Ordered Items
COMT Genetic Test

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<tr>
<th>TESTS</th>
<th>RESULT</th>
<th>FLAG</th>
<th>UNITS</th>
<th>REFERENCE INTERVAL</th>
<th>LAB</th>
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<tr>
<td>COMT Genetic Test</td>
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<tr>
<td>Predicted Metabolic Activity</td>
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<td>Interpretation</td>
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<tr>
<td>Additional Interpretation</td>
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COMT Genetic Test Information

The COMT gene on chromosome 22q11.2 encodes catechol-O-methyltransferase, COMT, an enzyme that metabolizes and inactivates catecholamine neurotransmitters (epinephrine, norepinephrine, and dopamine), catechol hormones (hydroxylated estradiol), and neuroactive drugs (e.g. L-DOPA). COMT deficiency variants are associated with varied responsiveness to pharmaceutical and behavioral treatments, pain susceptibility, and risk for certain psychiatric disorders (e.g., schizophrenia, eating disorders). Research use includes detecting susceptibility alleles for breast cancer risk when taking hormone replacement therapy.

Our laboratory developed COMT Genetic Test uses PCR and multiplex mini-sequencing to detect alleles for six single nucleotide polymorphisms (SNPs) that directly alter COMT activity (rs4680, rs6267, rs165774) or modulate its metabolic activity when specific alleles occur together as haplotypes (rs6269, rs4633, rs4818, rs4680). These SNPs, their locations in reference sequence NM_000754.3, and functional effects are:

- Low activity SNPs:
  1. rs4680: p.Val158Met (c.472G>A, exon 4) has decreased activity
  2. rs6267: p.Ala72Ser (c.214G>T, exon 3) has decreased activity
TESTS                        RESULT          FLAG        UNITS      REFERENCE INTERVAL   LAB
3. rs165774: c.615+739G>A, intron 5 and 3'UTR of alternatively spliced mRNA; the A allele has decreased dopamine-specific activity

Additional haplotype SNPs:
4. rs6269: c.1-98A>G, intron 2
5. rs4633: p.His62His (c.186C>T, exon 3)
6. rs4818: p.Leu136Leu (c.408C>G, exon 4)

Association studies suggest that the genetic background influences the phenotype of the key COMT SNP p.Val158Met. Diatchenko et al. (2005) describe haplotypes that modify COMT activity. Significantly, in vitro experiments showed that specific haplotypes from SNPs above (4, 5, 6, and 1), despite containing the p.158Val allele, have altered mRNA secondary structure leading to greatly reduced COMT protein synthesis (Nackley et al. 2006). This effect correlates with the presence of the C allele of rs4818. Due to altered expression of p.158Val, a majority of homozygous individuals would be re-categorized as having very low or intermediate COMT metabolic activity when the rs4680 genotype is combined with the additional haplotype SNP results. We use an additive model that includes the results for the rs4680 and rs6267 genotypes and the modifying effect of both haplotype alleles to express the predicted COMT metabolic activity: Normal (1.0), Intermediate (0.5 to <1.0), Low (0.15 to <0.5), and Very low (<0.15).

When the rare variant p.Ala72Ser is detected, this is noted in the interpretation section.

SNP rs165774 is located in intron 5 of COMT mRNA but also maps to the 3' untranslated region of an alternatively spliced transcript (Meloto et al. 2015). The encoded protein differs in its C' end and has a different substrate profile than full length COMT, with enzymatic activity towards dopamine but not epinephrine. The minor allele rs165774-A is associated with decreased protein levels of the altered protein and correlates with protection from pain, reduced risk for developing temporomandibular joint disorder, and a lower risk of schizophrenia and alcohol dependence. Individuals with the GG genotype are more responsive to duloxetine for major depression.

Comments

Common Drugs affected by COMT metabolic activity include, but are not limited to:
L-DOPA, used for treatment of Parkinson's disease - COMT methylation is the major degradation pathway for dopamine in the prefrontal cortex. Individuals homozygous for p.158Met may initially require a lower dose of L-DOPA to avoid cognitive decline due to drug toxicity. For individuals homozygous for p.158Val, co-administration with entacapone (a COMT inhibitor) may improve L-DOPA response.
OPIOIDS/MORPHINE, used for treatment of chronic pain - lower doses of morphine may be sufficient to achieve adequate pain relief in individuals with low COMT activity.

MODAFINIL - Individuals homozygous for p.158Val have been reported as having an improved response to modafinil. In sleep deprivation conditions, individuals homozygous for p.158Val responded better to modafinil and showed improved alertness compared to individuals homozygous for p.158Met. Homozygous results for p.158Met may warrant consideration of alternative drugs or choice of tasks.

ANTIPSYCHOTICS (olanzapine, clozapine) - Individuals homozygous for p.158Met have been reported to have an improved response to olanzapine and clozapine.

NICOTINE REPLACEMENT THERAPY - Caucasian individuals homozygous for p.158Met have significantly improved responses to nicotine replacement therapy.

4-HYDROXYESTROGENS - Individuals with low COMT activity may have adverse breast cancer outcomes when administered hormone replacement therapy. 4-hydroxyequilenin (Premarin(R)) inhibits COMT activity, which can cause excessive levels of endogenous estrogens.

Common compounds metabolized by COMT include, but are not limited to: L-dopa, dopamine, epinephrine, norepinephrine, 2-hydroxyestrogens, 4-hydroxyestrogens

Potential Drug Interactions:
Some common medications inhibit or induce metabolism by COMT. Caution should be used when co-administering a drug that inhibits or induces COMT with drug(s) that are metabolized by this enzyme. This list is not comprehensive, as there are additional medications that may affect COMT activity.

Common Medications that Inhibit COMT: entacapone, tolcapone, 4-hydroxyequilenin

Disclaimers:
As with all PCR tests, the possibility cannot be ruled out that a rare polymorphism or unusual mutation alters amplification and leads to a false negative result. Donor DNA from transplants and recent transfusions can lead to inaccurate results. Only six variants are detected by this assay. Haplotype phases are inferred based on our validation studies. Results should be interpreted in the context of each individual's clinical history. The metabolism of drugs is also influenced by ethnicity, diet, drug-drug interactions, age, nutrition, underlying chronic
diseases (liver, kidney or heart failure), alcoholism, illicit drug use, patient compliance, etc. All factors should be considered prior to initiating new therapy. This testing does not rule out the possibility of variant alleles in other drug metabolism pathways.

This test was developed and its performance characteristics determined by LabCorp. It has not been cleared or approved by the Food and Drug Administration.

This case has been reviewed, approved, interpreted and electronically signed by Toni R. Prezant, PhD.

References

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<td><strong>Interpretation</strong></td>
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<tr>
<td>This individual is heterozygous for p.Val158Met. In addition, the p.158Val allele occurs on a haplotype with normal COMT expression levels. COMT metabolic activity is predicted to be intermediate.</td>
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<tr>
<td>This individual is homozygous for the G-allele of rs165774. This variant has been associated with increased pain sensitivity and a greater response to duloxetine.</td>
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