Autosomal Dominant Hypermethioninemia in an ethnically diverse population

Graham Sinclair, PhD FCCMG
Biochemical Genetics and Newborn Screening Laboratories,
BC Children's Hospital
University of British Columbia

a place of mind

UBC

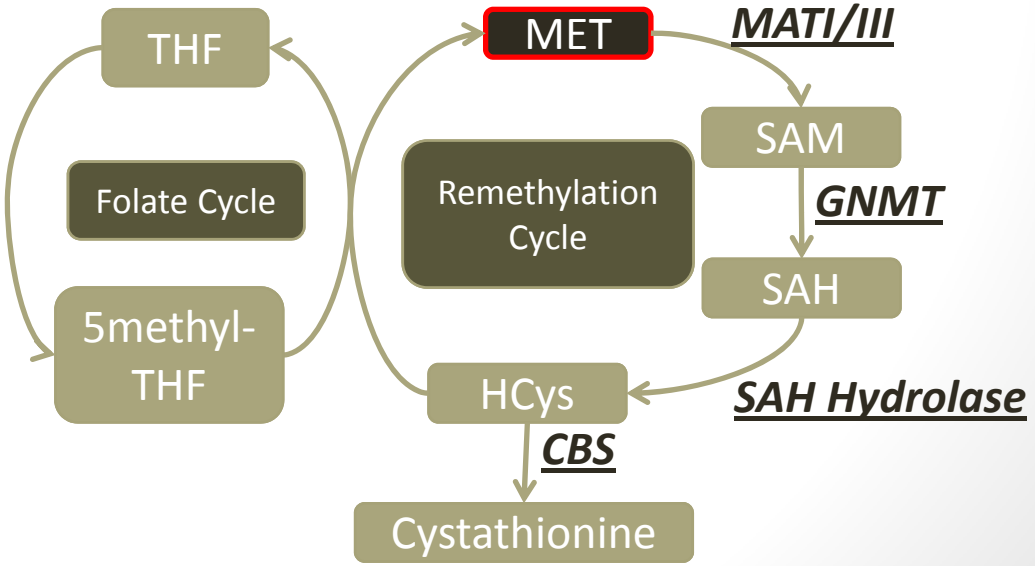
BC CHILDREN'S HOSPITAL
An agency of the Provincial Health Services Authority

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 (*MAT1a*)

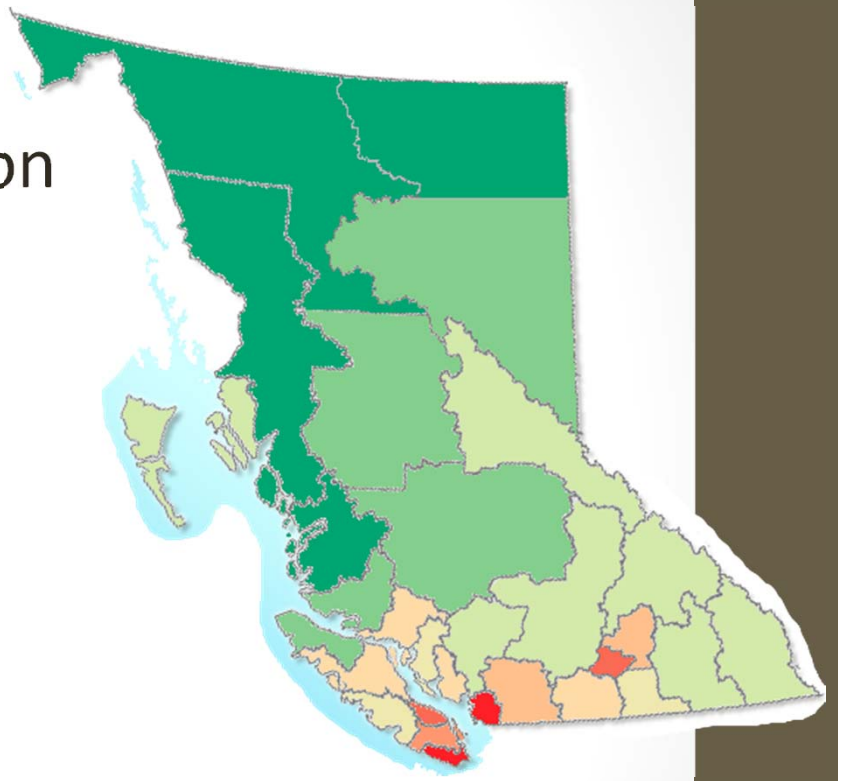
- **The primary outcome of many HCY screening programs**
  - Taiwan 1/100,000 (CBS 1/1.7 million)[1]
  - Galicia 1/28,000 (CBS 1/120,000)[2]
  - Portugal 1/26,000 (CBS (1/56,000)[3]
- **Clinical Features**
  - Highly variable
  - Vast majority of cases are asymptomatic
  - Reports of demyelination in 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
  - Galacia (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

