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SHORT REPORT

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An unusual combination of EEC syndrome and hypomelanosis Ito due to a *p63* mutation

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We describe a condition comprising the EEC syndrome and linear skin hypopigmentation in a boy who was found to carry a missense mutation in *p63*.

Mutations in the human *p63* gene are known to cause either isolated split hand/foot malformation (SHFM1, MIM 183600) or a number of syndromes such as ectrodactyly-ectodermal dysplasia-cleft lip/palate syndrome (EEC3, MIM 604292), ankyloblepharon-ectodermal dysplasia-clefting syndrome (AEC, MIM 106260), acro-dermato-ungual-lacrimal-tooth syndrome (ADULT, MIM 103285), limb-mammary syndrome (LMS, OMIM 603543), and Rapp-Hodgkin syndrome (RHS, MIM 129400) [1].

This patient was the first child of healthy and unrelated German parents. He was born at term after an uncomplicated pregnancy. Birth weight was 3770 g (75th percentile), length 54 cm (90th percentile), and head circumference 35 cm (50th percentile). During infancy and childhood, we had seen the patient several times at the clinical genetics unit. Physical examination showed ectrodactyly and syndactyly on hands and feet. The radiographs of the right hand revealed ectrodactyly with a missing central digit, double phalanges of the index finger, and a broad proximal phalanx of the third finger probably representing total synostosis of proximal phalanges III and IV (Fig. 1B). The left hand showed an almost total cutaneous syndactyly between fingers III and IV which was surgically corrected in childhood (Fig. 1C). A complete cutaneous syndactyly between the second and third toes of the right foot was present and both feet had hypoplastic fourth toes. Additionally, the boy presented with a cleft lip/palate on the left side, which was operated on early in infancy, and signs of mild ectodermal dysplasia such as hypoplastic brows and lashes (Fig. 1A), enamel dysplasia, and nail dysplasia. These signs and symptoms led to the initial diagnosis of EEC syndrome. Remarkably, the boy developed a striking pigmentary skin disorder with generalised streaky hypopigmentation during the first years of his life. The hypopigmented streaks and patches showed a linear distribution on arms, legs and back, thus resembling hypomelanosis of Ito (Fig. 1C, D, E). The boy's mental development is normal and he is attending regular school.

We performed a mutation analysis using DNA extracted from blood and revealed a heterozygous missense mutation C306Y located in exon 8 of the *p63* gene, which encodes the DNA-binding domain. A similar mutation (C306R) associated with EEC syndrome was reported previously by Celli et al. [2]. As patchy hypopigmentation is a non-specific phenotype and is often caused by chromosomal anomalies, we cytogenetically investigated fibroblasts from a hypopigmentated skin area. The patient's karyotype in 50 metaphases was 46,XY; a chromosomal mosaicism was not found. We considered a possible correlation between the skin hypopigmentation and the *p63* mutation. It appeared conceivable that a somatic mosaicism at the molecular level could be the cause of the pigmentary disorder in this patient. Thus, we sequenced the DNA sample obtained from the fibroblast culture of hypopigmentated skin and screened in particular for an additional second mutation in *p63*. However, the same heterozygous mutation C306Y was detected in fibroblasts as in the blood sample.

Two previous cases of individuals with a similar phenotype of hand malformation and hypopigmentation have been reported. Stewart et al. [6] in 1979 published a report on a girl showing an unilateral cleft lip/palate, ectrodactyly of both hands, bifid thumb on the right, a

