Kabuki Syndrome (KMT2D) Sequencing

Indications for Ordering

Confirm diagnosis of Kabuki syndrome (KS)

Test Description

Bidirectional sequencing of KMT2D coding regions and intron/exon boundaries

Tests to Consider

Primary test
Kabuki Syndrome (KMT2D) Sequencing 2009306
  • Detects most pathogenic variants

Related tests
Familial Mutation, Targeted Sequencing 2001961
  • Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Prevalence
  • Japanese population – 1/32,000
  • New Zealand and Australian populations – 1/86,000
  • KS has been reported in almost all ethnic groups
    0 Prevalence in other ethnic groups is likely similar to that of the Japanese population

Symptoms
  • Distinctive facial appearance, most prominent in early childhood
    0 Arched eyebrows with sparse lateral third, long palpebral fissures with eversion of the lower eyelid
    0 Blue sclerae
    0 Flat nasal tip
    0 Large dysplastic ears
    0 Long dense eyelashes
    0 Thin upper lip and full lower lip
  • Abnormal dentition
  • Attenuation and/or absence of the distal interphalangeal flexion crease
    0 Brachydactyly
  • Cryptorchidism
  • Dermatoglyphic pattern abnormalities
  • Developmental delay
  • Early breast development in infant girls
  • Feeding difficulties
  • Gastroesophageal reflux
  • Hearing loss
  • Hypospadias
  • Hypotonia
    0 Joint dislocations/hypermobility
  • Microcephaly
  • Ocular abnormalities
  • Palatal malformations
  • Persistent fetal fingertip pads
  • Renal and cardiac malformations
  • Repeated infections
  • Seizures
  • Short stature
  • Skeletal abnormalities
  • Structural brain abnormalities
    0 Varying degree of intellectual disability

Genetics

Gene – KMT2D (previously known as MLL2)
  • Most common cause of KS

Inheritance – autosomal dominant

Pathogenic variants
  • De novo variants
    0 Up to 80% of all identified KMT2D pathogenic variants
  • Mosaicism
    0 Low-level KMT2D gene mosaic pathogenic variants may occur
  • Large deletions/duplications
    0 Up to ~5% of all identified KMT2D pathogenic variants (Banka, 2012)
    0 Will not be detected by KMT2D sequencing
  • Up to 10% of individuals with KS and negative KMT2D testing have pathogenic variants in the KDM6A gene (Lederer, 2012; Miyake, 2013)
    0 Will not be detected by KMT2D sequencing

Test Interpretation

Sensitivity/specificity
  • Clinical sensitivity – ~70% (Banka, 2012; Hannibal, 2011)
  • Analytical sensitivity/specificity – 99%
Results

- Positive – one pathogenic variant detected in KMT2D gene
  - Confirms diagnosis and etiology
- Negative – no pathogenic variant detected in KMT2D gene
  - A diagnosis of KS is less likely but not excluded
- Uncertain – variants of unknown clinical significance may be identified

Limitations

- Deep intronic pathogenic variants and some regulatory region variants will not be detected
- Large deletions/duplications will not be detected
- KDM6A pathogenic variants or variants in other yet undiscovered genes associated with KS will not be detected
- Germline or somatic mosaicism will not be detected
- Diagnostic errors can occur due to rare sequence variations

References