CLINICAL REPORT

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Meier–Gorlin Syndrome: Growth and Secondary Sexual Development of a Microcephalic Primordial Dwarfism Disorder

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Meier–Gorlin syndrome (MGS) is a rare autosomal recessive disorder characterized by primordial dwarfism, microtia, and patellar aplasia/hypoplasia. Recently, mutations in the *ORC1*, *ORC4*, *ORC6*, *CDT1*, and *CDC6* genes, encoding components of the pre-replication complex, have been identified. This complex is essential for DNA replication and therefore mutations are expected to impair cell proliferation and consequently could globally reduce growth. However, detailed growth characteristics of MGS patients have not been reported, and so this is addressed here through study of 45 MGS patients, the largest cohort worldwide. Here, we report that growth velocity (length) is impaired in MGS during pregnancy and first year of life, but, thereafter, height increases in paralleled normal reference centiles, resulting in a mean adult height of −4.5 standard deviations (SD). Height is dependent on ethnic background and underlying molecular cause, with *ORC1* and *ORC4* mutations causing more severe short stature and microcephaly. Growth hormone therapy (n = 9) was generally ineffective, though in two patients with significantly reduced IGF1 levels, growth was substantially improved by GH treatment, with 2SD and 3.8 SD improvement in height. Growth parameters for monitoring growth in future MGS patients are provided and as well we highlight that growth is disproportionately affected in certain structures, with growth related minor genital abnormalities (42%) and mammary hypoplasia (100%) frequently present, in addition to established effects on ears and patellar growth.

Key words: Meier–Gorlin syndrome; ear-patella-short stature; growth; growth hormone therapy; abnormal secondary sexual development; genital underdevelopment

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INTRODUCTION

Meier–Gorlin syndrome (MGS; ear-patella-short stature syndrome) (OMIM#224690) is defined by the triad of microtia, patellar aplasia/hypoplasia and short stature. Other frequent findings include pulmonary emphysema and typical facial characteristics (Fig. 1). MGS is part of a group of autosomal recessive disorders called microcephalic primordial dwarfism [Klingseisen and Jackson, 2011], characterized by severe proportionate pre- and postnatal growth deficiency, and microcephaly.

Sixty-three cases of MGS have been described in literature, thus far [Meier et al., 1959; Gorlin et al., 1975; Hurst et al., 1988; Cohen et al., 1991; Boles et al., 1994; Lacombe et al., 1994; Buebel et al., 1996; Fryns, 1998; Loeys et al., 1999; Verhallen et al., 1999; Terhal et al., 2000; Bongers et al., 2001; Cohen et al., 2002; Feingold, 2002; Shalev and Hall, 2003; Dudkiewicz and Tanzer, 2004; Faqeih et al., 2005; Gezdirici et al., 2010; Guernsey et al., 2011; Bicknell et al., 2011a,b; de Munnik et al., 2012]. Recently, mutations in five different pre-replication complex genes (*ORC1*, *ORC4*, *ORC6*, *CDT1*, and *CDC6*) were identified in 67% (31/46) of patients with MGS described in literature [Bicknell et al., 2011a,b; Guernsey et al., 2011]. The pre-replication complex consists of the origin

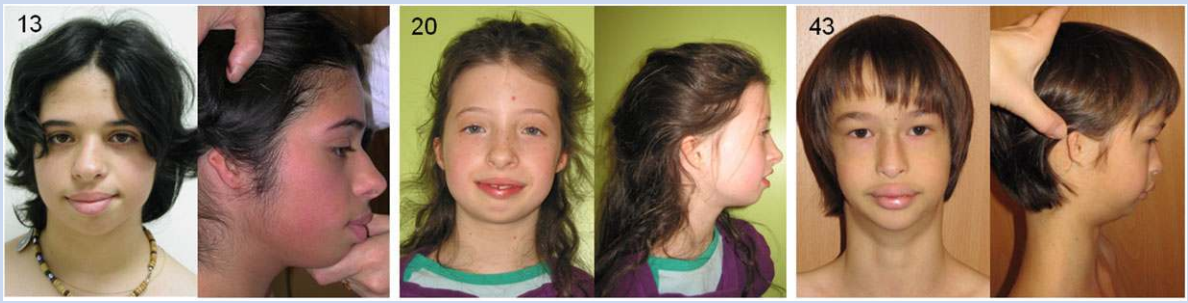

FIG. 1. Facial characteristics of three patients with Meier–Gorlin syndrome. Note the characteristic face with small, abnormally shaped ears, beaked nose, small mouth with full lips, and retrognathia. Patient 13 was previously described by Lacombe et al. [1994] and Bicknell et al. [2011a] (Case 3 and Patient 8, respectively). Patients 20 and 43 were previously described by Bongers et al. [2001] (patients 4 and 2, respectively).

