Maple Syrup Urine Disease

Not Something to Put on Your Pancakes!!!

What is Maple Syrup Urine Disease?

- It is also known as MSUD
- Metabolic disorder
- Autosomal recessive
- Incidence rate is 1:200,000 in live births
- The rate increases to 1:176 in inbred pop. like the Menonites

Effects of MSUD

- Urine that smells like maple syrup
- Increased levels of branched-chain α-ketoacids
- Progressive neurologic damage leading to high-pitched cry
- Irritability
- Spastic quadriparesis
- Seizures

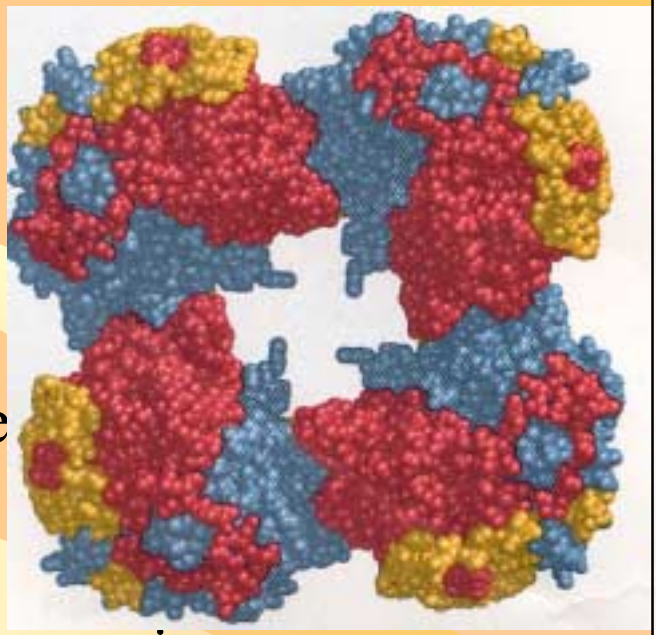
Effects cont….

- Central nervous system depression
- Coma
- Severe metabolic acidosis and Hypoglycemia
- Developmental disabilities: severe mental retardation
- Mortality: usually fatal within one month

