Hospital Infantil Universitario Niño Jesús

SaludMadrid

Comunidad de Madrid

AEFA KABUKI

Asociación Española de Familiares y Afectados

SÍNDROME DE KABUKI. GENERALIDADES

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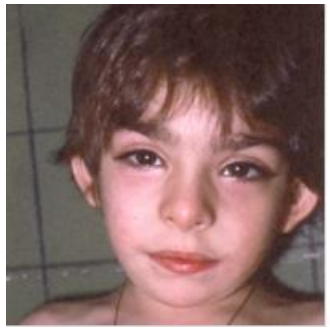
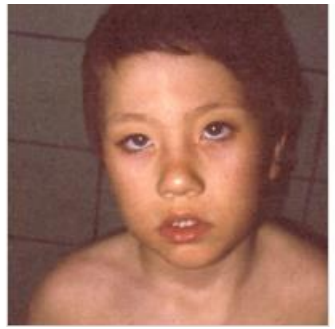
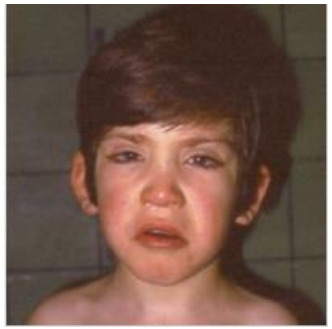
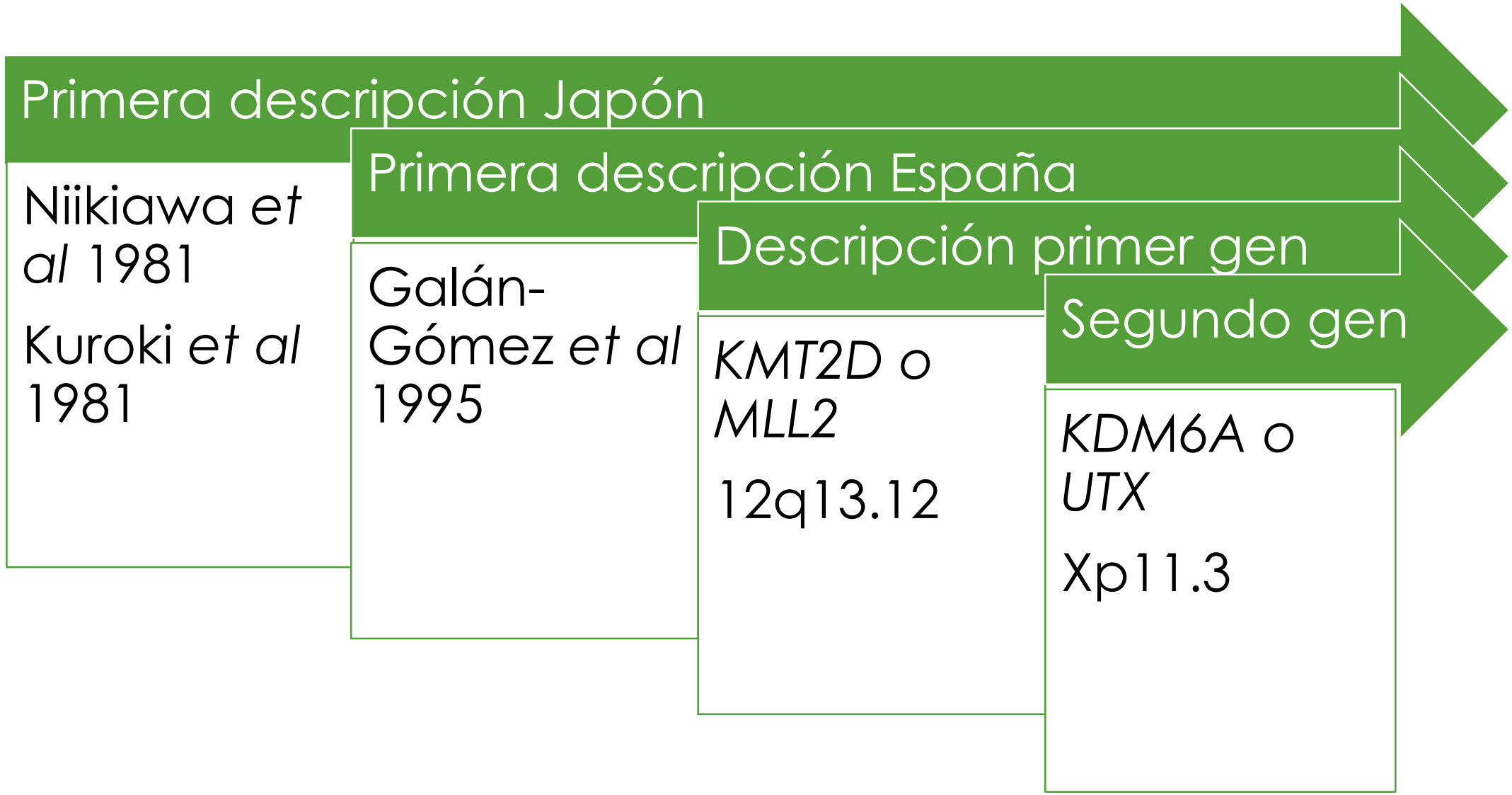
Síndrome Kabuki

- Síndrome polimalformativo caracterizado por la presencia de características faciales peculiares y distintivas, alteraciones del dermatoglifo, alteraciones esqueléticas, cardiovasculares, renales, endocrinas, oftalmológicas, inmunes, discapacidad intelectual leve-moderada y retraso del crecimiento y desarrollo



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/
Pascual-Castroviejo I1, Pascual-Pascual SI, Velázquez-Fragua R, Palencia R. Kabuki make-up syndrome. A report of 18 Spanish cases. Rev Neurol. 2005 Apr 16-30;40(8):473-8.


