Día Internacional Síndrome de Kabuki
23 Octubre 2020

S. de Kabuki: diagnóstico precoz y asesoramiento genético

Encarna Guillén Navarro

Presidenta de la Asociación Española de Genética Humana (AEGH)

Sección de Genética Médica. Servicio de Pediatría

Hospital Clínico Universitario Virgen de la Arrixaca

Universidad de Murcia

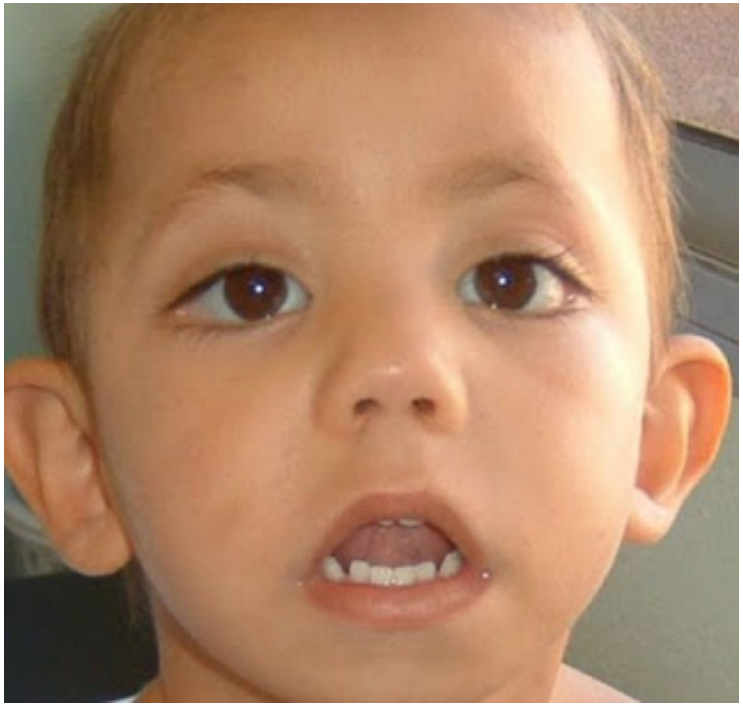
IMIB-Arrixaca. CIBERER-ISCIII

3ª Jornada médica-formativa sobre Síndrome de Kabuki

Dirigida a profesionales sanitarios, educadores, pacientes y familiares *

25 de Octubre de 2019. BURGOS

Síndrome de Kabuki



Discapacidad y Salud. Blog V. Velasco

- Descrito en 1981 por los investigadores japoneses Kuroki y Niikawa et al.
- Anomalías congénitas múltiples, rasgos faciales peculiares característicos, retraso de crecimiento y discapacidad intelectual de grado variable
- Origen: genético

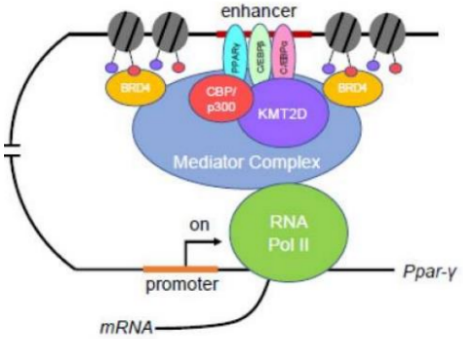
Base genética del Síndrome de Kabuki

- **75%: Gen *KMT2D*** (Bögershausen et al. 2010) en 12q13. **Herencia AD**

- **3-5%: Gen *KDM6A*** (Lederer et al. 2012) en Xp11.23. **Herencia ligada a X**

Las proteínas KMT2D y KDM6A son parte del complejo ASCOM actúan sobre regiones reguladoras favoreciendo la transcripción.

