E-TABLE 122-3 SELECTED METABOLIC MYOPATHIES

CLASS	NAME	ENZYME/GENE	PHENOTYPE	TESTING
GLYCOGEN STORAGE				
Type II	Pompe's disease	Acid maltase / *GAA*, 17q21	Infantile: hypotonia, cardiomegaly, hepatomegaly, fatal in 1st year without treatment. Adult: limb-girdle weakness, respiratory failure	Muscle biopsy with non-rimmed vacuoles, and PAS positive material. Decreased enzyme activity in muscle, lymphocytes, or fibroblasts
Type III	Cori-Forbes disease	Debrancher / *AGL*, 1p21	Infantile: hypotonia. Adult: Limb-girdle pattern with distal weakness, respiratory involvement	Muscle biopsy PAS positive glycogen deposits. Decreased enzyme activity in fibroblasts or lymphocytes
Type IV	Andersen disease	Branching / *GBE1*, 3p12	Infantile: hypotonia. Adult: limb-girdle pattern, ± distal	PAS-positive, diastase-resistant filamentous polysaccharides (polyglucosan bodies); decreased enzyme activity in skin fibroblasts, muscle or liver.
Type V	McArdle's disease	Myophosphorylase / *PYGM*, 11q13	Infantile: profound weakness. Adult: Exercise intolerance, cramps, fatigue, limb-girdle pattern, second wind phenomenon	Electrically silent muscle contractures; Subsarcollemal glycogen deposits; Decreased enzyme activity from muscle;
Type VII	Tauri's disease	Phosphofructokinase / PFKM, 12q13	Childhood: cramps, fatigue, exercise intolerance	Accumulation of free glycogen in muscle; hemolytic anemia; enzyme deficiency in muscle, erythrocytes
LIPID METABOLISM				
	Carnitine palmitoyltransferase II deficiency	CPT II, 1p32	Neonatal/infantile: severe, fatal. Adult: exercise or illness related, cramping, myoglobinuria, usually no fixed weakness	Low total serum carnitine; increased acylcarnitine fraction; reduced enzyme activity in skeletal muscle
	Very long chain acylcoenzyme A dehydrogenase deficiency	ACADVL, 17p13	Childhood: nonketotic hypoglycemia can have severe form with cardiomyopathy. Adult: rare, exercise/fasting induced myalgias or myoglobinuria.	Reduced VLCAD activity in fibroblasts; increased lipid staining in muscle
	Long chain acylcoenzyme A dehydrogenase deficiency	ACADL, 2q34	Infancy: failure to thrive, nonketotic hypoglycemia, cardiomegaly, encephalopathy. Adult: myopathy with cramps and myoglobinuria	Reduced total and free carnitine levels; increased long chain acylcarnitine esters; reduced enzyme activity in fibroblasts
	Medium chain acylcoenzyme A dehydrogenase deficiency	ACADM, 1p31	Infancy: failure to thrive, nonketotic hypoglycemia, cardiomegaly, encephalopathy. Adult: mild myopathy later in life.	Reduced total and free carnitine; decreased enzyme activity in lymphocytes, fibroblasts, and liver; excess lipid in muscle
MITOCHONDRIAL				
	Myoclonic Epilepsy associated with Ragged Red Fibers (MERRF)	Mitochondrial mutations, ~80% m.8344 A>G;	Onset usually childhood, epilepsy, myoclonus, ataxia, dementia, short stature, optic atrophy, wolf Parkinson white syndrome	Muscle biopsy ragged red fibers; elevated lactic acid; mitochondrial sequencing;
	Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)	Mitochondrial mutations, ~80% m. 3243 A>G	Childhood onset, normal psychomotor development, then episodes of encephalopathy, migraine, seizures, stroke like symptoms, anorexia and vomiting, short stature, deafness, myopathy with exercise intolerance	Muscle biopsy ragged red fibers; elevated lactic acid; mitochondrial sequencing;
	Mitochondrial neurogastrointestinal encephalopathy (MNGIE)	Genomic mutations, TYMP, 22q13	Onset childhood/teenage, visceral neuropathy (gastroparesis, obstipation, diarrhea), ptosis, external ophthalmoplegia, sensory > motor neuropathy, hearing loss, myopathy	Muscle biopsy ragged red fibers; elevated lactic acid; mitochondrial sequencing
	Kearns-Sayre Syndrome	Single large mitochondrial deletion (~80%); also individual mutations	Onset less than 20 years; external ophthalmoplegia; pigmentary degeneration of retina; heart block; myopathy	Muscle biopsy ragged red fibers; elevated lactic acid; mitochondrial sequencing
	Leigh Syndrome	Many genes nuclear (complex I-IV); SURF-1, 9q34; mitochondrial	Typical: Onset 1st year; hypotonia; episodic vomiting, ataxia; encephalopathy; hearing loss; visual loss; death often within 2 years of onset. Mitochondrial: variable age of onset; less severe;	Muscle normal histology but COX negative; elevated lactate (CSF >blood); MRI high T2 in lentiform and caudate nuclei
	Progressive External Ophthalmoplegia (PEO)	Nuclear: POLG 15q25; ANT1 4q35; Twinkle 10q23; POLG2 17q. Mitochondrial: deletions or depletion	Onset variable typically >20 years; ptosis; ophthalmoparesis often without double vision; plus syndromes have myopathy and variable organ involvement.	Muscle biopsy ragged red fibers; genetic testing or mitochondrial sequencing;

GAA, Acid α-glucosidase; GBE1, glycogen branching enzyme 1.