Hereditary disorders of carbohydrate metabolism

Disorders of metabolism of monosaccharides („small molecules“)

Fructose

Galactose

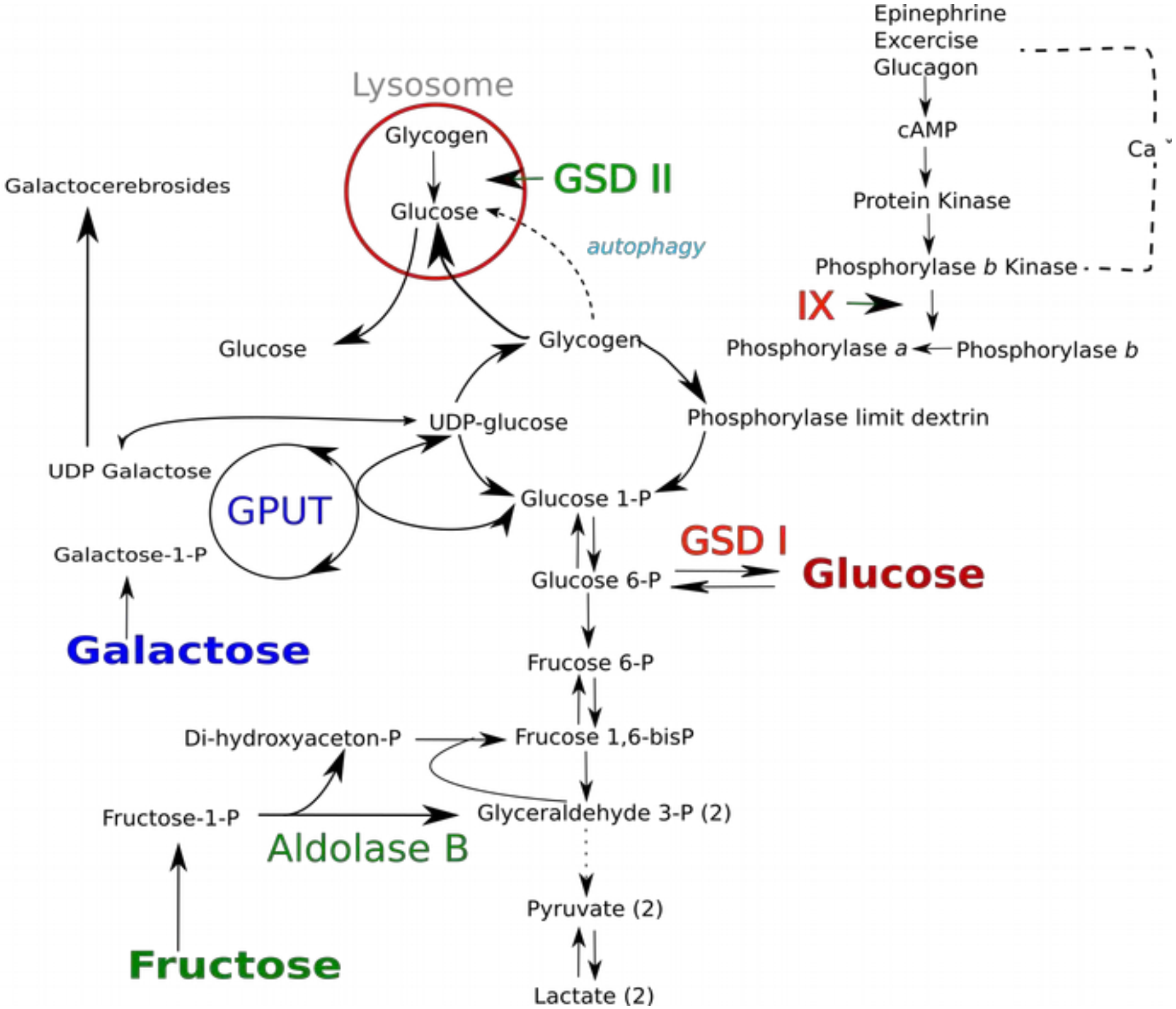
Glucose

Disorders of metabolism of polysaccharides („ large molecules“)

Glycogen storage disorders (also lack of product)

Disorders of glycosylation (proteins and lipids ...)

product deficiency


Epinephrine
Excercise
Glucagon
cAMP
Ca
Protein Kinase
Phosphorylase b Kinase
IX
Phosphorylase a
Phosphorylase b
Lysosome
Glycogen
GSD II
Glucose
autophagy
Galactocerebrosides
Glucose
Glycogen
UDP-glucose
Phosphorylase limit dextrin
UDP Galactose
GPUT
Glucose 1-P
GSD I
Glucose
Galactose-1-P
Glucose 6-P
Galactose
Frucose 6-P
Di-hydroxyaceton-P
Frucose 1,6-bisP
Fructose-1-P
Glyceraldehyde 3-P (2)
Aldolase B
Pyruvate (2)
Fructose
Lactate (2)

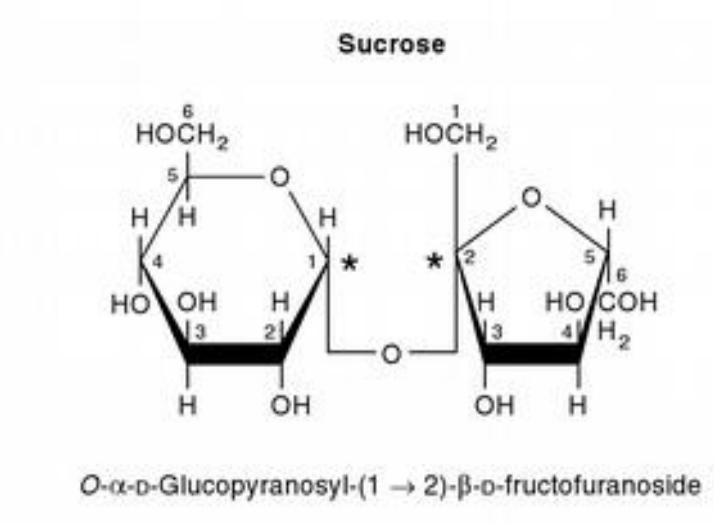
Inherited disorders of fructose metabolism

Fructose

Fructose (β-D-fructofuranose)

Honey, vegetables and fruits

Disaccharide sucrose containes a fructose moiety



sorbitol – sugar alcohol, derived from glucose, abundant in fruits. Sorbitol dehydrogenase converts sorbitol to fructose - a source of fructose.

GLUT5, GLUT-2 – glucose transporter isoforms responsible for fructose transport in the small intestine

Fructose is transported into liver cells mainly by GLUT-2

Inherited disorders of fructose metabolism

Daily intake of fructose in Western diets: 100 g

Metabolised in liver, kidney, intestine

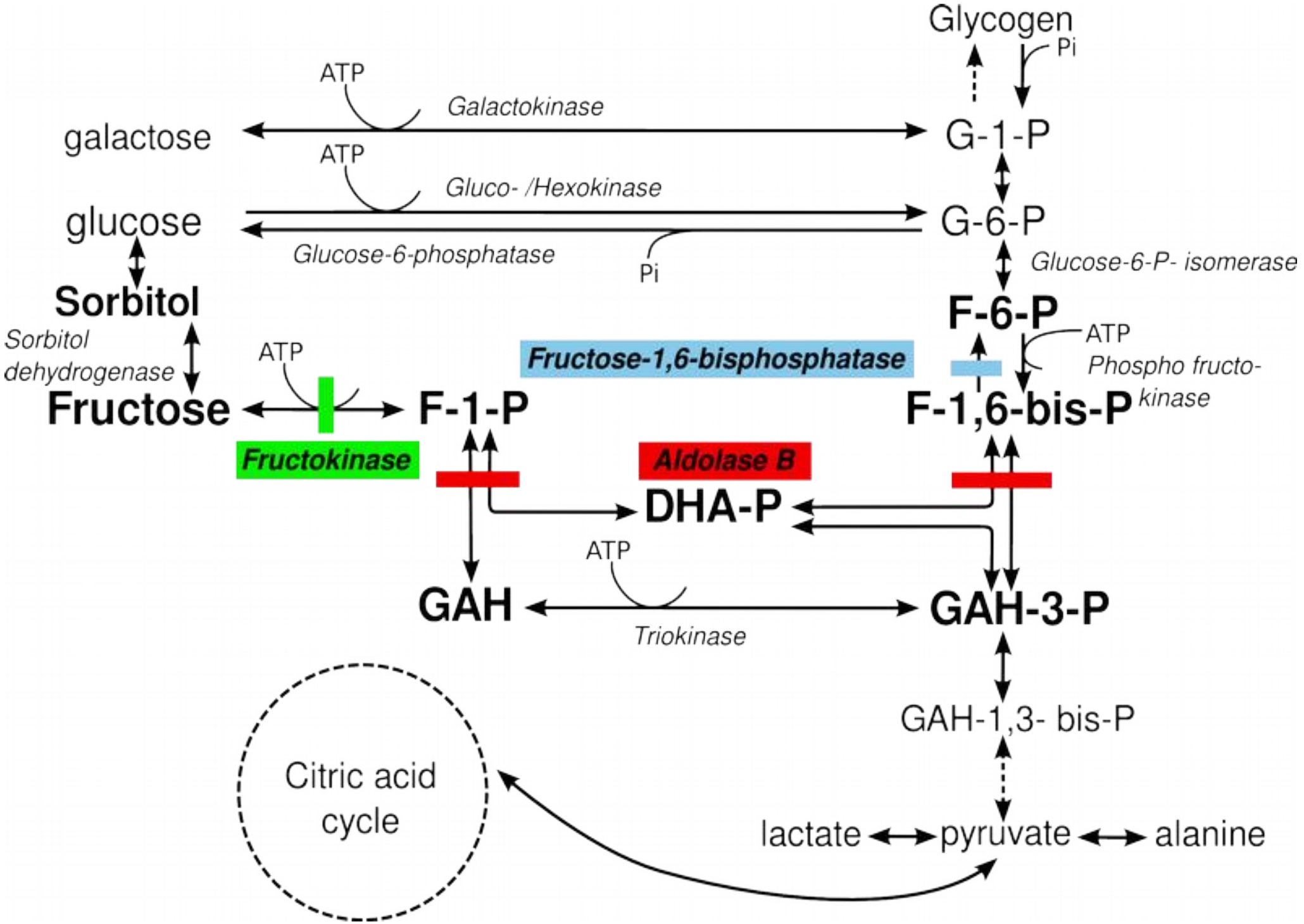
Intravenous fructose in high-doses is toxic: hyperuricemia, hyperlactacidemia, utrastructural changes in the liver.

Essential fructosuria

Hereditary fructose intolerance (aldolase B deficiency)

Hereditary fructose 1,6-bisphosphatase deficiency

Autosomal recessive disorders


Glycogen
Pi
ATP
Galactokinase
galactose
G-1-P
ATP
Gluco- /Hexokinase
glucose
G-6-P
Glucose-6-phosphatase
Pi
Glucose-6-P- isomerase
Sorbitol
F-6-P
Sorbitol dehydrogenase
ATP
Fructose-1,6-bisphosphatase
ATP
Phospho fructo-kinase
Fructose
F-1-P
F-1,6-bis-P
kinase
Fructokinase
Aldolase B
DHA-P
ATP
GAH
GAH-3-P
Triokinase
GAH-1,3- bis-P
Citric acid cycle
lactate
pyruvate
alanine

Toxicity of fructose

Rapid accumulation of fructose -1-phosphate

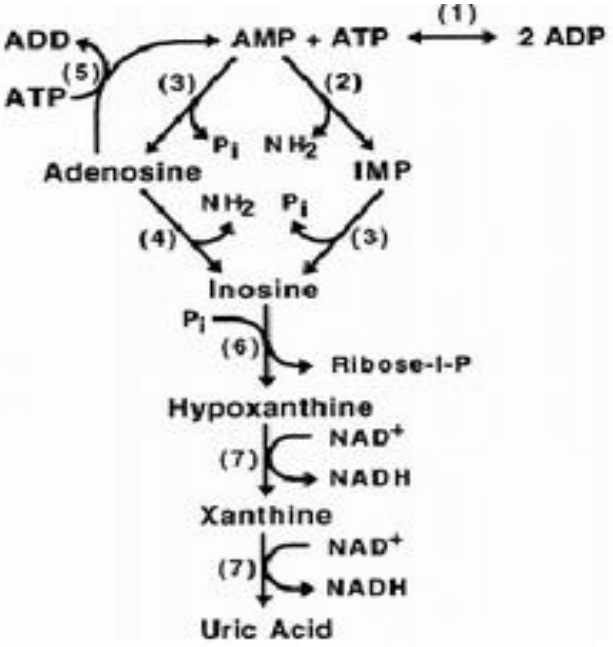
The utilization of F-1-P is limited by **triokinase**

Depletion af ATP

Hyperuricemia
Hyperuricemic effect of fructose results from the **degradation of adenine nucleotides (ATP)**.

Adenine dinucleotides → → → uric acid

Increase of lactate concentration



Hereditary fructose intolerance

Deficiency of **fructoaldolase B** of the liver, kidney cortex (isoenzymes A,B,C)

Severe **hypoglycemia** triggered by ingestion of fructose

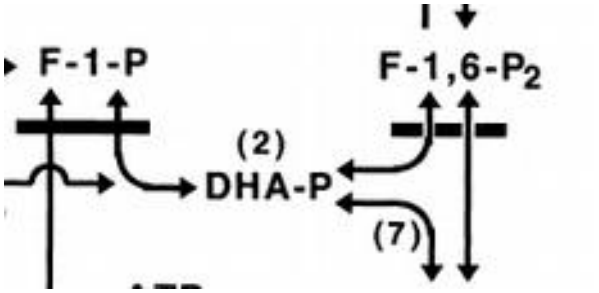
Prolonged fructose intake : poor feeding, vomiting, hepatomegaly jaundice hemorrage, proximal tubular renal syndrome, hepatic failure, death

Strong distaste for fructose-containing foods, may lead to psychiatric referrals

Fructose -1- phosphate inhibits gluconeogenesis (aldolase A), also glycogen phosphorylase

Patients are symptom-free on fructose-free diet

Diagnostics: (i.v. fructose tolerance test – abandoned), DNA analysis.



