Received: 3 September 2016 | Revised: 17 July 2017 | Accepted: 24 July 2017
DOI: 10.1002/ajmg.a.38417

ORIGINAL ARTICLE

WILEY AMERICAN JOURNAL OF medical genetics PART A

Congenital heart defects in molecularly proven Kabuki syndrome patients

Maria Cristina Digilio[1] | Maria Gnazzo[1] | Francesca Lepri[1] | Maria Lisa Dentici[1] | Elisa Pisaneschi[1] | Anwar Baban[1] | Chiara Passarelli[1] | Rossella Capolino[1] | Adriano Angioni[1] | Antonio Novelli[1] | Bruno Marino[2] | Bruno Dallapiccola[1]

[1] Medical Genetics Unit, Medical Genetics Laboratory, Pediatric Cardiology, Bambino Gesù Pediatric Hospital, IRCCS, Rome, Italy

[2] Department of Pediatrics, Pediatric Cardiology, Sapienza University, Rome, Italy

Correspondence
Maria Cristina Digilio, MD, Medical Genetics, Bambino Gesù Paediatric Hospital, IRCCS, Piazza S. Onofrio 4, 00165 Rome, Italy.
Email: digilio@opbg.net

The prevalence of congenital heart defects (CHD) in Kabuki syndrome ranges from 28% to 80%. Between January 2012 and December 2015, 28 patients had a molecularly proven diagnosis of Kabuki syndrome. Pathogenic variants in *KMT2D (MLL2)* were detected in 27 patients, and in *KDM6A* gene in one. CHD was diagnosed in 19/27 (70%) patients with *KMT2D (MLL2)* variant, while the single patient with *KDM6A* change had a normal heart. The anatomic types among patients with CHD included aortic coarctation (4/19 = 21%) alone or associated with an additional CHD, bicuspid aortic valve (4/19 = 21%) alone or associated with an additional CHD, perimembranous subaortic ventricular septal defect (3/19 = 16%), atrial septal defect ostium secundum type (3/19 = 16%), conotruncal heart defects (3/19 = 16%). Additional CHDs diagnosed in single patients included aortic dilatation with mitral anomaly and hypoplastic left heart syndrome. We also reviewed CHDs in patients with a molecular diagnosis of Kabuki syndrome reported in the literature. In conclusion, a CHD is detected in 70% of patients with *KMT2D (MLL2)* pathogenic variants, most commonly left-sided obstructive lesions, including multiple left-sided obstructions similar to those observed in the spectrum of the Shone complex, and septal defects. Clinical management of Kabuki syndrome should include echocardiogram at the time of diagnosis, with particular attention to left-sided obstructive lesions and mitral anomalies, and annual monitoring for aortic arch dilatation.

KEYWORDS
congenital heart defect, Kabuki syndrome, *KDM6A* gene, *KMT2D* gene

1 | INTRODUCTION

Kabuki syndrome is a genetically heterogeneous disorder characterized by developmental delay, growth defect with feeding difficulties, skeletal anomalies, congenital heart defects (CHDs), renal malformations, anorectal anomalies, persistence of fetal fingertip pads, and distinct facial anomalies, including sparse eyebrows, long palpebral fissures, eversion of the lateral third of the lower eyelids, pillowed lower lip, and large everted ears (Kawame, Hannibal, Hudgins, & Pagon, 1999; Kluijt et al., 2000; Kuroki, Suzuki, Chyo, Hata, & Matsui, 1981; Niikawa, Matsuura, Fukushima, Ohsawa, & Kajii, 1981; Niikawa et al., 1988; Philip et al., 1992; Schrander-Stumpel et al., 1994; Wilson, 1998).

In 2001, our group performed a clinical review of CHDs diagnosed in patients with Kabuki syndrome, when the underlying molecular

defect was still unknown (Digilio et al., 2001). According to the descriptions of the largest clinical series in the literature, the prevalence of CHD in Kabuki syndrome varies greatly, ranging between 28% and 80%, since not all the affected patients underwent specific cardiac evaluation (Digilio et al., 2001; Galan-Gomez et al., 1995; Hughes & Davies, 1994; Kawame et al., 1999; Niikawa et al., 1988; Philip et al., 1992; Schrander-Stumpel et al., 1994; Wilson, 1998). The spectrum of anatomic types of CHD is wide, including aortic coarctation and other left-sided obstructive lesions, septal defects, and conotruncal anomalies (Digilio et al., 2001; Niikawa et al., 1988; Philip et al., 1992; Schrander-Stumpel et al., 1994), with a predominance of aortic coarctation noted in several series (Armstrong et al., 2005; Digilio et al., 2001; Hughes & Davies, 1994).

At present, 4 genes causative of Kabuki syndrome and one related to a Kabuki-like phenotype are known. The first identified and more frequently involved gene is *KMT2D (MLL2)*, mapping to 12q13.12 (Ng et al., 2010). Our group has participated to the identification of the KS2 gene, the *KDM6A* gene mapping to Xp11.3 (Lederer et al., 2012). More recently, three additional genes involved in a minority of patients have been identified, including the *RAP1A* gene (Bögershausen et al., 2015), located within the region of a 12-Mb duplication of chromosome 1p13.1-p22.1 previously diagnosed in a Kabuki syndrome patient (Lo, Cheung, Ng, & Lam, 1998), the closely related *RAP1B* gene (Bögershausen et al., 2015), and the *HNRNPK* gene, associated with a Kabuki-like phenotype with nodular heterotopia (Au et al., 2015; Lange et al., 2016). Screening of large series of patients with Kabuki syndrome have shown that *KMT2D (MLL2)* pathogenic variants are responsible for 55–80% of the cases (Banka et al., 2012, 2013; Hannibal et al., 2011; Li et al., 2011; Micale et al., 2011; Ng et al., 2010; Paulussen et al., 2011), while pathogenic variants in *KDM6A* have been reported in 9–14% of *KMT2D (MLL2)*-negative patients (Lederer et al., 2012; Miyake et al., 2013), and in less than 5% of total Kabuki syndrome patients, respectively (Banka et al., 2015). *RAP1A*, *RAP1B*, and *HNRNPK* variants have been reported in single patients.

In this study, we analyzed the prevalence of CHD, their anatomic types and the genetic characteristics of 27 personal patients with Kabuki syndrome and pathogenic variants in *KMT2D (MLL2)*, and reviewed CHDs in patients with molecular diagnosis of Kabuki syndrome from the literature.

2 | MATERIALS AND METHODS

The patients were evaluated between January 2012 and December 2015. Complete physical examination for major and minor anomalies has been carried out by trained medical geneticists in all patients.The diagnosis of Kabuki syndrome is based on the presence of at least four of the following inclusion criteria: (i) long palpebral fissures with eversion of the lateral portion of lower eyelid; (ii) broad, arched eyebrows with sparseness; (iii) short nasal columella with depressed nasal tip; (iv) large, prominent or cupped ears; (v) developmental delay-mental retardation (Kawame et al., 1999). Cardiac evaluation included chest x-ray, electrocardiogram, and two-dimensional and color Doppler echocardiography in all patients.

