Bonuccelli *et al. J Transl Genet Genom* 2023;7:166-82
DOI: 10.20517/jtgg.2022.18

Journal of Translational Genetics and Genomics

Case Report

Open Access

Check for updates

Kabuki syndrome and rare tumors in a young girl carrying a frameshift *KMT2D* mutation

Alice Bonuccelli[1], Tommaso Baldaccini[5], Alessandro Orsini[1], Elisabetta Alberti[5], Marta Del Pistoia[5], Ugo Boggi[3], Benedetta Toschi[4], Andrea Santangelo[1], Emioli Randazzo[2], Diego Peroni[5], Giovanni Federico[2]

[1]Pediatric Neurology, University Hospital of Pisa, Pisa 56124, Italy.
[2]Pediatric Endocrinology, University Hospital of Pisa, Pisa 56124, Italy.
[3]Department of Surgery, University Hospital of Pisa, Pisa 56124, Italy.
[4]Medical Genetics, University Hospital of Pisa, Pisa 56124, Italy.
[5]Pediatric Clinic, University Hospital of Pisa, Pisa 56124, Italy.

Correspondence to: Dr. Tommaso Baldaccini, Pediatric Clinic, University Hospital of Pisa, via Roma 67, Pisa 56124, Italy. E-mail: tommasobaldaccini94@gmail.com

How to cite this article: Bonuccelli A, Baldaccini T, Orsini A, Alberti E, Del Pistoia M, Boggi U, Toschi B, Santangelo A, Randazzo E, Peroni D, Federico G. Kabuki syndrome and rare tumors in a young girl carrying a frameshift *KMT2D* mutation. *J Transl Genet Genom* 2023;7:166-82. https://dx.doi.org/10.20517/jtgg.2022.18

Received: 20 Aug 2022 **First Decision:** 24 Nov 2022 **Revised:** 17 Mar 2023 **Accepted:** 18 Apr 2023 **Published:** 20 Jul 2023

Academic Editor: Sanjay Gupta **Copy Editor:** Dan Zhang **Production Editor:** Dan Zhang

Abstract

Kabuki syndrome (KS) is a genetic disorder characterized by typical facial dimorphisms, various degrees of cognitive disability, and congenital anomalies involving the heart, kidneys, gastrointestinal system, and bones. It is accompanied by hypotonia, failure to thrive, obesity, and immunodeficiency. Association with neoplastic lesions has been recently described. We report a 13-year-old girl with KS, an insulinoma, and a benign phyllodes breast tumor with two hepatic lesions: a neuroendocrine tumor metastasis and a ciliated foregut cyst associated with hepatic fibrosis. She had a pilomatrixoma and a junctional melanocytic nevus with cytological atypia. Genetic analysis revealed a heterozygous frameshift variant in the *KMT2D* gene. Somatic K*MT2D* variants are in various types of tumors. The role of *KMT2D* variants in malignancies in KS appears to be related to defective transcription regulation and altered gene expression; however, the mechanism remains unclear. This aims to clarify the relationship between *KMT2D* gene variants, KS, and susceptibility to neoplastic lesions. For this purpose, a more extensive case series will be needed to accurately describe the patients' neoplastic phenotypes and precise genetic characterization.

Keywords: Kabuki syndrome, *KMT2D* gene, neoplastic lesions

© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, sharing, adaptation, distribution and reproduction in any medium or format, for any purpose, even commercially, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

INTRODUCTION

Kabuki syndrome (KS, OMIM ID: 147920; http://www.omim.org) is a congenital disorder characterized by atypical facies resembling Japanese traditional Kabuki actors. It is associated with mild-to-moderate cognitive disability, immunodeficiency, seizures, and internal malformations involving the heart, kidneys, eyes, skeleton, and gastrointestinal system.

Two genes are involved in KS: *KMT2D* (lysine methyltransferase 2D; NM_003482.3; formerly MLL2) at 12q13.12 (KS subtype-1; OMIM ID: 147920) and KDM6A (lysine (K)-specific demethylase 6A; NM_021140.2) at Xp11.3 (X-linked KS subtype-2; OMIM ID: 300867)[1,2]. Most patients (> 80%) with a clinical diagnosis of KS harbor pathogenic variants in *KMT2D*, whereas a smaller number (6%-10%) have KDM6A. Other genes in KS-like phenotypes include RAP1A/RAP1B, HNRNPK, and ZMZ1. Other genes associated may exist[3]. More than 650 genetic variants of the *KMT2D* gene have been described, including missense deletions, indels, duplications, frameshifts, and splice site variants; most of these variants lead to truncated protein synthesis[4] [Table 1].

Both genes affect chromatin opening and promote gene expression. Most pathogenic variants in *KMT2D* and KDM6A are associated with loss-of-function (resulting in haploinsufficiency) or missense variants[3]. Individuals with pathogenic missense variants of *KMT2D* involving exons 38 or 39 may have features atypical for KS. Patients may have choanal atresia, hypoplastic or absent nipples, external and internal ear anomalies with hearing loss, brachial sinus abnormalities, interstitial lung disease, hypothyroidism, hypoparathyroidism, variable developmental delay, and dysmorphic features. A possible gain-of-function mechanism has also been hypothesized. *KMT2D* variants may also be associated with isolated alobar holoprosencephaly[1,3]. No other phenotypes have been associated with germline pathogenic variants in KDM6A[1].

The clinical variability of KS may be attributable to differences in genotypes and unknown genetic and epigenetic factors[3]. Outcomes vary based on systemic involvement. Early recognition of eventual complications is essential to improving outcomes, mainly because the treatments for non-KS and KS patients are identical.

Interestingly, although the concurrence of neoplastic lesions in the context of KS has been limited to isolated and sporadic case reports, reports in the last ten years have allowed the drawing of associations between tumors and KS[6,7]. Only 18 cases of KS with malignancies have been reported, including cases of Wilms tumor[8], hepatoblastoma and neuroblastoma, pilomatrixoma[9], spinal ependymoma[10,11], Burkitt's lymphoma[12], and embryonal rhabdomyosarcoma[13] [Table 2]. Here, we describe a girl with KS who carries a *KMT2D* frameshift variant; she developed rare neoplasms in childhood, an insulinoma, liver metastasis, a benign phyllodes tumor of the breast, a pilomatrixoma, and an atypical melanocytic nevus.

CASE REPORT

Our patient is a 13-year-old girl born from a normal, full-term pregnancy from unrelated parents. At around three years old, she was diagnosed with KS due to the delay in psychomotor development, typical facial dysmorphisms, and other typical features, including tetralogy of Fallot, cleft lip and palate, congenital hip dysplasia, epilepsy, and immunodeficiency.

During school age, she presented sporadic focal seizures, which were well controlled by therapy with valproic acid.

Table 1. The known variants of *KMT2D* and KDM6A are associated with Kabuki syndrome[5]

