Original Article

Acanthosis nigricans in a Japanese boy with hypochondroplasia due to a K650T mutation in *FGFR3*

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Abstract. Acanthosis nigricans (AN) is observed in some cases of skeletal dysplasia. However, AN has occasionally been reported in patients with hypochondroplasia (HCH), and a clinical diagnosis is sometimes difficult when its physical and radiological features are mild. Mutations in the gene encoding the fibroblast growth factor receptor 3 (*FGFR3*) have been identified as the cause of some types of skeletal dysplasia, which is diagnostically useful. Here, we report the case of a 3-yr-old Japanese boy who presented with AN. His height, weight, head circumference, and arm span were 91.7 cm (–1.95 SD), 16.3 kg, 54.0 cm (+2.6 SD), and 88.0 cm, respectively. In addition to the AN, he also exhibited a mild height deficit and macrocephaly, which prompted a search for *FGFR3* mutations, although no skeletal disproportion, exaggerated lumbar lordosis, or facial dysmorphism was observed, and only slight radiological abnormalities were noted. A definitive diagnosis of HCH was made based on *FGFR3* gene analysis, which detected a heterozygous K650T mutation. Insulin insensitivity was not found to have contributed to the development of AN. In individuals with AN, careful assessments for symptoms of HCH are important, regardless of the presence or absence of a short stature, and *FGFR3* gene analysis is recommended in such cases.

Key words: hypochondroplasia, acanthosis nigricans, FGFR3

Introduction

Hypochondroplasia (HCH) is an autosomal dominant form of skeletal dysplasia and shares several phenotypic features with achondroplasia (ACH), including a disproportionately short stature, shortened limbs, lumbar lordosis, macrocephaly, and facial dysmorphism, etc. However, these features are less obvious than those of ACH, which often makes it difficult to make a definitive diagnosis for HCH, especially until early childhood (1). For these reasons, HCH is usually diagnosed later in childhood when the patient's short stature has become more obvious.

Acanthosis nigricans (AN) involves velvety and pigmented (brown) hyperkeratosis of the skin. It is usually found in bodily folds, such as

the posterior and lateral folds of the neck, the armpits, groin, navel, forehead, and other areas. AN is commonly observed in children with severe obesity and type 2 diabetes (2, 3). In addition, it is an important clinical feature of more severe forms of skeletal dysplasia than HCH, including ACH, thanatophoric dysplasia (TD), and severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) (4, 5). However, AN has occasionally been reported in patients with HCH.

Mutations in the gene encoding fibroblast growth factor receptor 3 (*FGFR3*) are known to cause skeletal dysplasia, including ACH, HCH, TD, and SADDAN, and *FGFR3* gene analysis allows for the early diagnosis of such conditions (6). Various mutations have been identified in codon 650 of *FGFR3*, including K650N and K650Q in HCH (7), K650M in TD1 and SADDAN, and K650E in TD2 (5).

We report the case of a Japanese boy who developed AN coexisting with a mild height deficit, which prompted us to perform an *FGFR3* mutation analysis. A K650T missense mutation was identified. To the best of our knowledge, this is the third reported case of HCH combined with AN due to a K650T mutation in *FGFR3*.

