BTN1A1 (NM_001732.3) — Integrated Sequence Investigation Portfolio

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Overview of Chosen Sequence / Accession

Chosen sequence/ACC: NM_001732.3 (RefSeq mRNA).

Organism: Homo sapiens.

Primary gene: BTN1A1 (butyrophilin subfamily 1 member A1).

Encoded protein: NP_001723.2 (Butyrophilin precursor).

Genomic location: Chromosome 6 (GRCh38: NC_000006.12, 26,500,303–26,510,425; T2T-CHM13: NC_060930.1, 26,368,710–26,378,831).

Cross-references: CCDS4614.1; Ensembl gene ENSG00000124557.

Length: 2945 bp (NM_001732.3).

History: Accession first seen at NCBI on Mar 24, 1999 (5:08 PM); current version v3 dated Jul 11, 2019; flatfile minor updates as recent as Apr 29, 2025.

Summary significance: BTN1A1 encodes butyrophilin, a major protein of the milk fat globule membrane (MFGM), essential for milk fat secretion; within the MHC class I region (immune context). Recent work suggests BTN1A1 may act as a novel immune checkpoint.

Flatfile References (Selected Literature)

Kim, Y. S., Lee, S. H., Park, A. H., Wu, C., Hong, B. K., Jung, H., Lin, S. H., & Yoo, S. S. (2024). BTN1A1 is a novel immune checkpoint mutually exclusive to PD-L1. Journal for Immunotherapy of Cancer, 12(3), e008303. https://doi.org/10.1136/jitc-2023-008303

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Mather, I. H., & Jack, L. J. (1993). A review of the molecular and cellular biology of butyrophilin, the major protein of bovine milk fat globule membrane. Journal of Dairy Science, 76(12), 3832–3850. https://doi.org/10.3168/jds.S0022-0302(93)77728-5

Vernet, C., Boretto, J., Mattei, M. G., Takahashi, M., Jack, L. J., Mather, I. H., Rouquier, S., & Pontarotti, P. (1993). Evolutionary study of multigenic families mapping close to the human MHC class I region. Journal of Molecular Evolution, 37(6), 600–612. https://doi.org/10.1007/BF00160406

Heid, H. W., Winter, S., Bruder, G., Keenan, T. W., & Jarasch, E. D. (1983). Butyrophilin, an apical plasma membrane–associated glycoprotein characteristic of lactating mammary glands of diverse species. BBA – Biomembranes, 728(2), 228–238. https://doi.org/10.1016/0005-2736(83)90566-1

Entrez Gene Findings (Summary)

BTN1A1 harbors numerous SNPs across coding and non-coding regions (including missense and regulatory variants), as well as occasional small indels in non-coding regions that may modulate expression.

Alternative splicing yields multiple mRNA isoforms that typically encode the same protein while differing in untranslated and regulatory regions; this likely supports context-specific regulation (e.g., lactation).

Orthologs are conserved across mammals, notably in human and cattle, reflecting BTN1A1's essential role in milk-fat secretion.

Reference: NCBI Gene — Btn1a1 (Mus musculus), Gene ID: 12231 (updated 2025).

DNA Marker Focus: Simple Sequence Repeats (SSRs)

Definition: SSRs (microsatellites/STRs) are 1–6 bp motifs repeated in tandem, typically <100 bp in total length, distributed across nuclear, chloroplast, and mitochondrial genomes.

Use in mapping: Repeat-number polymorphisms are highly informative for linkage analysis, inheritance tracking, and trait association in gene mapping.

Reference: NCBI Genes and Disease — Microsatellite (2023).

Module 2 Reflection — Two Things Learned & One Interesting Concept

Two things learned: (1) Orthologs — genes in other species with shared evolutionary origin; BTN1A1 has orthologs in hundreds of organisms. (2) SNP types — non-coding SNPs often influence regulation, coding SNPs affect codon usage, and missense SNPs can alter protein interactions.

Interesting concept: SSR DNA markers — short, tandemly repeated motifs that are abundant, distinct, and straightforward to genotype; highly useful for genome mapping.

Ensembl Gene Summary — BTN1A1 (ENSG00000124557)

Reported features: 2 splice variants, 1 gene allele, 98 orthologs, and 15 paralogs (Ensembl, 2025).

