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Clinical Report

Further Phenotypic and Genetic Variation in ADULT Syndrome

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ADULT (Acro-dermato-ungual-lacrimal-tooth) syndrome is characterized by ectrodactyly, syndactyly, fingernail and toenail dysplasia, hypoplasia of the breast and nipple, excessive freckling, lacrimal duct atresia, frontal alopecia, primary hypodontia, and/or early loss of permanent teeth. It is a rare autosomal dominant disorder which has been linked to mutation in the *p63* gene. The *p63* gene has been described in five overlapping limb malformation syndromes including the EEC syndrome (ectodermal ectrodactyly clefting). We report on the first case of ADULT syndrome of a mother and daughter with a new mutation R227Q in exon 6 of the *p63* gene. This has not been previously associated with ADULT syndrome but only seen in EEC. In addition to the previously reported features of ADULT syndrome this report also describes some additional findings including hyperextensibility at the distal interphalageal joints, bilateral thumb duplication, bifid toenails, symptoms of urinary retention, vesicoureteric reflux, prominent ears, conductive hearing loss, and an overgrowth of a patch of hair in the midline of the neck. This report expands the knowledge of genotype–phenotype data on the p63 gene and suggests there may be a considerable overlap between the EEC syndrome and the ADULT syndrome.

Key words: *p63*; ADULT syndrome; ectodermal dysplasia; deafness; mammary gland hypoplasia; EEC syndrome

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INTRODUCTION

In 1993, Propping and Zerres [1993] described a family with an autosomal dominant disorder that resembled EEC syndrome (ectodermal ectrodactyly clefting). They named this disorder acro-dermato-ungual-lacrimal-tooth (ADULT) syndrome. Clinically the disorder comprises syndactyly, ectrodactyly, and ectodermal abnormalities such as dysplasia of finger and toenails, primary hypodontia, loss of permanent teeth, sparse hair, lacrimal duct atresia, intensive freckling, and hypoplastic breasts and nipples. The disorder has been found to be associated with changes in the *p63* gene. There have been three mutations reported in the ADULT syndrome. Duijf et al. [2002] found an arginine-to-glycine substitution mutation (R298Q mutation) in exon 8 of the p63 gene in the original kindred described by Propping and Zerres. The same R298Q mutation was also found in an unrelated Italian family with ADULT syndrome [Van Bokhoven and Brunner, 2002], and in an 11-year-old male in England [Chan et al., 2004]. In a French kindred, Amiel et al. [2001] localized a p63 gene mutation in exon 3 causing an alanine-to-histidine substitution (N6H). More recently, a third mutation, V114M in exon 4, causing a single amino acid substitution G518A, was reported in a child of European American origin [Slavotinek et al., 2005].

Mutations of the *p63* gene have been found in five human malformation syndromes. In addition to ADULT, these include ankyloblepharon-ectodermal dysplasia-clefting (AEC) [McGrath et al., 2001], limb-mammary syndrome (LMS) [Van Bokhoven et al., 1999], EEC [Celli et al., 1999], and nonsyndromic split hand/foot malformation (SHFM) [Ianakiev et al., 2000].

We report on two patients (mother and child) with clinical features of the ADULT syndrome and a new

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mutation (R227Q) in exon 6 of the *p63* gene. This has not been previously associated with ADULT syndrome but has been seen associated with the EEC syndrome.

CLINICAL REPORT

Patient 1

The patient was born to nonconsanguineous, Caucasian parents. Labor was induced at 37 weeks' gestation because of maternal hypertension. The duration of labor was 4 hr 48 min and delivery was an unassisted, spontaneous cephalic vaginal delivery. The proposita weighted 2.14 kg with APGAR scores of 9 and 9 at the first and fifth minute, respectively.

At the time of birth, the mother and the father were 33 and 34 years old, respectively. Her older maternal and paternal half sisters did not have any features of ADULT syndrome.

Throughout her childhood, her growth and psychomotor development were within the normal range. She was noted to have persistent bilateral epiphora since birth and intermittent conjunctivitis. Under anesthesia, inspection of the eyes revealed bilateral mucocoels of significant size with no evidence of nasolacrimal ducts and on probing them, it was confirmed that there was a bony block in both nasolacrimal canals. This was corrected with dacryocystorhinostomy with good result. The rest of the ophthalmic examination was normal.

