INHERITED DISORDERS OF METABOLISM

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LYSOSOMAL STORAGE DISEASE

Lysosomal storage disorders

- Lysosomes degrade many materials:
- Mucopolysaccharides (glycosaminoglycans).
- Sphingolipids.
- Glycoproteins and glycolipids.
- Accumulate in tissues when not degraded.
- Can cause cell, tissue and organ dysfunction.
- Most are enzyme defects, some affect transport or targeting.

MUCOPOLYSACCHARIDOSES

Mucopolysaccharidoses

- Lysosomal storage disease.
- Ten enzymes cause six disorders.
- Enzyme deficiency is generalized, affecting all organ systems.
- Deficiency of lysosomal enzymes involved in the degradation of glycosaminoglycans
- Heparan sulfate, dermatan sulfate, keratan sulfate, or chondroitin sulfate accumulate
- Not generally apparent at birth.
- With the exception of Hunter syndrome, are autosomal recessive

Mucopolysaccharidoses

- Defects in the degradation of keratan sulfate and dermatan sulfate cause skeletal deformities and other connective tissue abnormalities.
- Only defects in heparan sulfate degradation cause mental retardation and neurological degeneration
- Presents early in childhood
- Coarsening of facial features and skeletal deformities
- Developmental delay and childhood dementia
- Restless, active with difficult behavior
- Sleep disorder

Mucopolysaccharidoses

- Myotonia
- Corneal clouding
- Inguinal and umbilical hernias early sign
- Organomegaly
- Carpal tunnel syndrome
- Spinal stenosis
- Generally dead within 8-12 years unless bone marrow transplant

Mucopolysaccharidoses

- Hurler (MPS-IH) syndrome
- Lack IDUA gene at 4p16.3 (α-L-iduronidase)
- Cannot degrade glycosoaminoglycans
- Hurler-Scheie (MPS-HIS), Scheie (MPS-IS) are milder forms
- Accumulate heparan sulfate and dermatan sulfate
- Hunter syndrome (MPS-II)
- X-linked recessive
- IDS gene at Xq28 (iduronate)
- Cannot degrade glycosoaminoglycans
- Accumulate heparan sulfate and dermatan sulfate

Mucopolysaccharidoses

- Sanfilippo (MPSIII)
- Type A lacks SGSH gene at 17q25.3 (heparan-N-sulfatase)
- Most common
- Type B lacks NAGLU gene at 17q21.2 (N-acetyl-alpha-D-glucosaminidase)
- Type C lacks HGSNAT gene at 8p11.21 (Heparin-α-glucosaminide N-acetyltransferase)
- Type D lacks GNS gene at 12q14.3 (N-acetylglucosamine 6-sulfatase)
- Accumulate heparan sulfate

Mucopolysaccharidoses

- Morquio syndrome (MPS-IV)
- Skeletal dysplasia
- Motor dysfunction
- Type A GALNS gene at 16p24.3 (galactose-6-sulfate sulfatase)
- Type B GLB1 gene at 3p22.3 (β-glucosidase)
- Accumulate keratan sulfate and chondroitin sulfate

Mucopolysaccharidoses

- Maroteaux-Lamy syndrome (MPS VI)
- Skeletal dysplasia and kyphosis
- Motor dysfunction
- Heart defects
- ARSB gene at 5q14.1 (N-acetylgalactosamine-4-sulfatase)
- Accumulate dermatan sulfate

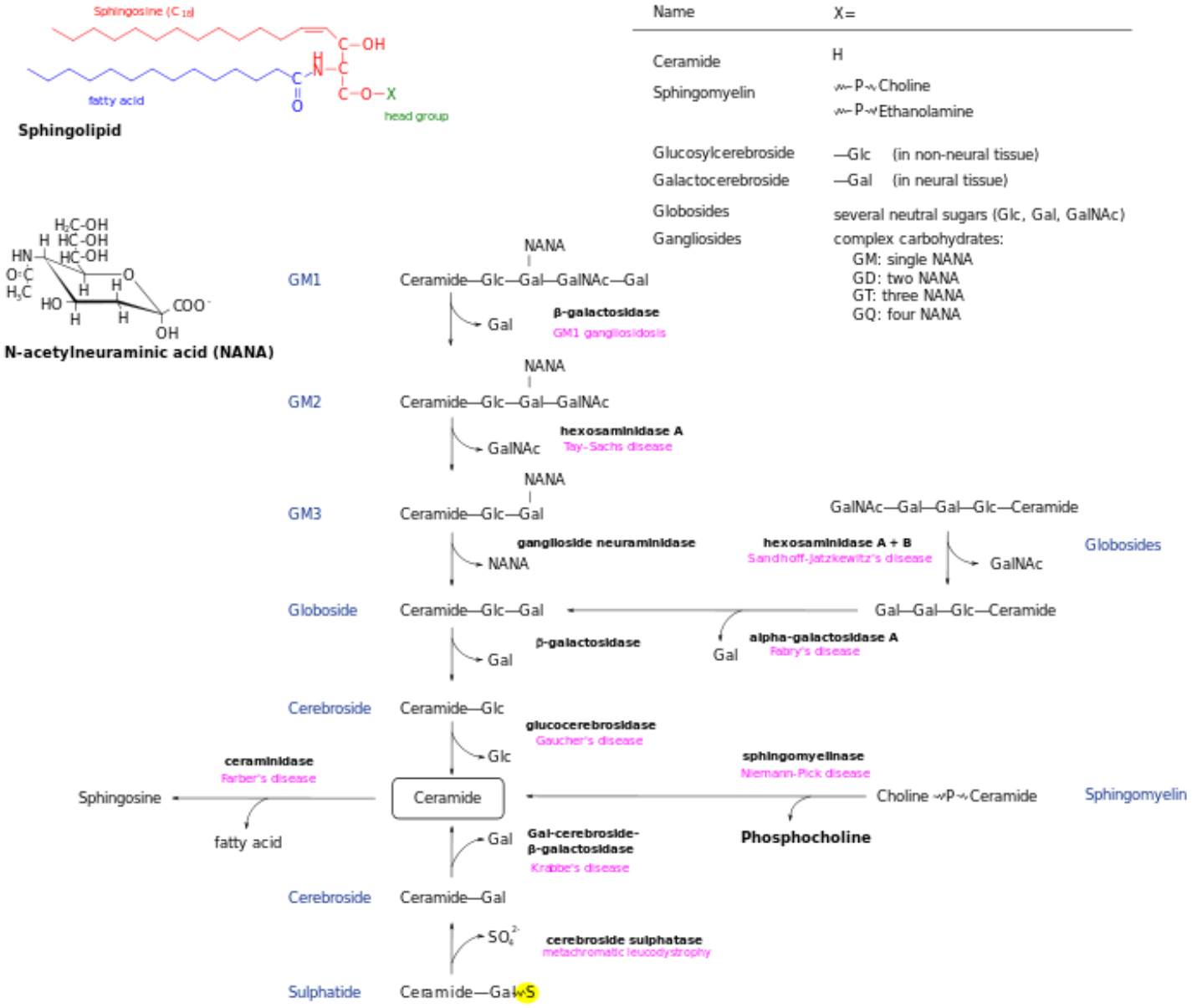
Mucopolysaccharidoses

- Natowicz syndrome (MPS IX)
- Nodular soft tissue masses around joints with painful swelling
- No intellectual impairment
- HYAL1 gene at 3p21.31 (hyaluronidase)
- Accumulate hyaluronic acid