ID	Inheritance	Exon/intron	Variant	AA change
KMT2D				
Non-sense				
KB49	NA	ex 5	c.669T > G	p. (Tyr223*)
KB343	NA	ex 8	c.1016G > A	p. (Trp339*)
KB35	NA	ex 10	c.1921G > T	p. (Glu641*)
KB33	NA	ex 16	c.4419G > A	p. (Trp1473*)
KB63	NA	ex 19	c.4895delC	p. (Ser1632*)
KB317	NA	ex 22	c.5212G > T	p. (Glu1738*)
KB336	*De novo*	ex 22	c.5269C > T	p. (Arg1757*)
KB262	NA	ex 26	c.5674C > T	p. (Gln1892*)
KB429	NA	ex 26	c.5707C > T	p. (Arg1903*)
KB26	NA	ex 31	c.6295C > T	p. (Arg2099*)
KB502	*De novo*	ex 31	c.7228C > T	p. (Arg2410*)
KB66	NA	ex 31	c.7246C > T	p. (Gln2416*)
KB59	NA	ex 31	c.7903C > T	p. (Arg2635*)
KB153	*De novo*	ex 31	c.7903C > T	p. (Arg2635*)
KB226	*De novo*	ex 31	c.7903C > T	p. (Arg2635*)
KB338	*De novo*	ex 31	c.7933C > T	p. (Arg2645*)
KB198	*De novo*	ex 31	c.7936G > T	p. (Glu2646*)
KB352	NA	ex 32	c.8227C > T	p. (Gln2743*)
KB323	NA	ex 33	c.8311C > T	p. (Arg2771*)
KB289	NA	ex 34	c.8743C > T	p. (Arg2915*)
KB422	*De novo*	ex 34	c.9396C > A	p. (Cys3132*)
KB186	*De novo*	ex 34	c.9961C > T	p. (Arg3321*)
KB56	*De novo*	ex 34	c.10135C > T	p. (Gln3379*)
KB168	*De novo*	ex 39	c.10750C > T	p. (Gln3584*)
KB46	*De novo*	ex 39	c.10841C > G	p. (Ser3614*)
KB41	NA	ex 39	c.11119C > T	p. (Arg3707*)
KB44	NA	ex 39	c.11119C > T	p. (Arg3707*)
KB42	*De novo*	ex 39	c.11269C > T	p. (Gln3757*)
KB25	NA	ex 39	c.11434 C > T	p. (Gln3812*)
KB244	*De novo*	ex 39	c.11674 C > T	p. (Gln3892*)
KB178	NA	ex 39	c.11704C > T	p. (Gln3902*)
KB425	*De novo*	ex 39	c.11731C > T	p. (Gln3911*)
KB461[a]	NA	ex 39	c.11749C > T	p. (Gln3917*)
KB463	NA	ex 39	c.11845C > T	p. (Gln3949*)
KB181	NA	ex 39	c.11869C > T	p. (Gln3957*)
KB358	NA	ex 39	c.11944C > T	p. (Arg3982*)
KB40	NA	ex 39	c.12274C > T	p. (Gln4092*)
KB114	*De novo*	ex 39	c.12274C > T	p. (Gln4092*)
KB65	NA	ex 39	c.12076C > T	p. (Gln4026*)
KB333	NA	ex 39	c.12703C > T	p. (Gln4235*)
KB410	NA	39	c.12760C > T	p. (Gln4254*)
KB82	*De novo*	ex 39	c.12844C > T	p. (Arg4282*)
KB350	*De novo*	ex 39	c.12844C > T	p. (Arg4282*)
KB189	*De novo*	ex 39	c.12955A > T	p. (Arg4319*)
KB183	*De novo*	ex 39	c.13450C > T	p. (Arg4484*)
KB450	NA	ex 39	c.13450C > T	p. (Arg4484*)
KB175	*De novo*	ex 39	c.13507C > T	p. (Gln4503*)

KB73	*De novo*	ex 40	c.13666A > T	p. (Lys4556*)
KB83	NA	ex 48	c.15022G > T	p. (Glu5008*)
KB377	NA	ex 48	c.15061C > T	p. (Arg5021*)
KB45	NA	ex 48	c.15079C > T	p. (Arg5027*)
KB72	NA	ex 48	c.15079C > T	p. (Arg5027*)
KB362	NA	ex 50	c.16018C > T	p. (Arg5340*)
KB130	NA	ex 52	c.16360C > T	p. (Arg5454*)
Frameshift				
KB454	NA	ex 3	c.234_235delGC	p. (Gln79Alafs*7)
KB469	NA	ex 3	c.345dupA	p. (Ser116Ilefs*7)
KB337	NA	ex 4	c.446_449delTATG	p. (Val149Glyfs*58)
KB75	*De novo*	ex 4	c.472delT	p. (Cys158Valfs*50)
KB8	*De novo*	ex 5	c.588delC	p. (Cys197Alafs*11)
KB58	NA	ex 6	c.705delA	p. (Glu237Serfs*24)
KB57	NA	ex 8	c.1035_1036delCT	p. (Cys346Serfs*17)
KB89	NA	ex 10	c.1345_1346delCT	p. (Leu449Valfs*5)
KB156	*De novo*	ex 10	c.1503dupT	p. (Pro502Serfs*7)
KB116	NA	ex 10	c.1634delT	p. (Leu545Argfs*385)
KB349	NA	ex 10	c.1634delT	p. (Leu545Argfs*385)
KB545	NA	10	c.2091dupC	p. (Thr698Hisfs*6)
KB369	NA	ex 11	c.3596_3597del	p. (Leu1199Hisfs*7)
KB48	*De novo*	ex 11	c.2993dupC	p. (Met999Tyrfs*69)
KB203	NA	ex 11	c.3161_3171del CGTTGAGTCCC	p. (Pro1054Hisfs*10)
KB309	NA	ex 11	c.3730delG	p. (Val1244Serfs*86)
KB142	*De novo*	ex 13	c.4021delG	p. (Val1341Leufs*35)
KB311	NA	ex 14	c.4135_4136delAT	p. (Met1379Valfs*52)
KB524	NA	14	c.4135_4136delAT	p. (Met1379Valfs*52)
KB188	*De novo*	ex 16	c.4454delC	p. (Pro1485Leufs*21)
KB159	NA	ex 19	c.4896_4905del AGATGCCCTT	p. (Asp1633Alafs*86)
KB443[a]	*De novo*	ex 25	c.5575delG	p. (Asp1859Thrfs*17)
KB3	NA	ex 26	c.5652dup	p. (Lys1885Glnfs*18)
KB84	NA	ex 26	c.5779delC	p. (Gln1927Lysfs120*)
KB146	*De novo*	ex 27	c.5857delC	p. (Leu1953Trpfs*94)
KB208	NA	ex 28	c.5954delC	p. (Thr1985Lysfs*62)
KB221	*De novo*	ex 29	c.6149_6150delGA	p. (Arg2050Lysfs*6)
KB525	NA	30	c.6212_6213delAC	p. (His2071Profs*10)
KB152	*De novo*	ex 31	c.6583delA	p. (Thr2195Profs*69)
KB267	NA	ex 31	c.6594delC	p. (Tyr2199Ilefs*65)
KB79	*De novo*	ex 31	c.6595delT	p. (Tyr2199Ilefs*65)
KB102	*De novo*	ex 31	c.6595delT	p. (Tyr2199Ilefs*65)
KB342	NA	ex 31	c.6595delT	p. (Tyr2199Ilefs*65)
KB67	*De novo*	ex 31	c.6638_6641delGCGC	p. (Gly2213Alafs*50)
KB176	NA	ex 31	c.6738delA	p. (Lys2246Asnfs*18)
KB253	NA	ex 31	c.6794delG	p. (Gly2265Glufs*21)
KB278	NA	ex 31	c.7481dupT	p. (Ala2496Serfs*10)
KB313	*De novo*	ex 32	c.8196delG	p. (Ser2733Valfs*24)
KB80	NA	ex 33	c.8273delG	p. (Gly2758Alafs*29)
KB243	*De novo*	ex 34	c.8430_8431insAA	p. (Gln2811Asnfs*41)
KB182	NA	ex 34	c.9203delA	p. (Gln3068Glyfs*3)
KB30	NA	ex 38	c.10606delC	p. (Arg3536Alafs*122)

