KASHI HEALTH

Delivering More Than a Test Result

ASHI No. 10-4-OR-03-1
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BEHAVIORAL HEALTH GENOTYPING REPORT

Patient Name:	Health, Sally	**Date Sample Collected:**	06/27/14
DOB:	09/05/1988	**Date Sample Received:**	07/04/14
Lab ID Number:	1400000001	**Date Reported:**	07/11/14
Ordering Physician:	Dr. Honeycrisp	**Ordering Facility:**	Apple-A-Day Clinic

Genes Tested:
MTHFR – C677T/A12698C
COMT – Val158/158Met
VITAMIN B12 – FUT2
VITAMIN D – GC, NADSYN1/DHCR7, CYP2R1
CYTOCHROME P450: CYP2D6, CYP2C19

KEY: **GREEN: NON-RISK ALLELE** **RED: RISK ALLELE**

Folate (Vitamin B9)
MTHFR Mutations

MTHFR1-1: C677T
Results: **T/T**

MTHFR1-2: A1298C
Results: **A/A**

INDICATIONS

MTHFR1-1: C677T
T/T Homozygous allele carriers are associated with increased homocysteine levels and a higher risk of depression, schizophrenia, bipolar disease

MTHFR1-2: A1298C
A/A Homozygous allele carriers have full enzymatic activity and typically do not exhibit high levels of homocysteine

BACKGROUND

The MTHFR (methylenetetrahydrofolate reductase) gene produces an enzyme that helps in processing folate and regulating homocysteine levels in the body. Folate is a critical nutrient involved in methylation, DNA synthesis and amino acid metabolism. Impaired folate metabolism due to MTHFR enzyme inactivity, or decreased folate, results in elevated plasma homocysteine which has been linked to depression.[8-10] The first of two common mutations in the MTHFR gene is the C677T polymorphism.[14] This mutation is characterized by a cytosine (C) to thymine (T) transition at mRNA position 677. The second mutation is a substitution of adenine (A) with cytosine (C) at mRNA position 1298.[15,16] There is no evidence to suggest that the A1298C mutation alone affects plasma homocysteine levels, however, it has been demonstrated that individuals who are compound heterozygotes for both the C677T and the A1298C mutations have increased plasma homocysteine concentrations.[15] Elevated homocysteine levels are inversely associated with memory score,[17] and directly related to brain atrophy[18] and depressive symptoms.[10] Folate levels are directly related to memory scores,[17] and inversely related to depressive symptoms in women.[9]

C677T: T/T homozygous allele carriers are associated with a higher risk of depression, schizophrenia, bipolar as compared to C/C genotype[10-12] Depressed, schizophrenic, bipolar individuals showed a significant increased frequency of the T allele[12] **C/T** heterozygous allele carriers may have an intermediate risk for depression.[11]
A1298C: C/C homozygous allele carriers are reported to have an increased risk of depression compared to homozygous non-variant allele carriers[12,13] **C/C** homozygotes showed an increased risk of schizophrenia compared to homozygous allele carriers **A/A**, while **A/C** heterozygous allele carriers did not show an increased risk of schizophrenia or depression[12,13]
C677T: C/T and A1298C: A/C Compound heterozygotes are associated with decreased folate levels as well as a potential for increase in depressive disorders.[15]

COMT Mutation Val/158Met	BACKGROUND
Results: **A/A** **INDICATIONS** **A/A** Homozygous allele carriers have an approximately 3-4 fold reduction in enzyme activity, and higher dopamine levels[1]	The COMT (catechol-*O*-methyltransferase) gene codes for an enzyme that is essential for the breakdown of several mood-associated neurotransmitters, most notably dopamine.[1-5] Scientific research has demonstrated that a common mutation in COMT results in the conversion of the amino acid valine to methionine at position 158, and causes a dramatic reduction in the enzyme's ability to break down neurotransmitters. The enzyme is predominantly active in the prefrontal cortex, or PFC; the area of the brain that gives rise to what we perceive as our personality, emotions, behavior inhibition, abstract thinking, and short-term memory. **G/G Val158** allele carriers typically have higher enzyme activity resulting in lower dopamine levels. This may be associated with reduced pre-frontal cognitive function.[5] This allele is also reported to be associated with propensity towards drug abuse and schizophrenia.[5] **A/A Met158** allele carriers have diminished enzyme activity and are more likely to have higher dopamine and norepinephrine levels, associated with higher alcohol intake, OCD, panic disorder, PTSD severity, phobic avoidance, and bipolar affective disorder.[5,7]

