Letter to the Editor

The first case of multiple pilomatricomas caused by somatic mutations of *CTNNB1* without any associated disorder

Pilomatricoma is a common benign epithelial tumor that originates from hair cells. The etiology of pilomatricomas remains to be fully elucidated, but stabilizing mutations in the beta-catenin gene (*CTNNB1*) have been reported to be involved in the formation of hair follicle-related skin tumors, including pilomatricomas [1]. Beta-catenin is a crucial component of the Wnt signal transduction cascade; mutations of *CTNNB1* lead to beta-catenin accumulation in the cytoplasm, which, in turn, forms complexes by binding to transcription factors. These complexes enter the nucleus and promote cell proliferation and differentiation, resulting in the formation of pilomatricomas [2]. Pilomatricomas are often solitary lesions, but they can also occur as multiple lesions. Multiple pilomatricomas are often associated with autosomal dominant disorders, such as myotonic dystrophy and familial adenomatous polyposis (FAP), but can also be associated with Rubinstein-Taybi syndrome (RTS), Turner syndrome, Gardner syndrome, Sotos syndrome, Kabuki syndrome, and Constitutional mismatch repair deficiency (CMMR-D). However, in contrast to cases of solitary pilomatricomas, those of multiple pilomatricomas caused by *CTNNB1* mutations are extremely rare.

A 26-year-old Japanese man was referred to our department with a 12-year history of multiple skin tumors occurring on the face, trunk, and extremities. On physical examination, seven tumors—cutaneous and subcutaneous—were observed on both cheeks (Fig. 1A, B), the left side of the neck (Fig. 1C), left shoulder, left cubital fossa (Fig. 1D), and upper back (bilateral; Fig. 1E). Clinical and histological features of the seven tumors are listed in Table 1. Serum levels of calcium, phosphorus, and parathyroid hormone were within the respective normal ranges. His medical history was unremarkable, and there was no known family history of skin tumors. Diagnosis of multiple pilomatricomas was made by skin biopsy (Table 1, Nos. 4 and 7), and all the tumors were surgically removed. Subsequently, the patient was examined for associated genetic disorders, but no abnormalities, except for the tumors, were detected. Screening gastroscopy and colonoscopy findings were unremarkable.

For genetic analyses, written informed consent was obtained from the patient, and genomic DNA was extracted from the resected tumors by using DNA Extraction from Paraffin-embedded Tissue (TaKaRa, Japan), according to the manufacturer's protocol. DNA samples were amplified by polymerase chain reaction, and direct sequencing of the amplified fragment of exon 3 of *CTNNB1* was performed using the ABI3130 Genetic Analyzer and GeneMapper Software 5 (both Applied Biosystems, CA, USA). Mutational analysis of *CTNNB1* demonstrated that 3/7 tumors (Table 1, Nos.1, 3, and 4) exhibited distinct heterozygous mutations in exon 3, viz. c.100G > A (p.Gly34Arg), c.94G > T (p.Asp32Tyr), and c.122C > T (p.Thr41Ile). All of these mutations have already been reported in pilomatricomas and are located at the hot spot of *CTNNB1* [1]. No mutations were detected in the other tumors. Furthermore, germline *CTNNB1* mutations were not detected in the genomic DNA of the patient's peripheral blood lymphocytes.

To our knowledge, this is the first case of *CTNNB1* mutations detected in multiple pilomatricomas, without clinical evidence of other disease conditions. Although multiple pilomatricomas often present with associated disorders, there are only a few reports of multiple pilomatricomas presenting without any other genetic diseases. Notably, some of the latter cases demonstrated a familial pattern with autosomal dominant inheritance [3,4]. It is likely that these familial cases had a spectrum of unidentified genetic abnormalities associated with multiple pilomatricomas.

Although somatic activating mutations in the *CTNNB1* have been found in a high percentage of solitary pilomatricomas [1,5,6], there are only two reported cases of multiple pilomatricomas harboring the same mutations [7,8]. First, we have previously reported a case of RTS with multiple pilomatricomas, in which one of the three pilomatricomas had a heterozygous mutation in *CTNNB1*, c.122C > T (p.Thr41Ile) [7]. RTS is caused by a mutation in *CREBBP*, which encodes cAMP-response element-binding protein–binding protein (CREBBP), or in *EP300*, which encodes p300. Hence, the development of multiple pilomatricomas in RTS may be explained by an activating mutation of *CTNNB1* as well as by the regulatory role of CREBBP/p300 in Wnt/beta-catenin signaling [9]. Secondly, Chmara et al. [8] reported three cases of CMMR-D due to *PSM2* mutations presenting with multiple pilomatricomas. CMMR-D results from germline mutations in one of four mismatch repair genes (*MLH1, MSH2, MSH6, or PMS2*), which leads to impaired DNA

