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Childhood overgrowth in patients with common *NF1* microdeletions

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While growth retardation and short stature are well-known features of patients with classical neurofibromatosis type 1 (NF1), we found advanced height growth and accelerated carpal bone age in patients with an *NF1* microdeletion. Our analysis is based on growth data of 21 patients with common 1.4/1.2 Mb microdeletions, including three patients with a Weaver-like appearance. Overgrowth was most evident in preschool children (2–6 years, $n = 10$, $P = 0.02$). We conclude that childhood overgrowth is part of the phenotypic spectrum in patients with the common 1.4/1.2 Mb *NF1* microdeletions and assume that the chromosomal region comprised by the microdeletions contains a gene whose haploinsufficiency causes overgrowth.

Introduction

Growth alterations in neurofibromatosis 1 (NF1) have first been described in the early 1950s.[1] Today, short stature and macrocephaly are well-recognized traits of this disorder.[2–9] Another form of growth anomaly associated with NF1 was reported by van Asperen *et al*, who observed the combination of NF1 with overgrowth and features resembling Weaver syndrome in a mother and her son. They attributed this unusual phenotype to a large *NF1* microdeletion in

17q11.2.[10] Weaver syndrome, first reported in 1974, is characterized by overgrowth in childhood (both height and occipitofrontal head circumference (OFC) above the 97th centile), markedly advanced carpal bone age, developmental delay, and distinctive facial appearance.[11] The genetic basis of this mostly sporadic syndrome has not been completely elucidated. Although Douglas *et al* (2003) and Rio *et al* (2003) found *NSD1* mutations in a group of patients with a diagnosis of Weaver syndrome, *NSD1* mutations could not be detected in other Weaver syndrome patients.[12–14]

In approximately 5% of all cases, NF1 is caused by microdeletions in 17q11.2.[15–17] The most common deletion (type I) encompasses 1.4 Mb and comprises 14 genes. The less frequent type II deletion spans 1.2 Mb and

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contains only 13 of these genes.[18,19] The breakpoints of type I deletions are localized within the *NF1* low-copy repeats (LCRs), those of type II deletions are within the *JJAZ1* gene and its pseudogene, suggesting that both deletions result from unequal homologous recombination.[19–21] Patients with *NF1* microdeletions present with a recognizable phenotype: (i) early and severe manifestation of NF1 signs, that is, development of neurofibroma and increased risk of malignancy, (ii) coarse facial appearance with prominent nose and large ears, and (iii) mild to moderate mental retardation.

Although a large number of reports dealing with *NF1* microdeletions have been published since the first report by Kayes *et al*[22] in 1992, little is known about growth profiles in such patients. Here, we report the growth data of 21 patients with the common 1.4/1.2 Mb *NF1* microdeletions. In contrast to classical NF1, overgrowth – particularly during childhood – is a frequent finding in these patients. Weaver-like features in three of them confirm a case report by van Asperen *et al*[10] (see above) and indicate that Weaver-like appearance belongs to the phenotypic spectrum associated with the common *NF1* microdeletions.

Patients and methods

Clinical data were taken into account up to the date of submission of the present paper. Values of height and OFC were available for 21 patients with the common 1.4/1.2 Mb *NF1* microdeletions (16 children and five adults, including three parent–child pairs, LIY-LIR, WEM-WER, KAA-KAE). The age of the 13 male patients ranged from 0 (birth) to 31 years, the age of the eight females from 2 to 45 years.

The presence and extension of the *NF1* microdeletions were determined as described by Tinschert *et al*.[23] In all, 19 patients had a type I deletion, as indicated by the lack of BAC 307A16 hybridization. In two patients (the parent–child pair LIY–LIR), this BAC clone produced a reduced signal intensity suggestive of a type II deletion.[19] Patients with unusual deletions (ie, smaller or larger than the 1.4/1.2 Mb common deletions) were not included in the study.

