

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



---

# CYLD Cutaneous Syndrome: Familial Cylindromatosis, Brooke-Spiegler Syndrome and Multiple Familial Trichoepithelioma

---

Takahiro Kurimoto, Naoki Oiso, Muneharu Miyake and Akira Kawada

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/53575>

---

## 1. Introduction

The concept of *CYLD* cutaneous syndrome was proposed by Rajan *et al.* in 2009 (Rajan *et al.*, 2009). The syndrome represents an uncommon autosomal dominant disease caused by a germline mutation in the cylindromatosis gene (*CYLD*) (Biggs PJ, *et al.* 1995). *CYLD* cutaneous syndrome is characterized by the development of multiple neoplasms originating from the skin appendages (Rajan *et al.*, 2009). It includes three appendageal tumor predisposition syndromes; familial cylindromatosis (FC, MIM 132700), Brooke-Spiegler syndrome (BSS, MIM 605041), and multiple familial trichoepithelioma (MFT, MIM 601606) (Rajan *et al.*, 2009). BSS is characterized by multiple skin appendage tumors such as cylindroma, trichoepithelioma, and spiradenoma. FC is typified by multiple cylindromas and MFT by multiple trichoepitheliomas. Here, we summarize current clinical and genetic recognition in *CYLD* cutaneous syndrome.

## 2. *CYLD* cutaneous syndrome

A genome search using two FC families identified strong evidence for linkage to the locus on chromosome 16q12-q13 (Biggs *et al.*, 1995). Subsequently, germline mutations in the tumor suppressor *CYLD* gene were identified in individuals having FC (Bignell *et al.* 2000). A combination of genetic linkage analysis and loss of heterozygosity in 15 FC families showed only the linkage to the locus, providing no evidence for genetic heterogeneity (Takahashi *et al.* 2000). The germline mutations were then detected in individuals with BSS (HU *et al.*, 2003; Poblete Gutiérrez *et al.*, 2002) and MFT (Salhi *et al.*, 2004; Zhang *et al.*, 2004; Zheng *et al.*, 2004). Affected family members with the same germline mutation in *CYLD* showed FC, BSS or MFT phenotypes, indicating the absence of genotype-phenotype

relationship (Fenske *et al.*, 2000; Rajan *et al.*, 2009; Young *et al.*, 2006). The phenotypic diversity from mild type to severe turban tumor is present in the affected family members with *CYLD* cutaneous syndrome (Biggs *et al.*, 1995; Oiso *et al.*, 2004; Rajan *et al.*, 2009; Young *et al.*, 2006). Bowen *et al.* suggested that FC, BSS, and MTF represent phenotypic variation of a single entity (Bowen *et al.*, 2005). Rajan *et al.* proposed the term, *CYLD* cutaneous syndrome, for unifying three skin appendage-associated disorders (Rajan *et al.*, 2009).

### 3. The function of CYLD

In 2003, *CYLD* was shown as a deubiquitinating enzyme that negatively regulates nuclear factor-kappa B (NF- $\kappa$ B) activation (Brummelkamp *et al.*, 2003; Kovalenko *et al.*, 2003; Trompouki *et al.*, 2003; Wilkinson, 2003). NF- $\kappa$ B is involved in controlling inflammation, the immune response, and apoptosis (Pasparakis, 2002). Nowadays, many different cellular functions have been ascribed to *CYLD* such as proliferation and cell cycle, Ca<sup>2+</sup> channel signaling, survival and apoptosis, inflammation, T-cell development and activation, antiviral response, and spermatogenesis (Pasparakis, 2002).

*CYLD* contains three cytoskeleton-associated protein-glycine-rich (CAP-Gly) domains, two proline-rich motifs, a tumor necrosis factor-alpha (TNF- $\alpha$ ) receptor-associated factor 2 (TRAF2) binding site, and ubiquitin-specific proteases (USP) domain responsible for its deubiquitinases (DUB) activity (Harhaj *et al.*, 2011; Pasparakis, 2002). The first two CAP-Gly domains mediate binding to microtubules (Gao *et al.*, 2008; Wickström *et al.*, 2010), and the third CAP-Gly domain regulates NEMO interactions. NEMO (also known as I $\kappa$ B kinase gamma (IKK $\gamma$ )) is the regulatory subunit of the I $\kappa$ B kinase (IKK) (Yoshida *et al.*, 2011). IKK plays crucial role in activating NF- $\kappa$ B in response to various inflammatory stimuli (Zheng *et al.*, 2011). TRAF2 regulates activation of the c-Jun N-terminal kinase (JNK)/c-Jun and the inhibitor of IKK/ NF- $\kappa$ B signaling cascades in response to TNF- $\alpha$  stimulation (Zhang *et al.*, 2011).

### 4. Conclusion

*CYLD* cutaneous syndrome represents familial cylindromatosis, Brooke-Spiegler syndrome, and multiple familial trichoepithelioma. Further studies for elucidating the function of *CYLD* will focus on defining the multifunctional activities including tumor suppression for neoplasms from the skin appendages.