Mucopolysaccharidoses

- Sly syndrome (MPS VII)
- Hydrops fetalis in severe cases
- Development delay
- Short stature
- Hepatomegaly
- Corneal clouding
- GUSB gene at 7q11.21 (β-glucoronidase)
- Accumulate heparan sulfate, chondroitin-4,6-sulfate, and dermatan sulfate

SPHINGOLIPIDOSES



https://en.wikipedia.org/wiki/Sphingolipidoses Accessed 03/20/2020

Sphingolipidoses

- GM_1 is the prototype ganglioside:
- Monosialotetrahexosylganglioside.
- Terminates in formation of ceramide.
- GM_1 gangliosidosis.
- Autsomal recessive.
- β-galactosidase deficiency
- accumulates GM_1
- Acute infantile disease
- Psychomotor retardation
- Hepatosplenomegaly
- Coarse features

GM_1 gangliosidosis

- Juvenile form
- Onset age 1
- Only cerebral accumulation of ganglioside
- No cherry-red spot
- No visceral or bone accumulation
- No visual disturbances

Sphingolipidoses

- Tay-Sachs disease is the prototype of a disease affecting gray matter primarily.
- Gray matter symptoms and signs are:
- Irritative
- Myoclonic seizures
- Inhibitory
- Apathy, lethargy and dementia.
- Cortical blindness if optic neurons involved

Sphingolipidoses

- Metachromatic leukodystrophy is the prototype of a disease predominantly of white matter.
- White matter symptoms and signs are:
- Long-tract involvement
- Spastic weakness with involvement of the corticospinal tract
- Pseudo-bulbar palsy with damage to the corticobulbar tract
- Incoordination from destruction of cerebellofugal fibers
- Cortical blindness from interruption of the optic radiations.

TABLE 1.—*Sphingolipidoses*

			Lipid	*Enzyme Defect*	*Disease*
CERAMIDE +	—P-choline (phosphorylcholine)		= sphingomyelin	sphingomyelinase	Niemann-Pick**
	—Hexoses	—galactose	= galactocerebroside	galactocerebrosidase	Krabbe's
		—glucose	= glucocerebroside	β-D-glucosidase	Gaucher's
		—gal-SO_4	= sulfatide	sulfatase	M.L.D. (sulfatide lipidosis)
		—trihexose	= ceremide trihexoside	ceremide trihexosidase	Fabry's
		—hexoses + NANA*	= gangliosides:		
			G_{M_2} ganglioside	Hexosaminidase A	Tay-Sachs***
			G_{M_1} ganglioside	β-galactosidase	Generalized gangliosidosis
		fucose		fucosidase	Fucosidosis
	CERAMIDE =	sphingosine + fatty acid	palmitic acid + serine		

*NANA = N-acetylneuraminic acid

**There are 4 clinically separate forms of Niemann-Pick and only type A is referred to above.

***There are now 5 gangliosidoses with varying ganglioside and lysosomal enzyme deficiencies.

Tay-Sachs disease

- Autosomal recessive.
- GM2A gene at 5q33.1 (ganglioside activator necessary for β-hexosaminidase A to function)
- Hexosaminidase A deficiency
- Accumulate ganglioside GM_2
- Type 1 (chronic non-neuronopathic)
- Most common presentation.
- Prevalent in Ashkenazi.
- Type 2 (acute neuronopathic) is characterized by central nervous system involvement.
- Rarely survive beyond age 2.

Tay-Sachs disease

- Type 3 (subacute neuronopathic) has a variable course.
- Cluster described in Norbotten, Sweden.
- “Ballooned” neurons filled with lipid staining material
- On electron microscopy, cells contain lamellated bodies

Tay-Sachs disease

- Early infantile form presents with:
- Cranio-facial abnormalities
- Seizures.
- 50% have cherry-red spot in macula.
- Between age 1-3 years, presents with:
- Flaccid paralysis
- Nystagmus
- Hepatosplenomegaly
- If presents after 3 years of age:
- Dystonia
- Angiokeratomas

Sandhoff's disease

- Sandhoff's disease.
- Infantile form presents at age 2-9 months.
- Lose motor skills.
- Retardation.
- Seizures.
- May have cherry-red spot in macula.
- Late onset disease is milder
- Autosomal recessive.
- HEXB gene at 5q13.3 (hexosaminidase A and B deficiency)
- Accumulate globoside (GM_2)

Fabry's disease

- X-linked recessive.
- GLA gene at Xq22.1 (α-galactosidase A deficiency)
- Globotriaosylceramide accumulates in endothelial cells as well as cells in kidneys, heart, and nervous system
- Sphingosine not formed.
- Pains in digits and abdomen.
- Diffuse angiokeratomas.
- Corneal opacities
- Tinnitus
- Milder disease in women
- Enzyme replacement therapy

Gaucher's disease

- Perinatal form associated with hydrops fetalis and is lethal
- Bulbar weakness
- Retroflexion of the head
- Hepatomegaly
- Present in childhood or adulthood

Gaucher’s disease

- Type 1 (non-neuronopathic)
- Most common
- Hepatosplenomegaly with pancytopenia
- Lung disease
- Skeletal abnormalities
- Psychomotor retardation

Gaucher's disease

- Types 2 and 3 (neuronopathic)
- Type 2 presents in infancy; Type 3 has later onset
- Hepatosplenomegaly with pancytopenia
- Lung disease
- Skeletal abnormalities
- Psychomotor retardation
- Abnormal eye movements and seizures
- There is also a cardiac form which is further associated with calcified valves

Gaucher’s disease

- All types are autosomal recessive
- GBA gene at 1q22 (β-glucocerebrosidase deficiency)
- Accumulate glucocerebroside rather than metabolize it further to ceramide
- Enzyme replacement therapy

Nieman-Pick disease

- Type A (Crocker's)
- Hepatomegaly by 3 months of age
- Failure to thrive
- Psychomotor retardation
- Interstitial lung disease
- Cherry-red spot in macula
- Rarely survive childhood
- Type A accounts for 85% of cases
- Only type with lipid abnormalities in the brain
- SMPD1 gene at 11p15.4 (sphingomyelinase deficiency)
- Accumulate sphingomyelin

Nieman-Pick disease

- Type B
- Presents in mid-childhood
- Hepatosplenomegaly with thrombocytopenia
- Short stature
- Recurrent lung infections
- 30% have Cherry-red spot in macula
- Survive into adulthood
- Type B does not produce neurologic symptoms.
- SMPD1 gene at 11p15.4 (sphingomyelinase deficiency)
- Accumulate sphingomyelin

Nieman-Pick disease

- Types C1 and C2
- Present in childhood
- Ataxia
- Supranuclear gaze palsy
- Dystonia
- Interstitial lung disease
- Severe liver disease
- Dysarthria
- Progressive intellectual decline
- 30% have seizures
- Survive into adulthood

Nieman-Pick disease

- Survive into adulthood
- NPC1 genes at 18q11.2 (defect in the cholesterol trafficking enzyme)
- NPC2 genes at 14q21.3 (defect in the cholesterol trafficking enzyme)
- Accumulate cholesterol

