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

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 cardiomypathy (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-
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.

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
recessively (Zernov et al., 2016). The manifestation in homozygotes, and transmit the nonhelical linker subdomains loinsufficiency. By contrast, variants in dominant-negative effects or haploinsufficiency. KRT25 affects the stability of the cytoskeleton. Further research will be beneficial to fully clarify the genetic and phenotypic heterogeneity of WH/hypotrichosis. In addition, such variable clinical severity might be the coordinated consequence of the nature of the pathogenic variant, modifier genes, and/or compensatory pathways.

Previous studies suggested that variants in the α-helical subdomains of keratin genes interfere with keratin heterodimer formation and cause dominant-negative effects or haploinsufficiency. By contrast, variants in the nonhelical linker subdomains interfere with the higher order formation of heterodimers into keratin IF, manifest in homozygotes, and transmit recessively (Zernov et al., 2016). The variant we identified within KRT25 exhibited moderate phenotypic expression and involved the scalp hairs alone with a clinically similar appearance to homozygous mutations in KRT25 albeit (Ansar et al., 2015; Zernov et al., 2016). We speculate that the mutation may act as a dominant negative in this pedigree. In addition, such variable clinical severity might be the coordinated consequence of the nature of the pathogenic variant, modifier genes, and/or compensatory pathways.

In summary, we report a Chinese ADWH/hypotrichosis pedigree that results from a heterozygous non-synonymous variant in KRT25. We conclude that mutation in KRT25 affects the stability of the cytoskeleton and hypothesize that this is how it affects hair in WH syndromes.

This study was approved by the Ethics Committees of Shanghai Jiaotong University School of Medicine and conducted in accordance with the principles of the Declaration of Helsinki. After obtaining written informed consent, we collected peripheral blood samples from the family members. Patients or guardians gave permission to publish their images and information.

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**CONFLICT OF INTEREST**
The authors state no conflict of interest.

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**REFERENCES**