KB101	*De novo*	ex 39	c.11066_11078delCT GGATCCCTGGC	p. (Ala3689Valfs*56)
KB504	*De novo*	ex 39	c.11093dupG	p. (Phe3699Leufs*14)
KB495	*De novo*	ex 39	c.11715delG	p. (Gln3905Hisfs*74)
KB172	NA	ex 39	c.12647delC	p. (Pro4216Leufs*62)
KB192	*De novo*	ex 39	c.12966delA	p. (Gln4322Hisfs*62)
KB54	NA	ex 39	c.13129dupT	p. (Trp4377Leufs*33)
KB121	*De novo*	ex 39	c.13277dupT	p. (Ala4428Serfs*59)
KB540	NA	41	c.13780delG	p. (Ala4594Profs*23)
KB123	*De novo*	ex 42	c.13884dupC	p. (Thr4629Hisf*18)
KB481	NA	ex 42	c.13895dupC	p. (Ser4633Ilefs*14)
KB197	*De novo*	ex 47	c.14592dupG	p. (Pro4865Alafs*48)
KB125	NA	ex 48	c.15031delG	p. (Glu5011Serfs*40)
KB16	*De novo*	ex 48	c.15374dupT	p. (Phe5126Leufs*12)
KB535	NA	50	c.16043_16044delAC	p. (His5348Leufs*14)
KB355	NA	ex 53	c.16438_16441delAACT	p. (Asn5480Val*6)
KB64	NA	ex 53	c.16469_16470delAA	p. (Lys5490Argfs*21)
KB533	NA	53	c.16469_16470delAA	p. (Lys5490Argfs*21)
Missense				
KB21[a]	inherited M	ex 3	c.346T > C	p. (Ser116Pro)
KB21[a,b]	inherited M	ex 4	c.510G > C	p. Gln170His
KB256	NA	ex 5	c.626C > T	p. (Thr209Ile)
KB458	NA	ex 8	c.1076G > C	p. (Arg359Pro)
KB269	inherited M	ex 10	c.1940C > A	p. (Pro647Gln)
KB126	NA	ex 10	c.2074C > A	p. (Pro692Thr)
KB374[c]	inherited M	ex 10	c.2074C > A	p. (Pro692Thr)
KB487	NA	ex 10	c.2654C > T	p. (Pro885Leu)
KB370[a]	Inherited P-M	ex 11	c.2837C > G	p. (Ala946Gly)
KB215	Inherited M	ex 11	c.3392C > T	p. (Pro1131Leu)
KB341	Inherited M	ex 11	c.3392C > T	p. (Pro1131Leu)
KB222	Inherited P-M	ex 11	c.3572C > T	p. (Pro1191Leu)
KB32	Inherited P	ex 11	c.3773G > A	p. (Arg1258Gln)
KB307	*De novo*	ex 14	c.4171G > A	p. (Glu1391Lys)
KB28[a]	Inherited M	ex 15	c.4249A > G	p. (Met1417Val)
KB28[a]	Inherited M	ex 15	c.4252C > A	p. (Leu1418Met)
KB174	Inherited M	ex 15	c.4283T > C	p. (Ile1428Thr)
KB138	NA	ex 16	c.4427C > G	p. (Ser1476Cys)
KB34	Inherited P	ex 16	c.4565A > G	p. (Gln1522Arg)
KB535	NA	25	c.5549G > A	p. (Gly1850Asp)
KB119	Inherited M	ex 31	c.6638G > A	p. (Gly2213Asp)
KB204[c]	Inherited M	ex 31	c.6638G > A	p. (Gly2213Asp)
KB330[a]	NA	ex 31	c.6733C > G	p. (Leu2245Val)
KB326[c]	Inherited M	ex 31	c.6811C > T	p. (Pro2271Ser)
KB107[a]	NA	ex 31	c.6970C > A	p. (Pro2324Thr)
KB430	NA	ex 31	c.7378C > T	p. (Arg2460Cys)
KB122	Inherited M	ex 31	c.7829T > C	p. (Leu2610Pro)
KB287	Inherited M	ex 31	c.7829T > C	p. (Leu2610Pro)
KB27	NA	ex 34	c.8521C > A	p. (Pro2841Thr)
KB330[a]	NA	ex 34	c.8774C > T	p. (Ala2925Val)
KB443[a]	Inherited M	ex 34	c.9971G > T	p. (Gly3324Val)
KB326[c]	Inherited P	ex 34	c.10192A > G	p. (Met3398Val)

KB357	Inherited P	ex 34	c.10192A > G	p. (Met3398Val)
KB297	NA	ex 35	c.10256A > G	p. (Asp3419Gly)
KB378	NA	ex 35	c.10256A > G	p. (Asp3419Gly)
KB292	*De novo*	ex 37	c.10499G > T	p. (Gly3500Val)
KB86[a]	NA	ex 39	c.10966C > T	p. (Arg3656Cys)
KB374[c]	Inherited P	ex 39	c.11380C > T	p. (Pro3794Ser)
KB293	Inherited P	ex 39	c.11794C > G	p. (Gln3932Glu)
KB204[c]	Inherited P	ex 39	c.12070A > G	p. (Lys4024Glu)
KB385	NA	ex 39	c.12302A > C	p. (Gln4101Pro)
KB247	NA	ex 39	c.12485G > A	p. (Arg4162Gln)
KB107[a]	NA	ex 39	c.12488C > T	p. (Pro4163Leu)
KB170	Inherited M	ex 39	c.13256C > T	p. (Pro4419Leu)
KB512	NA	45	c.14381A > G	p. (Lys4794Arg)
KB86[a]	NA	ex 48	c.14893G > A	p. (Ala4965Thr)
KB38[a]	*De novo*	ex 48	c.15084C > G	p. (Asp5028Glu)
KB154	NA	ex 48	c.15088C > T	p. (Arg5030Cys)
KB185	*De novo*	ex 48	c.15088C > T	p. (Arg5030Cys)
KB423	Inherited P	ex 48	c.15089G > A	p. (Arg5030His)
KB38[a]	*De novo*	ex 48	c.15100T > G	p. (Phe5034Val)
KB76	*De novo*	ex 48	c.15176A > C	p. (His5059Pro)
KB129	NA	ex 48	c.15292A > C	p. (Thr5098Pro)
KB462	*De novo*	ex 48	c.15310T > C	p. (Cys5104Arg)
KB171	Inherited M	ex 48	c.15565G > A	p. (Gly5189Arg)
KB264	NA	ex 48	c.15640C > T	p. (Arg5214Cys)
KB376	NA	ex 48	c.15640C > T	p. (Arg5214Cys)
KB24	*De novo*	ex 48	c.15641G > A	p. (Arg5214His)
KB219	NA	ex 48	c.15641G > A	p. (Arg5214His)
KB408	*De novo*	ex 48	c.15641G > A	p. (Arg5214His)
KB109	*De novo*	ex 48	c.15649T > C	p. (Trp5217Arg)
KB17	*De novo*	ex 50	c.16019G > A	p. (Arg5340Gln)
KB169	*De novo*	ex 51	c.16273G > A	p. (Glu5425Lys)
KB90	NA	ex 51	c.16295G > A	p. (Arg5432Gln)
KB467	NA	ex 51	c.16295G > A	p. (Arg5432Gln)
KB480	NA	ex 52	c.16385A > G	p. (Asp5462Gly)
KB177	*De novo*	ex 52	c.16412G > T	p. (Arg5471Met)
KB489	NA	ex 53	c.16498C > T	p. (Arg5500Trp)
KB120	*De novo*	ex 54	c.16528T > G	p. (Tyr5510Asp)
Indel				
KB404	Inherited M	ex 10	c.2283_2309del	p. (Ala765_Gln773del)
KB274	NA	ex 10	c.2532_2591del	p. (Arg845_Pro864del)
KB370[d]	*De novo*	ex 14	c.4202_4210del	p. (Ser1401_Cys1403del)
KB384	NA	ex 39	c.11220_11222dup	p. (Gln3745dup)
KB461[a,d]	NA	ex 39	c.11220_11222dup	p. (Gln3745dup)
KB281	Inherited M	ex 39	c.11714_11716dup	p. (Gln3905dup)
KB71	Inherited M	ex 39	c.11819_11836dup	p. (Leu3940_Gln3945dup)
KB227	Inherited P	ex 39	c.11843_11860del	p. (L3948_Q3953del)
KB228	Inherited P	ex 39	c.11854_11874dup	p. (Q3952_Q3958dup)
KB77	NA	ex 48	c.15163_15168dup	p. (Asp5055_Leu5056dup)
KB403	*De novo*	ex 53	c.16489_16491del	p. (Ile5497del)
KB53	NA	ex 53	c.16489_16491del	p. (Ile5497del)
Splice site				

