alleles, with possible implications for BP and metabolic pathways that influence reproductive efficiency and genetic progress in commercial populations.

Characterization of TRD across the genome

In total, 37,783 SNPs and 174,190 haplotypes were associated with TRD events (Table 2). The number of haplotypes showing patterns of TRD was higher than the number of SNPs due to the use of sliding windows of varying sizes to define haplotypes. A single SNP that shows evidence of TRD can appear in multiple sliding haplotype windows, potentially leading to multiple haplotypes sharing the same TRD effect. This is a common occurrence because haplotypes are defined as groups of SNPs that are inherited together due to their proximity and LD on the chromosome, and each haplotype window may contain the same TRD-associated SNP. Thus, while the number of SNPs reflects individual loci, the higher number of haplotypes reflects the multiple overlapping locations in which those SNPs contribute to TRD patterns.

The SNPs and haplotypes identified with TRD were further grouped into genomic regions based on LD between adjacent SNPs in the same BTA. As a result, 1,249 genomic regions distributed across all autosomal chromosomes were associated with TRD events (Table 2 and Figure 2). The genetic variant with the highest BF within each genomic region exhibiting evidence of TRD was selected to represent the TRD event in that region. These regions were categorized into three types based on the nature of the transmission distortion observed: overall TRD (802 regions), parent-specific TRD (191 regions), and genotypic TRD (256 regions). Overall TRD refers to regions where a general distortion in allele transmission is observed across both parents, suggesting the presence of alleles that are preferentially transmitted to offspring regardless of parental origin (Casellas et al., 2014, 2020). Parent-specific TRD is characterized by distortion patterns where one parent (either the sire or dam) exhibits a stronger transmission bias than the

other (Casellas et al., 2014, 2020). This type of TRD can indicate the involvement of imprinted genes or parent-of-origin effects, which can have implications for understanding complex inheritance patterns. Genotypic TRD, on the other hand, reflects variations in allele transmission depending on the genotype of the offspring, highlighting potential dominance or additive effects in genetic inheritance (Casellas et al., 2020).

The widespread distribution of TRD regions across all BTAs highlights the persistence of this phenomenon throughout the genome. In the context of the evaluated population, which is a closed herd with three selection lines subjected to distinct selection criteria for YW and RFI, the prevalence of TRD regions may be attributed to the cumulative effects of intense selection pressures. This could have driven deviations from Mendelian inheritance in loci associated with the targeted traits, particularly in genomic regions where alleles conferred either selective advantages or disadvantages. Furthermore, the presence of TRD regions may reflect BP influenced by deleterious alleles, such as embryonic lethality, reduced fertility, or impaired development, which can alter transmission patterns and disrupt normal inheritance (VanRaden et al., 2011; Schmidt et al., 2023). Additionally, the identification of TRD regions provides valuable insights into the genetic variation that may not be captured by traditional association studies, offering opportunities to refine genomic selection strategies (Id-Lahoucine et al., 2023a, 2023b).

The variation in TRD coefficients (α values) across the genome highlights the complexity of the underlying inheritance mechanisms. A diverse array of TRD patterns was observed, including regions with consistent transmission bias and others exhibiting contrasting transmission depending on the direction of inheritance. These patterns suggest the involvement of non-Mendelian processes, such as genomic imprinting, epistatic interactions, or other parent-of-origin effects that can influence allele segregation (Huang et al., 2013; Fishman and Mcintosh, 2019). Notably, one genomic region showed clear divergence in transmission direction depending on the parental origin of the allele, indicating potential interactions between distinct regulatory pathways during gametogenesis or early embryonic development. These effects may result from allele-specific interactions, disruptions in zygotic compatibility, or coordinated epigenetic modifications (Id-Lahoucine et al., 2019, 2023a, 2023c). Further investigation is necessary to determine whether such patterns reflect a unified TRD signal or distinct mechanisms acting concurrently in the same region. While sex-specific differences may be partially explained by sample size or LD, the consistency of directionally opposing transmission implies that additional biological factors likely contribute to these patterns.

The predominance of sire-specific TRD regions (183) compared to dam-specific regions (7) suggests a potential biological basis for this disparity. One contributing factor may be that males produce significantly more sperm cells than females produce ova (Siu et al., 2021). Furthermore, sperm cells undergo more rounds of cell division during spermatogenesis than oocytes do during oogenesis (Siu et al., 2021), increasing the likelihood of mutations that could distort allele transmission patterns. Understanding the nature of these TRD effects is crucial for developing more targeted genetic selection approaches, particularly in the context of traits influenced by complex genetic interactions and parent-of-origin effects (Huang et al., 2013; Casellas et al., 2017; Fishman and Mcintosh, 2019).

