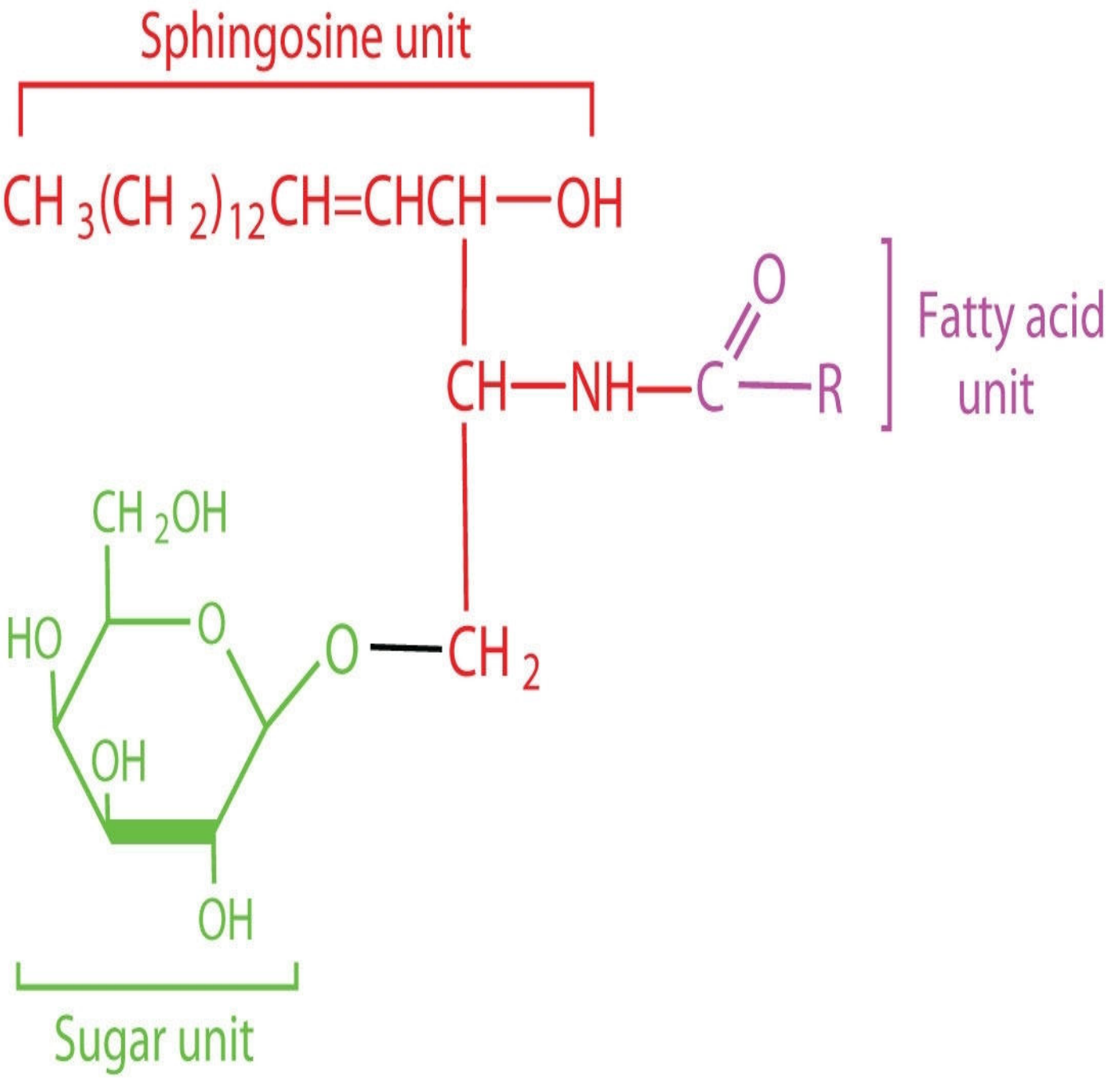
Glycolipids
OR
Glycosphingolipids

What are Glycolipids?

- Glycolipids are type of **compound Lipids.**

- **Chemically Esters of Fatty acids with Alcohol and contain additional group as Carbohydrate moieties**



Types Of Glycosphingolipids

Based Upon

- **Alcohol**
- **Fatty acid**
- **Number and Type of Carbohydrate moieties and there derivatives linked to a Ceramide**

Types OF Glycolipids
Based on Alcohol

1. Glycoglycerolipids
   (More In Plants)
   Glycerol as Alcohol

2. Glycosphingolipids
(Predominant in Animals and Human)
Sphingosine as Alcohol

Classification of glycolipids:

- **(A). Glycero-glycolipids:** *Glycerole backbone with carbohydrates*
  - *a) Galactolipids*
  - *b) Sulfolipids*

- **(B). Sphingo-glycolipids:** *Sphingosine backbone with carbohydrates*
  - *a) Cerebrosides*
  - *b) Gangliosides*
  - *c) Globosides*

Glycosphingolipids

Predominant Animal Glycolipids

- Ceramide linked with one or more sugar residues /there derivatives

Human Glycosphingolipids

All has Ceramide in Their Str

1) Cerebrosides
2) Gangliosides
3) Globosides

Cerebrosides

Simplest GlycoSphingolipids

Monoglycosylceramide

Cerebrosides

- **Cerebrosides** are **type of Glycosphingolipids**
- **Ceramide linked with one sugar residue**

Types of Cerebrosides

- **Depending upon Carbohydrate** moiety **Types of Cerebrosides** are:

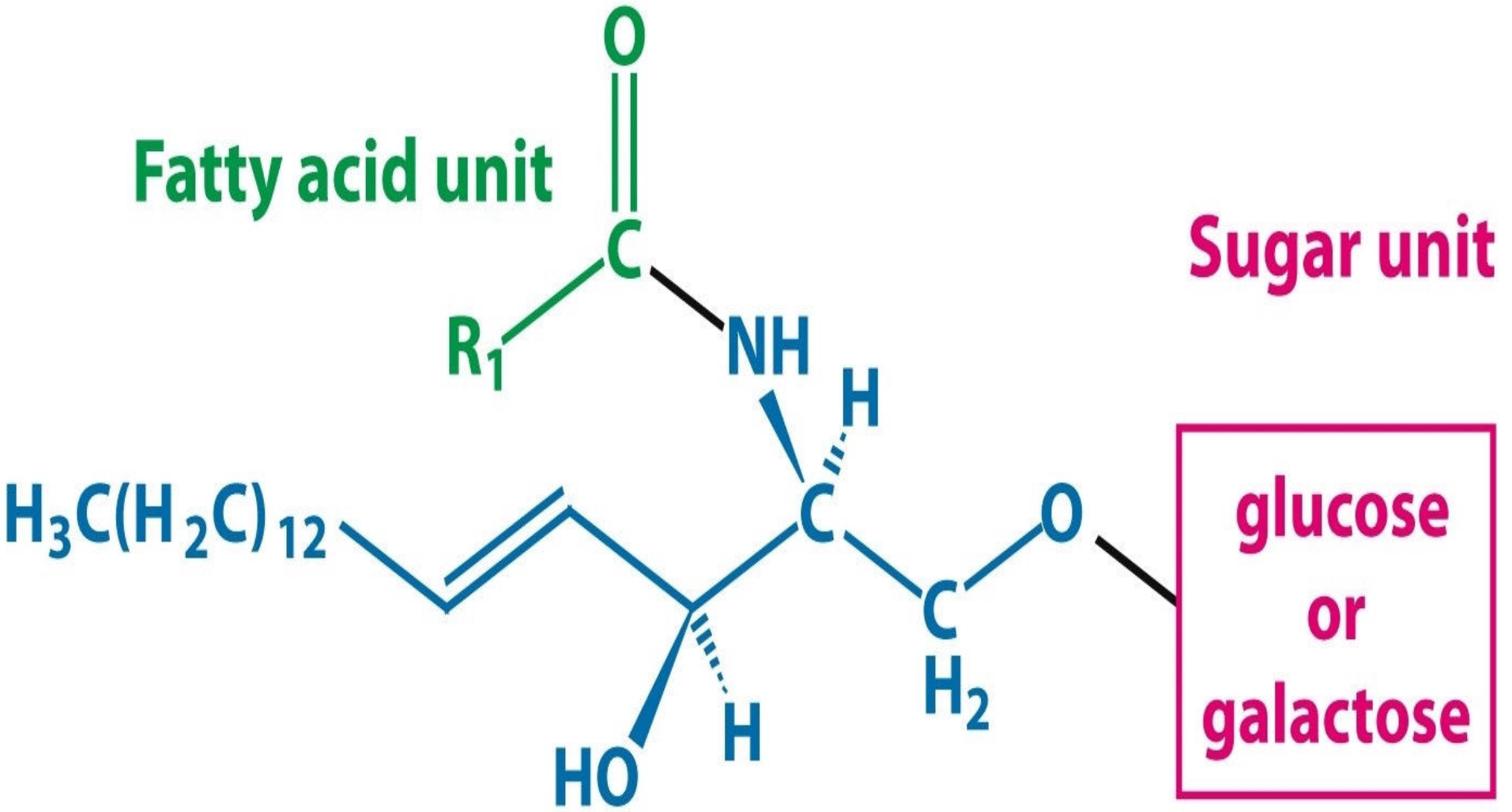
–Glucocerebrosides

(Occur In Extra neural/Other tissues)

–Galactocerebrosides

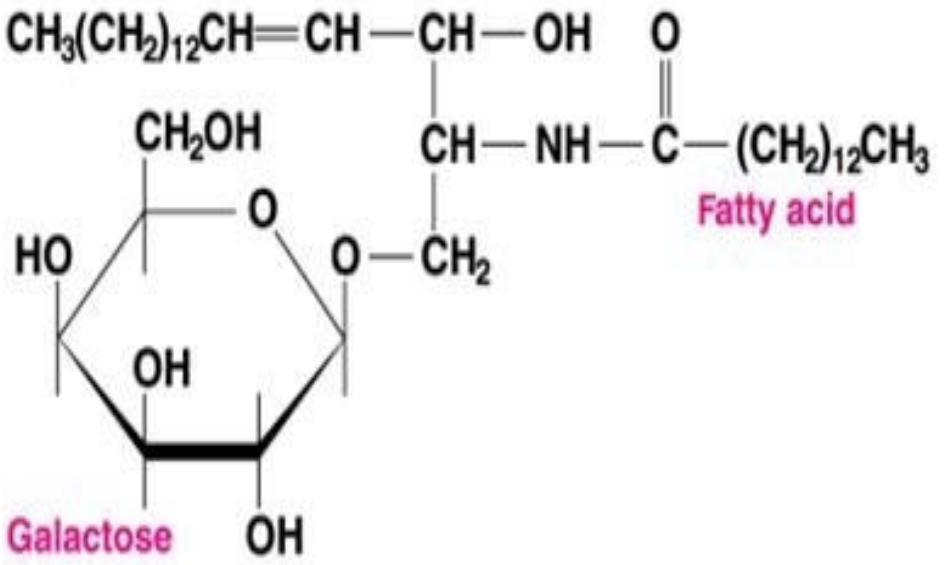
(Present In Neural)

Structures Of Cerebrosides

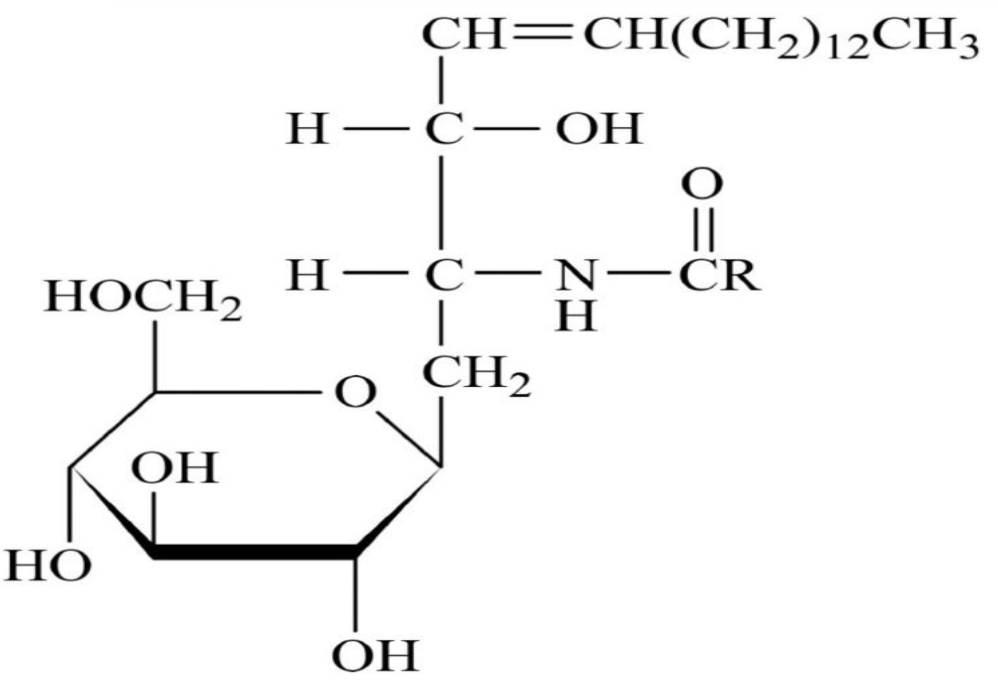


Cerebroside
(a glycolipid)

Sphingosine

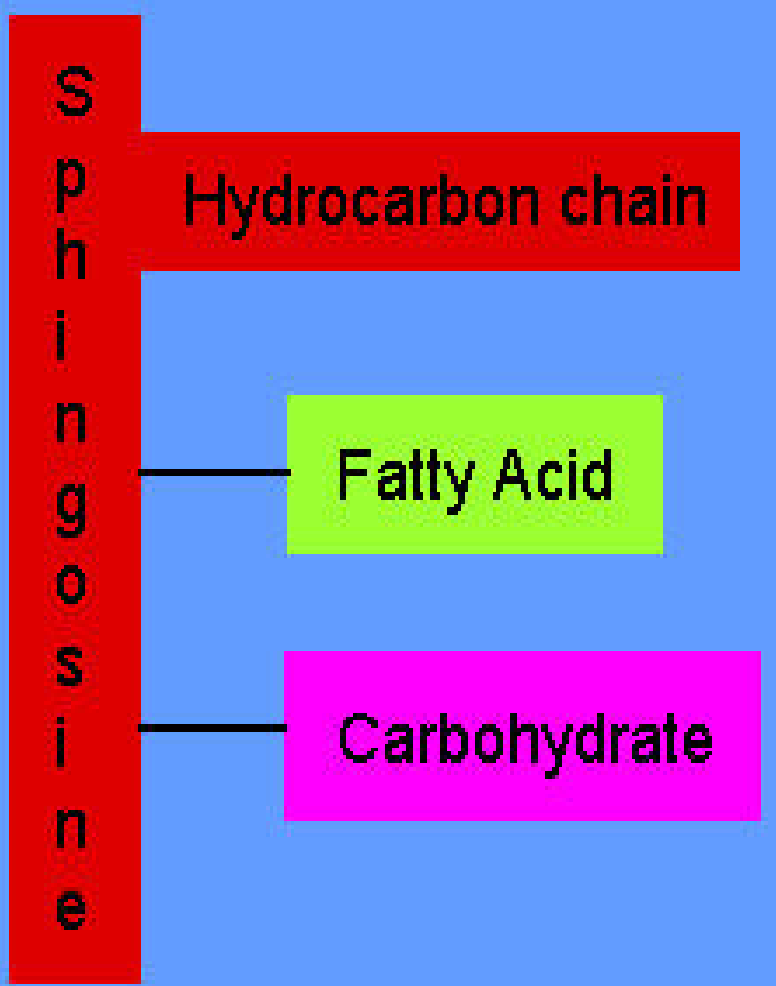


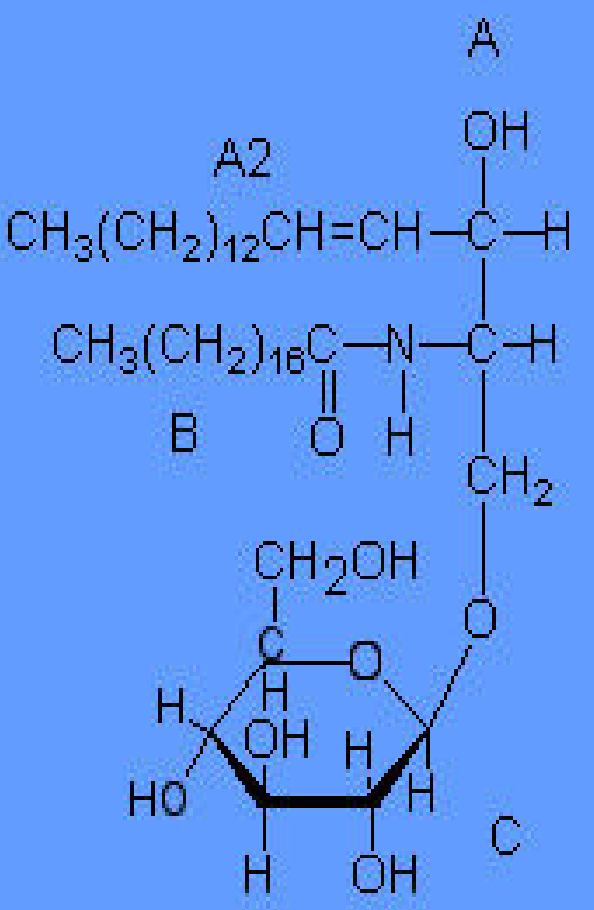
Galactocerebroside, a glycosphingolipid



A Glucocerebroside

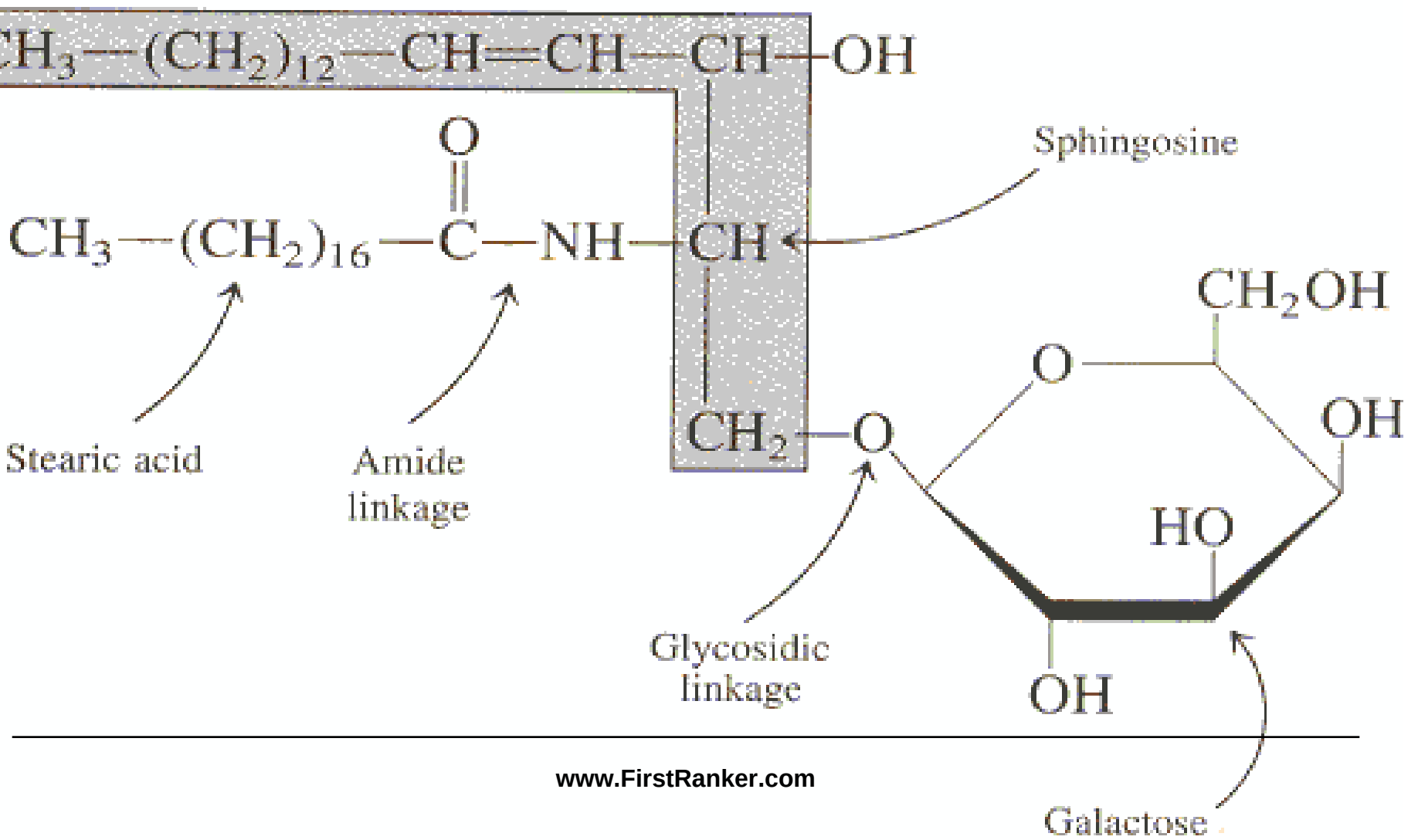
Glucocerebroside





C. Ophardt, c. 2003

Galactocerebroside



Cerebrosides	Fatty Acid Composed In
Kerasin	Lignoceric acid (C24) SFA
Cerebron	Cerebronic acid (C24) Hydroxy SFA
Nervon	Nervonic acid (C24) MUFA
Oxynervon	Oxynervonic acid (C24) MUFA

