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Review article

Journey toward unraveling the molecular basis of hereditary hair disorders

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ABSTRACT

Recent advances in molecular genetics have led to the identification of many genes expressed in hair follicle (HF), while the precise roles of these genes in the HF have not completely been disclosed. Using the methods of forward genetics, we and others have recently identified a series of genes responsible for hereditary hair disorders in humans, including monilethrix, woolly hair, and various ectodermal dysplasia syndromes. Furthermore, expression and functional analyzes have gradually revealed that these genes are directly or indirectly related with each other. As such, the journey toward unraveling the molecular basis of hereditary hair disorders will contribute to better understanding of the complex mechanisms for HF morphogenesis and development in humans.

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Abbreviations: HF, hair follicle; AD, autosomal dominant; AR, autosomal recessive; KIF, keratin intermediate filament; ch, chromosome; HIM, herix initiation motif; HTM, herix termination motif; ER, endoplasmic reticulum; WH, woolly hair; PPK, palmoplantar keratoderma; IRS, inner root sheath; LPA, lysophosphatidic acid; ED, ectodermal dysplasia; OODD, odonto-onycho-dermal dysplasia; PHNED, pure hair and nail ectodermal dysplasia; EEC, ectrodactyly-ectodermal dysplasia-cleft lip/palate; ADULT, acro-dermato-ungual-lacrimal-tooth; AEC, ankyloblepharon-ectodermal defects-cleft lip/palate; HJMD, hypotrichosis with juvenile macular dystrophy; EEM, ectodermal dysplasia-ectrodactyly-macular dystrophy.

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1. Introduction

Hair follicle (HF) is a skin appendage that is generated through close interaction between ectoderm and mesenchyme during embryogenesis [1]. The HF has a fascinating feature of regeneration and undergoes hair cycle throughout the postnatal life, which consists of three phases named anagen, catagen and telogen. It has previously been shown that the epithelial stem cells are localized in the bulge portion of the HF, where arrector pili muscle is attached [2]. During the anagen phase, daughter cells derived from the bulge move to the matrix region, and matrix cells actively proliferate and differentiate into several distinct layers of the HF including hair shaft, inner root sheath, and companion layer [3]. Recent advances in molecular genetics enabled us to identify numerous genes expressed in the HF [1,4,5]. However, a lot of questions remain to be answered. For example, we do not know completely which genes are critical for HF development and cycling. We also do not know well the mechanism responsible for determining hair texture, or the mechanism that causes HF miniaturization. To find the answers to these questions, mammalian genetics can become a powerful tool. There are two different approaches to mammalian genetics. One is forward or clinical genetics, in which we start from patients with some genetic diseases, and perform linkage studies and/or exome sequencing to identify the causative genes. By contrast, in reverse genetics, we first choose a gene of interest and make model animals. Then, we analyze the phenotype and try to make link to human diseases. Both approaches are equally important, while the forward genetics has an advantage in the point that genes identified via this approach are definitely crucial for human HFs. In the past 20 years, a number of genes responsible for various hereditary hair disorders in humans have been identified. In this review article, I will mainly describe the diseases and their causative genes, focusing on those that I myself was involved in the projects for them.

2. Monilethrix

Monilethrix is a non-syndromic hair disorder characterized by fragile scalp hair shafts which are frequently accompanied with perifollicular papules and erythema (Fig. 1A). Under microscopic observation, the patients' hair shaft shows a characteristic anomaly named beaded hair or moniliform hair with periodic changes in hair diameter, leading to form nodes and internodes (Fig. 1B) [6]. The disease typically shows an autosomal dominant (AD) inheritance pattern (OMIM #158000), while minority of cases can show an autosomal recessive (AR) inheritance trait (OMIM #252200). More than 30 years ago, it was predicted that monilethrix would be an anomaly resulting from disruption of keratin intermediate filaments (KIF) in the hair shaft cortex [6]. Indeed, AD monilethrix has been shown to be caused by heterozygous mutations in type II hair keratin genes *KRT81*, *KRT83*, or *KRT86* on chromosome (ch) 12q13 [7,8]. Importantly, all of these keratins are predominantly expressed in keratinizing zone of the hair shaft cortex [9], and most of the mutations reported to date are critical amino acid changes in either helix initiation motif (HIM) or herix termination motif (HTM) of each hair keratin. The HIM and HTM are highly conserved amino acid sequences in N-terminal and C-terminal regions of the central rod domain of keratins, respectively, and are well-known to be important for heterodimerization between type I and type II keratins. Mutations in these motifs result in causing disruption of the KIF formation in a dominant-negative manner [10,11].