KB286	*De novo*	int 2-3	c.177-2A > C	r.177_400del224; p. S59Rfs*86
KB31	NA	int 3-4	c.400 þ 1 G > A	r.177_400del224; p. Ser59Argfs*86
KB20	*De novo*	int 3-5	c.401-3 A > G	r.400_401insAG; p. Gly134Glufs*75
KB442	NA	int 6-7	c.840-6delC	r.?
KB519	NA	int 13-14	c.4132-2A > G	r.?
KB529	NA	int 16-17	c.4584-6C > G	r.?
KB210	*De novo*	in 17-18	c.4693 þ 1G > A	r.4681_4693del13; p. Val1561Argsfsplice*11
KB29	NA	int 42-43	c.13999 þ 5 G > A	r.13840_13999del160; p. Asn4614Ilefs*5
KB290	*De novo*	int 47-48	c.14643 þ 1G > A	r.14644_14875del232; p. Glu4882Profs*36
KB195	*De novo*	int 47-48	c.14644-3C > G	r.14644_14875del232; p. Gln4882Profs*36
KB7	*De novo*	int 44-45	c.14252-6_14252-5insGAAA	r.14252_14382del131; p. Val4751_Glufsplice*22
KB360	NA	int 47-48	c.14644-2A > T	r.?
KB496	NA	int 53-54	c.16520_16521 þ 1delAGG	r.?
Gross deletion				
KB43[e]	NA	ex 48-51	c.15785-238_16168delins	p.?
KDM6A				
Non-sense KB215[f]	*De novo*	ex 6	c.514C > T	p. (Arg172*)
KB341	*De novo*	ex 6	c.514C > T	p. (Arg172*)
Frameshift				
KB39	NA	ex 16	c.1846_1849del	p. (Thr616tyrfs*8)
KB141	NA	ex 17	c.2118_2119ins	p. (G707Hfs*13)
KB434	NA	ex 17	c.2515_2518del	p. (Asn839Valfs*27)
KB381	NA	ex 20	c.3044delC	p. (Thr1015Metfs*33)
Missense				
KB415	NA	ex 16	c.1843C > T	p. (Leu615Phe)
KB272	NA	ex 17	c.2326G > T	p. (Asp776Tyr)
KB131	*De novo*	ex 20	c.2939A > T	p. (Asp980Val)
KB380	*De novo*	ex 26	c.3743A > G	p. (Gln1248Arg)
Gross deletions				
KB11	NA	ex 1-2		p. ?
KB50	*De novo*	ex 5-9		p. ?
Splice site				
KB314	*De novo*	int 11-12	c.975-1G > A	r.876_1320del; p. Cys293IlefsX26
KB127	*De novo*	int 22-23	c.3384 þ 3_3384 þ 6del	r.3210_3284del; p. Asn1070_Lys1094del
KMT2D				
Non-sense				
KB49	NA	ex 5	c.669T > G	p. (Tyr223*)
KB343	NA	ex 8	c.1016G > A	p. (Trp339*)
KB35	NA	ex 10	c.1921G > T	p. (Glu641*)
KB33	NA	ex 16	c.4419G > A	p. (Trp1473*)
KB63	NA	ex 19	c.4895delC	p. (Ser1632*)
KB317	NA	ex 22	c.5212G > T	p. (Glu1738*)
KB336	*De novo*	ex 22	c.5269C > T	p. (Arg1757*)
KB262	NA	ex 26	c.5674C > T	p. (Gln1892*)
KB429	NA	ex 26	c.5707C > T	p. (Arg1903*)
KB26	NA	ex 31	c.6295C > T	p. (Arg2099*)

KB502	*De novo*	ex 31	c.7228C > T	p. (Arg2410*)
KB66	NA	ex 31	c.7246C > T	p. (Gln2416*)
KB59	NA	ex 31	c.7903C > T	p. (Arg2635*)
KB153	*De novo*	ex 31	c.7903C > T	p. (Arg2635*)
KB226	*De novo*	ex 31	c.7903C > T	p. (Arg2635*)
KB338	*De novo*	ex 31	c.7933C > T	p. (Arg2645*)
KB198	*De novo*	ex 31	c.7936G > T	p. (Glu2646*)
KB352	NA	ex 32	c.8227C > T	p. (Gln2743*)
KB323	NA	ex 33	c.8311C > T	p. (Arg2771*)
KB289	NA	ex 34	c.8743C > T	p. (Arg2915*)
KB422	*De novo*	ex 34	c.9396C > A	p. (Cys3132*)
KB186	*De novo*	ex 34	c.9961C > T	p. (Arg3321*)
KB56	*De novo*	ex 34	c.10135C > T	p. (Gln3379*)
KB168	*De novo*	ex 39	c.10750C > T	p. (Gln3584*)
KB46	*De novo*	ex 39	c.10841C > G	p. (Ser3614*)
KB41	NA	ex 39	c.11119C > T	p. (Arg3707*)
KB44	NA	ex 39	c.11119C > T	p. (Arg3707*)
KB42	*De novo*	ex 39	c.11269C > T	p. (Gln3757*)
KB25	NA	ex 39	c.11434 C > T	p. (Gln3812*)
KB244	*De novo*	ex 39	c.11674 C > T	p. (Gln3892*)
KB178	NA	ex 39	c.11704C > T	p. (Gln3902*)
KB425	*De novo*	ex 39	c.11731C > T	p. (Gln3911*)
KB461[a]	NA	ex 39	c.11749C > T	p. (Gln3917*)
KB463	NA	ex 39	c.11845C > T	p. (Gln3949*)
KB181	NA	ex 39	c.11869C > T	p. (Gln3957*)
KB358	NA	ex 39	c.11944C > T	p. (Arg3982*)
KB40	NA	ex 39	c.12274C > T	p. (Gln4092*)
KB114	*De novo*	ex 39	c.12274C > T	p. (Gln4092*)
KB65	NA	ex 39	c.12076C > T	p. (Gln4026*)
KB333	NA	ex 39	c.12703C > T	p. (Gln4235*)
KB410	NA	39	c.12760C > T	p. (Gln4254*)
KB82	*De novo*	ex 39	c.12844C > T	p. (Arg4282*)
KB350	*De novo*	ex 39	c.12844C > T	p. (Arg4282*)
KB189	*De novo*	ex 39	c.12955A > T	p. (Arg4319*)
KB183	*De novo*	ex 39	c.13450C > T	p. (Arg4484*)
KB450	NA	ex 39	c.13450C > T	p. (Arg4484*)
KB175	*De novo*	ex 39	c.13507C > T	p. (Gln4503*)
KB73	*De novo*	ex 40	c.13666A > T	p. (Lys4556*)
KB83	NA	ex 48	c.15022G > T	p. (Glu5008*)
KB377	NA	ex 48	c.15061C > T	p. (Arg5021*)
KB45	NA	ex 48	c.15079C > T	p. (Arg5027*)
KB72	NA	ex 48	c.15079C > T	p. (Arg5027*)
KB362	NA	ex 50	c.16018C > T	p. (Arg5340*)
KB130	NA	ex 52	c.16360C > T	p. (Arg5454*)
Frameshift				
KB454	NA	ex 3	c.234_235delGC	p. (Gln79Alafs*7)
KB469	NA	ex 3	c.345dupA	p. (Ser116Ilefs*7)
KB337	NA	ex 4	c.446_449delTATG	p. (Val149Glyfs*58)
KB75	*De novo*	ex 4	c.472delT	p. (Cys158Valfs*50)
KB8	*De novo*	ex 5	c.588delC	p. (Cys197Alafs*11)
KB58	NA	ex 6	c.705delA	p. (Glu237Serfs*24)

