The Great Plains Laboratory, LLC

CLIENT #:

Test requisition #
ORDER:
CLIENT REF:
PATIENT:
ID:
SEX:
AGE: DOB:

DNA Methylation Pathway Profile; Buccal Swab

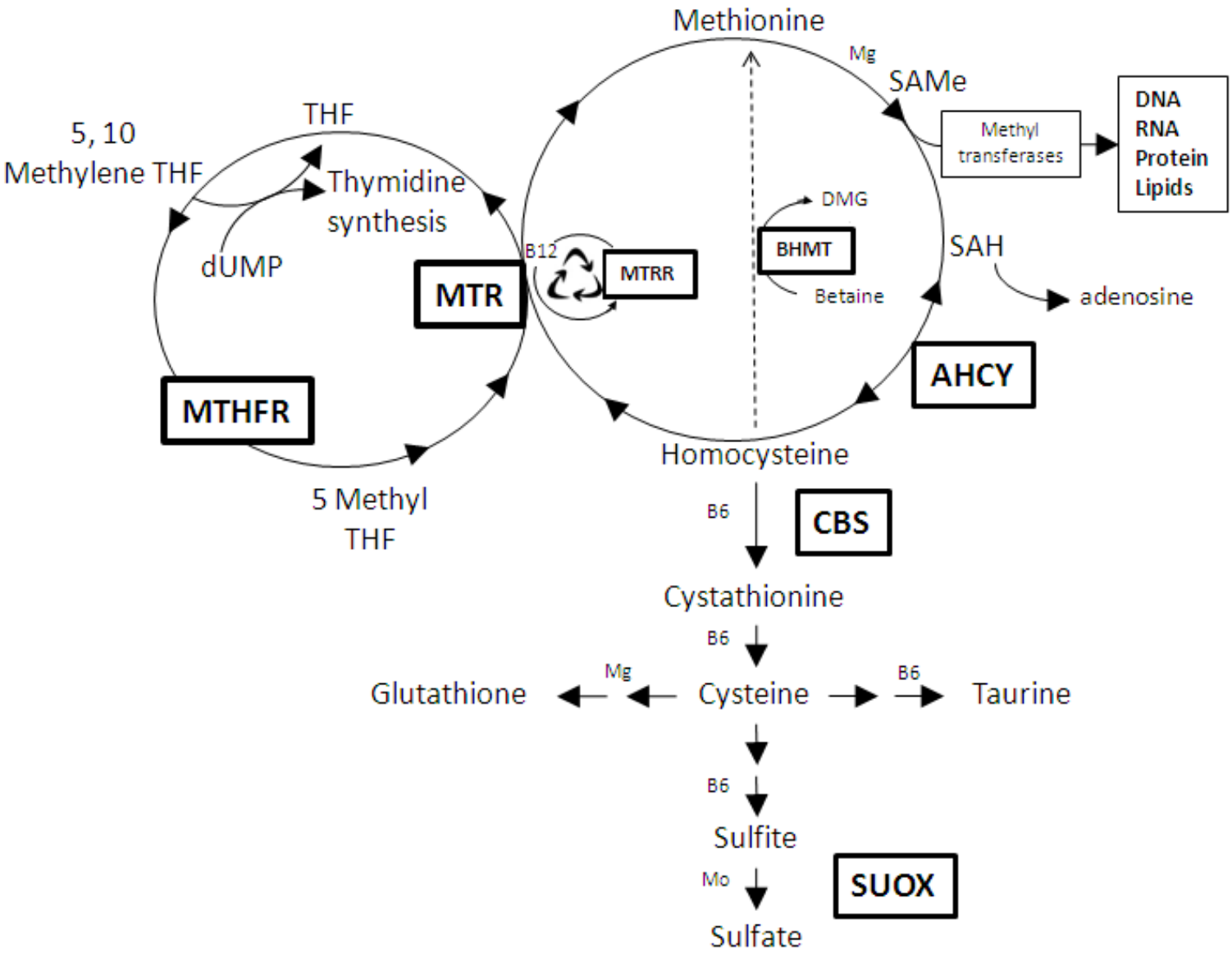
GENE NAME / VARIATION	MUTATION NOT PRESENT	MUTATION(S) PRESENT	CALL
SHMT/C1420T		+/-	Hetero
AHCY/1	-/-		A
AHCY/2	-/-		T
AHCY/19	-/-		A
MTHFR/C677T		+/-	Hetero
MTHFR/A1298C	-/-		A
MTHFR/3	-/-		C
MTR/A2756G		+/-	Hetero
MTRR/A66G		+/+	G
MTRR/H595Y	-/-		C
MTRR/K350A	-/-		A
MTRR/R415T	-/-		C
MTRR/S257T	-/-		T
MTRR/11	-/-		G
BHMT/1		+/-	Hetero
BHMT/2	-/-		C
BHMT/4	-/-		A
BHMT/8	-/-		C
CBS/C699T		+/+	T
CBS/A360A		+/-	Hetero
CBS/N212N	-/-		C
COMT/V158M	-/-		G
COMT/H62H	-/-		C
COMT/61	-/-		G
SUOX/S370S	-/-		C
VDR/Taq1	-/-		C
VDR/Fok1	-/-		C
MAOA		+/+	T
NOS/D298E	-/-		G
ACAT/1-02	-/-		G

