



Navigating MSUD: A Guide to Medical Management

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Disclosures

- No conflicts to declare

Outline

- What is MSUD?
- What are symptoms of MSUD?
- How is MSUD diagnosed?
- How to manage MSUD
 - Routine health
 - Sick day
 - Acute crisis
 - Other considerations

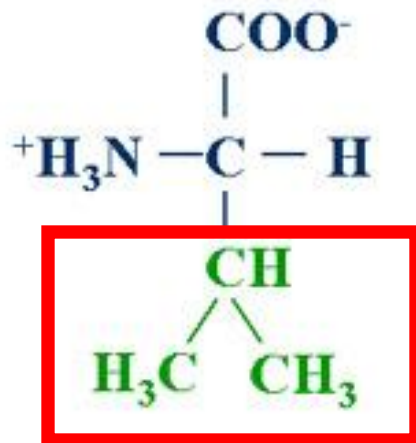
What is MSUD?
Biochemistry and Genetics

What is MSUD?

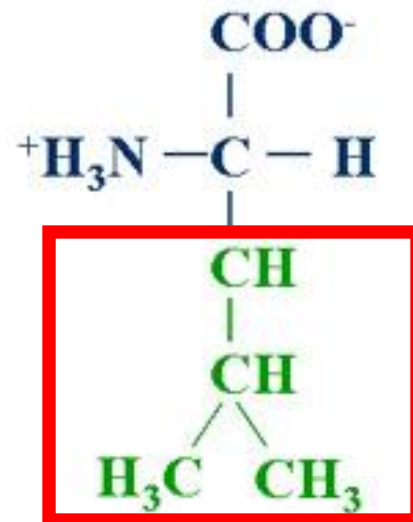
- Maple Syrup Urine Disease
- Caused by a reduced amount or a complete lack of an **enzyme** complex called Branched-Chain Keto-Acid Dehydrogenase (**BCKD**)
- This enzyme is needed in the breakdown of **branched-chain amino acids (BCAA)**

What are branched-chain amino acids (BCAA)?

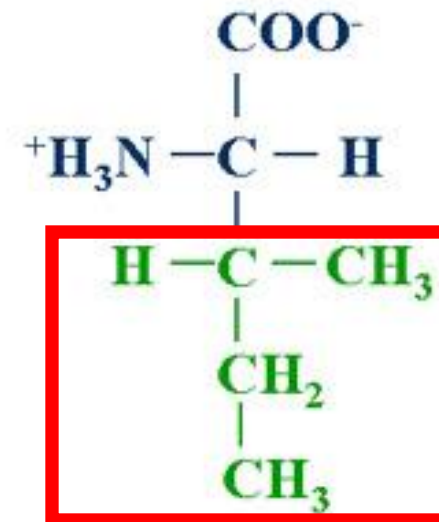
Amino acids are building blocks of protein