Hereditary fructose 1,6-bisphosphatase deficiency

Fructose 1,6-bisphosphatase catalyzes **the irreversible splitting of fructose 1,6-bisphosphate** into fructose 6-phosphate and inorganic phosphate (P)

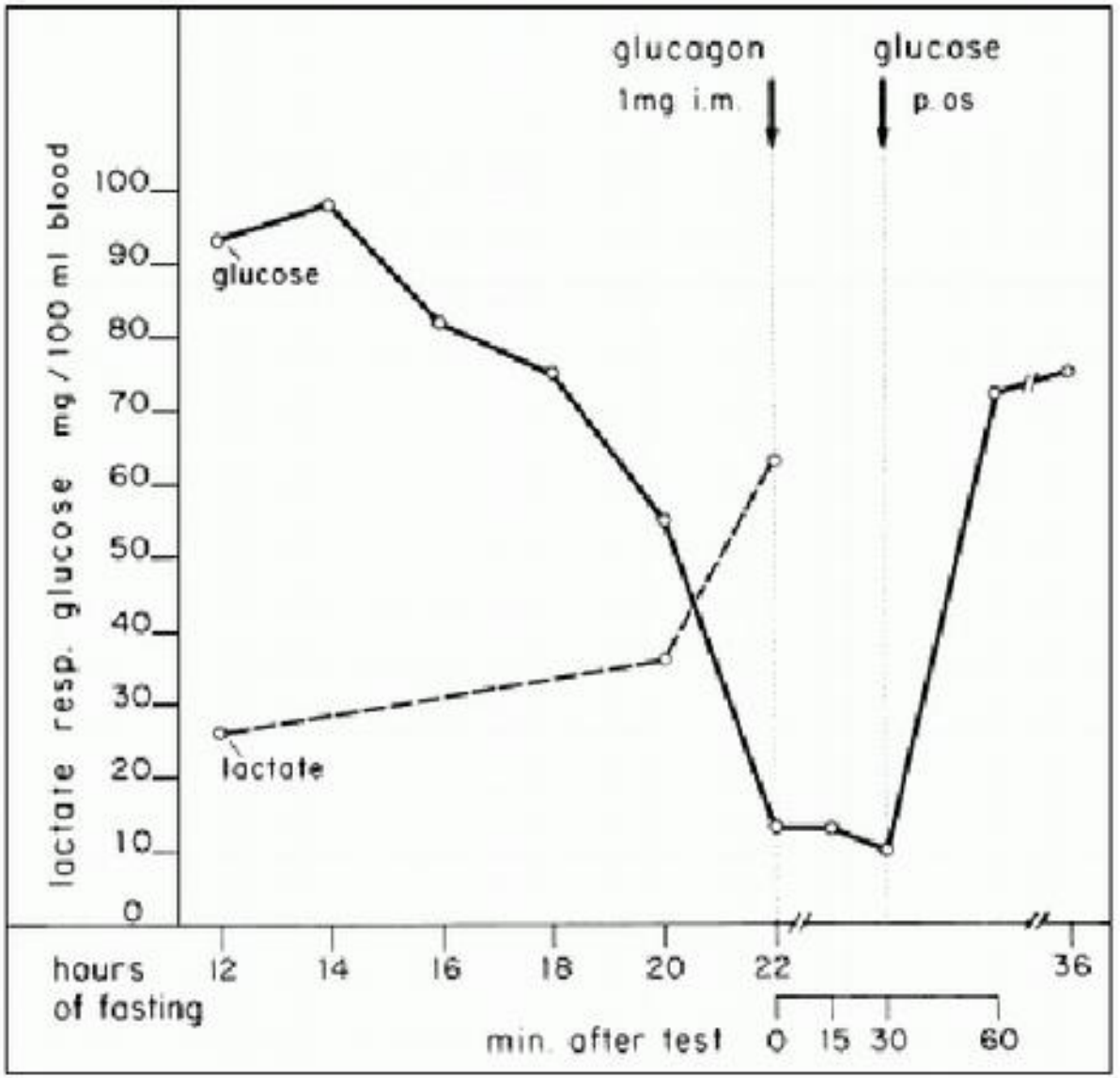
Episodes of hyperventilation, apnea, hypoglycemia, ketosis and lactic acidosis, with potentially lethal course

Episodes often triggered by fasting or infection, also by ingestion of larger amount of fructose. There may be chronic mild hyperlactacidemia

Aversion to sweets does not develop, tolerance to fasting improves with age

Autosomal recessive disorder

Severe disorder of <u>gluconeogenesis</u>, gluconeogenetic precursors (amino-acids, lactate, ketones) accumulate after depletion glycogen in the patients



Prolonged fasting in a 17-month-old boy (T.M.) with fructose 1,6-bisphosphatase deficiency. (Reprinted with permission from Baerlocher K, Gitzelmann R, Nüssli R, Dumermuth G. Helv Paediatr Acta 26:489, 1971. 338)

Essential fructosuria

Deficiency of liver fructokinase

Asymptomatic metabolic anomaly - benign

Hyperfructosemia and hyperfructosuria – important for differential diagnosis of other fructose metabolism disorders

Hereditary disorders of glucose transport

Glucose transport

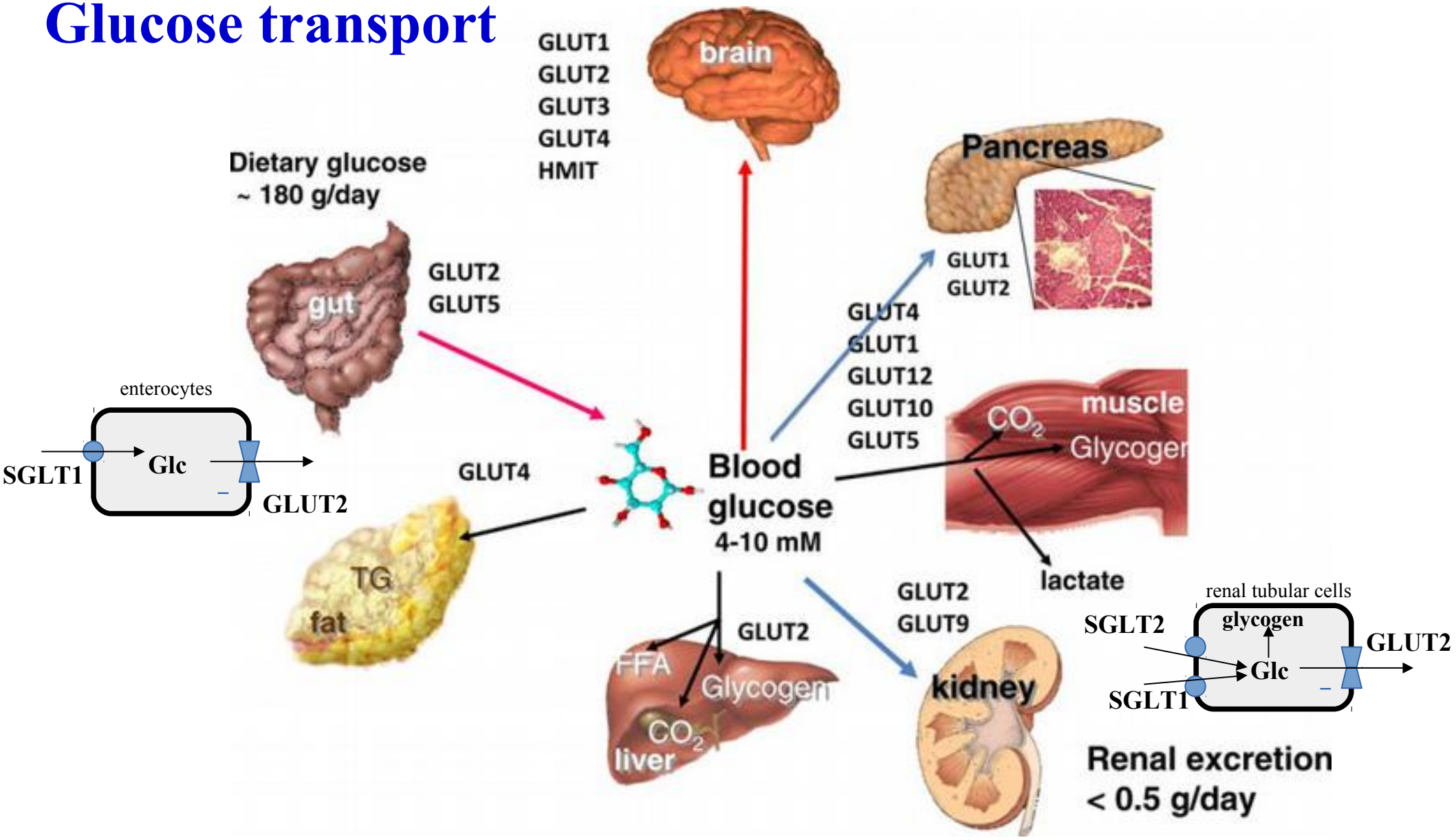
Hydrophillic glucose molecule does not cross easily lipohillic cellular membranes -> transporters are necessary to carry glucose across membranes

2 types of transporters:

a) **Sodium-dependent glucose transporters (SGLTs**, 'active' tranporters encoded by SLC5 family members) – couple sugar transport to sodium electrochemical gradient -> can transport against concentration gradient

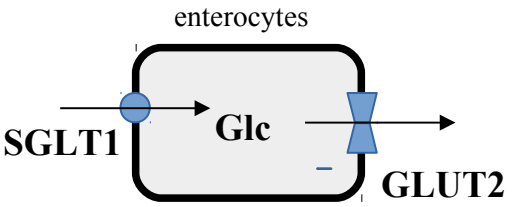
b) Facilitative glucose transporters (GLUTs, uniporter systems, 'passive' transporters) – transport glucose only along an existing gradient.

Glucose transport



Muecker and Thorens: Mol Aspects Med. 2013 Apr-Jun; 34(0): 121–138.

SGLT1 deficiency : Congenital Glucose/Galactose malabsorption



SGLT1 – sodium dependent transporter in the brush border of enterocytes
Promotes postprandial expression of GLUT2

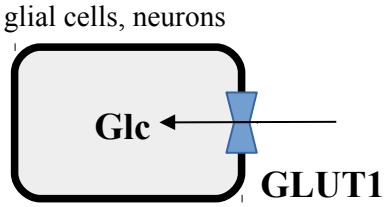
Rare, autosomal recessive disorder, no polyhydramnion in pregnancy

Profuse watery diarrhoea and bloating in the first days after birth
Severe hypertonic dehydration, often with fever
Typically, gastrointestinal infection is suspected, with **repeated failing attempts to switch patients from parenteral to oral feeds**
Chronic dehydration may lead to nephrolithiasis and nephrocalcinosis in some cases

Acidic stool pH, reducing substances in stools, mild intermitent glucosuria.
Glucose, galactose but not fructose provoke symptoms

Treatment : exclusion of glucose and galactose from the diet
Formula with fructose as the only saccharide

GLUT1 deficiency



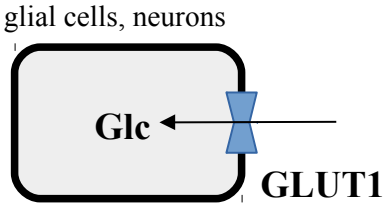
GLUT1 ***(SLC2A1)*** – membrane glucose facilitating transporter
GLUT1 deficiency results in **low CSF concentration (hypoglycorrhachia)**

Classic form: **early onset epileptic encephalopathy** developing during the first year of life
Various types and frequency of seizures:
Often refractory to anticonvulsants, sometimes aggravated by fasting
Developmental delay, complex motor disease, in most severe cases microcephaly

Non-classic form:
Complex movement disorder without epilepsy : spastic-atactic gait, action limb dystonia. chorea, cerebellar action tremor, myoclonus
Non-epileptic paroxysmal events of ataxia, weakness, parkinsonism, alternating hemiplegia, nonkinesogenic dystonia

GLUT1 is expressed in erythrocytes: exercise-induced enegy deficit may lead to haemolytic anemia

GLUT1 deficiency - continued



Treatment :

Ketone bodies are alternative fuel for the brain

Ketogenic', high-fat, low carbohydrate diets may restore brain energy metabolism (calories from fat/non-fat sources : 3/1 ... 4/1)

May control seizures and movement disorders, should be maintained throughout childhood into adolescence

Substances inhibiting GLUT1 should be avoided (anticonvulsants (phenobarbital, chlorahydrate, diazepam), methylxanthines (theophyllin, caffeine), alcohol and green tea.)

Genetics: both autosomal dominant and recessive inheritance described

About 80% of patients heterozygous for a GLUT1 mutation, most often de-novo

Diagnostics:

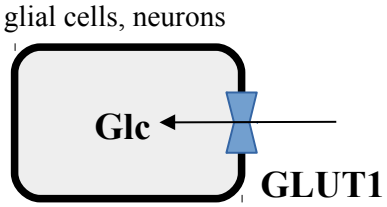
Low CSF glucose : < 2.5 mmol/l (normal >3.3 mmol/l)

Low CSF-to-blood ratio (< 0.5)

Low glucose uptake in erythrocytes, low GLUT1 expression in erythrocytes

GLUT1 mutation analysis

Suspicion for GLUT1 deficiency



- **any form of intractable epilepsy, in particular early onset absence epilepsy;**
- **global developmental delay, particularly in speech;**
- **complex movement disorders;**
- **paroxysmal events triggered by exercise, exertion, or fasting.**

http://www.g1dfoundation.org/youtube/

Hereditary disorders of galactose metabolism

Hereditary disorders of galactose metabolism

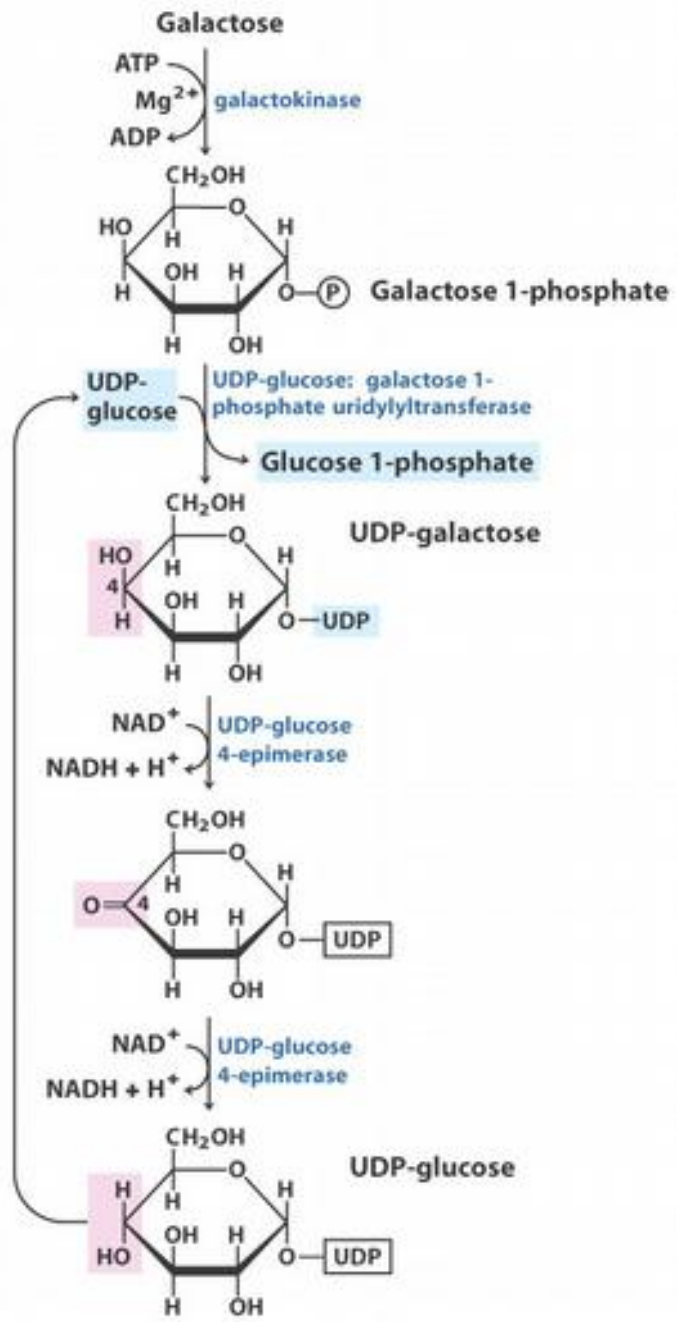
The main sources of galactose are milk and milk products.

Galactose is present as the disaccharide **lactose** (β-D-galactopyranosyl-(1→4)-D-glucose)

Genetic disorders:
Galactokinase

Galactose-1-phosphate uridyltransferase

Uridine diphosphate galactose 4-epimerase.



Classical galactosemia: galactose-1-phosphate uridyltransferase deficiency

In the first weeks of life: poor feeding and weight loss, vomiting, diarrhea, lethargy,and hypotonia.

Severe liver dysfunction, hepatomegaly, icterus (often conjugated hyperbilirubinemia), bleeding diathesis, septicemia, renal tubular syndrome

Cataracts : osmotic oedema of the lens due to galactitol

Elevated galactose, galactitol, galactose-1-phosphate

Late complications
Cognitive defects
Ovarian failure in females
Ataxia, low bone density.