In three patients (COS, ERS, PFA), the facial aspect reminded of Weaver syndrome (Figure 2). In two of them (COS and PFA), the deletion breakpoints were determined by deletion junction-specific PCRs and found to be located in the 4 kb hotspot interval of the type I deletion.[24,25]

Four patients with optic pathway glioma were not included in the present study since optic glioma is a rare cause of overgrowth and precocious puberty.[26–30] Precocious puberty was noticed in patient COS. However, it occurred at a borderline age of 7.8 years. Therefore, his early growth data (until the age of 6 years) and bone age data (determined at an age of 1.5 years) were taken into account. Other anatomical abnormalities reported to occur in *NF1* microdeletion patients such as callosal dysgenesis

(GUN) or agenesis (WEH), septum pellucidum cyst (SCH), moderate dilation of lateral ventricles (KRE, WEH), and non-occlusive aqueductal stenosis (WER) did not lead to exclusion.[31] Brain MRIs were available for the majority of patients in this study (BAH, BUC, COS, HIN, KRE, LIR, MUE, PFA, SCH, WEH, WEM, WER, and WOL).

Height and OFC data of the patients were compared to general population and NF1 standard growth charts (http://www.medgen.ubc.ca/friedmanlab/growthpatterns/growthpatterns.html).[8] Carpal and phalangeal bone age was assessed according to the standard method of Greulich and Pyle using X-ray images of the left hand.

Statistical analysis

The length data of male and female probands were compared to the respective distributions of both the general population and the NF1 population. Statistical analysis was performed in the age group of preschool children between 2 and 6 years. The mean $\mu(t)$ and standard deviation $\sigma(t)$ of every age t in this group were calculated from the $P_{50}(t)$ and $P_{95}(t)$ centiles of the reference populations (see Figure 1) by assuming normal distributions, that is, $\mu(t) = P_{50}(t)$ and $1.65\,\sigma(t) = P_{95}(t) - P_{50}(t)$.[8,32] Then, in order to overcome the age dependency of the data, the deviation of each proband's length $L_i(t)$ from the age-dependent mean $\mu(t)$ was divided by the age-dependent standard deviation $\sigma(t)$. Thus, an age-*in*dependent standard deviation score $z_i = (L_i(t) - \mu(t))/\sigma(t)$ was produced for each proband's length. If the length data of a proband were available from different ages, the average of the proband's z-scores was used in the statistical analysis. For calculation of the significance level P, $\bar{z}$ was divided by its estimated standard deviation and compared to a Student's distribution with $(n-1)$ degrees of freedom (ie, one-sample t-test).[32] Statistical analyses of head size (OFC) and of predicted adult height (ie, average of the parents' heights plus 6.5 cm in boys and minus 6.5 cm in girls, respectively[33]) were performed analogously.

