Tongue Tie (Ankyloglossia):  
Risk Reduction by Identifying MTHFR and Methylation Defects

Presenter:
Benjamin Lynch, ND

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I am founder of MTHFR.Net

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Purpose of this Presentation

- Provide a general overview of tongue tie

- Expand awareness of MTHFR and select other genetic defects which affect methylation

- Potentially reduce the risk of infants born with midline defects – including tongue tie

- Reduce lifelong suffering of various chronic diseases and conditions by identifying, addressing and supporting genetic mutations in the parents prior to pregnancy.
Overview of this Presentation

1) Genetics and Tongue Tie

2) Why L-Methylfolate is not enough

3) Important methylation steps needed to help reduce midline defects

4) Nutrients and cofactors for important methylation steps

5) Interference potential at methylation step via feedback inhibition or cofactor deficiency

6) Lab testing to help identify methylation deficiencies

7) How to discuss this with your doctor

8) Steps to support methylation in those with Tongue Tie (time dependent)
Ankyloglossia prevalence is approximately 4% in newborn population.

Appears to be a semi-dominant X-linked inheritable trait from gene TBX22 (T box 22).

Predominately male with a ratio of 3.8 males for every 1 female.

Commonly related to orofacial clefts in varying degrees.

Source: PMID 23071373, 22872835, 21248356
Tongue Tie: How to Get the X Linked TBX22?

Males more susceptible to X-linked conditions as they have only one x chromosome.

Women have two x chromosomes which ‘dilutes’ the effect of the x-linked trait – especially if recessive.
What happens to TBX22?

“An important functional role for rs41307258 (TBX22) results in a decreased promoter activity of up to 50%. CONCLUSIONS: CPX-like patients harboring this promoter haplotype are therefore associated with decreased TBX22 transcriptional activity. The risk haplotype, in concert with additional genetic and/or environmental factors, may contribute to the phenotypic variation observed and provide a novel causative mechanism for cleft palate, especially in patients with ankyloglossia.”

TBX22 activity is down-regulated. Why?

Decreased TBX22 transcriptional activity

“Loss of SUMO-1 modification is consistently found in all pathogenic x-linked cleft palate missense mutations. This implies a general mechanism linking the loss of SUMO conjugation to the loss of TBX22 function. Orofacial clefts are well known for their complex etiology and variable penetrance, involving both genetic and environmental risk factors. The sumoylation process is also subject to and profoundly affected by similar environmental stresses. Thus, we suggest that SUMO modification may represent a common pathway that regulates normal craniofacial development and is involved in the pathogenesis of both Mendelian and idiopathic forms of orofacial clefting.”

What is SUMOYLATION and how to affect it positively!?

Genetics and Environmental Factors

“For clefts of the lip and palate, a genetic contribution of 20%–50% has been estimated, with the remainder associated with a wide variety of environmental factors during early pregnancy, such as smoking, use of alcohol and chemotherapeutic drugs, lack of maternal nutritional supplements such as folic acid or other vitamins, viral infection, and exposure to agricultural chemicals or other teratogens.

More-complex factors have also been implicated, including maternal age, low socioeconomic status, psychological stress in the mother, altitude, and conditions of hypoxia, in some cases with good supporting evidence provided by animal models. It now seems likely that some of these factors may manifest through disturbance of the SUMO pathway.

Destabilizing the normal balance of expression and activity for genes such as TBX22, MSX1, SATB2, and p63 during early pregnancy is likely to provide a high-risk environment for occurrence of cleft lip and/or palate. Elucidating the relationship among environmental factors, the SUMO pathway, and the networks of craniofacial genes that are influenced by this posttranscriptional modification may be crucial to our understanding of idiopathic forms of orofacial clefts.”

