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Changes in glycosphingolipid levels in plasma and cerebrospinal fluid of individuals with Lysosomal Free Sialic Acid Storage Disorder

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ABSTRACT

Lysosomal free sialic acid storage disorder (FSASD) is a rare, multisystem disease caused by biallelic pathogenic variants in *SLC17A5*, encoding the lysosomal transmembrane sialic acid exporter, sialin. Defective sialin function leads to sialic acid accumulation in lysosomes, contributing to neurodegeneration. While glycosphingolipid (GSL) metabolism is altered in other lysosomal storage disorders, its role in FSASD remains poorly understood, especially due to the restricted availability of biospecimens. This study investigated GSL levels in FSASD plasma and cerebrospinal fluid (CSF) using two normal-phase high-performance liquid chromatography assays. In plasma, GM1a was significantly elevated, while GM2 was decreased, with no significant alterations in other GSL species. In CSF, total GSLs, GM1a, GM3, GD3, GD1a, and GD1b were significantly elevated compared to comparison samples. These results reveal dysregulated GSL metabolism and suggest the potential of gangliosides as biomarkers. Further research is warranted to elucidate the biological implications of these alterations and their contributions to FSASD pathogenesis.

1. Introduction

Lysosomal free sialic acid storage disorder (FSASD) is an ultra-rare, progressive, multisystem, neurodegenerative disorder caused by biallelic pathogenic variants in *SLC17A5* [1,2]. *SLC17A5* encodes SLC17A5 (sialin), a lysosomal proton-coupled cotransporter that exports sialic acid (N-acetylneuraminic acid) and other acidic hexoses from the lysosomal compartment into the cytosol [3–6]. Defective sialin transport activity results in the abnormal accumulation of unconjugated "free" sialic acid within lysosomes, leading to various clinical manifestations.

Historically, FSASD has been divided into three allelic disorders: infantile FSASD (MIM#269920); intermediate severe FSASD; and mild FSASD (MIM#604369; also known as Salla disease after a region in Finland) [2,7]. Individuals with mild FSASD typically appear normal at birth with no obvious neurologic symptoms. However, they gradually develop progressive neurologic deterioration characterized by mild-to-moderate psychomotor delays, spasticity, athetosis, and seizures [2]. In contrast, individuals with infantile FSASD present with severe developmental delay, coarse facial features, hepatosplenomegaly, and cardiomegaly shortly after birth, and often succumb to death in early childhood [2]. On brain MRI, individuals with FSASD display hypomyelination, corpus callosum hypoplasia, and atrophy [2,7–9]. Individuals with FSASD excrete 10–100 times normal amounts of unconjugated sialic acid in urine [7,10]. Worldwide, roughly 250 individuals with FSASD have been reported with biallelic *SLC17A5* variants; approximately 185 (75 %) of them carry the Finnish founder missense variant, *SLC17A5* c.115 C>T; p.(Arg39Cys) in a homozygous or compound heterozygous state, while nearly 65 individuals carry other biallelic variants; there exists incomplete molecular data on several other affected persons [1,11–14].

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Glycosphingolipids (GSLs), including the sialylated subclass of gangliosides, are found in the plasma membrane of all eukaryotic cells. With membrane turnover, the GSLs are routed to the lysosome for degradation via hydrolases [15,16] (Fig. 3). Although the biological role(s) of GSLs remain enigmatic, sphingolipids are known to serve as signaling lipids [17]. Mutations in the glycohydrolases and associated protein cofactors involved in GSL catabolism lead to a group of lysosomal disorders termed glycosphingolipidoses, which often present as progressive neurodegenerative diseases due to the abundant expression of GSLs in the central nervous system [18]. Beyond the primary glycosphingolipidoses, alterations in GSL levels have been described across several other lysosomal storage disorders including Niemann–Pick disease type C [16,19]. However, investigations into GSL metabolism in FSASD are limited, with prior studies reporting reduced gangliosides (sialioglycoconjugates and sphingolipids) turnover in FSASD fibroblasts [20,21]. This study aims to profile GSL levels in FSASD plasma and CSF relative to available comparison samples.