### Author details

Takahiro Kurimoto, Naoki Oiso\*, Muneharu Miyake and Akira Kawada  
Department of Dermatology,  
Kinki University Faculty of Medicine,  
Osaka-Sayama, Japan

---

\* Corresponding Author

## 5. References

- Biggs PJ, Wooster R, Ford D, *et al.* Familial cylindromatosis (turban tumour syndrome) gene localised to chromosome 16q12-q13: evidence for its role as a tumour suppressor gene. *Nat Genet* 1995; 11(4): 441-3.
- Bignell GR, Warren W, Seal S, *et al.* Identification of the familial cylindromatosis tumour-suppressor gene. *Nat Genet* 2000; 25(2): 160-5.
- Bowen S, Gill M, Lee DA, *et al.* Mutations in the CYLD gene in Brooke-Spiegler syndrome, familial cylindromatosis, and multiple familial trichoepithelioma: lack of genotype-phenotype correlation. *J Invest Dermatol* 2005; 124(5): 919-20.
- Brummelkamp TR, Nijman SM, Dirac AM, *et al.* Loss of the cylindromatosis tumour suppressor inhibits apoptosis by activating NF-kappaB. *Nature* 2003; 424(6950): 797-801.
- Fenske C, Banerjee P, Holden C, *et al.* Brooke-Spiegler syndrome locus assigned to 16q12-q13. *J Invest Dermatol* 2000; 114(5): 1057-8.
- Gao J, Huo L, Sun X, *et al.* The tumor suppressor CYLD regulates microtubule dynamics and plays a role in cell migration. *J Biol Chem* 2008; 283(14): 8802-9.
- Harhaj EW, Dixit VM. Deubiquitinases in the regulation of NF-kB signaling. *Cell Res* 2011; 21(1): 22-39.
- Hu G, Onder M, Gill M, *et al.* A novel missense mutation in CYLD in a family with Brooke-Spiegler syndrome. *J Invest Dermatol* 2003; 121(4): 732-4.
- Kovalenko A, Chable-Bessia C, Cantarella G, *et al.* The tumour suppressor CYLD negatively regulates NF-kappaB signalling by deubiquitination. *Nature* 2003; 424(6950): 801-5.
- Massoumi R. Ubiquitin chain cleavage: CYLD at work. *Trends Biochem Sci* 2010; 35(7): 392-9.
- Oiso N, Mizuno N, Fukai K, *et al.* Mild phenotype of familial cylindromatosis associated with an R758X nonsense mutation in the CYLD tumour suppressor gene. *Br J Dermatol* 2004; 151(5): 1084-6.
- Pasparakis M, Courtois G, Hafner M, *et al.* TNF-mediated inflammatory skin disease in mice with epidermis-specific deletion of IKK2. *Nature* 2002; 417(6891): 861-6.
- Poblete Gutiérrez P, Eggermann T, Höller D, *et al.* Phenotype diversity in familial cylindromatosis: a frameshift mutation in the tumor suppressor gene CYLD underlies different tumors of skin appendages. *J Invest Dermatol* 2002; 119(2): 527-31.
- Rajan N, Langtry JA, Ashworth A, *et al.* Tumor mapping in 2 large multigenerational families with CYLD mutations: implications for disease management and tumor induction. *Arch Dermatol* 2009; 145(11): 1277-84.
- Salhi A, Bornholdt D, Oeffner F, *et al.* Multiple familial trichoepithelioma caused by mutations in the cylindromatosis tumor suppressor gene. *Cancer Res* 2004; 64(15): 5113-7.
- Takahashi M, Rapley E, Biggs PJ, *et al.* Linkage and LOH studies in 19 cylindromatosis families show no evidence of genetic heterogeneity and refine the CYLD locus on chromosome 16q12-q13. *Hum Genet* 2000; 106(1): 58-65.
- Trompouki E, Hatzivassiliou E, Tschritzis T, *et al.* CYLD is a deubiquitinating enzyme that negatively regulates NF-kappaB activation by TNFR family members. *Nature* 2003; 424(6950): 793-6.

- Wickström SA, Masoumi KC, Khochbin S, *et al.* CYLD negatively regulates cell-cycle progression by inactivating HDAC6 and increasing the levels of acetylated tubulin *EMBO J* 2010; 29(1): 131-44.
- Wilkinson KD. Signal transduction: aspirin, ubiquitin and cancer. *Nature* 2003; 424(6950): 738-9.
- Yoshida M, Oiso N, Kimura M, *et al.* Skin ulcer mimicking pyoderma gangrenosum in a patient with incontinentia pigmenti. *J Dermatol* 2011; 38(10): 1019-21.
- Young AL, Kellermayer R, Szigeti R, *et al.* CYLD mutations underlie Brooke-Spiegler, familial cylindromatosis, and multiple familial trichoepithelioma syndromes *Clin Genet* 2006; 70(3): 246-9.
- Zhang L, Blackwell K, Altaeva A, *et al.* TRAF2 phosphorylation promotes NF- $\kappa$ B-dependent gene expression and inhibits oxidative stress-induced cell death. *Mol Biol Cell* 2011; 22(1): 128-40.
- Zhang XJ, Liang YH, He PP, *et al.* Identification of the cylindromatosis tumor-suppressor gene responsible for multiple familial trichoepithelioma. *J Invest Dermatol* 2004; 122(3): 658-64.
- Zheng C, Yin Q, Wu H. Structural studies of NF- $\kappa$ B signaling. *Cell Res* 2011; 21(1): 183-95.
- Zheng G, Hu L, Huang W, *et al.* CYLD mutation causes multiple familial trichoepithelioma in three Chinese families. *Hum Mutat* 2004; 23(4): 400.