TP63-related disorders: two case reports and a brief review of the literature

Arti Nanda[1] MD DNBE, Atlal AlLafi[1] MD, Sabrina Wolf[2], Iman M AlMasry[1] MD, Regina Betz[2] MD

Affiliations: [1]As'ad Al-Hamad Dermatology Center, Kuwait, [2]Institute of Human Genetics, University of Bonn, Medical Faculty & University Hospital, Bonn, Germany

Corresponding Author: Arti Nanda MD DNBE, PO Box: 6759, Salmiya, 22078, Kuwait, Tel: 965-97206272, Email: artinanda@hotmail.com

Abstract

TP63-related disorders comprise a group of six overlapping autosomal dominant syndromes caused by heterozygous pathogenic variants in the tumor protein p63 gene. The present report describes the identification of heterozygous de novo pathogenic variants in the DNA binding domain of the *TP63* gene in two patients diagnosed with ectodermal dysplasia-ectrodactyly-cleft lip/palate syndrome three and ankyloblepharon-ectodermal defects-cleft lip/palate syndrome, respectively. The report discusses the phenotypic and genotypic characteristics of these patients and provides a brief review of the *TP63*-related disorder literature.

Keywords: ankyloblepharon ectodermal defects cleft lip palate, dysplasia ectrodactyly, TP63 pathogenic variants

Introduction

TP63 (MIM *603273) encodes tumor protein 63 (p63), which is a member of the p53 transcription factor family. Research in humans and in animal models has demonstrated that p63 plays a key role in the development, proliferation, and stratified differentiation of epithelial tissues [1,2]. The heterozygous pathogenic variants in *TP63* are associated with a total of seven diseases: ectodermal dysplasia-ectrodactyly-Cleft lip/palate syndrome three (EEC3, MIM #604292); ankyloblepharon-ectodermal defects-cleft lip/palate syndrome (AEC, MIM #106260); Rapp-Hodgkin syndrome (RHS, MIM #129400); Limb Mammary syndrome (LMS, MIM #603543); Acro-Dermato-Ungual-Lacrimal-Tooth syndrome (ADULT, MIM #103285); Split-Hand/Foot Malformation type four (SHFM4, MIM #605289); and isolated cleft lip/cleft palate (orofacial cleft 8, MIM #129400). Full length p63 comprises six domains: 1) the transactivation (TA) domain; 2) the DNA binding domain (DBD); 3) the tetramerization (ISO) domain; 4) the second transactivation (TA2) domain; 5) the sterile-alpha-motif (SAM); and 6) transactivation inhibitory domain (TID). Localization of *TP63* pathogenic variants reveals a genotype-phenotype correlation [3]. Pathogenic variants in the DBD domain are responsible for the most prevalent *TP63* related sub-phenotypes, i.e., EEC3 and SHFM4. In most cases of AEC and RHS, the pathogenic variants are observed in the SAM domain. The ADULT and LMS phenotypes are rare and are usually attributable to specific pathogenic variants in *TP63* that differ from those associated with the other, *TP63*-related disorders. Although most *TP63*-related disorders display more precisely characterized features, cases with phenotypic and/or genotypic variability have been reported [4-7]. The present report describes one case each of EEC3 and AEC syndrome caused by de novo pathogenic variants in *TP63* (based on RefSeq NM_003722.4) with a genotype variability of the AEC case. In addition, the report provides a review of the *TP63*-related disorder literature.

Case Synopsis

Case 1

A 12-year-old girl presented to us with a history of hypotrichosis since birth and generalized dryness of

