

Re-evaluating GPRC6A Gene Loss: Implications for Milk Fat Synthesis and Functional Genomics in Dairy Cattle

Aswin S. Soman¹, Nagarjun Vijay¹,

1. Department of Biological Sciences, Indian Institute of Science Education and Research Bhopal, Bhopal, IND

Received: March 27, 2026 | Review began: April 07, 2026 | Review ended: June 23, 2026 | Published: July 15, 2026

© Copyright 2026

This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Accurate functional annotation of genes influencing livestock production traits is essential for advancing dairy science and agricultural genomics. Comparative genomics approaches often infer gene loss from sequence erosion; however, such inferences may conflict with experimental evidence for genes involved in economically important traits. The G protein-coupled receptor *GPRC6A* is a nutrient-sensing regulator implicated in lipid metabolism in bovine mammary epithelial cells, where it contributes to milk fat synthesis and dairy productivity. Despite this, genomic analyses have suggested that *GPRC6A* is eroded or lost in several mammalian lineages, including cattle. Here, we reconcile this discrepancy by evaluating five mechanistic scenarios that could permit protein function despite apparent gene-disrupting mutations: truncated protein translation, internal transcription initiation, translational recoding, RNA-level repair, and unresolved genomic copies. We propose that *GPRC6A* represents a “peripatetic molecular fossil,” a gene that retains biological activity despite genomic erosion. This case highlights the limitations of sequence-based gene-loss inference and underscores the need for integrative functional validation in livestock systems to identify genes that affect milk composition and agricultural productivity accurately.

Categories: Biodiversity conservation, Genomic selection, Livestock genetics & breeding

Keywords: dairy cattle, milk fat synthesis, livestock genomics, *gprc6a*, nutrient sensing, gene loss, functional annotation

Introduction

Improving milk composition and yield remains a central goal in dairy science, with milk fat content serving as a key determinant of product quality and economic value in cattle production systems [1,2]. Advances in livestock genomics have enabled the identification of genes underlying metabolic pathways that regulate milk synthesis, creating opportunities for genetic selection and precision breeding [3,4]. However, the functional annotation of such genes increasingly relies on comparative genomics approaches that infer gene presence or loss from sequence data alone, creating a critical challenge: genes classified as “lost” based on sequence erosion may still retain biological function in production-relevant tissues. Resolving this discrepancy is essential for accurately identifying molecular regulators of milk fat synthesis and for ensuring that genomics-informed breeding strategies do not overlook functionally important loci.

One such candidate is *GPRC6A*, a nutrient-sensing G protein-coupled receptor implicated in amino acid signaling and metabolic regulation [5,6]. In bovine mammary epithelial cells, *GPRC6A* has been shown to regulate lipid synthesis pathways directly linked to milk fat production. Recent evidence further supports the broader importance of amino-acid

How to cite this article:

Soman A S, Vijay N (July 15, 2026) Re-evaluating GPRC6A Gene Loss: Implications for Milk Fat Synthesis and Functional Genomics in Dairy Cattle. Cureus J. Agri. Food Sci 2 : es44497-026-00164-y. DOI <https://doi.org/10.7759/s44497-026-00164-y>

sensing GPCR pathways in bovine mammary epithelial cells and shows that L-theanine promotes bovine mammary epithelial cell(BMEC) proliferation, milk protein synthesis, and milk fat synthesis through the TAS1R1-FRMD6-mTOR signaling axis, with *TAS1R1* knockdown attenuating L-theanine-induced activation of mTOR and expression of lipogenic and lactogenic markers [7]. This finding complements the *GPRC6A* literature by demonstrating that nutrient-responsive GPCR signaling can directly regulate milk synthesis pathways in BMECs, reinforcing the need to functionally validate receptors implicated in lactation rather than relying solely on sequence-based annotation. Despite this functional evidence, comparative genomic analyses have produced conflicting conclusions regarding its evolutionary status, with some studies suggesting conservation in ruminants and others proposing widespread erosion or loss across mammals [8,9]. This inconsistency raises a broader question for livestock genomics - can genes inferred to be lost still contribute to economically important traits?

At a broader level, such discrepancies reflect a key limitation of sequence-based inference in functional genomics. Automated pipelines designed to detect gene loss rely heavily on coding sequence disruptions, such as premature stop codons and frameshifts, as indicators of inactivation. While effective at scale, these approaches may overlook alternative transcriptional and translational mechanisms that preserve protein function. Increasing evidence from pseudogene biology, ribosome profiling, and proteogenomics indicates that many loci previously classified as nonfunctional can be transcribed and translated into biologically active products [10-12]. These findings challenge the assumption that sequence erosion necessarily equates to functional loss.

This issue is particularly significant in agricultural genomics, where accurate gene annotation directly affects trait mapping, breeding decisions, and the identification of molecular targets to improve productivity. In dairy cattle, metabolic regulators of milk fat synthesis are of high economic importance, and misclassification of these genes may result in their exclusion from candidate gene analyses or genomic selection frameworks. The case of *GPRC6A* therefore provides an opportunity to examine how apparent gene-disrupting mutations can coexist with functional protein expression in a production-relevant context.

In this study, we evaluate a range of biologically plausible mechanisms that could reconcile sequence-based gene-loss predictions with experimental evidence of *GPRC6A* function in cattle [5-9]. These include truncated protein translation, translational recoding, RNA-level repair, internal transcription initiation, and the possibility of unresolved genomic copies. Rather than identifying a single explanatory mechanism, we aim to delineate the space of plausible solutions that current annotation frameworks collapse into binary outcomes. This work is intended as a hypothesis-generating effort rather than a definitive experimental validation of any single molecular mechanism. Our objective is not to demonstrate that one specific pathway restores canonical *GPRC6A* function in cattle, but to evaluate whether currently available sequence, annotation, and functional evidence justify treating *GPRC6A* as a binary case of gene presence or loss. Accordingly, the mechanisms discussed below should be interpreted as biologically plausible scenarios that require future validation using tissue-specific transcriptomic, ribosome-profiling, proteomic, and genome-resolved datasets. We propose that *GPRC6A* represents a “peripatetic molecular fossil,” a gene that retains functional activity while traversing the boundary between canonical gene presence and loss.

The novel contribution of this study is threefold. First, we integrate published functional evidence for *GPRC6A* activity in bovine mammary epithelial cells with sequence-based gene-loss predictions that classify the locus as disrupted. Second, we systematically organize five molecular mechanisms that could reconcile these conflicting observations, ranging from conservative explanations such as truncated protein production to more speculative possibilities such as RNA-level repair and unresolved genomic copies. Third, we propose operational criteria for recognizing “peripatetic molecular fossils,” genes that show sequence features associated with loss yet retain evidence of transcriptional, translational, or phenotypic activity in specific biological contexts.

