Propuesta de registro de pacientes España

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Base de datos conjunta HULP - HGUG

co	Problemas alimentación / GI	Anomalías renales	Paladar hendido	Dess psicomotor	Comunicación lenguaje	Cardiovascular	Neuro / crisis	Endo / crec	Probl ortopédicos	Inmuno / derma	Vist
M	si, gastrotomía	riñón ectópico	si	muy lento	Ausente a los 2a	CIV	alia (VDVP). Crisis parciales	dactilia	V dedo, hallux derech	?	?
S	NE / Ano anterior	Agenesia renal D	No	lento		No?	/ no		lux congénita caderas	no / no	miop
M											
M	?	?	?	muy lento		cardiopatía congénita	retraso importane	fallo medro	?	?	?
S	no	No	No	lento		No	No		No	No	No
S	no	no	no	lento	ento 2-3 palabras con 2 año	no	no	talla -2,5DE	lux congénita caderas	no	image
S	rto por vólvulo, candidata trasplan	No	No	lento	, escolaridad con adaptaci	sternosis aórtica-mit	rágico, hemiparesia	talla p10	No	No	Norm
S	ucción primeros meses, hepatopa	no	no	lento	scolaridad normal con apoy	no	no	talla -3DE	no	studio inmune norm	Norm
M	no	no	no	lento	scolaridad normal con apoy	CIV subaórtica	no	tall p10	no	otitis frecuentes	etropía
M	no	no	Si	lento	retraso moderado	subvalvular con disfu	una crisis epiléptica	tall -3,8DE	no	OMAs frec	Norm
S	si, sonda nasogástrica	enosis pieloureteral dere	Si	lento	, escolaridad con adaptación	curricular	no	talla p3	no		

Kabuki syndrome: a Spanish case series

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Introduction:

Kabuki syndrome is a clinically heterogeneous multiple congenital malformation syndrome with distinctive facial features and developmental delay.
Two histone methyltransferase genes have been identified as causes, *KMT2D* and *KDM6A* (X chromosome).

Material and methods:

We present 20 cases diagnosed with Kabuki syndrome, seen at two large hospitals in Madrid, Spain.

ID	Sex	Age (years)	Height (percentile)	DD/ ID	Heart	Renal	Gastro intestinal	Neurologic	Skeletal	Palate	Teeth	Eyes	Hearing	Endocrine / Immunology	Other
LP1	M	12	p10	+	VSD	N	N	N	N	N	hypodontia	Strabismus	bilateral SNHL	N	
GM1	F	3	SS	+	Ao coarctation; VSD; ASD	N	Feeding difficulties	Hypotonia; microcephaly	hemivertebra; hyperlaxity	VPI	N	retinal coloboma (unilateral)	preauricular tag	transient hypothyroidism	premature telarch
LP2	F	14	p10	+	Ao, MV stenosis	N	Volvulus; short bowel syndrome	stroke	N	N	hypodontia	N	N	N	genetic mosaicism
LP3	F	10	FTT	++	CHD										Deceased
GM2	F	8	SS	++	N	unilateral agenesis; ectopic dysplastic	GER	Hypotonia	-	cleft	hypoplastic	N	Transmissive HL	Low IgA	
LP4	M	6		+	N	N	N	N	N	N		N	N	N	
GM3	F	3	p25	++	VSD	N	-	Hypotonia; microcephaly	Trigonocephaly; hip dysplasia	N	N	NL duct obstruction			
GM4	F	4	p25	+	PFO	N	-	Hypotonia; microcephaly	hip dysplasia	VPI	N	N			
LP5	M	10													
LP6	M	16	SS	+	MV dysfunction	N	N	seizure	N	cleft	oligodontia	N	Transmissive HL	N	
GM5	M	3	SS	+	VSD	Horseshoe	-	Hypotonia	-	N	N	Strabismus	N	neonatal hypoglycemia	stereotypes
LP7	M	10	p3	+		unilateral pyeloureteral stenosis	feeding difficulties	N	N	cleft			N		hypospadias
LP8	F	7		++	VSD	ectopic kidney	PEG	Hydrocephaly; seizures	Vth finger clynodactyly	cleft					
GM6	M	10	p2-10	+	PFO	duplex renal pelvis (unilateral)	GER; PEG			high arched	Hypodontia	iris coloboma; corneal clouding (unilateral)	Transmissive HL	neonatal hypoglycemia	cryptorchidism
GM7	F	7	SS	++	Ao coarctation	N	GER; feeding difficulties ant placed anus	Hypotonia; EEG anomalies	-	high arched	Hypodontia	Strabismus		subclinical hypothyroidism	premature telarch; umbilical hernia; behavioural problems
LP9	F	5		+	N	unilat R agenesis	-	-	hip dysplasia	N	NA	Myopia	N	N	
LP10	F	5	SS	+	N	N	N	N	hip dysplasia	N	N	bull's eye	N	N	
GM8	M	5m	FTT	+	Tetraology of Fallot	N	feeding difficulties		clavicle hypoplasia	cleft	NA	microphtalmia; retinal coloboma	preauricular pits		
GM9	F	14	p25	+	N	N	-	Macrocephaly	-	N	N	Strabismus	preauricular pits	-	
LP11	F	9	SS	+	N	N	feeding difficulties	N	N	N	hypodontia	Anisochoria	N	AI sierosing cholangitis	ADHD