KB57	NA	ex 8	c.1035_1036delCT	p. (Cys346Serfs*17)
KB89	NA	ex 10	c.1345_1346delCT	p. (Leu449Valfs*5)
KB156	*De novo*	ex 10	c.1503dupT	p. (Pro502Serfs*7)
KB116	NA	ex 10	c.1634delT	p. (Leu545Argfs*385)
KB349	NA	ex 10	c.1634delT	p. (Leu545Argfs*385)
KB545	NA	10	c.2091dupC	p. (Thr698Hisfs*6)
KB369	NA	ex 11	c.3596_3597del	p. (Leu1199Hisfs*7)
KB48	*De novo*	ex 11	c.2993dupC	p. (Met999Tyrfs*69)
KB203	NA	ex 11	c.3161_3171del CGTTGAGTCCC	p. (Pro1054Hisfs*10)
KB309	NA	ex 11	c.3730delG	p. (Val1244Serfs*86)
KB142	*De novo*	ex 13	c.4021delG	p. (Val1341Leufs*35)
KB311	NA	ex 14	c.4135_4136delAT	p. (Met1379Valfs*52)
KB524	NA	14	c.4135_4136delAT	p. (Met1379Valfs*52)
KB188	*De novo*	ex 16	c.4454delC	p. (Pro1485Leufs*21)
KB159	NA	ex 19	c.4896_4905del AGATGCCCTT	p. (Asp1633Alafs*86)
KB443[a]	*De novo*	ex 25	c.5575delG	p. (Asp1859Thrfs*17)
KB3	NA	ex 26	c.5652dup	p. (Lys1885Glnfs*18)
KB84	NA	ex 26	c.5779delC	p. (Gln1927Lysfs120*)
KB146	*De novo*	ex 27	c.5857delC	p. (Leu1953Trpfs*94)
KB208	NA	ex 28	c.5954delC	p. (Thr1985Lysfs*62)
KB221	*De novo*	ex 29	c.6149_6150delGA	p. (Arg2050Lysfs*6)
KB525	NA	30	c.6212_6213delAC	p. (His2071Profs*10)
KB152	*De novo*	ex 31	c.6583delA	p. (Thr2195Profs*69)
KB267	NA	ex 31	c.6594delC	p. (Tyr2199Ilefs*65)
KB79	*De novo*	ex 31	c.6595delT	p. (Tyr2199Ilefs*65)
KB102	*De novo*	ex 31	c.6595delT	p. (Tyr2199Ilefs*65)
KB342	NA	ex 31	c.6595delT	p. (Tyr2199Ilefs*65)
KB67	*De novo*	ex 31	c.6638_6641delGCGC	p. (Gly2213Alafs*50)
KB176	NA	ex 31	c.6738delA	p. (Lys2246Asnfs*18)
KB253	NA	ex 31	c.6794delG	p. (Gly2265Glufs*21)
KB278	NA	ex 31	c.7481dupT	p. (Ala2496Serfs*10)
KB313	*De novo*	ex 32	c.8196delG	p. (Ser2733Valfs*24)
KB80	NA	ex 33	c.8273delG	p. (Gly2758Alafs*29)
KB243	*De novo*	ex 34	c.8430_8431insAA	p. (Gln2811Asnfs*41)
KB182	NA	ex 34	c.9203delA	p. (Gln3068Glyfs*3)
KB30	NA	ex 38	c.10606delC	p. (Arg3536Alafs*122)
KB101	*De novo*	ex 39	c.11066_11078delCT GGATCCCTGGC	p. (Ala3689Valfs*56)
KB504	*De novo*	ex 39	c.11093dupG	p. (Phe3699Leufs*14)
KB495	*De novo*	ex 39	c.11715delG	p. (Gln3905Hisfs*74)
KB172	NA	ex 39	c.12647delC	p. (Pro4216Leufs*62)
KB192	*De novo*	ex 39	c.12966delA	p. (Gln4322Hisfs*62)
KB54	NA	ex 39	c.13129dupT	p. (Trp4377Leufs*33)
KB121	*De novo*	ex 39	c.13277dupT	p. (Ala4428Serfs*59)
KB540	NA	41	c.13780delG	p. (Ala4594Profs*23)
KB123	*De novo*	ex 42	c.13884dupC	p. (Thr4629Hisf*18)
KB481	NA	ex 42	c.13895dupC	p. (Ser4633Ilefs*14)
KB197	*De novo*	ex 47	c.14592dupG	p. (Pro4865Alafs*48)
KB125	NA	ex 48	c.15031delG	p. (Glu5011Serfs*40)
KB16	*De novo*	ex 48	c.15374dupT	p. (Phe5126Leufs*12)

KB535	NA	50	c.16043_16044delAC	p. (His5348Leufs*14)
KB355	NA	ex 53	c.16438_16441delAACT	p. (Asn5480Val*6)
KB64	NA	ex 53	c.16469_16470delAA	p. (Lys5490Argfs*21)
KB533	NA	53	c.16469_16470delAA	p. (Lys5490Argfs*21)
Missense				
KB21[a]	inherited M	ex 3	c.346T > C	p. (Ser116Pro)
KB21[a,b]	inherited M	ex 4	c.510G > C	p. Gln170His
KB256	NA	ex 5	c.626C > T	p. (Thr209Ile)
KB458	NA	ex 8	c.1076G > C	p. (Arg359Pro)
KB269	inherited M	ex 10	c.1940C > A	p. (Pro647Gln)
KB126	NA	ex 10	c.2074C > A	p. (Pro692Thr)
KB374[c]	inherited M	ex 10	c.2074C > A	p. (Pro692Thr)
KB487	NA	ex 10	c.2654C > T	p. (Pro885Leu)
KB370[a]	Inherited P-M	ex 11	c.2837C > G	p. (Ala946Gly)
KB215	Inherited M	ex 11	c.3392C > T	p. (Pro1131Leu)
KB341	Inherited M	ex 11	c.3392C > T	p. (Pro1131Leu)
KB222	Inherited P-M	ex 11	c.3572C > T	p. (Pro1191Leu)
KB32	Inherited P	ex 11	c.3773G > A	p. (Arg1258Gln)
KB307	*De novo*	ex 14	c.4171G > A	p. (Glu1391Lys)
KB28[a]	Inherited M	ex 15	c.4249A > G	p. (Met1417Val)
KB28[a]	Inherited M	ex 15	c.4252C > A	p. (Leu1418Met)
KB174	Inherited M	ex 15	c.4283T > C	p. (Ile1428Thr)
KB138	NA	ex 16	c.4427C > G	p. (Ser1476Cys)
KB34	Inherited P	ex 16	c.4565A > G	p. (Gln1522Arg)
KB535	NA	25	c.5549G > A	p. (Gly1850Asp)
KB119	Inherited M	ex 31	c.6638G > A	p. (Gly2213Asp)
KB204[c]	Inherited M	ex 31	c.6638G > A	p. (Gly2213Asp)
KB330[a]	NA	ex 31	c.6733C > G	p. (Leu2245Val)
KB326[c]	Inherited M	ex 31	c.6811C > T	p. (Pro2271Ser)
KB107[a]	NA	ex 31	c.6970C > A	p. (Pro2324Thr)
KB430	NA	ex 31	c.7378C > T	p. (Arg2460Cys)
KB122	Inherited M	ex 31	c.7829T > C	p. (Leu2610Pro)
KB287	Inherited M	ex 31	c.7829T > C	p. (Leu2610Pro)
KB27	NA	ex 34	c.8521C > A	p. (Pro2841Thr)
KB330[a]	NA	ex 34	c.8774C > T	p. (Ala2925Val)
KB443[a]	Inherited M	ex 34	c.9971G > T	p. (Gly3324Val)
KB326[c]	Inherited P	ex 34	c.10192A > G	p. (Met3398Val)
KB357	Inherited P	ex 34	c.10192A > G	p. (Met3398Val)
KB297	NA	ex 35	c.10256A > G	p. (Asp3419Gly)
KB378	NA	ex 35	c.10256A > G	p. (Asp3419Gly)
KB292	*De novo*	ex 37	c.10499G > T	p. (Gly3500Val)
KB86[a]	NA	ex 39	c.10966C > T	p. (Arg3656Cys)
KB374[c]	Inherited P	ex 39	c.11380C > T	p. (Pro3794Ser)
KB293	Inherited P	ex 39	c.11794C > G	p. (Gln3932Glu)
KB204[c]	Inherited P	ex 39	c.12070A > G	p. (Lys4024Glu)
KB385	NA	ex 39	c.12302A > C	p. (Gln4101Pro)
KB247	NA	ex 39	c.12485G > A	p. (Arg4162Gln)
KB107[a]	NA	ex 39	c.12488C > T	p. (Pro4163Leu)
KB170	Inherited M	ex 39	c.13256C > T	p. (Pro4419Leu)
KB512	NA	45	c.14381A > G	p. (Lys4794Arg)
KB86[a]	NA	ex 48	c.14893G > A	p. (Ala4965Thr)

