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MINIREVIEWS

Knowledge explosion for monogenic skin diseases

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Abstract

During the past few decades, the investigative technologies of molecular biology - especially sequencing - underwent huge advances, leading to the sequencing of the entire human genome, as well as the identification of several candidate genes and the causative genetic variations that are responsible for monogenic skin diseases. These advances provided a solid basis for subsequent studies elucidating mechanisms of monogenic skin diseases and improving our understanding of common skin diseases. Furthermore, these discoveries also contributed to the development of novel therapeutic modalities for monogenic skin diseases. In this review, we have used the disease spectrum caused by mutations in the *CYLD* gene - Brooke-Spiegler syndrome, familial cylindromatosis and multiple familial trichoepithelioma type 1 - as a model for demonstrating the knowledge explosion for this group of diseases.

Key words: Familial trichoepitheliomatosis; Familial cylindromatosis; Brooke-Spiegler syndrome; Monogenic skin diseases

Core tip: Although dermatology is a morphology-orientated specialty, genetic investigation can help understand the events taking place in the skin of the affected patients. Genetic investigation of Brooke-Spiegler syndrome, familial cylindromatosis and multiple familial trichoepithelioma type 1 further supported the clinical hypothesis that these monogenic skin diseases are not different entities, but rather clinical variants of a disease spectrum caused by mutations in the cylindromatosis (*CYLD*) gene. In addition to understanding the underlying mechanisms of these allelic variants, genetic investigation can also accelerate the development of novel therapeutic modalities, such as therapy using tropomyosin-receptor-kinase specific lestaurtinib for patients with germline *CYLD* mutations.

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INTRODUCTION

From ancient times to the present, the basic approach for diagnosing skin diseases has been to classify the diseases according to their visible signs and symptoms. This approach highlights that dermatology is still a highly morphology-orientated specialty. The end of the 18th century saw great breakthroughs in dermatology: the first comprehensive textbook of modern dermatology was published in 1799 by Francesco Bianchi[1] and the first great school of dermatology was established in Paris in 1801[2]. Since that time, the desire to understand the nature of observed skin lesions constantly drives the development of dermatology and the incorporation of novel investigative methods into its everyday practice.

Among these methods, dermatohistopathology has had the highest impact on the diagnosis of skin diseases. Although the microscope was invented by Anton van Leeuwenhoek as early as 1673, the first standardized and classified nomenclature of dyes and stains was prepared only in 1924[3,4]. Since that time, enzyme histochemistry, electron microscopy, polarizing microscopy, immune-histochemistry and *in vivo* confocal microscopy have all become diagnostic tools in dermatohistopathology and have been integrated into everyday dermatology practices[3,4]. In recent decades, developments in the investigative fields of clinical genetics and genomics have further accelerated our knowledge about skin diseases.

Breeding agricultural plants and animals characterized the pre-Mendel era of genetics[5,6]. After Gregor Mendel established the basic rules of heredity in the nineteenth century[7], several major discoveries, such as the identification of DNA as the material encoding inheritable information, of the genetic code and of the mechanisms of gene expression, have initiated the era of molecular genetics[8,9]. Very recently, the enormous technical development of sequencing methods and platforms has resulted in large-scale genomic projects, which produce amounts of data that were unimaginable a few decades ago[10,11].

These discoveries and techniques have been used to identify several normal genetic variations, as well as candidate genes and their disease-causing mutations, accelerating the elucidation of the genetic background of several monogenic skin diseases. In this review, we present the knowledge explosion for monogenic skin diseases, using as an example the disease spectrum caused by mutations in the *CYLD* gene, which involves Brooke-Spiegler syndrome (BSS) (OMIM 605041), familial cylindromatosis (FC) (OMIM 132700) and multiple familial trichoepithelioma type 1 (MFT1) (OMIM 601606) (Table 1).

DISCUSSION

BSS is a rare monogenic skin disease characterized by the development of a wide variety of benign skin appendageal tumors, such as cylindromas, trichoepitheliomas and/or spiradenomas[12,13]. BSS was named after the two physicians who first reported these neoplasms in 1892 and 1899: Henry G Brooke and Eduard Spiegler, respectively[14,15]. FC, which was originally considered a separate rare disease, is characterized by the development of cylindromas[16]. FC was first reported in 1842 and 1899 by Henry Ancell and Eduard Spiegler, respectively[15,17]. MFT1, which was also reported as another rare entity, is characterized by the development of trichoepitheliomas[16] and was first reported in 1892 by Brooke[14] and Fordyce[18].