2. Materials and methods

2.1. Study population

FSASD blood and CSF samples were collected as part of the NIH FSASD Pilot Natural History Study under the Congenital Disorders of Glycosylation protocol (14-HG-0071; NCT04199000). Briefly, eight individuals with FSASD were recruited to the National Institutes of Health (Bethesda, MD, USA) to undergo a comprehensive clinical assessment and provide biospecimens for research investigations. The FSASD cohort ranged from 3 to 9 years old with clinical phenotypes spanning intermediate severe to mild FSASD (Supplementary Table 1). The individuals with FSASD were of diverse reported ancestry (nationalities included: American, Norwegian, Dominican, Brazilian) and have heterogeneous *SLC17A5* variant pairs (Supplementary Table 1). Note, CSF was not collected from one individual with FSASD (Individual 5) since the study participant was too medically fragile for sedated procedures. The biological parents of each affected individual were also consented and provided blood samples for research purposes. In this study, these samples were used as a comparison group (i.e., termed "parental group" in the associated plots). The parental comparison cohort consisted of 8 females and 8 males of diverse racial/ethnic backgrounds. The 14-HG-0071 protocol was approved by the NHGRI Institutional Review Board.

The pediatric CSF specimens used as an external comparison cohort for the individuals with FSASD were deidentified and collected as part of the 06-CH-0186 protocol (NCT00344331). Collected in 2009, the cohort ($n = 5$) included 3 male and 2 female subjects in the range of 3.5–8.25 years old at time of collection. One male subject had a diagnosis of leukemia and one female subject had a medical history of headaches. CSF samples with elevated cell count or positive culture were excluded. The 06-CH-0186 protocol was approved by the NICHD Institutional Review Board.

The collection of CSF from individuals affected by FSASD was carried out as a standard sedated clinical procedure. Age-appropriate CSF samples from pediatric individuals in the comparison group were obtained as residual samples from clinically indicated lumbar punctures performed for unrelated medical reasons. These samples were not specifically collected for the study, and, therefore, the collection process was not standardized.

2.2. Plasma isolation

As part of the NIH FSASD Pilot Natural History Study, whole blood samples were collected in EDTA tubes at room temperature. After collection, the whole blood was centrifuged at 980 g for 10 minutes at room temperature. Isolated plasma was placed at −20℃ for long-term storage.

2.3. Quantification of GSLs and GlcCer

Profiling of glycosphingolipids and glucosylceramide (GlcCer) in plasma and CSF was performed as previously described [22–24] (Supplementary Figure 5). Individual GSL species were identified by their glucose values and quantified by comparison of integrated peak areas with a known amount of 2AA-labeled BioQuant chitotriose standard (Ludger, UK). Results were normalized to sample volume, i.e., 75 μL plasma (¾ used for GSLs and ¼ used for GlcCer assays) and 125 μL CSF (¾ used for GSLs and ¼ used for GlcCer assays).

2.4. Quantification of β-hexosaminidase activity

In plasma, β-hexosaminidase lysosomal hydrolase activity was assayed fluorometrically using an artificial sugar-substrate (N-acetyl-β-D-glucosaminide) conjugated with the fluorophore 4-methylumbelliferone (4-MU) as previously described [22]. 25 μL plasma was assayed across three technical replicates after incubation with the sugar-substrate for 1 h at 37 ℃.

2.5. Quantification of CSF free sialic acid

Quantification of free and total sialic acid levels in CSF were performed using HPLC-MS/MS by LabCorp (https://mnglabs.labcorp.com/tests/620036/sialic-acid-csf) as a clinical test.

2.6. Statistical analyses

Statistical analyses were conducted using an unpaired *t*-test between FSASD and comparison samples using GraphPad Prism (GraphPad Software, Version 10.0.3). Correlations were analyzed with Pearson correlation analysis. A two-sided *p*-value significance was set at 0.05.

3. Results

We measured the levels of GSLs in FSASD plasma ($n = 8$; compared to $n = 16$ unaffected parental comparison samples) and cerebrospinal fluid ($n = 7$; compared to $n = 5$ external pediatric comparison samples) using two normal-phase high-performance liquid chromatography assays.

In FSASD plasma compared to parental comparison samples, GM1a was significantly elevated ($p < 0.005$) and GM2 was significantly decreased ($p < 0.005$) (Fig. 1). No statistically significant differences in other detected GSL species, including GlcCer or any other sialylated gangliosides, were found in FSASD plasma (Supplementary Figure 1). As a result of the change observed in GM2 (significantly decreased, Fig. 1), we examined total β-hexosaminidase activity in plasma since this glycohydrolase is responsible for converting GM2 to GM3 in the presence of GM2 activator protein [25]. No significant alterations in β-hexosaminidase activity in plasma were found (Supplementary Figure 2).