Minus "-" represents no mutation
Plus "+" represents a mutation
"-/-" indicates there is no mutation
"+/-" indicates there is one mutation
"+/+" indicates there is a double mutation

SPECIMEN DATA

Comments:
Date Collected: 05/14/2022
Date Received: 05/15/2022
Date Reported: 05/25/2022
Methodology: Real-time PCR technology for genotyping

Methionine Metabolism Transmethylation & Transsulfuration Diagram



Introduction

Single nucleotide polymorphisms (SNPs) are DNA sequence variations, which may occur frequently in the population (at least one percent of the population.) They are different from disease mutations, which are very rare. Huntington's disease is an example of a disease mutation- if you inherit the altered gene, the disease will develop. Certain SNPs may be associated with particular health conditions, but they are not known to cause disease. The majority of SNPs in this report affect protein, enzyme or cell receptor structure or function. Some SNPs may have modest and subtle but true biological effects and have been correlated with health concerns or disease risk. Their abundance in the human genome as well as their higher frequencies in the human population have made them targets to help explain variation in risk of common diseases. Often multiple SNPs need to be present to alter metabolic or biochemical functions in the body. SNPs and gene expression may often be modified by epigenetic factors (diet, lifestyle, nutrition, toxicant exposures). The influence of a single SNP may vary widely: for example, a specific SNP in MTHFR may influence enzyme function from 30-60%. In contrast, the SNP with the greatest known effect on human height only accounts for 0.04 percent of height variations.

Individuals are classified as homozygous (+/+) for the variant if they carry 2 mutated alleles, heterozygous (+/-) if they carry only one mutated allele, and homozygous (-/-) for the wild type gene if they have no mutant alleles. This panel of SNPs provides information about many facets of health and wellness, with an emphasis on important biochemical processes such as methionine metabolism (see diagram on the preceding page), detoxification, hormone and neurotransmitter balance, and Vitamin D function.

It is emphasized that SNPs are not imminently associated with abnormal metabolism or disease conditions. The presence or absence of a reported SNP is not the sole determinant of physiological function; it is simply one potential contributing factor. The results presented in this report should be interpreted in context with symptoms, epigenetic factors and other laboratory findings.

SHMT/ C1420T (Serine hydroxymethyltransferase)

Pathways/biochemistry

Serine hydroxymethyltransferase (SHMT) catalyzes the inter-conversion of serine and glycine, which has a role in neurotransmitter synthesis and metabolism and, moderates the activity of S-adenosyl methionine (SAM) synthesis. SHMT converts tetrahydrofolate into 5,10-methylene tetrahydrofolate. Folate-dependent one-carbon metabolism is critical for the synthesis of numerous cellular constituents required for cell growth, and SHMT is central to this process. Vitamin B-6 is an obligatory cofactor for SHMT activity.

Possible Health Implications

SHMT polymorphisms may disrupt cellular function leading to increased DNA damage, alterations in folate distribution for methylation reactions (inhibition of methylation), and competition with MTHFR. When

combined with MTHFR SNPs, SHMT SNPs may be associated with elevated plasma homocysteine which increases risk for cardiovascular disease, stroke, vascular dementia, and Alzheimer's disease; these cumulative effects are dependent on B-vitamin and folate status.

The maternal risk for Down's Syndrome is also altered with the SHMT mutation; the CC genotype is protective.

SHMT C1420 T genotypes may generally be considered protective for cancers, however the homozygous (TT) genotype may increase risk for colorectal cancers in cases of folate deficiency. The cancer protective effects of CT/TT genotypes may prove to be folate-dependent; research is ongoing. There is evidence that both SHMT/ C1420T and MTRR/ A66G polymorphisms
may decrease risk for autism.

In general, homozygotes are more influenced by SNPs than heterozygotes.

How to optimize the phenotype

Ensure adequate B-12, folate, betaine and B-6 to support methylation pathways. Monitor homocysteine levels and methylation pathways. Minimize cancer risks through lifestyle interventions.