Primera descripción Japón
Niikiawa *et al* 1981
Kuroki *et al* 1981
Primera descripción España
Galán-Gómez *et al* 1995
Descripción primer gen
KMT2D o *MLL2*
12q13.12
Segundo gen
KDM6A o *UTX*
Xp11.3

Kabuki make-up syndrome: A syndrome of mental retardation, unusual facies, large and protruding ears, and postnatal growth deficiency

A previously unrecognized mental retardation malformation syndrome was observed in five unrelated Japanese children. Consistent clinical features included moderate-to-severe mental retardation, progressive dwarfism of postnatal onset, a peculiar facies characterized by long palpebral fissures, with eversion of the lateral third of the lower eyelids, arched eyebrows, broad and depressed nasal tip, large prominent earlobes, short fifth fingers, abnormal dermatoglyphics including absence of digital triradius c or d, and frequent otitis media in infancy. Inconsistent abnormalities included epicanthal folds, cleft or high-arched palate, widely spaced teeth, low occipital hair line, scoliosis, and dislocation of the hip joint. Neither familial occurrence nor parental consanguinity was noted. The etiology of the malformation syndrome remains unknown.

Norio Niikawa, M.D.,* Nobuo Matsuura, M.D.,
Yoshimitsu Fukushima, M.D., *Sapporo, Japan,* **Tadashi Ohsawa, M.D.,**
Tochigi, Japan, **and Tadashi Kajii, M.D.,** *Ube, Japan*

Fig. 3. Kabuki actor's make-up.

comment. All of our patients were of normal size at birth. Shortness of stature became progressively apparent with increasing age. The palpebral fissures in our patients looked remarkably long, especially when seen from the side. In some of our patients the outer one-third of the lower eyelid turned outward to form an S-shaped lower ridge. These features are reminiscent of the make-up of actors in Kabuki, the traditional Japanese play (Fig. 3). Therefore, we propose that the malformation complex be called the "Kabuki make-up syndrome."

ADDENDUM

Since submitting the paper for publication, we have found three more patients with the syndrome: a 10-year-old boy, an 11-month-old male infant, and a 3-month-old male infant.

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2. Mann JR, Rayner PHW, and Gourevitch A: Insulinoma in childhood, Arch Dis Child **44:**435, 1969.
3. Smith DW: Recognizable patterns of human malformation, Philadelphia, 1976, WB Saunders Company.

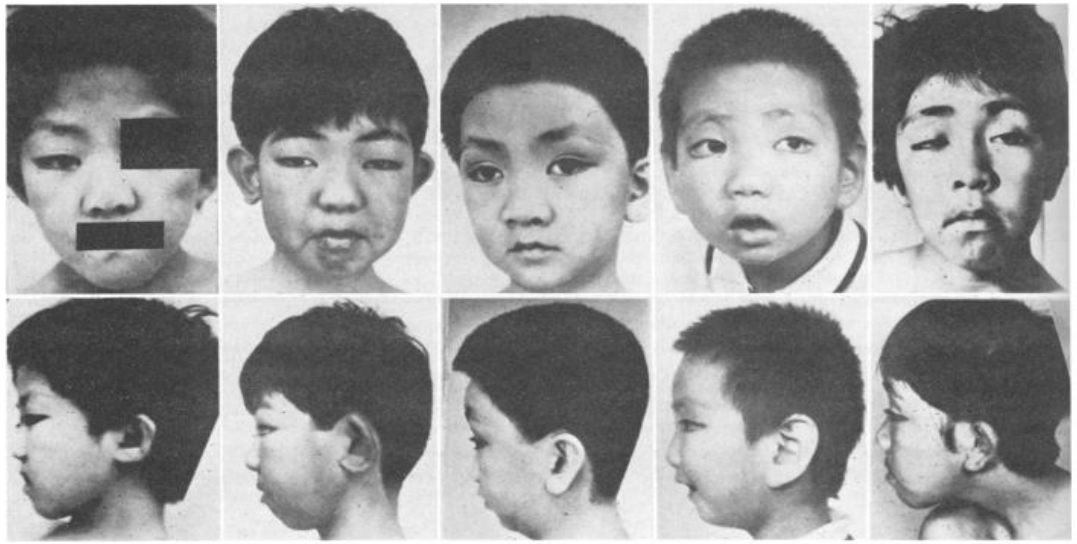

Fig. 1. Facies of the five patients. Consistent findings include: arched eyebrows, long palpebral fissures with eversion of the lateral one-third of the lower eyelids, broad and depressed nasal tip, and prominent ears with large earlobes. Inconsistent but prominent findings are: sparse lateral halves of the eyebrows (Patients 1 and 3 to 5), epicanthal folds (Patients 1 to 4), and retrognathia (Patients 2 to 4).

A new malformation syndrome of long palpebral fissures, large ears, depressed nasal tip, and skeletal anomalies associated with postnatal dwarfism and mental retardation

Five unrelated patients with a previously unrecognized mental retardation malformation syndrome are presented. Clinical features common to them include moderate mental retardation, postnatal dwarfism, susceptibility to infection in infancy, and peculiar craniofacial dysmorphia characterized by long palpebral fissures, high-arched and abnormal eyebrows, heavy and long eyelashes, large ears, short nasal septum and/or depressed nasal tip, and cleft palate. Other anomalies are stubby fingers, deformed vertebra and other bone and joint anomalies, and abnormal dermatoglyphics. The absence of familial occurrence and of consanguinity suggests some environmental causation, but the possibility of an autosomal dominant or X-linked mode of inheritance remains. Based upon our five patients and another five of Niikawa et al, we propose this syndrome as a new disease entity.

Yoshikazu Kuroki, M.D.,* Yasuyuki Suzuki, M.D., Hiroyuki Chyo, M.D., Akira Hata, M.D., and Ichiro Matsui, M.D., *Yokohoma, Japan*

