

Ganglioside GM3 Synthase Deficiency

Subjects: [Medicine](#), [Research & Experimental](#)

Contributor: Kei-ichiro Inamori , Jin-Ichi Inokuchi

Gangliosides (glycosphingolipids containing one or more sialic acids) are highly expressed in neural tissues in vertebrates, and four species (GM1a, GD1a, GD1b, GT1b) are predominant in mammalian brains. GM3 is the precursor of each of these four species and is the major ganglioside in many nonneural tissues. GM3 synthase (GM3S), encoded by *ST3GAL5* gene in humans, is a sialyltransferase responsible for synthesis of GM3 from its precursor, lactosylceramide. *ST3GAL5* mutations cause an autosomal recessive form of severe infantile-onset neurological disease characterized by progressive microcephaly, intellectual disability, dyskinetic movements, blindness, deafness, intractable seizures, and pigment changes.

gangliosides

GM3 synthase

glycosyltransferase

1. Introduction

Gangliosides—glycosphingolipids (GSLs) that contain one or more sialic acids—are fundamental components of cell membrane microdomains involved in dynamic regulation of various cell physiological processes [\[1\]](#). Ganglioside biosynthesis is initiated by the addition of a glucose residue to ceramide to form glucosylceramide (GlcCer); this process is catalyzed by GlcCer synthase (GlcCerS, encoded by *UGCG* gene) (**Figure 1**). Similarly, a galactose residue can be added to ceramide to form galactosylceramide (GalCer), catalyzed by GalCer synthase (GalCerS, encoded by *UGT8*). Synthesis of GlcCer occurs on the cytosolic surface of Golgi, whereas GalCer synthesis occurs on the luminal surface of endoplasmic reticulum [\[2\]\[3\]](#). Sulfation of GalCer by cerebroside sulfotransferase (CST, encoded by *GAL3ST1* gene) generates sulfatide SM4, a major lipid component of myelin sheath in both the central nervous system (CNS) and peripheral nervous system (PNS). GlcCer is galactosylated by lactosylceramide (LacCer) synthase (LacCerS, encoded by *B4GALT5* or *B4GALT6*) to form LacCer, the precursor of a variety of ganglioside species and other types of GSLs. GM3 synthase (GM3S, encoded by *ST3GAL5* gene) is a sialyltransferase that adds a sialic acid residue to LacCer to initiate synthesis of α- and β-series gangliosides. GD3 synthase (GD3S, encoded by *ST8SIA1* gene) is another sialyltransferase that catalyzes formation of disialoganglioside GD3. GM2 synthase (GM2S, encoded by *B4GALNT1* gene) adds N-acetylgalactosamine (GalNAc) to LacCer, GM3, or GD3 to generate (respectively) GA2, GM2, or GD2. Gangliosides are expressed in essentially all vertebrate tissues and cells, most abundantly in the nervous system. GM1, GD1a, GD1b, and GT1b in particular are the predominant ganglioside species in mammalian brain tissues [\[4\]](#).

