

CASE REPORT

Diabetes mellitus and insulin resistance associated with Kabuki syndrome—A case report and literature review

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Funding information

This work was supported by National Health and Medical Research Council (NHMRC, 1113188) and National Science Foundation of China (NSFC) 111 (81561128017) International Joint Program. Professor Assam El-Osta is a NHMRC Senior Research Fellow (1154650). The funder had no role in the study design, data collection and analysis

Abstract

Kabuki syndrome (KS) is a genetic disorder characterized by distinctive facies, intellectual disability, and multi-organ anomalies. This case report highlights the importance of clinical recognizable phenotype in patients with diabetes. The development of diabetes should be considered an endocrine complication in KS patients.

KEYWORDS

diabetes mellitus, insulin resistance, Kabuki syndrome, KMT2D

1 | INTRODUCTION

Kabuki syndrome (KS, OMIM#147920) is a genetically heterogeneous disorder characterized by striking facial features. The name of the disease originates from the resemblance of its characteristic facial appearance to stage makeup used in Japanese Kabuki theater. Features

include five cardinal manifestations—eversion of the lower lateral eyelid, arched eyebrows with the lateral one-third dispersed or sparse, a depressed nasal tip, and prominent ears), skeletal (deformed spinal column with or without sagittal cleft vertebrae and brachydactyly), dermatoglyphic abnormalities, intellectual disability, and postnatal growth deficiency.¹ The most frequently

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involved gene in more than 70% of individuals with the condition is the histone-lysine *N*-methyltransferase 2D (*KMT2D*, OMIM *602113) which located on chromosome 12q13. The *KMT2D* gene encodes a lysine methyltransferase responsible for catalyzing mono-methylation of lysine position 4 on histone H3.² A member of the SET1 family the histone H3 lysine 4 (H3K4) methyltransferase writes the methylation determinant at promoters and enhancers responsible for regulating gene transcription.³ Following the discovery of *KMT2D* gene in autosomal dominant inheritance of this syndrome, lysine-specific demethylase 6A (*KDM6A*, OMIM *159555) emerged as a causative pathogenic mutation in an X-linked dominant form of KS.⁴ Moreover, recent data have shown that 20%–40% of clinically diagnosed as KS might have unidentified genes.⁵ Therefore, the causative genes of KS are expected to expand in the future and the clinical phenotype of KS.

The underlying genetic mutation of KS is associated with abnormal embryonic and fetal development. As a result, the clinical phenotype and associated conditions are highly variable and range from congenital cardiac and renal anomalies, varying degrees of intellectual disability, failure to thrive, short stature, and immune dysfunction. The occurrence of diabetes mellitus (DM) both insulin-dependent and insulin-independent had been rarely reported. Indeed, a single case was previously reported with slow progressive form of type 1 DM and another case associated with obese diabetes.^{6,7} However, there are anecdotal reports of KS cases in recent years.^{8–10} The development of DM is considered one of the endocrine complications in KS patients. Limited information is available in the clinical course of DM associated with Kabuki syndrome. We report a 27-year-old Thai patient with molecular proven KS who developed youth-onset DM at the age of 19 years. Understanding the function of the genes that lead to KS would pave the way to create targeted therapies for the developmental origins of diabetes and also provide an opportunity for targeting epigenetic defects in KS.

2 | CASE REPORT

A 27-year-old male patient with unconfirmed diagnosis of Fragile X syndrome since childhood came to attend our diabetes clinic because of poorly controlled diabetes (HbA1c 69 mmol/mol, normal <36 mmol/mol). He was a preterm baby born at 7 months with birthweight 2240 g and had been clinically diagnosed with Fragile X syndrome due to delayed development and intellectual disability diagnosed from another hospital. At the age of 11 months, he underwent right nephrectomy from severe hydronephrosis. He was also diagnosed with moderate mental retardation (Intelligence Quotient = 43) at 8 years

of age. He later developed hypertension due to coarctation of the aorta at age 14. At the age of 19, he presented with polyuria and lost 10 kg within 6 months (baseline BMI at 26.3 kg/m²). Laboratory data showed HbA1c 137 mmol/mol, plasma glucose 24 mmol/L, and no ketonemia. At that time, youth-onset type 2 DM was diagnosed, and insulin treatment was prescribed before switching to oral metformin and glipizide. No detailed laboratory data were collected regarding the cause of diabetes. Furthermore, no family history of diabetes or other genetic disorders had been reported. The patient was the second child of non-consanguineous healthy parents. The patient was lost to follow-up until the age of 27 years and continued irregularly with anti-diabetic medications. At the age of 25, he developed moderate to severe sensorineural hearing loss requiring hearing aids in both ears. At the age of 26 years, plaque psoriasis without arthritis was diagnosed and only a topical retinoid was given.

