FG Syndrome Type 1 (**MED12** R961W Mutation)

**Indications for Ordering**
- Confirm a clinical diagnosis of FG syndrome type 1 (FGS1)
- Determine carrier or affected status in relatives of individuals with **MED12** R961W mutation

**Test Description**
Polymerase chain reaction (PCR)/fluorescence monitoring

**Tests to Consider**
- **FG Syndrome, FGS1 (**MED12**) R961W Mutation 0051752**
  - Diagnostic testing and carrier screening for FGS1

**Disease Overview**

**Incidence** – ~1/15,000

**Symptoms**
- Developmental delay PLUS minor congenital anomalies
  - Relative macrocephaly
  - High prominent forehead/upswung frontal hair
  - Congenital hypotonia
  - Deep-set eyes
  - Broad thumbs and great toes
  - Small, simple ears
  - Severe constipation
  - Persistent fetal fingertip pads
  - Joint hyperlaxity
- Rare malformations
  - Anal agenesis
  - Cryptorchidism/hypospadias
  - Heart defects
  - Vertebral/limb malformations
  - Pyloric stenosis
- Neurologic findings
  - Agenesis of the corpus callosum
  - Chiari 1 malformation
  - Tethered spinal cord
  - EEG abnormalities/rare seizures
  - Hyperactivity/poor attention span
  - Anxiety/depression/temper outbursts
- Pregnant FG syndrome carriers at risk for
  - Premature onset of labor
  - Preeclampsia/eclampsia/HELLP (hemolysis, elevated liver enzymes, and low platelet count)
- Diagnosis requires molecular confirmation
  - Clinical diagnostic criteria not established
  - High clinical variability/nonspecific clinical findings

**Genetics**

**Genes**
Seven X chromosomal loci have been associated with FG syndrome
- **FGS1** (Xq12-q21.31, **MED12** gene)
- **FGS2** (Xq28, **FLNA** gene)
- **FGS3** (Xp22.3)
- **FGS4** (Xp11.4-p11.3, **CASK** gene)
- **FGS5** (Xq22.3)
- **FGS6** (Xq25-26, **UPF3B** gene)
- **FGS7** (Xq21.1, **BRWD3** gene)

**Inheritance** – dependent on associated locus
- **MED12** is X-linked dominant, with variable penetrance

**Penetrance (**MED12** R961W)** – ~100% in males; variable in females

**Mutations**
- **MED12** R961W (c.2881C>T)
  - Most common molecular cause of FGS1
- Other **MED12** mutations – associated with FGS1 or Lujan syndrome

**Test Interpretation**

**Sensitivity/specificity**
- Clinical sensitivity – ~7% for FG syndrome (Risheg, 2007)
- Analytical sensitivity/specificity – 99%

**Results**
- Positive
  - Symptomatic individual – confirms a diagnosis of FGS1
  - Asymptomatic female – confirms carrier status for FGS1
- Negative – does not rule out FG syndrome
  - Tests for only the most common **MED12** gene mutation

**Limitations**
- Other **MED12** gene mutations are not detected
- Other genes associated with FG syndrome are not analyzed
- Diagnostic errors can occur due to rare sequence variations
References