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ADULT Syndrome Caused by a Mutation Previously Associated with EEC Syndrome

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Abstract: **Acro-Dermato-Ungual-Lacrimal-Tooth (ADULT) syndrome is a rare autosomal dominant syndrome characterized by ectrodactyly or syndactyly, excessive freckling and dry skin, dysplastic nails, lacrimal duct atresia, primary hypodontia and early loss of permanent teeth. ADULT syndrome is one of five such syndromes that result from mutations in *TP63*, encoding the transcription factor p63. Until now, only four families and three individuals with ADULT syndrome have been reported in the English literature. We present a 14-year-old female patient with ADULT syndrome and discuss phenotype-genotype correlations in the p63 syndromes.**

Acro-Dermato-Ungual-Lacrimal-Tooth (ADULT, OMIM 103285) syndrome is a rare autosomal dominant syndrome characterized by ectrodactyly or syndactyly, excessive freckling and dry skin, dysplastic nails, lacrimal duct atresia, primary hypodontia, and early loss of permanent teeth. Other variable manifestations are sparse hair, reduced sweating, hypoplastic breasts and nipples, and urinary tract abnormalities. ADULT syndrome is one of five syndromes which have been shown to result from mutations in *TP63*, encoding the transcription factor p63 and which include ectrodactyly–ectodermal dysplasia and cleft lip/palate (EEC, OMIM 604292), ankyloblepharon-ectodermal defects-cleft lip/palate (AEC, OMIM 106260), limb mammary syndrome (LMS, OMIM 603543), Rapp-Hodgkin syndrome (RHS, OMIM 129400), and ADULT syndrome. Nonsyndromic split hand and foot malformation (SHFM4, OMIM 605289) is also caused by mutations in *TP63*. Until now, only four families and three individuals with ADULT syndrome have been reported in the English literature.

CASE REPORT

A 14-year-old girl, the third daughter of nonconsanguineous healthy parents of Ashkenazi Jewish extraction was referred for evaluation. Her medical history was significant for syndactyly of the second and third fingers of the right hand. Repeated and unsuccessful attempts at correcting her hand deformity resulted in severe radial deviation of the right hand second finger (Fig. 1). The patient also displayed lacrimal duct obstruction (negative Schirmer's test) and congenital dental abnormalities (i.e., hypodontia with conical-shaped teeth) that had been

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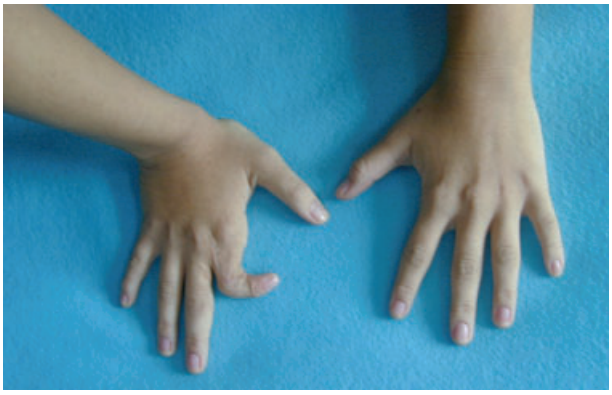

Figure 1. Severe radial deviation of the right hand second finger after unsuccessful attempts at correcting syndactyly.

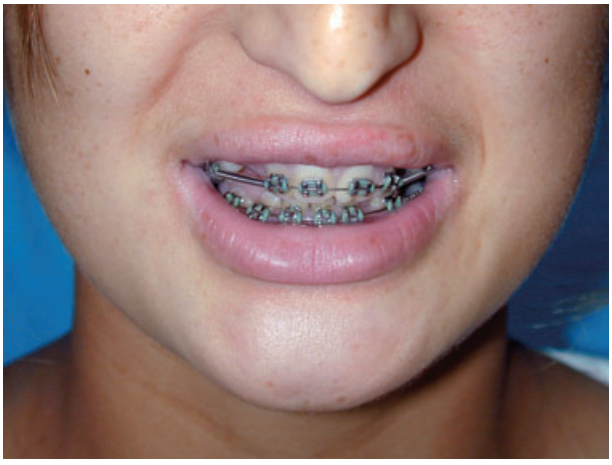

Figure 2. Hypodontia and conical-shaped teeth that had been treated with orthodontic braces. Freckling of the cheeks can be appreciated.

treated with orthodontic braces (Fig. 2). The patient's hair was lustreless, sparse, slowly growing, and her nails were brittle. No similar abnormalities were recorded in the family. Some family members were atopic.