recognition complex (subunits ORC1–ORC6), two regulatory proteins (CDT1 and CDC6), and the MCM helicase complex. The complex forms at origins of DNA replication and is essential for initiation of genome replication, a crucial step in cell cycle and cellular growth [Bell and Stillman, 1992; Nishitani et al., 2000]. Growth is globally reduced in MGS, presumably as a consequence of mutations slowing cell proliferation, with reported mean adult height in females of 131.6 cm (−5.6 standard deviation (SD) according to Prader et al.; range 127–148 cm, n = 5), and 147.8 cm in males (−3.3 SD according to Prader et al.; range 132–157.5 cm; n = 3) [Prader et al., 1989; Fryns, 1998; Shalev and Hall, 2003; Dudkiewicz and Tanzer, 2004; Guernsey et al., 2011; Bicknell et al., 2011a]. Growth did not improve during growth hormone (GH) therapy performed in six patients, thus far [Lacombe et al., 1994; Cohen et al., 2002; Faqeih et al., 2005; Guernsey et al., 2011; Bicknell et al., 2011b].

Reductions in growth of specific tissues are also evident, most notably affecting the patella and ear, given that microtia and patellar aplasia/hypoplasia are defining features of MGS. Microtia can vary profoundly, ranging from slightly small and normally positioned to abnormally shaped and positioned ears. Only one patient was reported to have normal sized and shaped ears [Bicknell et al., 2011b]. Additionally, genital growth may be specifically affected both evident at birth, resulting in minor genital anomalies, and during secondary sexual development, resulting in mammary hypoplasia [Gorlin et al., 1975; Lacombe et al., 1994; Buebel et al., 1996; Loeys et al., 1999; Terhal et al., 2000; Bongers et al., 2001; Shalev and Hall, 2003; Guernsey et al., 2011; Bicknell et al., 2011a].

Detailed longitudinal growth and endocrinological studies in patients with MGS have not been described and no reference curves for height, weight, and head circumference have been established. Here, we provide an overview of growth in a unique cohort of 45 MGS patients, the largest worldwide. Moreover, we describe the beneficial effect of GH treatment in two MGS patients with additional growth hormone insufficiency. Finally, we provide an overview of genital anomalies, secondary sexual characteristics, and disrupted growth of the ears in MGS.

MATERIALS AND METHODS

Patients

Pre- and postnatal growth measurements, endocrinological findings, and data regarding development of genitalia, secondary sexual characteristics, and ears of 45 patients with MGS were collected retrospectively by sending clinical questionnaires to the referring physicians and prospectively by physical examination and laboratory investigations. The cohort comprised 28 females (62%) and 17 males (38%), aged between 3 months and 47 years. Twenty patients had reached postpubertal or adult age (44%; 6 males, 14 females). Gynecologic examination, including a transvaginal ultrasound, was performed in five females. The demographic data of our cohort are summarized in Tables Ia and Ib. All patients were previously described in literature [Gorlin et al., 1975; Cohen et al., 1991; Lacombe et al., 1994; Verhallen et al., 1999; Terhal et al., 2000; Bongers et al., 2001; Feingold, 2002; Shalev and Hall, 2003; Guernsey et al., 2011; Bicknell et al., 2011a,b; de Munnik et al., 2012].

Anthropometric measurements at birth (length, weight, and head circumference for gestational age) were standardized using the growth charts from Niklasson and Albertsson-Wikland [2008]. Postnatal growth measurements (height, body mass index (BMI), and head circumference for age) were standardized according to the growth charts from Prader et al. [1989], as used by Ranke et al. [2007] in their international evaluation of growth and growth hormone therapy.

Endocrinological data (IGF1, stimulated GH, LH, FSH, estrogen, and testosterone levels) of 15 patients were available and standardized according to Rikken et al. [1998]. GH treatment was initiated in nine patients. Two of these patients (P43 and P44, Table II) were prospectively followed, seven were retrospectively analyzed.

In addition to a short stature and small head circumference, microtia is one of the most characteristic features of MGS. The ear length of 20 patients was compared to the normal values provided by Hall et al. [2007]. The ear morphology of 10 patients is shown in Figure 4. A detailed description of the ear morphology of 20 patients

TABLE Ia. Demographic Data and Data on Growth and Sexual Development of a Cohort of 45 Patients With Meier–Gorlin Syndrome