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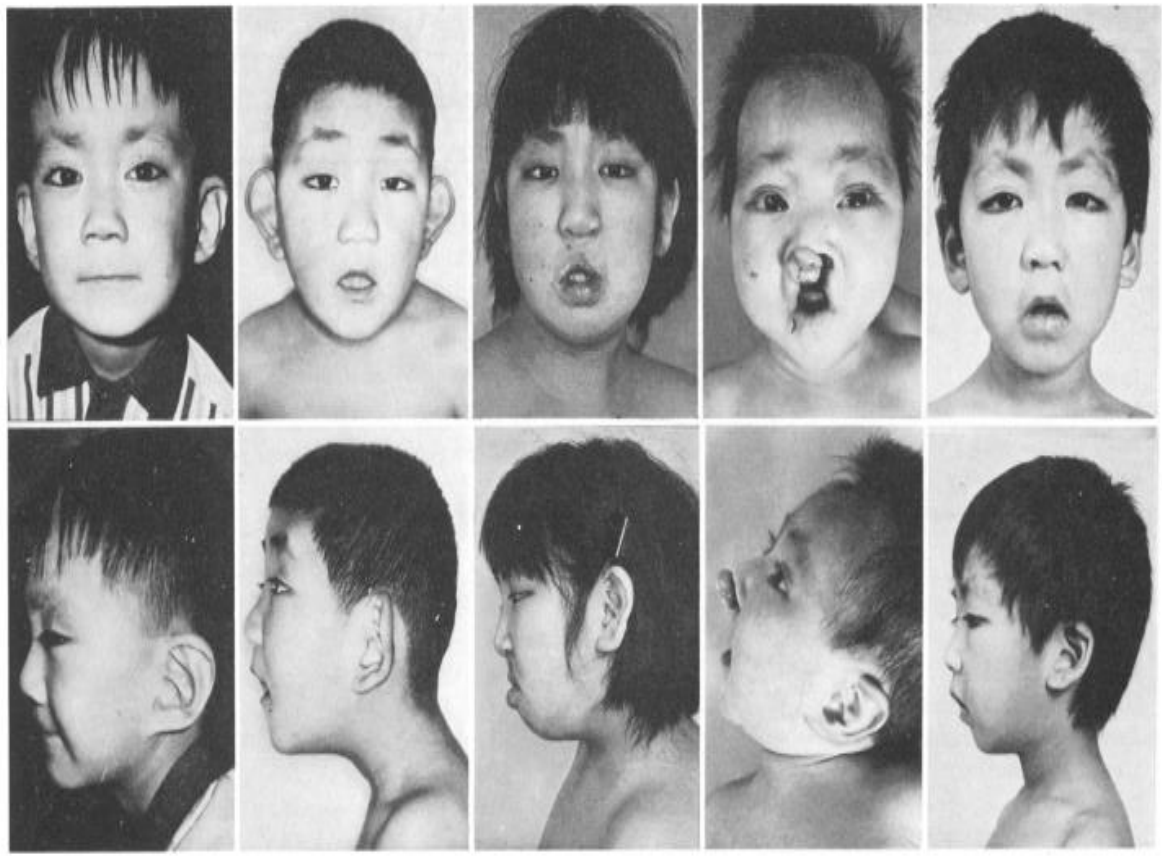

Fig. 1. Front and side view of our patients. Patients 1 through 5 from left to right. See the text in details.

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American Journal of Medical Genetics 59:276–282 (1995)

Kabuki Make-Up (Niikawa-Kuroki) Syndrome in Five Spanish Children

E. Galán-Gómez, J.J. Cardesa-García, F.M. Campo-Sampedro, C. Salamanca-Maesso, M.L. Martínez-Frías, and J.L. Frías

Departamento de Pediatría, Hospital Universitario Regional Infanta Cristina, Facultad de Medicina, Universidad de Extremadura, Badajoz (E.G.-G., J.J.C.-G., F.M.C.-S., C.S.-M.) and E.C.E.M.C. and Departamento de Farmacología, Facultad de Medicina, Universidad Complutense, Madrid (M.L.M.-F.), Spain; and Department of Pediatrics, University of South Florida, Tampa, Florida (E.G.-G., J.L.F.)

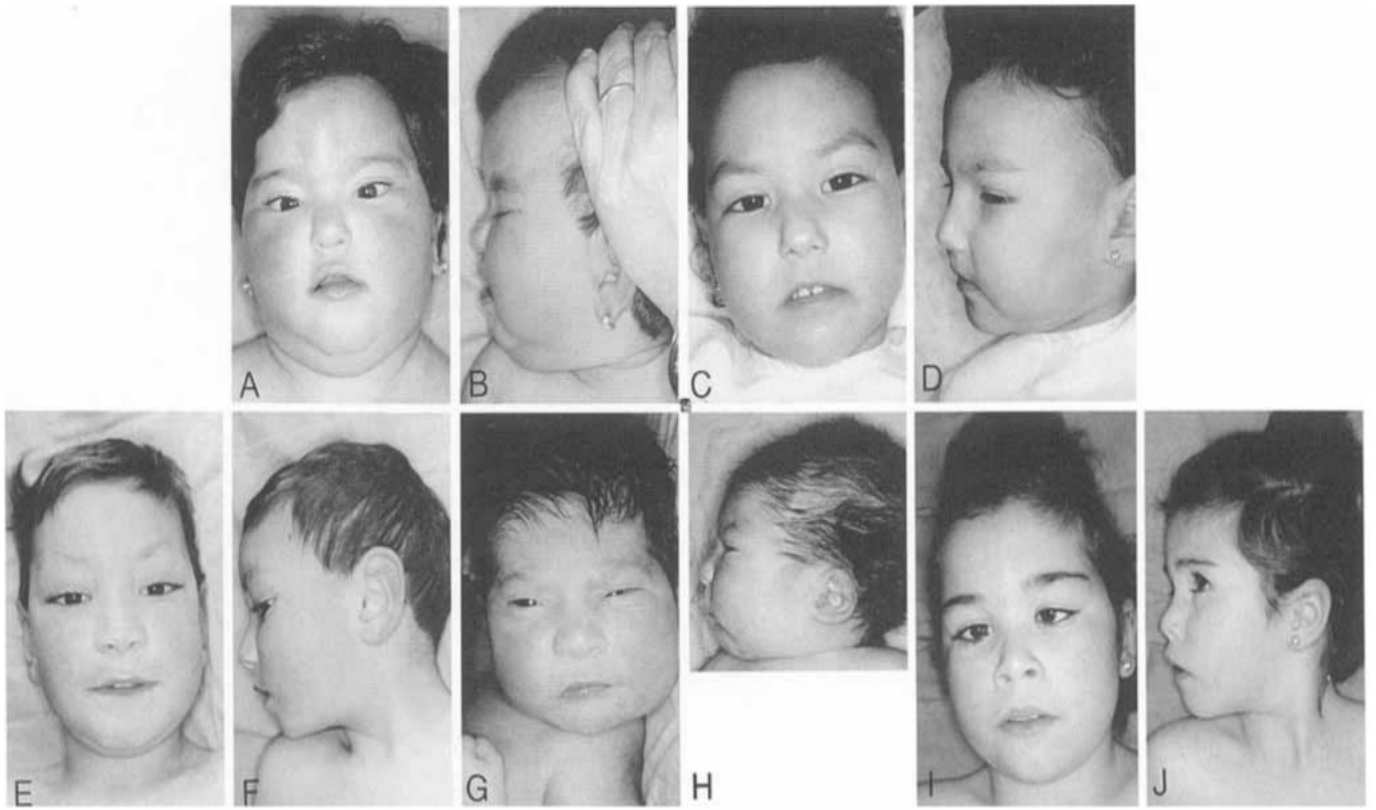

Fig. 2. Face (AP and lateral) in patients 1 (**A, B**), 2 (**C, D**), 3 (**E, F**), 4 (**G, H**), and 5 (**I, J**).

