Carnitine Palmitoyltransferase 1A Deficiency

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Alaska Newborn Metabolic Screening Program

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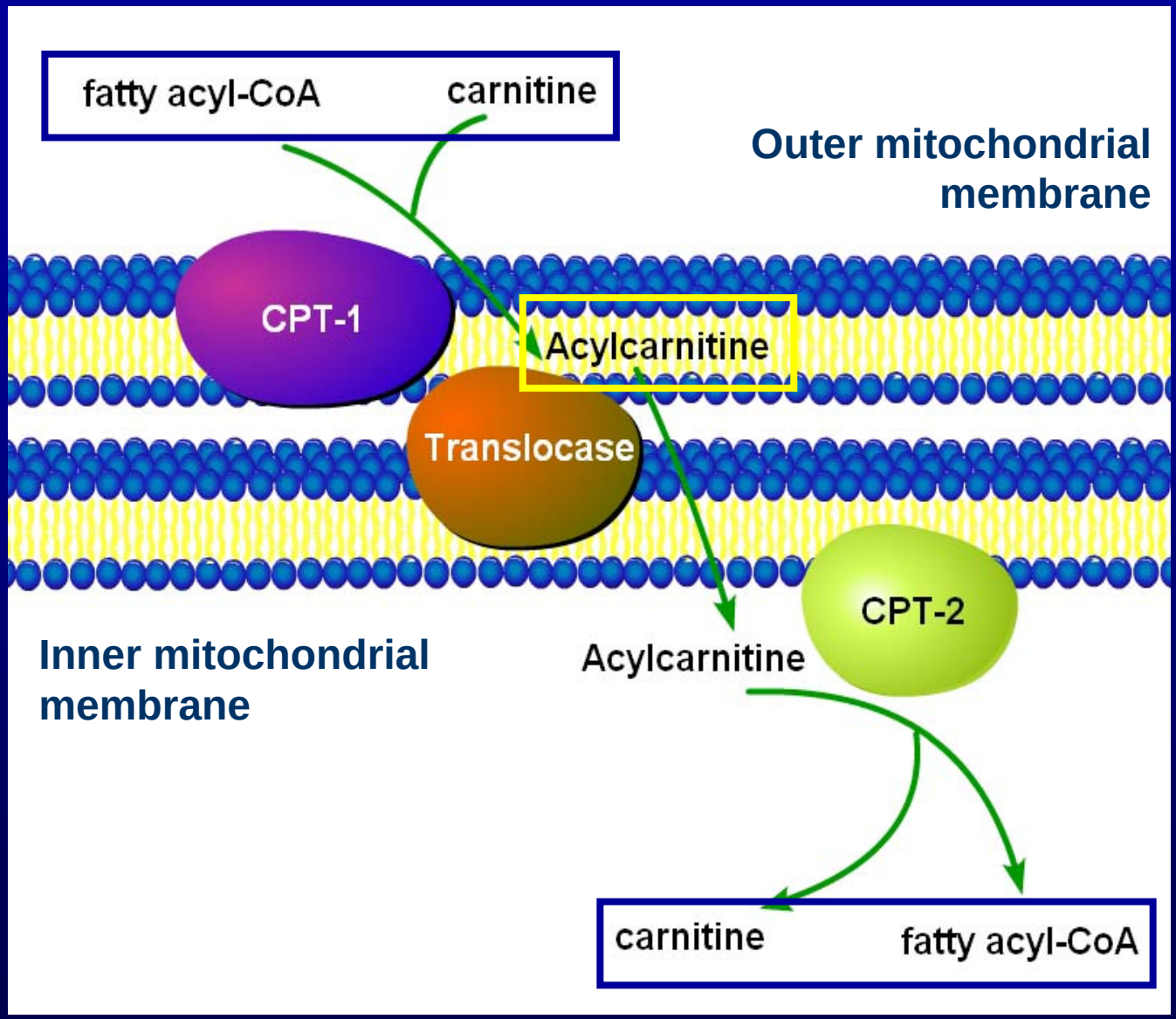
Goals

