* Do not include theses or articles with unknown journal

## Proposed EC/sub‐subclass

The accepted enzyme commission classification for Beta‐1,4 N‐acetylgalactosaminyltransferase 2 is EC 2.4.1.244. This assignment reflects its biochemical role as a glycosyltransferase that catalyzes the transfer of an N‐acetylgalactosamine moiety from a nucleotide sugar donor to an acceptor glycan bearing a terminal sialylated galactose residue (petit2021aphylogeneticview pages 9-10, petit2021aphylogeneticview pages 15-16).

## Accepted name

The recommended name for this protein is “Beta‐1,4 N‐acetylgalactosaminyltransferase 2.” It is also referred to as Sd(a) beta‐1,4‐GalNAc transferase or UDP‐GalNAc:Neu5Aca2–3Galb‐R β1,4‐N‐acetylgalactosaminyltransferase, reflecting its catalytic function in synthesizing the Sd(a) histo‐blood group antigen (dallolio2014theexpandingroles pages 3-3, duca2023thestoryof pages 3-4, duca2023thestoryof pages 1-3).

## Phylogeny

Beta‐1,4 N‐acetylgalactosaminyltransferase 2 is evolutionarily conserved among vertebrates, with well‐documented orthologs in human, mouse, pig, and other mammalian species (dallolio2014theexpandingroles pages 3-5, groux‐degroote2018theextendedcytoplasmic pages 9-12). Phylogenetic analyses place this enzyme within a conserved branch of glycosyltransferases that participate in the biosynthesis of glycan antigens on both glycoproteins and glycolipids (petit2021aphylogeneticview pages 4-4, petit2021aphylogeneticview pages 16-16). Within the broader context of glycan‐modifying enzymes, B4GALNT2 shows evolutionary relationships with closely related paralogs such as B4GALNT1, which synthesizes ganglioside GM2, yet its catalytic specificity and tissue distribution distinguish it functionally (cogez2023nglycanonthe pages 9-11, duca2023thestoryof pages 1-3). The gene is located on chromosome 17q21.33 and consists of multiple coding exons that have evolved by alternative exon usage to yield distinct isoforms (dallolio2014theexpandingroles pages 3-5, duca2023thestoryof pages 1-3).

## Glycosyltransferase family

B4GALNT2 belongs to the glycosyltransferase family GT31 within the CAZy classification. This family comprises enzymes that generally catalyze glycosyl transfer reactions via either retaining or inverting mechanisms. In particular, B4GALNT2 is grouped with other beta‐1,4‐N‐acetylgalactosaminyltransferases that participate in the biosynthesis of blood group antigens and complex glycan structures (petit2021aphylogeneticview pages 4-5, petit2021aphylogeneticview pages 4-4, petit2021aphylogeneticview pages 15-16).

## Reaction Catalyzed

Beta‐1,4 N‐acetylgalactosaminyltransferase 2 catalyzes the transfer of an N‐acetylgalactosamine (GalNAc) residue in a β1,4‐linkage from the donor substrate UDP‐GalNAc to the galactose residue of an acceptor glycan that features a terminal Neu5Acα2–3 linked sialic acid. The resulting product is the Sd(a) antigen, with the structure GalNAcβ1→4(Neu5Acα2→3)Gal‐R, which is displayed on both N‐ and O‐linked glycoproteins as well as glycolipids. This transfer reaction is critical for the biosynthesis of a distinct histo‐blood group antigen (dallolio2014theexpandingroles pages 3-3, duca2024thesdacarbohydrate pages 1-4, duca2023thestoryof pages 1-3).

## Cofactor Requirements

The catalytic activity of B4GALNT2 is dependent on divalent metal ion cofactors, with a requirement for ions such as Mn²⁺ (and in some cases Mg²⁺ is considered) that are essential for stabilizing the nucleotide sugar donor complex. The conserved DxD motif in the enzyme coordinates these metal ions, thereby facilitating the proper binding of UDP‐GalNAc during the transfer reaction (petit2021aphylogeneticview pages 9-10, petit2021aphylogeneticview pages 15-16, pqac-23e3b47b).

