# Capillary malformations in a child with Kabuki syndrome: A case report

Nikki C. Geers, MD,[a] H. Bing Thio, MD, PhD,[b] and Wim J. A. de Kort, MD[a]
*Breda and Rotterdam, The Netherlands*

***Key words:*** capillary malformations; genetic syndromes; Kabuki syndrome; KDM6A; KMT2D; mutations.

## INTRODUCTION

Certain genetic syndromes can result in characteristic cutaneous abnormalities, which may lead directly to the diagnosis of the underlying disease. Early diagnosis and treatment of these syndromes are often important to improve treatment and the patient's development.

Kabuki syndrome (KS) is a pediatric congenital disorder of genetic origin with complicated manifestations, occurring in approximately 1 of 32,000 newborns.[1] KS was first described in Japan in 1981 and is named after a Japanese dance drama.[2] The notable eyes characteristic for KS patients resembles the makeup used in Kabuki theater, showing eversion of the lateral lower eyelids and broad, arched eyebrows with lateral sparseness.[1]

The 5 main typical manifestations of KS include facial features, skeletal anomalies, dermatoglyphic abnormalities, mild-to-moderate intellectual disability, and postnatal growth deficiency.[3] The clinical features expressed vary widely between individual patients. Beside the main manifestations, other malformations are common, such as urogenital and cardiac malformations.[2]

Following recent advances in epigenetics, is it now known that KS is mainly caused by a dominant de novo pathogenic mutation. In 52% to 76% of patients, the mutation is located on the *KMT2D* gene of chromosome 12 and is called *KS type I*. In the other variant, the mutation is located on the *KDM6A* gene on chromosome X, which is inherited in an X-linked dominant pattern and is called *KS type II*.[3]

Both the *KMT2D* gene and the *KDM6A* gene regulate histone expression. Mutations in these genes result in abnormal histone functioning, resulting in impaired expression of certain other genes.

*Abbreviations used:*

| | |
|---|---|
| CM: | capillary malformations |
| CM-AVM: | capillary malformation-arteriovenous malformation syndrome |
| KS: | Kabuki syndrome |
| PWS: | Parkes-Weber syndrome |

The *KMT2D* gene plays a critical role in regulating development, differentiation, metabolism, and tumor suppression.[4] The *KDM6A* gene plays a critical role in developmental regulation.[5] Unlike in KS type I, developmental delay and learning disabilities are generally moderate to severe in boys but mild to moderate in girls with KS type II due because of the X-linked inheritance pattern.[6]

## CASE PRESENTATION

We report a case of a 4-year-old white girl with genetically proven KS type I, showing a mutation of the *KMT2D* gene on chromosome 12. The patient was a firstborn child, born at 37 weeks through vacuum-assisted vaginal delivery. She had orofacial cleft and mental retardation resulting in developmental disabilities. Despite speech therapy, only nonverbal communication was possible, as she remained unable to produce words. She walked since the age of 2. Her social skills were improving, and she was playing with other kids. We observed no difficulties with understanding and following instructions.

She was referred to the dermatology outpatient department with striking patchy capillary malformations (CM) (Figs 1 and 2) (para)medially on the (left) upper back and bilaterally along the lumbosacral

From the Department of Dermatology, Amphia Medical Center, Breda[a] and the Department of Dermatology, Erasmus University Medical Center, Rotterdam.[b]
Funding sources: None.
Conflicts of interest: None disclosed.
Correspondence to: Nikki C. Geers, MD, Department of Dermatology, Amphia Medical Center, PO Box 90158, 4800 RK Breda, The Netherlands. E-mail: nikki.c.geers@gmail.com.

JAAD Case Reports 2019;5:560-2.
2352-5126

https://doi.org/10.1016/j.jdcr.2019.05.004

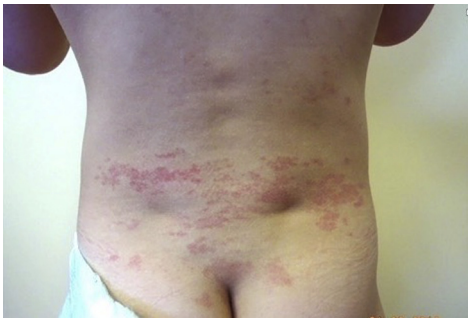

**Fig 1.** Capillary malformations on the lower back in a child with KS type I.

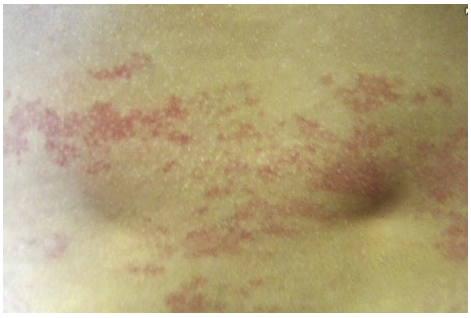

**Fig 2.** Capillary malformations on the lower back in a child with KS type I (close up).

region. These malformations were present since birth, were slowly expanding in width, and remained visibly unchanged to the patient's parents with regard to thickness and brightness. The malformations were asymptomatic; hence, no additional dermatologic analysis or treatment was applied.