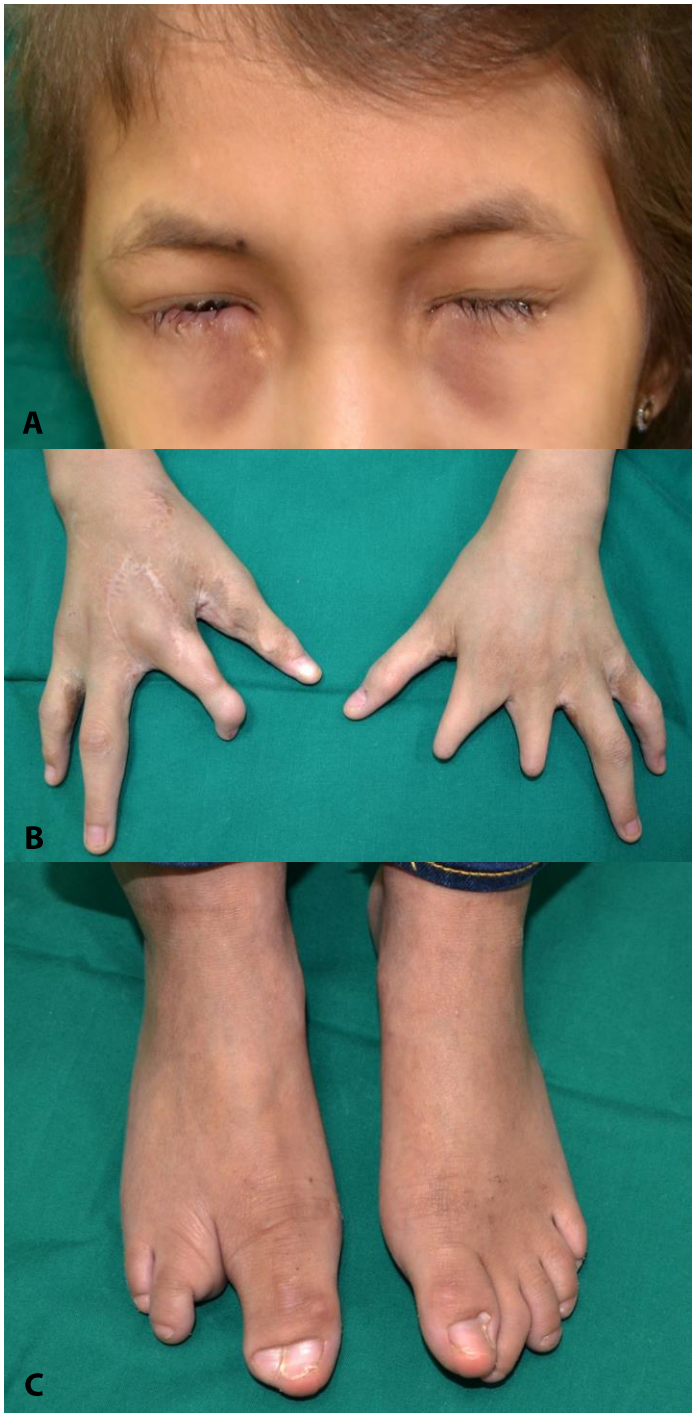

Figure 1. A) *Frontal bossing, sunken eyes with periorbital hyperpigmentation, a broad and flat nasal bridge, and narrow maxillae;* ***B)*** *Bilateral lobster claw hand deformity, anonychia, and surgical scarring, with a missing 3rd finger of the right hand and hypoplastic 2nd and 3rd fingers of the left hand; and* ***C)*** *Syndactyly of the 1st and 2nd toes of the right foot and ectrodactyly of the left foot.*

the skin with recurrent subacute dermatitis since early infancy. She was born with multiple congenital abnormalities. These included cleft lip and palate, which had been surgically corrected at the age of one year. In addition, she had exhibited bilateral syndactyly and ectrodactyly of the hands and feet, for which she had undergone web reconstructive surgery at the age of two and four years, respectively. She also had congenital bilateral dysgenesis of the nasolacrimal ducts, which had required repeat probing and dilatation. At the age of two years, she had been diagnosed with right-sided choanal atresia and moderate conductive deafness and had undergone tympanoplasty at the age of four years. The girl also had a history of delayed tooth eruption and poor dentition. Her family history was unremarkable.