In 2003, desmoglein 4 (*DSG4*) gene was identified on human ch18q12.1 as a new member of desmosomal cadherins, and it was simultaneously reported that a recessively-inherited mutation in the *DSG4* gene caused an AR form of hypotrichosis (OMIM #607903) [12]. Later on, we and others found that hair shaft of patients with *DSG4* mutations could frequently exhibit moniliform hair, thus it turned out that the *DSG4* was a causative gene for AR monilethrix [13–15]. DSG4 protein is abundantly expressed in the hair shaft, and its expression overlaps with K81, K83, and K86 in the keratinizing zone [16]. As desmosomes are known to play a role in supporting a correct distribution of the KIF in the cytoplasm, it makes sense that mutations in either these hair keratin genes or the *DSG4* gene lead to show similar clinical features. However, the precise mechanisms for formation of the moniliform hair had remained largely unknown. Most recently, Kato et al. identified a homozygous frameshift mutation (c.2119delG; p.Asp707Ilefs*109) in the *DSG4* gene in a Japanese patient with monilethrix [17]. They showed that the mutant DSG4 protein accumulated in the endoplasmic reticulum (ER) and underwent ER-associated degradation, suggesting that ER stress may have a role in the pathogenesis of monilethrix [17].

3. Woolly hair (WH)

3.1. Definition and classification of WH

WH is defined as an abnormal variant of tightly curled hair (Fig. 2A). Morphologically, WH is irregularly-curved with coarse hair shaft cuticle (Fig. 2B) [18]. In most cases, WH stops growing at a few inches, thus it is thought to be a certain hair growth deficiency. Furthermore, it is noteworthy that patients of WH can also show various degrees of sparse hair phenotype (hypotrichosis). There are both syndromic and non-syndromic forms of WH. During the past 15 years, more than 10 genes have been reported to underlie either form of WH. For example, recessively-inherited mutations in junctional plakoglobin (*JUP*) and desmoplakin (*DSP*) genes, encoding components of desmosomes, have been shown to underlie Naxos disease (OMIM #601214) and Carvajal syndrome

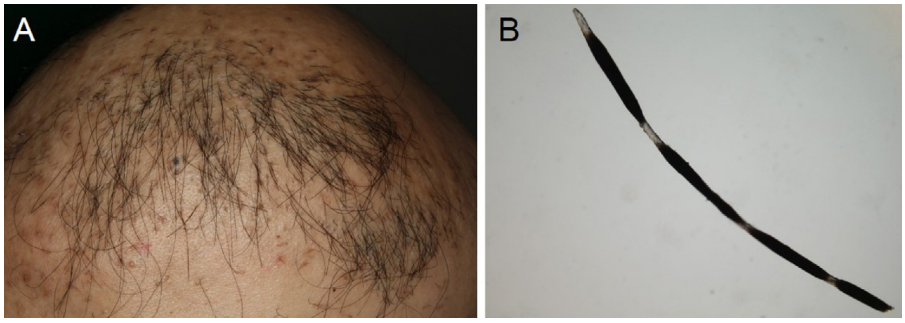

Fig. 1. Clinical features of monilethrix with a *DSG4* mutation. (A) Scalp hairs are sparse and fragile with perifollicular erythema and papules. (B) Moniliform hair under light microscopy. These pictures were kindly provided by Dr. Akira Shimizu in Gunma University, Japan.

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