- Carnitine Palmitoyltransferase 1 (CPT1)
- CPT1A deficiency
- Newborn Screening for CPT1A Deficiency
- Public Health Concerns

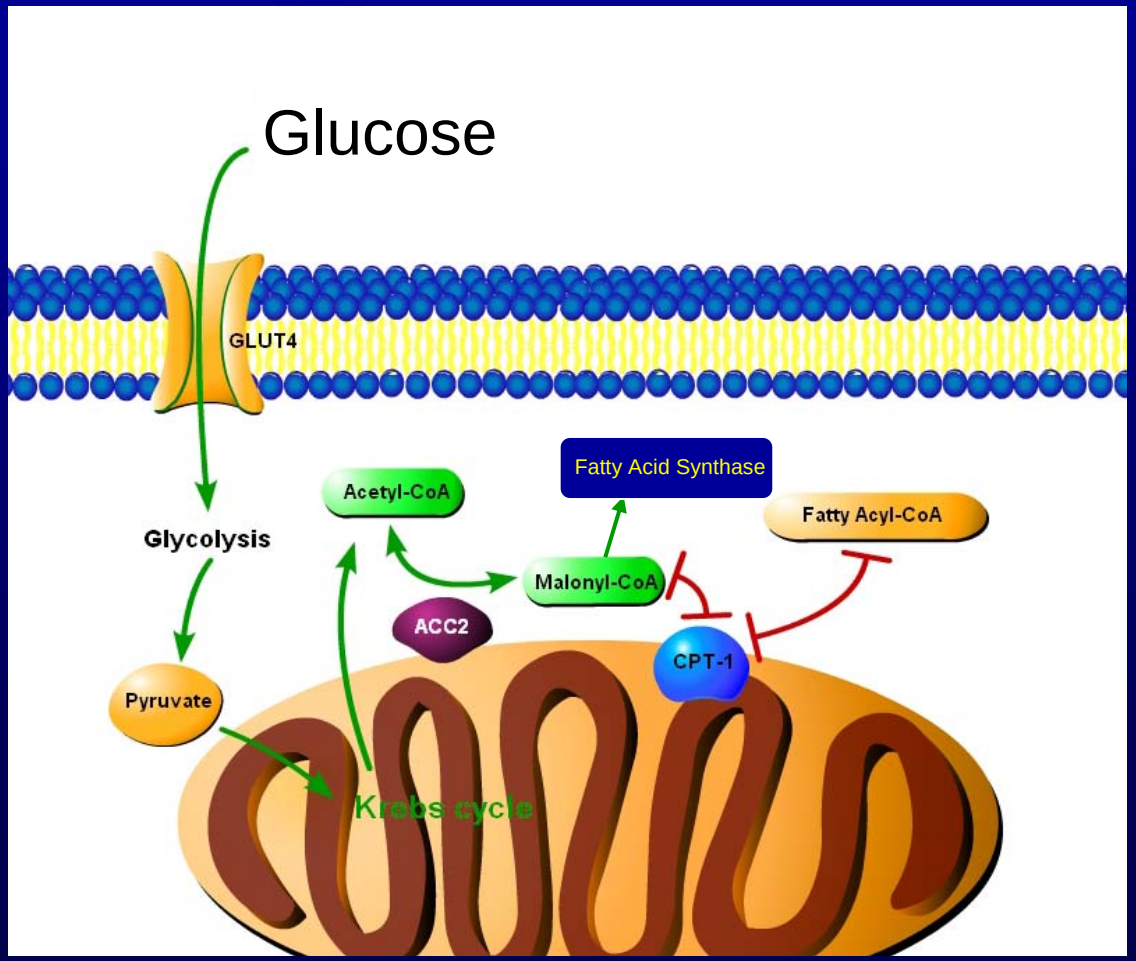
CPT1 is required for the import of long chain fatty acids into the mitochondrial matrix for oxidation


fatty acyl-CoA
carnitine
Outer mitochondrial membrane
CPT-1
Acylcarnitine
Translocase
CPT-2
Acylcarnitine
Inner mitochondrial membrane
carnitine
fatty acyl-CoA