On examination, her height and weight were at the 5th percentile. Facial dysmorphism was evident, as characterized by frontal bossing, sunken eyes with periorbital hyperpigmentation, a broad and flat nasal bridge, and narrow maxillae (**Figure 1A**). Her hair was relatively sparse, dry, and lusterless; excessive lacrimation was evident (**Figure 1A**). She presented with hypodontia, malformed and mal-aligned teeth, and angular cheilitis. Examination of the hands revealed bilateral lobster claw hand deformity, anonychia, and surgical scarring, with missing 3rd finger of the right hand, and hypoplastic 2nd and 3rd fingers of the left hand (**Figure 1B**). Examination of the feet revealed syndactyly of the 1st and 2nd toes of the right foot and ectrodactyly of the left foot (**Figure 1C**). A diagnosis of EEC was assigned and the genetic analysis of DNA from peripheral blood leukocytes revealed a heterozygous de novo pathogenic variant (c.727C>T;p.Arg243Trp) in exon 5 of *TP63*. Neither of the unaffected parents carried this pathogenic variant.

Case 2

A 2-week-old female infant was referred to us with a history of skin erosions and multiple congenital abnormalities. She had been delivered at term by normal vaginal delivery with a birth weight of 2.4kg. The antenatal and family history was unremarkable. On examination, her height and weight were at the 25th percentile. She had near total alopecia of the scalp, partial absence of eyebrows and eyelashes, a paramedian, left-sided cleft lip and palate, multiple erosions on the face (**Figure 2A**), trunk, and

