## 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 in transferring an N-acetylgalactosamine moiety from a nucleotide sugar donor to an acceptor glycan with 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 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 3-4, duca2023thestoryof pages 1-3).

## Phylogeny

Beta-1,4 N-acetylgalactosaminyltransferase 2 is evolutionarily conserved among vertebrates, with documented orthologs in humans, mice, pigs, and other mammals (dallolio2014theexpandingroles pages 3-5, groux-degroote2018theextendedcytoplasmic pages 9-12). Phylogenetic analyses place this enzyme within a conserved branch of glycosyltransferases involved in glycan antigen biosynthesis on glycoproteins and glycolipids (petit2021aphylogeneticview pages 4-4, petit2021aphylogeneticview pages 16-16). It shows evolutionary relationships with paralogs like B4GALNT1, which synthesizes ganglioside GM2, but differs in catalytic specificity and tissue distribution (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 includes enzymes that catalyze glycosyl transfer reactions via retaining or inverting mechanisms. B4GALNT2 is grouped with other beta-1,4-N-acetylgalactosaminyltransferases involved in blood group antigen and complex glycan structure biosynthesis (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 with a terminal Neu5Acα2–3 linked sialic acid. The resulting product is the Sd(a) antigen, with the structure GalNAcβ1→4(Neu5Acα2→3)Gal-R, displayed on N- and O-linked glycoproteins and glycolipids (dallolio2014theexpandingroles pages 3-3, duca2024thesdacarbohydrate pages 1-4, duca2023thestoryof pages 1-3).

## Cofactor Requirements

The catalytic activity of B4GALNT2 depends on divalent metal ion cofactors, requiring ions such as Mn²⁺ (and sometimes Mg²⁺) essential for stabilizing the nucleotide sugar donor complex. The conserved DxD motif in the enzyme coordinates these metal ions, facilitating proper UDP-GalNAc binding during the transfer reaction (petit2021aphylogeneticview pages 9-10, petit2021aphylogeneticview pages 15-16, pqac-23e3b47b).

## Substrate Specificity

B4GALNT2 displays strict substrate specificity, requiring the acceptor substrate to have 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 like sialylparagloboside. The enzyme does not transfer 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 experimentally and through computational modeling using tools like 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 in the Golgi lumen. Two major isoforms are produced by alternative first exon usage: a short form of 506 amino acids with higher enzymatic activity and a long form of 566 amino acids with an extended cytoplasmic tail critical for post-Golgi vesicle targeting (groux-degroote2018theextendedcytoplasmic pages 6-9, groux-degroote2018theextendedcytoplasmic pages 9-12, duca2023thestoryof pages 1-3). The catalytic domain contains typical glycosyltransferase motifs, including the conserved DxD motif for metal ion binding and UDP-GalNAc coordination, and conserved cysteine residues likely contributing 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 bulky N-glycans at non-consensus N-glycosylation sites, 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, facilitating 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 transcriptional and post-translational levels. Transcriptional regulation involves alternative promoter usage leading to distinct isoforms (exon 1S versus exon 1L), and CpG islands upstream of these exons indicate DNA methylation as an important modulator of gene expression. Transcription factors like ETS1, DMTF1, and SP1 contribute to B4GALNT2 regulation (groux-degroote2018theextendedcytoplasmic pages 17-20, cogez2023nglycanonthe pages 3-4). Post-translationally, B4GALNT2 undergoes N-glycosylation at an atypical, evolutionarily conserved non-consensus N-X-C motif, critical for proper protein folding, homodimerization, stability, and Golgi targeting (cogez2023nglycanonthe pages 13-14, cogez2023nglycanonthe pages 1-3, cogez2023nglycanonthe pages 9-11). The extended cytoplasmic tail in the long isoform contains specific motifs that modulate Golgi retention and 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 containing a Neu5Acα2–3Gal moiety. This reaction occurs on O- and N-linked glycoproteins and glycolipids, influencing the glycan composition of numerous cell surface molecules. B4GALNT2 expression is highest in the colon, contributing to mucin-type O-glycans and core 3 structures, and is also expressed in the ileum, stomach, and kidney (dallolio2014theexpandingroles pages 3-5, duca2024thesdacarbohydrate pages 7-9, duca2023thestoryof pages 1-3). The Sd(a) antigen modulates cell–cell recognition, protects host cells against pathogen adhesion, and restricts influenza A virus entry by modifying host receptor glycan structures (dallolio2014theexpandingroles pages 3-3, duca2024thesdacarbohydrate pages 1-4, dallolio2014theexpandingroles pages 10-10). In disease contexts, B4GALNT2 down-regulation in colon cancer is associated with tumor progression, while 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).

