LAB #: B000000-0000-0
PATIENT: Sample Patient
ID: PATIENT-S-00000
SEX: Female
AGE: 5

CLIENT #: 12345
DOCTOR:
Doctor's Data, Inc.
3755 Illinois Ave.
St. Charles, IL 60174, U.S.A.

DNA Methylation Pathway Profile; Buccal Cells

RESULTS

Gene Name / Variation	Mutation Not Present	Mutation(s) Present	Call
SHMT / C1420T		+/+	A
AHCY / 1	-/-		A
AHCY / 2	-/-		T
AHCY / 19	-/-		A
MTHFR / C677T	-/-		C
MTHFR / A1298C	-/-		A
MTHFR / 3	-/-		C
MTR / A2756G		+/-	Hetero
MTRR / A66G	-/-		A
MTRR / H595Y		+/-	Hetero
MTRR / K350A		+/-	Hetero
MTRR / R415T	-/-		C
MTRR / S257T	-/-		T
MTRR / 11	-/-		G
BHMT / 1	-/-		A
BHMT / 2	-/-		C
BHMT / 4		+/-	Hetero
BHMT / 8		+/+	T
CBS / C699T		+/-	Hetero
CBS / A360A		+/-	Hetero
CBS / N212N	-/-		C
COMT / V158M		+/-	Hetero
COMT / H62H		+/-	Hetero
COMT / 61	-/-		G
SUOX / S370S	-/-		C
VDR / Taq1		+/+	T
VDR / Fok1	-/-		C
MAO A / R297R		+/-	Hetero
NOS / D298E		+/-	Hetero
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

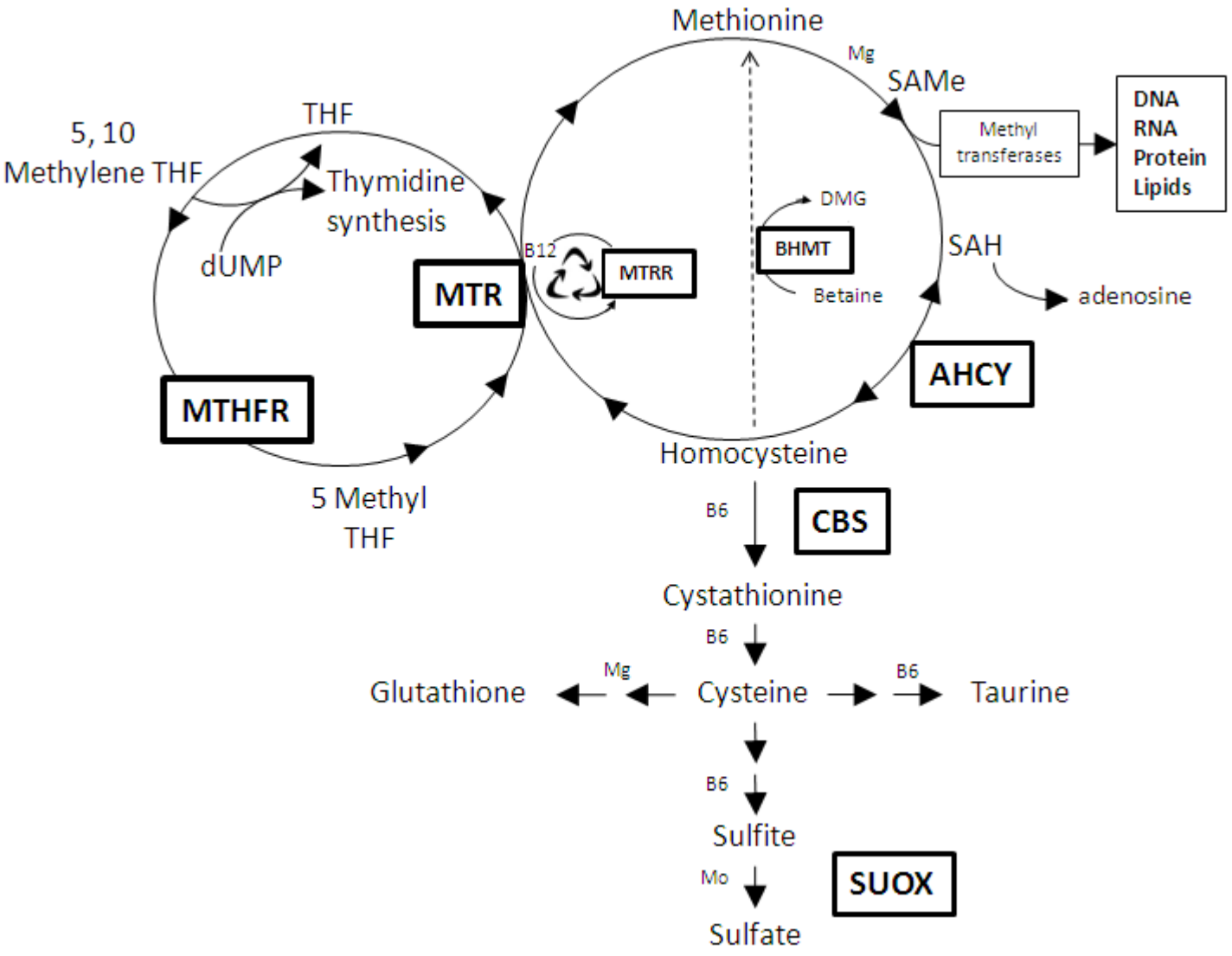
Comments:

