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Growth charts in Kabuki syndrome 1

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Abstract

Kabuki syndrome (KS, KS1: OMIM 147920 and KS2: OMIM 300867) is caused by pathogenic variations in *KMT2D* or *KDM6A*. KS is characterized by multiple congenital anomalies and neurodevelopmental disorders. Growth restriction is frequently reported. Here we aimed to create specific growth charts for individuals with KS1, identify parameters used for size prognosis and investigate the impact of growth hormone therapy on adult height. Growth parameters and parental size were obtained for 95 KS1 individuals (41 females). Growth charts for height, weight, body mass index (BMI) and occipitofrontal circumference were generated in standard deviation values for the first time in KS1. Statural growth of KS1 individuals was compared to parental target size. According to the charts, height, weight, BMI, and occipitofrontal circumference were lower for KS1 individuals than the normative French population. For males and females, the mean growth of KS1 individuals was −2 and −1.8 SD of their parental target size, respectively. Growth hormone therapy did not increase size beyond the predicted size. This study, from the largest cohort available, proposes growth charts for widespread use in the management of KS1, especially for size prognosis and screening of other diseases responsible for growth impairment beyond a calculated specific target size.

KEYWORDS
growth, growth hormone deficiency, Kabuki syndrome, parental target size, specific curves

1 | INTRODUCTION

Kabuki syndrome (KS, also called Niikawa–Kuroki syndrome) is a rare condition characterized by a distinctive facial phenotype, multiple congenital malformations such as visceral malformations, skeletal features, persistence of fetal fingertip pads, and intellectual disability. The first patients were simultaneously and independently described by Niikawa, Matsuura, Fukushima, Ohsawa, and Kajii (1981) and Kuroki, Suzuki, Chyo, Hata, and Matsui (1981). Numerous complications are also observed and include immunopathological manifestations, deafness, postnatal short stature but also overweight and endocrinological dysfunction such as growth hormone (GH) deficiency. Most of individuals diagnosed with KS have a heterozygous pathogenic variation in *lysine-specific methyltransferase 2D* (*KMT2D*, MIM *602113) responsible for Kabuki Syndrome 1 (KS1, autosomal dominant, MIM #147920) (Ng et al., 2010). Few individuals diagnosed with KS have a pathogenic variation in *lysine-specific demethylase 6A* (*KDM6A*, MIM*300128) responsible for Kabuki Syndrome 2 (KS2, unusual X-linked affecting males and females, MIM #300867) (Lederer et al., 2012; Miyake et al., 2013). *KMT2D* encodes for a H3K4 histone methyltransferase, and *KDM6A* encodes for a H3K27 histone demethylase, two proteins that are part of the ASCOM complex, a transcriptional regulator (Bögershausen & Wollnik, 2013).

Intrauterine growth retardation (IUGR) and postnatal growth retardation are observed in 19% to 65% and 35% to 71% of KS individuals, respectively. Microcephaly is observed in 24% to 65%, and overweight or obesity at puberty is present in 19% to 29%. In addition, GH deficiency is reported in 2% to 22% of KS individuals with or without the identified *KMT2D* pathogenic variation (Armstrong et al., 2004; Chu, Finley, Young, & Proud, 1997; Matsumoto & Niikawa, 2003; Schott et al., 2016; Schrander-Stumpel, Spruyt, Curfs, Defloor, & Schrander, 2005). A study of GH therapy efficacy compared for the first time the height of individuals with KS to their parental target size (PTS) and showed a difference of approximately −2 SD in 18 prepubertal KS children (eight males and seven females with the *KMT2D* pathogenic variant, one male and two females with the *KDM6A* pathogenic variant) (Schott, Gerver, & Stumpel, 2017).

In this study, we aimed to (a) confirm these observations in a large cohort of KS individuals with the *KMT2D* pathogenic variant, (b) present the first set of normative curves for height (H), weight (W), body mass index (BMI), and occipitofrontal circumference (OFC) in 95 individuals with KS and the *KMT2D* pathogenic variation, (c) assess the association between growth parameters and clinical or molecular features (sex, type of pathogenic variant),

(d) compare the height of KS individuals with their PTS, and (e) look for any effect of GH therapy on growth based on predicted size by using PTS.