AR, incidence 1:40 000- 60 000,
Neonatal screening for galactose in some countries

Variants (Duarte)

Galactitol formation by nonspecific aldose reductase

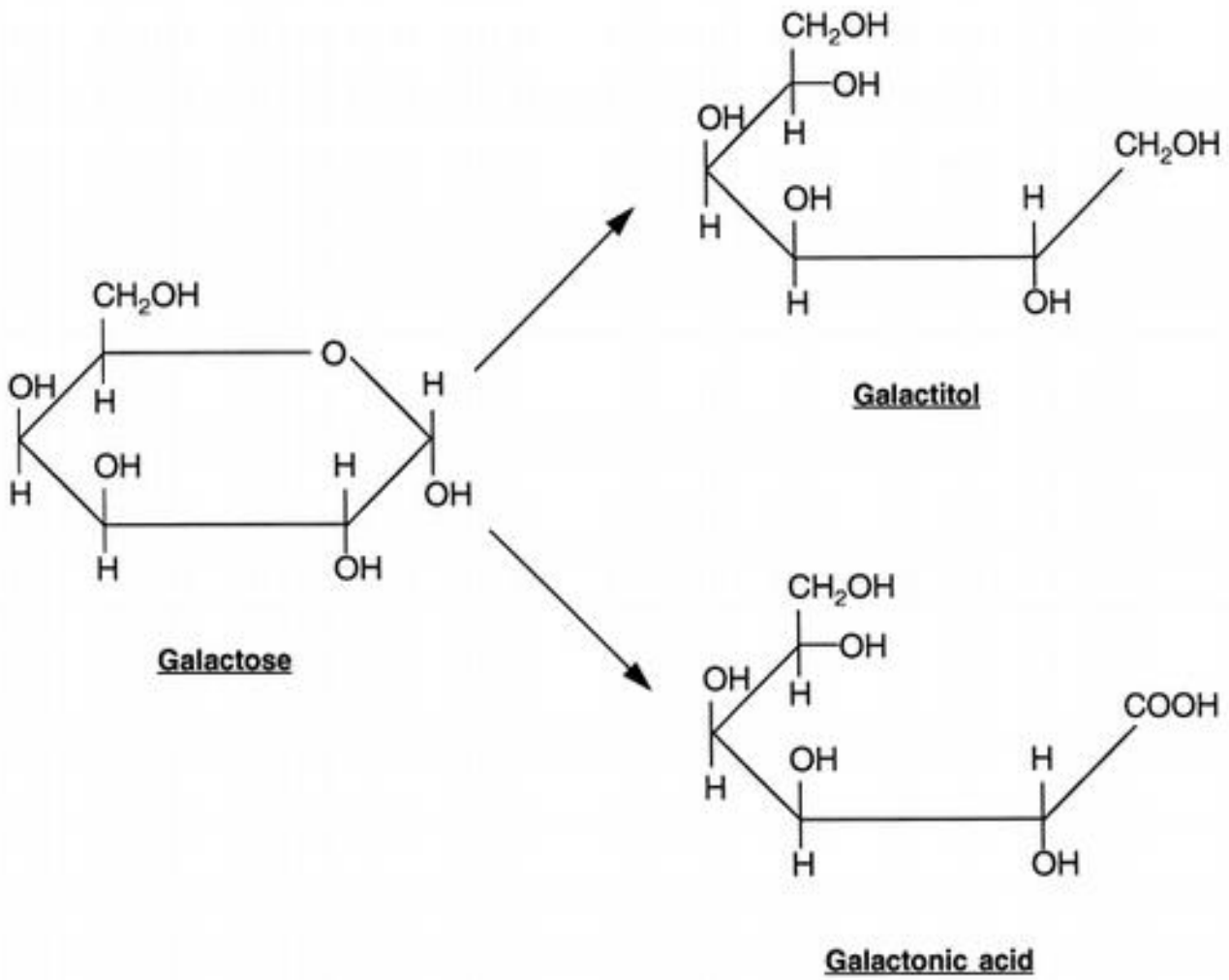


Fig. 72-3 The conversion of galactose to galactitol by a nonspecific aldose reductase and to galactonic acid by aldehyde dehydrogenase.

Brit. J. Ophthal. (1953) 37, 655.

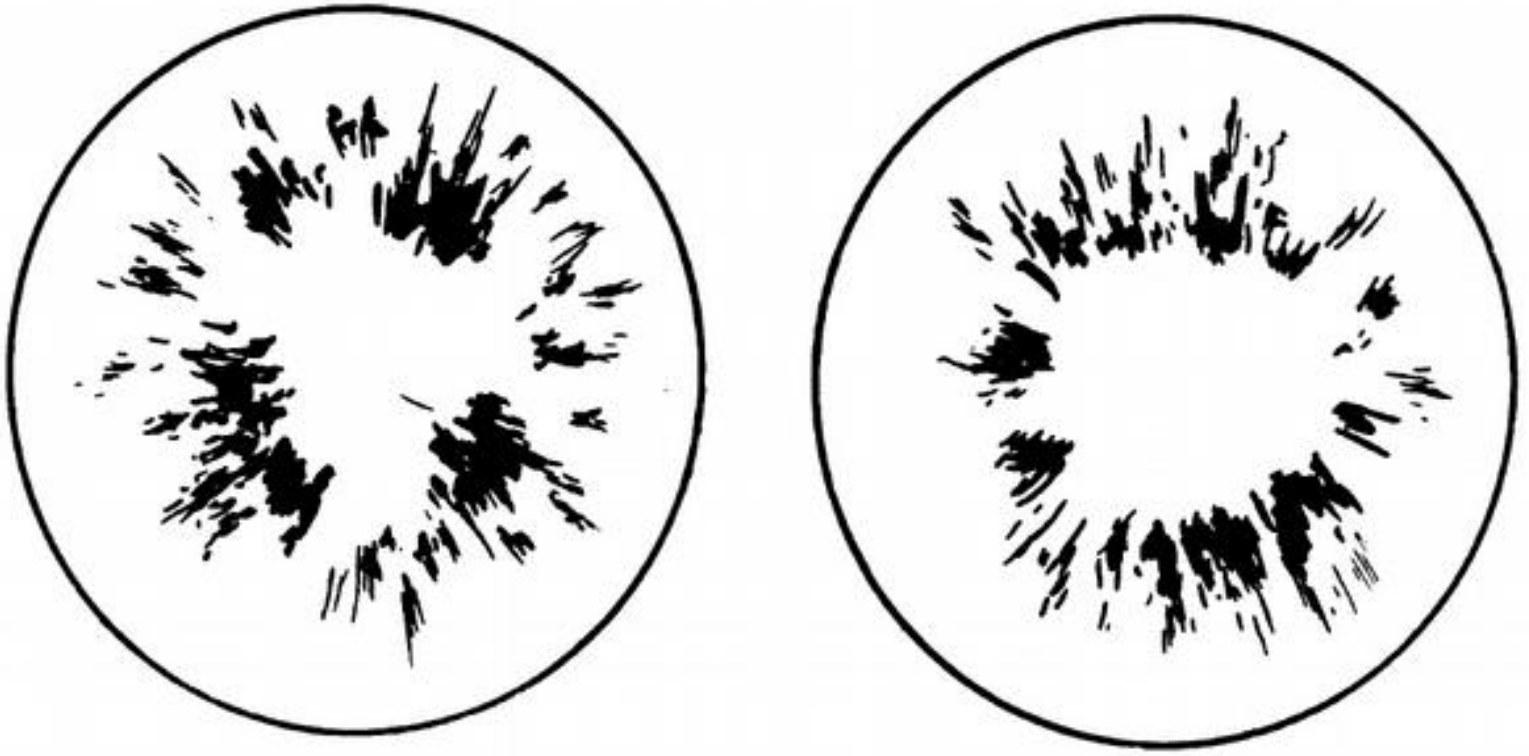
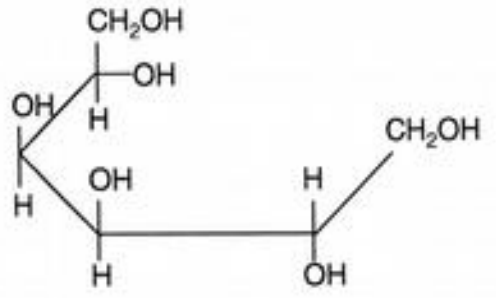


FIGURE.—Ophthalmoscopic appearance of the lenses at 6 weeks.

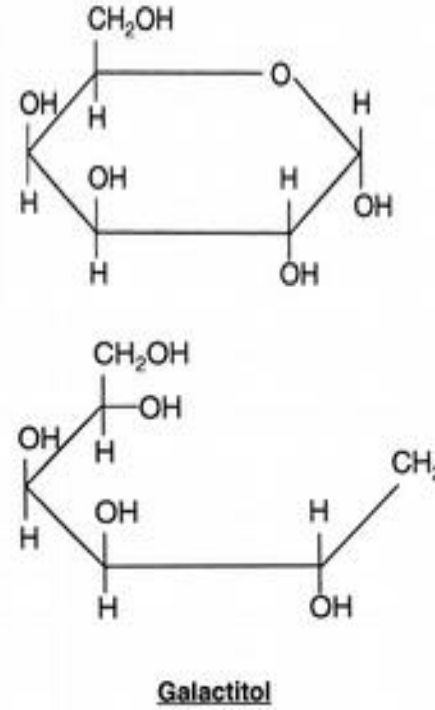
Cataracts in classical galactosemia

Galactitol – osmotic swelling of lens fibres



Galactitol

Galactokinase deficiency



Galactitol

Cataracts - usually bilateral and detectable in the early weeks of life

Pseudotumor cerebri

Galactitol – osmotic oedema of lens

Treatable by galactose-restricted diet, cataract can resolve

Autosomal recesive, rare condition (cca 1:200 000)

Uridine diphosphate galactose 4-epimerase deficiency

Severe form:

Severe deficiency of epimerase activity
Extremely rare

Newborns with vomiting, hepatopathy resembling classical galactosemia.
Mental retardation

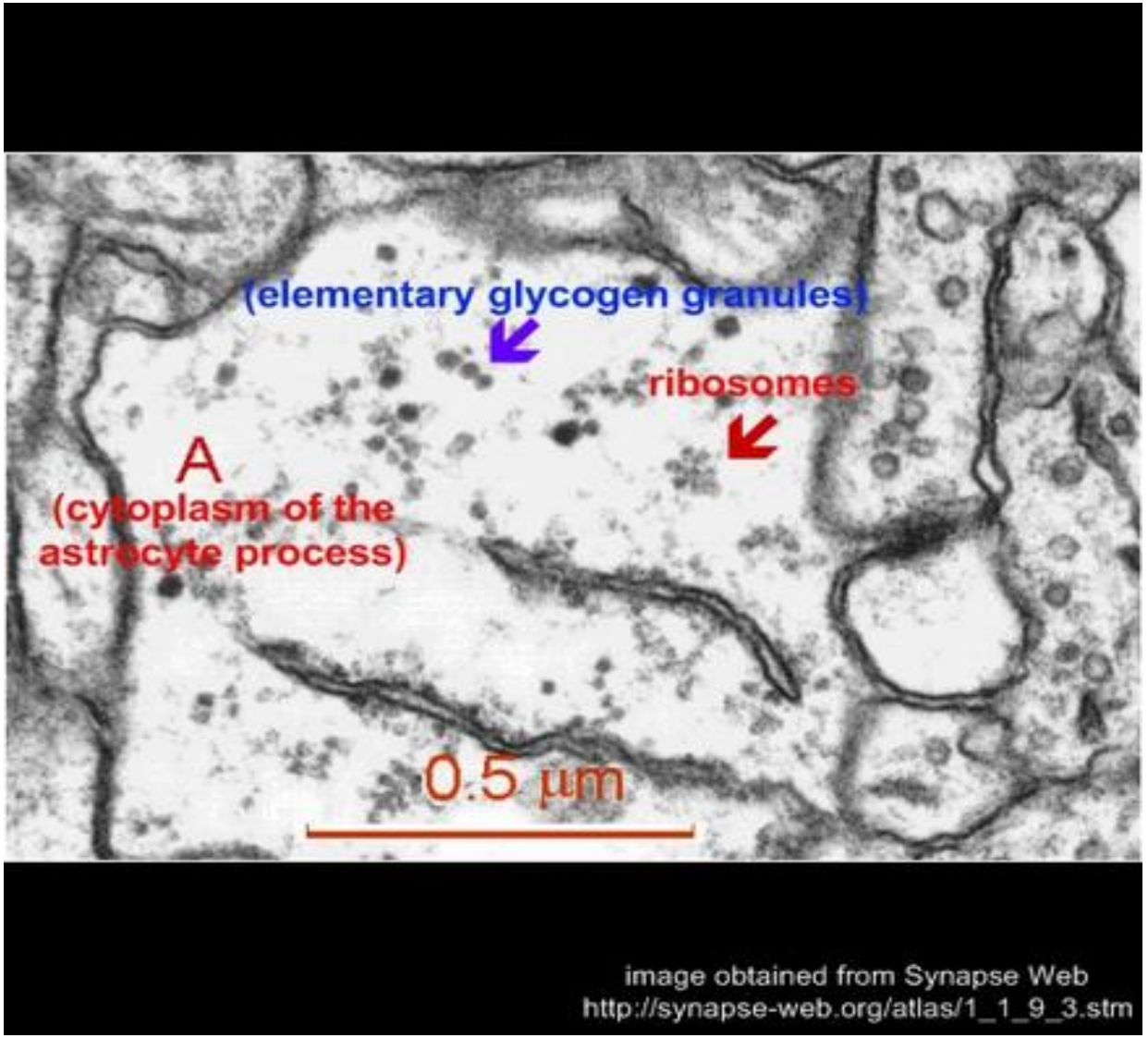
Mild form:

Partial deficiency of epimerase deficiency
In most patients apparently benign condition

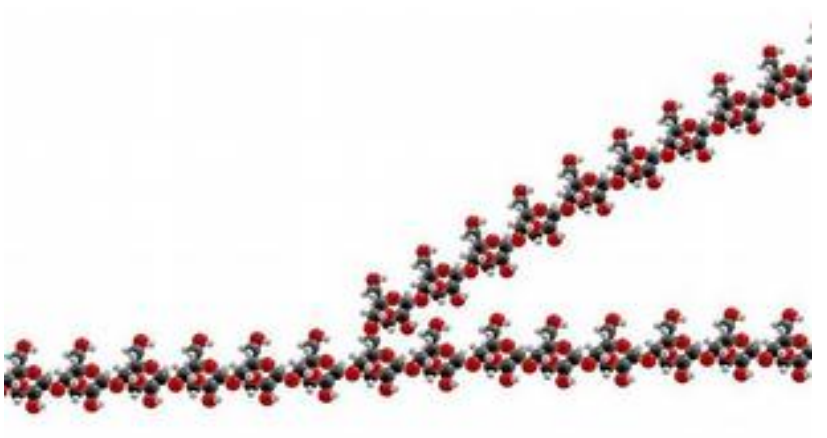
Intermediate forms

Autosomal recessive

Hereditary disorders of glycogen metabolism



Glycogenoses
Glycogen storage disorders



wikipedia

Glucose: primary source of energy for eukaryotic cells

Glycogen: macromolecular storage form of glucose
– branched chain polysacharide composed of glucose units.
Synthesis of glycogen starts at protein „primer“ - **glycogenin**

straight chains **α-1,4 linkages**
branching points **α-1,6 linkages** at intervals of 4-10 glucose residues

Only glucose from liver glycogen is released into circulation**.**

In the muscle: glycogen β particles- up to 60 000 glucose residues, up to 2% of wet weight,
In the liver: α particles „aggregates“ β particles, glycosomes, up to 8% of wet weight, glycogenin 2

Glycogenoses: hereditary enzymopathies that result in storage of abnormal amounts and/or forms of glycogen

Glycogen storage diseases - overview

Hepatic glycogenoses – present principally with ***hypoglycemia, ketosis, hyperlactacidemia, stunted growth*** (GSD I, GSD III, GSD 0) or mainly with ***hepatomegaly*** with hepatopathy(GSD VI, GSD IV, GSD IX)

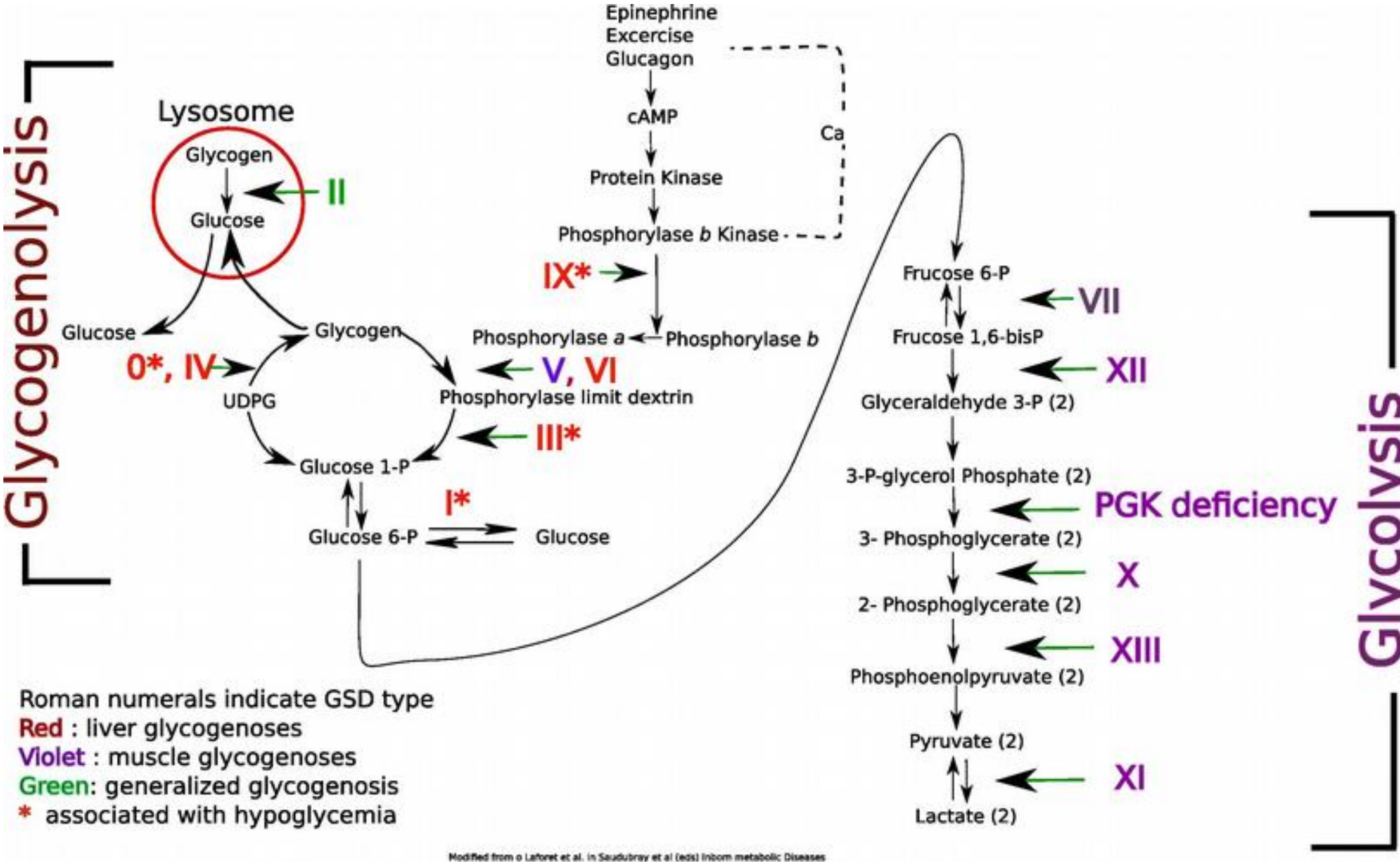
Muscle glycogenoses – present with *exercise intolerance, cramps after exercise, rhabdomyolysis* (GSD V, GSD VII and some very rare deficiencies)