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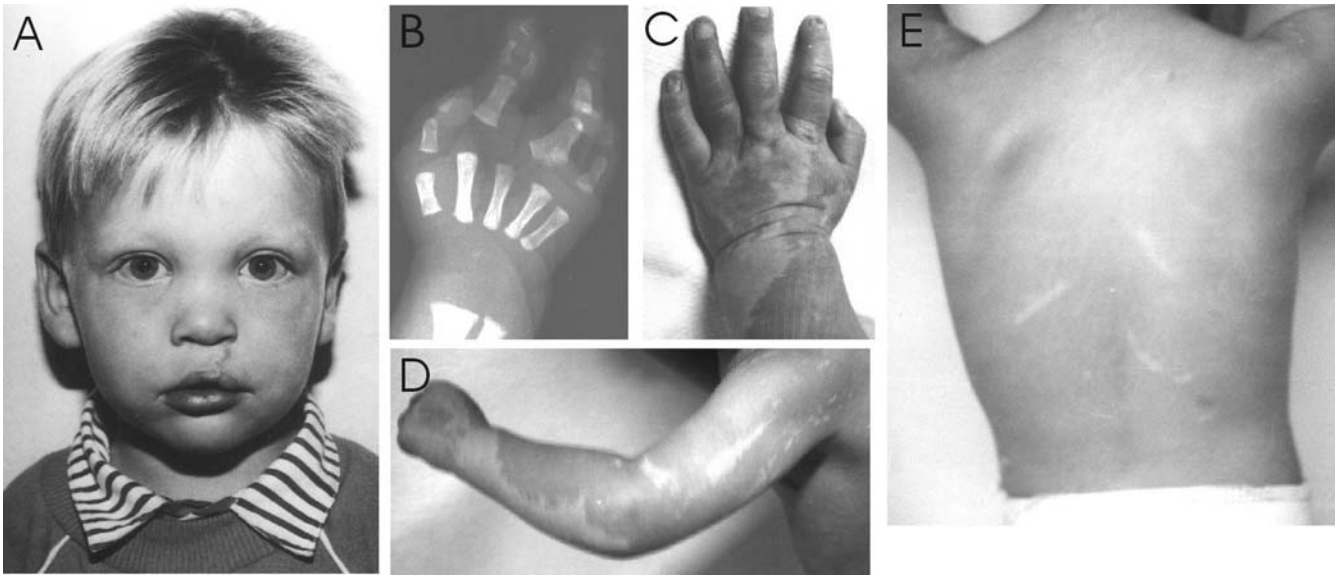

Fig. 1 **A** Note unilateral cleft lip after surgery as well as sparse eye brows and lashes at the age of 2 years. **B** Radiograph of the right hand of the newborn showing ectrodactyly, duplication of the middle phalanges of the index finger and broad, distally tapering proximal phalanx of the third finger. **C** Former syndactyly between fingers III and IV on the left. **D**, **E** Note generalised and linear distribution of hypopigmentation

rudimentary accessory digit II on the left, syndactyly of both feet, and hypomelanosis of Ito. Riccardi et al. [5] in 1980 reported a child presenting with brachysyndactyly of the hands and feet, postaxial polydactyly of the right hand, three nipples on each side, and streaky hypopigmentation of the limbs. Both children developed regularly and no evidence of mental problems was given. However, there is no information available whether those two patients carry a mutation in *p63* or a chromosomal mosaicism.

Occurrence of linear hypopigmentation associated with typical features observed in a p63-associated syndrome raises the question whether p63 has a specific function in melanocytes. An important role of p63 in the development and differentiation of the epidermis is known. P63 inactivation in mice results in major defects in their epithelial development. The skin of p63 knockout mice consists of a single cell layer without a stratified epidermis and does not express differentiation markers [3]. Could mutations in *p63* cause pigmentary abnormalities through a disturbance of melanocyte development in humans? This hypothesis is supported by patients affected with ADULT syndrome, another p63-related disease, who show hyperpigmentated patches and extensive freckling of their skin [4]. Therefore, we consider a coherence between the hypopigmentated skin anomalies and the EEC phenotype in our patient as one possibility. Given a linear distribution of pigmentary disorders, an early post-zygotic *p63* mutation might be an explanation for this phenotype; however, we cannot rule out a coincidental occurrence of both EEC syndrome and linear hypopigmentation. Future observations of patients with EEC syndrome will elucidate whether hypopigmentated skin anomalies may be an associated feature of this phenotype or if the combination of both conditions should be considered as a coincidence.

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References

1. Brunner HG, Hamel BC, Van Bokhoven (2002) The p63 gene in EEC and other syndromes. J Med Genet 39: 377–381
2. Celli J, Duijf P, Hamel BCJ, Bamshad M, Kramer B, Smits APT, Newbury Ecob R, Hennekam RCM, van Buggenhout G, van Haeringen A, Woods CG, van Essen AJ, de Waal R, Vriend G, Haber DA, Yang A, McKeon F, Brunner HG, van Bokhoven H (1999) Heterozygous germline mutations in the p53 homolog p63 are the cause of EEC syndrome. Cell 99: 143–153
3. Mills AA, Zheng B, Wang XJ, Vogel H, Roop DR, Bradley A (1999) P63 is a p53 homologue required for limb and epidermal morphogenesis. Nature 398: 708–713
4. Propping P, Zerres K (1993) ADULT-syndrome: an autosomal-dominant disorder with pigment anomalies, ectrodactyly, nail dysplasia, and hypodontia. Am J Med Genet 45: 642–648
5. Riccardi VM, Riccardi SL (1980) Hypomelanosis of Ito and ectrodactyly. Cleft Palate J 17: 337–339
6. Stewart RE, Funderburk S, Setoguchi Y (1979) A malformation complex of ectrodactyly, clefting, and hypomelanosis of Ito (Incontinentia pigmenti achromians). Cleft Palate J 15: 358–362