

Middle of the breasts pigmentation in a pedigree with POFUT1-related Dowling-Degos disease, expansion of the phenotype

Yingda Wu, Wanlu Zhang, Jianbing Wu, Yiping Ma, Pangen Cui, Chengrang Li

Department of Dermatology, Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College, Nanjing, Jiangsu, China

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Dowling-Degos disease (DDD [MIM: 179850, 615327 and 615674]), also called reticulate pigmented anomaly of the flexures (RPAF), is characterized by post-pubertal reticulate hyperpigmentation, particularly affecting the flexural areas and other great skin folds [1, 2]. As a rare autosomal dominant disorder, DDD-related genes include *KRT5*, *POFUT1* and *POGLUT1* genes [1–3].

We report a 37-year-old woman characterized by reticulated brown-black pigmented macules on the anterior chest, inframammary folds, dorsa of the neck, axillary folds, inguinal regions, flexor surfaces of the both wrist and inner sides of the thighs of 17 years' duration. All other systemic examinations were within normal limits. The parents of the proband were not consanguineous marriage. The family study unveiled that her paternal grandfather (I:1), father (II:1) and two aunts (II:3, II:4) suffer from a similar condition (Figure 1 A).

The proband's DDD-related genes (*KRT5*, *POFUT1* and *POGLUT1*) coding sequence and exon-intron junction analysis by Sanger sequencing revealed a heterozygous nonsense codon mutation c. 945T>G (p. Y315X) variant in exon 6 of the *POFUT1* (Figure 1 B). This mutation was not detected in unaffected family members and 100 normal individuals (Figure 1 C). The c. 945T>G mutation causes the premature termination of O-fucosyltransferase-1's polymerization. This variant was not present in the db-SNP or the HGMD.

Specifically, the proband presented with severe neck lesions and featured scattered comedones and pitted acneiform scars on the neck (Figure 1 D), which may hint the corresponding with acne inversa. A mixture of hyperpigmented and hypopigmented macules in the inner sides of wrists resembles features of dyschromatosis symmetrica

hereditaria (Figure 1 E). Notably, this report is the first one to find the middle of the breasts as a clinical feature of DDD (Figure 1 F). Though the middle of the breasts means a reticulate area, it has not been found before yet. In addition, inframammary folds involved in this report have been found in four already published articles.

The *POFUT1* gene, as a member of the glycosyltransferase O-Fuc family, encodes the protein O-fucosyltransferase-1, which is composed by 388 amino acid residues with seven exons. The protein O-fucosyltransferase-1 supplies O-fucose to EGF (epidermal growth factor-like), prompting O-fucosylation of the Notch receptor signaling protein, which requires GDP-fucose as a substrate [4]. There are totally 16 GDP-Fucose binding sites on a conserved domain of O-FucT-1 varying from 30 to 379 residues. This novel nonsense mutation c. 945T>G (p. Y315X) is located in the conserved domain instead of a binding site, ending up with the coding of just 11 binding sites and generating a truncated protein. This truncated protein is largely non-functional and this consequence is supported by online software analysis.

Recently, *PSENEN* mutation carriers have been partly found to be caught in DDD and the inner cause of coexistence between DDD and acne inversa remains a mystery [5]. DDD is hypothesized to increase the susceptibility of acne inversa when exposed to some risk factors [5]. Interestingly, DDD and acne inversa were deemed the different subphenotypes of *PSENEN* mutation, when the hyperpigmentation is the main feature, we view it DDD; whereas when the follicle keratosis occupies the main location, we consider it acne inversa [6]. Further pathogenesis studies are needed to understand the development of DDD and other related skin diseases.

Address for correspondence: Pangen Cui, Chengrang Li, Department of Dermatology, Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College, 12 Jiang Wang Miao St, Xuanwu District, Nanjing, 210042, China, e-mail: cui.pangen@126.com, dr_lcr72@163.com