KB38[a]	*De novo*	ex 48	c.15084C > G	p. (Asp5028Glu)
KB154	NA	ex 48	c.15088C > T	p. (Arg5030Cys)
KB185	*De novo*	ex 48	c.15088C > T	p. (Arg5030Cys)
KB423	Inherited P	ex 48	c.15089G > A	p. (Arg5030His)
KB38[a]	*De novo*	ex 48	c.15100T > G	p. (Phe5034Val)
KB76	*De novo*	ex 48	c.15176A > C	p. (His5059Pro)
KB129	NA	ex 48	c.15292A > C	p. (Thr5098Pro)
KB462	*De novo*	ex 48	c.15310T > C	p. (Cys5104Arg)
KB171	Inherited M	ex 48	c.15565G > A	p. (Gly5189Arg)
KB264	NA	ex 48	c.15640C > T	p. (Arg5214Cys)
KB376	NA	ex 48	c.15640C > T	p. (Arg5214Cys)
KB24	*De novo*	ex 48	c.15641G > A	p. (Arg5214His)
KB219	NA	ex 48	c.15641G > A	p. (Arg5214His)
KB408	*De novo*	ex 48	c.15641G > A	p. (Arg5214His)
KB109	*De novo*	ex 48	c.15649T > C	p. (Trp5217Arg)
KB17	*De novo*	ex 50	c.16019G > A	p. (Arg5340Gln)
KB169	*De novo*	ex 51	c.16273G > A	p. (Glu5425Lys)
KB90	NA	ex 51	c.16295G > A	p. (Arg5432Gln)
KB467	NA	ex 51	c.16295G > A	p. (Arg5432Gln)
KB480	NA	ex 52	c.16385A > G	p. (Asp5462Gly)
KB177	*De novo*	ex 52	c.16412G > T	p. (Arg5471Met)
KB489	NA	ex 53	c.16498C > T	p. (Arg5500Trp)
KB120	*De novo*	ex 54	c.16528T > G	p. (Tyr5510Asp)
Indel				
KB404	Inherited M	ex 10	c.2283_2309del	p. (Ala765_Gln773del)
KB274	NA	ex 10	c.2532_2591del	p. (Arg845_Pro864del)
KB370[d]	*De novo*	ex 14	c.4202_4210del	p. (Ser1401_Cys1403del)
KB384	NA	ex 39	c.11220_11222dup	p. (Gln3745dup)
KB461[a,d]	NA	ex 39	c.11220_11222dup	p. (Gln3745dup)
KB281	Inherited M	ex 39	c.11714_11716dup	p. (Gln3905dup)
KB71	Inherited M	ex 39	c.11819_11836dup	p. (Leu3940_Gln3945dup)
KB227	Inherited P	ex 39	c.11843_11860del	p. (L3948_Q3953del)
KB228	Inherited P	ex 39	c.11854_11874dup	p. (Q3952_Q3958dup)
KB77	NA	ex 48	c.15163_15168dup	p. (Asp5055_Leu5056dup)
KB403	*De novo*	ex 53	c.16489_16491del	p. (Ile5497del)
KB53	NA	ex 53	c.16489_16491del	p. (Ile5497del)
Splice site				
KB286	*De novo*	int 2-3	c.177-2A > C	r.177_400del224; p. S59Rfs*86
KB31	NA	int 3-4	c.400 þ 1 G > A	r.177_400del224; p. Ser59Argfs*86
KB20	*De novo*	int 3-5	c.401-3 A > G	r.400_401insAG; p. Gly134Glufs*75
KB442	NA	int 6-7	c.840-6delC	r.?
KB519	NA	int 13-14	c.4132-2A > G	r.?
KB529	NA	int 16-17	c.4584-6C > G	r.?
KB210	*De novo*	in 17-18	c.4693 þ 1G > A	r.4681_4693del13; p. Val1561Argsfsplice*11
KB29	NA	int 42-43	c.13999 þ 5 G > A	r.13840_13999del160; p. Asn4614Ilefs*5
KB290	*De novo*	int 47-48	c.14643 þ 1G > A	r.14644_14875del232; p. Glu4882Profs*36
KB195	*De novo*	int 47-48	c.14644-3C > G	r.14644_14875del232;

				p. Gln4882Profs*36
KB7	*De novo*	int 44-45	c.14252-6_14252-5insGAAA	r.14252_14382del131; p. Val4751_Glufsplice*22
KB360	NA	int 47-48	c.14644-2A > T	r.?
KB496	NA	int 53-54	c.16520_16521 þ 1delAGG	r.?
Gross deletion				
KB43[e]	NA	ex 48-51	c.15785-238_16168delins	p. ?
KDM6A				
Non-sense KB215[f]	*De novo*	ex 6	c.514C > T	p. (Arg172*)
KB341	*De novo*	ex 6	c.514C > T	p. (Arg172*)
Frameshift				
KB39	NA	ex 16	c.1846_1849del	p. (Thr616tyrfs*8)
KB141	NA	ex 17	c.2118_2119ins	p. (G707Hfs*13)
KB434	NA	ex 17	c.2515_2518del	p. (Asn839Valfs*27)
KB381	NA	ex 20	c.3044delC	p. (Thr1015Metfs*33)
Missense				
KB415	NA	ex 16	c.1843C > T	p. (Leu615Phe)
KB272	NA	ex 17	c.2326G > T	p. (Asp776Tyr)
KB131	*De novo*	ex 20	c.2939A > T	p. (Asp980Val)
KB380	*De novo*	ex 26	c.3743A > G	p. (Gln1248Arg)
Gross deletions				
KB11	NA	ex 1-2		p. ?
KB50	*De novo*	ex 5-9		p. ?
Splice site				
KB314	*De novo*	int 11-12	c.975-1G > A	r.876_1320del; p. Cys293IlefsX26
KB127	*De novo*	int 22-23	c.3384 þ 3_3384 þ 6del	r.3210_3284del; p. Asn1070_Lys1094del

[a]Detected together with pathogenic mutation; [b]Falls in the last base of exon, predicted to disrupt the donor splice site; [c]Patients with compound heterozygous variants; [d]Detected together with other variant; [e]Identified by MLPA; [f]Detected together with missense in *KMT2D*.

Table 2. The known solid organ malignancies reported in Kabuki syndrome patients

Tumor types	Reference
Wilms tumor	Teranishi *et al.*[8]
Hepatoblastoma	Bernier *et al.*[9]
Neuroblastoma	Bernier *et al.*[9]
Pilomatrixoma	Bernier *et al.*[9]
Spinal ependymoma	Roma *et al.*[10,11]
Burkitt's lymphoma	De Billy *et al.*[12]

During a recurrence of seizures at 13 years, a reduced blood glucose level [35 mg/dL (1.9 mmol/L)] was observed. In the subsequent six months, she was admitted to the hospital because of several episodes of transient confusion,NArrowing of consciousness, sialorrhea, and myoclonic seizures, occasionally prolonged with at least two episodes of status epilepticus requiring anesthesia support. Her adherence to therapy was good.

While hospitalized, an electroencephalogram revealed focal electrical anomalies in the right hemisphere in a poorly modulated tracing with an excess of rapid activity. Cerebral magnetic resonance imaging showed specific anomalies and a supra-vermian arachnoid cyst. Due to recurrent daily seizures, treatment with

valproic acid was started with topiramate but was later replaced with perampanel, followed by symptomatic improvement.

