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Trichothiodystrophy, complementation group A complicated with squamous cell carcinoma

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Running head: SCC complicated with TTDA

Abbreviations: Cockayne syndrome (CS); squamous cell carcinoma (SCC); trichothiodystrophy, complementation group A (TTDA); xeroderma pigmentosum (XP)

KEY WORDS: Cockayne syndrome; GTF2H5; squamous cell carcinoma; trichothiodystrophy, complementation group A; xeroderma pigmentosum

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There are three related, clinically defined disorders of DNA repair: xeroderma pigmentosum (XP), trichothiodystrophy (TTD) and Cockayne syndrome (CS).[1] Photosensitivity, neurological/developmental abnormalities, and skin cancer are important pathological features that can be used to distinguish between these three archetypes.[1,2] TTD is a rare, autosomal recessive disease characterized by brittle, sulfur-deficient hair and multisystem abnormalities.[3] The general TFIIH subunit 5 (GTF2H5) gene, *GTF2H5*, is known to be a causative gene of TTD, complementation group A (TTDA, OMIM#616395). None of five patients with mutations in TTDA showed skin cancers (Table 1).[4-6] Here, we describe a recurrent mutation in *GTF2H5* in a Japanese male suffering from TTDA complicated with squamous cell carcinoma (SCC).

The proband is a 44-year-old Japanese man, the oldest of four siblings born to related parents. At the age of 15 years, left sensorineural deafness was noted. On examination, he had short and somewhat brittle hair, with no hypotrichosis (Fig. 1a). He was found to have generalized scaling on the face, trunk and extremities, and palmoplantar keratoderma (Fig. 1b). A lesional skin biopsy revealed hyperkeratosis, acanthosis and thinned granular layers (Fig. 1g). Light microscopy and scanning electron microscopy demonstrated abnormal, irregular hair surfaces (Fig. 1d, e). He has short stature (-4.2 standard deviations) with normal weight. Other normal or negative

findings include the absence of all of the following: photosensitivity, teeth or visual abnormalities, micrognathia, developmental delay, recurrent infections, and abnormalities in maternal pregnancy and fetal development. Oral administration of etretinate (0.3 mg/kg/day) effectively resolved the ichthyosis eruptions.

When he was 42 years old, an ulcerated nodule with a fissure developed on the right neck (Fig. 1c). A biopsy specimen from the nodule showed the proliferation of atypical keratinocytes in the epidermis, and the invasion of these cells to the upper dermis was observed (Fig. 1h). The nodule was diagnosed as moderately differentiated SCC and was surgically excised.

Ethical approval was obtained and all research was performed in accordance with the Declaration of Helsinki principles. Genomic DNA from the patient's peripheral blood leukocytes was used for whole-exome sequencing analysis.[7] Analysis of the data revealed a homozygous nonsense mutation in *GTF2H5*, c.163G>T (p.Glu55*) (Fig. 1f). We did not identify any potentially pathogenic mutations in specific genes such as *MPLKIP* nor in other genes associated with trichothiodystrophy/photosensitivity. The mutation p.Glu55* identified in *GTF2H5* has been reported previously as a pathogenic mutation in a Japanese individual with TTDA.[6] In addition, a nonsense mutation of the adjacent arginine, p.Arg56*, has been reported in TTDA.[4] Taken together, these

pathogenic mutations potentially underscore the functional importance of the C-terminus. The reported Japanese boy with the identical *GTF2H5* mutation c.163G>T had photosensitivity, but no skin cancer.[6] There are phenotypic disparities between the two Japanese subjects with the homozygous mutation p.Glu55*, although we cannot exclude the possibility that skin cancer may develop later in the reported boy's life.

Our case has SCC, but no photosensitive dermatoses. We speculate that his cumulative sun exposure might have affected the development of SCC, since the neck region is continuously exposed to sunlight, potentially resulting in DNA damage. In XP patients, the median age of first nonmelanoma skin cancer was 9 years, compared with 67 years in the general population.[1] By contrast, CS patients have never been reported to develop cancer, although they often exhibit photosensitivity. Reid-Bayliss *et al.* reported that the lack of elevated UV-induced mutagenesis in cells cultured from CS patients revealed a transcription-coupled repair deficiency that was not mutagenic, despite cytotoxicity increases.[8] Although the malignancy in our case may be coincidental, there may be an association between TTDA by *GTF2H5* mutations and primary cutaneous SCC.

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Table I. Summary of reported trichothiodystrophy, complementation group A families with *GTF2H5* mutations.