Vitamin B12 FUT2 Mutations	BACKGROUND
FUT2-1 Results: **A/A** **INDICATIONS** **FUT2-1** **A/A** allele carriers are associated with higher vitamin B12 concentrations	Genetic variants of the FUT2 gene give rise to a non-functional FUT2 enzyme resulting in an inability to synthesize ABH blood group antigens on mucosal surfaces which is referred to as a 'non-secretor status'.[19] The non-secretor phenotype has been associated with higher vitamin B12 levels than the secretor phenotype.[20] Low B12 vitamin status has long been linked to depressive behavior.[21,22] Vitamin B12 supports the synthesis of a molecule known as S-adenosylmethionine (SAM) which is critical in regulating levels of neurotransmitters in the brain.[23] Scientific research suggests that B12 deficiency may contribute to a reduction in SAM leading to chemical imbalances in the brain resulting in depression. More recently, a large population based study reported that there was an approximately three-fold increase in risk for melancholic depressive symptoms in individuals with low B12 levels.[24] **A/A** and **A/G** individuals have been shown to have decreased function of the enzyme generating a non-secretor status, increased vitamin B12 levels, and therefore no significant association with increased risk for mood disorders.[25] **G/G** individuals generally have lower vitamin B12 levels, the latter being associated with depressive behavior, and specifically melancholic depressive symptoms.[24]

Vitamin D CYP2R1 Mutation	BACKGROUND
Results: **A/G** **INDICATIONS** **A/G** genotypes are reported to be associated with lower vitamin D levels	A locus containing a single nucleotide polymorphism (SNP) associated with vitamin D levels, the CYP2R1 gene encodes the hepatic enzyme 25-hydroxylase suggested to be responsible for the hydroxylation step of vitamin D metabolism in the liver.[36] The polymorphism is located in a coding region of this gene and may change the activity of the enzyme leading to a lowered 25(OH)D level.[27,28] Low vitamin D levels have been shown to be associated with impairments in cognitive function, and increased risk of developing depression in patients,[31,32] suggesting these variants can be used to indicate potential risk of mood disorders associated with low vitamin D levels. **A/A** individuals have been shown to have higher vitamin D serum levels and therefore may not be at increased risk for the development of depression. **A/G** and **G/G** individuals are more likely to have vitamin D insufficiency and be prone to developing depression.

Vitamin D NADSYN1/DHCR7 Mutation	BACKGROUND
Results: **T/T** **INDICATIONS** **T/T** homozygous allele carriers have higher levels of serum vitamin D levels	NADSYN1/DHCR7 is a novel locus for association with vitamin D status, but with direct biological relevance. A G->T SNP is found in an intron of NADSYN1 (nicotinamide adenine dinucleotide synthase 1), a gene that catalyzes the final step of NAD biosynthesis.[34] This SNP is in high linkage disequilibrium with SNPs in DHCR7 (7-dehydrocholesterol reductase), a gene that encodes the enzyme 7-dehydrocholesterol reductase, which converts the vitamin D precursor (7-DHC) to cholesterol.[35] By converting the 7-DHC into cholesterol the needed substrate used by the body to generate vitamin D is removed, leaving the individual at a higher risk of vitamin D deficiency.[30] Low vitamin D levels have been shown to be associated with impairments in cognitive function, and increased risk of developing depression in patients,[31,32] suggesting these markers can be used to indicate potential risk of mood disorders associated with low vitamin D levels. T/T and T/G allele carriers are reported to have higher levels of circulating 25(OH)D and lower frequency of vitamin D insufficiency, dyslipidemia and less risk of developing depression than G/G allele carriers. G/G homozygous individuals are associated with a greater risk of vitamin D insufficiency and therefore may be more prone to developing mood disorders.