He presented to our hospital at the age of 27 years old, seeking opinion regarding treatment options for diabetes. Physical examination revealed height of only 150 cm and weight of 56 kg (body mass index, BMI 24.9 kg/m²) with abdominal obesity. As shown in Figure 1, his facial features show long palpebral fissures with eversion of the lateral third of the lower eyelids, depressed nasal tip, and prominent ears. No coloboma or blue sclera was found. No cleft lip or cleft palate was detected. Based on his facial features and multi-organ involvements, KS was clinically suspected. Further examinations also revealed other KS-related typical clinical features as shown in Figure 2 (high-arched palate, enlargement of lower lip, increase in hypothenar patterns, absence of the digital tri-radius region, prominent finger pads in the 3rd and 4th fingers both hands, and shortening of the 5th fingers both hands). Skull, hand, and spine radiographs demonstrated abnormal skull contour, brachydactyly and clinodactyly of the fifth digit, scoliosis, and sacral spina bifida as shown in Figure 3. The patient was confirmed to have heterozygous frameshift deletion mutation (c.7524delA heterozygous mutation, p.(Lys2509Argfs*34)) in exon 31 of 54 of the *KMT2D* gene by exome sequencing (Agilent Sureselect QXT CREv2 kit, Illumina). This deletion is predicted to create a frameshift starting at amino acid position 2509, introducing a stop codon 34 residues downstream. This variant is also predicted to result in the loss of protein function through nonsense-mediated decay. *In-silico* analysis predicted damaging effect, classified as pathogenic by the American College of Medical Genetics and Genomics (ACMG) guideline. No other family members had been tested for genetic testing.

Evaluation of beta-cell function from mixed meal stimulation test revealed preserved beta-cell (fasting plasma C-peptide at 1026 pmol/L, normal range 260–1270 pmol/L

FIGURE 1 Distinctive facial features of Kabuki syndrome (long palpebral fissures, eversion of the lower lateral eyelids, depressed nasal tips)



and stimulated C-peptide was 2881 pmol/L, normal range 2500–9000 pmol/L). Fasting plasma insulin level was 77.8 pmol/L (normal <174 pmol/L), and stimulated plasma insulin level was 195.8 pmol/L (normal 125–1917 pmol/L). Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index which uses fasting measurements of plasma glucose and insulin concentrations to calculate indices of both insulin sensitivity suggested severe insulin resistance (HOMA-IR 5.5, normal <1.6). Pancreatic auto-antibodies (anti-GAD, anti-IA2, and anti-ZnT8) revealed negative results. Abdominal ultrasonography revealed moderately fatty liver and undescended right testes without mass. After molecular confirmation of KS and insulin resistance associated with diabetes, the patient was treated with combined oral anti-diabetic medications (Glipizide 5 mg/day, Metformin 2000 mg/day, Sitagliptin 50 mg/day, and Empagliflozin 12.5 mg/day). Oral pioglitazone had been attempted for a few months but discontinued due to pedal edema. Currently (at 30 years of age), the patient's diabetes has been moderately controlled (HbA1c varied from 57–61 mmol/mol) after loss of weight – 6 kg in the past three years as shown in Figure 4. No diabetic complications detected. During follow-up visits, asymptomatic hyperuricemia (512–636 $\mu\text{mol/L}$, normal <300 $\mu\text{mol/L}$)

was also found. Additional hormonal investigations revealed only mild hypogonadotropic hypogonadism (total testosterone 7.1 nmol/L, normal range 10.4–34.7 nmol/L). At the last follow-up, the patient underwent a 75 g oral glucose tolerance test (OGTT) to re-evaluation of OGTT-derived indices of insulin sensitivity. Fasting plasma insulin level was 29.9 pmol/L, and stimulated plasma insulin level was 139.6 pmol/L. These results showed markedly improvement of insulin resistance (HOMA-IR was 1.2) but assessment of insulin sensitivity by Matsuda index which used plasma glucose and insulin concentrations in fasting state and during OGTT to reflect a composite estimate of hepatic and muscle insulin sensitivity still revealed whole-body insulin resistance (Matsuda index 8.6, normal <4.5). The patient was advised to maintain his bodyweight together with closely regular follow-ups for further KS-related conditions.