Results

Height growth data are depicted in Figure 1. Overgrowth at preschool age (2–6 years) is evident. Data from this age were available for $n=7$ male patients. With one exception (NOI), all were at or above the 95th centile of classical NF1. Five of them even were at or above the 95th centile of the general population. The average standard deviation score $\bar{z}$ of male *NF1* microdeletion patients in the age group of 2–6 years was 1.4 ($P=0.01$) compared to the general population and 1.8 ($P=0.005$) compared to the classical NF1 population. The average predicted adult height of these patients as derived from the parents' heights did not differ significantly from male adult height in the general population (mean ± SD = 179.7 ± 5.5 cm, $\bar{z}=0.40$, $P=0.24$).
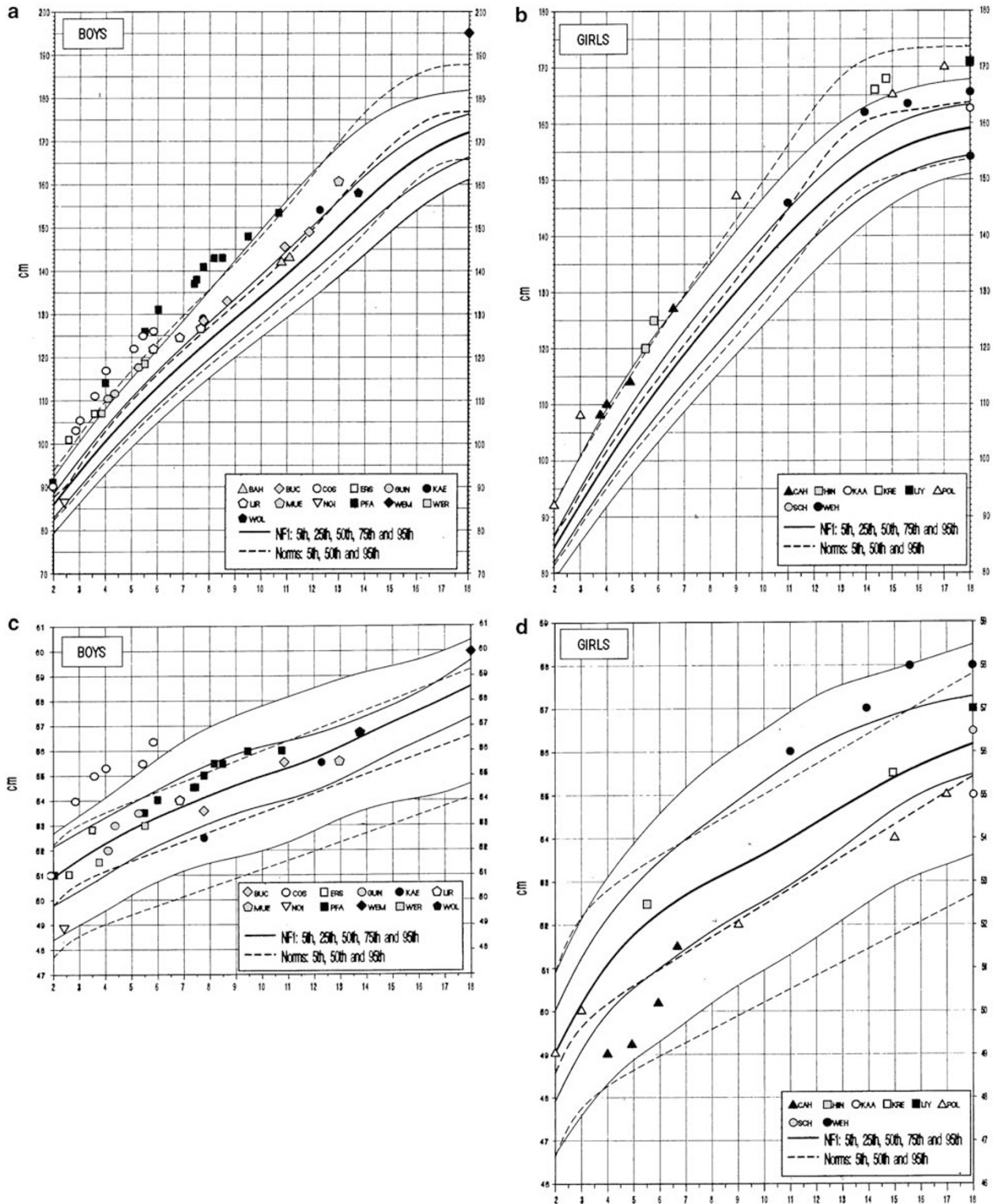
Figure 1 Growth of height and OFC in patients with common *NF1* microdeletions. Height, males (**a**) and females (**b**). OFC, males (**c**) and females (**d**). Growth charts are available at http://www.medgen.ubc.ca/friedmanlab/growthpatterns/growthpatterns.html.

Data were less abundant in older patients. However, during the second decade all patients were above the 50th, most of them at or above the 75th centile of classical NF1 and, with one exception (WOL), at or above the 50th centile of the general population. For adult male patients data were sparse.

Similar to the male patients, preschool height measures of female patients with common *NF1* microdeletions (available for $n = 3$ patients) were at or above the 95th centiles ($\bar{z} = 2.2$, $P = 0.01$, if compared to the general population; and $\bar{z} = 2.0$, $P = 0.01$, if compared to the classical NF1 population). As in the male group, the average predicted adult height of preschool girls did not differ significantly from female adult height in the general population (mean $\pm$ SD $= 167.5 \pm 3.6$ cm, $\bar{z} = 0.66$, $P = 0.09$). The height of five adolescent and adult females was above the 75th centile of classical NF1 and above the 50th centile of the general population. The short stature of patient SCH was at least in part due to her scoliosis.