How to cite this article:

Soman A S, Vijay N (July 15, 2026) Re-evaluating GPRC6A Gene Loss: Implications for Milk Fat Synthesis and Functional Genomics in Dairy Cattle. Cureus J. Agri. Food Sci 2 : es44497-026-00164-y. DOI <https://doi.org/10.7759/s44497-026-00164-y>

Materials And Methods

Study design and analytical framework

This study employed an integrative, literature-informed analytical framework to reconcile discrepancies between sequence-based gene-loss inference and experimentally observed gene function in cattle. The *GPRC6A* locus was selected as a case study due to its reported involvement in bovine milk fat metabolism and conflicting annotations regarding its evolutionary status. We combined comparative genomics evidence, gene annotation data, and published experimental findings with computational analyses of sequence features to evaluate biologically plausible mechanisms that may enable functional persistence despite apparent gene-disrupting mutations.

Identification of gene-disrupting mutations

Putative gene-inactivating mutations in the bovine *GPRC6A* locus were annotated based on previously reported comparative genomics analyses [9]. These included premature stop codons, frameshift mutations, and insertions or deletions within coding exons. Coordinates of these mutations were mapped onto the *Bos taurus* reference genome assembly, and their positions were examined relative to the exon-intron structure and predicted open reading frames (ORFs).

Prediction of transcription start sites

To evaluate the possibility of alternative transcription initiation, putative transcription start sites (TSSs) were predicted across the *GPRC6A* genomic region using Promoter 2.0 [13]. The analyzed sequence included the full annotated gene body (exons and introns) and upstream intergenic regions. Only TSS predictions classified as “highly likely” by the algorithm were retained. Predicted sites were categorized as upstream or downstream of the canonical start codon to assess their potential to bypass gene-disrupting mutations.

Transcriptional status of GPRC6A

To assess the transcriptional status of *GPRC6A* in *Bos taurus*, the genomic region corresponding to *GPRC6A* in the ARS-UCD2.0 reference assembly (GCA_002263795.4) was examined using the NCBI Genome Data Viewer (GDV) [14]. Pre-aligned RNA-seq and TSS tracks available within GDV were visualized and inspected. To comprehensively survey all publicly available RNA-seq data, MetaGraph, a scalable sequence-search framework based on annotated de Bruijn graphs, was utilized [15]. Exon sequences of *Bos taurus GPRC6A* were queried against the *Bos taurus* RNA-seq database indexed in MetaGraph, comprising 29,243 Sequence Read Archive (SRA) accessions (145.5 TB of sequence data; index size: 220 GB). Searches were performed using the default parameters (maximum results = 500; discovery threshold = 0.5). To provide comparative expression context, orthologous *GPRC6A* exon sequences from *Homo sapiens* and *Sus scrofa* were analyzed using the same approach. MetaGraph search results were exported as CSV files and visualized in R. Selected RNA-seq datasets were subjected to quality assessment using FastQC v0.12.1, followed by adapter trimming with fastp v1.1.0 [16]. Processed reads were aligned to the reference genome using STAR v2.7.11b [17]. Statistical analyses were performed in R using the ggplot2, dplyr, tidyr, and readr packages. Exon-wise abundance values were compared among *B. taurus*, *H. sapiens*, and *S. scrofa* using pairwise Welch's *t*-tests. Multiple-testing correction was performed using the Benjamini-Hochberg false discovery rate (FDR) procedure. Results were visualized as boxplots displaying the distribution of abundance values for each exon.

TSS annotations for *B. taurus* were obtained from GDV tracks, with histograms representing the 5' end counts of read alignments from experiments investigating TSS such as CAGE-Seq. In addition, CAGE-derived TSS data generated across 24 cattle tissues were obtained from the BOVReg/EuroFAANG resource (https://api.faang.org/files/trackhubs/BOVREG_CAGE_EUROFAANG/ARS-UCD1.2/) [18]. These data were visualized using igv-reports with the ARS-UCD1.2 genome assembly as the reference [19].

How to cite this article:

Soman A S, Vijay N (July 15, 2026) Re-evaluating GPRC6A Gene Loss: Implications for Milk Fat Synthesis and Functional Genomics in Dairy Cattle. Cureus J. Agri. Food Sci 2 : es44497-026-00164-y. DOI <https://doi.org/10.7759/s44497-026-00164-y>

Detection of ORFs

To identify potential coding capacity independent of the canonical reading frame, ORFs were detected using NCBI ORFfinder [14]. Default parameters were applied, with a minimum ORF length threshold of 75 nucleotides. ORFs were mapped across both forward and reverse strands, and their positions were compared with annotated exons and mutation sites to evaluate the potential for truncated protein or micropeptide production.

Identification of translational recoding signals

To assess the potential for programmed ribosomal frameshifting (PRF), the *GPRC6A* coding sequence was scanned for candidate heptanucleotide slippery motifs using Recode v2.0 [20]. Motifs conforming to the consensus pattern X XXY YYZ (where X = A, U, G, or C; Y = A or U; Z = A, U, or C) were queried. In addition, nearby RNA secondary structures, including stem-loop and pseudoknot-like configurations, were identified using the EMBOSS *einverted* program [21], with the following parameters: -match 3, -mismatch 4, -gap 6, and -threshold 15. Co-occurrence of slippery motifs and secondary structures was used as an indicator of potential PRF sites.

Tandem repeats and transposable element analysis

Tandem repeats within the *GPRC6A* locus were identified using the MISA-web server [22], with minimum repeat thresholds of four for mononucleotide motifs and three for all other repeat types. Transposable elements, including LINE and SINE insertions, were annotated using existing genome annotations. Particular attention was given to repetitive elements arranged in inverted orientations, as these configurations can form double-stranded RNA structures relevant to RNA editing and SOS splicing mechanisms.

Assessment of RNA-level mechanisms

Potential RNA-level repair mechanisms, including RNA editing and transposable element excision, were evaluated based on sequence context and known properties of repetitive elements in bovine genomes. Regions enriched for BovB-derived SINEs and LINE elements were examined for their capacity to form secondary structures conducive to adenosine-to-inosine (A-to-I) RNA editing or structure-dependent splicing. Evidence from published studies on RNA editing and SOS splicing was used to interpret the functional plausibility of these mechanisms.

Integration with experimental evidence

Experimental evidence for *GPRC6A* expression and function in bovine mammary epithelial cells was compiled from published studies reporting protein detection, gene knockdown, and functional assays related to lipid metabolism and milk fat synthesis. These data were used as a biological benchmark against which computational predictions were evaluated. Rather than prioritizing a single explanatory mechanism, all analyses were integrated to identify a set of plausible scenarios consistent with both sequence-level observations and functional outcomes.

Results And Discussion

Functional evidence supports a role for *GPRC6A* in milk fat synthesis

Experimental studies in bovine mammary epithelial cells demonstrate that *GPRC6A* is expressed and functionally active, mediating amino acid-induced lipid synthesis pathways relevant to milk fat production [5,6]. Specifically, activation of *GPRC6A* has been linked to intracellular signaling cascades involving PI3K and lipid-binding proteins, leading to enhanced fatty acid synthesis. These findings establish *GPRC6A* as a biologically relevant regulator of milk composition, a key determinant of dairy productivity. Given these observations, we adopt the conservative assumption that a biological mechanism must exist that permits protein production despite the gene-disrupting mutations reported by Gupta et al. [9]. The sections below examine five non-mutually exclusive mechanisms, ordered from the most conservative and well-established to the most speculative.