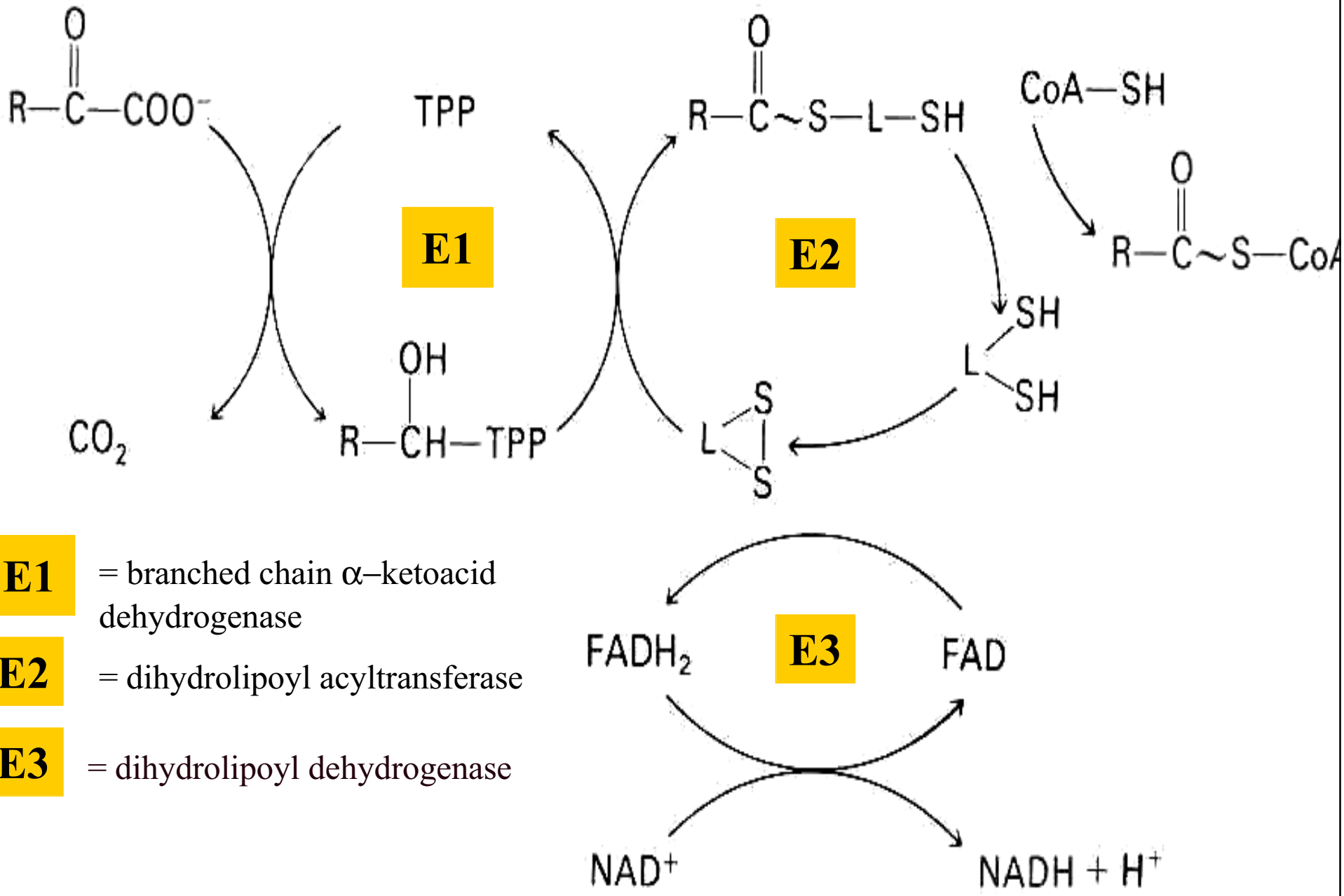
Cause of MSUD

- Decreased function of the BCKD complex

More on the BCKD Complex



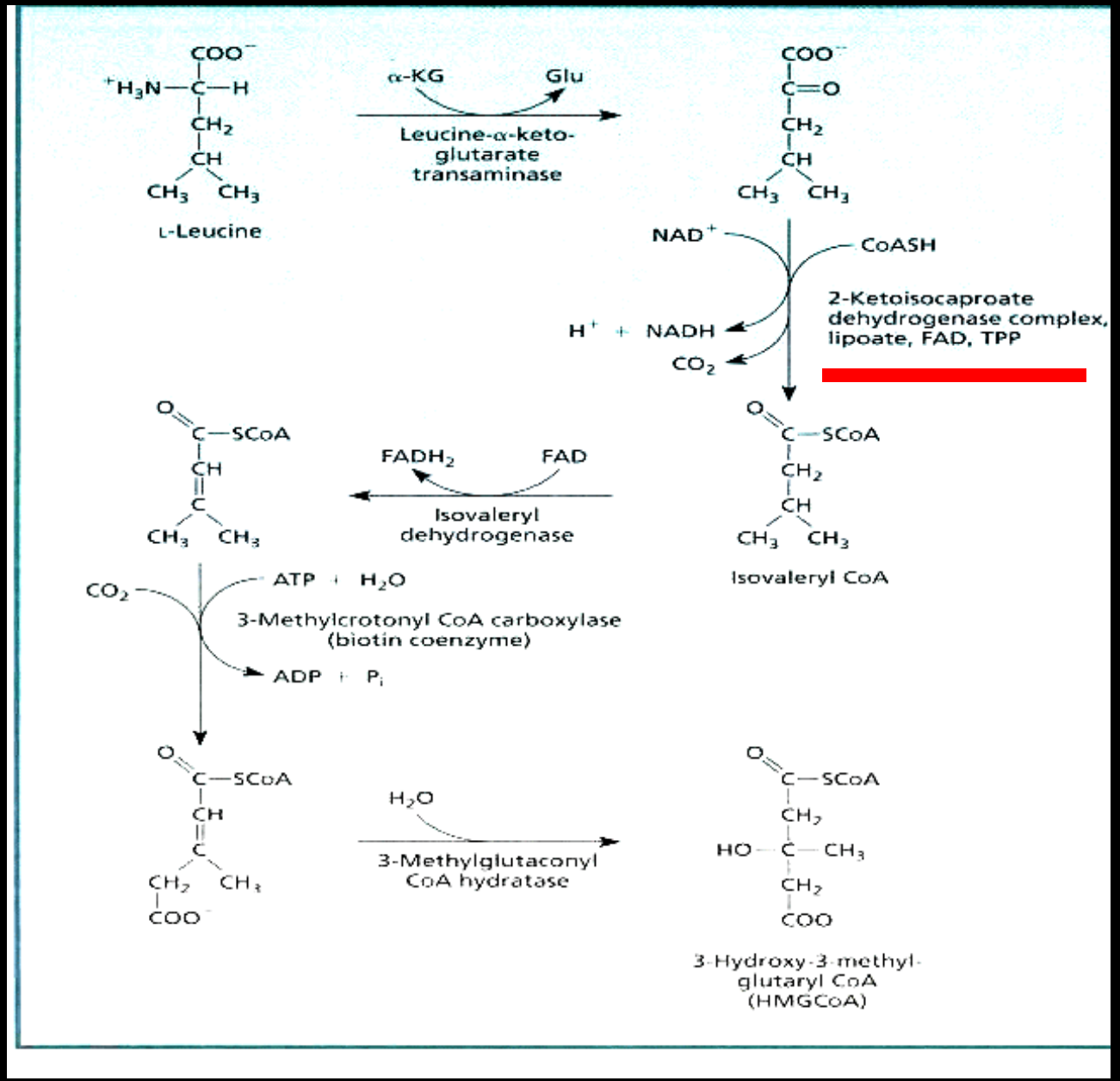
- Multienzyme complex w/ 3 catalytic subunits
- Specific kinase inactivates
- Specific phosphatase activates
- Oxidatively decarboxylates ketoacid substrate
- Located on matrix side of mito. inner membr.
- Genes located on sep. autosomes (autosomal recessive transmission)
- Similar to Pyruvate & α Ketoglut. Dehydrogenase complexes