Generalized glycogenosis and GSDs presenting with myopathy and cardiomyopathy
GSD II - deficiency of lysosomal alpha glucosidase , presents with myopathy and cardiomyopathy

(deficiency of LAMP 2 – disorder of autophagy – see lecture on lysosomal diseases)
AMP-activated protein kinase deficiency – presents with adult cardiomyopathy and Wolf-Parkinson-White syndrome

Brain glycogenoses – present with adult neurodegeneration, epilepsy and acumulation of polyglucosan bodies. also Lafora disease

Glycogen metabolism and glycogen storage disorders



Liver glycogenoses

Fasting hypoglycemia, hepatomegaly, growth retardation

5 types - most common is type I (von Gierke disease- glucose-6-phosphatase deficiency)

or hepatomegaly without tendency to hypoglycemia

Muscle glycogenoses

Intolerance of exercise , cramps induced by exercise, rhabromyolysis, the heart is not affected

6 types

Generalized glycogenosis and GSDs presenting with myopathy and cardiomyopathy

Type II (Pompe disease) Lysosomal α-1,4-glucosidase

- lysosomal storage of normal glycogen
- activated AMP protein kinase deficiency: W-P-W syndrome

Brain glycogenoses

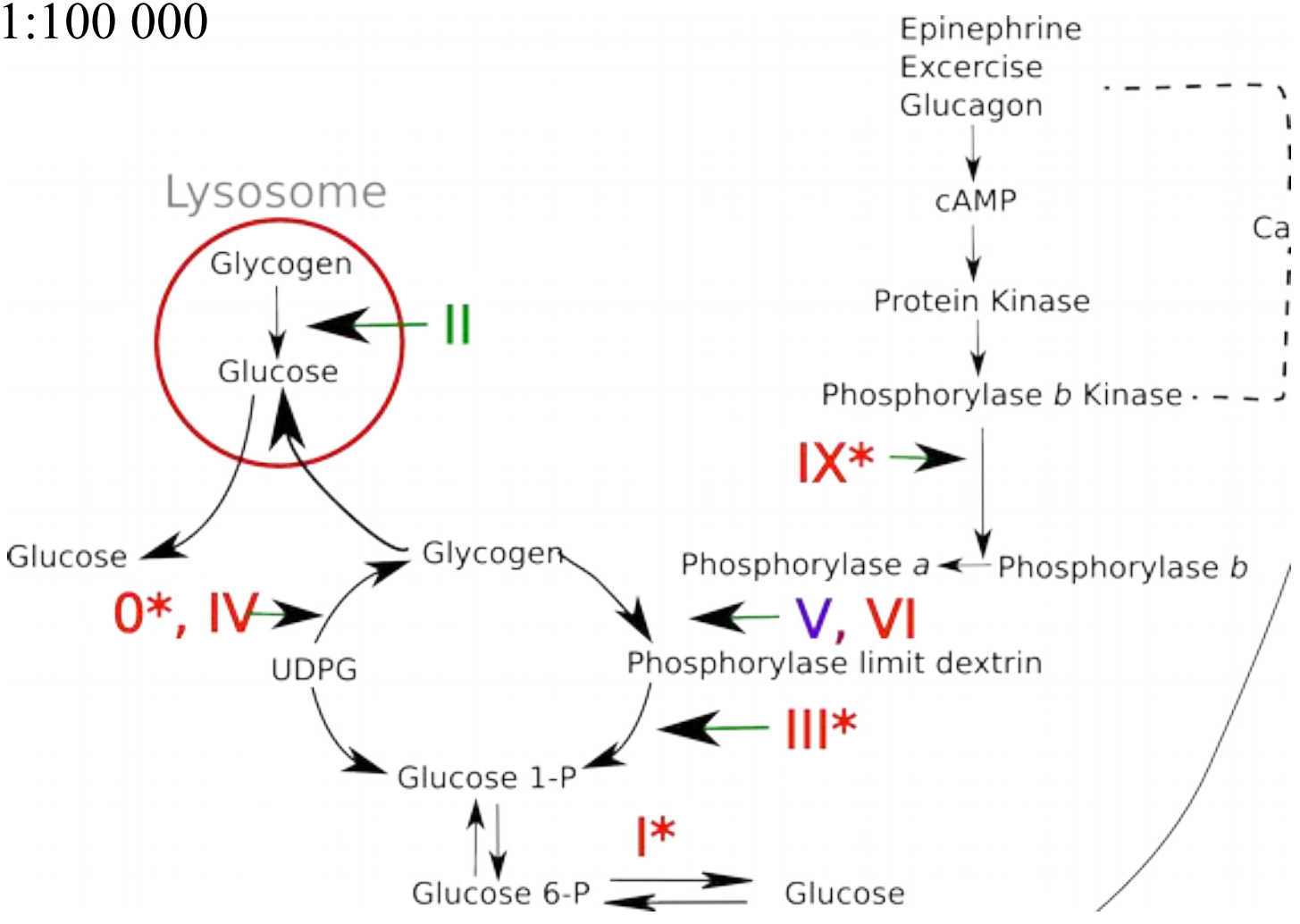
Adult polyglucosan body disease, Lafora disease and other disorders neurodegenerative disease with adult onset, epilepsy,

- accumulation of polyglucosan bodies

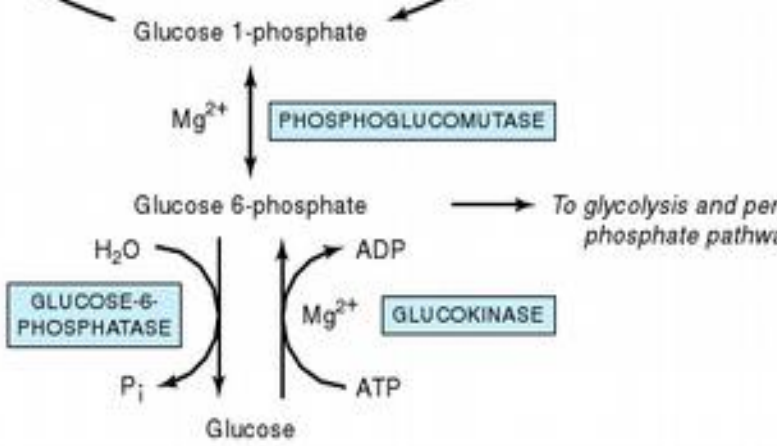
Liver glycogenoses

Fasting hypoglycemia, hepatomegaly, growth retardation
or *hepatomegaly without tendency to hypoglycemia*

prototypical GSD: GSD I? von Gierke disease- glucose-6-phosphatase deficiency), incidence approx. 1:100 000
common: GSD IX: phosphorylase kinase deficiency :
incidence approx. 1:100 000

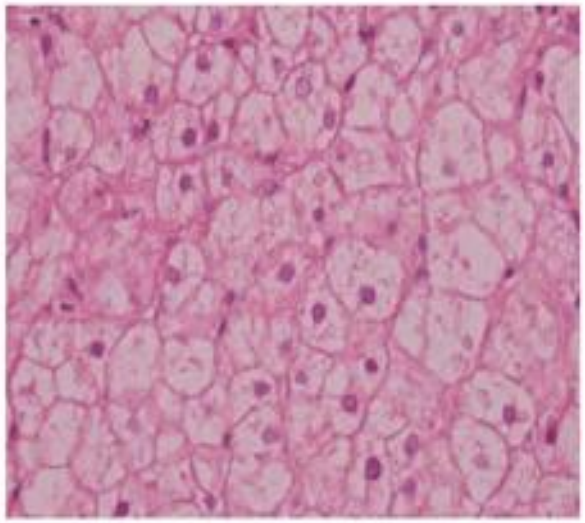


Type I Glycogen Storage Disease (Glucose 6-Phosphatase Deficiency, von Gierke Disease)



Excessive accumulation of glycogen in liver, kidney and intestinal mucosa

Patients usually present in infancy with hepatomegaly and/or hypoglycaemic seizures, hyperlactacidemia after a short fast, episodes of hyperpnoe and irritability



Gout, hyperlipidemia (hypertriglyceridemia), skin xanthomas

Doll-like face, thin extremities, short stature, protuberant abdomen (hepatomegaly), inflammatory bowel disease

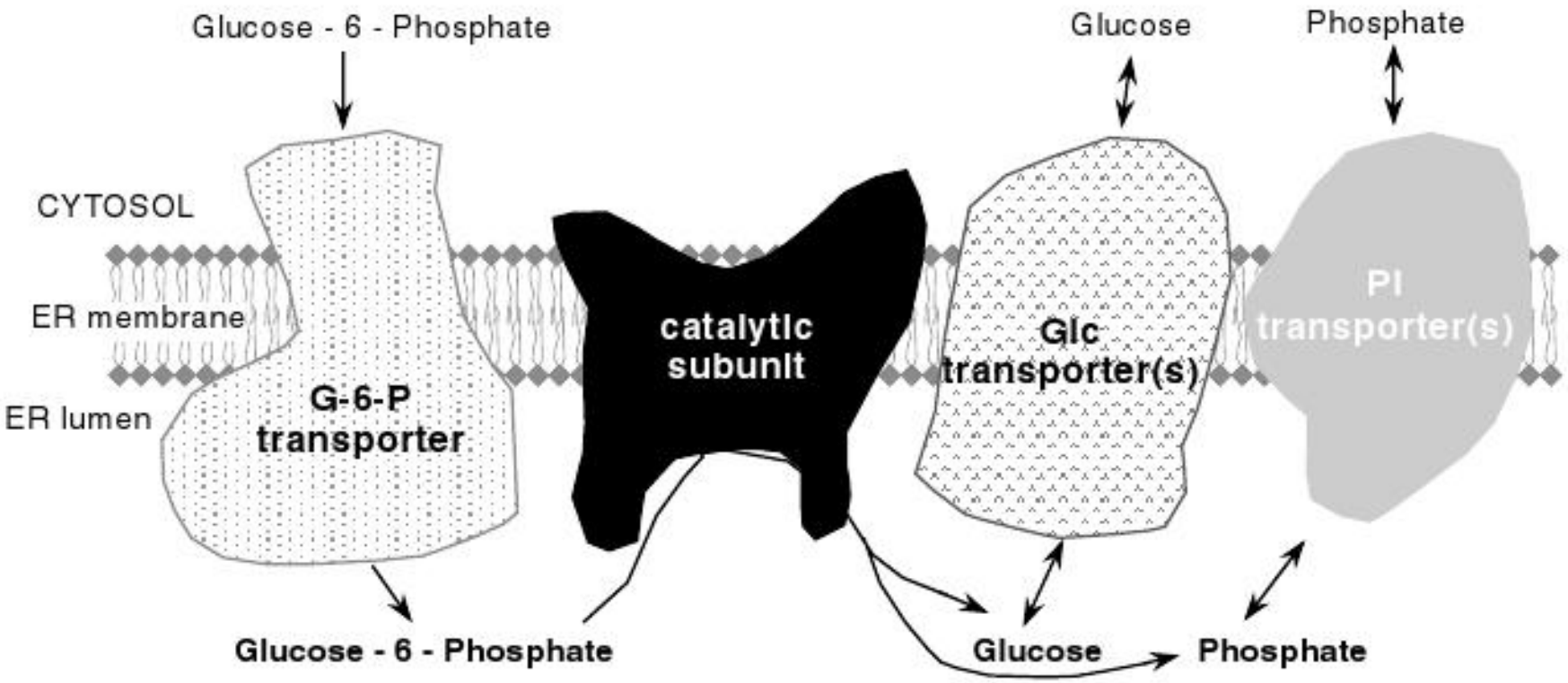
Later in life progressive fibrosis, liver adenomas -cave: malignant transformation. Atherosclerosis

Fasting tolerance improves with age, late complications

Treatment goal : **maintaining normoglycemia**, frequent feeding, nocturnal nasogastric drips in infancy, uncooked cornstarch, liver transplantation, kidney transplantation

Autosomal recessive, overall incidence is 1:10000, frequent in Ashkenazi
The diagnosis is based on clinical presentation, abnormal blood/plasma concentrations of glucose, lactate, uric acid, triglycerides, and lipids, and molecular genetic testing.

Glucose -6-phosphatase system

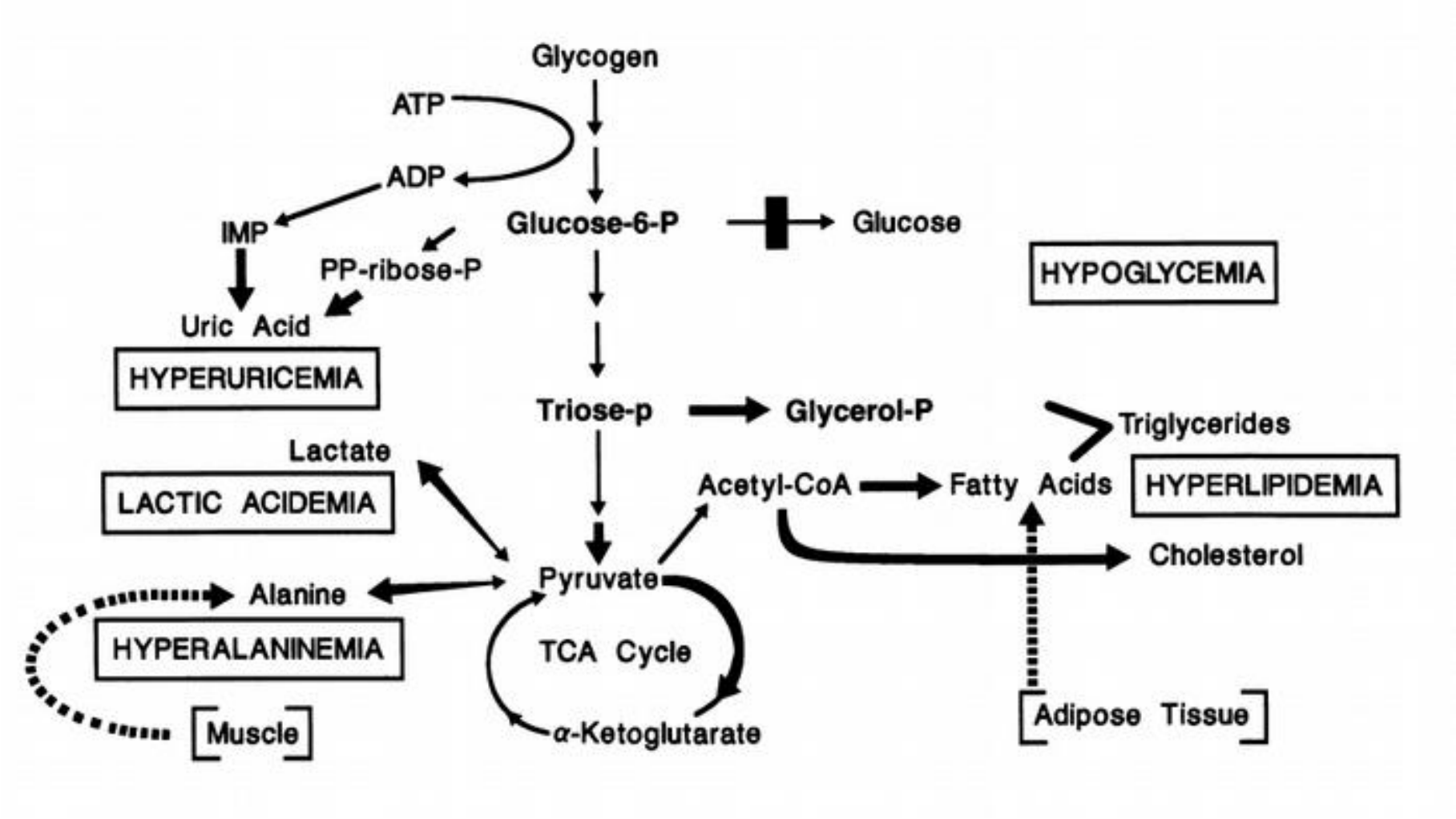


Localized to luminal face of ER

Type Ia GSD: deficient activity of phosphatase
Type Ib GSD: a defect in the microsomal membrane transport system of G-6-P