Demographic data	Meier–Gorlin syndrome	(% or range)
Total number of patients	45	
Number of females/males	28/17	(62%/38%)
Age range in years	0.3–4.7	
Region of descent		
Europe	21	(47%)
North America	14	(31%)
North Africa	4	(9%)
Middle East	3	(7%)
Asia	1	(2%)
Middle east/North America	1	(2%)
Oceania	1	(2%)
Gene mutated		
ORC1	10	(22%)
ORC4	7	(16%)
ORC6	7	(16%)
CDT1	10	(22%)
CDC6	1	(2%)
No known molecular cause	10	(22%)
Monoallelic mutation *ORC1*	1	
Monoallelic mutation *CDT1*	2	
No mutation	7	
Intrauterine growth retardation	42/43	(98%)
Mean birth weight in SD[1]	−3.4	(−6.5 to −0.3)
Mean birth length in SD[1]	−3.9	(−13.2 to 0.0)
Mean birth head circumference in SD[1]	−2.1	(−5.4 to 1.5)
Number of postpubertal/adult patients (14 F/6 M)	20	(44%)
Adult height (≥18 years)		
Mean female height in cm (7 females)	137.7	(127.0–150.8)
Mean male height in cm (2 males)	147.0	(136.5–157.5)
Mean in SD[2] for both sexes	−4.5	(−6.4 to −2.3)
Adult BMI		
Mean female BMI (5 females)	16.8	(14.3–19.8)
Mean BMI in SD[2] (5 females, 1 male)	−3.1	(−4.9 to −0.8)
Adult head circumference (≥15 years)		
Mean female head circumference in cm (12 females)	50.3	(45.6–53.0)
Mean male head circumference in cm (5 males)	51.9	(44.2–57.4)
Mean in SD[2] for both sexes	−2.4	(−5.8 to +1.3)

[1]SD calculated using the growth charts of Niklasson and Albertsson-Wikland [2008].
[2]SD calculated using growth charts of Prader et al. [1989].

according to the terminology of Hunter et al. [2009] is provided in Supplementary eTable I.

Statistical Analysis

A linear mixed model with random factor patient was used to analyze the standardized height and head circumference according to Prader et al. (random intercept model) [Leyland and Goldstein, 2001; Prader et al., 1989]. Independent fixed factors were sex, molecular cause, and region of descent. Age and age × age were included as fixed covariates. When the coefficient of age × age was not significant, that is, when there was no indication of a non-linear age trend, the analysis was repeated without age × age. In case of non-linearity, the relationships between age and growth during the first years and later years were estimated separately by including the variables age- and max (0, age-1; the latter variable represents the difference between the growth in the first year and second year). Growth data after the age of 20 years or after start of GH treatment were excluded from growth analysis. Five patients were completely excluded from analysis (three were treated with GH for an unknown duration; of one, no measurements before the age of 47 years were available; of one, no measurements were available after 17 weeks of gestation). Six patients were excluded from growth analysis after GH treatment was initiated. Four hundred fifty two measurements of 40 patients were obtained on different ages from birth throughout their childhood. Of six patients, only one measurement was available. Of 19 patients, five or more measurements were available.

TABLE Ib. Overview of Mutations Identified in a Cohort of 45 Patients With Meier–Gorlin Syndrome

Gene	Nucleotide alterations	Amino acid alterations	Hetero-/homozygous	Putative effect	Number of patients/ families
ORC1	c.266T>A	p.Phe89Ser	Homozygous	Missense	1/1
	c.314G>A	p.Arg105Gln	Homozygous	Missense	1/1
	[c.314G>A] + [c.1482-2A>G]	p.Arg105Gln + intron 9 splice acceptor site	Heterozygous	Missense + splice site	2/2
	[c.314G>A] + [c.1999_2000delGTinsA]	p.Arg105Gln + p.Val667*fs*X24	Heterozygous	Missense + frameshift	2/1
	[c.314G>A] + [c.1996C>T]	p.Arg105Gln + p.Arg666Trp	Heterozygous	Missense	1/1
	[c.314G>A] + [c.2159G>A]	p.Arg105Gln + p.Arg720Gln	Heterozygous	Missense	1/1
	c.380A>G	p.Glu127Gly	Homozygous	Missense	2/1
	[c.1721C>T]	p.Thr57Met	Monoallelic	Missense	1/1
ORC4	c.521A>G	p.Tyr174Cys	Homozygous	Missense	4/3
	[c.521A>G] + [c.874_875insAACA]	p.Tyr174Cys + p.Ala292*fs*X19	Heterozygous	Missense + frameshift	2/2
	[c.521A>G] + CNV del	p.Tyr174Cys + del	Heterozygous	Missense + deletion	1/1
ORC6	[c.2T>C] + [c.449 + 5G>A]	p.Met1? + p.?	Heterozygous	Missense + splice site	4/3
	[c.257_258delTT] + [c.695A>C]	p.Phe86X + p.Tyr232Ser	Heterozygous	Nonsense + missense	3/1
CDT1	[c.196G>A] + [c.351G>C]	p.Ala66Thr + p.Gln117His (exon 2 splicing donor site)	Heterozygous	Missense + splice site	1/1
	[c.351G>C] + [c.1385G>A]	p.Gln117His (exon 2 splicing donor site) + p.Arg462Gln	Heterozygous	Splice site + missense	1/1
	[c832G>T] + [c.1385G>A]	pGlu278X + p.Arg462Gln	Heterozygous	Nonsense + missense	2/1
	[c.1081C>T] + [c.1357C>T]	p.Gln361X + p.Arg453Trp	Heterozygous	Nonsense + missense	1/1
	[c.1385G>A] + [c1560C>A]	p.Arg462Gln + p.Tyr520X	Heterozygous	Missense + nonsense	4/2
	[c.1385G>A]	p.Arg462Gln	Monoallelic	Missense	2/1
	c.1402G>A	p.Glu468Lys	Homozygous	Missense	1/1
CDC6	c.968C>G	p.Thr323Arg	Homozygous	Missense	1/1