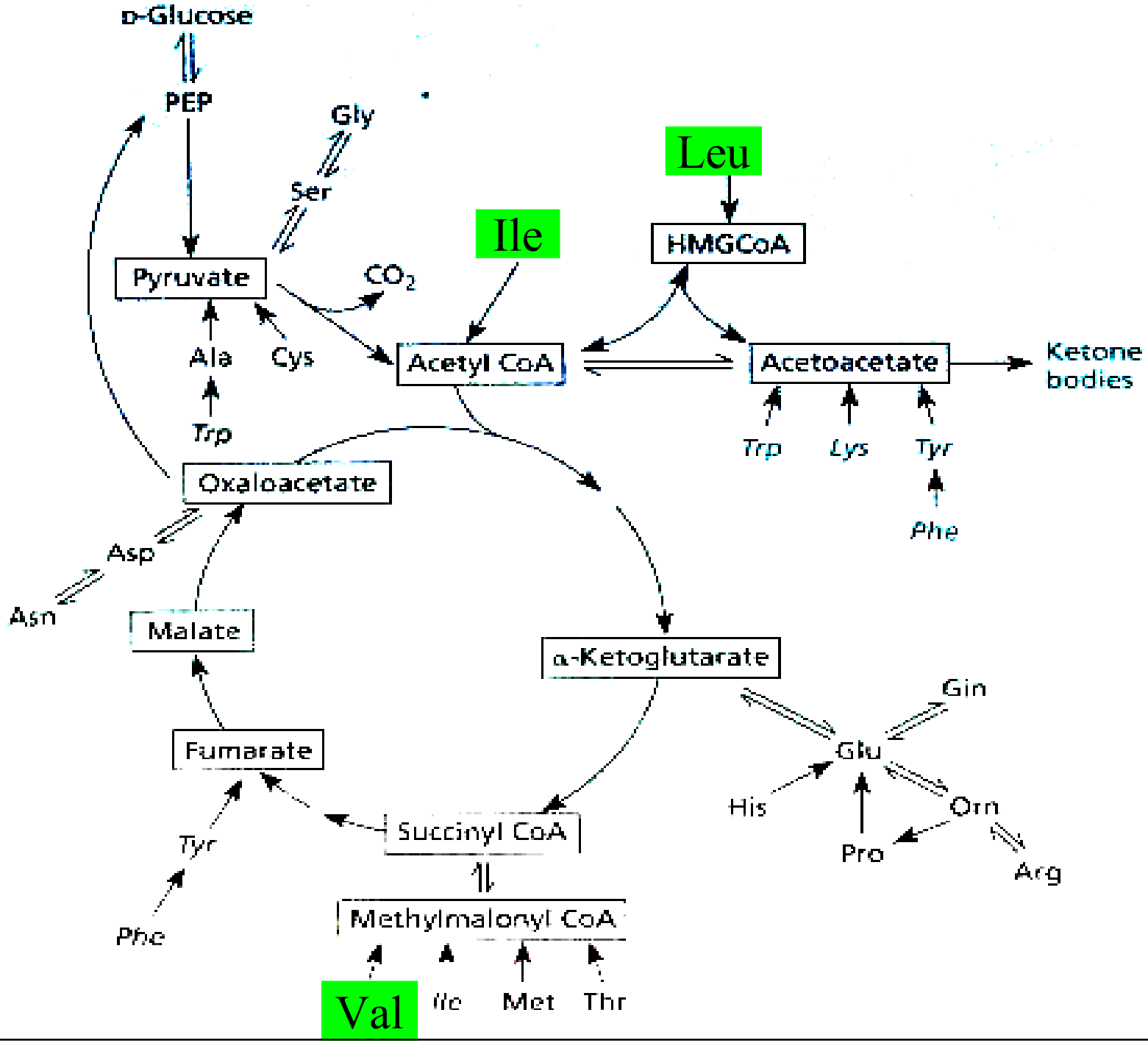


E1 = branched chain α–ketoacid dehydrogenase

E2 = dihydrolipoyl acyltransferase

E3 = dihydrolipoyl dehydrogenase


L-Leucine
α-KG
Glu
Leucine-α-keto-glutarate transaminase
NAD+
CoASH
H+ + NADH
CO2
2-Ketoisocaproate dehydrogenase complex, lipoate, FAD, TPP
Isovaleryl CoA
FADH2
FAD
Isovaleryl dehydrogenase
CO2
ATP + H2O
3-Methylcrotonyl CoA carboxylase (biotin coenzyme)
ADP + Pi
H2O
3-Methylglutaconyl CoA hydratase
3-Hydroxy-3-methyl-glutaryl CoA (HMGCoA)


D-Glucose
PEP
Gly
Ser
Leu
Ile
HMGCoA
Pyruvate
CO_2
Ala
Cys
Acetyl CoA
Acetoacetate
Ketone bodies
Trp
Trp
Lys
Tyr
Phe
Oxaloacetate
Asp
Asn
Malate
α-Ketoglutarate
Gln
Glu
His
Orn
Pro
Arg
Fumarate
Tyr
Phe
Succinyl CoA
Methylmalonyl CoA
Val
Ile
Met
Thr