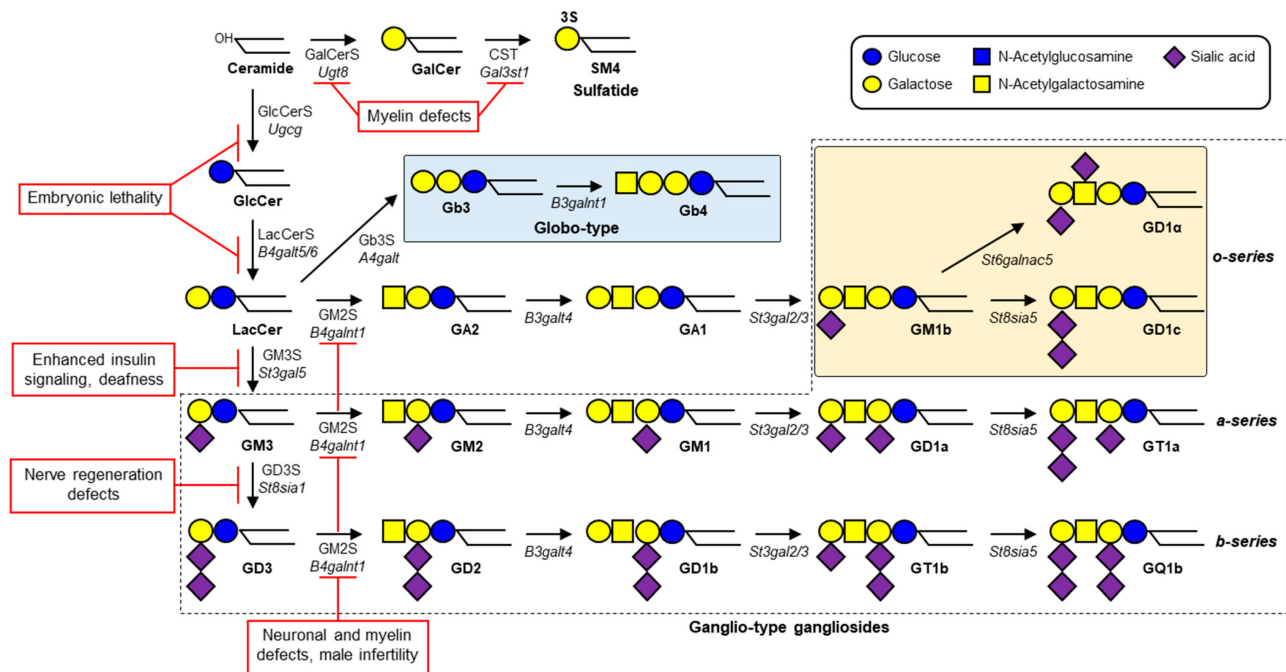


Figure 1. Biosynthetic pathway of gangliosides and sulfatide. GlcCerS catalyzes with the addition of glucose to ceramide, and LacCerS subsequently adds galactose to GlcCer to form LacCer. GalCerS catalyzes with the addition of galactose to ceramide to form GalCer, and CST subsequently adds a sulfate group to form sulfatide SM4. Expression of globo-type GSLs is elevated substantially in fibroblasts of human GM3S-deficiency patients. In contrast, in GM3S KO-mouse brains and fibroblasts, expression of globo-type GSLs is only slightly elevated, but that of o-series gangliosides (GM1b, GD1α, GD1c) is elevated substantially.

2. Human GM3S Deficiency

GM3S deficiency was first reported as an autosomal recessive infantile-onset epilepsy syndrome associated with developmental stagnation and blindness in Old Order Amish [5]. Biallelic pathogenic *ST3GAL5* variants led to disrupted synthesis of a- and b-series gangliosides, and consequently to severe infantile-onset neurological disorders characterized by progressive microcephaly, intellectual disability, choreoathetosis, blindness, deafness, intractable seizures, and/or pigment changes [5][6][7][8][9][10][11][12][13]. These patients appeared normal at birth, but all had psychomotor developmental delays, and most displayed consistent features of movement disorders and/or epilepsy. A “salt and pepper” syndrome sometimes seen in African American patients results from altered dermal pigmentation (hyper- or hypopigmented skin maculae) at various locations [8]. The human GM3S protein consists of 418 amino acids and includes sequences for L-(large), S- (small), and VS- (very small) sialyl motifs, which are highly conserved in mammalian sialyltransferases [14]. A nonsense variant, R288X, detected in numerous Amish GM3S-deficiency patients, two French patients, and three Pakistani patients results in a truncated protein that lacks S and VS. motifs, and was therefore predicted to be nonfunctional [5][7][10]. Plasma GSL analysis of the Amish patients revealed a total absence of GM3 and its downstream derivatives, whereas increased levels were observed for LacCer (the direct substrate of GM3S), o-series gangliosides (e.g., GM1b), and globosides [11]. Several missense variants are located in L or S motifs: E355K (found in African American patients with salt and pepper