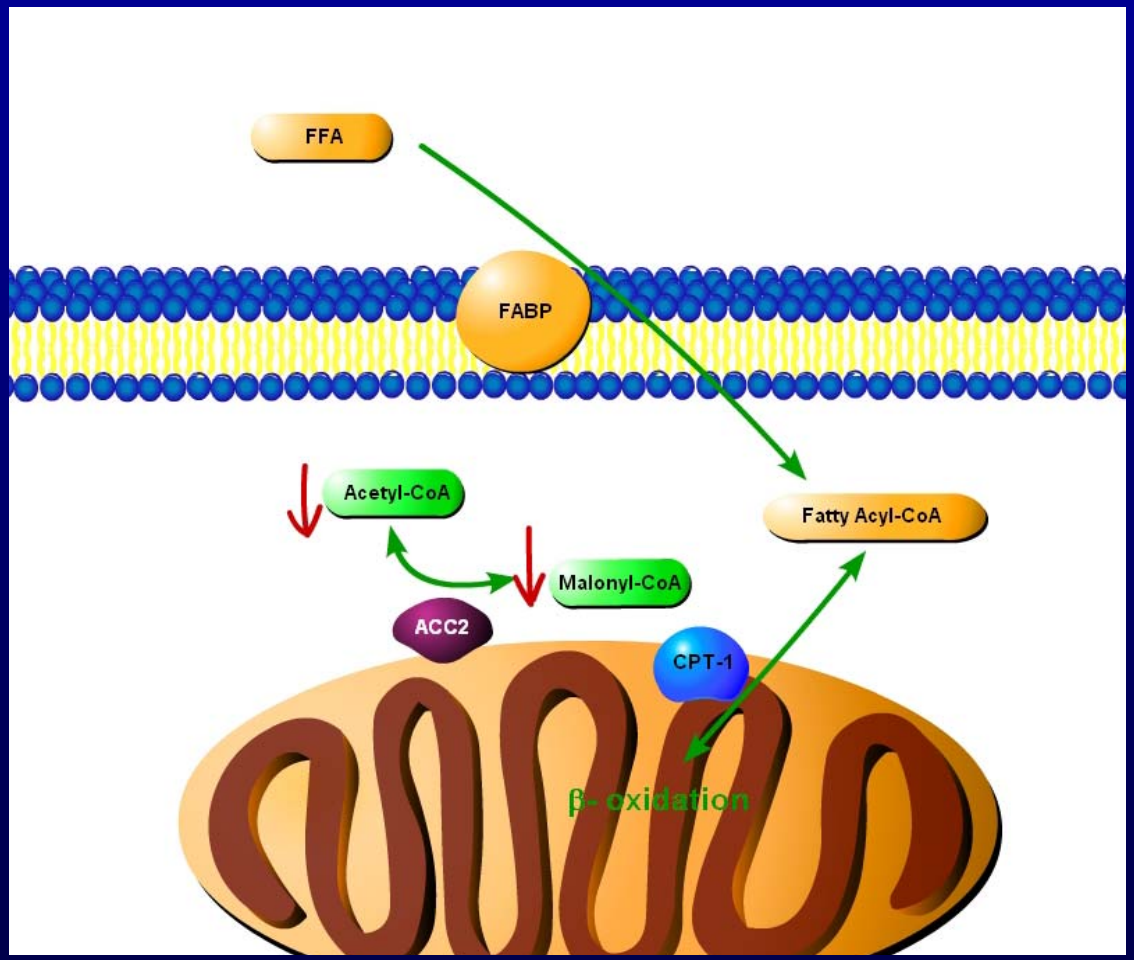
In the presence of an adequate glucose supply fatty acid oxidation is repressed