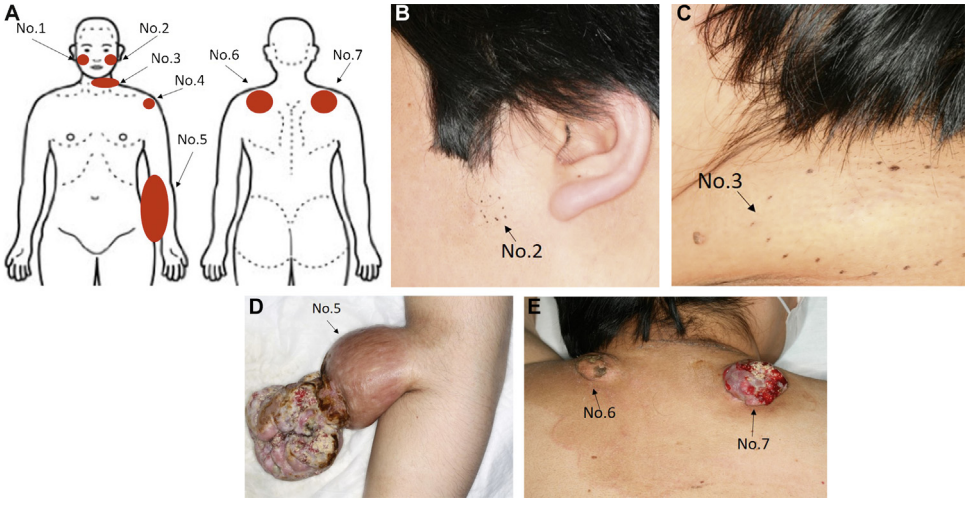

Fig. 1. Clinical manifestations of the present case. (A) Schematic representation of the distribution of seven pilomatricomas. (B–E) Clinical images of the pilomatricomas that developed on the patient's left cheek (B), left side of the neck (C), left cubital fossa (D), and upper back (E), representing sample Nos. 2, 3, 5, and 6 to 7 in Table 1 and Fig. 1A, respectively.

Table 1
Clinical and Pathological Features and Somatic *CTNNB1* Mutations in the Pilomatricomas.

No.	Location of pilomatricomas	Size (cm)	Clinical features	Pathological features	Somatic mutations *CTNNB1* exon 3
1	Rt. cheek	2.0 × 1.5	Subcutaneous tumor	SC, OS, CA, A few BC	c.100G > A (p.Gly34Arg)
2	Lt. cheek	1.2 × 1.0	Subcutaneous tumor	SC, OS, CA	WT
3	Lt. side of the neck	8.0 × 3.0	Subcutaneous tumor	SC, OS, CA	WT
4	Lt. shoulder	0.8 × 0.7	Subcutaneous tumor	SC, OS, CA, A few BC	c.94G > T (p.Asp32Tyr)
5	Lt. cuboidal fossa	25 × 15 × 10	Giant, Partially ulcerated, Pedunculated skin tumor	A lot of BC, CA A few SC	c.122C > T (p.Thr41Ile)
6	Lt. side of upper back	4.1 × 3.3	Dome-shaped skin tumor	SC, OS, CA	WT
7	Rt. Side of upper back	5.3 × 5.0	Ulcerated, Reddish, Dome-shaped skin tumor	BC, SC, OS	WT

Rt, Right; Lt, Left; SC, Shadow cells; OS, ossification; CA; Calcification; BC, Basophilic cells; WT, Wild type; G, Guanine; A, Adenine; T, Thymine; C, Cytosine; Gly, Glycine; Arg, Arginine; Asp, Asparatic acid; Tyr, Tyrosine, Thr, Threonine; Ile, Isoleucine.

mismatch repair and accumulation of somatic mutations that contributes to tumorigenesis [9]. In that study, nine pilomatricomas resected from three patients with CMMR-D demonstrated four different *CTNNB1* mutations, c.94G > T (p.Asp32Tyr), c.97T > C (p.Ser33Pro), c.121A > G (p.Thr41Ala), and c.122C > T (p.Thr41Ile), suggesting that mismatch repair defect by *PSM2* mutations increased the somatic mutation rate of *CTNNB1,* which may be the cause of the multiple pilomatricomas.

In the present study, 4/7 pilomatricomas demonstrated basophilic cells (Table 1, Nos.1, 4, 5, 7); three of these pilomatricomas (Table 1, Nos. 1, 4, 5) had activating *CTNNB1* mutations, whereas the three tumors without basophilic cells (Table 1, Nos. 2, 3, 6) were negative for *CTNNB1* mutations. These findings are consistent with previously published results that found *CTNNB1* mutations only in pilomatricomas containing basophilic cells [6,8]. Our patient had neither a known family history of pilomatricomas nor any associated genetic disorders. However, some of the tumors showed unusual clinical presentation; for example, tumors in the left cubital fossa and right side of the upper back were giant and ulcerative pilomatricomas (Table 1, Nos. 5, 7). Furthermore, similar to previously reported cases [8], three different somatic *CTNNB1* mutations in different pilomatricomas were observed in one individual, indicating that multiple somatic *CTNNB1* mutations can occur, resulting in multiple pilomatricomas. Therefore, further mutational analyses are required to detect unidentified genetic alterations that facilitate the Wnt/beta-catenin signaling or increase the susceptibility to somatic *CTNNB1* mutations.

In conclusion, we identified that somatic *CTNNB1* mutations can give rise to not only solitary, but also multiple pilomatricomas, without any associated genetic disorders. These findings may further the understanding of the pathogenesis of multiple pilomatricomas. Therefore, patients with multiple pilomatricomas should be carefully examined, investigated for associated disorders, and mutational analysis for somatic *CTNNB1* mutations should be performed in an attempt to elucidate the unknown mechanisms underlying the development of multiple pilomatricomas.

Conflicts of interest

The authors have no conflicts of interest to declare.

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