How to cite this article:

Soman A S, Vijay N (July 15, 2026) Re-evaluating GPRC6A Gene Loss: Implications for Milk Fat Synthesis and Functional Genomics in Dairy Cattle. Cureus J. Agri. Food Sci 2 : es44497-026-00164-y. DOI <https://doi.org/10.7759/s44497-026-00164-y>

Functionality of a truncated protein or micro-peptide

Gene loss is traditionally inferred from ORF disruptions and premature stop codons. However, ORF disruption alone is insufficient to establish loss of biological function, as many such loci are transcribed and translated, sometimes yielding stable protein products [11]. In the case of *GPRC6A*, even if disruptive mutations are present, truncated protein products may still be produced and detected by Western blotting in bovine mammary epithelial cells.

Notably, siRNA-mediated knockdown of *GPRC6A* is evaluated by Western blotting, and inspection of the coding region reveals that the siRNA target lies within exon 5 (Figure 1a). Several intact short ORFs occur across exons 4-6, including ORFs spanning the siRNA target site. Such convincing evidence raises the possibility that the detected signal corresponds not to a full-length receptor but to a truncated protein or a novel micropeptide. Micropeptides, typically ≤ 100 -150 amino acids in length and translated from short open reading frames, are increasingly recognized as functional biological entities with roles distinct from their parental proteins [23,24]. Such products could plausibly account for protein detection without requiring restoration of the canonical *GPRC6A* ORF [5,6].

Several independent proteomic investigations have previously identified *GPRC6A* peptides within mammalian sperm datasets [25,26]. Specifically, the mass spectrometry data from dataset PXD066938, which profiled the distinct proteomes of bull testicular, caput, and cauda epididymal spermatozoa, revealed the presence of a unique 12-amino-acid peptide sequence: "NDVFIVTNQETK" [25] that uniquely maps to the reviewed UniProt entry E1BPQ3, confirming its designation as the *B. taurus* *GPRC6A* ortholog. Encoded by exon 4, this peptide resides within a conserved family C GPCR ligand-binding domain belonging to the periplasmic binding protein type 1 superfamily (CDD ID: cl10011, appendix Figure 2) and shares the translational reading frame of the well-characterized human *GPRC6A* ortholog (appendix Figure 3). In another study investigating the proteomic profiles of spermatozoa from high- and low-fertility bulls, *GPRC6A* was actively detected but found to be significantly downregulated in the high-fertility cohort [26]. This observed reduction indicates a potential inverse relationship between *GPRC6A* abundance and bovine fertility, implying that overexpression of the protein could be detrimental to sperm competence. Although searches of the Veterinary Proteome Browser (VPBrowse) [27], a curated repository of experimentally validated bovine proteotypic peptides and proteins, did not identify any peptides corresponding to *GPRC6A*, the peptide detected in the present analysis provides direct translation-level evidence for *GPRC6A* expression. While these studies do not biochemically characterize the full-length *GPRC6A* protein in *B. taurus*, the identification of this highly specific peptide confirms the expression and post-translational existence of at least a truncated variant of this receptor.

How to cite this article:

Soman A S, Vijay N (July 15, 2026) Re-evaluating GPRC6A Gene Loss: Implications for Milk Fat Synthesis and Functional Genomics in Dairy Cattle. Cureus J. Agri. Food Sci 2 : es44497-026-00164-y. DOI <https://doi.org/10.7759/s44497-026-00164-y>

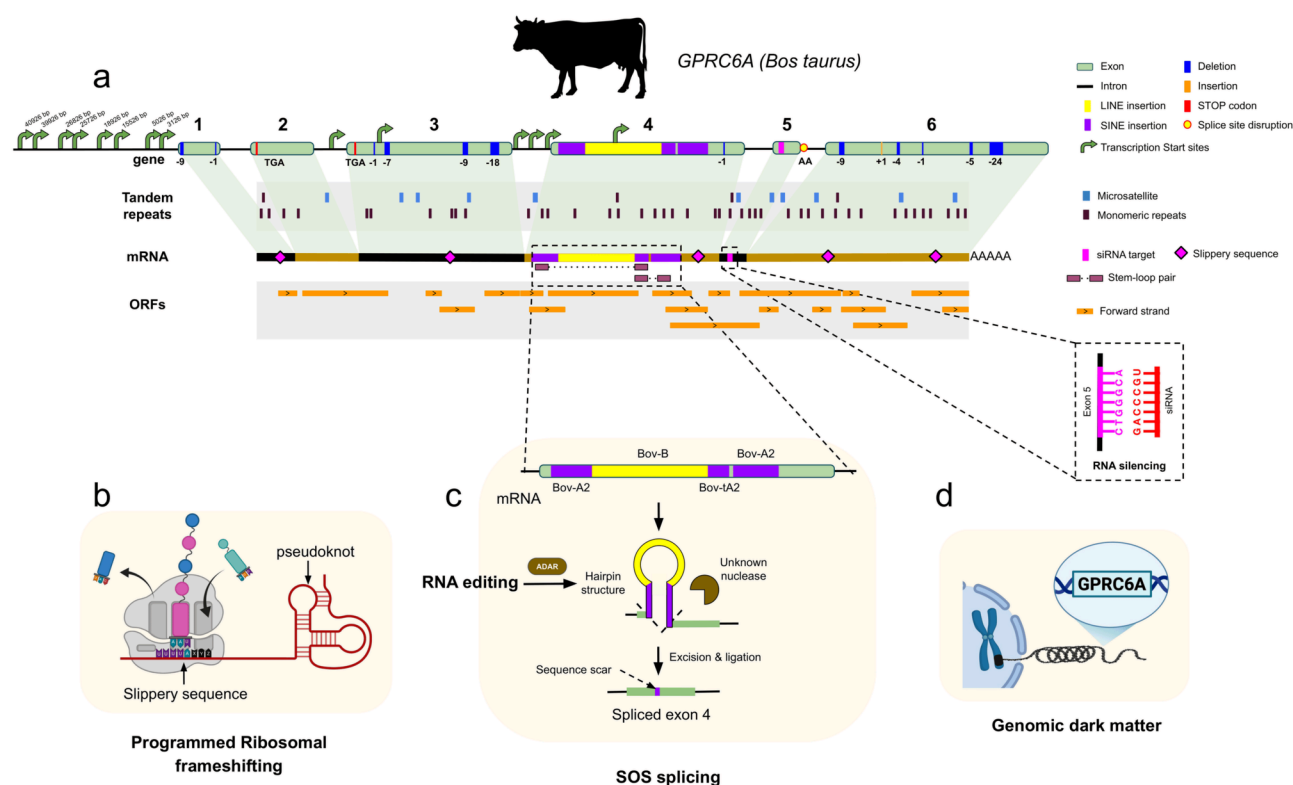


FIGURE 1: Biological scenarios permitting protein production despite gene-disrupting mutations.

