ORIGINAL ARTICLE

Kabuki syndrome: international consensus diagnostic criteria

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ABSTRACT

Background Kabuki syndrome (KS) is a clinically recognisable syndrome in which 70% of patients have a pathogenic variant in *KMT2D* or *KDM6A*. Understanding the function of these genes opens the door to targeted therapies. The purpose of this report is to propose diagnostic criteria for KS, particularly when molecular genetic testing is equivocal.

Methods An international group of experts created consensus diagnostic criteria for KS. Systematic PubMed searches returned 70 peer-reviewed publications in which at least one individual with molecularly confirmed KS was reported. The clinical features of individuals with known mutations were reviewed.

Results The authors propose that a definitive diagnosis can be made in an individual of any age with a history of infantile hypotonia, developmental delay and/or intellectual disability, and one or both of the following major criteria: (1) a pathogenic or likely pathogenic variant in *KMT2D* or *KDM6A*; and (2) typical dysmorphic features (defined below) at some point of life. Typical dysmorphic features include long palpebral fissures with eversion of the lateral third of the lower eyelid and two or more of the following: (1) arched and broad eyebrows with the lateral third displaying notching or sparseness; (2) short columella with depressed nasal tip; (3) large, prominent or cupped ears; and (4) persistent fingertip pads. Further criteria for a probable and possible diagnosis, including a table of suggestive clinical features, are presented.

Conclusion As targeted therapies for KS are being developed, it is important to be able to make the correct diagnosis, either with or without molecular genetic confirmation.

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INTRODUCTION

Kabuki syndrome (KS [MIM: 147920 and 300867]) was first described by Niikawa *et al*[1] and Kuroki *et al*[2] and has over the course of time become a well-recognised multiple congenital anomaly/intellectual disability disorder. Niikawa *et al*[3] initially defined five cardinal manifestations of KS, including postnatal growth restriction, dysmorphic facial features (long palpebral fissures with eversion of the lateral third of the lower eyelid; arched and broad eyebrows with the lateral third displaying notching or sparseness; large, prominent or cupped ears; and short columella with depressed nasal tip), skeletal anomalies (brachymesophalangy, brachydactyly V, spinal column abnormalities and fifth digit clinodactyly), dermatoglyphic abnormalities (most commonly persistent fingertip pads) and intellectual disability (typically in the mild to moderate range). Various combinations of these five cardinal manifestations should prompt the clinician to consider a diagnosis of KS; however, the cardinal manifestations were not developed in such a way as to constitute official clinical diagnostic criteria. A host of other congenital anomalies and functional differences have been described in association with KS, and various combinations of these features may also prompt consideration of the diagnosis.[4 5]

In 2010 heterozygous pathogenic variants in *KMT2D* (NM_003482.3; previously known as *MLL2*, *MLL4* or *ALR*) were reported as a cause of KS.[6] Two years later *KDM6A* (NM_001291415.1; also known as *UTX*) was identified as a second gene in which mutations can lead to features of KS.[7–9] Thereafter, Makrythanasis *et al*[10] developed a phenotypic scoring system with the purpose of predicting which individuals with features of KS were more likely to have a heterozygous pathogenic variant in *KMT2D* (see table 1). The authors then prospectively applied their proposed scoring system to a group of 86 individuals clinically diagnosed with KS; after performing genetic testing for *KMT2D* on their cohort, they compared the clinical score with the molecular genetic testing results. Individuals with heterozygous pathogenic *KMT2D* variants had a statistically significantly higher mean score (6.1) compared with those who did not have an identified pathogenic variant in *KMT2D* (4.5). While this system is useful in determining the utility of molecular genetic testing for pathogenic variants in *KMT2D* as opposed to *KDM6A* or other genes that lead to overlapping features of KS, it was not designed to be used as formal diagnostic criteria for KS.[11]

Understanding the function of the genes that lead to KS opens the door to the possibility of targeted therapies for affected individuals.[12–15] If specific therapeutic interventions for KS become available, high diagnostic certainty will acquire even more importance. While molecular genetic confirmation is considered the gold standard for diagnosis (with

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Table 1 Kabuki syndrome phenotypic scoring system*