Non-a type associated with neutropenia and inflamatory bowel disease with recurrent bacterial infections and oral ulcers

The metabolic consequences of GSD I



Type III Glycogen Storage Disease (Debrancher Deficiency; Limit Dextrinosis; Cori or Forbes Disease)

Both liver and muscle are affected: frequent cirrhosis, myopathy, often cardiomyopathy, with fasting ketotic hypoglycemia

about 15% percent of patients have only hepatic presentation

myopathic presentation - also in adulthood

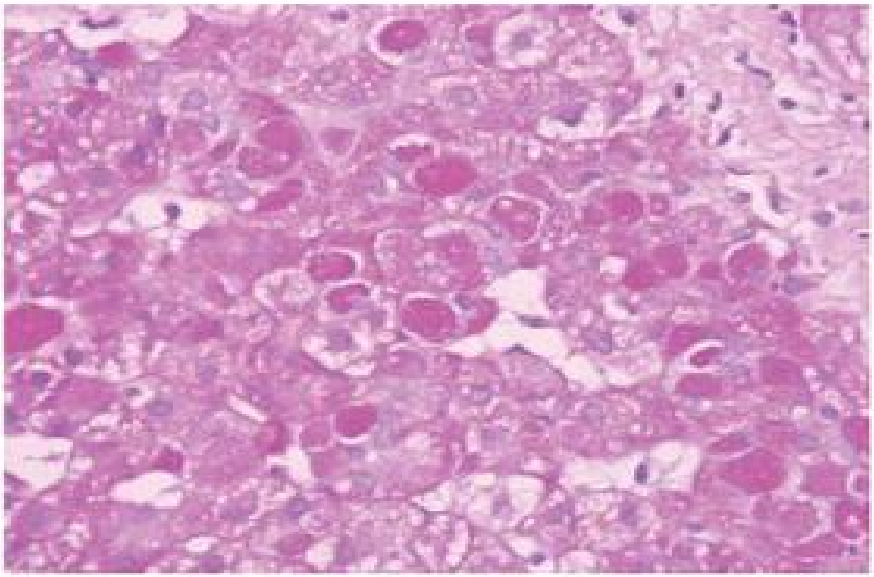
Abnormal glycogen: limit dextrin

Type IV (Branching Enzyme Deficiency, Amylopectinosis, or Andersen Disease)

Abnormal glycogen resembling amylopectin – fewer branching points

presents in infancy with progressive liver failure leading to cirrhosis, rare hypoglycemias, cardiomyopathy

death at 4-5 years without liver transplantation



Neuromuscular presentation - accumulation of polyglucosan bodies in tissues - myopathy, arthogyposis

adult polyglucosan body disease

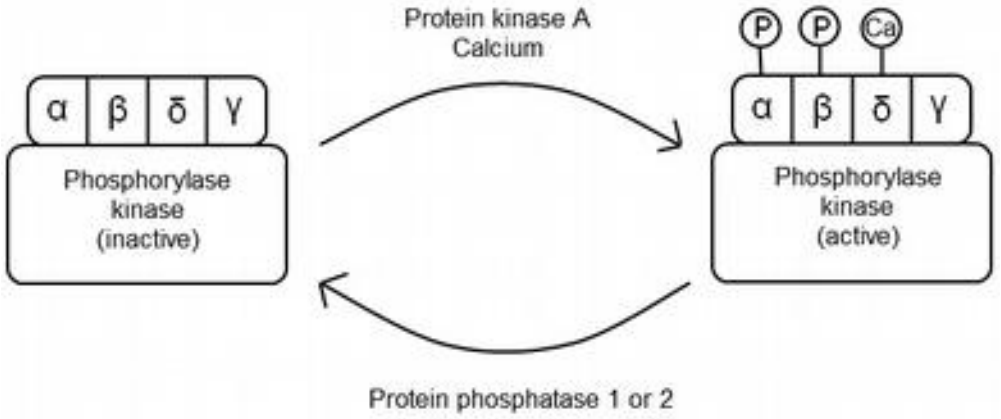
Type IX Glycogen Storage Disease (deficiency of phosphorylase kinase (PhK) and subunits)

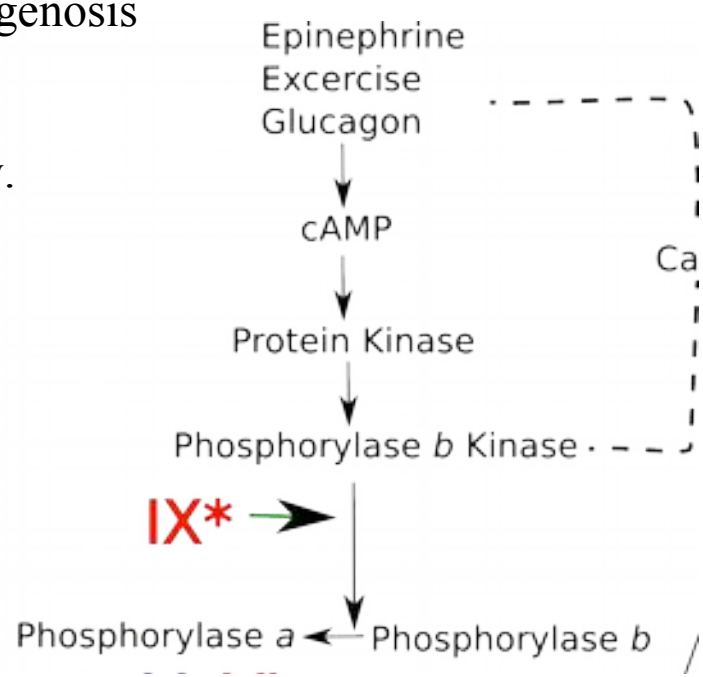
Degradation of glycogen is regulated by a metabolic cascade resulting in activation of glycogen phosphorylase by phosphorylase kinase

Phosphorylase kinase enzyme has four copies of 4 subunits each - α, β, γ, δ. Subunit γ is catalytic, subunits α and β are regulatory, δ is calmodulin.

The most common form (90% of cases), liver PhK deficiency (X-linked liver glycogenosis) is due to the deficiency of liver form of α subunit

deficiency of muscle form of α subunit: X - linked muscle glycogenosis
deficiency of subunit β: autosomal recessive PhK deficiency in liver and muscle;
deficiency of subunit γ, autosomal recessive liver PhK deficiency.



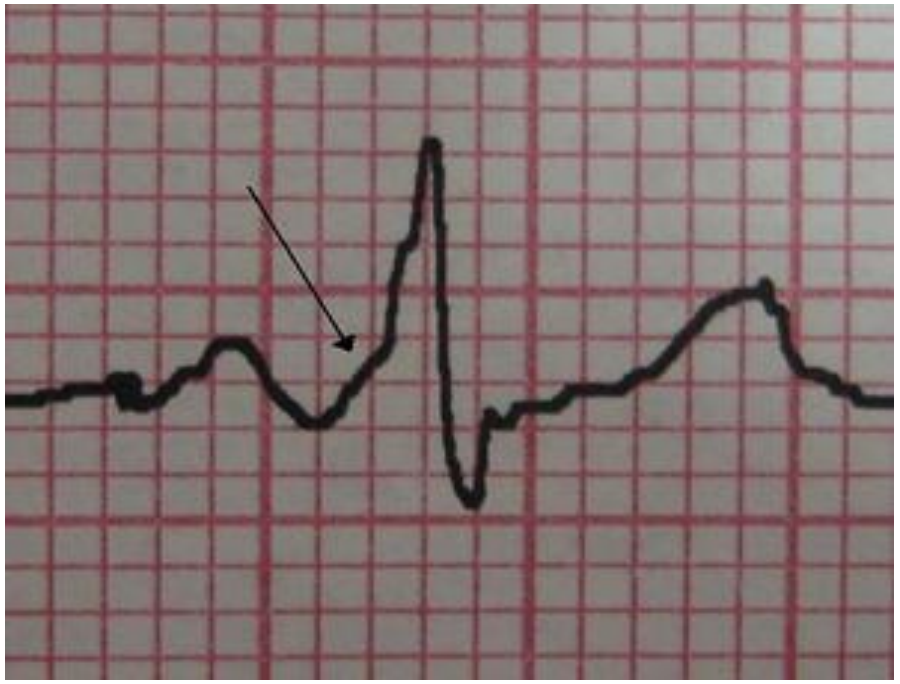


Activating mutations in PRKAG2, gene encoding γ subunit of AMP-activated Protein Kinase (AMPK), lead to glycogen accumulation in cardiac muscle and supraventricular arrythmias

Activated AMPK increases glucose influx into cells

AMPK is a cellular energy sensor. It is activated by exercise in muscle and an increase in the AMP/ATP ratio. Heterotrimeric complex: a catalytic subunit (α) and two regulatory γ.

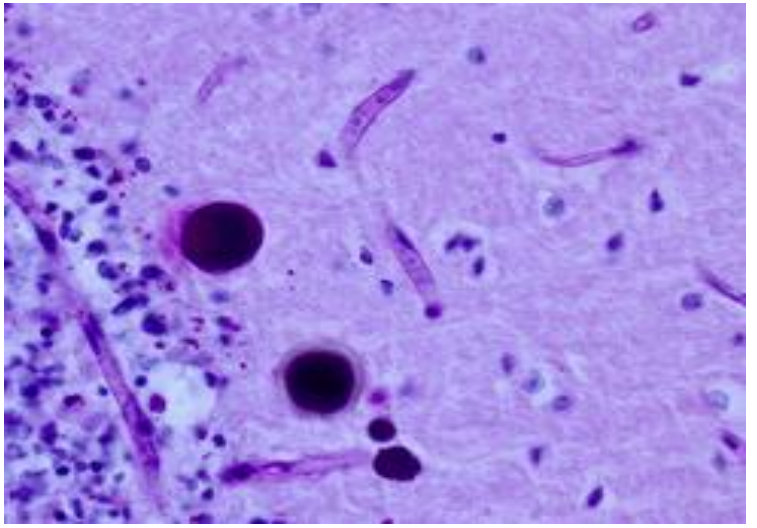
Mutations in the gene enconding γ subunit (PRKAG2) cause ventricular pre-excitation (Wolf-Parkinson-White syndrome) predisposing to supraventricular arrythmias. Fully penetrant autosomal dominant trait.



Other phenotypic features :
Hypertrophic cardiomyopathy

Mutant AMPK permanently stimulates glucose influx into cell, resulting elevation of G6P activates glycogen synthase.

Arrow : typical delta wave of W-P-W syndrome



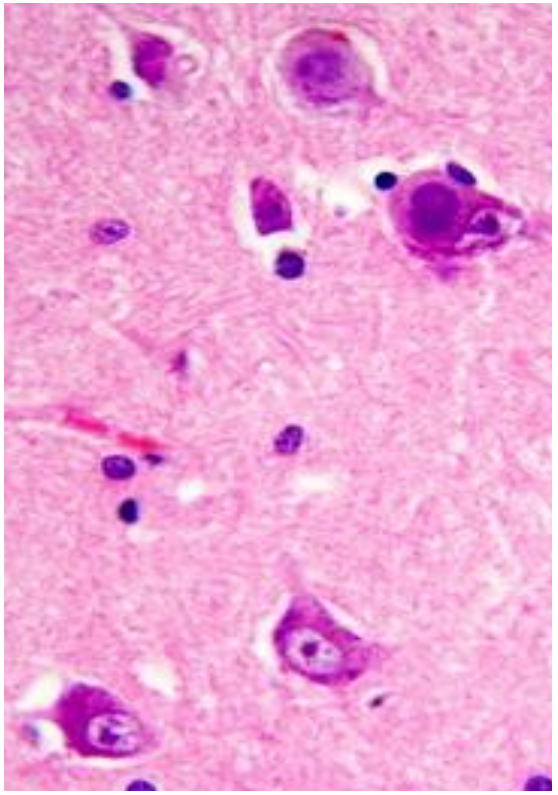
Brain glycogenoses

Adult polyglucosan body disease

Deficiency of the branching enzyme in astrocytes (GSD IV)
Slowly progressive gait disturbance, urinary incontinence,
loss of sensitivity in lower extremities, later cognitive decline

In peripheral nerves and in the brain storage of amylopectin-like glycogen in polyglucosan bodies

Rare, found almost exclusively in Ashkenazi Jewish patients, AR



Lafora disease

Progressive severe myocloclonic epilepsy with onset usually in adolescence, progressive dementia, aphasia, apraxia
Leads to vegetative state and death in 10 years from onset

Lafora bodies in neurons - abnormal glycogen storage

Mutations in laforin carbohydrate-binding phosphatase
and the malin E3 ubiquitin ligase
Enzyme deficiency is not known

Muscle glycogenoses (without cardiac involvement)

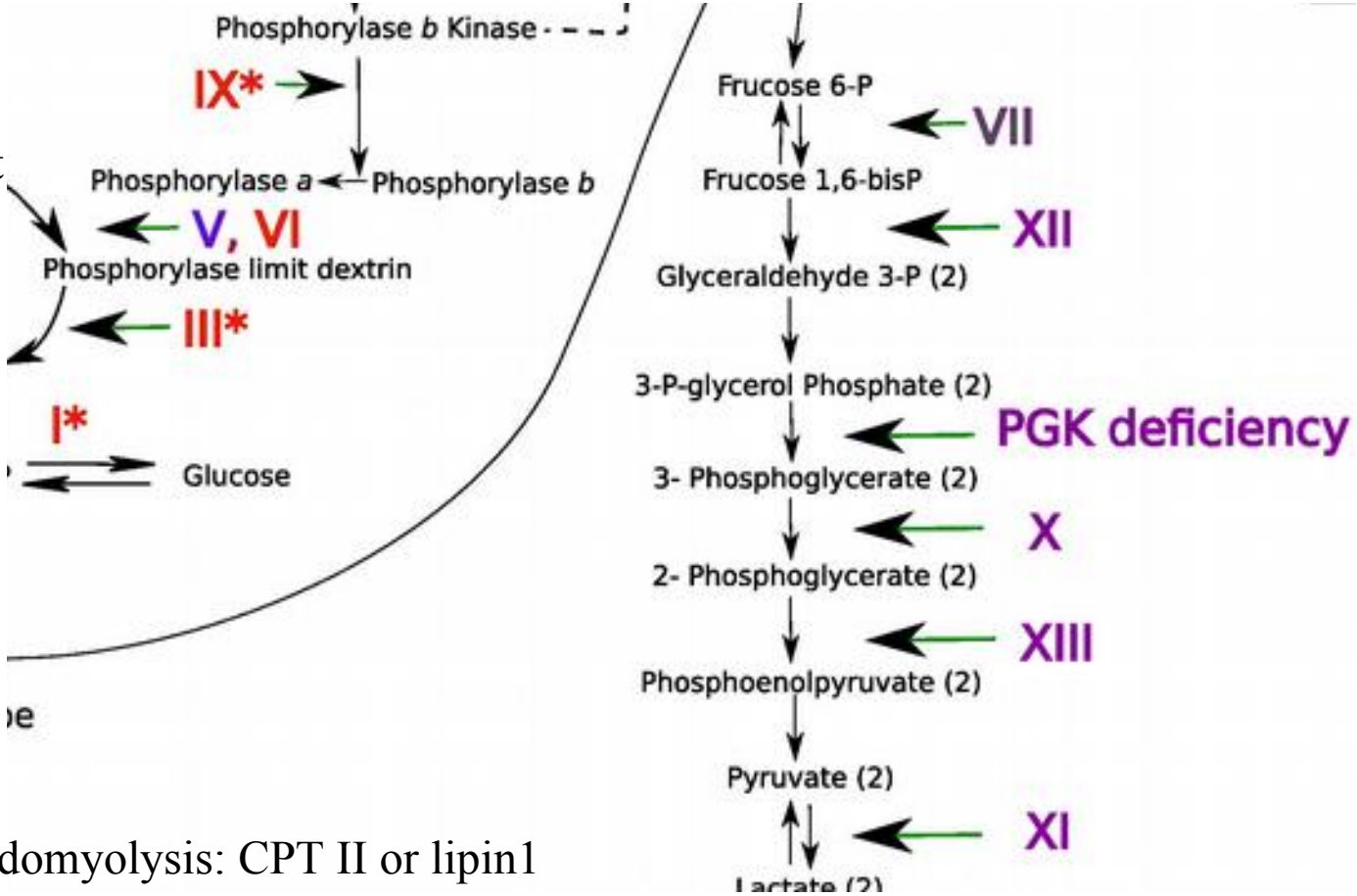
Excercise intolerance, often followed by rhabdomyolysis

prototypical disease : GSD V, McArdrle disease, deficiency of myophosphorylase

myalgia and stifness of exercising muscles relieved by rest, often rhabdomyolysis, later in life may be present muscle wasting