Intervienen en la diferenciación celular y el desarrollo embrionario



Síndrome de Kabuki

ORIGINAL ARTICLE

Kabuki syndrome: international consensus diagnostic criteria

Margaret P Adam,[1] Siddharth Banka,[2,3] Hans T Bjornsson,[4,5,6,7] Olaf Bodamer,[8,9] Albert E Chudley,[10,11] Jaqueline Harris,[12] Hiroshi Kawame,[13] Brendan C Lanpher,[1] Andrew W Lindsley,[16,17] Giuseppe Merla,[18] Noriko Miyake,[19] Nobuhiko Okamoto, Constanze T Stumpel,[21] Norio Niikawa,[22] the Kabuki Syndrome Medical Advisory Board

J Med Genet 2019;**56**:89–95.

KABUKY SYNDROME PHENOTYPIC SCORE SYSTEM:

No está diseñado para hacer el diagnóstico clínico de Síndrome de Kabuki. Su intención es identificar los pacientes en los que es más probable encontrar una variante patogénica en el gen *KMTD2*

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.

Síndrome de Kabuki
Diagnóstico Definitivo

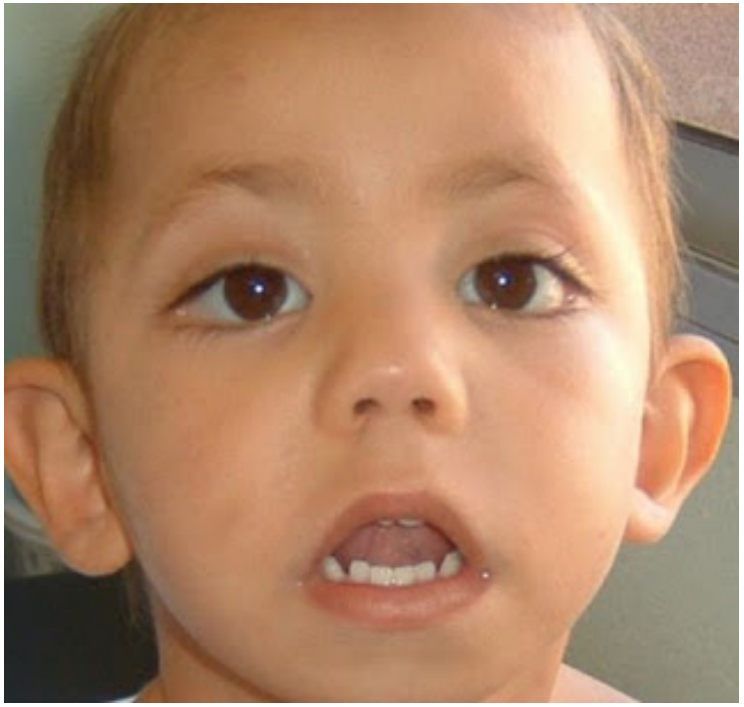
Mujeres y varones de cualquier edad con *hipotonía* en la infancia, *retraso psicomotor o discapacidad intelectual* y uno o ambos de los siguientes criterios mayores:

- Una variante patogénica o probablemente patogénica en *KMT2D* o *KDM6A*.

- Rasgos faciales característicos en algún momento de la vida

J Med Genet 2019;**56**:89–95.

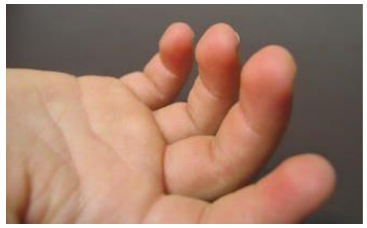
Síndrome de Kabuki
Rasgos típicos faciales



Discapacidad y Salud. Blog V. Velasco

Fisuras palpebrales elongadas con eversión del tercio lateral del párpado inferior, con dos o más de los siguientes rasgos:

- Cejas arqueadas con tercio externo ralo
- Columela corta con puente nasal deprimido
- Boca con apertura en tienda de campaña
- Pabellones auriculares grandes, de baja implantación
- Almohadillado fetal en dedos



J Med Genet 2019;**56**:89–95.