Clinical finding	Possible score	Scored features
Facial features	0–5 points†	Abnormal dentition.
		Arched eyebrows, sparse lateral one-third.
		Blue sclerae.
		Broad nasal root.
		Everted lower eyelids.
		Flat nasal tip.
		High or cleft palate.
		Large dysplastic ears.
		Lip nodules.
		Long palpebral fissures.
		Micrognathia.
		Oligodontia.
		Ptosis.
		Strabismus.
		Thin vermillion of the upper lip and full lower lip.
Limb/extremity features	Up to 1 point‡	Brachydactyly or clinodactyly.
		Hip dislocation.
		Lax joints.
		Persistent fetal pads.
Heart	1 point	
Kidney	1 point	
Microcephaly	1 point	
Short stature	1 point	
Sum	0–10 points	

*Adapted from Makrythanasis *et al*.[10]
†0–3 features=1 point; 4–6 features=2 points; 7–9 features=3 points; 10–12 features=4 points; 13–15 features=5 points.
‡0–1 feature=0 point; 2–4 features=1 point.

an analytical sensitivity of ~99% for sequence analysis), not all pathogenic variants that lead to a phenotype will be detected with current Sanger sequencing, next-generation sequencing and/or gene-targeted deletion/duplication analysis. This is made more difficult by the large size of the *KMT2D* (42 921 bases) and *KDM6A* (239 605 bases) genes. Genetic changes deep in an intron or in regulatory elements of a gene theoretically could lead to features of a condition but might not be detected with clinically available molecular genetic testing methodologies. Furthermore, molecular genetic testing is not universally available. Given that KS is a recognisable phenotype, it would be useful to define international consensus clinical diagnostic criteria that can be used when molecular methods are unavailable or if genetic testing is equivocal (eg, a variant of unknown clinical significance is identified).

METHODS

Clinical and molecular genetic experts on KS from Canada, the European Union, Japan, the UK and the USA were invited to a 1-day meeting in Boston, Massachusetts, which was teleconferenced to Japan and England, with the purpose of defining consensus diagnostic criteria for KS. Although the meeting was facilitated and organised by Takeda, Takeda did not have any influence on the content of this report. This paper summarises the recommendations of the international expert panel and proposes formal diagnostic criteria.

First the authors systematically reviewed available literature on KS. PubMed searches using the terms 'Kabuki', 'Kabuki make-up' and 'Niikawa-Kuroki' were performed. Each citation was reviewed for date of publication, relevance to clinical features of KS and whether molecular genetic testing of *KMT2D* and/or *KDM6A* was performed (figure 1). First, a review of the title and/or abstract was performed. Articles that clearly did not apply to KS specifically (eg, the use of next-generation sequencing to determine causes of congenital heart defects detected in a prenatal setting), focused solely on the cellular function of *KMT2D* and/or *KDM6A* without providing human phenotypic data, or were not available in English were excluded. Those reports published prior to the identification of *KMT2D* as a cause for KS were also excluded. Of the remaining 123 publications, a review of the full text was performed. Only those reports where at least one individual with KS had either a pathogenic variant in *KMT2D* or *KDM6A* without a second genetic diagnosis (eg, a concomitant chromosome abnormality) were retained and clinical information about mutation-positive individuals was reviewed. Fifty-three publications were excluded for the following reasons: data were given in a compiled format (eg, median height with SD); data for those with KS due to pathogenic variants in *KMT2D* and those with pathogenic variants in *KDM6A* were pooled together and compared with data in individuals who had neither a *KMT2D* nor a *KDM6A* pathogenic variant; or the reported patients were not unique and data on at least a portion of the cohort were reported previously.