In FSASD CSF compared to pediatric comparison samples, total GSLs and gangliosides subclass ($p < 0.005$), GM3 ($p < 0.0005$), GM1a ($p < 0.05$), GD3 ($p < 0.005$), GD1a ($p < 0.05$), and GD1b ($p < 0.05$) were elevated (Fig. 2A, Fig. 3). GSL species GT1b and GQ1b, as well as GM2 and GlcCer, also showed non-significant trends towards elevation in FSASD CSF (Fig. 2B, Fig. 3). Higher CSF free sialic acid concentrations do not significantly correlate with CSF ganglioside levels ($r = 0.6415$, $p = 0.1204$; Supplementary Figure 4). Interestingly, Individual 2, who harbors three *SLC17A5* mutations (see Supplementary Table 1 for *SLC17A5* variants), displayed one of the highest CSF free sialic levels and corresponding CSF ganglioside levels (Supplementary Figure 4). The levels of total gangliosides in CSF per individual are included in Supplementary Figure 3B; for comparison, total gangliosides in plasma per individual are represented in Supplementary Figure 3A.

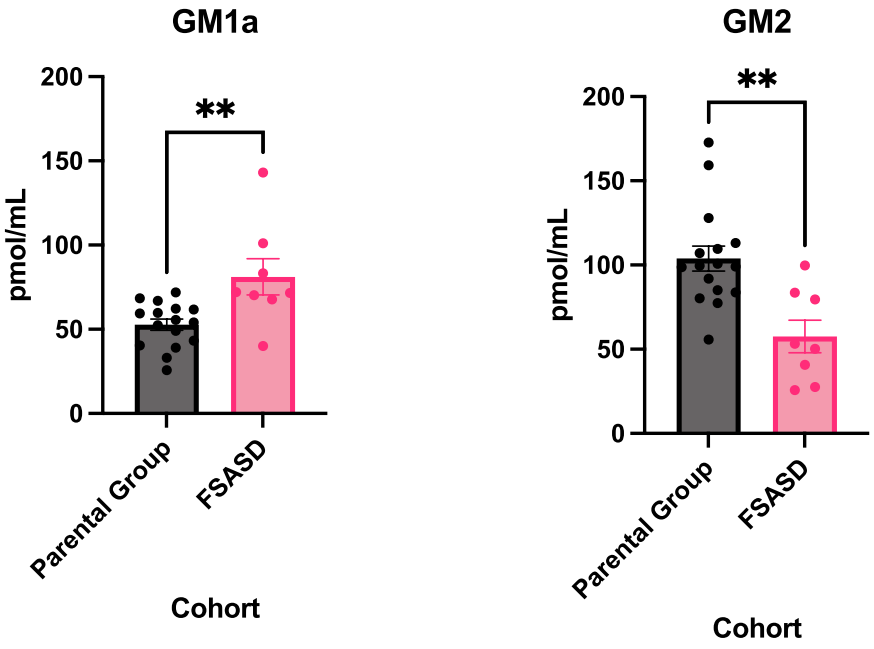

Fig. 1. Levels of GM1a and GM2 in plasma of FSASD versus parental comparison group. Mean ± SEM. Unpaired *t*-test with **representing *p*-value < 0.005.

4. Conclusions and discussion

This study describes alterations in glycosphingolipid (GSL) metabolism in FSASD, with a focus on its potential role in neurodegeneration and systemic metabolic imbalances, based on the limited available data. These findings point out the role of impaired sialin function in disrupting sialic acid recycling pathways and metabolic homeostasis, as evidenced by elevated GM1a and decreased GM2 in plasma and increased gangliosides in cerebrospinal fluid (CSF).

Gangliosides constitute the majority of the GSLs in the brain [27,28]. Gangliosides play critical roles in neuronal integrity, comprising up to 25 % of the outer membrane lipid layer [37]. Mouse models lacking GM2/GD2 synthase exhibit demyelination and axonal degeneration, supporting the role of gangliosides in maintaining myelin-axon communication [29]. The significant elevation of key brain gangliosides (e.g., GM1a, GD1a, GD1b) in FSASD CSF might contribute to the neurodegeneration and hypomyelination observed in FSASD [7] and animal models [26]; this finding could also support the potential of gangliosides as biomarkers for tracking disease progression and severity. Interestingly, measurement of CSF ganglioside levels in individuals with multiple sclerosis, a progressive neurological disorder characterized by demyelination, shows dynamic changes with disease state and progression [30,31].

