

Case report of syndromic multiple spiradenomas due to biallelic functional loss of *CYLD*



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INTRODUCTION

Multiple spiradenomas may arise in the setting of Brooke-Spiegler syndrome, due to mutations in *CYLD* gene; however, the genetic basis of multiple spiradenomas, without the presence of other adnexal tumors, has not been previously reported. In addition to Brooke-Spiegler syndrome (OMIM #605041), 2 other recognized cutaneous phenotypes are associated with *CYLD* mutations: Familial cylindromatosis (OMIM #132700) and multiple familial trichoepitheliomas (OMIM #601606). These *CYLD* cutaneous syndromes manifest exclusively as multiple cylindromas or trichoepitheliomas, respectively.¹ Herein, we describe germline and somatic mutations in a patient presenting exclusively with multiple eccrine spiradenomas.



Fig 1. Patient with multiple spiradenomas. Multiple pink and bluish papules on the scalp of a Caucasian man in his 60s.

Abbreviation used:

LOF: loss of function

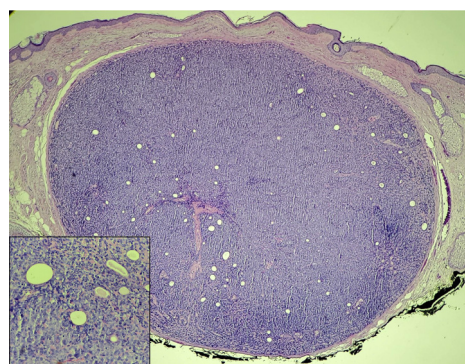


Fig 2. Spiradenoma. Hematoxylin-eosin–stained section at $\times 4$ and $\times 40$ (*inset*) magnification. A well-circumscribed nodule is present in the dermis with cells creating ductal structures, consistent with a spiradenoma.

CASE REPORT

A Caucasian man in his 60s presented with multiple painful nodules on his scalp and neck (Fig 1) and additional lesions on his trunk. He had a history of 5 spiradenomas previously removed via biopsy. The patient had no living relatives but reported that his mother and maternal uncle both had a history of multiple, disfiguring tumors on their scalps.

Informed consent was obtained, and 9 lesions were collected from the scalp via shave biopsy. The

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Table I. *CYLD* sequencing results from the patient's blood and 5 spiradenomas

Tissue source	Position (hg38)	Nucleotide change	Predicted effect on messenger Rna	Exon	Predicted effect on protein	Loss of heterozygosity at <i>CYLD</i>
Blood or normal skin	Chr16: 50781408	t/-	Frameshift	11	L561X	No
Tumor 1	Chr16: 50781408	t/-	Frameshift	11	L561X	Yes
Tumor 2	Chr16: 50781408	t/-	Frameshift	11	L561X	Yes
Tumor 3	Chr16: 50781408	t/-	Frameshift	11	L561X	Yes
Tumor 4	Chr16: 50781408	t/-	Frameshift	11	L561X	No
Tumor 5	Chr16: 50793665	g/a	Splice Junction	N/A		
	Chr16: 50781408	t/-	Frameshift	11	L561X	No
	Chr16: 50796443	c/t	Stop Gain	20	R936*	

Chr, chromosome; *N/A*, not applicable.

Table II. *CYLD* cutaneous syndromes, with newly proposed multiple spiradenomas

<i>CYLD</i> cutaneous syndromes	OMIM #	Disease features	Reported pathogenic germline mutations
Brooke-Spiegler syndrome	605041	Cylindromas, spiradenomas, trichoepitheliomas	Chr16, exons 9-20 of <i>CYLD</i> ⁴
Familial cylindromatosis	132700	Cylindromas	Chr16, exons 9-20 of <i>CYLD</i> ⁴
Multiple familial trichoepitheliomas	601606	Trichoepitheliomas	Chr16, exons 9-20 of <i>CYLD</i> ⁴
Multiple spiradenomas	N/A	Spiradenomas	Chr 16, exon 11 of <i>CYLD</i>

Chr, chromosome; *N/A*, not applicable.

lesions were selected for removal by the patient based on size and symptomatology. Complete or partial specimens from each lesion were submitted for routine histologic evaluation, and a diagnosis of spiradenoma was confirmed in all specimens (Fig 2). No overlapping features of cylindroma were observed in any of the specimens. All of the lesions were pure spiradenomas. In total throughout his life, this patient had 14 skin biopsies, the pathology of all of which showed spiradenomas. No cylindromas or trichoepitheliomas were present.

Five of the specimens were bifurcated, and tissue was submitted for exome sequencing along with normal-appearing skin and blood. Exome sequencing and bioinformatics were performed as previously described.² Germline variants and somatic mutations were confirmed by Sanger sequencing.

As shown in Table I, sequencing of the uninjured perilesional skin and blood both revealed a germline single base deletion in exon 11 of *CYLD*, predicted to cause a frameshift. Three of the 5 tumors exhibited loss of heterozygosity of *CYLD*. One of the 2 remaining tumors showed a somatic splice junction mutation, and the other showed a nonsense mutation in exon 20 of *CYLD*. In summary, all 5 tumors exhibited genetic changes predicted to cause loss of function (LOF) of both *CYLD* alleles.

DISCUSSION

The *CYLD* gene contains 20 exons encoding a deubiquitinating enzyme that functions as a tumor suppressor gene within the nuclear factor kappa-light-chain-enhancer of activated B cells pathway.³ A recent study by Nagy et al⁴ summarized the 107 germline variants that have been published to date associated with *CYLD* cutaneous tumor syndromes. The vast majority (99%) of mutations have been found within exons 9 to 20, with most of these occurring in exons 16, 17, and 20 (Table II).⁴ Little correlation exists between *CYLD* genotype and the cutaneous syndrome that the patient develops,⁵ and recent evidence indicates that expression of genes other than *CYLD*, such as *DKK2*, may influence whether tumors differentiate toward cylindromas or spiradenomas.⁶

Genetic analysis of the patient's blood and perilesional skin both showed a germline deletion in exon 11 of the *CYLD* gene, and all 5 spiradenomas that were sequenced exhibited genetic changes predicted to cause LOF of both *CYLD* alleles. The *CYLD* germline variant, in our patient, appears novel, but the R936* somatic mutation has previously been reported in a case of cylindroma.⁷ Our finding of different somatic mutations in multiple tumors, with similar histology, from a single patient has also been observed in other *CYLD* syndromes.⁷ These results

parallel the described mechanism of disease in other *CYLD* cutaneous syndromes, with a germline LOF of 1 allele and then a “second hit” resulting in LOF of the remaining normal allele. Discovery of additional variants in patients with multiple spiradenomas may help elucidate how a single genetic variant causing LOF of *CYLD* can lead to various clinical phenotypes.

In summary, LOF mutations in *CYLD* gene appear to provide the basis for the rare clinical presentation of multiple spiradenomas. This adds a genetic basis for a fourth clinical phenotype, multiple spiradenomas, to the previously characterized *CYLD* cutaneous syndromes, which include Brooke-Spiegler syndrome, familial cylindromatosis, and multiple familial trichoepitheliomas.

Conflicts of interest

None disclosed.

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