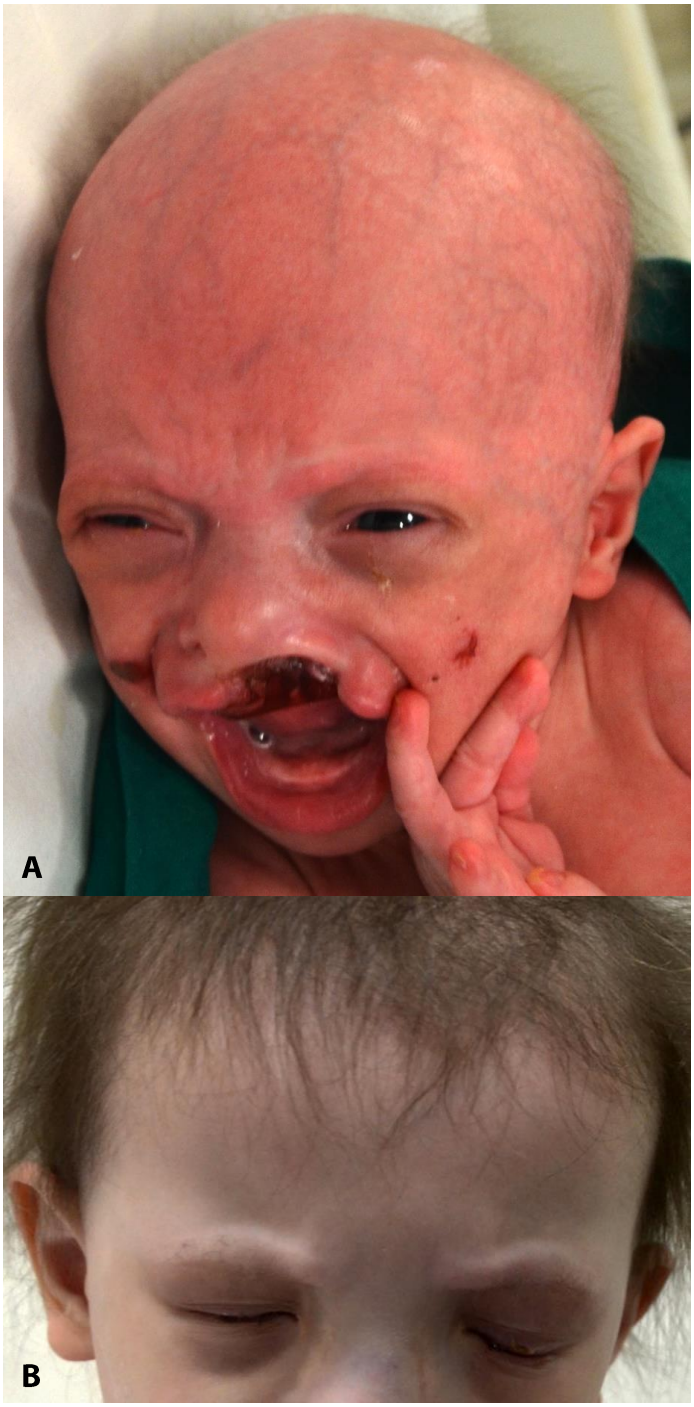

Figure 2. ***A)*** *Alopecia of the scalp, a partial loss of eyebrows and eyelashes, a left-sided paramedian cleft lip and palate, multiple facial erosions at the age 2 weeks and* ***B)*** *Frontal bossing, a broad and flat nasal bridge, hypotrichosis, and dry and brittle hair of the scalp, eyebrows, and eyelashes at 2-year follow-up.*

extremities, hypoplastic nails, and an anteriorly placed anus. At 2-year follow-up, she presented with sparse dry and brittle hair on the scalp, eyebrows, and eyelashes (**Figure 2B**). She also exhibited partial hypohidrosis and excessive dryness of the skin. The cleft lip and cleft palate had been corrected at the age of one year. Ophthalmological examination revealed bilateral dysgenesis of the nasolacrimal ducts. Bilateral dacryocystorhinostomy for nasolacrimal duct dysgenesis had been performed at the age of one-and-half years. Her parents reported that her skin fragility and erosions had shown a gradual improvement over time. A suspected diagnosis of AEC syndrome was assigned. Genetic analysis of peripheral blood DNA revealed a de novo C347F missense heterozygous pathogenic variant (c.1040G>T;p.Cys347Phe) of *TP63* gene. Neither of the unaffected parents carried this pathogenic variant.

Case Discussion

Table 1 shows the clinical characteristics of the present patients and those associated with all known *TP63*-related disorders.

Our Case one has all the clinical characteristics to fit in the diagnosis of EEC syndrome. EEC3 is an autosomal dominant (AD) disorder, whose cardinal signs are ectrodactyly, ectodermal dysplasia, and orofacial clefting [4]. Ectrodactyly manifests as a split hand/foot malformation and is often accompanied by syndactyly. Possible ectodermal defects in EEC3 include dry skin, sparse hair, dystrophic nails, hypoplastic "peg shaped" teeth, and lacrimal duct obstruction. Clefting of the lip and/or palate may occur. EEC3 was first described by Cockayne in 1936 [8]. Subsequently, multiple EEC3 cases have been reported [4,9]. Our review of the available literature revealed that the most common manifestations of EEC3 are ectrodactyly (84%), ectodermal dysplasia (77%), and cleft lip and/or palate (68%). Other prominent abnormalities include lacrimal tract abnormalities (59%), urogenital abnormalities (21%), and conductive hearing loss (14%), [4]. Both inter- and intra-familial phenotype variability has been demonstrated [4]. The present case displayed all of the major features of EEC3. In 1999, a study of nine unrelated families showed that EEC3 was caused by heterozygous pathogenic variants in the *TP63* [10]. Both familial and sporadic cases have been identified [4]. EEC3 syndrome is mainly caused by point

Table 1. *Phenotypic characteristics of the present cases and all known TP63-related disorders.*

Phenotypic characteristics	*TP63*-related disorders								
								Present Report	
	EEC3	AEC	RHS	LMS	ADULT	SHFM4	OFC8	Case 1	Case 2
Ectodermal defects									
Skin									
Dryness	+++	+++	++	±	++	-	-	+++	+++
Hypohidrosis	+++	+++	++	±	-	-	-	+	++
Erosions/erythema	-	+++	+	-	-	-	-	-	++
Nail dystrophy	+++	+++	++	±	++	-	-	++	+
Teeth abnormalities	+++	+++	++	±	++	-	-	++	+
Lacrimal duct abnormalities	++	++	+	+	++	-	-	++	+++
Cleft lip/palate	+++	+++	+	+	-	-	+++	+++	+++
Ectrodactyly/syndactyly	++	±	-	++	++	+++	-	+++	-
Ankyloblepharon	-	+++	±	-	-	-	-	-	-
Mammary gland hypoplasia and/or nipple aplasia	-	-	-	+++	-	-	-	-	-
External auditory canal stenosis	+	+	+	-	-	-	-	-	-