Valine



Leucine



Isoleucine

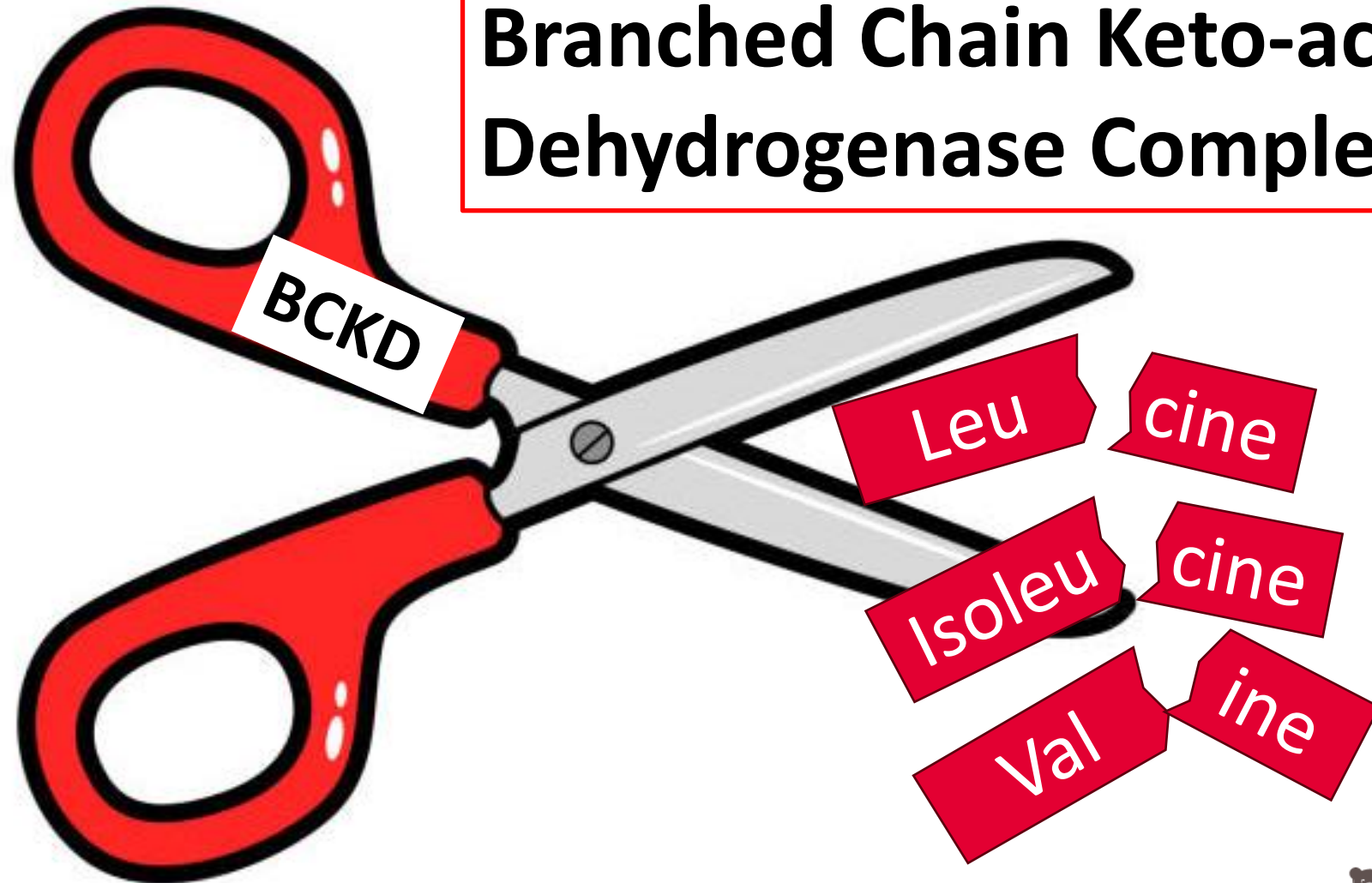
Where do branched-chain amino acids come from?



- Food!
- The human body cannot make new BCAA
 - The only source of BCAA is from dietary protein
 - All natural sources of protein have all amino acids, including BCAA

How does the body break down Branched Chain Amino Acids?