Case Report

The patient was a 3-yr-old healthy Japanese boy. He was born at 37 wk of gestation after an uneventful pregnancy and delivery. His height and weight at birth were 49.0 cm (0 standard deviations [SD]) and 2,883 g (–0.29 SD), respectively. His father's height was 178 cm, whereas his mother's height was 158 cm. He had no family history of a short stature or skin pigmentation. At 1 yr of age, skin pigmentation was noted on his whole body, especially his forehead, neck, and axilla, which had developed gradually. At 3 yr and 10 mo of age, he presented to the dermatology department with pigmentation, which was clinically diagnosed as AN (Fig. 1). He was then referred to our
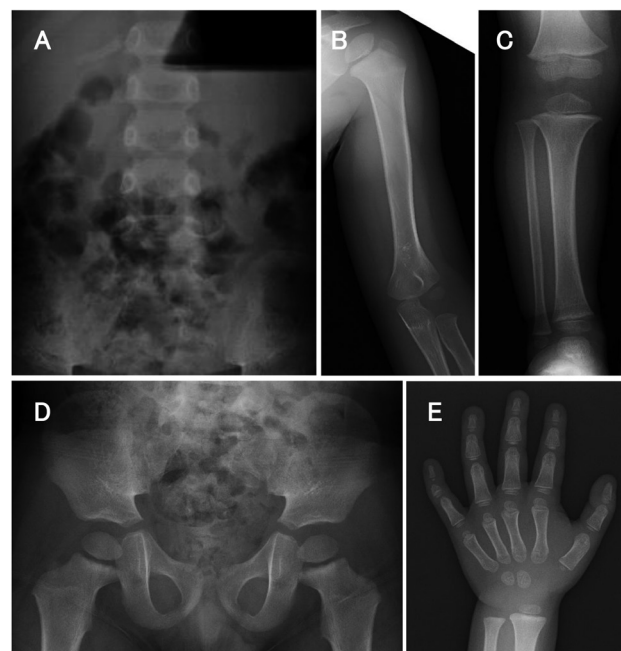

Fig. 1. The patient's overall appearance. Disproportionately short limbs, exaggerated lumbar lordosis, and facial dysmorphism were absent. Acanthosis nigricans was observed on the patient's flank (A), back (B), anterior neck (C), and axilla (D).

department to determine the cause of his illness. He had a stocky build, and his height, weight, head circumference, and arm span were 91.7 cm (–1.95 SD), 16.3 kg, 54.0 cm (+2.6 SD), and 88.0 cm, respectively. He was 23.9% overweight for his age. However, disproportionately short limbs, exaggerated lumbar lordosis, facial dysmorphism, trident-like hands, and psychomotor impairment were absent. A growth chart demonstrated that the patient's height had increased from –2.5 SD to –2.0 SD (Fig. 2). A radiological examination revealed characteristic features of HCH, including mild metaphyseal flaring, short femoral necks, and elongation of the distal fibula and horizontal acetabula, but
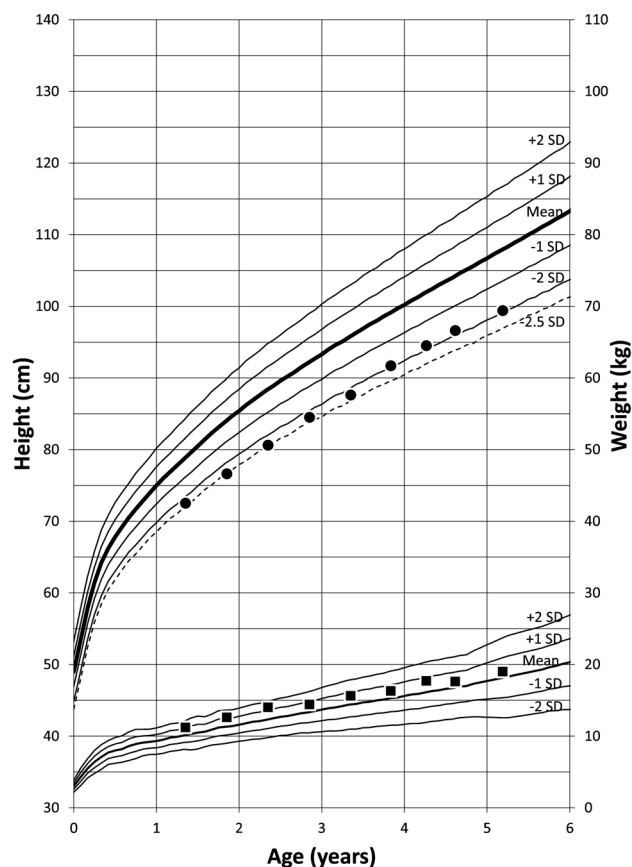
Fig. 2. The patient's growth chart. At the time of his initial admission (3 yr and 10 mo of age), his height SD score was −1.95 SD. His growth curve improved spontaneously.

