Lysosomal Diseases

Biochemical Defect	Deficiency in lysosomal enzyme → excess intracellular substrate (e.g., GAGs, MPS)
Presentation	• Substrate build-up → HSM, coarse facies, short stature, skeletal abnormalities • If nervous system involvement → intellectual disability, cataracts, neuropathy
Diagnosis	**Enzyme assay** on samples of WBCs, serum, or skin fibroblasts

Disorder	Enzyme Blockade	Accumulated Substrate(s)	Presentation (AR inheritance unless specified)	Treatment
Gaucher Disease	β-glucosidase (glucocerebrosidase)	Glucocerebroside	Type 1:HSM, bone disease, anemia & thrombocytopenia, absence of CNS disease Type 2&3: Primarily neurologic with DD, regression, early death	ERT, substrate reduction therapy
Tay-Sachs Disease	Hexosaminidase A	GM_2 gangliosides	By age 1 - DD, **exaggerated startle**, sz, macular cherry-red spot	Supportive
Niemann-Pick Disease	Sphingomyelinase	Sphingomyelin	Massive HSM, cherry red spot, interstitial lung disease; neuronopathic or non-neuronopathic	HSCT for non-neuronopathic
Krabbe Disease	Galactocerebrosidase	Galactocerebroside	Infantile-onset:By age 1 - irritability, rapid neurologic deterioration,early childhood death Later-onset: variable	Early HSCT
Metachromatic Leukodystrophy	Cerebroside sulfatase (arylsulfatase A)	Sulfatides	First years of life (late infantile form): DD/ regression; Juvenile form with regression, of dev and beh, then gait; Peripheral neuropathy in adult form	HSCT for juvenile and adult MLD
Fabry Disease	α-galactosidase	Globotriaosyl-ceramide (GL-3)	*XLR. Acroparesthesias, pain crises, corneal opacities, fatigue, angiokeratomas	ERT
Hurler Syndrome (MPS I)	α-L-iduronidase	Glycosamino-glycans (GAGs): dermatan + heparan sulfate	Coarse facies, DD, ID, corneal clouding, hearing loss, hernias, dysostosis multiplex	ERT, HSCT
Hunter Syndrome (MPS II)	Iduronate-2-sulfatase	GAGs as above	*XLR.Similar to MPSI r w/o corneal clouding.	ERT, HSCT

ERT = enzyme-replacement therapy. HSCT = hematopoietic stem-cell transplant.