Branched Chain Keto-acid Dehydrogenase Complex

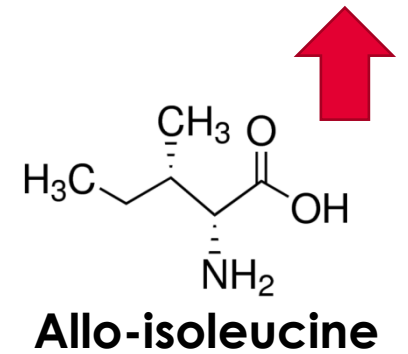
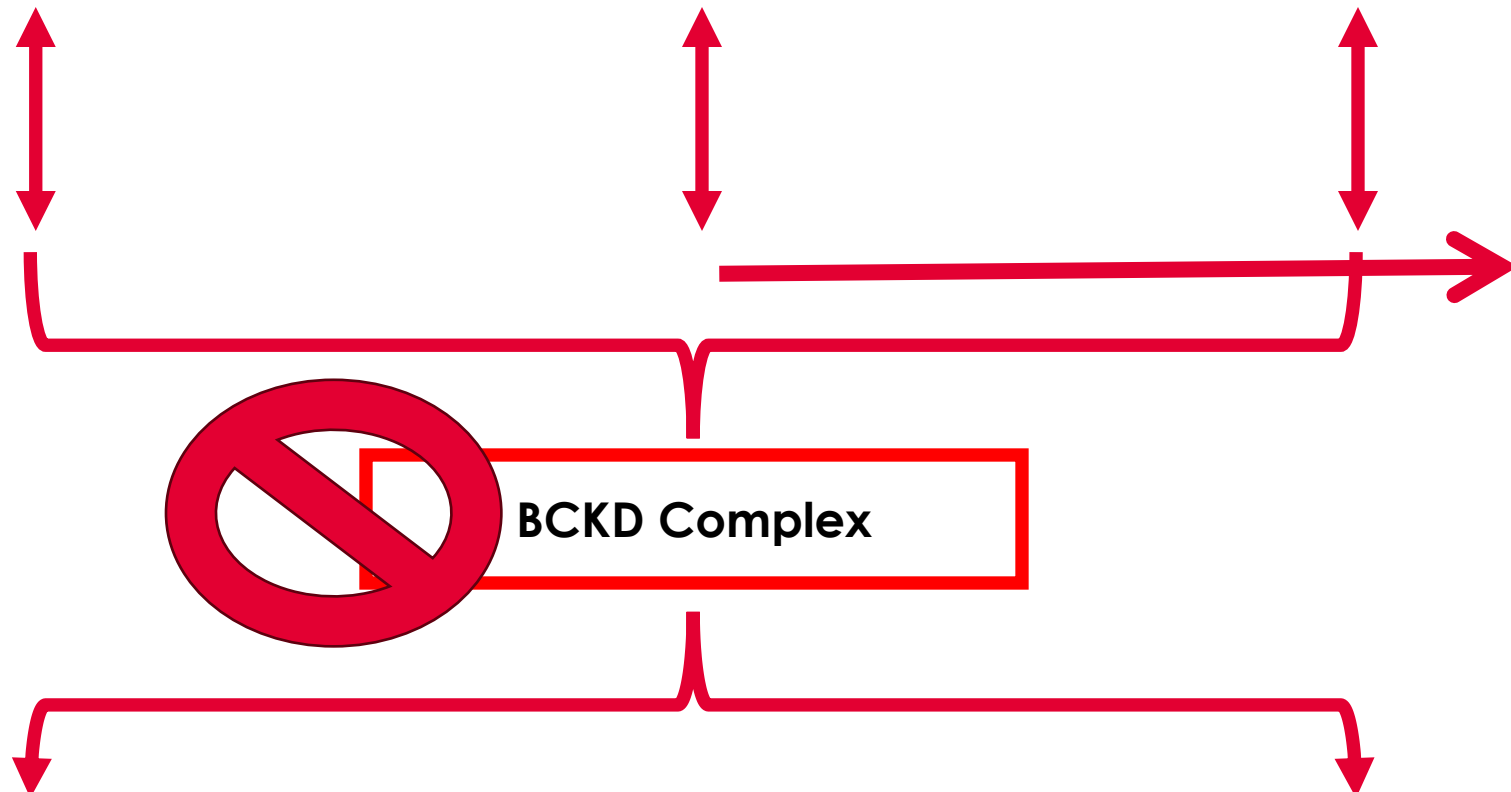


How does the body break down Branched Chain Amino Acids?