(a) Overview schematic showing four annotation tracks: gene structure (exons and introns), tandem repeats, mRNA features, and open reading frames (ORFs). In the gene structure track, putative gene-inactivating mutations are annotated following Gupta et al. [9]. Predicted transcription start sites (TSSs) are marked by green arrows. A total of six downstream and eight upstream TSSs relative to the *GPRC6A* start codon are shown, with distance labels provided exclusively for the upstream TSSs. The tandem repeat track highlights monomeric repeats (brown) and microsatellites (light blue) identified within exonic regions. The mRNA track marks candidate slippery sequences and adjacent stem-loop structures implicated in programmed ribosomal frameshifting (PRF), as well as features relevant to RNA editing and SOS splicing. The ORF track displays all potential ORFs longer than 75 nucleotides on the forward (orange) strand. A magnified view of exon 5 containing the predicted siRNA target site is shown within the dotted rectangle.

The schematics below depict biologically plausible mechanisms by which *GPRC6A* protein production could persist despite apparent gene-inactivating mutations:

(b) Programmed ribosomal frameshifting mediated by a heptanucleotide slippery sequence and a downstream stimulatory RNA secondary structure, such as a pseudoknot.

(c) SOS splicing of exon 4, in which a LINE element flanked by two SINEs forms a hairpin structure, enabling transposable element excision followed by transcript ligation. The inverted Bov-A2 and Bov-tA2 elements are also shown as potential substrates for ADAR-mediated RNA editing.

(d) A scenario in which *GPRC6A* resides within genomically complex or repetitive regions ("genomic dark matter"), potentially evading complete resolution by current genome assemblies.

Downstream internal TSSs or internal promoters

Beyond truncation, transcriptional reconfiguration offers another conservative explanation. Alternative downstream TSSs or internal promoters are widespread in eukaryotic genomes and are particularly common among loci annotated as pseudogenes or partial gene remnants. Internal promoters can generate transcripts that bypass upstream disruptive mutations, producing stable truncated proteins with retained or modified functionality.

How to cite this article:

Soman A S, Vijay N (July 15, 2026) Re-evaluating GPRC6A Gene Loss: Implications for Milk Fat Synthesis and Functional Genomics in Dairy Cattle. *Cureus J. Agri. Food Sci* 2 : es44497-026-00164-y. DOI <https://doi.org/10.7759/s44497-026-00164-y>

Large-scale ribosome profiling and proteogenomic studies demonstrate that many transcripts originating from annotated pseudogenes, lncRNAs, and untranslated regions initiate downstream of canonical start sites and are actively translated [10]. Such transcripts often evade detection in standard transcriptomic analyses due to low abundance, tissue specificity, or the exclusion of multimapping reads. Proteomics-focused reviews further highlight that annotation pipelines frequently misclassify such loci as nonfunctional, even when translation is supported by experimental evidence [12].

In the context of *GPRC6A*, an internal promoter downstream of the most disruptive mutations could plausibly generate a shorter, functional receptor fragment detectable by antibody-based assays. TSSs identified by CAGE sequencing in a previous study [18] revealed a total of 27 TSSs and an enhancer within the *Bos taurus GPRC6A* genomic region (appendix Figure 4). These TSSs exhibited strand specificity, with six located on the sense (+) strand containing *GPRC6A*, including five upstream and one downstream of the annotated start codon. In contrast, 21 TSSs were detected on the antisense (–) strand, of which nine were located upstream and twelve downstream of the *GPRC6A* start codon. The higher abundance of antisense TSSs raises the possibility of natural antisense transcript (NAT) activity within the *GPRC6A* locus. NATs have been increasingly recognized as important regulators of gene expression [28,29]. Although most studies report a negative correlation between sense and antisense transcript levels [30–32], few have demonstrated that antisense transcription can promote transcriptional activation and increased expression of the corresponding sense gene [33,34]. Notably, such activating effects have been observed when antisense transcription initiates within the first intron of the sense gene [35]. Interestingly, most TSSs identified in the *GPRC6A* region were tissue-specific, whereas a single antisense TSS located within intron 1 was detected across ten different tissues (appendix Figure 4). Given its broad tissue distribution and intronic location, this antisense promoter may represent a conserved regulatory element that contributes to the activation or maintenance of *GPRC6A* transcription. While direct evidence for such a mechanism is currently lacking, the observed pattern is consistent with a potential regulatory role for antisense transcription at the *GPRC6A* locus.

Beyond their proposed roles in transcriptional regulation, NATs can positively regulate protein expression through multiple post-transcriptional and translational mechanisms. They may sequester microRNAs, thereby preventing miRNA-mediated repression of target mRNAs [36,37], or directly pair with cognate transcripts to increase mRNA stability and half-life [38,39]. Certain NATs, such as SINEUPs, promote translation by facilitating recruitment of the translational machinery near the initiation site [40]. Additionally, NATs can increase protein stability by inhibiting components of the ubiquitin-proteasome pathway, thereby reducing protein degradation [41]. Collectively, these mechanisms provide plausible routes through which TSS and NATs could contribute to *GPRC6A* expression and potentially facilitate the production or persistence of truncated protein products or micropeptides despite the presence of gene-disrupting mutations.

Additionally, putative TSSs were predicted using Promoter 2.0 across the *B. taurus GPRC6A* genomic locus, encompassing annotated exons, introns, and the upstream intergenic region. Only sites classified as “highly likely” predictions were retained. A total of eight predicted transcription start sites were detected upstream of the canonical *GPRC6A* start codon, with an additional six located downstream. The downstream sites included one in intron 2, one in exon 3, one in exon 4, and three in intron 3. (Figure 1a). Collectively, these results are consistent with internal transcription initiation as a plausible mechanism for *GPRC6A* protein production despite apparent gene-disrupting mutations.

Stop-codon readthrough or programmed ribosomal frameshifting

At the level of translation, recoding mechanisms such as stop-codon readthrough and programmed ribosomal frameshifting (PRF) provide additional routes to protein production from disrupted loci (Figure 1b). While historically associated with viral genomes, both mechanisms are now recognized contributors to proteomic diversity in eukaryotes [42,43]. As PRF requires two key elements, a heptanucleotide slippery sequence and a downstream stimulatory RNA secondary structure, such as a stemloop or pseudoknot, we searched the *GPRC6A* coding sequence for both features [43]. Multiple candidate slippery motifs and nearby stem-loop structures were identified within exonic regions (Figure 1a). Together, these observations indicate that the structural prerequisites for PRF are present at this locus.

How to cite this article:

Soman A S, Vijay N (July 15, 2026) Re-evaluating GPRC6A Gene Loss: Implications for Milk Fat Synthesis and Functional Genomics in Dairy Cattle. *Cureus J. Agri. Food Sci* 2 : es44497-026-00164-y. DOI <https://doi.org/10.7759/s44497-026-00164-y>

Proteogenomic surveys reveal widespread translation of noncanonical ORFs embedded within pseudogenes, frequently involving recoding events that bypass premature stop codons or frame-disrupting mutations [10]. Proteomics-based analyses further show that truncated or frameshifted loci can yield stable peptides detectable across multiple datasets, even when absent from reference protein repositories [12]. In bacterial systems, proteogenomic studies have similarly uncovered extensive low-level expression of so-called “pseudo-pseudogenes,” reinforcing the principle that apparent gene disruption does not preclude regulated translation [44]. In *GPRC6A*, occasional readthrough or frameshifting events could yield sufficient protein for functional assays in specific tissues or physiological contexts.