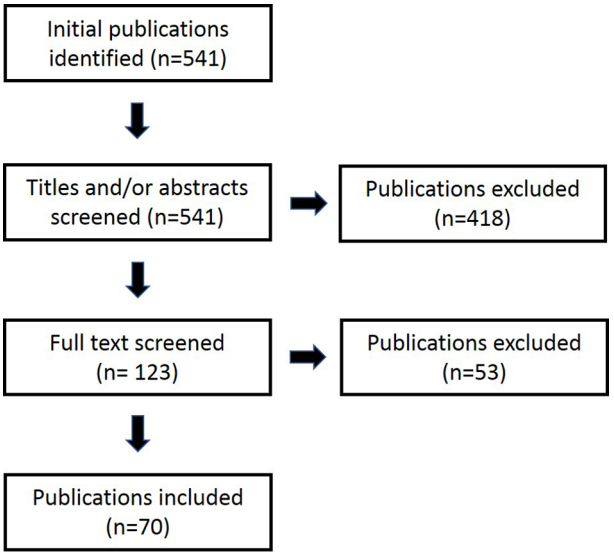

Figure 1 Summary of literature review algorithm. Reasons for exclusion after review of the title and/or abstract included the following: report was not specific to Kabuki syndrome; manuscript was focused solely on the cellular function of *KMT2D* and/or *KDM6A*; report was not available in English; or manuscript was published prior to the identification of the first gene that leads to Kabuki syndrome. Reasons for exclusion after review of the entire text included the following: data were reported as a compilation for the purposes of statistical analysis; reported data focused on a feature that we did not score (ie, manuscript discussed only seizure types and/or optimal antiseizure medication management); or clinical data from individuals with a pathogenic variant in *KMT2D* were pooled with clinical data on individuals with a pathogenic variant in *KDM6A*.

RESULTS

Seventy peer-reviewed publications on KS that met the criteria above were reviewed (online supplementary information). Clinical information on a variety of features that have been described in association with KS and have been used in various

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scoring systems was evaluated. Clinical information on a total of 449 individuals with molecularly confirmed KS was compiled (figure 2). Of the 449 individuals, 399 (172 females, 167 males and 60 individuals whose sex was not provided) had a pathogenic variant in *KMT2D* and 50 (30 females and 20 males) had a pathogenic variant in *KDM6A*.

In creating the proposed diagnostic criteria, the authors were particularly interested in articles that focused on clinical features, genotype–phenotype correlations and previously published scoring systems. The authors also discussed at length whether to use a scoring system, such as the type published by Makrythanasis *et al*,[10] or to use a system of major and minor findings, as is used to provide a clinical diagnosis in conditions such as tuberous sclerosis complex. Furthermore, the group weighed the likely sensitivity and specificity of the possible criteria, attempting to optimise both. Ultimately the group decided against using a scoring system, although the system developed by Makrythanasis *et al*[10] could help support a clinical diagnosis of KS in those patients who have either a probable or a possible diagnosis of KS using the diagnostic criteria proposed here.

The international expert panel proposes that a *definite diagnosis* of KS can be made in a male or female patient of any age with a history of infantile hypotonia, developmental delay and/or intellectual disability, *and* one or both of the following major criteria:

1. A pathogenic or likely pathogenic variant in *KMT2D* or *KDM6A*.[¥]
2. Typical dysmorphic features (defined below) at some point of life.[*]

Typical dysmorphic features include long palpebral fissures (a palpebral fissure measurement[§] greater than or equal to 2 SD above the mean for age) with eversion of the lateral third of the lower eyelid *and* two or more of the following:

1. Arched and broad eyebrows with the lateral third displaying notching or sparseness.
2. Short columella with depressed nasal tip.
3. Large, prominent or cupped ears.
4. Persistent fingertip pads.

[¥]The intent of the authors is that the genetic change in *KMT2D* or *KDM6A* is a pathogenic variant or a likely pathogenic variant as defined by Richards *et al*[16]; variants of unknown clinical significance cannot be used as a major criterion.

[*]The facial features of KS change over time. The features are most easily recognisable and classic in an individual who is between the ages of 3 and 12 years. In infants, the typical facial features may be more difficult to recognise.[5] In adolescents and adults, the eversion of the lower eyelid may resolve.

[§]In order to obtain a palpebral fissure measurement, ideally the examiner would sit at eye level with the patient. If the patient is cooperative and can follow directions, the patient is asked to keep the head in a neutral position while looking up to the ceiling with the eyes. A clear ruler is used to measure the distance from the medial canthus to the lateral canthus (figure 3).

