Disease Name	**Isovaleric acidemia**
Alternate name(s)	Isovaleric acid CoA dehydrogenase deficiency
Acronym	IVA
Disease Classification	Organic Acid Disorder
Variants	Yes
Variant name	Chronic intermittent form
Symptom onset	Infancy (in the acute neonatal form). The chronic intermittent form presents later in infancy or in childhood.
Symptoms	Episodic overwhelming illness with vomiting, ketosis, acidosis and coma. Hematological abnormalities include leucopenia, thrombocytopenia and possible anemia.
Natural history without treatment	About 50% of patients with the acute neonatal form will die during their first episode. Survivors may have neurological damage though several have made complete recoveries. Patients with the chronic form may have neurologic damage, but the majority of patients are developmentally normal.
Natural history with treatment	Intellectual prognosis depends on early diagnosis and treatment and subsequently on long-term compliance. If treated appropriately, most will have normal development.
Treatment	Low protein diet with restricted leucine intake, glycine supplementation and possible carnitine supplementation.
Other	Sometimes a “sweaty feet” odor is reported during an acute crisis.
Physical phenotype	No obvious dysmorphic features.
Inheritance	Autosomal recessive
General population incidence	1:230,000
Ethnic differences	None known
Population	N/A
Ethnic incidence	N/A
Enzyme location	N/A
Enzyme Function	Isovaleryl-CoA dehydrogenase is the first step in the branched chain organic acid metabolism of leucine.
Missing Enzyme	Isovaleryl-CoA dehydrogenase
Metabolite changes	Urinary isovaleryl glycine, 3-hydroxysoraline acid, increased isovaleric acid in blood. During acute attacks, 4-hydroxyisovaleric acid, mesaconic acid, and methylsuccinic acid, isovalerylglycine and 3-hydroxyisovaleric acid are present.
Prenatal testing	Enzyme analysis by GCMS in amniotic fluid or CVS tissue.
MS/MS Profile	Elevated C5 isovaleryl carnitine
OMIM Link	http://www.ncbi.nlm.nih.gov/omim/243500
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 C5 Acylcarnitine]
Isovaleric Acidemia

Differential Diagnosis: Isovaleric acidemia (IVA), 2-Methylbutyrylglycinuria (2MBG) (also referred to as short/branched chain acyl-CoA dehydrogenase deficiency or SBCAD deficiency); antibiotic-related (pivalic acid derived) artifact.

Condition Description: IVA and 2MBG result from different defects in the metabolism of the branched chain amino acids, leucine (**isovaleryl-CoA dehydrogenase** in IVA), and isoleucine (**short/branched chain acyl-CoA dehydrogenase** in 2MBG). In both conditions, specific metabolites accumulate and are potentially toxic.

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, odor of sweaty feet).
- Consult with pediatric metabolic specialists
- Evaluate the newborn; if 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 metabolic acidosis (poor feeding, vomiting, lethargy, tachypnea, odor of sweaty feet).
- Report findings to newborn screening program.

Diagnostic Evaluation: Plasma acylcarnitine analysis confirms the increased C5. Urine organic acid analysis will show isovalerylglycine in IVA and 2-methylbutyrylglycine in most cases of 2MBG. Urine acylglycine and acylcarnitine analysis may also be informative.

Clinical Considerations: Isovaleric acidemia presents in the neonate with metabolic ketoacidosis, a "sweaty feet" odor, dehydration, hyperammonemia, ketonuria, vomiting, hypoglycemia, and failure to thrive. Milder variants without neonatal illness exist. Long-term prognosis of IVA with appropriate therapy is good. The clinical spectrum of 2MBG is variable. To date, most patients identified by newborn screening with 2MBG are of Hmong descent and remain asymptomatic.

Additional Information:

New England Consortium of Metabolic Programs
Gene Reviews
Genetics Home Reference

Referral (local, state, regional and national):

Testing
Clinical Services