Metabolic Storage Disorders of the Nervous System

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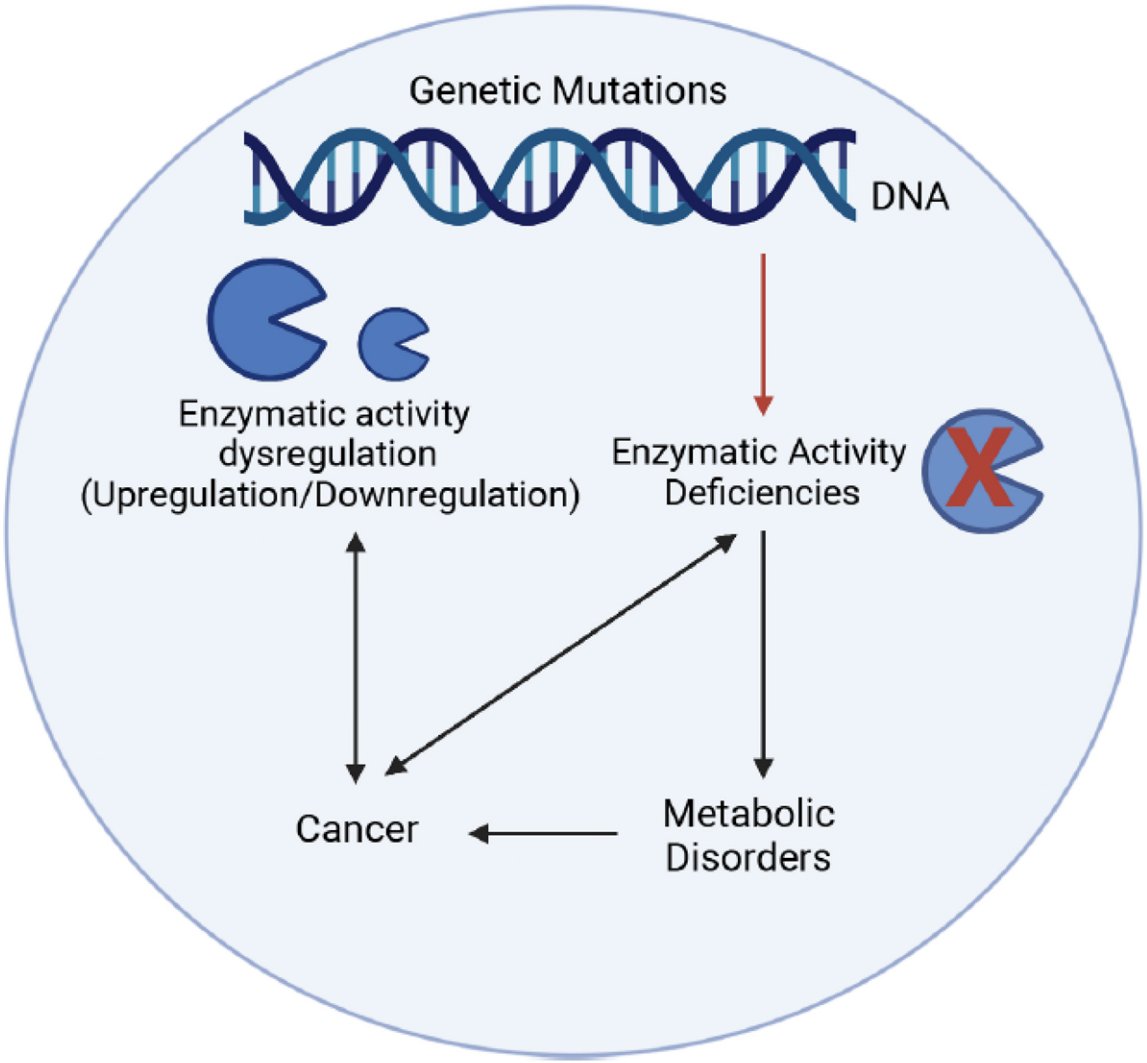
Disclosures

- I get a small royalty for sales of the book Perinatal Neuropathology

Learning Objectives

- Explain the normal turnover and recycling of proteins and lipids in the central nervous system
- Explain what happens when the recycling systems fail
- Give three examples of storage disorders of the CNS
- Explain a current approach to studying storage disorders



Altered Metabolic Pathways

- Urea Cycle
- Glycogen Storage
- Lysosome Storage
- TCA cycle
- Mitochondrial Fatty Acid Beta Oxidation

→ Brain disease

Mahé et al. 2023 doi: 10.3389/fonc.2023.1230934

AANP

Roche Biochemical Pathways

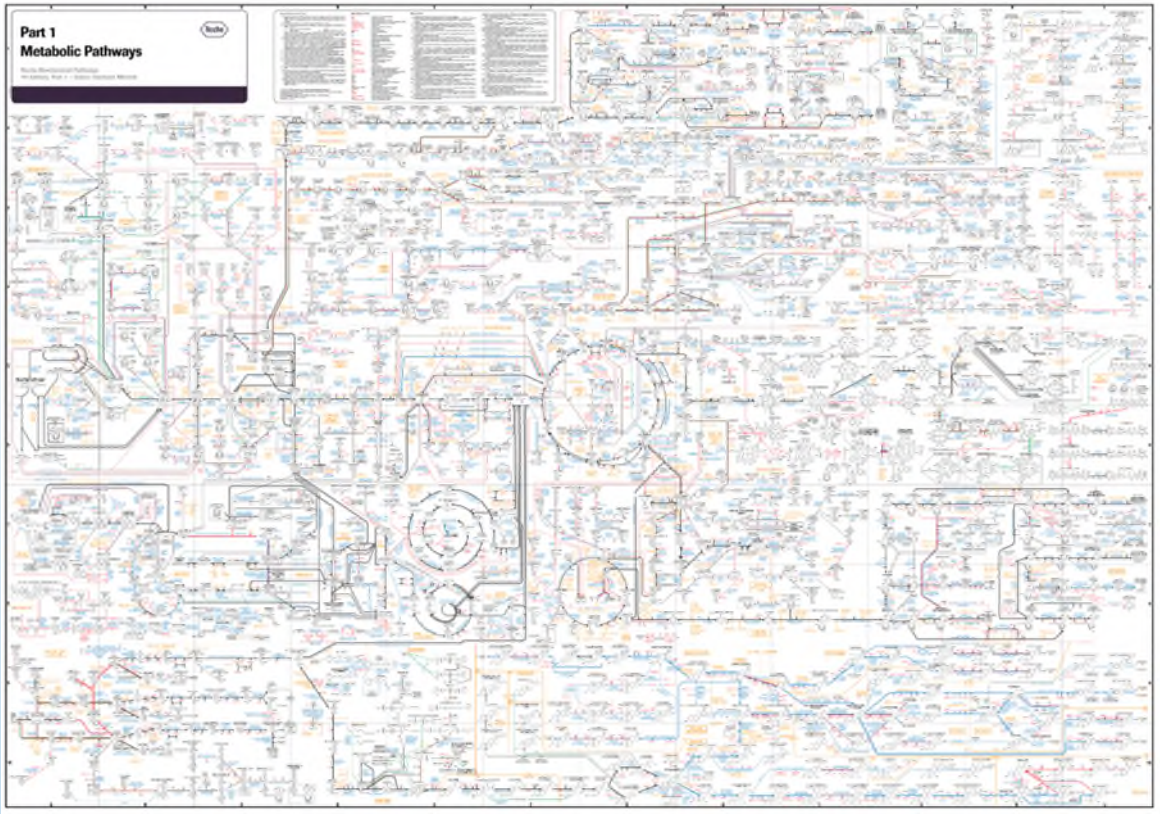
The Biochemical Pathways Wall Charts have enjoyed worldwide popularity as a standard reference for nearly 50 years.

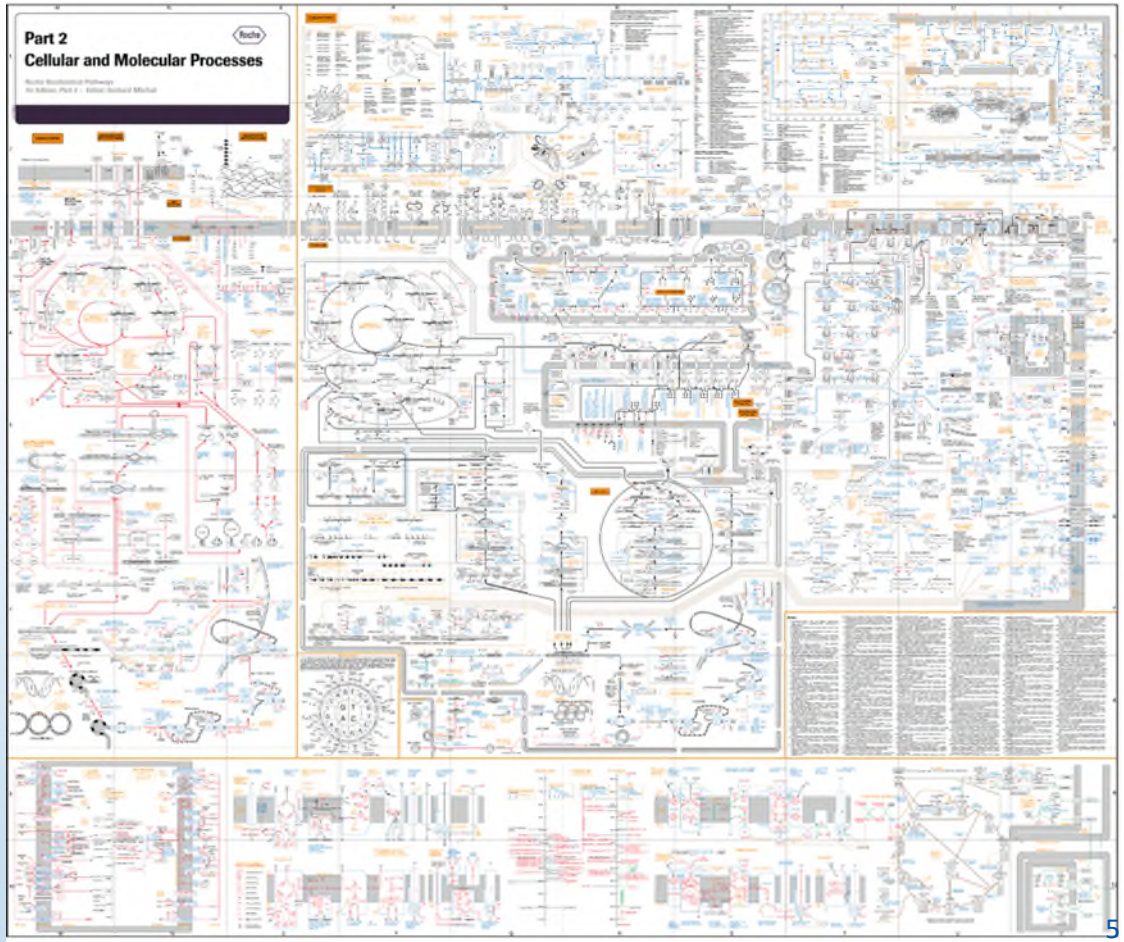
https://www.roche.com/sustainability/philanthropy/science_education/pathways.htm. 1965-2025 ??discontinued

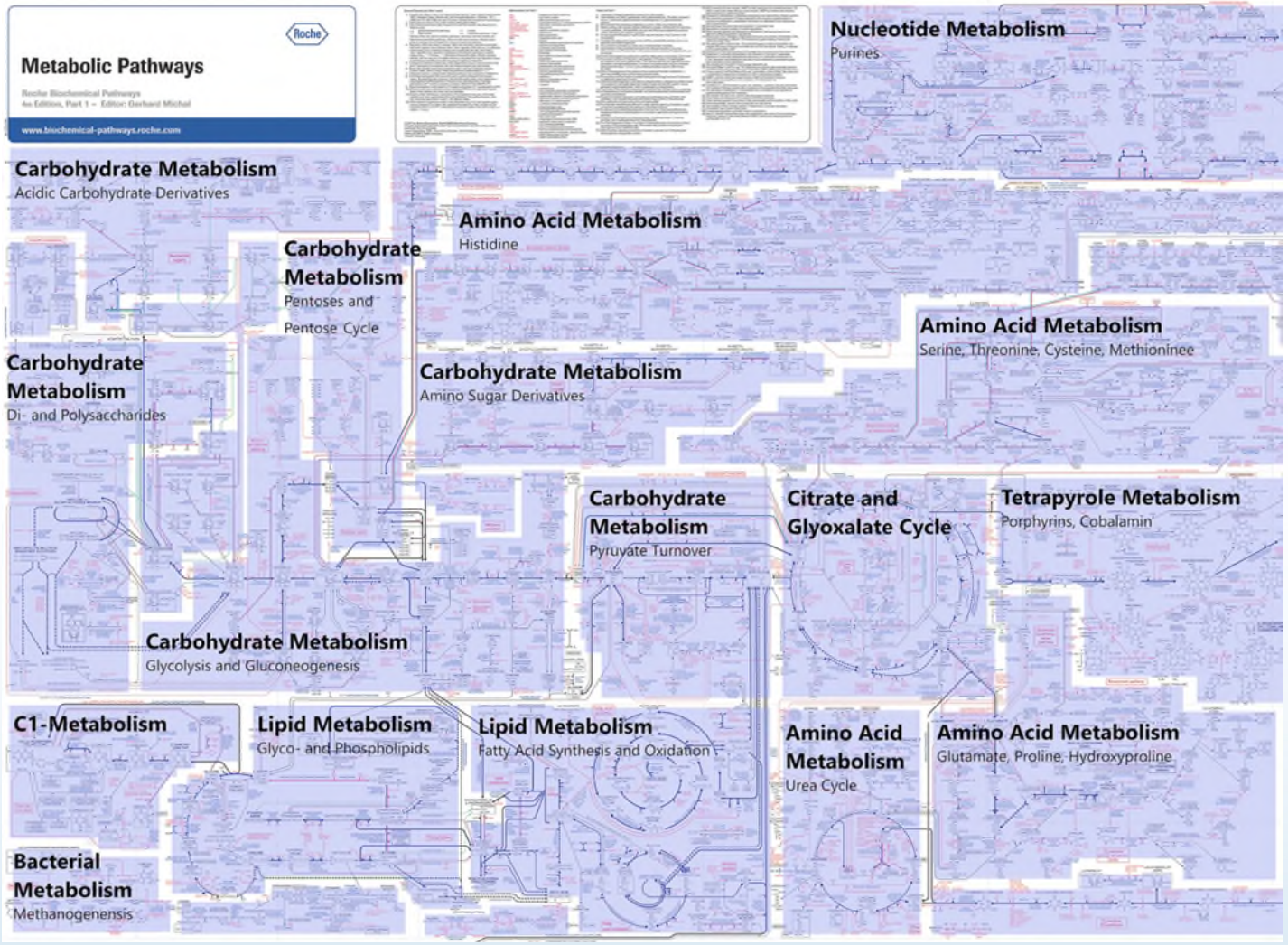
See also

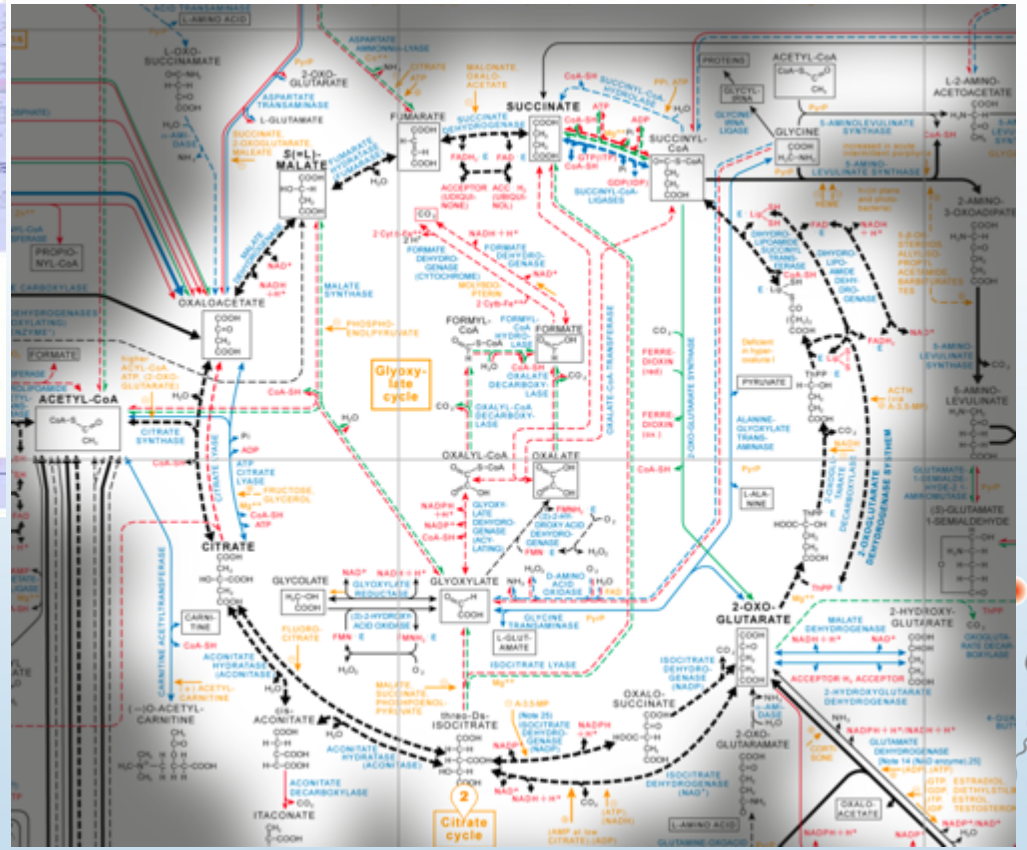
http://astrojan.nhely.hu/protein/bohr5.htm

https://www.vmh.life/#reconmap2



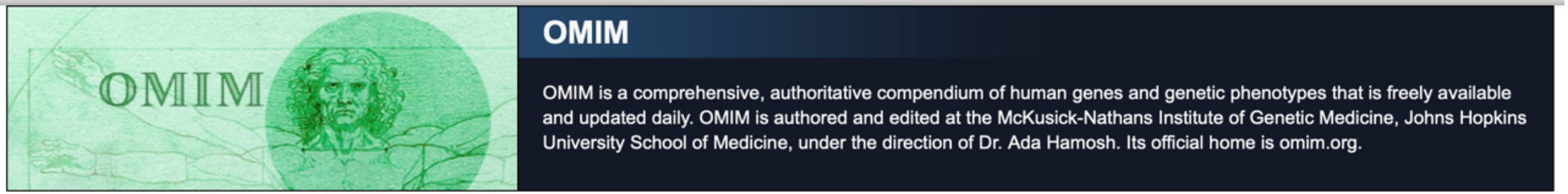



Roche
Metabolic Pathways
Roche Biochemical Pathways
4th Edition, Part 1 – Editor: Gerhard Michal
www.biochemical-pathways.roche.com
Nucleotide Metabolism
Purines
Carbohydrate Metabolism
Acidic Carbohydrate Derivatives
Amino Acid Metabolism
Histidine
Carbohydrate Metabolism
Pentoses and
Pentose Cycle
Amino Acid Metabolism
Serine, Threonine, Cysteine, Methioninee
Carbohydrate Metabolism
Di- and Polysaccharides
Carbohydrate Metabolism
Amino Sugar Derivatives
Carbohydrate Metabolism
Pyruvate Turnover
Citrate and Glyoxalate Cycle
Tetrapyrole Metabolism
Porphyrins, Cobalamin
Carbohydrate Metabolism
Glycolysis and Gluconeogenesis
C1-Metabolism
Lipid Metabolism
Glyco- and Phospholipids
Lipid Metabolism
Fatty Acid Synthesis and Oxidation
Amino Acid Metabolism
Urea Cycle
Amino Acid Metabolism
Glutamate, Proline, Hydroxyproline
Bacterial Metabolism
Methanogenesis


ACETYL-CoA
OXALOACETATE
CITRATE
SUCCINATE
FUMARATE
S(+L)-MALATE
GLYOXYLATE
GLYCOLATE
OXALYL-CoA
OXALATE
FORMYL-CoA
FORMATE
PYRUVATE
GLYCINE
2-OXO-GLUTARATE
SUCCINYL-CoA
Glyoxylate cycle
Citrate cycle

Enzymes

- Scientific databases list >3,400 human enzymes with specific commission numbers, the majority of which are non-digestive
- https://www.genome.jp/kegg/annotation/enzyme.html
- https://enzyme.expasy.org/
- https://www.brenda-enzymes.org/



- OMIM - Online Mendelian Inheritance in Man (https://www.ncbi.nlm.nih.gov/omim)
- continuously updated catalog of human genes and genetic disorders and traits, with a particular focus on the gene-phenotype relationship
- >25,000 entries
  - >9,000 represent phenotypes
  - >15,000 represent gene mutations

https://www.proteinatlas.org

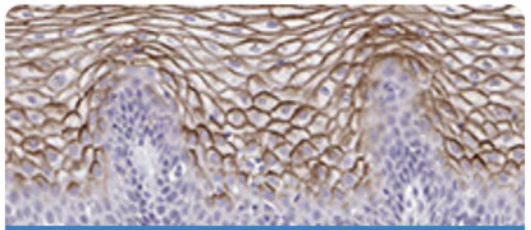
THE HUMAN PROTEIN ATLAS

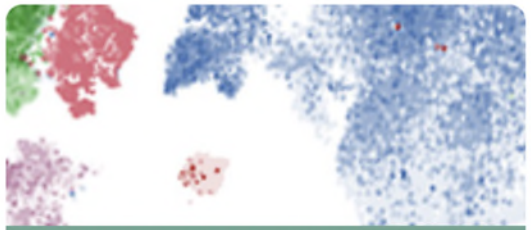
MENU HELP NEWS

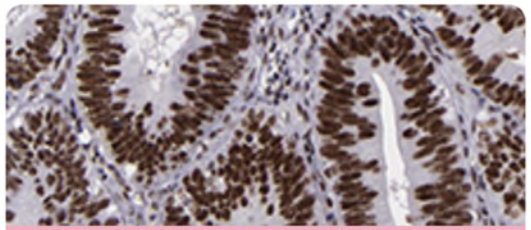
SEARCH[i]

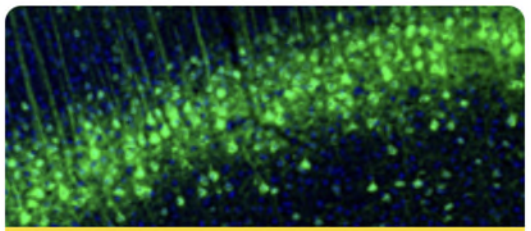
Search Fields »

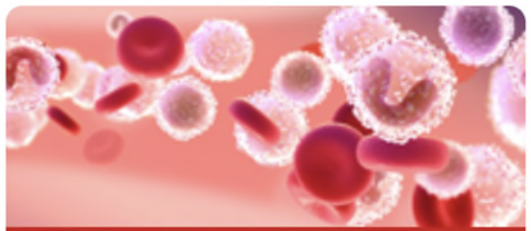
e.g. ACE2, GFAP, EGFR

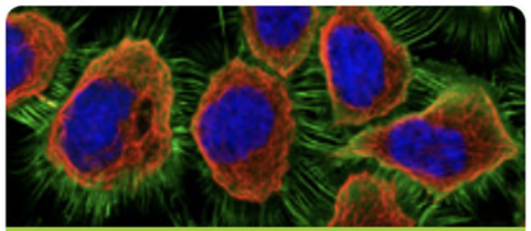

TISSUE ATLAS


SINGLE CELL TYPE ATLAS


PATHOLOGY ATLAS

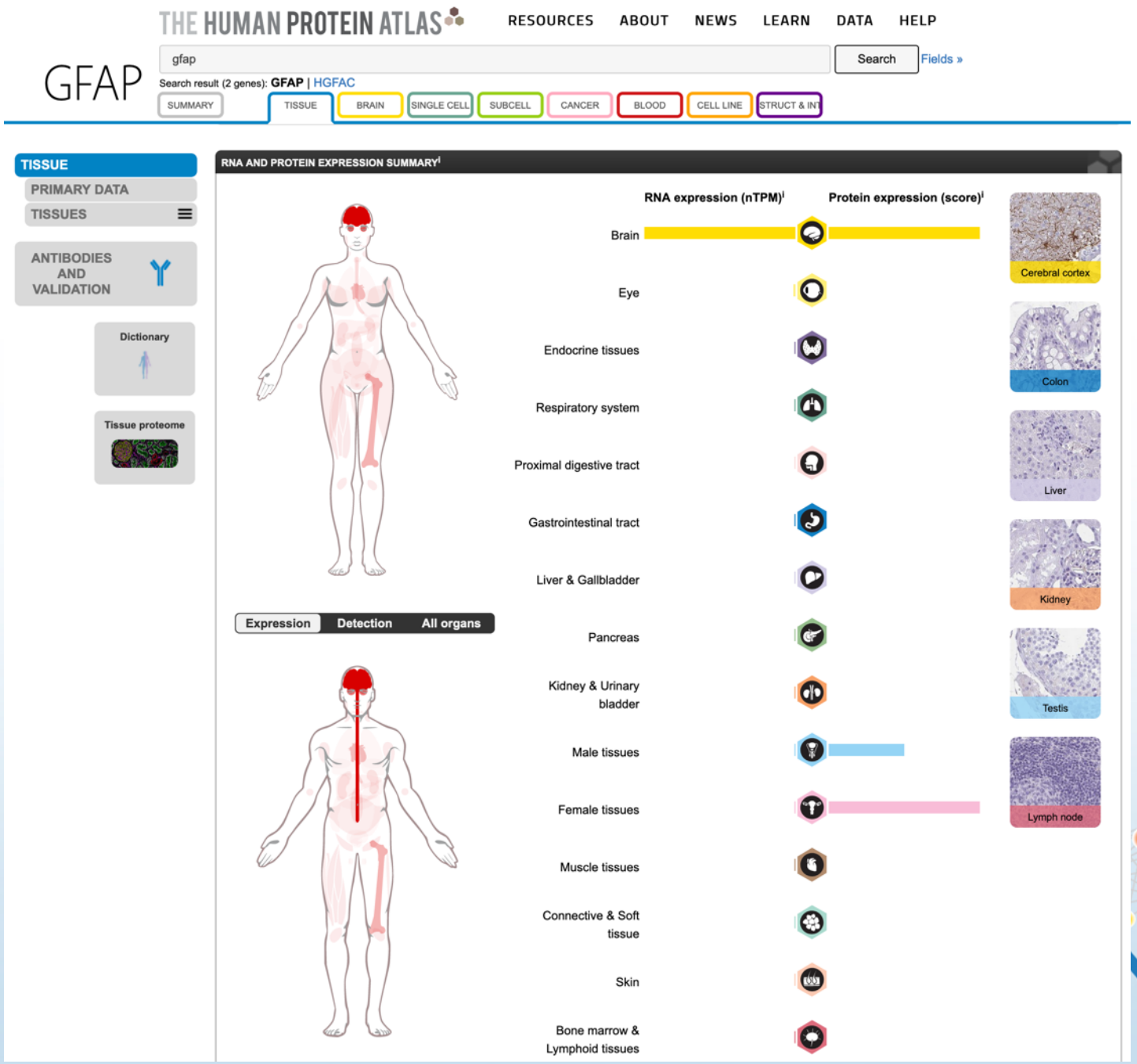

BRAIN ATLAS


BLOOD ATLAS


CELL ATLAS

RNA expression level indicates mRNA abundance, a reflection of turnover and ongoing necessity

Protein expression score is based on immunostaining; in the absence of high RNA expression this might be misleading



THE PRINCIPLES ARE MORE IMPORTANT THAN THE DETAILS BECAUSE IT IS IMPOSSIBLE (FOR NON-AI ENTITIES) TO KNOW ALL

All constituents of tissue are either incorporated or produced locally and must be degraded / recycled / disposed / expelled.