- All Nieman-Pick disorders are autosomal recessive

Metachromatic leukodystrophy

- Most common
- Occurs in infancy
- Autosomal recessive.
- ARSA gene at 22q13.33 (Arylsulfatase A deficiency from sulfatide).
- PSAP gene at 10q22.1 in a small number of cases (saposin B protein that works with arylsulfatase A)
- Myelin loss

Metachromatic leukodystrophy

- Initial presentation:
- Muscular weakness and wasting
- Stumbling gait
- Knock knees
- As the disease progresses:
- Spastic quadriparesis
- Cortical blindness and deafness
- Adult form presents with dementia

Krabbe disease

- Presents at 6 months of age
- Psychomotor retardation
- Hypertonia and opisthotonus
- Tonic seizures, spasticity, blindness
- Blindness and deafness.
- Autosomal recessive.
- GALC gene at 14q31.3 (β-galactosylceramidase deficiency)
- Cannot break down galactosylceramide or psychosine formed in myelin production
- Psychosine is toxic

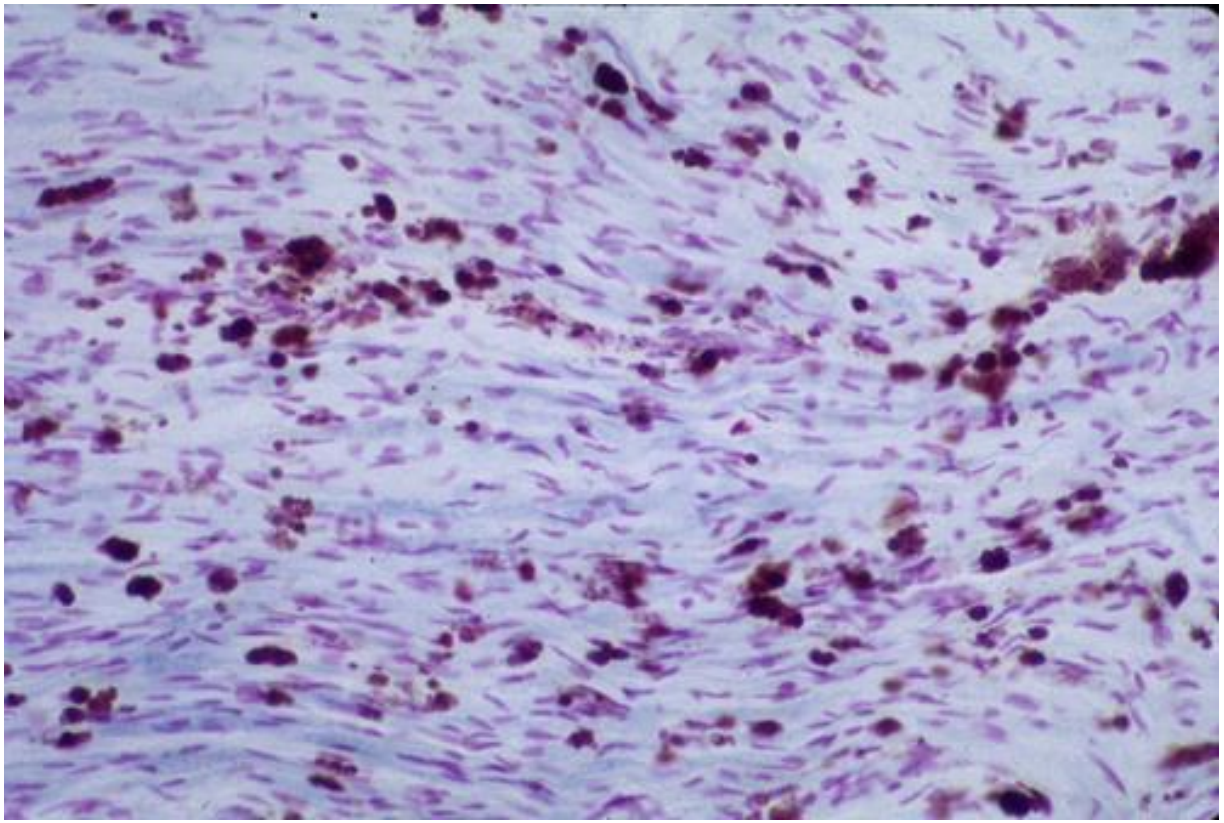
Krabbe disease

- Characterized histologically by nearly complete loss of oligodendroglia and myelin
- Epithelioid globoid cells found about blood vessels. In white matter
- Absence of myelin with sparing of arcuate fibers

Leukodsytrophy

- Krabbe disease.
- Autosomal recessive disorder
- Deficiency of galactocerebroside-β-galactosidase.

Leukodystrophy



Myelin loss.
Few oligodendroglial cells.
Lipid laden macrophages.

http://neuropathology-web.org/chapter10/images10/10-mldl.jpg
Accessed 11/26/2019

Leukodystrophy

- Adrenal leukodystrophy
- X-linked

- Cerebral form
- Presents between 4-10 years (males)
- Learning and behavioral disability
- Adrenal insufficiency

Leukodystrophy

- Adrenomyeloneuropathy form
- Presents between early adulthood and middle age
- 4% of females are symptomatic
- Paraparesis
- Bladder and bowel dysfunction
- Adrenal insufficiency

- Addison disease only form
- Presents any time between childhood and adulthood
- Adrenal insufficiency
- Paraparesis, bladder and bowel dysfunction appear later

Molecular change

- ABCD1 gene at Xq28 (ATP Binding Cassette Transporter)
- Adrenaleukodystrophy protein production impaired
- Elevated levels of long chain fatty acids in serum and tissues as a result of deficiency in enzyme that degrades very long chain fatty acids.
- Segmental demyelination with onion bulbs as well as myelinated and unmyelinated axonal degeneration noted.
- More severe in parietal and occipital regions
- Linear inclusions are present in Schwann cells.

Leukodystrophy

- Alexander disease.
- Neonatal form
- First month of life
- Hydrocephalus
- Seizures
- Infantile form
- Presents before age 2
- Megalencephaly
- Seizures
- Stiffness and spasticity in limbs
- Intellectual disability and developmental delay

Leukodystrophy

- Juvenile form
- Occurs from childhood to adulthood
- Speech and swallowing difficulties
- Ataxia
- Autosomal dominant
- GFAP gene at 17q21.31
- Rosenthal fibers (glial fibrillary acidic proteins in glial cells and around blood vessels)
- Demyelination.

Leukodystrophy

- Zellweger syndrome.
- Neonatal adrenoleukodystrophy
- May present later in life
- Infantile Refsum disease
- Neonates
- Lack of PEX1p (peroxin) gene at 7q21 (failure of membrane formation of peroxisome)
- Elevated levels of very long chain fatty acids
- Flattened face with broad nasal ridge
- Hyptonia, seizures, nystagmus, coma

Leukodystrophy

- Pelizaeus-Merzbacher disease
- X-linked recessive
- Duplicate PLP1 gene at Xq22.2
- Proteolipid 1 and DM20 genes needed for myelin formation in CNS and peripheral nervous system
- Do not form myelin
- Present within first year of life with nystagmus, hypotonia, and delayed motor development
- A more severe presentation occurs in neonates

Myoclonic epilepsy

- Progressive myoclonic epilepsy (Unverricht-Lundborg)
- Baltic myoclonus; Mediterranean myoclonus
- Presents between age 6-15 years
- Proximal muscle myoclonus, ataxia, emotional lability
- Autosomal recessive
- CTSB gene at 21q22.3
- 12 nucleotide repeat 5’-CCC-CGC-CCC-GCG-3’
- Variant has cytoplasmic inclusions of glycoprotein mucopolysaccharides (Lafora bodies) in brain, liver, muscle (EPM2 gene mutation) .