Source: TBX22 Missense Mutations Found in Patients with X-Linked Cleft Palate Affect DNA Binding, Sumoylation, and Transcriptional Repression
“... role of the SUMO pathway in mammals and, reporting in Developmental Cell, they show that it is essential for nuclear integrity, chromosome segregation and embryonic viability”
“Several members of the DNA virus families have been shown to modulate sumoylation, including papillomaviruses, adenoviruses and herpesviruses.”

Reduce risk of decreased sumoylation by combating viruses prior to pregnancy and preventing exposure during.

Evaluate presence and activity of EBV, influenza, HPV.

Methylation supports immunity so it is not coincidence that methylation defects increase risk of tongue tie.

Source: SUMO Regulation of Cellular Processes by Van Gene Wilson and PMID 22072786
**SAMe and Betaine improve early virological response** in chronic hepatitis C patients with previous nonresponse.

Establishment of **persistent Epstein-Barr virus** (EBV) infection **requires transition from a program of full viral latency gene expression (latency III) to one that is highly restricted** (latency I and 0) within memory B lymphocytes. **DNA methylation plays a critical role in EBV gene silencing**, and recently the chromatin boundary protein CTCF has been implicated as a pivotal regulator of latency via its binding to several loci within the EBV genome. One notable site is upstream of the common EBNA gene promoter Cp, at which CTCF may act as an enhancer-blocking factor to initiate and maintain silencing of EBNA gene transcription. It was previously suggested that increased expression of CTCF may underlie its potential to promote restricted latency, and here we also noted *elevated levels of DNA methyltransferase 1 (DNMT1) and DNMT3B associated with latency I.* (I = highly restricted)

Source: PMID 21079746 and 22072770
"Inhibition of DNA methylation by various dietary catechol-containing polyphenols. While we understand that the usual daily intake of caffeic acid or chlorogenic acid alone may not represent an overwhelming burden for the body’s COMT-mediated methylation system as well as for the intracellular SAM pool, it should be noted that SAH is a very potent non-competitive inhibitor of DNA methylation and only very low concentrations of intranuclear SAH may be needed to cause a meaningful inhibition of the enzymatic DNA methylation. Besides, there are many other catechol-containing polyphenolic compounds present in our daily diet, such as tea catechins and bioflavonoids, and they are excellent substrates for human COMT-mediated methylation. Undoubtedly, the total intake of various dietary catechol-containing polyphenols could be quite large in quantities, which could be a significant cumulative factor that may contribute to the increased intracellular accumulation of SAH, and these dietary chemicals may jointly contribute to the inhibition of DNA methylation in meaningful ways."

Tea, coffee, potatoes, sweet potatoes contain large amounts of chlorogenic acid.

Inhibition of DNA Methylation by Dietary Catechols
MTHFR and Cleft Palate

“No supplement use, low dietary folate intake, and maternal MTHFR 1298CC genotype increased the risk of CL(P) offspring almost sevenfold. Mothers carrying the MTHFR 677TT genotype and who either did not use folic acid supplements periconceptionally or had a low dietary folate intake, or both, had an increased risk of delivering a CL(P) child. Thus, the detrimental effect of low periconceptional folate intake on the risk of giving birth to a CL(P) child was more pronounced in mothers with the MTHFR 677TT or MTHFR 1298CC genotype.”

Univariate results suggest that low parental education, periconceptional maternal medication use and illnesses, paternal smoking, and first-trimester maternal common cold increased CL/P risk.

Source: PMID 12672677 and 16955502
“Higher levels of vitamin A intake from multivitamins and liver sources also seemed to protect against CL±P. Exploratory analyses suggested that the latter association was not entirely explained by the association between CL±P and multivitamin use, indicating that adequate levels of vitamin A may be required for normal development of the primary palate.”

Source: http://aje.oxfordjournals.org/content/158/1/69.full.pdf
Several Functions of Methylation:
1. Turn on and off genes (gene regulation)
2. Process chemicals and toxins (biotransformation)
3. Build neurotransmitters (dopamine, serotonin, epinephrine)
4. Process hormones (estrogen)
5. Build immune cells (T cells, NK cells)
6. DNA and RNA synthesis (Thymine aka 5-methyluracil)
7. Produce energy (CoQ10, carnitine, ATP)
8. Produce protective coating on nerves (myelination)
How is Methylation Disturbed?

