Understanding Inherited Cylindromas

Clinical Implications of Gene Discovery

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KEYWORDS

• CYLD • Cylindroma • Spiradenoma • *CYLD* cutaneous syndrome • Brooke-Spiegler syndrome

KEY POINTS

- Cylindromas, trichoepitheliomas, and spiradenomas are tumors of the skin appendages occurring in familial cylindromatosis, multiple familial trichoepithelioma, and Brooke-Spiegler syndrome.
- The tumor-suppressor gene *CYLD* was discovered in 2000 and mutations in this gene are responsible for the development of the three tumor syndromes, collectively termed CYLD cutaneous syndrome.
- This dominantly inherited syndrome is highly penetrant; however, severity may vary.
- Molecular characterization of CYLD function in skin biology has led to new mechanistic insights into tumorigenesis in the care of these patients and paved the way for novel therapeutic strategies.

INTRODUCTION

Tumors of the skin appendages occur sporadically and as part of inherited syndromes. Although these tumors have been described in the medical literature for many years, it is only recently that advances in genetics have allowed clinicians to further understand the origin of these lesions and delineate the clinical syndromes with which they are associated.

Skin appendages are derived from the embryonic ectoderm[1] and include three histologically distinct structures: (1) the pilosebaceous unit (hair follicle and sebaceous glands), (2) the eccrine sweat gland, and (3) the apocrine gland. Tumors of these adnexal structures are classified according to their differentiation as follicular, sebaceous, eccrine or apocrine. Cylindromas are a type of skin appendage tumor thought to arise from hair follicle stem cells.[2] Most present as papules on the skin, mainly on the face and scalp, which can be difficult to differentiate clinically. Diagnosis is often made on histologic assessment of skin biopsy. Although found only rarely on a sporadic basis, cylindromas are the characteristic tumor occurring in multiple numbers in several syndromes.

The autosomal-dominant condition familial cylindromatosis (FC; OMIM 132700) is now known to be caused by a germline mutation in the gene *CYLD*. The first reported case of a patient with FC was described by Ancell in 1842[3] (**Fig. 1**) and since then cylindroma, a benign skin appendage tumor, has continued to fascinate, with new mechanistic understandings and insights unfolding up to the present day.

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Abbreviations and acronyms

BCL3	B-cell lymphoma 3-encoded protein; a component of the NF-κB pathway, deubiquitinated by CYLD.
BSS	Brooke-Spiegler syndrome; a condition caused by a mutation in *CYLD* with cylindroma and trichoepithelioma occurring together with the related tumor spiradenoma.
CK	Cytokeratin; a protein that forms intermediate filaments, providing mechanical support to epithelial cells. Expression of particular cytokeratins is often tissue specific.
CYLD	The cylindromatosis gene
CYLD	The protein encoded by the cylindromatosis gene
FC	Familial cylindromatosis; a condition caused by a mutation in *CYLD* with the cylindroma as the main tumor type.
IKK	IκB kinase; this complex activates NF-κB.
MAP3K7	Mitogen-activated protein kinase kinase kinase 7; forms a complex that activates NF-κB.
MFT	Multiple familial trichoepitheliomas; a condition caused by a mutation in *CYLD* with the trichoepithelioma as the main tumor type.
NEMO (IKK-γ)	NF-kappa-B essential modulator (inhibitor of nuclear factor kappa-B kinase subunit gamma); a subunit of the IKK complex that activates NF-κB.
NF-κB	Nuclear factor-κB; a family of five transcription factors involved in a range of cellular functions, and negatively regulated by CYLD.
RELA/p65	v-rel avian reticuloendotheliosis viral oncogene homologue A; a transcription factor and member of the NF-κB family.
TRAF	Tumor necrosis factor receptor associated factor; proteins in this family interact with tumor necrosis factor receptors and are involved in activation of pathways, such as NF-κB.
TRK	Tropomysin receptor kinase or tyrosine receptor kinase; a signaling pathway that may be a potential target for cylindromas.

In addition to FC, cylindromas are also found in two additional related tumor syndromes. Multiple familial trichoepitheliomas (MFT; OMIM 601606) is a condition defined by the trichoepithelioma, a small skin-colored tumor mainly found on the face, with cylindromas coexisting in lower numbers. Brooke-Spiegler syndrome (BSS; OMIM 605041) is considered an overlap between FC and MFT, and here cylindroma and trichoepithelioma occur together with another related tumor, spiradenoma. Key early descriptions of these conditions, which led to the eponymous "BSS," include a report of a British family with multiple trichoepitheliomas by Brooke in 1892,[4] and an Austrian case of cylindromas by Spiegler in 1899.[5]

Cue forward to the year 2000, and the *CYLD* gene was discovered by positional cloning and Sanger sequencing. In-depth study of pedigrees with FC using a genetic technique called "linkage analysis" pinpointed the *CYLD* locus to chromosome 16q, which led subsequently to identification of the gene itself. With this came the confirmation that FC, MFT, and BSS are not in fact separate entities, but overlapping phenotypes resulting from mutations leading to loss of functional CYLD. *CYLD* functions as a recessive tumor-suppressor gene, and cylindromas show loss of heterozygosity at the *CYLD* locus as a result of a somatic second-hit on top of a pre-existing germline mutation.[6] Collectively, these conditions may be termed CYLD cutaneous syndrome, because individual labels do not prognosticate.[7]

The discovery of *CYLD* paved the way for several major steps forward that have occurred in the past 16 years. The mechanisms of tumor formation in the skin can now be investigated and understood on a molecular genetic basis. In addition, the wider role of *CYLD* has been explored and the cell signaling pathways it regulates have become better understood.

This article provides an overview of the features of the cutaneous tumors that arise in *CYLD* mutation carriers. Current knowledge of the gene and its function are reviewed, before considering how insights gained from this scientific information may be used toward investigating novel therapeutic strategies in patients.

SKIN TUMORS ASSOCIATED WITH GERMLINE CYLINDROMATOSIS MUTATIONS

Clinical Features

Cylindromas are benign, well-circumscribed, smooth, pale pink nodular tumors, often with arborizing vessels visible (**Fig. 2**). The tumors are slow growing and vary in size from a few millimeters to more than 5 cm. In severe cases, tumors may cover most of the scalp, which led to the previously used term "turban tumor."[8] Spiradenomas are benign nodular tumors that are often blue-black in color. They tend to be painful and can