Akira Hata, M.D., and Ichiro Matsui, M.D., *Yokohoma, Japan*

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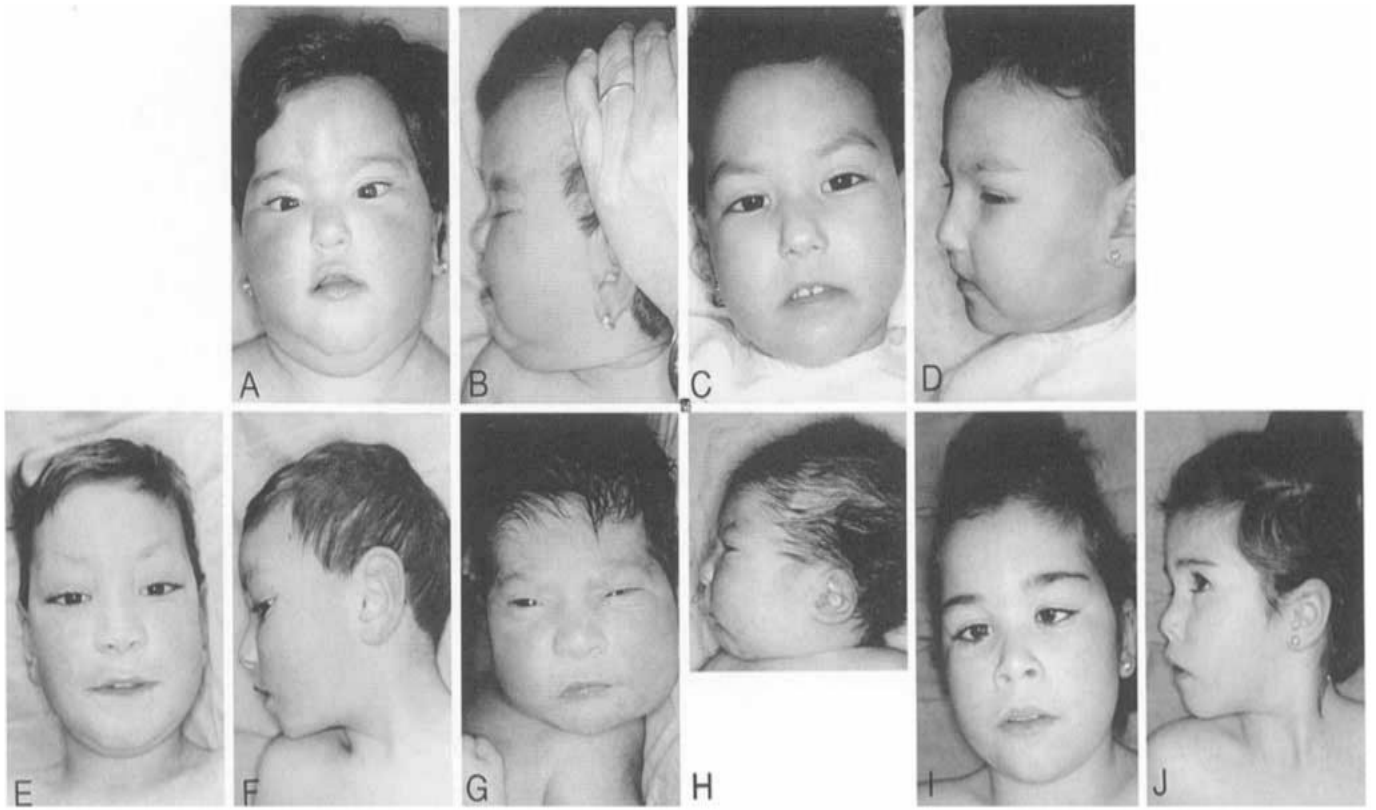

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nature genetics

Letter | Published: 15 August 2010

Exome sequencing identifies *MLL2* mutations as a cause of Kabuki syndrome

Sarah B Ng, Abigail W Bigham, Kati J Buckingham, Mark C Hannibal, Margaret J McMillin, Heidi I Gildersleeve, Anita E Beck, Holly K Tabor, Gregory M Cooper, Heather C Mefford, Choli Lee, Emily H Turner, Joshua D Smith, Mark J Rieder, Koh-ichiro Yoshiura, Naomichi Matsumoto, Tohru Ohta, Norio Niikawa, Deborah A Nickerson, Michael J Bamshad ✉ & Jay Shendure ✉