Failure of disposal can result from abnormal disposal system or abnormal waste that the disposal system cannot handle.

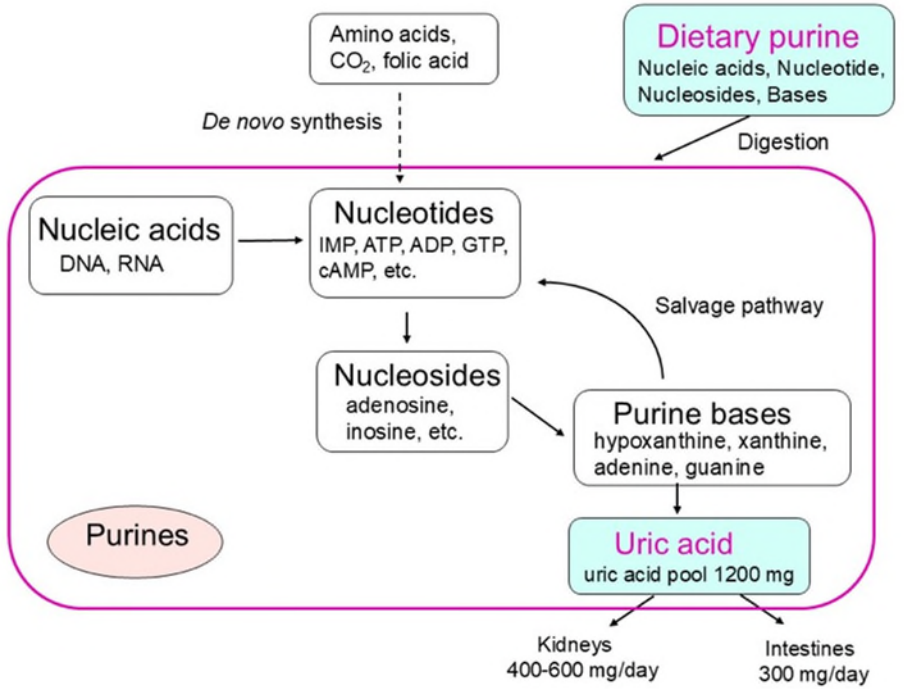
Materials not dealt with may be stored in the garbage piles in a non-toxic way (e.g. lipofuscin, corpora amylacea), or they may accumulate and become toxic

Even if aggregates themselves are not toxic, accumulation indicates a blocked metabolic pathway, the failure of which interferes with normal cell function / survival

Cell turnover in the normal CNS – generally low

- Difficult to study directly in humans
- Frisen et al. studied ^{14}C incorporation (radioactive fallout) in human brains
- Most experiments based on ^{3}H-thymidine administration, which is incorporated into DNA (mice most common)
- Younger animals have higher turnover rates (i.e. during growth)
- In adult mice (~9 months) +/- humans
  - Neurons postmitotic (dentate granule neurons ???)
  - Astrocytes: 0.4% per day (mouse McCarthy & Leblond 1988)
  - Oligodendrocytes: 0.04% per day (mouse ibid); 0.32% per year in human (Yeung et al. 2019)
  - Endothelial cells: 0.3% per day, longevity 1 to >10 years (Hobson & Denekamp 1984)
  - Microglia: 0.1% per day (human IdU and ^{14}C; Reu et al. 2017)
- Mitochondrial turnover: months (Poovathingal et al. 2012)

DNA synthesis and turnover



- Chromosome replication during cell division / mitotic activity
- Unscheduled DNA synthesis - DNA repair that occurs in response to DNA damage, independent of the normal cell cycle
- In mouse brain, nuclear DNA half life (overall) ~20 days (Williams et al. 1982)
- Faulty DNA repair associated with various neurological diseases and cancer
- Some nucleosides are recycled, some eliminated as uric acid
- Excess uric acid can cause gout, which carries increased risk of neurodegenerative disease (Topiwala et al. 2023)

- Ribonucleases degrade mRNA (and other forms) e.g. after protein synthesis
- If cell dies, most DNA is recycled locally - <1% of brain cell DNA reaches blood plasma as cell free DNA (Sender et al. 2024)

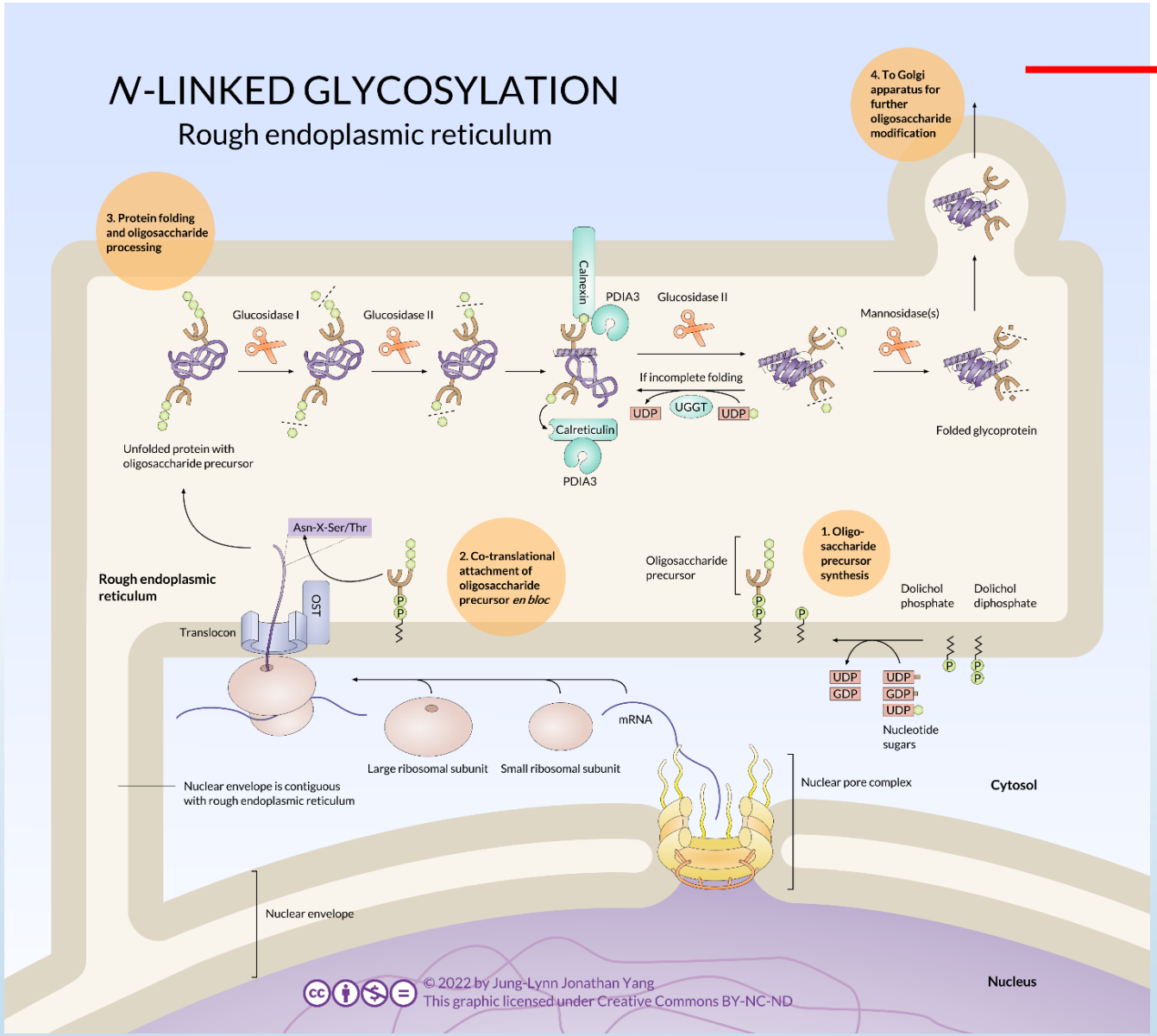
Protein synthesis and turnover

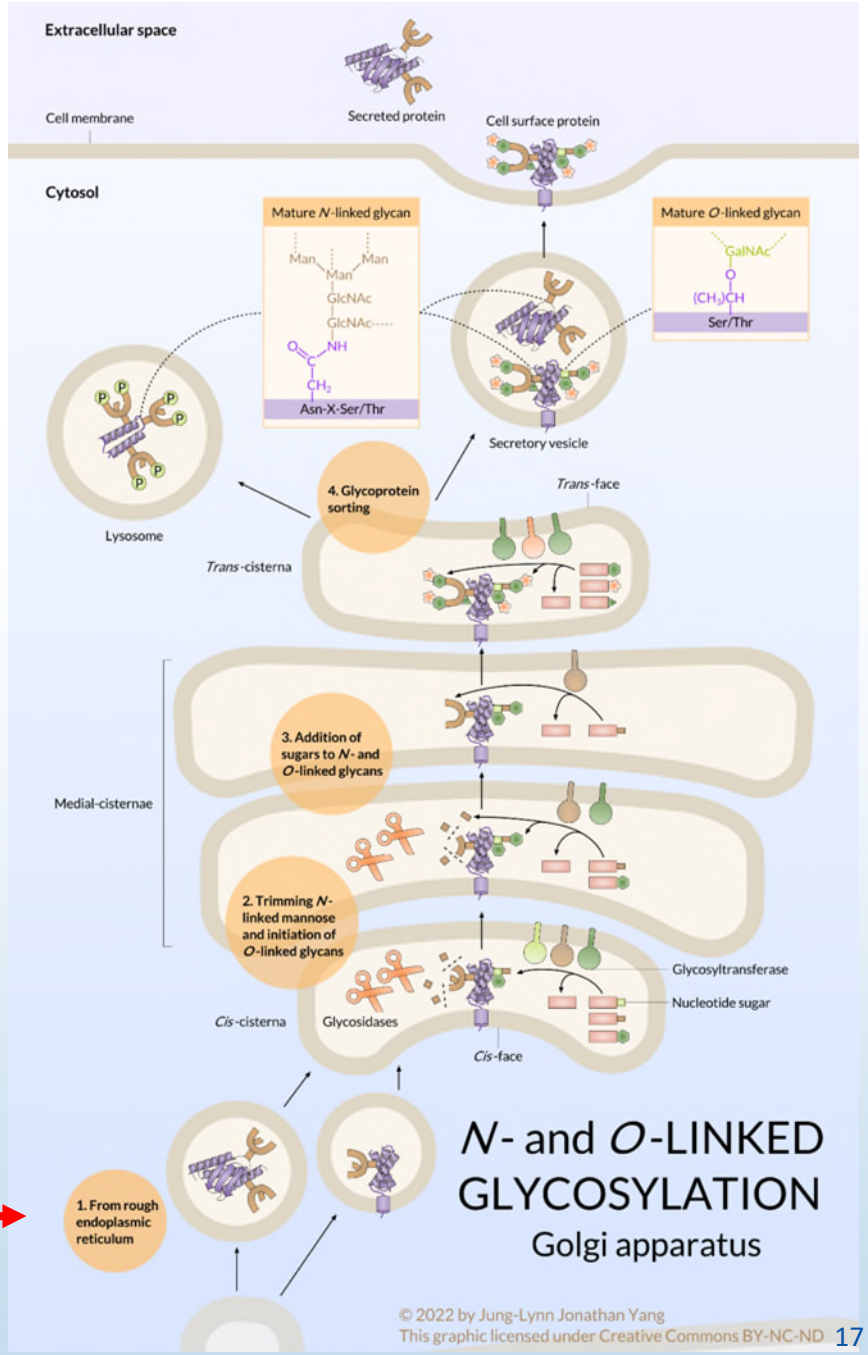
- Essential amino acids are transported across the blood-brain barrier (BBB) via specific carrier systems; many are solute carrier (SLC) family

Table 1
Transporters from SLC superfamily expressed in the BBB.

Transporters	Family	Physiological Substrate	Transport mechanism	Brain localisation
EAAT2 (SLC1A2)	SLC1	L-Glu, L-Asp	Symport	Abluminal membranes of BBB
EAAT1 (SLC1A3)	SLC1	L-Glu, L-Asp	Symport	Abluminal membranes of BBB
ASCT1 (SLC1A4)	SLC1	L-Ala, L-Ser, L-Cys, Gly, L-Met, L-Val, L-Leu, L-Ile, L-Thr, D-Ser, L-Glu	Antiport	Luminal and Abluminal sides of BBB
ASCT2 (SLC1A5)	SLC1	L-Ala, L-Ser, L-Cys, Gly, L-Met, L-Val, L-Leu, L-Ile, L-Thr, L-Glu	Antiport	Abluminal membranes of BBB
GLUT1 (SLC2A1)	SLC2	Glucose, galactose, mannose, 2-deoxy-d-glucose, 2-deoxy-2-[^{18}F]-d-glucose, glucosamine and dehydroascorbic acid	Uniport	Luminal and Abluminal membranes of BBB
CAT1 (SLC7A1)	SLC7	L-Arg, L-Lys, L-Orn	Unknown	Luminal and Abluminal membranes of BBB
LAT1 (SLC7A5)	SLC7	L-Leu, L-Phe, L-Cys, L-Tyr, L-Trp, L-His, L-Met, L-Ile, L-Val; Thyroid hormones, l-DOPA	Antiport	Luminal and Abluminal membranes of BBB, Neurons, Astrocytes, Microglia
MCT1 (SLC16A1)	SLC16	Lactate, pyruvate, ketone bodies	Symport	Luminal and Abluminal membranes of BBB, Neurons, Astrocytes,
MCT8 (SLC16A2)	SLC16	Thyroid hormones (T3 and T4)	Unknown	Luminal and Abluminal membranes of BBB, Neurons
OATP1A2 (SLC21A3)	SLC21	Organic anions, lipids	Unknown	Luminal membranes of BBB, Neurons
OATP2B1 (SLC21A9)	SLC21	Organic anions	Unknown	Luminal membranes of BBB
OCT1 (SLC22A1)	SLC22	Organic cations	Antiport	Luminal and Abluminal sides of the BBB endothelial cells
OCT2 (SLC22A2)	SLC22	Organic cations	Antiport	Luminal and Abluminal sides of the BBB endothelial cells
OCT3 (SLC22A3)	SLC22	Organic cations	Antiport	Luminal and Abluminal sides of the BBB endothelial cells
OCTN1 (SLC22A4)	SLC22	Acetylcholine, Ergothioneine, Carnitine	Symport	Luminal and Abluminal membranes of BBB
OCTN2 (SLC22A5)	SLC22	Carnitine, Acetylcholine	Antiport	Luminal and Abluminal membranes of BBB
OAT3 (SLC22A8)	SLC22	ketoglutarate, para-amino-hippuric acid, benzoyl penicillins, indoxyl sulfate, and homovanillic acid, prostaglandins	Unknown	Abluminal membranes of BBB
SNAT2 (SLC38A2)	SLC38	L-Pro, L-Asn, L-Cys, L-Glu, L-Gly, L-Met, L-Ser	Antiport	Abluminal sides of BBB
SNAT3 (SLC38A3)	SLC38	L-Gln, L-His, L-Asn	Antiport	Abluminal sides of BBB

Post-translational modifications





- Radioactive labelling of amino acids can give information about protein synthesis and degradation
- Lajtha et al. 1950s-1970s
- Radiolabeled amino acid (e.g. ^{14}C leucine, ^{14}C lysine, ^{14}C tyrosine) studies in young and adult mice
- Rapid (small proportion) and slow turnover proteins
- Brain - 5.7% of proteins have half-life of 15 hours and 94.3% have half-life of >10 days
- In adult mice, >97% of protein has turned over in 14-18 days
- Turnover of proteoglycan component may be same as protein backbone or faster (e.g. Roquemore et al. 1996)

Lajtha, J. Neurochem 3:358-365, 1959 (mouse)

TABLE 3.—HALF-LIFE TIME ($t_{1/2}$) OF PROTEINS AND FLUX (F) OF LEUCINE FROM N.P.N. INTO PROTEIN

Time after administration (min)	Brain				Liver			
	Adult		Newborn		Adult		Newborn	
	$t_{1/2}$	F	$t_{1/2}$	F	$t_{1/2}$	F	$t_{1/2}$	F
3	3·8	8·8	0·7	71	0·4	94	0·2	280
5	8·1	4·6	1·2	31	0·9	50	0·4	110
10	11	3·3	1·7	29	1·3	34	0·7	72
20	15	2·7	2·4	19	2·4	20	1·4	40
30	20	2·2	3·0	16	3·9	13	2·0	23
45	24	2·1	3·3	13	5·7	9·2	4·0	13
60	27	1·3	4·1	9·8			4·7	8

Flux = F = μg leucine/g dry protein per min. Half-life time = $t_{1/2}$ in days.

- In adult rat brain, almost 5% of protein breaks down daily (Goldspink 1988)
- Some proteins more stable; myelin basic protein (MBP) has >95% turnover after 3 months (Wood 1971)

Goldspink J. Neurochem. 50:1364- 1368,1988

TABLE 2. *Developmental changes in protein turnover in the brain*

Age	Protein/ DNA-P (mg/μg)	Fractional rate of synthesis (%/day)	Total protein synthesized (mg/day)	Total protein synthesized (mg/day/mg of RNA-P)	RNA-P/ protein (mg/g)	Growth rate (%/day)	Calculated rate of breakdown (%/day)
Foetal (days)							
16	0.18 ± 0.01	58.0 ± 3.0	—	90 ± 6.3	6.5 ± 0.2	—	—
18	0.22 ± 0.02	47.2 ± 1.7	3.8 ± 0.2 (9.0)	88 ± 3.8	5.4 ± 0.1	10.8	36.4
20	0.19 ± 0.01	41.2 ± 2.5	4.0 ± 0.2 (4.4)	71.6 ± 4.4	6.1 ± 0.2	8.9	32.3
Postpartum (weeks)							
3	1.18 ± 0.05	31.4 ± 1.1	57.5 ± 3.9 (3.3)	142 ± 6	2.2 ± 0.4	4.2	27.2
8	1.50 ± 0.1	16.2 ± 0.6	31.9 ± 1.2 (0.68)	116 ± 4	1.4 ± 0.1	1.8	14.4
44	2.35 ± 0.2	7.3 ± 0.7	24.5 ± 1.3 (0.25)	92 ± 12	0.90 ± 0.1	2.6	4.7
105	1.86 ± 0.05	6.8 ± 0.4	16.0 ± 1.2 (0.20)	49 ± 4	1.4 ± 0.1	2.7	4.1

Wood & King
Nature 229:56-58, 1971

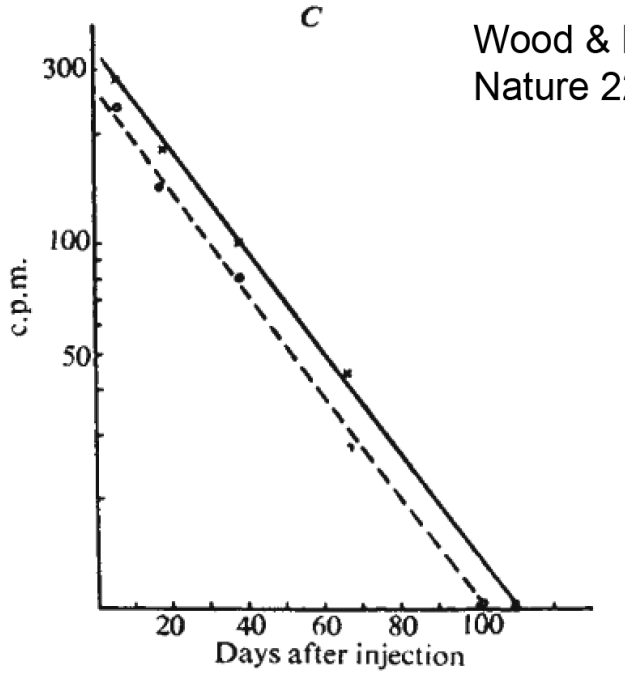


Fig. 2 *A*, Time course of loss of label from the basic protein isolated from whole brain. *B*, Loss of label from the basic protein isolated from myelin from mature animals. The myelin was washed twice with acetone, 1.5 ml./10 mg, and once with water, 0.5 ml./10 mg, before HCl extraction. *C*, Time course of loss of label from the basic protein purified by electrophoresis. ×—×, M. ture; ○ - - - ○, immature.

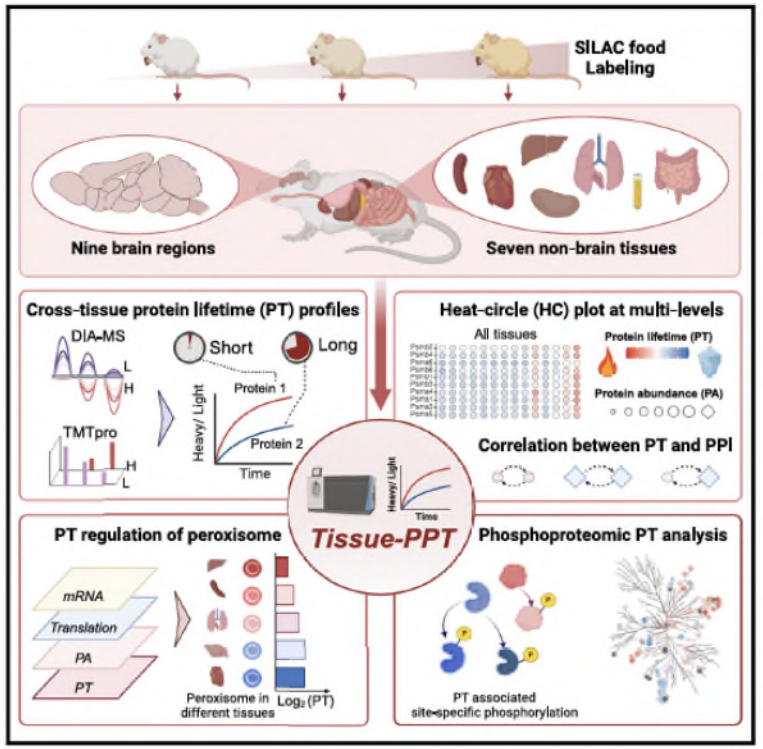
- Modern proteomic analysis of adult mouse brain (11,000 proteins and 40,000 phospho-sites in 9 brain regions)
- Protein abundance and lifetime together define tissue proteome function and stability
- Protein lifetime strongly correlates with protein-protein interactions in tissues
- Site-specific phosphorylation functionally shapes in vivo protein lifetime

- most of the proteome (66–80%) has a half life <10 days
- nine brain regions had higher median protein half life (5.89 ± 0.42 days) than other tissues
- 49 brain proteins in top 5% most long lived; enriched in tricarboxylic acid cycle (TCA), respiratory electron transport, myelin sheath, and chromatin assembly
- Examples: GFAP and synaptophysin ~15 days, MBP 80—180 days

Li et al. Cell 188:2267-2287.e21, 2025; DOI: 10.1016/j.cell.2025.02.021

Turnover atlas of proteome and phosphoproteome across mouse tissues and brain regions

Graphical abstract



Authors

Wenxue Li, Abhijit Dasgupta, Ka Yang, ..., Eugenio F. Fornasiero, Junmin Peng, Yansheng Liu

In brief

This study presents a comprehensive atlas of protein and phosphoprotein turnover across 16 mouse tissues and brain regions using advanced proteomics and isotope labeling. It reveals tissue-specific protein lifetimes, coordinated turnover within protein-protein interaction networks, peroxisomal turnover diversity, and the regulatory role of phosphorylation in protein stability, offering valuable insights into proteome homeostasis and tissue-specific functions.