References

Bailey, Lynn B. Ed. (15 June 2009) Folate in Health and Disease, Second Edition. CRC Press.
Hebbring, Scott J. et al. (2012) Serine hydroxymethyltransferase 1 and 2: gene sequence variation and functional genomic characterization. J Neurochem 120(6):881-90, PMID 22220685. Accessed 11/06/2012
http://pubget.com/paper/22220685/Serine_hydroxymethyltransferase_1_and_2__gene_sequence_variation_and_functional_genomic_characterization
Herbig K, Chiang EP, Lee LR, Hills J, Shane B, Stover PJ. (2002 Oct 11) Cytoplasmic serine hydroxymethyltransferase mediates competition between folate-dependent deoxyribonucleotide and S-adenosylmethionine biosyntheses. J Biol Chem.;277(41):38381-9. Accessed 11/05/2012
http://www.ncbi.nlm.nih.gov/pubmed/12161434
Marucci , GH. et al. (2012) Polymorphism C1420T of Serine hydroxymethyltransferase gene on maternal risk for Down syndrome. Mol Biol Rep. Mar;39(3):2561-6. Accessed 11/05/2012
http://www.ncbi.nlm.nih.gov/pubmed/21687976
Mohammad NS, Jain JM, Chintakindi KP, Singh RP, Naik U, Akella RR. (2009) Aberrations in folate metabolic pathway and altered susceptibility to autism. Psychiatr Genet. Aug;19(4):171-6. Accessed 11/06/2012 http://www.ncbi.nlm.nih.gov/pubmed/19440165
Sousa Guerreiro, Catarina et al. (2008) Risk of colorectal cancer associated with the C677T polymorphism in 5,10-methylenetetrahydrofolate reductase in Portuguese patients depends on the intake of methyl-donor nutrients. Am J Clin Nutr November vol. 88 no. 5 1413-1418. Accessed 11/05/2012
http://ajcn.nutrition.org/content/88/5/1413.full
OMIM Online Mendelian Inheritance in Man. SHMT http://omim.org/ Accessed 16 July 2013

MTHFR A1298C, C677T, 3

Pathways/biochemistry

Methylenetetrahydrofolate reductase (MTHFR) catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a co-substrate for remethylation of homocysteine to methionine. MTHFR helps pull homocysteine into the methionine synthesis cycle which facilitates maintenance of normal levels of homocysteine and essential methylation. MTHFR contains a bound flavin cofactor and uses NAD(P)H as the reducing agent.

Possible Health Implications

MTHFR enzyme activities may be reduced for homozygous (approximately 65%) and heterozygous C677T individuals (approximately 40%), respectively. The extent to which MTHFR C677T activity is actually suppressed is dependent upon folate status.

Mutations in MTHFR may cause MTHFR deficiency (an autosomal reccessive disorder) with a wide range of features including homocysteinuria, homocystinuria, developmental delay, severe mental retardation, peri-natal death, psychiatric disturbances, and later-onset neurodegenerative disorders. Elevated levels of homocysteine can result in excess formation of S-adenosyl homocysteine (SAH) which is a very potent inhibitor of methyl transferase enzymes that are involved in methylation of DNA, RNA, neurotransmitters, phospholipids and other important molecules.

Mutations in MTHFR may increase risk of ischemic stroke, cardiovascular disease and folate-sensitive neural tube defects. There is accumulating evidence that C677T may be an independent risk factor for hypertension.

MTHFR/677 CT/TT genotypes are more frequently associated with symptoms of Autism Spectrum Disorder (ASD); the effect may be cumulative with MTHFR/A1298C polymorphism. There is growing evidence that the MTHFR/A1298C homozygous mutation may be a genetic risk factor for male infertility. Studies indicate that hyperhomocysteinemia and the TT genotype may contribute to mood disorders.

Genotypic/Phenotypic expression

The C677T homozygous mutation is associated with decreased MTHFR activity and mild hyperhomocysteinemia, especially in the absence of adequate intake of folate. Low folate intake affects individuals with the 677TT genotype to a greater extent than those with the 677CC/CT genotypes. Those with coronary artery disease (about 17%), arterial disease (about 19%) and venous thromboembolism (about 11%) are more likely to carry the C677T homozygous (TT) mutation. MTHFR mutations in conjunction with genetic thrombophillic factors markedly increases risk for venous thrombosis.

The A1298C mutation is not associated with hyperhomocysteinemia, unless present in conjunction with the C667T mutation. The cumulative effect of the two mutations has been associated with decreased MTHFR activity and hyperhomocysteinemia. SHMT/ C1420T (homozygous) with MTHFR C677T polymorphysisms may have a cumulative effect on increased cardiovascular risk, and increased homocysteine levels.
MTHFR may demonstrate cumulative effects with MTR, MTRR, AHCY or CBS polymorphisms.
Studies indicate that MTHFR C677T may interact with environment and lifestyle to influence age of menarche and menopause for women.

There is mounting evidence that, especially within the folate and methylation pathways, multiple SNPs in multiple genes (haplotypes) may be necessary to alter metabolism or change health outcomes. In general, homozygotes are more influenced by SNPs than heterozygotes.

How to optimize the phenotype

Support methylation pathways and methionine metabolism with adequate B-12 (methyl B-12), folate (5-methylTHF), betaine and B vitamins (B-6, riboflavin). Monitor methionine metabolism and the Methylation index (DDI Methylation Profile).

