MOSAIC DIAGNOSTICS
Formerly Great Plains Laboratory

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ORDER:
CLIENT REF:
PATIENT:
ID:
SEX:
AGE: DOB:

CLIENT #:

DNA Methylation Pathway Profile; Buccal Swab

GENE NAME / VARIATION	MUTATION NOT PRESENT	MUTATION(S) PRESENT	CALL
SHMT/C1420T	-/-		G
AHCY/1	-/-		A
AHCY/2	-/-		T
AHCY/19	-/-		A
MTHFR/C677T		+/-	Hetero
MTHFR/A1298C	-/-		A
MTHFR/3	-/-		C
MTR/A2756G	-/-		A
MTRR/A66G	-/-		A
MTRR/H595Y		+/-	Hetero
MTRR/K350A		+/-	Hetero
MTRR/R415T	-/-		C
MTRR/S257T	-/-		T
MTRR/11	-/-		G
BHMT/1	-/-		A
BHMT/2		+/+	T
BHMT/4		+/+	C
BHMT/8		+/+	T
CBS/C699T		+/-	Hetero
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		+/-	Hetero
ACAT/1-02		+/-	Hetero

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: 04/18/2024
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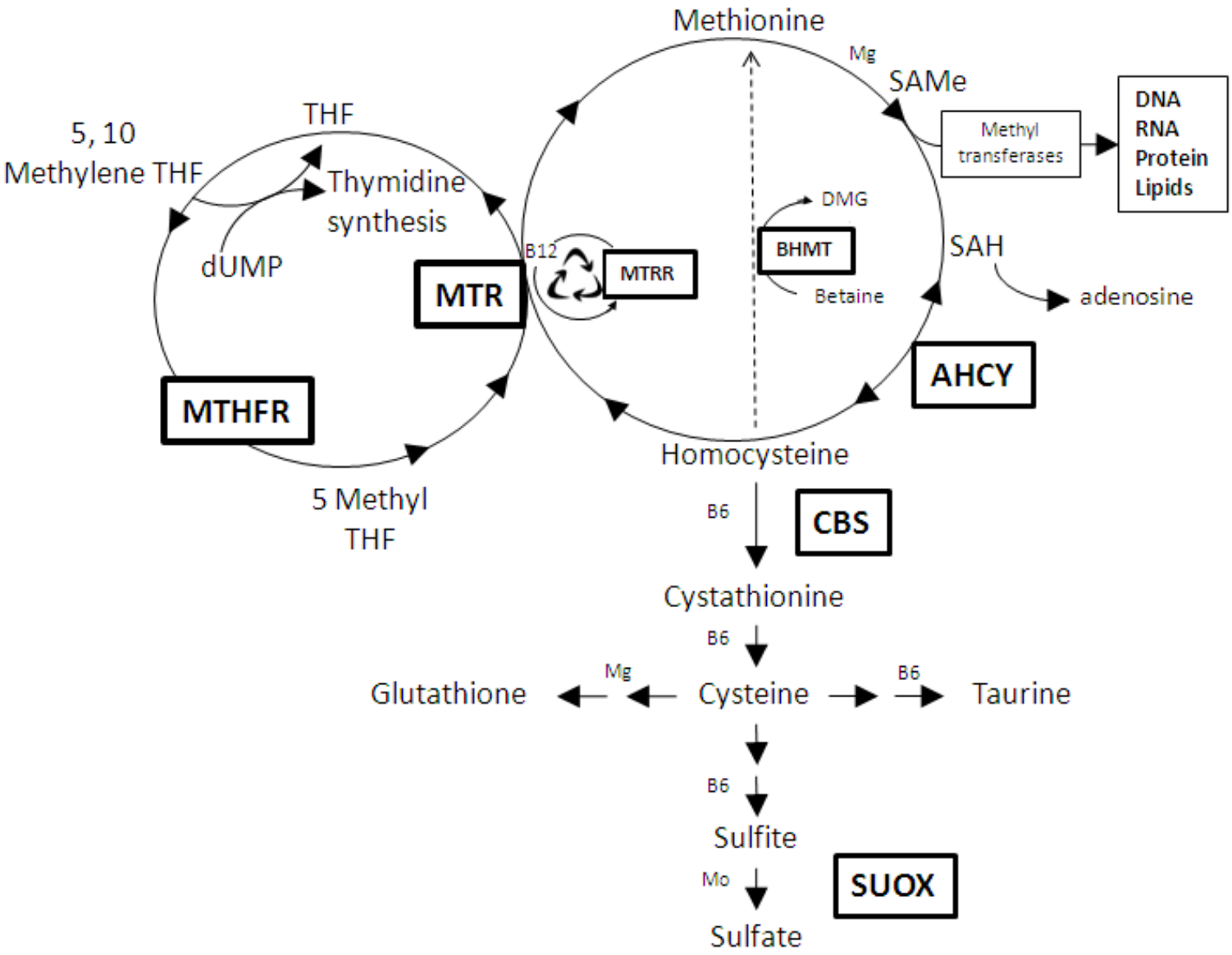
Methodology: Real-time PCR technology for genotyping

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.

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).

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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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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.

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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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ACAT /1 (acetyl coenzyme A acetyltransferase)

Pathways/biochemistry
ACAT is an enzyme found both in the cytoplasm (ACAT/2) and the mitochondria (ACAT/1). ACAT/1 is found in all tissues except intestinal tissue; ACAT/2 is found primarily in intestinal tissues. The ACAT/1 enzyme (mitochondrial) plays an important role beta-oxidation of fatty acids and protein metabolism; it is a step in the metabolic pathway for the amino acid isoleucine, and contributes to cellular energy production. ACAT/1 also completes ketone metabolism, synthesizing acetyl-Co-A for energy production.

ACAT/2 encodes a similar enzyme in the cytosol which is involved in the early steps of cholesterol biosynthesis and lipid metabolism.

Possible Health Implications
Polymorphism in ACAT/1 may increase the level of organic acids in the blood. Ketoacidosis may result from increased organic acidemia and may damage body tissues and organs, such as the nervous system. Mutations in ACAT/1 may cause the condition beta-ketothiolase deficiency. ACAT/1 may also be involved in foam cell formation and atherosclerosis.

Genotypic/Phenotypic expression
Based solely on the mutation, ACAT/1 may function poorly or not at all. However, published research indicates that genotype alone does not predict expression of the disorder; most patients develop normally and are able to manage symptoms. In general, homozygotes are more influenced by SNPs than heterozygotes.

How to optimize the phenotype
Monitor levels of organic acids, ketones, cholesterol and manage accordingly. Monitor plasma lipoproteins, especially oxidized low density lipoproteins (LDL), small dense LDL and apolipoproteins B.

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