Myoclonic epilepsy

- Lafora progressive myoclonic epilepsy
- Late childhood
- Myoclonus
- May have generalized seizures or occipital seizures
- Intellectual decline
- EPM2A gene at 6q24.3
- Loss of laforin leads to accumulation of polyglucosans
- Cytoplasmic inclusions (Lafora bodies) in brain, liver, muscle

MUCOLIPIDOSES

Mucolipidosis

- Inclusion cell disease
- Mucolipidosis II.
- Pseudo-Hurler syndrome
- Mucolipidosis III
- Autosomal recessive
- GNTPAB gene 12q32 (Glucose N-acetyl-phosphotransferase 1) is deficient
- Mannose-6 not produced in Golgi apparatus
- Hydrolases target to lysosome mannose-6-P receptor.

Mucolipidosis

- Are secreted from the cell rather than are sequestered in lysosomes.
- Undigested products accumulate in lysosome and appear as inclusions.
- Crowd out cytoplasm.
- Presents as birth with hypotonia and weak cry
- Kyphosis and club feet
- Coarse features
- Narrowed trachea
- Contractures

Mucolipidosis

- Dilated cardiomyopathy
- Umbilical and inguinal hernias
- Development stops by age 2 years
- Pseudo-Hurler syndrome less severe than is I-cell disease

LIPID DISORDERS

Neuronal ceroid lipofucsinosis

- Lipid pigment stored in lysosomes.
- Normal development in infancy
- Autosomal recessive.
- Type 1 Infantile
- By 18 months, present with developmental regression, hypotonia, and seizures
- PPT1 gene at 1p34.2 (palmitoyl-protein thioesterase 1 enzyme)
- Type 2 Late infantile
- At 24 months, present with ataxia and seizures
- TPP gene at 11p15.24 (tripeptidyl peptidase)

Neuronal ceroid lipofucsinosis

- Type 3 Juvenile (Spielmeyer-Vogt-Sjögren-Batten disease)
- Presents between 5-8 years of age with seizures and ataxia
- Most common
- CLN 3 gene at 16p12.1 (spans membrane surrounding lysosome, facilitating communication)
- Type 4 Adult
- Present at age 40 with milder symptoms
- CLN 6 gene at 15q23 (regulates transport from endoplasmic reticulum to lysosome)

Abetalipoproteinemia

- Autosomal recessive.
- Microsomal triglyceride transporting protein.
- MTTP gene at 4q23 (microsomal triglyceride transport)
- Defect in Apo B48 and B100 (formation of chylomycria and VLDL)
- Malabsorption
- Lordosis and kyphoscoliosis
- Clubfoot
- Retinitis pigmentosa
- Acanthocytotic anemia

GLYCOGEN STORAGE DISEASE

Type	Enzyme deficiency	Presentation
0	Glycogen synthase (not a storage disorder but failure to make glycogen) GYS1 gene at 19q13.33 (muscle) GYS2 gene at 12p12.1 (liver)	Muscle type presents in childhood and is associated with long QT syndrome and impaired ventricular function with sudden death. Liver type presents may present in early infancy with hypoglycemia, hyperketonemia and failure to thrive.
I	Glucose-6-phosphatase (Von Gierke' s disease) G6PC gene at 17q21.31 (GSD1a). Regulates glucose metabolism in liver. SLC37A4 gene at 11q23.3 (GSD1b). Works with G6P at endoplasmic reticulum. Associated with inflammatory bowel disease, gingivitis, neutropenia.	Fasting hypoglycemia, lactic acidosis, hyperuricemia, hyperlipidemia. Hepatomegaly with adenoma formation. Delayed puberty. Polycystic ovary disease

Type	Enzyme deficiency	Presentation
II	Acid maltase or α-acid glucosidase Unable to breakdown glycogen (Pompé's disease) GAA gene at 17q23	Classic infantile form presents shortly after birth with hypotonia, myopathy, hepatomegaly. Die of cardiac failure. Non-classic infantile form presents by age 1 with myotonia and cardiomegaly. Die in early childhood. Late onset form may present in childhood or adulthood. Muscle weakness of trunk and legs. Die of respiratory failure.
IIb	Danon syndrome LAMP2 gene at Xq24 (lack of fusion between autophagocytic and lysosomal vacuoles)	Myopathy of trunk and limb muscles, hypertrophic cardiomyopathy, Wolf-Parkinson-White syndrome, intellectual disability (not as common in women)

Type	Enzyme deficiency	Presentation
III	Amylo-1,6-glucosidase (debranching enzyme leads to accumulation of structurally abnormal glycogen; Cori's disease) AGL gene at 1p21.2 Types IIIa and IIIc (muscle) Types IIIb and IIId (liver)	Presents in infancy. Fasting hypoglycemia, hepatomegaly May develop hepatic adenoma Those with muscle disorder manifest with myopathy and cardiac problems
IV	Amylo-4,6-glucosidase (branching enzyme; deficiency leads to accumulation of polyglycosans; Andersen's disease) GBE1 gene at 3p12.2 Adult polyglucosan body disease associated with peripheral neuropathy, spasticity, neurogenic bladder, autonomic dysfunction.	Perinatal. Polyhydramnios. Severe Hypotonia and muscle atrophy. Fatal. Congenital. Early infancy. Hypotonia and dilated cardiomyopathy. Survive a few months. Progressive hepatic. Early infancy. Hepatomegaly leading to cirrhosis. Myotonia by age 2. Usually fatal early. Non-progressive hepatic. Childhood. Hepatomegaly but no cirrhosis. Hypotonia. Survive to adulthood. Childhood neuromuscular. Myopathy and dilated cardiomyopathy.

Type	Enzyme deficiency	Presentation
V	Myophosphorylase deficiency prevents glycogen breakdown to glucose-1-phosphate (McArdle's disease) PGYM gene at 11q13.1	Presents in late adolescence. Exercise induced muscle pain; rhabdomyolysis
VI	Liver glycogen phosphorylase (Hers' disease) PYGL gene at 14q22.1	Hepatomegaly; mild hypoglycemia
VII	Phosphofructokinase deficiency prevents development of fructose-1,6-biphosphate (Tarui syndrome) PFKM gene at 12q13.11	Classical form. Childhood. Exercise pain. Myoglobinuria, hyperuricemia, bilirubinemia Severe infantile form. Hypotonia and cardiomyopathy. Die by age 1. Late onset. Adults. Myopathy. Hemolytic form. No muscle component.