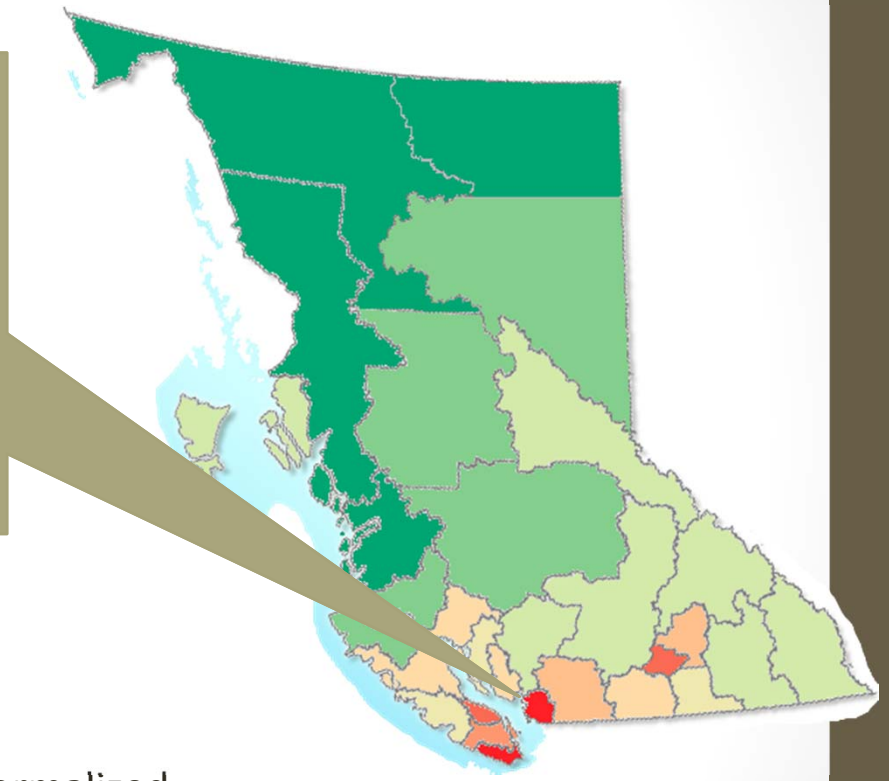


- Cover British Columbia and Yukon
- 45,000 Births per year
- Expanded program in 2009
  - (22 primary disorders)
- Includes Homocystinuria
  - Met > 70 uM
- All positive screens confirmed on a repeat card
- Single Metabolic Center for follow-up
  - BC Children's Hospital

