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
  - Prevalence in other ethnic groups is likely similar to that of the Japanese population

Symptoms
- Distinctive facial appearance, most prominent in early childhood
  - Arched eyebrows with sparse lateral third, long palpebral fissures with eversion of the lower eyelid
  - Blue sclerae
  - Flat nasal tip
  - Large dysplastic ears
  - Long dense eyelashes
  - Thin upper lip and full lower lip
- Abnormal dentition
- Attenuation and/or absence of the distal interphalangeal flexion crease
  - Brachydactyly
- Cryptorchidism
- Dermatoglyphic pattern abnormalities
- Developmental delay
- Early breast development in infant girls
- Feeding difficulties
- Gastroesophageal reflux
- Hearing loss
- Hypospadias
- Hypotonia
  - 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
  - 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
  - Up to 80% of all identified *KMT2D* pathogenic variants
- Mosaicism
  - Low-level *KMT2D* gene mosaic pathogenic variants may occur
- Large deletions/duplications
  - Up to ~5% of all identified *KMT2D* pathogenic variants (Banka, 2012)
  - 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)
  - 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

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