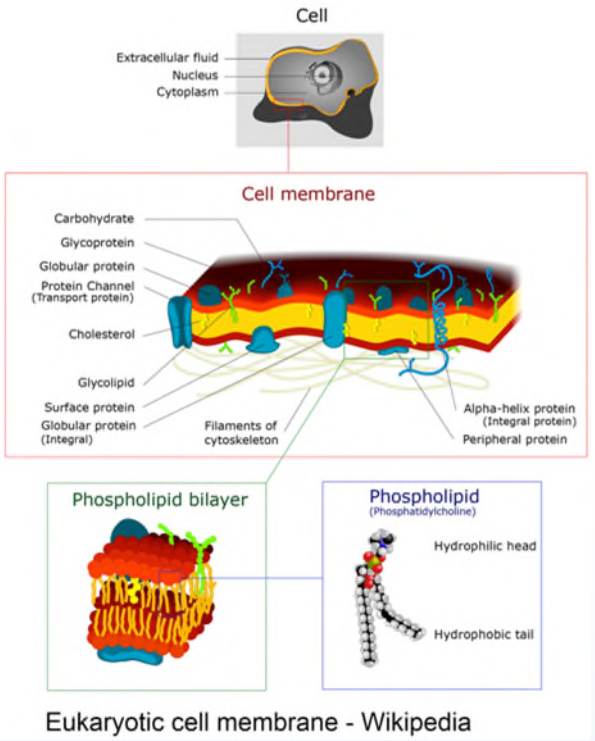
Highlights

- A high-quality comprehensive resource of protein turnover across mouse tissues

- Glycoproteomics reveal major protein modification differences in brain compared to other organs (Noel et al. 2025 doi.org/10.1093/glycob/cwaf054)

Lipid synthesis and turnover

- Lipid is major constituent of cell membranes (phospholipid bilayer with embedded proteins)
- Lipid components recycle at different rates
- Modern lipidomic assessment of lipid turnover
- Fatty acid turnover is slowest in brain (of mouse); e.g. palmitate $t_{1/2}$ 3.1 days
- See
  - Chen et al. 2023 doi.org/10.1016/j.cmet.2023.03.007
  - Kostyukevich et al. 2023 doi.org/10.3390/ijms241411725



Eukaryotic cell membrane - Wikipedia

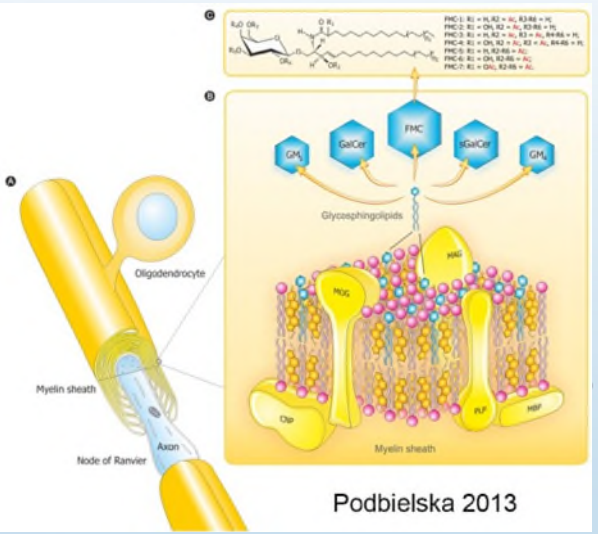
Myelin lipid turnover

- Myelin is specialized concentration of oligodendrocyte membranes
- Two metabolic pools of phosphatidylcholine (PC) in myelin, one with a half life of the order of days, and another with a half life of the order of weeks (Smith & Eng 1965; Morell & Ousley 1994).
- Compact r… membrane… ell

B. Half-Replacement Times (Days) for Lipid Components of Mouse Brain Myelin

Age (weeks)	5–9	30–36	60–66	106–112
Cholesterol	122.0	359.0	333.0	263.0
Phosphatidylcholine	20.0	20.4	20.8	20.8
Phosphatidylethanolamine	29.4	25.0	25.0	–
Cerebroside	28.6	94.3	250.0	151.0

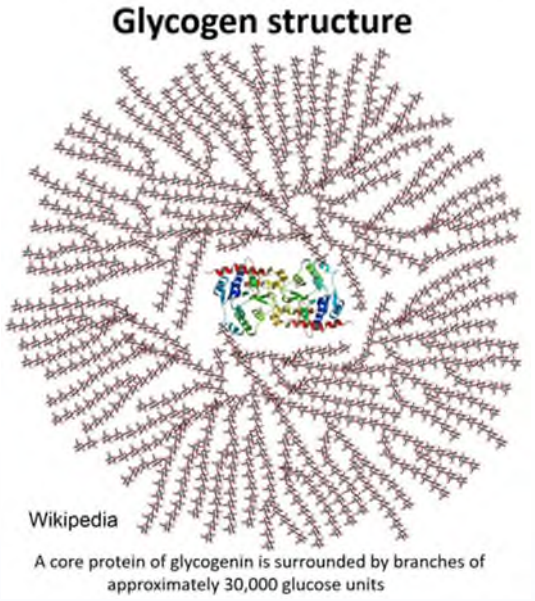
Ando 2003



Podbielska 2013

Glycogen synthesis and turnover

- D-glucose crosses BBB via GLUT1 transporter
- Incorporated into glycogen, mainly in astrocytes, within 1-6 hours
- Rapid turnover of astrocytic glycogen in response to local neuronal activity (Wu 2019)
- ^{14}C-glucose radiolabel experiments (Coxon 1965; Strang 1971) show ~50% degradation in 1 day



Coxon et al. Biochem. J. 97: 776-781,1965

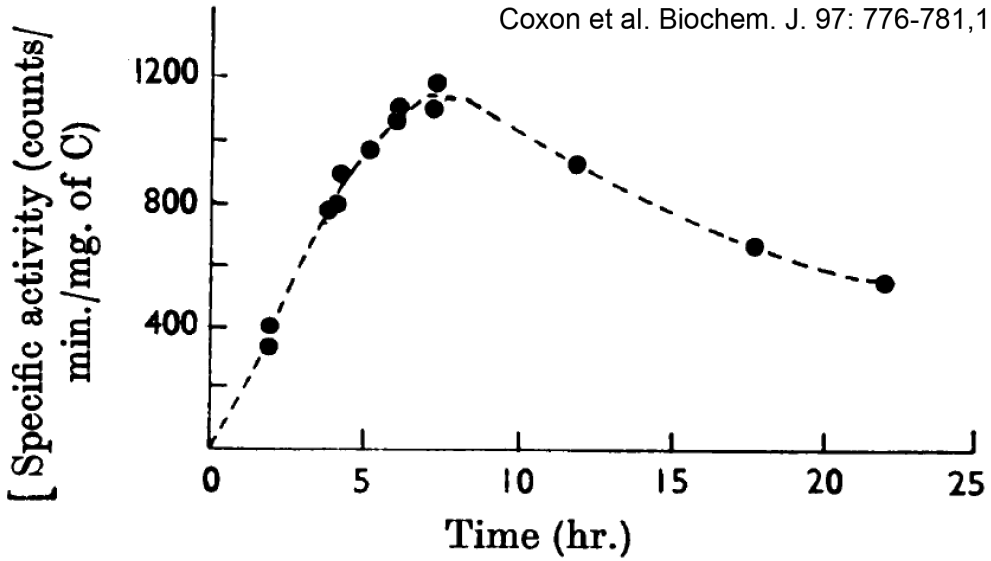


Fig. 1. Specific activity of brain glycogen after the injection of 8 μc of [U-^{14}C]glucose/kg. body wt. Each point shown represents the mean of duplicate samples from one rabbit's brain.

In vivo glycogen analysis using magnetic resonance spectroscopy (MRS)

- ^{13}C-glucose infused into animals (Morgenthaler 2008; van Heeswijk 2010)
- In humans, complete turnover of glycogen requires 3–5 days (Oz et al. 2007)

Every cell constituent degrades and must be repaired or disposed of through cellular waste recycling and disposal mechanisms

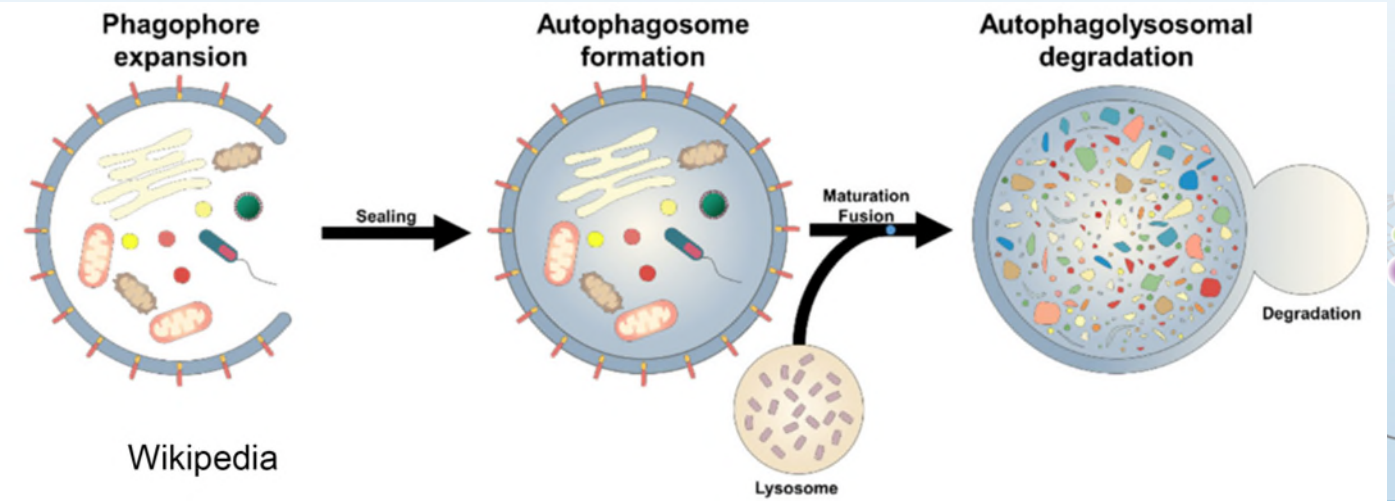
- Autosome / lysosome complex
- Peroxisome
- Proteosome
- Autophagy / mitophagy
- (Glymphatic clearance – after waste products are expelled from cells)

Autophagy / phagocytosis / lysosome

- Autophagy – orderly removal of unnecessary or dysfunctional cell components through a lysosome-dependent regulated mechanism
- Mitophagy – recycling of mitochondria
- Phagocytosis – engulfment of extracellular material for removal and recycling of debris
  - "Professional" phagocytes of the immune system include microglia and monocyte/macrophages
  - Astrocytes also play a limited role in phagocytosis (engulfment by endocytosis and pinocytosis) (Konishi et al. 2022 DOI: 10.1002/glia.24145)

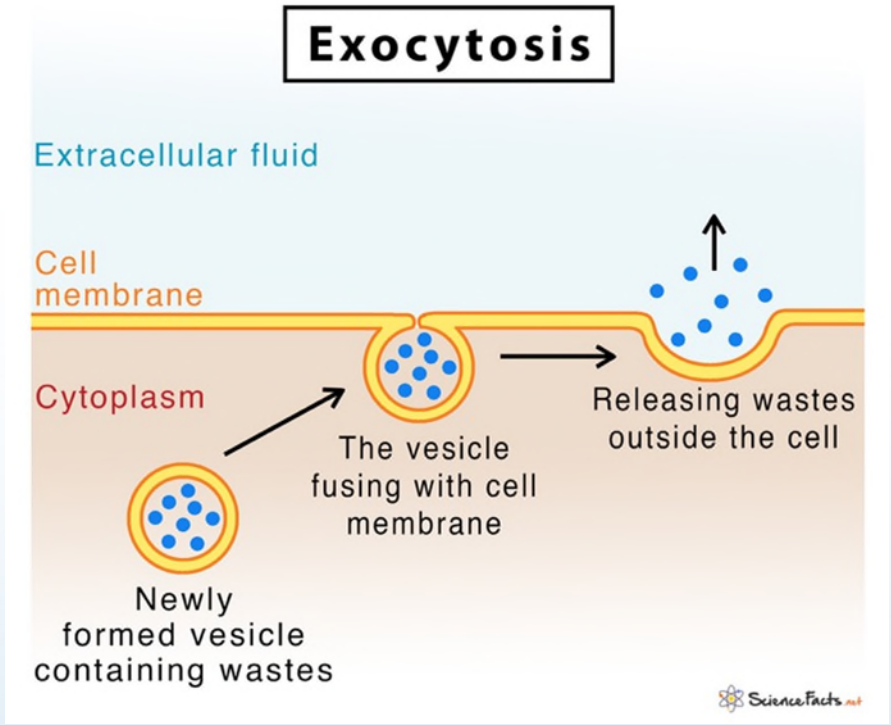
Lysosomes

- Membrane bound organelles (0.1-1.2 µm) that contain >60 hydrolytic enzymes to digest debris
- Formed in ER / Golgi
- Lysosomes fuse with endosomes or phagosomes - dependent on expression of targeting proteins on surfaces of latter (e.g. lipidated LC3 on autophagosomes)



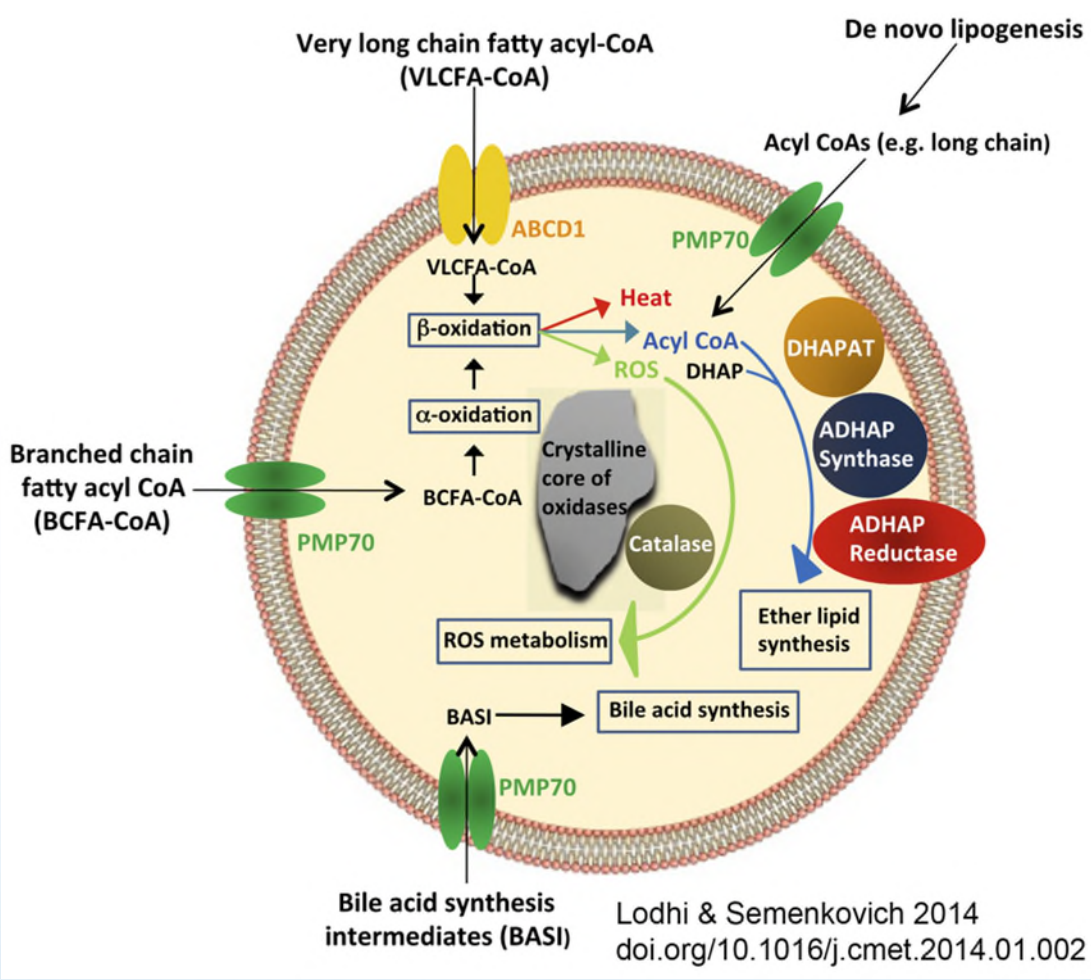
Neuroglial lysosomal exocytosis

- Most neuron – astroglial exocytosis is non-lysosomal exchange related to synaptic vesicle release and recycling
- Lysosomal contents can be released by exocytosis from neurons at synapses for synaptic remodeling (plasticity) (Ibata & Yuzaki 2021 doi.org/10.1016/j.neures.2021.03.011)
- Reactive astrocytes can release signaling molecules and enzymes necessary for tissue remodeling (Mielnicka & Michaluk 2021 doi.org/10.3390/biom11091367)



Peroxisomes

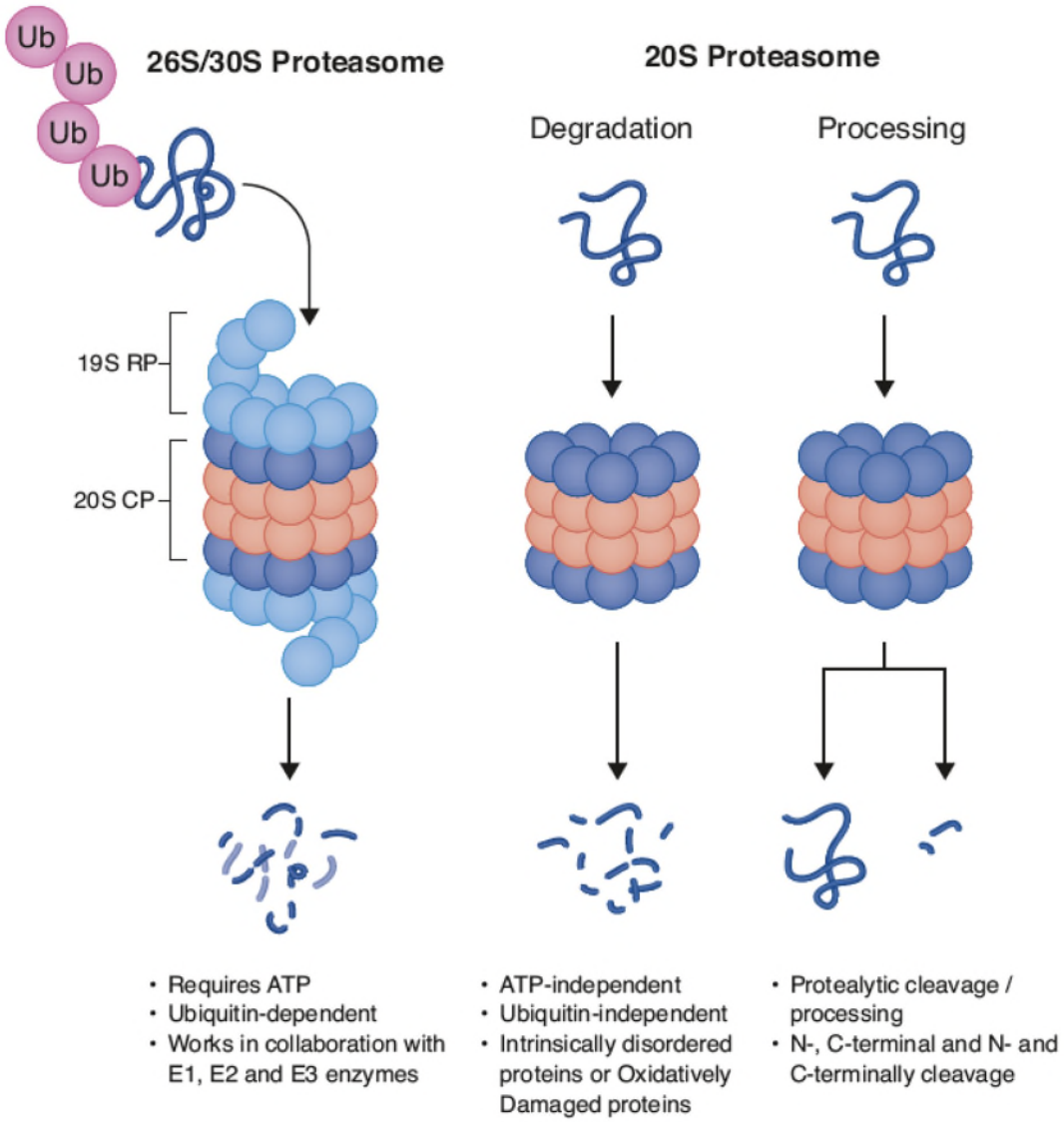
- Small (0.1–1 µm diameter) membrane bound organelles
- Contain ~60 enzymes
- Major functions:
  - hydrogen peroxide (H_2O_2) production and elimination (via catalase)
  - oxidative breakdown of very long chain fatty acids
  - synthesis of plasmalogens, including ethanolamine glycerophospholipids for myelin sheaths
- See Fujiki et al. 2022 doi.org/10.1016/j.bbamcr.2022.119330



Proteasome – ubiquitin system

- Proteasomes are nuclear and cytosolic protein complexes that degrade ubiquitin-tagged proteins by proteolysis
- Resulting peptides are hydrolyzed by downstream cytosolic aminopeptidases

- Important in neurodegenerative diseases (Davidson & Pickering 2023 DOI 10.3389/fcell.2023.1124907)



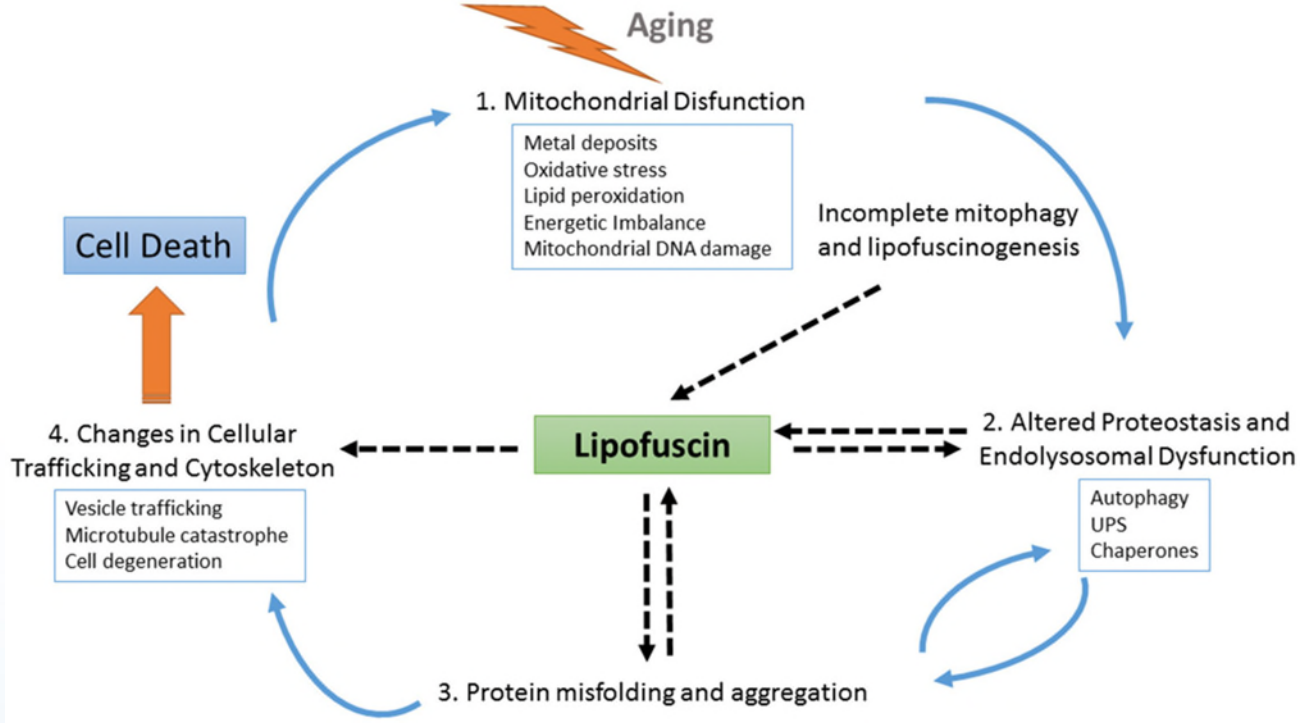
Church et al. 2024 doi.org/10.1038/s44320-024-00028-7

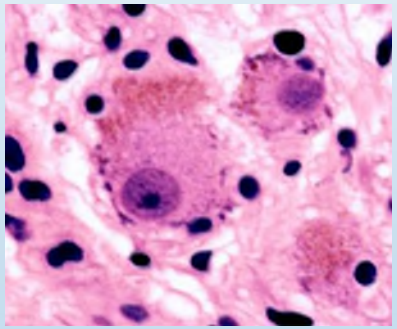
“Normal” tissue waste storage

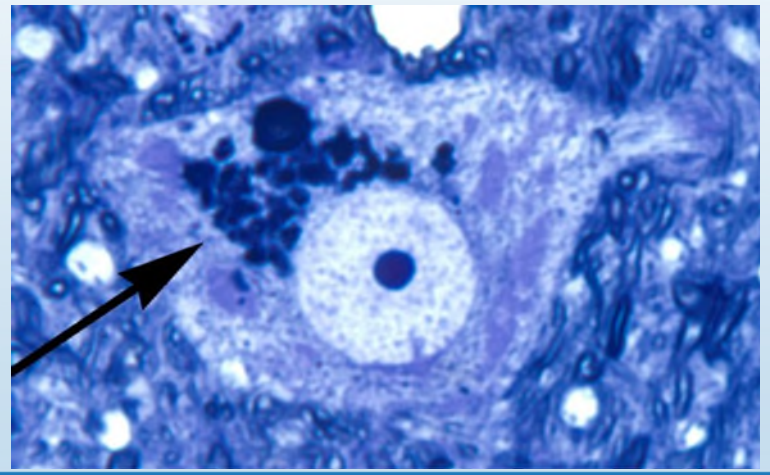
Cities have landfill sites – most cells, especially long lived ones, have equivalent structures