Biallelic mutations were found in 35 patients, monoallelic mutations in three patients. In seven patients, no mutations were detected.
Adapted from de Munnik et al. [2012].

RESULTS

Pre- and Postnatal Growth

At birth, mean length was −3.9 SD, with a mean weight of −3.4 SD, and mean head circumference of −2.4 SD according to Niklasson and Albertsson-Wikland [2008]. Mean birth length was −3.5 SD according to Prader et al. [1989]. In the first year after birth, length dropped significant with 1.7 SD ($P < 0.0001$) to −5.2 SD, relative to the general population. In other words, infants with MGS are small at birth, but become even smaller in the first year of life, compared to the general population. Thereafter, height remained below, but increased in parallel with the population centiles (nonsignificant gain of 0.08 SD/year, until age 15 years ($P > 0.05$)). Afterwards, (between age 15 and 18 years) no reliable trend could be calculated. Mean adult height (≥18 years of age) was −4.5 SD (females 137.7 cm, males 147.0 cm), with a BMI of −3.1 SD (females 16.8 kg/m^2, one male 15.0 kg/m^2), and head circumference of −2.4 SD (females 50.3 cm, males 51.9 cm). Stature was proportionate, except in two previously described adult females (P21 and P22) without known molecular cause [Terhal et al., 2000]. One of these females had a span of 136 cm and a height of 149 cm, the other had a span of 134 cm and a height of 143.6 cm.

Height appeared to be significantly affected by ethnic origin ($P < 0.0001$): patients from the Middle East were shortest, followed by patients from North America, Europe, and North Africa. In contrast, BMI and head circumference were not significantly influenced by age or ethnic background compared to normal ($P > 0.05$).

Height and head circumference were significantly influenced by the underlying molecular cause ($P < 0.0001$). Patients with mutations in *ORC1* or *ORC4* had a significantly shorter stature and smaller head circumference than patients with mutations in other genes (*ORC6*, *CDT1*, *CDC6*, or unknown genes), such that they were 4.7 SD (*ORC1*) and 3.1 SD (*ORC4*) shorter than the others (after adjustment for ethnic origin). For head circumference, the differences were 5.0 SD and 1.6 SD, respectively.

Prenatal and postnatal growth data are summarized in Table Ia. The trends for height, BMI, and head circumference for age, using the standardized growth charts according to Prader et al. [1989], are illustrated in Figure 2a. In Figure 2b, the proposed reference growth chart for height of MGS patients, derived from this data analysis, is shown. The difference between the reference growth curve and the normal curve corresponds to the average difference for our patient population. For individual patients the difference may depend on ethnic background, gender, and mutated gene. However, the slope of the curve (growth velocity) is independent of these factors.

Growth Hormone Levels and Growth Hormone Treatment

GH status, assessed by IGF1 and/or stimulated GH measurements, was normal in 12 out of 15 (80%) patients tested. Low IGF1 levels

TABLE II. Growth Hormone Levels and the Effect of Growth Hormone Treatment in Nine Patients With Meier–Gorlin Syndrome

Patient	Sex	Gene mutated	Mutations	IGF1 (SD)	GH stimulation	Skeletal age CA—SA (years)	Age at start GH treatment (years)	Height at start GH treatment (SD)	Age at end GH treatment (years)	Height at end GH treatment (SD)	Catch up ≥2 SD
5[1]	F	*ORC1*	[c.314G>A] [c.1482-2A>G]	−1.07	N	U	4.5	−7.3	6.1	−7.3	−
9	F	*ORC4*	[c.521A>G] [c.874_875insAACA]	U	N	3–1.2	3.1	−7.1	10	−5.3	−
10[3]	F	*ORC4*	[c.521A>G] [c.521A>G]	U	U	U	U	U	15	−5.5	−
11[3]	F	*ORC4*	[c.521A>G] [c.521A>G]	U	U	U	U	U	15	−5.8	−
27[4]	M	*ORC1*	[c.380A>G] [c.380A>G]	N	S	U	U	U	4.5	−5.2	−
38[2]	M	*CDT1*	[c.1385G>A] [c1560C>A]	U	U	U	3.5	U	7.5	−4.7	−
42[1]	M	*CDC6*	[c.968C>G] [c.968C>G]	−0.8	U	15–12.5	2.5 7.5	−4.0[7] −4.3	6.7 16	−4.1 −3.5	−
43[5]	M	U		−4.6	L	11.5–10	3	−6.8	14	−3.0	+
44[6]	M	U		−3.3	N	5.3–3	5.4	−5.7	7.4	−3.7	+