AR inheritance

no pharmacological treatment



(Dif.dg. of post-exercise rhabdomyolysis: CPT II or lipin1 deficiency)

Generalized glycogenosis: Morbus Pompe

M.Pompe

Deficiency of lysosomal acid alpha-glucosidase (acid maltase)
Lysosomal storage of glycogen with normal structure

Infantile type:
First symptoms in the first months of life: cardiomegaly, muscle weakness, macroglossia
Progressive course, death due to cardiopulmonary failure in the first two years of life

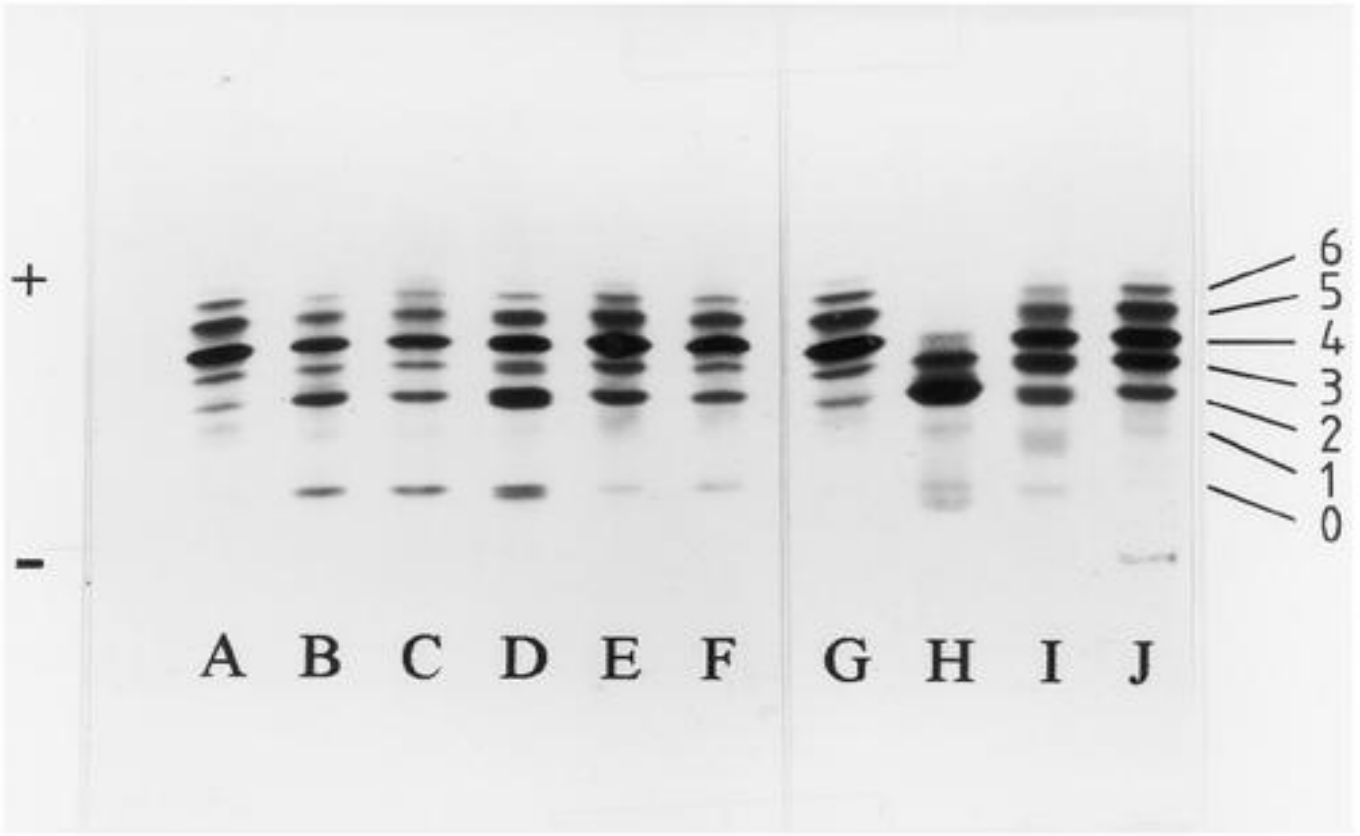
Adult type
Slowly progressive proximal myopathy and/or slowly progressive respiratory failure
Heart is not affected

Intermediate types
Myopathy, heart can be affected

Diagnostics:
Glycogen storage in tissues
measurement of enzyme activity
Mutation analysis
Treatment monitoring: glucose tetrasaccharide Glc4

Treatment
Enzyme supplementation therapy (Myozyme)

Congenital disorders of glycosylation (CDG)



Hereditary disorders of glycosylation

Disorders of protein glycosylation

N-glycosylation, O-glycosyltion, ….

Disorders of lipid glycosylation

Disorders of dolichol synthesis

Disorders glycophosphatidylinositol synthesis

Combined defects

Subcellular compartments:
ER, Golgi, cytosol

Overall more than 100 disorders

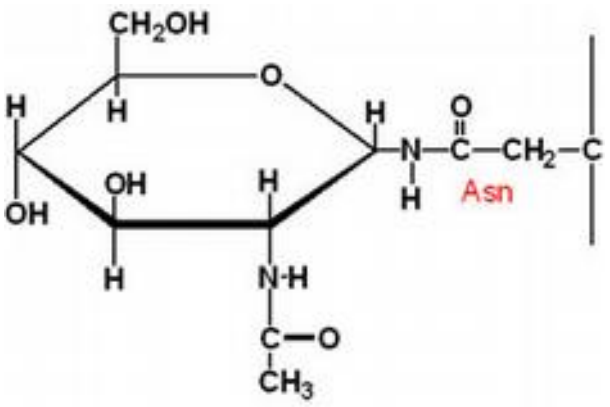
Scott K et.al. Congenital disorders of glycosylation: new defects and still counting. Journal of Inherited Metabolic Disease July 2014, Volume 37, Issue 4, pp 609–617

Glycoproteins

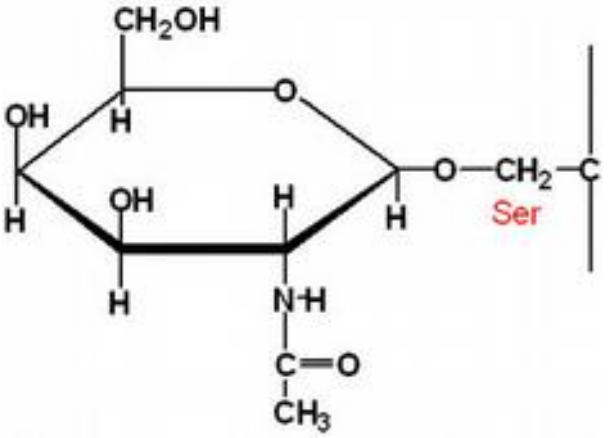
N-glycosylation

O-glycosylation

Disorders of glycosylation:
CDGs (previously known as carbohydrate-deficient glycoprotein syndromes)



N-glycosylation
Asn-X-Ser/Thr

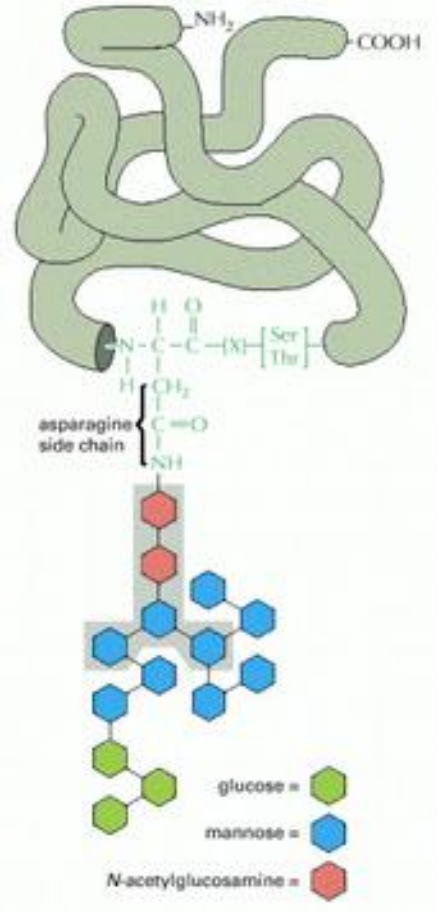


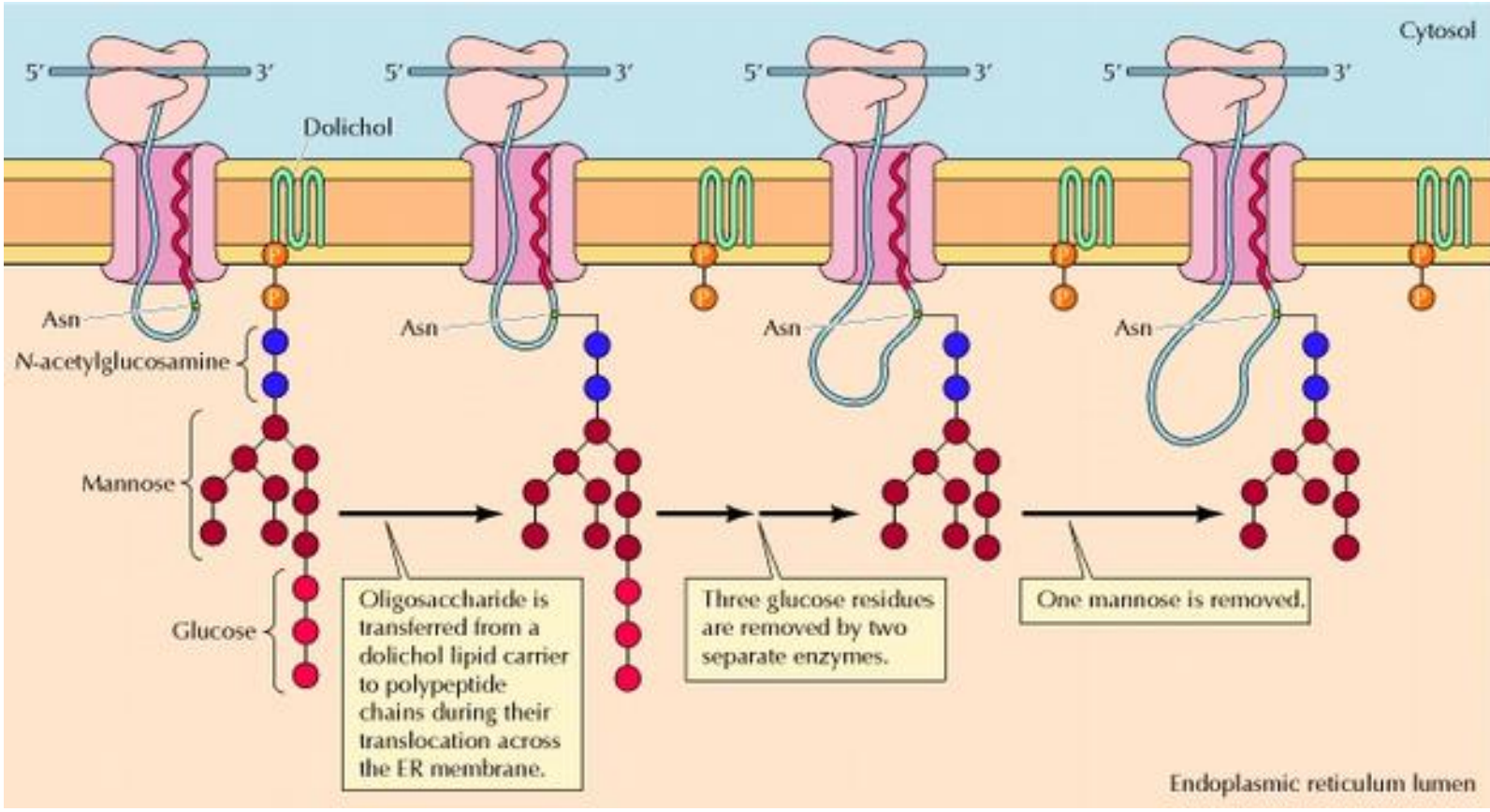
O-glycosylation
Thr, Ser

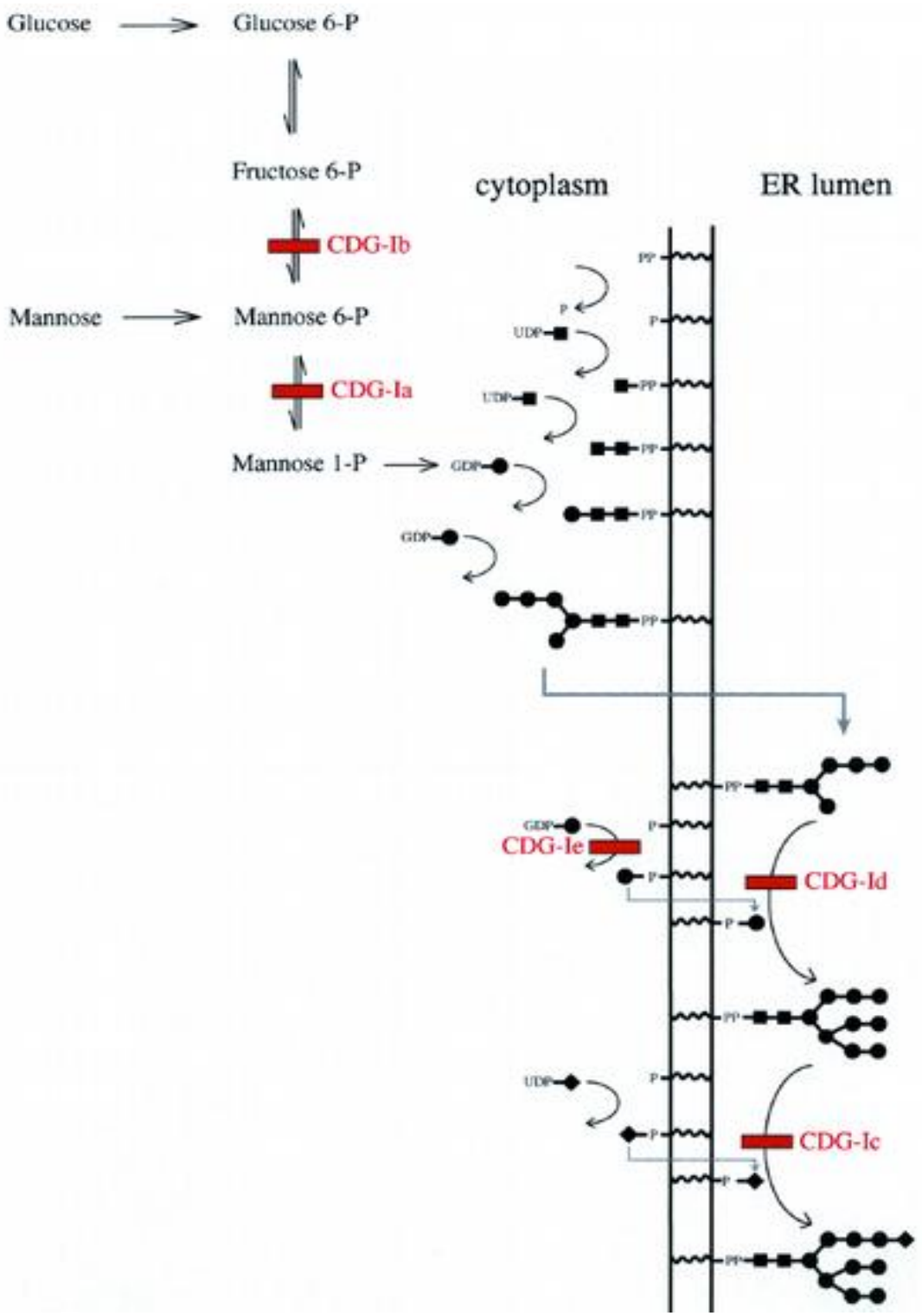
Most Proteins Synthesized in the Rough ER Are Glycosylated by the Addition of a Common N-linked Oligosaccharide

