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LETTER TO THE EDITOR

A novel missense mutation of CYLD gene in a Chinese family with multiple familial trichoepithelioma

KEYWORDS
Mutation; Trichoepithelioma; CYLD

Multiple familial trichoepithelioma (MFT, OMIM 601606) is an autosomal dominantly inherited disease characterized by numerous, skin-colored papules with pilar differentiation. The skin tumors usually occur on the face, especially around the nasolabial folds, and more commonly found in females between the first and second decade of the life. Mutations in the CYLD gene on chromosome 16q12-q13 have been identified as the molecular basis of MFT [1], which is also responsible for familial cylindromatosia (FC, cylindromas only) [2], and Brooke-Spiegler syndrome (BSS, a combination of cylindromas, trichoepitheliomas and spiradenomas) [3]. CYLD gene functions as a tumor suppressor, while CYLD protein is a deubiquitinating enzyme, which negatively regulates activation of the transcription factor NF-κB by removing lysine-63-linked ubiquitin chains from TRAF2 (tumor necrosis factor receptor-associated factor 2), TRAF6 and NEMO (NF-κB essential modulator, also known as IκB kinase γ, Ikkγ) [4—6]. Loss of the deubiquitinating activity of CYLD correlates with tumorigenesis.

In this study, we performed mutation analysis of the CYLD gene in one three-generation Chinese MFT family and summarized clinical features and CYLD gene mutations of the MFT families previously reported. The family (Fig. 1a), which included four affected individuals, was identified through the proband from Fujian province of China. The proband was a 29-year-old woman. Some small asymptomatic papules were firstly noticed on the back of nose when she was 16 years old, and the papules enlarged in size and increased in number gradually. Physical examination indicated numerous, skin-colored, dome-shaped papules and nodules of varying sizes on her face, mainly around the root and ala of her nose and on her forehead (Fig. 1b). Lesional skin biopsy revealed numerous horn cells, islands of basaloid cells with palisading periphery (Fig. 1c). The family history revealed that the four affected individuals belonging to three consecutive generations had similar clinical manifestations (Table 1a). All the patients had papules or nodules around the noses. The average onset age of this family was about 15 years old varying from 10 to 16. There was no consanguinity in the family.

After informed consent, blood samples were obtained from all available family members and 100 unrelated controls. Genomic DNA was extracted from peripheral blood using a kit (Promega, Madison, WI, U.S.A.). Coding exons 4—20 and exon—intron boundaries were amplified by polymerase chain reaction (PCR) using primers described previously [1]. The PCR products were purified using a QIA quick PCR Purification Kit (Qiagen, Valencia, CA, U.S.A.) and directly sequenced on CEQ8800 automated sequencer (Beckman Coulter, Inc.). Sequence comparisons and analysis were performed using Chromas Version 2.31 program. In addition, samples from 100 unrelated controls were sequenced to exclude the possibility of polymorphism in the CYLD gene.

A novel heterozygous missense mutation c.2711C → T in exon 20 of CYLD gene in all affected individuals of the Chinese family was found (Fig. 1d). This mutation results in replacement of proline (CCT) by leucine (CTT) at amino acid 904. It was not reported before and was not detected in unaffected family members or in 100 unrelated controls (Fig. 1e) showing that it is a novel pathogenic mutation, not a common polymorphism.

CYLD contains four recognizable groups of sequence motifs: CAP—GLY domains (aa127—203,