CA, chronological age; SA, skeletal age; GH, growth hormone; N, normal; S, suboptimal; L, low.
[1]Patients 5 and 42 were previously described by Bicknell et al. [2011a] (patients 4 and 18) and Bongers et al. [2001] (patients 1 and 3).
[2]Patients 9 and 38 were previously described by Bicknell et al. [2011a] (patients 5 and 11).
[3]Patients 10 and 11 were previously described by Bicknell et al. [2011a] (patients 6 and 7), Bongers et al. [2001] (P5 and 6), and Guernsey et al. [2011] (1,768 and 1,769).
[4]Patient 27 was previously described by Bicknell et al. [2011b] (patient 1).
[5]Patient 43 was previously described by Bongers et al. [2001] (patient 2).
[6]Patient 44 was not previously described.
[7]Measurement at the age of 4 years, 1.5 years after the start of GH therapy.

were detected in one female (−2.3 SD; P21) and two males (−4.6 and −3.3; P43 and P44, respectively, described below). The female was never treated with growth hormone.

GH therapy was initiated in 9 out of 45 patients (20%). An overview of their GH status, skeletal age, the period of GH treatment, and effect on height is presented in Table II. GH status was normal in seven patients, but abnormal in two (P43 and P44). Skeletal age according to Greulich and Pyle [1959] was delayed in four patients and unknown in five. A positive effect of GH treatment was seen in the two prospectively followed male patients (22%; P43 and P44, Fig. 3a,b, Table II). In both patients, height continued to decrease, even after the infancy period, up to the age of 1.5 years, and to standard deviations of −7 and −6.5. In both, strikingly low IGF1 levels were detected, up to −4.6 SD, with stimulated GH levels of 11.4 and 26 mIU/L. Growth hormone treatment resulted in an increase of height velocity in the first year of treatment from approximately 5 cm/year to more than 10 cm/year, with a total gain of 2 SD and 3.8 SD within 2 years after the start of treatment, respectively.

Abnormalities of Genital and Secondary Sexual Development

Minor anomalies of external genitalia were present in 19 out of 45 patients (42%). Cryptorchidism was seen in 11 out of 17 males (65%; 3 bilateral, 1 unilateral, 5 unknown), micropenis was present in two out of 17 males (12%), hypospadias in one (6%). Hypoplastic labia majora or minora were present in seven out of 28 females (25%).

Transvaginal ultrasound investigations were performed in 5 out of 14 postpubertal females. A small uterus and polycystic ovaries were observed in two females, while no abnormalities were detected in two others. In the fifth female (P22), ultrasound investigations, which were performed after premature delivery, showed a shortened uterus with a probe length of 4–5 cm. This female had two miscarriages after 17 and 18 weeks, respectively. No fetal anomalies were detected by ultrasound investigation and autopsy. These were the first two pregnancies in a patient with MGS.

Secondary sexual development was affected in 17 out of 20 patients (85%, males and females). Axillary hair was sparse or absent in 9 out of 12 patients (75%; 3 males, 6 females; 8 unknown), pubic hair was sparse in 1 out of 10 patients (10%; male; 10 unknown). Mammary hypoplasia was present in all 14 postpubertal females. However, menarche had occurred at a normal age (before age 14.5 years) and menstrual cycles were regular in these females. Though endogenous hormonal levels were normal, exogenous estrogen treatment was initiated in five females. An increase in breast size was reported in two females. A very mild increase was observed in a third female, after treatment with 100 μg ethinylestradiol between 16 and 18 years of age. In contrast, no increase in breast size was seen in two other females treated with 20 μg ethinylestradiol between 13.5 and 16 years of age. Hypoplastic nipples were reported in one male, but nipples were not hypoplastic in six postpubertal females (unknown in the other eight females).