Gangliosides

Complex Glycosphingolipids

Gangliosides

- **Gangliosides** are **Type of Glycosphingolipids**

- In comparison to **Cerebrosides, Gangliosides are more complex.**

NANA in Gangliosides

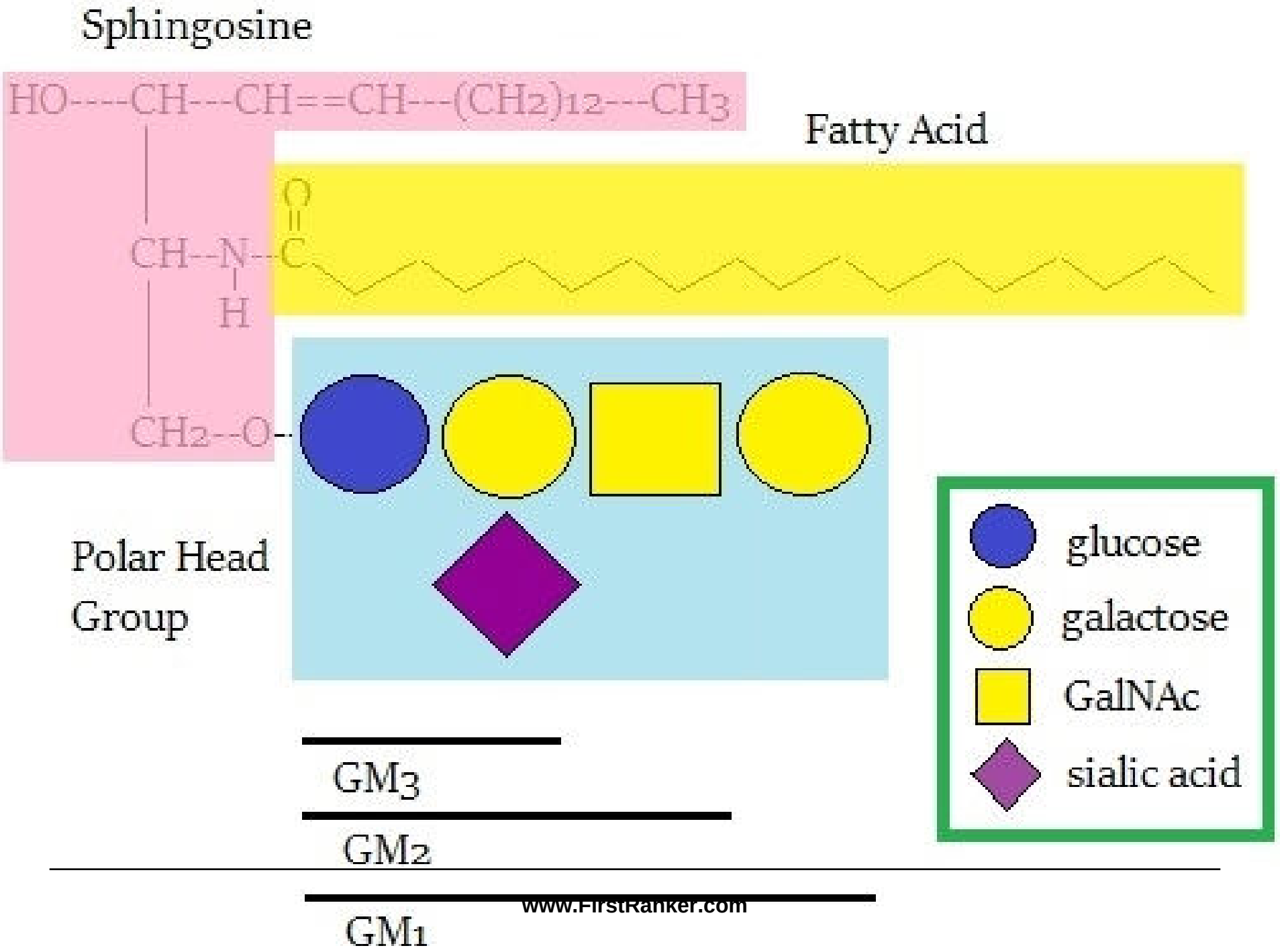
- Characteristic feature of Gangliosides is

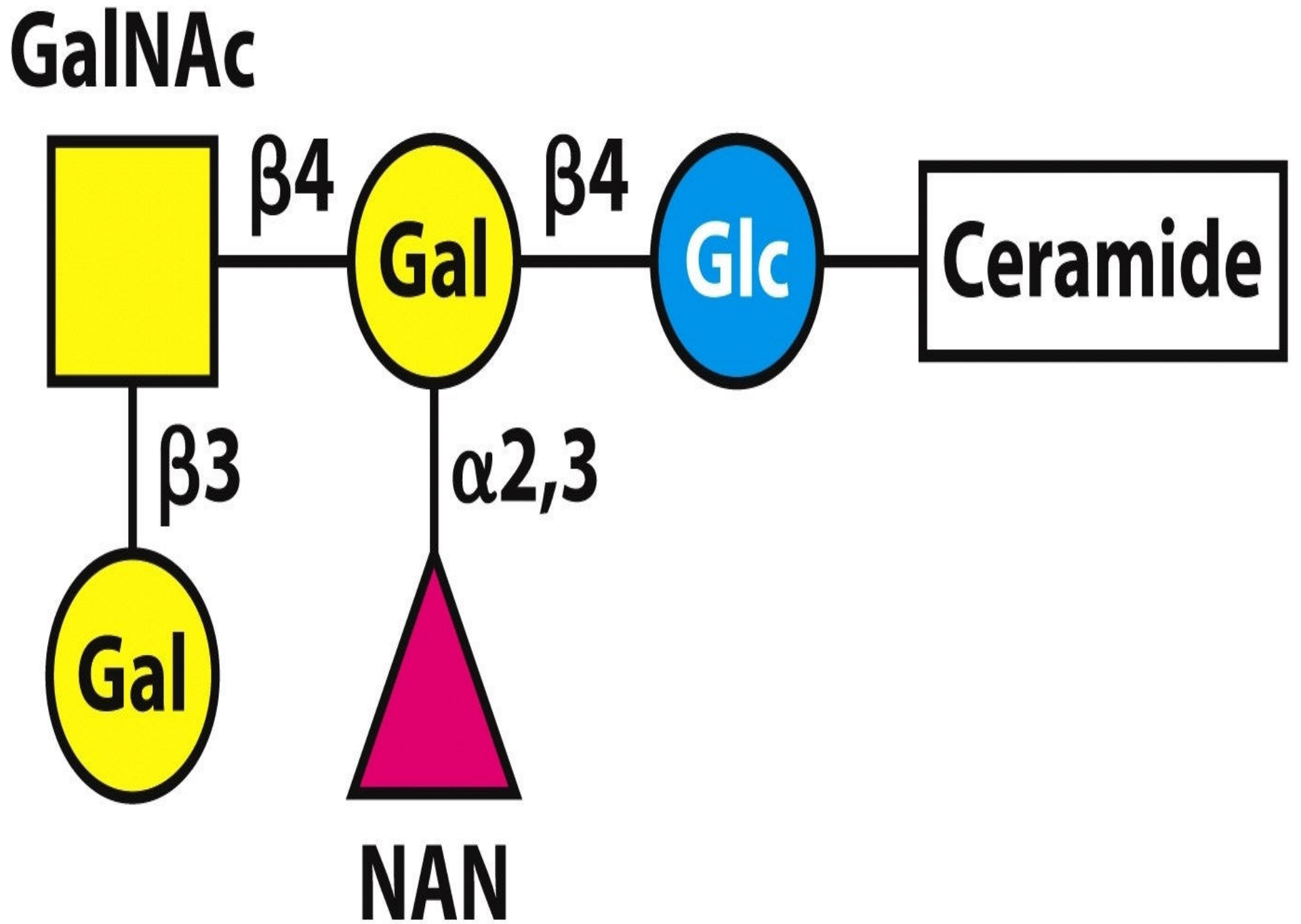
- Structure contains **one or more N-Acetyl Neuraminic Acid (NANA)/Sialic acid residues**

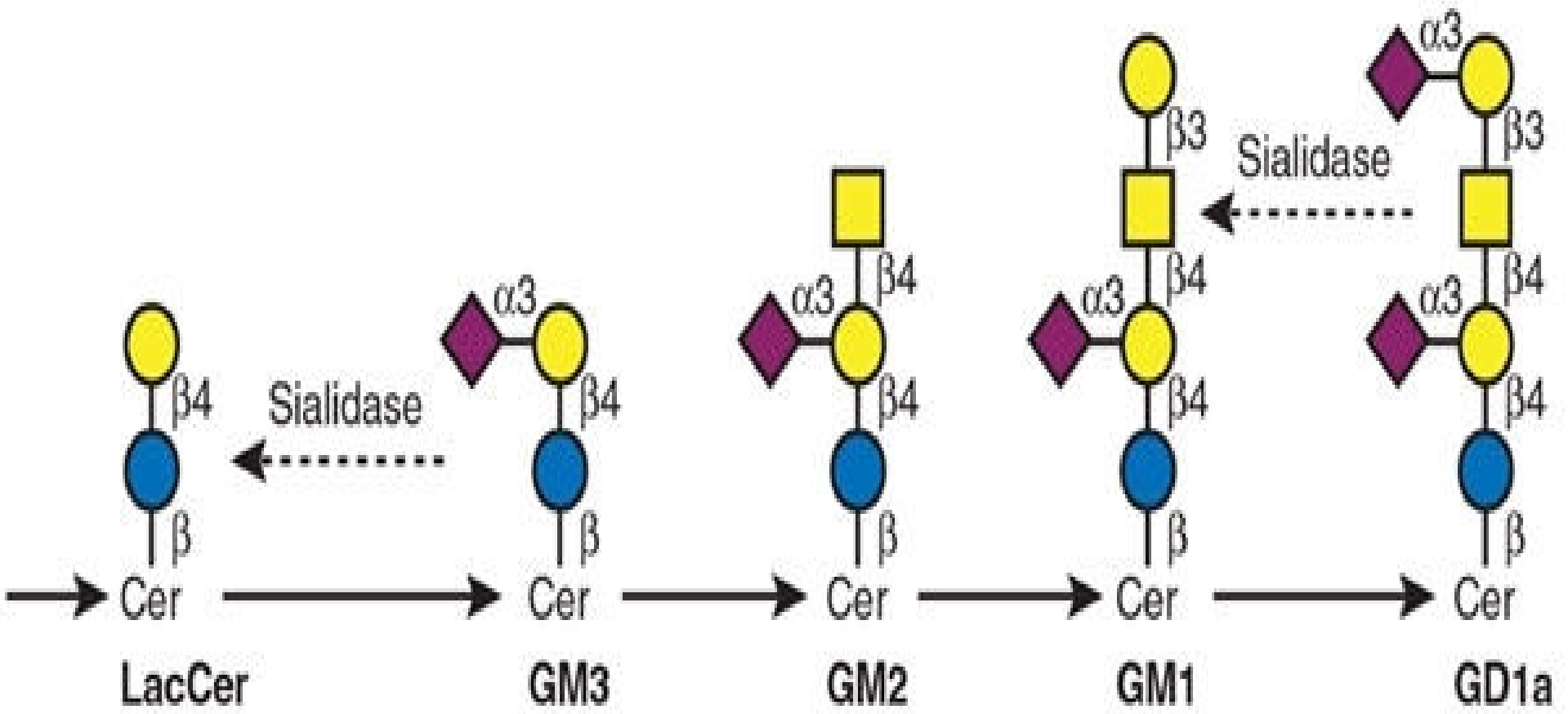
- **NANA**/Sialic acid is derived from **N-Acetyl Mannose and Pyruvate**.

- **Gangliosides** structure has Carbohydrate moieties as
  - **Glucose**
  - **Galactose**
  - **N-Acetyl Galactosamine**
  - **N-Acetyl Neuraminic Acid (NANA)/Sialic acid**.

Structure Of Gangliosides





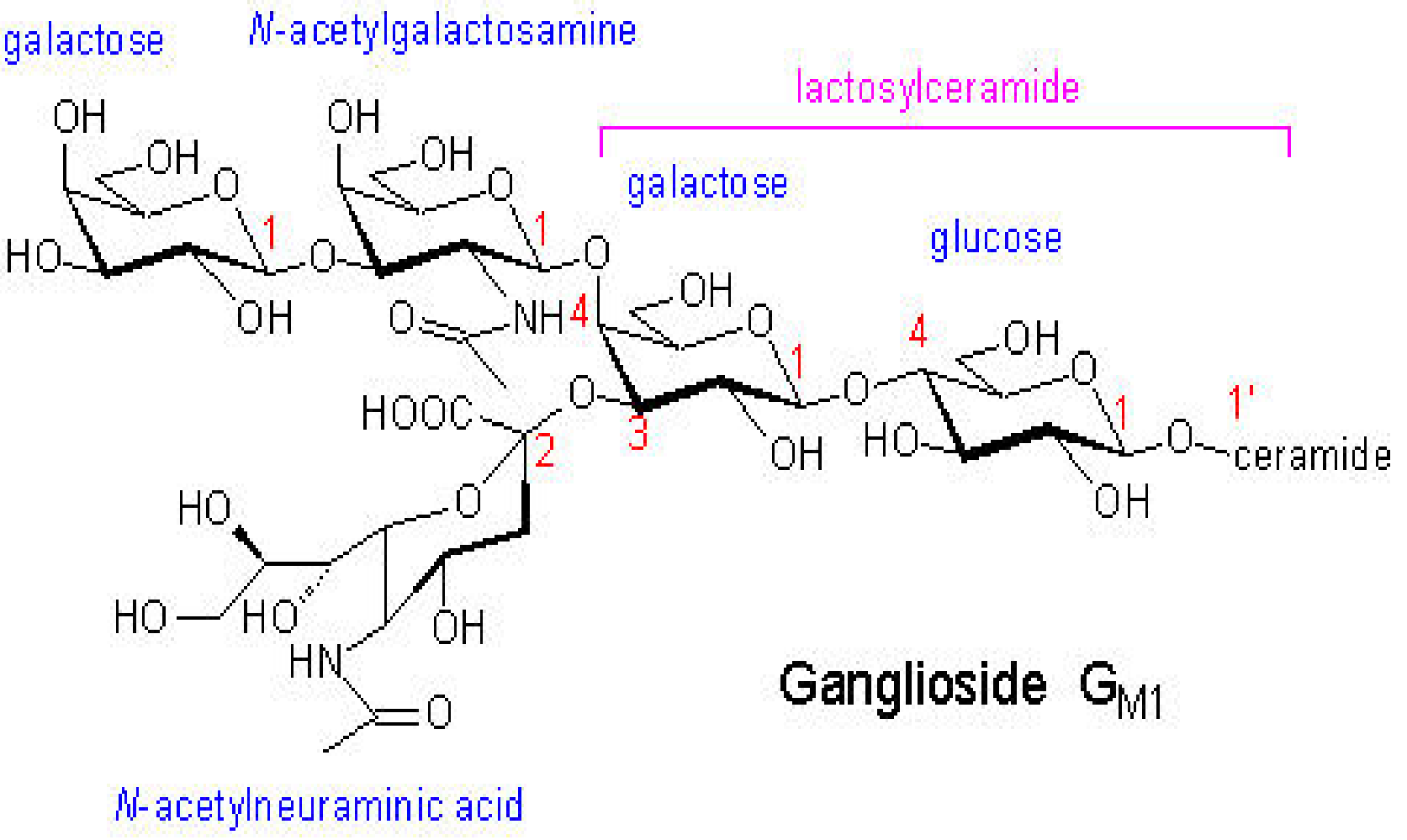


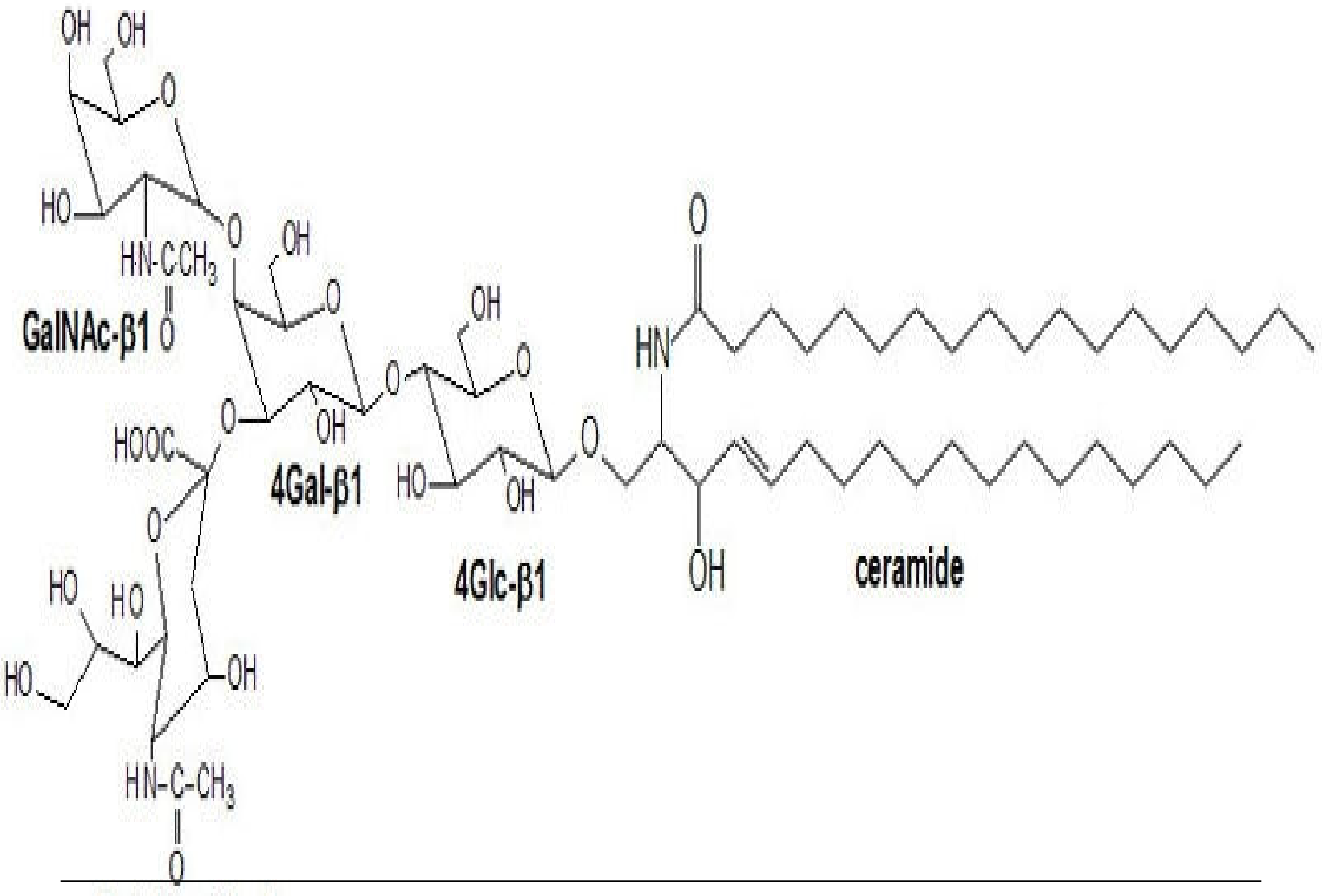
- **GM3 is more common and simplest Ganglioside.**

- GM3 has **single Sialic acid** and **less carbohydrate moieties**.