Nature Genetics **42**, 790–793 (2010) | Download Citation ↓

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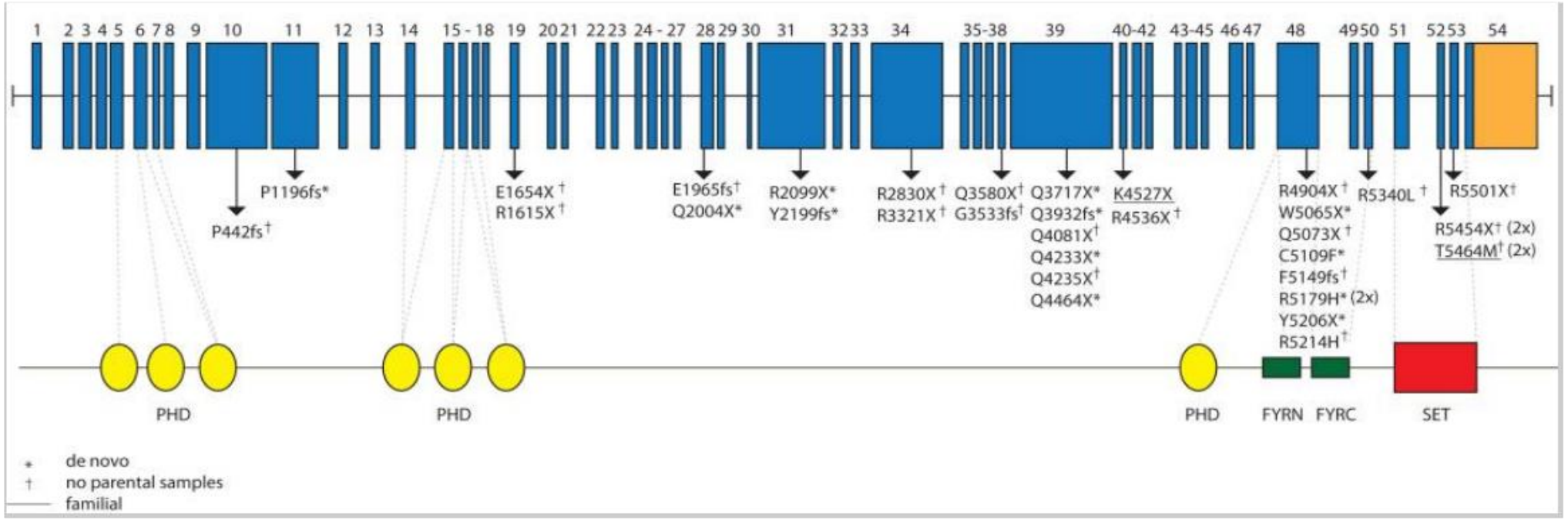
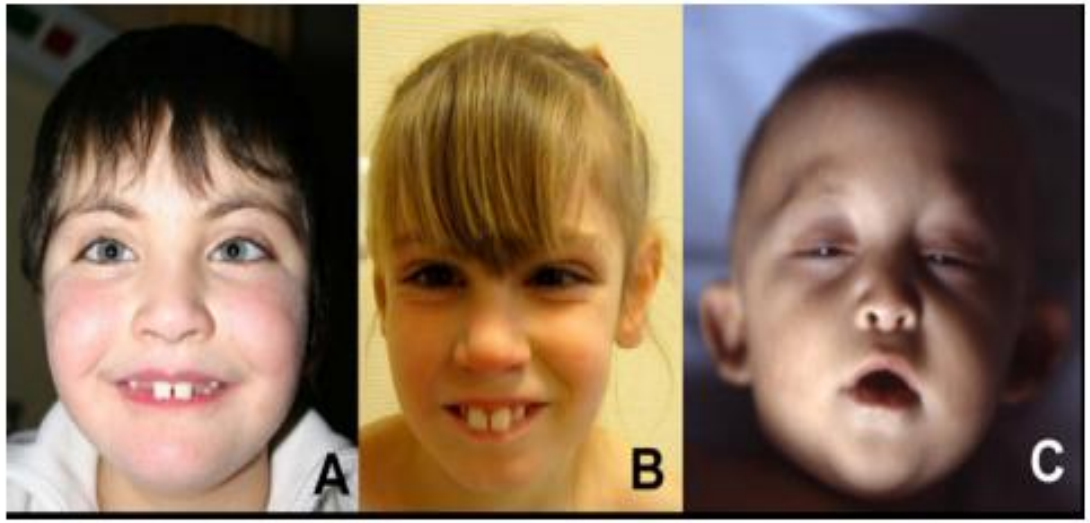




Kabuki in Five

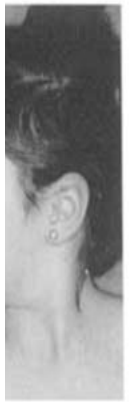
Am J Hum Genet. 2012 Jan 13;90(1):119-24. doi: 10.1016/j.ajhg.2011.11.021. Epub 2011 Dec 22.

Deletion of KDM6A, a histone demethylase interacting with MLL2, in three patients with Kabuki syndrome.

Lederer D[1], Grisart B, Digilio MC, Benoit V, Crespin M, Ghariani SC, Maystadt I, Dallapiccola B, Verellen-Dumoulin C.

Author information

1 Centre de Génétique Humaine, Institut de Pathologie et Génétique, Charleroi, Belgium. damien.lederer@ipg.be



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Journal of Medical Genetics

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Phenotypes
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[14, 15], Andrew W Lindsley[16, 17], Giuseppe Merla[18], Noriko Miyake[19], Nobuhiko Okamoto[20], Constanze T Stumpel[21], Norio Niikawa[22] the Kabuki Syndrome Medical Advisory Board

Author affiliations +

Clin Genet. 2013 Dec;84(6):539-45. doi: 10.1111/cge.12081. Epub 2013 Apr 26.

MLL2 mutation detection in 86 patients with Kabuki syndrome: a genotype-phenotype study.

Makrythanasis P[1], van Bon BW, Steehouwer M, Rodríguez-Santiago B, Simpson M, Dias P, Anderlid BM, Arts P, Bhat M, Augello B, Biamino E, Bongers EM, Del Campo M, Cordeiro I, Cueto-González AM, Cuscó I, Deshpande C, Frysira E, Izatt L, Flores R, Galán E, Gener B, Gilissen C, Granneman SM, Hoyer J, Yntema HG, Kets CM, Koolen DA, Marcelis CI, Medeira A, Micale L, Mohammed S, de Munnik SA, Nordgren A, Psoni S, Reardon W, Revencu N, Roscioli T, Ruiterkamp-Versteeg M, Santos HG, Schoumans J, Schuurs-Hoeijmakers JH, Silengo MC, Toledo L, Vendrell T, van der Burgt I, van Lier B, Zweier C, Reymond A, Trembath RC, Perez-Jurado L, Dupont J, de Vries BB, Brunner HG, Veltman JA, Merla G, Antonarakis SE, Hoischen A.

Score. No está diseñado para hacer el diagnóstico clínico de syndrome de Kabuki. Su intención es discriminar los pacientes en los que es más probable encontrar una variante causal en el gen *KMT2D*

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.