A *probable diagnosis* can be made in an individual with a history of infantile hypotonia, developmental delay, and/or intellectual disability *and* long palpebral fissures (a palpebral fissure measurement greater than or equal to 2 SD above the mean for age) with eversion of the lateral third of the lower eyelid *and* at least three supportive clinical features (see table 2). The three supportive clinical features can be in any combination and from any system listed in table 2 (eg, one feature each from three systems, all three features from one system or any other combination thereof). The presence of other typical dysmorphic features would increase the probability of the diagnosis, as would a score of 6.0 or more using the phenotypic scoring system proposed by Makrythanasis *et al*.[10]

A *possible diagnosis* should be entertained in an individual with a history of developmental delay and/or intellectual disability *and* at least two supportive clinical features (see table 2) *and* at least one of the following dysmorphic features at one point of life:

1. Arched and broad eyebrows with the lateral third displaying notching or sparseness.
2. Short columella with depressed nasal tip.
3. Large, prominent or cupped ears.
4. Persistent fingertip pads.

For individuals who have a probable or a possible diagnosis of KS, clinical genetic testing should be strongly considered, as the features listed above are not specific to KS. In this situation, other testing (eg, chromosomal microarray) may also be considered to evaluate for a condition with features that overlap with KS.

DISCUSSION

In developing diagnostic criteria for KS, the expert panel performed a systematic review of information from the published literature on the features that are more specific for KS, particularly those features that are seen in individuals who have a known pathogenic variant in *KMT2D*. There is limited information on the range of clinical features seen in individuals who have a heterozygous or hemizygous pathogenic variant in *KDM6A*. While the typical facial gestalt and many of the other common features of KS, including mild humoral immunodeficiency, have been reported in these individuals as well, the frequency of such findings in larger cohorts of affected individuals is unknown.[17–19]

The authors also took into account previously published suggestions for diagnostic criteria. For example, Cheon *et al*[20] suggested that the minimal clinical diagnostic criteria for KS regardless of ethnicity include the following: long palpebral fissures with lateral eversion of the lower eyelid, short columella with depressed nasal tip, broad and arched eyebrows with lateral sparseness, cupped or prominent ears, and developmental delay/cognitive impairment. The criteria proposed here also include this list of features in varying combinations.

Not surprisingly, individuals with typical facial features (the four original facial features described by Niikawa *et al*[3]) are more likely to have a pathogenic variant in *KMT2D*, which may reflect the fact that some individuals with features that are suggestive of KS may have other conditions. Consistent with this finding, Makrythanasis *et al*[10] identified 10 features found more commonly in individuals with pathogenic variants in *KMT2D*: blue sclerae, arched eyebrows, broad nasal root, depressed nasal tip, large dysplastic ears, thin vermilion of the upper lip and thick vermilion of the lower lip, joint laxity, short stature, frequent infections, and intellectual disability. Characteristic dental abnormalities (absent lateral upper incisors, absent lower incisors and/or second premolars, abnormal 'flat head' screwdriver shape of the upper incisors) may be more common in those with a heterozygous pathogenic variant in *KMT2D*.[21 22] Furthermore, renal anomalies, premature thelarche in females, palatal anomalies and feeding problems are seen more commonly in those with a pathogenic variant in *KMT2D* compared with those who do not have a pathogenic variant in *KMT2D*.[8 23–25]

Makrythanasis *et al*[10] developed a phenotypic scoring system with the purpose of determining which individuals were more likely to have a pathogenic variant in *KMT2D*. Two small

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Phenotypic Feature	Number of individuals reported with this feature who had a heterozygous pathogenic variant in *KMT2D*	Number of individuals reported with this feature who had a heterozygous or hemizygous pathogenic variant in *KDM6A*
Intellectual disability (IQ <70)	238	30
Fetal fingertip pads	224	28
Congenital heart defect	212	15
Long palpebral fissures	186	35
Large, prominent or cupped ears	159	25
Hypotonia	154	26
Eversion of the lower eyelid	149	24
Arched or broad eyebrows	134	16
Cleft palate	129	3
Brachydactyly	127	15
Short columella with depressed nasal tip	111	15
Short stature	108	30
Microcephaly	96	19
Oligodontia and/or abnormal incisors	94	15
Feeding difficulties	86	26
Developmental delay	82	8
Lateral eyebrows sparse or notched	65	21
Hearing loss	62	2
Nontraumatic joint dislocation	44	10
Hypogammaglobulinemia or low serum IgA	22	1
Hyperinsulinemic hypoglycemia in infancy	11	7
Lip pits	10	1
Malpositioned kidneys	8	0
Idiopathic thrombocytopenia purpura (ITP)	6	0
Hypospadias in males	2	0

Figure 2 Graphic representation of reported phenotypic features in 449 individuals with Kabuki syndrome, divided by molecular mechanism, as summarised from 70 publications (online supplementary information). Not every feature was reported or assessed in each reported individual and some data were not reported in a granular fashion. For example, the number of reported individuals with malposition of the kidney is likely an underestimate, as many publications reported 'renal anomalies' without specifying the type of anomaly.

