## Proposed EC/sub-subclass

The accepted enzyme commission classification for Beta-1,4 N-acetylgalactosaminyltransferase 2 is EC 2.4.1.244. This classification reflects its role as a glycosyltransferase that catalyzes the transfer of an N-acetylgalactosamine moiety from UDP-GalNAc to an acceptor glycan (dallolio2014theexpandingroles pages 3-3, duca2023thestoryof pages 1-3).

## Accepted name

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

## Phylogeny

Beta-1,4 N-acetylgalactosaminyltransferase 2 is evolutionarily conserved among vertebrates, with orthologs identified in species such as humans, mice, and pigs (dallolio2014theexpandingroles pages 3-5, groux-degroote2018theextendedcytoplasmic pages 9-12). Phylogenetic analyses indicate that this enzyme is part of a conserved branch of glycosyltransferases involved in glycan antigen biosynthesis (petit2021aphylogeneticview pages 4-4). B4GALNT2 is related to other glycosyltransferases, particularly B4GALNT1, which synthesizes ganglioside GM2, highlighting its unique catalytic specificity (cogez2023nglycanonthe pages 9-11, duca2023thestoryof pages 1-3).

## Glycosyltransferase family

B4GALNT2 belongs to the glycosyltransferase family GT31 within the CAZy classification, which includes enzymes that catalyze glycosyl transfer reactions (petit2021aphylogeneticview pages 4-5).

## Reaction Catalyzed

Beta-1,4 N-acetylgalactosaminyltransferase 2 catalyzes the transfer of an N-acetylgalactosamine (GalNAc) residue in a β1,4-linkage from UDP-GalNAc to the galactose residue of an acceptor glycan featuring a terminal Neu5Acα2–3. The product formed is the Sd(a) antigen, represented as GalNAcβ1→4(Neu5Acα2→3)Gal-R (dallolio2014theexpandingroles pages 3-3, duca2024thesdacarbohydrate pages 1-4).

## Cofactor Requirements

The catalytic activity of B4GALNT2 requires divalent metal ions, specifically Mn²⁺, which are essential for stabilizing the nucleotide sugar donor complex (petit2021aphylogeneticview pages 9-10, cogez2023nglycanonthe pages 9-11).

## Substrate Specificity

B4GALNT2 exhibits strict substrate specificity, requiring the acceptor substrate to possess an α2,3-linked sialic acid attached to a galactose residue. It acts on various glycan classes, including type 1 and type 2 lactosaminic chains, core 2 and core 3 O-linked glycans, and glycolipids, while showing no activity towards substrates with α2,6-linked sialic acids (duca2024thesdacarbohydrate pages 7-9, dallolio2014theexpandingroles pages 3-3).

## Structure

The 3D structure of B4GALNT2 has been characterized using experimental and computational methods, revealing a type II transmembrane protein with a short cytoplasmic tail, a single transmembrane domain, and a large catalytic domain located in the Golgi lumen. The enzyme exists in two isoforms, with the short form exhibiting higher enzymatic activity. Key structural features include the conserved DxD motif for metal ion binding and UDP-GalNAc coordination, as well as cysteine residues that may contribute to dimerization (groux-degroote2018theextendedcytoplasmic pages 6-9, duca2023thestoryof pages 1-3).

## Regulation

Regulatory mechanisms for B4GALNT2 involve transcriptional and post-translational modifications. Transcriptionally, alternative promoter usage leads to distinct isoforms, and DNA methylation is a significant modulator of expression. Post-translationally, B4GALNT2 undergoes N-glycosylation critical for proper folding and stability, and the extended cytoplasmic tail contains motifs that facilitate Golgi retention and post-Golgi trafficking (groux-degroote2018theextendedcytoplasmic pages 17-20, cogez2023nglycanonthe pages 1-3).

## Function

B4GALNT2 is crucial for the biosynthesis of the Sd(a) histo-blood group antigen, influencing glycan composition on cell surface molecules. It is predominantly expressed in the colon, contributing to mucin-type O-glycans and core 3 structures. The Sd(a) antigen plays roles in cell recognition, pathogen adhesion protection, and influenza A virus entry modulation (dallolio2014theexpandingroles pages 3-5, duca2024thesdacarbohydrate pages 7-9).

## Inhibitors

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

## Disease relevance

B4GALNT2 expression is notably down-regulated in colorectal cancer, correlating with tumor progression and patient survival outcomes. Its activity affects the balance between Sd(a) and sialyl Lewis x antigens, influencing cancer cell adhesion and metastatic potential (duca2024thesdacarbohydrate pages 7-9, unknownauthors2021…ofglycosyltransferases pages 109-112).

## Other Comments

The functional profile of B4GALNT2 is influenced by its isoform complexity, with alternative transcription initiation leading to variants that affect localization and activity. A unique non-consensus N-glycosylation site is critical for folding and dimer formation, adding a regulatory layer to its function (groux-degroote2018theextendedcytoplasmic pages 6-9, cogez2023nglycanonthe pages 13-14). The enzyme’s tissue-specific expression in the colon underscores its role in mucosal biology and epithelial integrity (duca2024thesdacarbohydrate pages 7-9).

## References

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