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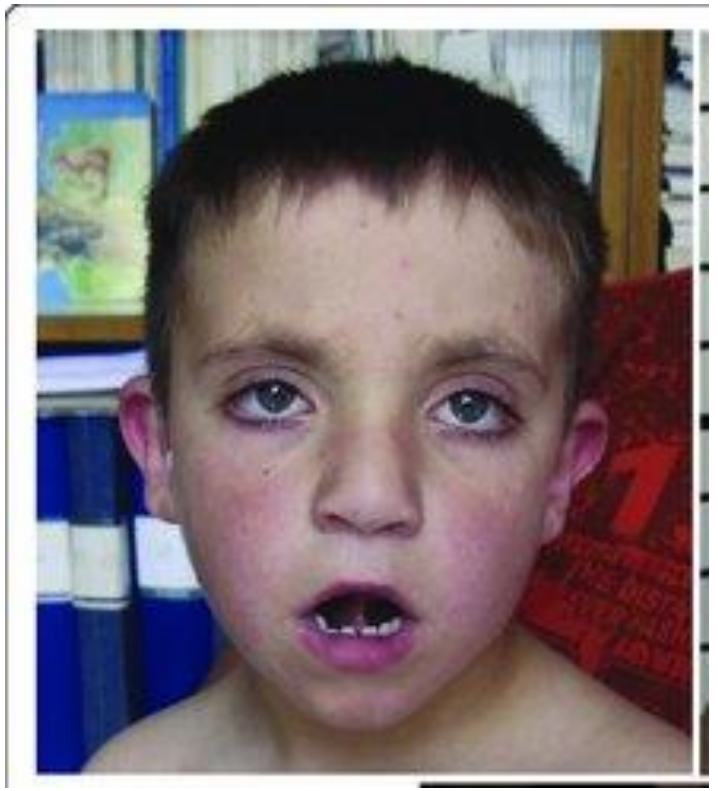
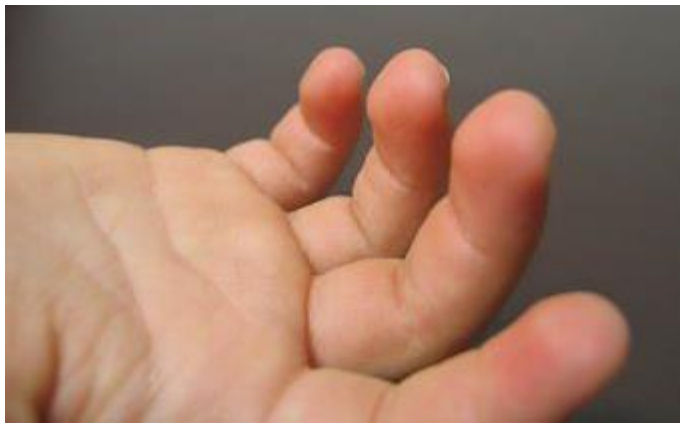


Diagnóstico definitivo de síndrome de Kabuki:

Individuos de cualquier sexo 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*.

- Dismorfias faciales características en algún momento de la vida



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Author affiliations +

Diagnóstico probable de síndrome de Kabuki:

Individuos de cualquier sexo con hipotonía en la infancia, retraso psicomotor o discapacidad intelectual y fisuras palpebrales largas y eversion del tercio lateral

+

3 características compatibles

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

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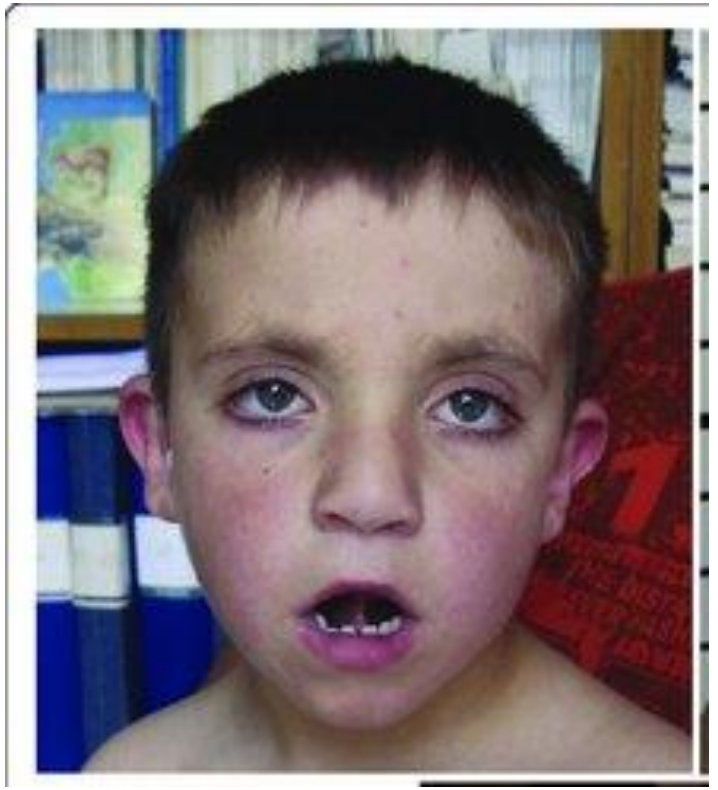
PDF

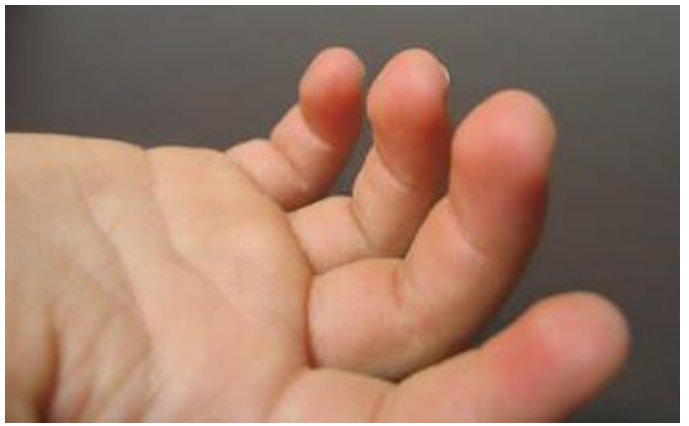
Diagnóstico posible de síndrome de Kabuki:

Individuos de cualquier sexo con retraso psicomotor o discapacidad intelectual y uno de las dismorfias características en cualquier momento de la vida

+

2 características compatibles





Síndrome Kabuki

Relación genotipo-fenotipo:

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

Patrón de herencia autosómico dominante, es decir, es suficiente con tener una variante patogénica en una de las dos copias del gen para manifestar la enfermedad. La mayoría de los pacientes presentan variants de novo, es decir que han ocurrido por primera vez en ellos y los padres no son portadores. El riesgo de repetición es muy bajo (<2%) y está confinado a la presencia de mosaicismo germinal, (la presencia de más de una línea celular, una de ellas con la variante patogénica, exclusivamente en gónadas sexuales).

