Based on these results, psoriasis patients identified in the clinic with BSA of greater than 10% should be targeted for preventative health interventions. Additionally, future research is needed to better elucidate the specific causes of mortality in patients with extensive psoriasis and determine the effects of psoriasis treatment on mortality risk.

ORCID

Megan H Noe: http://orcid.org/0000-0001-8481-4711

CONFLICT OF INTEREST

In the previous 12 months, JMG served as a consultant for Coherus (DSMB), Dermira, Janssen Biologics, Merck (DSMB), Novartis Corp., Regeneron, Dr Reddy's labs, Sanofi and Pfizer Inc., receiving honoraria; receives research grants (to the Trustees of the University of Pennsylvania) from Abbvie, Janssen, Novartis Corp., Regeneron, Sanofi, Celgene, and Pfizer Inc.; and received payment for continuing medical education work related to psoriasis that was supported indirectly by Lilly and Abbvie. JMG is a co-patent holder of resiquimod for treatment of cutaneous T-cell lymphoma. MHN, DBS, and MTW state no conflict of interest.

***Megan H. Noe*[1,*], *Daniel B. Shin*[1], *Marilyn T. Wan*[1] *and Joel M. Gelfand*[1,2]**

[1]*Department of Dermatology, University of Pennsylvania, Philadelphia, Pennsylvania, USA; and* [2]*Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, Pennsylvania, USA*

[*]*Corresponding author e-mail: megan.noe@uphs.upenn.edu*

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A Missense Mutation within the Helix Termination Motif of *KRT25* Causes Autosomal Dominant Woolly Hair/Hypotrichosis

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TO THE EDITOR

Woolly hair (WH)/hypotrichosis is an unusual condition characterized by sparse and tightly curled hair (Ramot and Zlotogorski, 2015a). WH may be isolated or be accompanied by additional complications including palmoplantar keratoderma, hypotrichosis, epidermal naevus, and cardiomyopathy (Ramot et al., 2014; Veraitch et al., 2016). Isolated WH can manifest with autosomal dominant (AD) or autosomal recessive trait of inheritance (Shimomura, 2016).

Keratins are scaffolding proteins that form a network of intermediate filaments (IFs). Heterodimerization between type I and II keratin to form keratin IFs is the basic building block for hair structure (Ramot and Zlotogorski, 2015b). The phenotypic heterogeneity caused by different keratin genes also depends on their location within different hair structures, including the cortex of the hair shaft, the cuticle, and the inner root sheath (Naeem et al., 2006).

Variants in keratins K71 and K74 were described in ADWH pedigrees, and polymorphisms in *KRT75* were implicated in the pathogenesis of pseudofolliculitis barbae (Fujimoto et al., 2012; Wasif et al., 2011; Winter et al., 2004). Recently, biallelic variants within *KRT25* were also related to autosomal recessive WH/hypotrichosis pedigrees (Ansar et al., 2015; Zernov et al., 2016).

Here, we describe a monoallelic pathogenic variant in a Chinese ADWH/hypotrichosis family, five-

Abbreviations: AD, autosomal dominant; IF, intermediate filament; WH, woolly hair

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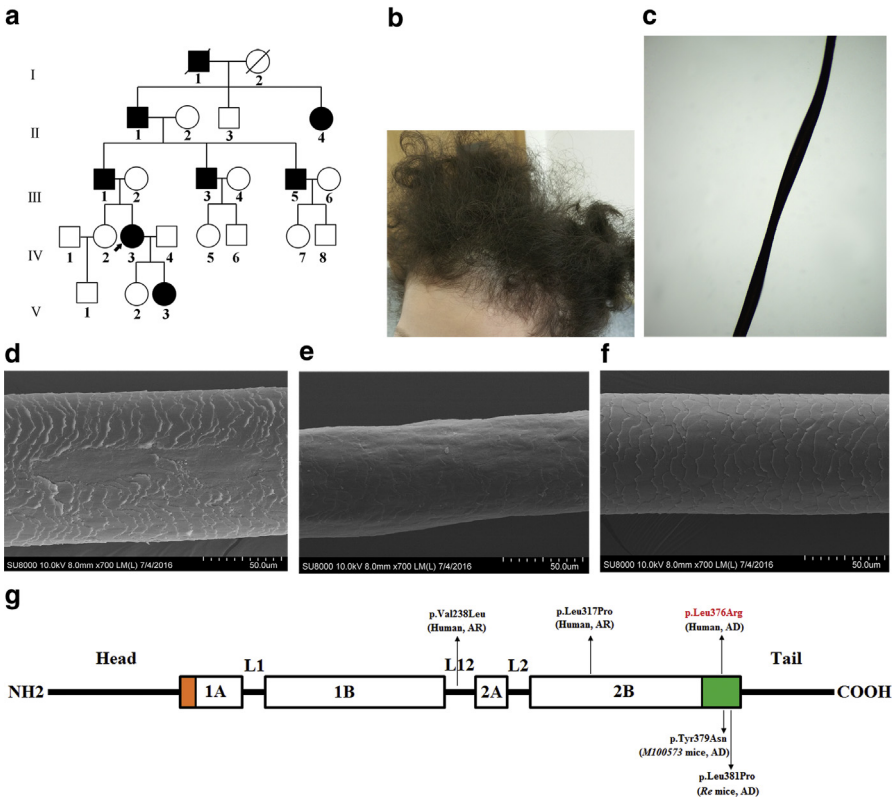