3 | DISCUSSION

Kabuki syndrome had been described in Japanese patients for 4 decades.¹ Its clinical variability and genetic heterogeneity pose a challenge for timely diagnosis. In

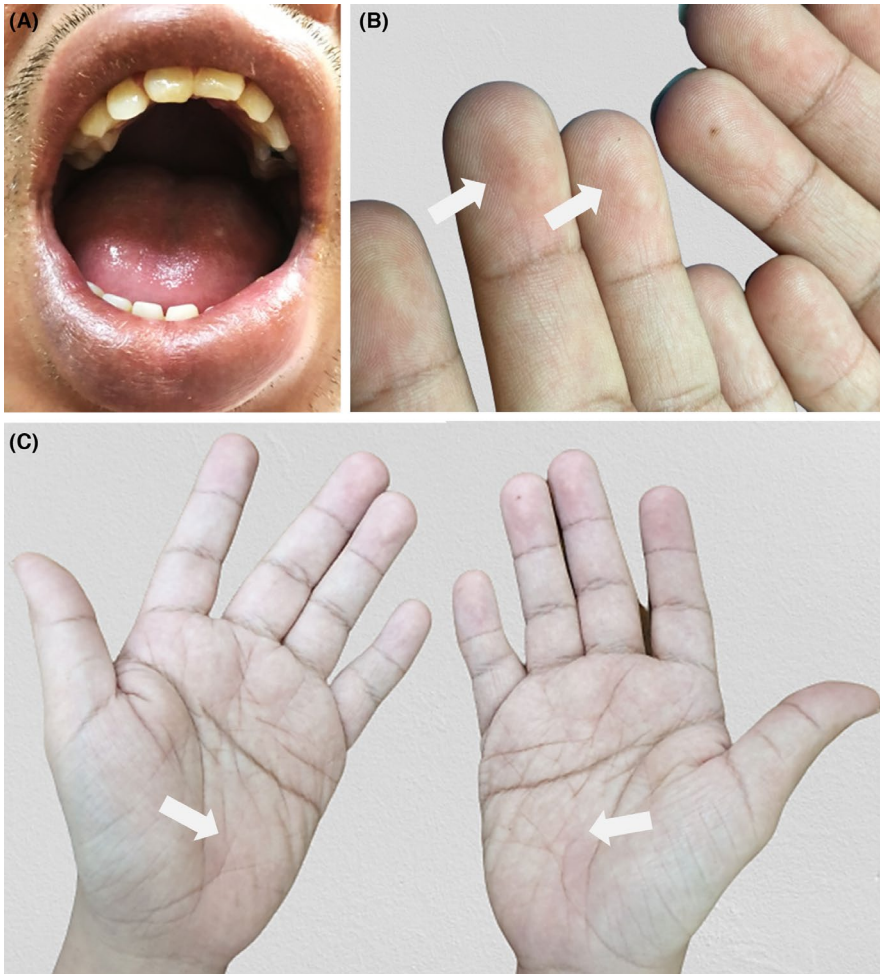


FIGURE 2 Kabuki syndrome-related clinical features which found in this patient A) High-arched palate and enlargement of lower lip B) Prominent finger pads in the 3rd and 4th fingers both hands (arrows) C) Typical dermatoglyphics (increase in hypothenar patterns (arrows) and absence of the digital tri-radius region with shortening of the 5th fingers both hands)

