Opioid Receptor, mu OPRM1 Genotype, 1 Variant

Indications for Ordering
Pretherapeutic identification of individuals who may
• Require higher or lower doses of opioid drugs to achieve adequate pain control
• Have a better response to naltrexone for the treatment of alcohol and/or opioid dependency

Test Description
Polymerase chain reaction and fluorescence monitoring
• Analyzes OPRM1 variant c.118A>G (p.Asn40Asp)

Tests to Consider
Primary test
Opioid Receptor, mu OPRM1 Genotype, 1 Variant 2008767
• Predict response to opioid agents

Related tests
Cytochrome P450 Genotype Panel 2013098
• Assess genetic risk of abnormal drug metabolism for drugs metabolized by CYP2D6, CYP2C9, CYP2C19, and CYP3A5
• May aid in drug selection and dose planning for many drugs
• Single tests for CYP2D6, CYP2C9, CYP2C19, and CYP3A5 are available separately

Drug monitoring tests using blood or urine specimens are available to assess individual’s metabolic phenotype and adherence for a specific opioid
• See ARUP’s Pain Management Test Menu
  (www.aruplab.com/pain-management/tests)

Overview
Treatment issues
• Opioid agonists (eg, morphine, fentanyl) are typically administered for pain control
• Opioid antagonists (eg, naltrexone) are often prescribed for the treatment of alcohol and/or opioid dependency
• Pharmacogenetic variation may affect pharmacokinetics or pharmacodynamics of a drug
  o May contribute to toxicity and risk for adverse drug reactions, including reduced therapeutic benefit
• Genetic and nongenetic factors may contribute to drug pharmacology and clinical response

• OPRM1 gene is associated with the pharmacodynamics of opioids
  o Variants in OPRM1 can result in different binding affinities to and clinical effects of opioids
  o Association of OPRM1 and drug sensitivity
    ▪ Is not definitive
    ▪ May be different for individual opioids

Genetics
Gene – OPRM1

Inheritance – autosomal codominant

Penetrance – drug dependent

Structure/function
• Encodes µ-opioid receptor 1 protein
• Primary binding site of action for various synthetic and endogenous opioids
  o Includes both agonists and antagonists
• One of three opioid receptors involved in this process

Alleles
• OPRM1 common allele at nucleotide position 118 is known as “A”; the variant allele is known as “G”
  o G allele frequency
    ▪ African Americans – 4%
    ▪ Caucasians – 14%
    ▪ Hispanics – 24%
    ▪ Asians – 25-47.4%
• c.118A>G variant (G allele) results in
  o Loss of a putative N-glycosylation site in the extracellular receptor region
  o Lower cell-surface receptor binding site availability compared to the A allele receptors
  o Thought to decrease mRNA and receptor protein concentrations
  o Lower sensitivity to opioid receptor agonists prescribed for pain control (eg, morphine)
  o Higher sensitivity to opioid receptor antagonists used in the treatment of alcohol and drug dependency (eg, naltrexone)

Test Interpretation
Sensitivity/specificity
• Clinical sensitivity/specificity – drug dependent
• Analytical sensitivity/specificity – >99%
Results

• Homozygous G/G
  o Two copies of OPRM1 c.118A>G variant detected
    ▪ Genotype is consistent with decreased sensitivity to opioid agonists and increased sensitivity to opioid antagonists
    ▪ Individual may require higher or more frequent doses of opioid agonists to achieve adequate pain control
    ▪ May be more likely to respond to opioid antagonists in treatment of alcohol and/or opioid dependency

• Heterozygous G/A
  o One copy of OPRM1 c.118A>G variant detected
    ▪ Further studies are needed to determine clinical significance of this genotype, but it is possible that
    ▪ Individual may require higher or more frequent doses of opioid receptor agonists to achieve adequate pain control
    ▪ May be more likely to respond to opioid antagonists in treatment of alcohol and/or opioid dependency

• Homozygous A/A
  o No copies of OPRM1 c.118A>G variant detected
    ▪ Genotype is consistent with increased sensitivity to opioid receptor agonists and decreased sensitivity to opioid receptor antagonists
    ▪ Individual may require lower or less frequent doses of opioid receptor agonists to achieve adequate pain control
    ▪ May be less likely to respond to opioid antagonists in treatment of alcohol and/or opioid dependency

Limitations

• OPRM1 variants other than c.118A>G are not evaluated by this test
• Diagnostic errors can occur due to rare sequence variations
• Risk of therapeutic failure or adverse reactions with opioids may be affected by genetic and nongenetic factors that are not detected by this test
• Genetic testing does not replace the need for therapeutic or clinical monitoring