Type	Enzyme deficiency	Presentation
IX d a b c	Phosphorylase b kinase deficiency PHKA1 gene at Xq13.1 PHKA2 gene at Xp22.13 is most commonly involved PHKB gene at 16q12.1 PHKG2 gene at 16q11.2	Childhood. Hepatomegaly; mild hypoglycemia. May see rhabdomyolosis with prolonged exercise. Type VIII (phosphorylase b kinase) included now with Type VI. 3’5’AMP dependent kinase X-linked
XI	Glucose transporter, GLUT 2(Fanconi-Bickel syndrome)	Failure to thrive. Hypoglycemia; hepatomegaly; osteopenia; renal tubular acidosis
XII	Aldolase A deficiency (failure to convert fructose-1,6-biphosphate) ALDOA gene at 16p11.2	Hemolytic anemia with or without myopathy; intellectual disability
XIII	β-enolase deficiency (failure to convert 2-phosphoglycerate and phosphoenolpyruvate) ENO3 gene at 17p13.2	Exercise intolerance

CARBOHYDRATE ENZYME DISORDERS

Galactosemia

- Most common carbohydrate defect.
- Failure to thrive and developmental delay.
- Hepatic insufficiency and jaundice.
- Cataracts.
- GALK1 gene at 17q25.1
- Deficiency in galactose-1-phosphate uridyl transferase.
- Galactose-1-phosphate to glucose-1-phosphate conversion diminished
- Incorporation into glycolipid and glycoprotein pathways diminished.
- Polyol pathway activated (galacitol, galactonate)
- Milk diet worsens condition.

Fructose metabolism disorders

- Fructose intolerance.
- Hypoglycemia, vomiting, jaundice.
- May develop cirrhosis.
- Autosomal recessive.
- ALDOB gene at 9q31.1 (aldolase B)
- Fructose-1-phosphate accumulates, resulting in diminished phosphate for metabolism.
- Diminish intake of fructose and sucrose (glucose and fructose).

Fructose metabolism disorders

- Essential fructosuria.
- Autosomal recessive.
- KHK gene at 2p23.3
- Deficiency of hepatic fructokinase
- Fructose does not enter cells and is found in blood and spills in urine
- Milder than galactosemia.

Glucose-6-phosphate deficiency

- Most common human enzyme deficiency.
- X-linked recessive
- Hemolytic anemia results from oxidation products.
- Heinz bodies (altered hemoglobin molecules precipitated within erythrocytes)
- Bite cells (phagocytized removal of Heinz bodies)
- Associated with resistance to malaria.
- G6PD1 gene at Xq28
- Deficiency of G6PD leads to diminished production of NADPH
- Glutathione not maintained in reduced state

METAL DISORDERS

Pantothelate kinase associated degeneration

- (Hallervorden-Spatz)
- Childhood presentation.
- Distorting muscle contractions (dystonia)
- Spasticity and rigidity
- Autosomal recessive.
- PAKN2 gene at 20p13 regulates production of AcetylCoA

Pantothelate kinase associated degeneration

- Late childhood
- Dementia and behavioral change
- Dysarthria more prominent.
- Parkinson-like symptoms
- Iron pigment accumulates in nigrostriatum
- MRI shows bilateral hypodensity of globus pallidus with central zone of hyperintensity (“tiger eye”).

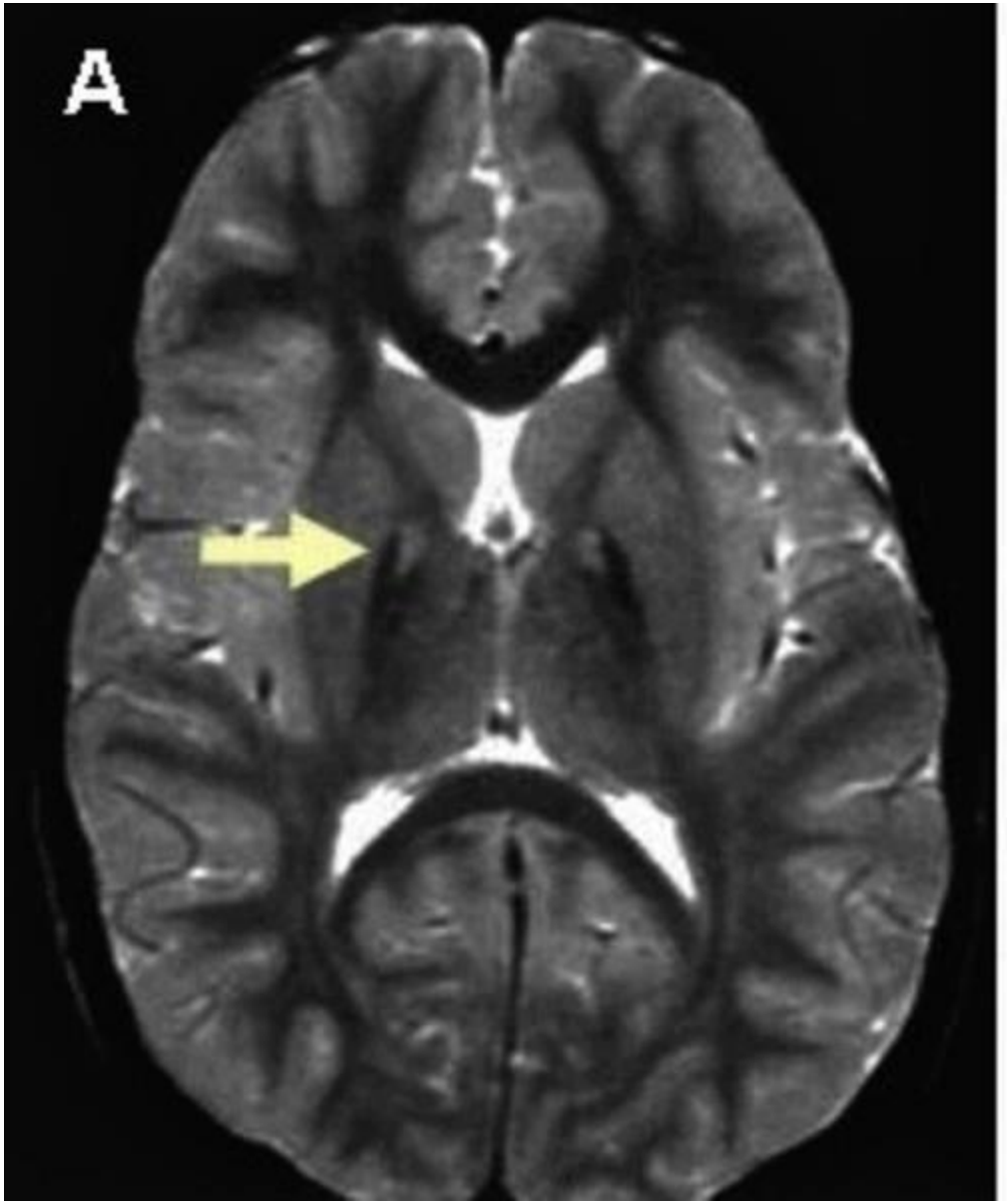
HARP syndrome

- Hypobetalipoproteinemia
- Acanthocytosis
- Retinitis pigmentosa
- Pallidal degeneration
- Parkinson-like symptoms
- Autosomal recessive
- PAKN2 at 20p13 (regulates production of AcetylCoA)
- Iron pigment accumulates in nigrostriatum.
- MRI shows bilateral hypodensity of globus pallidus with central zone of hyperintensity (“tiger eye”).

