Pediatrics and Neonatology (2019) 60, 686–688

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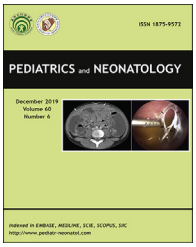

Short Communication

Mild osteochondrodysplasia with acanthosis nigricans in a short-statured Taiwanese family due to the p.Lys650Gln mutation in *FGFR3*

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Received Apr 8, 2019; received in revised form Jul 4, 2019; accepted Sep 10, 2019
Available online 17 September 2019

1. Introduction

Acanthosis nigricans (AN) is a condition characterized by velvety and pigmented hyperkeratosis of the skin at the neck, axillae, and groin. AN can occur as a symptomatic state of several diseases, including visceral malignancies, obesity, and endocrine disorders, including insulin resistance. Syndromic AN also includes familial AN that is associated with severe skeletal dysplasia caused by activating germline mutations in the fibroblast growth factor receptor 3 (*FGFR3*) gene.[1] *FGFR3* encodes a transmembrane tyrosine-kinase (TK) receptor that interacts with fibroblast growth factors and regulates chondrocyte differentiation, proliferation, and apoptosis in normal skeletal development. Genetic defects in distinct domains of *FGFR3* are associated with autosomal dominant human osteochondrodysplasia, such as achondroplasia (ACH), hypochondroplasia (HCH), and thanatophoric dysplasia types I and II (TDI and TD II). The clinical manifestations of *FGFR3* mutations can vary from mild unnoticed short stature to neonatal lethal dwarfism.[2] We herein report a Taiwanese family with a phenotype of mild short stature and AN associated with the p.Lys650Gln mutation in *FGFR3*.

2. Case

Our patient was a 12-year-old girl, who was the first child in the family from healthy, non-consanguineous parents in Taiwan. She presented extensive, velvety, thick, hyperpigmented plaques involving the neck, inguina, and axillae. She did not exhibit any neurological defects, intellectual impairment, clinically discernable skeletal abnormalities,

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https://doi.org/10.1016/j.pedneo.2019.09.008

or diabetes mellitus and related comorbidities. She also did not have a family history of cancer. Her body height and body mass index (BMI) were 137.0 cm (mildly below the 3rd percentile) and 21.3 kg/m^2 (around the 85th percentile), according to the New Growth Charts for Taiwanese Children and Adolescents.[3] Her mother was of normal height (158 cm), whereas her father was shorter (150 cm, far below the 3rd percentile). Her father also showed similar skin hyperpigmentation (Fig. 1A).

Her trunk was normal in appearance with relatively short limbs, and her forehead was mildly prominent without definite facial dysmorphism. Radiographic survey of the proposita skeleton excluded ACH, irrespective of the relatively large cranium, as well as the diagnosis of any other specific osteochondrodysplasia. Besides the relatively large head, her posture remained almost proportionate and her gait and muscle tone was normal (Fig. 1B). Her karyotype was 46, XX and laboratory tests were normal (Supplementary Table S1). These findings excluded the possibility of endocrine-related short stature and AN resulting from insulin resistance and type-2 diabetes. Based on the aforementioned clinical observation and evidence of possible parent-daughter transmission inheritance, mutation analysis of *FGFR3* was considered.

Informed consent was obtained from the patient's parents and genetic analyses were conducted. Detailed methods can be found elsewhere.[4] Through the analysis of *FGFR3* in the patient and her parents, an A-to-C transversion at nucleotide 1948 in exon 14 was found in the patient and her father, but not in her mother (Fig. 1C). This nucleotide variation converts a lysine at codon 650 to a glutamine (p.Lys650Gln). We concluded that this mutation was inherited from the father, who has a similar clinical phenotype to the index case.

3. Discussion

There are several different *FGFR3* mutations possibly associated with AN, of which p.Lys650Met causes SADDAN (severe achondroplasia with developmental delay and acanthosis nigricans). A p.Lys650Thr mutation has been linked to AN without significant craniofacial or skeletal abnormalities. Another p.Asn540Lys has been reported in HCH with AN. A p.Ser348Cys mutation has been described in patients with mild ACH/HCH and AN.[5] The mutation identified in our patient, p.Lys650Gln, usually causes AN with HCH or AN with mild short stature and less significant radiographic findings, without biochemical hyperinsulinemia.

In animal studies, transgenic mice carrying mutated *FGFR3* exhibited similar AN histology in skin lesions, suggesting a direct connection between AN in skeletal dysplasia and *FGFR3* mutations.[2,6] *FGFR3* mutations can increase the activation of STAT1 and MEK/MAPK pathways, both of which are relevant to the phenotypic consequence of skeletal dysplasia.[7] It has been speculated that activation of the MAPK pathway could affect keratinocyte proliferation and the PI3-K/Akt pathway could affect epidermal compartment expansion. Although they may play a role in AN development, the exact relationship between AN and FGFR3 mutations remains unclear (S1,S2).