Fig. 3. Radiographs of the patient. (A) No narrowing of the inferior lumbar interpedicular distances was observed. (B) Mild metaphyseal flaring was observed. (C) Elongation of the distal fibula was noted. (D) The patient exhibited short and broad femoral necks and elongation of the horizontal acetabula, but did not have square ilia. (E) The patient's bone age was 3.4 yr.

did not detect narrowing of the interpedicular distance or square ilia (Fig. 3). The patient's bone age was 3.4 yr. His serum insulin-like growth factor 1 and thyroid hormone levels were within normal ranges. His fasting blood glucose, and fasting insulin level were 76 mg/dL and 8.8 µU/ml, respectively. The homeostasis assessment index for insulin resistance (HOMA-IR) was 1.6, which indicated the absence of insulin resistance. Other laboratory examinations did not reveal any abnormalities. These findings excluded the possibility of endocrine disorders, including insulin resistance, type 2 diabetes, Cushing's syndrome, and hyperandrogenism. Based upon these physical and radiological features, a mutation analysis of *FGFR3* was performed to

detect HCH. At his most recent examination, which was conducted at 5 yr and 2 mo of age, his height and weight were 99.4 cm (−1.91 SD) and 19.0 kg, respectively. His height SD score gradually increased without GH treatment. Besides macrocephaly, his body parts exhibited almost normal proportions. His AN remained stable, and he did not require cosmetic treatment.

Methods

The genetic analysis was approved by the ethics committee of Okayama University Hospital. After informed consent was obtained from his parents, genomic DNA was extracted from the patient's peripheral leukocytes using the QIAamp DNA Blood Mini Kit (Qiagen Inc.,

Tokyo, Japan). We analyzed all of the coding exons and exon-intron boundaries of *FGFR3* using the standard PCR method. The sequences for the PCR primers used in this study are available upon request. The obtained PCR products were purified using the QIAquick PCR Purification Kit (Qiagen Inc.) and were sequenced using the BigDye Terminator v3.1 Cycle Sequencing Kit and an ABI PRISM® 310 Genetic Analyzer (Thermo Fisher Scientific Inc., Tokyo, Japan).

Results

We found a heterozygous base change, c.1949 A>C, which resulted in a p.K650T mutation (Fig. 4). This mutation was previously reported in patients with HCH combined with AN. No other mutations were found in *FGFR3*.

Discussion

We described the case of a Japanese boy with AN associated with HCH due to a K650T mutation in *FGFR3*. The coexistence of AN with a mild height deficit, macrocephaly, a stocky build, and radiological features of HCH prompted us to conduct an *FGFR3* gene analysis, which resulted in a definitive diagnosis for HCH. Various potential causes of the underlying AN, including insulin resistance and endocrine disorders, were excluded.
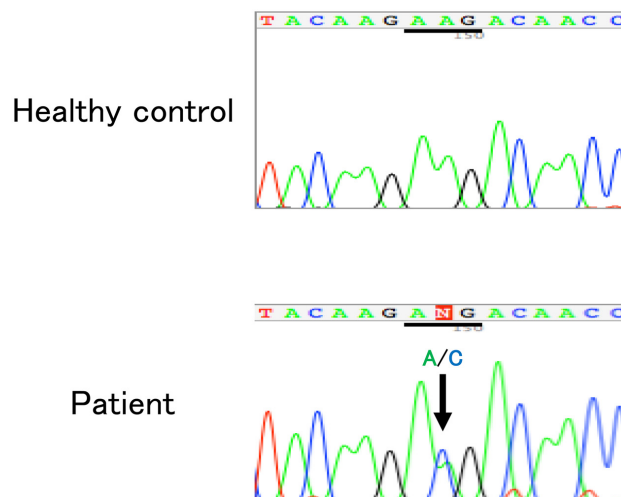
Fig. 4. Results of the *FGFR3* gene analysis. A heterozygous A1949C (black arrow) was identified in *FGFR3*. This base change resulted in K650T substitution in *FGFR3*. The black bar indicates codon 650.