- Insulin inhibits hormone sensitive lipase in adipose tissue, blocking release of free fatty acids into the blood
- Mitochondrial import of long chain fatty acids is blocked via inhibition of CPT1 by malonyl-CoA, which is generated from acetyl-CoA derived from glucose oxidation

Regulation of CPT1 activity



Regulation of CPT1 activity



There are 3 CPT1 Isoforms

CPT1A	Liver, kidney, leucocytes, fibroblasts, brain
CPT1B	Muscle, white adipose tissue
CPT1C	Brain, testes
60% homology between isoforms of CPT1A Only CPT1A deficiency identified in humans	

Goals

- CPT1A
- CPT1A deficiency
- Newborn Screening for CPT1A Deficiency
- Implications for Public Health

CPT1A Deficiency

- Affects ability to use long chain fatty acids for energy
- Symptoms precipitated by prolonged fasting, and exacerbated by metabolic stress
  - Fever
  - Infection
  - Dehydration
- Symptoms are similar to other fatty acid oxidation disorders
  - Hypoketotic hypoglycemia
    - Symptoms may be present before glucose drops
  - Hepatic encephalopathy
  - Acute and/or persistent seizures secondary to recurrent hypoglycemia
  - Sudden unexplained death: SIDS
- HELLP Syndrome (hypertension, elevated liver enzymes, low platelets)

CPT1A Deficiency: Treatment

- Avoid fasting
  - Feeds infants every 3-4 hours during first 3 months of life and then allow fasting equal to age in months up to ten months (10 hours).
  - From 12-24 months should go no longer than 10 hours
  - After 24 months can go for 12 hours and probably longer
- Fasting guidelines apply only in times of good health; illness and surgical stress decrease the length of time fasting can be tolerated
- Avoidance of long chain fats is often recommended but unproven - and likely impractical in the Alaska Native population

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Newborn Screening for CPT1A Deficiency

- CPT1A deficiency is identified by a high ratio of free carnitine (C0) to the sum of palmitoylcarnitine (C16) plus stearoylcarnitine (C18)
- The C0 / (C16+C18) is elevated as a direct result of a decreased ability to make acylcarnitines
- The ability to identify infants with CPT1A deficiency resulted from the switch to expanded newborn screening using tandem mass spectrometry (MS/MS) in the Fall of 2003

Newborn Screening for CPT1A Deficiency

- Since October of 2003 there have been 129 infants identified with CPT1A deficiency in Alaska (8/15/08)
- All have been homozygous for the C1436T DNA variant that results in the substitution of proline 479 with leucine (P479L)
- All affected infants have been born to Mothers that identified themselves as Alaska Native on their newborn screening card

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- CPT1A deficiency
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The Big Questions:

- What is the clinical impact of the P479L sequence variant ?
- What is the true incidence of CPT1A deficiency in Alaska
- Do we need to identify and treat affected infants ?

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Case Reports:

Retrospective genotyping of newborn screening cards for the P479L carnitine palmitoyltransferase (CPT1) variant: Correlation with acylcarnitine profiles and estimation of incidence in BC

G. Sinclair, J. Ma , P. MacLeod, L. Arbour, H. Vallance.

Departments of Pathology, University of British Columbia, Vancouver, Canada; Medical Genetics, University of British Columbia, Vancouver, Canada.

Introduction: A common variant of CPTI deficiency (P479L) first identified in the Canadian Inuit population has also been identified in 21 First Nations children in British Columbia. All BC cases presented with one or more of the following: hypoglycemia, liver disease, and sudden unexpected death.

