

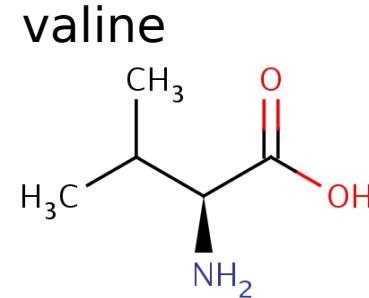
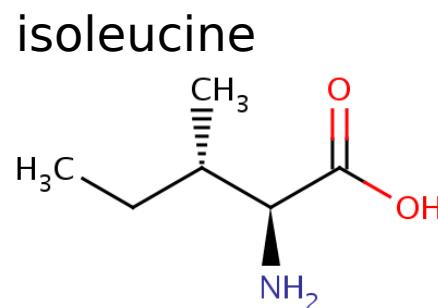
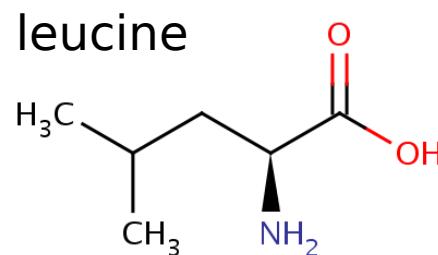
Maple Syrup Urine Disease

Master practical 'Protein Structure
and Function Analysis' SS 2013

Laura Schiller & Shen Wei

MSUD: Introduction

- deficiency in branched chain alpha-keto acid dehydrogenase complex (BCKDC)
- BCAAs (leucine, isoleucine and valine) and alpha-keto acids accumulate
- mental and physical retardation

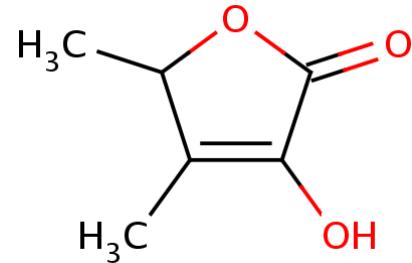


Phenotype

- sweet smell of newbornes urine resembling maple syrup
- BCAAs, alpha-keto acids increased → toxic:
 - ketonuria
 - lethargy
 - seizures
 - vomiting
 - problems in feeding
 - neurological dysfunctions
- if untreated: coma / death



sotolone



MSUD: disease types

depending on the BCKDC enzyme activity

- classic severe form
- intermediate form
- intermittend form
- thiamine-responsive form

MSUD: disease types

depending on the subunit of the BCKDC

- type IA : E1 subunit (alpha-keto acid dehydrogenase), alpha chain
- type IB: E1 subunit, beta chain
- type II: E2 subunit (dihydrolipoyl transacetylase)
- type III: E3 subunit (dihydroliponamide dehydrogenase)

Diagnosis

- presence of clinical features
- decreased levels of BCKDC enzyme activity
- accumulation of BCAAs, allo-isoleucine, and branched-chain ketoacids (BCKAs) in plasma
- BCKAs in urine: dinitrophenylhydrazine (DNPH) → precipitate
- sequencing of genes encoding BCKDC subunits