## Disease relevance

Alterations in B4GALNT2 expression are relevant to colorectal cancer. The enzyme is down-regulated in colon cancer tissues compared to normal colon epithelium, and higher B4GALNT2 expression correlates with improved survival outcomes, supporting its role as a prognostic indicator in colorectal cancer (duca2024thesdacarbohydrate pages 7-9, unknownauthors2021…ofglycosyltransferases pages 109-112, duca2024thesdacarbohydrate pages 1-4). B4GALNT2 activity influences the balance between Sd(a) and sialyl Lewis x antigens, affecting cancer cell adhesion and metastatic potential (unknownauthors2021…ofglycosyltransferases pages 109-112, dallolio2014theexpandingroles pages 3-3, unknownauthors2021…ofglycosyltransferases pages 102-106). B4GALNT2-mediated glycosylation also protects against influenza A virus by altering glycan structures on cell surface receptors, reducing viral binding and entry (duca2024thesdacarbohydrate pages 1-4, dallolio2014theexpandingroles pages 10-10).

## Other Comments

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

## References

1. (petit2021aphylogeneticview pages 9-10): Daniel Petit, Roxana Elin Teppa, and Anne Harduin-Lepers. A phylogenetic view and functional annotation of the animal β1,3-glycosyltransferases of the gt31 cazy family. Glycobiology, 31:243-259, Sep 2021. URL: https://doi.org/10.1093/glycob/cwaa086, doi:10.1093/glycob/cwaa086. This article has 21 citations and is from a peer-reviewed journal.
2. (petit2021aphylogeneticview pages 15-16): Daniel Petit, Roxana Elin Teppa, and Anne Harduin-Lepers. A phylogenetic view and functional annotation of the animal β1,3-glycosyltransferases of the gt31 cazy family. Glycobiology, 31:243-259, Sep 2021. URL: https://doi.org/10.1093/glycob/cwaa086, doi:10.1093/glycob/cwaa086. This article has 21 citations and is from a peer-reviewed journal.
3. (dallolio2014theexpandingroles pages 3-3): Fabio Dall’Olio, Nadia Malagolini, Mariella Chiricolo, Marco Trinchera, and Anne Harduin-Lepers. The expanding roles of the sda/cad carbohydrate antigen and its cognate glycosyltransferase b4galnt2. Biochimica et Biophysica Acta (BBA) - General Subjects, 1840:443-453, Jan 2014. URL: https://doi.org/10.1016/j.bbagen.2013.09.036, doi:10.1016/j.bbagen.2013.09.036. This article has 72 citations.
4. (duca2023thestoryof pages 3-4): Martina Duca, Nadia Malagolini, and Fabio Dall’Olio. The story of the sda antigen and of its cognate enzyme b4galnt2: what is new? Glycoconjugate Journal, 40:123-133, Oct 2023. URL: https://doi.org/10.1007/s10719-022-10089-1, doi:10.1007/s10719-022-10089-1. This article has 9 citations and is from a peer-reviewed journal.
5. (duca2023thestoryof pages 1-3): Martina Duca, Nadia Malagolini, and Fabio Dall’Olio. The story of the sda antigen and of its cognate enzyme b4galnt2: what is new? Glycoconjugate Journal, 40:123-133, Oct 2023. URL: https://doi.org/10.1007/s10719-022-10089-1, doi:10.1007/s10719-022-10089-1. This article has 9 citations and is from a peer-reviewed journal.
6. (dallolio2014theexpandingroles pages 3-5): Fabio Dall’Olio, Nadia Malagolini, Mariella Chiricolo, Marco Trinchera, and Anne Harduin-Lepers. The expanding roles of the sda/cad carbohydrate antigen and its cognate glycosyltransferase b4galnt2. Biochimica et Biophysica Acta (BBA) - General Subjects, 1840:443-453, Jan 2014. URL: https://doi.org/10.1016/j.bbagen.2013.09.036, doi:10.1016/j.bbagen.2013.09.036. This article has 72 citations.