References

www.uniprot.org [Accessed 10/31/2012]
Sibani S et al. Characterization of six novel mutations in the methylenetetrahydrofolate reductase (MTHFR) gene in patients with homocystinuria.Hum. Mutat. 15:280-287(2000
Kluijtmans L et al. Identification of four novel mutations in severe methylenetetrahydrofolate reductase deficiency. Eur. J. Hum. Genet. 6:257-265(1998)
Goyette P et al. Severe and mild mutations in cis for the methylenetetrahydrofolate reductase (MTHFR) gene, and description of five novel mutations in MTHFR."
Am. J. Hum. Genet. 59:1268-1275(1996).
Goyette P et al. Seven novel mutations in the methylenetetrahydrofolate reductase gene and genotype/phenotype correlations in severe methylenetetrahydrofolate reductase deficiency. Am. J. Hum. Genet. 56:1052-1059(1995).
Arruda V et al. (1997). The mutation Ala677-->Val in the methylene tetrahydrofolate reductase gene: a risk factorfor arterial disease and venous thrombosis. Thromb Haemost 77: 818-821.
Cattaneo M. (1999). Hyperhomocysteinemia, atherosclerosis and thrombosis. Thromb Haemost 81:165-176.
Frosst P et al. (1995). A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nat Genet 10:111-113.
Jacques P et al. (1996). Relation between folate status, a common mutation in methylenetetrahydrofolate reductase,and plasma homocysteine concentrations. Circulation 93:7-9.
van der Put NM et al. (1998) A second common mutation in the methylenetetrahydrofolate reductase gene: an additional risk factor for neural-tube defects(c) Am J Hum Genet 62:1044-1051.
Szczeklik A et al. (2001). Mutation A1298C of methylenetetrahydrofolate reductase: risk for early coronary disease not associated with hyperhomocysteinemia. Am J Med Genet 101:36-39.
Eloualid, Abdemajid, et al. (2012) Association of the MTHFR A1298C Variant with Unexplained Severe Male Infertility. PLoS One. 2012; 7(3): e34111. Published online 2012 March 23. doi: 10.1371/journal.pone.0034111 . Accessed 12/12/12
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3311580/
OMIM Online Mendelian Inheritance in Man. MTHFR http://omim.org/ Accessed 16 July 2013

MTR/A2756G (methionine synthase)

Pathways/biochemistry

Methionine synthase (MTR) catalyzes the re-methylation of homocystiene to methionine utilizing methylcobalamin (methyl B-12) as a cofactor. Important in folate metabolism, MTR maintains intracellular levels of methionine which is the precursor to S-adenosylmethionine (SAM). SAM is a vital methyl group donor involved in hundreds of methylation reactions, including methylation of DNA. Studies indicate that methionine synthase reductase (MTRR) may be required as a molecular chaperone for proper MTR function.

Possible Health Implications

Under- or over-methylation of the DNA for tumor suppressor or promoter genes may contribute to the selective growth or transformation of cells. Approximately 50% of cancer cells types are methionine dependent; low MTR function, while increasing plasma homocysteine levels, would decrease available methionine; this may influence cancer risk and tumor growth.

The MTR/A2756G polymorphism has been associated with increased maternal risk of neural tube defect; the risk increases with the number of high-risk alleles, and may be cumulative with MTHFR polymorphisms. The risk of hyperhomocysteinuria is also increased. A plasma homocysteine level greater than 14 ìmol/L is associated with increased risk of Alzheimer's disease.

MTR/A2576G is associated with male infertility and, it is more prevalent in patients with Celiac Disease. The SNP is generally cancer-protective (GI tract, lymphomas), and may be protective against dementia in the AG or GG genotypes; this protection may be population-specific to those of European descent and the reverse may be true of Asian populations. The AG/GG phenotype is associated with folate-deficient hypertension in Chinese males and, with increased risk of Inflammatory Bowel Disease in Asians.

Genotypic/Phenotypic expression

There is mounting evidence that, especially within the folate and methylation pathways, multiple SNPs in multiple genes (haplotypes) and/or low folate or B-vitamin status are necessary to alter metabolism or change health outcomes. MTR may have cumulative effects with MTHFR/C677T, MTRR/A66G, AHCY or CBS polymorphisms.

In general, homozygotes are more influenced by SNPs than heterozygotes.

How to optimize the phenotype

Provide adequate B-12 (or methylcobalamin) and nutritional support for methylation pathways. Minimize cancer risks with lifestyle interventions.

References

Yu, Ke et al. (2010) Methionine synthase A2756G polymorphism and cancer risk: a meta-analysis. Eur J Hum Genet. 2010 March; 18(3): 370-378. Accessed 11/08/2012 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2987221/
Genetics Home Reference. MTR. Accessed 11/09/2012 http://ghr.nlm.nih.gov/gene/MTR
Chen, Min et al. (2008) Methionine synthase A2756G polymorphism may predict ulcerative colitis and methylenetetrahydrofolate reductase C677T pancolitis, in Central China. BMC Med Genet. 2008; 9: 78. Accessed 11/08/2012 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2533647/
Villanueva, J.A.; Halstead, C.H. (2004) Hepatic transmethylation reactions in micropigs with alcoholic liver disease. Hepatology (2004).
Lee, Han-Chul, et al. (2006) Association study of four polymorphisms in three folate-related enzyme genes with non-obstructive male infertility. Hum. Reprod. 21 (12): 3162-3170. doi: 10.1093/humrep/del280. Accessed 11/12/2012 http://onlinelibrary.wiley.com/doi/10.1002/hep.20168/full http://humrep.oxfordjournals.org/content/21/12/3162.long
De Lim, E.L. et al. (2010) MTR polymorphic variant A2756G and retinoblastoma risk in Brazilian children. Pediatr Blood Cancer. 2010 Jul 1;54(7):904-8. Accessed 11/08/2012 http://www.wikigenes.org/e/ref/e/15122759.htmlhttp://www.ncbi.nlm.nih.gov/pubmed/20310006
Niclot, Sidonie et al. (2006) Implication of the folate-methionine metabolism pathways in susceptibility to follicular lymphomas. Blood July 1, 2006 vol. 108 no. 1 278-285. Accessed 11/09/2012