Gene sequencing was performed based on the clinical picture. Genetic analysis revealed a heterozygous c.446_449del variant in the *KMT2D* gene, confirming the diagnosis of KS-1. Continuous glucose monitoring (CGM; Ipro2, Medtronic, Milan, Italy) revealed several prolonged episodes of low blood glucose at night, early morning, and lunchtime. Blood insulin levels during two hypoglycemic episodes on two consecutive days were low (18.5 μU/mL and 20.3 μU/mL). She started diazoxide (10 mg/kg/day divided into three doses per day) but discontinued it due to the lack of benefit and the development of adverse effects (hypotension, tachycardia, and cold sweats). Ultrasound of the abdomen revealed no abnormalities; contrast-enhanced computer tomography revealed a 2.4 × 2.0 cm lesion at the head of the pancreas without local invasion and two small hepatic lesions.

Laboratory data were notable for increased circulating chromogranin A (29 U/L, n.v. 2-18 U/L), normal gastrin (50 pg/mL, n.v 6-108 pg/mL), neuron-specific enolase (NSE; 14.8 ng/mL, n.v. < 16.3 ng/mL), vasoactive intestinal peptide (33 ng/mL, n.v. < 200 ng/mL), and glucagon (30 pg/mL, n.v. 25-250 pg/mL).

The patient underwent pylorus-preserving pancreatoduodenectomy, partial hepatectomy, and microwave ablation of the remaining hepatic lesions. Histological examination of the pancreatic lesion confirmed the presence of a well-differentiated neuroendocrine tumor of intermediate grade, expressing insulin, chromogranin, CD56, and synaptophysin [Figure 1A-D]. One of the two hepatic lesions was a neuroendocrine tumor metastasis (3 mm) with a solid immunoreactivity for chromogranin with mitosis count (seven per ten high-power fields). The remaining metastasis-free liver tissue of the specimen showed some degree of fibrosis, diffuse neogenesis of intrahepatic bile ductules, and diffuse dilation and congestion of the portal veins [Figure 1E and F]. The other hepatic lesion was a ciliated hepatic foregut cyst (CHFC) [Figure 1G]. After surgery, her blood glucose levels returned to the normal range.

Two months later, during a physical examination, we perceived two small nodules in the left breast. Ultrasound examination confirmed the presence of two rounded masses of 50 mm and 16 mm (without malignant appearance). Because of the growth pattern over the subsequent 12 months, the nodules were removed. Histological examination showed they were benign phyllodes tumors, a rare fibroepithelial breast tumor at a young age [Figure 1H and I]. Follow-up revealed another neoplasm in the right shoulder, diagnosed as a pilomatrixoma and a junctional melanocytic nevus with cytological atypia, which was completely excised.

At the six-year follow-up, the girl showed no neoplasms and presented reasonable control of epileptic seizures. The Array-CGH was negative, and no other variants associated with predisposition to cancer were detected. However, whole exome sequencing was not performed.

DISCUSSION

The genetic analysis in our patient revealed a heterozygous c.446_449del frameshift variant in the *KMT2D* gene, predicted to generate the p.(Val149Glyfs*58) protein. Frameshift variants are the most common mechanisms of gene loss-of-function, reported in 36.67% of cases[14].

The c.446_449del variant of the *KMT2D* gene has been described only in one previous KS case; however, the precise clinical description is lacking[5]. Our KS patient is notable because she developed very rare tumors. Insulinoma, phyllodes tumor of the breast, CHFC, and melanocytic nevus with cytological atypia have never

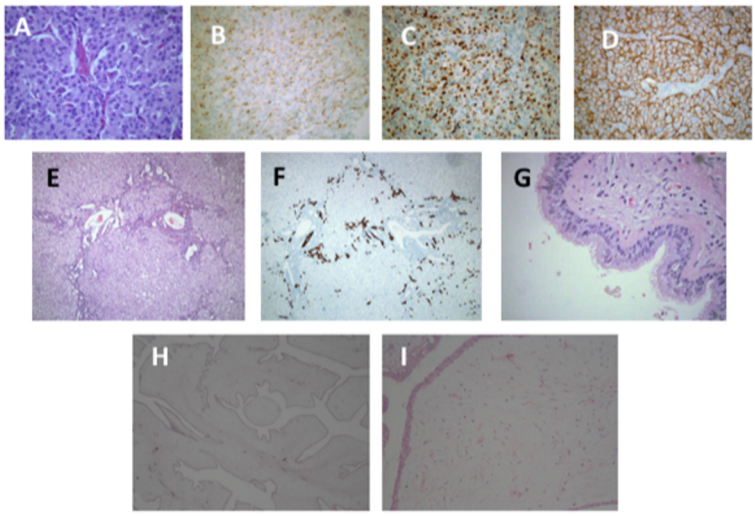

Figure 1. (A) Hematoxylin-eosin (H&E) stained section of the pancreatic endocrine neoplasm. Immunostaining revealed a strong expression of insulin; (B) chromogranin (C) and CD56 (D). The section was also strongly positive for Ki-67 and synaptophysin staining (not shown). The morphology indicates a well-differentiated neuroendocrine tumor and a mitotic count of 20 per 10 high-power fields and a Ki-67 index (%) of 20 % indicates a tumor of intermediate-grade (G2). (A, H&E, original magnification × 200; B-D, immunohistochemistry, original magnification × 200); (E) H&E stained section of the metastasis-free liver tissue showing fibrous bands encircling small islets of hepatic tissue; (F) Numerous small bile ducts were scattered in the fibrous tissue well evidenced by cytokeratin 7 immunostaining. We also observed a diffuse, pronounced, dilation and congestion of the portal veins (E, H&E, original magnification × 100; F, immunohistochemistry, original magnification × 100); (G) Liver tissue with a cyst entirely lined with ciliated columnar epithelium, showing pseudo-stratification, surrounded by smooth muscle (G, H&E, original magnification ×400); (H) H&E x25 Leaf-like processes with a moderately cellular stroma phyllodes tumour; (I) H&E x200 cellular spindle cell stroma. No evidence of mitoses or necrosis in low-grade phyllodes tumor.

been described in patients with KS.

Benign tumors, especially pilomatrixoma, have rarely been described in patients with KS[9]. Associations between KS and other tumors are uncommon; however, there have been significant reports in the last ten years.

Somatic variants of *KMT2D*, particularly loss-of-function, have been reported in gastric cancer, lymphoma, and medulloblastoma; somatic variants of KDM6A have recently been described in some malignancies (most commonly in urothelial carcinoma, T-cell acute lymphoblastic leukemia, and breast cancer)[1]. *KMT2D* encodes a lysine-specific methyltransferase, responsible for post-translational histone 3 lysine 4 (H3K4) mono-, di- and tri-methylation, which is exclusively associated with actively transcribed genes[3,6]. KDM6A encodes an X-linked H3K27 demethylase that removes repressive epigenetic marks and interacts with *KMT2D* in regulating gene expression in the activating signal integrator-2-containing complex[3]. Defective demethylation dysregulates gene expression with the proliferation of neoplastic cells. However, the significance of germline (i.e., present in all tissues) pathogenic variants in neoplasms of KS patients is yet to be determined[6,11].

Insulinoma, the most common functioning neoplasm of the endocrine pancreas, is infrequent in childhood (about 30 cases have been reported) and usually affects individuals in their late 50 s and early 60 s. The clinical presentation is characterized by neuroglycopenic symptoms due to severe hypoglycemia, i.e., irrational behavior, somnolence, impaired school performance, and refractory seizures. Hyperinsulinemic hypoglycemia should be considered in cases of unexplained psychiatric and neurologic disorders or worsening neurologic conditions (e.g., increased seizures or seizures becoming refractory to treatment, as in

our case). Diazoxide (5-20 mg/kg/day given orally) may reduce the frequency and severity of hypoglycemic events, although tumor resection is the gold standard.