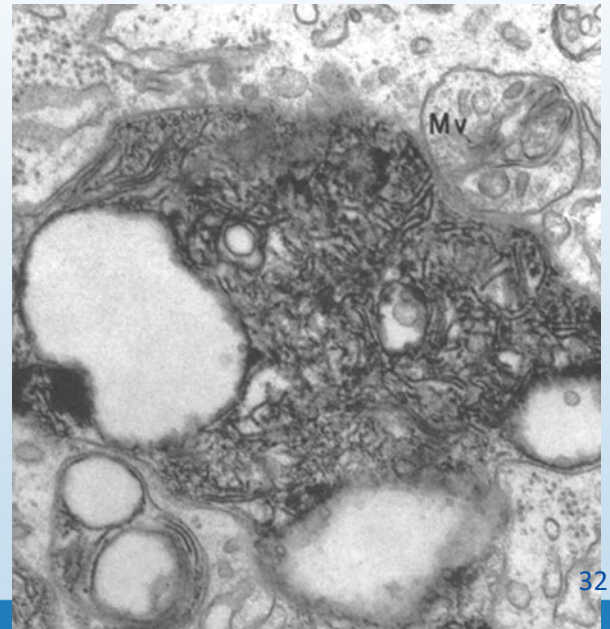
Lipofuscin

- Mixture of highly oxidized, cross-linked macromolecules including proteins (30–70%), lipids (20–50%), metals cations (2%), and sugar residues
- Cannot be degraded or cleared by exocytosis
- Accumulate within lysosomes and cell cytoplasm during normal aging (and more in disease states)
- Typically yellowish; autofluorescent
- Ceroid = lipofuscin; term “ceroid” used by some to mean pathological
- (reviewed by Moreno-García 2018 doi: 10.3389/fnins.2018.00464)



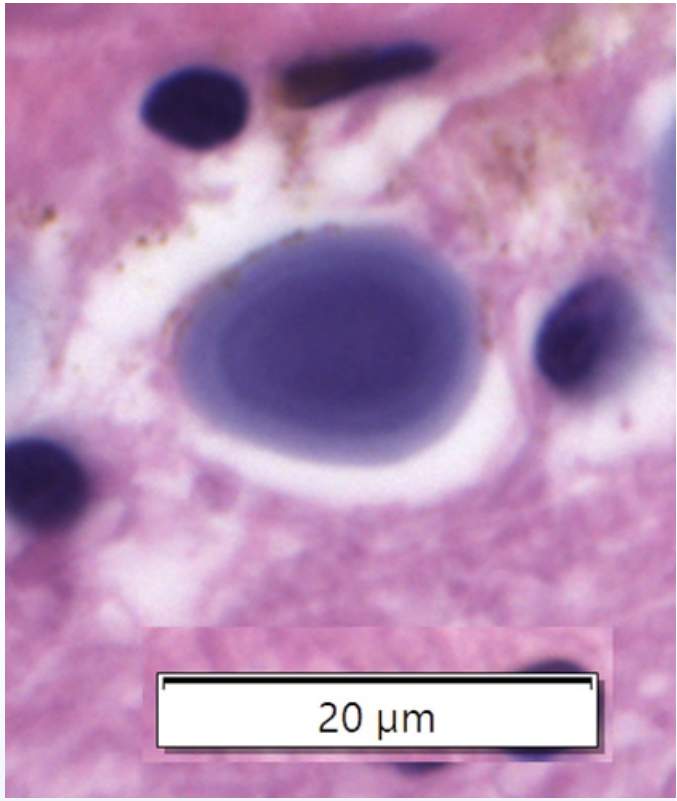






Corpora amylacea

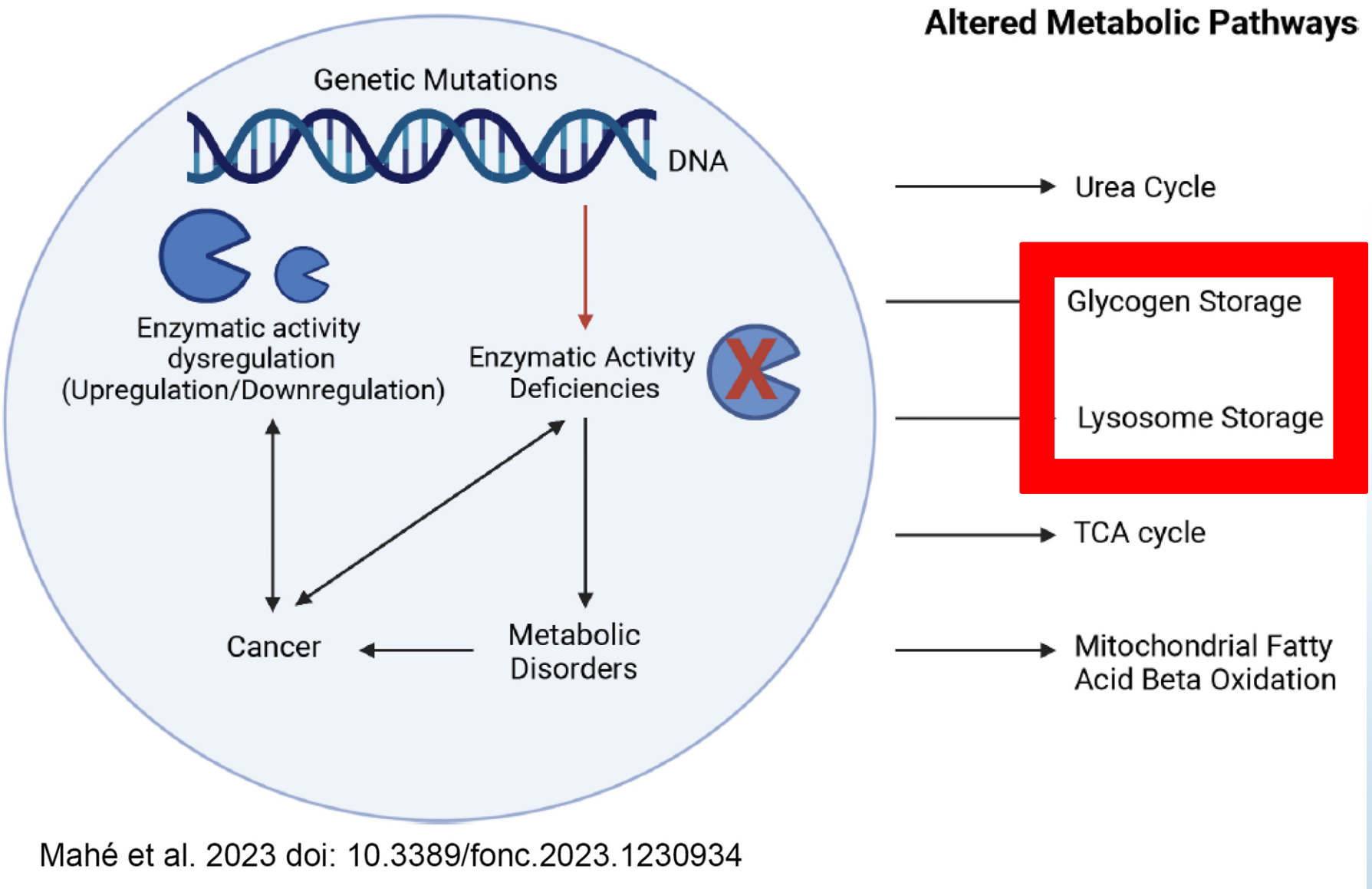
- Lamellated “pearls”; mainly within astrocytes
- Glucose polymer (polyglucosan) >90% + protein
- Stain with periodic-acid Schiff (PAS) et al.
- Degenerating material (from neuron) incorporated into astrocytes; may be recirculated through CSF and then macrophage digestion



- Reviews by Auge 2017, DOI: 10.1038/srep41807
- Riba 2019, doi.org/10.1073/pnas.1913741116

AANP

Storage diseases of the nervous system



Brain disease

Mahé et al. 2023 doi: 10.3389/fonc.2023.1230934

Categorization of metabolic / enzymatic disease

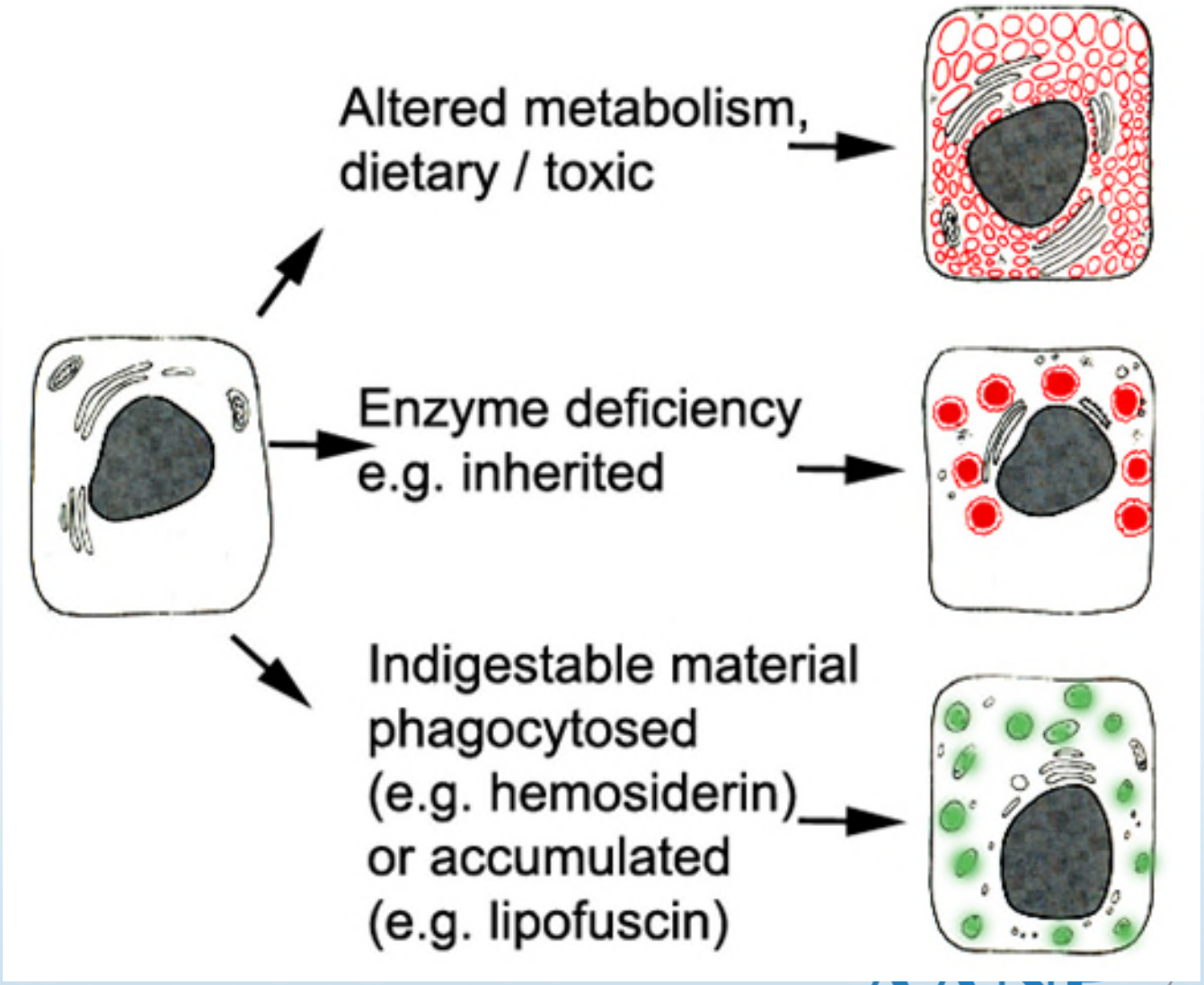
- By metabolic ‘pathway’ involved (e.g. lipid metabolism, amino acid metabolism, energy supply)
- By organelle involved (e.g. lysosomal, mitochondrial)
- By end result (e.g. leukodystrophy, storage disorder, epilepsy)
- By inheritance (e.g. X linked, autosomal dominant, autosomal recessive)

- Many carry eponymous names of people who described the disease

Cellular storage material

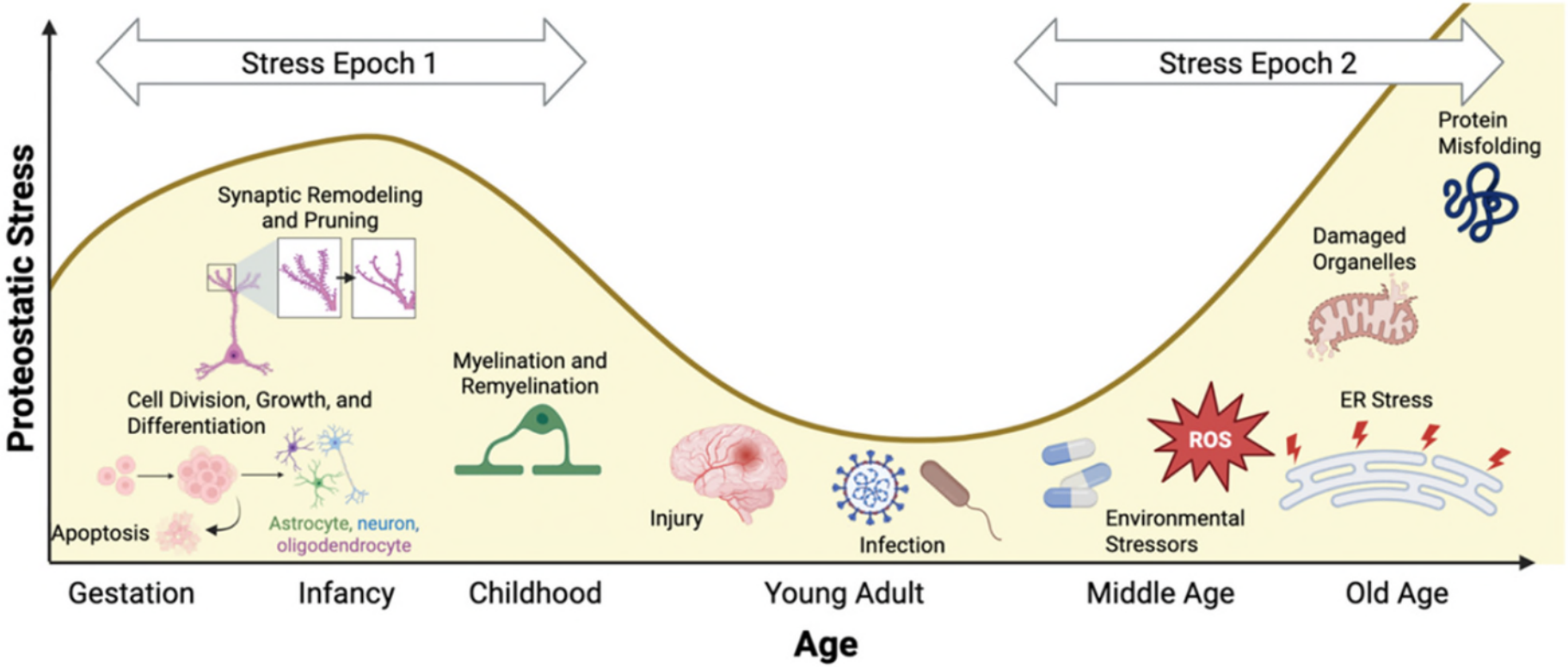
Particles of aggregated protein, lipid, or carbohydrate

Size is context specific, but generally visible within cells at the light microscopic level



Why do storage disorders often present in youth?

- Growing up is hard
- Homeostatic (proteostasis etc.) mechanisms are stressed by developmental physiology



Proteostatic stress peaks during two life epochs that require enhanced lysosomal functional capacity.

Lane-Donovan et al. 2025 doi.org/10.1016/j.pneurobio.2025.102854

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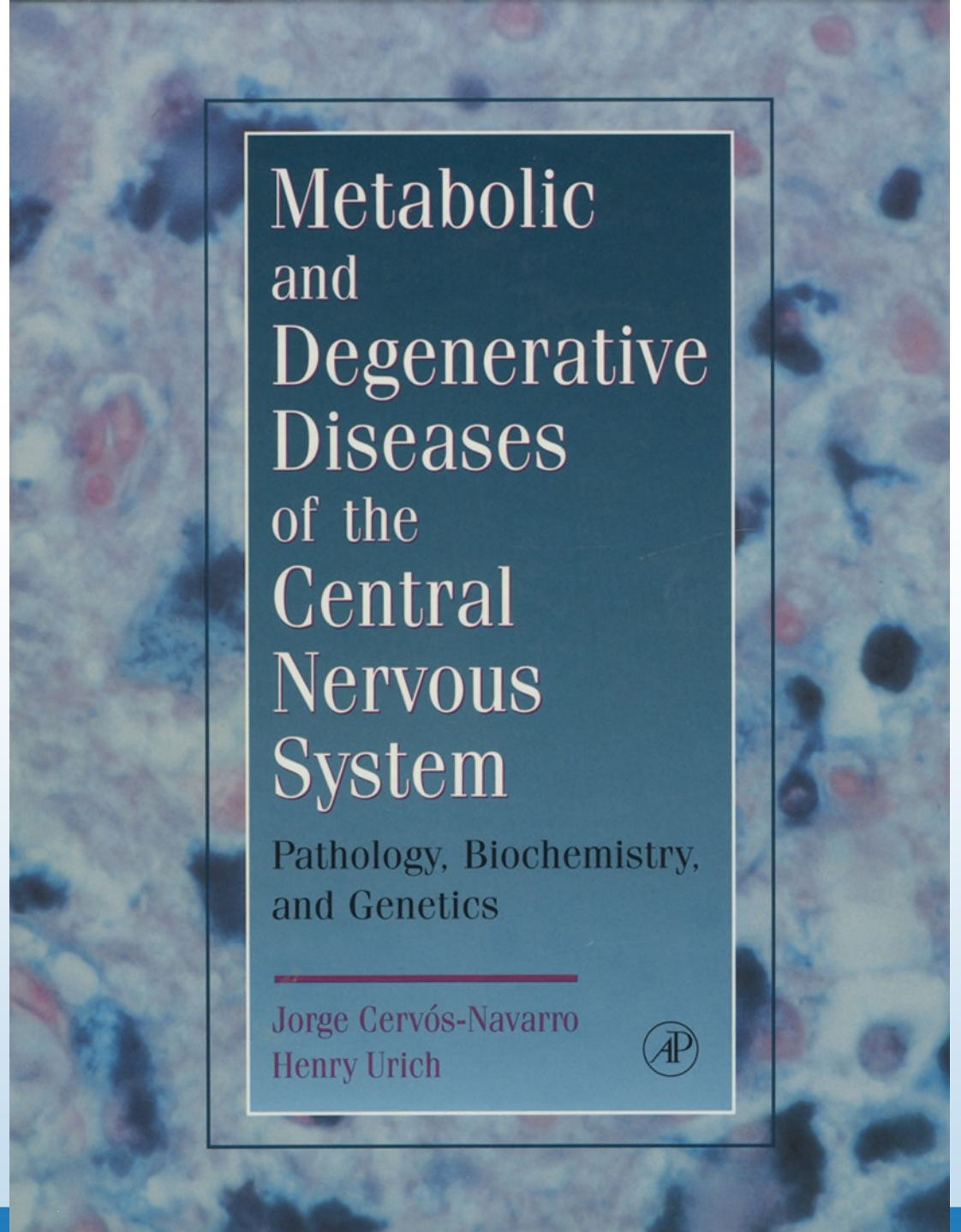
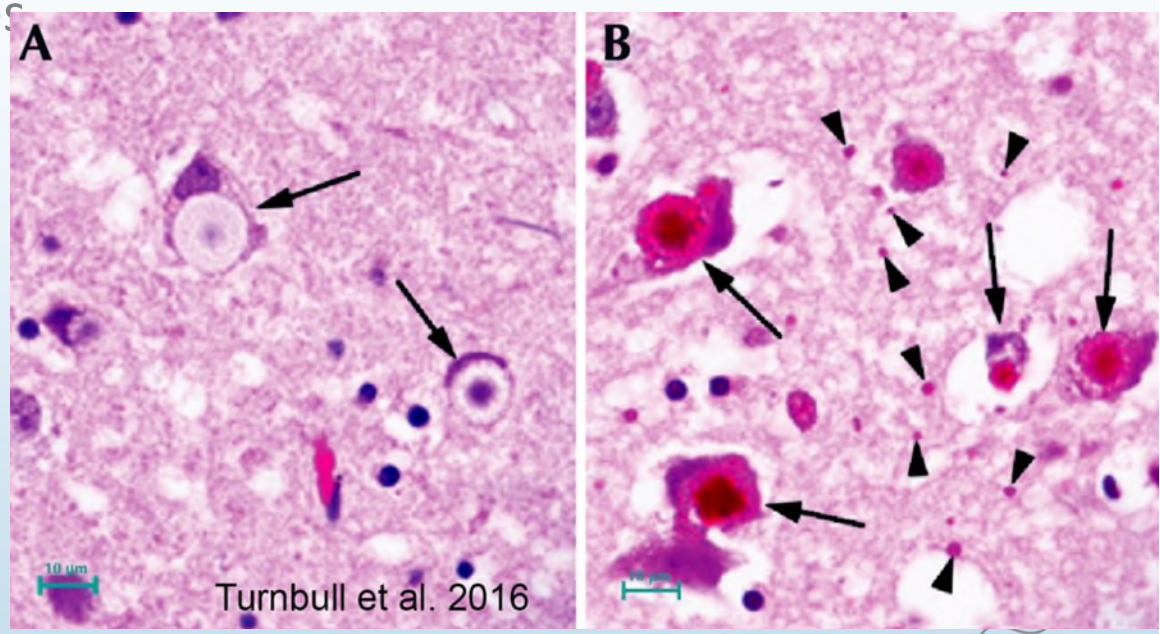

Metabolic
and
Degenerative
Diseases
of the
Central
Nervous
System
Pathology, Biochemistry,
and Genetics
Jorge Cervós-Navarro
Henry Urich
AP

1995

AANP

Glycogen storage - Lafora (polyglucosan body) disease

- Most often caused by loss-of-function mutations in EPM2A and NHLRC1 (encode laforin and malin, respectively)
- Normal – malin (E3 ubiquitin ligase) binds laforin (dual specificity protein phosphatase) to protect against intracytoplasmic polyglucosan accumulation
- Mutations result in poorly branched, hyperphosphorylated glycogen that and accumulates into Lafora bodies (in brain, liver, myocytes, myoepithelial glands of sweat glands).
- Seizures followed by decline and death in ~10 years

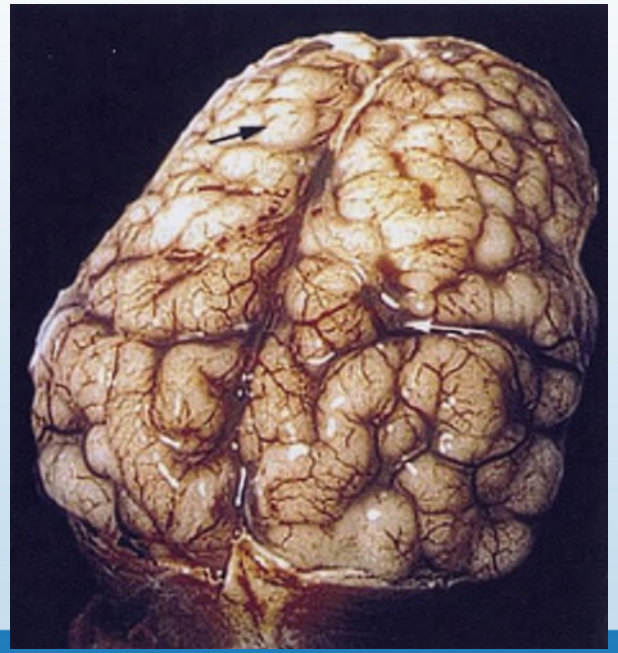


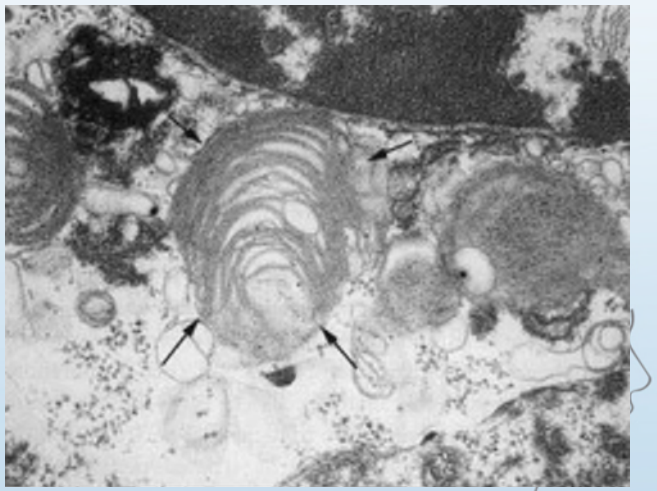
Peroxisome dysfunction

- Peroxisome biogenesis (multiple protein deficiencies, abnormal peroxisome morphology)
  - Zellweger spectrum
  - Neonatal adrenoleukodystrophy
  - Refsum disease, infantile
- Single protein deficiency (normal peroxisome morphology)
  - Adrenoleukodystrophy
  - Refsum disease, adult