Date Collected: **06/14/2015**
Date Received: **06/17/2015**
Date Completed: **07/03/2015**

*For Research Use Only. Not for use in diagnostic procedures.

Methodology: **MassARRAY iPLEXT platform by Sequenom**

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.

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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.

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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.

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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.

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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

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COMT V158M, H62H, 61 (catechol-O-methyltransferase)

Pathways/biochemistry

Catechol-O-methyltransferase catalyzes the transfer of a methyl group (using SAM as the methyl donor), an important step in the inactivation of biological and xenobiotic catechols.
COMT is found in nerve cells, and in the liver, kidneys and red blood cells. In the brain COMT functions to break down catecholamine neurotransmitters such as dopamine, epinephrine, and norepinephrine. In the liver, COMT helps inactivate 2- and 4-hydroxyestrodiols prior to excretion in bile.

Possible Health Implications

SNPs in COMT/ V158M/ H62H may affect neurologic processes (particularly prefrontal processing), including mood and pain tolerance. The V158M VV homozygous variant is associated with deviations in thought processes that are common in people with schizophrenia, including problems with working memory, inhibition of behavior, and attention. The V158Met polymorphism has also been associated with other

disorders that affect thought (cognition) and emotion. It is still being evaluated as a risk factor for bipolar disorder, panic disorder, anxiety, obsessive-compulsive disorder (OCD), eating disorders, and attention deficit hyperactivity disorder (ADHD).

COMT plays a key role in processes associated with the placebo effect such as reward, pain, memory and learning. The homozygous COMT /V158M (MM) has the strongest placebo response.

COMT function will affect the half-life of neurologic pharmaceuticals such as L-Dopa, alpha-methyl DOPA and isoproterenol, as well as some asthma medications and anti-hypertensives. Polymorphism of V158M in the COMT gene has been related to increased cancer risk. In the liver, COMT helps inactivate 2- and 4-hydroxyestrogens prior to excretion in bile. SNPs may affect the efficiency of COMT function; increased enzyme function may be protective against benign prostatic hypertrophy and other hormone-mediated diseases. TheV158M variant (MM) confers low COMT activity and contributes to postmenopausal breast cancer in women, particularly those with a higher body mass index.

Genotypic/Phenotypic expression

There is a decrease in enzyme function in COMT/V158M with methionine substitution, with up to a four-fold decrease in enzyme function for V158M homozygotes (MM).

In general, homozygotes are more influenced by SNPs than heterozygotes, and multiple COMT polymorphisms may increase the likelihood for adverse effects. COMT polymorphisms may have cumulative effects with MAO A polymorphisms.

How to optimize the phenotype

Adjust medication dosages to accommodate difference in enzyme functions. Minimize cancer risks through lifestyle interventions. Evaluate risks of hormone therapies with COMT/V158M genotypes prior to implementation.

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VDR /Taq 1/Fok 1 (Vitamin D receptor)

Pathways/biochemistry

The vitamin D receptor (VDR) is a nuclear receptor that binds 1,25-dihydroxy vitamin D (vitamin D), influencing gene transcription patterns in target organs. It has been estimated that the expression of as much as one third of the human genome is influenced by vitamin D. When vitamin D is bound to VDR it regulates the expression of genes involved in the regulation of bone metabolism, oxidative stress, inflammatory responses, immune function, xenobiotic detoxification and, the growth of skin and hair. The vitamin D receptor is a component of some anti-cancer properties. Lithocholic acid, a secondary bile acid that is liver-toxic and potentially carcinogenic, also binds to VDR and activates cytochrome P450 enzymes that metabolize (detoxify) the bile acid. VDR may interact with the microflora of the gastrointestinal tract (GIT); animal studies have recently shown VDR to inhibit pathogens in the GIT tract and, to moderate inflammation in the bowel. Vitamin D and VDR are directly involved in (1) T cell antigen receptor signaling, (2) modulation of the T cell antigen receptor, (3) mucosal immunity, (4) inflammation, and (5) autoimmune responses.