Elevated brain gangliosides in FSASD CSF, despite defective lysosomal sialic acid recycling, may reflect attempts to clear excess gangliosides due to neurodegeneration into the CSF. This might be considered paradoxical since pathogenic variants in *SLC17A5* decrease sialin efflux activity [32]. Excess free sialic acid may cause inhibition of lysosomal sialidase with a consequent decrease in the overall rate of ganglioside degradation and turnover. However, studies examining sialidase activity in FSASD fibroblasts report conflicting results, from no change to significantly elevated activity [33–36]. It is important to note that regulation of sialidase activity in fibroblasts may not directly reflect neural cell activity due to differences in ganglioside composition and metabolic rates. Neural cells, where gangliosides are significant components of membranes, may exhibit distinct metabolic vulnerabilities. For example, gangliosides constitute 10–12 percent of the total lipid content in neuronal membranes and up to 25 percent in the outer membrane layer [37]. The potential interplay between impaired lysosomal sialidase activity and compensatory mechanisms in neural cells warrants further investigation. Rat cerebellar granule cell studies supplemented with radiolabeled gangliosides demonstrate efficient recycling of ganglioside-derived sialic acid [37], indicating the energy efficiency of this process. We postulate that in FSASD, ganglioside degradation may be impaired due to lysosomal sialidase inhibition [38,39], while ganglioside turnover rates may be decreased to reduce reliance on the energetically costly *de novo* biosynthetic pathway of sialic acid. Collectively, these disruptions may contribute to the observed neurodegeneration and neural cell death.

5. Limitations and future directions

This study represents the first study to examine GSL levels in FSASD fluid biospecimens; however, there exist several limitations. The comparison group for the plasma studies consisted of the biological parents of the individuals enrolled in the NIH FSASD Pilot Natural History Study. A more fitting cohort would be age and sex-matched pediatric control subjects as several studies have shown that levels of GSLs decrease with normal aging [22,40,41]. Furthermore, the levels of GSLs in *SLC17A5* carriers (i.e., heterozygotes) have not been studied. Our pediatric comparison group for the CSF studies included only five individuals from a historical clinical investigation and the collection process was not standardized. Obtaining normal pediatric CSF samples is precluded by statutory and ethical restrictions posing a major challenge in obtaining a robust control cohort. Furthermore, due to the ultra-rare nature of FSASD, collecting samples from individuals with similar pathogenic variants, racial/ethnic backgrounds, etc. is challenging and resource intensive, precluding genotype-phenotype correlation. Finally, the limited availability of biospecimens prevented the measurement of free sialic acid levels in the pediatric comparison group, which could have enabled more comprehensive correlations with ganglioside levels.

Despite these limitations, this study pinpoints dysregulation of glycosphingolipid metabolism as a secondary biochemical defect in FSASD. Future studies should consider focusing on the levels, distribution, and metabolism of gangliosides in specific brain cell types, such as iPSC-derived neural cells, from individuals with FSASD. This approach would help clarify the consequences of defective sialic acid transport in neural cells and elucidate the vulnerability of specific brain cell types. Expanding the cohort size to validate findings and correlating ganglioside levels with clinical outcomes will further clarify the