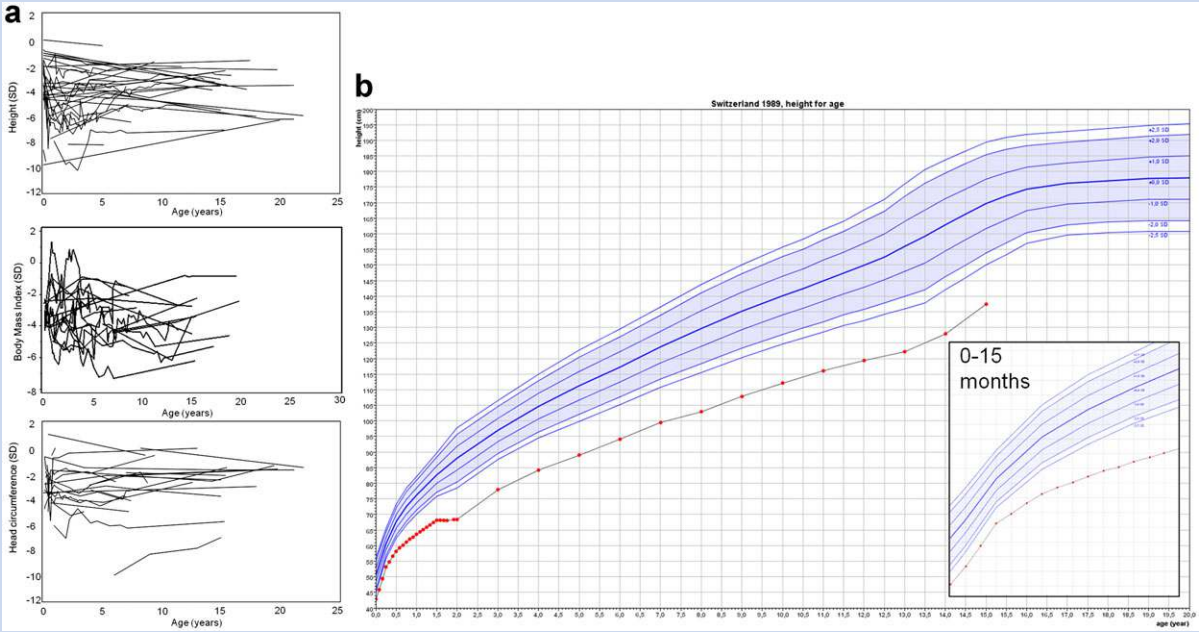

FIG. 2. a: Trends for height, body mass index, and head circumference of 33 patients with Meier–Gorlin syndrome. Growth measurements for both sexes were standardized according to the growth charts of Prader et al. [1989]. Height dropped significantly with 1.7 SD in the first year after birth ($P < 0.0001$) and increased with an average of 0.08 SD per year afterwards, until age 15 years ($P > 0.05$). Between age 15 and 18, insufficient data were available for statistical analysis. Head circumference and BMI were not significantly influenced by age ($P > 0.05$). There were no differences in growth patterns between males and females. b: Proposed growth charts for patients with Meier–Gorlin syndrome. This growth chart is based on the trends in a cohort of 33 patients with Meier–Gorlin syndrome. Here, the growth pattern (height for age) is shown in comparison to the growth charts for boys of Prader et al. [1989]. This growth pattern is the same for males and females. After 15 years of age, insufficient data were available to calculate a reliable statistical trend. These data can be applied to predict height in an individual MGS patient: the growth chart of an individual patient will differ from this chart in actual height (i.e., in distance relative to the normal growth chart), but follow the same pattern of growth velocity (i.e., shape) as our proposed chart.

Ears

Microtia (ear length < -2 SD) was present in 44 out of 45 MGS patients (98%). The mean right ear length was -5.8 SD (20 patients, range -7.3 to -3.1 SD), the mean left ear length -5.3 SD (20 patients, range -7.9 to -3.2 SD). Most ears were small, with a shelved antihelix, prominent crus, and small or absent ears lobes. The ear anomalies of 10 MGS patients are shown in Figure 4. A detailed description according to the morphology of Hunter et al. [2009] of the ear malformations of 20 patients is provided in Supplementary eTable I.

DISCUSSION

In this first retrospective and partially prospective study of growth in patients with MGS, we show that the growth retardation in MGS predominantly arises prenatally and in early infancy. Mean birth length was -3.5 SD [Prader et al., 1989]. In the first year of life, relative length further decreased to -5.2 SD. In the following years, growth velocity stayed normal with a height curve nearly parallel to normal and a mean adult height of -4.5 SD. This pattern is consistent with an intrinsic growth problem of reduced cellular proliferation, though, surprisingly, growth velocity post infancy is not perturbed. Alternatively, placental dysfunction could potentially cause growth impairment in MGS prenatally, while feeding problems, present in almost all MGS patients during the first year of life, might contribute to the growth retardation.

Global growth, as reflected by both height and head circumference, was influenced by the underlying molecular cause: *ORC1* mutations caused the most severe growth retardation, followed by *ORC4* mutations. This might represent a differential sensitivity to efficient DNA replication, of mutations in different pre-replication complex subunits, or simply reflect the strength of specific mutations, of which there are a limited number in each subunit so far reported. However, the limited number of patients with a mutation in one of the five pre-replication complex genes and the inclusion of patients with all features of the classical triad of clinical characteristics might have introduced ascertainment bias in these results. Centile charts for height, weight, and head circumference cannot be established given the rarity of this condition, the restricted size of our cohort and the lack of measurements at standardized ages.

