Original Article

Expanding the Phenotypic Spectrum of *TP63*-Related Disorders including the First Set of Monozygotic Twins¹

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¹ This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi:[10.1002/ajmga.38516](https://doi.org/10.1002/ajmga.38516)

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None of the authors have a conflict of interest to report.

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ABSTRACT

Individuals with *Tumor Protein P63 (TP63)*-related disorders are known to present with a range of phenotypic features, including ectrodactyly, ectodermal dysplasia, cleft lip/palate, Rapp-Hodgkin, Hay-Wells, and limb-mammary syndromes. We present six individuals from three families, including a set of monozygotic twins, with pathogenic *TP63* variants who had novel clinical findings. The twins were discordant for cleft lip and palate, and the type of hand malformations, but concordant for choanal atresia, and bilateral volar nail. Both failed newborn screening for severe combined immunodeficiency (SCID) due to T-cell lymphopenia. The second family included three family members across two generations. Two of these three family members had orofacial clefting, but the remaining child had a laryngeal web and hydrocele with no clefting or hand anomalies, highlighting the variable expressivity and penetrance in *TP63*-related disorders. The individual from the third family had unilateral cleft lip and palate, hydronephrosis, and bilateral volar nails. Together, these cases illustrate that: there is significant familial variability including discordant major but concordant minor anomalies in the first ever reported set of molecularly confirmed monozygotic twins with pathogenic variants in *TP63*; pathogenic variants in *TP63* should be considered in individuals with volar nail, which was previously only strongly associated with 4q34 deletion syndrome; and failed SCID newborn screening due to abnormal immune functioning may be part of the phenotypic spectrum of *TP63*-related disorders, as it was reported in one prior individual and two of the individuals in our case series.

INTRODUCTION

Tumor Protein P63 (TP63)-related disorders can be phenotypically divided into six or more overlapping categories, including acro-dermo-ungual-lacrima-tooth (ADULT) syndrome (OMIM 103285), ectrodactyly, ectodermal dysplasia, cleft lip/palate syndrome 3 (EEC3) (OMIM 604292), limb-mammary syndrome (OMIM 603543), nonsyndromic orofacial cleft 8 (OMIM 129400), ankyloblepharon-

ectodermal defects-cleft lip/palate syndrome (AEC syndrome) including Rapp-Hodgkin syndrome and Hay-Wells syndrome (OMIM 106260), and split-hand/foot malformation 4 (OMIM 605289). These are all autosomal dominant conditions caused by heterozygous pathogenic variants in *TP63*. Each condition was described based on their phenotypic features, before it was established that the distinct diagnostic categories likely represent phenotypic heterogeneity of *TP63* pathogenic variants.

The majority of pathogenic variants are missense with occasional nonsense variants (Rinne, Bolat et al. 2009), small deletions (Giampietro, Baker et al. 2013), splice site variants (Kantaputra, Matangkasombut et al. 2012), and one large deletion (Aradhya, Lewis et al. 2012). There is a large amount of intra- and inter-familial phenotypic variability, but common findings across *TP63*-related disorders include cleft lip and/or palate, ectodermal dysplasia, hand and/or foot abnormalities, skin pigmentary differences, and hypoplastic breasts and nipples. A single individual with a *TP63* pathogenic variant was reported with failed T-cell receptor excision circle (TREC)-based newborn screening was later found to have T-cell lymphopenia. That individual was treated with intravenous immunoglobulin (IVIG) in infancy, but ultimately had normalization of T-cell subsets and was able to stop IVIG treatment (Giampietro, Baker et al. 2013).

Although there are common features in most individuals with *TP63*-related disorders, there is significant phenotypic variability across the various named syndromes. This present case series describes six individuals across three families with pathogenic variants in *TP63* who were identified because of syndromic cleft lip and palate in the proband, but there was wide phenotypic variability in affected family members (Figure 1). Individuals in the present study were enrolled in an IRB-approved research study on the molecular characterization of undiagnosed craniofacial syndromes through the Children's Hospital of Philadelphia.