RNA-level repair: editing, SOS splicing, or trans-splicing

More radical solutions operate at the RNA level. Frame-altering deletions and insertions could, in principle, be corrected through site-specific RNA editing or transcriptional slippage, although such mechanisms have not yet been characterized at this locus. Of particular interest is a repeat insertion consisting of a LINE element embedded within a SINE element in the fourth coding exon. The recently described SOS splicing mechanism excises transposable elements from mRNAs in a structure-dependent manner, protecting transcripts from transposon-mediated disruption [45]. While SOS splicing has not yet been shown to act on this specific configuration, its existence establishes precedent for RNA-level rescue of otherwise disrupted genes.

Analysis of pre-aligned RNA-seq data of *B. taurus* in NCBI showed a lack of robust exon coverage in all 167 samples comprising 99 unique tissues (appendix Figure 5) of *GPRC6A*. Although a few tissues, including lactating milk somatic cells and testis, showed detectable histogram peaks, the signals were of low coverage, dispersed across the entire track rather than confined to exonic regions, and consisted primarily of fragmented, short stretches of small peaks. Notably, even within these tissues, peak abundance was markedly higher toward the 3' end of the gene, particularly in exons three to six. Coverage was also biased toward the 3' end of the region, particularly across exons 3-6. Consistent with this observation, ORFfinder identified a higher density of short open reading frames downstream of exon 6 within the annotated *GPRC6A* locus (Figure 1).

To further assess transcriptional activity across the broader *B. taurus* RNA-seq landscape, including datasets not represented in publicly available pre-aligned resources, all six *GPRC6A* exons were queried against archived SRA datasets using MetaGraph. MetaGraph reports mean exon abundance values for individual RNA-seq samples, providing a measure of transcript representation across the archive. Across all six examined exons, *B. taurus* consistently showed the lowest transcript abundance (appendix Figures 6-8). Notably, no individual RNA-seq sample showed expression across all exons. Furthermore, analysis of the sample with the highest transcript abundance (SRR9136449) revealed no RNA-seq reads mapping to exons 2, 3, and 4, with reads detected only in exons 1, 5, and 6 (appendix Figure 9). This expression pattern raises the possibility of a shorter transcript capable of encoding a truncated peptide, although its biological significance remains to be determined. Peak expression values in *B. taurus* remained low across all exons, ranging from 9 (exon 4) to 46 (exon 6) (appendix Figure 10). By comparison, *S. scrofa*, a close relative of ruminants that retains an intact *GPRC6A*, exhibited higher transcript abundance, with peak values reaching 108. This trend was further accentuated in *H. sapiens*, where maximum abundance values ranged from 890 to 1,225 across exons 1 to 6. These marked differences in transcript abundance were supported by pairwise Welch's *t*-tests across the six examined exons. Comparisons between *B. taurus* and *H. sapiens* showed consistently strong statistical support, with adjusted *P*-values ranging from 6.6×10^{-13} to 3.5×10^{-36} (appendix Figure 10). Differences between *B. taurus* and *S. scrofa* were less pronounced but remained significant for exons 1, 2, 4, and 5, further supporting reduced expression in cattle relative to its functional artiodactyl relative. Notably, although *Sus scrofa* retains an intact open reading frame, previous studies have suggested relaxed selective constraint on this gene, which may contribute to its intermediate transcript abundance relative to the highly expressed *H. sapiens* ortholog.

In the *GPRC6A* locus, this region comprises a Bov-B LINE element flanked by SINEs, specifically Bov-A2 and Bov-tA2, with an additional Bov-A2 element located downstream (Figure 1a and c). Both Bov-A2 and Bov-tA2 are retrotransposons widely distributed across ruminant genomes [46]. Bov-tA2 is a tRNA-derived SINE composed of a tRNA-related sequence at its 5' end and a Bov-A unit at its 3' end, whereas Bov-A2 consists of two Bov-A units linked by short internal repeats

How to cite this article:

Soman A S, Vijay N (July 15, 2026) Re-evaluating GPRC6A Gene Loss: Implications for Milk Fat Synthesis and Functional Genomics in Dairy Cattle. *Cureus J. Agri. Food Sci* 2 : es44497-026-00164-y. DOI <https://doi.org/10.7759/s44497-026-00164-y>

[47,48]. Notably, the Bov-A2 and Bov-tA2 elements are arranged as inverted repeats, a configuration that permits intramolecular base pairing and the formation of stable RNA hairpin structures. Such secondary structures are thought to be substrates for SOS splicing, in which transposable-element derived sequences are excised from mRNAs in a structure-dependent manner and the remaining transcript ligated by nuclease-mediated repair. Although this process can introduce short “scar” sequences into the mRNA, protein production may be preserved provided that the resulting alterations are tolerated at the amino acid level.

RNA editing sites are preferentially enriched within repetitive elements, most notably primate-specific Alu repeats [49,50]. In bovine genomes, however, RNA editing events are predominantly localized to BovB and BovB-derived SINEs, including Bov-tA and Bov-A2, with a particularly strong enrichment in the Bov-tA2 family [51]. Structural analyses indicate that A-to-G editing events within these repetitive regions are frequently associated with double-stranded RNA conformations, such as hairpin structures, which provide favorable substrates for ADAR-mediated editing (Figure 1c). These observations are consistent with a role for repetitive elements in shaping RNA secondary structures that could permit compensatory RNA-level processing.

Trans-splicing provides an additional, albeit speculative, mechanism by which disrupted exons could be replaced through ligation with exons from separate transcripts. Although Gupta et al. [9] did not detect *GPRC6A* transcripts in the tissues they surveyed, expression restricted to specific tissues or physiological states cannot be excluded. Evaluating these RNA-level processes remains challenging but underscores the diversity of mechanisms capable of decoupling genomic disruption from functional outcome.

Genomic dark matter is impervious to current sequencing methods

Finally, it remains possible that the apparent disruptions occur at the annotated locus, while an intact copy of *GPRC6A* resides elsewhere in the genome. However, this possibility should be regarded as the least supported of the five scenarios considered here. Gene duplication followed by divergence is a well-established evolutionary process [52]. Although extensive searches of short- and long-read datasets have identified only the paralog CaSR [9], current sequencing technologies may fail to resolve structurally complex or repetitive genomic regions (Figure 1d). Future improvements in genome assembly may yet uncover cryptic copies contributing to observed protein expression. Therefore, an unresolved genomic copy remains a testable but currently speculative explanation. Its evaluation will require haplotype-resolved long-read assemblies, targeted sequence capture, and orthogonal structural validation rather than inference from current annotations alone.

