The Novel Tetratricopeptide Repeat Domain 7 Mutation, *Ttc7*$^{fsn\text{-}Jic}$, with Deletion of the TPR-2B Repeat Causes Severe Flaky Skin Phenotype

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We carried out molecular analyses of the novel flaky skin mutation, *Ttc7*$^{fsn\text{-}Jic}$ (a synonym for *fsn*^{Jic}), which we found in a previous study. It was revealed that this mutation involved a genomic in-frame deletion including exons 9 and 10 of the *Ttc7* gene, and that the genomic deletion in *Ttc7*$^{fsn\text{-}Jic}$ may disrupt the tetratricopeptide repeat-2B domain of the TTC7 protein. Based on a comparison of three *Ttc7* mutations, including *Ttc7*$^{fsn\text{-}J}$ (a synonym for *fsn*) and *Ttc7*$^{fsn\text{-}hea}$ (a synonym for *hea*), it was suggested that either exon 9 or exon 10 or both may play a more important role than the other exons of the *Ttc7* gene. *Ttc7* gene expression analyses using Northern blotting revealed that *Ttc7* mRNA is expressed in 11 tissues, except muscle. In conclusion, we confirmed that the *Ttc7*$^{fsn\text{-}Jic}$ mutation, as well as the *Ttc7*$^{fsn\text{-}J}$ and *Ttc7*$^{fsn\text{-}hea}$ mutations, is responsible for abnormal phenotypes observed in various tissues of mice with the flaky skin mutation. Exp Biol Med 232:695–699, 2007

Key words: flaky skin; psoriasis; *fsn*; *Ttc7*; TPR; exon deletion

Introduction

Flaky skin (*fsn*) mice are used as an animal model of human psoriasis because they develop thick scales with associated patchy alopecia (1, 2). So far, three flaky skin mutants have been reported. The *fsn* mutation (hereafter referred to as *Ttc7*$^{fsn\text{-}J}$) arose spontaneously in A/J mice (3), and during study of this mutant the *fsn* locus was assigned to chromosome 17 (3, 4). The *hea* mutant (hereafter referred to as *Ttc7*$^{fsn\text{-}hea}$) was reported by Shimizu *et al*. (5) and White *et al*. (6), and *fsn*^{Jic} (hereafter referred to as *Ttc7*$^{fsn\text{-}Jic}$) was reported by us (7). Recently, it was demonstrated that the *Ttc7*$^{fsn\text{-}J}$ mutation is caused by the insertion of an ETn transposon (8, 9), and that the *Ttc7*$^{fsn\text{-}hea}$ mutation is caused by a large deletion of exons 1–14 of 20 exons (8).

It is well known that flaky skin mice have a pleiotropic disease phenotype, with such features as a smaller body; anemia; low iron metabolism; low hematocrit; enlargement of the liver, spleen, and heart; increased nucleated red blood cells; fragile erythrocyte membranes; and lymphocyte infiltration in the liver and kidneys (3, 10–14). Studies using *Ttc7*$^{fsn\text{-}J}$ mice have focused on immunologic dysfunction (10, 11, 14, 15) and autoimmunity (16–23). As a result, it has been recognized that the TTC7 protein may be an important regulator of lymphocyte development and function.

Different life spans of three *Ttc7* congenic mice with the BALB/c genetic background have been found. *Ttc7*$^{fsn\text{-}hea}$ homozygotes have the shortest life span (about 7 days; Ref. 6), and *Ttc7*$^{fsn\text{-}Jic}$ homozygotes live about 10 days (7). In contrast, the life span of the *Ttc7*$^{fsn\text{-}J}$ homozygotes is about 3 months. This phenomenon suggests that these three mutant alleles are generated by different mutations.

In the present study we attempted a mutation search of the novel mutation, *Ttc7*$^{fsn\text{-}Jic}$, in order to identify differences between it and the other *Ttc7* mutations. We also carried out expression studies in 12 tissues using Northern blotting.