http://bloodjournal.hematologylibrary.org/content/108/1/278.short
Bosco, P. et al. (2004) Association of IL-1 RN*2 allele and methionine synthase 2756 AA genotype with dementia severity of sporadic Alzheimer's disease. J Neurol Neurosurg Psychiatry 2004;75:1036-1038 doi:10.1136/jnnp.2003.025866. Accessed 11/08/2012 http://jnnp.bmj.com/content/75/7/1036.short
Hozyasz KK, Mostowska A, Szaflarska-Poplawska A, Lianeri M, Jagodzinski PP. (2012) Polymorphic variants of genes involved in homocysteine metabolism in celiac disease. Mol Biol Rep. Mar;39(3):3123-30. Epub 2011 Jun 19 Accessed 11/09/2012 http://www.ncbi.nlm.nih.gov/pubmed/21688148(c)dopt=Abstract
Qin, Xianhui et al. (2012) MTHFR C677T and MTR A2756G polymorphisms and the homocysteine lowering efficacy of different doses of folic acid in hypertensive Chinese adults. Nutrition Journal 2012, 11:2 doi:10.1186/1475-2891-11-2. Accessed 11/08/2012 http://www.nutritionj.com/content/11/1/2
Shi Q, Zhang Z, Li G, Pillow PC, Hernandez LM, Spitz MR, Wei Q. (2005) Polymorphisms of methionine synthase and methionine synthase reductase and risk of lung cancer: a case-control analysis. Pharmacogenet Genomics. Aug;15(8):547-55. Accessed 11/08/2012 http://www.ncbi.nlm.nih.gov/pubmed/16006998
Doolin, Marie-Therese; Barbaux, Sandrine; Maeve; Hoess, Katy; Whitehead, Alexander S. and Mitchell, Laura E. (2002) Maternal Genetic Effects, Exerted by Genes Involved in Homocysteine Remethylation, Influence the Risk of Spina Bifida. Am J Hum Genet. 2002 November; 71(5): 1222-1226 Accessed 11/08/2012 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC385102/
http://www.uniprot.org/uniprot/Q99707 METH_HUMAN. Accessed 11/09/2012
OMIM Online Mendelian Inheritance in Man. MTR http://omim.org/ Accessed 16 July 2013

MTRR A66G/H595Y/K350A/R415T/S257T/11 (methionine synthase reductase)

Pathways/biochemistry

Methionine synthase reductase (MTRR) is one of two enzymes involved in the regeneration of methionine (with MTR) from homocysteine. MTRR regenerates methionine synthase (MTR) via a reductive methylation reaction that uses S-adenosylmethionine (donor) and NADPH. MTRR supports methionine synthase (MTR) activity by "recycling" vitamin B-12. Studies indicate that MTRR may also be required as a molecular chaperone for proper methionine synthase (MTR) function.

Possible Health Implications

MTRR/A66G produces an MTRR enzyme with a lower affinity for MTR and some studies have found it to be associated with homocysteine levels; further studies have shown that MTR requires MTRR to function properly. The 66AG/GG SNPs are also associated with increased micronucleation, a marker for chromosome damage and developmental delays.

MTRR/66 AA is considered a risk factor for folate-related neural tube defects and increased risk of Down's syndrome, specifically as a maternal risk factor when homocystiene levels are high.
MTRR/66 AA is associated with a higher rate of micronucleation, a marker for cell damage and developmental delays. The rate of micronucleation increases with a history of smoking.
MTRR/66 AA is more frequently associated with symptoms of Autism Spectrum Disorder(ASD).

MTRR/66GG is associated with male infertility (as are MTHFR and MTR).
Polymorphisms in MTRR- /66/AG/GG and /H595Y-have been associated with the risk of cancers (breast, colon, prostate, pancreatic); the 66GG SNP appears to reduce the risk of acute lymphoblastic leukemia and,

Alzheimer disease.

MTRR/66 AG/GG is associated with an increased risk of gastric cancers -this association is currently only documented for Asian populations (Korean); the risk increases further with obesity.
MTRR/A66G polymorphism may reduce risk for autism.

There is mounting evidence that, especially within the folate and methylation pathways, multiple SNPs in multiple genes (haplotypes) and low folate or B-vitamin status are necessary to alter metabolism or change health outcomes. MTRR polymorphisms may have cumulative effects with MTHFR/C677T, MTR, AHCY or CBS polymorphisms.

The clinical significance of MTRR polymorphisms /K350A/, R415T, /S257T, and /11 is currently unknown; research is ongoing.