RESULTS

Family 1:

Individuals 1 and 2 in family 1 are monozygotic twin boys who initially presented prenatally with cleft lip and palate in individual 1. During the pregnancy, there was also transient concern for pelviectasis in both boys, but this had normalized on repeat ultrasound. Due to concern for pelviectasis and cleft lip and palate, prenatal SNP-based chromosomal microarray was performed and found to be normal.

The twins were born at 33 weeks gestation due to preterm labor, weighing 1.59kg (35th percentile) and 1.41kg respectively (10th percentile). Individual 1 was found to have right-sided unilateral cleft lip and palate, left-sided choanal atresia, and absent lacrimal ducts (Figure 2 A, B). He also had right-sided 3, 4 syndactyly of the fingers and toes, bilateral volar nails [fifth fingers did not fully extend, and the nail was long and abnormally extended towards the palmar surface of the finger] (Figure 3 A-D). Individual 2 was emergently intubated at birth due to respiratory distress and was found to have bilateral choanal atresia, and lacrimal duct atresia (Figure 1 C, D). In addition, he had right-sided ectrodactyly with transverse defect of the third digit and a mesomelic finger remnant and both of his hands have stiff fifth digits with a volar nail that extended towards the palmar surface of the finger (Figure 2 E-H). The ears of both twins had minor helical anomalies. Shortly after birth, both boys failed their TREC-based newborn screening for Severe Combined Immunodeficiency (SCID). While subsequent testing revealed that they did not have SCID, it did confirm T-cell lymphopenia in both boys.

Both boys had prolonged hospitalizations due to prematurity, choanal atresia requiring multiple surgical revisions and feeding difficulties requiring G-tubes. Individual 1 underwent uncomplicated repair of his cleft lip and palate in the first year of life. Individual 2 had additional medical problems, including necrotizing enterocolitis and identification of two simple venous malformations which were confirmed with ultrasound (one on the forehead, one in the right cheek extending towards the neck). The vascular malformations are visible with crying or Valsalva. Each twin had an additional hospitalization due to a

serious infection. Individual 1 was hospitalized with a Methicillin-resistant *Staphylococcus aureus*- (MRSA)-associated abscess accompanied by widespread rash consistent with toxin-mediated *Staphylococcal Scalded Skin Syndrome*. Individual 2 developed pyelonephritis and was found to have vesicoureteral reflux. Both boys required treatment with multiple courses of antibiotics for MRSA-associated eye infections. As their teeth erupted, both boys had evidence of enamel defects and subsequently developed multiple dental caries despite excellent dental hygiene. They are both very fair and have relatively coarse hair. By the age of 15 months, they were both able to take all nutrition by mouth, and their G-tubes were removed. They received physical, occupational and speech therapies, which were felt to be required due to prematurity. At the age of 2 years, they were both developmentally normal except for mild speech delay, and continued to have mild persistent T-cell lymphopenia.

Maternal family history was unremarkable for birth defects or developmental delays. Paternal family history was not available.

Due to their combination of hand malformations, clefting, absent lacrimal ducts and features suggestive of ectodermal dysplasia, *TP63* sequencing was undertaken. It revealed a pathogenic variant that has previously been described in individuals with EEC syndrome (c.1028G>A, p.Arg343Gln). Variants affecting the same amino acid (p.Arg343Pro, p.Arg343Trp) were also found in other patients with EEC (Ianakiev, Kilpatrick et al. 2000, de Mollerat, Everman et al. 2003). Individuals 1 and 2 have a phenotypically normal mother, although the father is not available for phenotypic evaluation or genetic testing, so it is unclear if the variant is inherited or *de novo* in the twins.

Family 2:

This family came to the attention of genetics as there were anomalies in five family members across two generations, including the proband with unilateral cleft lip and palate who has a son with unilateral cleft

lip and palate, another son with ankyloglossia and laryngeal web but without cleft lip / palate, as well as his unaffected brother who has a daughter with cleft lip and palate as well as a laryngeal cleft.

The proband (Individual 3) was a 36-year-old male with left unilateral cleft lip and palate (Fig 2 G, H). By report his only other notable feature was subjectively long fingers and toes, with normal mobility and did not have volar nail anomaly (Fig 3 K, L). He had normal development and had graduated from college.