Feb 2010 First HyperMet Case

Case 1: Newborn Male

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

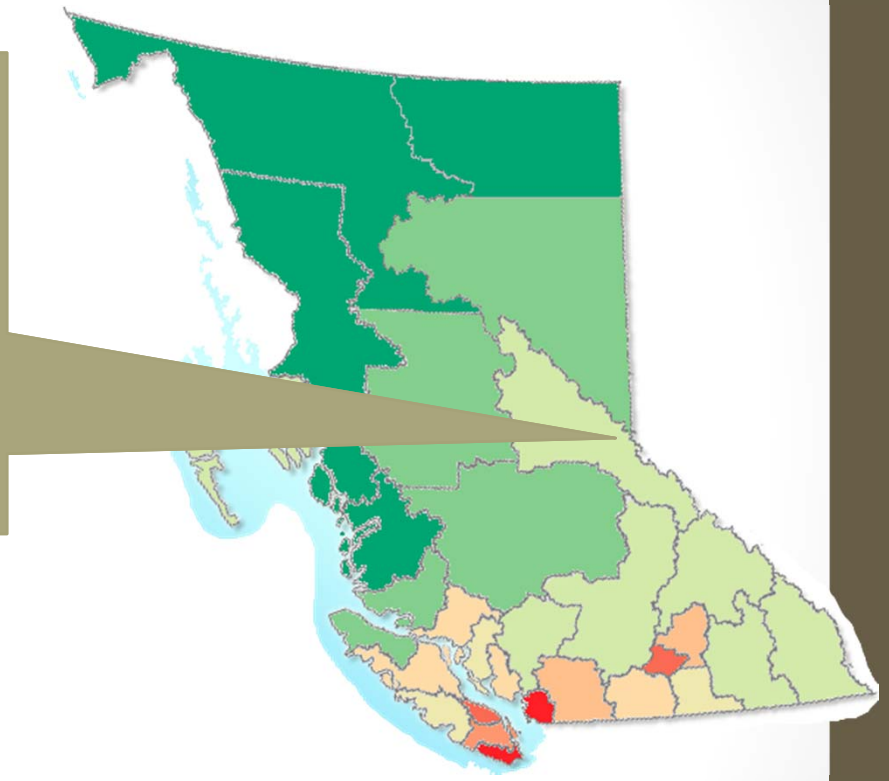


- Followup Testing
  - Plasma MET = 119 uM (Ref<36)
  - Plasma tHCys normal
  - SAM slightly increased initially then normalized
  - SAH normal
  - Maternal MET = 53 uM (Father normal)
  - MAT1a Sequencing = Het c.776C>T (p.A259V)
  - Mother also heterozygous (Father non-carrier)

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)

Subequent HyperMet Cases

Case 3: Newborn Female

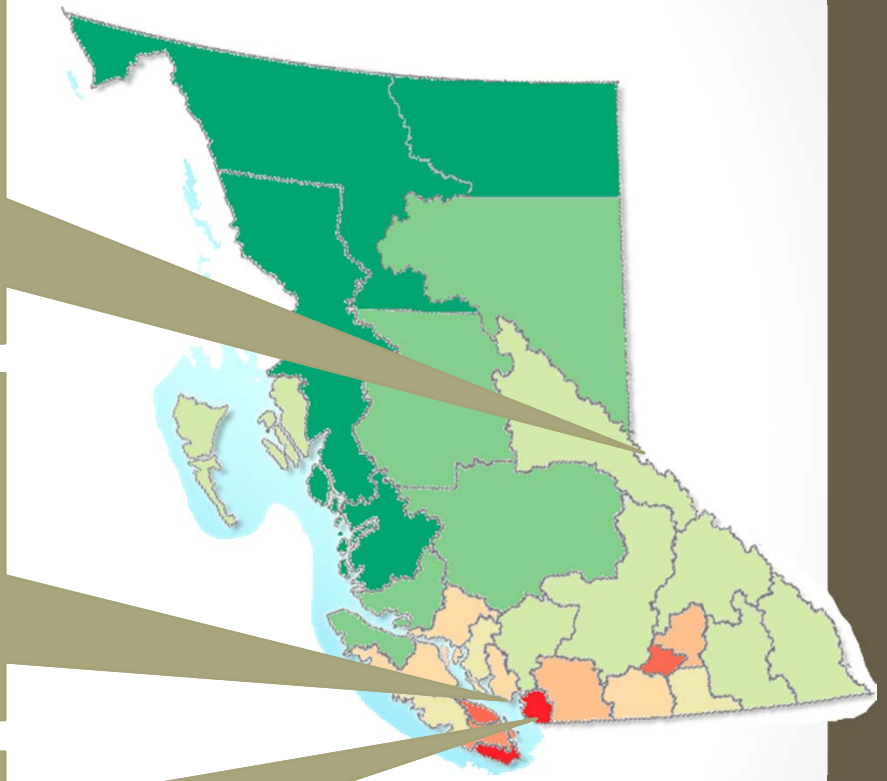
First Nations Descent
Northern BC (same community as #2)
Initial Card: MET = 108 uM (Cutoff <70)
MAT1a = p.A259V (Shared with Mom)

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

Location	Ethnicity	Plasma Met uM (Ref <36)	Parental Met uM (Ref<36)	*MAT1α* Genotype
Vancouver	Caucasian	119	53	c.776C>T (p.A259V)
Northern BC	First Nations	139	53	c.776C>T (p.A259V)
Northern BC	First Nations	95	49	c.776C>T (p.A259V)
Vancouver	Chinese	65	38	c.341C>T (p.S114F)
Vancouver	Vietnamese	137	89	c.757G>C (p.G253R)

