Familial Acanthosis Nigricans Due to K650T FGFR3 Mutation

David R. Berk, MD; Elaine B. Spector, PhD; Susan J. Bayliss, MD

Background: Acanthosis nigricans is a feature of several syndromes caused by activating mutations of the fibroblast growth factor receptor 3 gene (FGFR3), including Crouzon syndrome with acanthosis nigricans, thanatophoric dysplasia, and severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN syndrome).

Observations: We describe a healthy 4-year-old African American girl with generalized acanthosis nigricans since infancy. Her father had a history of acanthosis nigricans since childhood, in addition to Crohn disease, obesity, and adult-onset diabetes mellitus. A pedigree with numerous affected family members was constructed. Other than slightly short stature, no associated anomalies were found, including dysmorphic features or skeletal or neurologic defects. Genetic testing revealed a previously undescribed, heterozygous lysine to threonine mutation at codon 650 of the FGFR3 gene in the 4 affected family members who were tested.

Conclusion: Extensive acanthosis nigricans in early childhood, especially with a family history of acanthosis nigricans, may warrant testing for FGFR3 mutations.

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Numerous genetic syndromes are associated with acanthosis nigricans (AN), particularly syndromes characterized by obesity, hyperinsulinemia, and/or craniosynostosis.1 In a recent review, Torley et al1 divided these genetic syndromes into insulin resistance syndromes and fibroblast growth factor (FGF) defects. Insulin resistance syndromes are caused by mutations in the insulin receptor (leprechaunism and Rabson-Mendenhall syndrome), peroxisome proliferator-activated receptor-γ (insulin-resistant diabetes mellitus with AN and hypertension), 1-acylglycerol-3-phosphate O-acyltransferase-2 (Berardinelli-Seip syndrome), seipin (Berardinelli-Seip syndrome), lamin A/C (Dunnigan syndrome), and Alstrom syndrome genes. Fibroblast growth factor defects associated with AN include specific activating mutations of FGFR2 (Beare-Stevenson syndrome) and FGFR3 (Crouzon syndrome with AN and thanatophoric dysplasia [TD], and severe achondroplasia with developmental delay and AN [SADDAN syndrome]).

REPORT OF CASES

A 4-year-old African American girl was referred for evaluation of generalized, minimally pruritic skin thickening since infancy. She was diagnosed as having atopic dermatitis by her pediatrician years earlier but had not responded to treatment with topical corticosteroids. She was otherwise healthy without diabetes mellitus and was taking no medications. Neurological development was normal. Her father (age, 25 years) described having a similar skin condition since early childhood. He was slightly obese and had Crohn disease and mild adult-onset diabetes mellitus (diet controlled). There was no history of consanguinity.

On physical examination, the patient had generalized, thick, velvety, hyperpigmented plaques that were most prominent on her neck, back, and axillae (Figure 1). There was no erythema or li-
chenification. Her oral mucosa, palms, and external genitalia were normal. Height and weight at age 5.5 years were 105.5 cm (eighth percentile) and 17.3 kg (20th percentile), respectively. Results from laboratory evaluations (complete blood cell count, urinalysis, and random glucose and hemoglobin A1c measurements) were normal. Examination of the patient’s father revealed similarly thick, velvety, hyperpigmented plaques localized to the neck, back, and axillae. His height was 156 cm (<fifth percentile). Over the past few years, his weight had fluctuated from 48 to 106 kg due to his Crohn disease. Neither the patient nor her father had facial dysmorphism (eg, frontal bossing) or tibial bowing. Familial AN was diagnosed.

Because activating FGFR3 mutations have been identified in several forms of syndromic AN, this gene was evaluated for mutations. Genetic testing was performed on DNA isolated from saliva (Oragene; DNA Genotek Inc, Ottawa, Ontario, Canada) followed by sequencing of exons 10, 13, and 15 of the FGFR3 gene. A single nucleotide change was observed in exon 15 (Figure 2). The patient and her father both demonstrated a previously undescribed lysine to threonine mutation at codon 650 (K650T) in one FGFR3 gene, suggesting autosomal dominant inheritance. No mutation was identified in the patient’s mother or the patient’s 3-year-old sister, both of whom were clinically unaffected. Genetic counseling was performed. There was no change with topical pimecrolimus and steroids.

The father’s 29-year-old cousin (Figure 3) and her 11-year-old daughter (Figure 4) were subsequently evaluated for the same condition and diagnosed as having familial AN, resulting in a pedigree with multiple affected relatives (Figure 5). The daughter’s height and weight at age 11 years were 139 cm (26th percentile) and 40.9 kg (68th percentile), respectively. Her mother’s height and weight were 145 cm (<fifth percentile) and 64.2 kg (25th-50th percentile), respectively. No further associated anomalies were identified in these 2 patients or reported in their relatives, including dysmorphic features, diabetes mellitus, Crohn disease, or skeletal or neurologic defects. Both this child and her mother demonstrated heterozygous K650T mutations on genetic testing, identical to their 2 relatives who had been previously tested.

Acanthosis nigricans is characterized by velvety, hyperpigmented plaques often accentuated in the flexures. Numerous forms of AN have been described including be-

Figure 1. Patient at age 4 years with thick, velvety, hyperpigmented plaque involving the neck and chest.