- **GM1** is a **more complex Ganglioside.**

- **GM1 is obtained from GM3.**





Types Of Gangliosides

- Depending upon the Chemical structure and Chromatographic separations

- **More than 30 Types of Gangliosides** are isolated:

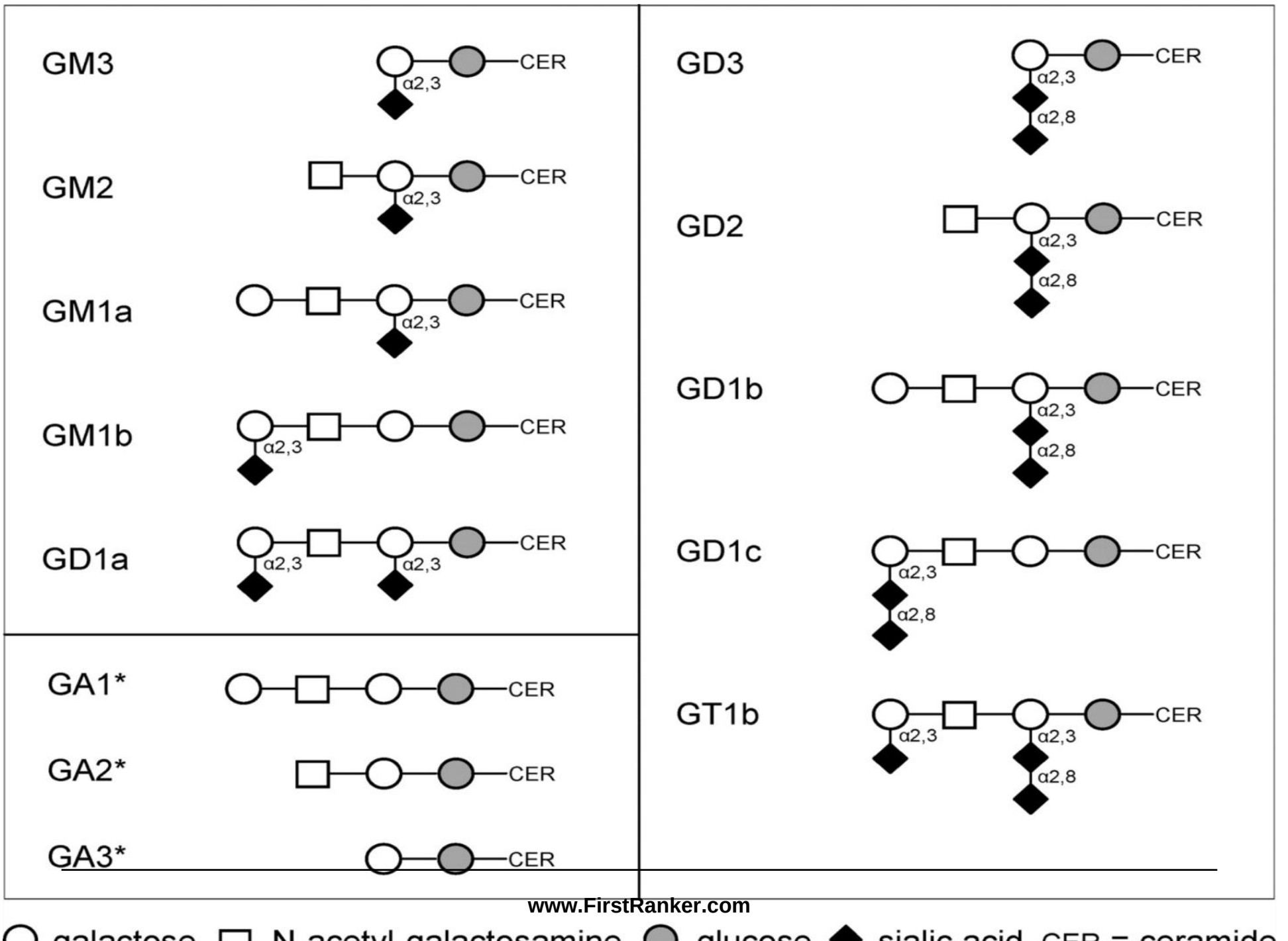
Types Of Gangliosides

- Based on **Number and Position of NANAs** in Ganglioside structure

- Various types and subtypes of Gangliosides are existing in human body

Types of Gangliosides

- Gangliosides with one NANA residue
  - GM1
  - GM2
  - GM3
- Gangliosides with two NANA residues
  - GD
- Gangliosides with three NANA residues
  - GT

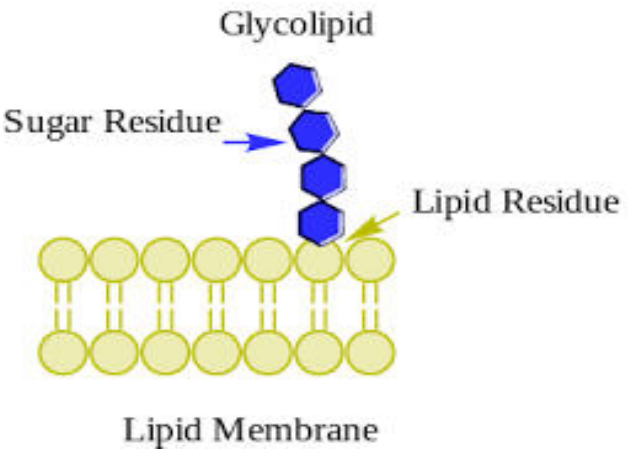


○ galactose, □ N-acetyl-galactosamine, ● glucose, ◆ sialic acid, CER = ceramide

Sources Of GlycoSphingolipids

- Dietary has **no much role**
- All forms of Glycolipids **Endogenously Biosynthesized**
- Utilized for **Structure and Functional Role**

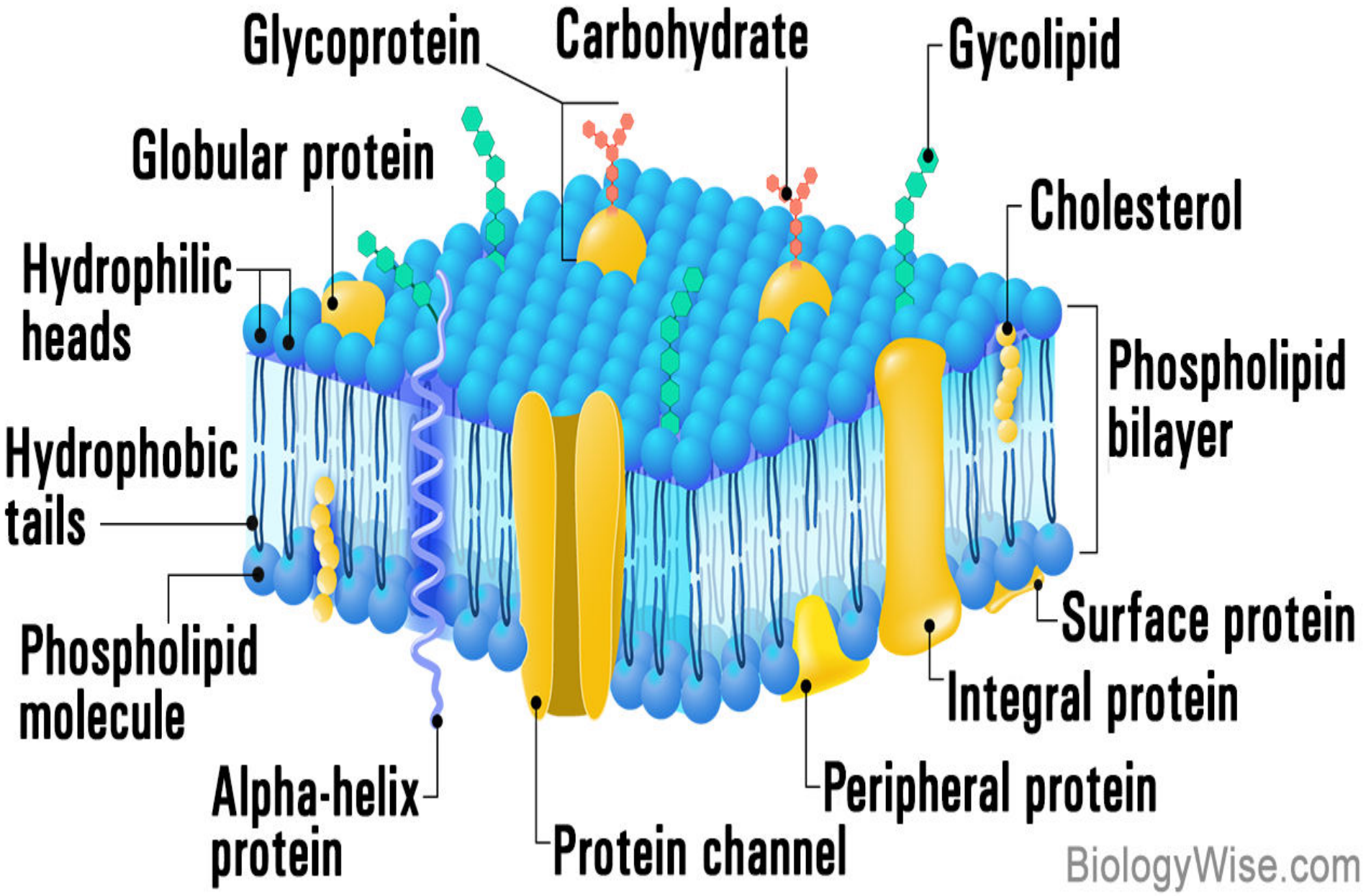
Occurrence/Distribution Of Glycolipids



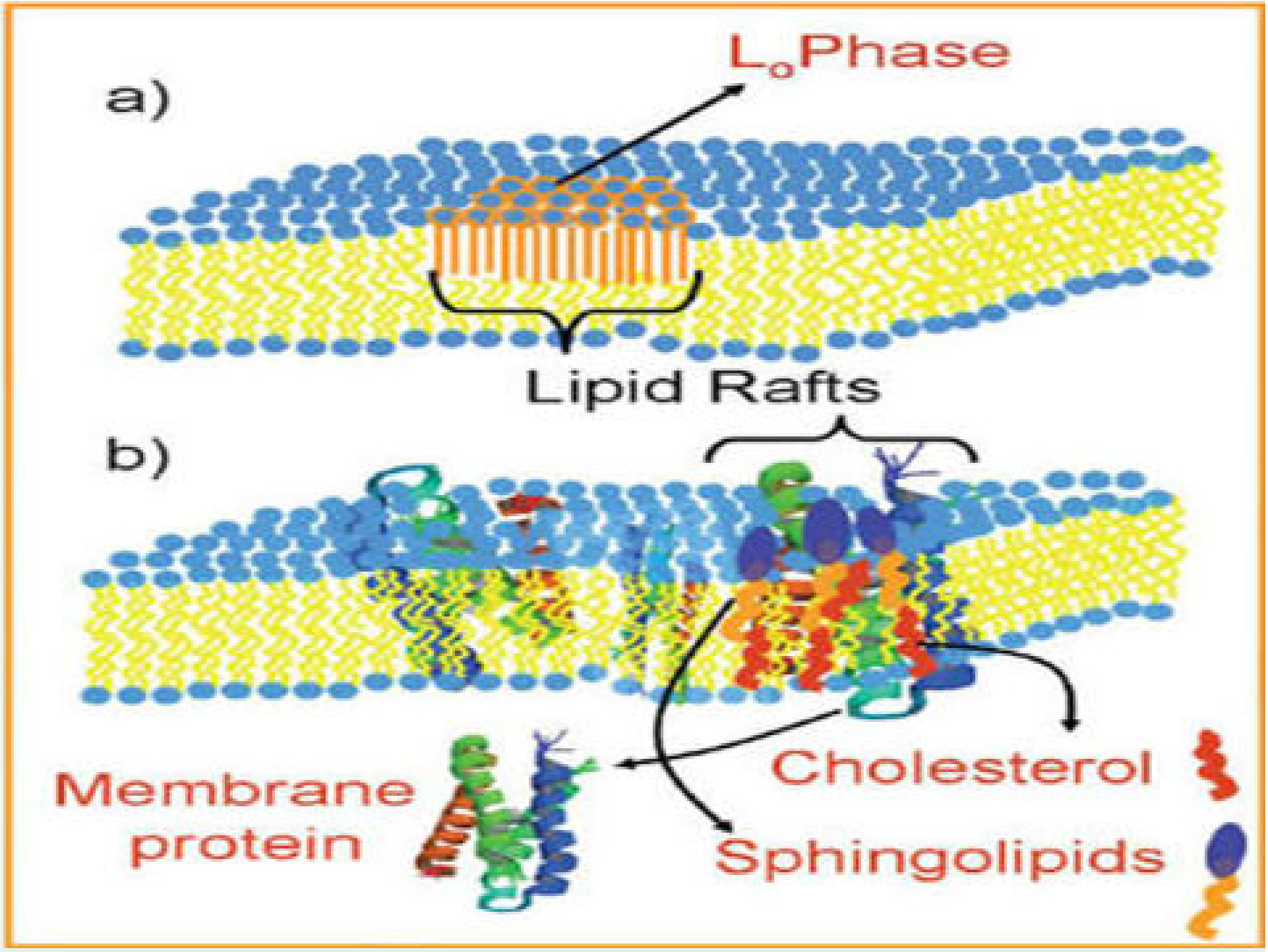
- **Glycosphingolipids** are widely distributed
- In **every cell and tissue of human body**
- **Occur particularly in outer leaflet of Cell membrane/Glycocalyx /Cell Rafts**

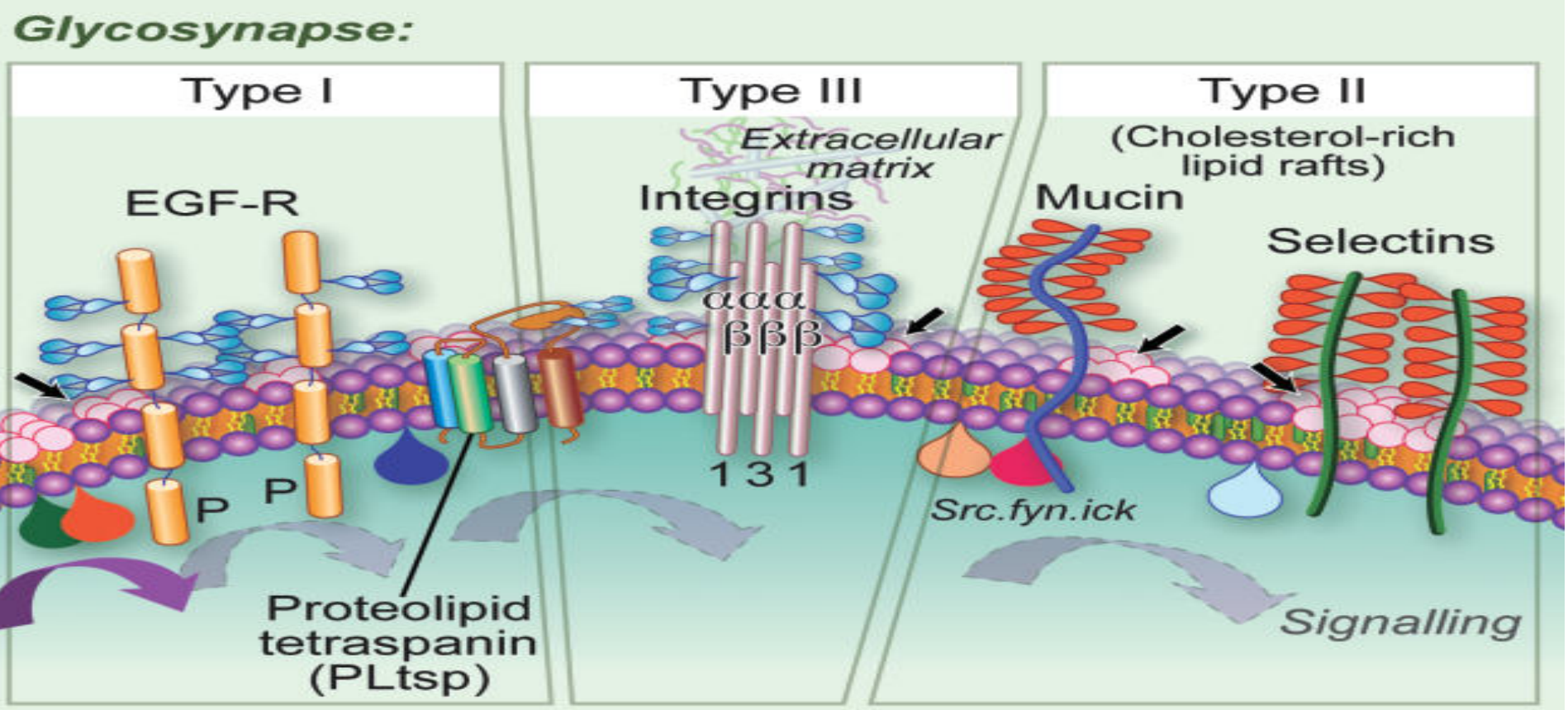
- They are **richly present in nervous cells.**