During the first years of life the girl suffered from recurrent urinary tract infections, starting from age 5 months. Investigation at the time with micturating cystogram showed a very minor degree of vesicoureteric reflux at the lower end of the left ureter (grade I reflux), with slight prominent left calyceal system but with no evidence of cortical scarring on a renal DMSA scan. Renal ultrasound showed a slight prominence of both renal pelvises although the intracalyceal collecting systems on both sides were not dilated. The reflux and subsequent ultrasonographic and urographic evaluations improved on follow-up without specific treatment except for 2 years of prophylactic antibiotics for the urinary tract infection.

There have also been episodes of intermittent acute urinary retention. As a result, at 2 years of age, a cysto-urethroscopy showed no abnormalities of the urethra or bladder with normal external genitalia and perineum.

The urethra was dilated, but this did not resolve the problem of urinary retention and abdominal pain. However, the symptoms responded to propantheline, leading to the belief that the problem was possibly due to inappropriate detrusor contraction or an inability to relax the sphincter mechanism. Abdominal pain was investigated with a barium enema and meal studies in the first year of life. These were normal with no evidence of any stricture or Hirschsprung disease. The abdominal pain still persists till this date and is being further investigated. To date, she has normal complete blood count, Helicobacter pylori antibodies, ESR, serum electrolytes and urinalysis, urine culture, and normal repeat barium meal and abdominal ultrasound. In addition, a cause for lower genitalia pain/discomfort has not been accounted for and is being investigated as well. Full skeletal survey showed simple, partial syndactyly between the hallux and 2nd toe of the right foot with a smaller 2nd toe in comparison to the left 2nd toe. At the age of 10 years of age she had a Zadeck's procedure to correct the broad distal phalanx with the bifid nail in the left 2nd toe. Radiological investigation confirmed duplication of the distal phalanx of the left 2nd toe with only one distal bony outgrowth (Fig. 1A,B). Hand abnormalities were

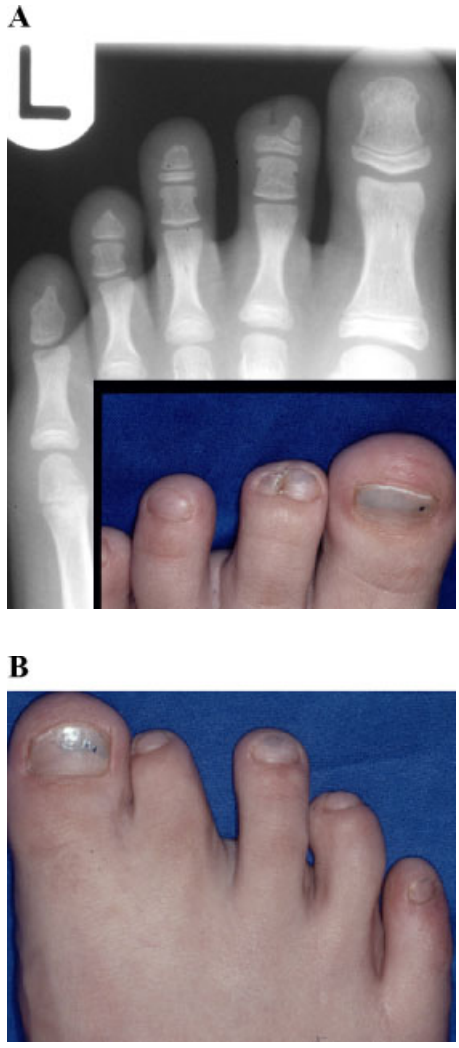

FIG. 1. **A**: Patient 1 left foot displaying a broad distal phalanx with a bifid nail in the 2nd toe. This is superimposed on the left foot radiograph showing duplication of the distal phalanx of the 2nd toe with only one distal bony outgrowth. **B**: Right foot with cutaneous syndactyly of the hallux and 2nd toe and a display of a smaller 2nd toe. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