syndrome), C195S and G201R (found as compound heterozygotes in Korean patients), and G342S (found in an Italian patient). In vitro GM3S assay for LacCer using homogenate of HEK293T cells transfected with mutated ST3GAL5 constructs revealed an absence of enzymatic activity in these variants [12]. A recent study revealed four more novel variants: missense variants G247D and H389R, nonsense variant R344X, and stop-loss variant X419RextX38, which disrupts the stop codon and causes 37-codon extension of the reading frame [13]. Plasma GSL analysis of patients with these four variants showed significant reduction of GM3 levels; however, GM3 was still present, as well as residual GM2—which was not observed in Amish patients with the R288X variant. The pathogenic mechanisms of these variants will be clarified by in vitro GM3S assay and analysis of intracellular localization and/or stability of ST3GAL5 protein. Two patients, homozygous for the above stop-loss variant, had the highest plasma GM3 levels among the studied patients, and the least severe phenotype [13]. Plasma GM3 levels thus appear to be inversely related to severity of GM3S-deficiency disease.

References

1. Jin-Ichi Inokuchi; Kei-Ichiro Inamori; Kazuya Kabayama; Masakazu Nagafuku; Satoshi Uemura; Shinji Go; Akemi Suzuki; Isao Ohno; Hirotaka Kanoh; Fumi Shishido; et al. Biology of GM3 Ganglioside. *Progress in Molecular Biology and Translational Science* **2018**, 156, 151-195, 10.1016/bs.pmbts.2017.10.004.
2. Hein Sprong; Boudewijn Kruithof; Richtje Leijendekker; Jan Willem Slot; Gerrit van Meer; Peter van der Sluijs; UDP-Galactose:Ceramide Galactosyltransferase Is a Class I Integral Membrane Protein of the Endoplasmic Reticulum. *Journal of Biological Chemistry* **1998**, 273, 25880-25888, 10.1074/jbc.273.40.25880.
3. D Jeckel; A Karrenbauer; K N Burger; Gerrit van Meer; F Wieland; Glucosylceramide is synthesized at the cytosolic surface of various Golgi subfractions. *Journal of Cell Biology* **1992**, 117, 259-267, 10.1083/jcb.117.2.259.
4. Ronald L. Schnaar; The Biology of Gangliosides. *Advances in Carbohydrate Chemistry and Biochemistry* **2018**, 76, 113-148, 10.1016/bs.accb.2018.09.002.
5. Michael Simpson; Harold Cross; Christos Proukakis; David A Priestman; David C A Neville; Gabriele Reinkensmeier; Heng Wang; Max Wiznitzer; Kay Gurtz; Argyro Verganelaki; et al. Anna PrydeMichael A PattonRaymond A DwekTerry D ButtersFrances PlattAndrew H Crosby Infantile-onset symptomatic epilepsy syndrome caused by a homozygous loss-of-function mutation of GM3 synthase. *Nature Genetics* **2004**, 36, 1225-1229, 10.1038/ng1460.
6. Heng Wang; Alicia Bright; Baozhong Xin; J.R. Bockoven; Amy S. Paller; Cutaneous dyspigmentation in patients with ganglioside GM3 synthase deficiency. *American Journal of Medical Genetics Part A* **2013**, 161, 875-879, 10.1002/ajmg.a.35826.

