

From a Gene Mutation to Pathology and Targeted Therapy in a Patient with Therapy-resistant Porokeratosis

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The term “porokeratoses” describes a heterogeneous group of diseases that represent a chronic keratinization disorder of the epidermis. Porokeratoses are generally classified as genodermatoses with disseminated superficial actinic porokeratosis (DSAP) being the most common variant (1). It is currently assumed that either autosomal-dominantly inherited or *de novo* mutations in genes of the mevalonate metabolic pathway are responsible for the development of the clinical picture of DSAP (2). However, the details of the underlying mechanism are still not fully understood. Here, we further investigated the genetic basis of DSAP in 1 affected patient with clinical and histological diagnosed DSAP by performing panel sequencing and subsequent evaluation of mevalonate pathway genes (*MVD*, *MVK*, *PMVK*, and *FDPS*) for pathogenic variations. Additionally, we successfully treated DSAP with topical 2% simvastatin/2% cholesterol ointment, achieving complete response within a timeframe of 5 weeks.

CASE REPORT

A 60-year-old woman presented to our clinic with erythematous papules surrounded by a fine peripheral keratotic rim distributed on her lower legs. The lesions first appeared 2 years before. The patient's medical history revealed chronic sun exposure with increasing intensity and number of lesions during the summer. No further symptoms were reported. Previous treatments including cryotherapy and 5-fluorouracil cream were ineffective. Cryotherapy showed no therapeutic effect after 6 sessions and 5-fluorouracil was applied once daily for 8 weeks without success. No other previous dermatological diseases were reported. Arterial hypertension and hypercholesterolemia, as cardiovascular risk factors, were treated with ramipril and simvastatin. Histology from a punch biopsy of her left leg revealed epidermal invagination with a parakeratotic column, also known as cornoid lamella. In addition, dyskeratotic keratinocytes and a lymphocytic dermal infiltrate were observed. Her family history was unremarkable for disseminated superficial actinic porokeratosis and other dermatological diseases. Based on clinical and histological evidence, the diagnosis of disseminated superficial actinic porokeratosis was made. Loss of function mutations in genes of the mevalonate pathway have earlier been described as causative for DSAP. Therefore, genetic analyses from peripheral blood of the affected patient were performed employing next-generation-sequencing to gain new insight into potential mutations driving the pathogenesis of porokeratosis. Using an exome-based approach, genomic DNA was screened for variants in 4 genes of the mevalonate pathway, namely *MVK*, *MVD*, *PMVK*, and *FDPS*. We identified the heterozygous likely pathogenic variant

c.415G>T; p.(Glu139*) [NM_002004.4] in the *FDPS* gene, which encodes farnesyl diphosphate synthase. This truncating variant was absent in GnomAD and clinical databases suggesting that presentation as a sporadic case of DSAP was due to an underlying autosomal dominant porokeratosis in our patient. Based on earlier evidence (3), the patient was treated with topical 2% simvastatin/2% cholesterol ointment applied once daily to the lower extremities. The patient experienced a significant improvement, and a complete resolution of all porokeratotic lesions was achieved after 5 weeks of therapy (Fig. 1). After the treatment was stopped, our patient reported isolated lesions, which continued to occur sporadically on both legs. After topical re-application of simvastatin/cholesterol ointment, lesions again completely resolved within a short time. The treatment was well tolerated with no reported side effects.

DISCUSSION

In this study, we identified a previously unreported variant within the *FDPS* gene encoding farnesyl diphosphate synthase as likely cause for a DSAP. In the past years, heterozygous pathogenic germline variants of the mevalonate pathway genes *MVD* (mevalonate decarboxylase), *MVK* (mevalonate kinase), *PMVK* (phosphomevalonate kinase), and *FDPS* have been reported in familial and sporadic cases of porokeratosis (2). The mevalonate pathway is involved in cholesterol biosynthesis and plays a vital role in various cellular processes, such as cell growth, gene expression, cytoskeleton assembly, and post-translational modification of proteins involved in intracellular signalling (4).

Previously, it was postulated that keratinocytes carrying a germline pathogenic variant undergo a UV-radiation-induced second hit mutation, forming pathogenic epidermal clones. Preferably in sun-exposed areas, as in our patient, expansion of these clones into the surrounding epidermis leads to characteristic lesions of the diseased phenotype (5).