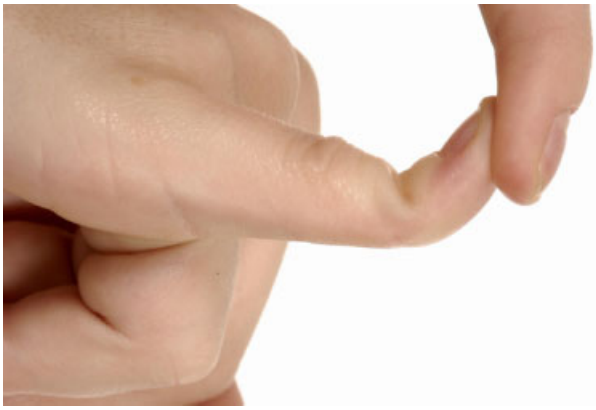

FIG. 2. Right little finger photograph displaying hyperflexibility at the distal interphalangeal joints. This is characteristic to all other fingers except for the thumbs. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

limited to bilateral fingers hyperflexibility at the distal interphalangeal joints (thumbs were spared) (Fig. 2); radiological evaluation of both hands showed the presence of Wassel type I duplication of the thumbs (bifid terminal phalanx), and left middle finger abortive duplication of the distal phalanx (Fig. 3A,B).

There were no other joints hyperextensibility; pronation and supination of the forearms were normal and so was the gait.

Oral examination revealed normal lips, hard and soft palate, and uvula. The patient complained of reduced saliva secretion and subsequent difficulty in swallowing solids without the aid of fluids. The deciduous teeth erupted with no delay but they were small, pointed, and spaced apart. There was evidence of considerable amount of decay and occlusive wear of the deciduous teeth with radiological evidence of enamel hypoplasia. The deciduous teeth were all present, however, the permanent teeth displayed primary hypodontia and some of these teeth were spread apart and pegshaped. Both maxillary lateral incisors, 2nd premolars and 3rd molars were missing, and her mandibular right lateral incisor, and both the 2nd and 3rd molars were missing (Fig. 4). The permanent premolars had asymmetrical and pointy abnormal cusp pattern. Several teeth were carious needing fillings. It remains to be seen if she will develop early loss of her permanent teeth as her mother did.

Clinical examination was noteworthy for identification of breast asymmetry with right breast hypoplasia and right nipple-areola complex underdevelopment (Fig. 5A,B). Secondary sexual characteristics were present.

The ears were prominent due to dysplastic helices, and hearing was unimpaired. At puberty, all her fingernails became brittle and dystrophic with horizontal grooves along the length of the nails. With time this progressively got worse (Fig. 6A,B). The toenails were unaffected. She was found to have sparse, thin blond hair with sparse hair in the front of her scalp, and there was an overgrowth of a patch of fine blond hair in the midline of the neck which she regularly trimmed. There was evidence of light freckling around the face, and a single café au lait spot in her right elbow (Fig. 7). There was reduced axillary sweating.

Patient 2

The mother of Patient 1 is a 48-year-old woman with normal height and intellect. She is the fourth child of unrelated parents; her three older brothers had no malformations. She has had two pregnancies. The first produced an unaffected child and the second was Patient 1. Previously, she had been normotensive apart from a transiently raised blood pressure at 38 weeks with the first pregnancy, and at 37 weeks gestation with Patient 1. Like her daughter, chronic right-sided epiphora and repeated instances of conjunctivitis occurred during infancy and childhood. This was due to congenital distortion of canaliculi and nasolacrimal obstruction for which surgery had been performed. Subsequently she had only occasional tearing and very infrequent eye infections. Her teeth were all extracted by 4 years of age because of extensive caries. There was also a history of primary hypodontia of the permanent teeth and poor enamel leading to severe teeth caries. This resulted in a full dental prosthesis in her 3rd decade. The amount of saliva was reduced and as a result had difficulties with eating.

Like Patient 1, at the age of 2 years, she developed acute urinary retention on several occasions requiring intermittent catherization, which she grew out of. Investigation at the age of 4 years revealed normal cystoscopy. Renal ultrasound at the age of 35 years was normal as well. She also had left breast hypoplasia with underdeveloped nipple-areola complex. Clinical examination revealed a right breast vertical mastopexy scar, and left inframammary scar from previous breast augmentation with a small nipple-areola complex.

