Kabuki Syndrome (KMT2D) Sequencing

Kabuki syndrome (KS) is a genetic disorder that results in particular dysmorphic facial features and often includes developmental delay or intellectual disability. Pathogenic variants in the \textit{KMT2D} gene are the most common etiology, accounting for about 56-75\% of cases. Causative variants in the \textit{KDM6A} gene have also been reported.\textsuperscript{1} In approximately 30\% of individuals, the genetic cause cannot be determined.\textsuperscript{2}

Disease Overview

Prevalence

- In Japan: \textasciitilde 1:32,000\textsuperscript{2}
- In other ethnic groups: likely similar to that of the Japanese population\textsuperscript{2}

Incidence

New Zealand and Australian populations: 1:86,000\textsuperscript{2}

Diagnostic Criteria

A definitive diagnosis of KS requires\textsuperscript{3}:

- Developmental delay and/or intellectual disability
- Infantile hypotonia
- One or both of the following:
  - Pathogenic variant of \textit{KMT2D} or \textit{KDM6A}
  - Dysmorphic features
    - Arched eyebrows with sparse lateral third, long palpebral fissures with eversion of the lower eyelid
    - Flat nasal tip
    - Large dysplastic ears
    - Persistent fingertip pads

Genetics

Gene

\textit{KMT2D} (previously known as \textit{MLL2})\textsuperscript{2}

Inheritance

Autosomal dominant\textsuperscript{2}
Pathogenic Variants

- Over 400 pathogenic *KMT2D* variants have been reported, including:
  - Nonsense mutations
  - Small deletions
  - Small insertions or duplications
  - Missense variants
  - Splice-site variants
  - Several large deletions/insertions (not detected by *KMT2D* sequencing)
- Percentage of de novo variants is unknown but likely high

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity: ~75%
- Analytical sensitivity/specificity: 99%

Results

<table>
<thead>
<tr>
<th>Results</th>
<th>Result Description</th>
<th>Interpretive Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>One pathogenic variant detected in <em>KMT2D</em> gene</td>
<td>Confirms diagnosis and etiology</td>
</tr>
<tr>
<td>Negative</td>
<td>No pathogenic variant detected in <em>KMT2D</em> gene</td>
<td>Diagnosis of KS less likely but not excluded</td>
</tr>
<tr>
<td>Uncertain</td>
<td>Variant(s) of unknown clinical significance identified</td>
<td>Inconclusive</td>
</tr>
</tbody>
</table>

Limitations

- Large deletions/duplications, deep intronic pathogenic variants and some regulatory region variants 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