Methylation is often disturbed by various mechanisms
1. Lack of cofactors driving methylation forward (zinc, B2, magnesium, B6, methylcobalamin)
2. Medications (antacids, methotrexate, metformin, nitrous oxide)
3. Specific nutrients depleting methyl groups (high dose Niacin)
4. Environmental toxicity, heavy metals, chemicals (acetylaldehyde, arsenic, mercury, high copper)
5. Excessive substrate (feedback inhibition – eg. DMG, glutathione, SAMe, Methylfolate)
6. Genetic mutations
Which Genes to Suspect and/or Screen for?

- MTHFR: produces methylfolate
- COMT: processes neurotransmitter catabolism and estrogens
- CBS: depletes homocysteine and if upregulated, depletes methyl groups, increases taurine
- MTR/MTRR: recycles B12 and processes B12 for methionine production
- GSTM1 and SOD: major detoxification enzymes
- CYT P450: major detoxification liver enzymes
- SUOX: processes sulfites/sulfur and this mutation is made worse from CBS upreg
Prevalence of homozygous TT genotype (two 677C>T alleles) among newborns by area and ethnic background, ICBDMS 2003

What is MTHFR?

MTHFR = methylenetetrahydrofolate reductase

- An enzyme produced by the MTHFR gene found on Chromosome 1
- Converts 5,10 methylenetetrahydrofolate to 5-methyltetrahydrofolate

**Clinical Relevance:**
- Produces the most active form of folate:
  - 5-methyltetrahydrofolate (L-5-MTHF)
Promoters of MTHFR

- Low SAMe levels
- Low Methionine levels

Clinical Relevance:
MTHFR produces Methylfolate which:
- supports SAMe
- reduces Homocysteine
- recycles BH4

Source: http://www.peds.ufl.edu/divisions/genetics/_style/images/autism-B12-methionine.jpg
Inhibitors of MTHFR

High SAMe levels¹
High Methionine levels¹
DHF (Dihydrofolate)²

Source:
(1) Folate in Health and Disease, Second Edition (Clinical Nutrition in Health and Disease)

(2) PMID: 7051769
Inhibitors of MTHFR: Why are they there?

The MTHFR enzyme is irreversible so it must be inhibited at times to produce and repair DNA.

source: Folate in Health and Disease, 2nd Ed (Clinical Nutrition in Health and Disease)

Clinical Relevance: Do not supplement with excessive methylfolate levels or you may increase DNA production – unless this is what you want. There are risks.

Source: http://www.rbej.com/content/figures/1477-7827-2-7-1.jpg
Inhibitors of MTHFR: DHF

The MTHFR enzyme is inhibited by Dihydrofolate which is a predominate form of folate in food.

source: Folate in Health and Disease, 2nd Ed (Clinical Nutrition in Health and Disease)
MTHFR Variants and Effects

Beyond 677 and 1298, there are other MTHFR variants that are being evaluated. If MTHFR variants are in combination with each other, methylfolate production may be limited.

Clinical Relevance:
- If your patient tests negative for 677 and/or 1298 MTHFR defects yet has signs and symptoms of methylation defects, treat anyway as we do not have the ability to identify all genetic mutations – nor do we have the knowledge of how severely these mutations affect our physiology.

- Using synthetic folic acid should not be used in anyone; only the active forms of Folinic acid and L-5-MTHF should be used.
MTHFR Variants: Bypass the Defect
Decreased thymidine increases uracil incorporation into DNA causing strand breaks. 
MTHFR is not only about Homocysteine

“Having two MTHFR variants is much more common than having high homocysteine or any health conditions linked to high homocysteine.”