At the molecular level, loss-of-function mutations of involved key enzymes of the cholesterol pathway lead to an accumulation of potentially harmful upstream metabolites, especially mevalonate, which subsequently accumulates and exerts toxic effects on keratinocytes with apoptosis and altered epidermal differentiation. In addition, increased intracellular concentration of mevalonate promotes macrophage activation with increased release of macrophage-derived cytokines (like

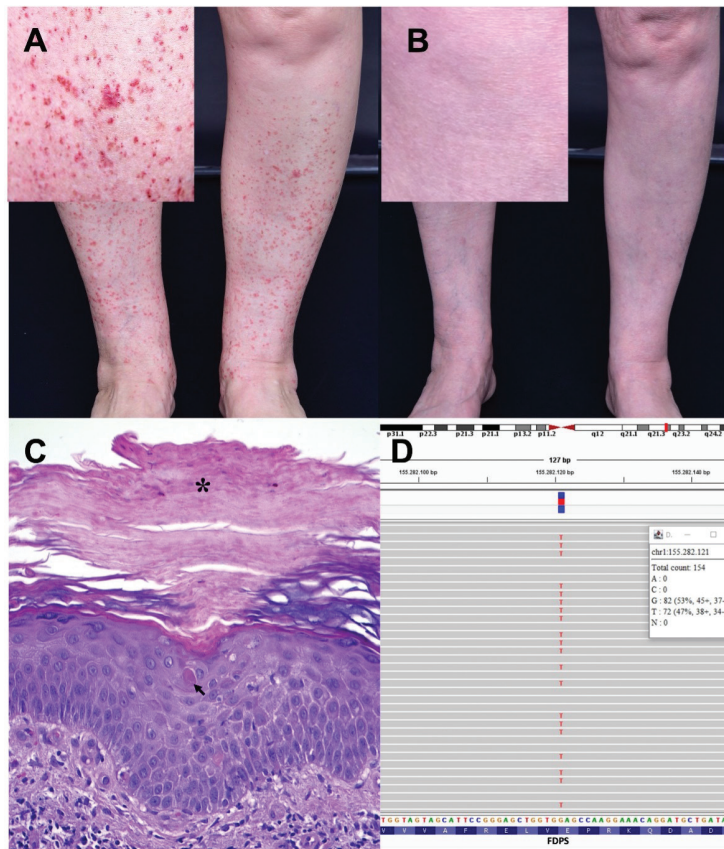


Fig. 1. Clinical picture and treatment success with topical simvastatin/cholesterol ointment, histology, and the underlying likely pathogenic gene variant. (A) Before treatment both legs show numerous annular, reddish-brown plaques and papules with a hyperkeratotic border surrounding a central atrophic area, close-up view depicted by insert. (B) The lesions resolved completely after 5 weeks of topical therapy, close-up view depicted by insert. (C) Haematoxylin and eosin (H&E) stained punch biopsy revealed a typical cornoid lamella (*) in the epidermis. Dyskeratotic (apoptotic) keratinocytes (→) and mild lymphocytic infiltration were present in the upper dermis. (D) Alignment of next-generation-sequencing areas of proband (displayed as grey bars) to reference sequence (row of letters, below). The c.415G > T likely pathogenic variant is highlighted by the red T and accounts for 47% of the reads suggesting heterozygosity.

IL-1 β , IL-6 and TNF- α), enforcing skin inflammation (6). Furthermore, a decrease in enzyme activities of the mevalonate pathway disrupts cholesterol production, one of the end-products of this pathway. Cholesterol is essential for maintaining a functional epidermal barrier and lower levels of cholesterol increase the sensitivity of keratinocytes to ultraviolet A (UVA)-induced apoptosis (7). While topical simvastatin/cholesterol unfolds its effect via local transcutaneous absorption, oral statins are most likely ineffective due to hepatic first-pass metabolism. This is consistent with the observation that pre-treatment of our patient with an oral statin did not lead to any improvement in lesions.