Our data have clinical utility and will be useful in predicting the growth pattern during different stages of life of future patients with MGS. Our data can be used to predict the height of a patient, since height decreases with 1.7 SD during the first year of life and the growth velocity is nearly equal to the normal growth velocity

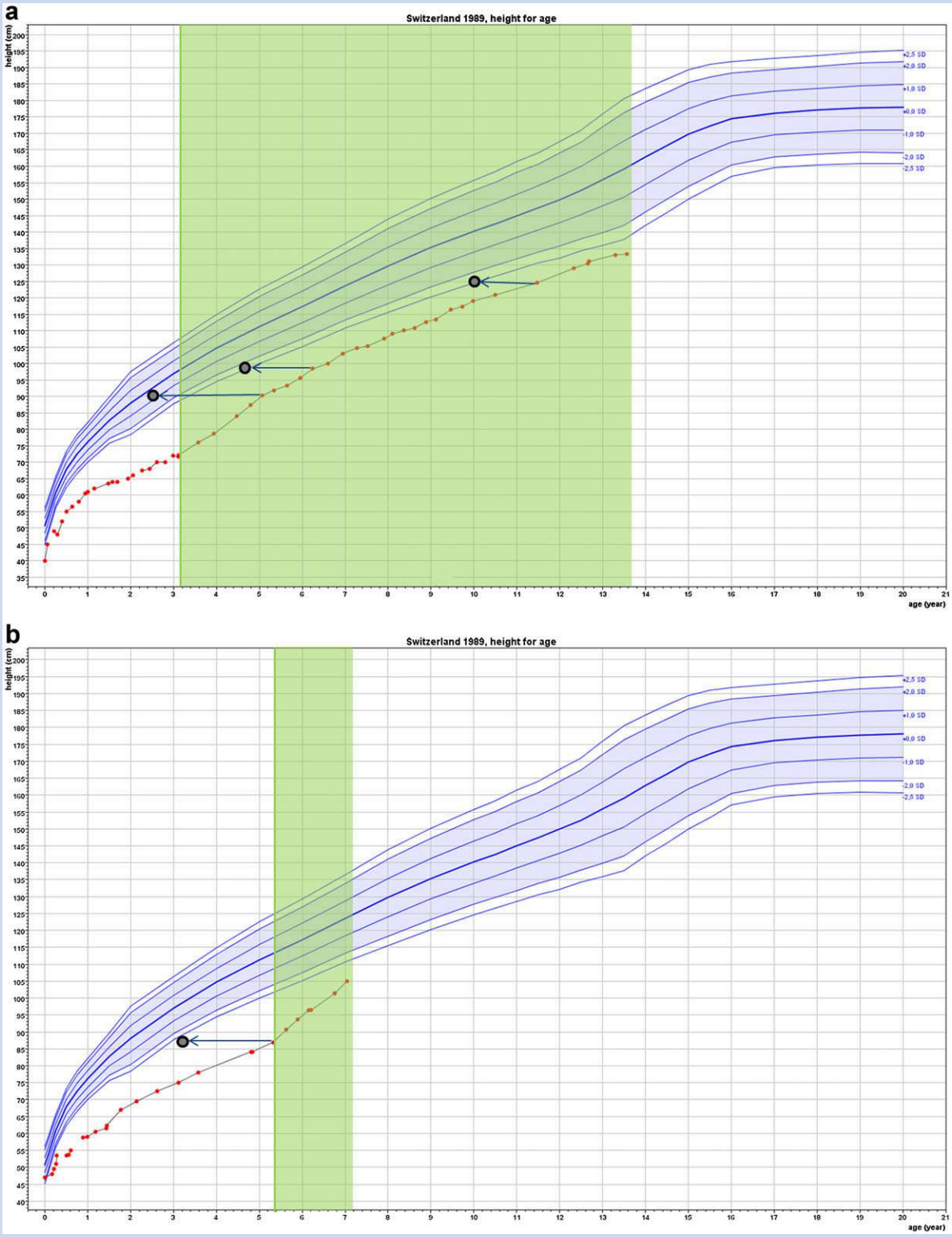

FIG. 3. a,b: Growth charts of two patients with Meier–Gorlin syndrome showing a positive response to growth hormone treatment. Height for age is compared to the growth charts of Prader et al. [1989]. The green highlighted areas represent the period of GH treatment. The black/gray dots and arrows represent the bone age at that age. a: Growth chart of Patient 43 (Table II; Bongers et al. [2001] Patient 3), height improved 3.8 SD during GH therapy. b: Growth chart of Patient 44 (Table II; de Munnik et al. [2012] individual i) height improved 2 SD during GH therapy.