General physical examination found that the patient had a small length (96 cm [-1.94 standard deviation (SD)]) and normal weight (14,4 kg [-0.03 SD]), head circumference (49 cm [-0.63 SD]) and body mass index (15,6 kg/m$^2$ [0,18 SD]). Cardiac ultrasonography and lumbar and thoracic spine ultrasonography found no abnormalities. Abdominal ultrasonography unveiled a urogenital malformation, showing a duplicated ureter. No additional magnetic resonance imaging scan was made, which would be indicated to rule out other dysgraphia defects associated with CM in the lumbosacral region.

## DISCUSSION

Multiple malformations have been associated with KS, but typically no CM are seen. CM are localized abnormalities that occur during vascular development. CM may cause aesthetic problems and can continue to grow throughout life. CM are commonly called *port wine stains* and are the most common cutaneous vascular malformations, affecting 0.3% of newborns.[7] Based on the abnormal microanatomy seen in vascular malformations, the underlying genes may have encoded structural proteins of the endothelial or smooth muscle cells or possibly extracellular matrix proteins.[8] CM may occur as solitary findings or may be associated with other malformations as part of genetic syndromes.

Four syndromes are known to be characterized by CM: Sturge-Weber syndrome, Klippel-Trenaunay syndrome, Parkes-Weber syndrome (PWS), and capillary malformation–arteriovenous malformation syndrome (CM-AVM). Uncovering the genetic basis for Sturge-Weber syndrome, Klippel-Trenaunay syndrome, PWS, and CM-AVM has posed a challenge, as these syndromes usually occur sporadically, although some cases of autosomal-dominant inheritance of PWS and CM-AVM have been described.[9]

To our knowledge, CM have not yet been associated with KS. The CM described in the presented case may be an incidental coexisting finding apart from KS. This case might also point at a yet-unknown link between KS and CM. Even though no proof for a link was found in this case, a link would be important in recognizing KS in an earlier stage, leading to timelier medical and developmental patient support.

## CONCLUSION

The authors report an atypical case of KS showing CM in a child with genetically proven KS type I. To our knowledge, these malformations have not yet been associated with KS. The malformations may be an incidental coexisting finding apart from KS or point at a yet-unknown link with KS. A link would be clinically important to help ensure timely diagnosis of KS, enabling earlier medical and developmental patient support.

### REFERENCES

1. Long A, Sinkovskaya ES, Edmondson AC, Zackai E, Schrier Vergano SA. Kabuki syndrome as a cause of non-immune fetal hydrops/ascites. *Am J Med Genet A*. 2016;170(12):3333-3337.
2. Moon JE, Lee SJ, Ko CW. A de novo KMT2D mutation in a girl with Kabuki syndrome associated with endocrine symptoms: a case report. *BMC Med Genet*. 2018;19(1):102.
3. Sakata S, Okada S, Aoyama K, et al. Individual clinically diagnosed with CHARGE syndrome but with a mutation in KMT2D, a gene associated with Kabuki syndrome: a case report. *Front Genet*. 2017;8:210.
4. Froimchuk E, Jang Y, Ge K. Histone H3 lysine 4 methyltransferase KMT2D. *Gene*. 2017;627:337-342.
5. Micale L, Augello B, Maffeo C, et al. Molecular analysis, pathogenic mechanisms, and readthrough therapy on a large

cohort of Kabuki syndrome patients. *Hum Mutat*. 2014;35(7):841-850.
6. Banka S, Lederer D, Benoit V, et al. Novel KDM6A (UTX) mutations and a clinical and molecular review of the X-linked Kabuki syndrome (KS2). *Clin Genet*. 2015;87(3):252-258.
7. Jacobs AH, Walton RG. The incidence of birthmarks in the neonate. *Pediatrics*. 1976;58(2):218-222.
8. Wetzel-Strong SE, Detter MR, Marchuk DA. The pathobiology of vascular malformations: insights from human and model organism genetics. *J Pathol*. 2017;241(2):281-293.
9. Eerola I, Boon LM, Mulliken JB, et al. Capillary malformation-arteriovenous malformation, a new clinical and genetic disorder caused by RASA1 mutations. *Am J Hum Genet*. 2003;73(6):1240-1249.