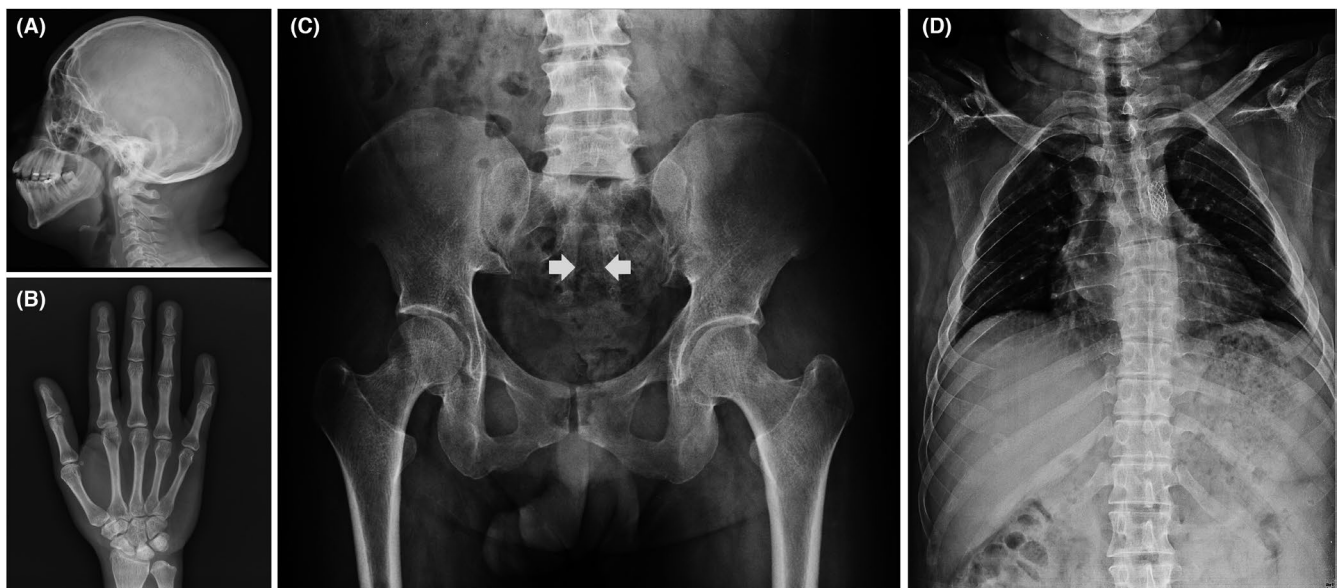


FIGURE 3 A) Lateral skull radiograph showed thick cortical bone and abnormal skull contour B) X-ray of right hand showed shortening and clinodactyly of the fifth digit C) Anteroposterior view of pelvis revealed sacral spina bifida (arrows) without hip dislocation D) Anteroposterior view of spine radiograph showed mild scoliosis of thoracolumbar spine

