Freeman-Sheldon Syndrome, *MYH3* Exon 17 Sequencing

Indications for Ordering

Confirmation of clinical diagnosis of Freeman-Sheldon syndrome (FSS), distal arthrogryposis type 2A (DA2A)

Test Description

Polymerase chain reaction followed by bidirectional sequencing of exon 17 of *MYH3* gene

Tests to Consider

Primary test

Freeman-Sheldon Syndrome (*MYH3*) Sequencing Exon 17 2002662

- Diagnostic testing for FSS

Disease Overview

Prevalence – rare (~100 cases reported)

Symptoms

- Muscle/joint contractures
  - Face ("whistling facies")
  - Fingers/hands/elbows
  - Hips/ankles/feet/toes
    - Above defects lead to difficulty with feeding, walking, hand function, articulation
- Dysmorphic facial features
- Scoliosis
- Limited neck motion
- Strabismus
- Dental crowding
- Hearing loss
- Cryptorchidism
- Inguinal hernia
- Risk for life-threatening malignant hyperthermia associated with general anesthesia

Genetics

Genes – *MYH3*

Inheritance – primarily autosomal dominant

De novo mutations – ~70%

Mutations

- 93% of FSS cases have an *MYH3* gene mutation
- Two common missense mutations occur in exon 17
  - c.2014C>T (p.R672C) and c.2015G>A (p.R672H)
  - Account for 72% of FSS cases
- Some individuals with FSS have *MYH* mutations outside of exon 17

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity – ~70%
- Analytical sensitivity/specificity – 99%

Results

- Positive – mutation detected
  - Predicts individual is affected with FSS
- Negative – no mutation detected
  - Risk for FSS is reduced but not eliminated
- Undetermined – mutation detected, but whether it is pathogenic is unknown

Limitations

Detects mutations only in exon 17 of *MYH3* gene

- No other mutations will be detected