A combination of male and female probands' height data at age 2–6 years ($n = 10$) resulted in $\bar{z} = 1.7$, $P < 0.001$, compared to the general population; and $\bar{z} = 1.8$, $P < 0.001$, compared to the classical NF1 population, whereas the average predicted adult height based on parent's heights was not significantly increased ($\bar{z} = 0.48$, $P = 0.11$). If (in order to exclude an influence of familial growth patterns definitively) for each proband the predicted height score (based on parent's heights) was subtracted from the presented height score (based on individual lengths data), childhood overgrowth was also significant ($\bar{z} = 1.2$, $P = 0.02$, compared to the general population; and $\bar{z} = 1.3$, $P = 0.01$, compared to the classical NF1 population).

Head sizes (OFC) of *NF1* microdeletion patients were similar to patients with intragenic mutations and, as expected, larger than those of the general population. In boys, the difference from the general population was significant ($P = 0.03$) already at the age of 2–6 years and became obvious in both genders when older probands were included in the analysis (males, $P = 0.002$; females, $P = 0.05$; data not shown).

Table 1 Carpal and phalangeal bone age acceleration

Patient	Chronological age (years)	Carpal bone age acceleration (years)	Phalangeal bone age acceleration (years)
COS	1.42	+1.58	+1.08
PFA	1.58	+0.42	−0.08
	6.25	+2.75	−0.25
ERS	2.66	+0.84	+0.16
	3.50	+1.00	+1.00
WER	4.25	+1.25	+0.75
GUN	4.50	+2.00	+2.00
LIR	6.83	+0.77	+1.17
KAE	12.25	+1.75	+1.75
MUE	13.00	+0.50	+0.50

Bone age data were available from eight patients (Table 1). In six patients (COS, ERS, GUN, KAE, PFA, WER), carpal bone age was advanced by more than one year, four of them (COS, GUN, LIR, KAE) also showed advanced phalangeal age.

Discussion

Macrocephaly and short stature are regarded as distinctive traits of NF1 and result from *NF1* haploinsufficiency. Several groups published anthropometric measurements and growth charts for NF1 patients.[6–9,34] It was shown that height growth was nearly normal during childhood but decreased with increasing age.[6,7,9] Patients with the common *NF1* microdeletions, however, display distinct growth anomalies. In contrast to classical NF1 patients, childhood overgrowth occurs in these patients. Previously published data on individual patients with *NF1* microdeletions are sparse and an age dependency of their growth patterns has not been reported. Fragmentary information on 43 patients can be found in the literature. In support of our results, 12 of those were also reported with overgrowth or advanced growth (above the 90th centile of the general population).[10,16,35–40]

In addition to childhood overgrowth, we found evidence of bone age acceleration in *NF1* microdeletion patients. This also contrasted with findings in classical NF1 patients whose prepubertal bone age is delayed by 1–2 years.[6]

The cause of childhood overgrowth in patients with *NF1* microdeletions remains to be elucidated. Precocious puberty is a possible explanation. However, precocious puberty occurred only in one of our patients (COS) and not before he was 7.8 years old. Optic glioma, a rare cause of overgrowth in some patients with classical NF1, cannot serve as a general explanation of the observed overgrowth in *NF1* microdeletion patients; furthermore, optic glioma led to exclusion from the present study.[26–30] Incidentally, however, the boy reported by van Asperen *et al*[10] had an optic glioma.[16]

We suggest that haploinsufficiency of a gene located within the common *NF1* microdeletions – but different from the *NF1* gene itself – may cause increased growth during childhood, possibly by influencing skeletal maturation. On the basis of our data, it is not yet possible to make a definitive statement concerning adolescent height growth of patients with common *NF1* microdeletions.

