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/upswept 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 I 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

- Battaglia A, Chines C, et al. The FG syndrome: report of a large Italian series. Am J Med Gen. 2006;140(19):2075-2079
- Graham JM Jr, Superneau D, et al. Clinical and behavioral characteristics in FG syndrome. Am J Med Gen. 1999;85:470-475
- Risheg H, et al. A recurrent mutation in MED12 leading to R961W causes Opitz-Kaveggia syndrome. Nat Genet. 2007;39:451-453