Eye of the tiger sign compatible with iron accumulation

https://ghr.nlm.nih.gov/condition/pantothenate-kinase-associated-neurodegeneration

Accessed 03/20/2020



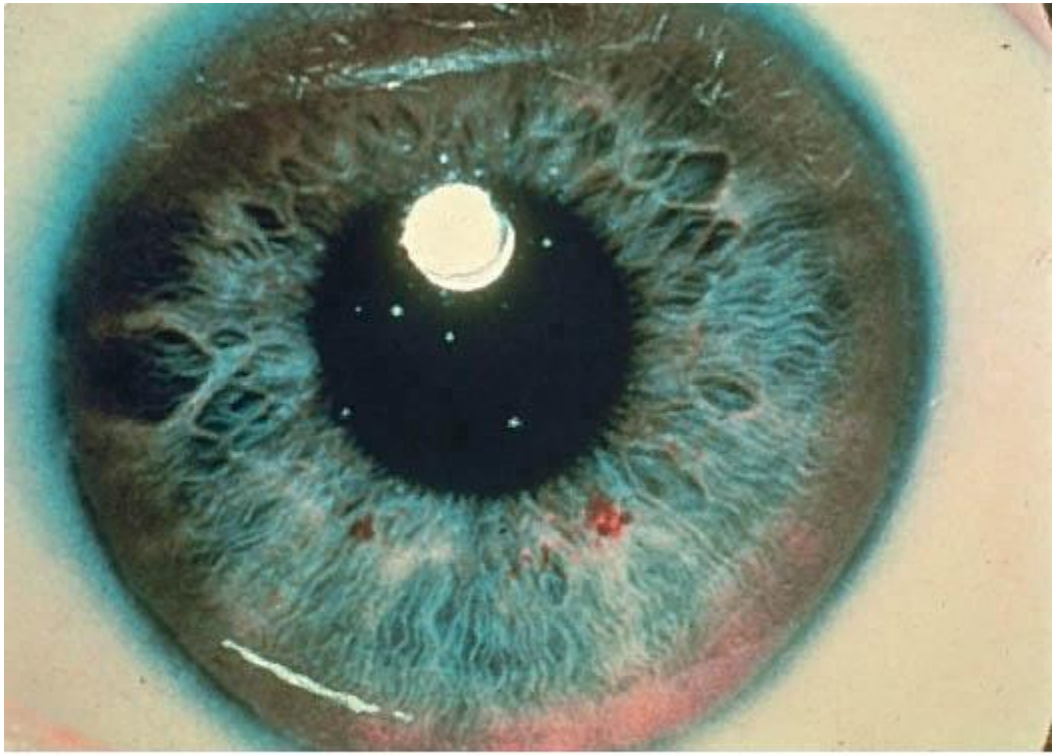
Wilson's disease

- Mild behavioral changes
- Parkinson-like syndrome or
- Psychosis
- May see atrophy and cavitation of the putamen.
- May lead to acute liver failure
- Green-brown deposits of Copper in Descemet's membrane in the limbus of the Cornea is diagnostic (Kayser-Fleischer ring).
- May be absent in 50% of patients

Wilson's disease

- Autosomal recessive.
- ATP7B gene at 13q14.3 (ATPase 2 Copper transporting enzyme)
- 40% of cases in Northern Europeans have same mis-sense mutation.
- Microscopically mimics hepatitis.
- Ratio of alkaline phosphatase to total bilirubin <4.0 with AST/ALT > 2.2 is diagnostic (in liver failure)

Kayser-Fleischer ring



Source: McPhee SJ, Papadakis MA: *Current Medical Diagnosis and Treatment 2010,* 49th Edition: http://www.accessmedicine.com

(Reproduced, with permission, from Yarze JC, Martin P, Munoz SJ, Friedman LS: Wilson's disease: Current status. Am J Med 1992;92:643.)

Fig. Ch. 16
Accessed 03/01/2010

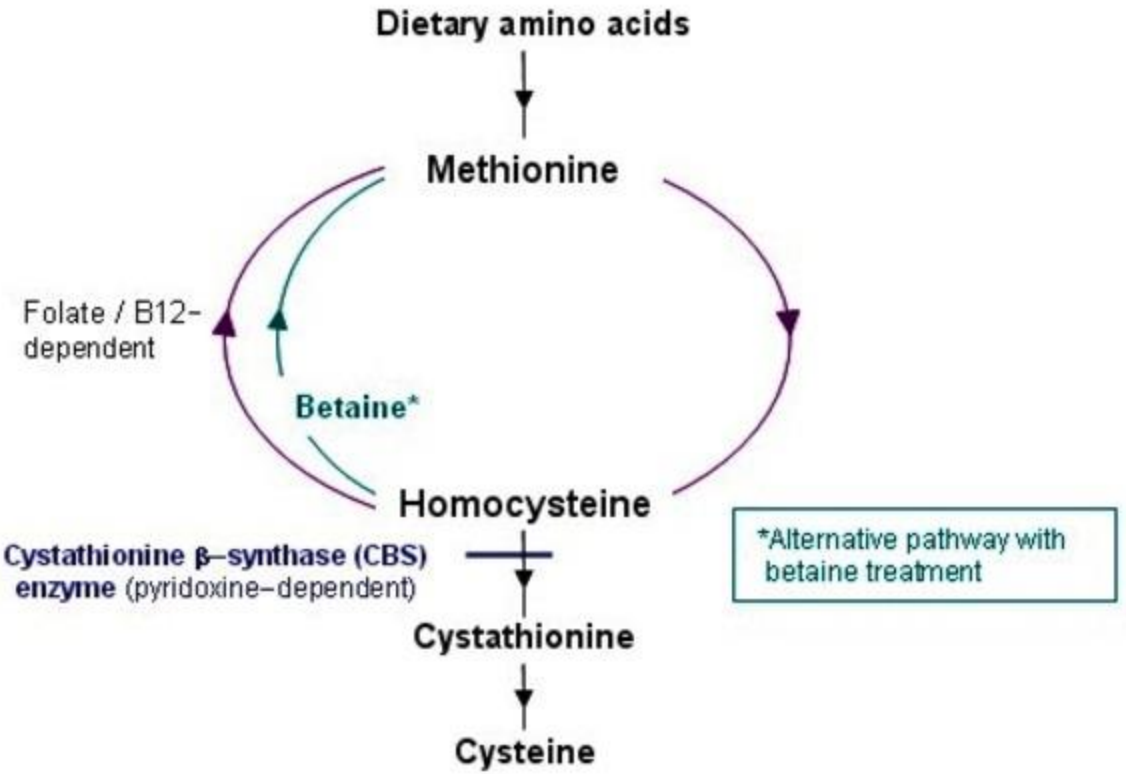
Wilson's disease

- Majority of patients are compound heterozygotes containing different mutations of the disease gene (ATP7B) on each allele at13q14.3.
- ATP7B codes for a transmembrane Cu^{2+} transporting ATPase located on the hepatocyte canalicular membrane.
- Permits binding to ceruloplasmin.