Simultaneous occurrence of NF1 and overgrowth reminiscent of Weaver syndrome was reported before in a mother and her son who had a large microdeletion in 17q11.2.[10,16] Weaver syndrome was suspected because in addition to overgrowth there was advanced skeletal maturation, craniofacial dysmorphism, developmental delay, prominent fingerpads, and umbilical hernia.[11,41] In
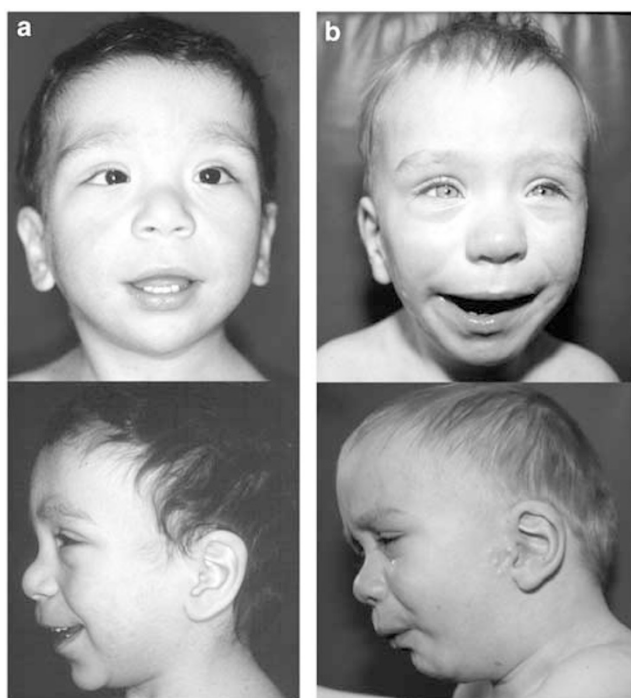
Figure 2 Facial appearance of patients COS (**a**) and PFA (**b**) with features resembling Weaver syndrome, that is, coarse face, broad forehead, broad nasal bridge, epicanthus, long and prominent philtrum, retrognathia, large ears, and short neck. Other features typical of Weaver syndrome but not present in other *NF1* microdeletion patients were not observed.

their facial appearance, the patients COS, PFA (Figure 2), and ERS closely resemble this overlapping NF1-Weaver-like phenotype. As determined by FISH analysis, all three patients have the common 1.4 Mb spanning deletion type I. For patients COS and PFA, it was possible to assign the breakpoints within the *NF1* LCRs to a 4 kb hotspot interval of deletion breakpoints.[25]

Patients with *NF1* microdeletions usually present with learning disability or mental retardation, coarse face with broad nasal bridge, down-slanting palpebral fissures, large nose, small/pointed chin, large ears with thick helices, and macrocephaly.[16,22,35,37–39,42–48] Our data indicate that childhood overgrowth and, in some cases, Weaver-like facial appearance belong to the phenotypic spectrum associated with the common *NF1* microdeletions. If occurring in patients with NF1, these signs should prompt the appropriate molecular cytogenetic evaluation.

At present, most of the genes from the deleted interval are completely uncharacterized and information on their expression during bone maturation and growth is not available. Overgrowth and anomalies of bone maturation have been observed in autosomal dominant syndromes such as Sotos syndrome (associated with *NSD1* mutations, OMIM #117550), and Bannayan–Riley–Ruvalcaba syn-

drome (*PTEN*, OMIM #153480). These syndromes are caused by anomalies in receptor-mediated signalling pathways (*PTEN*) or transcriptional regulation (*NSD1*). With these dominantly inherited syndromes in mind, we are being enticed to speculate that one of the partially characterized genes, centaurin alpha-2 (*CENT2A*), a regulator of phosphoinositide signalling or *JJAZ1/SUZ12*, a regulator of histone methylation, is modifying the NF1 phenotype due to a partial loss of functional activity.[49–52] The hemizygous expression of such a gene may also facilitate the growth and progression of neurofibromas after the loss of the second normal *NF1* allele. Further evaluation of these genes during bone development and maturation will clarify whether the deletion of one or both of them is a genuine cause of overgrowth including a Weaver-like phenotype and of the accelerated tumor growth in patients with the 17q11.2 common microdeletions.

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