- A 2 year old Alaska Native boy came to the Shriner's Hospital in Portland for Achilles tendon release
- Pre and Post-Op IV fluids = normal saline, no glucose
- Post-Op lethargy led to transfer to the PICU at OHSU
- Admission labs: glucose = 34, serum HCO_3 = 10
- Developed severe lactic acidosis, and a coagulopathy
- He had a generalized seizure shortly after admission
- DNA testing: homozygous 1436T = affected
- He was born three months prior to the start of expanded newborn screening in Alaska

Summary

- There is evidence suggestive of an increased risk of morbidity and mortality in infants homozygous for the P479L variant.

The Big Questions:

- What is the clinical impact of the P479L sequence variant ?
- What is the true incidence of CPT1A deficiency in Alaska
- Do we need to identify and treat affected infants ?

Previous Reports of the P479L variant

- Cheryl Greenberg reported a three generation Inuit kindred
  - 18/22 homozygous for P479L
  - 3/22 heterozygous
- Collected 500 samples from an Inuit village for DNA testing
  - 70% homozygous for P479L
  - 28% heterozygous
- Early data from BC suggests at least 18% of First Nations infants are homozygous for P479L
  - Hilary Vallance, UBC, Vancouver

Are we finding all of the affected infants?

- We have identified 129 affected infants
- Many infants were picked up on third screens that were done as a result of an abnormal thyroid or other test
- Infants identified on a third screen had two previously normal screens

Due to concern that routine newborn screening was missing a significant number of affected infants we did a formal analysis of the sensitivity of MS/MS to detect CPT1A deficiency due to the P479L variant

- Goal: To determine ascertainment rate of MS/MS
- Analyzed 2,500 consecutive newborn screening cards collected over a period of 3 months
- All cards had routine expanded screening and DNA testing for the C1436T variant
- DNA results were compared with MS/MS data
- Funding provided by ANMC, and the Alaska Division of Public Health

Results:

- The P479L variant is due to a C to T change at nucleotide 1436 in the cDNA of CPT1A
- 2063 homozygous 1436C = 83%
- 248 heterozygous 1436C/T (carriers) = 10%
- 173 homozygous 1436T (affected) = 7%
- 10,000 births per year = 700 affected infants / year