In general, homozygotes are more influenced by SNPs than heterozygotes.

How to optimize the phenotype

Provide adequate B-12, folate and nutritional support for methylation pathways. Hydroxycobalamin may be the preferred form of B-12 for this SNP. Minimize cancer risks with lifestyle interventions.

References

http://www.uniprot.org/uniprot/Q9UBK8 MTRR_HUMAN. Accessed 11/09/2012
Yoo, Jae-Youg, et al. (2012) Association Study between Folate Pathway Gene Single Nucleotide Polymorphisms and Gastric Cancer in Koreans. Genomics Inform. Sep;10(3):184-193. Accessed 11/09/2012 http://synapse.koreamed.org/search.php(c)where=aview&id=10.5808/GI.2012.10.3.184&code=0117GNI&vmode=FULL
Dutta, S. et al. (2011) Importance of gene variants and co-factors of folate metabolic pathway in the etiology of idiopathic intellectual disability. Nutr Neurosci. Sep;14(5):202-9. Accessed 11/12/2012 http://carcin.oxfordjournals.org/content/28/3/625.abstract
Lee, Han-Chul, et al. (2006) Association study of four polymorphisms in three folate-related enzyme genes with non-obstructive male infertility. Hum. Reprod. 21 (12): 3162-3170. doi: 10.1093/humrep/del280. Accessed 11/12/2012 http://humrep.oxfordjournals.org/content/21/12/3162.long
Gemmati D. et al. (2004) Common gene polymorphisms in the metabolic folate and methylation pathway and the risk of acute lymphoblastic leukemia and non-Hodgkin's lymphoma in adults. Cancer Epidemiol Biomarkers Prev. May;13(5):787-94. Accessed 11/12/2012 http://www.ncbi.nlm.nih.gov/pubmed/15159311
Ishikawa, Hitoshi ; Ishikawa, Takashi ; Miyatsu, Yu ; Kurihara, Kazuo ; Fukao, Akira ; Yokoyama, Kazuhito. (2006) A polymorphism of the methionine synthase reductase gene increases chromosomal damage in peripheral lymphocytes in smokers. Mutation research. Fundamental and molecular mechanisms of mutagenesis. 2006, vol. 599, no1-2, pp. 135-143. Accessed 11/12/2012 http://cat.inist.fr/(c)aModele=afficheN&cpsidt=17978661
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2610366/pdf/nihms68264.pdf
http://www.uniprot.org/uniprot/Q9UBK8 MTRR_HUMAN. Accessed 11/12/2012
OMIM Online Mendelian Inheritance in Man. MTRR http://omim.org/ Accessed 16 July 2013

BHMT 1,2,3,4 (betaine-homocysteine methyltransferase)

Pathways/biochemistry

Betaine-homocysteine methyltransferase (BHMT) catalyzes the transfer of a methyl group from betaine to homocysteine to produce methionine and dimethylglycine. This is commonly referred to as the ”short route” in the regeneration of methionine from homocysteine. The ”long route”requires folate (MTHFR) and B-12 (MTR and MTRR). BHMT and its polymorphisms are involved in the regulation and metabolism of homocysteine. The BHMT pathway is folate-independent, although levels of folate, choline, and dimethyl glycine (DMG) are predictive for plasma betaine levels. DMG inhibits BHMT by product inhibition, but does not affect the BHMT2 variant. The enzyme is found almost exclusively in liver and kidney tissues; the reaction is involved in choline oxidation as well as the methylation of homocysteine. The BHMT-2 polymorphism product is rapidly degraded unless it is bound to BHMT and is stabilized by homocysteine to become a functional product. BHMT2 cannot use betaine, rather it converts homocysteine to methionine using S-methylmethionine as a methyl donor. Methionine levels regulate BHMT2 activity by product inhibition.

Possible Health Implications

BHMT and its polymorphisms are involved in the regulation and metabolism of homocysteine. BHMT has been reported to protect the liver from homocysteine-induced injury. Elevated levels of homocysteine are a known risk factor for vascular disease and neural tube defects. Elevated circulating homocysteine levels are also being studied as a possible risk factor for osteoporosis, dementia, and complications of pregnancy. Animal studies have shown BHMT2 to be protective, with adequate nutrition, against acetaminophen-induced liver toxicity.

Preliminary research indicates that BHMT1 may have some function in immune response and reactivity.

Genotypic/Phenotypic expression

Polymorphisms will likely be present with altered elevated homocysteine levels.
In general, homozygotes are more influenced by SNPs than heterozygotes.

How to optimize the phenotype

Consider the DDI Methylation Profile to assess the components of the methylation pathway. Zinc-dependent BHMT requires adequate levels of betaine to function optimally. Support the methionine synthase dependent methylation pathway (”Long route”) with adequate B-12 and folate.