7. (groux-degroote2018theextendedcytoplasmic pages 9-12): Sophie Groux-Degroote, Céline Schulz, Virginie Cogez, Maxence Noël, Lucie Portier, Dorothée Vicogne, Carlos Solorzano, Fabio Dall’Olio, Agata Steenackers, Marlène Mortuaire, Mariano Gonzalez-Pisfil, Mélanie Henry, François Foulquier, Laurent Héliot, and Anne Harduin-Lepers. The extended cytoplasmic tail of the human b4galnt2 is critical for its golgi targeting and post-golgi sorting. The FEBS Journal, 285:3442-3463, Aug 2018. URL: https://doi.org/10.1111/febs.14621, doi:10.1111/febs.14621. This article has 22 citations.
8. (petit2021aphylogeneticview pages 4-4): Daniel Petit, Roxana Elin Teppa, and Anne Harduin-Lepers. A phylogenetic view and functional annotation of the animal β1,3-glycosyltransferases of the gt31 cazy family. Glycobiology, 31:243-259, Sep 2021. URL: https://doi.org/10.1093/glycob/cwaa086, doi:10.1093/glycob/cwaa086. This article has 21 citations and is from a peer-reviewed journal.
9. (petit2021aphylogeneticview pages 16-16): Daniel Petit, Roxana Elin Teppa, and Anne Harduin-Lepers. A phylogenetic view and functional annotation of the animal β1,3-glycosyltransferases of the gt31 cazy family. Glycobiology, 31:243-259, Sep 2021. URL: https://doi.org/10.1093/glycob/cwaa086, doi:10.1093/glycob/cwaa086. This article has 21 citations and is from a peer-reviewed journal.
10. (cogez2023nglycanonthe pages 9-11): Virginie Cogez, Dorothée Vicogne, Céline Schulz, Lucie Portier, Giulia Venturi, Jérôme de Ruyck, Mathieu Decloquement, Marc F. Lensink, Guillaume Brysbaert, Fabio Dall’Olio, Sophie Groux-Degroote, and Anne Harduin-Lepers. N-glycan on the non-consensus n-x-c glycosylation site impacts activity, stability, and localization of the sda synthase b4galnt2. International Journal of Molecular Sciences, 24:4139, Feb 2023. URL: https://doi.org/10.3390/ijms24044139, doi:10.3390/ijms24044139. This article has 8 citations and is from a peer-reviewed journal.
11. (petit2021aphylogeneticview pages 4-5): Daniel Petit, Roxana Elin Teppa, and Anne Harduin-Lepers. A phylogenetic view and functional annotation of the animal β1,3-glycosyltransferases of the gt31 cazy family. Glycobiology, 31:243-259, Sep 2021. URL: https://doi.org/10.1093/glycob/cwaa086, doi:10.1093/glycob/cwaa086. This article has 21 citations and is from a peer-reviewed journal.
12. (duca2024thesdacarbohydrate pages 1-4): Martina Duca, Nadia Malagolini, and Fabio Dall’Olio. The sda carbohydrate antigen and its biosynthetic enzyme b4galnt2 in health and disease. Unknown journal, Feb 2024. URL: https://doi.org/10.20944/preprints202402.1754.v1, doi:10.20944/preprints202402.1754.v1.
13. (duca2024thesdacarbohydrate pages 7-9): Martina Duca, Nadia Malagolini, and Fabio Dall’Olio. The sda carbohydrate antigen and its biosynthetic enzyme b4galnt2 in health and disease. Unknown journal, Feb 2024. URL: https://doi.org/10.20944/preprints202402.1754.v1, doi:10.20944/preprints202402.1754.v1.
14. (duca2024thesdacarbohydrate pages 14-15): Martina Duca, Nadia Malagolini, and Fabio Dall’Olio. The sda carbohydrate antigen and its biosynthetic enzyme b4galnt2 in health and disease. Unknown journal, Feb 2024. URL: https://doi.org/10.20944/preprints202402.1754.v1, doi:10.20944/preprints202402.1754.v1.
15. (groux-degroote2018theextendedcytoplasmic pages 6-9): Sophie Groux-Degroote, Céline Schulz, Virginie Cogez, Maxence Noël, Lucie Portier, Dorothée Vicogne, Carlos Solorzano, Fabio Dall’Olio, Agata Steenackers, Marlène Mortuaire, Mariano Gonzalez-Pisfil, Mélanie Henry, François Foulquier, Laurent Héliot, and Anne Harduin-Lepers. The extended cytoplasmic tail of the human b4galnt2 is critical for its golgi targeting and post-golgi sorting. The FEBS Journal, 285:3442-3463, Aug 2018. URL: https://doi.org/10.1111/febs.14621, doi:10.1111/febs.14621. This article has 22 citations.