Isoforms BTN1A1-204 (2945 bp) and BTN1A1-203 (2895 bp) differ primarily in non-coding regions; core domains are preserved.

Observed SNPs span coding (potential amino-acid changes) and non-coding regions (potential expression effects).

Conservation across mammals (e.g., cattle, mouse) underlines functional constraints.

Ensembl Synteny Example — Ubtd1 (Mouse ENSMUSG00000025171)

Ubtd1 in mouse (chr19: 41,970,202–42,023,082, forward strand) illustrates conserved synteny with human UBTD1 (chr10: 97,498,913–97,571,206).

Synteny and homology views show conservation across additional mammals (e.g., Chinese hamster, naked mole-rat, Eurasian red squirrel).

UCSC Genome Browser — BTN1A1 Locus

Coordinates: chr6:26,500,303–26,510,425 (hg38), positive strand.

Transcripts: RefSeq NM_001732.3, NM_013483.4; GENCODE isoforms (e.g., ENST00000684113.1) with distinct exon structures.

Variation: dbSNP153 shows multiple SNPs (e.g., rs2076530 intronic; rs1050634 in the 3′ UTR).

Conservation: Strong mammalian conservation consistent with lactation function; resides on primary chr6 contig (hg38) without alt-haplotype placement.

Reference: Kent et al., 2002, Genome Research (UCSC Browser).

Example SNP Record

dbSNP ID: rs50942201.

Chromosome 12, position 57,798,985 (positive strand).

Observed alleles: A/G; Reference allele: G.

Genomic context: intronic.

BLASTN Summary — BTN1A1 Genomic Sequence (GRCh38)

Parameters: megablast with defaults (E-value 1e-10, DUST on, masking for lookup on, max targets 100); also ran discontiguous megablast for distant mammals.

Findings: 99–100% identity with human BTN1A1 genomic records (E=0.0); close primates next; more distant mammals (cow, mouse) align strongly in exons with expected intron gaps.

Interpretation: Coding exons are highly conserved across mammals; UTRs and introns more variable — consistent with functional constraints on protein domains.

Reference: NCBI Gene — BTN1A1 (Homo sapiens), Gene ID 696.

FASTA Summary — BTN1A1

Initial plan used strict parameters (match/mismatch 2/-3; gap open -16; gap extend -4; ktup 3; E upper limit 1e-10) but default settings were used due to runtime.

Results: High similarity between human BTN1A1 and mammalian homologs (Bos taurus, Mus musculus). Additional similar sequences noted in butyrophilin and ubiquitin-ligase families.

Reference: Pearson (2013) — FASTA sequence comparison at NCBI.

Multiple Sequence Alignment — Clustal Omega, T-Coffee, MUSCLE

Input sequences: NM_001732.3 (Homo sapiens), XM_054685653.2 (Bos taurus), U39576.1 (Homo sapiens), XM_004043429.4 (Ovis aries).

Clustal Omega: near-continuous conservation across central coding region; Ovis aries shows unique 5′ extension in first ~200 nt.

T-Coffee (Nightingale): highlights short, weakly conserved tracts within the variable 5′ region, suggesting partial similarity rather than true homology.

MUSCLE: aligns closely with T-Coffee visualization; high-quality, low-gap alignment emphasizing conserved residues.

Note: Removing Ovis aries sequence could slightly increase early-region alignment uniformity, but inclusion displays evolutionary diversity.

Conserved Domains — NCBI CDD / Pfam

Identified domain: Butyrophilin immunoglobulin-like domain (CDD:293991) in the extracellular region, characteristic of the butyrophilin/MHC superfamily.

Architecture aligns with Pfam: immunoglobulin-like domains plus a transmembrane region typical of BTN proteins.

Functional implication: conserved motifs support dual roles in lipid-droplet secretion and immune signaling.

Overall Interpretation

BTN1A1 is a highly conserved, structurally constrained gene across mammals. Concordant evidence from BLAST, FASTA, MSA tools, and conserved domain analysis supports strong selective pressure on its immunoglobulin-like and transmembrane domains.

Its genomic position within the MHC class I region and emerging literature on immune-checkpoint function suggest immunological relevance in addition to its canonical role in milk fat globule membrane biology.

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