ADULT Phenotype and rs16864880 in the *TP63* Gene: Two New Cases and Review of the Literature

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Keywords

ADULT syndrome · Genotype-phenotype correlation ·
rs16864880 · *TP63*

Abstract

The *TP63* gene has been described in 5 overlapping limb malformation disorders, including a rare autosomal dominant ectodermal disorder named acro-dermato-ungual-lac-rimal-tooth (ADULT) syndrome. This article describes 2 patients with ectrodactyly and variable features related to ectodermal dysplasia/ADULT syndrome, and the polymorphism rs16864880 in the *TP63* gene, which was not present in their parents. The role of this variant in the genesis of this condition is discussed, based upon a review of 40 cases. The results suggested that rs16864880 may not be directly related to ADULT syndrome. However, it is not possible to exclude its participation in gene interactions in the limb development pathway.

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In 1993, Propping and Zerres reported a disorder in a large German family, characterized by excessive freckling, ectrodactyly, nail dysplasia, hypodontia and/or early loss of permanent teeth, neurodermic signs, obstructed lacrimal ducts, and hypoplastic breasts and nipples. Moreover, they proposed the acronym ADULT syndrome (acro-dermato-ungual-lacrimal-tooth syndrome; MIM 103285).

This disorder was described as being extremely variable, and there was some phenotypic overlap with ectrodactyly-ectodermal dysplasia-cleft lip/palate syndrome (EEC1; MIM 129900), limb-mammary syndrome (MIM 603543), ankyloblepharon-ectodermal dysplasia-cleft palate syndrome (MIM 604732), and Rapp-Hodgkin syndrome (MIM 129400). These conditions are part of a heterogeneous group of ectodermal dysplasias caused by *TP63* mutations, showing autosomal dominant inheritance [Rinne et al., 2007; Yin et al., 2015].

This article describes 2 cases with ectrodactyly and variable features related to ectodermal dysplasia/ADULT syndrome, and the polymorphism rs16864880 in the *TP63* gene. In order to investigate the role of this variant in the genesis of this condition, a review of 40 cases from the literature was performed.

Fig. 1. The clinical features of patient 1. **A** Facial asymmetry, synophrys, telecanthus, long eyelashes, and perioral hirsutism on the left corner. Hypochromic spots and hirsutism on thorax (**B**) and back (**C**). **D, E** Ectrodactyly of the right hand.

Fig. 2. The clinical features of patient 2. **A** Facial appearance shows hair and teeth unchanged. **B** Preauricular appendage of the left ear. **C** Auricular appendage of the right ear. **D, E** Ectrodactyly with agenesis of 3rd ray in the left hand.

Case Reports

Case 1

The patient was referred at 2 years of age for investigation of a malformation of the right hand, increased hair growth on the back and atrophy in the left deltoid region. The girl is the second child of a healthy, young (father 30 and mother 20 years old) nonconsanguineous couple from the Brazilian admixed population. The family history was unremarkable. Pregnancy and delivery were uneventful and the newborn weighed 2,800 g (10th percentile [P]), with a length of 45 cm (<P10) and a head circumference of 32.5 cm (P2). She had normal neuropsychomotor development and normal hearing. At physical examination, the anthropometric data were: weight 10,000 g (P10), length 82 cm (P25), and head circumference 44 cm (<P2). However, facial asymmetry, synophrys, telecanthus, and long eyelashes; ectrodactyly in the right hand; large hypochromic spots on thorax, feet, and hands; increased hair growth in face, buttocks, thigh root, and back were observed (Fig. 1). Teeth were normal, and no sweating dysfunction was reported. The echocardiogram, brain-evoked auditory response, and cranial CT scan were normal. G-banding revealed a 46,XX karyotype.

Case 2

The patient was evaluated for the first time at 6 months of age for investigation of a hand malformation, renal agenesis, and auricular appendices. The boy is the first child of a young (both father and mother were 23 years old) nonconsanguineous couple from

the Brazilian admixed population. His family history had a maternal second-degree cousin with polydactyly in the left hand and a paternal third-degree cousin with preauricular appendage (family not evaluated). Prenatal care was adequate, but there were recurrent urinary tract infections which were treated with antibiotics; delivery was by cesarean section due to oligoamnios at term. His birth weight was 1,870 g (<P3), length 44 cm (<P3), and his head circumference was 31 cm (<P2). The patient had a normal development. At physical examination, the anthropometric data were: weight 6,400 g (P3), length 61 cm (P3), and head circumference 41 cm (P2). Preauricular appendage of the left ear and auricular appendage of the right ear were observed (Fig. 2). Teeth were normal, and no sweating dysfunction was reported. The echocardiogram showed a tortuous ascending aorta, patent foramen ovale (2 mm) and patent ductus arteriosus (1 mm). Brain-evoked auditory response, spine radiography and ophthalmologic evaluations were normal. Ultrasound imaging and scintigraphy showed left kidney agenesis. Hand radiographs showed absence of the 3rd ray in the left hand. G-banding revealed a 46,XY karyotype.

Materials and Methods

The aCGH technique was performed using the CytoScan 750K chip (Affymetrix, Santa Clara, CA, USA). The *TP63* gene was investigated by direct DNA sequencing (ABI BigDye Terminator kit on ABI 3130 Sequencer Genetic Analyzer; Applied Biosystems, Foster City, CA, USA) in both the patients and their parents. The PCR prim-

Fig. 3. Chromatogram of the sequence of the *TP63* gene in case 1. The changed S – C/G – rs16864880 in patient 1 (A), and normal in her mother (B) and father (C).

ers were designed based on the sequence described in the Ensembl Genome Browser (<http://www.ensembl.org/index.html>; for online suppl. material, see www.karger.com/doi/10.1159/000470025).