16. (dallolio2014theexpandingroles pages 1-2): Fabio Dall’Olio, Nadia Malagolini, Mariella Chiricolo, Marco Trinchera, and Anne Harduin-Lepers. The expanding roles of the sda/cad carbohydrate antigen and its cognate glycosyltransferase b4galnt2. Biochimica et Biophysica Acta (BBA) - General Subjects, 1840:443-453, Jan 2014. URL: https://doi.org/10.1016/j.bbagen.2013.09.036, doi:10.1016/j.bbagen.2013.09.036. This article has 72 citations.
17. (cogez2023nglycanonthe pages 13-14): Virginie Cogez, Dorothée Vicogne, Céline Schulz, Lucie Portier, Giulia Venturi, Jérôme de Ruyck, Mathieu Decloquement, Marc F. Lensink, Guillaume Brysbaert, Fabio Dall’Olio, Sophie Groux-Degroote, and Anne Harduin-Lepers. N-glycan on the non-consensus n-x-c glycosylation site impacts activity, stability, and localization of the sda synthase b4galnt2. International Journal of Molecular Sciences, 24:4139, Feb 2023. URL: https://doi.org/10.3390/ijms24044139, doi:10.3390/ijms24044139. This article has 8 citations and is from a peer-reviewed journal.
18. (groux-degroote2018theextendedcytoplasmic pages 17-20): Sophie Groux-Degroote, Céline Schulz, Virginie Cogez, Maxence Noël, Lucie Portier, Dorothée Vicogne, Carlos Solorzano, Fabio Dall’Olio, Agata Steenackers, Marlène Mortuaire, Mariano Gonzalez-Pisfil, Mélanie Henry, François Foulquier, Laurent Héliot, and Anne Harduin-Lepers. The extended cytoplasmic tail of the human b4galnt2 is critical for its golgi targeting and post-golgi sorting. The FEBS Journal, 285:3442-3463, Aug 2018. URL: https://doi.org/10.1111/febs.14621, doi:10.1111/febs.14621. This article has 22 citations.
19. (cogez2023nglycanonthe pages 3-4): Virginie Cogez, Dorothée Vicogne, Céline Schulz, Lucie Portier, Giulia Venturi, Jérôme de Ruyck, Mathieu Decloquement, Marc F. Lensink, Guillaume Brysbaert, Fabio Dall’Olio, Sophie Groux-Degroote, and Anne Harduin-Lepers. N-glycan on the non-consensus n-x-c glycosylation site impacts activity, stability, and localization of the sda synthase b4galnt2. International Journal of Molecular Sciences, 24:4139, Feb 2023. URL: https://doi.org/10.3390/ijms24044139, doi:10.3390/ijms24044139. This article has 8 citations and is from a peer-reviewed journal.
20. (cogez2023nglycanonthe pages 1-3): Virginie Cogez, Dorothée Vicogne, Céline Schulz, Lucie Portier, Giulia Venturi, Jérôme de Ruyck, Mathieu Decloquement, Marc F. Lensink, Guillaume Brysbaert, Fabio Dall’Olio, Sophie Groux-Degroote, and Anne Harduin-Lepers. N-glycan on the non-consensus n-x-c glycosylation site impacts activity, stability, and localization of the sda synthase b4galnt2. International Journal of Molecular Sciences, 24:4139, Feb 2023. URL: https://doi.org/10.3390/ijms24044139, doi:10.3390/ijms24044139. This article has 8 citations and is from a peer-reviewed journal.
21. (dallolio2014theexpandingroles pages 10-10): Fabio Dall’Olio, Nadia Malagolini, Mariella Chiricolo, Marco Trinchera, and Anne Harduin-Lepers. The expanding roles of the sda/cad carbohydrate antigen and its cognate glycosyltransferase b4galnt2. Biochimica et Biophysica Acta (BBA) - General Subjects, 1840:443-453, Jan 2014. URL: https://doi.org/10.1016/j.bbagen.2013.09.036, doi:10.1016/j.bbagen.2013.09.036. This article has 72 citations.
22. (unknownauthors2021…ofglycosyltransferases pages 109-112): … of Glycosyltransferases on the Phenotype, Signaling and Transcriptome of Colorectal Cancer Cell Lines. Focus on the role of glycosyltransferases B4GALNT2 …
23. (unknownauthors2021…ofglycosyltransferases pages 102-106): … of Glycosyltransferases on the Phenotype, Signaling and Transcriptome of Colorectal Cancer Cell Lines. Focus on the role of glycosyltransferases B4GALNT2 …