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Intermediate Phenotype between ADULT Syndrome and EEC Syndrome Caused by R243Q Mutation in TP63

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Summary: A patient who had ectrodactyly, dry skin, exfoliative dermatitis, and hypodontia with peg-shaped teeth, but not cleft lip and palate, is described. Ectrodactyly with a tooth anomaly is recognized in both acro-dermato-ungual-lacrimal-tooth (ADULT) syndrome and ectrodactyly-ectodermal dysplasia-cleft (EEC) syndrome. These 2 syndromes are caused by heterozygous mutations in the transcriptional factor gene *p63*. Mutation analysis of *p63* gene showed a heterozygous mutation c.728G>A, p.Arg243Gln (previously referred to as R204Q) in the patient, but not in his parents. Therefore, this was a sporadic case of the *p63* mutation–associated disorder. Although the mutation has been mostly reported in EEC syndrome patients, the present case did not have cleft lip and palate. Furthermore, the present case did not exhibit freckling or some of the other ectodermal dysplasia phenotypes typical of ADULT syndrome. The concept of ELA syndrome proposed by Prontera in 2011 resolves the problem confronted in diagnosing the present case. ELA syndrome is an acronym of EEC/limb–mammary syndrome/ADULT syndromes, and these 3 syndromes are united into a unique entity. This system can classify *p63* mutation–associated disorders simply without interfering with treatment. *(Plast Reconstr Surg Glob Open 2016;4:e1185; doi: 10.1097/GOX.0000000000001185; Published online 22 December 2016.)*

The presence of defects in the central digits of the hands and feet is recognized as ectrodactyly or split hand/foot malformation, which has a prevalence of approximately 1 in 18,000 newborns.[1] It can occur as an isolated malformation or in combination with other anomalies. Ectrodactyly with tooth anomaly is recognized in some syndromes such as acro-dermato-ungual-lacrimal-tooth (ADULT) syndrome and ectrodactyly-ectodermal dysplasia-cleft (EEC) syndrome, both of which are categorized in the group of developmental syndromes, ectodermal dysplasia. ADULT syndrome was first described by Propping and Zerres in 1993[2] and characterized by congenital limb malformations including ectrodactyly, tooth abnormalities, dysplasia of nails, lacrimal duct atresia, and skin disorders. EEC was first described in 1936 by Cockayne[3] and defined by ectrodactyly, facial clefting, and ectodermal dysplasia with multiple congenital anomalies, including tooth dysplasia. Facial clefting is a major manifestation of EEC, whereas a familial case without orofacial clefting has been reported as ectrodactyly and ectodermal dysplasia syndrome.[4]

These syndromes are caused by heterozygous mutations in the transcriptional factor gene *p63*, a member of the *p53* family that is well known for its role as a tumor suppressor. However, *p63*, and *p73*, in this family does not preferentially function in tumor repression but rather works in development. The expression of *p63* is found in developing epidermis, and its deletion in mice results in limb truncations, impaired development of the epidermis and urogenital system, and lack of hair follicles, teeth, and mammary glands. Recent reports of *p63* mutation–associated disorders have led to disputes over the discrepancy between genotype and phenotype.

Here, an intermediate phenotype between ADULT and EEC syndromes is reported, and the classification of

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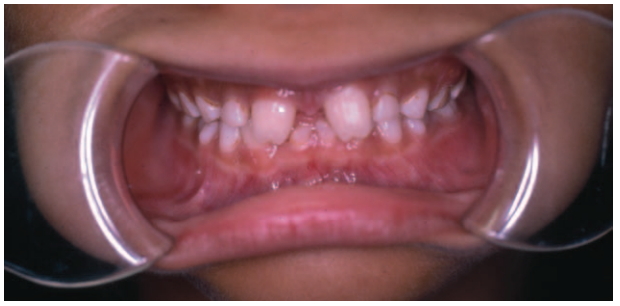

Fig. 1. The patient's teeth at 13 years. The intraoral photograph shows peg-shaped teeth.

p63 mutation syndromes is discussed based on the current case and previous literature.