Why?
MTHFR is **more** than Elevated Homocysteine = Other Routes to Lower Hcy
Betaine and Homocysteine

Betaine does lower Homocysteine

“Betaine can act as a methyl donor in the remethylation of homocysteine in the liver by the enzyme betaine-homocysteine methyltransferase (BHMT), and that human intervention studies consistently show a significant decrease in plasma concentrations of homocysteine following betaine administration . . . 1.5 g of betaine should be consumed daily.”


Foods Highest in Betaine (per 100 gram serving)

- Quinoa  630 mg
- Spinach  577 mg
- Lamb     332 mg
- Beets    256 mg

Looks like a great dinner that is most likely hypoallergic and very supportive of methylation

Source: [http://nutritiondata.self.com/foods-000145000000000000000000-w.html](http://nutritiondata.self.com/foods-000145000000000000000000-w.html)
Betaine and Homocysteine

Use the Right Form of Betaine
• TMG aka Betaine anhydrous = best form
• Betaine HCl will work also but not ideal
• DMG causes feedback inhibition of BHMT
  • increase homocysteine levels (PMID: 11380830)

Source: [http://annals.org/data/Journals/AIM/19940/5FF1.jpeg](http://annals.org/data/Journals/AIM/19940/5FF1.jpeg)
Increased levels may decrease NK cell activity. PMID: 16365081

Caused by excessive fortification programs and supplementation

May mask a vitamin B12 deficiency
Nitrous oxide inhibits MTR enzyme.

Those with MTHFR and methylation defects already have limited MTR enzyme function so further reducing it may cause significant neurological or cardiovascular damage.
Starting the Methylation Protocol

History! Lifestyle! Diet!
Must start with foundational health first – ideally. If not, then side effects are likely.
• Dietary intake? Switch them to modified GAPS or Paleo – or simply whole foods diet w/o Gluten/Dairy
• Toxin and Chemical Exposure? Reduce it
• Digestion? Improve it
• Bowel Movements? Two a day or more well formed
• Meds? Look for folic acid and vitamin B12 antagonists
• Supplements? Which making them worse? May need to stop all and restart to identify problem nutrients.
• Eating? Chew you water, drink your food.
• Sensitive to Sulfur supplements? Possible CBS, SUOX or Molybdenum deficiency

Testing?
Shouldn’t be necessary right away. Order testing when you are stuck.

Typically enough work to do with foundational steps first
- Reduce methylation burden
Approach for Each Patient: Key Points

1. Thorough History
   • Diet, Lifestyle, Occupation, Stressors, Medical Hx, Family Hx, Current Labs (3 mos), ALL signs/sxs

2. Improve Diet and Lifestyle (ie. Reduce methylation demand)
   • Remove Wheat and Dairy for all
   • Ideally Gluten but tough to do in beginning – need to win trust first
   • Evaluate sensitive to sulfur-containing foods and/or sulfites (CBS screening)

3. Provide Therapeutic Interventions
   • Castor Oil Packs, Contrast Hydro, Electrolyte Drink
   • Positive Mindset, Educate about Epigenetics (show Bruce Lipton’s ‘New Biology’ on YouTube)

4. Provide Basic Supplementation to Start
   • Hit all key areas: Digestive, Mental, Physical, Mitochondrial
   • Start in safest part first
   • Introduce one supplement every other day to every 4 days
   • Start low amounts and work up
   • Clearly inform how they should feel
     • Needs to feel better. If bad in anyway, then protocol is incorrect. Adjust.

5. ‘Intuition’
   • Wake up and ‘feel’ how they are doing for the day. Listen to their sxs. Take only what is needed for that moment
   • Do not supplement daily once feeling better.
   • Can become easily overmethylated requiring need for Niacin (methylation ‘sponge’)


Which Therapies to use for Methylation Support?