Her ears were normally shaped and placed; an audiogram at 42 years of age showed an average of H91.5 bilateral conductive hearing loss and a left-sided high-frequency sensorineural hearing loss in the frequencies over 4 kHz. Otoscopy was normal and clinical tests of balance were normal. The hands were normal with no clinical anomalies of the digits apart from transverse ridging of all fingernails with nail dystrophy and onycholysis. The feet were normal, as were the toenails, and hard and soft palate. There was evidence of light freckling over sun-exposed areas such as her upper chest, arms, and shoulders; the hair growth was normal and not particularly thin. She noticed reduced axillary sweating and in adolescence suffered from lower

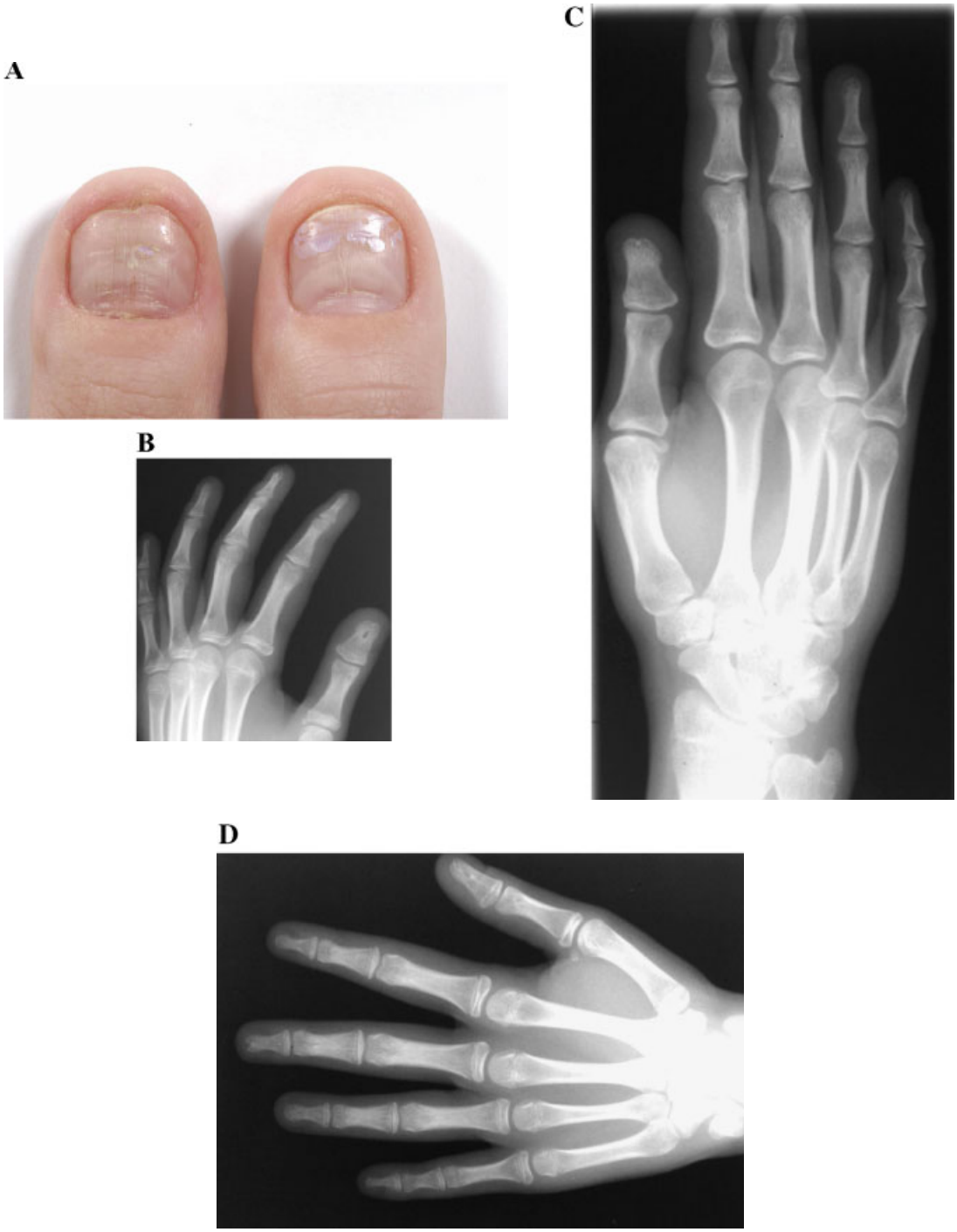

FIG. 3. **A:** Clinical photograph of Patient 1 thumbs with dystrophic thumbnail with horizontal grooves along the length of the nails and a single longitudinal ridge in the middle of the nail, where the bifurcation is. **B** and **C**: Right and left hands respectively with radiographic evidence of Wassel type I duplication. **D**: Radiograph displaying left middle finger incomplete duplication of the distal phalanx. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

genitalia pain/discomfort, which she grew out off in her early twenties.