Mutations in *FGFR3* are identified in approximately 70% of HCH cases, 60% of which involve the N540K mutation (6). However, few studies have examined the mutations in *FGFR3* that are found in patients with HCH combined with AN (Table 1). To the best of our knowledge, there have been 7 case reports about the coexistence of HCH and AN. Of these cases, 2, 3, and 2 were caused by N540K, K650Q (8–10), and K650T mutations, respectively (11, 12). Here, we report the third case of HCH combined with

Table 1 Reports on AN with or without HCH

FGFR3	Diagnosis	Age	Sex	Ht	BMI	Insulin sensitivity	Ref.
N540K	HCH+AN	14	M	−3.1SD	24.5	Normal	(15)
N540K	HCH+AN	9	M	−3.3SD	22.6	Insulin resistance	(16)
K650Q	HCH+AN	5	F	−3.5SD	N/A	N/A	(8)
K650Q	HCH+AN	10	F	−2.0SD	N/A	N/A	(9)
K650Q	HCH+AN	15	F	−3.4SD	26.3	Insulin resistance	(10)
K650T	HCH+AN *	14	M	−2.0SD	21.5	N/A	(12)
K650T	HCH+AN *	16	M	−3.4SD	24.2	Normal	(11)
K650T	AN *	5	F	8%ile	N/A	N/A	(13)
K650T	AN *	15	F	N/A	N/A	N/A	(14)
K650T	HCH+AN	3	M	−1.95SD	19.4	Normal	Current case

* Data of the proband. M, male; F, female; N/A, not available.

AN to involve a K650T mutation. A previous study has reported that 10 patients with K650T mutations exhibited moderately to severely short statures (–2.90 ± 1.0 SD; –1.53 ~ –4.57 SD) (11). However, another study reported 4 patients with K650T mutations who had moderately short statures (–2.0 SD for the proband) (12) and whose physical features were similar to those of our case. Interestingly, the same mutation was also detected in cases of AN that did not involve any obvious skeletal abnormalities, including a short stature, and these patients were not diagnosed with HCH (13, 14). Taken together, we speculate that AN might be prevalent in patients with HCH harboring K650 mutations, and that some individuals with K650T mutations might present with no skeletal manifestations other than AN. These issues should be studied further by examining patients with HCH for AN and patients with AN for HCH.

Previous reports have described both normoinsulinemic and hyperinsulinemic individuals with HCH combined with AN. Normal insulin sensitivity was observed in an adolescent boy with a N540K mutation (15) and in a family with K650T mutations (11). In contrast, insulin resistance was detected in two patients with HCH; a 14-yr old girl with a K650Q mutation (10), and a 13-yr old boy with an N540K mutation who was treated with recombinant human GH (16). Although our patient exhibited normal insulin sensitivity, we could not conclude whether the development of AN in patients with HCH was due to skeletal dysplasia-related insulin resistance. The FGFR3 signals through the activation of STAT1 and MEK/MAPK pathways were reported to be relevant to the phenotypic consequence of skeletal dysplasia (17), but the mechanisms involved in the development of AN in patients with HCH remain unclear.

We described the third reported case of HCH combined with AN due to a K650T mutation in *FGFR3*. In individuals with AN, regardless of the presence or absence of a short stature, it is important to perform careful assessments for symptoms of HCH, and radiological examinations or even a *FGFR3* mutation analysis should be considered. Furthermore, AN can sometimes be used as a marker for skeletal dysplasia.

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