Materials and Methods

Mice and Genetic Nomenclature. The B6.INT-*Ttc7*$^{fsn\text{-}Jic}$ mice maintained in our laboratory were used in

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Table 1. Primer Sets Used for Genomic PCR (5′-3′)[a]

Exon no.	Forward primer	Reverse primer	Product size (bp)
1	GTCAAGCCTGCTGGAGAGTGCTC	GGACAGACGACTTTCCTAACTG	430
2	GAATGCACCTTTATCGTCTCAGAC	CTTCTCCATATCCACTGGAGCTAC	388
3	CATCCTGGAAGACTTCCTGGAG	CCCAACATGGCTTTCACTACCC	409
4	GTATTCCCTCAGATGCACCTAC	CAGGAGAGGAGATGCTTTCTTC	322
5	GACGTCTCCTTCAAGCCACATG	CCCACAACTTGGTTCTCTGAAC	357
6	CCTGTTAGTGCTGGACTCTGAG	GTCTGCTGAGAGCAGAAGAAG	286
7	GGATTTGCCAGTTGGGAAACAG	ATGTCTGCCTGGTCCTGTACAG	371
8	GGGATGCTGTTGTGTTTTCCAG	CGCTCCATAACCTCAACCCA	133
9	TCGCCAAACTCCATTTCACC	AGGTAGGCTGAGTGACTGAC	188
10	AGTGCTGACTGCGTGTTCCT	ACGTCTCCAGCACCAAACTCTG	201
11	CCAGTGATTGTGTTCCCTACT	CCACCATACCCTCATCTCAC	169
12	CGTTGCCTACAGTTGCAGTTTGG	GCGTGTCTGTGGAAAAGCAAGG	362
13	GATAGGTTCCTTCCTTACCAAGG	CTGGCAATTGGGTTTCCTTATCC	285
14	CTGGCAGAATCTCCCACCATAATG	CCCTTCACAAAGATGCTCACTTG	265
15	CCATTCAAGATGCTTGCTTCTGG	GCAGTGGACACTTTACCCTGTG	386
16	GAAAGCTAGCATCCGATGAGTGTG	GCTGAGTTCCACATCTCCCTTC	363
17	GTCCTTCCCTGCTATTCTAGCTTG	GGAGGGACTTTCTTTCTGTTGC	322
18	GGTGGAGTCCAGTGAACATCTTTG	CCAGAAATCTCCACCTCCTTCATC	375
19	GTGTCCTCTGTTGACTTCCTGG	GGAAATCACCTCCTAGAGATGC	427
20	GCACAGTCATTTGTCTGTGGCC	CACTTGTCATCTATTCCCTGAGG	475

[a] The primer sets were designed based on the sequence data from the National Center for Biotechnology Information database (http://www.ncbi.nih.gov/).

this study. The flaky skin phenotypes of the mice are described elsewhere (7). CBy.A-*Ttc7*$^{fsn\text{-}J}$ was purchased from the Jackson Laboratory (Bar Harbor, ME). C57BL/6JJcl mice were purchased from CLEA Japan (Tokyo, Japan) and were used as the normal mice in this study.

In accordance with information in the Mouse Genome Informatics Database (http://www.informatics.jax.org/mgihome/nomen/), the following gene symbols are used in this paper: *Ttc7*$^{fsn\text{-}J}$ for *fsn*^{J}, *Ttc7*$^{fsn\text{-}hea}$ for *fsn*^{hea}, and *Ttc7*$^{fsn\text{-}Jic}$ for *fsn*^{Jic}.

Mutation Search. *Extraction of Genomic DNA and Messenger RNA.* Genomic DNA was extracted using the standard method. Extraction of messenger RNA was performed using Trizol reagent (Invitrogen, Carlsbad, CA) in accordance with the manufacturer's instruction.

Genomic Polymerase Chain Reaction (PCR) and Reverse Transcriptase (RT)-PCR. Genomic PCR was performed to amplify the *Ttc7* exons. The primer sets derived from flanking sequences 50 bp upstream and downstream of *Ttc7* are shown in Table 1. Conditions for genomic PCR were: 35 cycles of 30 secs at 94°C, 30 secs at 60°C, and 30 secs at 72°C, using Ex-Taq polymerase (TaKaRa, Kyoto, Japan) in accordance with the manufacturer's instruction. Two-percent agarose gels (Nippon Gene, Tokyo, Japan) were used as analytical gels and were prepared in Tris-acetate-EDTA buffer.

RT-PCR was carried out using a Superscript III First-Strand cDNA synthesis kit (Invitrogen) in accordance with the manufacturer's instruction. Agarose gels (0.8% and 2%) were used as described above.