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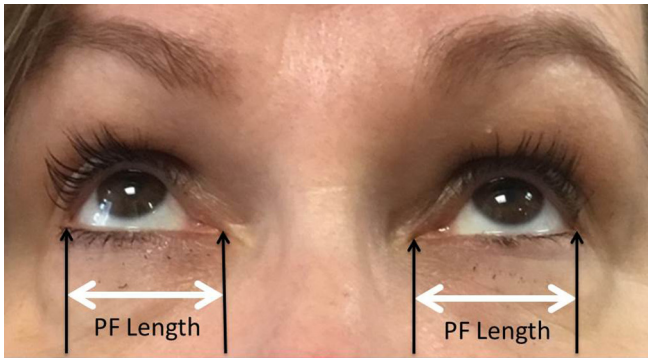

Figure 3 The patient is asked to keep the head in a neutral position while looking up to the ceiling. A clear ruler is used to measure the distance between the inner and outer canthus (black arrows), which is the palpebral fissure (PF) length (white arrows).

validation studies of the scoring system were then published by Paděrová *et al*[26] and Paderova *et al*.[11] In both studies the number of individuals included was small and overlapping. In the first study 14 individuals with features of KS were given a clinical score using the system reported by Makrythanasis *et al*.[10] Genetic testing found a pathogenic variant in 6 out of 14 individuals. The mean score in *KMT2D*-positive individuals was 8.0 (range 7.0–9.0), while the mean score in *KMT2D/KDM6A*-negative individuals was 4.8 (range 4.0–7.0).[26] It should be noted, however, that a score of 7.0 was given to one individual with a pathogenic variant in *KMT2D* and to one individual who did not have a pathogenic variant in either *KMT2D* or *KDM6A*.

Table 2 Supportive clinical features

System	Clinical feature
Constitutional	Short stature.*
Craniofacial	Microcephaly.†
	Cleft palate.
	Lip pits.
	Oligodontia and/or abnormal incisors.‡
	Progressive sensorineural hearing loss.
Cardiac	Congenital heart defect§, excluding a patent ductus arteriosus.
Gastrointestinal	Feeding difficulties.¶
Genitourinary	Malpositioned kidneys.
	Hypospadias in males.
Musculoskeletal	Brachydactyly.
	Non-traumatic joint dislocation, including congenital hip dislocation.
Endocrinological	Hyperinsulinaemic hypoglycaemia in infancy.
Immunological	Hypogammaglobulinaemia or low serum IgA.**
	Idiopathic thrombocytopaenia purpura.

*Length or height less than or equal to 2 SD below the mean for age and sex, particularly after 1 year of age.[38]
†Head circumference less than or equal to 2 SD below the mean for age and sex.
‡Absent lateral upper incisors, absent lower incisors, missing second premolars, ectopic upper 6-year molars and/or 'flat head' screwdriver-shaped appearance of the upper incisors.
§Approximately 70% of individuals with a heterozygous pathogenic variant in *KMT2D* will have a congenital heart defect, in particular left-sided obstructive lesions and mitral anomalies.[39]
¶Poorly coordinated suck and swallow, often requiring nasogastric or gastrostomy tube feeding for a period of time.
**Lindsley *et al*. Defects of B-cell terminal differentiation in patients with type-1 Kabuki syndrome. *J Allergy Clin Immunol* 2016;137:179–87.