Genomic DNA was extracted from circulating leukocytes with Qiagen protocol, and quantified using fluorescent dyes. Mutational analysis of *MLL2* (NM_003482) and *KDM6A* (NM_021140) genes was performed through targeted resequencing, using a customized design, Truseq Custom Amplicon panel, and analyzed with MiSeq® sequencing platform (Illumina, San Diego, CA). The probe design was performed over a cumulative target region of 33,255 bp and generated a panel of 135 amplicons 500 bp long with coverage of 99% of the cumulative region. Each variant identified by Illumina Variant Studio has been evaluated for call quality score, coverage and visualized by Integrative Genome Viewer (IGV). All variants identified were validated by Sanger sequencing using standard protocols. To predict the consequences of the unknown missense variants we used in silico methods (Alamut Software) and, when available, DNA of the parents' patients with variants was screened to investigate whether the change was de novo or inherited. Informed consent was obtained from all patients or their parents. Standard chromosome analysis was performed in all patients, and CGHarray at a resolution of 75 kb in 14 patients.

We ascribed as pathogenic the variants resulting in truncated protein or obvious splicing error or missense changes that were proven to be de novo in at least one patient. If both parental samples were unavailable, a missense change was considered to be pathogenic if it has been identified in more than one patient or pathogenicity was consistent accordingly to ACMG criteria. Variants with uncertain significance (VUS) and changes that were inherited from a clinically unaffected parent were excluded from the study.

During the collection period, 28 patients had a molecularly proven diagnosis of Kabuki syndrome. Pathogenetic variants in *KMT2D (MLL2)* gene were detected in 27 patients, and a deletion of part of *KDM6A* gene in an additional patient which was previously reported by Lederer et al. (2012) (Table 1). Previously published Kabuki syndrome subjects are patients 2,3 (Dentici et al., 2015; Micale et al., 2011), 5 (Cappuccio et al., 2014; Dentici et al., 2015), 6,7,9,21 (Dentici et al., 2015), 26 (Roma et al., 2015) (Table 1). Patient 2 (Table 1) had 47,XXY karyotype, additionally to the variant in *KMT2D (MLL2)*. CGHarray was normal in the 14 patients analyzed.

Both parents of the affected patients have been analyzed in 13 families, the mother only in 2. The variant was "de novo" in 12 families with *KMT2D (MLL2)* variant and in the family with *KDM6A* deletion. The mother was not carrying the proband's variant in the two families where the mother only was tested.

3 | RESULTS

3.1 | Present series

3.1.1 | Cardiac evaluation

CHD was diagnosed in 19/27 (70%) patients with *KMT2D (MLL2)* variant, while the single patient with *KDM6A* change had a normal

TABLE 1 Molecular defects and congenital heart defects in patients with Kabuki syndrome with pathogenetic variant in *KTMD2D* (*MLL2*) and *KDM6A* from the present series

Patient	Sex	*KMT2D* (*MLL2*) nucleotide substitution/exon deletion or duplication	*KMT2D* (*MLL2*) amino acid change	Karyotype and/or CGHarray	Family	Congenital heart defect
1	F	c.177-2A>C		Normal	Parents NT	Perimembranous subaortic ventricular septal defect
2	M	c.721delC	p.Leu241Cysfs*19	47,XXY	de novo	Atrial septal defect ostium secundum
3	M	c.1345_1346del	p.Leu449Valfs*5	Normal	Mother negative	Bicuspid aortic valve, subaortic restrictive ventricular septal defect, atrioventricular valves (mitral and tricuspidal) prolapse, right ventricle divided in two chambers
4	M	c.1814_1815delAG	p.Glu605Valfs*7	Normal	Parents NT	Normal heart
5	M	c.3161_3171delCGTTGAGTCCC	p.Pro1054Hisfs*9	Normal	de novo	Aortic coarctation
6	F	c.3318dup	p.Ser1107Glnfs*7	Normal	Mother negative	Bicuspid aortic valve, aortic root dilatation
7	F	c.3532C>T	p.Gln1178*	Normal	Parents NT	Aortic coarctation
8	F	c.4435C>T	p.Gln1479*	Normal	de novo	Infundibular pulmonary stenosis, perimembranous subaortic ventricular septal defect, atrial septal defect ostium secundum
9	M	c.5707C>T	p.Arg1903*	Normal	de novo	Restrictive perimembranous subaortic ventricular septal defect
10	M	c.6595delT	p.Tyr2199Ilefs*65	Normal	de novo	Dilatation of the aortic root, dysplastic mitral valve, persistent left superior vena cava draining in coronary sinus
11	F	c.7879del	p.Tyr2627Thrfs*64	Normal	Parents NT	Normal heart
12	M	c.9828_9833dup	p.Gln3281_3282dup	Normal	Parents NT	Normal heart
13	F	c.10825_10827dupCAA	p.Gln3609dup	Normal	Parents NT	Normal heart
14	M	c.11149C>T	p.Gln3717*	Normal	de novo	Hypoplastic left heart syndrome
15	F	c.11215_11220delCAGCAG	p.Gln3739_Gln3740del	Normal	Parents NT	Normal heart
16	M	c.11475_11478delACAG	p.Gln3826Cysfs*2	Normal	Parents NT	Normal heart
17	F	c.12725C>G	p.Pro4242Arg	Normal	de novo	Aortic coarctation, bicuspid aortic valve, mitral valve stenosis with supramitralic ring (Shone complex)
18	M	c.12800delC	p.Pro4267Leufs*10	Normal	de novo	Bicuspid aortic valve, aortic insufficiency, aortic root dilatation
19	M	c.12811_12814delACAG	p.Thr4271Alafs*5	Normal	Parents NT	Atrial septal defect ostium secundum
20	F	c.13328delC	p.Pro4443Glnfs*75	Normal	Parents NT	Pulmonary atresia with ventricular septal defect
21	M	c.13450C>T	p.Arg4484*	Normal	Parents NT	Perimembranous subaortic ventricular septal defect
22	F	c.14710C>T	p.Arg4904*	Normal	de novo	Double outlet right ventricle
23	M	c.15163_15168dupGACCTG	p.Asp5055_Leu5056dup	Normal	de novo	Aortic coarctation, small perimembranous ventricular septal defect

(Continues)

TABLE 1 (Continued)

Patient	Sex	*KMT2D* (*MLL2*) nucleotide substitution/exon deletion or duplication	*KMT2D* (*MLL2*) amino acid change	Karyotype and/or CGHarray	Family	Congenital heart defect
24	F	c.15461G>A	p.Arg5154Gln	Normal	Parents NT	Normal heart
25	F	c.15461G>A	p.Arg5154Gln	Normal	de novo	Atrial septal defect ostium secundum
26	F	c.16085_16086del	p.Lys5362Serfs*96	Normal	Parents NT	Normal heart
27	M	c.16501C>T	p.Arg5501*	Normal	de novo	Bicuspid aortic valve
		KDM6A nucleotide substitution/ exon deletion or duplication	KDM6A amino acid change			
28	M	intragenic deletion (exons 5–9) from base 44,866,302 to base 44,912,718		Normal	de novo	Normal heart

F, female; M, male; NT, not tested.

heart. Cardiac anatomy, clinical diagnosis, and molecular details of the patients are reported in Table 1. Anatomic types among patients with CHD included aortic coarctation (4/19 = 21%) alone or associated with an additional CHD, bicuspid aortic valve (4/19 = 21%) alone or associated with an additional CHD, perimembranous subaortic ventricular septal defect (3/19 = 16%), atrial septal defect ostium secundum type (3/19 = 16%), conotruncal heart defects (3/19 = 16%). Additional CHDs diagnosed in single patients were aortic dilatation with mitral anomaly and hypoplastic left heart syndrome.

