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ORIGINAL ARTICLE

A Mongolian patient with hypohidrotic ectodermal dysplasia with a novel P121S variant in *EDARADD*

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Structured Abstract

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Introduction – Hypohidrotic ectodermal dysplasia is a genetic disorder characterized by diminished or a lack of sweating, congenital missing teeth, and sparse or absent hair. Three genes, *EDA*, *EDAR*, and *EDARADD*, all related to tumor necrosis factor signaling, have been reported as responsible genes for this disorder. Among them, the largest numbers of mutations have been identified in *EDA*, and only two mutations identified in *EDARADD*.

Materials and Methods – DNA analysis of *EDA*, *EDAR*, and *EDARADD* was performed on a Mongolian patient by polymerase chain reaction-direct sequencing.

Results – The 5-year-old Mongolian individual had no erupted deciduous or permanent teeth. A panoramic radiograph showed only one tooth in the right mandible. His hair and eyebrows were sparse, but he did not have a short stature. He showed diminished sweating. The nails of his fingers and toes were normal. Based on these conditions, he was diagnosed with hypohidrotic ectodermal dysplasia. There was no gene mutation of *EDA* or *EDAR*. A novel heterozygous variant (P121S; c.361C > T) was identified in the death domain of *EDARADD* (NM_080738). No other member of his family was affected, and this variant was not identified in his parents or maternal grandparents.

Conclusion – This study reports an individual affected with hypohidrotic ectodermal dysplasia with a novel heterozygous P121S variant in the death domain of *EDARADD*.

Key words: death domain; ectodermal dysplasia; *EDARADD*; gene mutation; tumor necrosis factor

Introduction

Ectodermal dysplasias are heterogeneous genetic disorders that display different combinations of congenital defects in teeth, nails, sweat glands, and hair (1, 2). The hypohidrotic (or anhidrotic) ectodermal dysplasias (MIM #129490, #224900, #305100) are a subgroup showing abnormalities of the eccrine sweat glands.

It has been reported that the ectodysplasin (Eda) pathway initiates development of the hair, teeth, and other ectodermal derivatives (3, 4). Three genes, *EDA*, *EDAR*, and *EDARADD*, are related to this pathway. *EDA* encodes Eda, which is a ligand of Edar (encoded by *EDAR*) belonging to the tumor necrosis factor (TNF) receptor family (5). The adaptor protein, Edaradd, encoded by *EDARADD*, interacts with the death domain of Edar and transduces the downstream signaling (6–8). Both Edar and Edaradd are known to have a death domain related to the apoptosis signal (6, 8, 9).

The X-linked form of hypohidrotic ectodermal dysplasia (MIM #305100) is mainly caused by *EDA* mutation. The autosomal hypohidrotic ectodermal dysplasias (MIM #129490 and #224900) are caused by the mutations of *EDAR* and *EDARADD*. Among them, only two mutations have been identified in *EDARADD* (6, 8). One is a homozygous E142K mutation in the death domain (6), and the other is a heterozygous L112R mutation (8).

In this report, we describe an individual affected by hypohidrotic ectodermal dysplasia with a novel heterozygous P121S variant (c.361C > T) in the death domain of *EDARADD*.

Materials and methods

Genomic DNA was isolated from nail samples from the affected patient, his parents, and maternal grandparents, after obtaining informed consent. Isolated DNA was amplified by the polymerase chain reaction (GeneAmp PCR System 9700; Applied Biosystems, Foster City, CA, USA) using specific primers for *EDA* (10), *EDAR* (11), and *EDARADD* (8). Amplified products were sequenced using BigDye Terminator v.3.1 cycle sequencing kit (Applied Biosystems).

Results

The 5-year-old Mongolian boy (III-6) was born to healthy parents, and his birth weight was 2980 g (Fig. 1). He was a monozygotic twin, and his counterpart (III-7) had died of cardiac failure at 1 years of age (Fig. 1). Because of his short life, it was not clear whether the counterpart had also been affected with ectodermal dysplasia. His father (II-1) had six younger brothers, and his mother (II-10) had two older sisters. No family member was affected with ectodermal dysplasia.