Precursor oligosaccharide is bound to dolichol in the ER membrane

Oligosacchariders are further processed in ER and Golgi



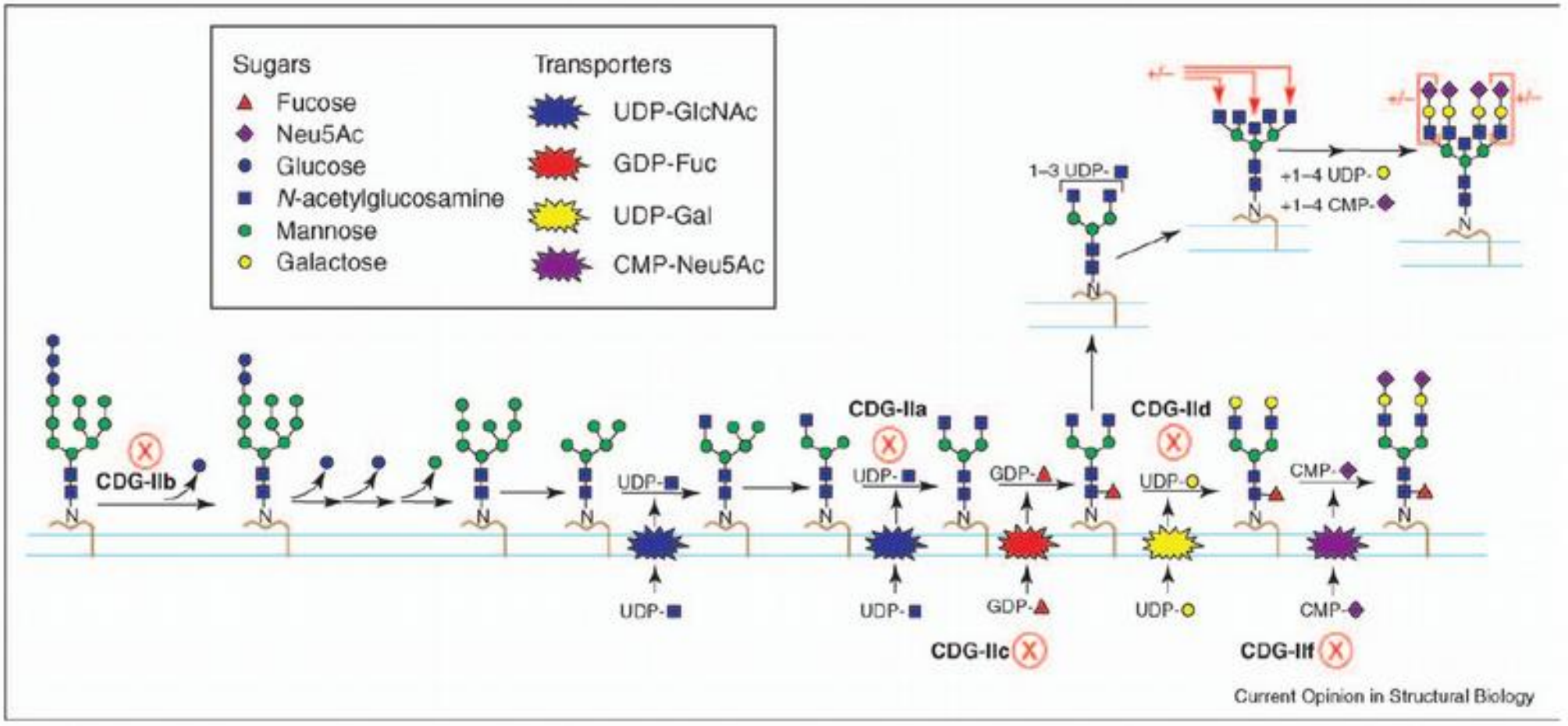




$Man_5GlcNac_2$

$Glc_3Man_9GlcNac_2$

Processing of oligosaccharide chains of glycoproteins in ER and Golgi



O-glycosylation

Saccharide units are bound to Thr or Ser hydroxyl

Threonin
Serin

7 groups (classification after the first saccharide)

Glycosyltransferases add other saccharide unit in the Golgi apparatus

Jaak Jaeken

Congenital disorders of N-glycosylation

CGD I: >16 disorders of N-glycan assembly (CDG Ia-m) including dolichol-phosphate synthesis defects

(CDGIa : phosphomannomutase 2 deficiency)

CDGII: >8 disorders of processing of N-glycans

Congenital disorders of O-glycosylation

> 6 disorders

Disorders of glycolipid glycosylation

3 disorders: GM3 synthase deficiency, ...

Highly variable phenotype
Autosomal recessive disorders
Autosomal dominant : 1 disorder (hereditary multiple exostoses sy.)

Congenital disorders of glycosylation

Aberrant protein glycosylation

Diagnostic paradigm:
analysis of glycans → molecular defect

Screening:
Isolectric focusing of **sialyltransferin** in defects of N-linked glycans
Isolectric focusing of **apo CIII** in defects of N-linked glycans

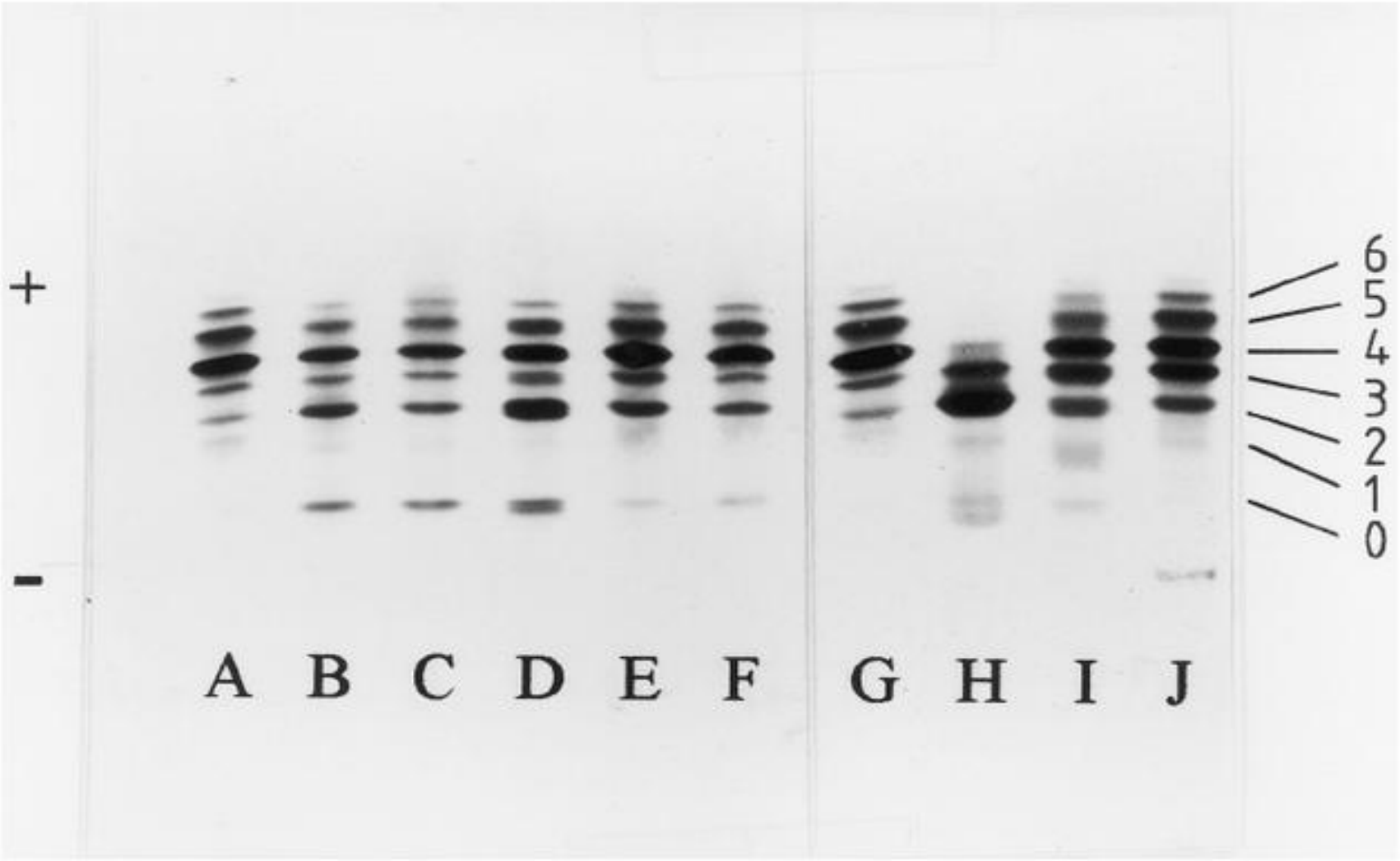
Structural analysis of glycans

Measurement of enzyme activities

Mutation analysis

CDG-x: abnormal glycosylation detected by screening techniques, but with unknown molecular defect

Isoelectrofocusing of serum sialotransferins



A, G controls,
B to F : **type-I pattern**
B phosphomannomutase def., C phosphomannose isomerase (PMI) deficiency D, hypoglucosylation defect; E, F unidentifed
H to J : **type-II pattern**
H, N-acetylglucosaminyltransferase (GnT II) def; I, Junidenti®ed

Glycoproteins Reported to Be Abnormal in Phosphomannomutase Deficiency and Showing an Abnormal Pattern on Isoelectrofocusing, Two-dimensional Electrophoresis, Western Blotting, and/or Decreased or Increased Concentration or Enzymatic Activity

Serum

Transport Proteins

Apoprotein B, apoprotein CII, apoprotein E, ceruloplasminhaptoglobin, α2-macroglobulin, retinol-binding protein, sehormone-binding globulin, thyroxine-binding globulin, transcobalamin II, transcortin, transferrin, vitamin D-binding globulin

Coagulation and Anticoagulation Factors

Antithrombin, α2-antiplasmin, coagulation factors II, V, VI, VIIIIX, X, XI, and XII, heparin cofactor II, plasminogen, protein C, protein S

Hormones

Follicle-stimulating hormone, l

Lysosomal Enzymes

Arylsulphatase A, α-fucosidase

Other Enzymes

N-Acetylglucosaminidase, carb

Other Glycoproteins

Amyloid P α1-acid glycoprotein, α1-antichymotrypsin, α1-antitrypsin, α1-B glycoprotein, clusterin, complement C3a, complement C4a, complement C1 esterase inhibitor, α2-HSglycoprotein, immunoglobulin G, orosomucoid, peptide PLS:29peptide PLS:34, Zn-a2-glycoprotein

Glycosylation defects lead to abnormal glycoproteins, which normally have diverse functions