References

http://www.uniprot.org/uniprot/Q93088 BHMT1_HUMAN. Accessed 10/30/2012
http://www.uniprot.org/uniprot/Q9H2M3 BHMT2_HUMAN. Accessed 11/12/2012
Feng, Qiping et al. (2011) Betaine-homocysteine methyltransferase: human liver genotype-phenotype correlation. Mol Genet Metab. February; 102(2): 126-133. Accessed 11/01/2012.
Li, Fang et al. (2008) Human Betaine-Homocysteine Methyltransferase (BHMT) and BHMT2: Common Gene Sequence Variation and Functional Characterization. Mol Genet Metab. July; 94(3): 326-335. Accessed 11/01/2012 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2515933/
Szegedi SS, Castro CC, Koutmos M, Garrow TA. (2008) Betaine-homocysteine S-

methyltransferase-2 is an S-methylmethionine-homocysteine methyltransferase. J Biol Chem. Apr 4;283(14):8939-45. Accessed 11/02/2012 http://www.ncbi.nlm.nih.gov/pubmed/18230605
Liu, Hohg-Hsing et al. (2010) An integrative genomic analysis identifies Bhmt2 as a diet-dependent genetic factor protecting against acetaminophen-induced liver toxicity. Genome Res. January; 20(1): 28-35 Accessed 11/02/2012 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2798828/
We have never put a color diagram in commentaries. This is useful but perhaps we can re-do in black and white.

CBS /C699T/A360A/N212N (Cystathionine beta-synthase)

Pathways/biochemistry

CBS catalyzes the first irreversible step of the transsulfuration pathway. CBS catalyzes the vitamin B6-dependent reaction between serine and homocysteine, producing cystathionine enroute to taurine, cysteine, sulfate and glutathione. CBS function is influenced by betaine levels via re-methylation of homocysteine.
Possible Health Implications

Some defects in CBS are responsible for homocystinuria and altered sulfur metabolism. The SNPs evaluated are found in various tissues and have different functions in the body. Mutations in CBS may alter homocysteine levels and risk for CVD; there may also be changes in cancer risks. Health implications are related to the individual SNPs.

CBS/699TT (homozygous) is significantly associated with lower fasting total homocysteine levels and is associated with a decreased risk of coronary artery disease.

CBS/A360A is associated with a reduced risk of breast cancer. Paradoxically, it may be associated with an increased risk of lung cancer - current research indicates that CBS/A360A serves as a marker for the yet-unidentified CBS SNP responsible for the increased risk.

CBS/N212N is currently under investigation for an association with Ehlers-Danlos syndrome and other collagen disorders.

Genotypic/Phenotypic expression

In general, homozygotes are more influenced by SNPs than heterozygotes.

How to optimize the phenotype

CBS function is influenced by B-6, betaine and folate status; may have cumulative effects with MTHFR

References

http://www.uniprot.org/uniprot/P35520 Cystathionine beta-synthase. Accessed 11/02/2012
Kraus, Jan P. et al. (1998) The Human Cystathionine â-Synthase (CBS) Gene: Complete Sequence, Alternative Splicing, and Polymorphisms. Genomics. Volume 52, Issue 3, 15 September 1998, Pages 312-324. Accessed 11/02/2012 http://www.sciencedirect.com/science/article/pii/S0888754398954374
Stevens, Victoria L.; McCullough, Marjorie L.; Pavluck, Alexandre L.; Talbot, Jeffrey T.; Feigelson, Heather S.; Thun, Michael J. and Calle, Eugenia E. (2007) Association of Polymorphisms in One-Carbon Metabolism Genes and Postmenopausal Breast Cancer Incidence Cancer Epidemiol Biomarkers

Prev. June 2007 16; 1140. Accessed 11/02/2012 http://cebp.aacrjournals.org/content/16/6/1140.long
D'Angelo, Armando; Mazzola, Giuseppina; Fermo, Isabella. (2003) Gene-Gene and Gene-Environment Interactions in Mild Hyperhomocysteinemia. Pathophysiol Haemost Thromb 2003/2004 33: 337-341. Accessed 11/02/2012
http://content.karger.com/produktedb/produkte.asp(c)typ=pdf&file=PHT20030335_6337
Kery, V., Poneleit, L., Meyer, J. D., Manning, M. C., Kraus, J. P.Binding of pyridoxal 5-prime-phosphate to the heme protein human cystathionine beta-synthase. Biochemistry 38: 2716-2724, 1999.
Christopher SA, Melnyk S, James SJ, Kruger WD. S-adenosylhomocysteine, but not homocysteine, is toxic to yeast lacking cystathionine beta-synthase. Mol Genet Metab. 2002 Apr;75(4):335-43.
Scott, John W. et al. (2004) CBS domains form energy-sensing modules whose binding of adenosine ligands is disrupted by disease mutations. J. Clin. Invest. 113:274-284 (2004). doi:10.1172/JCI200419874
Summers et al. (2008) Influence of the cystathionine â-synthase 844ins68 and methylenetetrahydrofolate reductase 677C>T polymorphisms on folate and homocysteine concentrations. European Journal of Human Genetics (2008) 16, 1010-1013; doi:10.1038/ejhg.2008.69; published online 9 April 2008
Anthony J. Barak, Harriet C. Beckenhauer*, Mark E. Mailliard, Kusum K. Kharbanda* and Dean J. Tumar (2003) Betaine Lowers Elevated S-Adenosylhomocysteine Levels in Hepatocytes from Ethanol-Fed Rats. J. Nutr. September 1, 2003 vol. 133 no. 9 2845-2848
Kruger, W.D. et al. (2000) Polymorphisms in the CBS gene associated with decreased risk of coronary artery disease and increased responsiveness to total homocysteine lowering by folic acid. Mol Genet Metab. May;70(1):53-60. Accessed 11/02/2012
http://www.ncbi.nlm.nih.gov/pubmed/10833331(c)dopt=Abstract