• Colonics
• Sauna (low temperature as long as tolerable then get out)
• Castor Oil Packs
• Coffee Enemas (once feeling better – then begin – as they are very strong)
• Epsom Salt Baths
• Rebounding
• Dry Skin Brushing
• Hot Yoga
• Breath Therapy
• Mindful Eating
• Paleo, GAPS or Adventure Diet with focus on uncooked leafy greens, grass fed beef, vegetables, seeds
• Detox Home (air purifier, water purifier, wood floor, tile, dust mite covers, bathroom fans, natural soaps/cleaners
• Avoid Folic Acid (fortified foods)
• Avoid Vaccinations (screening newborns)

Source: http://mthfr.net/mthfr-c677t-mutation-basic-protocol/2012/02/24/
Drugs to Avoid with MTHFR

Common Drugs to Avoid with MTHFR

- Antacids (deplete B12)
- Cholestyramine (deplete cobalamin and folate absorption) – common in gallbladder issues during pregnancy!
- Colestipol (decrease cobalamin and folate absorption)
- Methotrexate (inhibits DHFR)
- Nitrous Oxide (inactivates MS)
- Niacin (depletes SAMe and limits pyridoxal kinase = active B6) → useful during times of over-methylation
- Theophylline (limits pyridoxal kinase = active B6)
- Cyclosporin A (decreases renal function and increases Hcy)
- Metformin (decreases cobalamin absorption)
- Phenytoin (folate antagonist)
- Carbamazepine (folate antagonist)
- Oral Contraceptives (deplete folate)
- Antimalarials JPC-2056, Pyrimethamine, Proguanil (inhibits DHFR)
- Antibiotic Trimethoprim (inhibits DHFR)
- Ethanol
- Bactrim (inhibits DHFR)
- Sulfasalazine (inhibits DHFR)
- Triamterene (inhibits DHFR)

Source: Fischbach, Laboratory Diagnosis and BMJ http://heart.bmj.com/content/83/2/127/T1.expansion.html
Common Meds used for MTHFR

Common Meds used with MTHFR
- Cerefolin
- CerefolinNAC
- Neevo
- NeevoDHA
- Metanx → personal favorite out of all of them but still don’t like it
- Deplin
- Folbee
- Folplex
- Folgard
- Foltx
- FABB

Common ‘Other Ingredients’ in MTHFR Meds
Dibasic Calcium Phosphate Dihydrate, Microcrystalline Cellulose 90, Microcrystalline Cellulose HD 90, Pyridoxal-5’-Phosphate, Opadry II Purple 40L10045 (Polydextrose, Titanium Dioxide, Hypromellose 3cP, Hypromellose 6cP, Glycerol Triacetate, Hypromellose 50cP, FD&C Blue #2, FD&C Red #40, Polyglycol 800), Microcrystalline Cellulose 50, Opadry II Clear Y-19-7483 (Hypromellose 6cP, Maltodextrin, Hypromellose 3cP, Polyglycol 400, Hypromellose 50cP), Lmethylfolate Calcium, Magnesium Stearate, Methylcobalamin, and Carnauba Wax.

Which Methylfolate to use for MTHFR?

Quality forms of Methylfolate
- L-5-MTHF (L is important to avoid racemic R forms)
- Quatrefolic (glucosamine form)
- Metafolin (calcium form)
- L-Methylfolate
- (6S)-5-Methylfolate

Issues to Understand about Methylfolate
1. Maximum of 1,000 mcg of L-Methylfolate may be used solo
2. Maximum of 800 mcg of L-Methylfolate may be used in a formula
3. If no ‘L’ or (6S) or Quatrefolic or Metafolin is used on the label, avoid it!

Source: http://mthfr.net/l-methylfolate-methylfolate-5-mthf/2012/04/05/
Which Supplements to use for MTHFR and Methylation?