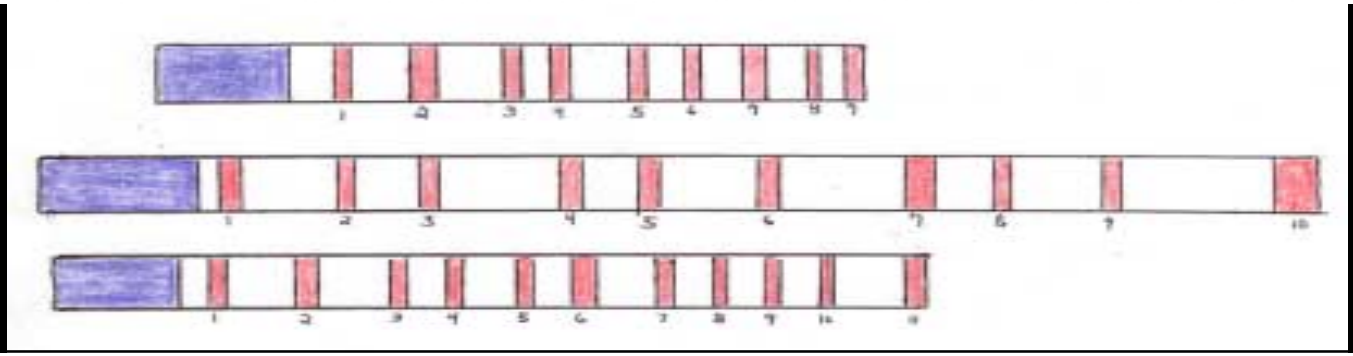
Why does this decreased function occur?

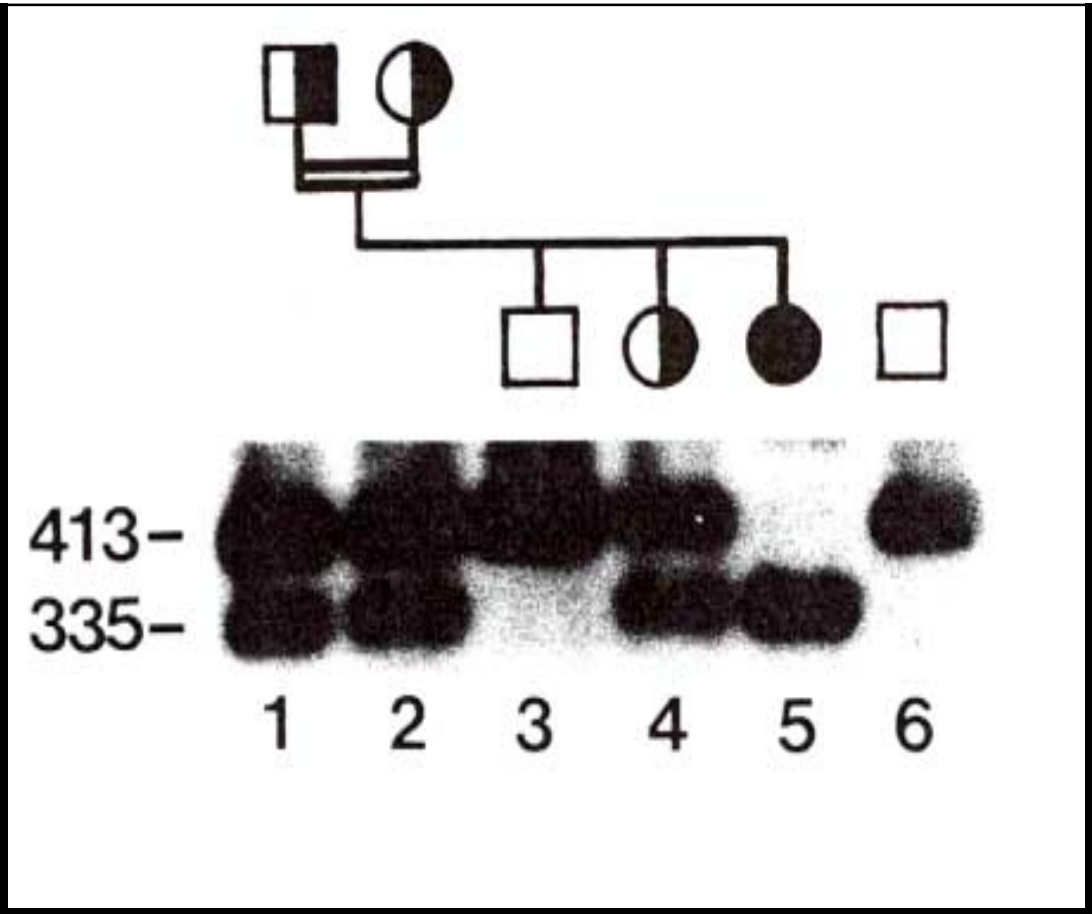
Gene rearrangement & Point mutations

- Affect gene txn, transcript processing, and transcript stability by abberant splicing or early termination
- Pt. Mutations can lead to unstable prtns or a prtn that can not be imported into the mito.