Síndrome de Kabuki

ANOMALÍAS ASOCIADAS

Sistema	Característica Clínica
Constitucional	Talla baja
Craneofacial	Microcefalia
	Paladar hendido
	Pits labiales
	Oligodontia y/o anomalía de los incisivos
	Hipoacusia progresiva
Cardíaco	Cardiopatía congénita, excluyendo ductus arterioso persistente
Gastrointestinal	Trastornos alimentarios
Genitourinario	Malposición renal
	Hipospadias en varones
Musculoesquelético	Braquidactilia
	Luxaciones articulares no traumáticas
Endocrinológico	Hipoglucemia hiperinsulínica en la infancia
Inmunológico	Hipogammaglobulinemia o IgA sérica disminuida
	Púrpura trombocitopénica inmune

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Kabuki Syndrome

System/Concern	Evaluation	Comment
Growth	Measurement of height, weight, & head circumference	FTT is a common sequela of feeding difficulties.
Ophthalmologic	Ophthalmology evaluation	For assessment of strabismus, refractive error, ptosis, & corneal abnormalities
Hearing	Baseline audiology evaluation	To assess for conductive &/or sensorineural hearing loss
Mouth	Directed evaluation of the palate for palatal anomalies	Consider referral to a craniofacial specialist if palatal anomalies are suspected.
	Consider dental evaluation for those age >3 yrs.	
Cardiac	Echocardiogram w/visualization of the aortic arch	To assess for congenital heart defects incl coarctation of the aorta
	Consider EKG.	If arrhythmia is suspected
Respiratory	Consider chest radiographs to assess for diaphragmatic eventuation.	In those w/respiratory issues, chronic cough, or recurrent pneumonia
Gastrointestinal/ Feeding	Assess nutritional status, feeding, GERD.	• Consider assessment by feeding team &/or VFSS for those w/suspected dysphagia. • Infants may have FTT; adolescents & adults may have obesity.
Genitourinary	Baseline renal ultrasound	To evaluate for renal anomalies & hydronephrosis
	Physical examination for hypospadias &/or cryptorchidism in males	

S. KABUKI

SEGUIMIENTO

Adam MP, Hudgins L, Hannibal M. Kabuki Syndrome. 2011 Sep 1 [Updated 2019 Feb 28]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available from: https://www.ncbi.nlm.nih.gov/books/NBK62111/

System/Concern	Evaluation	Comment
Musculoskeletal	Consider radiographs of the spine in those w/scoliosis.	To assess for vertebral anomalies
Endocrinologic	Assess for hyperinsulinism. [1]	In neonates & infants w/persistent hypoglycemia
	Assess for hypothyroidism & growth hormone deficiency. [2]	In those w/abnormal growth velocity
Immunologic	T cell count, T cell subsets, & serum immunoglobulin levels at time of diagnosis or at age 1 yr (whichever is later)	Refer to immunologist if: • Levels are abnormal; or • Patient has history of recurrent infections.
Neurologic	EEG	In those w/suspected seizures
	Head MRI	To evaluate for: • Structural brain malformation in those w/ seizures • Chiari I malformation in those w/suggestive symptoms [3]
Psychiatric/ Behavioral	Neuropsychiatric evaluation	Screen individuals age >12 mos for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD.
Miscellaneous/ Other	Developmental assessment	Evaluate motor, speech/language, general cognitive, & vocational skills.
	Consultation w/clinical geneticist &/or genetic counselor	

