USCAP Head & Neck Companion Society Meeting

Brooke-Spiegler syndrome and phenotypic variants

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ACCME/Disclosure

Dr. Kazakov has nothing to disclose

HISTORY
OF A REMARKABLE CASE OF
TUMOURS,
DEVELOPED ON THE HEAD AND FACE:
ACCOMPANIED WITH A SIMILAR MALIGN IN THE ANOGENITAL PARTS.
BY HENRY ANCELL,
SURGEON TO THE VAUXHALL AND SOUTH KENSINGTON HOSPITAL.

1899 E. Spiegler: Endothelioma capitis

„Ancell-Spiegler Cylindromas“

1892 Brooke HG: Epithelioma adenoides cysticum

1892 Fordyce JA: Multiple benign cystic epithelioma

„Brooke-Fordyce trichoepitheliomas“

Ancell H. 1842

Fordyce JA, 1892
Variation in severity
Spiradenoma and cylindroma

Spiradenocylindroma

“Hybrid” histopathologic features
**CYLD gene**

- 20 exons (3 first are untranslated)
- Codes 956 amino acid protein
- Tumor suppressor gene
- Second hit: LOH and somatic mutations

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Brooke-Spiegler Syndrome: Report of 10 Patients From 8 Families With Novel Germline Mutations

Evidence of Diverse Somatic Mutations in the Same Patient Regardless of Tumor Type

Rahel Silve, MSc,*, Tomas Vannec, PhD,*, Dominika Kuczerowska, MD, PhD,† Patrice Trebaol, MSc,‡ Bernard Collet, MD,*, Ana Barrio, MD,‖ Maria de la Guardia, MD,‖
Dominic V. Spanu, MMBS,§ Radek Littik, MD,‖ Yvonne Vynckier, MD,‖
Wolfgang Wyrsch, MD,*,‡‡ Robert L. Peere, MD,‡‡ John Piero, MD,‡‡ Michel Michal, MD,‡‡§ and Darcy V. Kizakos, MD, PhD*†

Diagn Med Pathol 2016;19:83-81

Novel and Recurrent Germline and Somatic Mutations in a Cohort of 67 Patients From 48 Families With Brooke–Spieglер Syndrome Including the Phenotypic Variant of Multiple Familiar Inchoepithelomas and Correlation With the Histopathologic Findings in 379 Biopsy Specimens

Peter Großmann, MSc,*§ Tomas Vannec, PhD,*§ Peter Steinhe, BSc,* Dominika Kuczerowska, MD, PhD,*§ Dominic V. Spanu, MD,‡‡ Bernard Collet, MD,‖ Christian Booc, MD,‖ Maria de la Guardia, MD,‖§ J. Andrea Garcia, MD,‖ Michael Dahmke, MD,‡‡ John Piero, MD,‡‡ Michel Michal, MD,‡‡§ and Darcy V. Kizakos, MD, PhD†
The CYLD p.R758X worldwide recurrent nonsense mutation detected in patients with multiple familial trichoepithelioma type 1, Brooke-Spiegler syndrome and familial cylindromatosis represents a mutational hotspot in the gene.

Farkas et al. JBC Genetics. (2018) 17:36

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<thead>
<tr>
<th>CYLD cDNA</th>
<th>CYLD protein</th>
<th>Detected in patients with</th>
<th>Reference</th>
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<tr>
<td>pR758X</td>
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<td>Classical Brooke-Spiegler syndrome</td>
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Why?

• Large deletions

CYLD germline mutation rate (PCR based approach: exons & exon-intron junctions)

Classical Brooke-Spiegler syndrome 80-85%

Why?

• Large deletions

• Mutations in introns
**CYLD germline mutation rate**

- Classical Brooke-Spiegler syndrome 80-85%

**Why?**
- Large deletions
- Mutations in introns
  - Another gene

---

**A Case of Brooke–Spiegler Syndrome With a Novel Germline Deep Intronic Mutation in the CYLD Gene Leading to Intronic Exonization, Diverse Somatic Mutations, and Unusual Histology**

Dmitry E. Kozlov, MD, PhD; Sybilla Thomas-Uczynski, MD; Tomasz Tanczek, PhD; Denis Kowalowka, MD, PhD; Petr Grossmann, MSc; and Michal Michal, MD

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**CYLD germline mutation rate**

- Classical Brooke-Spiegler syndrome 80-85%

**Why?**
- Large deletions
- Mutations in introns
  - Another gene
  - Epigenetic mechanisms
**Large Germline Deletions of the CYLD Gene in Patients With Brooke-Spiegler Syndrome and Multiple Familial Trichoepithelioma**

Tomas Vymazal, MD,* Zbynек Hallakner, PhD‡,†,‡,§ Denisa Bučková, MD, PhD,* Peer Martinek, MD,* Monika Sedláčková, MD,* Richard A. Cari, FRCP,C†,‡,§ David Stella, MD,* Michal Mihalek, MD, and Dmitry V. Kasedov, MD, PhD,*

**Malignant transformation: sudden rapid growth, ulceration and bleeding**

Courtesy of Bernhard Zeiger, MD, Austria

**Malignant transformation : 5-10%**

Courtesy of Bernhard Zeiger, MD, Austria
Inclusion criteria

1) a residuum of an unequivocally benign neoplasm regardless of size

2) a malignant neoplasm regardless of its histological type.