MAO A/R297R (monoamine oxidase type A)

Pathways/biochemistry

Monoamine oxidase type A (MAO A) catalyzes the oxidative deamination of biogenic, dietary and xenobiotic amines and, degrades the neurotransmitters serotonin, dopamine, epineprine, and norepinephrine. MAO A has important functions in the metabolism of neuroactive and vasoactive amines in the central nervous system and peripheral tissues. MAO enzymes also deaminate dietary amines, such as tyramine.

Possible Health Implications

MAO A preferentially oxidizes biogenic amines such as 5-hydroxytryptamine (serotonin), norepinephrine and epinephrine. Serotonin is involved with mood, and aberrant serotonin metabolism is associated with depression, aggression, anxiety, and OCD behavior. Impairment in the central dopamine pathways and metabolism has been suggested as a factor in the pathogenesis of restless legs syndrome (RLS).

Several studies indicate a genetic influence on stress-related disorders. There is evidence that a functional polymorphism in MAO A may influence adult response to childhood abuse or trauma. The association between childhood maltreatment, aggression and mental health problems is significantly stronger in males with the genotype conferring low (TT) vs. high (GG) MAOA activity. Females with childhood trauma and high MAO A (GG) activity may be more aggressive in conjunction with sad mood.

Studies indicate that the high-activity MAOA (GG) genotypes may have less severe autistic symptoms or behaviors.

Genotypic/Phenotypic expression

The G allele encodes for the higher activity form of the enzyme. GT/GG phenotypes have significantly decreased placebo responses. The effects may be cumulative with COMT H62H polymorphisms.
MAO A is inherited with the X chromosome and is considered a dependent trait; it may not show standard inheritance characteristics in males. Since the X chromosome in males can only come from the mother, there is no paternal contribution to the genotype. For females, since one X chromosome is inherited from each parent, the genetics tend to reflect the MAO A status of both parents.

How to optimize the phenotype

Monitor clinical indications of abnormal serotonin metabolism and plasma tryptophan. Individuals with genotypic variations may not respond to therapies that rely on placebo effect, and may need pharmaceutical support for mood disorders.

References

www.uniprot.org [Accessed 10/30/2012]
Kim-Cohen, J.; A Caspi, A.; A Taylor, A.; Williams, B.; Newcombe, R.; Craig, I.W.; and Moffitt, T.E. (2006) MAOA, maltreatment, and gene-environment interaction predicting children's mental health: new evidence and a meta-analysis. Molecular Psychiatry (2006) 11, 903-913. doi:10.1038/sj.mp.4001851; published online 27 June 2006. Accessed 12/10/2012
http://www.nature.com/mp/journal/v11/n10/full/4001851a.html
Tipton, K.F. (1997) Monoamine oxidase inhibitors and pressor response to dietary amines. Vopr Med Khim. 1997 Nov-Dec;43(6):494-503. Accessed 12/21/2012
http://www.ncbi.nlm.nih.gov/pubmed/9503566
Verhoeven FE, Booij L, Kruijt AW, Cerit H, Antypa N, Does W. (2012) The effects of MAOA genotype, childhood trauma, and sex on trait and state-dependent aggression. Brain Behav. 2012 Nov;2(6):806-13. doi: 10.1002/brb3.96. Epub 2012 Oct 5. Accessed 12/10/2012
http://www.ncbi.nlm.nih.gov/pubmed/23170243
Xu Z, Zhang Z, Shi Y, Pu M, Yuan Y, Zhang X, Li L. (2011) Influence and interaction of genetic polymorphisms in catecholamine neurotransmitter systems and early life stress on antidepressant drug response. J Affect Disord. 2011 Sep;133(1-2):165-73. Epub 2011 Jun 16. Accessed 12/10/2012
http://www.ncbi.nlm.nih.gov/pubmed/21680027(c)dopt=Abstract
Leuchter AF, McCracken JT, Hunter AM, Cook IA, Alpert JE. (2009) Monoamine oxidase a and catechol-o-methyltransferase functional polymorphisms and the placebo response in major depressive disorder. J Clin Psychopharmacol. 2009 Aug;29(4):372-7. Accessed 12/10/2012
http://www.ncbi.nlm.nih.gov/pubmed/19593178(c)dopt=Abstract
OMIM Online Mendilian Inheritance in Man. MOA http://www.omim.org/ accessed 16 July 2013
Cohen, I. L., Liu, X., Schutz, C., White, B. N., Jenkins, E. C., Brown, W. T., Holden, J. J. A. Association of autism severity with a monoamine oxidase A functional polymorphism. Clin. Genet. 64: 190-197, 2003.