CASE REPORT

We report a 13-year-old boy who was delivered normally at 38 weeks of gestation, weighing 2950 g. His parents and other family members did not have any congenital disorders. His mental development and intelligence were normal. Ectrodactyly was seen in both hands and feet (Fig. 1), with skin disorders involving dry skin and exfoliative dermatitis, and also tooth-shape abnormalities in which the edge of the incisors was notched and narrower than the cervical area, giving a peg-shaped appearance (Fig. 2). Cleft lip and palate, mammary gland hypoplasia/aplasia, and lacrimal duct atresia, ankyloblepharon, were not seen. Both the patient and his parents did not have any history of carcinomas.

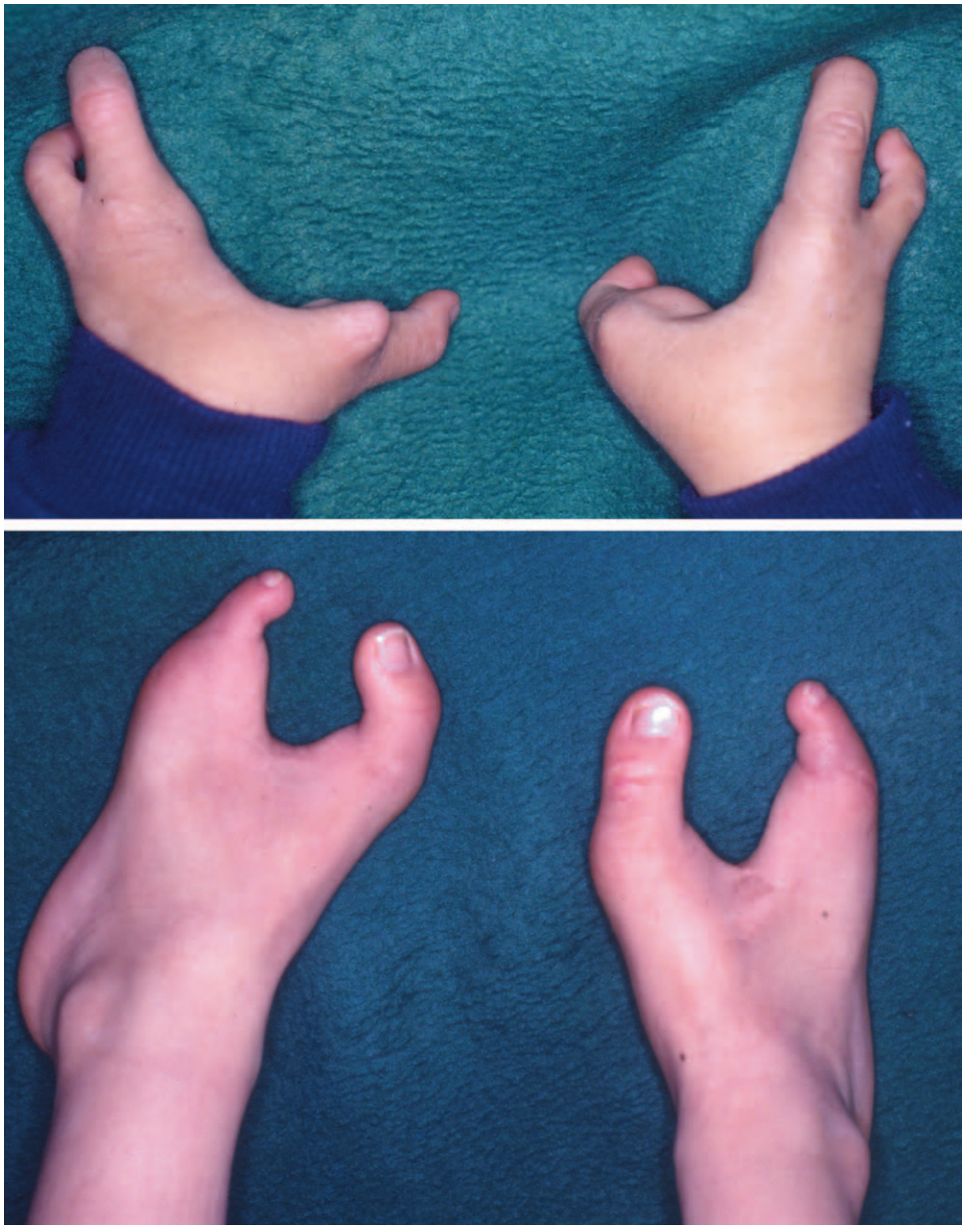

Fig. 2. The hand and foot disorder of the patient. The clinical photographs show severely split hand and foot malformations.