7. Konstantina Fragaki; Samira Ait-El-Mkadem; Annabelle Chaussenot; Catherine Gire; Raymond Mengual; Laurent Bonesso; Marie Bénateau; Jean Ehrland Ricci; Valérie Desquirit-Dumas; Vincent Procaccio; et al. Agnes Rotig V Refractory epilepsy and mitochondrial dysfunction due to GM3 synthase deficiency. *European Journal of Human Genetics* **2012**, 21, 528-534, 10.1038/ejhg.2012.202.
8. Luigi Boccuto; Kazuhiro Aoki; Heather Flanagan-Steet; Chin-Fu Chen; Xiang Fan; Frank Bartel; Marharyta Petukh; Ayla Pittman; Robert Saul; Alka Chaubey; et al. Emil Alexov Michael Tiemeyer Richard Steet Charles E. Schwartz A mutation in a ganglioside biosynthetic enzyme, ST3GAL5, results in salt & pepper syndrome, a neurocutaneous disorder with altered glycolipid and glycoprotein glycosylation. *Human Molecular Genetics* **2013**, 23, 418-433, 10.1093/hmg/ddt434.
9. Jin Sook Lee; Yongjin Yoo; Byung Chan Lim; Ki Joong Kim; Junghan Song; Murim Choi; Jong-Hee Chae; GM3 synthase deficiency due to ST3GAL5 variants in two Korean female siblings: Masquerading as Rett syndrome-like phenotype. *American Journal of Medical Genetics Part A* **2016**, 170, 2200-2205, 10.1002/ajmg.a.37773.
10. Eliza Gordon-Lipkin; Julie S. Cohen; Siddharth Srivastava; Bruno P. Soares; Eric Levey; Ali Fatemi; ST3GAL5-Related Disorders: A Deficiency in Ganglioside Metabolism and a Genetic Cause of Intellectual Disability and Choreoathetosis. *Journal of Child Neurology* **2018**, 33, 825-831, 10.1177/0883073818791099.
11. Lauren E. Bowser; Millie Young; Olivia K. Wenger; Zineb Ammous; Karlla W. Brigatti; Vincent J. Carson; Teresa Moser; James Deline; Kazuhiro Aoki; Thierry Morlet; et al. Ethan M. Scott Erik Puffenberger Donna L. Robinson Christine Hendrickson Jonathan Salvin Steven Gottlieb Adam D. Heaps Michael Tiemeyer Kevin A. Strauss Recessive GM3 synthase deficiency: Natural history, biochemistry, and therapeutic frontier. *Molecular Genetics and Metabolism* **2019**, 126, 475-488, 10.1016/j.ymgme.2019.01.013.
12. Rossella Indellicato; Rossella Parini; Ruben Domenighini; Nadia Malagolini; Maria Iascone; Serena Gasperini; Nicoletta Maserà; Fabio Dall'Olio; Marco Trincherà; Total loss of GM3 synthase activity by a normally processed enzyme in a novel variant and in all ST3GAL5 variants reported to cause a distinct congenital disorder of glycosylation. *Glycobiology* **2019**, 29, 229-241, 10.1093/glycob/cwy112.
13. Solveig Heide; Marie-Line Jacquemont; David Cheillan; Michel Renouil; Marilyn Tallot; Charles E. Schwartz; Juliette Miquel; Marc Bintner; Diana Rodriguez; Françoise Darcel; et al. Julien Buratti Damien Haye Sandrine Passemard Domitille Gras Laurence Perrin Yline Capri Bénédicte Gérard Amélie Piton Boris Keren Christel Thauvin-Robinet Yannis Duffourd Laurence Faivre Charlotte Poe Anne Pervillé Delphine Héron Julien Thévenon Lionel Arnaud Eric LeGuern Lorita La Selva Annalisa Vetro Renzo Guerrini Caroline Nava Cyril Mignot GM3 synthase deficiency in non-Amish patients. *Genetics in Medicine* **2021**, 24, 492-498, 10.1016/j.gim.2021.10.007.

14. James C. Paulson; Christoph Rademacher; Glycan terminator. *Nature Structural & Molecular Biology* **2009**, *16*, 1121-1122, 10.1038/nsmb1109-1121.
-

Retrieved from <https://encyclopedia.pub/entry/history/show/55472>