Comparing the clinical features of these tumors, cylindromas are benign, skin-colored tumors usually present as multiple turban-like protrusions on the scalp, trichoepitheliomas are small, benign, skin-colored tumors, typically located at the center of the face, and spiradenomas are purple, benign, nodular tumors, usually located on the trunk or limbs[19]. The histological characteristics of cylindromas are dermal nodules of epithelial cells lined by membrane-like basement material and arranged in a "jigsaw puzzle" pattern, of trichoepitheliomas are dermal nodules of basaloid cells with peripheral palisades arranged in nests or cribriform patterns and of spiradenomas are dermal nodules comprised of large light-colored epithelial cells with abundant cytoplasm at the center and small darker epithelial cells at the periphery[20-22]. Hybrid tumors can also occur, such as spiradenocylindromas, which exhibit the characteristics of both cylindromas and spiradenomas[23].

The candidate gene for BSS was first mapped to chromosome 16q12-q13 in 2000[24], and the causative *CYLD* gene and its first pathogenic mutation was identified in an affected German pedigree in 2002[25]. The candidate gene for FC was first mapped to chromosome 16q12-q13 in 1995[26]; however, the causative *CYLD* gene and the first 21 pathogenic mutations were identified as late as 2000[27]. It was first suggested in 1995 that MFT1 and FC may be caused by the dysfunction of the same gene, since both type of tumors can occur in the same patient or in different patients within a single family[28]. The causative gene for MFT1 was identified as *CYLD,* and the first pathogenic mutation was detected in an affected Turkish family in 2003[29].

These clinical variants - BSS, FC and MFT1 - were originally described as distinct clinical entities. However, due to their overlapping clinical symptoms and their manifestation within the same family, they are currently considered as part of a phenotypic spectrum of the same entity[30-32]. This hypothesis is supported by genetic evidence: several mutations - the c.1112C/A p.S371X, the c.2272C/T p.R758X and the c.2806C/T p.R936X nonsense mutations - lead to the development of all three clinical variants (Table 2)[33-42].

Presumably, this is due to the fact that the nonsense mutations of the *CYLD* gene are in general recurrent ones and develop due to *de novo* events indicating mutational hotspots on the gene[35]. Patients carrying the same nonsense mutation from different mutational events often exhibit extreme phenotypic differences, which might be the consequences of yet unknown genetic factors that modify the development of the phenotype.

To date, a total of 99 disease-causing *CYLD* mutations have been reported worldwide (Figure 1)[43-46]. The majority (82%) of *CYLD* mutations identified to date

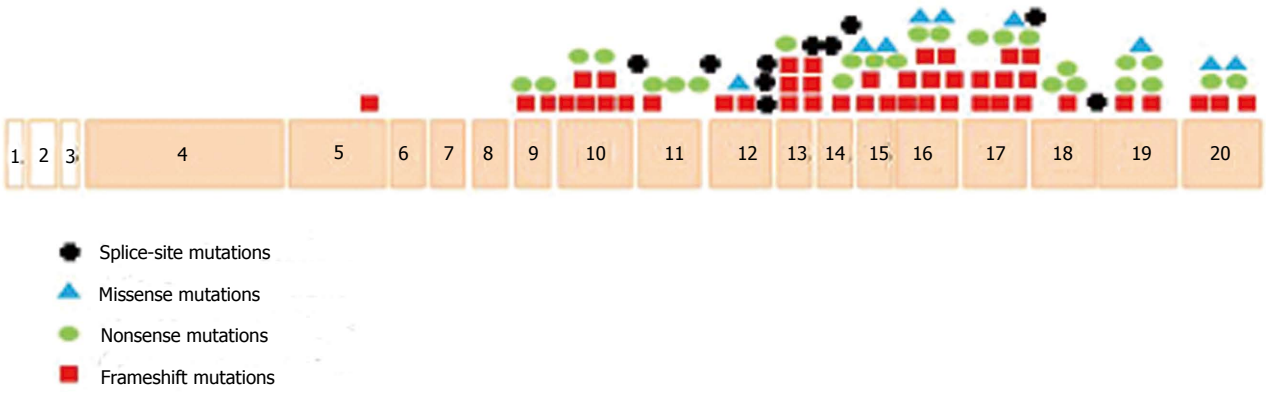

Figure 1 ***CYLD*** **gene mutations identified to date.**

Table 1 Classification of the clinical variants within the disease spectrum caused by *CYLD* mutation

Name of clinical variant	Familial cylindromatosis	Brooke-Spiegler syndrome	Multiple familial trichoepithelioma type 1
Clinical symptoms	Cylindromas	Cylindromas Trichoepitheliomas Spiradenomas	Trichoepitheliomas
Genetic background	Any type of mutation	Any type of mutation	Any type, but mainly missense mutations

Table 2 Reported clinical variants and geographic distributions of the most common recurrent mutations of the *CYLD* gene