In the second validation study, a total of 24 individuals (7 of whom were in the Paděrová *et al*[26] study) were evaluated. Of 15 individuals with a score above 6.0, 10 (66.7%) had a pathogenic variant in *KMT2D* and no individual with a score below 5.0 was found to have a pathogenic variant in *KMT2D*.[11]

Intellectual disability is another feature that is common in individuals with KS. The degree of intellectual disability typically falls in the mild to moderate range, with severe intellectual disability being uncommon. However, not every person with KS will have intellectual disability,[7 27–33] and this feature cannot be assessed in a newborn or infant.[27] Caciolo *et al*[28] performed standardised neuropsychiatric testing on a cohort of 17 individuals with KS (9 of whom had a confirmed heterozygous pathogenic variant in *KMT2D* and 8 of whom had a clinical diagnosis of KS) and found that there were no significant differences in the neuropsychological profile between those with a molecular diagnosis and those with a clinical diagnosis. They again confirmed that a majority of affected individuals (11/17; 66%) had an IQ level that was below 80, similar to previous findings by Matsumoto and Niikawa[34] that 84% of affected individuals had an IQ level below 80. However, individuals with KS also have substantial weakness in motor skills, which may stem from a combination of joint laxity and hypotonia.[28 34 35] Therefore, to address the neurological and developmental issues in the newborn and young child, hypotonia and/or developmental delay can substitute for intellectual disability in the proposed diagnostic criteria.

When establishing the suggestive findings listed in table 2, the authors tried to balance the information above with the specificity of the finding to KS in particular. For example, while blue sclera is one of the 10 features that Makrythanasis *et al*[10] found to be more common in individuals with a heterozygous pathogenic variant in *KMT2D* compared with mutation-negative individuals, this feature can be seen in a variety of connective tissue disorders and is also a normal finding in infants under the age of 1 year. Similarly, premature thelarche (isolated breast development in a female under the age of 8) is not seen frequently in other genetic syndromes but is present in up to 90% of normal neonates.[36] Therefore, these features were not felt to be specific enough to KS to be included in table 2. Conversely, long palpebral fissures with eversion of the lateral third of the lower eyelid is a relatively specific (although not pathognomonic) feature for KS that is seen in few other genetic syndromes or in the general population as a whole. The other facial features seen in KS are less specific. Therefore, in order to make a definitive or probable clinical diagnosis of KS, long palpebral fissures with eversion of the lateral third of the lower eyelid at some point of life is required.

The authors applied our proposed diagnostic criteria to three individuals with mosaic KS reported in the literature.[37] Each reported patient had a mosaic heterozygous pathogenic variant in *KMT2D* and was reported to have mild clinical features of KS. Using our proposed clinical diagnostic criteria (ignoring the molecular confirmation), two out of three of these reported individuals would have been given a definitive clinical diagnosis of KS. Less information on physical phenotype was presented for the third patient in this report, so this patient would not have qualified for a clinical diagnosis of KS but would have been assigned the diagnosis based on molecular genetic testing results.

In choosing which features to include in the diagnostic criteria, the authors have attempted to balance the need for specificity without significantly decreasing the sensitivity. However, the authors realise that these criteria may need to be modified in the future, particularly as evaluations of the diagnostic sensitivity and specificity are studied and as more information is learnt

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about the clinical features in individuals with a heterozygous pathogenic variant in *KDM6A*. Because targeted treatments for KS are currently being developed, however, consensus diagnostic criteria are needed now.

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Contributors MPA, SB, HTB, OF, AEC, CTS and NN planned the study and created the study design, including reviewing and compiling relevant clinical and molecular features of large cohorts of individuals with Kabuki syndrome. JH, HK, BCL, AWL, GM, NM and NO reviewed and interpreted the data. Based on the data, JH, HK, BCL, AWL, GM, NM, NO, MPA, SB, HTB, OF, AEC, CTS and NN constructed the diagnostic criteria, including multiple discussions around using a scoring system versus a system of major and minor criteria. JH, HK, BCL, AWL, GM, NM, NO, MPA, SB, HTB, OF, AEC, CTS and NN also determined which features should be listed in table 2, which outlines supportive findings in those who do not qualify for a definitive diagnosis of Kabuki syndrome based on major criteria. The Kabuki Syndrome Medical Advisory Board approved the consensus diagnostic criteria as presented in this manuscript. MPA wrote majority of the manuscript and is responsible for manuscript submission.

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Competing interests The clinical and molecular genetic experts on Kabuki syndrome who collaborated on this manuscript were all participants of the Kabuki Syndrome Medical Advisory Board organised and sponsored by Takeda in January 2018. Although the meeting was facilitated and organised by Takeda, Takeda did not have any influence on the content of this report.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement There are no unpublished data from this study.

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