Among the 19 patients with pathogenic variant and CHD, 11 (58%) were males and 8 (42%) females. Male patients with left-sided obstructive lesions were 7/11 (64%), male patients with other CHDs 4/11 (36%).

3.2 | Literature review

Cardiac and molecular details on patients with Kabuki syndrome, CHD and pathogenic changes in *KMT2D (MLL2)*, *KDM6A*, *RAP1B*, and *HNRNPK* genes from the literature papers in comparison with those of patients with CHD in the present series are shown in Tables 2 and 3. Cited literature papers included those reporting information about CHD. The prevalence of the different anatomic types of CHD in *KMT2D (MLL2)* mutated patients with Kabuki syndrome from the present series and in the literature are reviewed in Table 3. The anatomic types of CHD were concordant in present and literature cases. The prevalence of left-sided obstructive lesions was similar in the two groups, septal defects were more frequently diagnosed in literature cases, conotruncal heart defects were more frequently found in our patients.

CHDs in patients with KS2 gene (*KDM6A*) anomalies are reviewed in Table 2. Anatomic types included ventricular and atrial septal defects, hypoplastic right ventricle, pulmonary stenosis and abnormalities of the aorta (abnormal shape, subaortic membrane, bicuspid aorta, and coarctation). One patient with *RAP1B* variant had an unspecified type of CHD (Table 2). The patients with *HNRNPK* gene variant had heterogeneous types of CHD, including ventricular septal defects, bicuspid aortic valve with aortic root dilatation, and atrioventricular septal defect (Table 2).

4 | DISCUSSION

The prevalence of CHD in the present series of patients with Kabuki syndrome and *KMT2D (MLL2)* variant is 70% which included 47% with left-sided obstructive lesions, 32% with septal defects, and 16% with conotruncal defects (Table 3). The high occurrence of left-sided obstructions seen in this study has been noted (Armstrong et al., 2005; Digilio et al., 2001; Digilio, Baban, Marino, & Dallapiccola, 2010).

4.1 | Left-sided obstructive CHD

Aortic coarctation and bicuspid aortic valve are prevalent among left-sided obstructive CHDs in Kabuki syndrome, although patients with aortic or mitral stenosis have also been reported (Tables 2 and 3). Additionally, the diagnosis of hypoplastic left heart syndrome in several patients (Digilio et al., 2010; Kung, Chang, Sklansky, & Randolph, 2010; Shahdadpuri, Lynch, Murchan, & McMahon, 2008) suggests that the entire spectrum of cardiac left-sided obstructive lesions can be a marker for Kabuki syndrome. In this regard, the clinical review by Armstrong et al. (2005) confirmed that the prevalence of left-sided obstructions in Kabuki syndrome (31%) is significantly ($p < 0.001$) higher in comparison to that in the general population (14%).

Patients with aortic valve defects can have additional anomalies of the mitral valve, consisting in mitral stenosis with supramitral ring, dysplastic mitral valve, and bicuspid aortic valve. These multiple left-sided obstructions are similar to those observed in the spectrum of the so-called Shone complex (Shone et al., 1963), classically defined as the association of aortic coarctation, membranous subaortic stenosis, bicuspid aortic valve, mitral stenosis with "parachute" mitral valve with single papillary muscle and supramitral ring.

TABLE 2 Cardiac and molecular data of patients with Kabuki syndrome and congenital heart defect with pathogenetic changes in *KMT2D (MLL2)*, *KDM6A*, *RAP1B*, and *HNRNPK* genes from the literature papers reporting cardiac information in comparison with mutated patients with congenital heart defect in the present series

MLL2 (*KMT2D*) nucleotide substitution/exon deletion or duplication	*MLL2* (*KMT2D*) amino acid change	Congenital heart defect	Reference
c.177-2A>C	–	*Perimembranous subaortic ventricular septal defect*	*Present series*
c.241G>T	p.Glu81*	Aortic coarctation, ventricular septal defect	Yoon et al. (2015)
c.721delC	p.Leu241Cysfs*19	*Atrial septal defect ostium secundum*	*Present series*
c.589del	p.Cys197Alafs*11	Ventricular septal defect	Makrythanasis et al. (2013)
c.1345_1346del *ventricle (Shone), hypertension*	p.Leu449Valfs*5	*Bicuspid aortic valve, subaortic restrictive ventricular septal defect, atrioventricular valves (mitral and tricuspidal) prolapse, right ventricle divided in two chambers*	*Present series*
c.1512_1513delTC	p.Pro506Thrfs*2	Cardiomegaly	Li et al. (2011)
c.1628C>T	p.Ser543Leu	Patent ductus arteriosus/Patent foramen ovale	Li et al. (2011)
c.2819C>A	p.Ser940*	Aortic regurgitation	Yoon et al. (2015)
c.3161_3171delCGTTGAGTCCC	*p.Pro1054Hisfs*9*	*Aortic coarctation*	*Present series*
c.3318dup	*p.Ser1107GlnfsX7*	*Bicuspid aortic valve, aortic root dilatation*	*Present series*
c.3532C>T	*p.Gln1178**	*Aortic coarctation*	*Present series*
Exons 14–15 deletion		Atrial septal defect, small ventricular septal defect	Riess et al. (2012)
Exons 14 – 15 deletion		Atrial septal defect, small ventricular septal defect	Riess et al. (2012) (patient's 12 monozygotic twin)
c.4135_4136delAT	p.Met1379Valfs*52	Mitral stenosis	Yoon et al. (2015)
c.4168dup	p.Ala1390Glyfs*40	Aortic coarctation	Makrythanasis et al. (2013)
c.4271G>T	p.Cys1424Phe	Scimitar syndrome	Cheon et al. (2014)
c.4358A>G	p.His1453Arg	Atrial septal defect/Ventricular septal defect, Patent foramen ovale	Li et al. (2011)
c.4435C>T	*p.Gln1479**	*Perimembranous subaortic ventricular septal defect, atrial septal defect ostium secundum, infundibular pulmonary stenosis*	*Present series*
Exons 15–34 duplication		Patent foramen ovale	Banka et al. (2013)
c.5135_5136del	p.Lys1712Argfs*22	Ventricular sepal defect, atrial septal defect, arrhythmia	Makrythanasis et al. (2013)
c.5153C>T	p.Ala1718Val	Atrial septal defect/Ventricular septal defect	Li et al. (2011)
c.5256_5257delGA	p.Lys1753Alafs*34	Bicuspid aortic valve	Kim et al. (2013)
c.5707C>T	*p.Arg1903**	*Restrictive perimembranous subaortic ventricular septal defect*	*Present series*
c.5775_5776insT	p.Leu1926Serfs*31	Hypoplastic left heart syndrome	Cheon et al. (2014)
c.6595delT	*p.Tyr2199Ilefs*65*	*Dysplastic mitral valve, dilatation of the aortic root, persistent left superior vena cava draining in coronary sinus*	*Present series*
c.6595delT	p.Tyr2199Ilefs*65	Atrial septal defect/Ventricular septal defect	Li et al. (2011)
c.6613_6614insG	p.Ala2205Glyfs*38	Ventricular septal defect, atrial septal defect, mitral valve stenosis	Takagi, Ishii, Torii, Kosaki, and Hasegawa (2014)
c.8107G>T	p.Glu2703*	Aortic coarctation, ventricular septal defect	Cheon et al. (2014)
c.8431C>T	p.Gln2811*	Patent ductus arteriosus/Patent foramen ovale	Li et al. (2011)
c.8743C>T	p.Arg2915*	Atrial septal defect/Ventricular septal defect	Li et al. (2011)
c.8743 C>T	p.Arg2915*	Atrial septal defect	Lin et al. (2015)
c.9931C>T, c.10101G>T	p.Gln3311*, p.Leu3367Phe	Patent ductus arteriosus/Patent foramen ovale	Zarate, Zhan, and Jones (2012)