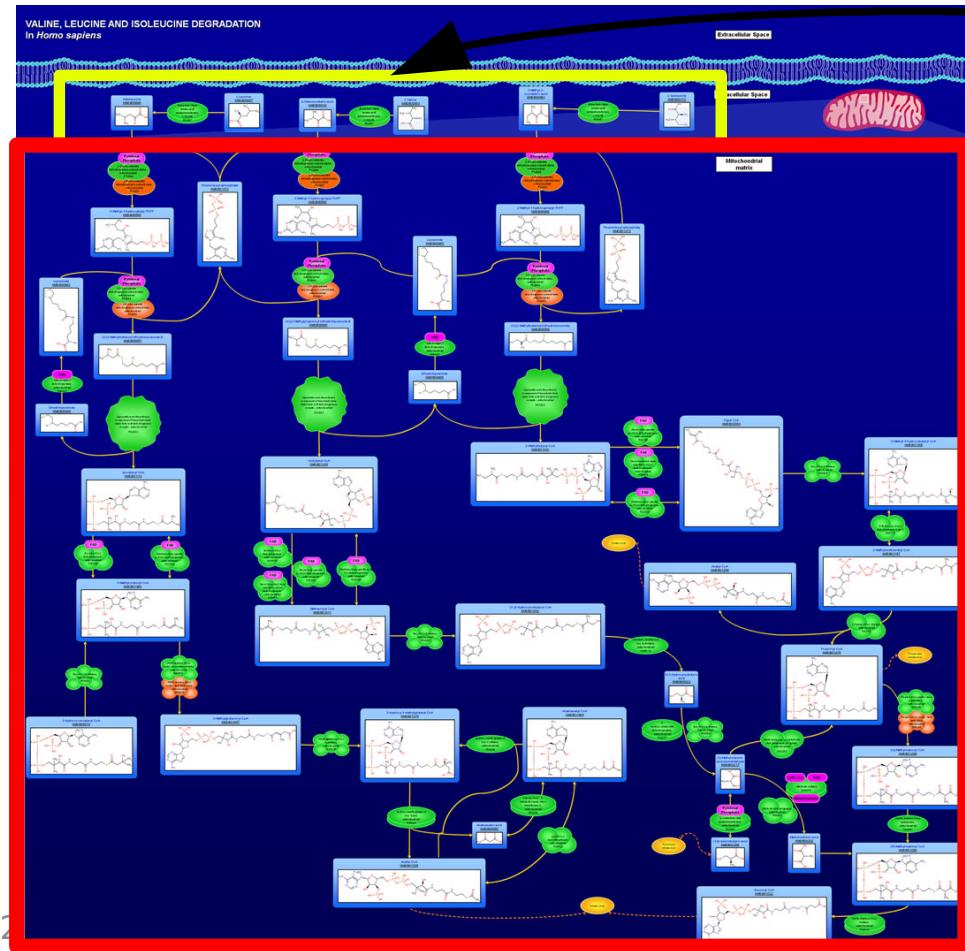
Treatment

- special diet
- low levels of the amino acids leucine, isoleucine, and valine
- frequent blood tests and close supervision



Degradation of Valine, Leucine and Isoleucine

- Reactions in cytosol and mitochondria

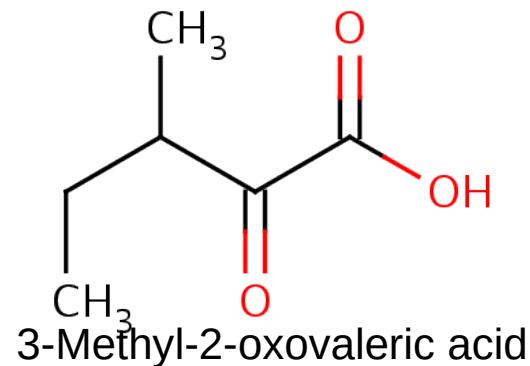
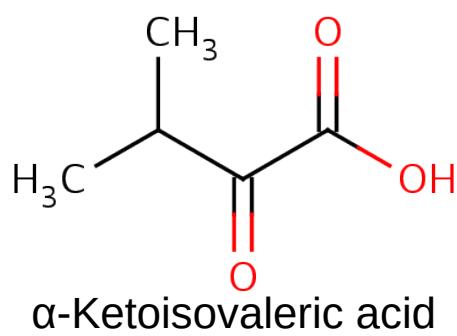
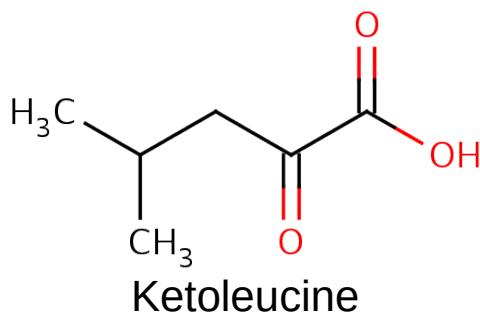


