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1. Aktuelle Fachinformation TREMFYA®. **2.** Reich K et al. Lancet. 2019;394(10201):831–839. **3.** Reich K et al. Br J Dermatol. 2021 Jun 9. doi: 10.1111/bjd.20568.
4. Mease P et al. The Lancet 2020; https://doi.org/10.1016/S0140-6736(20)30263-4 (Supplementary)

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Clinical Letter

Phenotype diversity associated with *TP63* mutations

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Dear Editors,

A 41-year-old man from Southern India (index) and his 10-year-old son were referred to our department with a history of diverse cutaneous and extracutaneous symptoms affecting the ectodermal appendages.

The index patient presented with sparse scalp hair, eyebrows, and eyelashes (Figure 1a). His son had fragile and brittle scalp hair, as well as sparse eyebrows and eyelashes (Figure 2a). Both had dysplastic and brittle nails; (pseudo) acanthosis nigricans (Figures 1b, 2b); generalized maculo-papular hyperpigmentation (Figure 1b and 2c); xerosis cutis; increased skin fragility; and hypohidrosis (Figures 1, 2). The index patient also had dental malformations and supernumerary teeth (Figure 1d), while his son had dysplastic mammillae, lacrimal duct stenosis, and a unilateral impairment of conductive hearing. Both patients had syndactyly of the second and third toes, and a widening of the gap between the first and second toes, of both feet (Figure 1c). Ectrodactyly was excluded via radiography (data not shown). The personal and family medical history of both patients was otherwise unremarkable.

Molecular genetic investigations were performed in both patients and in selected relatives, in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the ethics committee of the Medical Faculty of the University of Bonn. Whole-exome sequencing (WES) was performed at the Cologne Center for Genomics (CCG). Details of the sequencing protocol are provided elsewhere [1]. Sanger sequencing was performed to verify the variants and enable segregation analyses. WES identified the heterozygous variant c.1922C>T p.(Ala641Val) in exon 14 of *TP63* encoding Tumor Protein P63 (NM_003722.5) in the index patient and his son. This variant leads to the substitution of an alanine residue at the transactivation inhibition domain (TID) of the α isoforms of p63, and is annotated as likely pathogenic in a single entry in the ClinVar database, although no description of the respective phenotype is provided. The variant was not detected in the unaffected parents of the index patient, or in his unaffected wife. This indicates that the mutation was a *de novo* event in the index patient, and was transmitted from him to his son.