Limitations and future validation

Several limitations temper the conclusions of this study. The analyses presented are primarily computational and literature-informed, and no new primary experimental or proteomic data were generated to directly validate these models. While data mining of public repositories identified a candidate *GPRC6A* peptide sequence via mass spectrometry, its definitive biochemical and structural characterization remains unverified. Consequently, the proposed internal promoter configurations, translational recoding events, and RNA-level repair mechanisms must be viewed as provisional, testable hypotheses deduced from sequence context and archival datasets rather than empirically demonstrated pathways of protein production in bovine mammary tissue. Furthermore, the “genomic dark matter” scenario remains speculative until evaluated using high-quality long-read assemblies, optical mapping, or targeted capture sequencing. Future investigation should therefore prioritize targeted proteomic characterization of the identified candidate peptide, tissue-specific isoform-resolved transcriptomics, and high-quality long-read genomic reconstruction of the *GPRC6A* locus to accurately elucidate the mechanisms underlying its functional expression.

Conclusions

The present study demonstrates that sequence-based inference of gene loss can fail to accurately capture functional reality in livestock genomes. Using *GPRC6A* as a case study, we show that apparent gene-disrupting mutations can coexist with experimentally validated protein expression and biological activity in bovine mammary epithelial cells,

How to cite this article:

Soman A S, Vijay N (July 15, 2026) Re-evaluating GPRC6A Gene Loss: Implications for Milk Fat Synthesis and Functional Genomics in Dairy Cattle. *Cureus J. Agri. Food Sci* 2 : es44497-026-00164-y. DOI <https://doi.org/10.7759/s44497-026-00164-y>

where the gene contributes to lipid metabolism and milk fat synthesis. This disconnect highlights a fundamental limitation of comparative genomics approaches that rely primarily on coding sequence erosion to infer functional inactivation. Our analysis outlines multiple, nonmutually exclusive mechanisms that may enable functional persistence despite genomic disruption, including the production of truncated proteins or micropeptides, alternative transcription initiation, translational recoding, and RNA-level repair processes. In addition, the possibility of unresolved genomic copies underscores the influence of assembly limitations on gene annotation. Collectively, these mechanisms illustrate that gene function can be maintained through diverse molecular pathways that are not captured by standard annotation frameworks. From an agricultural perspective, these findings have direct implications for dairy genomics and livestock improvement. Genes involved in nutrient sensing and metabolic regulation, such as *GPRC6A*, are integral to traits, such as milk fat composition, that determine both product quality and economic value. Misclassification of such genes as nonfunctional may lead to their exclusion from candidate gene discovery, genomic selection programs, and functional studies, thereby limiting progress in breeding strategies aimed at improving productivity.

We therefore propose the concept of “peripatetic molecular fossils” to describe genes that retain biological activity while exhibiting sequence features typically associated with loss. We specifically define a “peripatetic molecular fossil” as a locus that satisfies three criteria: first, it contains sequence features that would normally support a gene-loss annotation, such as premature stop codons, frameshifts, or disruptive insertions; second, independent evidence indicates transcription, translation, or functional activity in at least one biologically relevant tissue or physiological condition; and third, the available evidence does not yet establish whether the active product derives from the annotated disrupted locus, an alternative transcript, a truncated ORF, RNA-level rescue, or an unresolved genomic copy. This category differs from a conventional translated pseudogene because it explicitly links apparent sequence erosion to retained trait-relevant biological activity and highlights unresolved mechanistic ambiguity rather than assuming a single origin of the functional product. Recognizing this intermediate category shifts the interpretation of gene status from a binary framework toward a continuum that incorporates functional evidence alongside sequence data. More broadly, our findings emphasize the need for integrative approaches that combine comparative genomics with transcriptomics, proteomics, and experimental validation to accurately identify genes influencing agriculturally important traits. In this sense, a peripatetic molecular fossil is not merely a degraded remnant, but a locus that appears genomically eroded while retaining evidence of biological activity. Analogous to biogeographically unexpected fossils, such as the “kangaroos in Kashmir” metaphor used to describe palaeontological anomalies, these genes appear out of place within a binary framework of gene presence versus gene loss. The concept is intended to highlight loci that occupy this unsettled middle ground: sequence-disrupted, functionally suggestive, and mechanistically unresolved.

In conclusion, the *GPRC6A* case underscores the importance of re-evaluating gene-loss inference in livestock systems and highlights the need for functionally informed annotation to advance dairy science and agricultural genomics.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Nagarjun Vijay, Aswin S. Soman

Drafting of the manuscript: Nagarjun Vijay, Aswin S. Soman

Critical review of the manuscript for important intellectual content: Nagarjun Vijay, Aswin S. Soman

Supervision: Nagarjun Vijay

Acquisition, analysis, or interpretation of data: Aswin S. Soman

How to cite this article:

Soman A S, Vijay N (July 15, 2026) Re-evaluating GPRC6A Gene Loss: Implications for Milk Fat Synthesis and Functional Genomics in Dairy Cattle. *Cureus J. Agri. Food Sci* 2 : es44497-026-00164-y. DOI <https://doi.org/10.7759/s44497-026-00164-y>

Disclosures

Plant subjects: All authors have confirmed that this study did not involve any herbarium specimen. **Human subjects:** All authors have confirmed that this study did not involve human participants or tissue. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** Nagarjun Vijay, Aswin S Soman declare(s) a grant from Ministry of Human Resource Development for the fellowship to A.S. , The Department of Biotechnology, Ministry of Science and Technology, India, Science and Engineering Research Board . We thank the Ministry of Human Resource Development for the fellowship to A.S. The Department of Biotechnology, Ministry of Science and Technology, India (Grant no. BT/11/IYBA/2018/03) and Science and Engineering Research Board (Grant no. ECR/2017/001430) provided funds for procuring computational resources (i.e., Har Gobind Khorana Computational Biology cluster) used. Any resemblance to any talent found in nature is purely coincidental. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Data Availability Statements

The data (and/or code) supporting this study are openly available in GitHub repository at <https://github.com/saumyagupta09/GPRC6A/tree/c655a98b3ba1e4dd729a96206f59b9eb68a973ae/Peripatetic>.

Acknowledgements

We thank the Ministry of Human Resource Development for the fellowship to A.S. The Department of Biotechnology, Ministry of Science and Technology, India (Grant no. BT/11/IYBA/2018/03) and Science and Engineering Research Board (Grant no. ECR/2017/001430) provided funds for procuring computational resources (i.e., Har Gobind Khorana Computational Biology cluster) used. Any resemblance to any talent found in nature is purely coincidental.