cytosol

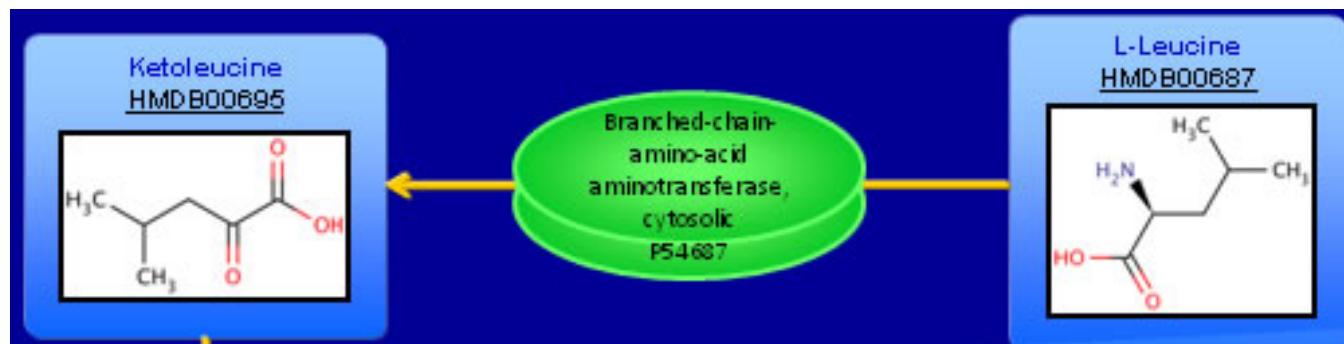
mitochondrial
matrix

Degradation of Valine, Leucine and Isoleucine

- **in cytosol:** α -amino acids \rightarrow α -keto acids



HMDB

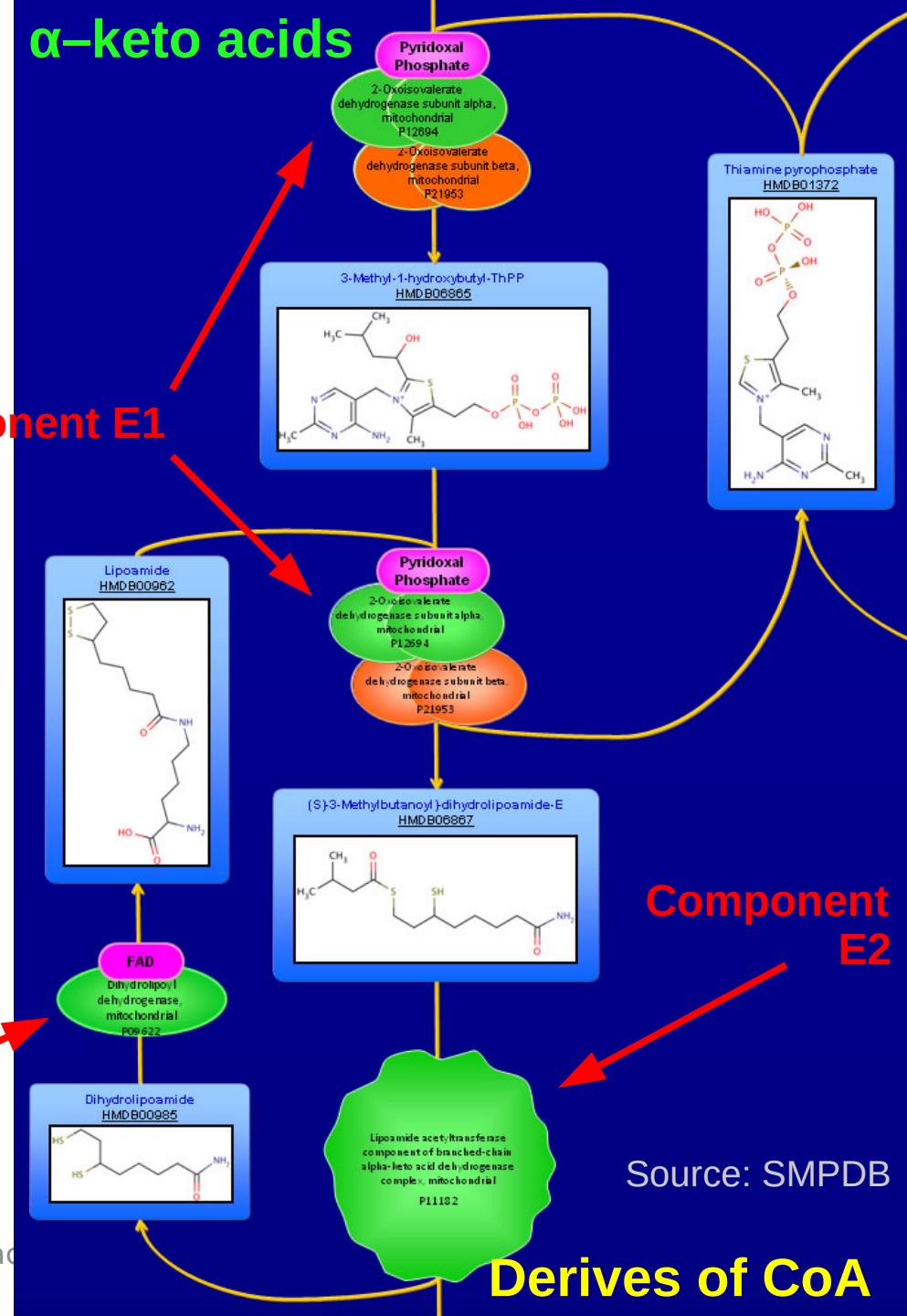


Leucine \rightarrow Ketoleucine (α -keto acid)