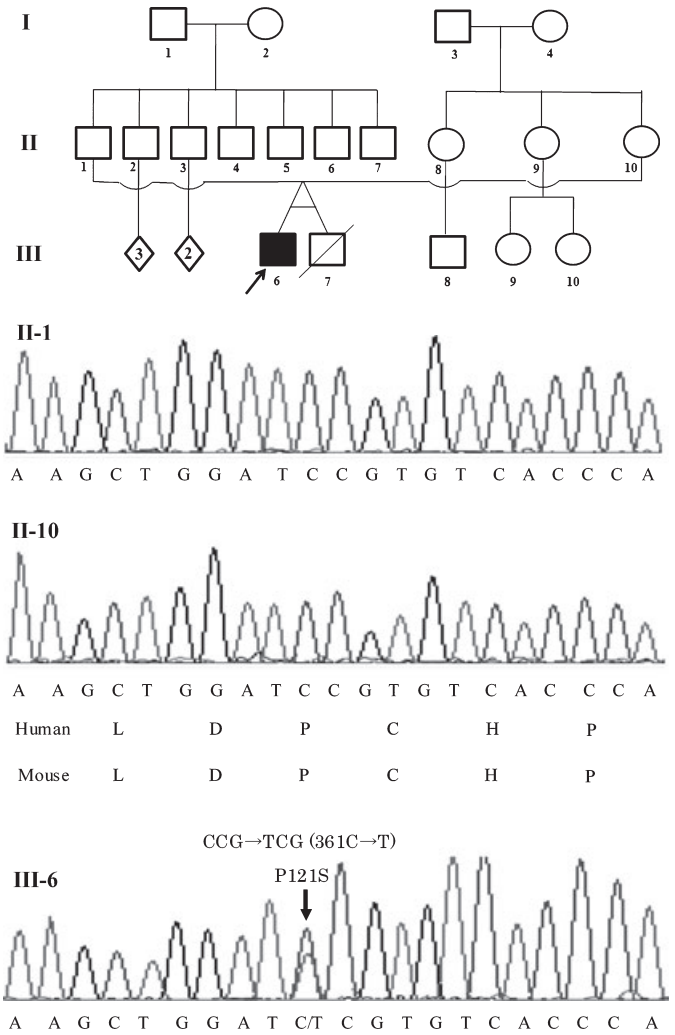

Fig. 1. The pedigree of the Mongolian individual with hypohidrotic ectodermal dysplasia. DNA sequences of *EDARADD* in II-1 (father), II-10 (mother), and III-6 (proband) are shown. III-6 showed a heterozygous P121S (c.361C > T) variant, which was not in II-1 or II-10. N-terminus amino acid sequences of the death domain (start from L119) of human and mouse Edaradd are shown under II-10.

He did not show short stature, and his mental development was normal. His hair and eyebrows were sparse. The nails on his fingers were normal, but he was unable to sweat. He did not show any cardiac abnormality. He had no erupted deciduous or permanent teeth. A lateral cephalogram and panoramic radiograph showed only one mandibular molar on the right side (Fig. 2). The alveolar bone height of the maxilla and mandible was extremely low. Based on these conditions, he was diagnosed with hypohidrotic ectodermal dysplasia.