Up to now, only 2 nonsense mutations in *FDPS* have been described in patients with porokeratosis (8–12). The truncating variant reported herein converts the glutamic acid at position 139 into a termination codon, resulting in domain deletion with an anticipated functional decline of the *FDPS* enzyme activity. Furthermore, the pathway of nonsense-mediated mRNA decay (NMD) present in eukaryotic cells recognizing and eliminating mRNAs with translation termination codons is another potential mechanism to explain decrease in enzyme activity. The wildtype *FDPS* gene codes for an enzyme that is responsible for the production of geranyl pyrophosphate and farnesyl pyrophosphate key intermediates in the cholesterol and isoprenoid biosynthesis (Fig. 2). In consequence, the mevalonate pathway, which regulates

cell growth, division, and differentiation in keratinocytes, is impaired. Furthermore, geranyl pyrophosphate deficiency likely leads to inflammasome activation, a

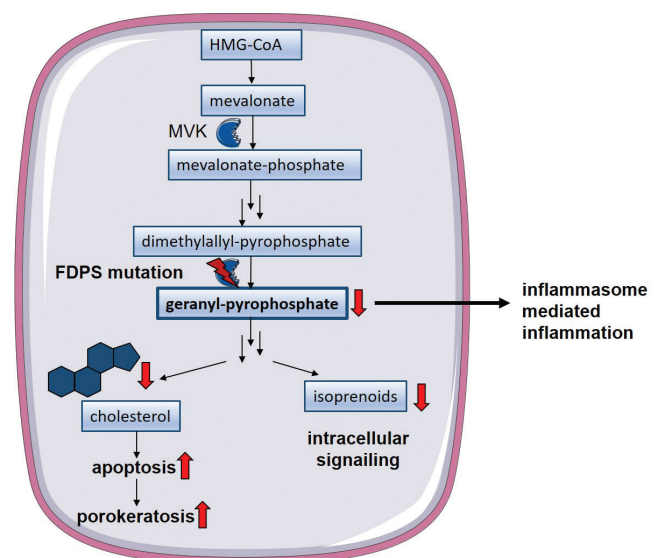


Fig. 2. Schematic overview of mevalonate pathway impairment caused by a mutation within the *FDPS* gene (farnesyl diphosphate synthase). *FDPS* plays a decisive role in the synthesis of geranyl-pyrophosphate in the mevalonate pathway and if mutated leads to inflammasome activation and reduced cholesterol synthesis with impaired growth, differentiation of keratinocytes disrupting the epidermal barrier. *MVK*: mevalonate-kinase. Created with Smart.Servier.com (accessed May 2024).

crucial component of the innate immune system, which activates the pro-inflammatory IL-1 β . Similar to earlier reported mutations in the mevalonate pathway (13), the here described mutation in the *FDPS* gene likely enforces increased inflammation, abnormal keratinocyte differentiation, and the lack of cholesterol/isoprenoid biosynthesis underlying the development of the observed inflammatory porokeratotic phenotype.

Porokeratosis follows a chronic course and treatment has proven challenging in the past. Current treatment options focus on either lesion destruction using cryotherapy, photodynamic therapy, CO₂ lasers, and/or 5-fluorouracil, or impacting on epidermal differentiation and suppression of inflammation with acitretin corticosteroids and vitamin D analogues (1).

In terms of a pathogenesis-directed therapy, topical cholesterol-lovastatin ointment leads to clearance of lesions in patients suffering from various subtypes of porokeratosis (10). Hydroxymethylglutaryl-CoA reductase is the responsible enzyme for mevalonate synthesis. Inhibition of hydroxymethylglutaryl-CoA reductase activity by statins results in a decrease in mevalonate and, in the here presented case, to reduced dimethylallyl-pyrophosphate concentrations. Reduced concentrations of dimethylallyl-pyrophosphate are likely better processed by the rest activity of the farnesyl diphosphate synthase enzyme encoded by the heterozygous wild type *FDPS* allele. In addition, topical application of cholesterol helps to restore the epidermal barrier (14). We show that topical application of simvastatin/cholesterol can fully reverse clinical signs of DSAP in a patient with a described *FDPS* variant with no reported side effects. This treatment confirms previous reports and helps to understand the link between gene mutation, biochemical changes in the mevalonate pathway, with the corresponding histological and clinical pathology, and a targeted treatment approach for a so far difficult-to-treat condition of porokeratosis (15).

In summary, we have here identified a previously unreported *FDPS* truncating variant leading to DSAP, which responded to topical combination therapy with simvastatin/cholesterol. For further confirmation, vehicle-controlled randomized trials are essential in future.

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The authors have no conflicts of interest to declare.

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