Table 3 Mutations affecting the human branched-chain α-ketoacid dehydrogenase complex

		Nucleotide change	*Exon*	*Intron*	*Functional change*	*Reference*
E1α						
GM649		$T_{1339} \rightarrow A$	9	–	Y393N	Zhang et al(1989) Fisher et al (1991) Matsuda et al (1990)
E1β						
LK		11 bp del	1	–	Early stop codon	(Nobukuni et al (1991b)
E2						
GM1366		$G_{684} \rightarrow T$	6	–	E163*	Fisher et al (1989) Fisher et al (1993)
GM612	A1	2 bp del	2	–	Stop	Chuang et al (1991)
	A2	$G_{684} \rightarrow T$	6	–	E163*	Fisher et al (1993)
WG34	A1	17 bp insert	–	4	Splice error	Fisher et al (1989)
	A2	$T_{841} \rightarrow G$	7	–	F215C	Fisher et al (1991) Chuang et al (1991)
Ech	A1	2 bp del	2	–	Stop	Fisher et al (1989)
	A2	2 bp del	–	5	Splice error	Chuang et al (1991) Fisher et al (1993)
AL	A1	3 bp del	4	–	E27 lost	Fisher et al (1989)
	A2	$T_{427} \rightarrow C$	5	–	I77T	Chuang et al (1991)
TH1		G del	–	8	Splice error, Exon 8 del	Mitsubuchi et al (1991a) Nobukuni et al (1991a)
LF	A1	20 kb genomic del	6–11	6–10	Truncated	Herring et al (1992)
	A2	$G_{1031} \rightarrow A$	8	–	Splice error Exon 8;8–10 del	
BH	A1	?	2	–	Splice error Exon 2 del	Herring et al (1991)
	A2	?			No transcript	
TH2		$G_{684} \rightarrow T$	6	–	E163*	Fisher et al (1993)
HJ		$G_{684} \rightarrow T$	6	–	E163*	Fisher et al (1993)
Etty MF		2 bp del	2	–	Stop	Fisher et al (1993)





- Mitsubuchi and colleagues did PCR analysis of the E2 subunit cDNA on the patient's family

Types of MSUD

Three types related to branched-chain α-ketoacid dehydrogenase complex (BCKD)

- Type IA: defect in the E1-alpha subunit
- Type IB: defect in the E1-beta subunit
- Type II: defect in the E2 subunit

Note that E3 is not mentioned b/c it's involved in 3 major pthwys and infants die w/severe lactic acidosis

Forms of MSUD

MSUD is also classified by age of onset, decarboxylase activity, and blood levels of BCKA

Three clinical phenotypes

- Mild intermediate form: decarboxylase activity 5-25% of normal; blood levels of Leu, Ile, and Val 5-10 fold normal; developmentally normal to moderately retarded
- Intermittent form: occurs later in childhood as a result of infection or stress; crisis resembles classic MSUD and can be fatal
- Thiamine-responsive form: decarboxylase activity 20% of norma; blood leucine levels of BCKA 3 fold normal

Treatment

- Restricted diet in branched-chain amino acids and prtn
- Daily Pharmacological doses of B1 increase tolerance for prtn while keeping norm leucine levels
- High doses of Thiamine increase tolerance for BCAA

Future Goals

- To understand how gene products interact w/each other in given genetic environment
- Identify which tissues require func. of BCKD
- Use gene therapy to get the wild type gene, gene replacement, or correct the mutation w/in tissue to the improve quality of life

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11. http://www.vtmednet.org/~m145037/vhgi_mem/nbsman/msud.htm

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