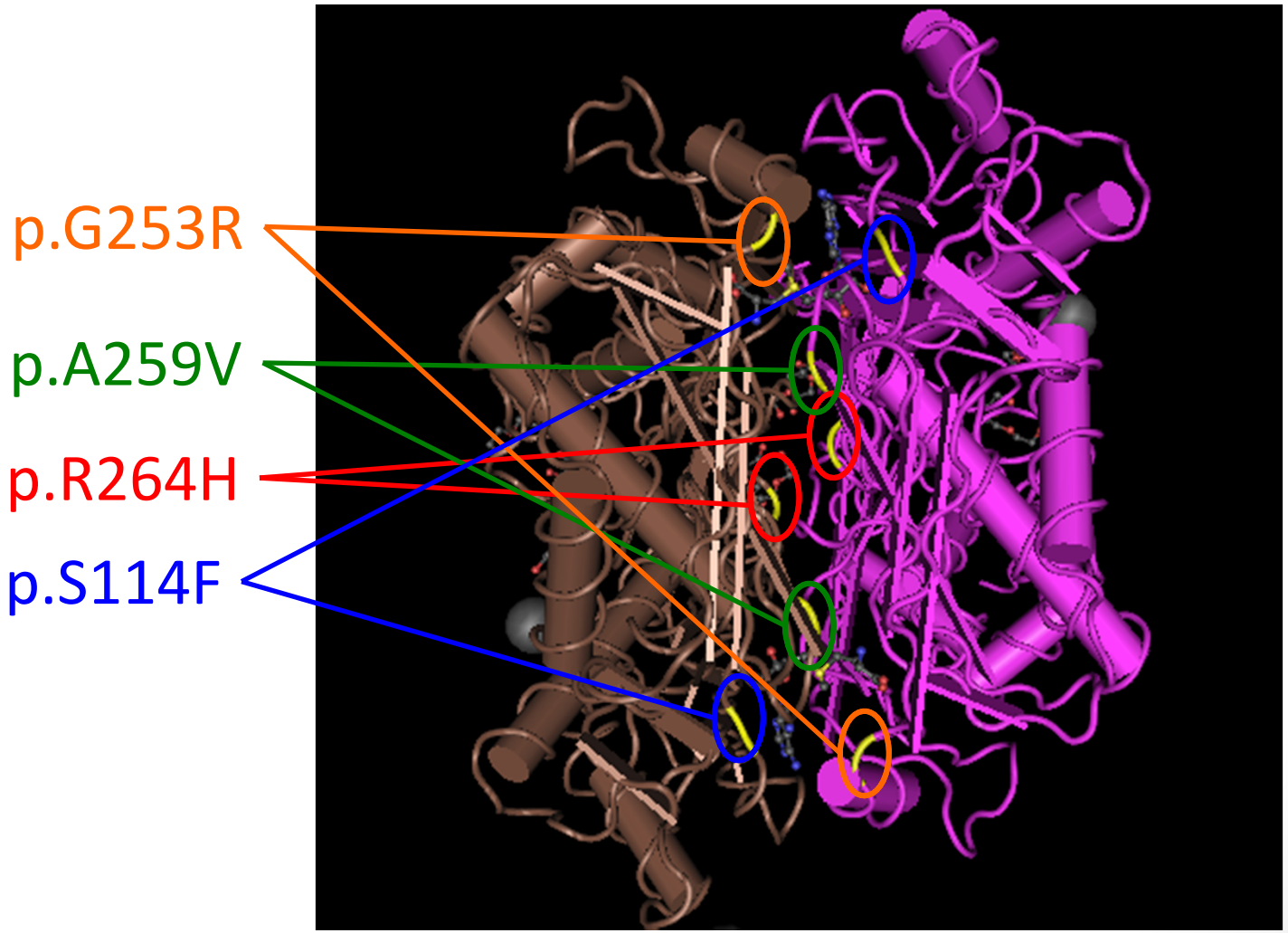
Dominant MATI/III (p.R264H)

- 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

Pilka et al. Structural Genomics Consortium

Perez Mato et al. (2001) J of Biol Chem 276(17): 13803-9

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)**

Acknowledgements

- BC Children's Hospital
  - Hilary Vallance
  - Saadet Mahmutoglu
  - Ramona Salvarinova
  - Sylvia Stockler

- NIH
  - Harvey Mudd

a place of mind

UBC

BC CHILDREN'S HOSPITAL

An agency of the Provincial Health Services Authority