Figure 2. Sequencing of exon 15 of the FGFR3 gene was performed using the following primers: forward, 5’ GTA AAA CGA CGG CCA GT AGG TGT GGG TGG AGT AGG; and reverse, 5’ CAG GAA ACA GCT ATG ACC TC AGG CGC CAT CCA CT T5’ CGA CGG CAT CGG TGA AG. Sequencing was performed with an ABI 3130 sequencer (Applied Biosystems, Foster City, California). A, The arrow indicates K650T mutation; A→C change at nucleotide 1950, amino acid 650. B, Normal sequence.
nign (nonsyndromic, insulin resistance-associated AN), malignant (paraneoplastic), obesity-associated (pseudo-AN), acral, medication-induced (corticosteroids, estrogens, oral contraceptives, niacin, triazinate, somatotrophin, and diethylstilbestrol), and syndromic AN (including isolated, “pure” familial AN).2,3

Generalized AN is rare and often paraneoplastic,4 even in very early childhood. However, generalized AN in early childhood may also suggest isolated (nonsyndromic, non-insulin resistance–associated) familial AN.4-8 Furthermore, there are reports of benign, generalized AN in early childhood without a positive family history, malignancy, associated syndrome, causative medication, or comorbid condition.9-15

Only a few families with isolated (nonsyndromic, non-insulin resistance–associated) familial AN have been reported in the literature.3-8 Inheritance tends to be autosomal dominant with variable penetrance. This “pure” familial AN usually appears in infancy, stabilizes at puberty, and is not associated with obesity or diabetes mellitus. The term familial AN is confusing because AN associated with insulin resistance also tends to be hereditary and the term familial AN has been used in the literature in such cases.16-17 Comorbid conditions have rarely been reported with isolated familial AN. Chuang et al18 reported a family with AN and ectodermal defects including madarosis. In addition, 2 cases of benign AN (no family history) in early childhood have been associated with pyramidal tract degeneration.11,15 Familial AN may be confused with ichthyosis hystrix,2 generalized epidermal nevi, or lichenification in atopic dermatitis.

The pathogenesis of AN is poorly understood. In patients with hyperinsulinemia, excess insulin may directly or indirectly stimulate epidermal proliferation through the insulin-like growth factor 1 receptor.19 Growth factors (particularly transforming growth factor-α) produced by tumors may cause malignant AN through the epidermal growth factor receptor.20

Fibroblast growth factors are involved in angiogenesis, embryogenesis, mitogenesis, and wound healing. There are more than 20 human FGF ligands and 4 human FGF receptors. The FGFR3 gene is located at 4p16.3 and encodes a transmembrane receptor tyrosine kinase, which down-regulates long-bone growth. FGFR3 mutations have been reported in several dermatologic conditions including seborrheic keratoses,21 epidermal nevi,22 and syndromic AN. Several autosomal dominant syndromes are caused by specific FGFR3 mutations, including achondroplasia, Muenke syndrome, hypochondroplasia, TD I and II, Crouzon syndrome with AN, and SADDAN syndrome. The latter 3 disorders demonstrate AN.

Codon 650 of FGFR3 is located in its tyrosine kinase domain II. Mutations of this codon have been reported in skeletal disorders including hypochondroplasia (K650N and K650Q), SADDAN syndrome (K650M), TD I (K650M), and TD II (K650E), as well as malignant conditions including bladder cancer and multiple myeloma (K650M, K650E, and K650T). Germline K650T mutations have never been reported. Bellus et al23 studied the effects of various amino acid changes on the activation of FGFR3 in vitro. Constructs were made that contained all of the possible FGFR3 mutations at amino acid 650.
In a \(^{32}\)P-ATP autophosphorylation assay, the relative activity of the mutations compared with that of a wild-type construct was as follows: K650R, 1.5x; K650N, 3.7x; K650Q, 4.9x; K650T, 3.1x; K650E, 9.6x; and K650M, 18.1x. These data suggest that the K650T mutation was a relatively weak activator of FGFR3, it would have a less severe effect on phenotype than the mutations found in hypochondroplasia, SADDAN syndrome, TD I, and TD II, as was observed in the patients described herein.

Activating FGFR3 mutations and/or ectopic overexpression have been reported in a number of tumors, such as bladder, cervical, multiple myeloma, and colorectal cancers. Tyrosine kinase inhibitors of FGFR3 are being tested in several hematologic malignancies with positive results. Topical preparations of these inhibitors may prove beneficial for seborrheic keratoses, epidermal nevi, and/or AN.

In summary, we describe a family with AN caused by an autosomal dominant K650T mutation in the FGFR3 gene. Extensive AN in early childhood, especially with a family history of AN, may warrant testing for FGFR3 mutations.

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Correspondence: David R. Berk, MD, Division of Dermatology, Washington University School of Medicine, 660 S Euclid, Campus Box 8123, St Louis, MO 63110 (DBerk@im.wustl.edu).

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REFERENCES


Figure 5. Pedigree of family. Shaded boxes indicate affected family members. The asterisks indicate family members tested for FGFR3 mutations.