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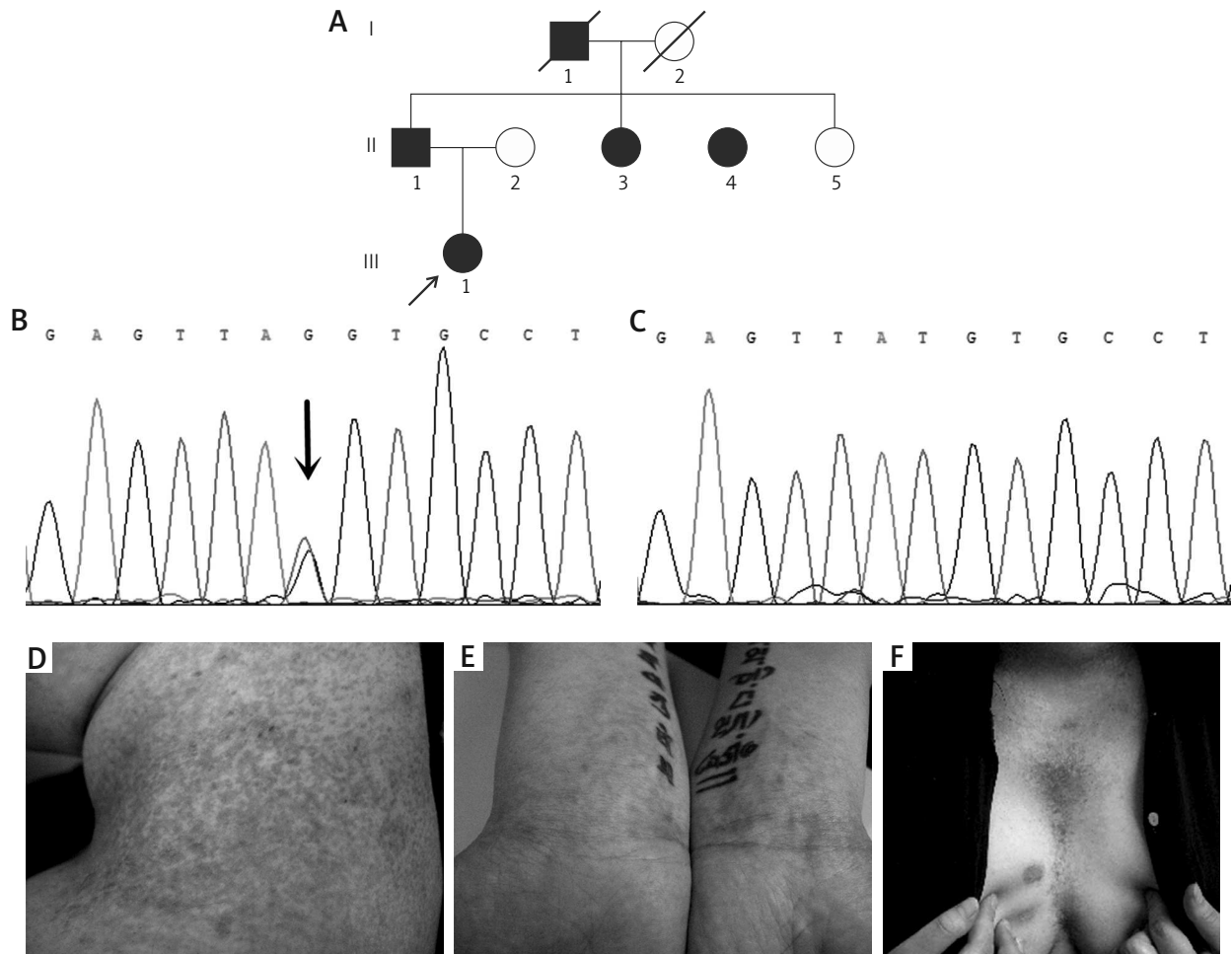


Figure 1. POFUT1 mutations and clinical appearance of the patients. **A** – Genealogical tree of the proband’s family. **B** – The gene mutation result: c. 945T>G (p. Y315fs). **C** – Wild-type sequence of the gene mutation. **D** – Proband’s neck lesions. **E** – Proband’s inner sides of wrists presentation. **F** – Proband’s chest lesions

In conclusion, we report a DDD family with a novel gene mutation and we are first to find a new clinical feature involving areas in the middle of breasts, which enrich the phenotype, gene mutation database and contribute to genetic counselling to the patients’ family.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Li M, Cheng R, Liang J, et al. Mutations in POFUT1, encoding protein O-fucosyltransferase 1, cause generalized Dowling-Degos disease. *Am J Hum Genet* 2013; 92: 895-903.

2. Betz RC, Planko L, Eigelshoven S, et al. Loss-of-function mutations in the keratin 5 gene lead to Dowling-Degos disease. *Am J Hum Genet* 2006; 78: 510-9.
3. Basmanav FB, Oprisoreanu A, Pasternack SM, et al. Mutations in POFUT1, encoding protein o-glycosyltransferase 1, cause autosomal-dominant Dowling-Degos disease. *Am J Hum Genet* 2014; 94: 135-43.
4. Zhang J, Li M, Yao Z. Updated review of genetic reticulate pigmentary disorders. *B J Dermatol* 2017; 177: 945-59.
5. Ralser DJ, Basmanav FB, Tafazzoli A, et al. Mutations in γ -secretase subunit-encoding PSENEN underlie Dowling-Degos disease associated with acne inversa. *J Clin Invest* 2017; 127: 1485-90.
6. Li C, Li W, Xu H, et al. PSENEN mutation carriers with co-manifestation of acne inversa (AI) and Dowling-Degos disease (DDD): is AI or DDD the subphenotype? *J Invest Dermatol* 2017; 137: 2234-6.