2 | MATERIALS AND METHODS

2.1 | Biological and data collection

With the French research program PHRC AOM-09-070 (ClinicalTrials.gov identifier: NCT01314534), we collected clinical data for 95 individuals (54 males) with a diagnosis of KS1. The project was approved by the ethics committee "Comité de Protection des Personnes Ile de France II". All individuals, parents or legal guardians gave their written informed consent to this study. The diagnosis for all individuals was ascertained by a cohort of geneticists and fulfilled the clinical criteria and facial features of KS1. All diagnoses were genetically confirmed: all individuals had the *KMT2D* pathogenic variant (Table S1). Data for H (centimeters), W (kilograms), BMI, and OFC (centimeters) were collected for individuals at birth and at each visit to the geneticist (Table 1). GH deficiency was recorded. Each measurement at different ages was counted as one data point. PTS was calculated as mother's H plus father's H (centimeters) divided by two, plus 6.5 cm for a male or minus 6.5 cm for a female.

2.2 | Growth chart generation

We used a normal modelization with curve smoothing by cubic splines. The package gamlss in R software was used to construct the growth curves (Stanisopoulos, Rigby, & Akantziliotou, 2008). Growth reference curves for H, W, OFC, and BMI were from French curves, obtained from the PC PAL society (https://www.pcpal.eu/) (Deheeger & Rolland-Cachera, 2004; Sempé, Pédron, & Roy-Pernot, 1979). This methodology was used to construct the World Health Organization (WHO) Child Growth Standards (Bulletin of WHO, 1995) and the WHO growth reference for school-aged children and adolescents (de Onis, 2007).

TABLE 1 Growth data for 95 individuals with Kabuki syndrome 1 (KS1) and a *KMT2D* pathogenic variant

Growth data		Males	Females	Total
Weight	Individuals	41	30	71
	Measurements	273	196	469
Height	Individuals	44	29	73
	Measurements	328	216	544
BMI	Individuals	37	29	66
	Measurements	203	153	356
OFC	Individuals	32	25	57
	Measurements	143	112	255

Abbreviations: BMI, body mass index; OFC, occipitofrontal circumference.

3 | RESULTS

3.1 | Data collection

W, H, BMI, and OFC data were collected from 41, 44, 37, and 32 males and from 30, 29, 29, and 25 females, respectively (Table 1). At least one birth parameter was collected from 54 of 54 males and 39 of 41 females. Parents' height was collected and allow to calculate PTS for 37 of 54 males and 25 of 41 females. A truncating variant (i.e., nonsense, frameshift or splicing variant) in *KMT2D* was observed in 42 males and 31 females, and a nontruncating variant (i.e., missense or inframe deletion) in 12 males and 10 females (Table S1). GH deficiency was observed in 12 individuals (nine males), all who received GH therapy. None of the individuals without GH deficiency received GH therapy.

3.2 | Birth parameters

Mean gestational age at delivery is 38 weeks of amenorrhea (WA) and 5 days with no difference between males and females. Four KS1 individuals (5% of those for whom we had data on birth H and W) showed IUGR, defined by birth H and birth W < −2 SD from French curves. For males, mean birth H was −0.3 SD (48.2 cm), mean birth W −0.8 SD (3.01 kg) and mean birth OFC -0.9 SD (33.1 cm). For females, mean birth H was −0.5 SD (47.9 cm), mean birth W −1.2 SD (2.98 kg), and mean birth OFC −1.4 SD (32.9 cm). Birth parameters did not differ by sex (Table S2) or truncating or nontruncating pathogenic variant (Table S3).

3.3 | Postnatal growth

In total, 35 of 89 (39%) individuals (17 of 51 males and 18 of 38 females) showed postnatal growth retardation at the last

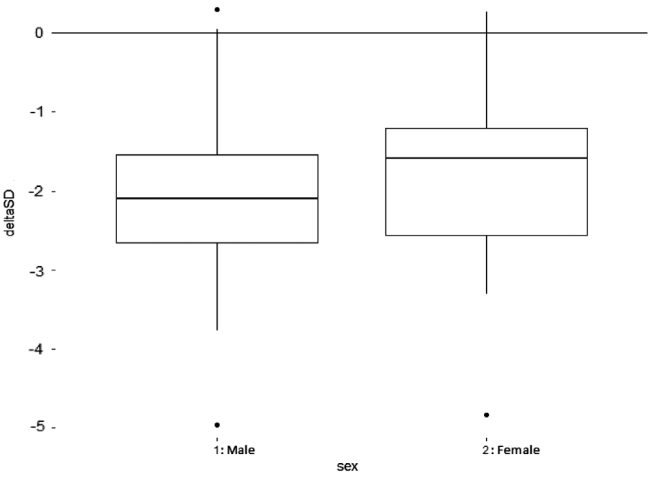

FIGURE 1 Height for participants with Kabuki syndrome 1 (KS1) with reference to parental target size (PTS). Bold lines represent median difference between PTS and participant height in standard deviations (SDs), boxes represent interquartile range (IQR). Vertical lines represent lower and upper range, calculated as 1.5× IQR. Dots represent extreme data (higher and lower)