↑ Leucine

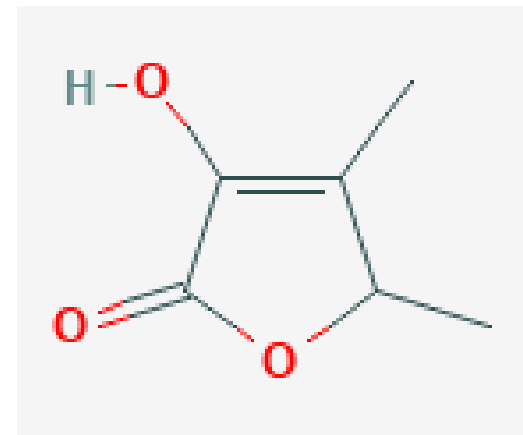
↑ Isoleucine

↑ Valine

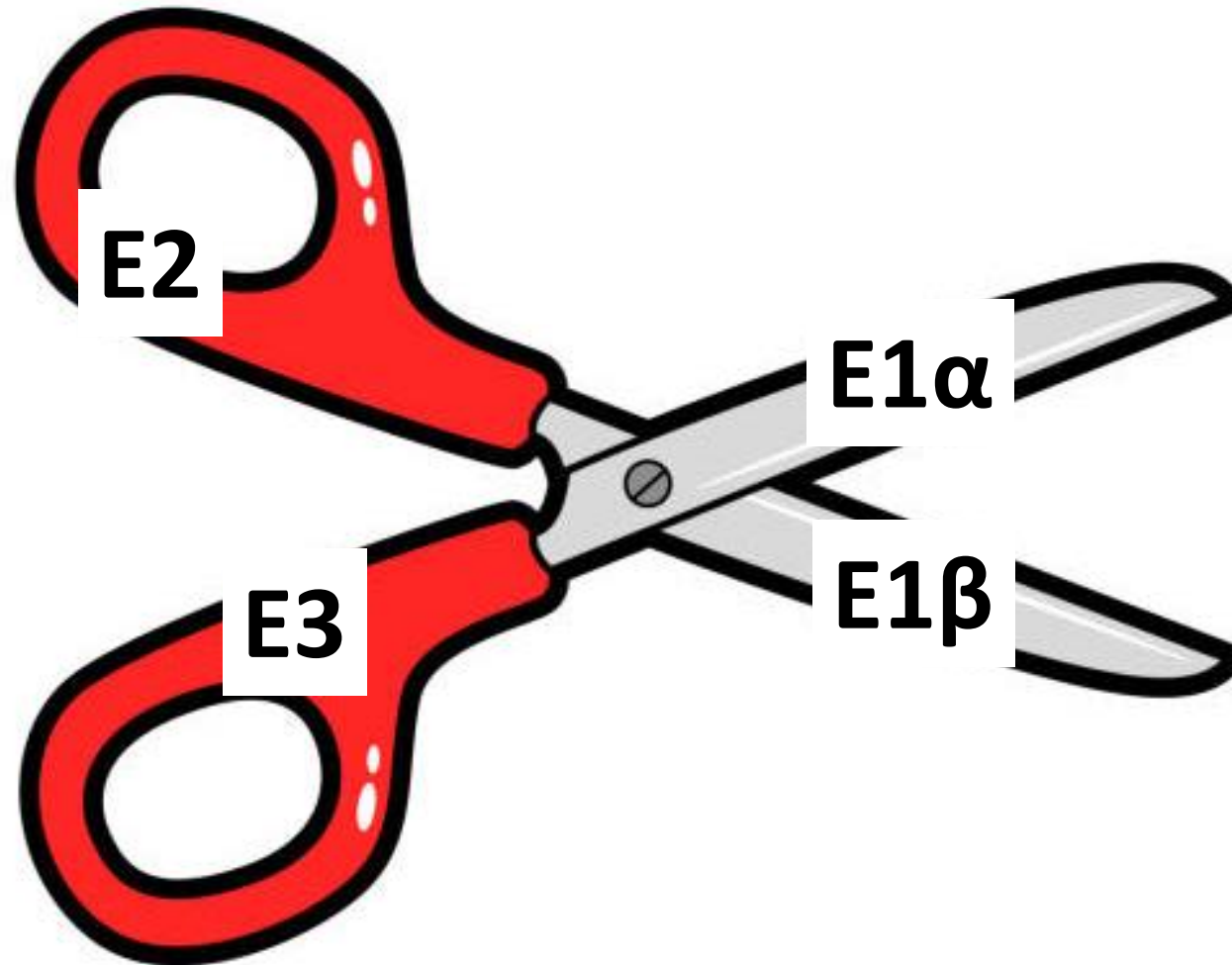


Why is it called Maple Syrup Urine Disease?