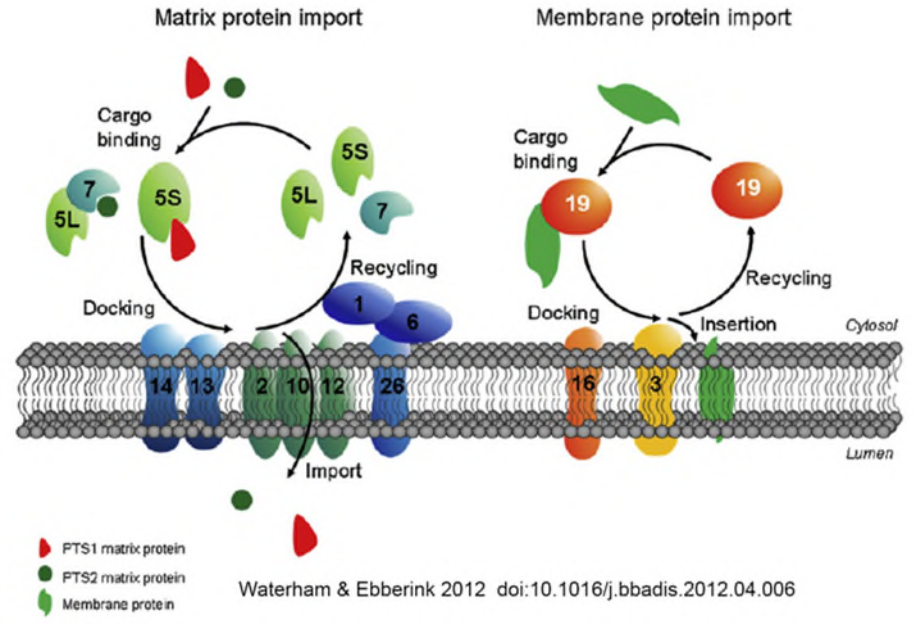
Zellweger Syndrome (Cerebro-hepato-renal syndrome)

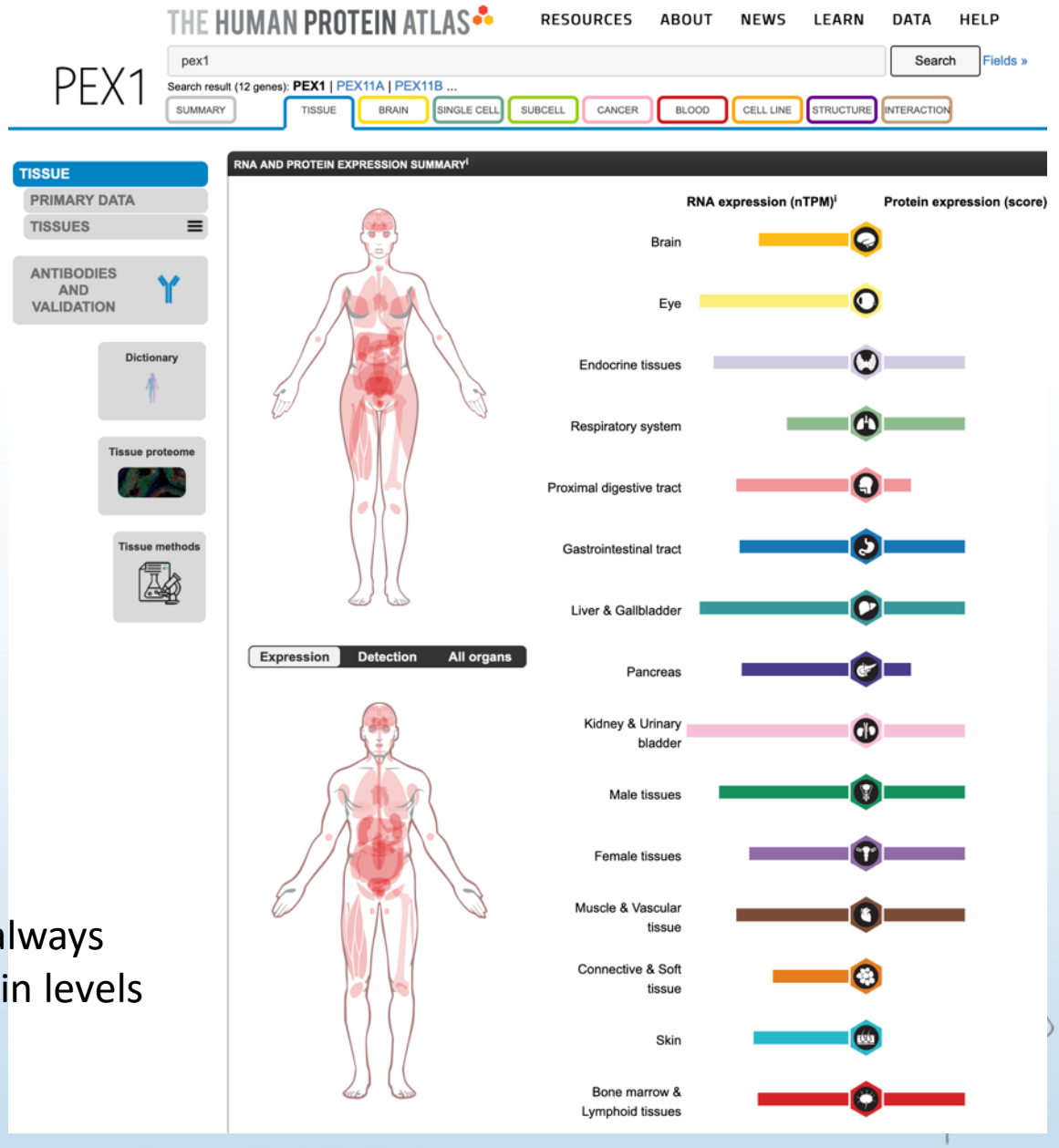
- most severe of the peroxisomal biogenesis disorders
- homozygous or compound heterozygous mutation PEX1 gene
- Evident at birth with distinctive facial features and skeletal abnormalities
- Brain abnormalities include pachygyria, abnormal lipid membrane like autophagosomes (Faust 2018)





PEX1 is involved in peroxisome protein import



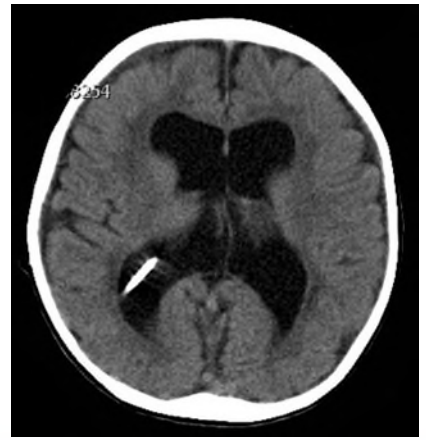


- PEX1 protein expression is low in brain
- relative disease effect on organs is not always easily explained simply by normal protein levels

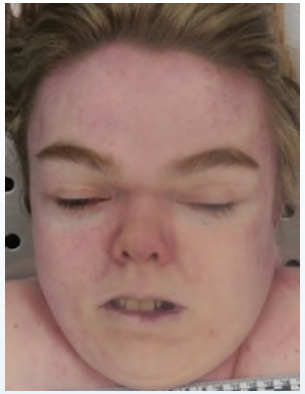
Mucopolysaccharidoses (MPS)

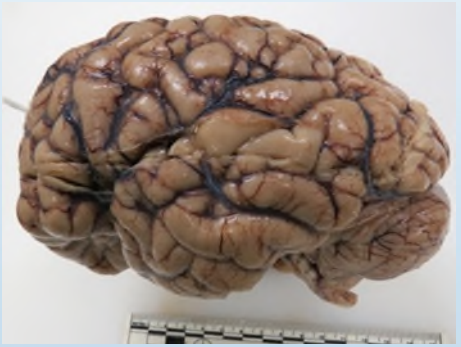
- Clinical onset and severity typically depends on enzyme activity level
- Progressive neurologic decline in childhood or adulthood
- MPS I (3 sub-groups: Hurler, Hurler-Scheie, and Scheie syndromes); absent or deficient alpha-L-iduronidase (break down of glycosaminoglycans dermatan sulphate and heparan sulphate)
- MPS II (Hunter syndrome); X-linked; absent iduronate-2-sulfatase
- MPS III (Sanfilippo syndrome, 4 types A - D); deficient break down of heparan sulfate
- MPS IV (Morquio syndrome); missing or deficient N-acetylgalactosamine-6-sulfatase (Type A) or beta-galactosidase (Type B) needed to break down chondroitin-6-sulfate and keratan sulfate. Skeletal dysplasia (CNS not directly affected)
- Also MPS VI to IX

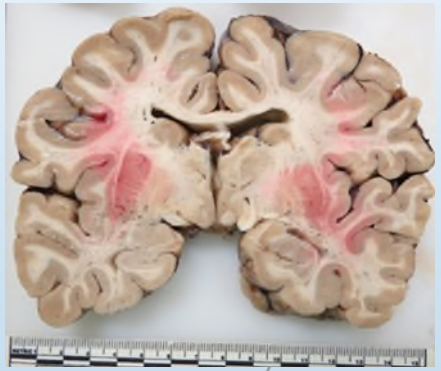
MPS I case



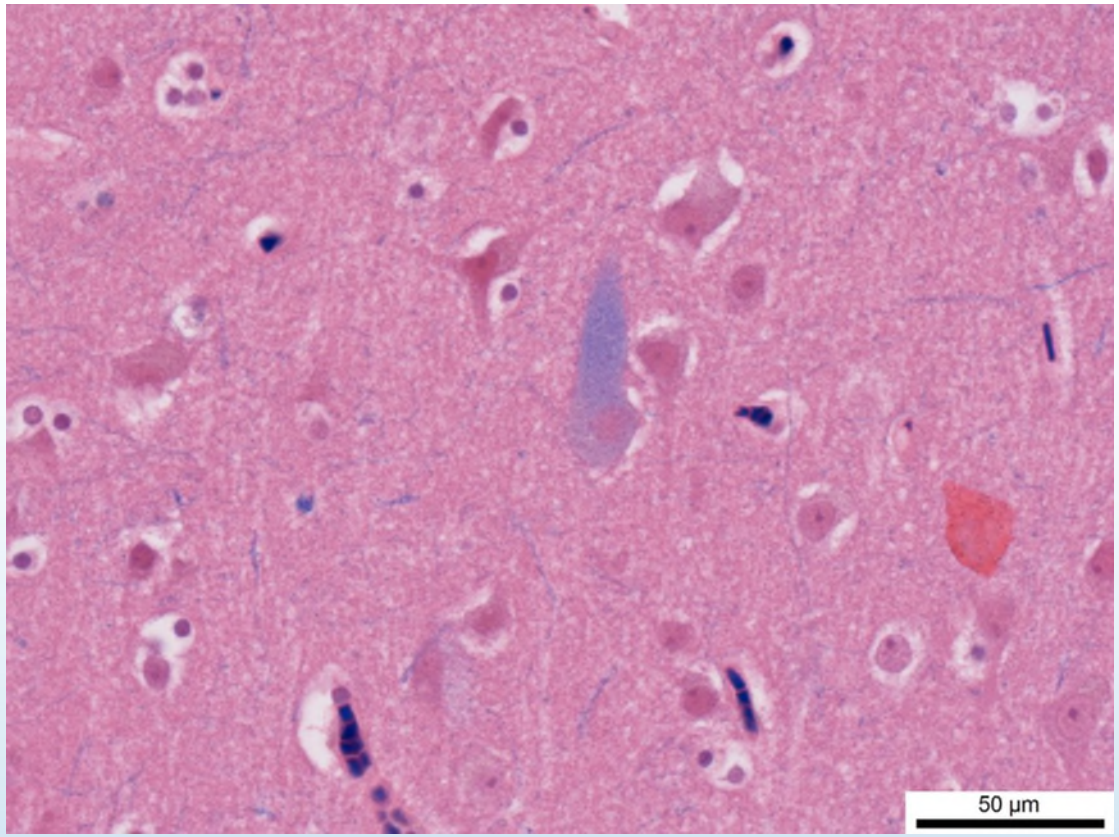
- Female, large head in infancy, severe hydrocephalus shunted at 5 months
- Diagnosed with MPS type I (alpha-iduronidase deficiency; Hurler syndrome; IDUA mutation)
- stem cell transplantation at 1 year with normalization of circulating cell alpha-iduronidase activity.
- infrequent seizures, intellectual impairment, talkative; ambulate with walker / wheelchair (scoliosis)
- Died at 20 years age; coarse facial features
- Brain small 1162g; shunted small ventricles, normal white matter



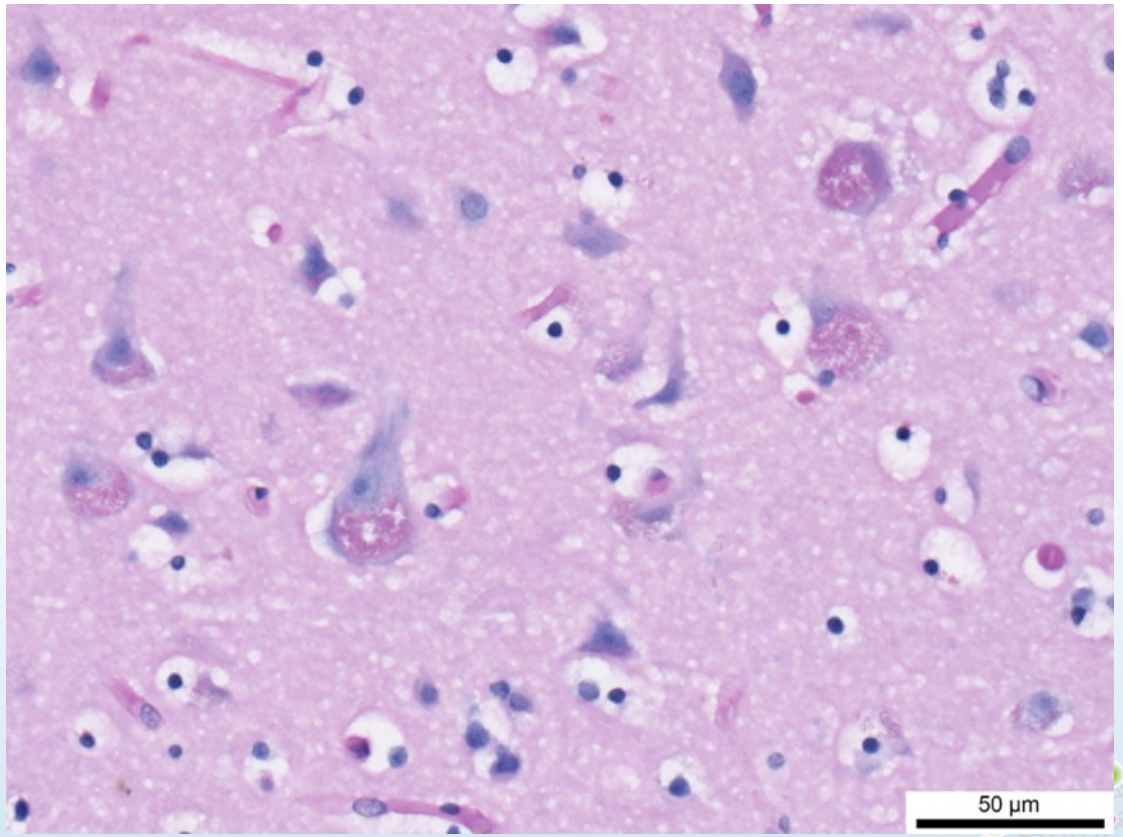




MPS I (marrow transplant) histology



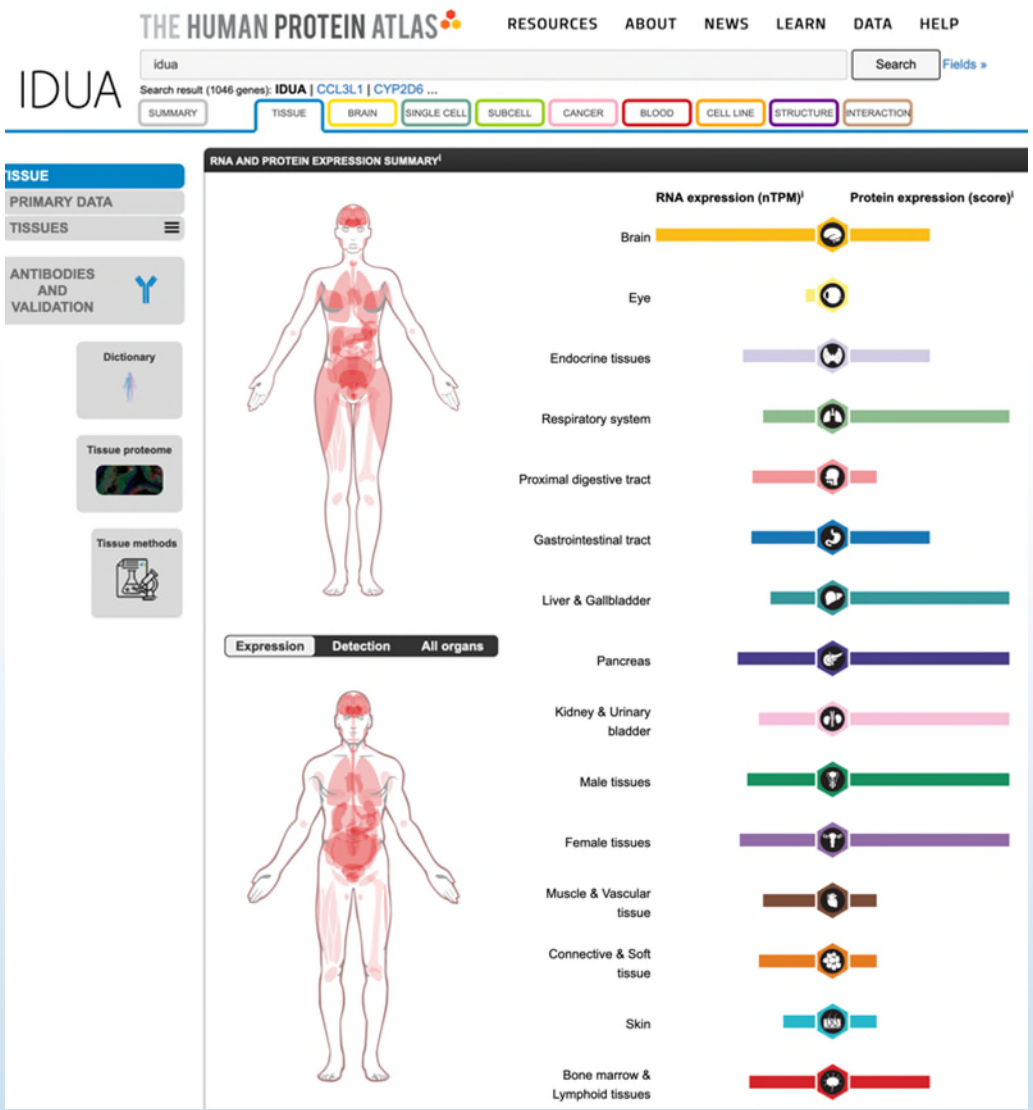
LFB – H&E

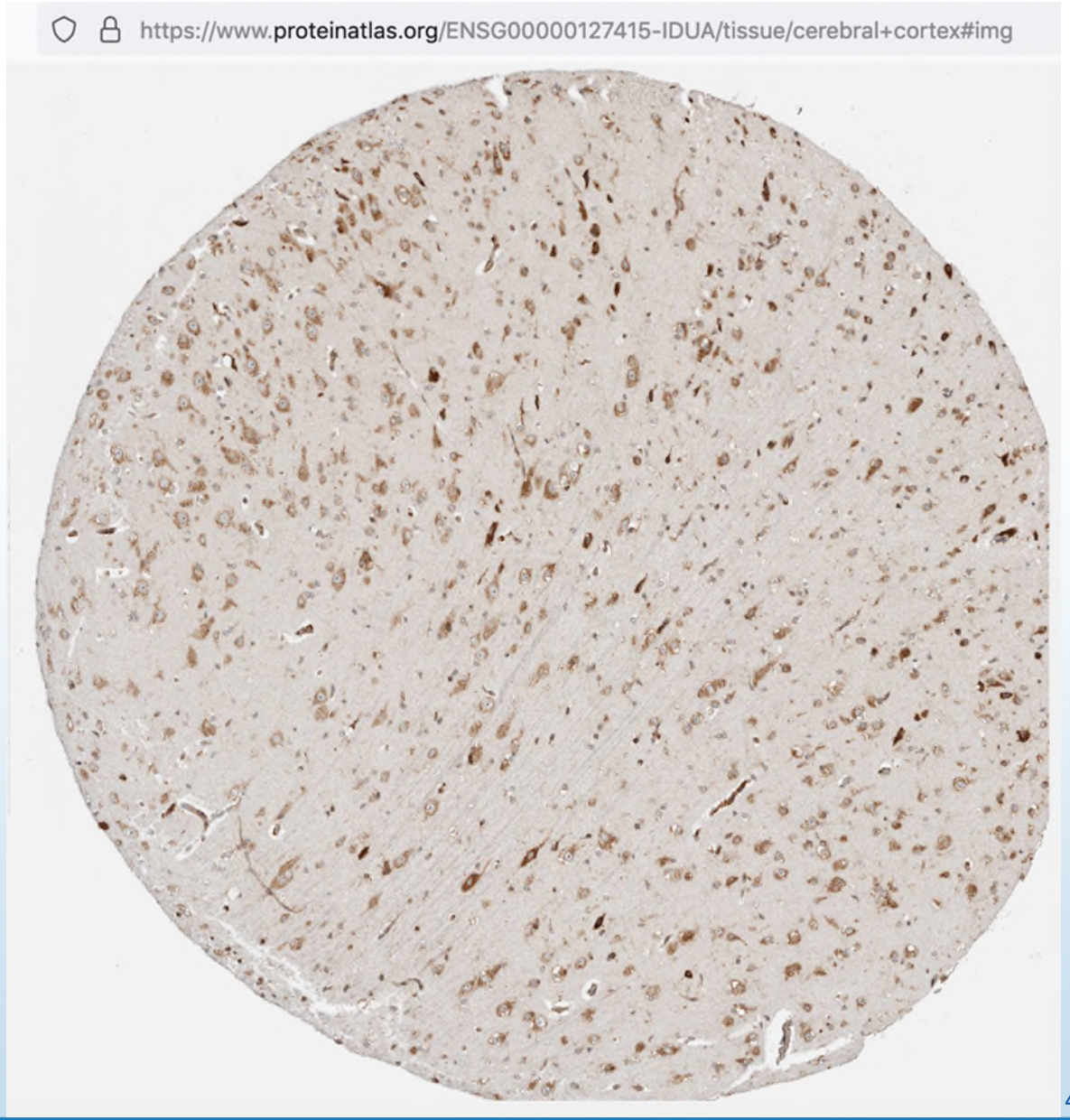


PAS + hematoxylin

Abnormal storage in cortical neurons

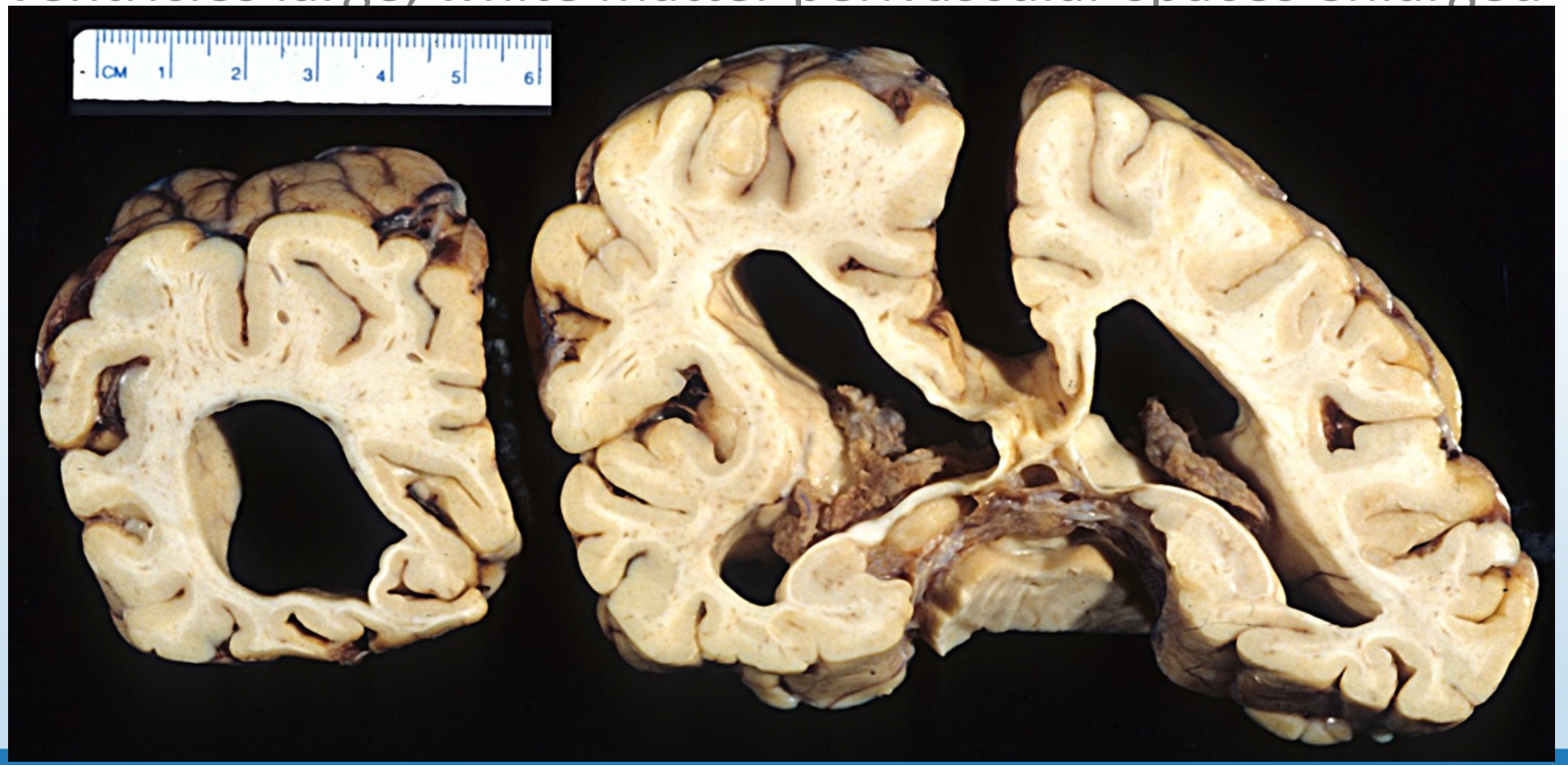
IDUA is abundant in brain, mainly in neurons



