Disease Name	Methylmalonic acidemia, Cbl A, B
Alternate name(s)	Methylmalonic acidemia, Vitamin B-12 responsive, due to defect in adenosylcobalamin, cblA complementation type; Methylmalonic acidemia, cblA type; Methylmalonic acidemia, Vitamin B-12 responsive, due to defect in synthesis of adenosylcobalamin, cbl B complementation type
Acronym	MMA, MMAA/MMAB
Disease Classification	Organic Acid Disorder
Variants	Yes
Variant name	Methylmalonic acidemia, Vitamin B-12 non-responsive; Combined deficiency of methylmalonyl-CoA mutase and homocysteine
Symptom onset	Variable. Ranges from the first days of life to completely asymptomatic.
Symptoms	Episodic ketoacidosis with vomiting accompanied by lethargy and coma which can lead to death. Survivors can have developmental delays, growth delays, spastic quadriparesis, dystonia and seizures. Neutropenia, thrombocytopenia and osteoporosis are common complications.
Natural history without treatment	Variable depending on the enzyme defect. Some will die in the newborn period, others will survive with deficits and others will be asymptomatic.
Natural history with treatment	**CblA:** Good prognosis with injections of hydroxy-cobalamin (OH-cbl) which reverses biochemical and clinical abnormalities in about 90% of patients. **CblB:** Equal fractions of affected patients are alive and well, alive and impaired, or deceased. The age of onset of symptoms can help prognosticate outcome – those patients with a later onset of symptoms have a more benign course. Approximately 40% of patients will respond with a drop in MMA level when given OH-cbl injections.
Treatment	Protein restricted diet, OH-cbl injections, carnitine supplementation, oral antibiotic therapy to decrease proprionate and medical foods. Liver transplant or combined liver/kidney transplant may increase metabolic control, but may not prevent neurologic complications.
Physical phenotype	Minor facial dysmorphisms including high forehead, broad nasal bridge, epicanthal folds, long, smooth philtrum and triangular mouth. A variety of skin lesions can be seen in patients due to moniliasis.
Inheritance	Autosomal recessive
General population incidence	1:48,000
Ethnic differences	No known population at increased risk
Population	N/A
Ethnic incidence	N/A
Enzyme location	Mitochondria
Enzyme Function	Production of adenosylcobalamin
Missing Enzyme	Cobalamin A (cblA) deficiency: cobalamin reductase Cobalamin B (cblB) deficiency: cobalamin adenosyltransferase
Metabolite changes	Elevated glycine in urine
Prenatal testing	Possible via enzyme assay on amniocytes or CVS.
MS/MS Profile	Elevated C3 propionyl carnitine, elevated C4 DC methylmalonyl carnitine.
OMIM Link	http://www.ncbi.nlm.nih.gov/omim/251000
Genetests Link	www.genetests.org
Support Group	Organic Acidemia Association www.oaanews.org Save Babies through Screening Foundation www.savebabies.org Genetic Alliance www.geneticalliance.org Fatty Oxidation Disorder (FOD) Family Support Group www.fodsupport.org

Newborn Screening ACT Sheet
[Elevated C3 Acylcarnitine]
Propionic Acidemia and Methylmalonic Acidemia

Differential Diagnosis: Propionic acidemia (PA); Methylmalonic acidemias (MMA) including defects in B_{12} synthesis and transport; maternal severe B_{12} deficiency.

Condition Description: PA is caused by a defect in **propionyl-CoA carboxylase** which converts propionyl-CoA to methylmalonyl-CoA; MMA results from a defect in **methylmalonyl-CoA mutase** which converts methylmalonyl-CoA to succinyl-CoA or from lack of the required B_{12} cofactor for methylmalonyl-CoA mutase (cobalamin A, B, C, D, and F).

YOU SHOULD TAKE THE FOLLOWING ACTIONS IMMEDIATELY:

- Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy, tachypnea).
- Consult with pediatric metabolic specialist.
- Evaluate the newborn; check urine for ketones and, if elevated or infant is ill, initiate emergency treatment as indicated by metabolic specialist and transport immediately to tertiary center with metabolic specialist.
- Initiate timely confirmatory/diagnostic testing as recommended by specialist.
- Educate family about signs, symptoms and need for urgent treatment of hyperammonemia and metabolic acidosis (poor feeding, vomiting, lethargy, tachypnea).
- Report findings to newborn screening program.

Diagnostic Evaluation: Plasma acylcarnitine confirms the increased C3. Blood amino acid analysis may show increased glycine. Urine organic acid analysis will demonstrate increased metabolites characteristic of propionic acidemia or increased methylmalonic acid characteristic of methylmalonic acidemia. Plasma total homocysteine will be elevated in the cobalamin C, D and F deficiencies. Serum vitamin B_{12} may be elevated in the cobalamin disorders.

Clinical Considerations: Patients with PA and severe cases of MMA typically present in the neonate with metabolic ketoacidosis, dehydration, hyperammonemia, ketonuria, vomiting, hypoglycemia, and failure to thrive. Long-term complications are common, early treatment may be lifesaving and continued treatment may be beneficial.

Additional Information:

Emergency Protocols (New England Consortium of Metabolic Programs)
- PA
- MMA

Gene Reviews
- PA (Organic Acidemias Overview)
- MMA

Genetics Home Reference
- PA
- MMA

Referral (local, state, regional and national):

Testing
- PA
- MMA

Clinical Services