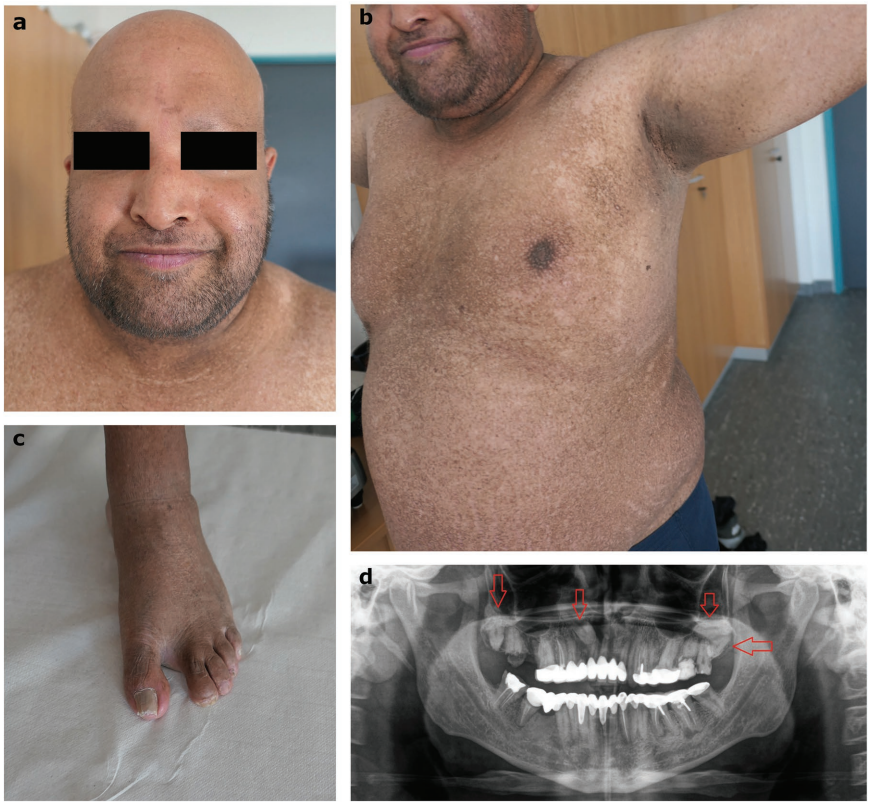

Figure 1 The index patient presented with: sparse scalp hair (reported to have been coarse and wiry hair during childhood, with progressive hair loss having commenced around puberty), as well as sparse eyebrows and eyelashes (a); (pseudo)acanthosis nigricans and maculo-papular hyperpigmentation (b); and a widening of the gap between the first and second toes of both feet (c). Orthopantomographic radiograph of the index patient after extensive prosthetic rehabilitation, with the presence of metal-ceramic crown and bridge work being evident in the upper and lower jaw. Some teeth also show apical lesions as a result of root canal treatment and a post insertion procedure. The X-ray reveals multiple retained, and in part supernumerary, teeth in the retromolar as well as anterior incisor/canine region of the maxilla, with orthogonal or mesial inclination. All retained teeth appear malformed, with a peg-shaped crown morphology and tap root formation in the molar region (d).

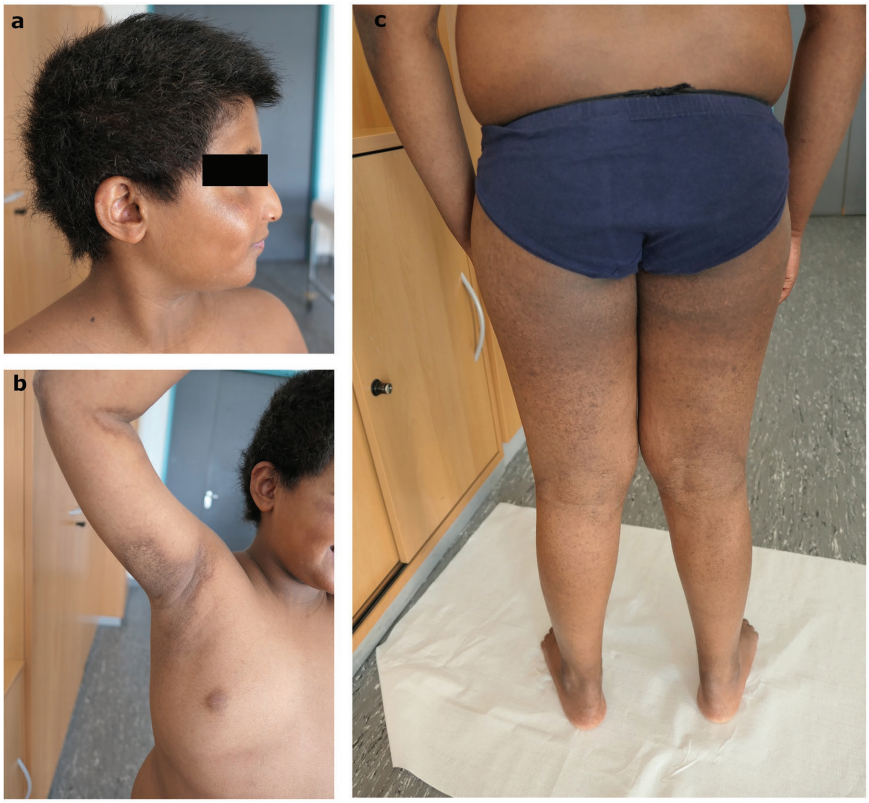

Figure 2 The 10-year-old son of the index patient presented with: fragile and brittle scalp hair, sparse eyebrows and eyelashes (a); (pseudo)acanthosis nigricans (b); and maculo-papular hyperpigmentation (c).

Ectodermal dysplasias are a group of clinically and genetically heterogeneous hereditary disorders that are characterized by a developmental defect in at least two tissues originating from the ectoderm [2]. In 1968, Rapp and Hodgkin were the first to report a family with anhydrotic ectodermal dysplasia and cleft lip/palate, a condition now termed Rapp-Hodgkin syndrome (RHS) [3]. Subsequently, multiple phenotypically similar ectodermal dysplasias have been described in the literature, which present with or without the involvement of skin appendages, limb anomalies, and/or clefting of the lip/palate. Prior to 2006, six additional forms of ectodermal dysplasia were reported and listed in the OMIM database, as depicted in chronological order in Table 1. Interestingly, only later were *TP63* variants identified as the underlying molecular genetic defect in all of these disorders [4–6].

Since the first description of a *TP63* variant by Celli et al. research has identified a large number of clinically-relevant mutations within this gene [7]. Each novel patient with a *TP63* mutation has displayed a plethora of distinct and broad-ranging cutaneous and extra-cutaneous symptoms [8], reflecting the clinical heterogeneity of disorders caused by mutations in *TP63* (Table 1).

The two cases described in the present report further expand this phenotypic variability, since to our knowledge, their particular constellation of clinical features have not yet been described in the scientific literature. These included a maculo-papular rash resembling that observed in Dowling-Degos disease [1, 9], and dental malformations with supernumerary teeth.