The genotypic parametrization of TRD revealed the relative contributions of additive and dominance effects to transmission patterns. Notably, additive genetic effects emerged as the prevalent factor influencing genotypic TRD events, as evidenced by higher BF values for additive effects compared to dominance effects. This emphasizes the central role of additive variation, which reflects the cumulative contribution of individual alleles in driving TRD and shaping allele transmission patterns. In contrast, dominance effects, resulting from interactions between alleles at a locus, played a comparatively minor role in these regions. These findings have important implications for breeding programs, as additive effects are more straightforward to estimate and are consistently transmitted to subsequent generations. Due to their direct influence and predictability, additive genetic effects are included in selection indexes to enhance traits through animal breeding (Falconer and Mackay, 1996). Recognizing the predominance of additive effects in genotypic TRD events can be useful for refining breeding strategies, ultimately improving the efficiency of genomic selection in traits regulated by complex inheritance mechanisms.

Identification of potential candidates for semilethal or lethal alleles in TRD regions

The identification of TRD regions harboring potential semilethal or lethal alleles represents opportunities for livestock breeding. From a population genetics standpoint, these alleles are likely subject to purifying selection, which would normally reduce their frequency over time in natural populations (Cvijović et al., 2018; Buffalo and Kern, 2024; Hasan and Whitlock, 2024). However, in the context of animal breeding programs, lethal alleles could persist or even accumulate within subpopulations if not carefully managed (VanRaden et al., 2011; Schmidt et al., 2023; Rodrigues et al., 2025). Therefore, incorporating TRD analyses into breeding strategies is crucial for the effective management of genomic regions that may impact the long-term viability and sustainability of beef cattle production.

By employing criteria to select allelic TRD genomic regions potentially harboring semilethal or lethal alleles—defined as regions with a minimum of 1,000 underrepresented offspring and a TRD effect magnitude of |0.20|, a total of 73 genomic regions were identified (Table 3 and Supplementary File S2, Supplementary Table S2). Of these, 45 were associated with overall TRD, while 28 were linked to parent-specific TRD (27 sire-specific and 1 dam-specific), highlighting the diversity of the mechanisms driving the TRD phenomena. The identification of these genomic regions underscores their potential consequences for animal breeding, as they may harbor alleles that disrupt normal transmission patterns, leading to reduced reproductive success or the perpetuation of harmful genetic variants. Understanding these mechanisms is crucial for refining breeding programs, as it allows for the strategic management of alleles that can significantly impact livestock efficiency and sustainability. The TRD region on BTA23 (32.46 to 32.66 Mb) exhibited 1,092 underrepresented offspring ($\alpha_s = -0.379 \pm 0.010$), suggesting its association with a lethal or semilethal allele. Furthermore, this region has also been associated with pregnancy loss in Nellore cattle based on a genome-wide association study (**GWAS**) (Rodrigues et al., 2024b). Similarly, the TRD region on BTA19 (59.76 to 59.96 Mb), which exhibited 1,114 underrepresented offspring

($\alpha = 0.373 \pm 0.008$), was also identified in a GWAS for stillbirth in Nellore cattle (Rodrigues et al., 2024b).

The genotypic parametrization of TRD also revealed 59 genomic regions potentially harboring semilethal or lethal alleles (Table 4 and Supplementary File S3, Supplementary Table S3). These regions showed strong evidence of additive TRD effects and in some of these regions, heterozygous-by-heterozygous matings ($AB \times AB$) resulted in the complete absence of homozygous offspring (AA or BB), exhibiting signs of lethal outcomes. For instance, genomic regions on BTA1, BTA8, BTA13, BTA24, and BTA27 exhibited this pattern, suggesting the presence of alleles that impair viability when homozygous. This finding emphasizes the potential biological consequences of TRD regions, as such alleles may disrupt key developmental or physiological pathways, leading to embryonic lethality or severe fitness reductions. The genotypic TRD region on BTA18 (64.52 to 64.72 Mb) was also detected in a GWAS for preweaning mortality in Nellore cattle (Rodrigues et al., 2024b).