MS/MS data for affected infants

MS/MS data for all genotypes

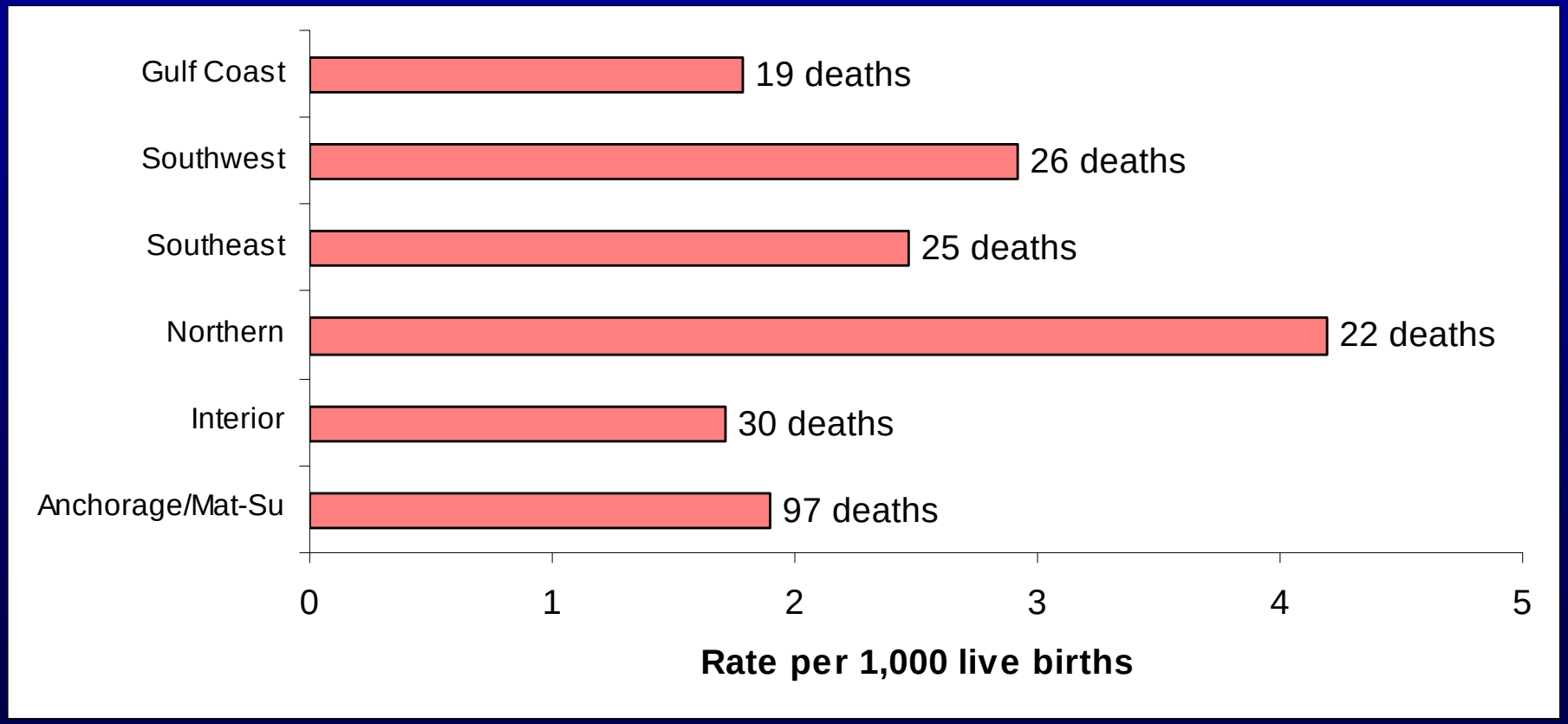
Summary

- 7% of Alaska infants are homozygous for the C1436T sequence variant (P479L)
- Newborn screening identified only _% of affected infants in this sample
- Newborn screening by MS/MS is not an effective means to identify infants with CPT1A deficiency due to the P479L variant

The Big Questions:

- What is the clinical impact of the P479L sequence variant ?
- What is the true incidence of CPT1A deficiency in Alaska
- Do we need to identify and treat affected infants ?