(Continues)

TABLE 2 (Continued)

MLL2 (*KMT2D*) nucleotide substitution/exon deletion or duplication	*MLL2* (*KMT2D*) amino acid change	Congenital heart defect	Reference
c.11149C>T	*p.Gln3717**	Hypoplastic left heart syndrome	*Present series*
c.11743C>T	p.Gln3915*	*Patent forame ovale*	Makrythanasis et al. (2013)
c.11833C>T	p.Gln3945*	*Aortic coarctation, bicuspid aortic valve*	Yoon et al. (2015)
c.12592C>T	p.Arg4198*	Aortic valve stenosis, bicuspid aortic valve	Cheon et al. (2014); Yoon et al. (2015)
c.12725C>G	*p.Pro4242Arg*	*Aortic coarctation, bicuspid aortic valve, mitral valve stenosis with supramitralic ring (Shone)*	*Present series*
c.12800delC	*p.Pro4267Leufs*10*	*Bicuspid aortic valve, aortic insufficiency, aortic root dilatation*	*Present series*
c.12811_12814delACAG	*p.Thr4271Alafs*5*	*Atrial septal defect ostium secundum*	*Present series*
c.12986_13010del25	p.Gln4329Leufs*47	Bicuspid aortic valve	Verhagen, Oostdijk, Terwisscha van Scheltinga, Schalij-Delfos, and van Bever (2014)
c.12994_12995insT	p.Thr4332Ilefs*2	Aortic coarctation, ventricular septal defect	Yoon et al. (2015)
c.13328delC	*p.Pro4443Glnfs*75*	*Pulmonary atresia with ventricular septal defect*	*Present series*
c.13450C>T	*p.Arg4484**	*Perimembranous subaortic ventricular septal defect*	*Present series*
Exons 43–54 deletion		Bicuspid aortic valve	Banka et al. (2013)
c.14404delG	p.Ala4802Glnfs*6	Interrupted aortic arch type B, ventricular septal defect, patent ductus arteriosus	Cheon et al. (2014)
c.14710C>T	*p.Arg4904**	*Double outlet right ventricle*	*Present series*
c.15163_15168dupGACCTG	*p. Asp5055_Leu5056dup*	*Aortic coarctation, small perimembranous ventricular septal defect*	*Present series*
c.15326G>T	p.Cys5109Phe	Atrial septal defect	Lin et al. (2015)
c.15461G>A	p.Arg5154Gln	Patent ductus arteriosus/Patent foramen ovale	Li et al. (2011)
c.15461G>A	p.Arg5154Gln	Atrial septal defect/Ventricular septal defect	Li et al. (2011)
c.15461G>A	*p.Arg5154Gln*	*Atrial septal defect ostium secundum*	*Present series*
c.16294C>T	p.Arg5432Trp	Atrial septal defect	Makrythanasis et al. (2013)
c.16501C>T	*p.Arg5501**	*Bicuspid aortic valve*	*Present series*
KDM6A Exon deletion/ nucleotide substitution	*KDM6A* amino acid change		
Deletion, 815.7 kb from 44,377,858 to 45,193,629		Aortic coarctation	Lederer et al. (2012)
Deletion, 283.5 kb from 44,941,324 to 45,224,829		Atrial septal defect, ostium secundum	Lederer et al. (2012)
Exon 6 deletion		Perimembranous subaortic ventricular septal defect	Banka et al. (2015)
c.190G>T	p.Glu64*	Atrial septal defect, ventricular septal defect	Bögershausen et al. (2016)
c.443 + 5G>C		Atrial septal defect, ventricular septal defect, left ventricular hypertrophy	Bögershausen et al. (2016)
c.563A>G	p.Lys188Arg	Bicuspid aortic valve	Banka et al. (2015)
c.619 + 6T>C		Atrial septal defect, ventricular septal defect, persistent left superior vena cava	Bögershausen et al. (2016)
c.2515_2518del	p.Asn839Profs*38	Severe subpulmonary right ventricular outflow obstruction with a critical pulmonary stenosis, hypoplastic right ventricle, atrial septal defect, ventricular septal defect	Lederer et al. (2014)
c.2515_2518del	p.Asn839Profs*38 Inherited	Atrial septal defect, pulmonary valve stenosis	Lederer et al. (2014) (patient's 61 brother)

(Continues)

TABLE 2 (Continued)

MLL2 (*KMT2D*) nucleotide substitution/exon deletion or duplication	*MLL2* (*KMT2D*) amino acid change	Congenital heart defect	Reference
c.3717G>A	p.Trp1239*	Atrial septal defect	Miyake et al. (2013)
c.3763C>T	p.Arg1255Trp	Aortic coarctation, bicuspid aortic valve	Bögershausen et al. (2016)
c.3876_3878delTAA c.3878 + 11delG (g.217351_4delTAAG)		Atrial septal defect	Cheon et al. (2014)
c.3878 + 3_3878 + 6delAAGT		Abnormal aorta	Banka et al. (2015)
RAP1B nucleotide substitution	*RAP1B* amino acid change		
c.451A>G	p.Lys151Glu	Congenital heart defect (type unpecified)	Bögershausen et al. (2015)
HNRNPK nucleotide substitution	*HNRNPK* amino acid change		
c.257G>A	p.Arg85His	Bicuspid aortic valve, aortic root dilatation	Au et al. (2015)
c.931_932insTT	p.Pro311Leufs*40	Atrioventricular septal defect	Lange et al. (2016)
c.953 + 1dup	p.Gly319Argfs*6	Two small ventricular septal defects	Au et al. (2015)

The preponderance of male patients in comparison to females among those with Kabuki syndrome and left-sided obstructive lesions previously noted in the clinical series (Digilio et al., 2001) is confirmed also in *KMT2D (MLL2)* mutated patients, although the molecular basis for these evidence remains difficult to be explained.