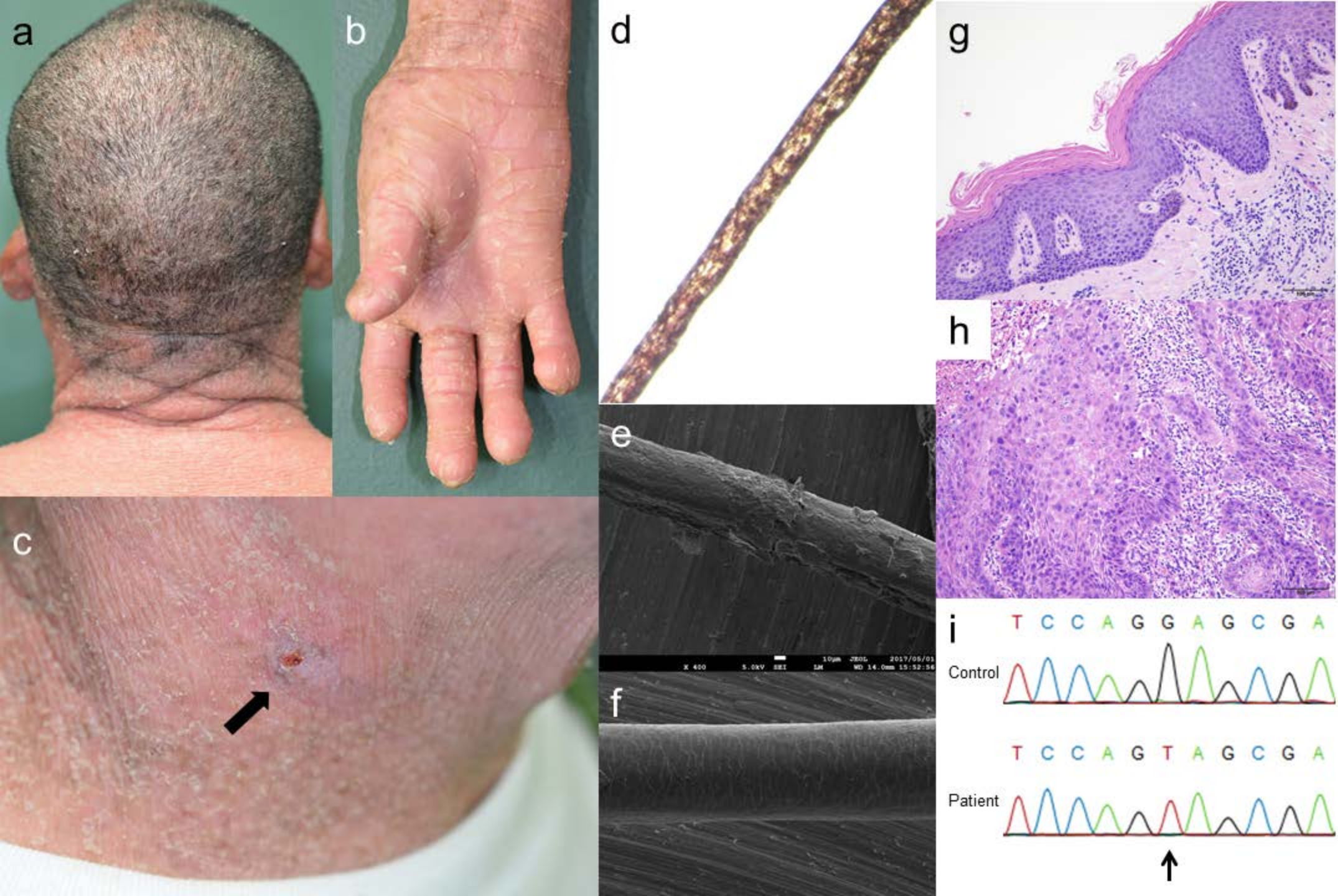
Pedigree	1 (ref. 4, 5)	2 (ref. 5)	3 (ref. 5)	4 (ref. 6)	Present case
Mutations	p.Arg56*/p.Leu21Pro	p.Arg56*/p.Arg56*	p.Met1Thr/p.Met1Thr	p.Glu55*/p.Glu55*	p.Glu55*/p.Glu55*
Family members	1 patient	1 patient	2 patients	1 patient	1 patient
Age (y.o.)	20	NS	NS	5	44
Skin cancer	-	-	-	-	squamous cell carcinoma
Photosensitive dermatosis	+	+	+	+	-
Other features	asthma, cataracts, contracture of fingers, developmental delay, mental retardation, short stature	cataracts, developmental delay, deafness, mental retardation, short stature, caries	developmental delay, mental retardation, deafness	cataracts, developmental delay, mental retardation	contracture of fingers, unilateral deafness, elevated serum IgE, short stature

Abbreviations: y.o., years old; NS, not stated; ND, not described

Figure legends

Figure 1. Clinical and molecular features of the proband with trichothiodystrophy, complementation group A.

(a) The patient has short, bright hair on the scalp. (b) His right palm shows diffuse, severely scaly hyperkeratosis, and his fingers are shortened and contractured. (c) An ulcerated red nodule (9 x 12 mm) is seen in the neck (the arrow indicates the tumor). (d) Polarizing microscopy reveals characteristic bright and dark regions on the hair. (original magnification ×40) (e) Scanning electron microscopy of the hair shows surface irregularities in comparison with the normal control (f). (original magnification ×400) (g) A haematoxylin-eosin stained section of the skin biopsy specimen from his ichthyotic skin shows partial parakeratosis, mild acanthosis and moderate hyperkeratosis in the epidermis. Scale bar: 100 μm. (h) A skin biopsy from the nodule in the neck demonstrates the proliferation of atypical keratinocytes of various sizes with large nuclei, and severe lymphocytic infiltration in the upper dermis. Scale bar: 100 μm. (i) Sanger sequencing reveals a homozygous mutation within *GTF2H5,* c.163G>T (p.Glu55*) in the proband.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Control
T C C A G T A G C G A
Patient