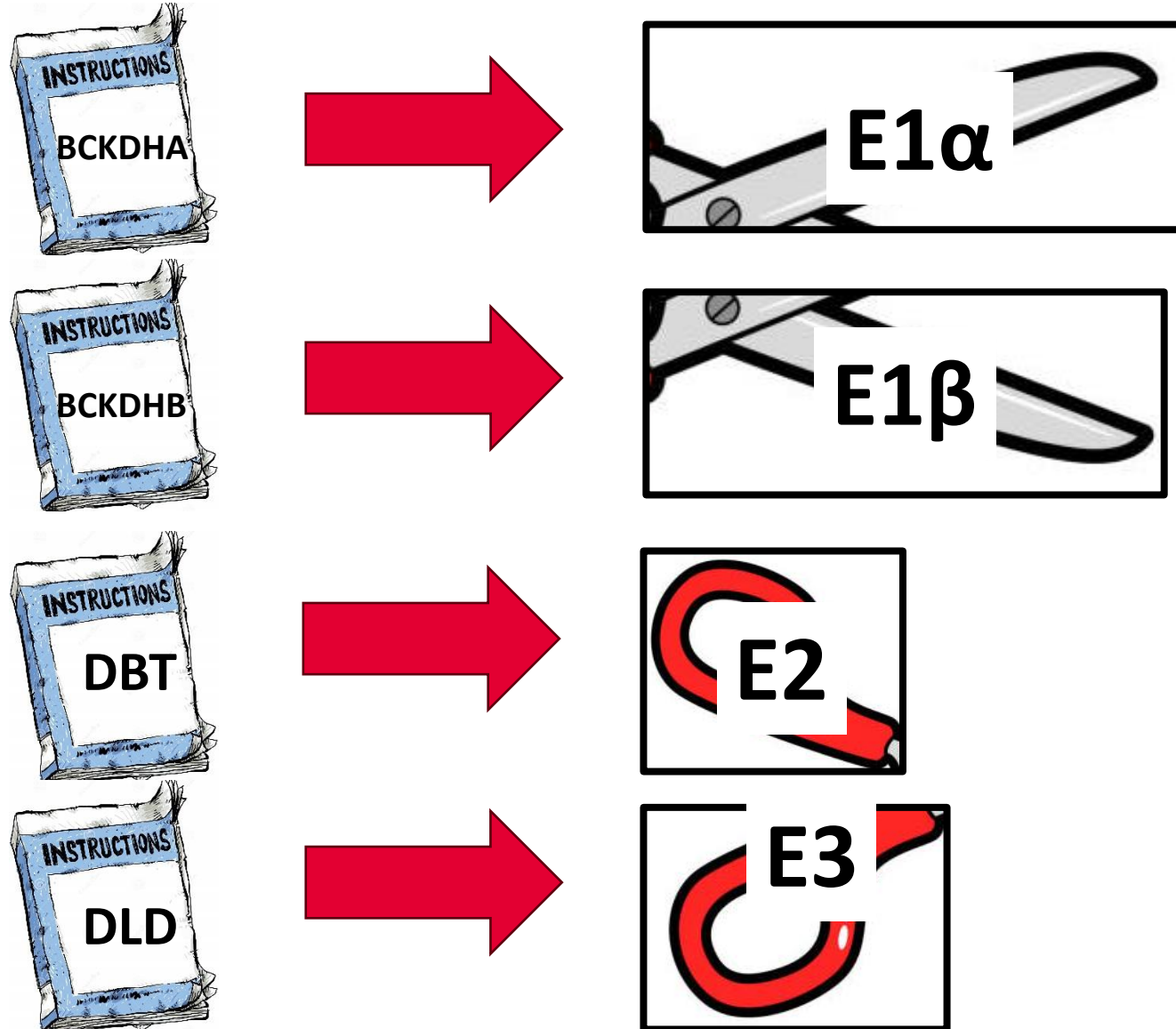
- Characteristic “sweet” “burnt sugar” odor
- Comes from a by-product of isoleucine (sotalone)
- Present in urine, ear wax