Main Support Nutrients for MTHFR

- L-Methylfolate (good forms)
- Sublingual Methylcobalamin, Adenosylcobalamin and/or Hydroxycobalamin
- Vitamin E
- Choline
- Krill Oil
- Fish Oil
- Silymarin
- Selenium
- Zinc
- NAC, MSM, SAMe, Methionine, Inositol, TMG, CoQ10, Alpha Lipoic Acid, L-Carnitine, Ribose
- Glutathione
- Probiotics (strong – consider GAPS compliant)
- Multivitamin with minerals and complete B’s (if patient can handle it)
- Vitamin D3
- Vitamin C
- Niacin
- Electrolytes
- Magnesium
- Adaptogens (Ashwagandha)
- Digestive Repair
- Potassium

Source: http://mthfr.net/l-methylfolate-methylfolate-5-mthf/2012/04/05/
Common Side Effects with Methylfolate

**Side Effects / Signs to Look For When Starting Methylfolate Meds or Supplements**

- Muscle Pain
- Irritability
- Anxiety
- Depression
- Joint Pain
- Nausea
- Headache
- Insomnia
- Seizures
- Vomiting
- Stomach Pain
- Sweating
- ‘Herxheimer Reaction’
- Rash
- Hypokalemia
- Palpitations

Source: [http://mthfr.net/methylfolate-side-effects/2012/03/01/](http://mthfr.net/methylfolate-side-effects/2012/03/01/)
Dealing with Side Effects from Methylfolate

Neutralize Side Effects from Methylfolate ASAP
There are two things to quickly quench most of the methylfolate side effects:

1. Consider 50 to 100 mg of nicotinic acid every 30 minutes to 1 hour.
   - Why? Niacin is broken down through methylation – by SAMe. This means that excessive methylation is quenched by taking niacin. Niacin also helps break down glutamate and therefore increase GABA.
   
   **NOTE of CAUTION**: One may experience flushing for 20 to 30 minutes. This is not harmful and is a result of histamine release. Since likely overmethylated, the histamine flush will likely be minimal.

2. Consider 250 mg of liposomal curcumin to help quench inflammation. If one takes methylfolate before inflammation is controlled, the methylfolate may worsen it.

3. Lowered potassium levels. Why? Increased folate increases DNA production which requires higher K+ demand.

   Use Potassium Chloride powder or Potassium Citrate. Consider 700 mg twice daily or as needed. Safest is supplementing with high potassium foods (apricots, avocados, dates, carrot juice, almonds, baked beans, lima beans, potatoes).

Zero Tolerance to Methylcobalamin or Methylfolate?

**Zero Tolerance to Methylfolate?**

*Not ready to take it yet. Stop.*
- Heal the gut
- Change diet
- Do foundational steps first
- Check for H Pylori
- Consider further genetic testing for: COMT, CBS, MAO A
- Do lab testing as mentioned in Slide 26

**Zero Tolerance to Methylcobalamin?**

- Switch to Hydroxycobalamin – start low and work up.
- Heal the gut
- Change diet
- Do foundational steps first
- Check for H Pylori
- Test for Transcobalamin Deficiency (Vitamin B12 Unsaturated Binding Capacity)
- Consider further genetic testing for: COMT, CBS, MAO A
- Do lab testing as mentioned in Slide 26
Zero Tolerance to Methylcobalamin and/or Methylfolate?

MethylB12 and Methylfolate combined support SAM levels.

High SAM levels increase transulfuration (CBS activity) ~ 5 fold which reduces the transmethylation cycle thus depleting methylation production.

This leads to imbalanced SAM:SAH ratio which induces DNA methylation problems.

Combined with CBS 699 – even worse.

High Dose Folic Acid Affects SAM:SAH Ratio

“Exposure of normal human cells to supra-physiological folic acid concentrations present in commercial cell culture media perturbs the intracellular SAM:SAH ratio and induces aberrant DNA methylation.”

Why do some people do well with Deplin or high dose L-Methylfolate?