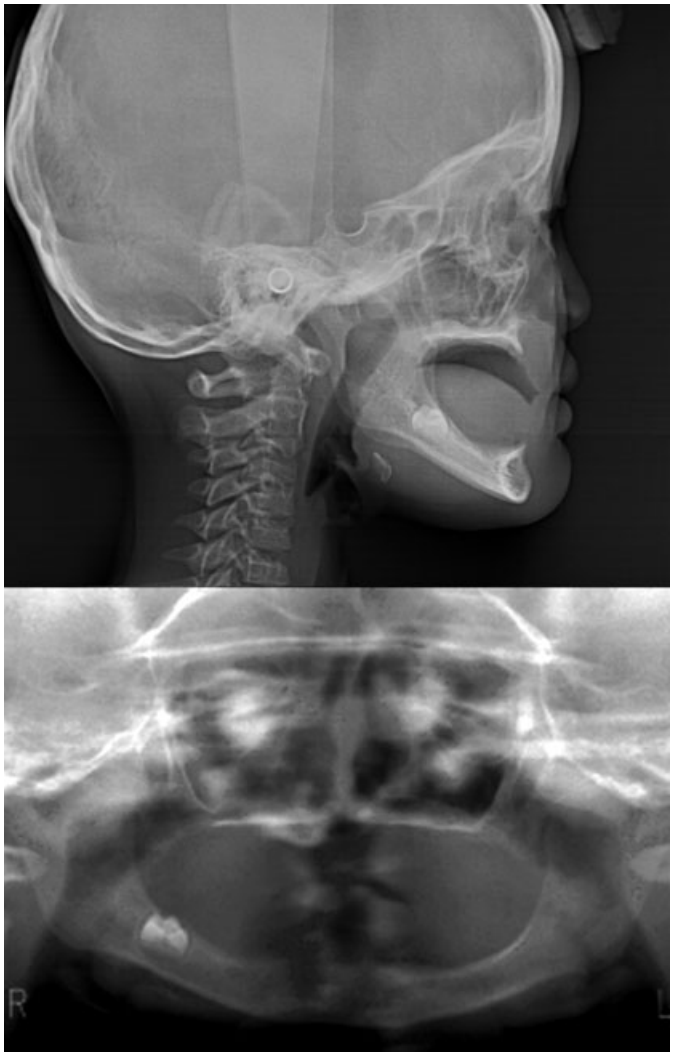

Fig. 2. Lateral cephalogram (upper panel) and panoramic radiograph (lower panel) of the Mongolian individual with hypohidrotic ectodermal dysplasia. Note the extremely short alveolar height of both jaws and only one tooth in the right mandible.

There was no mutation of *EDA* (NG_009809) or *EDAR* (NG_00825). In *EDARADD* gene (NM_080738), there was a heterozygous P121S variant (c.361C > T, starting from ATG) (Fig. 1). P121 is located in the death domain, which starts from the 119th amino acid, in *EDARADD* (Fig. 2). This variant had not been credited in the NCBI database for SNPs. This variant was not found in his parents (father: II-1, mother: II-10) or maternal grandparents (grandfather: I-3, grandmother: I-4).

Discussion

Hypohidrotic ectodermal dysplasia is known to have varying degrees of ectodermal defects such as hypodontia, alopecia, hypohydrosis, and nail abnormalities (1, 2). This patient exhibited sparse hair and eyebrows, an inability to sweat, and severe oligodontia (Fig. 2). Although he had no family history or nail abnormalities, these clinical symptoms were sufficient to diagnose him with a hypohidrotic ectodermal dysplasia.

Three genes, *EDA*, *EDAR*, and *EDARADD*, have so far been associated with hypohidrotic ectodermal dysplasia. Among them, only two mutations have been identified in *EDARADD*: a heterozygous L112R mutation (8) and a homozygous E142K mutation (6). Edar can interact with Edaradd, and it has been reported that this interaction was markedly impaired by L112R (8). The principle function of the death domain is to induce apoptosis (9), and this domain starts from the amino acid position of L119 in Edaradd (Fig. 1), as previously reported (6). E142 is located in this domain, and E142K mutation is reported to diminish the interaction with Edar (6).

The Eda pathway is related to hair and tooth development (12). Mouse models of hypohidrotic ectodermal dysplasia (known as *tabby*, *downless*, *sleek*, and *crinkled*) are known (13). The cloning of Eda signaling demonstrated that *Eda*, *Edar*, and *Edaradd* were mutated in these mutant mice (4, 6, 14, 15). These mutant mice show abnormalities of tooth, hair, and sweat glands, which are similar to those in hypohidrotic ectodermal dysplasia. As the downstream pathway of Edaradd, another adaptor molecule, TNFR-associated factor 6 (TRAF6), recruits TGF-β activated kinase (TAK1), and finally activates NFκ-B (16). NFκ-B is thought to be a transcriptional regulator, and some genes have been reported as targets of NFκ-B. These genes include *Bmp4* (Bone morphogenic protein-4), *Dkk4* (Dickkopf-4), and *Shh* (Sonic hedgehog), and all of them are related to hair, skin, or tooth development (12).

The death domain of *ERARADD* is highly conserved among species, indicating an important function of this domain (6). The P121S variant has not credited in the NCBI Web site for SNPs. Moreover, this variant was not seen in the parents or grandparents of the affected patient. Considering these points, it is likely that the P121S variant was a *de novo* germ-line mutation of either II-1 or II-10, and it was responsible for hypohidrotic ectodermal dysplasia in III-6. However, the frequency and function of this variant is not known. P121S might be merely a polymorphism in *EDARADD*,

which is more than 1% in the general population. Studies are required to clarify the frequency of the P121S variant together with its gene function during hair and tooth development.

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