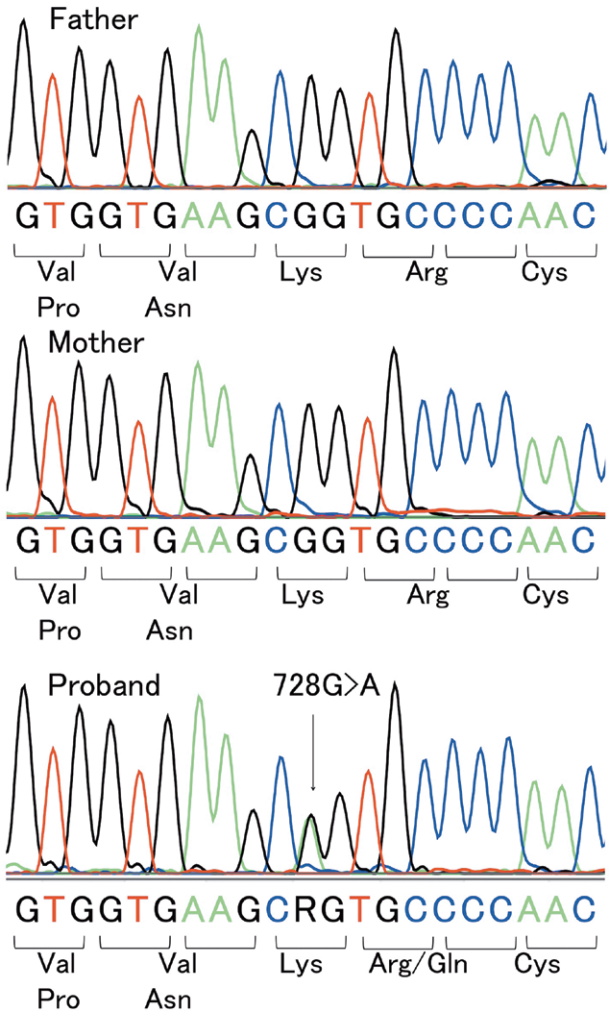

Fig. 3. *p63* mutation analysis. A heterozygous G>A transition at cDNA position 728 of the TP63 gene is found in the patient, but this mutation is not present in his parents.

After ethical approval from the ethics committee of Osaka Medical College and written informed consent from the patient and his parents, peripheral blood samples were obtained for direct sequencing of the whole exon of *p63* gene, which showed a de novo heterozygous missense G>A mutation at nucleotide 728 (ENST00000264731), which is predicted to result in amino acid substitution p.R243Q (Fig. 3). This mutation was previously referred to as R204Q associated with ADULT or EEC syndrome, and the patient was diagnosed as having *p63* mutation syndrome.

DISCUSSION

There are 3 characteristic features in *p63* mutation syndrome: ectodermal dysplasia, limb anomalies, and orofacial cleft, and the combination of the phenotypes has been used for diagnosis of the syndrome. Because the present case did not show a cleft, but had ectrodactyly and ectodermal dysplasia (Table 1), it was fair to diagnose that the patient has ADULT syndrome, in which cleft lip/palate has never been reported.[5] Although extensive freckling in addition to skin lesions is often found in ADULT syndrome, the present case did not have freckling, lacrimal atresia, or nail dysplasia. EE syndrome might be a candidate diagnosis, but skin disorders are not common in EE syndrome.[6] It is especially difficult to diagnose the *p63* mutation syndromes in sporadic cases, because the spectrum of the phenotypes in family members cannot be used for diagnosis.

