

Mosaic *TP63* variant and associated ectodermal dysplasia features



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Key words: DNA copy number variations; ectodermal dysplasia; mosaicism; transcription factors.

INTRODUCTION

Ectodermal dysplasia (ED) is a broad group of genodermatoses involving developmental defects of tissues derived from the ectoderm. The conditions vary in genetic etiology and phenotype, since there are multiple developmental pathways and genes that contribute to normal formation and function of ectodermal structures. Proposed classification systems for ED organize conditions based on genotype, molecular pathway, and phenotype.¹ One group of ED conditions consists of disorders associated with the tumor protein p63 (TP63) pathway, which is essential to epidermal development and differentiation.^{1,2} Reports of genetic mosaicism in ED are rare, but they further contribute to the diverse clinical presentations among ED. We present the case of a young adult man with patterned hypopigmentation, alopecia, and dental anomaly who was found to have a variant of the *TP63* gene with mosaic distribution on genomic analysis.

CASE REPORT

A 31-year-old African American man presented to the clinic for evaluation of hypopigmented patches on the body, with a history of alopecia of the scalp, scoliosis, and an unspecified childhood deformity of the lower extremity treated with leg orthosis. The hypopigmented patches on the body were present since the first few years of life. The patient noted having straighter hair texture and lighter hair color in the hypopigmented areas on his scalp since childhood. He also began noticing hair loss, particularly in the hypopigmented areas, in his mid-20s. A biopsy of the areas of hair loss confirmed the presence of nonscarring alopecia with a mild increase of telogen

Abbreviations used:

ED: ectodermal dysplasia
TP63: tumor protein p63

hairs, associated with sparse lymphocytic infiltrate and trichomalacia without lichenoid interface changes. The patient also reported losing his right lower deciduous canine tooth at 25 years of age, followed by growth of a hypoplastic permanent tooth. He also described a history of possible seizure-like activity or parasomnias in his twenties, when he would open his eyes while sleeping but was unable to move. The episodes stopped spontaneously a few years ago, without medical workup. He denied having abnormal sweating or overheating, despite being a former athlete. He also denied visual, hearing, or genitourinary problems. Although there was no family history of a disease or symptoms similar to those of the patient, he reported having a sister with hypoplastic index, long, and ring fingers.

The physical examination revealed hypopigmented patches following a Blaschkoid distribution on the body, which were most pronounced on the hands and feet and spared the face (Fig 1). Evaluation of the hair revealed vellus and dystrophic hairs in the hypopigmented patches on the scalp and body (Fig 2). Examination of the mouth revealed only a hypoplastic inferior right canine tooth (Fig 3). No nail abnormalities were seen. No deformity, hypertrophy, or hypotrophy of the face, trunk, or limbs was observed. The patient had normal intellect. Based on the clinical history and examination, ED was considered as a potential diagnosis. Using

From the Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine.

Funding sources: None.

IRB approval status: Not applicable.

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JAAD Case Reports 2021;17:52-4.
2352-5126

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<https://doi.org/10.1016/j.jdc.2021.09.016>



Fig 1. Linear hypopigmented patches on bilateral hands following Blaschkoid lines.



Fig 2. Whorled pattern of hypopigmentation and alopecia or vellus hairs on the scalp.



Fig 3. Bottom right canine tooth, hypoplastic with conical shape.

DNA extracted from the patient's saliva, a genomic assay panel was performed for ED-associated genes, which revealed a *TP63* gene copy number variant with the presence of mosaicism.

The patient had presented to the clinic seeking a diagnosis, particularly counseling in regard to the risk to future offspring. In the setting of a genetic mosaicism, further evaluation would have to be

completed to determine the additional presence of germline mosaicism.

DISCUSSION

The *TP63* gene encodes for transcription factor p63, a key regulator of epidermal development that plays important roles in embryonic epidermal stratification and in keratinocyte differentiation and proliferation.^{2,3} Mice lacking *TP63* expression have developmental defects, including truncated limbs, undifferentiated epidermis, and abnormalities in epidermal adnexal structures such as the teeth, hair follicles, and mammary glands. In humans, germline *TP63* mutations have been associated particularly with a group of ectodermal-related disorders, including ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome 3; limb mammary syndrome; acrodermato-ungual-lacrimal-tooth syndrome; split hand foot malformation; and ankyloblepharon-ectodermal defects-cleft lip/palate syndrome. This family of *TP63*-related ectodermal disorders involves varying combinations and presentations of 3 hallmark defects: ED, limb malformation, and orofacial clefting.^{3,4}

The dermatologic phenotype of *TP63*-related ED has been observed to include erosions, erythroderma, and linear or reticulated skin hyperpigmentation, the latter affecting up to 32% of patients.⁵ The role of p63 in pigmentary anomalies is unclear, although given its essential involvement in epidermal development, p63 may have a specific function in melanocyte differentiation.⁶ Reports of patients with ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome 3 or ankyloblepharon-ectodermal defects-cleft lip/palate syndrome presenting with generalized hypopigmented patches in linear distribution on the body include no information regarding the presence of mosaicism and consider the patterned hypopigmentation as a feature of *TP63*-associated syndromes.^{5,6} There have been few reported cases of ED with mosaicism. In these cases, the dermatologic findings follow Blaschko distributions on the body. A case series of hypohidrotic ED patients identified 2 patients with postzygotic mutations, demonstrated by the starch-iodine test confirming a mosaic distribution of

functional sweat glands following Blaschko lines.⁷ Mosaicism in the *PKP1* gene was reported in a child with ED-skin fragility syndrome, showing unilateral superficial erosions, plantar keratoderma, and nail dystrophy in a Blaschkoid distribution.⁸ In this case, the hypopigmented patches may be considered a characteristic of *TP63*-related ED; however, the heterogenous presentation of hair also follows similar patterns along Blaschko lines, suggesting mosaic distribution. The absence of other classic features of *TP63*-related ectodermal disorders, such as characteristic orofacial cleft or limb anomalies, may also be explained by p63 mosaicism. It is also important to note that in postzygotic mutations and genetic mosaicism, one is unable to predict which tissue derivatives will be affected.

To our knowledge, this is the first reported case of a copy number variant of *TP63* resulting in mosaic expression of ED. We present this case to exemplify the complex diversity of ED presentations that should be considered during clinical evaluation and to demonstrate the utility of genetic panels in the workup of suspected ED.

Conflicts of interest

None disclosed.

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