# A novel germline mutation in the *CYLD* gene in a Slovak patient with Brooke-Spiegler syndrome

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**SUMMARY**
The authors report a 64-year-old female with Brooke-Spiegler syndrome who presented with multiple cutaneous nodules and tumors mostly involving the scalp. Histopathological examination of one of the lesions located in a periauricular area revealed a typical cylindroma. In some neoplastic nodules ductal differentiation and occasional bilayered glands composed of the dark abluminal basal/myoepithelial cells and luminal mucinous cells might be recognized. Apocrine secretion was focally noted. Molecular biologic study of the *CYLD* gene performed from the peripheral blood identified a novel splice site c.2041+1 G>T mutation. This new germline mutation in the *CYLD* gene of a Slovak patient with Brooke-Spiegler syndrome extends the catalogue of known *CYLD* germline mutations in this condition.

**Keywords:** adnexal neoplasms – Brooke-Spiegler syndrome – *CYLD* – cylindroma – apocrine secretion – basal cell carcinoma

## Nová zárodečná mutace v *CYLD* genu u slovenského pacienta s Brookeovým-Spieglerovým syndromem

**SOUHRN**
Autoři prezentují případ 64 leté ženy s Brookeovým-Spieglerovým syndromem s mnohočetnými kožními noduly a tumory lokalizovanými ve kštici. Histopatologické vyšetření projevu z periaurikulární krajiny odhalilo typický obraz cylindromu. V některých nádorových uzlech mohla být navíc detekována duktální diferenciace a příležitostně i přítomnost dvouřadých žlázek složených z tmavých bazálních/myoepitelálních buněk uložených periferně a luminálních mucinózních buněk. Místy byla detekována apokrinní sekrece. Molekulárně-biologická studie genu *CYLD* provedená z periferní krve prokázala mutaci v sestřihovém místě c.2041+1 G>T. Jedná se o zcela novou zárodečnou mutaci genu *CYLD* poprvé popsanou u slovenského pacienta s Brookeovým-Spieglerovým syndromem, která tak rozšiřuje spektrum dosud známých zárodečných mutací u tohoto onemocnění.

**Klíčová slova:** adnexální tumory – Brookeův-Spieglerův syndrom – *CYLD* – cylindrom – apokrinní sekrece – bazocelulární karcinom

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Brooke-Spiegler syndrome (BSS) is an inherited autosomal dominant disease characterized by the occurrence of multiple adnexal cutaneous neoplasms, including spiradenoma, cylindroma, spiradenocylindroma and trichoepithelioma (cribriform trichoblastoma) (1–7). In its phenotypic variant, multiple familial trichoepitheliomas (MFT), only trichoepitheliomas without accompanying cylindromas, spiradenomas and spiradenocylindromas are seen (8,9). Rarely, malignant tumors develop from preexisting benign cutaneous neoplasms (10–15). In addition to cutaneous lesions, the affected patients present on rare occasions with salivary gland neoplasms that are histopathologically similar to their cutaneous counterparts (10,16–21). Exceptionally rare is the occurrence of cylindroma in the breast (20,22).

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BSS/MFT is characterized by a common genetic alteration, namely mutations in the *CYLD* gene, a tumor suppressor gene located on chromosome 16q12-q13 (23–29). The *CYLD* gene contains 20 exons (the smallest being 9 bp), of which the first 3 are untranslated, and extends over approximately 56 kb of genomic DNA. Exon 3 (in the 5` untranslated region) and the 9-bp exon 7 (which is coding) show alternative splicing. *CYLD* encodes a deubiquitinating enzyme that negatively regulates the nuclear factor-kappaB and c-Jun N-terminal kinase pathways by removing lysine 63-linked polyubiquitin chains from several specific substrates. The CYLD protein contains 2 essential domains: 3 cytoskeletal-associated protein-glycine-conserved (CAP-Gly) repeats, which are found in proteins that coordinate the attachment of organelles to microtubules and one zinc-finger-like B-box motif within the ubiquitin carboxy-terminal hydrolases (UCH or USP; Ub-specific proteases) domain. In addition, CYLD contains 2 conserved proline-rich segments that can potentially mediate interactions with Src homology 3 (SH3) domains found in other proteins. It has been suggested that the CYLD protein may play a role in immunity, lipid metabolism, spermatogenesis, osteoclastogenesis, antimicrobial defense, and inflammation (25).

To date, a total of 85 distinct germline *CYLD* mutations have been reported in over 100 BSS families originating from the USA, UK, Russia, Belorussia, Ukraine, Czech Republic, France, China, Ire-