Sequencing. To perform direct sequencing, the PCR products were purified using a MinElute PCR purification kit (Qiagen, Valencia, CA). Sequencing was carried out using an ABI3700 automated sequencer (Applied Biosystems, Foster City, CA). Analyses of sequence data were carried out using Sequencher software (Gene Codes, Ann Arbor, MI).

Northern Blotting. The cDNA probe (approximately 0.46 kb and including exons 17–20) for Northern blotting was prepared using RT-PCR. Purification of the cDNA was carried out using Quiaquick Gel Extraction Kit (Qiagen) and labeled with ^{32}P-2′-deoxycytidine 5′-triphosphate (^{32}P-dCTP) using a Prime-It Labeling kit (STRATAGENE; Roche Molecular Biochemicals, Mannheim, Germany) in accordance with the manufacturer's instructions. Northern blot membrane was purchased from OriGene Technologies (Rockville, MD).

Results

Identification of the *Ttc7*$^{fsn\text{-}Jic}$. Genomic PCR was performed using 20 primer sets designed to detect 20 exons of the *Ttc7* gene. As shown in Figure 1, exons 9 and 10 were not detected in the *Ttc7*$^{fsn\text{-}Jic}$ mutation.

RT-PCR also was carried out to confirm the deletion. As shown in Figure 2, two mutation bands were indicated by gel electrophoresis. One is a 786-bp band deleting 222 bp, which is equivalent to 74 amino acids, including exons 9 and 10, and the other is a 681-bp band deleting 327 bp, which is equivalent to 109 amino acids, including exons 9–11. Genomic DNA sequencing was performed to clarify the reason why two different deletions were present. As a result, a 10-base deletion from –32 to –41 of the 5′ sequence near exon 11 was observed, as shown in Figure 3.

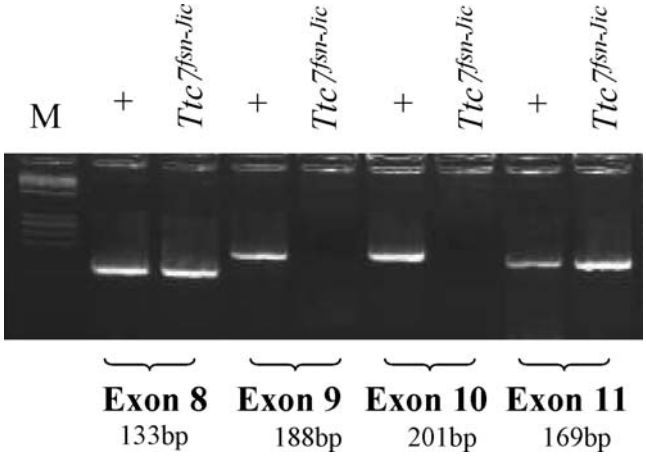

Figure 1. Exon deletion in the *Ttc7*$^{fsn\text{-}Jic}$ mutation. Using genomic PCR, exons 1–20 were detected in the normal mice (+), but exons 9 and 10 were not detected in the mutant mice (*Ttc7*$^{fsn\text{-}Jic}$). M indicates the φX174 phage DNA digested with *Hae*III enzyme.

Expression Studies of *Ttc7* mRNA. We studied expression of the *Ttc7* gene in 12 tissues of the normal mouse. As shown in Figure 4, *Ttc7* mRNA was strongly expressed in kidney and liver; was moderately expressed in the skin, spleen, stomach, intestine, thymus, and lung; was weakly expressed in the brain, heart, and testis; and was absent in muscle.

Comparison of Genomic DNA and mRNA of *Ttc7*$^{fsn\text{-}Jic}$, *Ttc7*$^{fsn\text{-}hea}$, and *Ttc7*$^{fsn\text{-}J}$. Possible structures of genomic DNA and mRNA of the *Ttc7*$^{+}$, *Ttc7*$^{fsn\text{-}Jic}$, *Ttc7*$^{fsn\text{-}hea}$, and *Ttc7*$^{fsn\text{-}J}$ mutations are shown in Figure 5. As a result of comparing these structures, it was supposed that the deletion of exons 9 and 10 in the *Ttc7*$^{fsn\text{-}Jic}$ mutation