The TRD analyses conducted in this study identified 44 genomic regions that overlap with the findings of Schmidt et al. (2023) and Rodrigues et al. (2025) (Table 5), both of which examined genomic regions as potential candidates harboring lethal haplotypes based on the absence of homozygous carriers of recessive haplotypes. These findings emphasize the consistency of TRD as a marker for identifying genomic regions that may influence survival and reproduction. Furthermore, these genomic regions are potential hotspots for lethal or semilethal alleles and may have potential mutations in specific genes associated with early mortality of specific genotypes in Nellore cattle. The identification of these common regions across independent studies provides strong groundwork for subsequent investigations using WGS, gene expression, and/or transcriptomic analyses to comprehend the genetic mechanisms underlying lethal alleles. Notably, genomic regions on BTA1 and BTA22 were consistently identified across this study as containing lethal alleles, and in the study of Schmidt et al. (2023) and Rodrigues et al. (2025) as candidate regions harboring lethal haplotypes, suggesting their pivotal role in reproductive fitness and embryonic viability in Nellore cattle.

From an animal breeding perspective, monitoring TRD regions associated with semilethal or lethal alleles is essential to avoid the spread of deleterious alleles, which could reduce genetic gains and compromise long-term herd efficiency. By identifying TRD regions, it is possible to design mating strategies that minimize the transmission of deleterious alleles. For instance, avoiding matings that are likely to produce homozygous recessive offspring can reduce embryonic lethality and improve reproductive efficiency. Future research should focus on the functional characterization of these TRD regions to elucidate the specific biological mechanisms by which deleterious alleles influence fitness, thereby enabling more effective management strategies in cattle breeding programs. By accounting for TRD in breeding programs, it may be possible to enhance genetic progress while mitigating undesirable outcomes, such as the inadvertent propagation of deleterious alleles. This approach could lead to more sustainable genetic improvement in commercial populations.

Biological aspects of TRD regions: genes, QTLs, and functional enrichment

The annotation of 2,265 genes overlapping with TRD regions reveals a diverse array of gene biotypes, each potentially contributing to the transmission bias observed in these loci (Supplementary File 4, Supplementary Table S4). Protein-coding genes were predominant in TRD regions, reflecting their likely role in fundamental biological pathways such as metabolism, structural integrity, and regulatory functions. These genes are often key players in processes influencing key traits in cattle (Brunes et al., 2021; Mota et al., 2022; Rodrigues et al., 2024b; Souza et al., 2024). Regulatory noncoding RNAs, including 90 miRNAs, 18 snoRNAs, and one lncRNA, underscore the complexity of gene regulation within TRD regions. Noncoding RNAs regulate gene expression through transcriptional repression, RNA splicing, and posttranscriptional modification (Kaikkonen et al., 2011; Zhao et al., 2016). These elements could mediate the genetic imbalance aspect of TRD by modulating key developmental or reproductive processes. For instance, miRNAs are known to influence developmental timing and stress responses, roles that are critical during early embryogenesis—a period particularly sensitive to genetic imbalances (Mendell and Olson, 2012; Marsico et al., 2023). Additional biotypes, such as rRNAs, pseudogenes, and Y RNAs, emphasize the involvement of fundamental cellular processes in TRD. Ribosome biogenesis and RNA modification, driven by snoRNAs and rRNAs, are essential for cellular growth and function (Sloan et al., 2017; Ojha et al., 2020), linking these elements to the observed enrichment of QTLs for production traits. These QTLs include growth (e.g., average daily gain, metabolic body weight, and maturity rate) and feed efficiency (e.g., RFI and dry matter intake), suggesting that TRD regions may influence phenotypes associated with energy utilization and developmental efficiency. Such traits are under strong selection pressure in cattle breeding programs, making TRD regions key targets for further exploration.

Reproductive traits also showed significant associations with TRD regions, underscoring their importance to fertility and survival. QTLs linked to female reproductive performance, such as age at first calving, calving ease, and gestation length, and male reproductive traits, such as scrotal circumference, emphasize the genetic mechanisms underlying reproductive success. The TRD region on BTA10 (86.13 to 86.33 Mb) shows this connection, indicating a significant association with calving ease and overlapping with 366 QTLs for this trait. This region may harbor alleles with pleiotropic effects, influencing maternal and neonatal viability during calving through variations in the uterine environment, fetal growth, or pelvic structure. Associations between TRD regions and QTLs for stillbirth further suggest a role in calf survival. These findings support the hypothesis that some TRD loci harbor alleles with deleterious effects, which are maintained in populations through balancing selection or heterozygote advantage (Hedrick, 2012; Derks and Steensma, 2021). For example, alleles that impair early development when homozygous but confer advantages in heterozygous individuals could persist due to their net fitness benefit (Hedrick, 2012; Derks and Steensma, 2021).