The proband's older son (Individual 4) was a 6½ year-old male with right-sided cleft lip and palate, bilateral entropion with distichiasis, small ear lobes and stenotic external ear canals (Figure 2 E, I, J). His cleft lip and palate repair was unremarkable, but he required tonsillectomy and adenoidectomy, had chronic otitis media with effusion requiring multiple bilateral myringotomy tubes and resulting in low-frequency conductive hearing loss. He did not have any abnormalities of his limbs (Fig 3, M, N). His development was normal at the age of six years. His first tooth erupted at the slightly delayed age of 16 months, and he is now reported to have "very little enamel" and brownish discoloration of his teeth. Prior to the diagnosis, he had normal SNP-based chromosomal microarray and *IRF6* sequencing with deletion and duplication analysis.

The proband's 4 year-old son (Individual 5) was found to have a laryngeal web, type IV ankyloglossia, hydrocele, and a small umbilical hernia at birth. He does not have cleft lip or palate (Figure 2, F, K, L). His first tooth erupted at the typical age of 9 months. At 3 weeks of age, he underwent microlaryngoscopy with excision of the laryngeal web and division of the tongue fold. On examination, he was minimally dysmorphic with mild retrognathia but not micrognathia, and a thin vermilion of the upper lip. Both ears were normal in position and set, but the antihelix was prominent and the ear lobes were small.

Examination of his upper and lower extremities was unremarkable (Figure 3, F, K, L). Gross neurologic exam was normal. *TBX1* sequencing and deletion/duplication analysis was normal. SNP-based

chromosomal array revealed only a maternally-inherited chromosome 17q25.1 gain (~900kb), thought to be noncontributory.

Other family history showed that the affected boys' mother has a history of high hyperopia and astigmatism, but no significant learning or intellectual issues, and they have an unaffected 8-year-old sister.

The proband's full brother is reportedly phenotypically normal, but he has a 3-year-old daughter with unilateral cleft lip and palate as well as a laryngeal cleft, laryngomalacia, and duplex right kidneys; he also has an unaffected 7 year-old daughter. Neither the proband's brother nor did his niece consent to a genetics evaluation, including molecular testing. The proband's mother had no relevant medical history, and his father was healthy but had not been tested.

A *TP63* c.1334_1337delACTT;p.Leu446Phefs*20 (RefSeq accession # NM_003722.4) pathogenic variant was found by exome sequencing of the proband and his oldest son (Individual 4), by standard filtration methods assuming an autosomal dominant inheritance model. Sanger sequencing was subsequently used to determine that the proband and his affected sons all carried the variant; his wife, unaffected daughter, and mother did not carry the variant.

Family 3:

Individual 6 is the second child of non-consanguineous Caucasian parents. His prenatal evaluation was notable for bilateral hydronephrosis and a left cleft lip and cleft palate. He was delivered at 37 weeks' gestation, weighing 2.3 kg (10th-25th centile). His cleft lip and palate have been repaired, and he has normal growth and development at age four years. He continues to have bilateral hydronephrosis and minor hypospadias. He has had normal MRI of the brain, ophthalmologic examination, and echocardiogram. His facial features included down-slanting palpebral fissures and low-set ears, in

addition to the repaired cleft lip and associated nasal deformity. He also had broad thumbs and an unusual indentation in the left little finger representing a volar nail (Figure 3 I, J). Both parents are unaffected and there is no family history of cleft lip and palate or kidney issues. Previous to the diagnosis, he had normal SNP-based chromosomal microarray and *SF3B4* sequencing. Whole exome sequencing revealed a *de novo* *TP63* variant, c.1027C>T;p.Arg34Trp, which was previously reported in an individual with EEC syndrome (Celli, Duijf et al. 1999, Ianakiev, Kilpatrick et al. 2000).

For both familial variants identified by whole exome sequencing (Individuals 3-6), variants were absent from the 1000 Genomes Project, COSMIC v80, ESP6500SI, gnomAD dataset with more than 120,000 individuals, and additional exome-sequence data from more than 3,000 samples that we had previously sequenced in our in-house database. The variants identified in Individuals 1, 2 and 6 had been previously reported in individuals with EEC syndrome (Celli, Duijf et al. 1999, Ianakiev, Kilpatrick et al. 2000).