Abbreviations:
FTT: Failure to thrive
DD: Developmental delay
ID: Intellectual disability
N: Normal
SS: Short stature
PFO: Patent Foramen Ovale
VPI: Velopharyngeal insufficiency
SNHL: Sensorineural Hearing Loss

Table 1: Clinical data

ID	Gene	Mutation	Protein	Change	Other
LP1	KMT2D	c.1790C>G (ph)	p.Ser597Ter	missense	
GM1	KMT2D	c.10990dupT (ph)	p.Pro3667Ufs*10	small insertion	
LP2	KMT2D	c.12750delA (ph)	p.Gln4125Hisfs*10	small deletion	mosaicism 30-40%
LP3	KMT2D	c.1448dupT (ph)		small insertion	
GM2	KMT2D	c.9662_9683delGG		small deletion	
LP4	KMT2D	c.4150G>C (ph)	p.Arg1384Pro	missense	
GM3	KMT2D	c.7991delC	p.Thr2668Profs*59	small insertion	
GM4	KMT2D	c.8295C>T (ph)	p.Arg2999Ter	Nonsense	
		c.3392C>T (pat)	p.Pro1131Leu	Missense	
		c.6752C>T (pat)	p.Ser2251Leu	Missense	
LP5	KMT2D	c.7228C>T (ph)	p.Arg2410Ter	Nonsense	
LP6	KMT2D	c.7909C>G (ph)	p.Ser2636*	Nonsense	
GM5	KMT2D	c.8306G>A (ph)	p.Arg2769Gln	Missense	
LP7	KMT2D	c.1012C>T	p.Gln1674Ter	Nonsense	
LP8	KMT2D	c.11103delC (ph)		small deletion	
GM6	KMT2D	c.11119C>T	p.Arg3707Ter	Nonsense	
GM7	KMT2D	c.15341A>G (ph)	p.His5114Arg	Missense	
LP9	KMT2D	c.15401G>A (ph)	p.Arg5140Gln	Missense	
LP10	KMT2D	c.15403_15404delTG (ph)		small deletion	
GM8	undersea				aCGH normal
GM9	Negative for both genes				aCGH normal
LP11	KDM6A	c.3407G>A (ph)	p.Arg1169Asn	Missense	

Table 2: Genetic testing results: 18 confirmations of 19 tested

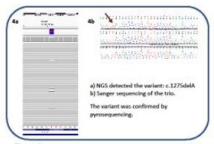

Figure 4:
Case LP2: Mosaicism for a *KMT2D* mutation in blood.

Results:

Age at diagnosis ranged from 5 months to 16 years. Female:male ratio was 12:8.
Eighteen cases had a molecular confirmation (17 *KMT2D* and 1 *KDM6A* mutation), one test is ongoing and one result was negative for both genes. Of the 17 *KMT2D* mutations 8 (47%) were truncating (either nonsense or frameshift producing a downstream stop codon).
One case was found to carry 3 variants in *KMT2D*: 1 *de novo* nonsense (clearly pathogenic) and 2 missense variants inherited from an unaffected parent.

The combination of congenital anomalies, developmental delay and characteristic facial features was variable but the distinctive eyebrows and long palpebral fissures reminiscent of the Kabuki make-up of Japanese theatre were present in all.
Additional features found in our series, rarely or not previously described as part of the syndrome, were trigonocephaly in one case, unilateral corneal opacity and iris coloboma in another, and autoimmune cholangitis in the girl with *KDM6A* mutation. One patient died at 10 years from complications of her heart anomalies. Interestingly, one case with a milder phenotype and less characteristic facial dysmorphism was found to be mosaic for a *KMT2D* frameshift mutation.

Conclusions:

This is the first series of cases with Kabuki syndrome in Spain. Additional cranial, ophthalmological and hepatic features are shown. A case with mosaicism for Kabuki syndrome is presented.

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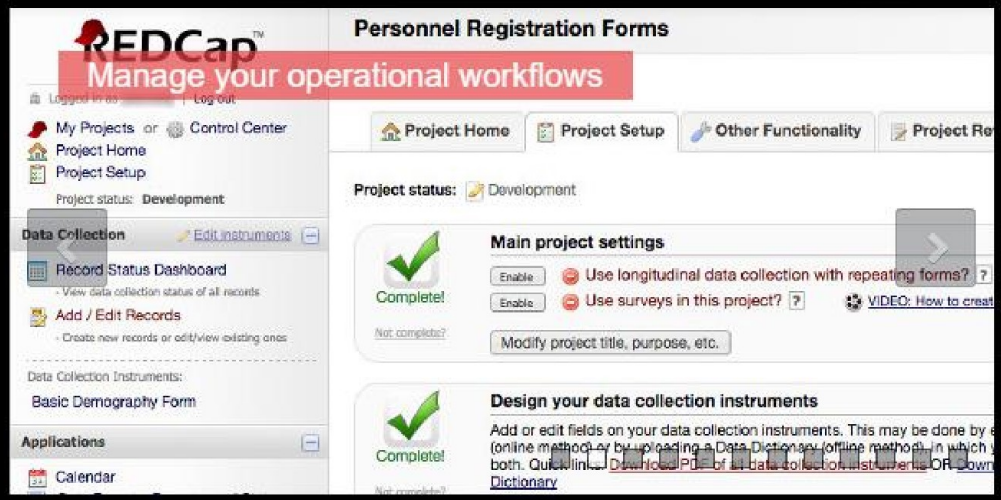

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