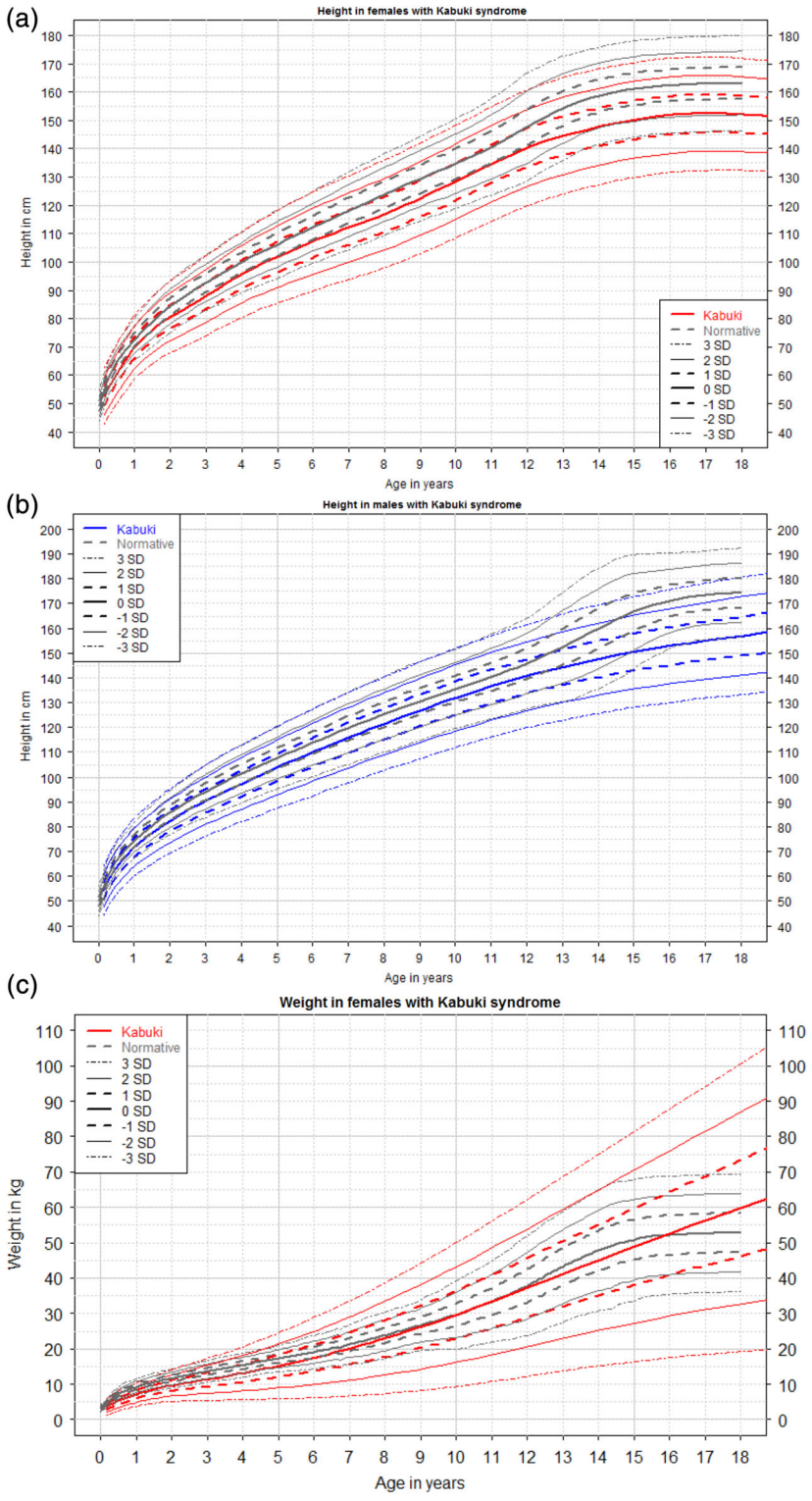

FIGURE 2 (a) Height for females with KS1. (b) Height for males with KS1. (c) Weight for females with KS1. (d) Weight for males with KS1. (e) Occipitofrontal circumference (OFC) for females with KS1. (f) OFC for males with KS1. (g) Body mass index (BMI) for females with KS1. (h) BMI for males with KS1 [Color figure can be viewed at wileyonlinelibrary.com]

