

Freeman-Sheldon Syndrome (MYH3) Sequencing, Exon 17

TO CONFIRM A CLINICAL DIAGNOSIS OF FREEMAN-SHELDON SYNDROME

Test Highlight

Includes testing for two common mutations: R672C and R672H.

Disease Overview

- Freeman-Sheldon syndrome (FSS), distal arthrogyposis type 2A, is a congenital contracture disorder with variable clinical presentation.
- Affected individuals display muscle contractures in the face (“whistler appearance”) as well as in the joints of the fingers, hands, elbows, hips, ankles, feet, and toes. Other characteristic features include dysmorphic facial features, scoliosis, limited neck motion, strabismus, dental crowding, hearing loss, cryptorchidism, and inguinal hernia.
- Life-threatening respiratory complications occur frequently due to oropharyngeal and thoracic cage abnormalities.
- Difficulties with feeding, walking, hand function, and articulation may require early intervention, including occupational, physical, and speech therapy.
- Craniofacial, orthopedic, or plastic surgery may correct the size of the mouth and frontal bone or eye openings, or reduce spinal curvature and contractures.
- Any surgery requiring general anesthesia should be performed in tertiary care centers due to the risk of adverse reactions in individuals with FSS.

Epidemiology

Uncertain incidence and prevalence; approximately 100 cases have been reported to date.

Genetics

- Autosomal dominant; approximately 70 percent of cases represent new mutations.
- Mutations identified in the embryonic myosin heavy chain (*MYH3*) gene account for 93 percent of cases. No other FSS-associated genes have been identified.
- MYH3* mutations affect the structure of the myosin head near the ATP-binding sites, disrupting the normal function of myosin in muscle contraction.

- Two common missense mutations, c.2014C>T (p.R672C) and c.2015G>A (p.R672H), occur in exon 17 of *MYH3* and account for 72 percent of FSS cases.

Indication for Ordering

To confirm a clinical diagnosis of FSS.

Interpretation

- Positive: Individuals with a pathogenic *MYH3* mutation are predicted to be affected with FSS.
- Negative: If no exon 17 *MYH3* mutations are identified, the risk for FSS is reduced but not eliminated.
- MYH3* exon 17 sequencing may identify mutations with unknown clinical significance.

Methodology

- Polymerase chain reaction (PCR) followed by bidirectional sequencing of *MYH3* exon 17.
- Analytical sensitivity and specificity are 99 percent.
- Clinical sensitivity is approximately 70 percent.

References

- Stevenson DA, et al. Clinical characteristics and natural history of Freeman-Sheldon syndrome. *Pediatr* 2006;117(3):754–62.
- Tajsharghi H, et al. Embryonic myosin heavy-chain mutations cause distal arthrogyposis and developmental myosin myopathy that persists postnatally. *Arch Neurol* 2008;65(8):1083–90.
- Toydemir RM, et al. Mutations in embryonic myosin heavy chain (*MYH3*) cause Freeman-Sheldon syndrome and Sheldon-Hall syndrome. *Nat Genet* 2006;38(5):561–65.
- Vimercati A, et al. Prenatal diagnosis of Freeman-Sheldon syndrome and usefulness of an ultrasound fetal lip width normogram. *Prenat Diagn* 2006;26(8):679–83.

Test Information

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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.