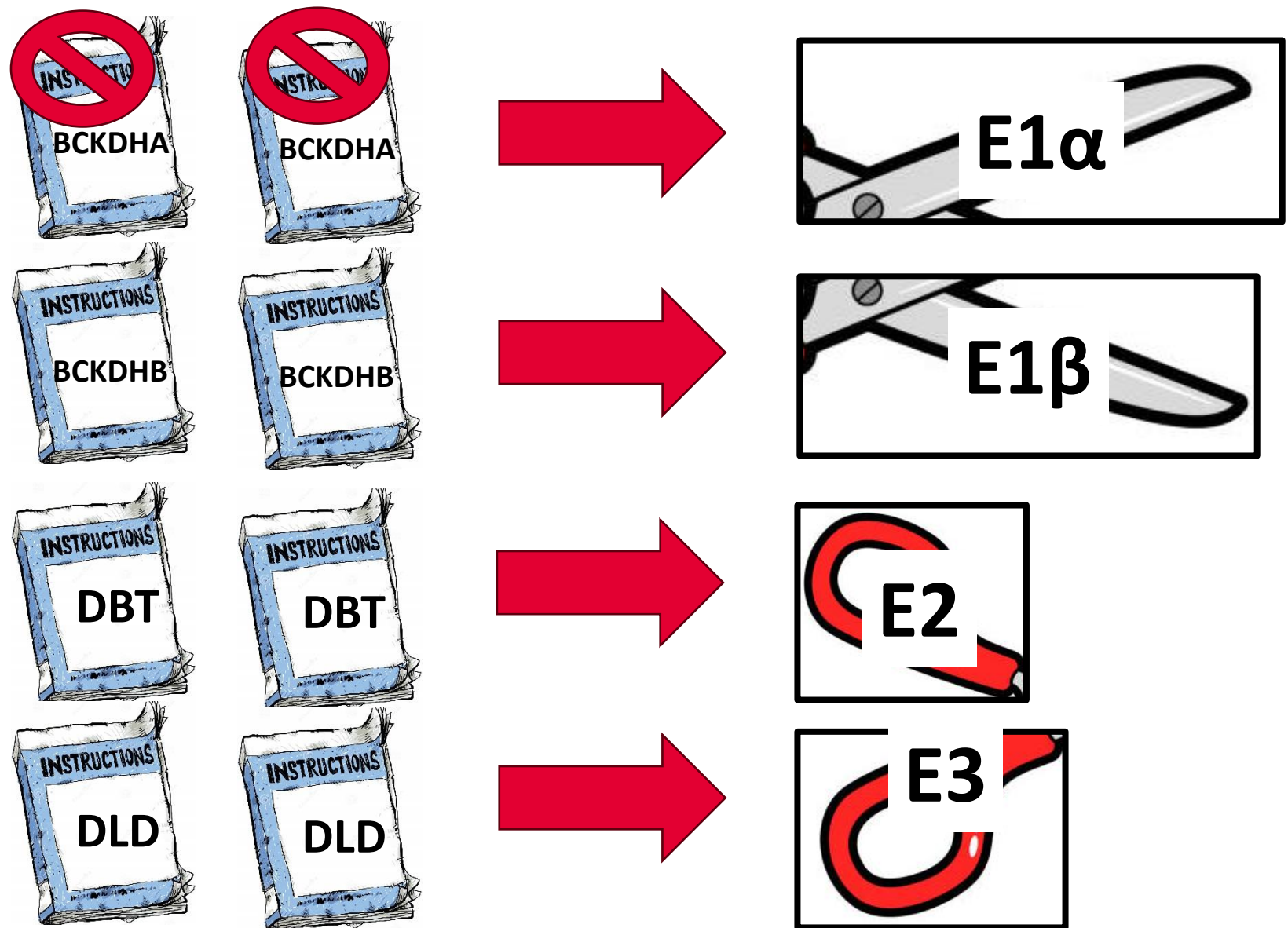
Why does ____ have MSUD?
(Nobody else in our family has MSUD)