S. KABUKI

SEGUIMIENTO

Seguimiento Síndrome de Kabuki

Surveillance

Table 5. Recommended Surveillance for Individuals with Kabuki Syndrome

System/Concern	Evaluation	Frequency
Growth	Measurement of at least height & weight [1]	At each appointment
Ophthalmologic	Ophthalmology or optometry to assess vision	At least annually
Hearing	Hearing assessment	At least annually
Musculoskeletal	Clinical evaluation for scoliosis	At each appointment until skeletal maturity
Endocrinologic	Thyroid function tests	Every 2-3 yrs
Immunologic	Assessment of complete blood count	Every 2-3 yrs
Miscellaneous/ Other	Monitor developmental progress & educational needs.	At each visit during childhood & adolescence

1. Adolescents and adults may develop obesity.

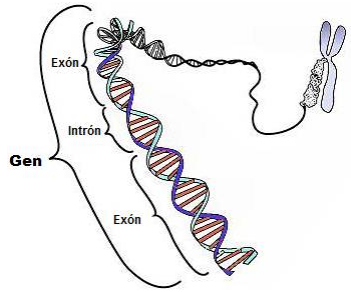
Adam MP, Hudgins L, Hannibal M. Kabuki Syndrome. 2011 Sep 1 [Updated 2019 Feb 28]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available from: https://www.ncbi.nlm.nih.gov/books/NBK62111/

Síndrome de Kabuki

Tratamiento

Manifestation/Concern	Treatment	Considerations/Other
Cleft lip &/or palate	Standard treatment	• Management through a specialized craniofacial clinic is ideal. • The palate may be shorter, which can lead to velopharyngeal insufficiency after typical cleft repair.
Dental anomalies	Orthodontic referral if hypodontia or significant malocclusion is noted	
Congenital heart defects &/or arrhythmia	Standard treatment per cardiologist	It is unclear whether risk for aortic aneurysm is ↑; however, if catheterization or angioplasty is being considered, a potential ↑ risk of aortic aneurysm should be communicated to treating team.
Feeding difficulties/GERD	Standard treatment, which may incl thickening feeds & appropriate positioning after meals in infants & toddlers	Pharmacologic treatment for GERD may be considered.
	Consider gastrostomy tube.	In those w/severe feeding difficulties &/or poorly coordinated suck & swallow
Chronic diarrhea	Refer to gastroenterologist.	Consider evaluation for malabsorption &/or celiac disease.
Hypospadias/ Cryptorchidism	Standard treatment per urologist	
Hyperinsulinism & hypothyroidism	Standard treatment per endocrinologist	
Short stature	Consider growth hormone therapy.	Refer to endocrinologist.
Recurrent infections	Intravenous immunoglobulin therapy may be considered in those w/documented immunoglobulin deficiency.	Refer to immunologist.
Seizure disorder	Standard antiepileptic treatment per neurologist	
Short stature	Growth hormone treatment may be considered. [2]	Refer to endocrinologist.
Premature thelarche	No treatment is warranted if there are no other signs of premature puberty.	
Need for anesthesia	Care in positioning during intubation due to joint laxity, which can affect the cervical spine	Educate regarding potential structural airway anomalies that could make intubation difficult.