Malignant tumors from preexisting benign spiradenomas and cylindromas

1. Salivary gland type basal cell adenocarcinoma-like pattern, low-grade
2. Salivary gland type basal cell adenocarcinoma-like pattern, high-grade
3. Invasive adenocarcinoma, not otherwise specified
4. Sarcomatoid (metaplastic) carcinoma

1&2: most common in Brooke-Spiegler syndrome
Salivary gland type basal cell adenocarcinoma-like pattern, low-grade (n=11)
Salivary gland type basal cell adenocarcinoma-like pattern, high-grade (n=14)

Invasive adenocarcinoma, not otherwise specified (n=3)
Adenocarcinoma in situ (1 case)

Metaplastic (sarcomatoid carcinoma)

Metaplastic (sarcomatoid) carcinoma

Metaplastic (sarcomatoid) carcinoma
Other malignant neoplasms are rare in classic Brooke-Spiegler syndrome.

Multiple familial trichoepitheliomas

and

Brooke-Spiegler syndrome

How many syndromes are there?

Mutations in the CYLD gene in Brooke-Spiegler Syndrome, Familial Cylindromatosis, and Multiple Familial Trichoepithelioma: Lack of Genotype–Phenotype Correlation

Sarah Bowen,* Melissa Gill,† David A. Lee,* Galen Fisher,‡ Roy G. Geronemus,* Maria Luisa Espinel-Vázquez,* and Julide Tolun-Cerda*†

Departments of Dermatology and Pediatrics, Columbia University, New York, New York, USA, The Laser and Skin Surgery Center of New York, New York, New York, USA, Instituto Guzmán de la Sierra, Caxixi, Spain

Short Report

CYLD mutations underlie Brooke–Spiegler, familial cylindromatosis, and multiple familial trichoepithelioma syndromes

Multiple familial trichoepithelioma: papules in nasolabial folds
Confluence in nasolabial folds and inner aspects of eyebrows

Confluence in nasolabial folds and inner aspects of eyebrows
Multiple familial trichoepithelioma: mild phenotype

Multiple familial trichoepithelioma: severe phenotype

Multiple familial trichoepithelioma: severe phenotype

Multiple familial trichoepithelioma, disease progression

1987 (3 yo)  1991 (7 yo)  2008 (24 yo)

Courtesy of Jorg Schaller, Germany

Courtesy of J. Andrew Carlson, USA

Courtesy of J. Andrew Carlson, USA
Multiple familial trichoepithelioma

Twins: 11 yo

Trichoepithelioma/cribiform trichoblastoma (WHO 2006)

Courtesy of Martin Sangueza, MD, Bolivia
"Hybrid" morphology occasionally (spiradenoma-like area)

**CYLD or PTCH?**

- 1996, Johnson et al, identified the PTCH gene (Drosophila patched gene) located at 9q22.3.
- 1996-1999 mutations in PTCH in sporadic BCC and in nevoid basal cell carcinoma syndrome (Gorlin-Goltz syndrome).

- 1999, Aszterbaum et al, studied a Ptch+/- mice who develop primordial follicular neoplasms resembling human trichoblastomas, which after exposure to ultraviolet radiation or ionizing radiation manifested an increase in the number and size of these tumors and resembled human BCC.

- 2000, Matt et al identified LOH at 9q22.3 in 14 (48%) of 29 cases of sporadic trichoepitheliomas, whereas LOH at 9p21 could not be demonstrated.
Multiple (Familial) Trichoepitheliomas: A Clinicopathological and Molecular Biological Study, Including CYLD and PTCH Gene Analysis, of a Series of 16 Patients

Dmitry V. Kuzukov, MD, PhD,* Tomas Vanek, PhD,** Bernhard Zelger, MD, MS;† J. Andrew Carlisle, MD,‡ Dominique V. Spagnolo, MMBS,§ Jorg Schaefer, MD,§ Anna Nemecova, MSc,** Danuta Kaczenowska, MD, PhD,* Martina Kizmioz, MD,** Martin Sangierka, MD,** Michael Emberger, MD,*†† Irena Belotorska, MD, PhD,** Maria Teresa Fernandez-Figueras, MD,** Werner Kempt, MD,** Dale R. Meyer, MD,*** Arno Ritten, MD,***†† Mehmet Babaci, MD,** and Michael Michal, MD,**

Am J Dermatopathol 2011;33:251–265

6 patients – mutations in CYLD
9 patients – no mutations in PTCH

Multiple familial trichoepithelioma: malignant transformation
Multiple familial trichoepithelioma: malignant transformation

Rare aggressive basaloid neoplasms can occur

a) Before treatment with Vismodegib. b) After two months of treatment with Vismodegib 150 mg/d partial regression of trichoepitheliomas in the face is evident.

Influence of CYLD on Hedgehog signalling, (from Masoumi et al., 2011)

a: CYLD tumour suppressor gene is active and leads to deubiquination and thus stabilisation of SUFU. Consequently Hedgehog signalling is absent.

b: In the case of a CYLD mutation, SUFU is ubiquinated which leads to its proteasomal degradation. Thus, Gli is translocated to the nucleus, where it promotes the transcription of target genes leading to tumour progression.
Extracutaneous lesions in Brooke-Spiegler syndrome

- Salivary glands
- Breast
- Lung (single case of cylindroma reported in the literature)

Salivary gland involvement
- Rare (1%)
- Usually parotis
- After age of 40 yrs
- Subcutaneous mass
- Maybe bilateral
- Rarely multicentric
- Basal cell adenoma, membranous type
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So far no reports of salivary gland tumors in multiple familial trichoepithelioma.
Thank you!