Novel *POFUT1* mutation in patient with flexural and acral hyperpigmented reticulated macules presenting in adolescence

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INTRODUCTION

Dowling-Degos disease (DDD) is an autosomal dominant pigmentary disorder characterized by reticular hyperpigmentation, hypopigmentation, and hyperkeratotic papules of the flexures, including the neck, axillae, antecubital fossae, inframammary area and groin, and acral sites typically presenting between ages 20 and 50.[1] The clinical presentation is variable and is partly attributable to mutations causing DDD, including loss-of-function mutations in *KRT5*, *POGLUT1,* or *POFUT1*, involved in melanin synthesis and transport.[1-4] Here we report a case of DDD presenting in adolescence with prominent acral hyperpigmentation caused by a novel heterozygous truncating mutation and potential modifying single nucleotide polymorphism (SNP) in *POFUT1*.

CASE REPORT

A 27-year-old woman of Asian descent presented with hyperpigmented macules since adolescence on ventral wrists (Fig 1, *A*), ankles (Fig 1, *B*), dorsal hands and feet, face, neck, and axillae and hypopigmented macules on the ankles. Family history was notable for similar macules in the patient's mother, maternal aunt, and grandmother.

Genomic DNA was extracted from the patient's peripheral blood. Whole exome sequencing found a heterozygous truncating mutation, NM_015352.1:c.342delC (NP_056167.1:p.Thr115fs) in *POFUT1* (Fig 2).[5] An SNP, NP_056167.1:p.Met251Val in *POFUT1,* was also present, but no other pathogenic mutations were found in *KRT5*, *POGLUT1*, *ADAM10*, or *ADAR*. Together, the findings confirmed a diagnosis of DDD.

Abbreviations used:

DDD: Dowling-Degos disease
SNP: single nucleotide polymorphism

DISCUSSION

DDD, caused by mutations in *KRT5*, *POGLUT1,* or *POFUT1,* has a variable clinical presentation, which is likely related to the heterogeneity of the mutation landscape.[6,7] The phenotype of DDD caused by *POFUT1* mutations appears particularly complex.[1] Similar to other reported cases, our patient showed prominent acral involvement but lacked hyperkeratotic papules, erythematous macules, palmar pits, or interrupted dermatoglyphics.[1] The frameshift mutation described here results in a truncated and likely dysfunctional POFUT1 protein. These proteins are thus far the most common type of mutation described in *POFUT1* and include 9 other truncating mutations on *POFUT1*.[6] It is possible that the *POFUT1* SNP identified in our patient may contribute to the phenotype given it is likely to impact POFUT1 function as determined by several prediction tools of genomic variants, SIFT, PolyPhen-2, and CADD.[8-10] This SNP is rare in all populations with the exception of those of East Asian descent, 0.004 to 8 versus 0.04

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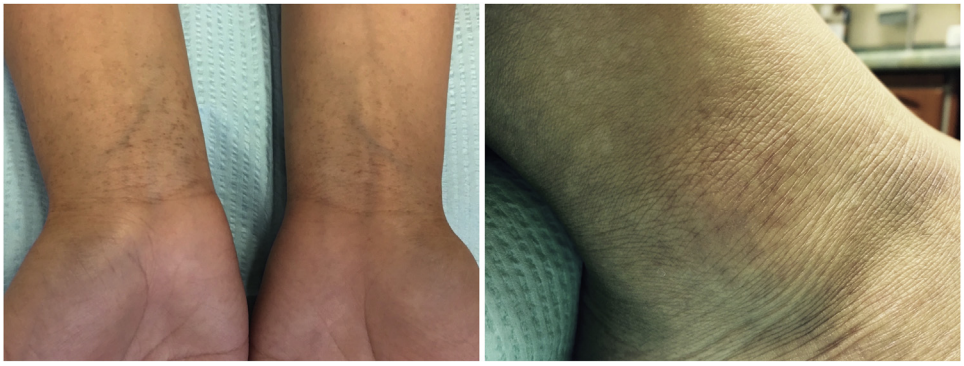

Fig 1. **A**, Hyperpigmented macules of the ventral wrists. **B**, Hyperpigmented macules of the ankles.

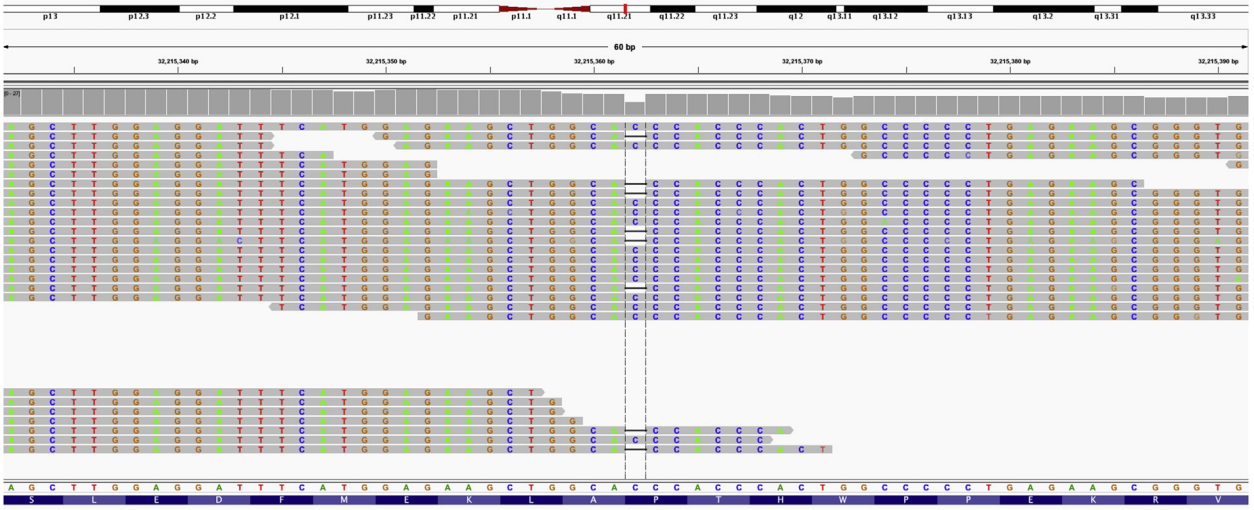

Fig 2. The heterozygous frameshift *POFUT1* mutation NM_015352.1:c.342delC (NP_056167.1:p.Thr115fs) identified in the patient through whole-exome sequencing (Integrative Genomics Viewer v2.3.93; GRCh38).[5]

to 0.05, respectively. Our study highlights the phenotypic heterogeneity seen in DDD, particularly when it is caused by mutations in *POFUT1* and a potential modifying SNP.

Distribution of skin lesions, associated clinical findings, and age of onset can be helpful in differentiating DDD from other inherited reticulate pigmentary disorders, including reticulate acropigmentation of Kitamura, dyschromatosis symmetrica hereditaria (reticulate acropigmentation of Dohi), dyschromatosis universalis hereditaria, X-linked reticulate pigmentary disorder, epidermolysis bullosa simplex with mottled pigmentation, dermatopathia pigmentosa reticularis, and dyskeratosis congenita,[1] but given the phenotypic variability, genetic testing is needed to confirm the diagnosis. Early recognition and genetic testing are important for patient counseling. The treatment of DDD remains difficult with limited efficacy of therapies such as hydroquinone, retinoids, or adapalene. Laser treatments, such as erbium- yttrium aluminum garnet and intense pulsed light, show some promise.[1] Further studies are needed to ascertain the pathogenesis of this group of diseases for development of targeted treatment options.

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