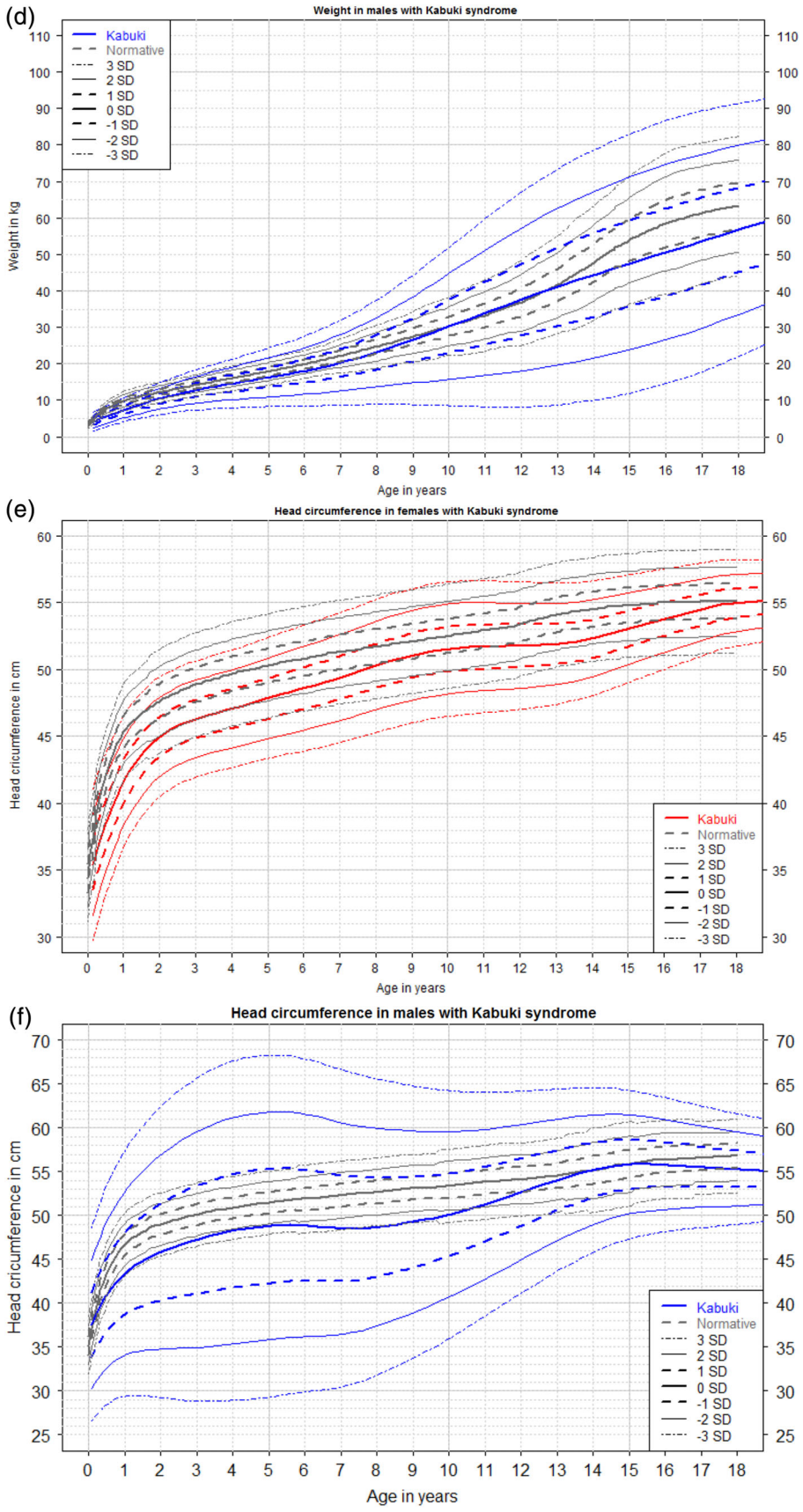

FIGURE 2 (Continued)

