# A recurrent R936X mutation of *CYLD* gene in a Chinese family with multiple familial trichoepithelioma

Sir,

Multiple familial trichoepithelioma (MFT; OMIM 601606) is an autosomal dominant skin disease characterized by the presence of many small benign tumors with pilar differentiation predominantly on the face. Mutations of the cylindromatosis (*CYLD*) gene have been first identified as the cause of multiple familial trichoepithelioma from Chinese Han populations in 2004. Loss of the deubiquitinating activity of CYLD protein is correlated with tumorigenesis.[1] Herein, we report a Chinese family with multiple familial trichoepithelioma with a recurrent mutation of *CYLD*, designated c. 2806C>T.

In this study, a large Chinese family consisting of six multiple familial trichoepithelioma patients in three generations was investigated [Figure 1a]. The proband in the family was a 25-year-old female. She initially developed trichoepitheliomas at the age of 11 years. Dermatological examination showed numerous, dome-shaped, firm skin-colored papules and nodules involving the surface of nose, and the nasolabial folds [Figure 1b]. Lesional skin biopsy from the proband revealed the typical histopathological characteristics of trichoepithelioma, such as palisade-like arrangement of small basaloid cells and multiple horn cysts with a fully keratinized center [Figure 1c]. Blood samples were obtained from available family members and 100 unrelated controls.

After informed consent and approval of human medical and ethics committee of Southern Medical University, genomic DNA was extracted from peripheral blood with a DNA isolation kit (Simgen Inc., Hangzhou, China). Polymerase chain reactions were performed as described in a previous study.[2] All polymerase chain reaction products were directly sequenced using dye terminator chemistry on an ABI 3730xl DNA Analyzer (Applied Biosystems, Foster City, CA). In addition, samples from 100 unrelated controls were sequenced to exclude the *CYLD* polymorphisms possibilities.

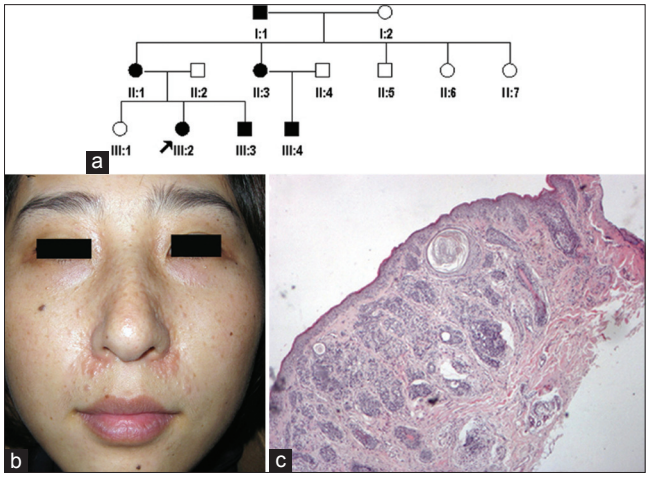


**Figure 1: The circles indicate females, the squares males. Blackened symbols represent affected individuals, open symbols represent unaffected individuals. The proband in the family (Individual III:2) is indicated by an arrow (a). Numerous trichoepitheliomas in the nasal region and nasolabial folds (b); Histology of trichoepithelioma excised from the face of the proband (H and E, 100×). Well-demarcated nodules consist of small basaloid cells that are arranged in a palisade-like pattern; multiple horn cysts with a fully keratinized center surrounded by basaloid cells lie free in the fibrous stroma. (c)**

Sequence analysis identified a recurrent nonsense mutation, a change of C to T at nucleotide position 2806 in exon 20 in *CYLD* gene, resulting in a substitution of arginine (CGA) to terminal code (TGA) at position 936(p.R936X) in the proband [Figure 2a]. The same mutation was not found in 100 unrelated individuals [Figure 2b].

The mutation c. 2806C>T (p.R936X) in *CYLD* has been reported in several studies. Bowen *et al*. identified a heterozygous R936X mutation in a Canadian woman with Brooke–Spiegler syndrome (BSS) who had cylindromas and trichoepitheliomas.[3] In a 73-year-old male with cylindromatosis and turban tumor syndrome, the heterozygous 2806C>T transition in the *CYLD* gene was identified. His two children, also carrying the mutation, had multiple familial trichoepithelioma without cylindromas. The findings suggested phenotypic variation of a single genetic defect.[4] The same nonsense mutation was identified in a woman of Czech ethnic background, who was one case from a series of 24 cases who developed malignant neoplasms arising in preexisting benign spiradenoma ($n$ = 20), cylindroma ($n$ = 2), or spiradenocylindroma ($n$ = 2).[5] The development of malignant transformation in benign neoplasms in patients with p.R936X mutation of *CYLD* gene may be due to a second mutation in the tumor tissue or a homozygous c. 2806C>T mutation. Unfortunately, none of the previous studies were able to provide evidence of such mutation in patients who developed the malignant neoplasms.

In this study, we reported a large Chinese family with multiple familial trichoepithelioma and identified a

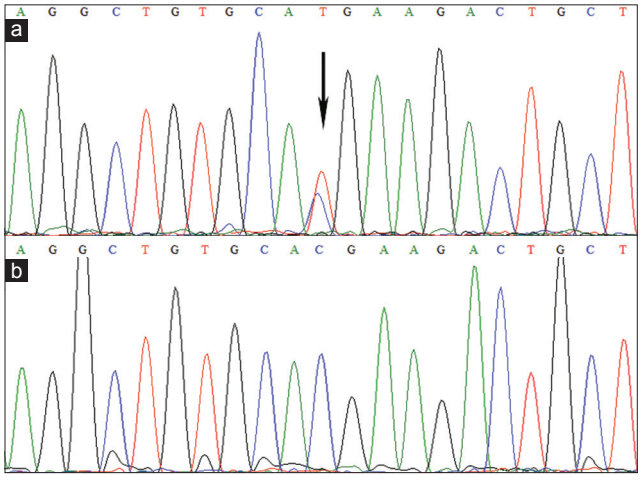


**Figure 2: (a) Heterozygous c.2806(C>T) (p.R936X) mutation in exon 20 of the CYLD gene in proband of the pedigree. (b) Sequence of exon 20 of the CYLD gene in normal controls**

recurrent nonsense mutation c. 2806C>T, leading to p.R936X in exon 20 of *CYLD* gene. This study expands the clinical heterogeneity of multiple familial trichoepitheliomas due to the same mutation (c. 2806C>T) in *CYLD* and contributes to enrichment of the database of the *CYLD* mutations underlying multiple familial trichoepitheliomas in the Chinese population. In the light of previous studies, our findings also suggest that though the mutation c. 2806C>T in *CYLD* mainly leads to a 'benign' phenotype such as multiple familial trichoepithelioma Brooke–Spiegler syndrome, but may also result in a malignant phenotype.

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