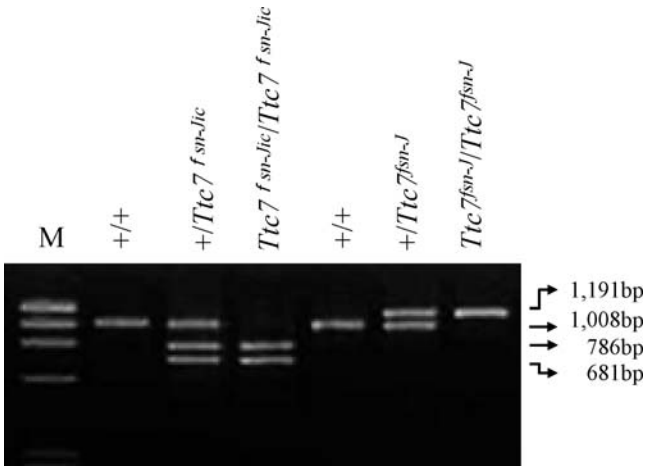

Figure 2. Two types of deletion mutation in the *Ttc7*$^{fsn\text{-}Jic}$ mutation. Primers TCACCTCTACGAAGGGGACAA (forward) and AGAGTCAGGTGGATACCGTT (reverse) that were designed based on sequence data in the National Center for Biotechnology Information (NCBI) database (http://www.ncbi.nih.gov/) were used to amplify 1008 bp, including exons 7–17. RT-PCR using this primer pair amplified two different PCR products, 681 bp and 786 bp, from the *Ttc7*$^{fsn\text{-}Jic}$ mutation. *Ttc7*$^{+}$ and *Ttc7*$^{fsn\text{-}J}$ were clearly identified by the different sizes of their PCR products (1008 bp and 1191 bp, respectively). M indicates the φX174 phage DNA digested with *Hae*III enzyme.

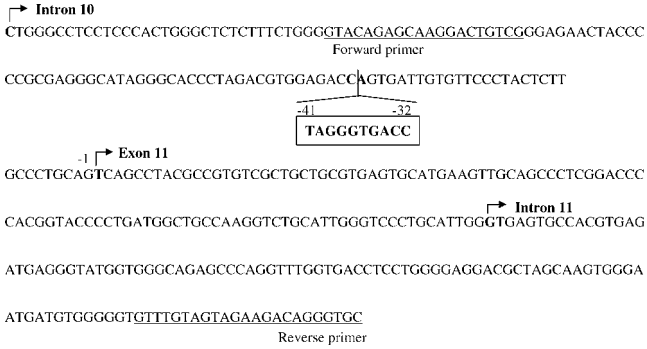

Figure 3. A 10-base deletion exists in intron 10 near exon 11 of *Ttc7*$^{fsn\text{-}Jic}$. The PCR product used for sequencing was amplified using the primers designed in intron 10 and intron 11. Rectangles shown the 10 bases from –41 to –32 at the 5′ end near exon 11.

leads to a lack of tetratricopeptide repeat-2B (TPR-2; Fig. 5f), and that the deletion of exons 1–14 in the *Ttc7*$^{fsn\text{-}hea}$ mutation leads to a lack of TPR-2A, TPR-2J, TPR-2B, TPR-1C, and TPR-2D (Fig. 5g).

Discussion

Molecular analyses performed in the present study revealed that the *Ttc7*$^{fsn\text{-}Jic}$ mutation is caused by a genomic in-frame deletion of exons 9 and 10. Comparing *Ttc7*$^{fsn\text{-}J}$ mice and *Ttc7*$^{fsn\text{-}hea}$ mice showing a large deletion of exons 1–14, there are few differences in their disease phenotypes, except a slightly different life span. This result leads to the conclusion that exon 9 and/or 10 of the *Ttc7* gene may play an important role in biologic function of the TTC7 protein.

Two different amplicons were equally produced in the *Ttc7*$^{fsn\text{-}Jic}$ homozygotes by RT-PCR, as shown in Figure 2. It may be supposed that a 10-base deletion in intron 11 causes two different splicing events leading to two transcripts, deleting exons 9 and 10 and exons 9–11. We used a website (http://www.fruitfly.org/seq_tools/splice.html) to search specific sequences for splicing mutation. However, a query result showed this 10-base sequence does not predict any splicing mutations.