Vitamin D GC Mutations	BACKGROUND
GC-1 Results: **G/G** **GC-2** Results: **C/C** **INDICATIONS** **GC-1 / GC-2 isoforms** are associated with Vitamin D level status **G/C** – isoform GC1s; individuals with this haplotype have an intermediate risk for vitamin D deficiency	The GC gene encodes the group-specific component which functions to tightly bind and carry vitamin D metabolites to their target organs. A two-SNP combination in this gene is directly associated with variability in vitamin D [25(OH)D] concentrations.[26-29] These well-studied GC SNP variants result in allelic combinations (haplotypes) that give rise to three common GC isoforms, GC1f, GC1s, and GC2.[26] These variants in particular, change the amino acid sequence and alter protein function. Several studies have shown that vitamin D serum levels differ significantly depending on the genotype. [28,30] Low vitamin D levels have been shown to be associated with impairments in cognitive function, and increased risk of developing depression in patients,[31,32] suggesting these variants can be used to indicate potential risk of mood disorders associated with low vitamin D levels. GC-1 / GC-2 isoforms: T/C (GC1f) is considered the non-risk isoform and has the highest affinity for 25(OH)D. Individuals with this genotype are typically not associated with increased risk for vitamin D deficiency, and subsequently may not be at increased risk for mood disorders. G/C (GC1s) isoform has intermediate affinity for 25(OH)D. Individuals with this genotype typically have an intermediate risk profile for vitamin D deficiency. T/A (GC2) isoform has the lowest affinity for 25(OH)D. It is suggested that individuals with this genotype have lower vitamin D concentrations due to reduced binding capacity of the transport protein, and thus may be at risk for mood disorders susceptibility.[28,33]

Cytochrome P450	BACKGROUND
CYP2D6 Results: ***2/*41** **CYP2C19** Results: ***1/*17**	CYP450 (CYP450) enzymes are necessary for the metabolism of drugs. A specific gene encodes each CYP450 enzyme. Every person inherits one genetic allele from each parent. A normal metabolizer has received two copies of wild-type alleles. Polymorphism occurs when a variant allele replaces one or both wild-type alleles. Variant alleles usually encode a CYP450 enzyme that has reduced or no activity.[40] Persons with two copies of variant alleles are "poor" metabolizers, whereas those with one wild-type and one variant allele have reduced enzyme activity. Finally, some persons inherit multiple copies of wild-type alleles, which results in excess enzyme activity. This phenotype is termed an "ultrarapid" metabolizer.[41] **CYP2D6**[37-38] Cytochrome P450 enzyme 2D6 (CYP2D6) is thought to be active in the enzymatic breakdown of antidepressants, antipsychotics, opioids, beta-blockers, antiarrhythmics and tamoxifen. Commonly prescribed medications that are metabolized by this enzyme include Codeine, Oxycodone, Duloxetine (Cymbalta), Fluoxetine (Prozac), Tramadol and many others. **CYP2C19**[37, 39] Cytochrome P450 enzyme 2C19 (CYP2C19) is involved in the metabolism of drugs including clopidogrel, anticonvulsants, diazepam, omeprazole, tricyclic antidepressants and proton pump inhibitors. Commonly prescribed antidepressant and antipsychotic medications that are metabolized by CYP2C19 include Sertraline (Zoloft), Citalopram (Celexa), Carisoprodol (Soma), Diazepam (Valium), Amitriptyline (Elavil), and several others.
INDICATIONS **CYP2D6 - Normal Metabolizer** Individuals with this phenotype have normal metabolism of most antidepressants and antipsychotic drugs. Standard dosing practices is recommended. **CYP2C19 - Ultrarapid Metabolizer** Individuals with this phenotype have increased enzymatic activity. Selection of a medication not metabolized by CYP2C19 or administration of an elevated dose of drugs metabolized by CYP2C19 along with therapeutic drug monitoring may be warranted to achieve the desired effect.	

For more information about gene/drug interactions visit www.pharmgkb.org

*The Cytochrome P450 test only detects specific targeted mutations. There is a possibility that other mutations in these genes are present that are not detected by this test. The content of this report is only provided as a guideline and does not supersede the judgment of the patient's pharmacist or physician. Drug metabolism is affected by many non-genetic factors so mutation testing is not a substitute for therapeutic drug monitoring. *Methodology: Multiplexed PCR reactions were utilized to detect the most common, clinically significant variants in the genes of interest. Variants tested include: CYP2D6-*1,*2,*3, *4, *5, *6, *7, *8, *9, *10, *11, *15, *17, *29, *35, *41, Dup CYP2C19:*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *13, *17*

***Additional information will be supplied to your provider to help inform treatment options.**

This test was developed and its performance characteristics determined by Kashi Clinical Laboratories. It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research.

Reported and Reviewed By:

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