DISCUSSION

The main clinical features of ADULT syndrome include ectrodactyly, syndactyly, fingernail and toenail dyplasia, hypoplastic breasts and nipples, excessive freckling, lacrimal duct atresia, frontal alopecia, primary hypodontia, and/or early loss of permanent teeth. We describe a mother and daughter with features consistent with ADULT syndrome. In addition there are a number of previously unreported clinical signs which may represent part

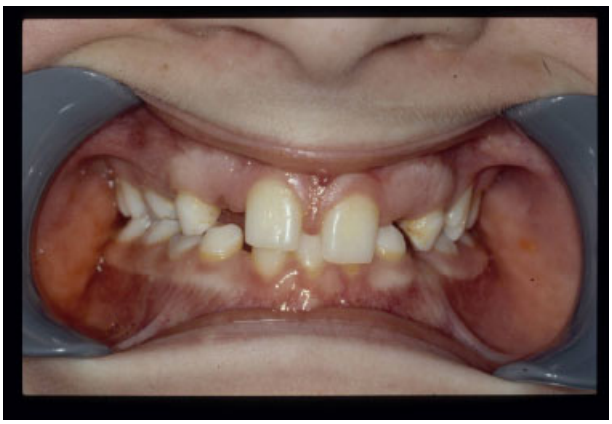

FIG. 4. Intraoral photograph showing permanent teeth primary hypodontia of both maxillary lateral incisors. Not seen in this photograph, the 2nd premolars and 3rd molars were missing as well. Missing mandibular right lateral incisor, and both the 2nd and 3rd molars. In addition, there is an eruption delay of the mandibular left 1st premolar which in subsequent years erupted. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

of a wider spectrum of features in this syndrome viz. (i) fingers hyperextensibility at the distal interphalageal joint, (ii) bilateral Wassel type I thumb duplication, (iii) bifid toenail, (iv) urinary retention, (v) grade I vesicoureteric reflux, (vi) prominent ears, (vii) conductive hearing loss, and (viii) an overgrowth of a patch of hair in the midline of the neck. The pattern of urinary retention is unusual in females and it is of considerable interest to note that similar urinary problems have been reported in EEC syndrome and have been attributed to a dysplastic bladder epilethium and have responded well to medical treatment by a synthetic sulfonated glycosaminoglycan [Maas et al., 1996]. At the present time this treatment has not been tried in the reported family.

The genetic test in this family showed a mutation R227Q in exon 6 of the *p63* gene. This has not been previously associated with ADULT syndrome but has been reported in the EEC syndrome [Van Bokhoven et al., 2001].

The overlap between syndromes caused by *p63* provides an insight into the function of the gene [Brunner et al., 2002]. Previously reported mutations in ADULT syndrome have affected the transactivation (TA) region of the *p63* gene, while the mutations causing EEC have been located in the DNA binding region of the gene. The R227Q mutation reported

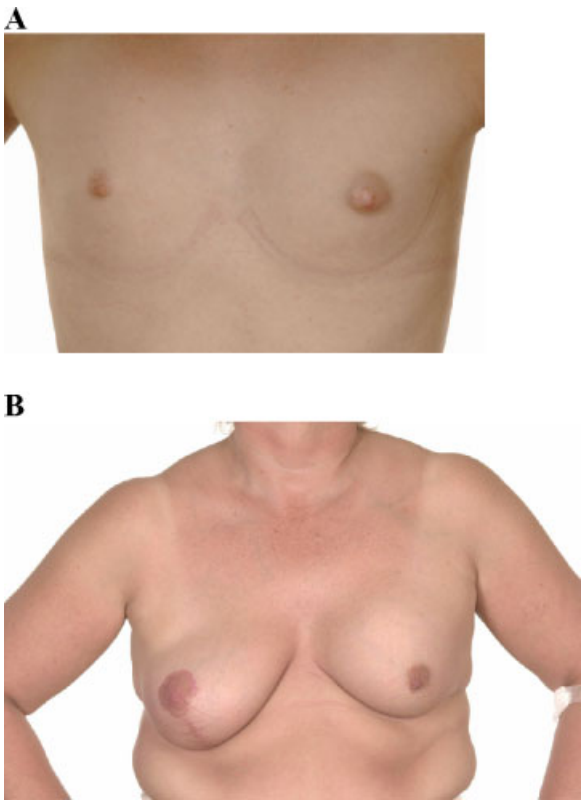

FIG. 5. **A**: Photos of case 1 chest. Note the right breast and nipple-areola complex underdevelopment. **B**: Chest photograph of patient 2 showing right breast vertical mastopexy scar, and implant augmented left breast with a small nipple-areola complex in comparison to the right nipple-areola complex. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