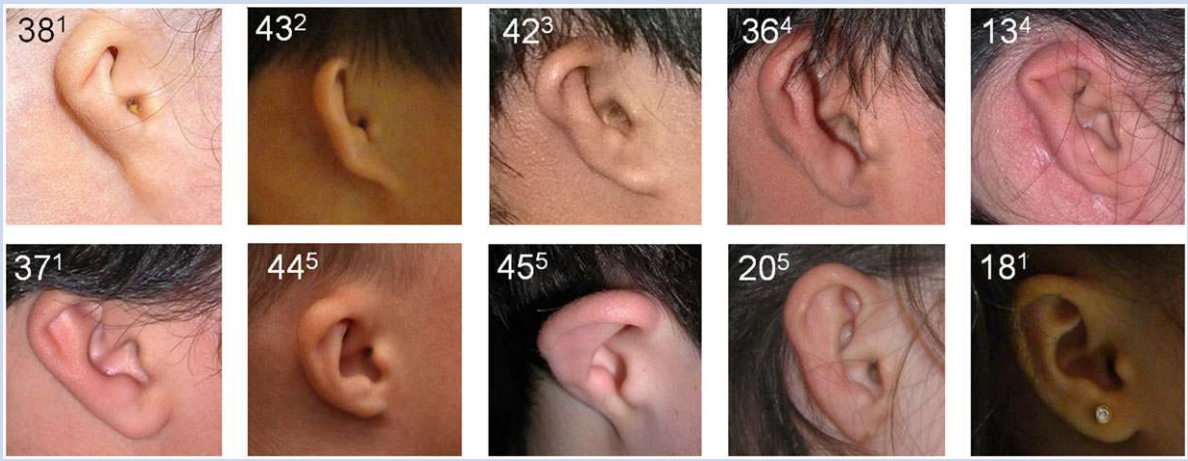

FIG. 4. The ear morphology of 10 patients with Meier–Gorlin syndrome. The ears are arranged from most (P38) to least underdeveloped (P18, only microtia). Common features were microtia (10; 100%), a shelved antihelix (4; 40%), prominent crus helix (5; 50%), and small or absent ear lobes (6; 60%). A detailed description of the ear anomalies in 20 MGS patients is provided in Supplementary eTable I. [1]Patients 38, 37, and, 18 were previously described by Bicknell et al. [2011a] (patients 10, 11, and 17). [2]Patient 43 and 20 were previously described by Bongers et al. [2001] (Patient 4 and 2, respectively). [3]Patient 42 was previously described by Bicknell et al. [2011a] (Patient 18) and Bongers et al. [2001] (Patient 3). [4]Patients 36 and 13 were previously described by Bicknell et al. [2011a] (patients 8 and 9) and Lacombe et al. [1994] (patients 2 and 3). [5]Patients 44 and 45 were previously described by de Munnik et al. [2012] (individual i).

thereafter (Fig. 2b). The actual height of the proposed growth chart of Figure 2b corresponds to the average height of our patient group. Corresponding curves for individual patients with different gender, ethnic background, or mutated gene, would lie closer to or further away from the normal curve according to Prader et al. [1989], but the growth velocity is independent of these factors, so they would all run parallel to our proposed growth chart of Figure 2b. This is in contrast to growth curves in other syndromes, such as Achondroplasia or Turner's syndrome [Horton et al., 1978; Park et al., 1983].

In two MGS patients, growth hormone treatment turned out to be successful in improving height. Growth patterns in these patients differed from the general pattern in our cohort, because growth velocity continued to be reduced after early infancy and in particular, extremely low IGF1 levels were found (Table II). Notably though, these two patients had a classic MGS phenotype with microtia and patellar aplasia and the underlying molecular cause is currently unknown for both of them. It is tempting to speculate that the gene causing MGS in these two patients might play an important role in the growth hormone axis. Furthermore, this suggests that IGF1 measurements can be used to target treatment to a subset of MGS patients that will respond to GH therapy, in contrast to those with mutations in the pre-replication complex, who appear unlikely to benefit from GH therapy.

Mammary hypoplasia was present in all postpubertal females. Besides an early disturbance of embryonic development, (partial) insensitivity to estrogen as a cause of secondary sexual underdevelopment may be considered. This would explain the lack of response to estrogen treatment in two patients with mammary hypoplasia. However, the presence of normal menstrual cycles in these patients contradicts this theory.

In the future, further prospective growth studies would be useful to confirm our results and establish more detailed growth charts, as well as more systematically assessing the effect of GH treatment in MGS patients. Further studies of an increased number of MGS patients with a known molecular cause and elucidation of the genetic defect in MGS patients with a yet unknown molecular cause will further define the phenotypic spectrum of MGS, including growth.

Finally, animal studies (mouse models) might contribute to gain insight into the embryonic development of MGS patients and unravel pathogenic mechanisms underlying the growth retardation and underdevelopment of genitalia, secondary sexual characteristics, and ears in MGS.

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