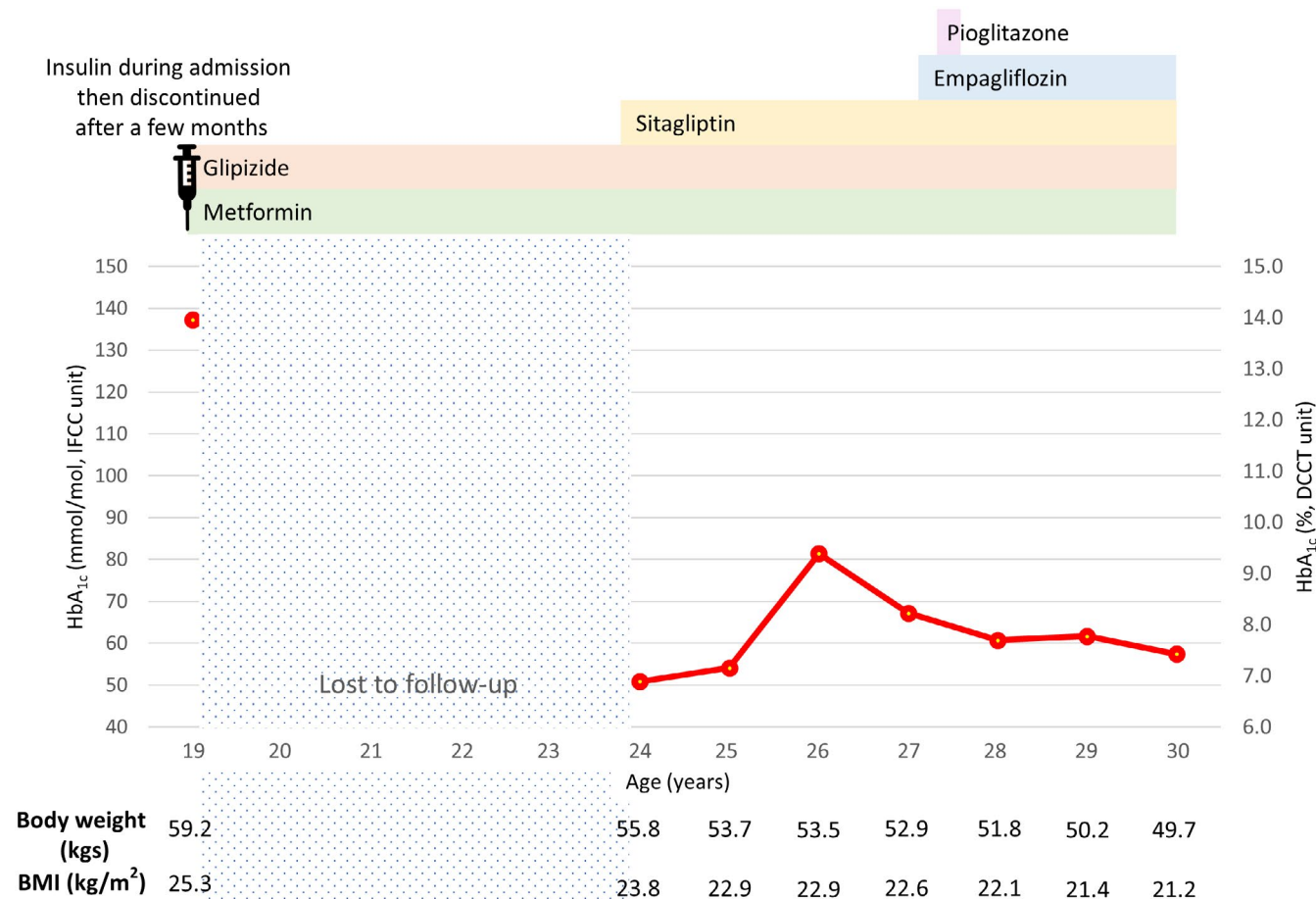


FIGURE 4 Clinical course and treatments of diabetes mellitus (DM) in this patient from the onset of DM until at the time of last follow-up

a recent consensus report, this syndrome could be diagnosed by a history of infantile hypotonia, developmental delay, and/or intellectual disability combined with molecular testing or typical dysmorphic features.⁵ To date, more than 800 different mutations in *KMT2D* gene have been reported. The pathogenesis of this complex and multi-organs developmental phenotype is not fully understood due to our incomplete knowledge in the role of causative gene during developmental process.

While detailed investigations on the phenotypic manifestations of KS had been carried out in European, American, and East Asian countries patients,^{5,9,10} studies on patients from the Southeast Asian region are rarely reported. Our case highlights that the presumptive diagnosis should be reconsidered if atypical features arise. Delayed diagnosis could lead to suboptimal care and create uncertainty for families. In the era of molecular testing, genomic sequencing could lead to accurate diagnosis and appropriate medical interventions for complex disorders. Although various barriers exist to accessing genomic testing in resource-limited settings, further research is warranted for early genetic testing for individuals with suspected rare genetic syndromes. Additionally, a greater

number of patients with complex genetic syndrome are now reaching adult age and knowledge of health problems and referral centers for multidisciplinary care are required to provide best care. Because there is no KS phenotype in other family members of this patient, genetic testing was not performed. Therefore, the possibility of *de novo* mutation in this patient had been suspected but it should be further confirmed with additional genetic data in other family members.

KMT2D protein belongs to the SET1 family of lysine methyltransferases enzymes involved in mono-methylation and gene regulation.² Preclinical studies show this protein is important for the formation of craniofacial structures, heart formation, and neural crest migration.¹¹ Interestingly, pro-inflammatory gene expression associated with transient hyperglycemic response and diabetic memory was previously demonstrated for the SET7 methyltransferase and conferred by mono-methylation of H3K4.¹² Both insulin-dependent and insulin-independent DM in KS have been occasionally reported^{6–10} as summarized in Table 1. While a first case of insulin-dependent DM had been initially linked with type 1 DM in a Japanese patient,⁶ the recent cases linked this type of DM with

TABLE 1 Clinical features and genetic mutation of diabetes-associated Kabuki syndrome in the previous reports

