

FG Syndrome (*MED12*) R961W Mutation

TO CONFIRM DIAGNOSIS OR CARRIER STATUS FOR *FGS1*(*OPITZ-KAVEGGIA*) SYNDROME

Disease Overview

- The FG syndromes are characterized by developmental delay/mental retardation and a collection of minor congenital anomalies, including: relative macrocephaly (95 percent), high prominent forehead (95 percent), congenital hypotonia (90 percent), upswept frontal hair (85 percent), deep-set eyes (70 percent), broad thumbs and great toes (60 percent), small, simple ears (55 percent), severe constipation (55 percent, in *FGS1*), persistent fetal fingertip pads (50 percent), joint hyperlaxity (50 percent).
- Malformations are relatively rare but include: anal agenesis, cryptorchidism, heart defects, vertebral malformations, pyloric stenosis, limb malformations, and hypospadias.
- Neurologic findings include brain anomalies, commonly agenesis of the corpus callosum or Chiari I malformation. About 50 percent of patients have an abnormal EEG, and some patients have a tethered spinal cord. Seizures are a rare finding.
- Patients often exhibit hyperactivity, poor attention span, anxiety, temper outbursts, and poor social interactions during childhood. Behavioral issues and interpersonal skills often improve over time.
- Diagnosis of FG syndrome is complex, due to high clinical variability and the fact that many of the associated findings are common in individuals with mental retardation.
- Many carrier women or girls show subtle manifestations, including high forehead, upswept frontal hair/cowlick, broad thumbs/halluces, constipation, depression, and anxiety.
- Female FG carriers are also at risk for pregnancy complications, including premature onset of labor and high blood pressure/preeclampsia, which may result in HELLP syndrome and other signs of fetal distress.
- Death may occur during infancy due to respiratory infection or bronchopulmonary problems. Patients surviving infancy do not appear to be at risk for premature death.
- An accurate diagnosis is important for genetic counseling and assessment of reproductive risk. FG syndromes are suspected to demonstrate transmission ratio distortion, where a greater number of offspring from carrier women are affected than expected under a hypothesis of Mendelian segregation.
- Symptomatic treatment and educational assistance are available for patients with FG syndrome.

Epidemiology

- Estimated incidence of all FG syndromes is one in 1,000 in the United States and Italy.
- Due to extreme clinical variability in affected individuals (both male and female), FG syndrome is likely underdiagnosed.

Genetics

- There are seven known X chromosomal loci that appear to be associated with FG syndrome: *FGS1* (Xq12-q21.31), *FGS2* (Xq28, *FLNA* gene), *FGS3* (Xp22.3), *FGS4* (Xp11.4-p11.3, *CASK* gene), *FGS5* (Xq22.3), *FGS6* (Xq25-26, *UPF3B* gene), and *FGS7* (Xq21.1, *BRWD3* gene). The clinical variability in FG syndrome may be partially explained by this genetic heterogeneity.
- The mediator subunit 12 gene, *MED12* (also known as HOPA and TRAP230), is located on chromosome Xq13 and maps to the *FGS1* locus. *MED12* encodes a thyroid hormone receptor-associated protein thought to regulate the expression of other genes involved in neuronal development. The *MED12* R961W (c.2881C>T) mutation has been identified in several FG families.
- The *Filamin A* (*FLNA*) gene is located at the *FGS2* locus, and mutations have been identified in males with periventricular nodular heterotopias and FG-associated anomalies.
- FG-associated genes at the *FGS3* and *FGS5* loci have not been identified.
- The inheritance pattern of FG syndrome may differ depending on the associated locus.
 - *MED12*: X-linked dominant with variable penetrance
 - *FLNA*, *CASK*, *UPF3B*, and *BRWD3*: X-linked
- Most cases are inherited; de novo mutations are suspected to be rare.
- FG syndrome appears to be allelic with Lujan-Fryns syndrome, as *MED12* and *UPG3B* mutations have also been reported in these patients.

Indications for Ordering

- To confirm a clinical diagnosis of FG syndrome.
- To determine carrier or affected status in relatives of individuals with a *MED12* R961W mutation.

Contraindications

Carrier testing when the familial mutation is either unknown or not identified as *MED12* R961W.

Interpretation

- Detection of the *MED12* R961W mutation in a symptomatic individual confirms a diagnosis of FG syndrome (*FGS1*).
- Identification of the *MED12* R961W mutation in an asymptomatic female indicates carrier status.
- Lack of detection of the *MED12* R961W mutation does not rule out a diagnosis of FG syndrome, since *MED12* mutations other than R961W and mutations in other causative genes will not be identified.

Limitations

- *MED12* mutations other than R961W are not evaluated by this assay.
- Mutations in other genes associated with FG syndrome will not be detected.
- Rare diagnostic errors can occur due to probe site mutations.

Methodology

- Polymerase chain reaction and fluorescence monitoring.
- Analytical sensitivity and specificity are 99 percent.
- Clinical sensitivity is approximately 7 percent for FG syndrome.

References

1. Risheg H, et al. A recurrent mutation in *MED12* leading to R961W causes Opitz-Kaveggia syndrome. *Nat Genet* 2007; 39(4):451–3.
2. Battaglia A, et al. The FG syndrome: report of a large Italian series. *Am J Med Gen* 2006; 140A:2075–9.
3. Graham JM, et al. Clinical and behavioral characteristics in FG syndrome. *Am J Med Gen* 1999; 85:470–5.
4. Opitz JM, et al. The FG syndrome (FGS; OMIM 305450)-perspective in 2008. *Adv Pediatr* 2008 (in press).

Test Information

0051752 FG Syndrome FGS1 (MED12) R961W Mutation

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.