Using Northern blotting we demonstrated that *Ttc7* transcripts are ubiquitously expressed in the normal mice in

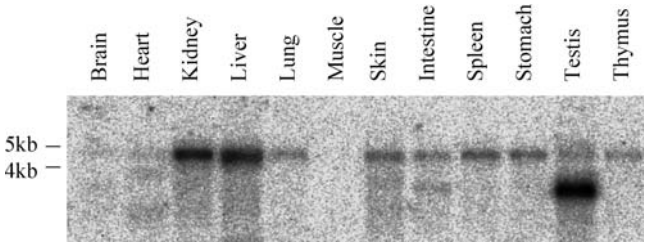

Figure 4. *Ttc7* mRNA expression using Northern blotting. The cDNA probe for Northern blotting was prepared using RT-PCR with the primers 5′-GAAGAAACAGAACGGTATCCAC-3′ (forward) and 5′-TCCACAGCATCCCGCAGCACCT-3′ (reverse), which were designed based on sequence data in the NCBI database (http://www.ncbi.nih.gov/). A high-density band in a small size was observed in testis. This band also was observed by Helms *et al.* (9).

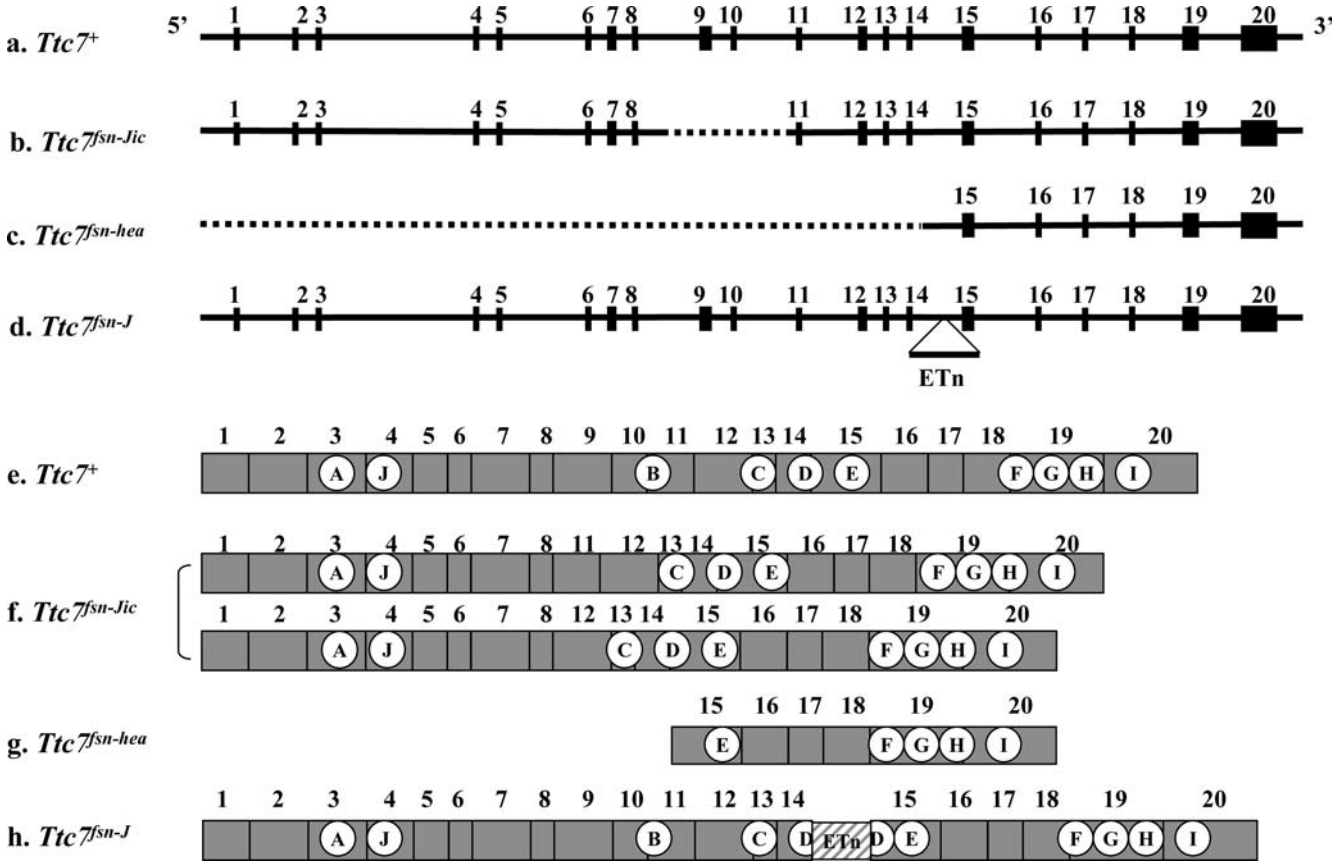

Figure 5. Comparison of the genomic DNA and mRNA of *Ttc7*$^{+}$, *Ttc7*$^{fsn\text{-}Jic}$, *Ttc7*$^{fsn\text{-}hea}$, and *Ttc7*$^{fsn\text{-}J}$. (a) and (e) are the possible structures of genomic DNA and mRNA of *Ttc7*$^{+}$, (b) and (f) are those of *Ttc7*$^{fsn\text{-}Jic}$, (c) and (g) are those of *Ttc7*$^{fsn\text{-}hea}$, and (d) and (h) are those of *Ttc7*$^{fsn\text{-}J}$. Dotted lines indicate the deleted genomic regions observed in *Ttc7*$^{fsn\text{-}Jic}$ and *Ttc7*$^{fsn\text{-}hea}$. Two *Ttc7*$^{fsn\text{-}Jic}$ transcripts (f) were detected using RT-PCR, as shown in Figure 2. However, existence of the *Ttc7*$^{fsn\text{-}hea}$ transcript has not been found (8). The *Ttc7* genomic DNA is approximately 100 kb in length, consisting of 20 exons. The *Ttc7* mRNA is approximately 4.6 kb in length, including the 2577-bp coding region (858 amino acids). Among the letters A through I enclosed in circles, C and I are the TPR-1 repeats; B, E, F, G, and H are the TPR-2 repeats; and A and D are TPR-2 repeats determined from sequence context. This figure was drawn based on the report of Helms *et al.* (9).

