## Proposed EC/sub-subclass

2.4.1.92

## Accepted name

Beta-1,4 N-acetylgalactosaminyltransferase 1

## Synonyms

GM2 synthase, GM2/GD2 synthase, GalNAc-T, (N-acetylneuraminyl)-galactosylglucosylceramide transferase

## Phylogeny

B4GALNT1 is evolutionarily conserved across vertebrates, with known orthologs in species such as humans, mice, and rats. Phylogenetic analyses reveal significant sequence conservation with other glycosyltransferases involved in ganglioside synthesis, indicating its essential role in the formation of complex glycolipids in the nervous system. B4GALNT1 is classified within the GT31 family of glycosyltransferases, which specialize in glycolipid modification.

## Glycosyltransferase family

GT31

## Reaction catalyzed

The enzyme catalyzes the transfer of N-acetylgalactosamine (GalNAc) from UDP-GalNAc to glycolipid acceptors, converting GM3, GD3, GT3, and GA3 into GM2, GD2, GT2, and GA2, respectively.

## Cofactor requirements

B4GALNT1 requires manganese ions (Mn²⁺) for its catalytic activity.

## Substrate Specificity

B4GALNT1 specifically acts on glycolipid substrates, particularly those that are precursors to complex gangliosides. It incorporates an N-acetylgalactosamine residue into gangliosides such as GM3, GD3, GT3, and GA3, generating GM2, GD2, GT2, and GA2. The enzyme does not exhibit activity toward glycoprotein substrates.

## Structure

B4GALNT1 is a type II transmembrane glycosyltransferase localized in the Golgi apparatus. It features a short cytosolic tail, a single transmembrane helix, and a large C-terminal catalytic domain. The catalytic domain contains conserved motifs, including a DXD motif critical for metal ion coordination and donor substrate binding. Structural studies suggest that the catalytic domain adopts a GT-A fold, although no experimentally solved 3D structure is currently available. The enzyme forms homodimers, which are important for its enzymatic function and localization.

## Regulation

B4GALNT1 is regulated at multiple levels, including transcriptional and post-translational mechanisms. The gene undergoes alternative splicing, producing transcripts with varying N-terminal domains that may influence subcellular localization. Post-translational modifications, particularly N-glycosylation at three critical sites, are essential for the enzyme’s maturation and activity. Increased expression of B4GALNT1 has been observed in malignant melanomas and certain T cell subsets, indicating a response to cellular transformation and immune activation.

## Function

B4GALNT1 is crucial for the biosynthesis of complex gangliosides, which are vital components of neural cell membranes. The enzyme’s activity is essential for the development and function of the nervous system, as it participates in cell–cell recognition and signal transduction. B4GALNT1 is predominantly expressed in neural tissues, correlating with the enrichment of gangliosides in these areas. Aberrant expression of B4GALNT1 has been linked to various cancers, suggesting its role in tumor cell behavior.

## Disease relevance

Loss-of-function variants in B4GALNT1 are associated with early-onset complex hereditary spastic paraplegia, characterized by impaired ganglioside synthesis and neurological deficits. Increased expression of B4GALNT1 has been noted in adult T-cell leukemia, neuroblastomas, and malignant melanomas, indicating that dysregulation of ganglioside biosynthesis may contribute to tumor progression.

## Other comments

B4GALNT1 exclusively acts on glycolipid substrates and does not exhibit activity toward glycoprotein acceptors. The enzyme’s expression is under complex regulatory control, including alternative promoter usage and splicing. Although detailed structural data from X-ray crystallography are not yet available, modeling studies suggest that the catalytic domain adopts a GT-A-like fold. The strict requirement for Mn²⁺ and the enzyme’s specificity for ganglioside substrates highlight its critical role in the neural ganglioside biosynthetic pathway.

## References

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