EEC3, Ectodermal dysplasia-Ectrodactyly-Cleft lip/palate syndrome 3; AEC, Ankyloblepharon-Ectodermal defects-Cleft lip/palate syndrome; RHS, Rap-Hodgkin syndrome; LMS, Limb Mammary syndrome; SHFM4, Split-Hand/Foot Malformations type 4; OFC8, orofacial cleft 8; +++, characteristic finding; ++, regularly observed; +,occasionally observed; ±, rarely observed; -, not associated.

pathogenic variants in the DBD domain of the *TP63* gene and a genotype-phenotype correlation has been proposed [5, 11]. The present case carried a heterozygous pathogenic variant in the DBD domain of *TP63,* which had been reported in earlier EEC3 cases [5,12].

The phenotypic characteristics of Case 2 are compatible with AEC syndrome. AEC syndrome, also known as Hay-Wells syndrome, is an AD disorder that was first described in 1976 in seven unrelated patients who presented with ankyloblepharon, atresia of the lacrimal ducts or absence of the lacrimal puncta, absent eye lashes, coarse, wiry hair, pili torti, nail dystrophy, cleft palate, cleft lip, hypodontia, anodontia, and mild hypohidrosis [13]. Prior to the AEC report by Hay and Wells, Rapp and Hodgkin had described the occurrence of an autosomal dominant form of dyshidrotic ectodermal dysplasia and cleft lip and palate in a single family [14]. Subsequent authors speculated that AEC and RHS do not represent clinically distinct entities [15]. This hypothesis was later confirmed by molecular genetic analysis [16]. However, overlapping features of AEC with other *TP63* related disorders and wide inter- and intrafamilial phenotypic variability have been reported [7,17,18].

The main clinical features of AEC syndrome are listed in **Table 1**. Minor features include hypoplasia of the maxillary region, a broad nasal bridge, a short philtrum, a small mouth, and cup shaped ears [5]. In a small number of cases, additional abnormalities, such as supernumerary nipples, limb abnormalities, short stature, heart defects, and genitourinary abnormalities, have been reported [5]. Compared to individuals with other *TP63*-related disorders, patients with AEC show a higher incidence of skin abnormalities, including skin fragility and a tendency to milder and more localized limb abnormalities. The

present case displayed all of the typical clinical features of AEC (**Table 1**). An interesting finding of the present analyses was a heterozygous de novo pathogenic variant (C347F missense pathogenic variant) in the DBD domain of *TP63*. Previous research identified other missense pathogenic variants at the same position (C347S and C347Y) in patients with EEC3 and in one patient with characteristics of both EEC and AEC [8,17]. However, to our knowledge, no previous study had identified missense pathogenic variant at this position for AEC alone. Most of the pathogenic variants reported for AEC to date were located in the SAM domain [3,16].

The prognosis of the patients with *TP63*-related disorders is determined by the associated abnormalities. Treatment is directed to the specific signs and symptoms that are present in the respective patients and in most a multidisciplinary approach is warranted. They do not have intellectual impairment but based on associated abnormalities, these patients are likely to have a greatly impacted quality of life. Prenatal diagnosis and preimplantation testing, in families with known pathogenic variants, is possible. Being an AD disorder, the proband carries a 50% risk of passing the disease to the offspring. Once diagnosed, it is mandatory to provide the genetic counselling to the families.

Conclusion

Over recent years, an increasing number of publications have reported that the various *TP63*-related disorders show overlapping clinical features and that wide phenotypic variability is present both within and between families affected by a specific *TP63* mutation. Further research is warranted to determine whether these findings are attributable to epigenetic processes or to genetic modifiers. Another aim for future research is to determine whether the term *TP63*-related ectodermal dysplasia or *TP63*-related disorder should be retained for all conditions arising secondary to *TP63* mutations or whether separate and more specific disease classification is required.

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Potential conflicts of interest

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