The functional enrichment analyses of genes within TRD regions highlight their potential roles in fertility, early embryogenesis, and reproductive success. Reproductive terms such as embryo development and embryonic morphogenesis underscore the importance of genes involved in early developmental stages for producing viable offspring. The TRD phenomena may arise from alleles that either enhance or disrupt these critical processes, leading to selection-driven distortions

in allele transmission. The presence of enriched terms such as the development of primary female sexual characteristics suggests that TRD regions harbor genes crucial for the formation and function of reproductive traits. These genes likely regulate processes such as ovarian folliculogenesis, hormonal signaling pathways, and uterine receptivity, which are functions essential for reproductive success (Christensen et al., 2012; Fiorentino et al., 2023). Mutations or variations within these regions might lead to reduced fertility or embryonic lethality, particularly when deleterious alleles are homozygous. Processes related to cell differentiation and cell morphogenesis play key roles in early embryonic development. These mechanisms control the specialization and organization of cells into functional tissues and organs, which are essential for zygotic development and successful implantation (Huang et al., 2025). Mutations in these processes may delay the development of the embryo, potentially leading to embryonic loss (Das and Holzer, 2012; Huang et al., 2025). Ion channel activity, particularly voltage-gated ion channel activity, appears to be another important process enriched in TRD regions. Ion channels regulate key events such as oocyte maturation, sperm motility, and calcium oscillations during oocyte activation and early embryogenesis (Darszon et al., 2011; Xu and Yang, 2017). Dysfunctions in ion transport mechanisms caused by mutations in these loci could impair reproductive processes and contribute to allele transmission distortions.

Future directions for research

The identification of TRD regions within the Nellore cattle genome, particularly those harboring lethal or semilethal alleles, opens up significant possibilities for advancing animal breeding strategies. The incorporation of TRD regions into genomic selection models represents an important advance in animal breeding. Genomic selection, which has already revolutionized breeding programs by selecting animals based on their genomic information, can be further optimized using TRD information. By monitoring the transmission of alleles, breeders can make more informed decisions, avoiding the perpetuation of lethal alleles that may result in reduced fertility or embryonic mortality. Moreover, while this study has identified several candidate genes within TRD regions, the functional characterization of nearly all these genes in Nellore cattle is still in its early stages, especially regarding their role in reproductive mechanisms. Future research should focus on experimentally validating these candidate genes, using techniques such as transcriptomics and proteomics, to gain a deeper understanding of their biological functions and their contribution to generating TRD patterns.

Conclusions

We identified 1,249 TRD regions distributed across the Nellore cattle genome. Of these, 73 and 59 TRD regions were classified as potential genomic hotspots harboring semilethal or lethal alleles, identified through allelic and genotypic parametrizations of TRD effects, respectively. Enrichment analyses revealed that TRD regions are strongly associated with key QTLs, including growth, feed efficiency, and reproductive performance, underscoring their importance in livestock productive efficiency. Functional annotation of genes within TRD regions highlighted significant BP, such as early embryogenesis, gametogenesis, cellular signaling, and ion transport. These findings emphasize the importance of incorporating TRD information into genomic selection strategies to enhance productivity while minimizing the segregation of deleterious alleles in cattle populations.

Supplementary Data

Supplementary data are available at *Journal of Animal Science* online.

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Author Contributions

Gustavo Rodrigues (Conceptualization, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing—original draft, Writing—review & editing), Luiz F. Brito (Conceptualization, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing—review & editing), Lucio F. M. Mota (Conceptualization, Formal analysis, Investigation, Supervision, Visualization, Writing—review & editing), Joslaine Cyrillo (Conceptualization, Data curation, Investigation, Supervision, Visualization, Writing—review & editing), João B. Silva Neto (Formal analysis, Investigation, Writing—review & editing), Milena A. F. Campos (Formal analysis, Investigation, Writing—review & editing), Lenira Faro (Funding acquisition, Resources, Writing—review & editing), Lucia Galvao de Albuquerque (Funding acquisition, Resources, Writing—review & editing), and Maria Zerlotti Mercadante (Conceptualization, Data curation, Funding acquisition, Investigation, Project administration, Resources, Supervision, Validation, Visualization, Writing—review & editing)

Data Availability

The raw data can be required by contacting MEZM (e-mail: mezmercadante@gmail.com) upon a reasonable request for research purposes.

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