The clinical overlap between the pattern of CHDs in Kabuki syndrome and other syndromes includes the overlap with Turner syndrome since both can have aortic coarctation and aortic dilation (Gotzsche, Krag-Olsen, Nielsen, Sørensen, & Kristensen, 1994; Mazzanti & Cacciari, 1998; McGinniss, Brown, Burke, Mascarello, & Jones, 1997; Sybert, 1998). The occurrence of a Shone-like complex in Kabuki syndrome has been reported with Adams-Oliver syndrome which has been linked to variants in *NOTCH* (Digilio, Marino, & Dallapiccola, 2008; Lin, Westgate, van der Velde, Lacro, & Holmes, 1998; Southgate et al., 2015; Stittrich et al., 2014), although no additional extracardiac clinical overlap has been observed.

4.2 | Septal defects

Septal defects are also frequent in Kabuki syndrome, and include atrial septal defect ostium secondum type and perimembranous subaortic ventricular septal defect. This group of CHDs is more frequently diagnosed in literature cases in comparison to the present series, but it should be considered that clinical description of literature cases is often limited, referring to "atrial septal defect/ventricular septal defect type unspecified" and several patients with patent foramen ovale.

4.3 | Rare defects

Additional CHDs found in Kabuki syndrome with *KMT2D (MLL2)* variant are represented by conotruncal heart defects (Tables 1 and 2), including tetralogy of Fallot—classic or with pulmonary atresia, double aortic arch, double outlet right ventricle, and interrupted aortic arch type B. Cardiac conduction anomalies are also reported in Kabuki syndrome (Ng et al., 2010; Shah, Bogucki, Mavers, deMello, & Knutsen, 2005).

4.4 | Vascular anomalies

Aortic dilatation has also been seen in association with congenital aortic lesions in patients with Kabuki syndrome, so as potential increased risk of aortic aneurysm (Okada et al., 2001). For this reason, the clinical guidelines for managingKabuki syndrome should include annual monitoring for aortic dilatation because of the theoretical risk of dissection (Dyscerne Guidelines, 2010).

Weir et al. (2014) highlighted an association between Kabuki syndrome and premature atherosclerosis, suggesting that the syndrome itself may contribute to the predisposition also in absence of classical different risk factors. A case report of Henoch-Schonlein purpura causing thrombosis has also been reported (Oto et al., 2008). In addition, the growth hormone deficiency described in patients with Kabuki syndrome (Devriendt, Lemli, Craen, & de Zegher, 1995) should be mentioned as an additional risk factor, since it known to be associated with endothelial dysfunction, increased intima medial thickness and reduced aortic distensibility. A predisposition to vascular hypertension should also be considered in patients with Kabuki syndrome (Dyscerne Guidelines, 2010).

4.5 | Other Kabuki syndrome genes

The single patient in the present series with pathogenic variant in the KS2 gene (*KDM6A*) has normal heart. The review of the patients with variants in the KS2 gene (*KDM6A*) reported in the literature showed that the frequency of CHDs, corresponding to around 45%, is lower in comparison to that in patients with *KMT2D (MLL2)* variant. Anatomic types included ventricular and atrial septal defects, hypoplastic right

TABLE 3 Prevalence of different anatomic types of congenital heart defects in patients with *KMT2D (MLL2)* pathogenic variants and cardiac malformation in the present series and in the literature review

Congenital heart defect	Present series (number of patients with congenital heart defect)	Present series (%)	Present series and literature review (number of patients with congenital heart defect)	Present series and literature review (%)
Left-sided obstructive lesion	9/19	47	22/52	42
Aortic coarctation (total)	4 /19	21	9/52	17
−Without additional CHDs	2		3	
+Bicuspid aortic valve, mitral stenosis, supramitral ring (Shone complex)	1		1	
+VSD	1		4	
+Bicuspid aortic valve	0		1	
Bicuspid aortic valve (total)	4/19	21	7/52	13
−Without additional CHDs	1		4	
+Mitral anomaly, VSD	1		1	
+Aortic dilatation	1		1	
+Aortic insufficiency + aortic dilatation	1		1	
Mitral stenosis (total)	0		2/52	4
−Without additional CHDs	0		1	
+VSD/ASD	0		1	
Hypoplastic left heart syndrome	1/19	5	2/52	4
Aortic regurgitation	0		1/52	2
Aortic stenosis, bicuspid aortic valve	0		1/52	2
Septal defects	6/19	32	24/52	46
ASD/VSD unspecified	0		8/52	15
ASD, ostium secundum	3/19	16	6/52	12
VSD, perimembranous subaortic	3/19	16	4/52	8
PDA, PFO	0		4/52	8
PFO	0		2/52	4
Conotruncal heart defects	3/19	16	4/52	8
Double outlet right ventricle	1/19	5	1/52	2
Tetralogy of Fallot with pulmonary atresia	1/19	5	1/52	2
Infundibular pulmonary stenosis, subaortic VSD, ASD	1/19	5	1/52	2
Interrupted aortic arch type B	0		1/52	2
Others	1/19	5	3/52	6
Scimitar syndrome	0		1/52	2
Cardiomegaly	0		1/52	2
Dysplastic mitral valve, dilatation aortic root, persistent left superior vena cava	1/19	5	1/52	2

CHDs, congenital heart defects; VSD, ventricular septal defect; ASD, atrial septal defect ostium secundum; PDA, patent ductus arteriosus; PFO, patent foramen ovalis.

ventricle, pulmonary stenosis and abnormalities of the aorta (abnormal shape, subaortic membrane, bicuspid aorta, and coarctation) (Table 2) (Banka et al., 2015; Lederer et al., 2012; Lederer, Shears, Benoit, Verellen-Dumoulin, & Maystadt, 2014; Miyake et al., 2013). A higher prevalence of right sided-lesion is noticeable in patients with KS2 in comparison to those with KS1.

In regard to the two Kabuki syndrome genes (*RAP1A* and *RAP1B*) recently identified using whole exome sequencing (Bögershausen et al., 2015), the authors determined that their dysfunction results in aberrant MEK/ERK signalling, suggesting that the Kabuki syndrome pathophysiology in these cases overlaps with the RASopathies. The patient with *RAP1B* variant had a CHD, but the anatomic type was not specified.

The patients with *HNRNPK* variant had heterogeneous types of CHD, including ventricular septal defects, bicuspid aortic valve with aortic root dilatation, and atrioventricular septal defect. It is possible that this latter CHD can be specifically associated with *HNRNPK* gene, since atrioventricular canal defect is reported also in a patient carrying a deletion 9q21.32-q21.33 extending for 2 Mb and including *HNRNPK* (Hancarova et al., 2015).