CYLD cDNA	CYLD protein	Detected in patients with	Nationality	Ref.
c.1112C > A	p.S371X	BSS, FC, MFT1	American, African American, Irish, Dutch, Austrian, Czech, Slovak, Chinese	Bignell *et al*[27], 2000; Bowen *et al*[30], 2005; Saggar *et al*[32], 2008; Linos *et al*[40], 2011; Kazakov *et al*[39], 2011; Grossmann *et al*[33], 2013; Kacerovska *et al*[51], 2013; Lv *et al*[41], 2013; Van den Ouweland *et al*[36], 2011
c.2272C > T	p.R758X	BSS, FC, MFT1	American, South African, Austrian, Czech, Dutch, Chinese, Japanese	Bignell *et al*[27], 2000; Kazakov *et al*[38], 2009; Kazakov *et al*[39], 2011; Grossmann *et al*[33], 2013; Oiso *et al*[42], 2004; Zhang *et al*[37], 2006; van den Ouweland *et al*[36], 2011
c.2806C > T	p.R936X	BSS, FC, MFT1	American, Canadian, Anglo-Saxon, Czech, Hungarian, Chinese	Bignell *et al*[27], 2000; Bowen *et al*[30], 2005; Saggar *et al*[32], 2008; Kazakov *et al*[38], 2009; Grossmann *et al*[33], 2013; Young *et al*[31], 2006; Nagy *et al*[35], 2013

BSS: Brooke-Spiegler syndrome; FC: Familial cylindromatosis; MFT1: Multiple familial trichoepithelioma type 1.

are located between exon 12 and 20. This finding has a significant diagnostic relevance, as mutation screening of the affected individuals should begin with examination of the exon 12-20 region. Within this region, exons 16 and 17 contain the highest number of mutations (16%). Now that, because the causative mutation can be identified prenatally as well as preimplantation, diagnosis can be offered to affected families. This information can have a huge impact on family planning, since the symptoms of all clinical variants can be very stigmatizing[35].

Several functional studies have been performed to elucidate the underlying mechanism of the *CYLD*-mutation disease spectrum. The *CYLD* gene encodes an enzyme with deubiquitinase activity, which is involved in the post-translational modification of its target proteins by removing Lys63-linked ubiquitin chains[47]. CYLD interacts with several members of the NF-κB signaling pathway, including the TRAF2, TRAF6, NEMO and BCL3 proteins, acting as a negative regulator[48]. Mutations of the *CYLD* gene, in general, result in decreased activity of the CYLD enzyme. The reduced activity leads to the hyperubiquitination of interaction partners and influences several signaling pathways, such as the NF-κB pathway, as well as affects several biological processes, such as the development of the skin appendages and tumor formation[34].

It is interesting to note that, although the CYLD protein is expressed in a wide range of human tissues, the reason why dysfunction manifests only in skin symptoms is still unclear[49-51]. Moreover, patients carrying the same mutation from different mutational events often exhibit extreme differences in their clinical and histological manifestations[35]. These differences might be the consequences of yet unknown genetic, environmental and/or lifestyle factors that modify the development of the phenotype. Further

studies are needed to elucidate the putative factors that are responsible for the observed late onset of the symptoms, for the development of only skin manifestations and for the great variation in phenotypes and histological findings.

To date, no causative therapy is available for BSS. However, recent gene expression studies demonstrated that tumors with somatic *CYLD* mutation have impaired *TRK* signaling and treatment with a small *TRK*-inhibiting molecule, lestaurtinib, can reduce colony formation and proliferation of tumor cells with somatic *CYLD* mutation[52]. These data may have huge clinical significance, since lestaurtinib treatment might be a novel therapeutic modality for patients suffering from symptoms caused by germline *CYLD* mutations.

CONCLUSION

Although dermatology and genetics are considered separate disciplines, the combination of these two fields has already resulted in enormous improvement in the understanding of monogenic skin diseases, such as the skin-disease spectrum caused by mutations in the *CYLD* gene. Genetic studies have proved that BSS, FC and MFT1, which were originally considered different entities, result from mutations of the same gene. Moreover, mutations of the *CYLD* gene have been reported in patients presenting all clinical variants. Genetic screening and the identification of the disease-causing mutation have already been of great significance for family planning in prenatal and preimplantation diagnosis. Furthermore, molecular biological investigation demonstrated that all known *CYLD* mutations lead to decreased activity of the encoded CYLD deubiquitinase enzyme and, thus, influence several signal transduction pathways. Currently, only symptomatic surgical treatment is available for patients with BSS, FC or MFT1. Gene expression studies of solid tumors carrying the *CYLD* mutation identified modifications in the TRK signaling pathway and raised the possibility that treatment with lestaurtinib could potentially be a novel therapeutic modality for patients with germline *CYLD* mutation. Future genetic studies could also provide a solid basis for the development of novel causative therapies that will be more specific and effective than the symptomatic treatments currently available for patients with the FC, BSS and MFT1 variants.

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