AMINO ACID DISORDERS

Homocystinuria

- Presents in first year of life
- Myopia, lens dislocation, osteoporosis in most common form
- Autosomal recessive
- CSB gene at 221q22.3
- Cystathione-β-synthase deficiency prevents further metabolism of homocysteine to cysteine and methionine
- Less common form associated with failure to grow, intellectual disability, megaloblastic anemia, and increased risk of stroke.
- Associated with mutations in tetrahydofolate and cobalamin pathways



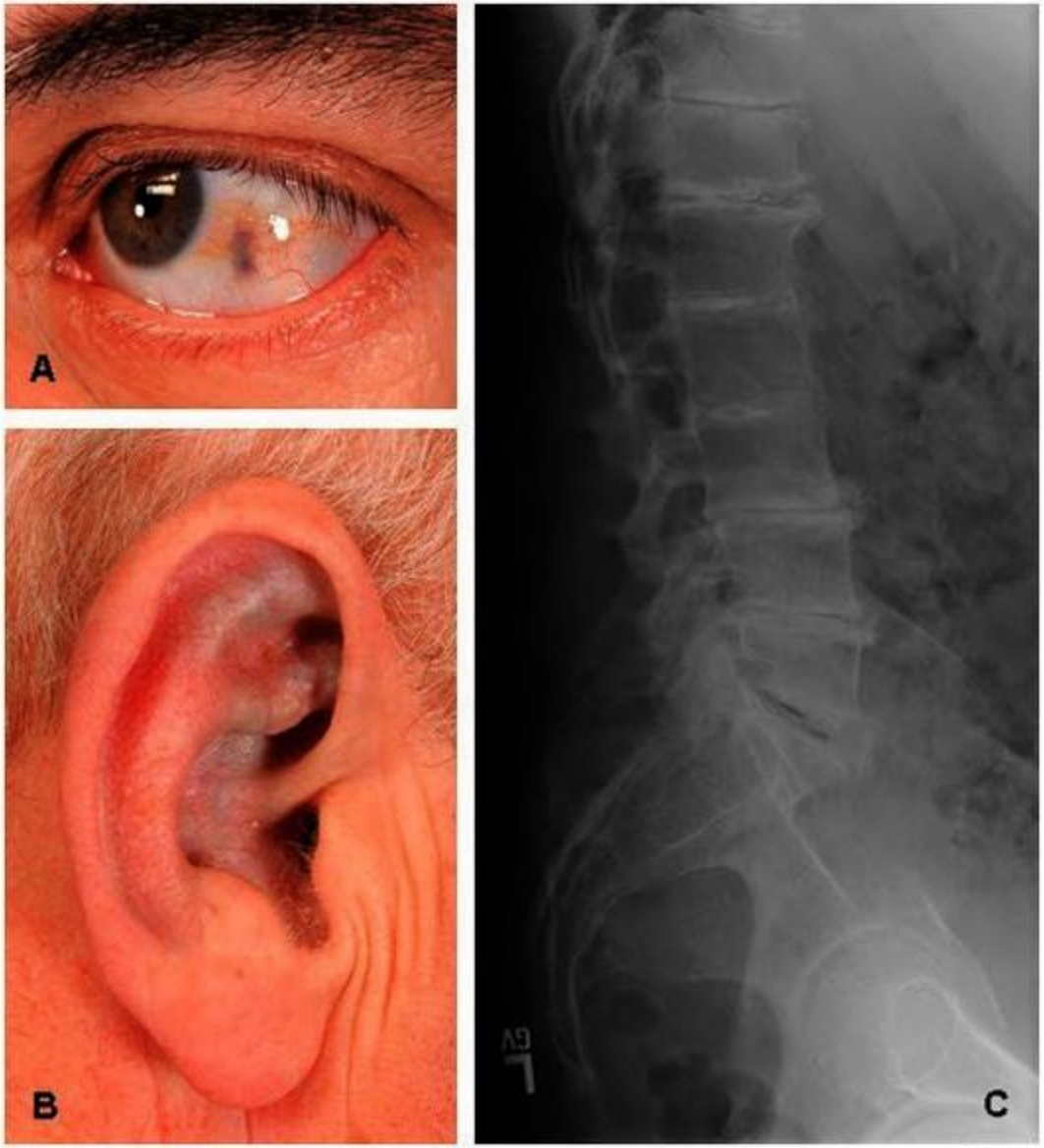
https://ghr.nlm.nih.gov/condition/homocystinuria#genes
Accessed 03/20/2020

Maple syrup urine disease

- Presents in infancy
- Ketoacidosis
- Hypotonia
- Seizures and coma.
- Distinctive sweet aroma of urine
- Autosomal recessive
- BCKDHA gene at 19q13.2 or BCKDHB gene at 6q14.1 affects EC1 complex in mitochondria
- DBT gene at 1p22 affects EC2 complex in mitochondria
- Defective α-keto acid dehydrogenase impedes breakdown of branched chain amino acids (leucine, isoleucine, valine).

Alkaptonuria

- Neonates.
- Blue-black pigmentation of skin and sweat glands appears about age 30
- Black ear wax
- Cartilage deposition associated with arthritis in large joints and spine
- Degrades heart valves
- Kidney and prostate stones
- Autosomal recessive
- HGD gene at 3q13.33
- Defect in homogentisate-1,2-dioxygenase impairs metabolism of tyrosine and phenylalanine
- Homogentisic acid accumulates in tissues



A shows ochronosis of the eye.
B shows ochronosis of the ear.
C shows an x-ray image of the lower spine with disc flattening, calcification, and osteophyte formation.

https://ghr.nlm.nih.gov/condition/alkaptonuria#inheritance
Accessed 03/20/2020

Hartnup disease

- Aminoaciduria usually
- Autosomal recessive
- May present with other signs temporarily if stressed, febrile, or consuming a nutrient poor diet:
- Red, scaling skin rash (exposed skin).
- Episodic ataxia.
- Depression
- SLC6A19 gene at 5p15.33
- Deficiency of B(0) neutral amino acid transporter 1 (B^0AT1) impairs renal and intestinal transport of neutral amino acids.

Phenylketonuria

- Classic form presents within months after birth
- Milder versions occur
- Psychomotor retardation.
- Musty odor to skin.
- Autosomal recessive
- PAH gene at 12q23.2
- Phenylalanine hydroxylase deficiency.
- Failure to convert phenylalanine to tyrosine.

Phenylketonuria

- May also see elevated phenylalanine with tetrahydrobiopterin (a cofactor) deficiency
- GCH1 gene at 14q22.2 (GTP cyclohydrolase 1)
- Impair dopamine and serotonin formation
- PCBD1 gene at 10q22.1 (pterin-4 alpha-carbinolamin dehydratase)
- PTS at 11q23.1 (6-pyruvoyltetrahydropterin synthase)
- Both PCBD1 and PTS impair cofactor formation
- QDPR gene at (Quinoid dihydropteridine reductase)
- Unable to recycle cofactor

Acidurias

- Non-ketotic hyperglycinemia.
- Presents shortly after birth
- Hypotonia, myoclonus, seizures.
- Autosomal recessive
- PCCA gene at 13q32.2 (Proprionyl carboxylase CoA)
- Defective breakdown of isoleucine, methionine, threonine, and valine as well as conversion proprionylCoA to methylmalonylCoA.

Acidurias

- Glutaric acidemia Type 1.
- Infancy
- Spasticity, rigidity, hypotonia
- May bleed spontaneously in brain or eyes
- Autsomal recessive
- GCDH gene at 19p13.13 (Glutaryl-CoA dehydrogenase)
- Found in mitochondria
- Unable to degrade lysine, tryptophan, hydroxylysine.
- Accumulation of intermediate (3-hydroxyglutaric acid) leads to basal ganglia damage.
- Carnitine deficiency as organic acids detoxified by carnitine.