The type of gene mutation is of help in diagnosis, but accumulation of data on gene mutation analysis of patients has revealed that the identical gene mutation is found in patients diagnosed to have different syndromes by their phenotypes. In the present case, R243Q (referred to in the previous literature as R204Q), which was previously reported to be associated with EEC syndrome, was identified. Recently, R243W (previously referred to in the literature as R204W) mutation, reported as an EEC syndrome mutation, was also identified as the causative gene mutation of ADULT syndrome.[7,8]

Rinne et al[9] reported on the phenotype–genotype correlations of EEC syndrome in great detail. Cleft lip and palate are seen in 81% of R304-mutated EEC syndrome cases, but the prevalence falls to 26% in R204 mutation, which suggests that R204 is one of the most frequently found mutations in EEC syndrome patients, and orofacial clefting is not a predominant phenotype of the syndrome. Furthermore, skin lesions are present in only 38% of R204-mutated EEC syndrome cases. These findings suggest that orofacial clefting and skin lesions are not very typical features in EEC syndrome, especially when caused by R204

Table 1. Phenotypic Characteristics of *p63* Mutation Syndromes

			***p63* Mutation Syndromes**						
		Our Case	**ADULT**	**EE**	**EEC**	**LMS**	**SHFM**	**AEC**	**RHS**
Ectrodactyly		+++	++	+++	++	++	+++	–	–
Ectodermal	Teeth	+++	++	++	+	±	–	++	++
	Skin	+++	+++	–	+	–	–	+++	+
	Hair	–	+	++	+	–	–	+++	+++
	Nail	–	+	–	+	±	–	++	++
	Lacrimal duct	–	+	–	+	+	–	+	++
	Breast	–	+	–	±	+++	–	–	–
	Sweat gland	–	±	–	+	+	–	+	++
Cleft lip and palate		–	–	–	+	+	–	+	++
Fused eyelid		–	–	–	–	–	–	+++	–

The patient has peg-shaped teeth, ectrodactyly, and a skin disorder. This suggests an intermediate phenotype between ADULT syndrome and EEC syndrome.
AEC, ankyloblepharon-ectodermal dysplasia-clefting syndrome; RHS, Rapp-Hodgkin syndrome; LMS, limb–mammary syndrome; SHFM, split hand/foot malformation.

mutation. Of note, none of the characteristic features of the syndrome was present at full penetrance in any of the patients with common causative mutations.

Prontera et al[5] reported a case that had the ADULT syndrome phenotype accompanied by cleft palate with a G134V mutation of *p63*. Through this case, they proposed that EEC, limb–mammary syndrome, and ADULT syndromes could be united into a unique entity known as ELA syndrome, which is distinguished from the other *p63* mutation syndromes such as AEC and RHS by its different clinical spectrum (Table 1). Because the concept of ELA syndrome could well explain the current case and other recent cases that were difficult to diagnose because of the uncertain correlations between phenotype and genotype of *p63*-mutated syndromes, categorization of the syndromes needs to be considered.

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REFERENCES

1. Celli J, Duijf P, Hamel BC, et al. Heterozygous germline mutations in the p53 homolog p63 are the cause of EEC syndrome. *Cell* 1999;99:143–153.
2. Propping P, Zerres K. ADULT-syndrome: an autosomal-dominant disorder with pigment anomalies, ectrodactyly, nail dysplasia, and hypodontia. *Am J Med Genet.* 1993;45:642–648.
3. Cockayne EA. Cleft palate–lip, hare lip, dacryocystitis and cleft hand and foot. *Biometrika* 1936;28:60–63.
4. Wallis CE. Ectrodactyly (split-hand/split-foot) and ectodermal dysplasia with normal lip and palate in a four-generation kindred. *Clin Genet.* 1988;34:252–257.
5. Prontera P, Garelli E, Isidori I, et al. Cleft palate and ADULT phenotype in a patient with a novel TP63 mutation suggests lumping of EEC/LM/ADULT syndromes into a unique entity: ELA syndrome. *Am J Med Genet A* 2011;155A:2746–2749.
6. van Bokhoven H, Brunner HG. Splitting p63. *Am J Hum Genet.* 2002;71:1–13.
7. Avitan-Hersh E, Indelman M, Bergman R, et al. ADULT syndrome caused by a mutation previously associated with EEC syndrome. *Pediatr Dermatol.* 2010;27:643–645.
8. Berk DR, Armstrong NL, Shinawi M, et al. ADULT syndrome due to an R243W mutation in TP63. *Int J Dermatol.* 2012;51:693–696.
9. Rinne T, Hamel B, van Bokhoven H, et al. Pattern of p63 mutations and their phenotypes–update. *Am J Med Genet A* 2006;140:1396–1406.