

# Idiopathic extensive acanthosis nigricans with a variant of the epidermal growth factor receptor



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**Key words:** acanthosis nigricans; epidermal growth factor receptor; familial acanthosis nigricans; fibroblast growth factor receptor; paraneoplastic acanthosis nigricans; severe acanthosis nigricans; TGF alpha.

## INTRODUCTION

Acanthosis nigricans (AN) is a common condition seen in individuals as a consequence of insulin resistance states, other metabolic disorders, malignancy, genetic syndromes, and drugs. This article presents a severe, childhood-onset case of AN that was of unclear etiology. Whole-genome sequencing identified a variant of epidermal growth factor receptor (EGFR), a receptor involved in keratinocyte proliferation and fibroblast migration.<sup>1</sup>

## CASE REPORT

A 23-year-old white woman was referred to the dermatology clinic for evaluation of severe AN. The plaques first appeared around the age of 6 years on the posterolateral neck. They had progressively gotten darker and thicker, involving additional areas, particularly during menarche and pregnancy. The plaques were neither painful nor pruritic. The patient described having a normal weight throughout her childhood and adolescence but reported a 60-pound weight gain that she maintained after her 2 recent pregnancies. She had regular menses since menarche at the age of 12 years. Findings from a complete review of systems were negative except for progressive worsening of AN.

Past medical history was significant for reported hyperinsulinemia diagnosed at age 4 years after a corticosteroid injection for contact dermatitis caused by poison ivy. She did not have any chronic medical conditions. She was not taking any medications at the time of presentation except for a Mirena intrauterine device (Bayer, Whippany, NJ). Past use of an

### Abbreviations used:

|       |                                   |
|-------|-----------------------------------|
| AN:   | acanthosis nigricans              |
| EGFR: | epidermal growth factor receptor  |
| FGFR: | fibroblast growth factor receptor |
| IGF:  | insulin-like growth factor        |
| IR:   | insulin resistance                |

oral contraceptive pill was not associated with a change in AN. Over the years, she was treated with metformin (up to 2000 mg), isotretinoin, and various topical regimens, including 40% urea, 0.025% tretinoin cream, and 4% hydroquinone cream, all without improvement. There was no family history of AN or other genetic conditions.

Physical examination showed that the patient was a nondysmorphic female with a height of 170 cm and body mass index of 32 kg/m<sup>2</sup>. She was Fitzpatrick skin type II. An examination of the skin showed symmetric, extensive, papillomatous, hyperpigmented velvety plaques on the neck and axillae (Fig 1). Additionally, she had hyperpigmented velvety plaques on the lateral eyes, perioral region, inframammary folds, antecubital fossae, volar wrists, and inguinal folds. There was no evidence of masculinization, lymphadenopathy, cushingoid features, or organomegaly.

A biopsies of the left side of the neck and left side of the upper back were performed. Histology results were consistent with AN. Immunohistologic staining for human papillomavirus was negative. An extensive endocrinology evaluation excluded diabetes mellitus, hyperinsulinemia, hyperandrogenemia,

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**Fig 1.** Extensive, papillomatous, hyperpigmented velvety plaques on (A) the left axilla and (B) the posterior aspect of the neck.

**Table I.** Laboratory evaluation results

| Laboratory evaluation (serum)        | Value    | Normal range |
|--------------------------------------|----------|--------------|
| Hemoglobin A1c, %                    | 5.0      | <5.7         |
| Insulin, $\mu$ U/ml                  | 16.8     | 3-25         |
| Nonfasting glucose, mg/dl            | 86       | 70-100       |
| IGF-1, ng/ml                         | 185      | 107-367      |
| IGF-II                               | Normal   |              |
| C-peptide, ng/ml                     | 5.07     | 0.9-7.1      |
| Antipancreatic islet cells           | Negative |              |
| GAD-65 antibody, IU/ml               | <5       | <5           |
| ICA-512, U/ml                        | <1       | <1           |
| Testosterone total, ng/dl            | 23       | 14-76        |
| Sex hormone binding globulin, nmol/L | 43       | 18-144       |
| TSH, $\mu$ U/ml                      | 1.393    | 0.350-5.5    |
| Leptin, ng/ml                        | 15.5     | 4.7-23.7     |
| Adiponectin, $\mu$ g/ml              | 93       | 4-22         |

GAD, Glutamic acid decarboxylase; IGF, insulin-like growth factor; ICA, islet cell antibody; TSH, thyroid-stimulating hormone.

lipodystrophy, and thyroid function abnormalities (Table D). Abdominal computed tomography scan showed no abnormalities. Whole-exome sequencing, a genetic test that provides sequencing for all of the protein-coding regions of genes known as *exons*, was obtained. It showed a single, heterozygous variant of uncertain significance (c.2648T>C, p.Leu883Ser) in the *EGFR* gene (Fig 2). Sanger sequencing confirmed the finding.