DISCUSSION:

In this case series, we present six additional individuals from three families that expand the phenotypic spectrum for *TP63*-related disorders. The unique features seen in these families, along with their implications for *TP63*-related disorders, will be discussed individually below.

This series includes the first set of molecularly-confirmed monozygotic twins with this group of disorders. Interestingly, the twins were discordant for some of the major anomalies that are considered integral to the diagnosis of *TP63*-related disorders. The major category of hand anomalies was discordant, with individual 1 having syndactyly of digits 3 and 4 on the right hand, bilateral volar nails, but otherwise no anomalies of the left hand. Individual 2 had ectrodactyly, a transverse defect of the third digit and a mesomelic nubbin of the right hand. He also had bilateral volar nails, but his left hand

was otherwise normal. Individual 1 also had 3, 4 syndactyly of the right foot, but a normal left foot. Individual 2 had no foot abnormalities. The volar nail sign, a minor anomaly that was previously thought to be pathognomonic for chromosome 4q34 deletion syndrome, was present on the fifth digits of both hands in both boys. Other concordant features included choanal atresia, lacrimal duct atresia, severe feeding difficulty requiring G-tube feedings in infancy, enamel defects and multiple dental caries, fair complexion with coarse hair, and at least one serious infection requiring hospitalization and numerous eye infections with Methicillin Resistant *Staphylococcus Aureus* in the setting of known T-cell lymphopenia. Other discordant features included necrotizing enterocolitis in Twin B that was likely due to prematurity and two venous vascular malformations of the forehead and right cheek, which are likely unrelated to their *TP63* variants. Both twins have normal development. It is worth noting that the major features that are considered central to the diagnosis of *TP63*-related disorder were discordant, while features that are minor (e.g. volar nail sign, complexion) or less common (e.g. choanal atresia, T-cell lymphopenia) were concordant. While this is the first report of discordant major malformations but concordant minor and less common malformations in monozygotic twins with *TP63*-related disorders, there are many other examples in the literature of discordant anomalies in monozygotic twins with genetic syndromes (McDonald-McGinn, Tonnesen et al. 2001, Burgemeister, Zirn et al. 2015, Votava-Smith, Pitukcheewanont et al. 2016, Zhou, Xie et al. 2016).

Previous reports suggest variability in expressivity and penetrance in *TP63*-related disorders (Cole, Hatef et al. 2009). These individuals demonstrate that within a single family, there can be wide variability in the types of abnormalities that are seen. This is consistent with other syndromic forms of clefting. For example, van der Woude syndrome, due to pathogenic variants in *IRF6*, can cause cleft lip and/or palate with or without lip pits. Individuals within the same family may have cleft lip, cleft palate, and lip pits, either in isolated or combination. In addition, pathogenic variants in *IRF6* can cause popliteal pterygium syndrome, which has a much more severe phenotype (Busche, Hehr et al. 2016).

The volar nail sign, in which a stiff fifth digit is accompanied by a hooked nail that extends towards the palmar surface of the finger, had only been closely linked in the literature to chromosome 4q34 deletion syndrome (Vogt, Ryan et al. 2006, McKay and Fryer 2014). This condition was considered for individuals 1, 2 and 6, who were found to have volar nails, as cleft lip/palate may also be seen with these deletions. Both the finger and fingernail are fundamentally different in our cohort than in individuals with Coffin-Siris syndrome, as the finger in the *TP63* cases has severe camptodactyly and the nail is longer and hooked (i.e., volar nail sign) rather than being hypoplastic. The presence of the volar nail sign in three of our individuals from two unrelated families suggests that it may be a feature of *TP63*-related disorders. *TP63*-related disorders should be in the differential diagnosis for individuals with volar nail and a normal chromosomal microarray.