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 Kabuki

Relación genotipo-fenotipo:

- *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 en la única copia del gen que portan (hemicigotos) manifiestan la enfermedad de una manera grave, y con alta tasa de mortalidad temprana; mientras que las mujeres que portan una variante patogénica en una de las 2 copias del gen que poseen (heterocigotas) 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%, la descendencia de sexo masculino manifestará la enfermedad de una manera más grave y la de sexo femenino la manifestará con un grado variable de intensidad.

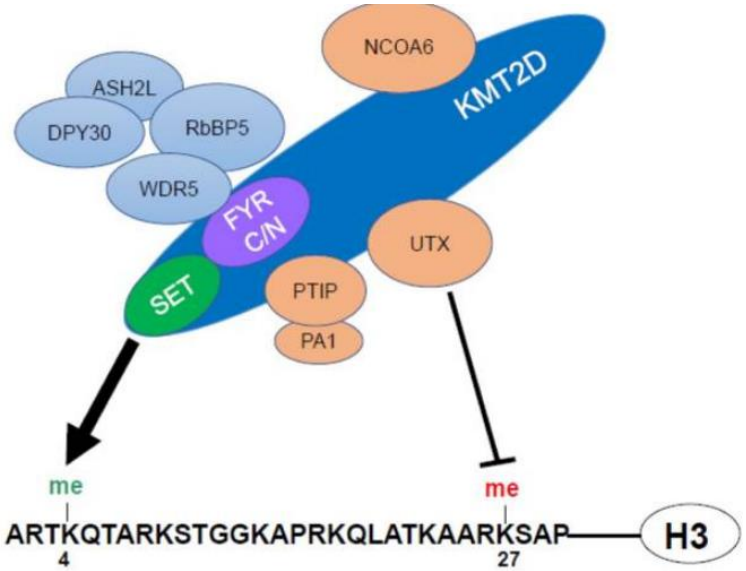
Adam MP, Hudgins L, Hannibal M. Kabuki Syndrome. 2011 Sep 1 [Updated 2019 Feb 28]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available from: https://www.ncbi.nlm.nih.gov/books/NBK62111/

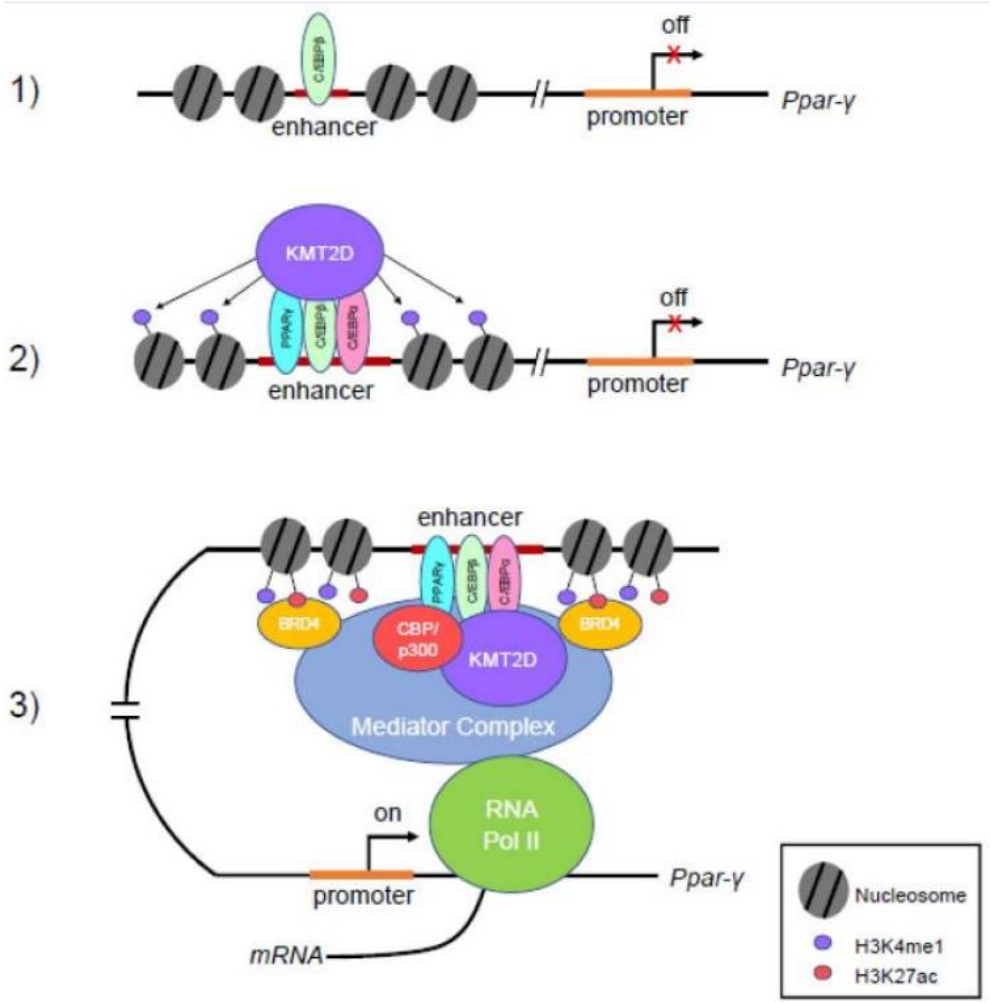
Phenotypic Feature	Number of individuals reported with this feature who had a heterozygous pathogenic variant in *KMT2D*	Number of individuals reported with this feature who had a heterozygous or hemizygous pathogenic variant in *KDM6A*
Intellectual disability (IQ <70)	238	30
Fetal fingertip pads	224	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

Adam et al. Kabuki syndrome: international consensus diagnostic criteria. J Med Genet. 2019 Feb;56(2):89-95

Síndrome Kabuki. Causas

- Las proteínas **KMT2D y KDM6A** son parte del complejo ASCOM actúan sobre regiones reguladoras favoreciendo la transcripción.
- Intervienen en la diferenciación cellular y el desarrollo embrionario