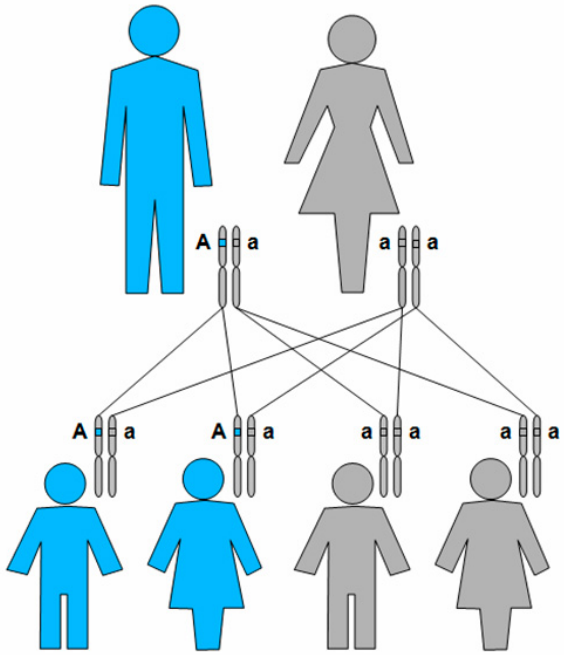
RELACIÓN GENOTIPO-FENOTIPO S. KABUKI



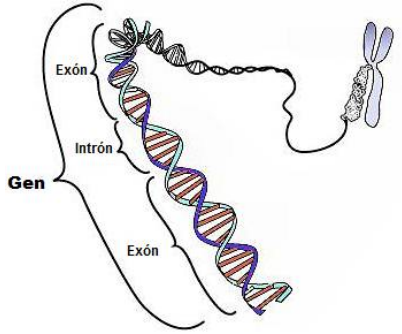
KMT2D: rasgos faciales característicos, alteraciones renales, trastornos de la alimentación, paladar hendido, telarquia precoz, luxaciones articulares.

- Patrón de herencia **autosómico dominante**.

- La mayoría de los pacientes presentan variantes genéticas ***de novo***, es decir, que han ocurrido por azar en ellos y los padres no son portadores. El riesgo de recurrencia es muy bajo para los progenitores. Para los afectados, sin embargo, sería de un 50% en el caso de tener descendencia



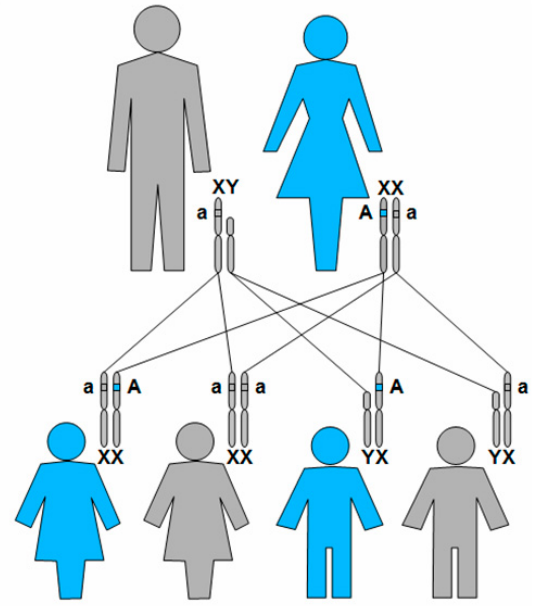
RELACIÓN GENOTIPO-FENOTIPO S. KABUKI



KDM6A: hipoglucemia, hipertricosis, halluces largos, incisivos centrales largos, mayor afectación cognitiva en varones.

- **Patrón de herencia ligado al cromosoma X** dominante, es decir, que los varones portadores de una variante patogénica manifiestan la enfermedad de una manera grave; mientras que las mujeres pueden manifestar la enfermedad con un grado variable de gravedad.

- Las mujeres portadoras tienen un riesgo de transmitir la enfermedad a su descendencia de un 50%,



Asesoramiento genético

- Propósito: proporcionar información y apoyo a las familias en riesgo de tener o que ya han tenido miembros afectados por defectos congénitos o enfermedad genética

ANTES Y DESPUÉS DEL ANÁLISIS GENÉTICO

Consentimiento informado

La identificación del defecto molecular permite opciones reproductivas seguras en caso de riesgo de recurrencia aumentado con Diagnóstico prenatal y/o preimplantatorio---**PREVENCIÓN**

IMPORTANCIA DEL DIAGNÓSTICO PRECOZ EN S. KABUKI

ESTABLECER DIAGNÓSTICO Y ETIOLOGÍA

ADECUADO MANEJO

MEJOR PRONÓSTICO/CALIDAD DE VIDA

ASESORAMIENTO GENÉTICO

MENSAJE FINAL

PREVENCIÓN NUEVOS CASOS EN LA FAMILIA

Muchas gracias por la atención