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
  - 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
  - Variants in *OPRM1* can result in different binding affinities to and clinical effects of opioids
  - 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
  - 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"
  - G allele frequency
    - African Americans – 4%
    - Caucasians – 14%
    - Hispanics – 24%
    - Asians – 25-47.4%
- c.118A>G variant (G allele) results in
  - Loss of a putative N-glycosylation site in the extracellular receptor region
  - Lower cell-surface receptor binding site availability compared to the A allele receptors
  - Thought to decrease mRNA and receptor protein concentrations
  - Lower sensitivity to opioid receptor agonists prescribed for pain control (eg, morphine)
  - 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
  - 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
  - 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
  - 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