The genes (“instructions”) to make the BCKD enzyme



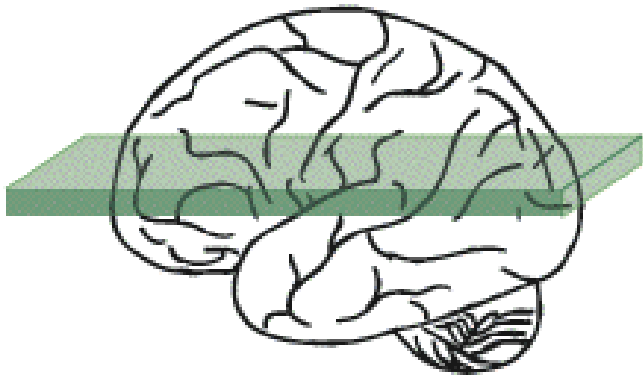
Autosomal Recessive Inheritance of MSUD



Symptoms and Diagnosis of Classic MSUD

Why is a high leucine level bad?

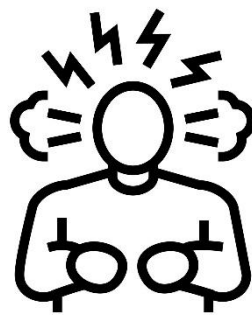
During acute crisis, high blood levels of leucine (and its keto-acid) causes brain swelling (edema)



Symptoms of acute crisis in MSUD



**Poor Feeding
Nausea/Vomiting**



Irritability



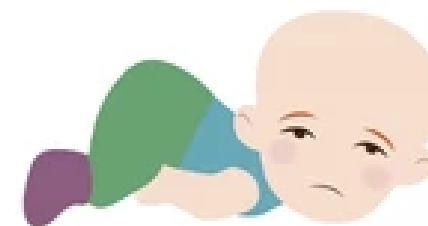
Unusual behavior



Abnormal tone



Seizures



Lethargy

How do you diagnose MSUD?

- Confirmation with plasma amino acid profile
- High leucine, isoleucine, valine and **allo-isoleucine**
- DNA sequencing of MSUD genes
 - BCKDHA, BCKDHB, DBT, (DLD)

Newborn Screening for MSUD

- State public health service
- Screen for treatable conditions
- All US states screen for MSUD
- Allows treatment to start as early as possible, before symptoms or harmful effects occur



Thiamine (Vitamin B1) Challenge

- High-dose thiamine (100mg daily) for 30 days
- Periodic measurements of BCAA with diet record to assess leucine tolerance
- Positive response: lower BCAA and/or increased leucine intake
- Changes in diet during the challenge can make results difficult to interpret

Management of MSUD

Goals of Day-to-day management of MSUD



- Provide just enough leucine, isoleucine, valine for normal growth but not too much
- Provide enough calories, vitamins, minerals to support normal growth
- Prevent acute crises

Day-to-day management of MSUD



- Exact amount of regular protein (“natural”, “intact”, “complete”)
 - Some teams may measure exact amount of BCAA
- Synthetic formula with everything except leucine, isoleucine, valine
 - Provides calories, essential fats, vitamins, minerals
- Valine and isoleucine supplementation
- Protein-free foods
 - Provides additional calories, essential fats, vitamins, minerals

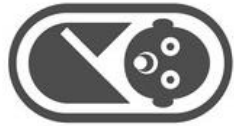
How often are outpatient visits?