4.6 | Cardiac experimental models

Experimental models for *KDM6A* mutants performed by Lee et al. (2012) showed that female knockout mice exhibited severe cardiac malformations, anterior neural tube closure defects, and growth retardation, while female heterozygous mice displayed normal cardiac morphogenesis. Additionally, the test of the effect of *kmt2d*, *kdm6a*, and *kdm6al* knockdown on cardiac development in the zebrafish performed by Van Laarhoven et al. (2015) did observe morphological defects in cardiac development in *kmt2d* and *kdm6al* morphants, with a milder defect in *kdm6a* morphants. Morphants in all three experimental groups exhibited abnormal development of the atria and/or ventricle, as well as prominent bulging of the myocardial wall. This was most pronounced in the *kmt2d* morphants, whereas effects in *kdm6a* and *kdm6al* morphants were less severe. A defective progression of cardiac looping involution was found in morphants compared with wildtype embryos (Van Laarhoven et al., 2015). Further studies in mice indicated that *kmt2d* is essential for regulating cardiac gene expression during heart development primarily via H3K4 di-methylation (Ang et al., 2016). The authors observed that the developing embryonic heart of haploinsufficient mice had no differences in cardiac morphology compared to wild-type controls, but a significant narrowing of the diameter of the ascending aorta and increased aortic valve peak velocity were noted (Ang et al., 2016).

4.7 | Genotype–phenotype correlations

No specific hot spots for CHD have been identified, and variants have not shown significant clustering in a certain exon or a known protein-domain. In general, it should be noted that variants in patients with cardiac anomaly are preferentially located in proximal exons (1–28) and in the terminal end (52–54 exons) of *KMT2D (MLL2)*.

Variants in patients with conotruncal anomalies include the p.Gln1479*, and the p.Pro4443Glnfs*75, and the p.Arg 4904*.

The majority of patients from the present series are carrying a private *KMT2D (MLL2)* pathogenic variant, with the exception of patients with the p.Arg5154Gln variant, which is known to be recurrent in Kabuki syndrome (Li et al., 2011; Ng et al., 2010), and a patient with the p.Arg4484* variant (Makrythanasis et al., 2013; Paulussen et al., 2011). Cardiac expression of these variants is heterogeneous, since different anatomic types of CHD and normal heart are described in patients with the same variant.

5 | CONCLUSIONS

This is the first review of CHDs in Kabuki syndrome patients with alterations in *KMT2D (MLL2)*which reports a prevalence of 70%. The most distinctive CHDs which characterize Kabuki syndrome include multiple left-sided obstructions similar to those observed in the spectrum of the Shone complex, aortic dilatation, and perimembranous subaortic ventricular septal defect. No specific hot spots for CHD have been identified. Pathogenic variants in patients with cardiac anomaly are preferentially located in proximal exons (1–28) and in the terminal end (52–54 exons) of *KMT2D (MLL2)*. Our review of the literature suggests that the prevalence of CHD in KS2 patients is lower, about 45%, with an higher prevalence of right sided-lesions in comparison to KS1. Clinical management of Kabuki syndrome should include an echocardiogram at the time of diagnosis, with particular attention to left-sided obstructive lesions and mitral anomalies, and monitoring for aortic arch dilatation, although it is premature to prescribe a schedule.

ORCID

Maria Cristina Digilio http://orcid.org/0000-0002-0205-9634

REFERENCES

Ang, S.-Y., Uebersohn, A., Spencer, C. I., Huang, Y., Lee, J.-E., Ge, K., & Bruneau, B. G. (2016). KMT2D regulates specific programs in heart development via histone H3 Lysine 4 di-methylation. *Development*, *143*, 810–821.

Armstrong, L., El Moneim, A. A., Aleck, K., Aughton, D. J., Baumann, C., Braddock, S. R., … Allanson, J. E. (2005). Further delineation of Kabuki syndrome in 48 well-defined new individuals. *American Journal of Medical Genetics Part A*, *132A*, 265–272.

Au, P. Y. B., You, J., Caluseriu, O., Schwartzentruber, J., Majewski, J., Bernier, F. P., … Kline, A. D. (2015). GeneMatcher aids in the identification of a new malformation syndrome with intellectual disability, unique facial dysmorphisms, and skeletal and connective tissue abnormalities caused by de novo variants in *HNRNPK*. *Human Mutation*, *36*, 1009–1014.

Banka, S., Veeramachaneni, R., Reardon, W., Reardon, W., Howard, E., Bunstone, S., … Donnai, D. (2012). How genetically heterogeneous is Kabuki syndrome? MLL2 testing in 116 patients, review and analyses of mutation and phenotypic spectrum. *European Journal of Human Genetics*, *20*, 381–388.

Banka, S., Howard, E., Bunstone, S., Chandler, K. E., Kerr, B., Lachlan, K., McKee, S., … Donnai, D. (2013). *MLL2* mosaic mutations and intragenic deletion-duplications in patients with Kabuki syndrome. *Clinical Genetics*, *83*, 467–471.

Banka, S., Lederer, D., Benoit, V., Jenkins, E., Howard, E., Bunstone, S., … Donnai, D. (2015). Novel *KDM6A* (UTX) mutations and a clinical and molecular review of the X-linked Kabuki syndrome (KS2). *Clinical Genetics*, *87*, 252–258.

Bögershausen, N., Tsai, I.-C., Pohl, E., Simsek Kiper, P. O., Veleggia, F., Perciò, E. F., … Wollnik, B. (2015). RAP1-mediated MEK/ERK pathway defects in Kabuki syndrome. *Clinical Investigation*, *125*, 3585–3599.

Bögershausen, N., Gatinois, V., Riehmer, V., Kayserili, H., Becker, J., Thoenes, M., … Wollnik, B. (2016). Mutation update for Kabuki syndrome genes *KMT2D* and *KDM6A* and further delineation of X-linked Kabuki syndrome subtype 2. *Human Mutation*, *37*, 847–864.

Cappuccio, G., Rossi, A., Fontana, P., Acampora, E., Avorio, V., Merla, G., … Melis, D. (2014). Bronchial isomerism in a Kabuki syndrome patient with a novel mutation in MLL2 gene. *BMC Medical Genetics*, *15*, 15.

Cheon, C. K., Sohn, Y. B., Ko, J. M., Lee, Y. J., Song, J. S., Moon, J. W., … Jeong, S.-Y. (2014). Identification of KMT2D and KDM6A mutations by exome sequencing in Korean patients with Kabuki syndrome. *Journal of Human Genetics*, *59*, 321–325.

Dentici, M. L., Di Pede, A., Lepri, F. R., Gnazzo, M., Lombardi, M. H., Auriti, C., … Dallapiccola, B. (2015). Kabuki syndrome: Clinical and molecular diagnosis in the first year of life. *Archives of Disease in Childhood*, *100*, 158–164.

Devriendt, K., Lemli, L., Craen, M., & de Zegher, F. (1995). Growth hormone deficiency and premature thelarche in a female infant with Kabuki Makeup sundrome. *Hormone Research*, *43*, 303–306.

