CASE REPORT

Novel mevalonate kinase missense mutation in a patient with disseminated superficial actinic porokeratosis

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INTRODUCTION

Disseminated superficial actinic porokeratosis (DSAP) is a genodermatosis with autosomal dominant inheritance and near-complete penetrance clinically featuring uniform 3- to 7-mm annular lesions with scaly borders on sun-exposed face and extremities. The hyperkeratotic rim correlates histopathologically with the presence of a cornoid lamella.1 Dermoscopy may be used to noninvasively visualize the cornoid lamella, which appears as a distinctive thin white annular structure at the periphery of each lesion.2 Several causal DSAP mutations have previously been reported in members of the mevalonate/isoprenoid biosynthesis pathway,1,3,4 although the exact mechanism is not well understood. We report a patient who presented with classic clinical and histopathologic features of DSAP in which a novel mutation in a coding region of the mevalonate kinase (MVK) gene was identified via Sanger sequencing of the skin biopsy specimen.

CASE REPORT

A 50-year-old Eastern European woman presented to the clinic with a 15-year history of small, round asymptomatic but cosmetically bothersome lesions on her arms and legs. The patient reported similar lesions in her mother and maternal grandmother. On physical examination, numerous 2- to 3-mm annular brown-to-red papules and plaques with a scaly keratotic rim were identified on her extremities; her face and trunk were spared (Fig 1, A, B). Shave biopsy of a representative lesion on the leg found a cornoid lamella, dermal lymphocytic infiltrate, and epidermal dyskeratosis (Fig 1, C). The diagnosis of DSAP was made based on clinical presentation and characteristic histopathologic findings.

To identify the patient’s causal mutation, sequencing of the MVK gene was performed on genomic DNA extracted from formalin-fixed paraffin-embedded biopsy specimens of DSAP (lesional) skin and histologically uninvolved perilesional skin and unaffected abdominal skin. The wild-type MVK sequence was obtained as a
reference standard from the National Center for Biotechnology Information (NCBI)'s RefSeq database under accession no. NG_007702. Sequencing analysis of all specimens found an identical novel heterozygous missense point mutation in exon 5 (c.455:G>A), resulting in the substitution of tyrosine for cysteine (p.C152Y) in a predicted functional domain of the MVK enzyme (Fig 2). This variant was not present in NCBI's dbSNP150 database of single nucleotide polymorphisms. Biomaterials were not available for sequencing of other affected family members.

MATERIALS AND METHODS

DNA isolation
DNA was extracted from formal-fixed, paraffin-embedded skin biopsy specimen tissue using the QIAmp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany) following the manufacturer's protocol.

Polymerase chain reaction amplification and Sanger sequencing
Primers for MVK exons were synthesized using previously published sequences1 (Sigma-Aldrich, St Louis, MO). Polymerase chain reaction amplification of each coding exon was performed using Q5 High-Fidelity 2x Master Mix (New England Biolabs, Ipswitch, MA) per manufacturer's standard protocol, with 35 cycles of amplification, on an Eppendorf 5331 MasterCycler Gradient Thermal Cycler (Eppendorf, Hamburg, Germany). Amplified DNA quality and quantity were assessed with a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA). The MVK exon polymerase chain reaction products were then gel purified using the QIAquick Gel Extraction Kit (Qiagen, Hilden, Germany) and sequenced via Sanger sequencing with an ABI 3730xl DNA analyzer (Applied Biosystems, Foster City, CA). Sequences were aligned to the MVK reference (NCBI RefSeq NG_007702) and analyzed using CLC Main Workbench 7.0 (Qiagen).

DISCUSSION

DSAP is a genodermatosis now recognized as the most common form of porokeratosis.5 It usually appears in the third or fourth decade of life in individuals with a history of extensive sun exposure.5 DSAP is inherited in an autosomal dominant fashion with near-complete penetrance,1 and there is evidence implicating mutations in members of the mevalonate/isoprenoid biosynthesis pathway as the primary cause.4 Several MVK variants have been previously described in DSAP patients of Asian descent.1,3,4 Here we report a novel heterozygous MVK mutation in an Eastern European patient who presented with cutaneous and histopathologic features of DSAP. This missense mutation was identified in the patient’s DSAP lesions as well as in perilesional and nonlesional skin, supporting its germline status. Although homozygous loss-of-function MVK mutations are associated with a severe systemic autoinflammatory phenotype and failure to thrive,6 heterozygous MVK mutations appear to be associated only with the classic skin lesions of DSAP.

Identification of a new mutation in a functional domain of MVK in our patient supports a growing body of evidence implicating the mevalonate/isoprenoid biosynthesis pathway in the DSAP phenotype. Aberrant MVK function and consequent decrease in production of the farnesyl pyrophosphate intermediate are predicted to impair cholesterol biosynthesis as well as protein isoprenylation.7 These processes have important roles in keratinocyte differentiation and apoptosis.

Fig 1. DSAP features. A, Characteristic DSAP lesions on the bilateral lower extremities. B, Representative annular lesions with hyperkeratotic rims. C, Lesional biopsy specimen shows the characteristic cornoid lamella. (Hematoxylin-eosin stain; original magnification, ×20.)
during physiologic epidermal stratification. Impaired barrier formation may thus partially account for the clinical and histopathologic features of DSAP.

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Fig 2. MVK sequencing in DSAP lesional and nonlesional skin. Alignment of the patient’s amplified MVK exons from lesional DSAP skin, histologically normal perilesional skin, and unaffected abdominal skin to the wild-type MVK reference sequence identified an identical heterozygous mutation in exon 5 (c.455:G>A), resulting in the predicted substitution of tyrosine for cysteine (p.C152Y) in a functional domain of MVK. Sequence tracings, alignments, and protein predictions were generated using CLC Bio software.

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