Fluid Mosaic Model

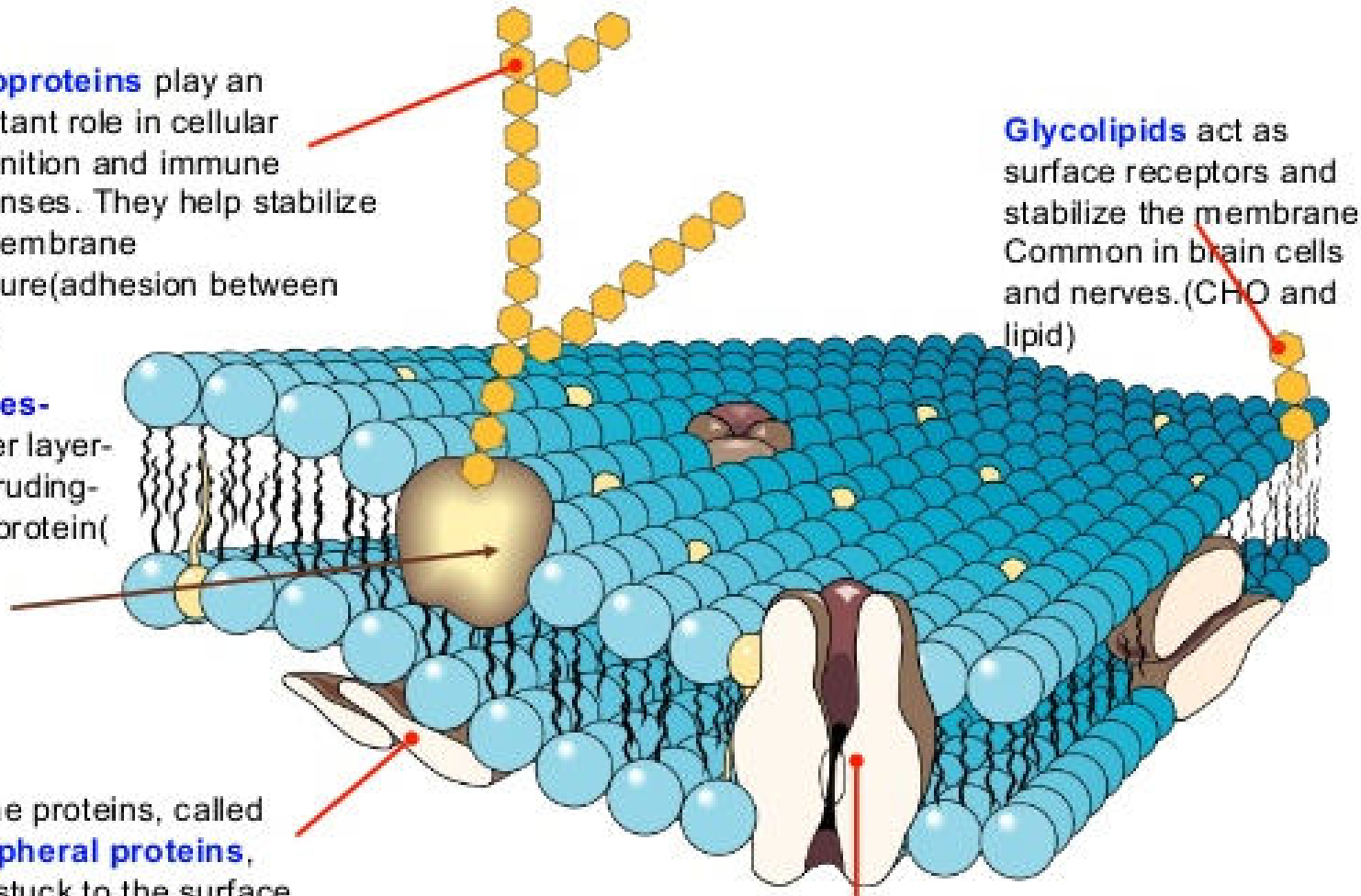


- **Glycolipids** occur on the outer surface of every cell membrane as component of **Glycocalyx /(Cell raft).**





Membrane Structure



– **Cerebrosides**: Richly present in
  - **White matter of brain**
  - **Myelin sheath**

– **Gangliosides:** Predominantly present in
  - **Grey matter of brain**
  - **Ganglions and Dendrites**

Functions Of Glycolipids

- Glycolipids are **richly present in nervous tissue,** they help in:
- **Development** and **function of brain**.
- **Nerve impulse conduction**

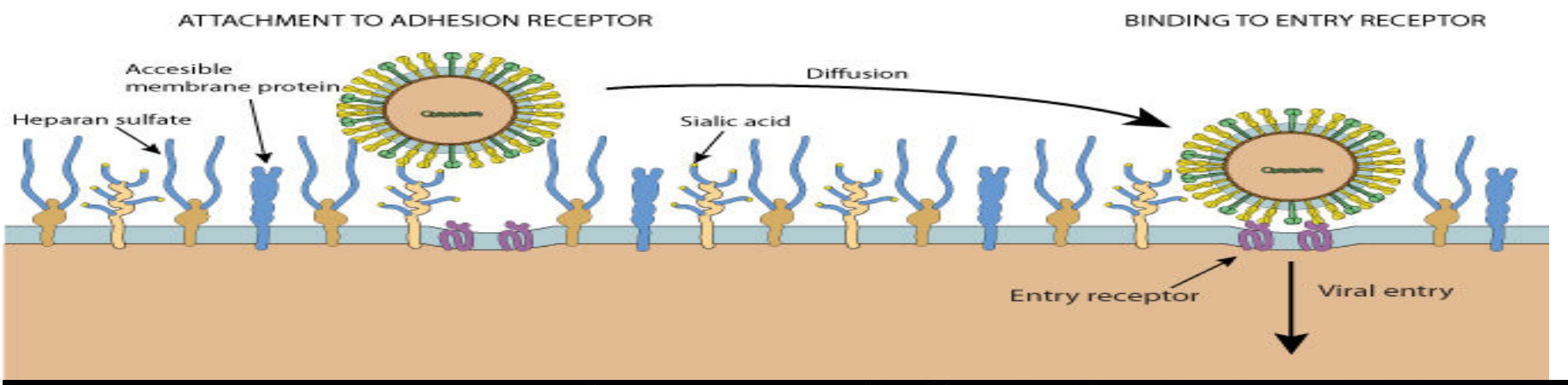
- **Glycolipids present in cell membranes Serve as :**

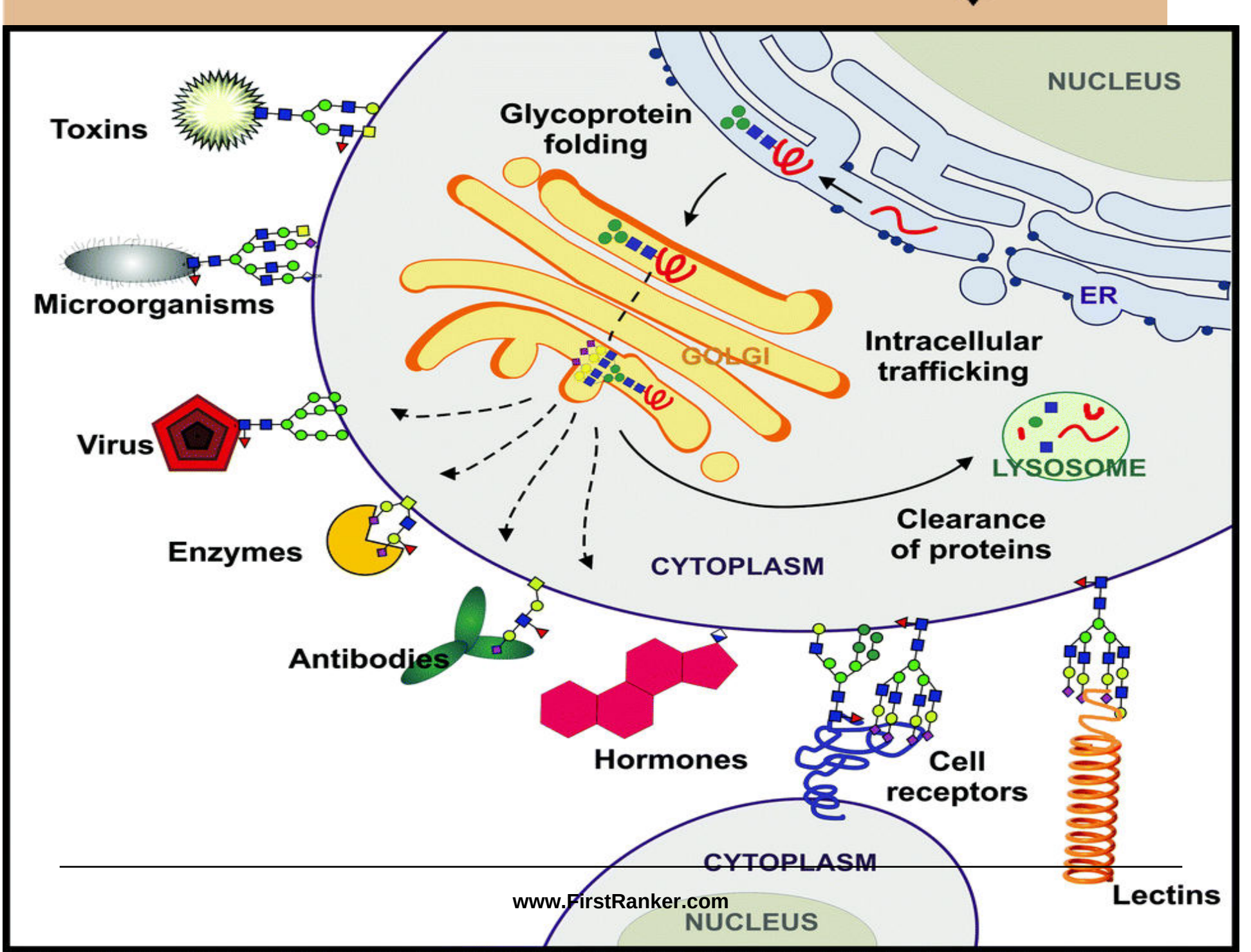
  - **Antigens**
    - **Blood group Antigens**
    - **Embryonic Antigen**

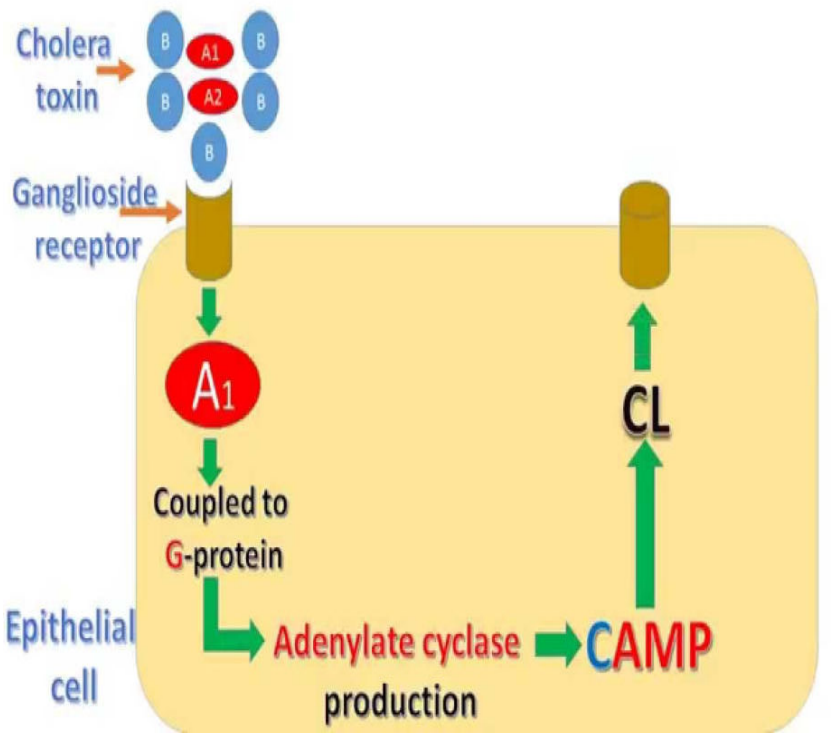
  - **Receptor sites for Hormones.**

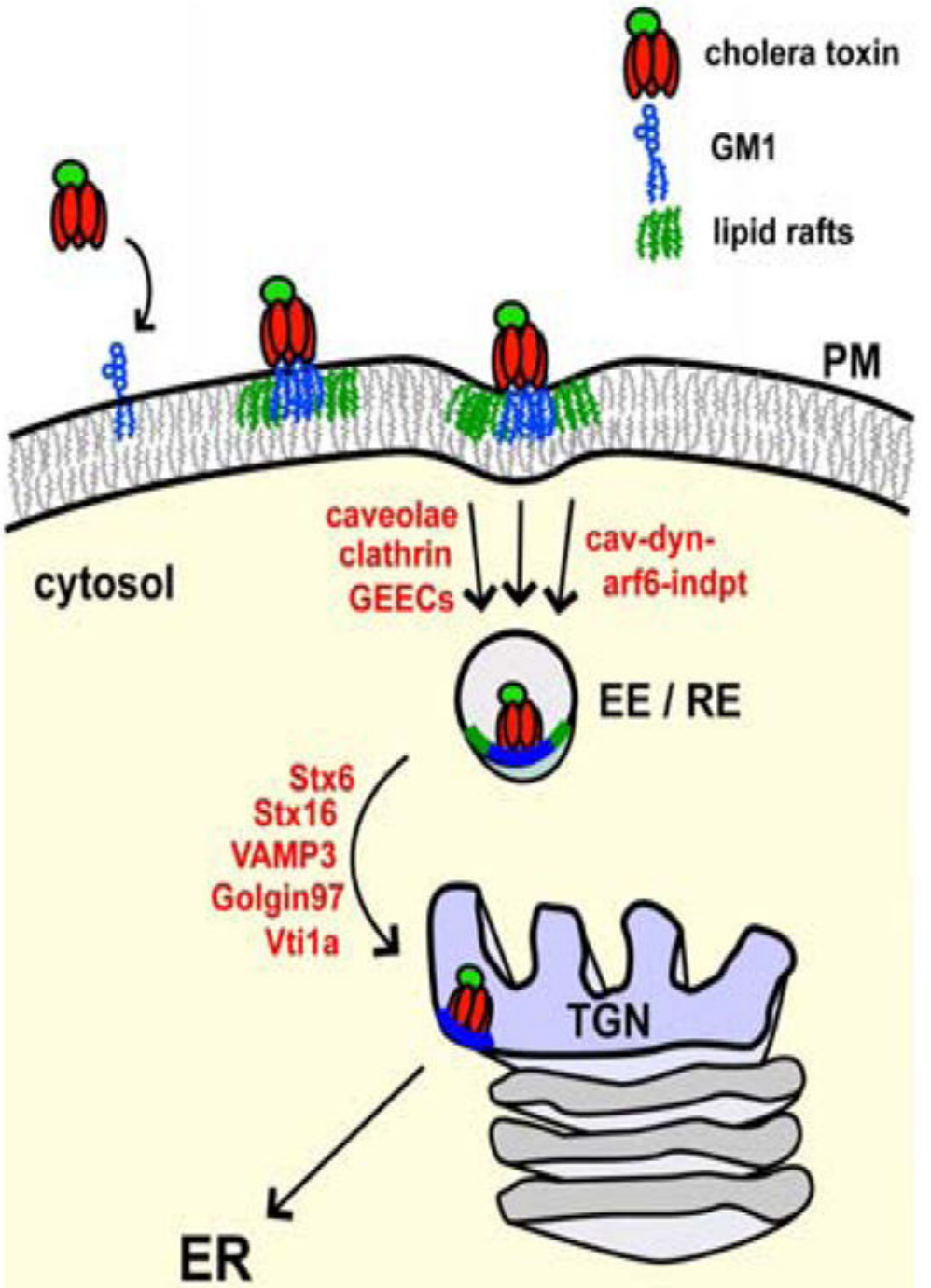
- **Glycolipids of cell membrane serve as:**
- **Markers for cellular recognition which helps in:**
  - **Cell Functioning**
  - **Cell-Cell interaction**
  - **Cell Signaling/Signal Transduction**
  - **Anchoring sites for Antigens, Toxin and Pathogens**
  - **Cell Growth and Differentiation**

- **GM1** serve as **receptor /anchoring** site to :
  - **–Cholera toxin**
  - **–Tetanus toxin**
  - **–Influenza viruses**

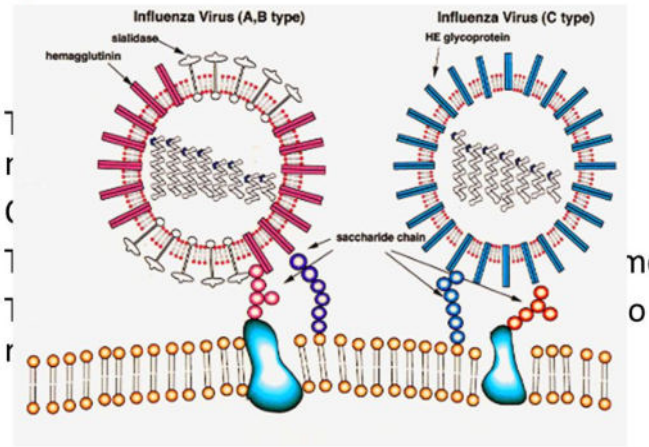








- Influenza viruses bind through hemagglutinin onto sialic acid sugars on the surfaces of epithelial cells



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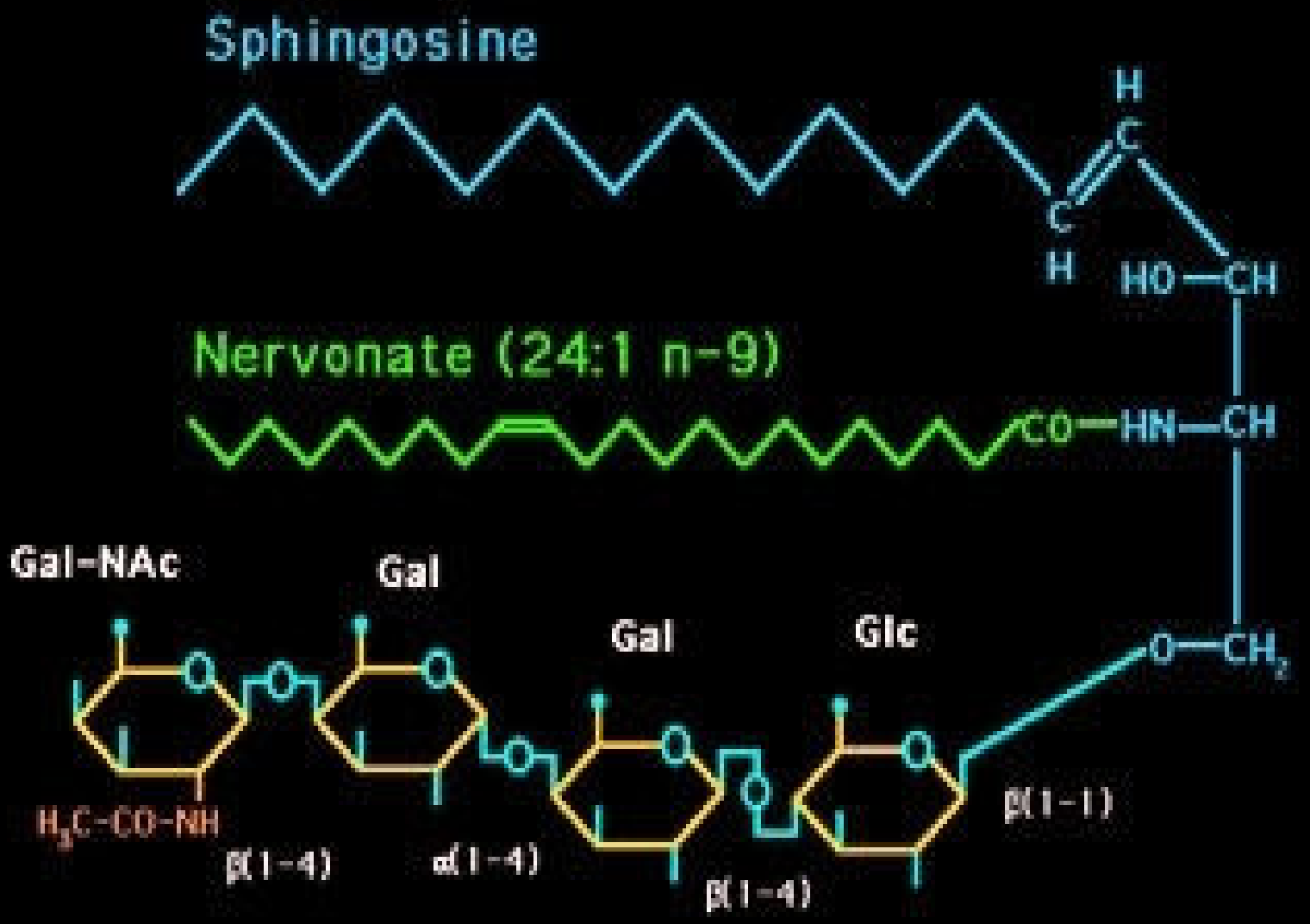
- The **Cholera toxin** on binding to intestinal cells
- **Stimulates secretion of Chloride ions into gut lumen.**
- **Resulting in copious diarrhea of Cholera.**

