Autosomal Dominant Hypermethioninemia in an ethnically diverse population

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NBS for Homocystinuria

- **Classical Homocystinuria (cystathionine β-synthase def.)**
  - Analyte = Methionine
  - tHCys not amenable to current high throughput methods

- **Meets most screening criteria**
  - Well characterized natural history
    - *Risk of stroke, lens dislocation, developmental delay*
  - Effective treatment
    - *Protein restriction, close monitoring*
  - Evidence of improved outcomes from early intervention

- **Test performance is suboptimal**
  - Mild cases can be missed (sensitivity)
  - Methionine elevations are not specific
HyperMethioninemias

• Classic Homocystinuria (cystathionine β-synthase)
• Methionine aminotransferase (MAT I/III)
• Glycine N-methyltransferase (GNMT)
• S-adenosylhomocysteine hydrolase (SAM Hydrolase)

• Secondary Causes
  • Tyrosinemia type I (FAH)
  • Citrin deficiency
  • Liver disease
  • Prematurity
  • Low birth weight
MAT I/III Deficiency (MAT1α)

• **The primary outcome of many HCY screening programs**
  - Taiwan 1/100,000 (CBS 1/1.7 million)\(^1\)
  - Galicia 1/28,000 (CBS 1/120,000)\(^2\)
  - Portugal 1/26,000 (CBS 1/56,000)\(^3\)

• **Clinical Features**
  - Highly variable
  - Vast majority of cases are asymptomatic
  - Reports of demyelination in some (SAM deficiency?)

• **Treatment**
  - Monitoring only, in many cases
  - Protein restriction if Met >150 uM
  - Anecdotal evidence that SAM treatment may improve outcomes in those with symptoms

\(^1\)Chien et al. Early Hum Dev 2005; 81,6:529-33
\(^2\)Couce et al. JIMD 2008; 31 Suppl2:S233-9
\(^3\)Martins et al. JIMD 2012;6:107-112
Autosomal Dominant MAT I/III

- **p.R264H Mutation**
  - Heterozygotes with hypermet detected by NBS
    - Mild hypermet (80-250 uM)
    - No other mutations on full sequencing
    - Hypermet in parent sharing the genotype
    - Mild homocystine elevations in most cases
  - Galicia (5), Portugal (12), Taiwan (1)
  - Mutation likely a dominant negative
    - Affects interface of the two dimers
- **No other dominant mutations reported**
  - Hypermet reported with heterozygosity for p.A295V but autosomal dominant transmission not confirmed
  - Some heterozygote hypermet cases reported with an assumed second mutation not identified
BC Screening Program

- Cover British Columbia and Yukon
- 45,000 Births per year
- Expanded program in 2009
  - (22 primary disorders)
- Includes Homocystinuria
  - Met > 70 uM
- All positive screens confirmed on a repeat card
- Single Metabolic Center for follow-up
  - BC Children’s Hospital
Feb 2010 First HyperMet Case

Case 1: Newborn Male
European Descent
Vancouver
Initial Card: MET = 95 uM (Cutoff <70)
Repeat Card: MET = 167 uM

- Followup Testing
  - Plasma MET = 119 uM (Ref<36)
  - Plasma tHCys normal
  - SAM slightly increased initially then normalized
  - SAH normal
  - Maternal MET = 53 uM (Father normal)
  - MAT1a Sequencing = Het c.776C>T (p.A259V)
  - Mother also heterozygous (Father non-carrier)
Mar 2010 2nd HyperMet Case

Case 2: Newborn Male
First Nations Descent
Northern BC
Initial Card: MET = 105 uM (Cutoff <70)
Repeat Card: MET = 186 uM

• Followup Testing
  • Plasma MET = 139 uM (Ref<36)
  • tHCys Normal
  • SAM slightly increased initially then normalized
  • SAH normal
  • Maternal MET = 53 uM (Father normal)
  • MAT1a Sequencing = Het c.776C>T (p.A259V)
  • Mother also heterozygous (Father non-carrier)
Subsequent HyperMet Cases

**Case 3: Newborn Female**
First Nations Descent
Northern BC (same community as #2)
Initial Card: MET = 108 uM (Cutoff <70)
MAT1a = p.A259V (Shared with Mom)

**Case 4: Newborn Male**
Chinese Descent
Vancouver
Initial Card: MET = 136 uM (Cutoff <70)
MAT1a = p.S114F (Shared with Dad)

**Case 5: Newborn Female**
Vietnamese Descent
Vancouver
Initial Card: MET = 126 uM (Cutoff <70)
MAT1a = p.G253R (Shared with Dad)
Summary of BC Experience

<table>
<thead>
<tr>
<th>Location</th>
<th>Ethnicity</th>
<th>Plasma Met uM (Ref &lt;36)</th>
<th>Parental Met uM (Ref&lt;36)</th>
<th>MAT1a Genotype</th>
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<tr>
<td>Vancouver</td>
<td>Caucasian</td>
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<td>c.776C&gt;T (p.A259V)</td>
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<td>Vietnamese</td>
<td>137</td>
<td>89</td>
<td>c.757G&gt;C (p.G253R)</td>
</tr>
</tbody>
</table>
Dominant MATI/III (p.R264H)

- MATI/III functions as a dimer.
- AA 264 is at the dimer interface.
- p.R264H subunits fail to dimerize with each other.
- Heterodimers with the WT subunit are inactive.
- Dominant Negative effect

MAT I/III Structure

Madej et al. Nucleic Acids Res 2012 40:D461-4
Conclusions

• **Hypermethioninemia on NBS (1/26,000)**
  • Mild but persistent

• **Autosomal Dominant**
  • One parent with hypermethioninemia in all cases

• **Heterozygosity for MAT1a mutations**
  • 3 different mutations
  • All showing autosomal dominant hypermet
  • No other sequence changes detected

• **Only p.A259V previously reported**
  • Taiwan, heterozygote, dominant transmission not explored

• **All 4 dominant mutations are located at the dimer interface**
• **This is the ONLY outcome of our HCY screening algorithm to date (56% PPV)**
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