

## Whole exome sequencing in a multi-generation family from India reveals a genetic variation c.10C>T (p.Gln4Ter) in keratin 5 gene associated with Dowling–Degos disease

Sir,

Dowling–Degos disease (OMIM: 179850) is a rare genodermatosis characterized by reticulate pigmentation of the flexures.<sup>1</sup> This disease is inherited in an autosomal dominant pattern,<sup>2</sup> with onset typically in early adulthood. The clinical presentation is with development of hyperpigmented, reticular macules on the face, trunk, axillae and groin.<sup>1,3</sup> The mutations causing the disease are usually found in the keratin 5 (*KRT5*)<sup>4</sup> gene and rarely in the protein O-fucosyl transferase 1 (*POFUT1*)<sup>5</sup> and protein O-glucosyltransferase 1 (*POGLUT1*) genes.<sup>6</sup> *POGLUT1* and *POFUT1* are components of the *Notch* signaling pathway, involved in the differentiation and migration of cells. Mutations in these genes affect the skin more than the hair.<sup>5</sup> Only a few cases suffering from this disease have been described previously from India, as it is a rare disorder with an unknown population frequency.<sup>7,8</sup> In the current report, we emphasize the utility of whole exome sequencing in the molecular characterization of the genetic defect, in a rare familial case of a reticular pigmentation disorder.

The multi-generational family comprised over 30 individuals in four generations, with 14 members suffering from a reticular pigmentation abnormality [Figure 1a-d] affecting the face, axillae and the trunk. Some members of the family have been previously reported in a recent case series.<sup>7</sup> The Proband (III.9) was a 42-year-old female who presented with multiple hyperpigmented papules and macules localized to the face, neck and abdomen. Acantholysis was seen on histopathology. Her father (II.5) had multiple wide-spread itchy erythematous papules and plaques involving the face, upper and lower limbs and trunk [Figure 1a-d]. Her daughter (IV.10) had similar lesions, while her son (IV.9) was asymptomatic. Another member (III.2) of the family had multiple erythematous and hyperpigmented itchy papules and patches over the face, abdomen and limbs, clinically suspected to be a case of Galli–Galli disease. Her

mother (II.4) and both the affected children (IV.1 and IV.2) showed similar features.

Because there were three genes typically mutated in Dowling–Degos disease and *KRT5* mutation screening was not readily available in India, we attempted whole exome sequencing to characterize the genetic variation. In addition, our selection of the technique was guided by the fact that reticular pigmentation disorders have overlapping phenotypes and genes involved. The study was approved by the Institutional human ethics committee of CSIR-IGIB (IHEC proposal no. 8). DNA was isolated from whole blood using salt-precipitation method and whole exome sequencing (WES) was performed for one affected individual following manufacturer's instructions (Illumina Inc., USA). WES analysis revealed a G to A transition (chr12:g.52914071G>A) in exon 1 of *KRT5* gene, which also corresponds to C to T change at position 10 in *KRT5* cDNA (c.10C>T). The mutation resulted in the substitution of glutamine by a stop codon at fourth residue (p.Gln4Ter). This variant was not present in 1000 genome, ExAC and al mena<sup>9</sup> datasets and was also absent in the internal control database of South Asian Genomes and Exomes. The variant was present in ClinVar (RCV000056543.1) with no clinical assertions provided. We also attempted to systematically curate literature evidence for genetic variants associated with Dowling–Degos disease. Detailed literature analysis revealed that the genetic variant *KRT5*:c.10C>T was previously reported from India<sup>8</sup> and China<sup>10</sup> in patients suffering from Dowling–Degos disease and presenting with similar clinical features. The variant was further confirmed by capillary sequencing in the index case (III:9) and two other affected members (III.2 and IV: 2), and was found to be absent in one unaffected member (IV:9) [Figure 1e].