**Genetics**
- Absence of COMT and MAO A
- Absence of CBS
- Likely more than one MTHFR mutation

**Methylfolate Receptor Binding Inadequate**
- Presence of Cerebral Folate Antibodies\(^1\)
- Stopping Dairy Intake Reduces Cerebral Folate Antibodies\(^2\)
- Test for Cerebral Folate Antibodies $100 + shipping
  - Edward V. Quadros, Ph.D. Edward.Quadros@downstate.edu
  - Research Professor, (BSB 7-15)
  - Departments of Medicine/Cell Biology/Biochemistry
  - SUNY-Downstate Medical Center
  - 450 Clarkson Avenue
  - Brooklyn, NY 11203
  - Ph: 718-270-4203
  - FAX: 718-270-3316

2) [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2715943/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2715943/)
Why do some people do well with Deplin or high dose L-Methylfolate? (cont’d)

Multifaceted Approach Not Done

- Demand for Methylation is very high
  - Poor Diet and Lifestyle – not improved
  - Digestive Dysfunction – not repaired
  - Poor Absorption
Functional Lab Testing

- Biopterin and Neopterin (Metametrix)
- Transcobalamin aka Vitamin B12 Unsaturated Binding Capacity (Quest)
- UMFA (Metametrix)
- Folinic Acid (Vitamin Diagnostics)
- 5-MTHF (Metametrix)
- Ammonia (any)
- Amino Acids (Doctor’s Data 24 hr urine – longer term measure vs blood)
- Glutathione – reduced and oxidized (Vitamin Diagnostics)
- SAM (Doctors Data)
- SAH (Doctors Data)
- Homocysteine (Doctors Data, Quest)
- Urea Breath Test (Metsol)
- CDSA (Doctor’s Data)
- Minerals – zinc, copper, molybdenum, selenium, magnesium, calcium
- Pyroluria
- CBC with Chem Panel (noting potassium)
- ApoA1 and IFN gamma
# Methylation Profile; plasma

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<tr>
<th>PRIMARY &amp; INTERMEDIATE METABOLITES</th>
<th>RESULT/UNIT</th>
<th>REFERENCE INTERVAL</th>
<th>2.5&lt;sup&gt;th&lt;/sup&gt;</th>
<th>16&lt;sup&gt;th&lt;/sup&gt;</th>
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<tr>
<td>Cysteine</td>
<td>22 µmol/dL</td>
<td>21 - 38</td>
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<td>S-adenosylmethionine (SAM)</td>
<td>90 nmol/L</td>
<td>86 - 150</td>
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<tr>
<td>S-adenosylhomocysteine (SAH)</td>
<td>32 nmol/L</td>
<td>10 - 25</td>
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<td>Homocysteine</td>
<td>9 µmol/L</td>
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<td>Cystathionine</td>
<td>&lt;dl µmol/dL</td>
<td>&lt; 0.05</td>
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## Methylation Index

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<th>RESULT</th>
<th>REFERENCE INTERVAL</th>
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<tr>
<td>SAM : SAH</td>
<td>2.8</td>
<td>&gt; 4</td>
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Homocysteine Lab Test Preparation (SAH is better…)

Get Accurate Homocysteine Levels

- Do not do Home Homocysteine Tests!
- High Methionine Foods can falsely elevate homocysteine. Limit them day before test.
- Fast 12 hours prior to having blood drawn
- Schedule blood draw in morning
- Get blood drawn
- Lab Tech must spin out red blood cells immediately to prevent false elevation of homocysteine
- If not spinning down immediately, then must put blood on ice until centrifuged – then spin out RBC later.
- Send sample by overnight mail to lab
- Retest in 6 weeks

Source: [http://mthfr.net/elevated-homocysteine-level-or-laboratory-error/2012/03/02/](http://mthfr.net/elevated-homocysteine-level-or-laboratory-error/2012/03/02/)
List of Don’ts

**Avoid Doing These!**

- Prescribing high dose methylfolate without tapering up
  - Massive side effect potential or hospitalization

- Giving methylfolate first instead of methylcobalamin (or hydroxycobalamin)
  - Methyl-trapping potential

- Being aggressive (can overdrive methylation causing symptoms)
  - Prescribing multiple supplements starting the same day
  - Performing potent therapies such as coffee enemas, sauna, epsom salt baths without foundational work in place

- Guessing after foundational work is done
  - Working without laboratory testing

- Blame everything on MTHFR (especially in recurrent miscarriage)
  - Patients (and docs) ready to blame all symptoms and signs on MTHFR yet may be totally unrelated.