FGFR3 structure comprises three extracellular immunoglobulin-like loops, one hydrophobic transmembrane domain, and two cytoplasmic TK sub-domains (TK1 and TK2) that are related to catalytic function. Lys650 residue is located within a critical region of the TK domain activation loop (S3). Mutations at this site result in different severe phenotypes in patients. Missense mutations p.Lys650Glu and p.Lys650Met strongly activate the receptor and result in TD2 and SADDAN, respectively. In contrast, p.Lys650Asn,

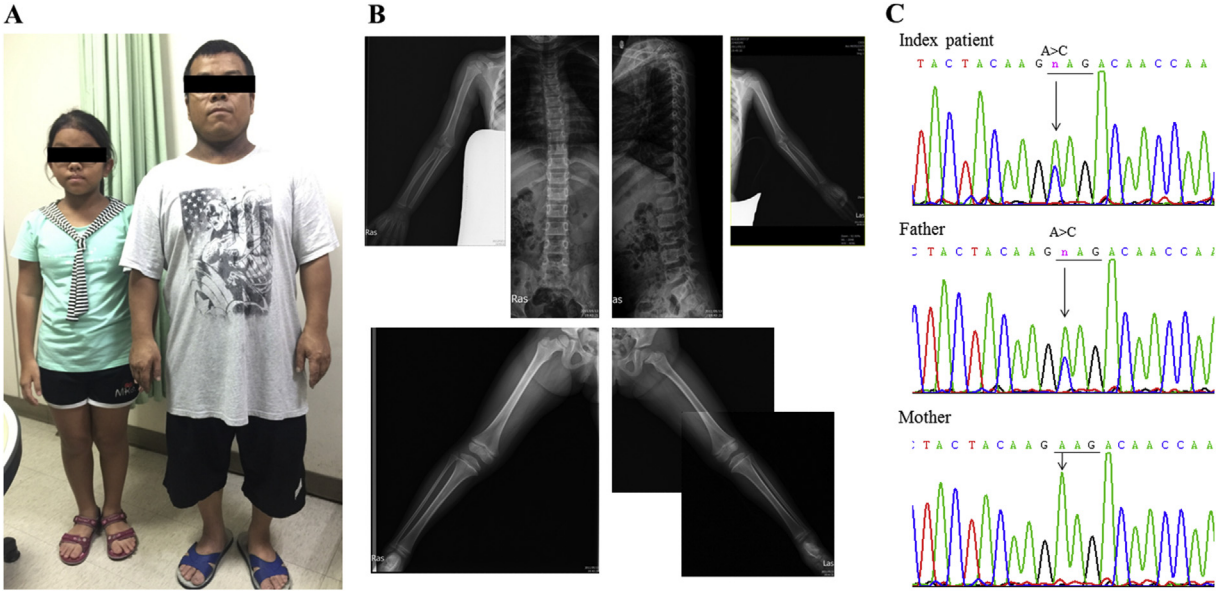

Figure 1 (**A**) The index patient (age 12) and her father were both short statured with relatively short limbs. Acanthosis nigricans could be seen clearly around the neck. (**B**) X-ray images of the index patient at five years of age revealed mild scoliosis of the spine with contour preservation of vertebral bodies and no evidence of narrowing of intervertebral disc space for the thoracolumbar spine. Long bone series disclosed appropriate alignment of bony structure in appearance. (**C**) Sequencing results of the *FGFR3* gene indicated a mutation in the index case and her father (c.1948A $>$ C, arrow indicated), but not in her mother.

p.Lys650Thr, and p.Lys650Gln mutations affect the receptor activity to a lesser extent, and the presentations of skeletal dysplasia are usually milder (S4).

According to our literature review, only five cases of p.Lys650Gln mutation have been reported to date: four were sporadic and one was a familial case (S4—S6). Ours is the second familial case and the first one reported in the Taiwanese population having AN with a mild phenotype. To our knowledge, limited cases of the p.Lys650Gln mutation in *FGFR3* along with AN were reported (S4—S6). No definite follow-up plan was formulated and from only ten cases, even though the *FGFR3* mutation and AN have been linked to an increased risk of malignancy (S7). We recommend that it would suffice to track the patients' BMI, blood sugar, insulin and skin changes yearly. In this study, we presented the known *FGFR3* mutations in patients with mild osteochondrodysplasia and AN, which may extend our knowledge on the phenotype-genotype spectrum of *FGFR3* gene mutations. In the future, *FGFR3* mutational profiling may be considered and subsequent genetic counseling for short-statured patients with AN and their affected families can be performed.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

The work was supported by grants from China Medical University Hospital, Taichung, Taiwan (# DMR106-134).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2019.09.008.