

DNA Test Summary

Patient Name: John Smith

January 21, 2007

What tests were performed:

DNA tests for:

Bipolar disorder

Therapeutic response to the SSRI type of antidepressant

GRK3 (G protein Receptor Kinase 3)

**P-5
E/H haplotype**

**Positive
Negative**

These two mutations in the GRK3 gene are associated with bipolar disorder. Patients who have either of these two mutations, are Caucasian, of Northern European ancestry and have a family history of bipolar disorder, are three times more likely to have bipolar disorder.

Serotonin transporter

Promoter L allele

Positive (S/L genotype)

This mutation in the serotonin transporter gene is associated with response to SSRI antidepressants, as well as, several other traits including vulnerability to stress induced major depression. Presence of either the l/l or s/l genotype is a positive test. Patients with one of these two genotypes that are Caucasian and suffering from depression, are twice as likely to benefit from treatment with an SSRI type of antidepressant.

Information About DNA Tests

No DNA test presently can provide a definitive diagnosis for any psychiatric disorder. Many genes act together in combination with environmental stress to increase the risk of a psychiatric disorder. In the context of your history and symptoms, DNA tests can indicate whether your patient has a higher or lower probability of having a given psychiatric diagnosis. Psynomics provides DNA test results or genotypes for several specific genes. The interpretation of these results depends on scientific studies and may change as more studies are conducted. Psynomics provides information from the existing medical studies to aid in interpretation.

Two genes were tested that are involved in mood disorders:

GRK3 (G protein Receptor Kinase 3)

GRK3 is involved in regulating the intensity of neurotransmitter signaling in the brain. Stress or other factors can increase the release of many neurotransmitters. This increase in neurotransmitters can in turn lead to the development of mania, depression or other psychiatric disorders. The GRK3 gene operates as a “brake” in the brain that decreases the brain’s sensitivity to some neurotransmitters. GRK3 therefore, plays a key role in maintaining balance in the brain. Two different variations in the GRK3 gene have been found that affect its ability to maintain balance: The P-5 mutation and the E/H haplotype. The frequency and effect of these variants are shown below:

GRK3 variants	Frequency		Increase in likelihood of having Bipolar Disorder
	Bipolar Disorder	Unaffected	
P-5	3%	1%	3x
E/H haplotype	15%	7%	2x

Interpretation

Patients who have psychiatric symptoms, a family member with Bipolar Disorder and the P-5 variant, are 3 times more likely to have Bipolar Disorder. Similarly, patients with the E/H haplotype are 2 times more likely to have Bipolar Disorder.

The GRK3 test is most useful clinically when there are some psychiatric symptoms present, but the diagnosis is unclear. In this situation, as described above, a positive GRK3 test may indicate a higher probability of Bipolar Disorder. The table below indicates how the GRK3 test should be interpreted in different scenarios of behavioral symptoms and gene test results.

Symptoms by History	GRK3 Test (P-5 or E/H)	
	Positive	Negative
No psychiatric symptoms	No psychiatric disorder. There is no data to enable interpretation of a positive GRK3 test in someone without symptoms.	No psychiatric disorder.
Some psychiatric symptoms, but not enough for diagnosis or diagnosis unclear.	Bipolar Disorder should be strongly considered. A positive GRK3 test in the context of a family history of Bipolar Disorder makes a diagnosis of Bipolar Disorder 2-3 times more likely.	Indeterminate. A negative GRK3 test cannot rule out Bipolar Disorder as other genes for Bipolar Disorder may be present.
DSM-IV diagnosis of Bipolar Disorder based on symptoms	Bipolar Disorder. A positive GRK3 test helps confirm the diagnosis based on symptoms.	Bipolar Disorder. Even though the GRK3 test is negative, the patient meets criteria for Bipolar Disorder. Genes other than GRK3 may be involved.