## Substrate Specificity

B4GALNT2 displays strict substrate specificity that requires the acceptor substrate to possess an α2,3‐linked sialic acid attached to a galactose residue. It acts on multiple glycan classes, including type 1 and type 2 lactosaminic chains, core 2 and core 3 O‐linked glycans, and glycolipids such as those found in sialylparagloboside. The enzyme does not catalyze the transfer of GalNAc to substrates with α2,6‐linked sialic acids or gangliosides like GM3, emphasizing its selectivity for α2,3‐sialylated structures (duca2024thesdacarbohydrate pages 7-9, dallolio2014theexpandingroles pages 3-3, duca2024thesdacarbohydrate pages 14-15, duca2023thestoryof pages 1-3).

## Structure

The domain organization of B4GALNT2 has been characterized both experimentally and through computational modeling using tools such as AlphaFold2. The protein is a type II transmembrane glycosyltransferase, comprising a short cytoplasmic tail, a single transmembrane domain, a stem region, and a large catalytic domain located in the Golgi lumen. Two major isoforms are produced by alternative first exon usage: a short form of 506 amino acids, which exhibits higher enzymatic activity, and a long form of 566 amino acids that contains an extended cytoplasmic tail critical for additional post‐Golgi vesicle targeting (groux‐degroote2018theextendedcytoplasmic pages 6-9, groux‐degroote2018theextendedcytoplasmic pages 9-12, duca2023thestoryof pages 1-3). The catalytic domain contains the typical glycosyltransferase motifs, including the conserved DxD motif integral for metal ion binding and UDP‐GalNAc coordination, as well as conserved cysteine residues that likely contribute to intersubunit disulfide bonding and homodimer formation (dallolio2014theexpandingroles pages 1-2, cogez2023nglycanonthe pages 13-14, groux‐degroote2018theextendedcytoplasmic pages 9-12). Structural modeling indicates that the catalytic pocket remains accessible despite the presence of bulky N‐glycans at non‐consensus N‐glycosylation sites, thereby ensuring efficient catalysis (dallolio2014theexpandingroles pages 3-5, cogez2023nglycanonthe pages 9-11). The extended cytoplasmic tail of the long isoform contains sorting signals, such as an ER‐exit dibasic RGR motif and a vesicular targeting heptapeptide, which facilitate its localization to post‐Golgi vesicles and the plasma membrane in addition to the Golgi (groux‐degroote2018theextendedcytoplasmic pages 6-9, groux‐degroote2018theextendedcytoplasmic pages 17-20, groux‐degroote2018theextendedcytoplasmic pages 9-12).

## Regulation

Regulatory mechanisms controlling B4GALNT2 expression and activity occur at both the transcriptional and post‐translational levels. Transcriptional regulation involves alternative promoter usage leading to the production of distinct isoforms (exon 1S versus exon 1L), and the presence of CpG islands upstream of these exons indicates that DNA methylation is an important modulator of gene expression. Moreover, transcription factors such as ETS1, DMTF1, and SP1 have been reported to contribute to B4GALNT2 regulation (groux‐degroote2018theextendedcytoplasmic pages 17-20, cogez2023nglycanonthe pages 3-4). At the post‐translational level, B4GALNT2 undergoes N‐glycosylation at an atypical, evolutionarily conserved non‐consensus N‐X‐C motif, and this glycosylation is critical for proper protein folding, homodimerization, stability, and correct targeting to the Golgi apparatus (cogez2023nglycanonthe pages 13-14, cogez2023nglycanonthe pages 1-3, cogez2023nglycanonthe pages 9-11). In addition, the extended cytoplasmic tail in the long isoform contains specific motifs that not only modulate Golgi retention but also facilitate dynamic post‐Golgi trafficking, underscoring the importance of subcellular localization in the enzyme’s functional regulation (groux‐degroote2018theextendedcytoplasmic pages 6-9, groux‐degroote2018theextendedcytoplasmic pages 9-12).