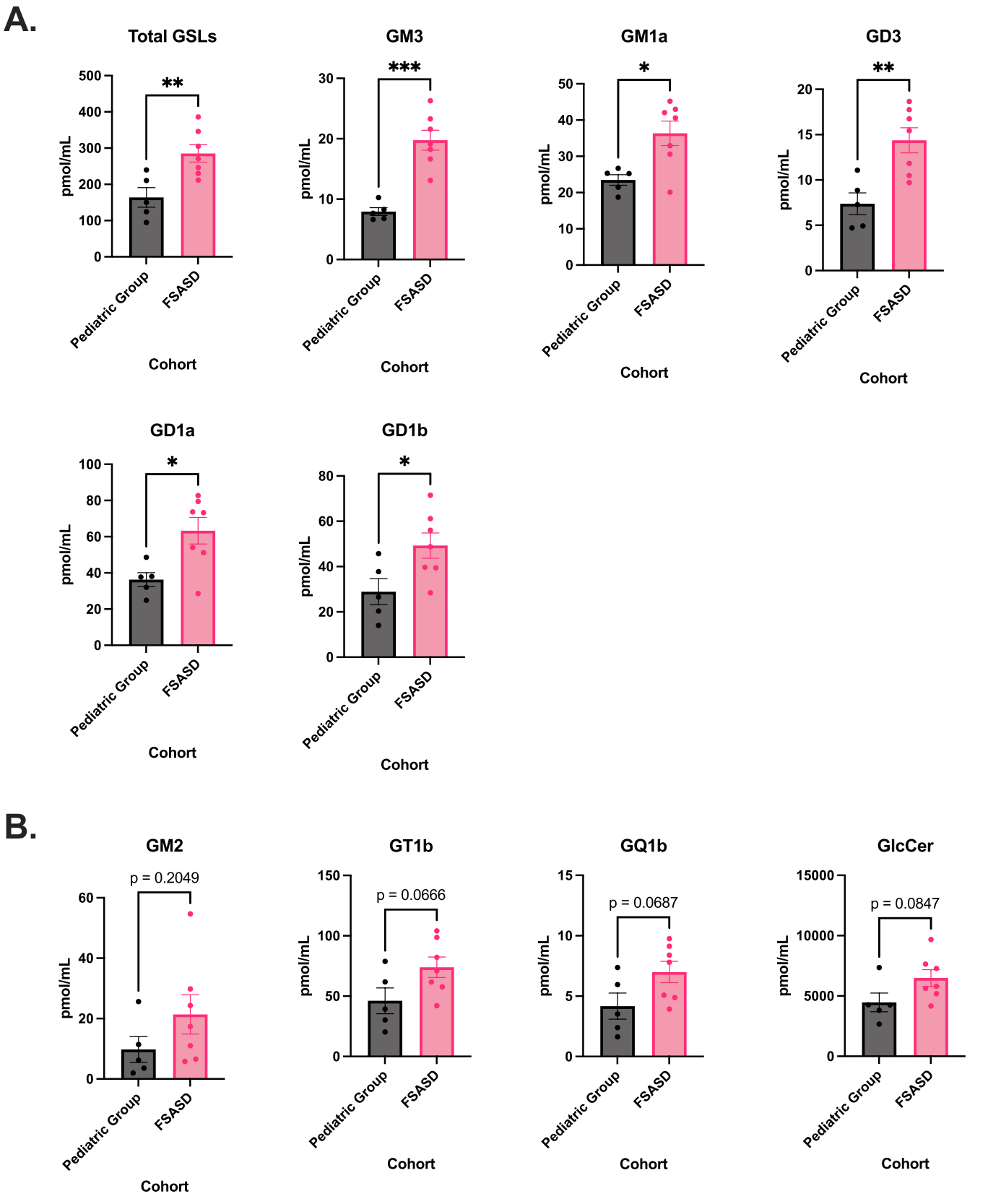

Fig. 2. Levels of total GSLs (total excludes LacCer and GlcCer; all other detected GSL species were gangliosides) and individual GSL species in CSF of FSASD versus pediatric comparison group. (A) Significantly altered groups and GSL species. (B) Non-statistically significant GSL species. Mean ± SEM. Unpaired *t*-test with *p*-values as indicated for non-statistically significant GSL species, otherwise $*p < 0.05$, $**p < 0.005$, $*** p < 0.0005$.