Cerebrospinal Fluid

β-Trace protein, transferrin

Leukocytes

Lysosomal Enzymes

α-Fucosidase, β-glucuronidase, α-iduronidase, α-mannosidase, β-mannosidase

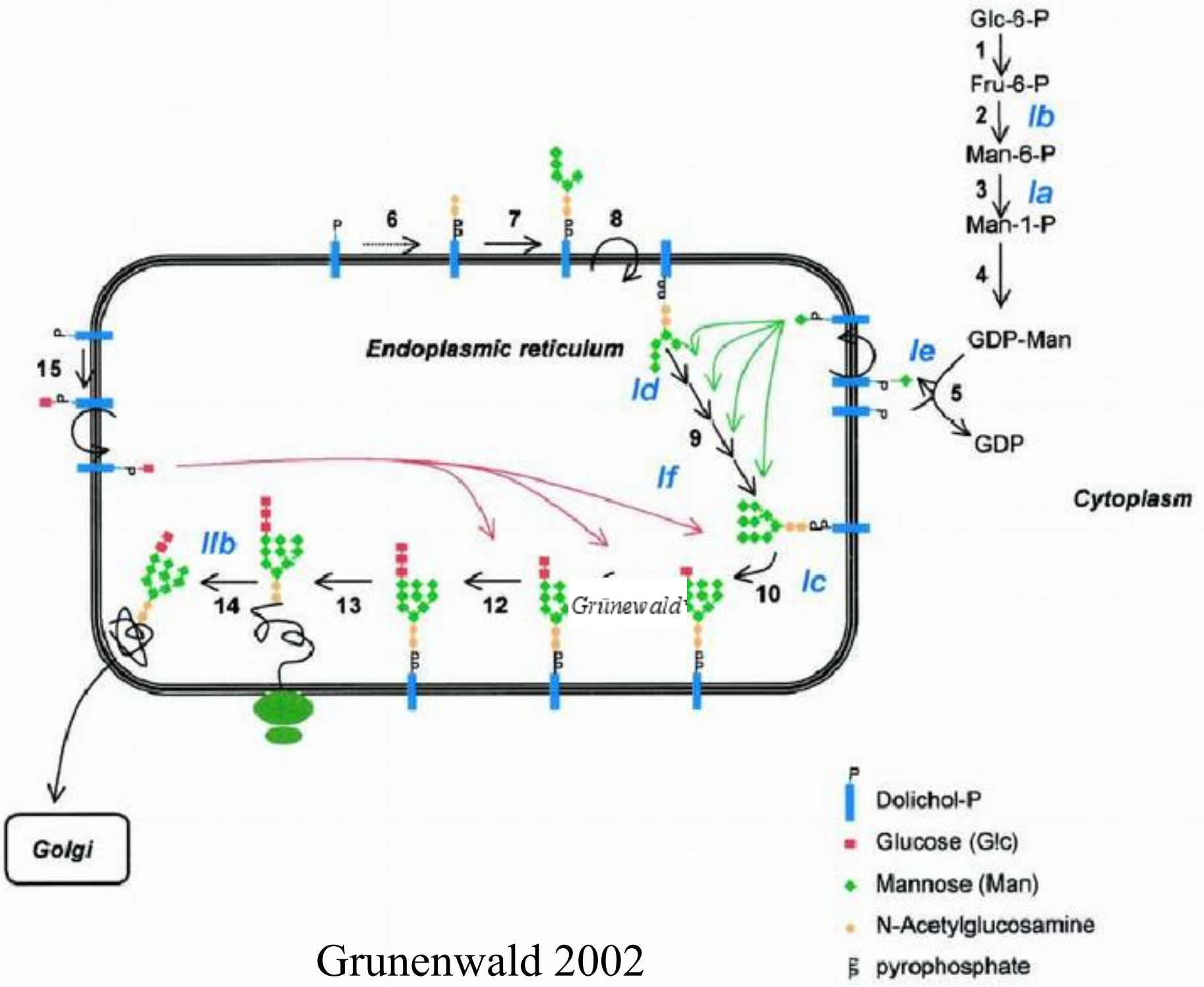
Sialoglycoproteins on B lymphocytes

Fibroblasts

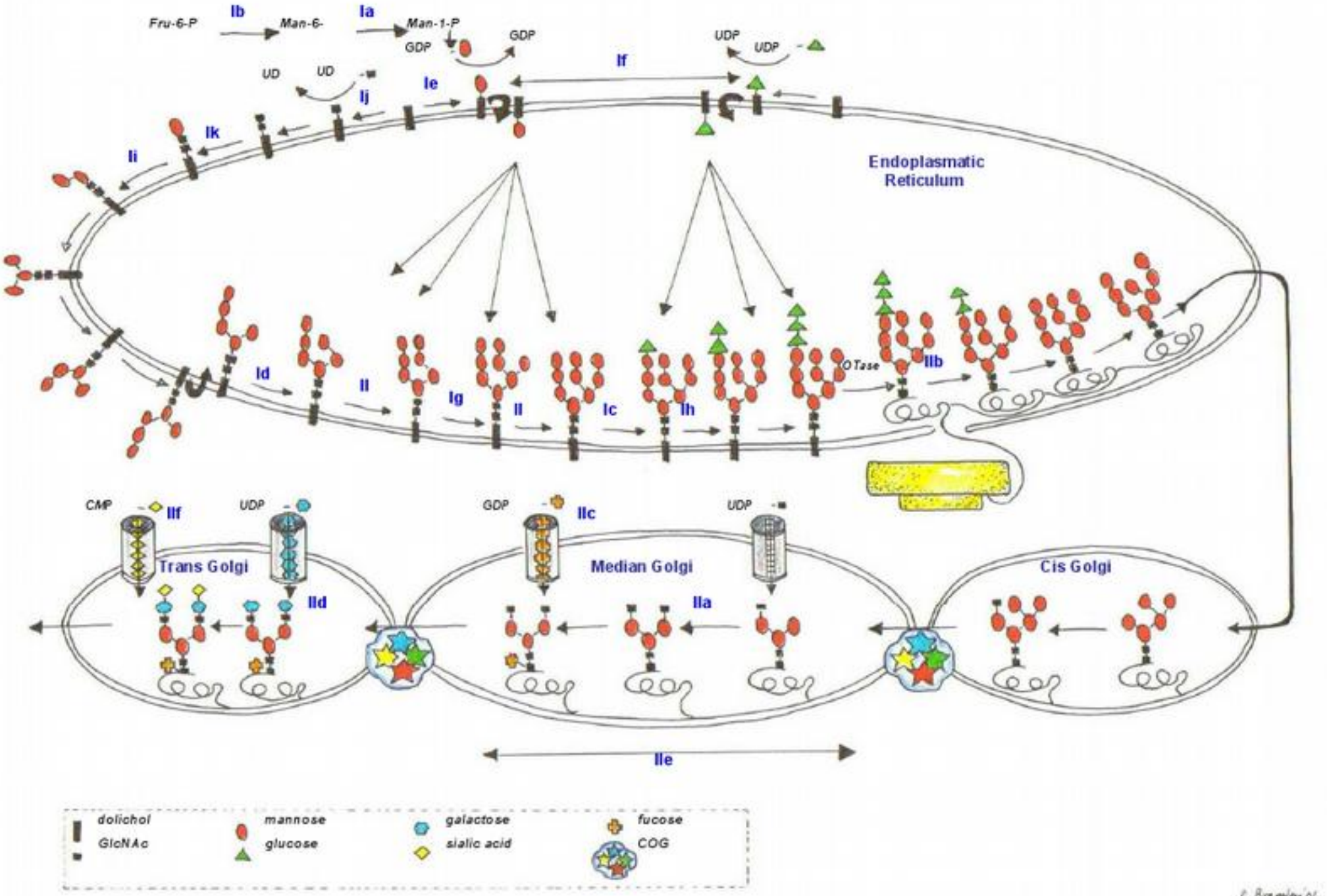
Biglycan, decorin

Liver

α1-Acid glycoprotein, α1-antitrypsin, haptoglobin, transferrin



Grunenwald 2002



Grünewald 2007

Neurology	axial hypotonia; hyporeflexia; developmental delay; seizures; stroke-like events; micro- and macrocephaly; myopathy
Gastroenterology/ Hepatology	failure to thrive; vomiting; protein-losing enteropathy; liver dysfunction; hepatomegaly; cholangitis; chronic diarrhoea
Neonatology	hydrops; ascites; multiorgan failure; failure to thrive; floppy baby
Haematology	thrombocytosis, thrombocytopenia; coagulopathy; thrombosis; anaemia; leukocytosis, thrombocytopenia
Endocrinology	hyperinsulinemic hypoglycemia; hypothyroidism; hypergonadotropic hypogonadism; growth retardation
Clinical genetics	dysmorphic features
Orthopaedics	osteopenia; joint contractures; kyphosis/scoliosis; short limbs; arthrogryposis
Ophthalmology	abnormal eye movements; squint; cataract; retinitis pigmentosa; nystagmus; iris coloboma; cortical blindness
Radiology	cerebellar hypoplasia; calcification of white matter; delayed myelinisation; micropolygyria; renal hyperechogenecity
Histology	liver fibrosis; liver cirrhosis; lamellar inclusions in hepatocytes; intestinal villus atrophy
Dermatology	ichthyosis; abnormal fat distribution
Nephrology	nephrotic syndrome; tubulopathy; cystic kidneys
Immunology	recurrent infections; hypogammaglobulinaemia
Cardiology	cardiomyopathy; pericardial effusions
Biochemistry	hypoalbuminaemia; elevated transaminases; low cholesterol, triglycerides; decreased antithrombin III; decreased factor VIII and XI; decreased protein C and S; elevated FSH, LH and prolactin; elevated TSH, low free T4

Patients with CDGs can be referred to specialists in different fields of medicine

Symptoms of CDGs due to defects of N-linked glycans

CDG-Ia.
In infancy : Inverted nipples, abnormal subcutaneous fat distribution, and cerebellar hypoplasia, facial dysmorphism, hypotonia, and psychomotor retardation. Alternating strabism and other eye movement disorders, skeletal abnormities.
After infancy : Stroke-like episodes, pigment retinitis, ataxia, peripheral neuropathy

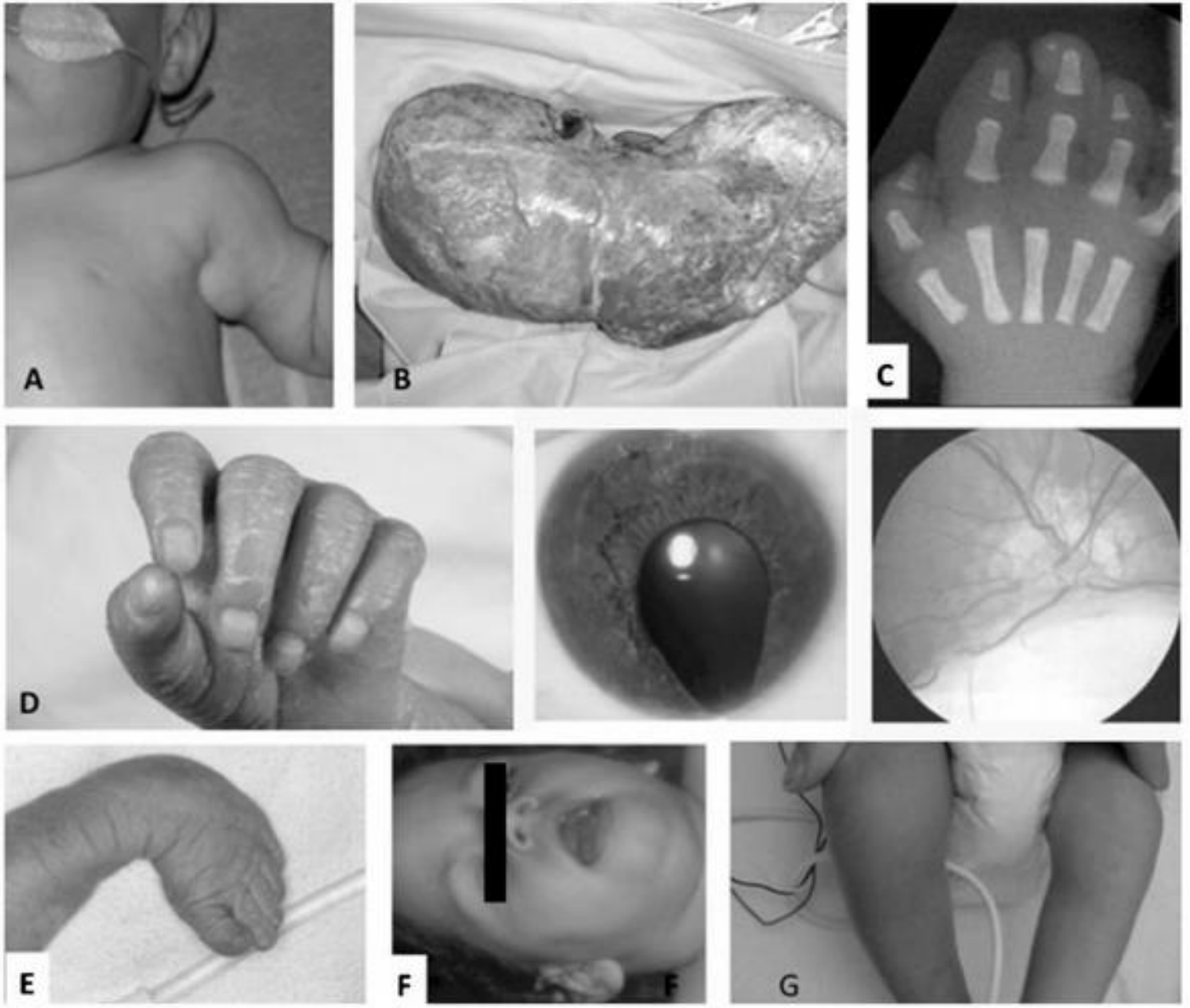
Clinical course:
infantile multisystem stage, late-infantile and childhood ataxia-mental retardation stage, and adult stable disability stage.

CDG-Ib. Phosphomannoisomerase deficiency
Cyclic vomiting, profound hypoglycemia, failure to thrive, liver fibrosis, and protein-losing enteropathy, occasionally coagulation disturbances without neurologic involvement,

Treatment: mannose 50-1g/kg/day

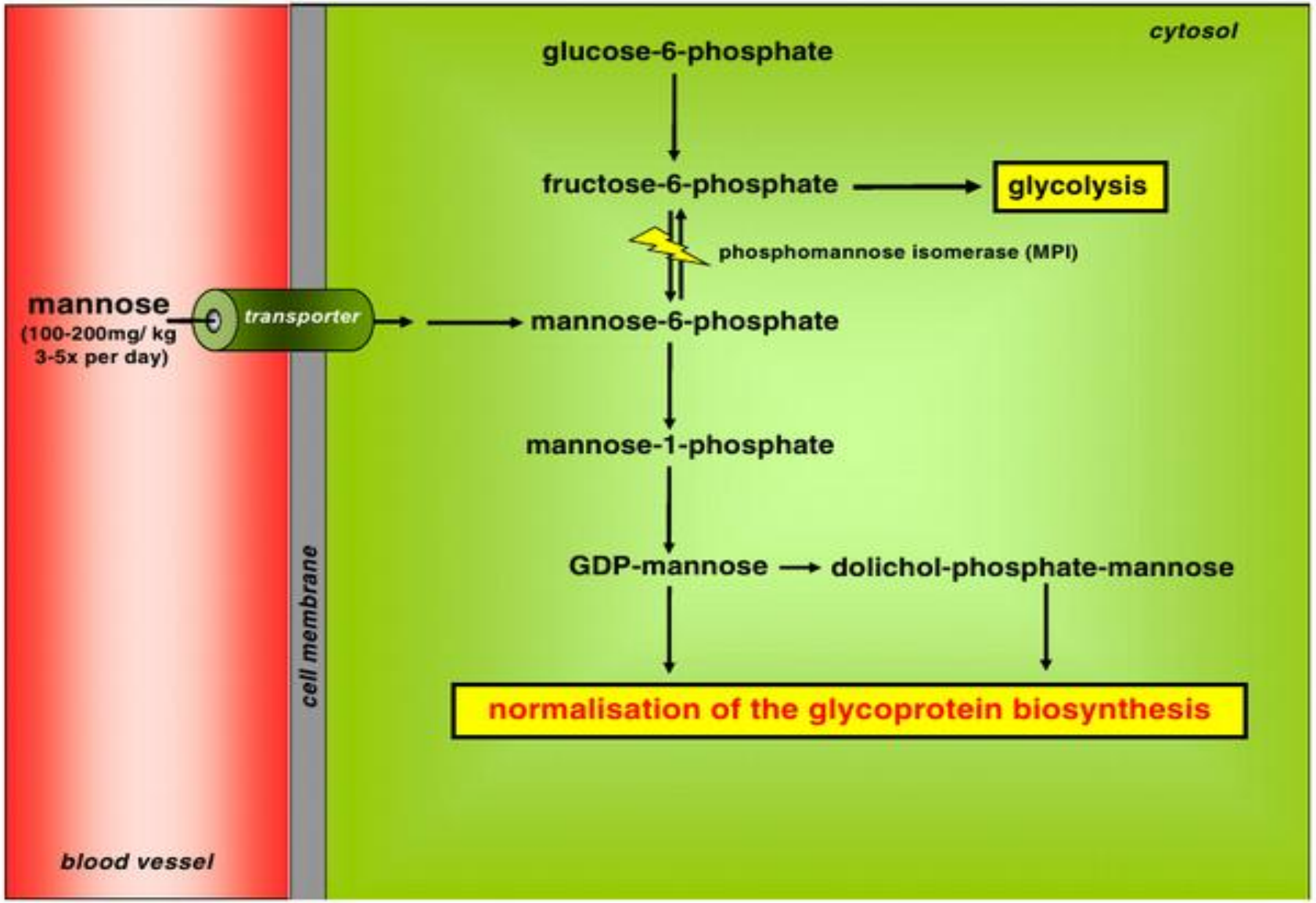
CDG-Ic.
Mild to moderate neurologic involvement with hypotonia, poor head control, developmental delay, ataxia, strabismus, and seizures, ranging from febrile convulsions to epilepsy
The clinical presentation is milder than in CDG-Ia;

…

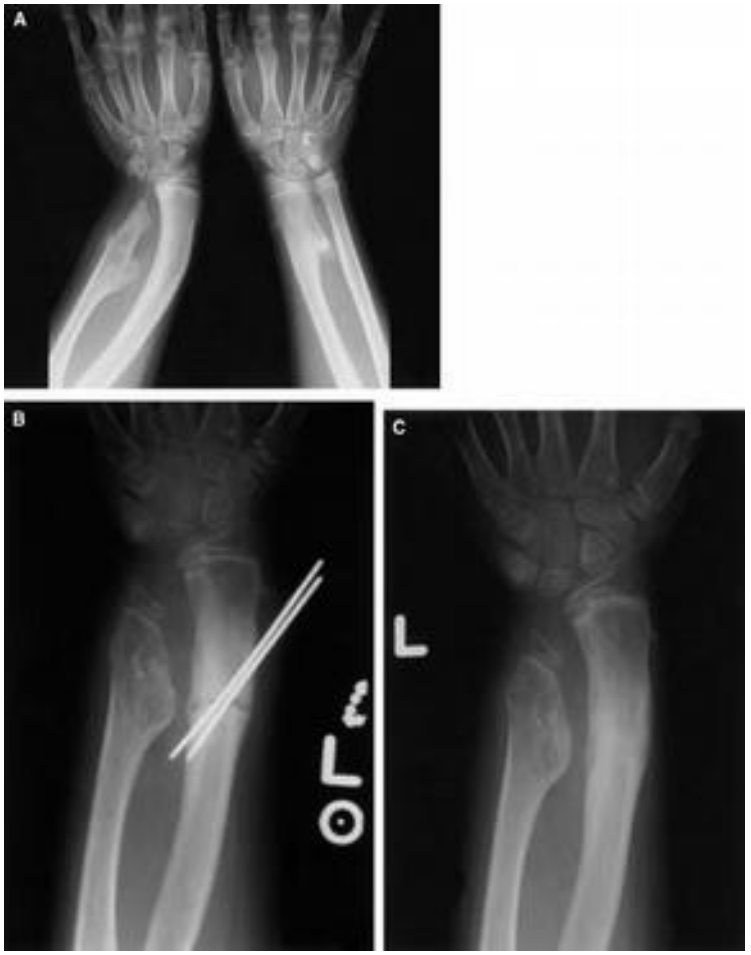


Recognizable clinical features in different N-linked glycosylation defects. a Abnormal fat distribution in phosphomannomutase 2 (PMM2)-CDG; CDG-Ia). b Liver cirrhosis in phosphomannose isomerase (MPI)-CDG (CDG-Ib). c Distal phalangeal aplasia in ALG6-CDG (CDG-Ic). d Ichthyosis and iridial and retinal coloboma are characteristic for SRD5A3-CDG. e Distal arthrogryposis in ALG8-CDG (CDG-Ih). f Myasthenic face and ptosis are common in DPAGT1-CDG (CDG-Ij). g Venous thrombosis leads to asymmetry in limb circumference in ALG1-CDG (CDG-Ik). Scott K et.al. JIMD 2014, Volume 37, Issue 4, pp 609–617

Treatment of phosphomannose isomerase deficiency by mannose supplementation



Selected O-glycosylation disorders



Multiple hereditary exostoses
Autosomal dominant
Incidence 1/50 000
Osteochondromas of long bones
Compression of peripheral nerves and blood vessels
Limited joint movements
Increased probability of malignant transformation

Mutations in exostosin 1 and exostosin 2 genes

Walker-Warburgův syndrom
A neuronal migration disorder
Lissencephyly, corpus callosum agenesis, cerebellar agenesis
Brain and eye dysgenesis
Muscular dystrophy
Testicular dysgenesis in males
Death often before 1 year of age
A defect in glycosylation of **α-dystroglycan**
O-manosyltransferase I deficiency