Phyllodes tumors are rare fibroepithelial tumors of the breast, representing only 0.3%-0.9% of all breast tumors and 2%-3% of fibroepithelial neoplasms in adults. The tumor usually occurs in women aged 35-55; only 35 cases have been reported in girls under 20. Phyllodes tumors are often benign but may be borderline and malignant. Although it presents as a well-delimited, rapidly growing, painless, and mobile mass with an overall good outcome, it often recurs[15], and surgery is the standard treatment[16].

Congenital hepatic malformations have been rarely described in patients with KS[17]. Our patient showed the presence of a CHFC and some degree of hepatic fibrosis. CHFCs are rare cystic lesions of embryological origin. Because metaplastic and malignant epithelial lining has been described in CHFC, complete surgical excision is recommended, given the potential for metaplastic or malignant squamous carcinoma[18]. While CHFC has not been reported in KS, hepatic fibrosis has been described, supporting that hepatic abnormalities may be common in KS[1]. *KMT2D* is mutated in hepatocellular carcinoma cases, with earlier disease recurrence, more significant microvascular invasion, and a more aggressive phenotype. Therefore, the potential development of malignant liver cancer must be considered in KS patients[11].

Pilomatricoma is a cystic follicular lesion that commonly arises on the head and neck in children. This lesion has been linked to various syndromes (Turner, Gardner, RubinsteinTaybi, Sotos, Trisomy 9, myotonic dystrophy, spina bifida, sarcoidosis, and gliomatosis cerebri); however, only three cases of pilomatrixoma associated with KS have been reported[8]. All three cases had common facial and syndromic features; they were referred to dermatology for lesions described as cutaneous skin-colored papulonodular lesions, which were subsequently diagnosed as pilomatrixoma following biopsy. A somatic variant in CTNNB1 causes the only known mutation confirmed in pilomatrixoma. Predisposition to pilomatrixoma in KS may not be coincidental because CTNNB1 plays a pivotal role in the Wnt pathway, encoding b-catenin, which may recruit *KMT2D* to regulate Wnt pathway target genes involved in morphogenesis and tumorigenesis[11]. The case of the junctional melanocytic nevus with cytological atypia is the first described in the literature associated with KS. The only previous association was a Becker nevus.

In our patient, the aCGH was negative; no other searches for cancer susceptibility genes were performed; further investigations will be needed to clarify the relationship between KS variants and neoplastic lesion development.

CONCLUSION

Our case broadens the phenotypic spectrum of KS, especially the neoplasms associated with this syndrome. This case agrees with the most recent literature showing a significant association between KS and tumors, even if the molecular basis of this relationship is not well understood.

A large case series with an accurate description of the neoplastic phenotypes and precise genetic characterization of the patients are needed to clarify the relationship between *KMT2D* gene variants, KS, susceptibility to neoplastic lesions, and eventual specific tumor phenotypes associated with KS. To date, there are no indications for oncologic screening in KS patients. Studies are needed in this regard. Finally, although a second genetic syndrome in the patient is unlikely, we cannot rule out a tumor predisposition syndrome.

DECLARATIONS

Acknowledgments

We thank the family for their continuing interest and cooperation. We also thank the Genomic and Genetic Disorders Biobank, a Telethon Network of Genetic Biobanks member funded by Telethon Italy (project no. GTB12001G) for biospecimens banking.

Authors' contributions

Substantial contributions to the conception and design of the study and performed data analysis and interpretation: Bonuccelli A, Federico G, Orsini A, Boggi U

Data acquisition, administrative, technical, and material support: Baldaccini T, Santangelo A, Alberti E, Del Pistoia M

Contributed to reviewing the manuscript: Peroni D, Randazzo E

Provided genetic counseling: Toschi B

Availability of data and materials

Data regarding the case report can be found in the database of the Pediatric Clinic of Pisa. Data regarding the literature review are referenced in the manuscript as footnotes and can be found on PubMed.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The article consists of the retrospective description of a clinical case. In these cases the approval of the ethics committee is not required. Consent to partecipate has been obtained from the parents of the patient.

Consent for publication

Consent for publication has been obtained from the parents of the patient.

Copyright

© The Author(s) 2023.

REFERENCES

1. Adam MP, Hudgins L, Hannibal M. Kabuki syndrome. GeneReviews®. Seattle: University of Washington; 2011. PubMed
2. Adam MP, Banka S, Bjornsson HT, et al; Kabuki Syndrome Medical Advisory Board. Kabuki syndrome: international consensus diagnostic criteria. *J Med Genet* 2019;56:89-95. DOI
3. Barry KK, Tsaparlis M, Hoffman D, et al. From genotype to Phenotype-A review of kabuki syndrome. *Genes* 2022;13:1761. DOI PubMed PMC
4. Aristizábal E, Diaz-Ordóñez L, Candelo E, Pachajoa H. A novel intronic *KMT2D* variant as a cause of kabuki syndrome: a case report. *Appl Clin Genet* 2021;14:409-16. DOI PubMed PMC
5. Cocciadiferro D, Augello B, De Nittis P, et al. Dissecting *KMT2D* missense mutations in Kabuki syndrome patients. *Hum Mol Genet* 2018;27:3651-68. DOI PubMed PMC
6. Wang YR, Xu NX, Wang J, Wang XM. Kabuki syndrome: review of the clinical features, diagnosis and epigenetic mechanisms. *World J Pediatr* 2019;15:528-35. DOI
7. Froimchuk E, Jang Y, Ge K. Histone H3 lysine 4 methyltransferase *KMT2D*. *Gene* 2017;627:337-42. DOI PubMed PMC
8. Teranishi H, Koga Y, Nakashima K, et al. Cancer management in kabuki syndrome: the first case of wilms tumor and a literature review. *J Pediatr Hematol Oncol* 2018;40:391-4. DOI
9. Bernier FE, Schreiber A, Coulombe J, Hatami A, Marcoux D. Pilomatricoma associated with kabuki syndrome. *Pediatr Dermatol* 2017;34:e26-7. DOI PubMed

10. Roma D, Palma P, Capolino R, et al. Spinal ependymoma in a patient with Kabuki syndrome: a case report. *BMC Med Genet* 2015;16:80. DOI PubMed PMC
11. Boniel S, Szymańska K, Śmigiel R, Szczałuba K. Kabuki syndrome-clinical review with molecular aspects. *Genes* 2021;12:468. DOI PubMed PMC
12. de Billy E, Strocchio L, Cacchione A, et al. Burkitt lymphoma in a patient with Kabuki syndrome carrying a novel *KMT2D* mutation. *Am J Med Genet A* 2019;179:113-7. DOI
13. Aukema SM, Glaser S, van den Hout MFCM, et al. Molecular characterization of an embryonal rhabdomyosarcoma occurring in a patient with Kabuki syndrome: report and literature review in the light of tumor predisposition syndromes. *Fam Cancer* 2023;22:103-18. DOI PubMed PMC
14. Herodež Š Š, Varda NM, Krgović D. De novo *KMT2D* heterozygous frameshift deletion in a newborn with a congenital heart anomaly. *Balkan J Med Genet* 2020;23:83-90. DOI PubMed PMC
15. Wang H, Wang X, Wang CF. Comparison of clinical characteristics between benign borderline and malignant phyllodes tumors of the breast. *Asian Pac J Cancer Prev* 2014;15:10791-5. DOI
16. Strode M, Khoury T, Mangieri C, Takabe K. Update on the diagnosis and management of malignant phyllodes tumors of the breast. *Breast* 2017;33:91-6. DOI PubMed
17. Bögershausen N, Altunoglu U, Beleggia F, et al. An unusual presentation of Kabuki syndrome with orbital cysts, microphthalmia, and cholestasis with bile duct paucity. *Am J Med Genet A* 2016;170:3282-8. DOI
18. Bishop KC, Perrino CM, Ruzinova MB, Brunt EM. Ciliated hepatic foregut cyst: a report of 6 cases and a review of the English literature. *Diagn Pathol* 2015;10:81. DOI PubMed PMC