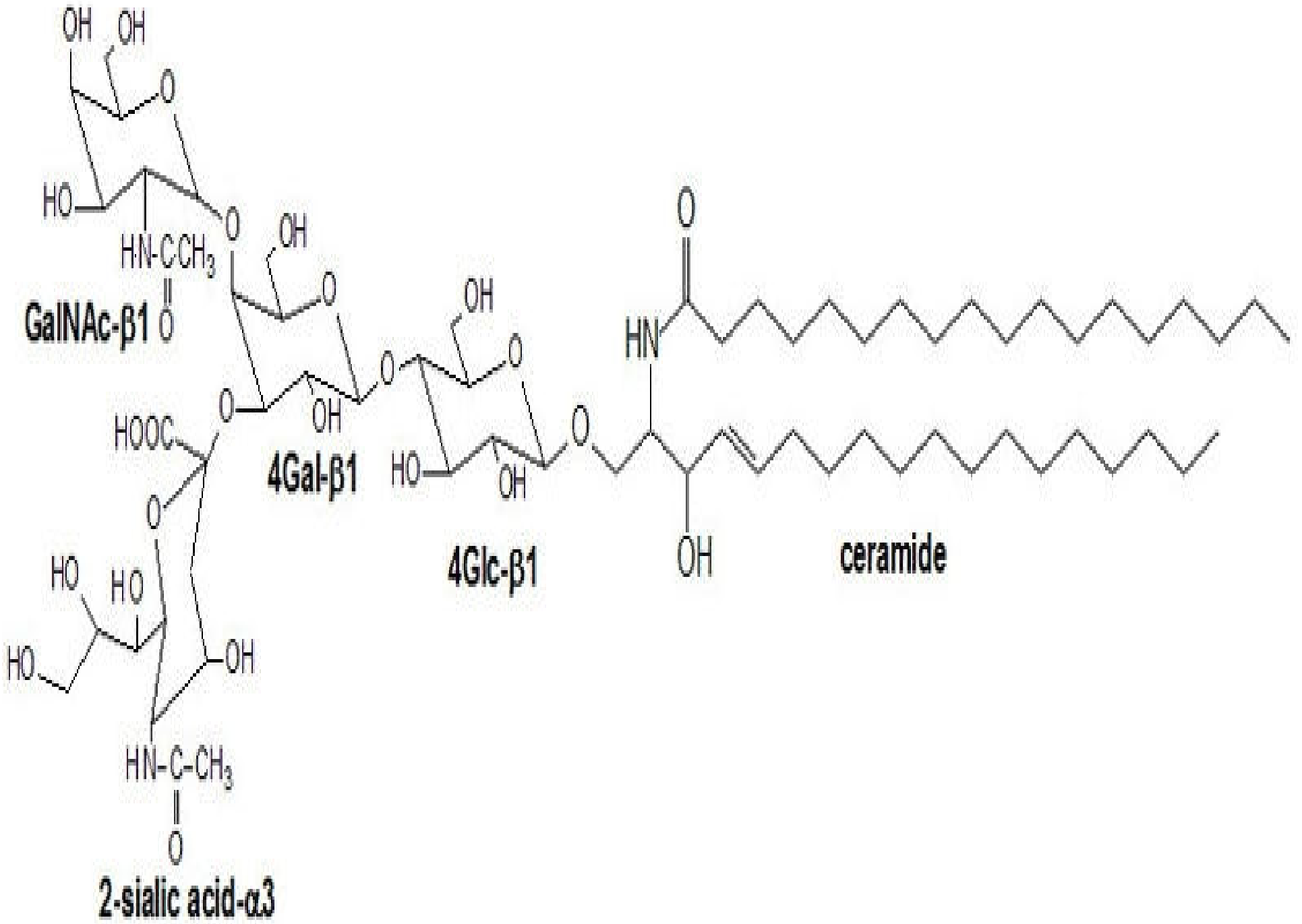
- In various malignancies dramatic **changes** in **membrane Glycolipid** composition are noted.

Globosides

- Globosides are **type of Glycolipids.**
- Structurally **Ceramide linked with Oligosaccharide** is Globosides.



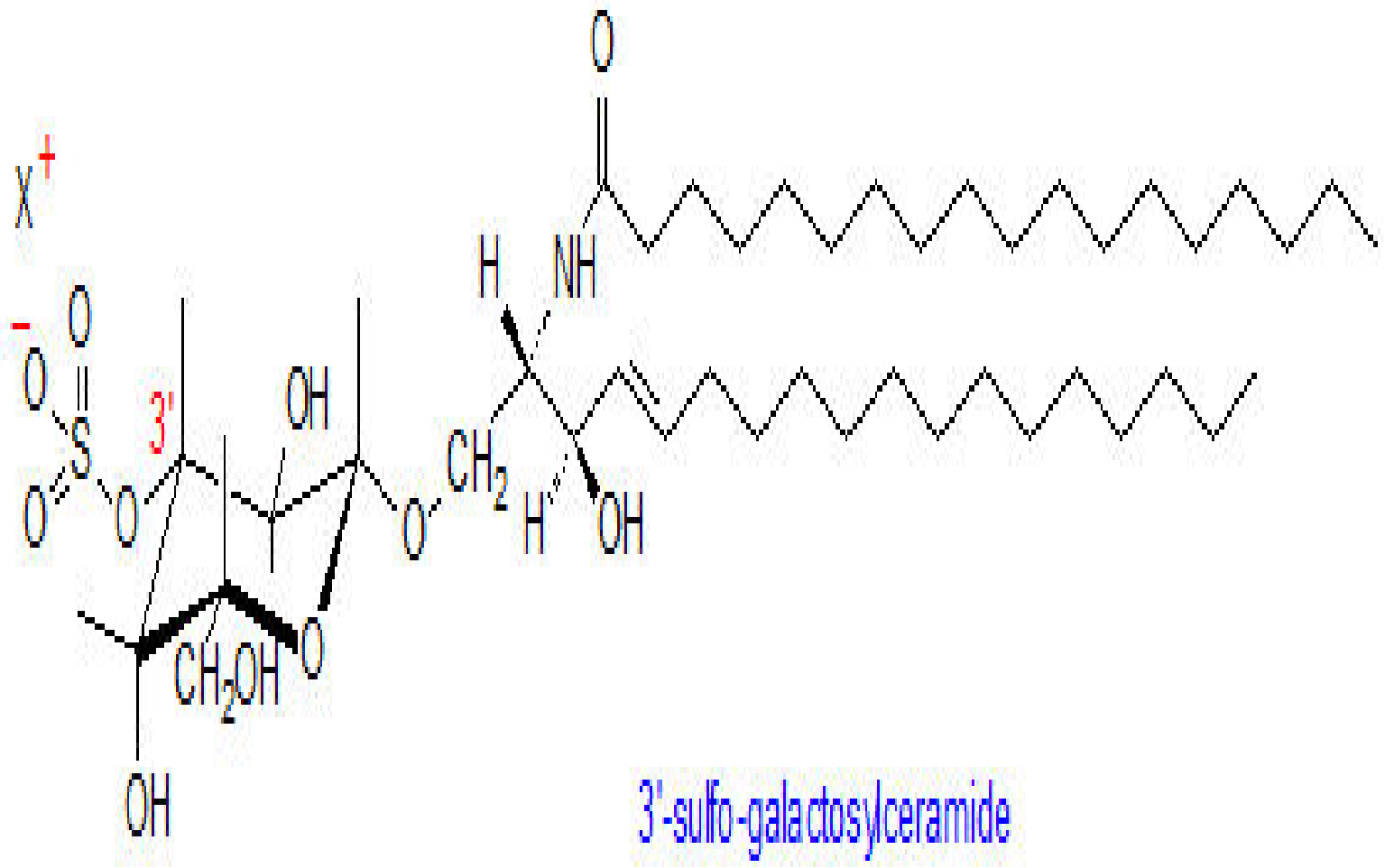
Globoside



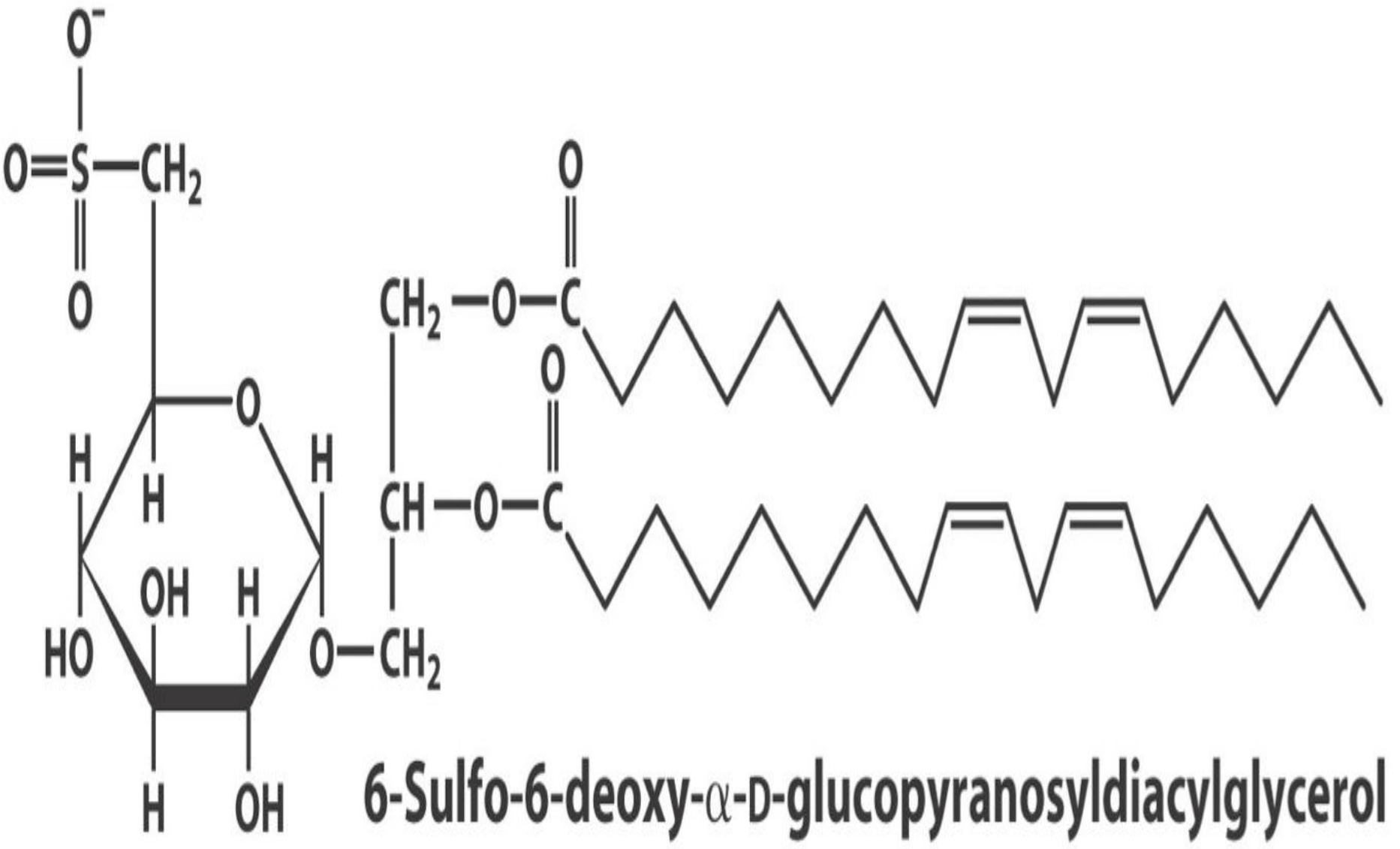
Sulfatides/Sulfolipids

- **Sulfolipids** are **compound Lipids**.
- **Sulfolipids** are **Ceramide** linked to **Sulfated sugar units/ Oligosaccharides**.

- Structurally Sulfolipids may also has Glycerolipids containing **Sulfate groups**.
- Sulfolipids are component of **nervous tissue.**



3'-sulfo-galactosylceramide



6-Sulfo-6-deoxy-α-D-glucopyranosyldiacylglycerol
(a sulfolipid)

Lipidosis

Lipid Storage Disorders

Inborn Errors Of Lipid Metabolism

Lysosomal Storage Disorders

Rare Genetic Lipid Associated Disorders

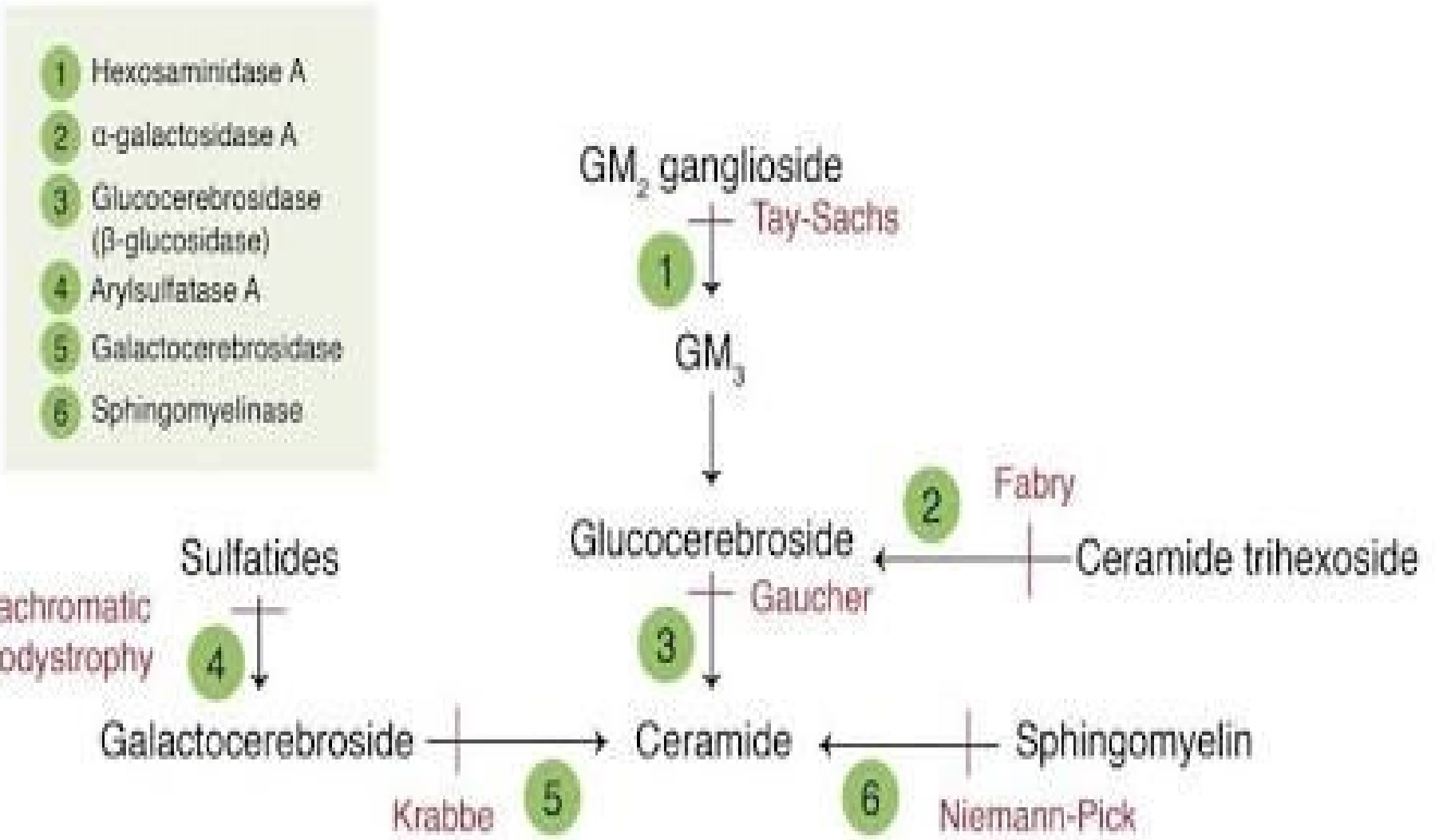
- Niemann Picks Disease
- Tay Sach's Disease
- Gauchers Disease
- Farbers Disease
- Krabbes Disease
- Sandhoff's Disease

SPHINGOLIPIDOSES

- **Tay-Sachs disease** **AR** **Hexosaminidase -A**
  - Developmental regression, Blindness,
  - Cherry-red spot, Deafness
- **Gaucher' s disease** **AR** **Glucosylceramide Type I**
  - Joint and limb pains, Splenomegaly

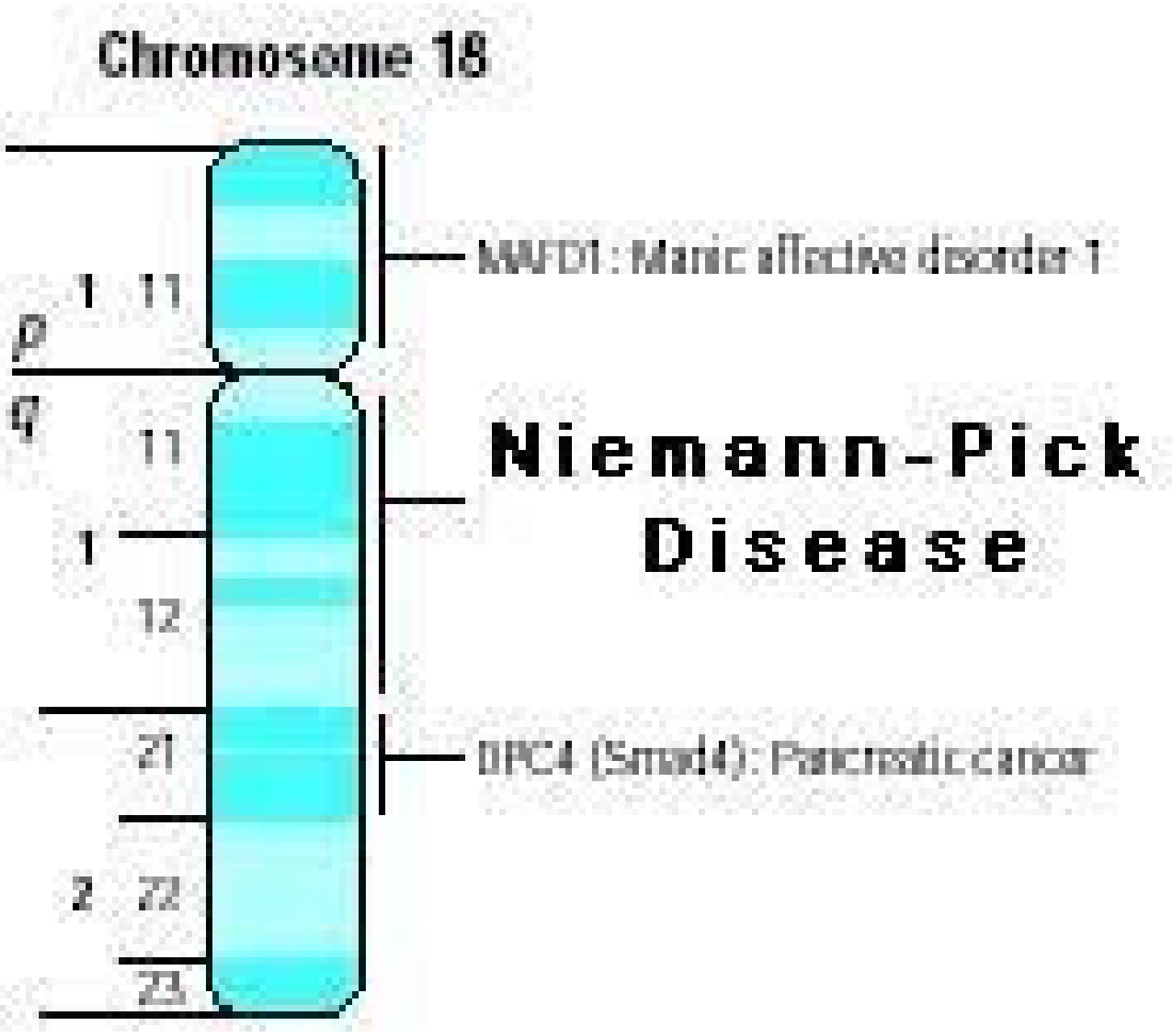
  β- Glucosidase Type II
  - Spasticity, fits; death
- **Niemann-Pick disease** **AR** **Sphingomyelinase**
  - Failure to thrive, Hepatomegaly
  - Cherry-red spot, Developmental