Acidurias

- Glutaric acidemia Type 2.
- Infancy
- Acidosis, hypoglycemia, hyperammonemia
- Hepatomegaly
- Dilated cardiomyopathy
- Autsomal recessive
- ETFA gene at 15q24.2-3 and ETFB gene at 19q13.41 (electron transfer flavoprotein) or EFTDH gene at 4q32.1 (electron transfer flavoprotein dehydrogenase)
- Found in mitochondria
- Acyl carnitines increased

Acidurias

- Isovaleric acidemia.
- Infancy
- Poor feeding, seizures, lethargy
- Odor of sweaty feet during acute illness.
- Milder or asymptomatic forms also are found.
- Autosomal recessive
- IVD gene at 15q15.1 (isovalerylCoA dehydrogenase)
- Unable to degrade leucine

Kearns-Sayre syndrome

- Appears before age 20
- Chronic progressive external ophthalmoplegia
- Ptosis
- Pigmentary retinopathy (salt and pepper retinal pigmentation)
- 2^{o} and 3^{o} grade heart block
- Ataxia
- Proximal myopathy
- Ragged red muscle fibers
- Cerebral folic acid levels diminished
- Electron transfer genes (12) deleted in X chromosome
- Oxidative phosphorylation impaired

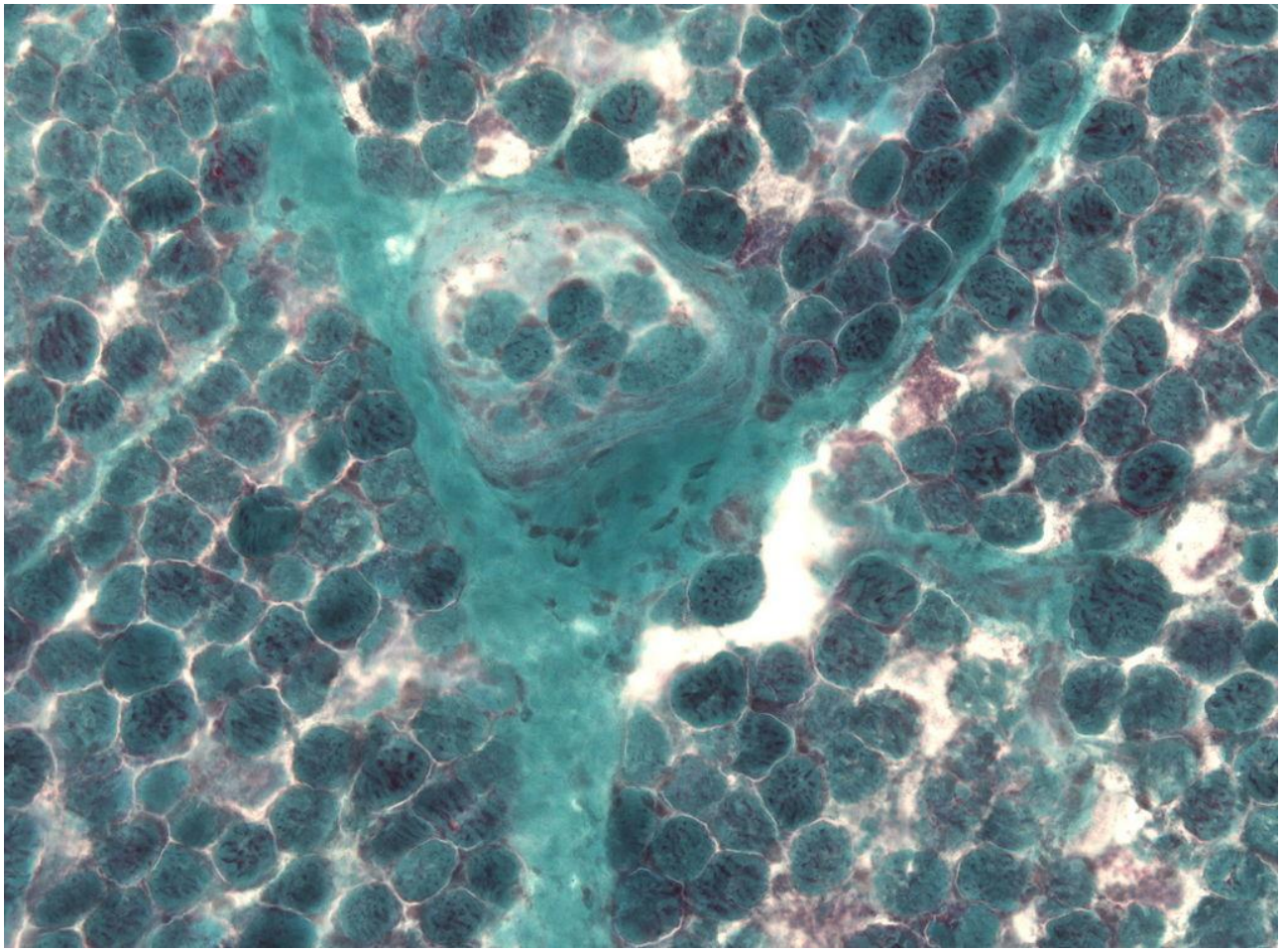
Leigh syndrome

- Infants
- Hypotonia and dystonia
- Psychomotor regression
- Ophthalmoparesis
- Optic atrophy
- Hypertrophic cardiomyopathy
- CSF lactate increased

Leigh syndrome

- Most common is MTP-A6 gene (X-linked)
- 33% of cases involve NADH-ubiquinone oxidoreductase
- Transfer electrons from NADH to CoQ10
- Transfer H+ across membrane
- 15% of cases involve SURF1 gene at 9q34.2 (cytochrome c oxidase – CoQ10)
- Mitochondrial respiratory chain and protein synthesis defects.

Ragged red fibers



https://en.wikipedia.org/wiki/Leigh_syndrome#/media/File:Leigh_Trichrom.jpg Accessed 03/20/2020

Urea cycle disorders

- Type I hyperammonemia.
- Newborn
- Lethargic, needs stimulation to feed
- Vomiting
- Increasing lethargy
- Hypothermia
- Hyperventilation.
- CPSD gene at 2q34. (Carbamoylphosphate synthetase I)
- Unable to incorporate excess nitrogen into urea cycle
- Treatment with arginine activates N-acetylglutamate synthetase

Urea cycle disorders

- N-acetylglutamate synthetase deficiency.
- Severe hyperammonemia, acidosis, hypoglycemia
- Recurrent diarrhea
- Ataxia
- Deep coma
- hyper-ornithinemia.
- Treatment includes administration of carbamoyl glutamate to activate CPS I.

Urea cycle disorders

- Increased serum orotic acid due to mitochondrial carbamoylphosphate entering cytosol, incorporated into pyrimidine nucleotides.
- Leads to excess production and consequently excess catabolic products
- Treat with high carbohydrate, low protein diet
- Ammonia detoxification
- Sodium phenylacetate or sodium benzoate

Urea cycle disorders

- Classic citrullinemia.
- Infancy
- Episodic hyperammonemia
- Vomiting
- Lethargy
- Ataxia
- Seizures
- Eventual coma.
- ASS1 gene at 9q34.11(Argininosuccinate synthetase)
- Treat with arginine administration to enhance citrulline excretion, also with sodium benzoate for ammonia detoxification.

Urea cycle disorders

- Hyperargininemia.
- Infancy
- Lethargy, hypotonia, seizures, and stunted growth
- Ammonia and arginine high in cerebral spinal fluid and serum.
- Arginine, lysine and ornithine high in urine
- Autosomal recessive
- ARG1 gene at 6q23.2 (Arginase deficiency)
- Treatment includes diet of essential amino acids excluding arginine, low protein diet.