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
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>
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<th>Mutations affecting the human branched-chain α-ketoacid dehydrogenase complex</th>
<th>Nucleotide change</th>
<th>Exon</th>
<th>Intron</th>
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<tr>
<td><strong>E1α</strong></td>
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| GM649 | $T_{1339} \rightarrow A$ | 9 | – | Y393N | Zhang et al (1989)  
| **E1β** |  |  |  |  |  |
| LK | 11 bp del | 1 | – | Early stop codon | (Nobukuni et al (1991b)) |
| **E2** |  |  |  |  |  |
Chuang et al (1991)  
Chuang et al (1991)  
| GM612 A1 | 2 bp del | 2 | – | Stop | |
| A2 | $G_{684} \rightarrow T$ | 6 | – | E163* | |
| **WG34** |  |  |  |  |  |
Chuang et al (1991)  
| A2 | $T_{841} \rightarrow G$ | 7 | – | F215C | |
| **Ech** |  |  |  |  |  |
| A1 | 2 bp del | 2 | – | Stop | |
| A2 | 2 bp del | – | 5 | Splice error | |
| **AL-** |  |  |  |  |  |
Chuang et al (1991)  
Mitsubuchi et al (1991a)  
Nobukuni et al (1991a) |
| A2 | $T_{427} \rightarrow C$ | 5 | – | I77T | |
| **TH1** |  |  |  |  |  |
| G del |  | 8 | – | Splice error,  
Exon 8 del | Herring et al (1992) |
| **LF** |  |  |  |  |  |
| A1 | 20 kb genomic del | 6–11 | 6–10 | Truncated  
Splice error  
Exon 8,8–10 del | Herring et al (1991) |
| A2 | $G_{1931} \rightarrow A$ | 8 | – |  |
| **BH** |  |  |  |  |  |
| A1 | ? | 2 | – | Splice error  
Exon 2 del | |
| A2 | ? |  |  | No transcript | |
| **TH2** |  |  |  |  |  |
| $G_{684} \rightarrow T$ | 6 | – | E163* | Fisher et al (1993)  
| **EHy** |  |  |  |  |  |
| $G_{684} \rightarrow T$ | 6 | – | E163* | Fisher et al (1993)  
| **MF** |  |  |  |  |  |
- 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 $\alpha$-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 pathways 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 normal; 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 with each other in given genetic environment

• Identify which tissues require functional BCKD

• Use gene therapy to get the wild type gene, gene replacement, or correct the mutation within tissue to improve quality of life
References


The End