Lysosomal Storage Disorders



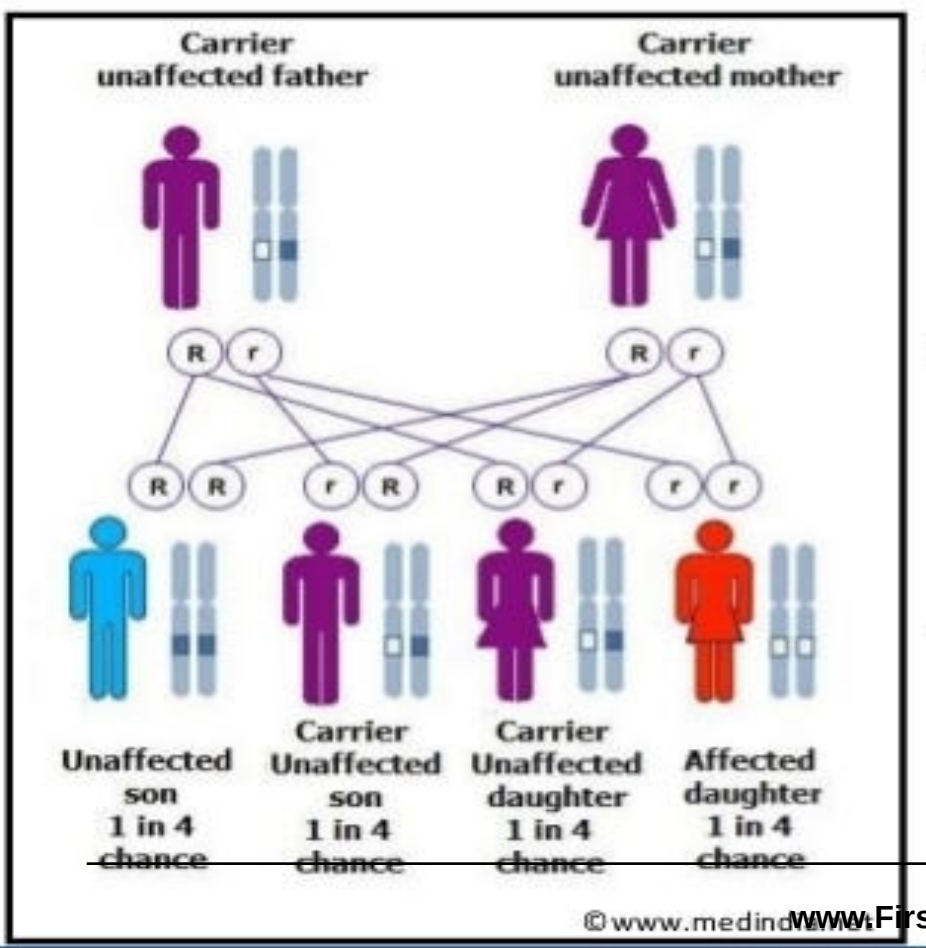
Niemann-Pick disease

- Sphingomyelinase deficiency causes **sphingomyelin** accumulation within mononuclear phagocyte system (and neurons and glial cells)
  - Autosomal recessive
  - **cherry red spot** similar to Tay-Sachs disease.



Niemann Picks Disease
Autosomal Recessive Disorder

Is it Hereditary?



- The disease has an **autosomal recessive** pattern of inheritance.
- Both alleles of the gene must be mutated in such a way that function is impaired.
- If both parents are carriers, there is a 25% chance for an affected child with each pregnancy.

Niemann-Pick disease

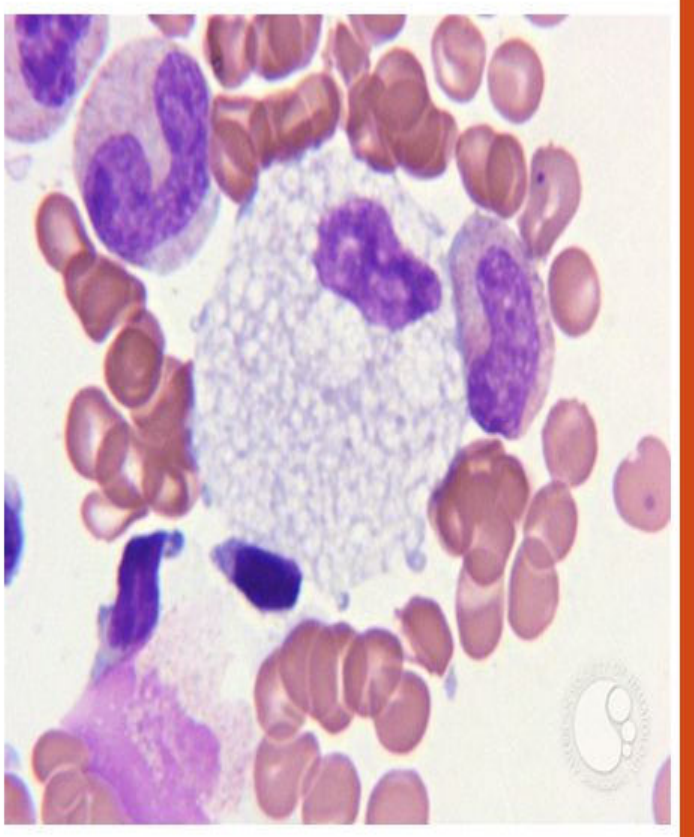
Heterogeneous group of disorders

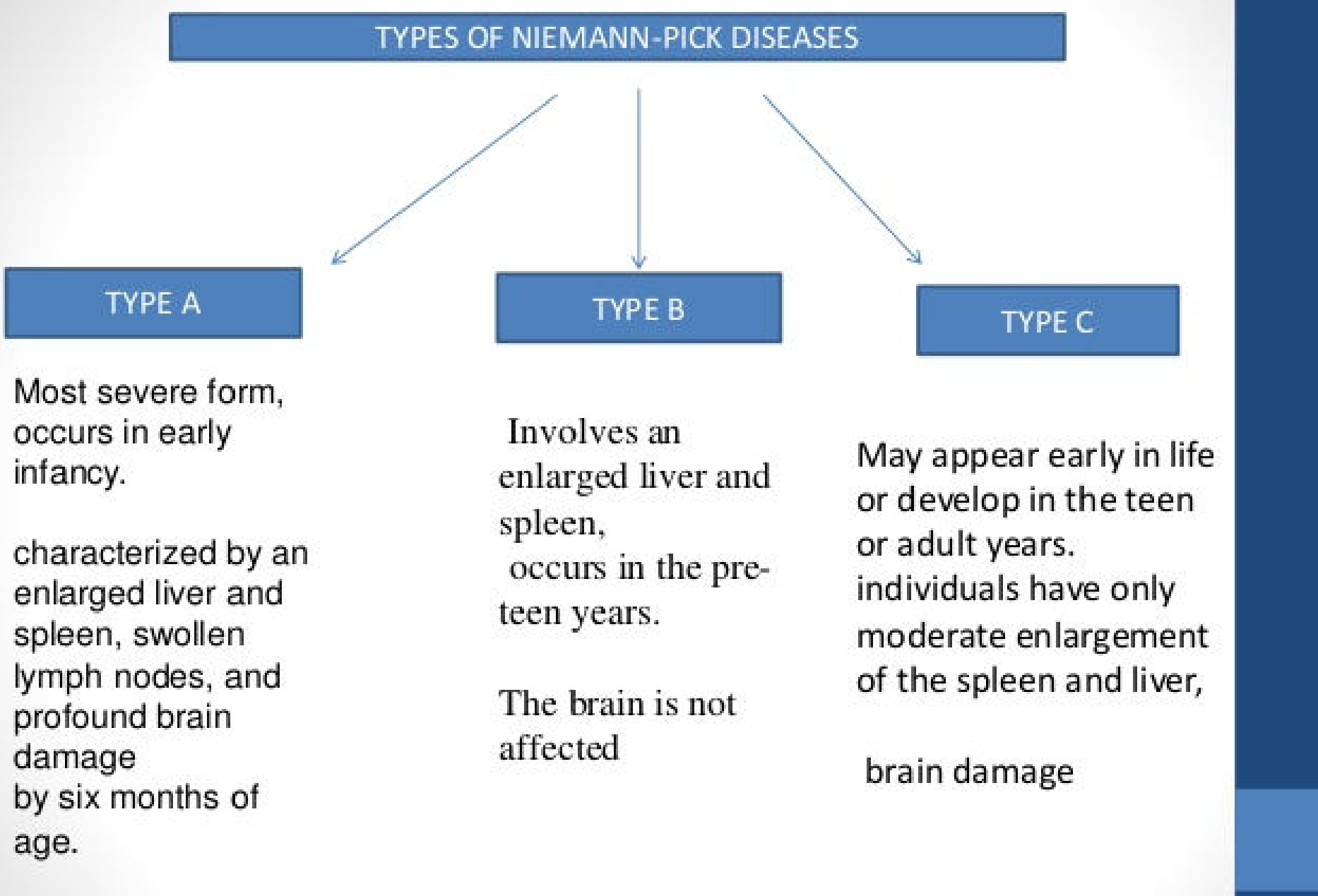
Increased incidence in Jewish population

This disorder is divided into five main types based on the genetic cause and the signs and symptoms (A,B,C,D,E)

Clinical manifestation

- Retardation
- Hepatoslenomegaly
- Lymphadenopathy
- Pigmentation
- Impaired neurologic function
- Niemann-Pick cells – lipid-laden giant foam cells found in affected tissues

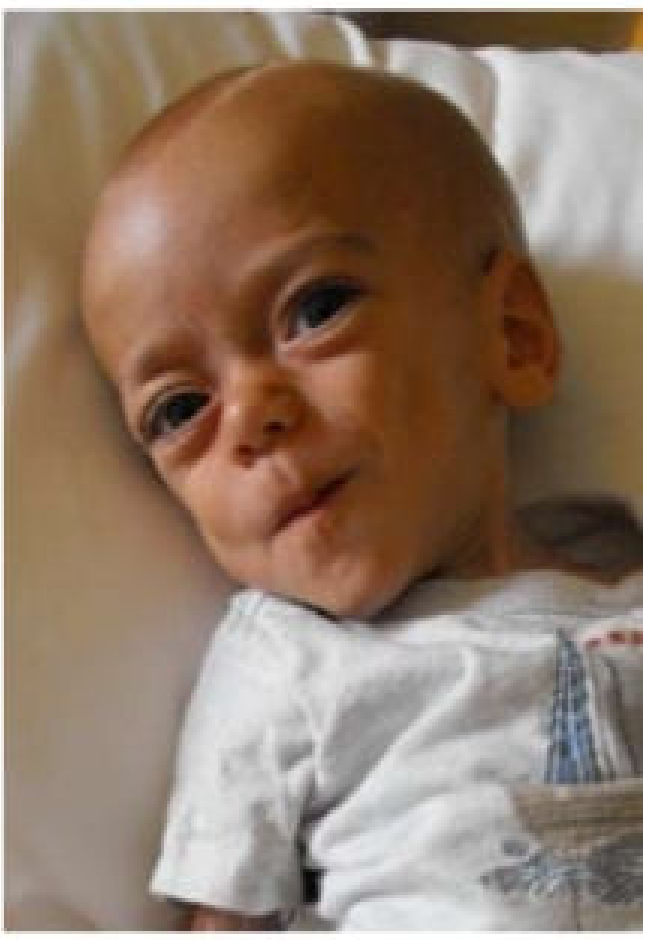




Signs and Symptoms

(related to the **organs** in which they accumulate)

Type A



- ✓ Large abdomen within 3-6 months
- ✓ Cherry red spot in the eye
- ✓ Feeding difficulties *(**dysphagia**)*
- ✓ Loss of early motor skills (***ataxia***)
- ✓ Rapid decline in the child after 6 months

Type B

- ✓ Abdominal swelling may occur in early childhood
- ✓ No brain and nervous system involvement
- ✓ Some may develop repeated respiratory infections and breathing problems

Diagnosis

Type A and B:

* ***Measurement of ASM amount in WBC***
  - by using a blood/bone marrow sample.
  - can detect patients, not carriers.
* ***DNA tests*** (to determine if carriers have type A or type B)

Type C:

* **Skin biopsy :** scientists closely examine how the skin cells grow, keep track of how they move & store cholesterol.
* **DNA tests**

- Few centers offer tests for **prenatal diagnosis.**
- Other tests might include:
  * Bone marrow aspiration
  * Liver biopsy
  * Slit-lamp eye exam

Ⓟ-choline

Ceramide → Sphingomyelin

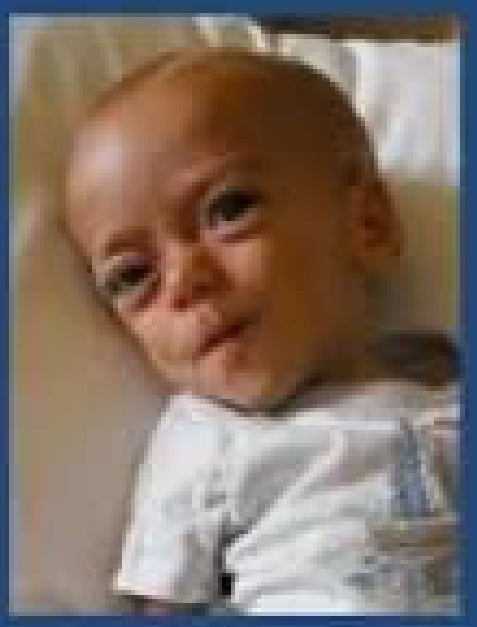
(Cer-Ⓟ-choline)

degradation ✕ Niemann-Pick A & B

(defect in sphingomyelinase)

ceramide + phosphorylcholine

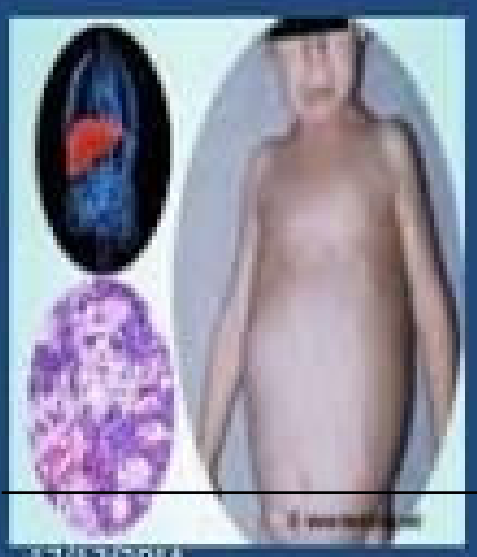
Niemann-Pick Disease[1,6]

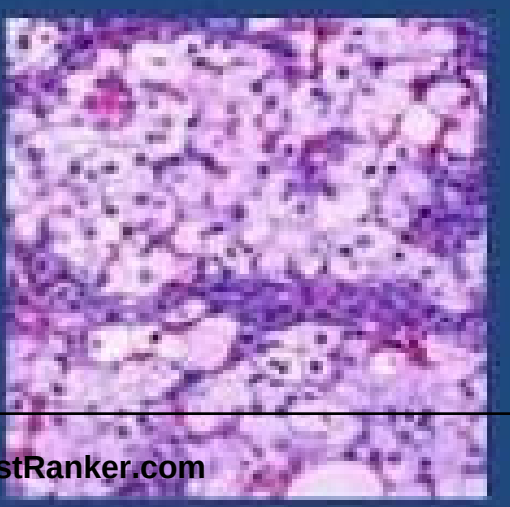


Clinical Manifestations

Neurological Detoriation
Cherry-red spot on the retina the eye
Enlarged liver and spleen
Lipid-laden cells in bone marrow
Pulmonary disease
Liver dysfunction

