Disease Name	**Trifunctional protein deficiency**
Alternate name(s)	N/A
Acronym	**TFP**/LCHAD
Disease Classification	Fatty Acid Oxidation Disorder
Variants	Yes
Variant name	Mitochondrial trifunctional protein deficiency
Symptom onset	Neonatal, infancy
Symptoms	Hypoketotic hypoglycemia, hypotonia, cardiomyopathy, hepatic disease, peripheral neuropathy and pigmentary retinopathy, rhabdomyolysis, sudden death
Natural history without treatment	Possible developmental delay due to damage from hypoglycemic episodes, possible death due to cardiomyopathy or hepatic failure.
Natural history with treatment	Intelligence is usually normal if there is no damage due to hypoglycemic crisis. Peripheral neuropathy, if present, may not improve with treatment.
Treatment	Avoidance of fasting, use of uncooked starch, MCT treatments, carnitine supplementation, DHA supplementation (may prevent retinopathy, but this has not been proven)
Other	Maternal complications in pregnancy include acute fatty liver of pregnancy, HELLP syndrome, and pre-eclampsia
Physical phenotype	Hypotonia, cardiomyopathy and possible retinal changes
Inheritance	Autosomal recessive
General population incidence	Rare
Ethnic differences	Yes
Population	Finnish
Ethnic incidence	1:240 carrier rate for common mutation G1528C in Finland
Enzyme location	Inner mitochondrial membrane, liver, heart, fibroblasts
Enzyme Function	Metabolizes long chain fatty acids (C-12 to C-16 in length)
Missing Enzyme	Long-chain 3-hydroxyacyl-CoA dehydrogenase or mitochondrial trifunctional protein
Metabolite changes	Increased 3-hydroxydicarboxylic acids in urine, increased saturated and unsaturated 3-hydroxy organic acids, possible elevated CPK during acute illness.
Prenatal testing	Enzyme analysis, protein analysis and direct DNA (when applicable).
MS/MS Profile	C18:OH, C16:1OH, C16OH
OMIM Link	http://www.ncbi.nlm.nih.gov/omim/600890
Genetests Link	www.genetests.org
Support Group	FOD Family Support Group http://www.fodsupport.org Save Babies through Screening Foundation http://www.savebabies.org Genetic Alliance http://www.geneticalliance.org

Newborn Screening ACT Sheet
[Elevated C16-OH +/- C18 and Other Long Chain Acylcarnitines]
Long-chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency (LCHADD)

Differential Diagnosis: Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency; Trifunctional protein (TFP) deficiency.

Condition Description: LCHADD and TFP deficiencies are fatty acid oxidation (FAO) disorders. Fatty acid oxidation occurs during prolonged fasting and/or periods of increased energy demands (fever, stress) after glycogen stores become depleted and energy production relies increasingly on fat metabolism. Fatty acids and potentially toxic derivatives accumulate in FAO disorders which are caused by deficiency in one of the enzymes involved in FAO.

YOU SHOULD TAKE THE FOLLOWING ACTIONS:

- Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy).
- Consult with pediatric metabolic specialist.
- Evaluate infant (hepatomegaly, cardiac insufficiency; history of sudden unexpected death in a sibling; maternal liver disease during pregnancy; hypoglycemia). If signs are present or infant is ill, initiate emergency treatment in consultation with metabolic specialist.
- Educate family about need for infant to avoid fasting. Even if the infant becomes mildly ill (poor feeding, vomiting, or lethargy), immediate treatment with IV glucose is needed.
- Report findings to newborn screening program.

Diagnostic Evaluation: Plasma acylcarnitine analysis will show a characteristic pattern consistent with LCHADD or TFP deficiency. Urine organic acid analysis may also show an abnormal profile. Differentiation between both disorders requires further biochemical and molecular genetic testing

Clinical Considerations: LCHAD and TFP deficiencies may present acutely and are then associated with high mortality unless treated promptly. Hallmark features include hepatomegaly, cardiomyopathy, lethargy, hypoketotic hypoglycemia, elevated liver transaminases, elevated creatine phosphokinase (CPK), lactic acidosis, and failure to thrive. Rhabdomyolysis (a serious and sometimes fatal complication) may occur. Milder variants exist. Consider that cefotaxime treatment in the baby or mother may alter lab results.

Additional Information:

Emergency Treatment Protocol (New England Consortium of Metabolic Programs)

Genetics Home Reference:

LCHAD

TFP

Referral (local, state, regional and national):

Testing

Clinical Services