Digilio, M. C., Marino, B., Toscano, A., Giannotti, A., & Dallapiccola, B. (2001). Congenital heart defects in Kabuki syndrome. *American Journal of Medical Genetics*, *100*, 269–274.

Digilio, M. C., Marino, B., & Dallapiccola, B. (2008). Autosomal dominant inheritance of aplasia cutis congenita and congenital heart defect: A possible link to the Adams-Oliver syndrome. *American Journal of Medical Genetics*, *146A*, 2842–2844.

Digilio, M. C., Baban, A., Marino, B., & Dallapiccola, B. (2010). Hypoplastic left heart syndrome in patients with Kabuki syndrome. *Pediatric Cardiology*, *31*, 1111–1113.

DYSCERNE: A Network of Centres of Expertise in Dysmorphology (www.dyscerne.org); Management of Kabuki Syndrome. A Clinical Guideline, Kabuki Syndrome Guideline Development Group, 2010.

Galan-Gomez, E., Cardesa-Garcia, J. J., Campo-Sampedro, F. M., Salamanca-Maesso, C., Martinez-Frias, M. L., & Frias, J. L. (1995). Kabuki make up (Niikawa-Kuroki) syndrome in five spanish children. *American Journal of Medical Genetics*, *59*, 276–282.

Gotzsche, C. O., Krag-Olsen, B., Nielsen, J., Sørensen, K. E., & Kristensen, B. O. (1994). Prevalence of cardiovascular malformations and association with karyotypes in Turner's syndrome. *Archives of Disease in Childhood*, *71*, 433–436.

Hancarova, M., Puchmajerova, A., Drabova, J., Karaskova, E., Vlckova, M., & Sedlacek, Z. (2015). Deletions of 9q21.3 including NTRK2 are associated with severe phenotype. *American Journal of Medical Genetics Part A*, *167A*, 264–267.

Hannibal, M. C., Buckingham, K. J., Ng, S. B., Ming, J. E., Beck, A. E., McMillin, M. J., … Bamshad, M. J. (2011). Spectrum of MLL2 (ALR) mutations in 110 cases of Kabuki syndrome. *American Journal of Medical Genetics Part A*, *155A*, 1511–1516.

Hughes, H. E., & Davies, S. J. (1994). Coarctation of the aorta in Kabuki syndrome. *Archives of Disease in Childhood*, *70*, 512–514.

Kawame, H., Hannibal, M. C., Hudgins, L., & Pagon, R. A. (1999). Phenotypic spectrum and management issues in Kabuki syndrome. *Journal of Pediatrics*, *134*, 480–485.

Kim, S. J., Cho, S. Y., Maeng, S. H., Sohn, Y. B., Kim, S. J., Ki, C. S., & Jin, D. K. (2013). A novel MLL2 gene mutation in a Korean patient with Kabuki syndrome. *Korean Journal of Pediatrics*, *56*, 355–358.

Kluijt, I., van Dorp, D. B., Kwee, M. L., Toutain, A., Keppler-Noreuil, K., Warburg, M., & Bitoun, P. (2000). Kabuki syndrome—Report of six cases and review of the literature with emphasis on ocular features. *Ophthalmic Genetics*, *21*, 51–61.

Kung, G. C., Chang, P. M., Sklansky, M. S., & Randolph, L. M. (2010). Hypoplastic left heart syndrome in patients with Kabuki syndrome. *Pediatric Cardiology*, *31*, 138–141.

Kuroki, Y., Suzuki, Y., Chyo, H., Hata, A., & Matsui, I. (1981). A new malformation syndrome of long palpebral fissures, large ears, depressed nasal tip, and skeletal anomalies associated with postnatal dwarfism®sm and mental retardation. *Journal of Pediatrics*, *99*, 570–573.

Lange, L., Pagnamenta, A. T., Lise, S., Clasper, S., Stewart, H., Akha, E. S., … Kini, U. (2016). A *de novo* frameshift in *HNRNPK* causing a Kabuki-like syndrome with nodular heterotopia. *Clinical Genetics*, *90*, 258–262.

Lederer, D., Grisart, B., Digilio, M. C., Benoit, V., Crespin, M., Ghariani, S. C., … Verellen-Dumoulin, C. (2012). Deletion of *KDM6A*, a histone demethylase interacting with MLL2, in three patients with Kabuki syndrome. *American Journal of Human Genetics*, *90*, 119–124.

Lederer, D., Shears, D., Benoit, V., Verellen-Dumoulin, C., & Maystadt, I. (2014). A three generation X-linked family with Kabuki syndrome phenotype and a frameshift mutation in KDM6A. *American Journal of Medical Genetics Part A*, *164A*, 1289–1292.

Lee, S., Lee Jae, W., & Lee, S.-K. (2012). UTX, a histone H3-lysine 27 demethylase, acts as a critical switch to activate the cardiac developmental program. *Developmental Cell*, *22*, 25–37.

Li, Y., Bogershausen, N., Alanay, Y., Simsek Kiper, P. O., Plume, N., Keupp, K., … Wollnik, B. (2011). A mutation screen in patients with Kabuki syndrome. *Human Genetics*, *130*, 715–724.

Lin, A. E., Westgate, M. N., van der Velde, M. E., Lacro, R. V., & Holmes, L. B. (1998). Adams–Oliver syndrome associated with cardiovascular malformations. *Clinical Dysmorphology*, *7*, 235–241.

Lin, J. L., Lee, W. I., Huang, J. L., Chen, P. K., Chan, K. C., Lo, L. J., … Wu, M. C. (2015). Immunologic assessment and KMT2D mutation detection in Kabuki syndrome. *Clinical Genetics*, *88*, 255–260.

Lo, I. F., Cheung, L. Y., Ng, A. Y., & Lam, S. T. (1998). Interstitial Dup 1p) with findings of Kabuki make-up syndrome. *American Journal of Medical Genetics*, *78*, 55–57.

Makrythanasis, P., van Bon, B. W., Steehouwer, M., Rodríguez-Santiago, B., Simpson, M., Dias, P., … Hoischen, A. (2013). MLL2 mutation detection in 86 patients with Kabuki syndrome: A genotype–phenotype study. *Clinical Genetics*, *84*, 539–545.

Mazzanti, L., & Cacciari, E. (1998). Congenital heart disease in patients with turner's syndrome. italian study group for turner syndrome (ISGTS). *Journal of Pediatrics*, *133*, 688–692.

McGinniss, M. J., Brown, D. H., Burke, L. W., Mascarello, J. T., & Jones, M. C. (1997). Ring chromosome X in a child with manifestations of Kabuki syndrome. *American Journal of Medical Genetics*, *70*, 37–42.

Micale, L., Augello, B., Fusco, C., Selicorni, A., Loviglio, M. N., Cirillo Silengo, M., … Merla, G. (2011). Mutation spectrum of MLL2 in a cohort of Kabuki syndrome patients. *Orphanet Journal of Rare Diseases*, *6*, 38.