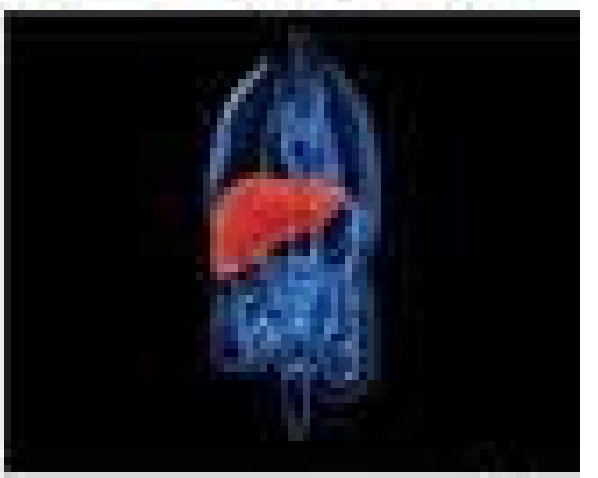
Foam Cells



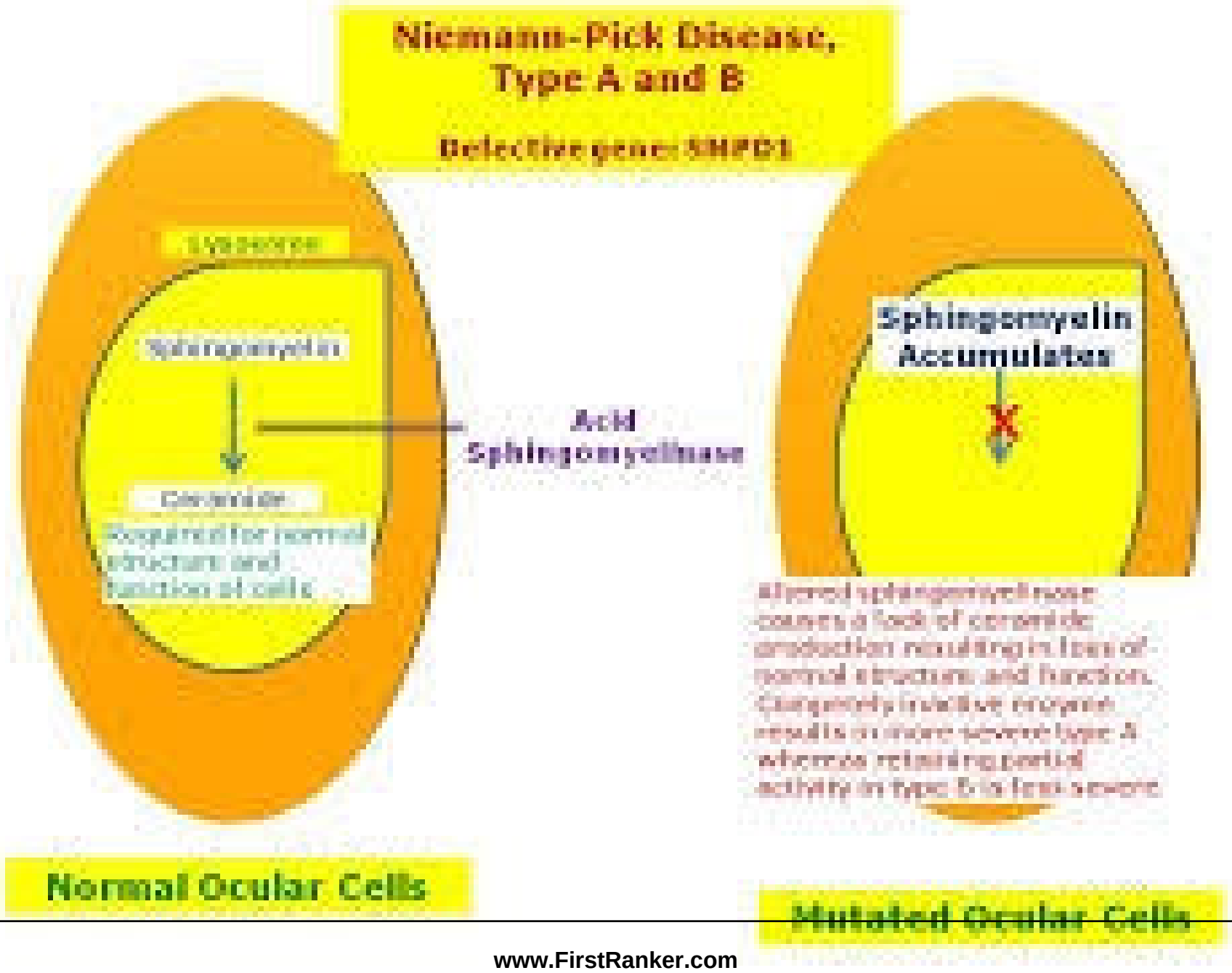


Introduction

Niemann–Pick disease refers to
- a fatal inherited metabolic disorder
- classified in a subgroup of lysosomal storage disorders called **sphingolipidoses**
- involves dysfunctional metabolism of sphingolipids



- accumulation of harmful quantities of lipids in the spleen, liver, lungs, bone marrow, and brain.



Lipid Storage Disorders Related To Glycosphingolipids

Disorders Of GlycoSphingolipids

- Gaucher's Disease
- Tay Sach's Disease
- Farbers Disease
- Krabbes Disease

- **Gaucher's Disease:**

- **Defect:** Deficiency of Cerebroside degrading enzyme **Glucocerebrosidase.**

- **Biochemical Alteration:** Abnormal **accumulation of Cerebrosides** in tissues.

- **Consequences: Affect normal function** of tissues where it is accumulated.

Gaucher Disease: A Lysosomal Storage Disorder

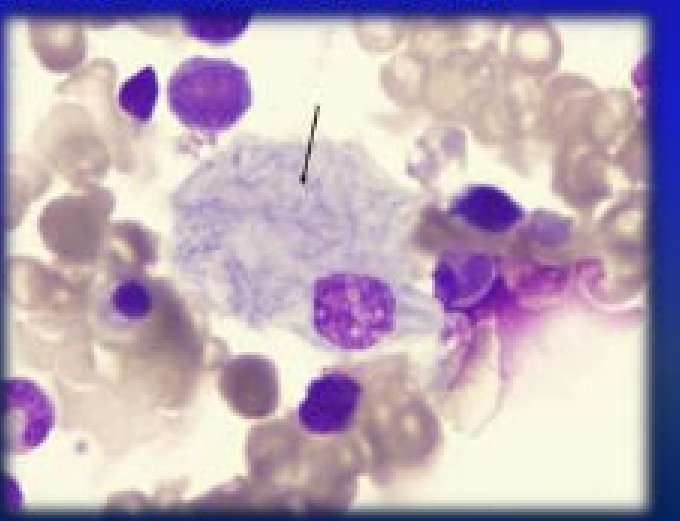
Gaucher Disease:

- Most common lysosomal storage disorder
- Autosomal recessive
- Genetic defect on chromosome 1
- Enzyme deficiency
- Reticuloendothelial system
- Progressive, multisystemic, multiorgan dysfunction

Philippe Gaucher
1854 – 1918

Gaucher Disease: Overview

- The most common lysosomal storage disease
  - Incidence: approximately 1 in 40,000 for non-Jewish populations
- Caused by a deficiency of the enzyme glucocerebrosidase
- The glycolipid glucocerebroside accumulates in lysosomes of macrophages
- Lipid-filled Gaucher cells displace normal cells in
  - Bone marrow
  - Spleen
  - Liver
  - Lungs
  - CNS*

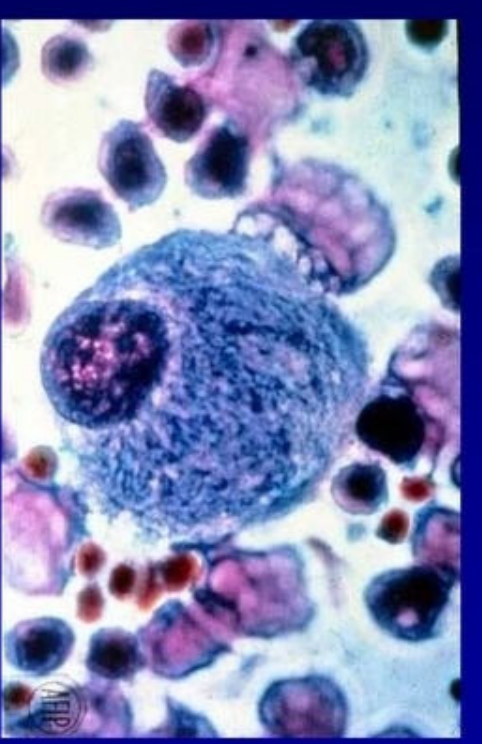


Gaucher disease

- defect of glucocerebrosidase - 3 types (type 1 - survival, type 2 - lethal, type 3 - intermediate)
- accumulation of glucocerebroside (Glc-ceramide) - kerasin
- Gaucher cells - spleen (red pulp), liver (sinuses), bone marrow

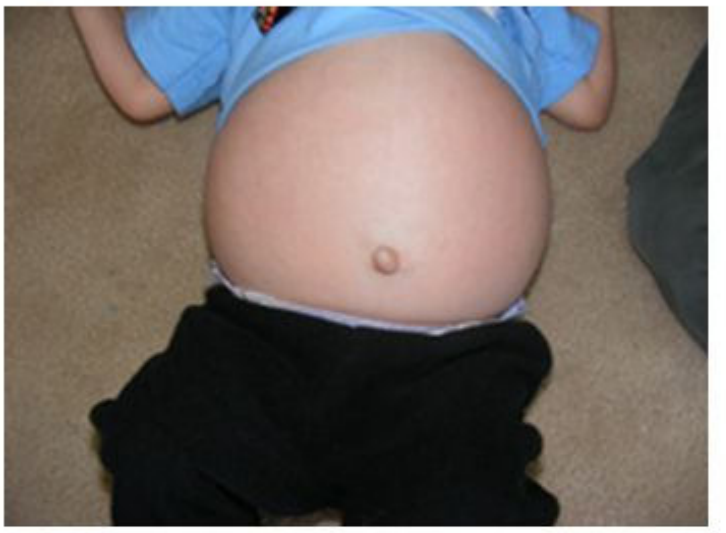
GAUCHER DISEASE (TYPE II)

- Can diagnosed by ***Gaucher cells*** in bone marrow
- Neuropathology:
  - Little lipid storage
  - Neuron loss, especially in *brainstem*



Gaucher Disease (this is a hereditary disease)

- Symptoms
  - Distended abdomen
  - Bone pain
  - Anemia
  - Cognitive impairment



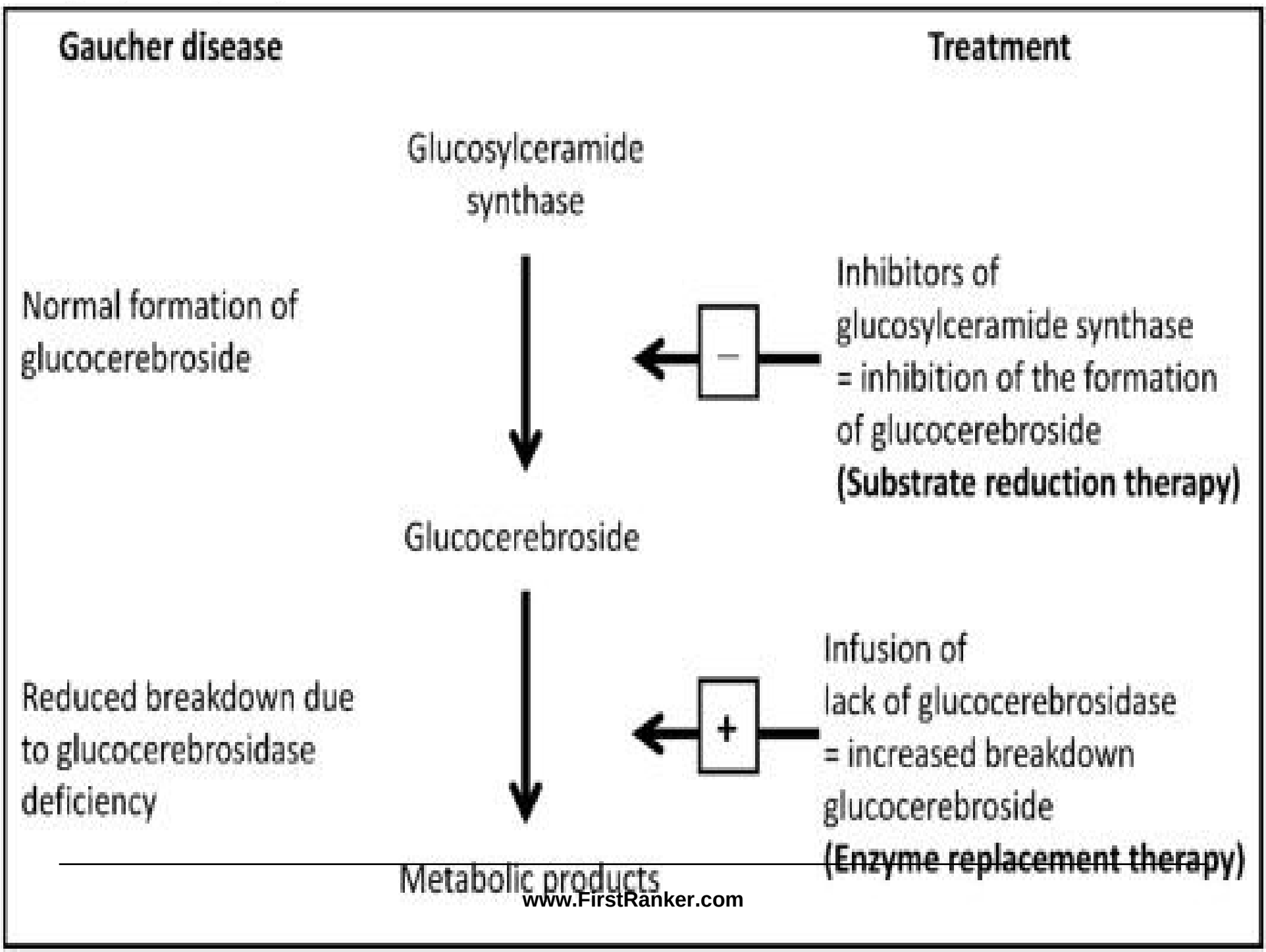
When to Suspect Gaucher Disease and Establishing the Diagnosis

Observations

- Splenomegaly in any age group
- Nosebleeds and unexplained bruising
- Persistent anemia or thrombocytopenia
- Bone pain
- Failure to thrive
- Neurologic deterioration in a young infant
- Congenital ichthyosis
- Horizontal gaze disorder or visual apraxia

After clinical suspicion has been raised, diagnosis can be confirmed by

- Enzymatic analysis in white blood cell pellet in expert lab
- Mutation analysis
- Bone marrow biopsy is NOT required for the diagnosis



- **Tay Sach's Disease:**

- **Defect:** Deficiency of Ganglioside degrading enzyme: **Hexoseaminidase-A.**

- **Biochemical Alteration:** Abnormal **accumulation of Gangliosides** in the tissues.

- **Consequences: Affect normal function of tissues.**

Tay Sach's features:

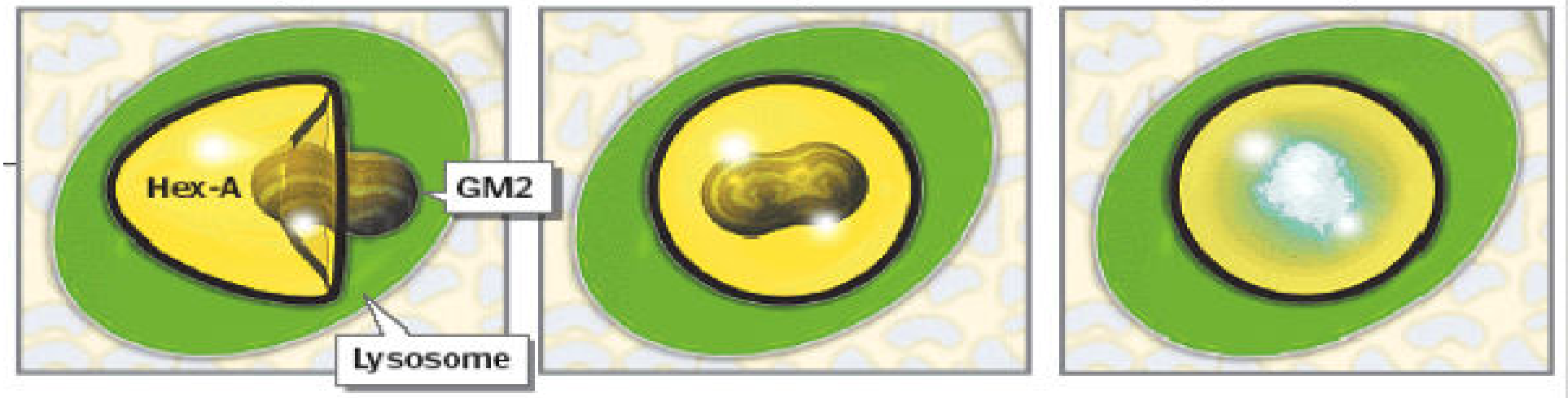
TAY SACHS

- **T**esting recommended
- **A**utosomal recessive
- **Y**oung death (<4 yrs.)
- **S**pot in macula (cherry red spots)
- **A**shkenazi Jews
- **C**NS degeneration
- **H**ex A deficiency
- **S**torage disease

Cells in healthy children

In a healthy child, a lipid, or fat, called **GM2 ganglioside** enters the nerve cell as a source of food. Among the components of the cell are **lysosomes**, which might be thought of as the "stomachs" of the cell. They contain an enzyme called Hexosaminidase A, or **Hex-A**, that digests the GM2.

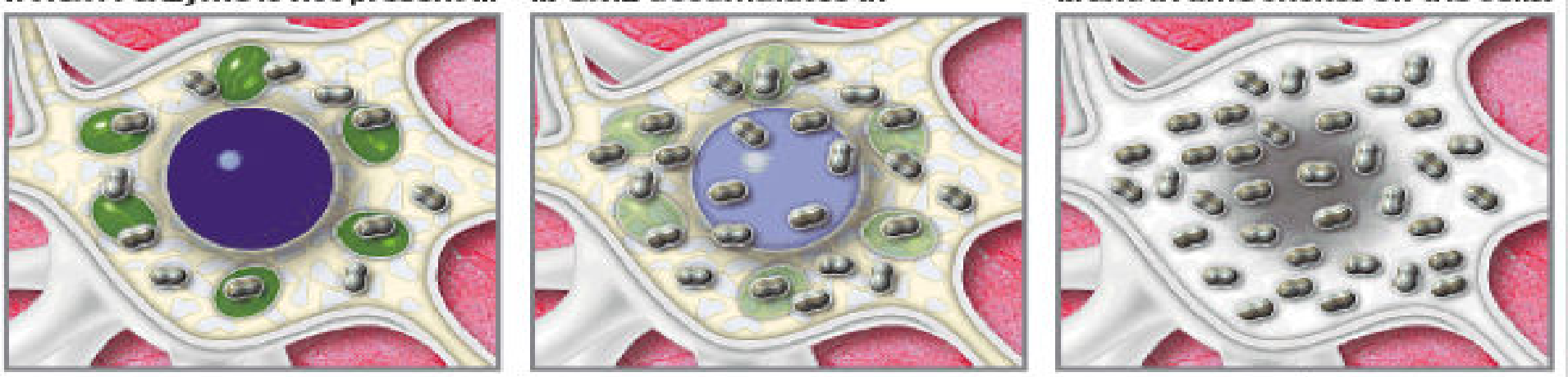
GM2 enters the lysosome ... **... where it is engulfed ...** **... and digested by the Hex-A.**



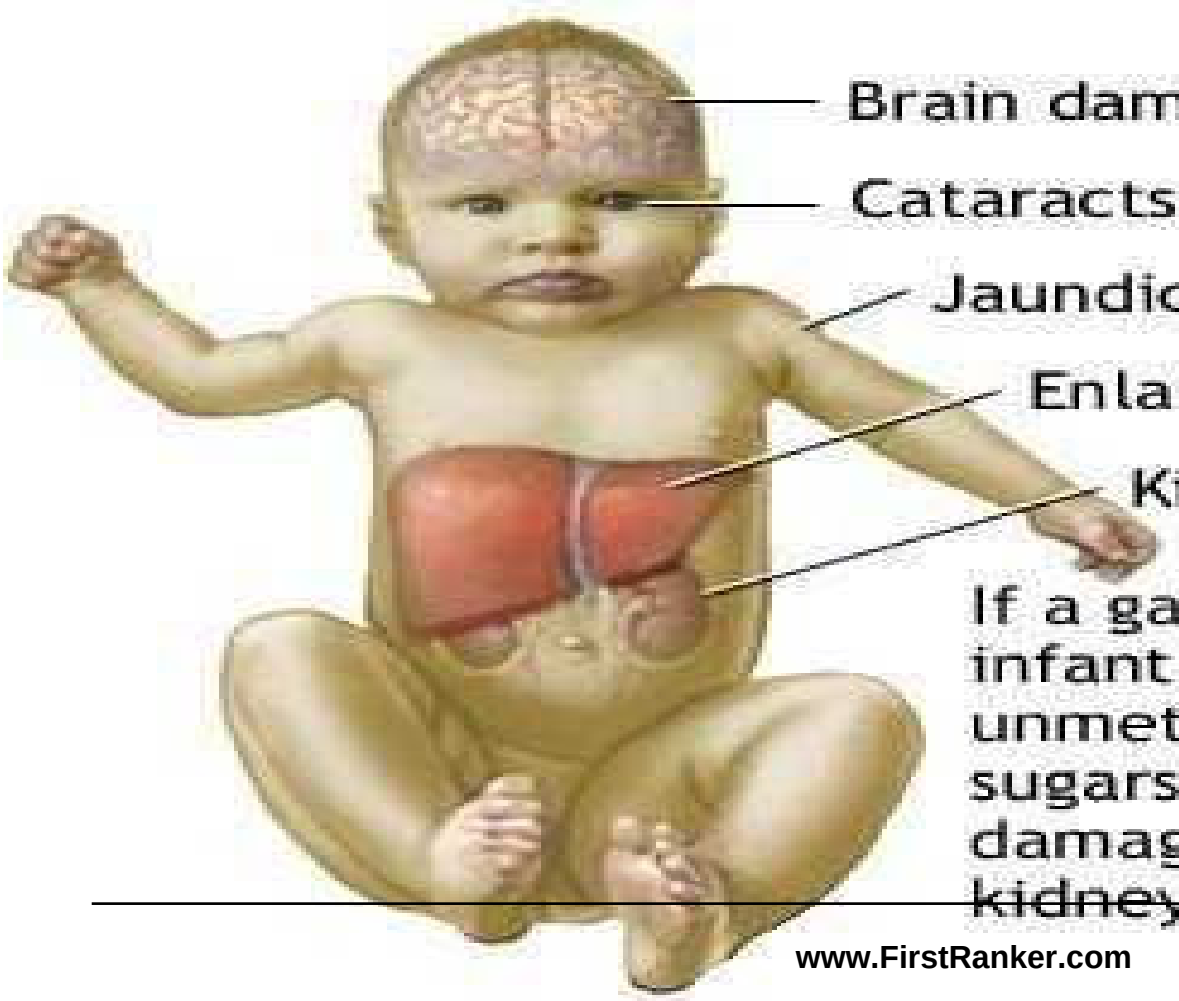
Cells in children with Tay-Sachs disease

Children with Tay-Sachs lack Hex-A, so the GM2 proliferates to such a degree that it eventually kills the cell, gradually shutting down the central nervous system.