- 1-3 times per week in infants
- Every 1 – 6 months in children < 8 years
- Every 6 – 12 months in those > 8 years

- More frequent visits if sick or if levels unstable



What happens during an outpatient visit?



Measure Growth



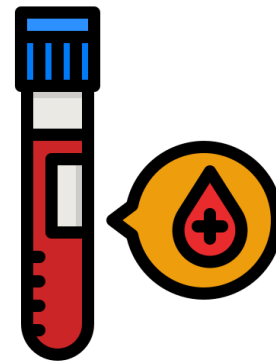
Medical History



Physical Exam



Test Development



Blood Tests



Diet adjustment

What are target BCAA levels?

- Leucine 75-300 $\mu\text{mol/L}$
- Isoleucine 200-400 $\mu\text{mol/L}$
- Valine 200-400 $\mu\text{mol/L}$

Preventing acute crises

- Infections are often the cause for metabolic instability
- To reduce the risk of infections:
- Good hand washing habits
- Vaccinations!
 - Routine vaccinations
 - Yearly flu shot

“Sick day” plan



- “Sick day”: Patient is ill, but:
 - Acting normally
 - Taking normal amount of of food/formula
- **Decision to use “sick day” plan should be discussed with your metabolic team**

What's in a “Sick day” plan?

- Modified diet plan may include:
 - Less leucine or natural protein (50-100% less)
 - More leucine-free formula (10% to 50% more)
 - More calories
 - More fluids (5–15% more)
 - More isoleucine/valine
- Fever control
- Nausea control (e.g., ondansetron)
- Treat underlying cause of illness (e.g., infection)

When to go straight to the hospital

- Change in alertness
- Unable to tolerate oral or tube feeding
- Abundant urine ketones
- Caregiver is not comfortable at home



Management of Acute MSUD Crises

Provide all amino acids except leucine

- BCAA-free formula (by mouth or tube)
- May give BCAA-free IV solution (parenteral nutrition)
- Supplement isoleucine and valine

Reverse catabolism: Give lots of calories

- BCAA-free formula (by mouth or tube)
- If not tolerating formula: Intravenous calories

Dialysis

- Different types of dialysis: e.g. intermittent vs. continuous hemodialysis vs peritoneal dialysis
- Advantages:
 - Quickest method of reducing leucine
- Disadvantages
 - Requires special IV access and special equipment and trained team
 - Takes several hours to set up
 - Higher risk of complications

Protecting the brain

- Brain CT/MRI is needed if there is a concern for brain swelling (edema)
- If edema is present:
 - Reduce fluid intake
 - Use of Normal Saline or Hypertonic Saline
 - Mannitol
 - Diuretics

Long-term Considerations

- Developmental delays
 - Referral to early intervention
- ADHD, anxiety or mood disorders
 - May require referral to psychiatrist
- Executive functioning difficulties
- Movement disorders
 - e.g. tremor, dystonia (abnormal tone), spasticity (stiffness), parkinsonism)
 - Referral to neurologist / movement disorder specialist
- Successful pregnancies in adult women with MSUD

Liver Transplantation

- Can be performed when patient:
 - Is clinically stable
 - Has reached a certain size
- New liver can “restore” some BCKD activity
 - Enough to allow unrestricted diet and prevent acute crisis
- Risk of complications and need for immunosuppression



Questions?