References

1. Bauman DE, Griinari JM: [Nutritional regulation of milk fat synthesis](#). Annual Review of Nutrition. 2003, 23:203-227. [10.1146/annurev.nutr.23.011702.073408](#)
2. Lock AL, Bauman DE: [Modifying milk fat composition of dairy cows to enhance fatty acids beneficial to human health](#). Lipids. 2004, 39:1197-1206. [10.1007/s11745-004-1348-6](#)
3. Georges M, Charlier C, Hayes B: [Harnessing genomic information for livestock improvement](#). Nature Reviews Genetics. 2018, 20:135-156. [10.1038/s41576-018-0082-2](#)
4. Xiang R, Berg IVD, MacLeod IM, Goddard ME: [Quantifying the contribution of sequence variants with regulatory and evolutionary significance to 34 bovine complex traits](#). Proceedings of the National Academy of Sciences of the United States of America. 2019, 116:19398-19408. [10.1073/pnas.1904159116](#)
5. Li X, Li P, Wang L, Zhang M, Gao X: [Lysine enhances the stimulation of fatty acids on milk fat synthesis via the GPRC6A-PI3K-FABP5 signaling in bovine mammary epithelial cells](#). Journal of Agricultural and Food Chemistry. 2019, 67:7005-7015. [10.1021/acs.jafc.9b02160](#)
6. Jin X, Zhen Z, Wang Z, Gao X, Li M: [GPRC6A is a key mediator of palmitic acid regulation of lipid synthesis in bovine mammary epithelial cells](#). Cell Biology International. 2022, 46:1747-1758. [10.1002/cbin.11886](#)
7. Zhou X, Sun M, Jiang N, et al.: [L-theanine activates the mTOR signaling pathway through TAS1R1-FRMD6 to promote milk synthesis in bovine mammary epithelial cells.](#) The Journal of Nutritional Biochemistry. 2026, 156:110395. [10.1016/j.jnutbio.2026.110395](#)
8. Turakhia Y, Chen HI, Marcovitz A, Bejerano G: [A fully-automated method discovers loss of mouse-lethal and human-monogenic disease genes in 58 mammals](#). Nucleic Acids Research. 2020, 48:e91. [10.1093/nar/gkaa550](#)

How to cite this article:

Soman A S, Vijay N (July 15, 2026) Re-evaluating GPRC6A Gene Loss: Implications for Milk Fat Synthesis and Functional Genomics in Dairy Cattle. Cureus J. Agri. Food Sci 2 : es44497-026-00164-y. DOI <https://doi.org/10.7759/s44497-026-00164-y>

9. Gupta S, Patil ABj, Soman AS, Vijay N: [Master of none: GPRC6A gene loss is more widespread than previously known](#). *Genetica*. 2026, 154:1-16. [10.1007/s10709-026-00258-7](#)
10. Ji Z, Song R, Regev A, Struhl K: [Many lncRNAs, 5'UTRs, and pseudogenes are translated and some are likely to express functional proteins](#). *eLife*. 2015, 4:1-21. [10.7554/elife.08890](#)
11. Xu J, Zhang J: [Are human translated pseudogenes functional?](#). *Molecular Biology and Evolution*. 2015, 33:755-760. [10.1093/molbev/msv268](#)
12. Vasylieva V, Arefiev I, Bourassa F, Trifiro FA, Brunet MA: [Proteomics can rise to the challenge of pseudogenes' coding nature](#). *Journal of Proteome Research*. 2024, 23:5233-5249. [10.1021/acs.jproteome.4c00116](#)
13. Knudsen S: [Promoter2.0: for the recognition of PolII promoter sequences](#). *Bioinformatics*. 1999, 15:356-361. [10.1093/bioinformatics/15.5.356](#)
14. Sayers EW, Beck J, Bolton EE, et al.: [Database resources of the National Center for Biotechnology Information in 2025](#). *Nucleic Acids Research*. 2024, 53:D20-D29. [10.1093/nar/gkae979](#)
15. Karasikov M, Mustafa H, Danciu D, et al.: [Efficient and accurate search in petabase-scale sequence repositories](#). *Nature*. 2025, 647:1036-1044. [10.1038/s41586-025-09603-w](#)
16. Chen S, Zhou Y, Chen Y, Gu J: [fastp: an ultra-fast all-in-one FASTQ preprocessor](#). *Bioinformatics*. 2018, 34:i884-i890. [10.1093/bioinformatics/bty560](#)
17. Dobin A, Davis CA, Schlesinger F, et al.: [STAR: ultrafast universal RNA-seq aligner](#). *bioinformatics (oxford, england)*. 2012, 29:15-21. [10.1093/bioinformatics/bts635](#)
18. Salavati M, Clark R, Becker D, et al.: [Improving the annotation of the cattle genome by annotating transcription start sites in a diverse set of tissues and populations using cap analysis gene expression sequencing](#). *G3: Genes, Genomes, Genetics*. 2023, 13:1-15. [10.1093/g3journal/jkad108](#)
19. Robinson JT, Thorvaldsdottir H, Mesirov JP: [igv-Reports: embedding interactive genomic visualizations in HTML reports to aid variant review](#). *Bioinformatics*. 2026, 42:1-4. [10.1093/bioinformatics/btag125](#)
20. Bekaert M, Firth AE, Zhang Y, Gladyshev VN, Atkins JF, Baranov PV: [Recode-2: new design, new search tools, and many more genes](#). *Nucleic Acids Research*. 2009, 38:D69-D74. [10.1093/nar/gkp788](#)
21. Rice P, Longden I, Bleasby A: [EMBOSS: the European Molecular Biology Open Software Suite](#). *Trends in Genetics*. 2000, 16:276-277. [10.1016/s0168-9525\(00\)00204-2](#)
22. Beier S, Thiel T, Münch T, Scholz U, Mascher M: [MISA-web: a web server for microsatellite prediction](#). *Bioinformatics*. 2017, 33:2583-2585. [10.1093/bioinformatics/btx198](#)
23. Makarewich CA, Olson EN: [Mining for micropeptides](#). *Trends in Cell Biology*. 2017, 27:685-696. [10.1016/j.tcb.2017.04.006](#)
24. ME Sousa Maria E., MH Farkas Michael H.: [Micropeptide](#). *PLoS Genetics*. 2018, 14:1-7. [10.1371/journal.pgen.1007764](#)
25. Leites I, Diniz P, Fardilha M, Santiago J, Ferreira-Dias G, Lopes-da-Costa L, Silva E: [Proteomic dynamics of bull sperm during post-testicular maturation](#). *BMC Genomics*. 2026, 27:1-19. [10.1186/s12864-026-12614-0](#)
26. Singh R, Sengar GS, Singh U, et al.: [Functional proteomic analysis of crossbred \(Holstein Friesian × Sahiwal\) bull spermatozoa](#). *Reproduction in Domestic Animals*. 2018, 53:588-608. [10.1111/rda.13146](#)
27. Selvam P, Ashick M, Dudley KJ, Satake N, Mills PC, Sadowski P, Nagaraj SH: [VPBrowse: genome-based representation of MS/MS spectra to quantify 10,000 bovine proteins](#). *Proteomics*. 2024, 24:1-7. [10.1002/pmic.202300431](#)
28. Xu JZ, Zhang JI, Zhang WG: [Antisense RNA: the new favorite in genetic research](#). *Journal of Zhejiang University-SCIENCE B*. 2018, 19:739-749. [10.1631/jzus.b1700594](#)
29. Faghihi MA, Wahlestedt C: [Regulatory roles of natural antisense transcripts](#). *Nature Reviews Molecular Cell Biology*. 2009, 10:637-643. [10.1038/nrm2738](#)
30. Rosikiewicz W, Makalowska I: [Biological functions of natural antisense transcripts](#). *Acta Biochimica Polonica*. 2016, 63:665-673. [10.18388/abp.2016_1350](#)
31. Werner A, Cockell S, Falconer J, Carlile M, Alnumeir S, Robinson J: [Contribution of natural antisense transcription to an endogenous siRNA signature in human cells](#). *BMC Genomics*. 2014, 15:1-12. [10.1186/1471-2164-15-19](#)