Source: SMPDB

Degradation in Mitochondria

- main catalyst: **BCKDC**
 - α -keto acids --> Acetyl-CoA, Succinyl-CoA and others
 - cooperate with citrate cycle and other pathways



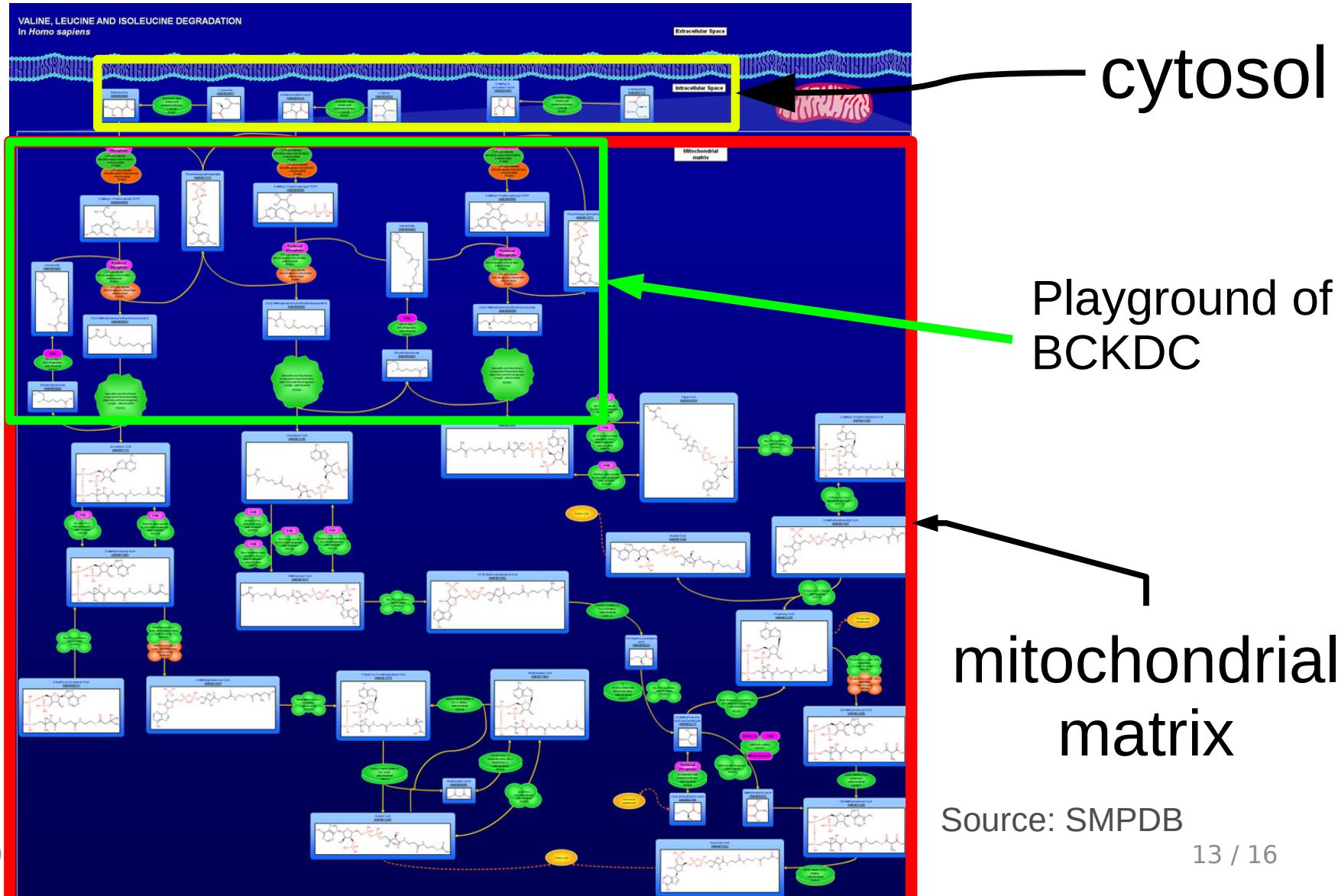
The Enzyme Complex

- Branched-chain α -keto acids dehydrogenase complex (BCKDC)
- Catalyze key mitochondrial reactions of BCAA degradation
- Three different component enzymes
- E1: α -ketoisovalerate dehydrogenase
 - Two subunits: E1A(**BCKDHA**) and E1B(**BCKDHB**)
- E2: dihydrolipoyl transacetylase (**DBT**)
- E3: dihydrolipoamide dehydrogenase (**DLD**)