Infant mortality rates for SIDS/asphyxia

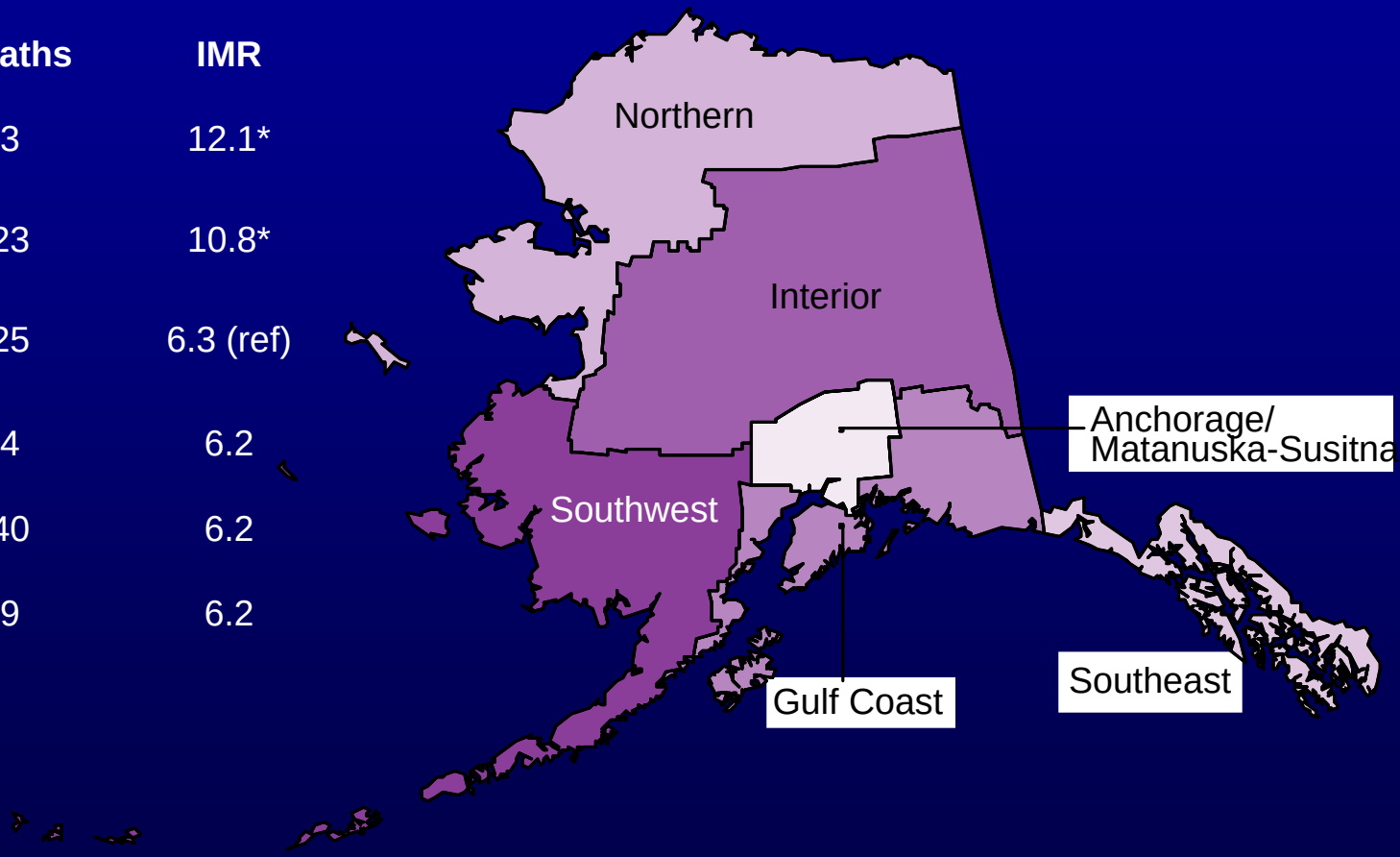


Source: Alaska MIMR, 1992-2001

Infant Mortality Rates
(1992-2004)

Infant Mortality Rates
(1992-2004)

Region	# deaths	IMR
Northern	83	12.1*
Southwest	123	10.8*
Anchorage/Mat-Su	425	6.3 (ref)
Gulf Coast	84	6.2
Interior	140	6.2
Southeast	79	6.2



*Rate is significantly different from IMR for residents of Anchorage/Mat-Su region

Data source: Alaska Bureau of Vital Statistics

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Ongoing Studies

- Retrospective analysis of infant deaths in Alaska to determine whether CPT1A deficiency due to the P479L variant is a risk factor for infant mortality
  - In collaboration with Dr. Brad Gessner, MCH-Epidemiology Unit Chief

Ongoing Studies

- Impact of CPT1A deficiency due to the P479L variant on the metabolic response to fasting

- A Collaboration with
  - Drs. Melanie Gillingham & Cary Harding - OHSU
  - Dr. Matt Hirschfeld - ANMC

Future Studies

- Long-term follow up of infants identified by newborn screening with CPT1A deficiency due to the P479L variant

- A Collaboration with
  - Drs. Melanie Gillingham, Cary Harding, and Bill Lambert - OHSU
  - Dr. Matt Hirschfeld and colleagues - ANMC
  - Dr. Brad Gessner, Thalia Wood, and colleagues at Womens, Children's, and Family Health, Alaska Division of Public Health
  - Families, friends, and concerned citizens of Alaska!

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