## Function

Beta‐1,4 N‐acetylgalactosaminyltransferase 2 plays a pivotal role in the biosynthesis of the Sd(a) histo‐blood group antigen by mediating the terminal transfer of GalNAc to acceptor glycans that contain a Neu5Acα2–3Gal moiety. This reaction occurs on both O‐ and N‐linked glycoproteins as well as on glycolipids, thereby influencing the glycan composition of numerous cell surface molecules. Expression of B4GALNT2 is highest in the colon, where it contributes to the synthesis of mucin‐type O‐glycans and core 3 structures, and it is also expressed, albeit at lower levels, in the ileum, stomach, and kidney (dallolio2014theexpandingroles pages 3-5, duca2024thesdacarbohydrate pages 7-9, duca2023thestoryof pages 1-3). Functionally, the Sd(a) antigen has been implicated in modulating cell–cell recognition processes, protecting host cells against pathogen adhesion, and restricting influenza A virus entry through modification of host receptor glycan structures (dallolio2014theexpandingroles pages 3-3, duca2024thesdacarbohydrate pages 1-4, dallolio2014theexpandingroles pages 10-10). In addition to its role in normal physiology, B4GALNT2 has significant implications in disease; for example, its down‐regulation in colon cancer is associated with tumor progression, whereas higher expression correlates with improved patient survival, suggesting a potential tumor‐suppressive role (duca2023thestoryof pages 3-4, duca2024thesdacarbohydrate pages 7-9, duca2024thesdacarbohydrate pages 1-4).

## Inhibitors

No specific inhibitors for B4GALNT2 have been reported in the literature available from the provided sources (duca2024thesdacarbohydrate pages 7-9, duca2024thesdacarbohydrate pages 1-4).

## Disease relevance

Alterations in the expression of B4GALNT2 are particularly relevant to colorectal cancer. The enzyme is notably down‐regulated in colon cancer tissues compared to normal colon epithelium, and patients exhibiting higher levels of B4GALNT2 expression tend to have improved survival outcomes. This correlation supports the role of B4GALNT2 as a prognostic indicator in colorectal cancer (duca2024thesdacarbohydrate pages 7-9, unknownauthors2021…ofglycosyltransferases pages 109-112, duca2024thesdacarbohydrate pages 1-4). Furthermore, because the enzyme’s activity influences the balance between Sd(a) and sialyl Lewis x antigens—glycan structures that are functionally antagonistic in tumor metastasis—the modulation of B4GALNT2 expression has downstream effects on cancer cell adhesion and metastatic potential (unknownauthors2021…ofglycosyltransferases pages 109-112, dallolio2014theexpandingroles pages 3-3, unknownauthors2021…ofglycosyltransferases pages 102-106). In addition to its role in cancer, B4GALNT2‐mediated glycosylation is implicated in host protection against influenza A virus by altering glycan structures on cell surface receptors, thereby reducing viral binding and entry (duca2024thesdacarbohydrate pages 1-4, dallolio2014theexpandingroles pages 10-10).

## Other Comments

The functional profile of B4GALNT2 is further diversified by its isoform complexity; alternative transcription initiation produces variants with differing cytoplasmic tail lengths, thus impacting subcellular localization, enzymatic activity, and potentially interactions with other Golgi‐resident proteins (groux‐degroote2018theextendedcytoplasmic pages 6-9, groux‐degroote2018theextendedcytoplasmic pages 9-12). Notably, a unique non‐consensus N‐glycosylation site within the stem region is critical for proper folding and homodimer formation, providing an additional regulatory layer that distinguishes B4GALNT2 from other glycosyltransferases (cogez2023nglycanonthe pages 13-14, cogez2023nglycanonthe pages 1-3, cogez2023nglycanonthe pages 9-11). The enzyme’s tissue‐specific expression, particularly its markedly high levels in the colon, underpins its role in mucosal biology and highlights its importance in maintaining epithelial integrity. Moreover, the exquisite substrate specificity—requiring the presence of an α2,3‐linked sialic acid—ensures that B4GALNT2 selectively modifies glycan structures that are functionally essential for cell recognition and immune modulation (duca2024thesdacarbohydrate pages 7-9, dallolio2014theexpandingroles pages 3-3, duca2023thestoryof pages 1-3). Finally, despite the absence of directly characterized inhibitors, the detailed understanding of its catalytic mechanism, domain organization, and conserved regulatory motifs establishes a robust framework for future studies that might target B4GALNT2 therapeutically in contexts such as cancer and viral infections (dallolio2014theexpandingroles pages 3-5, duca2024thesdacarbohydrate pages 1-4, petit2021aphylogeneticview pages 9-10).

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