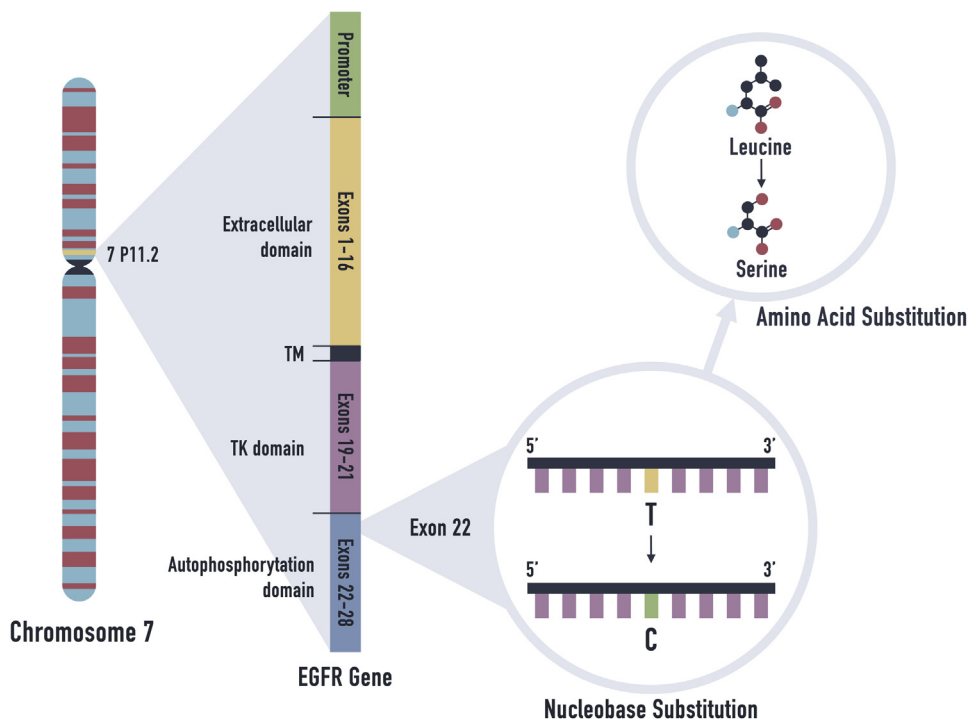
## DISCUSSION

Most theories of the pathogenesis of AN have focused on insulin-like growth factor (IGF), tyrosine

kinase receptors, EGFR, and fibroblast growth factor receptor (FGFR), all of which stimulate keratinocyte and fibroblast growth and proliferation.

Similar to the disease in adults, the vast majority of AN in early childhood occurs in the setting of obesity and insulin resistance (IR).<sup>2</sup> This includes genetic defects in insulin-signaling pathways (type A IR) and blocking autoantibodies against the insulin receptor (type B IR). High concentrations of insulin cause keratinocyte proliferation by binding to IGF-1R. Hence, AN has been reported at skin sites where insulin has been injected.<sup>3</sup>

Our patient's Homeostatic Model Assessment of Insulin Resistance score was 1, indicating insulin sensitivity and an overall low metabolic risk. Normal glucose, insulin, and IGF-1 levels excluded other causes of IR because IR requires significant abnormalities of glucose metabolism.<sup>4</sup> Although this patient had a reported history of hyperinsulinemia secondary to corticosteroid use, medication-associated AN is unlikely because, in that situation, the lesions regress after discontinuation of the offending medication, and they did not in this patient. In addition, the onset occurred years after exposure, and subsequent testing showed no evidence of hyperinsulinemia. The patient's normal height and anatomy, lack of significant family history, and absence of an FGFR mutation excluded familial AN. This form of AN is exceedingly rare and manifests early in life in the absence of obesity and endocrinopathies, the clinical presentation seen in this case. Familial cases of Beare-Stevenson syndrome, Crouzon syndrome, and severe achondroplasia with developmental delay and acanthosis



**Fig 2.** The *EGFR* mutation at nucleotide c.2648 was detected with whole-genome sequencing. *EGFR*, Epidermal growth factor receptor; *TK*, tyrosine kinase; *TM*, transmembrane.

nigricans, which have mutations in *FGFR*, have also been associated with AN. All reported cases of familial AN, with the exception of a de novo case from China, are inherited in an autosomal dominant manner.<sup>5</sup> In addition, *FGFR* defects and/or skeletal abnormalities are associated with familial AN.<sup>5</sup>

Paraneoplastic AN was excluded in this patient by the lack of laboratory evidence of cancer and by the long duration of its presence. The onset of paraneoplastic AN is sudden and rapidly progressive. It most commonly occurs with adenocarcinoma, especially adenocarcinoma of the stomach, lung, and breast.<sup>6</sup> It is exceedingly rare in children.<sup>7</sup> Gastric tumors with AN have been reported to secrete high levels of transforming growth factor alpha, leading to the amplification of *EGFR*.<sup>8</sup> Also, biopsy specimens of paraneoplastic AN exhibited an enhanced expression pattern of *EGFR* that included most of the suprabasal keratinocytes.<sup>9</sup>

Our patient fit none of the known causes of AN. For this reason, we performed whole-exome sequencing and observed that she had a mutation in *EGFR*. To our knowledge, this is the first report of an *EGFR* mutation associated with AN. *EGFR* is a transmembrane protein that is a member of the receptor tyrosine kinase family of signal transduction molecules. It is expressed mainly in the basal layer of normal epidermis, and its role in modulating

keratinocyte proliferation, migration, and survival is well established.<sup>1</sup>

### CONCLUSION

Despite a thorough medical evaluation, the cause of this severe case of AN was unknown and, for this reason, whole-exome sequencing was performed. Because the clinical findings were identical to those of other mutations that cause overactivation of the receptor, we speculate that this mutation was an activating mutation that enhances *EGFR* signaling by its known ligands or even causes activation of the signal transduction pathway without the requirement for its ligands. Profiling *EGFR* activity may provide additional answers as to how this mutation is involved in the pathogenesis of AN. Furthermore, whole-exome sequencing of other patients with AN, for which the cause is unknown, may generate additional information about the pathogenesis of this disease. It also provides an excellent example of how, in the future, whole-exome and genome sequencing may be used for personalized medicine.

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