The mode of inheritance, familial segregation, functional consequences and the extreme rarity of the variation in



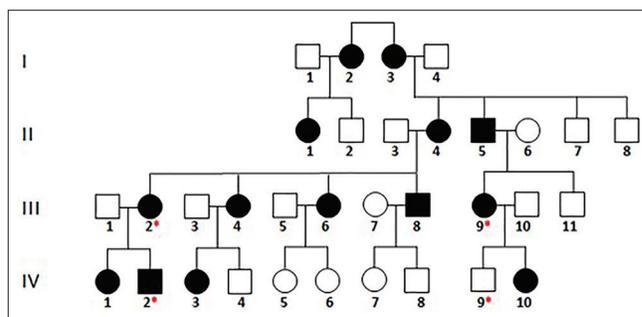
**Figure 1a:** Representative clinical image showing reticular pigmentation of the face



**Figure 1b:** Representative clinical image showing pigmentation of the axilla



**Figure 1c:** Representative clinical image showing the chest. The representative clinical images are for patient II:5



**Figure 1d:** Representative clinical images showing pedigree of the family. The members for whom genetic testing was performed are marked with a red asterisk

population frequency databases provides ample evidence that the variation c.10C>T<sup>8,10</sup> in *KRT5* is associated with Dowling–Degos disease. Apart from confirming the association of the variant through familial segregation, our analysis suggests that the variant could potentially be quite prevalent in the population, given another report from an unrelated family.<sup>4</sup> Therefore, we suggest that a systematic screening for the mutation could potentially benefit a large number of patients and families. Given the cost-effectiveness, speed and ease of use, we propose that whole-exome sequencing could be of clinical utility for effective molecular diagnosis in rare cases of genodermatoses, especially in cases where overlapping clinical features could preclude an accurate diagnosis.

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**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

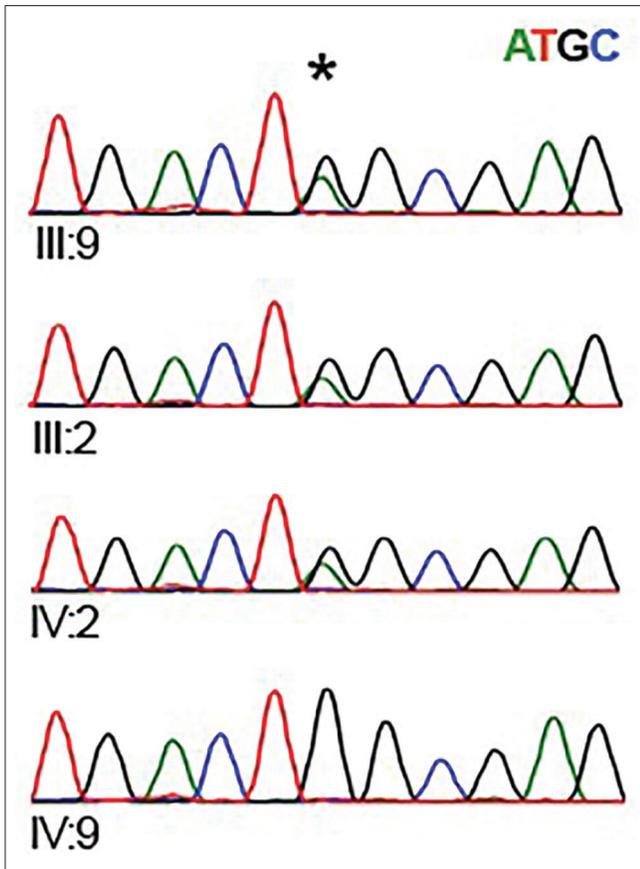
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**Conflicts of interest**

There are no conflicts of interest.

*Neha Virmani,  
Shamsudheen Karuthedath Vellarikkal<sup>1</sup>,  
Ankit Verma<sup>1</sup>, Rijith Jayarajan<sup>1</sup>, Jagdish Sakhiya,  
Chirag Desai<sup>2</sup>, Sridhar Sivasubbu, Vinod Scaria*



**Figure 1e:** Representative clinical images of independent validation of the variant keratin 5:c.10C>T (marked with black asterisk) in the index case (III:9) and two other affected members (III:2 and IV:2) of the family

Department of Dermatology, Sakhiya Skin Clinic, Surat, Gujarat,  
<sup>1</sup>Genomics and Molecular Medicine, CSIR Institute of Genomics and Integrative Biology, New Delhi, <sup>2</sup>Department of Dermatology, Seth GSMC and KEM Hospital, Mumbai, Maharashtra, India

**Correspondence:** Dr. Vinod Scaria,  
 CSIR Institute of Genomics and Integrative Biology, Mathura Road,  
 New Delhi - 110 025, India.  
 E-mail: vinods@igib.in

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