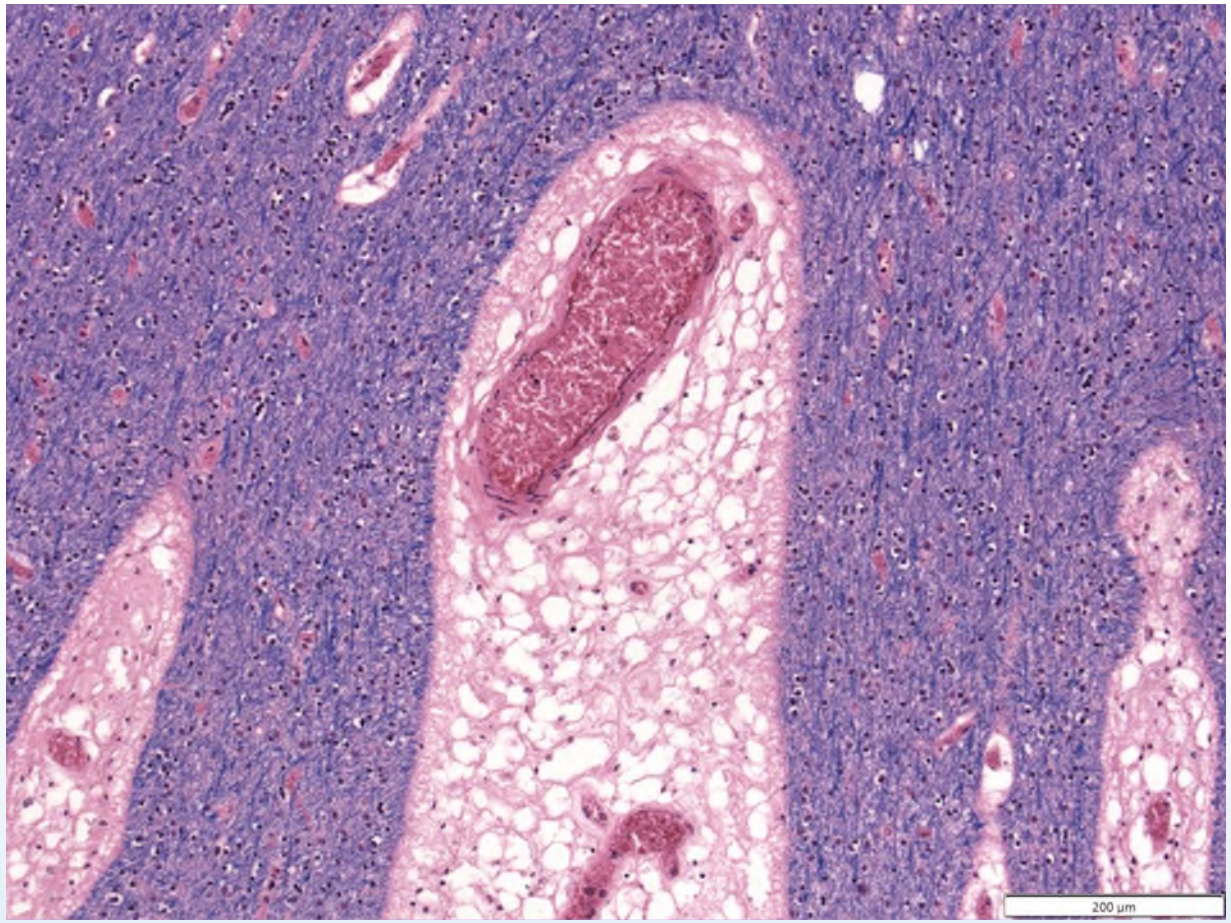


MPS II (Hunter disease; iduronate 2-sulfatase deficiency; IDS mutation)

- 12 year male with severe neurologic decline
- Ventricles large, white matter perivascular spaces enlarged

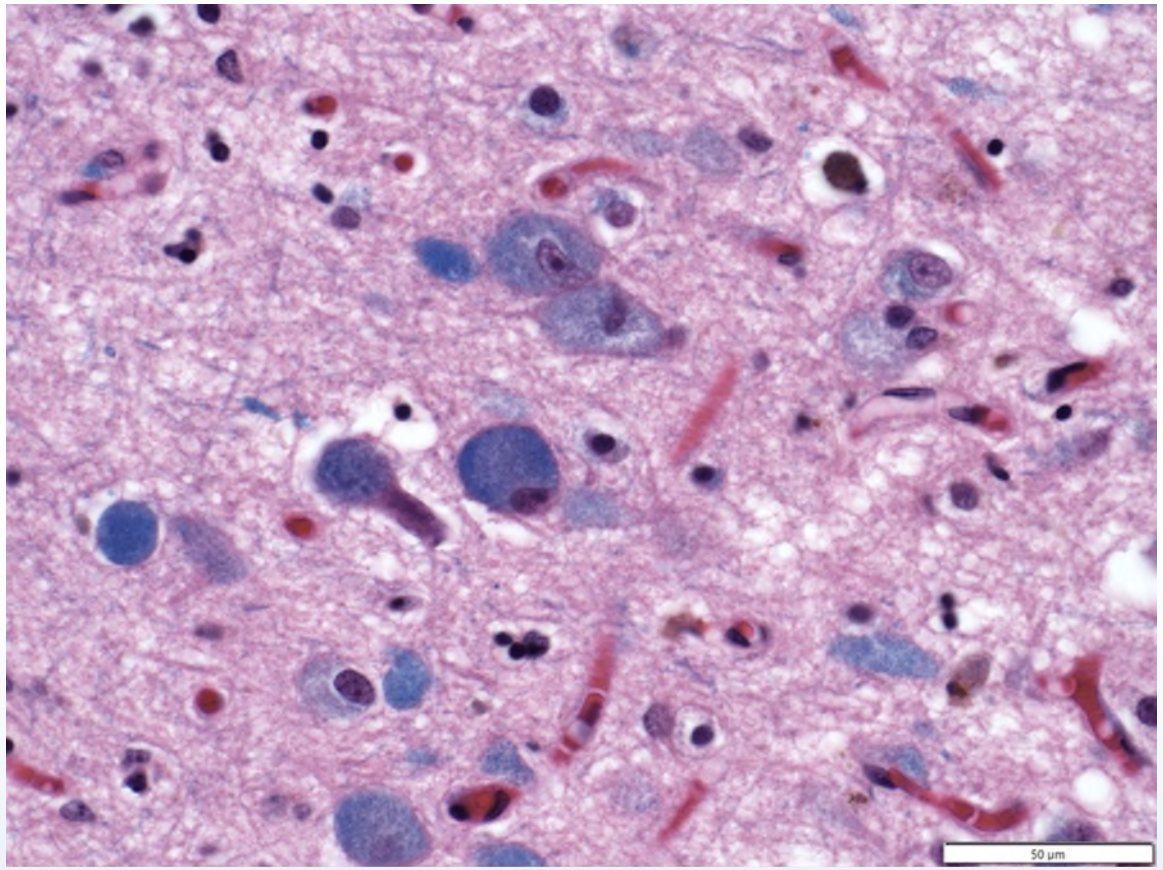


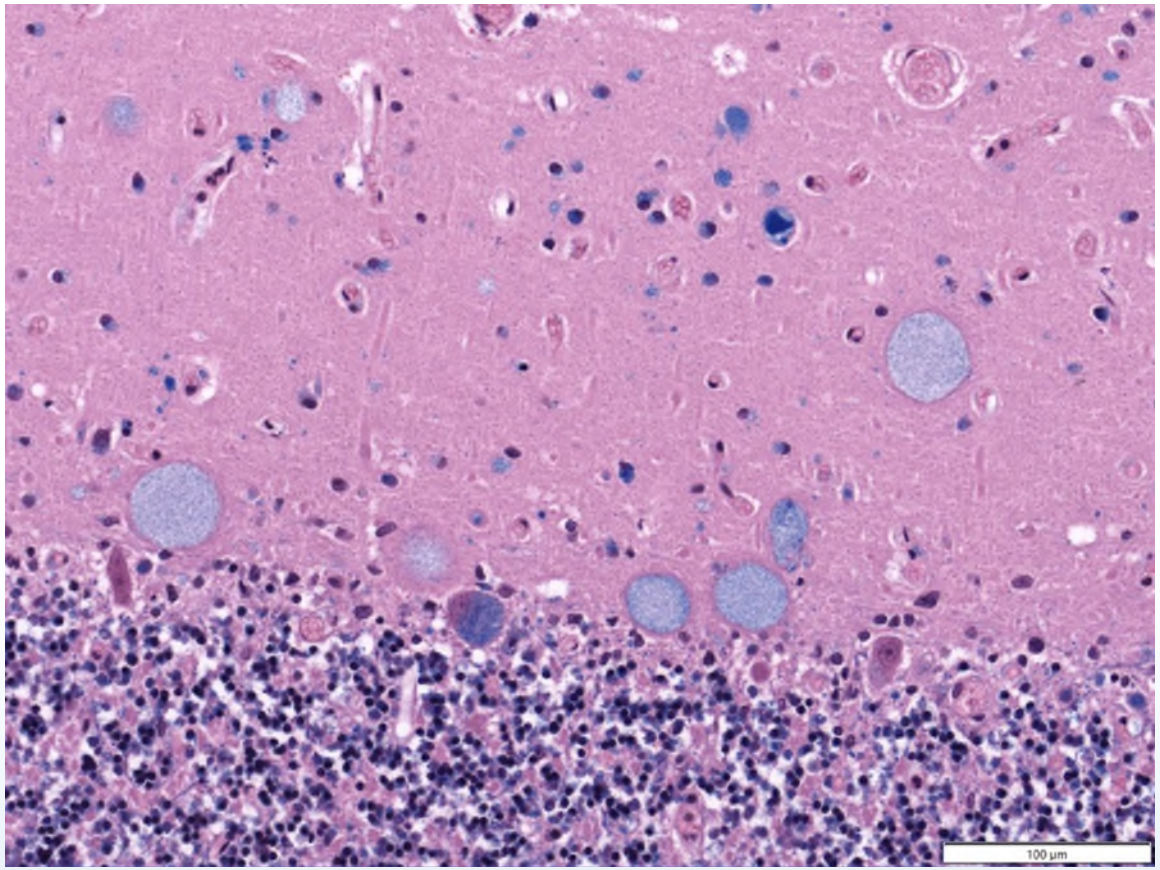
MPS II



Thick dura / arachnoid

White matter well myelinated, but perivascular spaces filled with macrophages





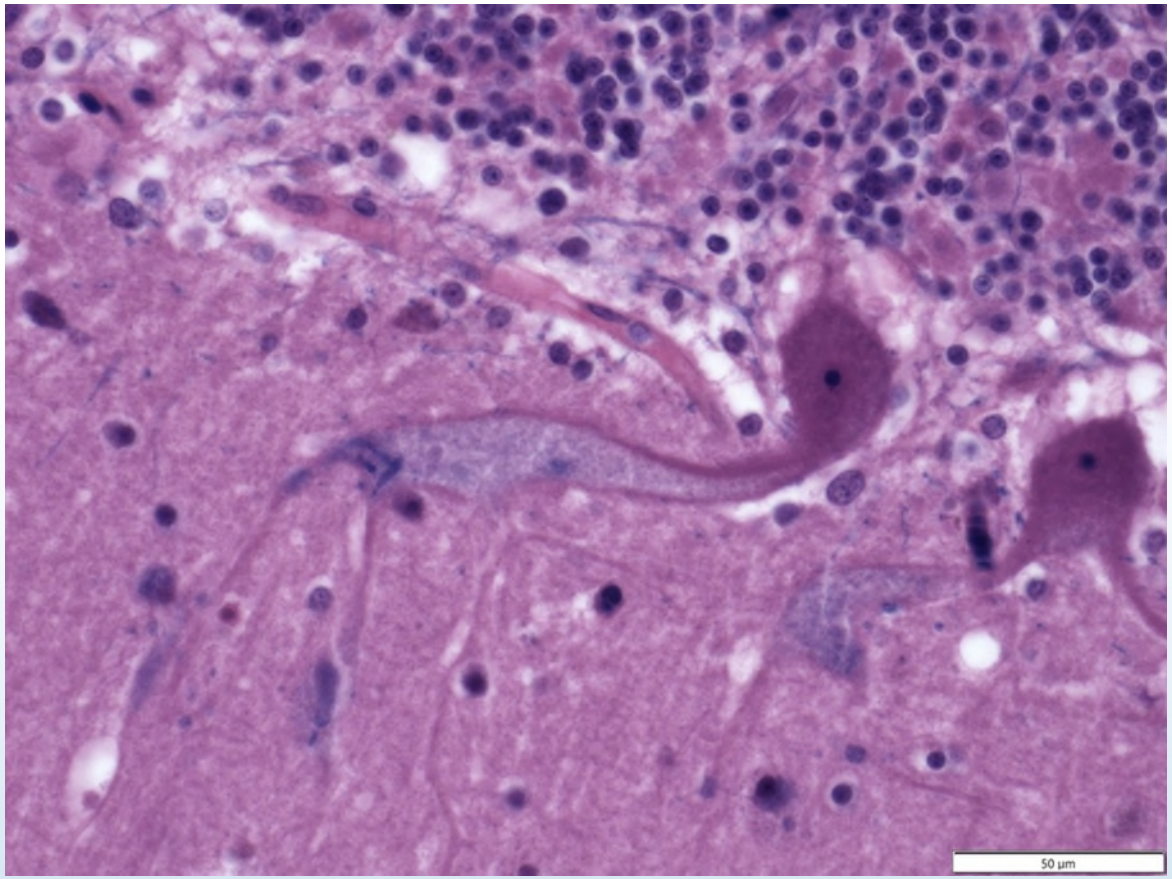
Neuron somata in neocortex (et al.) and Purkinje dendrites packed with Luxol fast blue stained storage material

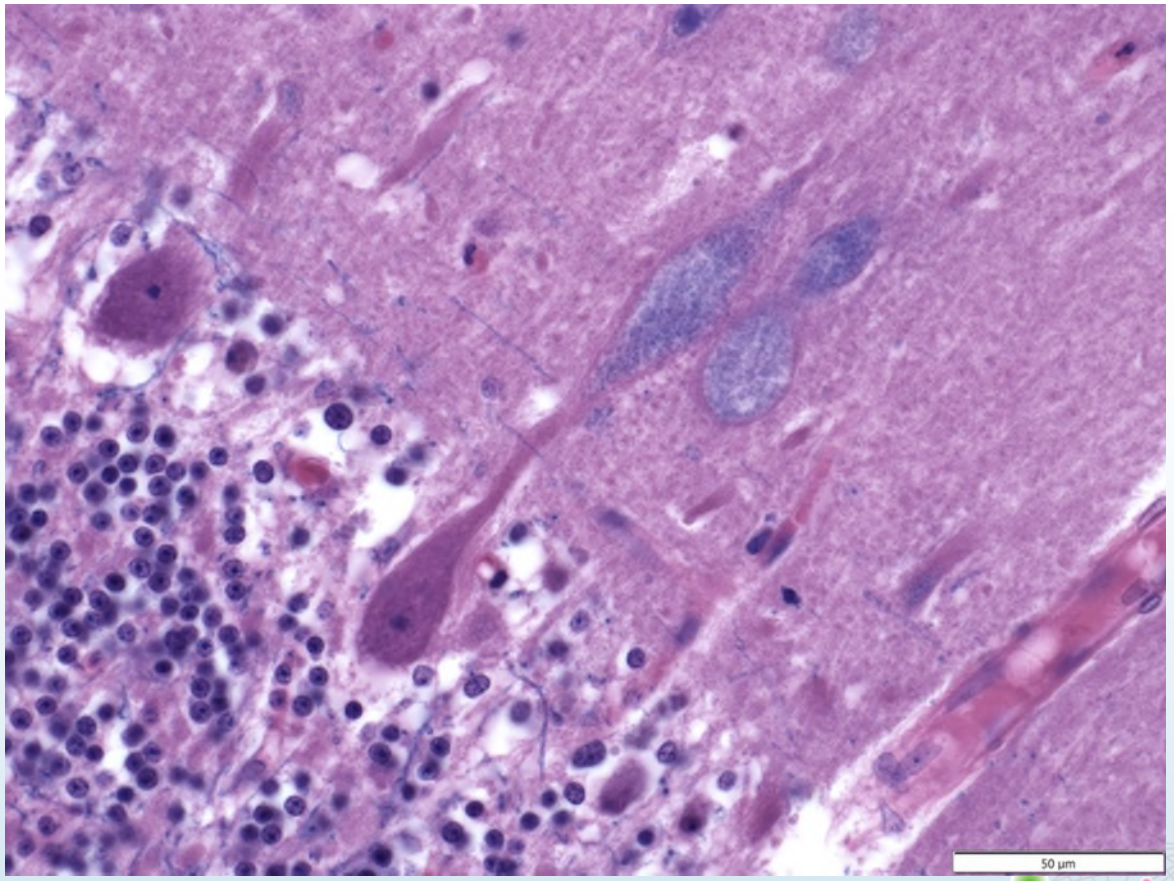
MPS III (Sanfilippo disease)

- 4 different genes coding for lysosomal enzymes that breakdown heparan sulfate (HS)
- progressive accumulation of partially degraded HS in lysosomes, which ultimately damages the cells

Sanfilippo syndrome type	Gene	Enzyme
Type A	SGSH	heparan N-sulfatase[15]
Type B	NAGLU	Alpha-N-acetylglucosaminidase[15]
Type C	HGSNAT	acetyl-CoA:alpha-glucosaminide N-acetyltransferase[15]
Type D	GNS	N-acetylglucosamine-6-sulfatase[15]

MPS III (11 year male) – LFB stained storage material in Purkinje dendrites



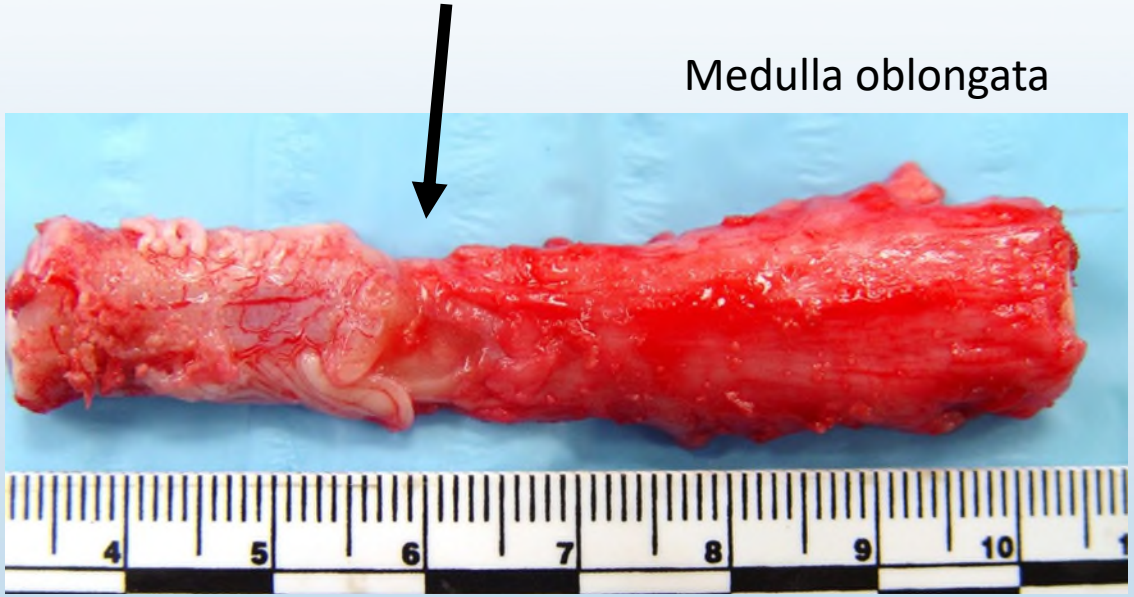


MPS IV (Morquio)

- GALNS gene (MPS IVA) or GLB1 gene (MPS IVB)
- Mainly skeletal (brain not directly affected)
- Despite the clinical syndrome, both proteins are highly expressed in brain

MPS IV case

- 33 year male
- Severe scoliosis, short stature, cognitively normal
- Atlanto-axial instability since age 16 years – occiput to C2 fusion
- Respiratory arrest during dental procedure
- At autopsy, severe atlanto-occipital instability with C1-C2 cervical spinal cord compression

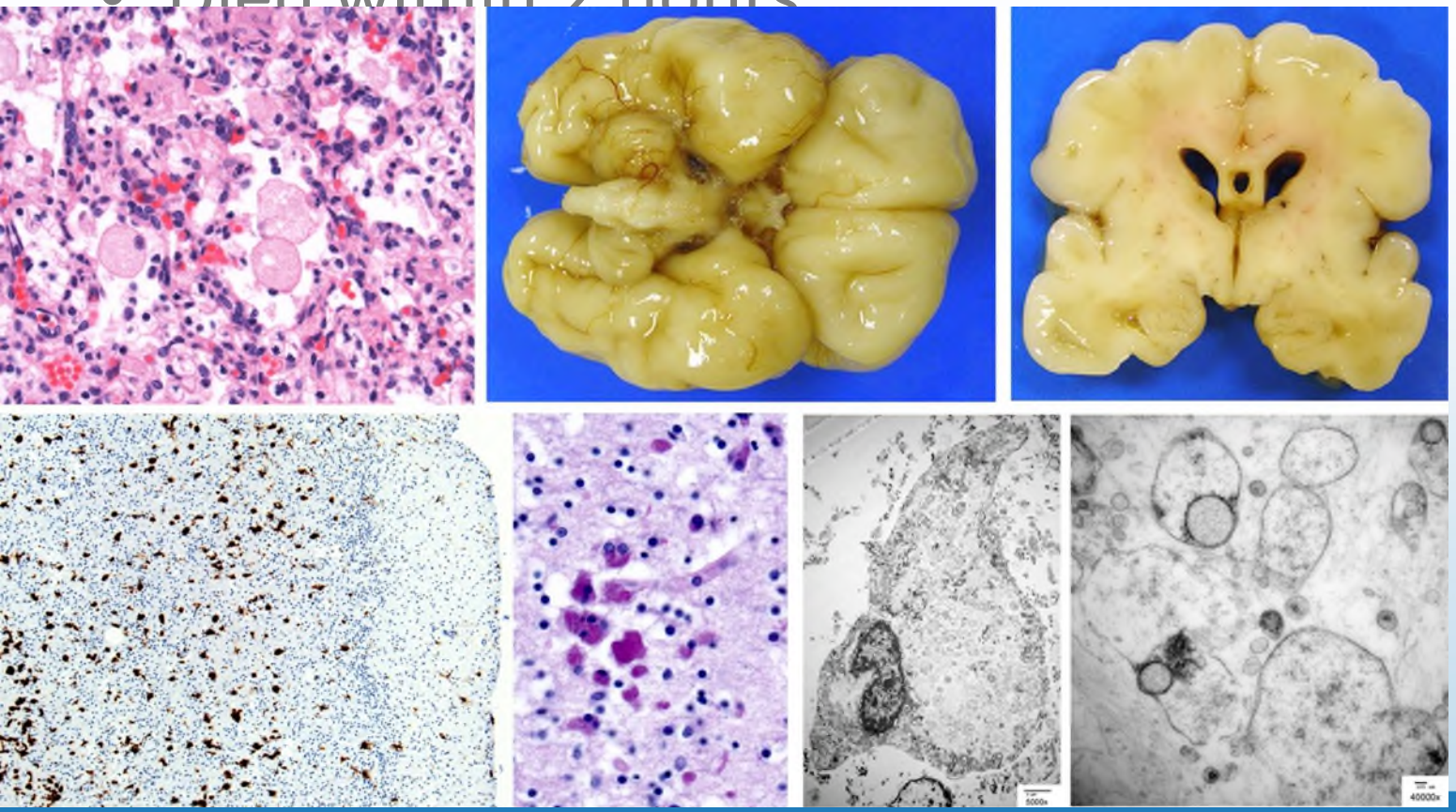


Gaucher disease

- Mutation in GBA1 gene, which codes for lysosomal glucocerebrosidase (glucosylceramidase beta 1)
- Autosomal recessive
- Type 1 - varied phenotype; storage of lipids in spleen, liver, and bones (most cases)
- Type 2 - severe early onset and rapidly fatal form that affects the brain (rare)
- Type 3 - skeletal problems, enlarged liver and spleen, seizures, and neurological decline, death in adolescence or early adulthood

Gaucher type 2, perinatal

- Born at 35 weeks gestation with a prenatal diagnosis of fetal akinesia, abnormal facial features, and hepatomegaly
- Died within 2 hours



Periodic acid Schiff (PAS)+ inclusion material in perivascular macrophages

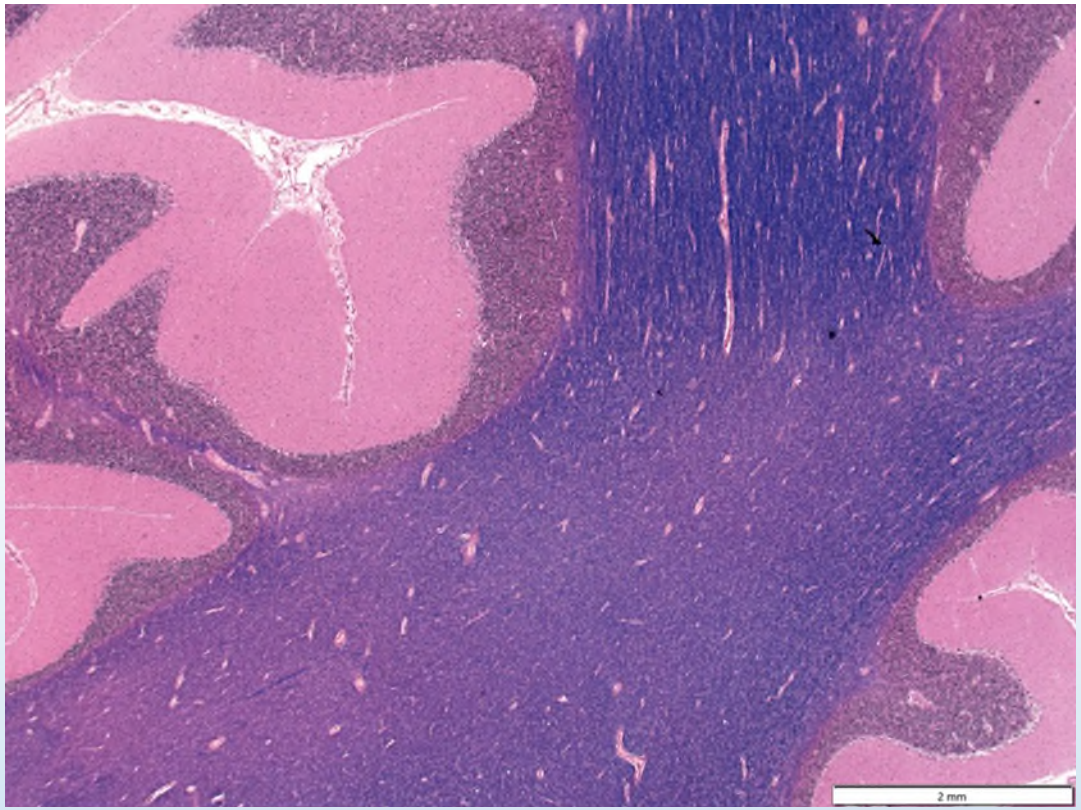
EM showed granular lysosomal debris but NOT typical Gaucher cells.