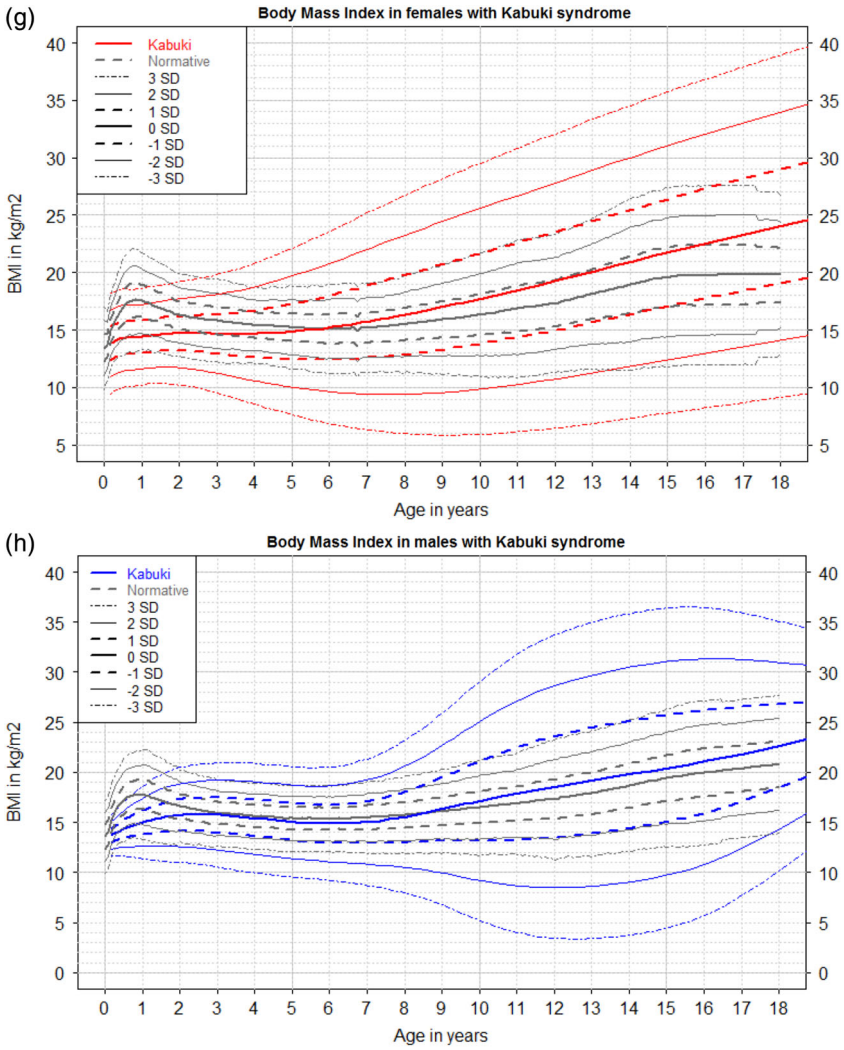

FIGURE 2 (Continued)

examination, with H below −2 SD. Individuals with the truncating or nontruncating pathogenic variant did not differ in parameters of growth (H, W, BMI, and OFC) (Table S4).

3.4 | Prediction of size in KS1 individuals

Using PTS data, we identified that KS1 males had a mean growth −2 SD of their PTS and KS1 females a mean growth −1.8 SD of their PTS, with no significant difference by sex (p = .39 by Student t test) (Figure 1). These data seem reliable to predict a specific KS1 target size. Individuals with and without GH treatment did not differ in predicted size (p = .71 by Student t test) (Table S5 and S6).

3.5 | Set of normative curves in KS1

Figure 2a–2h illustrate growth curves for males and females with KS1 in comparison with reference curves used in France for H, W, BMI, and OFC.

4 | DISCUSSION

These specific KS1 growth charts could be used as new tools to improve care in individuals with KS1. Overall 19% to 65% of KS individuals from the literature show IUGR. In our cohort, 18% had birth H < −2 SD and 6.5% birth W < −2 SD from French curves. IUGR, defined as birth W and birth H < −2 SD, was found in only 5% of individuals.

In this series, 39% of KS1 individuals showed postnatal growth retardation, with H < −2 SD (35 of 89:17 of 51 males and 18 of 38 females) (Table S7). Our data are consistent with the literature (−2 SD in 35–71% individuals) (Armstrong et al., 2004; Matsumoto & Niikawa, 2003; Schott et al., 2016; Schrander-Stumpel et al., 2005).