Animal studies (mice) indicate that elevated levels parathyroid hormone may inhibit VDR expression.

Possible Health Implications

VDR polymorphisms are associated with functional, but significantly less efficient receptors. In general, homozygotes are more influenced by SNPs than heterozygotes.

The vitamin D endocrine system is involved in a wide variety of biological processes including bone metabolism, modulation of the immune response, and regulation of cell proliferation and differentiation. Variations in this endocrine system have been linked to several common health concerns, including osteoarthritis, diabetes, cancer, cardiovascular disease, bone loss and tuberculosis susceptibility. Polymorphisms in both Fok 1 and Taq 1 may be associated with an increased risk of renal stones, as well as a decreased immune response to Mycobacterium tuberculosis infection. Occupational health studies have shown that in workers with lead exposures, VDR/Fok1 mutations are associated with increased white matter brain lesions and increased lead-induced hypertension. Research is ongoing to determine how VDR polymorphisms may affect lead deposition into bone. VDR/Fok1 is most strongly associated with the regulation of blood glucose; these polymorphisms may predispose for diabetes. Fok1 SNPs are associated with plasma rennin activity, and may increase risk of hypertension. Mutations in VDR/Fok1 may influence

the efficacy of vitamin D therapy in breast cancers. In Caucasians Fok1 polymorphisms may increase cancer risk for colorectal adenoma, prostate, skin, ovarian and breast cancers, as well as non-Hodgkin's lymphoma.

VDR/Taq1 plays a role in calcium homeostasis, osteocalcin levels and bone metabolism; it also acts to regulate the growth of skin cells and hair. The Taq1 polymorphisms affect how the receptor binds vitamin D, which affects immune function and responses. Taq1 SNPs may decrease melanoma risk.

Genotypic/Phenotypic expression

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

How to optimize phenotype

Diet and lifestyle choices (such as NSAID use and Body Mass Index) seem to influence the protective functions of Fok1 and Taq1. Monitor and support Vitamin D status. Monitor blood glucose, HbA1c and blood pressure. Assess gastrointestinal health (Comprehensive Stool Analysis) if gastrointestinal symptoms are present. Assess exposure to lead (whole blood) and chelatable lead because demineralization of bone can result in increased release of the vast bone lead stores back into circulation with uptake by "soft tissues."

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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 (immediate precursor of 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.

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ENOS (NOS3)/D298E (endothelial nitric oxide synthase)

Pathways/biochemistry

Endothelial nitric oxide synthase (ENOS/NOS3) synthesizes nitric oxide (NO) from arginine. NO mediates smooth muscle relaxation and angiogenesis and, promotes blood clotting via platelet activation. Endothelial NOS3 is calcium dependent. Cobalamin (B-12) is required for NOS regulation, and ENOS/NOS3 polymorphisms may be influenced by omega-3 fatty acid status and oxidative stress. ENOS/NOS3 serves as a substrate for other enzymes involved in glucose metabolism, apoptosis, cell proliferation, transcription and cell migration.

Possible Health Implications

There have been many studies regarding this polymorphism and a large number of controversial reports have been published. These inconsistent findings might be explained in part by the genetic and environmental differences among populations. It is also possible that ENOS/NOS3 SNPs only contribute to atherosclerosis through interactions with other genes. The NO pathway may play a role in the expression of congenital urea cycle disorders.

SNPs in both NOS3 and apolipoprotein E are associated with increased risk of atherosclerosis. When present with coronary artery disease (CAD) and hyperhomocysteinuria, the NOS3 /D298E SNP increases the severity of disease. NOS3/D289E is associated with hypertension, changes in coronary artery vasodilation, post-stroke dementia risk, increased oxidative stress (due to air particulate pollution), and increased risk of Left Ventricular Hypertrophy. In general, homozygotes are more influenced by SNPs than heterozygotes.

Tibolone, (a synthetic steroid hormone used in post-menopausal women for hormone replacement therapy), and its metabolites, has been shown to activate ENOS/NOS3 and NO synthesis.

Genotypic/Phenotypic expression

Homozygous expression may be more common in those of Asian and Caucasian descent.
In women of Japanese descent NOS3/D298E is an independent risk factor for hypertension during pregnancy. Estrogen or hormone replacements may also play a role in gene regulation and expression.

How to optimize the phenotype

Endothelial NOS is calcium dependent. Vitamin B-12 is required for NOS regulation, and NOS3/D298E polymorphisms may be influenced by poor omega-3 fatty acid status and oxidative stress. Smoking status and omega-3 fatty acid status may play a role in the phenotypic expression of the NOS polymorphism. Estrogen or hormone replacements may also play a role in gene regulation and expression.

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