Disease Name	**Methylmalonic acidemia mutase deficiency**
Alternate name(s)	Methylmalonic aciduria due to methylmalonic CoA mutase deficiency, Complementation group mut0, Methylmalonyl-CoA mutase
Acronym	MUT
Disease Classification	Organic Acid Disorder
Variants	Yes
Variant name	Vitamin B12 metabolic defect with methylmalonic acidemia and homocystinuria
Symptom onset	Eighty percent of infants become ill during the first week or life and 90% will present by the end of the first month. Infants with the less severe *mut*- may present later than the first month. A few may remain asymptomatic or present much later in life depending on the residual enzyme activity and the metabolic stressors.
Symptoms	Most common signs and symptoms are lethargy, failure to thrive, recurrent vomiting, dehydration which leads to profound metabolic acidosis, respiratory distress, hypotonia and death if not recognized. Complications of acute episodes can include metabolic stroke, extrapyramidal signs, dystonia and bilateral lucencies of globus pallidus. Survivors may have significant neurological damage. Renal failure may appear during childhood. Clinical spectrum is wide, ranging from fatal neonatal disease to asymptomatic individuals. Patients do not have to have clinical crises in order to have neurological or other organ compromise.
Natural history without treatment	Variable depending on the enzyme defect and the patient. Some will die as a neonate, others will survive with deficits and a few others will remain asymptomatic.
Natural history with treatment	About 60% of patients die within the first year of life and of those that survive, 40% are distinctly developmentally impaired. Age of onset of symptoms can help prognosticate – those with later onset tend to have a more benign course. Liver and liver/kidney transplant are one treatment option. However, liver transplants have significant preoperative risk and there is documentation of neurological problems after transplant despite improved biochemical values. Renal transplants have shown good response with drops in methylmalonic acid levels, normalization of the diet and absence of acute episodes of metabolic decompensation. However, the effect of any type of transplant is limited because the MMA enzyme is in all tissues and the transplants do not affect the levels made in the cerebrospinal fluid and brain.
Treatment	Protein restricted diet, OH-Cbl injections, carnitine supplementation and oral antibiotic therapy to decrease gut production of propionate. Special medical foods (formula) deficient in methionine, threonine, valine, isoleucine, odd chain fatty acids and cholesterol. Liver transplant and liver/kidney transplant.
Physical phenotype	Most patients have no obvious dysmorphic features. Some patients, in whom there is known consanguinity, have had associated birth defects, congenital heart defects, hydronephrosis and facial dysmorphisms.
Inheritance	Autosomal recessive
General population incidence	1:48,000
Ethnic differences	None known
Population	N/A
Ethnic incidence	N/A
Enzyme location	Liver, kidneys, cerebrospinal fluid, brain
Enzyme Function	Catalyzes methylmalonyl-CoA to succinyl-CoA
Missing Enzyme	Methylmalonyl-CoA mutase
Metabolite changes	Increased methylmalonic acid in blood and 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

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