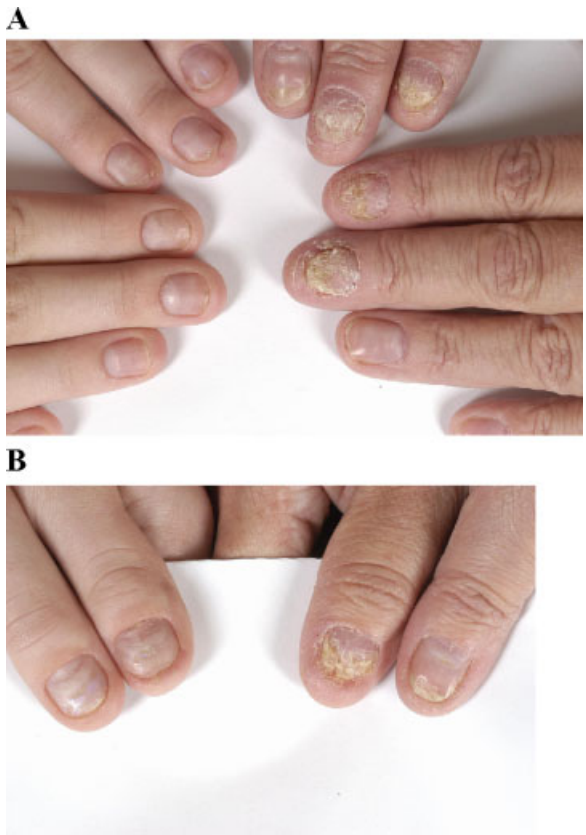

FIG. 6. **A**: Patient 1 fingernails, on the left of the photograph, displaying brittle finger nail tips. On the right side of the photograph, patient 2, the mother of patient 1, showing severe nails dystrophy and onycholysis. **B**: Close-up photograph of both patients' index and middle fingers with clear evidence of brittle nail dystrophy and horizontal grooves along the length of the nails. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

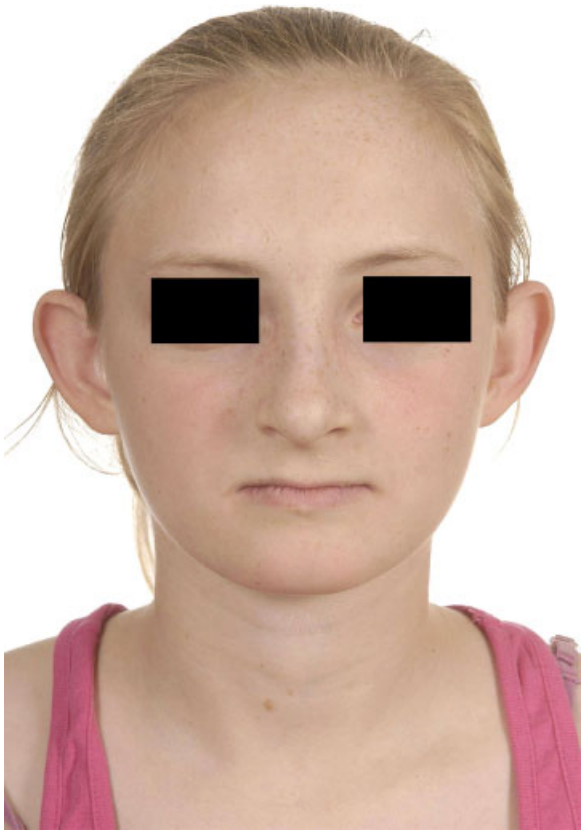

FIG. 7. Patient 1 at 14 years of age displaying facial freckling, thin blond hair with sparse hair in the front of scalp, and prominent ears. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

here is in the DNA binding region, but has produced phenotypic features more suggestive of ADULT syndrome than EEC syndrome. It is becoming increasingly clear that there is a considerable overlap in the phenotypic features of p63 mutations [Rinne et al., 2006]. It may be appropriate to reclassify the syndromes associated with *p63* mutations and accept there is an argument for "lumping" the *p63* mutation syndromes together.

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