How to cite this article:

Soman A S, Vijay N (July 15, 2026) Re-evaluating GPRC6A Gene Loss: Implications for Milk Fat Synthesis and Functional Genomics in Dairy Cattle. *Cureus J. Agri. Food Sci* 2 : es44497-026-00164-y. DOI <https://doi.org/10.7759/s44497-026-00164-y>

32. Zong X, Nakagawa S, Freier SM, Fei J, Ha T, Prasanth SG, Prasanth KV: [Natural antisense RNA promotes 3' end processing and maturation of MALAT1 lncRNA](#). Nucleic Acids Research. 2016, 44:2898-2908. [10.1093/nar/gkw047](#)
33. de Jesus BB, Marinho SP, Barros S, Sousa-Franco A, Alves-Vale C, Carvalho T, Carmo-Fonseca M: [Silencing of the lncRNA Zeb2-NAT facilitates reprogramming of aged fibroblasts and safeguards stem cell pluripotency](#). Nature Communications. 2018, 9:1-11. [10.1038/s41467-017-01921-6](#)
34. Boque-Sastre R, Soler M, Oliveira-Mateos C, et al.: [Head-to-head antisense transcription and R-loop formation promotes transcriptional activation](#). Proceedings of the National Academy of Sciences of the United States of America. 2015, 112:5785-5790. [10.1073/pnas.1421197112](#)
35. Postepska-Igielska A, Giwojna A, Gasri-Plotnitsky L, Schmitt N, Dold A, Ginsberg D, Grummt I: [LncRNA Khps1 regulates expression of the proto-oncogene SPHK1 via triplex-mediated changes in chromatin structure](#). Molecular Cell. 2015, 60:626-636. [10.1016/j.molcel.2015.10.001](#)
36. Wang X, Zhang C, Gong M, Jiang C: [A novel identified long non-coding RNA, lncRNA MEF2C-AS1, inhibits cervical cancer via regulation of miR-592/RSP01](#). Frontiers in Molecular Biosciences. 2021, 8:1-11. [10.3389/fmolb.2021.687113](#)
37. Liao L, Chen J, Zhang C, et al.: [LncRNA NEAT1 promotes high glucose-induced mesangial cell hypertrophy by targeting miR-222-3p/CDKN1B axis](#). Frontiers in Molecular Biosciences. 2021, 7:1-12. [10.3389/fmolb.2020.627827](#)
38. Nishizawa M, Ikeya Y, Okumura T, Kimura T: [Post-transcriptional inducible gene regulation by natural antisense RNA](#). Frontiers in Bioscience-Landmark. 2015, 20:1-36. [10.2741/4297](#)
39. Jadaliha M, Gholamalamdari O, Tang W, et al.: [A natural antisense lncRNA controls breast cancer progression by promoting tumor suppressor gene mRNA stability](#). PLoS Genetics. 2018, 14:1-24. [10.1371/journal.pgen.1007802](#)
40. Podbevšek P, Fasolo F, Bon C, et al.: [Structural determinants of the SINE B2 element embedded in the long non-coding RNA activator of translation AS Uchl1](#). Scientific Reports. 2018, 8:1-13. [10.1038/s41598-017-14908-6](#)
41. Wang CL, Li JC, Zhou CX, et al.: [Long non-coding RNA ARHGAP5-AS1 inhibits migration of breast cancer cell via stabilizing SMAD7 protein](#). Breast Cancer Research and Treatment. 2021, 189:607-619. [10.1007/s10549-021-06286-5](#)
42. Clark MB, Jänicke M, Gottesbühren U, Kleffmann T, Legge M, Poole ES, Tate WP: [Mammalian gene PEG10 expresses two reading frames by high efficiency-1 frameshifting in embryonic-associated tissues](#). The Journal of Biological Chemistry. 2007, 282:37359-37369. [10.1074/jbc.M70567200](#)
43. Ren G, Gu X, Zhang L, et al.: [Ribosomal frameshifting at normal codon repeats recodes functional chimeric proteins in human](#). Nucleic Acids Research. 2024, 52:2463-2479. [10.1093/nar/gkae035](#)
44. Feng Y, Wang Z, Chien KY, Chen HL, Liang YH, Hua X, Chiu CH: ["Pseudo-pseudogenes" in bacterial genomes: proteogenomics reveals a wide but low protein expression of pseudogenes in Salmonella enterica](#). Nucleic Acids Research. 2022, 50:5158-5170. [10.1093/nar/gkac302](#)
45. Zhao LW, Nardone C, Chang C, Paulo JA, Elledge SJ, Kennedy S: [An RNA splicing system that excises DNA transposons from animal mRNAs](#). Nature. 2025, 649:496-504. [10.1038/s41586-025-09853-8](#)
46. Ohshima K, Okada N: [SINEs and LINEs: symbionts of eukaryotic genomes with a common tail](#). Cytogenetic and Genome Research. 2005, 110:475-490. [10.1159/000084981](#)
47. Adelson DL, Raison JM, Edgar RC: [Characterization and distribution of retrotransposons and simple sequence repeats in the bovine genome](#). proceedings of the national academy of sciences of the united states of america. 2009, 106:12855-12860. [10.1073/pnas.0901282106](#)
48. Lenstra JA, Vanboxtel JAF, Zwaagstra KA, Schwerin M: [Short interspersed nuclear element \(SINE\) sequences of the Bovidae](#). Animal Genetics. 1993, 24:33-39. [10.1111/j.1365-2052.1993.tb00916.x](#)
49. Nishikura K: [A-to-I editing of coding and non-coding RNAs by ADARs](#). Nature Reviews Molecular Cell Biology. 2015, 17:83-96. [10.1038/nrm.2015.4](#)
50. Eisenberg E, Levanon EY: [A-to-I RNA editing — immune protector and transcriptome diversifier](#). Nature Reviews Genetics. 2018, 19:473-490. [10.1038/s41576-018-0006-1](#)
51. Cai W, Shi L, Cao M, Shen D, Li J, Zhang S, Song J: [Pan-RNA editing analysis of the bovine genome](#). RNA Biology. 2020, 18:368-381. [10.1080/15476286.2020.1807724](#)

How to cite this article:

Soman A S, Vijay N (July 15, 2026) Re-evaluating GPRC6A Gene Loss: Implications for Milk Fat Synthesis and Functional Genomics in Dairy Cattle. Cureus J. Agri. Food Sci 2 : es44497-026-00164-y. DOI <https://doi.org/10.7759/s44497-026-00164-y>

52. Qian W, Zhang J: [Genomic evidence for adaptation by gene duplication](https://doi.org/10.1101/gr.172098.114). Genome Research. 2014, 24:1356-1362. [10.1101/gr.172098.114](https://doi.org/10.1101/gr.172098.114)

How to cite this article:

Soman A S, Vijay N (July 15, 2026) Re-evaluating GPRC6A Gene Loss: Implications for Milk Fat Synthesis and Functional Genomics in Dairy Cattle. Cureus J. Agri. Food Sci 2 : es44497-026-00164-y. DOI <https://doi.org/10.7759/s44497-026-00164-y>