In 2006, Rinne et al. attempted to overcome the difficulties encountered in characterizing diseases associated with *TP63* variants and in establishing the respective genotype-phenotype correlations. They noted a clustering of mutations in specific domains of the *TP63* gene, depending on the clinical phenotype. In particular, mutations in patients with EEC clustered in the DNA-binding domain, whereas in AEC syndrome or RHS, mutations were mainly found at the TID or Sterile Alfa Motif (SAM) domain [7, 10]. However, their attempt revealed inconsistencies. This was mainly due to the poor specificity of most features, clinical images of questionable quality, incomplete clinical descriptions in previous reports, in particular regarding the cutaneous phenotype (Table 1), and marked clinical variability associated with single mutations. Some of the clinical features observed in these patients show considerable inter- and intrafamilial divergence – as was the case in the two individuals described in the present report.

In summary, since their initial clinical characterization, our understanding of the spectrum of *TP63*-associated disorders has advanced substantially. This has been largely attributable to the identification of the underlying molecular defects,

Table 1 Clinical characteristics, OMIM (database Online Mendelian Inheritance in Man) entries, and historical terminology of the *TP63*-related disorders. Note the extensive phenotypic overlap.

Disorder, abbreviation and synonyms	Rapp-Hodgkin syndrome (RHS); ectodermal Dysplasia anhidrotic with cleft lip/ palate	Ankyloplepharon-ectodermal defects-cleft lip/palate (AEC) syndrome; Hay-Wells syndrome	Split-hand/foot malformation 4	Acro-dermato-ungual-lacrimal-tooth (ADULT) syndrome	Ectrodactyly, ectodermal dysplasia and cleft lip/palate (EEC) syndrome	Limb mammary syndrome (LMS)	Orofacial cleft 8	Present index patient	Son of present index patient
Initial clinical description	Rapp and Hodgkin (1968)	Hay and Wells (1976)	Spranger and Schapera (1988)	Propping and Zerres (1993)	Maas et al. (1996)	Van Bokhoven et al. (1999)	Leoyklang et al. (2006)	Present case report	
Identification of the underlying genetic cause	Kantapura et al. (2003)	McGrath et al. (2001)	Ianakiev et al. (2000)	Amiel et al. (2001)	Celli et al. (1999)	Van Bokhoven et al. (2001)	Leoyklang et al. (2006)	Present case report	
OMIM number	129400	106260	605289	103285	604292	603543	618149		
Ectodermal involvement	+++	+++		+++	++	+		•	•
– skin	+	+++		+++	+	(+)		•	•
– hair anomalies/ alopecia	+++	+++		++	++	(+)		•	•
– nail anomalies	++	+++		+++	++	+		•	•
– tooth anomalies	+++	+++		+++	++	+		•	
Limb deformation				++	++	++			
– ectrodactyly			+++	++	++	++			
– syndactyly	+	(+)		++	+	+		•	•
Cleft lip/palate	++	+++			+	+	+++		
Mammary gland/ nipple hypoplasia		(+)		+++	(+)	+++			•
Hypohydrosis	+	(+)			(+)	+		•	•
Lacrimal duct obstruction	+++	+		++	++	++			•
Ankyloblepharon		+							
Hearing impairment	(+)	+				(+)			•

as facilitated by the use of next-generation sequencing. These disorders represent a challenging example of how defects in a single gene can be associated with a broad range of phenotypic variability. Consequently, recent data from other groups [11], together with data generated from the two present cases, provide support for the use of a merged molecular and clinical classification of those diseases that are associated with *TP63* variants. Therefore, to overcome the diverse and confusing nature of the terminology that has been applied in the field to date, we propose the use of the term *TP63*-associated disorder, in combination with a thorough description of the respective phenotypes, in particular the presence or absence of cutaneous symptoms. In our opinion, this approach would better reflect the heterogeneous nature of these disorders.

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Conflict of interest

None.

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JA, ICH HABE MEINE VITILIGO AKZEPTIERT. SCHLIESSLICH HABE ICH KEINE WAHL.

65 % aller Menschen mit Vitiligo wird gesagt, ihre Erkrankung sei nicht behandelbar.[1] Noch gravierender ist, dass nahezu die Hälfte aller Betroffenen eine Behandlung überhaupt nicht mehr in Betracht zieht.[1] Wie Sie wissen, tritt Vitiligo meist im Teenageralter auf – und ohne zugelassene Therapie fühlen sich viele Betroffene in einem Zustand der Ungewissheit gefangen. Deshalb forschen wir an neuen wissenschaftlichen Ansätzen. Denn wenn wir uns alle mehr mit der Erkrankung Vitiligo befassen, haben Ihre Patientinnen und Patienten eines Tages vielleicht wieder eine Wahl.

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1. Bibeau K, et al. Diagnosis and Management of Vitiligo From the Perspectives of Patients and Healthcare Professionals: Findings From the Global VALIANT Study. Maui Derm for Dermatologists. Maui, HI. January 24th–28th 2022.