- Measuring Homocysteine to provide a ‘therapeutic guide post’
  - Totally inaccurate marker as there are other routes to reduce levels
List of Don’ts (continued)

• Using high dose Folic Acid
  ❖ The standard of 4 mg of folic acid for recurrent miscarriage (or any condition) is dated.
  ❖ Risks increasing UMFA which does two things:
    ❖ Reduces NK cells
    ❖ May Inhibit MTHFR

• Using Lab Tests to Identify Every Problem and Solution
  ❖ Take a VERY thorough history
  ❖ Lifestyle and Dietary habits play a HUGE role here

• Telling patients to take their methylation supplements every day – and in the same amounts
  ❖ They will need to ‘listen’ to how they are feeling so they know if they should supplement or not
  ❖ Supplement yourself daily to see how you feel so you understand how your patients will feel.

• Long Duration Between Follow Up Visits
  ❖ Working with methylation provides RAPID changes.
  ❖ Encourage your patients to check in regularly with how they are feeling: good or bad and adjust quickly

• Thinking that More Methylation is Better than Some
  ❖ Too much of anything is bad – including methylation. Balance it.
List of Don’ts (continued)

- Using high dose Niacin daily
  - Use PRN in small doses
  - Depletes SAMe
  - Upregulates COMT
    - Reduces Dopamine, Serotonin, Norepi and Epi
  - Don’t use it to lower cholesterol. Plenty of other tools.
    - Address the cause

- Using Specific Amino Acid Therapy
  - Try to avoid using targeted amino acids: eg. GABA, Tyrosine, Glycine
  - Can Swing Moods Radically
  - If diet optimized along with absorption, neurotransmitters will balance with needed nutrients:
    - Mg, Zinc, Methylcobalamin, Vitamin C, Methylfolate, P5P, Niacin

- Following Lab Recommendations Precisely
  - Labs use common ‘average’ recommendations
  - Labs are not perfect – have errors
  - Samples not obtained properly – fasting? Foods alter values? Supplements alter values?
  - Start low and work up and use your judgement – not what is on the paper
“....data are consistent for Mexico and northern China, which not only have a very high frequency of the TT genotype but also high rates of neural tube defect.”

“...In the United States, the rates of neural tube defects historically have been higher among Hispanics, intermediate among non-Hispanic whites, and lower among African-Americans, a trend that follows the relative frequency of the TT homozygous genotype.”

There are, however, notable exceptions.

“In southern Italy, the TT genotype is common, but the rate of neural tube defects is not particularly high. Nevertheless, such exceptions are not entirely unexpected, because environmental and nutritional factors are likely to modulate considerably the genetic risk.”
Overall Picture

**Lifestyle, Diet, Genetics and Supplementation**

Treating disease and dysfunction from all angles is a must.

Leaving one aspect out = ineffective treatment outcomes

**Lot to Learn Still**

Nutrigenomics is a new field and biochemistry is constantly evolving – as are laboratory tests.

Keep researching and staying as current as possible.
Thank You
Tongue Tie Care

**Pre-Op**
1. No nitrous oxide
2. Arnica 30C
3. Rescue Remedy
4. Calm Forte for Kids

**Post-Op**
1. Arnica 30C
2. Rescue Remedy
3. Breastfeed
4. Thiosinaminum 30C
5. Silicea 30C
6. Centella asiatica

Jennifer Tow, IBCLC has a full pre-op and post-op protocol. These are some other suggestions to consider.