Failed TREC-based newborn screening for SCID was found in individuals 1 and 2, and was previously reported for another child with *TP63* pathogenic variant (Giampietro, Baker et al. 2013). Individuals 1 and 2, in addition to the previously reported individual, were shown not to have SCID with follow up testing, but were found to have T-cell lymphopenia. The individual in the literature received treatment with IVIG, though his counts normalized over the first year and he was able to discontinue treatment. Our patients have each had one serious infection over the first year as well as a number of more minor, self-limited infections. The types of infections in these individuals included abscess, Methicillin Resistant *Staphylococcus Aureus* eye infections and pyelonephritis. Previous reports of children with *TP63*-related disorders attributed increased numbers of infections to altered skin barrier or genitourinary abnormality. As TREC-based newborn screening for SCID is relatively new, it is possible that the abnormal infections in prior cases were felt to be secondary to these other abnormalities when they may have been at least partially due to T-cell lymphopenia. As TREC-based newborn screening is becoming more widespread, it is likely that additional individuals with *TP63*-related T-cell lymphopenia will be diagnosed on newborn screening. Moreover, individuals with abnormal SCID newborn screening

and T-cell lymphopenia who also have birth defects should be referred to a geneticist to evaluate for features suggestive of *TP63*-related disorders.

Additional new features in the present report include laryngeal web (which should be considered in any child with *TP63*-related disorder with respiratory or feeding issues that are not easily explained by other malformations) and vascular malformation. Laryngeal web is an uncommon finding, but could be related to malformations of other parts of the airway seen in *TP63*-related disorders. It is possible that the vascular malformations are related to their *TP63* variants, but more likely is unrelated, as vascular malformations are common and often due to somatic variants. Additional individuals with *TP63* pathogenic variants should be evaluated for vascular malformations in the future to determine if they occur at a higher rate than in the general population.

CONCLUSIONS:

Individuals with *TP63*-related disorders can have a significant variability in penetrance and expressivity – across families, within families, and even between affected monozygotic twins. These individuals provide additional support for T-cell lymphopenia as a feature of *TP63*-related disorders, and suggest that the volar nail sign and laryngeal web may be new associated features.

FIGURE LEGENDS:

Figure 1: Pedigree of three affected families, black shading indicates common manifestations of *TP63*-related disorders, grey indicates uncommon manifestations of *TP63*-related disorders (AI: affected individual).

Figure 2: Facial photographs of affected individuals. (A, B, C, D) Individuals 1 and 2 at 8 months. Though they have many similarities as monozygotic twins, individual 1 can be easily distinguished by his cleft lip

and palate. Both twins have fair complexion, shortened palpebral fissures and abnormality of helical folding. Individual 2 is also demonstrated to have a simple venous malformation that is visible when crying. (E, I, J) Facial photographs of the individual 4 demonstrate a slightly tall forehead with a prominent occiput, deeply-set eyes with normal palpebral fissures slant. His eyelids demonstrate postsurgical changes associated with his correction of entropion and distichiasis. His remaining eyelashes on the upper lid appeared slightly prominent and curved upwards, while the lashes on the lower lid were relatively short and sparse. He had a relatively large nose with a broad nasal tip, while the vermilion of his upper lip was thin but vermilion of his lower lip was normal. He had mild maxillary prominence and possibly mild retrognathia. His ears were generally normal in position and set. (F, K, L) Photographs of individual 5 demonstrated his square face, short nose, telecanthus, micro- and retrognathia, a long philtrum, small mouth, thin upper lip vermilion and small ear lobes.

Figure 3: Hand photographs of affected individuals. (A-D) Individual 1 has 3,4 syndactyly on the right hand and bilateral volar nails. (E-H) Individual 2 has ectrodactyly, transverse defect of the third digit, a mesomelic nubbin and bilateral volar nails. (I, J) Note the volar nail on the 5th digit of individual 6, without other associated anomalies. By comparison, the hands of individual 3 (K, L), individual 4 (M,N), and individual 5 (O,P), are without major anomalies.

Table 1: Molecular and clinical features of the individuals describes in this case series.

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Figure Captions

Figure 1

Figure 2

Figure 3

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TP63 Fig 1 .

TP63 Fig2 .

TP63 Fig 3 .

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Date:

2018-01

Citation:

Wenger, T., Li, D., Harr, M. H., Tan, W. -H., Pellegrino, R., Stark, Z., Hakonarson, H. & Bhoj, E. J. (2018). Expanding the phenotypic spectrum of TP63-related disorders including the first set of monozygotic twins.. *Am J Med Genet A*, 176 (1), pp.75-81. <https://doi.org/10.1002/ajmg.a.38516>.

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