Limitations

The association of the GRK3 gene and Bipolar Disorder has been shown in several studies, but only in Caucasians of Northern European ancestry. If your patient does not have a family member with bipolar disorder or is not a Caucasian of Northern European ancestry, then there is no data at this time to enable interpretation of this result.

The GRK3 gene has not been well studied in other psychiatric disorders. It may also be associated with other illnesses such as schizophrenia or major depression. Therefore, these other disorders cannot be clearly ruled out. It is most likely to indicate a higher likelihood of Bipolar Disorder if there are other family members with Bipolar Disorder. For this reason, it cannot be interpreted if your patient does not have other family members with Bipolar Disorder.

Serotonin Transporter

The Serotonin Transporter regulates the levels of the neurotransmitter serotonin in the brain. It is the site of action of Selective Serotonin Reuptake Inhibitor (SSRI) types of antidepressant medication. These include medications such as: Prozac™, Paxil™, Zoloft™, Celexa™ and others. These drugs block the Serotonin Transporter and thereby increase the level of serotonin. This in turn treats depression in most people. The Serotonin Transporter has a variation referred to as HTTLPR which has a short (S) and a long (L) form. The L form makes more Serotonin Transporter and has been

associated with better response to SSRI antidepressant medications. One simple interpretation is that people with the L form have more sites in the brain for SSRI antidepressants to work. Everyone has two copies of each gene. Therefore, there are three possible combinations or genotypes: SS, SL and LL. Both SL and LL are associated with good SSRI response and therefore reported as positive by Psynomics, while SS is reported as negative.

Interpretation

The frequency of the variants and their interpretation are summarized in the table below:

	Serotonin Transporter (HTTLPR) Genotype		
	SS (Negative)	SL (Positive)	LL (Positive)
Frequency	19%	48%	33%
SSRI response	Poor	Good – about twice as likely to respond as SS	Good – about twice as likely to respond as SS

The Serotonin Transporter has also been reported to be associated with several other clinical features and responses. These have not been as widely validated as response to SSRI's but still are worth consideration. They include:

1. Patients with Bipolar Disorder and the SS genotype (Negative test) are at higher risk for hypomania or mania in response to antidepressant medication
2. People with the SS genotypes (Negative test) are at higher risk for developing depression in response to major stresses in life

Limitations

These results have been validated only in Caucasians. Several studies have suggested that this marker may not be associated with SSRI response in Asians. Hence, if your patient is of Asian descent, these results should not be interpreted to mean they are either more or less likely to respond to SSRI antidepressants.

The association with SSRI response has been validated only in patients with Major Depression. It is not clear that it has the same implications for patients with Bipolar Disorder.

What does this mean for your patient's family

Bipolar disorder is largely a hereditary disorder. Inherited factors may explain as much as 60-70% of the incidence of this disorder. If your patient's history and DNA test indicate that they have Bipolar Disorder, this indicates that an inherited risk for bipolar disorder may run in their family. DNA testing presently cannot detect the risk for illness in relatives who have no psychiatric symptoms. However, a diagnosis of Bipolar Disorder indicates that your patient's family members may be at higher risk. Bipolar disorder commonly has its onset in the early 20's. Family members who may be having symptoms of depression or mania, should be seen by a psychiatrist for evaluation.

DNA Test Data Reviewed by:

[Scanned electronic signature]

Dr. Linda Wasserman

Laboratory Testing and Certification

These tests were adopted and their performance characteristics determined by the Molecular Genetics Laboratory at UCSD. This testing was performed by the Molecular Genetics Laboratory at UCSD, and the results were reviewed and approved by the laboratory director, Dr. Linda Wasserman. These tests have not been cleared or approved by the Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. These tests are used for clinical purposes. They should not be regarded as investigational or for research. The laboratory is regulated by the Clinical Laboratory Improvement Act of 1988. Possible sources of error in this analysis include erroneous specimen identification and genotyping errors. Genotyping errors may result from trace contamination of PCR reactions and rare genetic variation.