Figure 1. Family pedigree, clinical features, LM, and SEM observation of the HS from the proband's younger daughter. SEM observation of the HS from the proband's elder daughter, and schematic representation of K25 protein. (**a**) Family pedigree. (**b**) The proband's younger daughter showed ADWH/hypotrichosis: wiry, coarse, curled, dry, hypopigmented, and fragile. (**c**) Under LM, the HS of affected individuals characteristically showed local variations in diameter, irregular curled HS contours, sharp corners (×40). (**d**) Under SEM, the cortex of affected HS was partially exposed with irregular overlay of the cuticle. Desquamation of lifting cuticle layers was obvious. (**e**) HS of affected individuals frequently showed longitudinal grooves. (**f**) The proband's elder daughter showed intact hair with regular overlay of the cuticle. Scale bar = 50 μm. (**g**) Schematic representation of K25 protein. The location of mutation p.Leu376Arg in human K25 is shown above the scheme and is indicated in red. The two variants of K25 identified in the mice are shown below the scheme. Mutations in the *M100573* mice and the *Re* mice are dominantly inherited, whereas the other two variants (Val238Leu and Leu317Pro) in human are recessive variants. The HIM and HTM are colored in orange and green, respectively. AD, autosomal dominant; AR, autosomal recessive; HS, hair shaft; LM, light microscopy; SEM, scanning electron microscopy; WH, woolly hair.

generation pedigree consisting of 23 individuals (Figure 1a). The proband (IV-3) was a 40-year-old woman, born with sparse, soft, and curled scalp hairs. Her hairs were less dense and slower to grow compared with age-matched individuals. Her hairs looked wiry, coarse, curled, dry, hypopigmented, and fragile. The frontotemporal hairline was normal. There were no other obvious abnormalities. Other patients showed similar manifestation (Figure 1b). Light microscopy of the patients demonstrated local variations in diameter, showing irregular curled contours and sharp corners (Figure 1c). Scanning electron microscopy showed that the cortex was partially exposed with irregular overlay of the cuticle. Desquamation of lifting cuticle layers was obvious (Figure 1d). More frequent longitudinal grooves suggested a tendency to break at the delicate location (Figure 1e and f). The damage level was 10 out of the 12-point scale classification system (Lee et al., 2016), or 4 out of the five-grading system (Kim et al., 2010).

The genomic DNA was extracted from four patients (III-1, III-3, IV-3, and V-3) and six unaffected individuals (III-2, IV-1, IV-2, IV-4, V-1, and V-2). We sequenced the exomes of three patients (IV-3, III-1, V-3) and two unaffected individuals (V-2 and IV-2) (Supplementary Material S1 online). Sequence variants were initially filtered against dbSNP146, the 1000 Genomes Project, ExAC, and our internal database. Assuming AD transmission, the downstream variant filtering strategy was as follows: heterozygous variants present in the patients but not in the unaffected individuals were treated as possible candidates (Supplementary Material S1). This strategy reduced the number of variants to eight missense variants. Finally, only one out of the eight single nucleotide polymorphisms passed through the conservation assay. Sanger sequencing also confirmed that the heterozygous missense mutation in *KRT25* (c.1127T>G, p.Leu376Arg) fully co-segregated with the disease status in this family. No mutation detection in 200 ethnically matched normal controls suggested the likely deleterious variant (Supplementary Figure S1a and b online).

KRT25 encodes a member of the type I keratin family with a characteristic structure: the N-terminal head domain, the central α-helical rod domain, and the C-terminal tail domain. The central α-helical rod domain starts with the helix initiation motif and ends with the helix termination motif. Leu residue at position 376 is located within the helix termination motif (Figure 1g), where it is highly conserved amongst all human type I keratin members (Supplementary Figure S1c). Besides, sequence alignment of K25 among various mammals indicates that Leu376 is highly conserved (Supplementary Figure S1d). A single missense substitution in the helix termination motif of the type I inner root sheath gene *krt25* was shown to underlie wavy/curly coat phenotype in *M100573* and *Re* mice (Figure 1g) (Tanaka et al., 2007).

To predict the potential effect of p.Leu376Arg variant on the function of human K25, we integrated multiple bioinformatics tools. The results suggested that p.Leu376Arg variant influenced the structure of K25 and the binding between K25 and its partner K71. Because K25 and K71 belong to the superfamily of intermediate filament proteins that form an integral part of the cytoskeleton, changes in their binding may affect a variety of cellular characteristics (Supplementary Material S1). To determine the impact at the cellular level, we transfected the