If Hex-A enzyme is not present ... **... GM2 accumulates ...** **... and in time chokes off the cells.**



REID BROWN | THE PLAIN DEALER



If a galactosemic infant is given milk, unmetabolized milk sugars build up and damage the liver, eyes, kidneys and brain

WHAT IS KRABBE'S DISEASE?

- Krabbe's disease (globoid cell leukodystrophy) is a degenerative disorder that affects the nervous system.
- It's hereditary autosomal recessive disease.
- Occurrence of 1 in 100,000 newborns.
- It affects the myelin sheath of the nervous system.
- Knud Haraldsen Krabbe.

HOW IS KRABBE DISEASE CAUSED?

- Mutations in the GALC gene, causing deficiency of enzyme galactosylceramidase.
- This effects the growth and maintenance of myelin, which causes severe degeneration of motor skills.

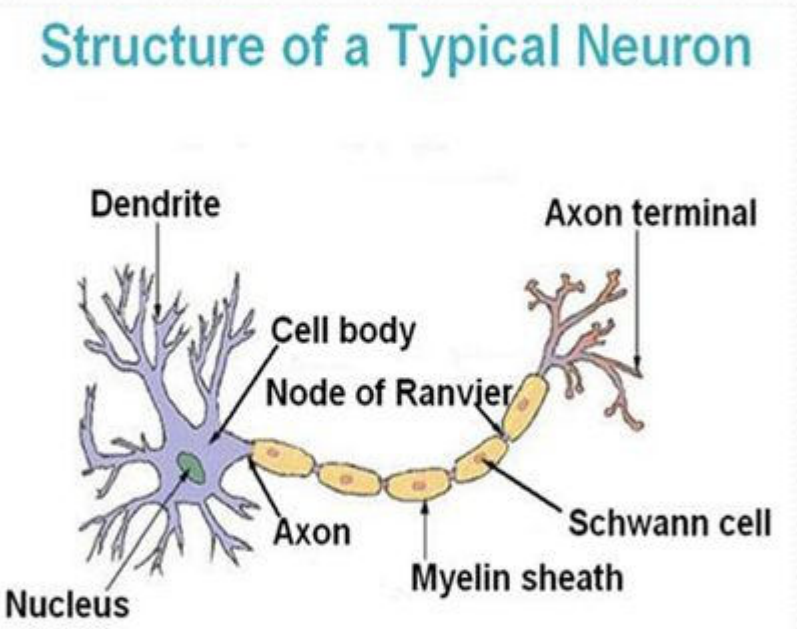
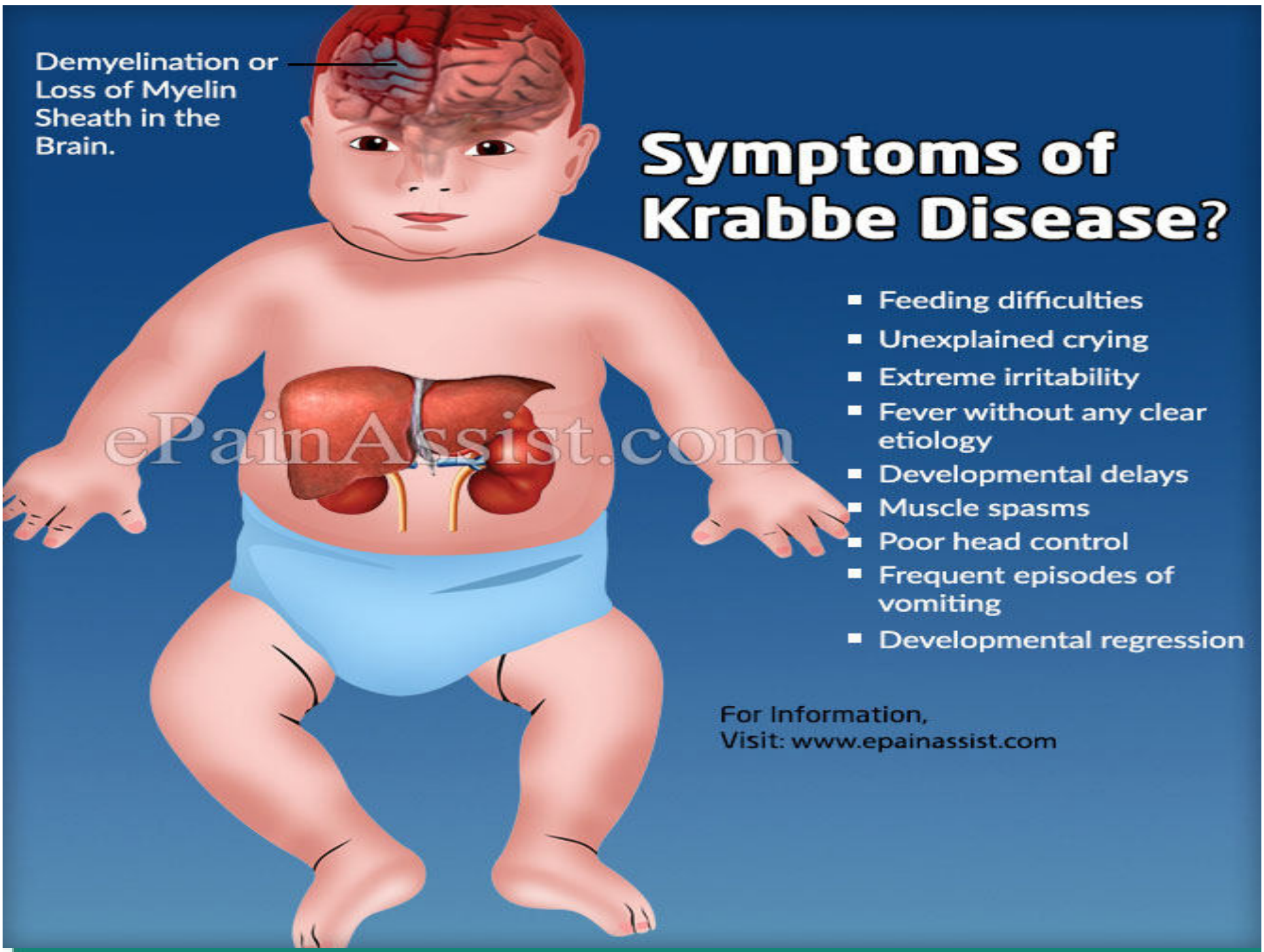


Fig.1 – www[1].

- Krabbe disease is a leukodystrophy.



Farber Disease

- Autosomal recessive disorder
- Results from deficiency of lyzozomal enzyme ceramidase & the accumulation of ceramide in various tissues especially joints.
- Symptoms begin as early as 1st year of life with painful jt. swelling & nodule formation.
- It's diagnosis should be suspected in patients who have nodule formation over jt's. but no other finding of RA.

Farber's Disease

Cause

- Deficiency of the enzyme called ceramidase
- Resulting in accumulation of ceramide in joints , tissues and central nervous system

Clinical features

- Dyspnea
- Dysphagia
- Vomiting
- Arthritis
- Horseness
- Xenthemas

Treatment

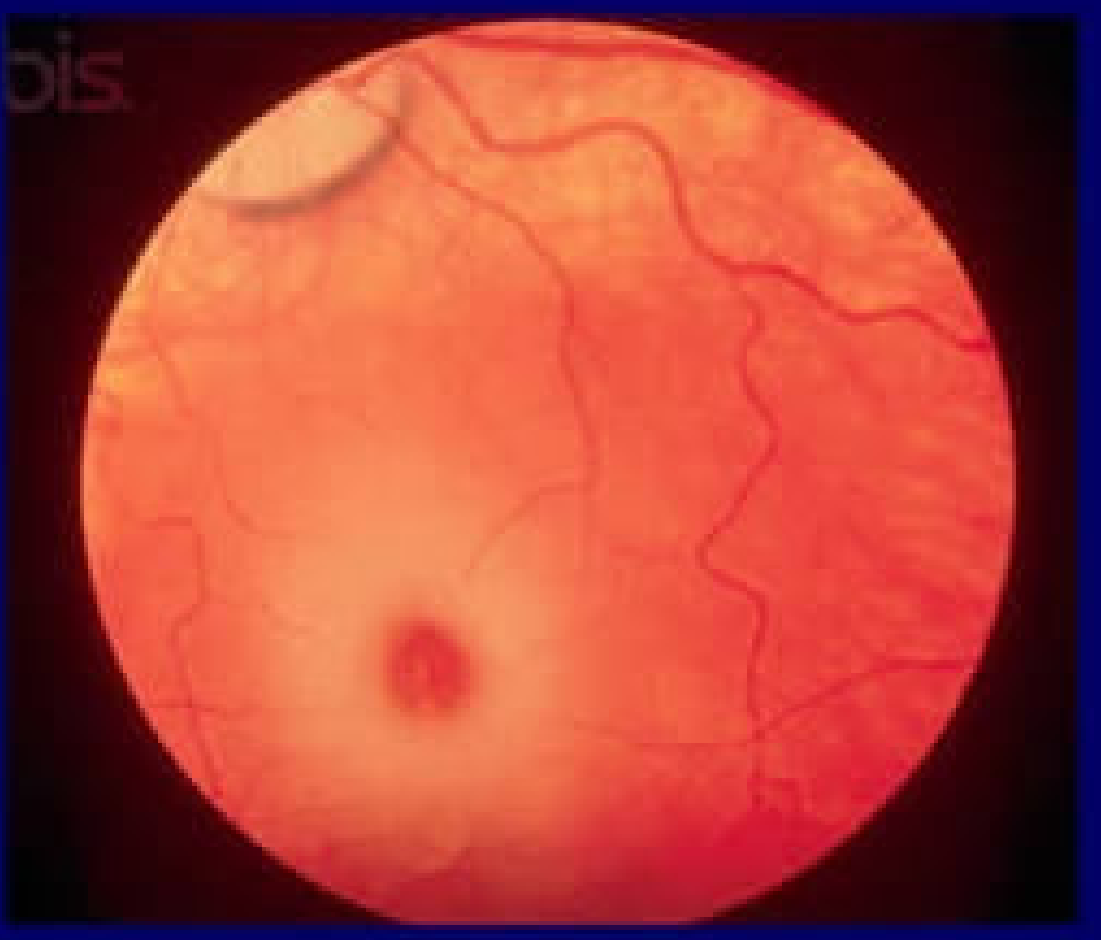
- no specific treatment for Farber's disease
- Most children with the disease die by age 2
- Joint contractures

Farber's Lipogranulomatosis

Lysosomal storage disease: ocular features

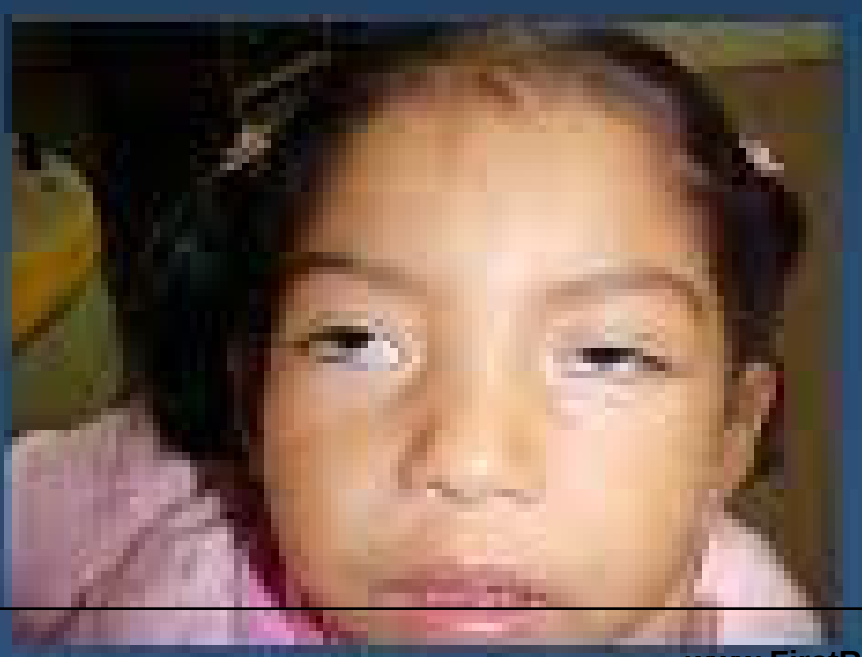
Lysosomal lipid storage disorders associated with cherry red macula:

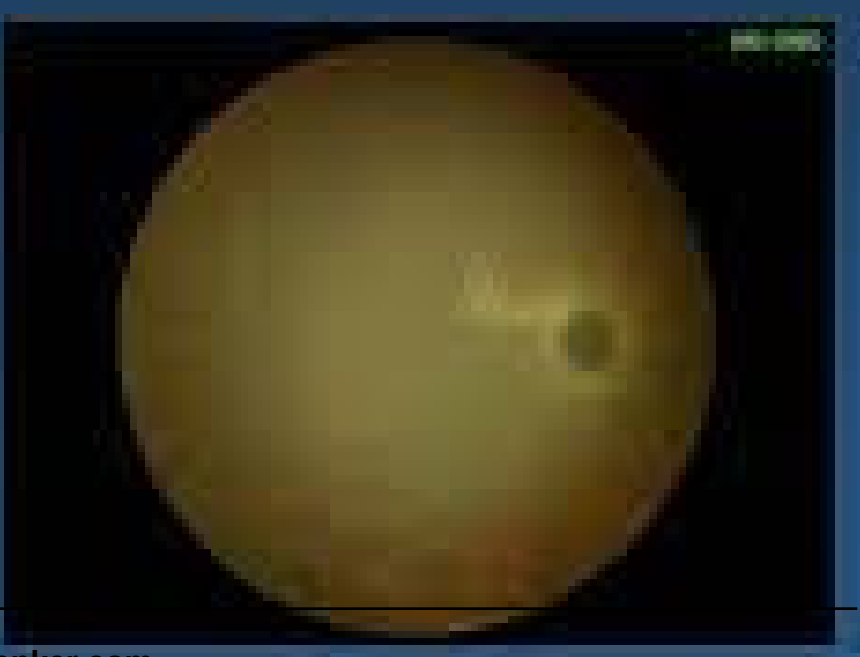
- Niemann-Pick A
- GM1 gangliosidosis
- Tay-Sachs disease
- Sandhoff disease
- Farber lipogranulomatosis
- Sialidosis



Sandhoff Disease

- Deficiency of both Hexosaminidase A and B.
- Clinical course is very similar to Tay-Sachs





Sialidosis

- AR
- Accumulation of a **sialic acid oligosaccharide** complex secondary to a deficiency in the lysosomal enzyme **neuraminidase**
- Urinary excretion of sialic acid containing oligosaccharides is increased
- Sialydosis type 1
  - Cherry red spot-myoclonus syndrome
  - Visual deterioration
  - Myoclonus
- Sialydosis type 2
  - Infantile
  - Juvenile
  - Cherry red spots, myoclonus, somatic involvement, coarse facial features
  - Lymphocytes show vacuoles in the cytoplasm
  - Liver biopsy
    - Cytoplasmic vacuoles

CASE REPORT 1

A 19 months old child from Rajasthan came with a history of apparently normal growth and development upto 5 months of age. There after the child developed gradual distension of abdomen, unable to hold neck and unable to recognized her parents.

On examination :

- Liver and spleen were enlarged by 10 and 12 cm respectively.
- Blood examination showed reduced haemoglobin.
- All the deep reflexes were diminished and there was hypotonia in all four limbs.
- Bone marrow examination showed infiltration of foamy cells in macrophages.

➢ **Fundus examination** revealed cherry red spot in the macula of both eyes. Hence, this characteristic is seen in many types of storage diseases so this cannot simply confirm the presence of Niemann-Pick.

Expected Diseases according to above information- 1) Gaucher Disease
2) Tay Sachs Disease
3) Hurler's syndrome
4)Niemann-pick disease

➢ **Further Enzymatic and gene studies** revealed the presence of Niemann-Pick Type A disease. In gene study, gene expression was studied.

CASE REPORT 2

An Afghan girl was growing normally till 1 year of age. Later on, hepatomegaly with developmental delay was observed. Parents also noticed unexplained frequent falls without any sign of seizure.

She was the 5th sibling with one elder sister dying of respiratory failure and hepatosplenomegaly at the age of 5 years. Two elder brothers and one sister were normally growing till that date.

On examination: At the age of 4 yrs, she had

- neurological regression
- hypotonia
- facial dyskinesia
- Bone-marrow examination revealed presence of storage cells

Expected Diseases related to these symptoms- 1) Gaucher Disease
2) Niemann-Pick Disease

Similarities and Dissimilarities Of Cerebrosides and Gangliosides

Similarities Of Cerebrosides and Gangliosides

- **Both are Glycolipids** containing Carbohydrate moieties.
- Both contain S**phingosine/Ceramide** in their structures.
- Both are richly present in **Nervous tissue.**

Dissimilarities Of Cerebroside and Gangliosides.

S.No	Cerebrosides	Gangliosides
1	**Structurally Simple** Ceramide linked with Glucose or Galactose.	**Structurally complex** Ceramide linked to Glucose, Galactose , NAGalactosamine ,and NANA
2	Occur in **White matter** of brain and **Myelin Sheaths.**	Occur in **Grey matter** of brain and **Ganglions**.
3	Types : Glucocerebrosides Galactocerebrosides	Types : GM1,GM2, GM3,GM4
4	Function : Conducts nerve impulse	Transfer Biogenic Amines
5	Related Disorder: **Gauchers Disease**	Related Disorder: **Tay Sachs Disease**