See Frosk et al. Neuropathol Appl Neurobiol. 2014 40:946-50. doi: 10.1111/nan.12122.

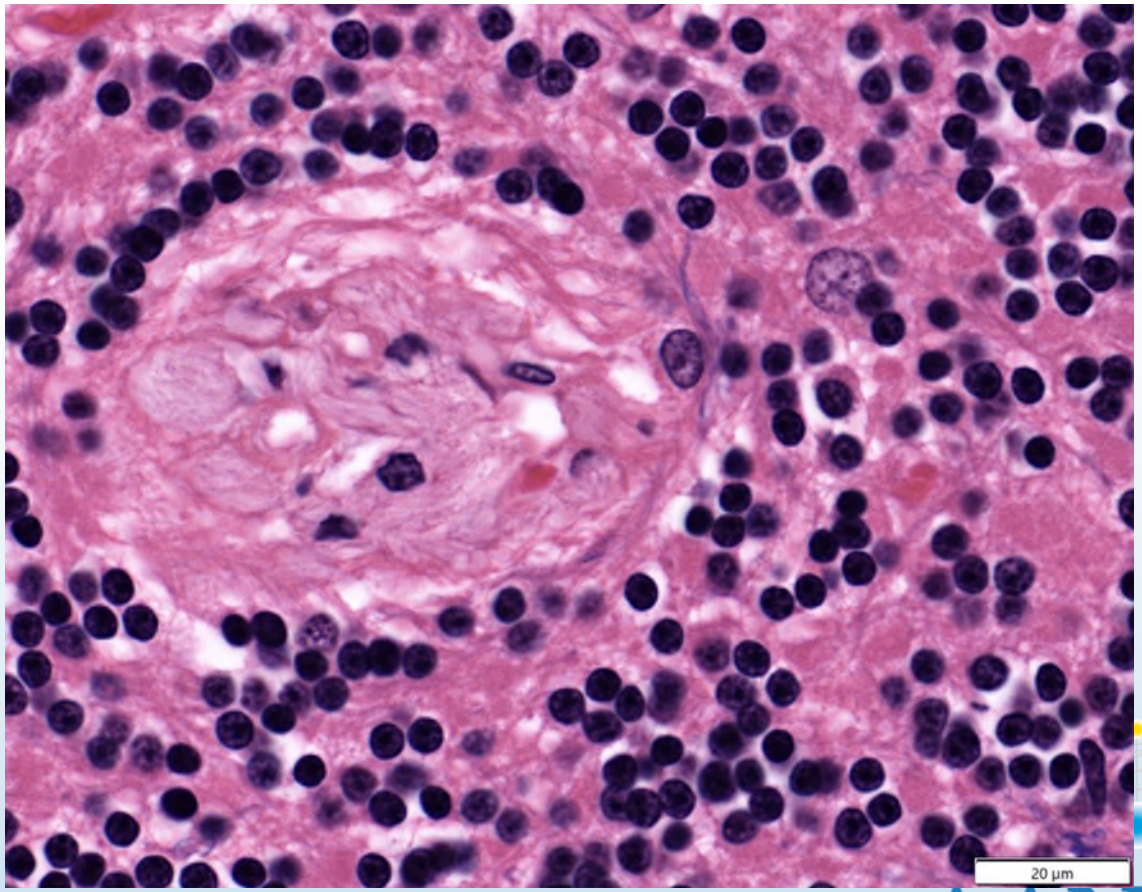
AANP

Gaucher type 3

- 22 year female with seizures for 4 years; died of progressive liver failure

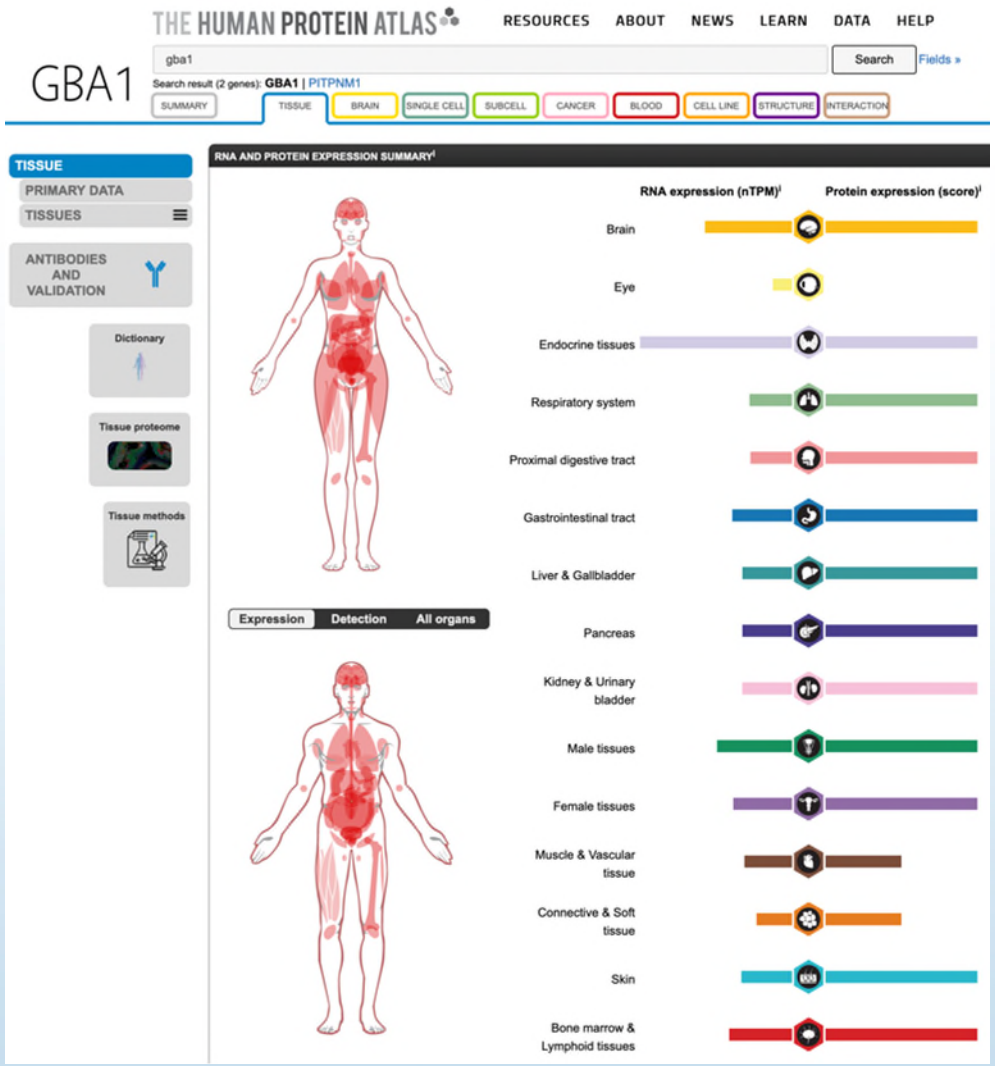


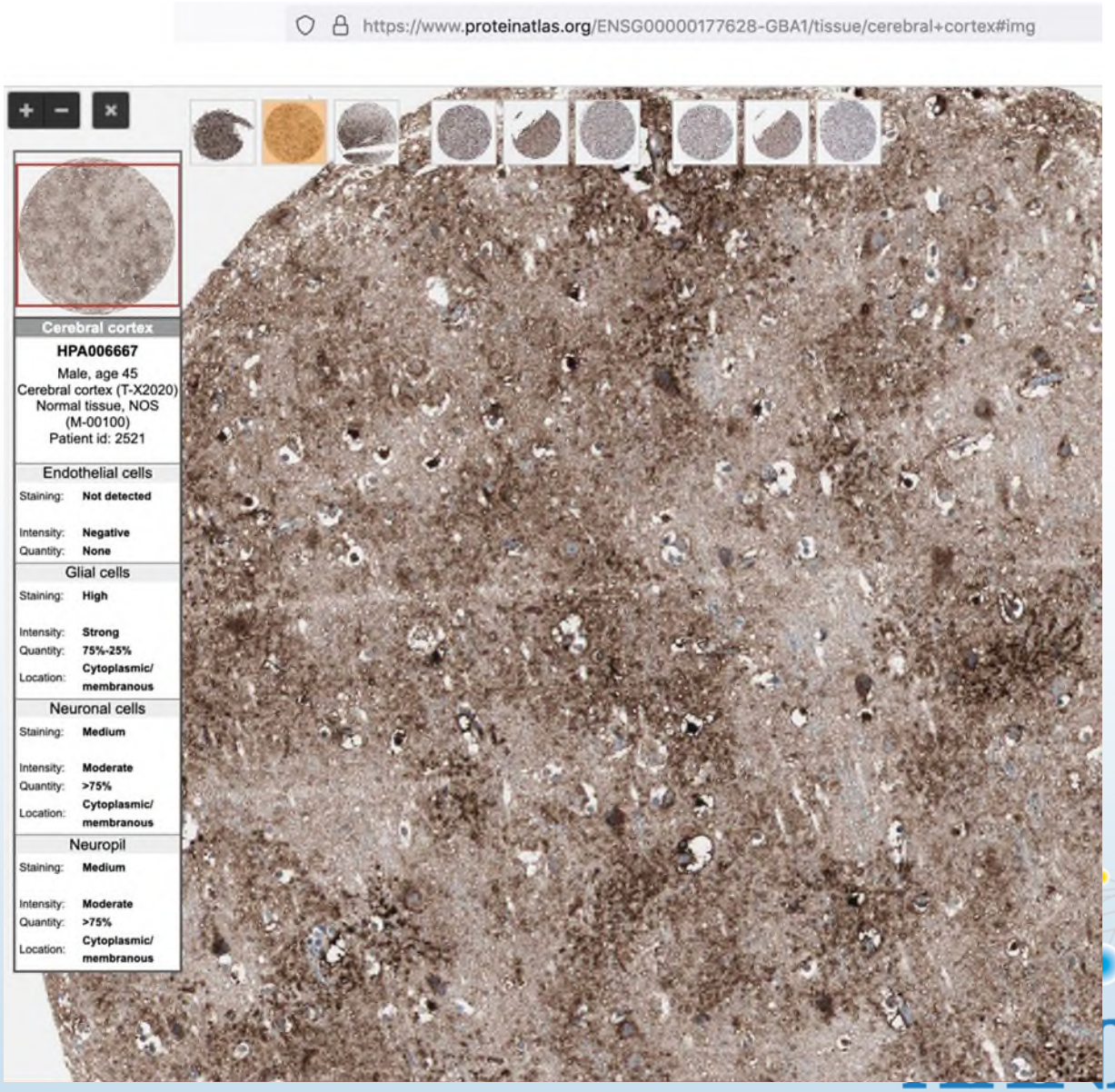
Slight decrease cerebellar myelin (LFB H&E)



Perivascular “Gaucher” cells (macrophages with lamellar inclusions)

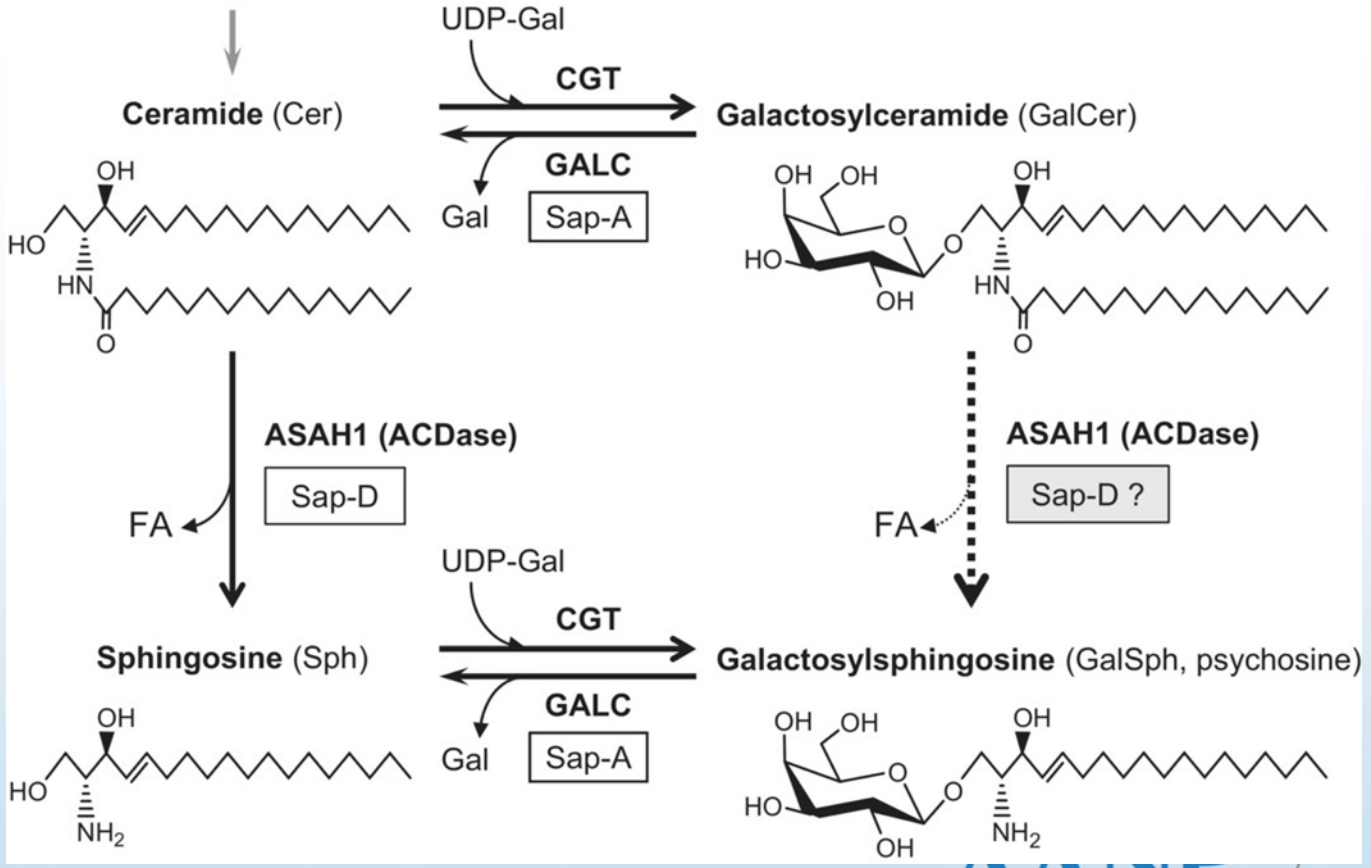
GBA1 highly expressed in all organs and in almost all cell types



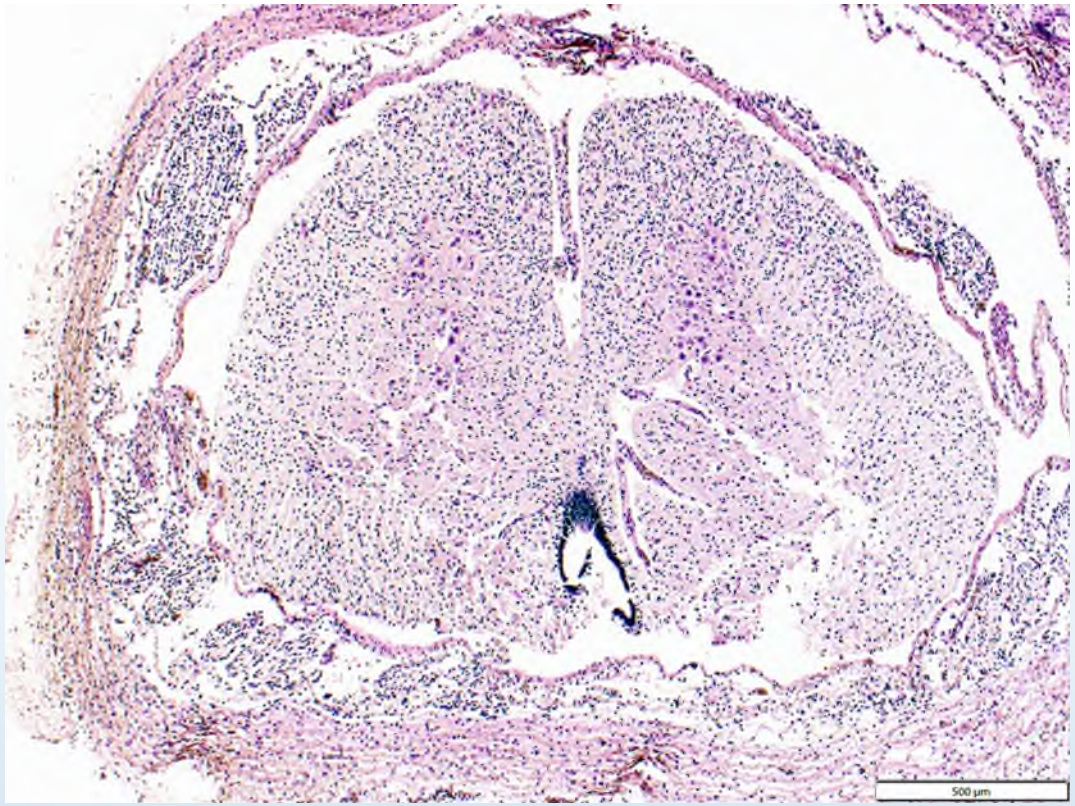


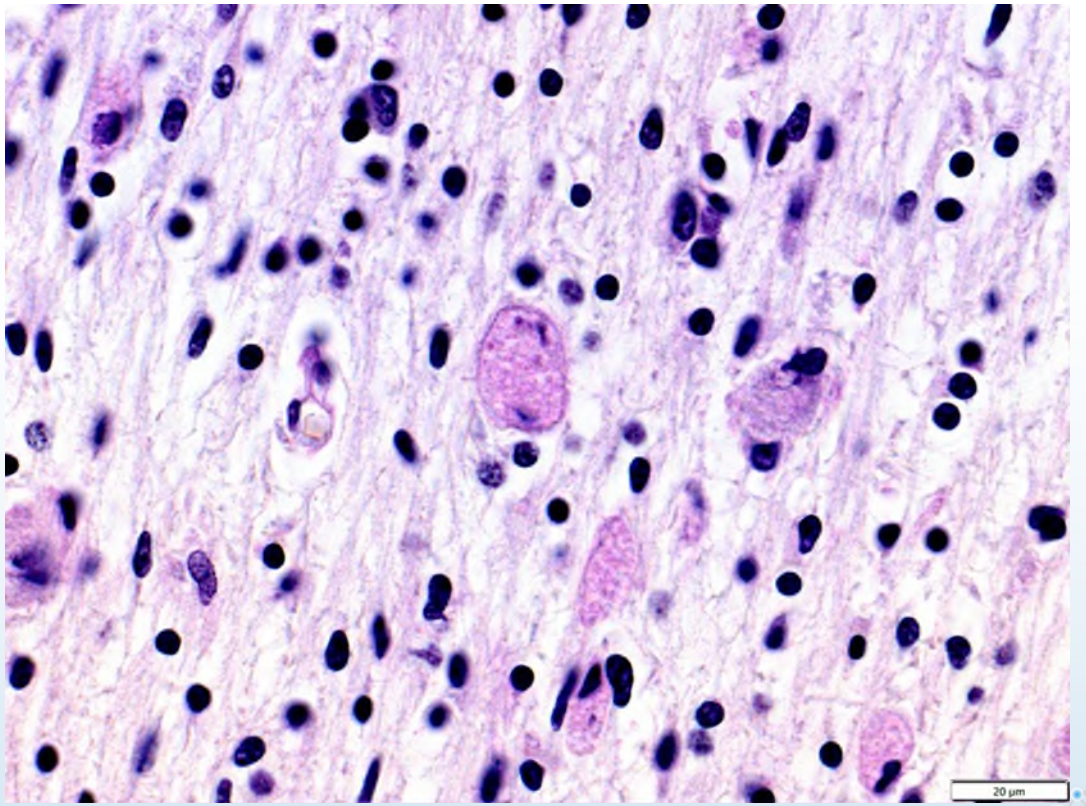
Krabbe disease (globoid cell leukodystrophy)

- galatocerebroside-ß-galactosidase enzyme deficiency (lysosomal)
- GALC mutation
- Failure to break down membrane lipids (galactocerebroside and galactosylceramide)
- Accumulation of toxic lipid, psychosine

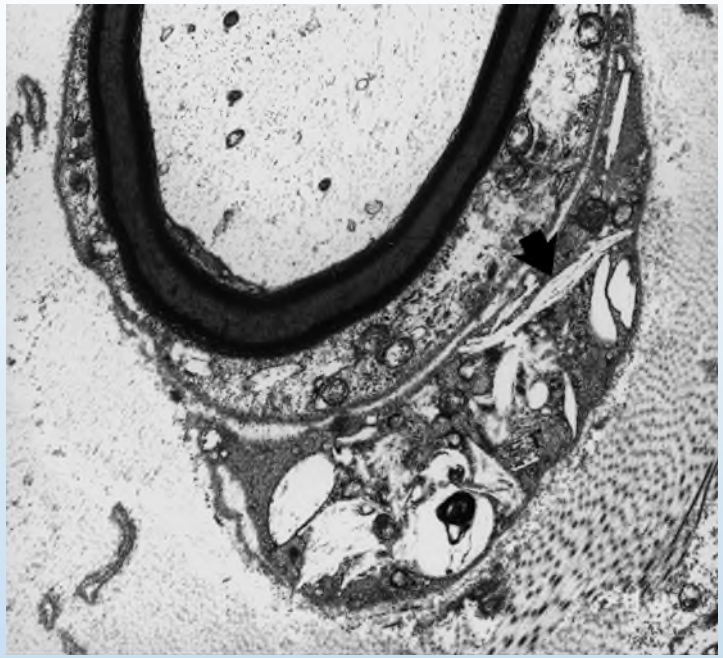


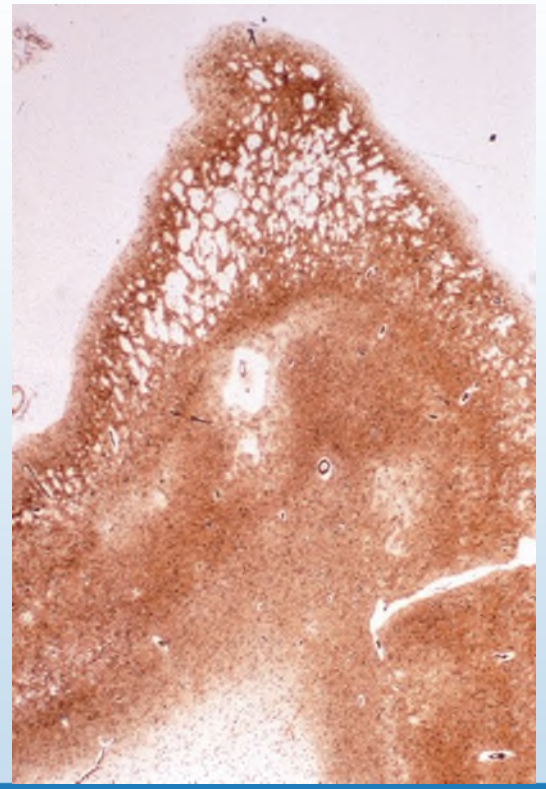
- 19 week fetus with GALC mutation
- Globoid cells in spinal cord