Metabolic Pathogenesis

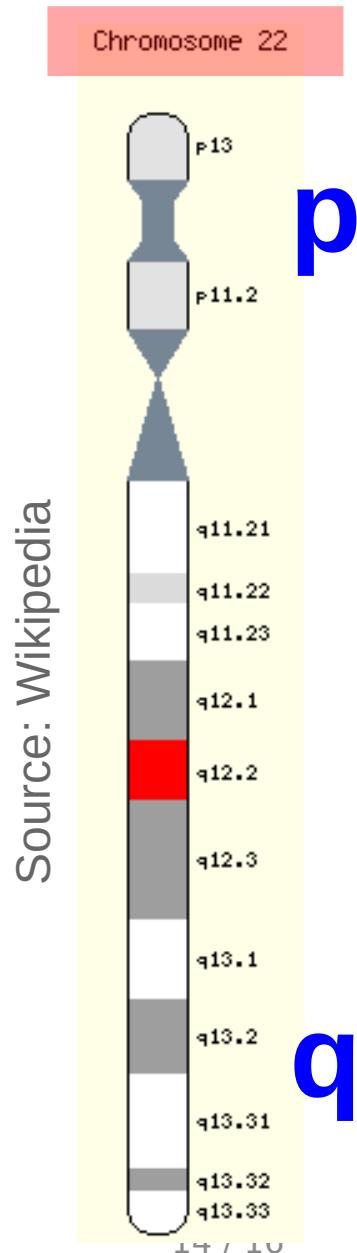
- Deficiency of human BCKDC
- Blocks pathway in mitochondria
- Reactions in cytosol continue
 - branched-chain AA → α -keto acids
- Consequence:
 - Accumulation of α -keto acids in cell
 - Pathogenesis of MSUD

Metabolic Pathogenesis



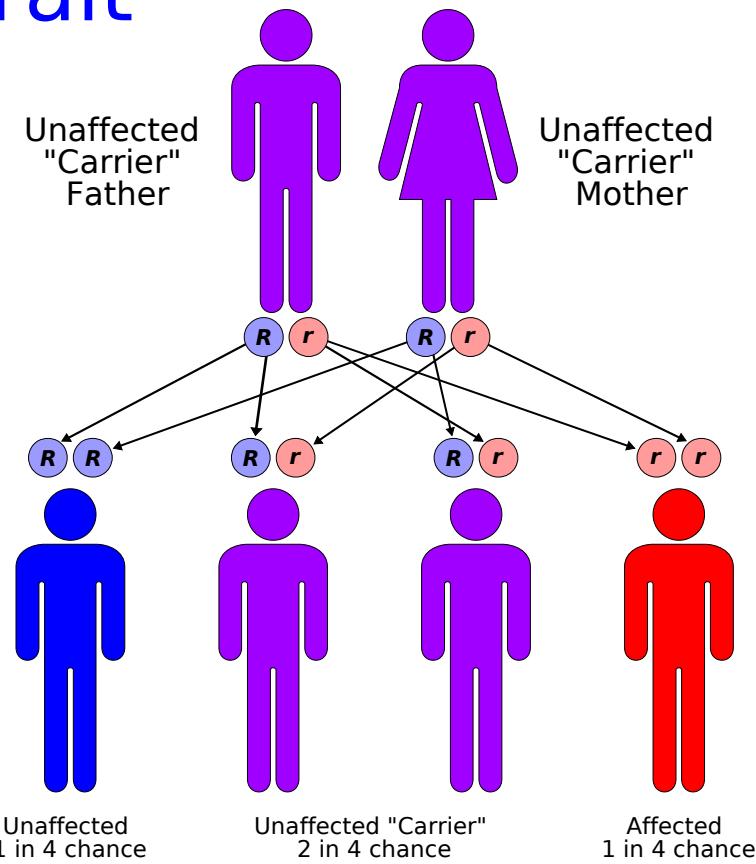
The Genes

- E1 component:
 - BCKDHA: locus **19q13.1-q13.2**
 - BCKDHB: locus **6q14.1**
- E2 component:
 - DBT: locus **1p31**
- E3 component:
 - DLD: locus **7q31-q32**



Inheritance of MSUD

- Autosomal recessive trait
- Higher prevalence in some ethic groups
 - Mennonite and Jews



Source: Wikipedia

Disease Causing Mutations

- BCKDHA
 - 7 mutations and 2 deletions **reported** in OMIM
- BCKDHB
 - 2 deletions, 1 insertion and 3 mutations **reported**
- DBT
 - 4 deletions, 2 insertions and 6 mutations **reported**
- DLD
 - 13 allelic variants **reported**