Also, 32.1% of individuals >2 years old (17 of 53: seven of 30 males and 10 of 23 females) showed OFC < −2 SD, with no significant difference by sex (p = .21) (Table S6). In the literature, 24 to 65% of individuals with KS have microcephaly (Armstrong et al., 2004; Chu et al., 1997).

The type of genetic variation (truncating or not) did not allow for predicting birth parameters or future H, W, BMI and OFC after birth (Tables S3 and S4).

PTS is additional data to monitor growth. Schott et al. (2017) first compared H in KS individuals to their PTS and showed a difference of approximately −2 SD but in an inhomogeneous *KMT2D* and *KDM6A* cohort of 18 individuals. We confirm this observation: individuals with KS1 due to a *KMT2D* pathogenic variant showed a mean growth of about −2 SD and −1.8 SD of their PTS for males and females, respectively (Table S5). This finding allows for predicting the size of KS1 individuals and to monitor growth. It also allows clinicians to search for a growth disruptor such as GH deficiency with children with H less than their predicted size using PTS.

Possible causes of postnatal growth restriction in KS include hormonal dysregulation or peripheral organ involvement. In the literature, GH deficiency is reported in 2 to 22% KS individuals with or without a *KMT2D* variant (Armstrong et al., 2004; Matsumoto & Niikawa, 2003; Schott et al., 2017; Schrander-Stumpel et al., 2005). In this series, GH deficiency was observed in 13% of KS1 individuals (nine males). GH therapy did not increase size beyond the predicted size: −2 SD and −1.8 SD for males and females, respectively (Table S6). All individuals from this series who had GH deficiency received GH therapy. It is therefore impossible to predict whether individuals with GH deficiency would be the same size without GH therapy.

Weight was below average in young KS1 individuals. However, although mean BMI is almost similar to that in the general population, the distribution is much wider in KS1, which suggests more overweight or obesity in this population than in the French general population. These data agree with prior publications showing overweight or obesity in 19 to 29% of KS individuals at puberty (Armstrong et al., 2004; Matsumoto & Niikawa, 2003). In our series, 27.7% of individuals <15 years old had BMI > +2 SD from French curves (18 of 65: 12 of 37 males and 6 of 28 females) as compared with 3.9% in the general pediatric French population (Matta, Carette, Rives Lange, & Czernichow, 2018), with no significant difference by sex (p = .43) (Table S7). Furthermore, BMI curves show an onset of obesity of about age 4 years for some individuals and about puberty for others. Therefore, early dietary advice is primordial to prevent obesity in KS1 individuals. In this series, we had BMI data for only five adults: two were overweight and none was obese. This lack of data does not allow for comparing obesity in adult KS1 individuals to the 17.2% obesity rate in adult general French population.

The limitations of this study are the small number of individuals with KS1 due to a low prevalence of this syndrome and are compounded by the lack of reliable growth data and the small number of measurements for some individuals. Especially, for two curves, OFC for females and W for males, we had only few measurements after age 10 years, so monitoring of growth is not as precise as wished.

In conclusion, we present the first normative growth curves for individuals with KS1. These charts are consistent with prior findings of growth anomalies in KS: 5% IUGR, 39% postnatal short stature, 32% microcephaly, and 21% obesity during childhood. These results confirm the importance of monitoring food and dietary advice for KS1 individuals to avoid obesity, which is more frequent in KS1 individuals than the general population, and its complications. Use of PTS allows for predicting the size of KS1 individuals and monitoring growth. We confirm also the need for a search for GH deficiency with growth < −2 SD of the PTS.

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CONFLICT OF INTEREST

D.G. is a consultant for the Takeda Society. The society did not have any influence on the content of this report or its publication.

AUTHORS' CONTRIBUTION

V.R. wrote the paper. C.D., S.A., V.G., M.B.-H., G.B., E.S., I.T., V.G. performed the analysis. C.C., M.A., Y.A., E.A., J.A., C.A., C.B., A.B., O.B., L.B., T.B., M.-P.C., V.C.-D., M.-A.D., B.D., L.F., M.F., B.G.-D., F.G., A.G., S.G., D.H., B.I., M.-L.J., A.J., C.J., D.L., M.L.M., K.H.L.Q.S., S.L., S.M., C.M., A.M., S.M., S.O., A.P., N.P., L.P., J.R., J.R., D.S., P.S., E.S., M.T., A.T., M.W. collected the data. D.G conceived and designed the study.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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