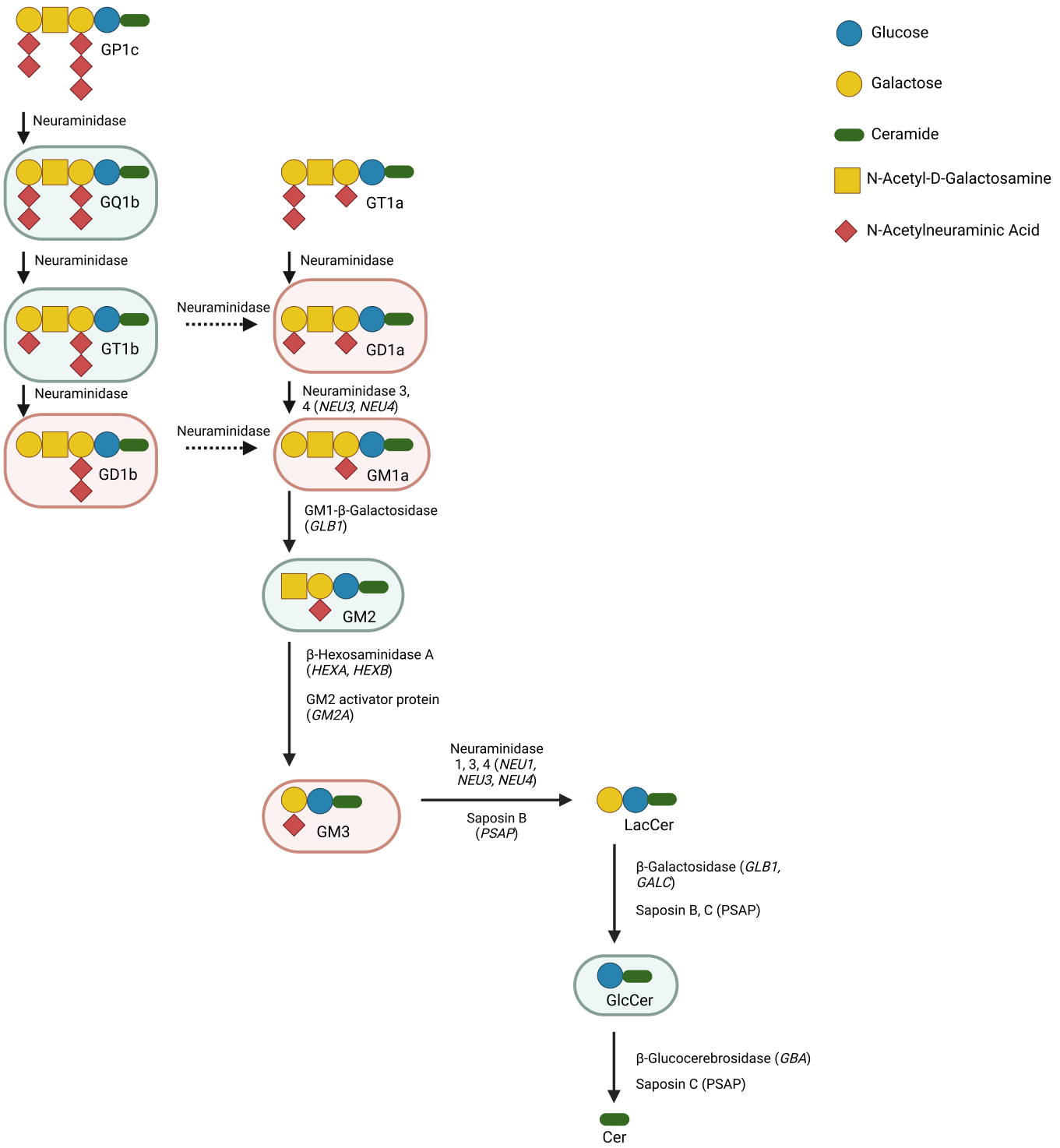

Fig. 3. Simplified representation of GSL catabolism. The catabolic enzymes and co-factors are listed next to each arrow. Sialic acid moieties are denoted in red diamond shapes. The species that are elevated (red oval shading) or trending up (green oval shading) in FSASD CSF are indicated; not all species depicted are detected in CSF and GD3 is also elevated in FSASD CSF. Figure adapted from Platt [16] and created using BioRender.com.

pathophysiological role of these molecules in FSASD. These efforts are essential for advancing our understanding of FSASD and developing targeted therapeutic strategies.

Ethics statement

The 14-HG-0071 protocol was approved by the NHGRI Institutional Review Board. The 06-CH- 0186 protocol was approved by the NICHD Institutional Review Board.

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CRediT authorship contribution statement

Marya S. Sabir: Writing – review & editing, Writing – original draft, Visualization, Project administration, Formal analysis, Data curation, Conceptualization. **Lynne Wolfe:** Writing – review & editing, Resources. **David R. Adams:** Writing – review & editing, Resources. **Carla Ciccone:** Writing – review & editing, Resources. **Forbes D. Porter:** Writing – review & editing, Resources. **William A. Gahl:** Writing – review & editing, Funding acquisition. **Marjan Huizing:** Writing – review & editing, Project administration, Conceptualization. **Frances M. Platt:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **May Christine V. Malicdan:** Writing – review & editing, Project administration, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The graphical abstract was created using BioRender.com (July 2024).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.rare.2025.100065.

Data availability

Data will be made available on request.

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