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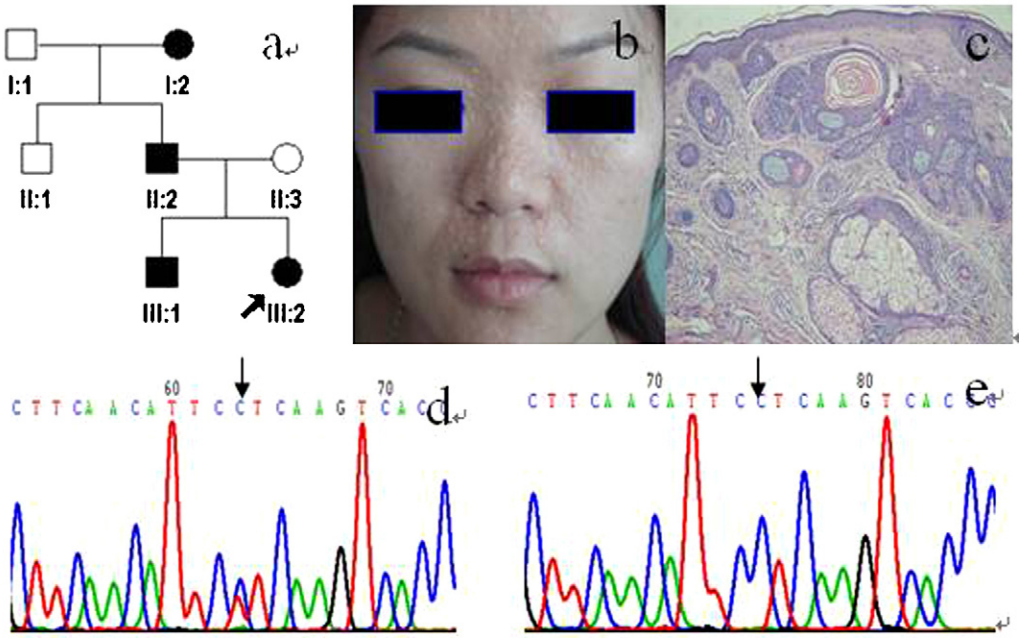

Fig. 1 (a) Pedigree of the family with MFT, the arrow designates the proband. (b) Clinical findings of proband: numerous, firm skin-colored, dome-shaped papules and nodules of varying sizes on her face. (c) Histological features: numerous horn cells, islands of basaloid cells with palisading periphery (haematoxylin and eosin; original magnification: 100×). (d) c.2711C → T(p.P904L) mutation in exon 20 of CYLD gene. (e) Wild type sequence of CYLD.

232—285 and 472—540, which is responsible for microtubute binding); proline-rich repeat (aa 388—413 and 446—471, which may constitute an SH3- binding domain); four Cys—X—X—Cys pairs (between aa 788 and 856, which may be metal-binding finger-like domains); a split domain with similarity to UCH type 2 catalytic sites (aa 593—610 and 871—889) [2]. To date, a total of 33 mutations of CYLD gene have been identified in families with MFT, FC and BSS, but only eight mutations led to the clinical features of MFT (Table 1b). All of the 33 mutations were located in 3′ two-thirds of the coding sequence (exon 9—20). Most mutations led to a premature translational stop, which disrupted the protein function. The mutation c.2711C → T(P904L) in our study was on exon 20 and did not seemed to have effect on the four recognizable groups discussed above; however, it was possible that the mutation influenced CYLD function by acting on some unrecognizable groups of sequence motifs, which were not known at present.

In summary, we have reported a Chinese MFT family and identified a novel missense mutation P904L of CYLD gene. This study should be useful for genetic counseling and prenatal diagnosis for the families with MFT; at the same time, the result may contribute to expanding database of CYLD mutations and be helpful in elucidating the molecular consequences of CYLD mutation in MFT.

Table 1a Summary of clinical findings in the family of MFT

Affected individual	Age (years)/ sex	Onset age (year)	Dermatological findings		Subjective symptom	With other disease?
			Distribution	Color		
I:2	80/F	16	Nose, left ear	Skin-colored	Itch	None
II:2	59/M	10	Nose	Skin-colored	None	None
III:1	31/M	17	Nose, eyelid	Skin-colored	None	None
III:2[a]	29/F	16	Nose, forehead, eyelid, chin	Skin-colored	None	None

M, male; F, female; III: 2[a], the proband.