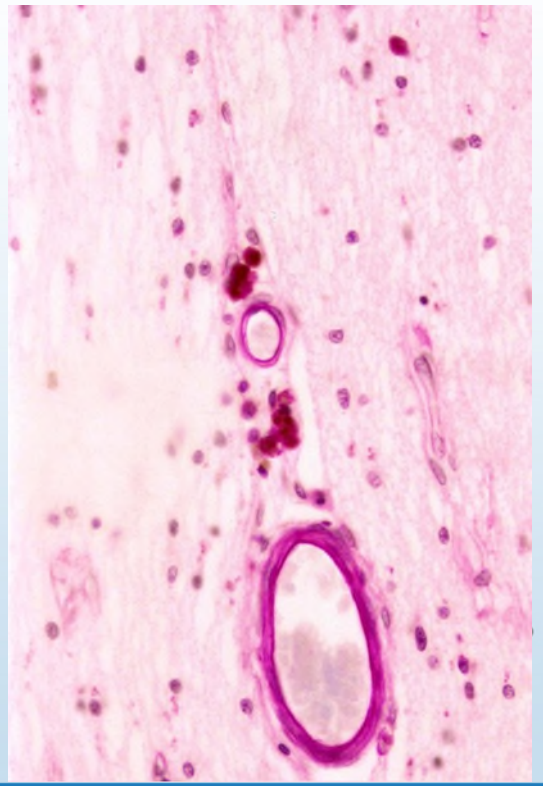




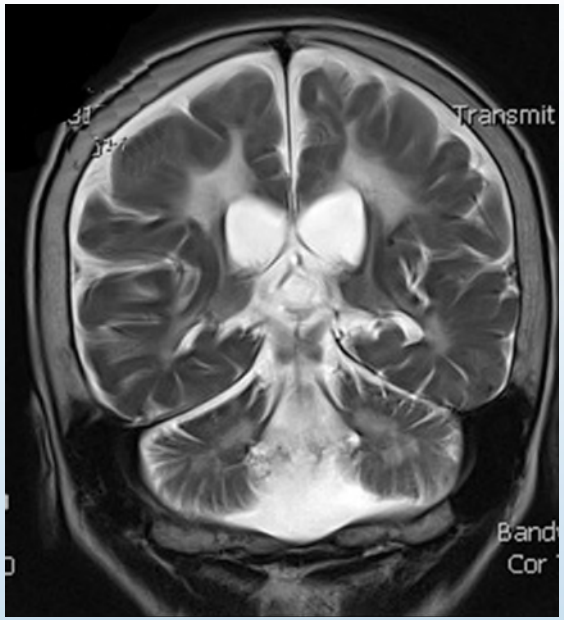
- Female developmental delay noted at 6 months
- 17 months speaking 5-10 words, regressed at 20 months
- Sural nerve biopsy at 22 months – large axons with thin myelin, Schwann cells with needle shaped inclusions characteristic of Krabbe disease
- Died at 9 years, brain small (820g) with severe white matter atrophy and spongiform degeneration in cortex, but no globoid cells in any organ
- Del Bigio et al. 2004 Neuropediatrics. 2004 35:297-301. doi: 10.1055/s-2004-821172



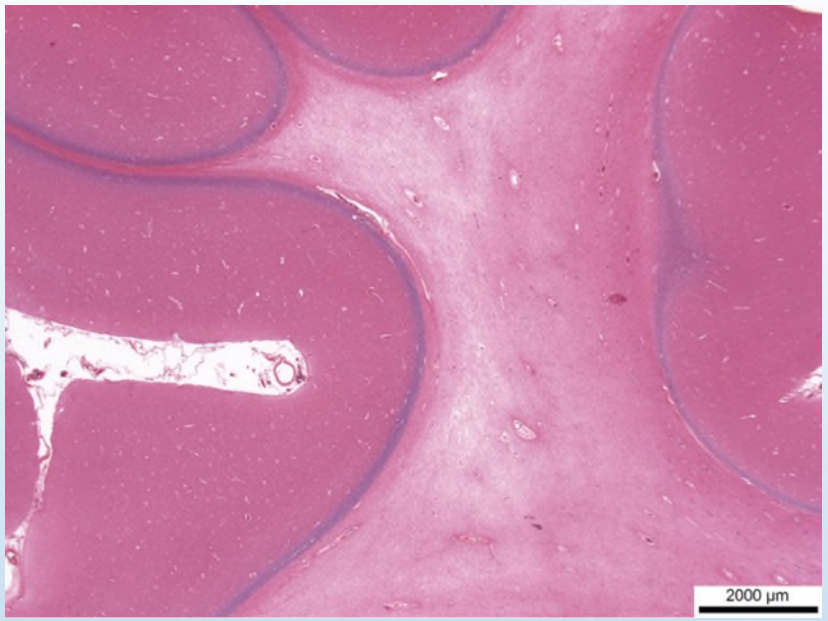




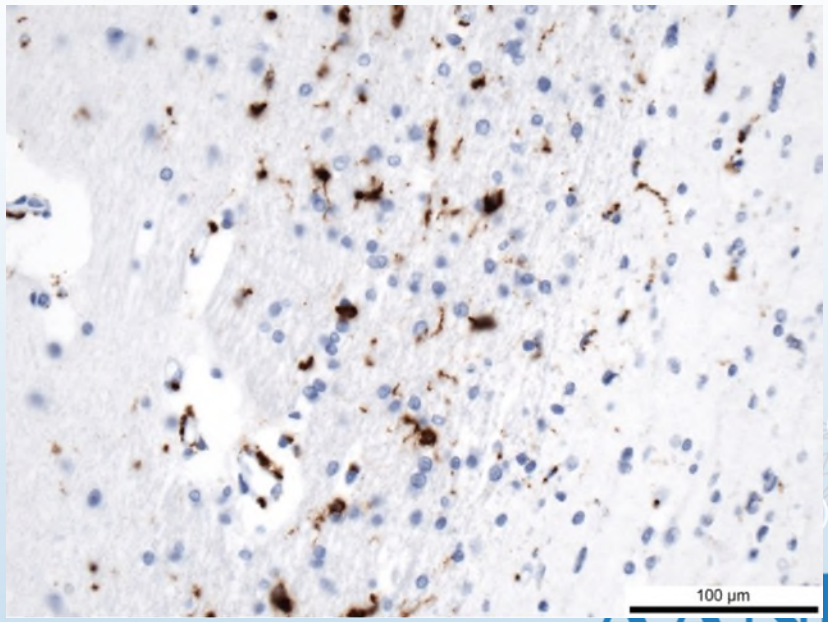
- 12-year-old boy with severe developmental delay, scoliosis, peripheral neuropathy, spasticity, intractable seizures, and visual impairment
- Galactocerebroside-ß-galactosidase enzyme deficiency.
- Heterozygous GALC mutations.
- Severe degeneration of deep cerebral white matter and descending tracts.
- Regional atrophy of cerebellum
- Absence of globoid cells - macrophages do not necessarily persist in long survivors
- Del Bigio MR. Pediatr Neurol. 2018 82:51-52. doi: 10.1016/j.pediatrneurol.2018.03.002



MRI T2 weighted



Frontal cerebrum (LFB H&E)

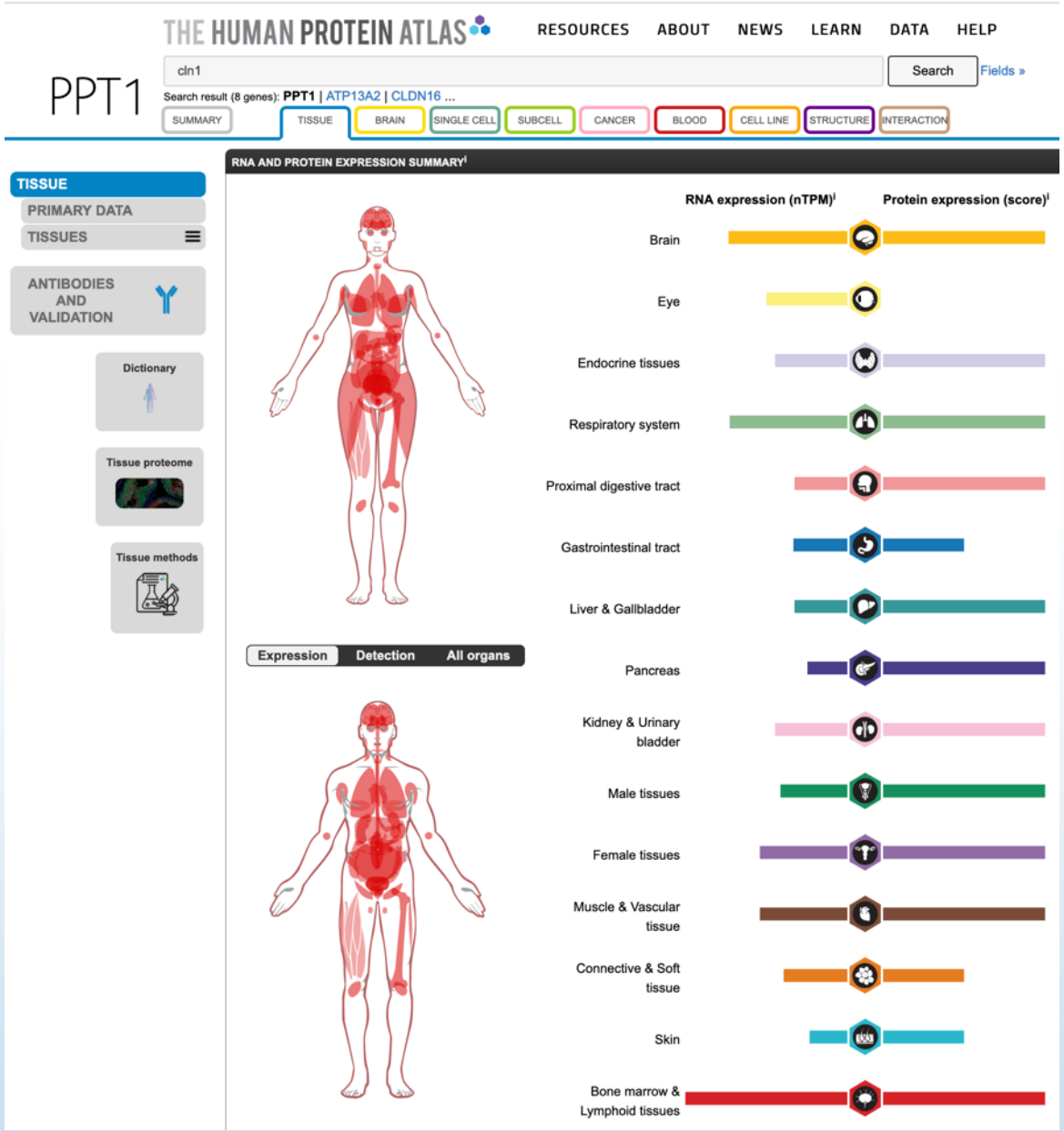


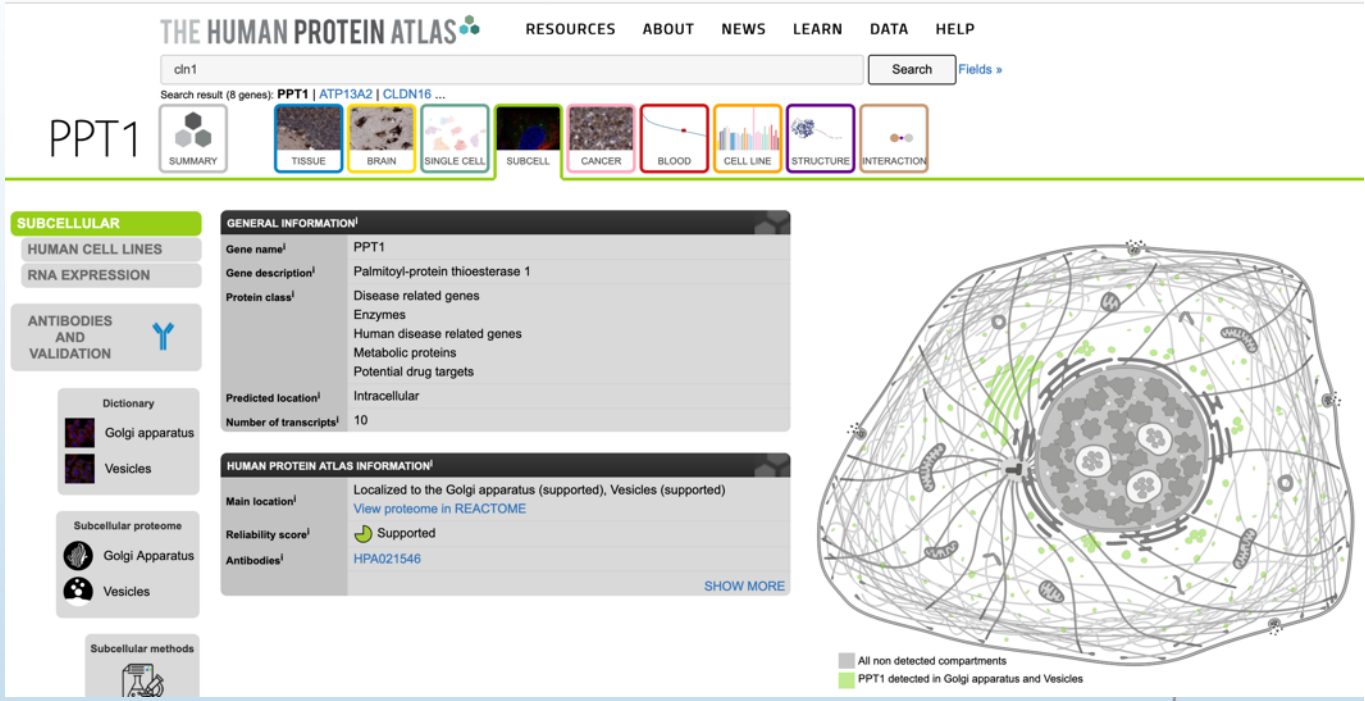
White matter (CD68)

Neuronal ceroid lipofuscinosis (NCL)

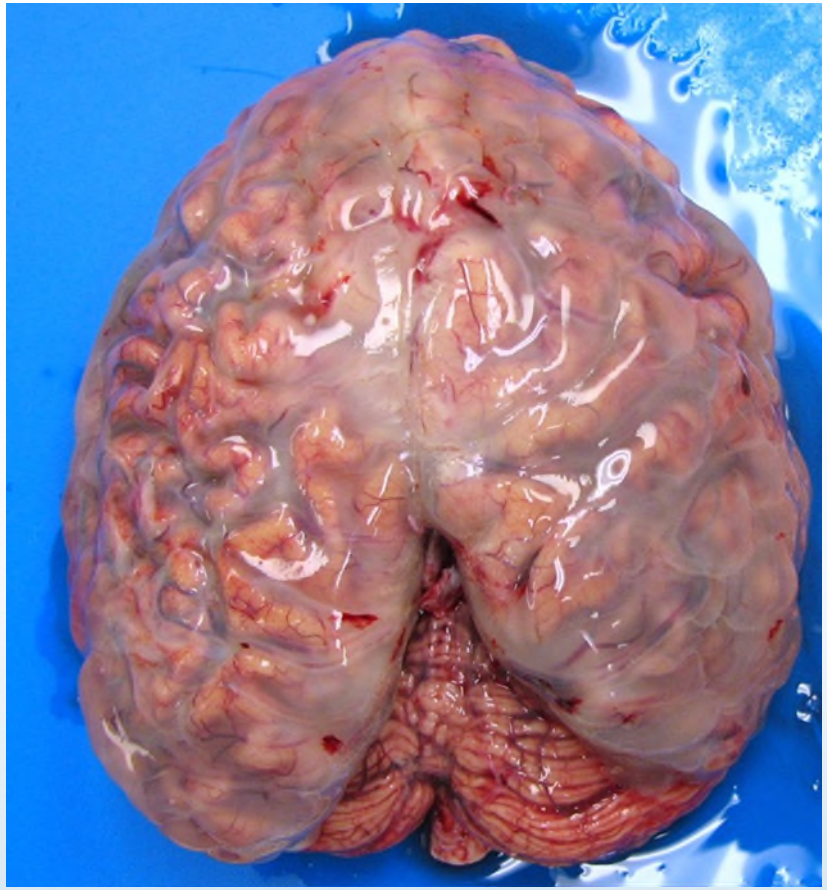
- old classification of NCL divided the condition into four types based upon age of onset, new classifications divide it by the associated gene:
  - infantile (most PPT1 gene (previously CLN1), also CTSD), onset 6 months to 2 years (Santavuori–Haltia disease)
  - late infantile (most TPP1 gene (previously CLN2), also CLN5 CLN6 CLN8), onset 2 to 4 years (Jansky–Bielschowsky disease)
  - juvenile (CLN3 gene), onset 5 to 8 years (Batten disease)
  - adult (various mutations)
- All are highly expressed in brain tissue (glia and neurons) and most other organ systems

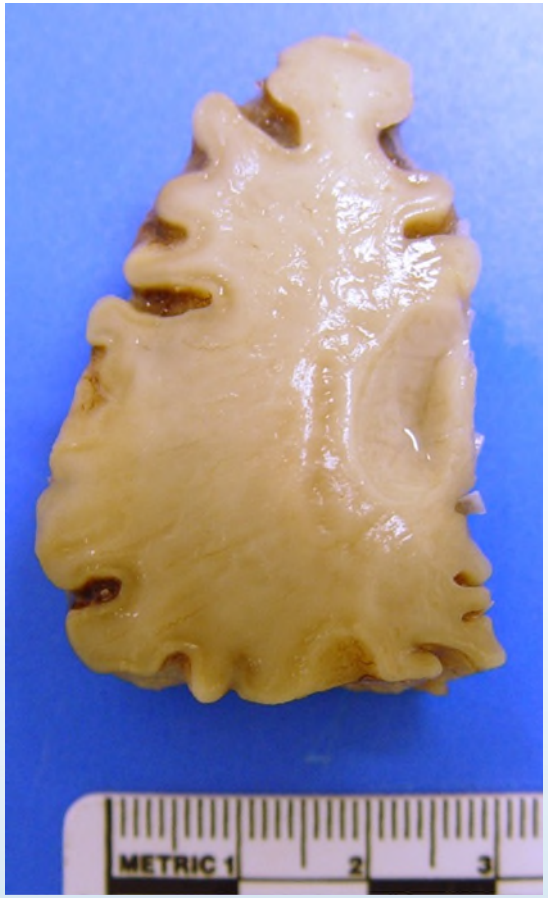
PPT1 (CLN1) expressed in all organs, in Golgi and lysosomes

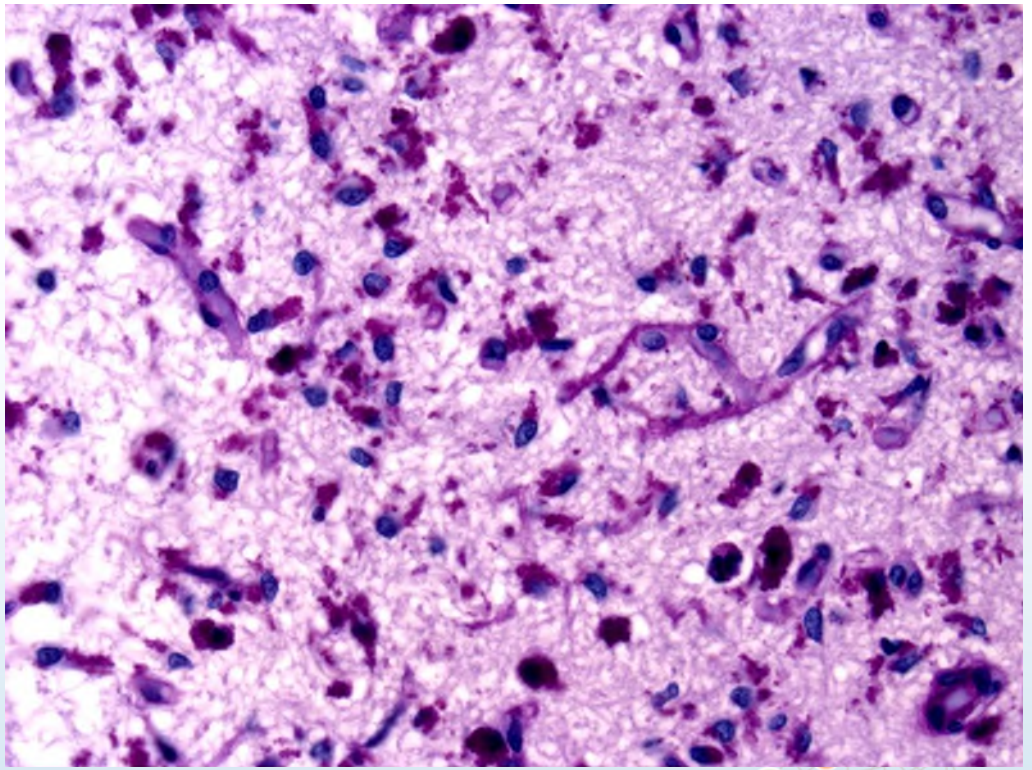




Late infantile onset NCL







Atrophic brain

Negligible myelin

abundant PAS+ storage material in frontal cortex

Etc. etc.

CNS storage disorder investigation

- In the past:
  - Metabolic / storage disease suspected by clinical history and neurologic phenotype
  - ± enzyme analysis
  - ± muscle / nerve / skin / cornea biopsy ± electron microscopy
  - Autopsy to “prove” disease with microscopy, electron microscopy etc.
- Current:
  - Clinical suspicion → genetic testing
  - Possible marrow transplant or enzyme replacement therapy
  - Clinical and MR imaging monitoring of CNS status
  - Autopsy rare – unless:
    - tissue donation for research
    - unexpected death requiring medicolegal autopsy
    - fetal / perinatal case not yet diagnosed

Phenotypic variability – gene correlation

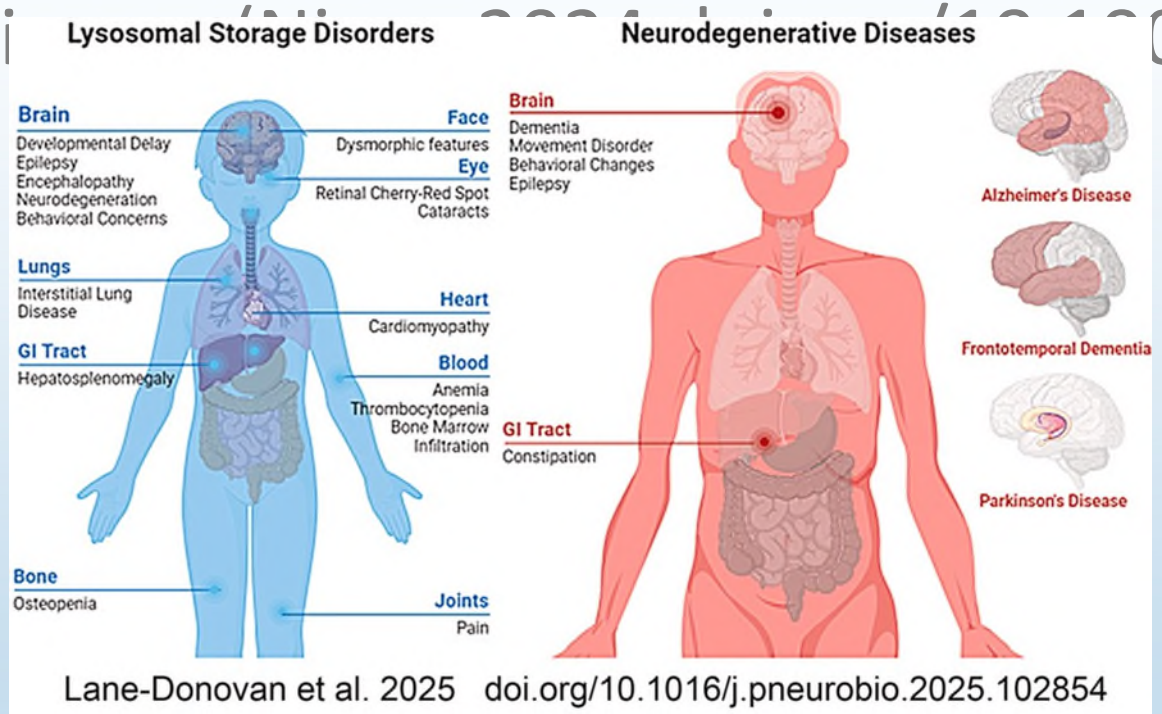
- Age of onset / severity typically depends on severity of enzyme deficiency; e.g. 0% activity could be embryonic lethal or present early, 50% activity might present in adolescence or adulthood
- Factors include:
  - specific mutation
  - multiple genetic variants (e.g. autosomal recessive disorder with two different mutations)
  - modifier genes
  - epigenetic modifications
  - random (stochastic) events in gene expression
  - environmental influences
- (Girirajan & Eichler 2010 doi:10.1093/hmg/ddq366)

Phenotypic variability – storage diseases

- Classic storage material might not persist in chronic cases (macrophages emigrate, neurons die)
- Specificity of classic electron microscopic features may be overstated
  - e.g. Goebel et al. Mechan. Ageing Devel. 10:53-70, 1979
  - Mole et al. Correlations between genotype, ultrastructural morphology and clinical phenotype in the neuronal ceroid lipofuscinoses. Neurogenetics 6:107-26, 2005.
- Organ / tissue phenotype is not always obviously explained by relevant gene / protein distribution.

Neurodegenerative diseases of aging

- In some respects, these are similar to pediatric storage disorders
- Abnormal processing (recycling system or mutant protein), accumulation, toxicity)
- Autophagy–lysosomal-associated neuron death in neurodegenerative di[illegible]07/s00401-024-02799-7)



Other useful references

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- Ellison et al. Advances in therapies for neurological lysosomal storage disorders. J Inherit Metab Dis. 46:874–905, 2023
- Spencer et al. Non-canonical roles of lysosomes in neurons. Trends Neurosci. 2025 doi: 10.1016/j.tins.2025.10.009.
- Viana et al. Brain Pathology in Mucopolysaccharidoses (MPS) Patients with Neurological Forms. J. Clin. Med. 2020, 9:396; doi:10.3390/jcm9020396
- Bosch et al. Neuroinflammatory paradigms in lysosomal storage diseases. Front. Neurosci.9:417, 2015; doi: 10.3389/fnins.2015.00417
- Carmichael et al. Peroxisome dynamics and inter-organelle interactions in neuronal health and disease. Front. Mol. Neurosci. 18, 2025; doi: 10.3389/fnmol.2025.1603632