	Our case	Fujishiro et al. 2003 ⁶	Lin et al. 2015 ⁷	Sakata et al. 2017 ⁸	Baldridge et al. 2020 ⁹	So et al. 2021 ¹⁰
Age at the first diagnosis of DM	19 years	20 years	N/A	11 years	10 years	Early adulthood (reported 4 cases)
Age at the last evaluation	30 years	31 years	31 years	24 years	Deceased at 14 years	N/A
Sex	Male	Female	Male	Female	Female	N/A
BMI at the diagnosis of DM (kg/m ²)	26.3	16.6	N/A but obese	N/A	N/A	N/A
DKA	No	Yes	No	No	No	N/A
Insulin-dependent	No	Yes	No	Yes	Yes	No
Associated endocrine problems	Hypogonadotropic hypogonadism	Hypogonadotropic hypogonadism	N/A	Primary hypothyroidism	Central hypothyroidism Hypogonadotropic hypogonadism	Primary hypothyroidism
Type of <i>KMT2D</i> mutation	Frameshift	N/A	Missense	Missense	Missense	N/A

hypoplasia of pancreas.⁹ Interestingly, the latest report of Chinese patients with KS describes the development of type 2 DM in early adulthood representing up to 20% (4/21) of all patients.¹⁰ In the case presented, we observe insulin resistance reminiscent of type 2 DM but the occurrence of severe hyperglycemia at the onset of diabetes reflected for glucose toxicity which did not fit with typical type 2 DM. Interestingly, a role of *KMT2D* gene in the pathogenesis of insulin resistance and non-alcoholic fatty liver disease (NAFLD) was previously reported in knockout mice.¹³ Of interest, a marked decrease in insulin secretion in response to the glucose challenge was observed in the pre-clinical studies. Therefore, we propose the development of DM in KS could be considered as diabetes-associated genetic syndromes.

Low birthweight in KS patients due to intrauterine growth retardation may also lead to low adult beta-cell mass,¹⁴ which together with insulin resistance contribute to beta-cell failure. KS patients commonly present with failure to thrive and feeding problems during infancy. In contrast, these children commonly present with obesity in late childhood and consistent with observations in this case report. Indeed, multiple comorbidities, including psoriasis, fatty liver, and hyperuricemia, are also associated with metabolic syndrome. The underlying psoriasis and metabolic syndrome had been postulated as a model of overlapping inflammatory pathways and genetic predisposition.¹⁵ While there are no reports of psoriasis in KS individuals, these patients are predisposed with recurrent infections, autoimmune diseases, and immune pathway changes.⁵ The long follow-up period into adulthood could delineate KS-related endocrine problems and immunological disorders. Growth hormone (GH) deficiency is one of the most common endocrine complications in KS patients (but not seen in the present case), and recombinant human GH had been recently found to be beneficial on linear height without adverse effects.¹⁶ However, the association between GH administration and worsening insulin resistance should be cautioned in high-risk patients as shown in a recent Japanese case report.⁸

4 | CONCLUSION

Our case highlights the importance of clinical recognizable phenotype in patients with diabetes and expand the development of diabetes as an endocrine complication in KS and particularly in patients with low birthweight. KS patients should be advised to maintain healthy lifestyle together with regular follow-ups for further KS-related conditions. The continued study of lysine methyltransferases in this syndrome is warranted to understand the regulation of insulin signaling pathways defects in Kabuki syndrome.

ACKNOWLEDGMENTS

We are grateful to the patient for participating in this publication. Written informed consent has been obtained from the patient for publication of the submitted article and accompanying images. We also would like to thank Dr. Veekij Veerasomboonsin for his expert reviews of skeletal radiographs.

CONFLICT OF INTEREST

The authors do not have any conflict of interest to declare. Parts of this manuscript had previously been presented as a poster at ENDO 2021, the Endocrine Society's annual meeting 2021, Virtual Meeting.

AUTHOR CONTRIBUTIONS

Y.T. wrote the initial draft of the article. E.W. was involved in the direct care of the patient. I.K. and AEO. facilitated genetic testing. All authors contributed to the acquisition and interpretation of data, manuscript revision, final approval of manuscript, and are accountable for accuracy of manuscript; and contributed to the editing process.

CONSENT

The patient and his family gave written consent for publication.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no relevant data were created or analyzed in this study.

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How to cite this article: Thewjitcharoen Y, Wanothayaroj E, Nakasatien S, et al. Diabetes mellitus and insulin resistance associated with Kabuki syndrome—A case report and literature review. *Clin Case Rep*. 2022;10:e05736. doi:10.1002/ccr3.5736