Miyake, N., Mizuno, S., Okamoto, N., Ohashi, H., Shiina, M., Ogata, K., … Matsumoto, N. (2013). *KDM6A* point mutations cause Kabuki syndrome. *Human Mutation*, *34*, 108–110.

Ng, S. B., Buckingham, K. J., Hannibal, M. C., McMillin, M. J., Gildersleeve, H. I., Beck, A. E., … Shendure, J. (2010). Exome sequencing identifies MLL2 mutations as a cause of Kabuki syndrome. *Nature Genetics*, *42*, 790–793.

Niikawa, N., Matsuura, N., Fukushima, Y., Ohsawa, T., & Kajii, T. (1981). Kabuki make-up syndrome: A syndrome of mental retardation, unusual facies, large and protruding ears and postnatal growth deficiency. *Journal of Pediatrics*, *99*, 565–569.

Niikawa, N., Kuroki, Y., Kajii, T., Matsuura, N., Ishikiriyama, S., Tonoki, H., … Schmid, E. (1988). Kabuki make-up (Niikawa-Kuroki) syndrome: A study of 62 patients. *American Journal of Medical Genetics*, *31*, 565–589.

Okada, Y., Ono, S., Tomomasa, T., Inoue, Y., & Morikawa, A. (2001). Balloon angioplasty in a patient with Kabuki make-up syndrome. *Pediatrics International*, *43*, 694–696.

Oto, J., Mano, A., Nakataki, E., Yamaguchi, H., Inui, D., Imanaka, H., & Nishimura, M. (2008). An adult patient with Kabuki syndrome presenting with Henoch-Schönlein purpura complicated with pulmonary hemorrhage. *Journal of Anesthesia*, *22*, 460–463.

Paulussen, A. D. C., Stegmann, A. P. A., Blok, M. J., Tserpelis, D., Posma-Velter, C., Detisch, Y., … Schrander-Stumpel, C. T. (2011). MLL2 mutation spectrum in 45 patients with Kabuki syndrome. *Human Mutation*, *32*, 2018–2025.

Philip, N., Meinecke, P., David, A., Dean, J., Ayme, S., Clark, R., … Tariverdian, G. (1992). Kabuki make-up (Niikawa-Kuroki) syndrome: A study of 16 non-Japanese cases. *Clinical Dysmorphology*, *1*, 63–77.

Riess, A., Dufke, A., Riess, O., Beck-Woedl, S., Fode, B., Skladny, H., Klaes, R., & Tzschach, A. (2012). Mirror-image asymmetry in monozygotic twins with Kabuki syndrome. *Molecular Syndromology*, *3*, 94–97.

Roma, D., Palma, P., Capolino, R., Figà-Talamanca, L., Diomedi-Camassei, F., Lepri, F. R., … Mastronuzzi, A. (2015). Spinal ependymoma in a patient with Kabuki syndrome: A case report. *BMC Medical Genetics*, *16*, 80.

Schrander-Stumpel, C., Meinecke, P., Wilson, G., Gillessen-Kaesbach, G., Tinschert, S., Koènig, R., … Fryns, J. P. (1994). The Kabuki (Niikawa-Kuroki) syndrome: Further delineation of the phenotype in 29 non-Japanese patients. *European Journal of Pediatrics*, *153*, 438–445.

Shah, M., Bogucki, B., Mavers, M., deMello, D. E., & Knutsen, A. (2005). Cardiac conduction abnormalities and congenital immunodeficiency in a child with Kabuki sydrome: Case report. *BMC Medical Genetics*, *6*, 28.

Shahdadpuri, R., Lynch, S. A., Murchan, H., & McMahon, C. J. (2008). A novel constellation of cardiac findings for Kabuki syndrome: Hypoplastic left heart syndrome and partial anomalous pulmonary venous drainage. *Pediatric Cardiology*, *29*, 820–822.

Shone, J. D., Sellers, R. D., Anderson, R. C., Adams, P., Jr, Lillehei, C. W., & Edwards, J. E. (1963). The developmental complex of parachute mitral valve, supravalvular ring of the left atrium, subaortic stenosis and coarctation of the aorta. *American Journal of Cardiology*, *11*, 714–725.

Southgate, L., Sukalo, M., Karountzos, A. S., Taylor, E. J., Collinson, C. S., Ruddy, D., … Trembath, R. C. (2015). Haploinsufficiency of the NOTCH1 receptor as a cause of adams-Oliver syndrome with variable cardiac anomalies. *Circulation Cardiovascular Genetics*, *8*, 572–581.

Stittrich, A.-B., Lehman, A., Bodian, D. L., Ashworth, J., Zong, Z., Li, H., & Patel, M. S. (2014). Mutations in NOTCH1 cause Adams-Oliver syndrome. *American Journal of Human Genetics*, *95*, 275–284.

Sybert, V. P. (1998). Cardiovascular malformations and complications in Turner syndrome. *Pediatrics*, *101*, E11.

Takagi, M., Ishii, T., Torii, C., Kosaki, K., & Hasegawa, T. (2014). A novel mutation in SOX3 polyalanine tract: A case of Kabuki syndrome with combined pituitary hormone deficiency harboring double mutations in MLL2 and SOX3. *Pituitary*, *17*, 569–574.

Van Laarhoven, P. M., Neitzel1, L. R., Quintana, A. M., Geiger, E. A., Zackai, E. H., Clouthier, D. E., … Shaikh, T. H. (2015). Kabuki syndrome genes KMT2D and *KDM6A*: Functional analyses demonstrate critical roles in craniofacial, heart and brain development. *Human Molecular Genetics*, *24*, 4443–4453.

Verhagen, J. M., Oostdijk, W., Terwisscha van Scheltinga, C. E., Schalij-Delfos, N. E., & van Bever, Y. (2014). An unusual presentation of Kabuki syndrome: Clinical overlap with CHARGE syndrome. *European Journal of Medical Genetics*, *57*, 510–512.

Weir, R. A. P., Alston, A. F., & Al-Dalla Ali, M. (2014). Acute myocardial infarction in Kabuki syndrome: Chance occurrence or a novel risk factor for premature atherosclerosis? *International Journal of Cardiology*, *176*, e26–e28.

Wilson, G. N. (1998). Thirteen cases of Niikawa-Kuroki syndrome: Report and review with emphasis on medical complications and preventive management. *American Journal of Medical Genetics*, *79*, 112–120.

Yoon, J. K., Ahn, K. J., Kwon, B. S., Kim, G. B., Bae, E. J., Noh, C. I., & Ko, J. M. (2015). The strong association of left-side heart anomalies with Kabuki syndrome. *Korean Journal of Pediatrics*, *58*, 256–262.

Zarate, Y. A., Zhan, H., & Jones, J. R. (2012). Infrequent manifestations of kabuki syndrome in a patient with novel MLL2 mutation. *Molecular Syndromology*, *3*, 180–184.

How to cite this article: Digilio MC, Gnazzo M, Lepri F, et al. Congenital heart defects in molecularly proven Kabuki syndrome patients. *Am J Med Genet Part A*. 2017;173A:2912–2922.
https://doi.org/10.1002/ajmg.a.38417