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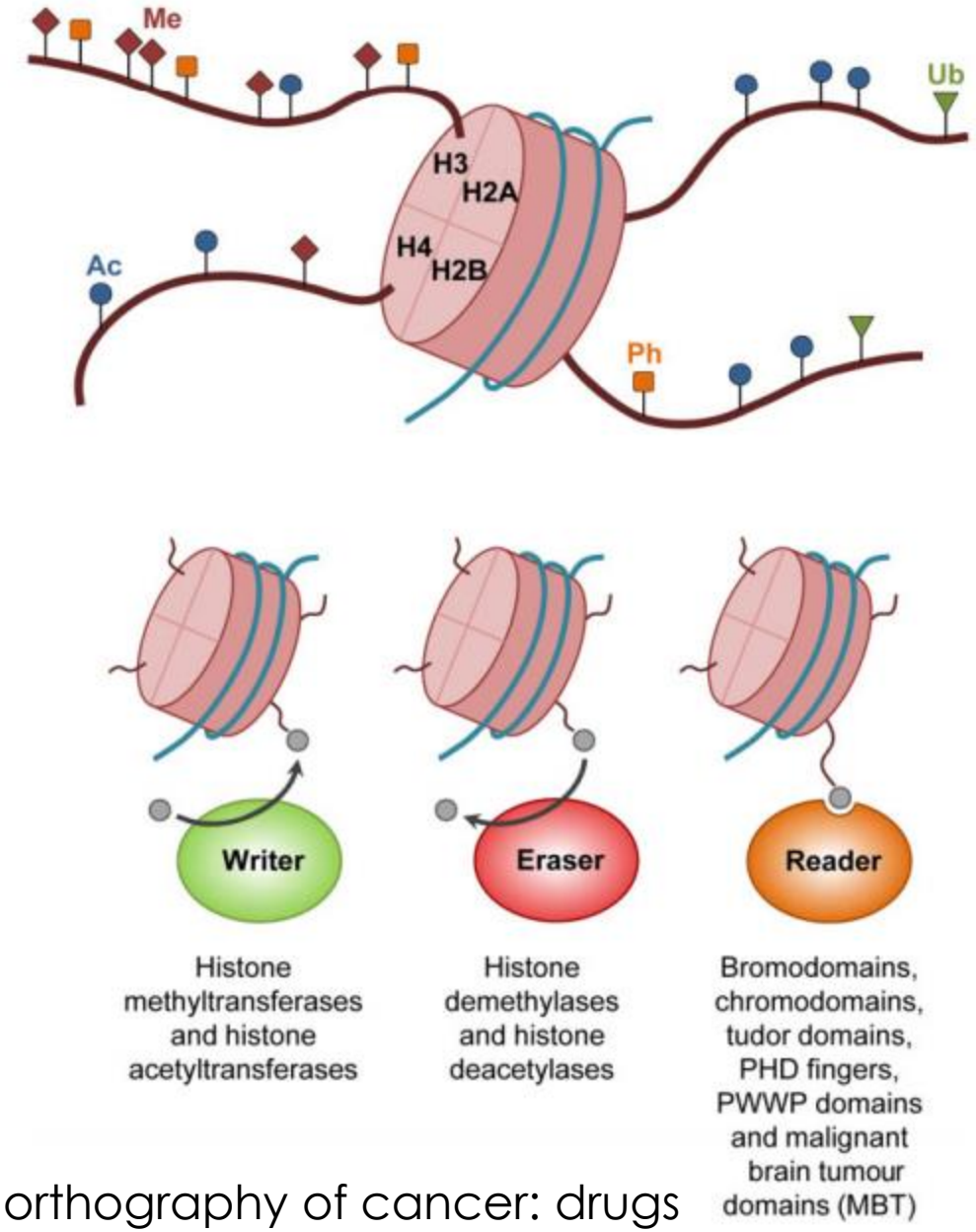
Síndrome Kabuki.

- *KMT2D* Histona metil-transferasa (escritor epigenético) H3K4

12q13.12 Autosómico dominante

- *KMD6A* demetilasa, (borrador epigenético) elimina la trimetilación H3K27

Xp11.3 Ligado al X dominante, escapa a la inactivación del X



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Síndrome Kabuki. Pruebas

Síndrome de Kabuki. Pruebas

- **Secuenciación:** variantes de uno o pocos nucleótidos.

- **Arrays o MLPA:** ganancias o pérdida de material genético de muchos nucleótidos, exones o genes completos.

Clase 1	**Benigna**
Clase 2	**Probablemente Benigna**
Clase 3	**Variante de significado clínico incierto (VUS)**
Clase 4	**Probablemente patogénica**
Clase 5	**Patogénica**

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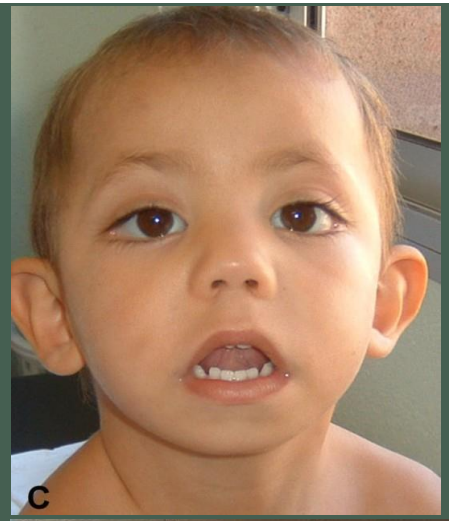
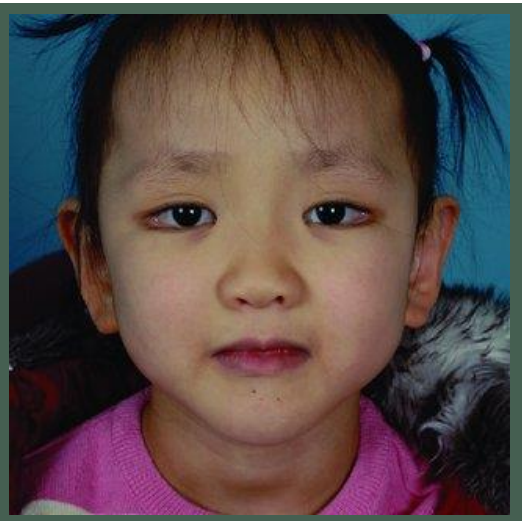
GRACIAS….
¿PREGUNTAS?





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