Results

Using the aCGH technique, no rare CNVs were observed in either of the cases. DNA sequencing showed a SNP in the downstream flanking region of exon 8 of *TP63* (rs16864880) in both patients (Fig. 3, 4), but not in their parents.

Discussion

Clinical data of 40 cases of ADULT syndrome were reviewed [Amiel et al., 2001; O'Brien et al., 2002; Chan et al., 2004; Slavotinek et al., 2005; Eter et al., 2006; Reisler et al., 2006; Rinne et al., 2006; Kier-Swiatecka et al., 2007; van der Zwaag et al., 2009; van Zelst-Stams et al., 2009; Wang et al., 2009; de Almeida et al., 2010; Avitan-Hersh et al., 2010; Prontera et al., 2011; Serra et al., 2011; Berk et

al., 2012; Kiritsi et al., 2015]. Table 1 shows the comparison of ADULT syndrome findings with our patients.

Additionally, there are some rare clinical findings related to ADULT syndrome, which were not identified in both patients reported here. These include watch glass nails [Propping and Zerres, 1993]; small mouth and multiple oral frenula [Amiel et al., 2001]; bifid phalanx [O'Brien et al., 2002; Reisler et al., 2006]; imperforate anus, brachydactyly, and incomplete fusion of the right inner canthus [Slavotinek et al., 2005]; sensorineural and conductive hearing loss [Reisler et al., 2006; Prontera et al., 2011]; arrhythmogenic right ventricular cardiomyopathy, trichorrhexis nodosa [van der Zwaag et al., 2009]; alacrima [van Zelst-Stams et al., 2009]; pre-axial polydactyly [Berk et al., 2012] as well as vesicoureteral reflux and urinary retention [Reisler et al., 2006]. ADULT syndrome was described as extremely variable, and there was a phenotypic overlap with other ectodermal dysplasias caused by *TP63* mutations.

The cases described herein had ectrodactyly, sparse and thin hair, skin changes, and absence of oral clefting or ankyloblepharon in common. Due to the age of the patients, hypoplastic breasts could not be confirmed.

Fig. 4. Chromatogram of the sequence of the *TP63* gene in case 2. The changed S – C/G – rs16864880 in patient 2 (**A**), and normal in his mother (**B**) and father (**C**).

Table 1. Features described in ADULT syndrome and present cases

Defect	ADULT syndrome cases, <i>n</i>	Case 1 (female)	Case 2 (male)
Ectrodactyly (hand)	13/40	+	+
Ectrodactyly (foot)	8/40	–	–
Syndactyly (hand)	10/40	–	–
Syndactyly (foot)	11/40	–	–
Excessive freckling	23/40	–	–
Onychodysplasia	27/40	–	–
Tear duct abnormality	27/40	–	–
Hypodontia/small peg-shaped incisors	28/40	–	–
Hypoplastic breast/nipple	22/40	–	–
Sparse, thin fine hair	23/40	+	+
Sweating dysfunction	9/40	–	–
Broad nasal bridge, midfacial hypoplasia	9/40	+	+
Ecematous skin changes	24/40	–	–
No clefting	38/40	+	+
No ankyloblepharon	40/40	+	+

The ADULT syndrome cases comprised 22 females and 18 males. +, present; –, absent.

Therefore, the clinical findings indicate that the diagnosis of ADULT syndrome is more likely among the conditions of the group of ectodermal dysplasias caused by *TP63* mutations. Next-generation sequencing would be an excellent strategy to improve the knowledge in these cases; however, it was not available.

Earlier genetic studies have demonstrated a clear genotype-phenotype correlation for EEC and EEC-linked syndromes. The majority of EEC syndrome cases occur due to missense mutations in the DNA-binding domain, such as an R298Q mutation that has been described, not in EEC syndrome but in ADULT syndrome [Propping and Zerres, 1993; Chan et al., 2004].

Both our patients have the same de novo variant (rs16864880) that was previously described in an ADULT syndrome case in one Chinese family [Wang et al., 2009]. In this family, besides this variant, the authors identified the R298Q mutation, proposing a significantly higher rs16864880 C/G genotype frequency. They suggested a possible closer genetic association between the patient with ADULT syndrome and the paternal transmission in that family.

Considering the phenotype of ADULT syndrome, the family reported by Wang et al. [2009] and the findings in both the patients described here show that rs16864880 may not be directly related to ADULT syndrome. However, it is not possible to exclude its participation in the gene interactions in the limb development pathway.

Acknowledgments

We would like to thank the patients and their families for their participation in this study. We would also like to acknowledge the financial support by the Fundação de Amparo à Pesquisa do Estado de São Paulo – FAPESP (No. 2011/23794-7) and the Conselho Nacional de Desenvolvimento Científico e Tecnológico –

CNPq (No. 471422/2011-8). V.L.G.-d.-S.-L. is supported by CNPq (No. 304455/2012-1), and T.K.d.A. is supported by CNPq (No. 141083/2011-5).

Statement of Ethics

The patients' parents have given written informed consent, and the study protocol was approved by the local Institutional Review Board and the National Research Ethics Committee (CEP 714/2008).

Disclosure Statement

The authors declare they have no conflicts of interest.

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