this study. Our results agreed with that of Helms *et al*. (9). Abnormalities observed in blood, skin, and other organs of the flaky skin mice lead to a hypothesis that *Ttc7* mutations could cause the widespread flaky skin disease phenotypes, including hematopoietic and autoimmune disorders. Therefore, the TTC7 protein may play a fundamental role in the development or regulation of the immune system. This is in agreement with the multi-immunologic abnormalities in flaky skin mice. We conclude that various flaky skin diseases are brought about not by immunologic dysfunction but by the mutated TTC7 protein expressed ubiquitously in almost all tissues and organs.

TPR is a structural motif present in a wide range of proteins (24–26). It mediates protein-protein interactions and the assembly of multiprotein complexes (27). The *Ttc7* gene codes 10 TPR domains that consist of 34 to 37 amino acids (8, 9). Five TPRs (2A, 2J, 2B, 1C, and 2D) are deleted in *Ttc7*$^{fsn\text{-}hea}$ (8), and one TPR (2B) is deleted in *Ttc7*$^{fsn\text{-}Jic}$, as shown in this study. In *Ttc7*$^{fsn\text{-}J}$, TPR-2D is disrupted due to insertion of the ETn transposon into intron 14 (8, 9). Helms *et al*. noted that the disruption of TPR-2D may affect its interaction with an as yet unidentified protein partner (9). They also found that a subset of *Ttc7* transcripts in *Ttc7*$^{fsn\text{-}J}$ mice are wild type, indicating that the splicing of the ETn exon is leaky. This leaky splicing may bring about the longer life span of the *Ttc7*$^{fsn\text{-}J}$ mouse. These findings may suggest that a deletion of TPR-2B leads to a nearly complete loss of TTC7 function, which causes not only pleiotropic pathologic changes but also early postnatal death in both *Ttc7*$^{fsn\text{-}hea}$ and *Ttc7*$^{fsn\text{-}Jic}$ mutants.

In an association study of single nucleotide polymorphisms within *TTC7A*, the human ortholog of mouse *Ttc7*, Helms *et al*. (9) concluded that the *TTC7A* locus did not have a major role in psoriasis susceptibility in human psoriasis. However, even if *TTC7* is not the gene responsible for human psoriasis, the mechanisms underlying psoriasis-like inflammatory skin lesions and the biologic roles of each TPR domain in the functions of the TTC7 protein should still be studied further.

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