Physical examination revealed fine sparse hair, facial freckles (Fig. 2), hypodontia with missing teeth, conical-shaped teeth, xerosis, small ears, and hooked nose. There was no clinical evidence of cleft lip or palate. Laboratory analyses revealed IgA immunoglobulin deficiency.

Blood samples were obtained from both parents and proband after written informed consent was obtained. We identified a heterozygous C > T transition at cDNA position 727 of the *TP63* gene (accession number: NM_003722). This mutation is predicted to result in amino acid substitution p.R243W (accession number: NP_003713). The mutation was not present in the patients' parents, suggesting that it represents a de novo change. This mutation has not been previously associated with ADULT syndrome. Nevertheless it was previously described by Celli et al (1) in three unrelated patients diagnosed with ectrodactyly-ectodermal dysplasia and cleft lip/palate (EEC) syndrome.

DISCUSSION

ADULT syndrome was first described by Propping and Zerres (2). They reported a family having members either with both hypodontia and early loss of permanent teeth together or with either one of the conditions, and also ectrodactyly, obstruction of lacrimal ducts, onychodysplasia, and excessive freckling. Other signs that are variably associated with the syndrome include brittle hair alone or concurrently with alopecia, hypoplastic breast and nipples, urinary tract abnormalities, and possibly prominent ears and conductive hearing loss (3,4).

ADULT syndrome has been shown to result from mutations in *TP63*, encoding the transcription factor p63.

Transcription factor p63 is thought to have a critical role in ectodermal development and maintenance. It is expressed very early during embryogenesis and epidermal development and plays an essential role in the induction of epidermal stratification program (5,6). In addition, its has been shown to regulate the expression of P-cadherin, a critical regulator of hair development (7).

In the mature epidermis, p63 expression is important for maintaining the proliferative potential of the basal cell layer (6) as it represses some of the genes required for keratinocyte terminal differentiation (8).

The role of p63 in epidermal-mesenchymal interactions is not well understood. It was suggested that some of p63 target genes are responsible for basement membrane formation and for maintaining its integrity (8). Support for the role of p63 in epidermal-mesenchymal interactions is evident in the extracutaneous manifestations of p63 syndromes (i.e., limb malformation, cleft lip/palate) (5).

Ectrodactyly-ectodermal dysplasia and cleft lip/palate (EEC) is considered the prototype of p63 syndromes (3). EEC and ADULT syndromes are considered allelic disorders with overlapping features as ectodermal dysplasia, limb abnormalities and dental changes. The main differentiating sign is orofacial clefting, which is absent in ADULT syndrome. Other features that have been associated with ADULT syndrome and less commonly with EEC are lacrimal duct atresia and breasts and nipples hypoplasia (9).

The mutation that was found in our patient has not been previously associated with ADULT syndrome. Nevertheless, it has been described by Celli et al in three

patients with EEC (1). p.R243 (referred to in the literature as p.R204) is one of the most frequently mutated amino acid residues in p63 (26 of 152 EEC cases [1,3,9]). This mutation had been reported in patients affected with EEC and LMS (9) but not with ADULT syndrome.

Conversely, cases of ADULT syndrome and EEC resulting from the same mutation have been reported (3,9). Reisler et al (3) described patients with phenotypic features of ADULT syndrome and a mutation that had been previously reported in EEC and LMS patients (9). However, only a minority of EEC patients with mutations reported in both EEC and ADULT syndromes display cleft lip or palate, as compared with others carrying mutations found in EEC only (9). Similarly, a single *TP*63 mutation had been shown to be associated with varying p63 syndromes (10,11). These findings illustrate the complexity of phenotype-genotype correlations across the various p63 syndromes and emphasize the tremendous phenotypic overlap between all p63 syndromes.

The possible reasons for the phenotypic variations on one hand, and overlapping features on the other, are not well understood. The influence of modifier genes and, possibly, of environmental factors on gene expression is likely. Some, however, suggest that p63 syndromes should be considered as spectrum of one entity, and should be reclassified (3,4,9).

A better delineation of the elements governing the expression pattern of *TP63* mutation is likely to improve the quality of genetic counseling provided to affected families, and possibly to pave the way for novel therapeutic approaches.

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