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Beyond the triad: inheritance, mucocutaneous phenotype, and mortality in a cohort of patients with dyskeratosis congenita

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To the editor

Dyskeratosis congenita (DC) is a telomere biology disorder (TBD) associated with bone marrow failure (BMF) and the classic triad of reticulate skin pigmentation, nail dystrophy, and oral leukoplakia. Disease-causing variants in at least 11 telomere biology genes have been implicated in DC and exhibit autosomal dominant (AD), autosomal recessive (AR), and X-linked recessive (XLR) inheritance, as well as *de novo* occurrence (*TINF2*). Patients with XLR, AR or *TINF2* DC tend to manifest more severe hematologic outcomes than patients with AD DC.[1, 2] We sought to assess the sensitivity of the clinical triad for DC diagnosis, quantify additional mucocutaneous features, and examine the relationship between DC genotype and mucocutaneous phenotype.

This study included 60 patients with genetically-proven DC in an IRB-approved longitudinal cohort study, NCT-00027274 (Table 1).[3] The prevalence of triad features and eight

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CONFLICT OF INTEREST

The authors state no conflict of interest

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additional mucocutaneous findings (adermatoglyphia, palmoplantar hyperkeratosis, hyperhidrosis, premature graying, scalp or eyelash hair loss, epiphora, and lash irritation/blepharitis) were elicited from comprehensive medical photographs and dermatology evaluations. Hematologic and mortality outcomes data were gathered prospectively. Telomere length data were obtained for 58/60 patients as previously described.[4] Patients with XLR/AR and AD DC were compared. Because *TINF2* variants can be AD inherited or *de novo* and typically have severe phenotypes, patients with *TINF2* DC were excluded from the AD group and analyzed separately.[2]

Patients displayed a wide spectrum of clinical findings (range 0–9 features out of a possible 11; median 3 features: 2 triad, 1 non-triad). While triad features were most common, six non-triad features were present in more than 20% of the cohort: epiphora, adermatoglyphia, early graying, palmoplantar hyperkeratosis, eyelash loss, and hair loss from scalp (Figure 1a). The complete clinical triad manifested in only 37% (22/60) of patients, while 10% (6/60) lacked all triad features. Patients with higher numbers of triad and total mucocutaneous features were more likely to have AR DC or heterozygous *TINF2* mutations ($p < 0.01$, chi squared test). All 6 patients lacking any triad features had AD DC. The number of triad features was strongly inversely associated with telomere length ($p=0.002$). Patients with 2–3 triad features had a greater cumulative incidence of BMF compared with patients with 0–1 triad features (Figure 1b, $p < 0.0001$). A higher number of total features was also associated with cumulative incidence of BMF and overall mortality ($p < 0.0001$).

This study specifically focused on mucocutaneous phenotypes in a large cohort of patients with DC. Severe mucocutaneous phenotypes, as defined by number of triad features and additional findings, are associated with higher risk genotypes and poorer prognosis compared with milder mucocutaneous phenotypes. We believe careful detection of all mucocutaneous features of DC is important for early referral, confirmatory testing and appropriate clinical management.

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Patients are enrolled in an IRB approved longitudinal cohort study, Etiologic Investigation of Cancer Susceptibility in Inherited Bone Marrow Failure Syndromes (NCT-00027274)

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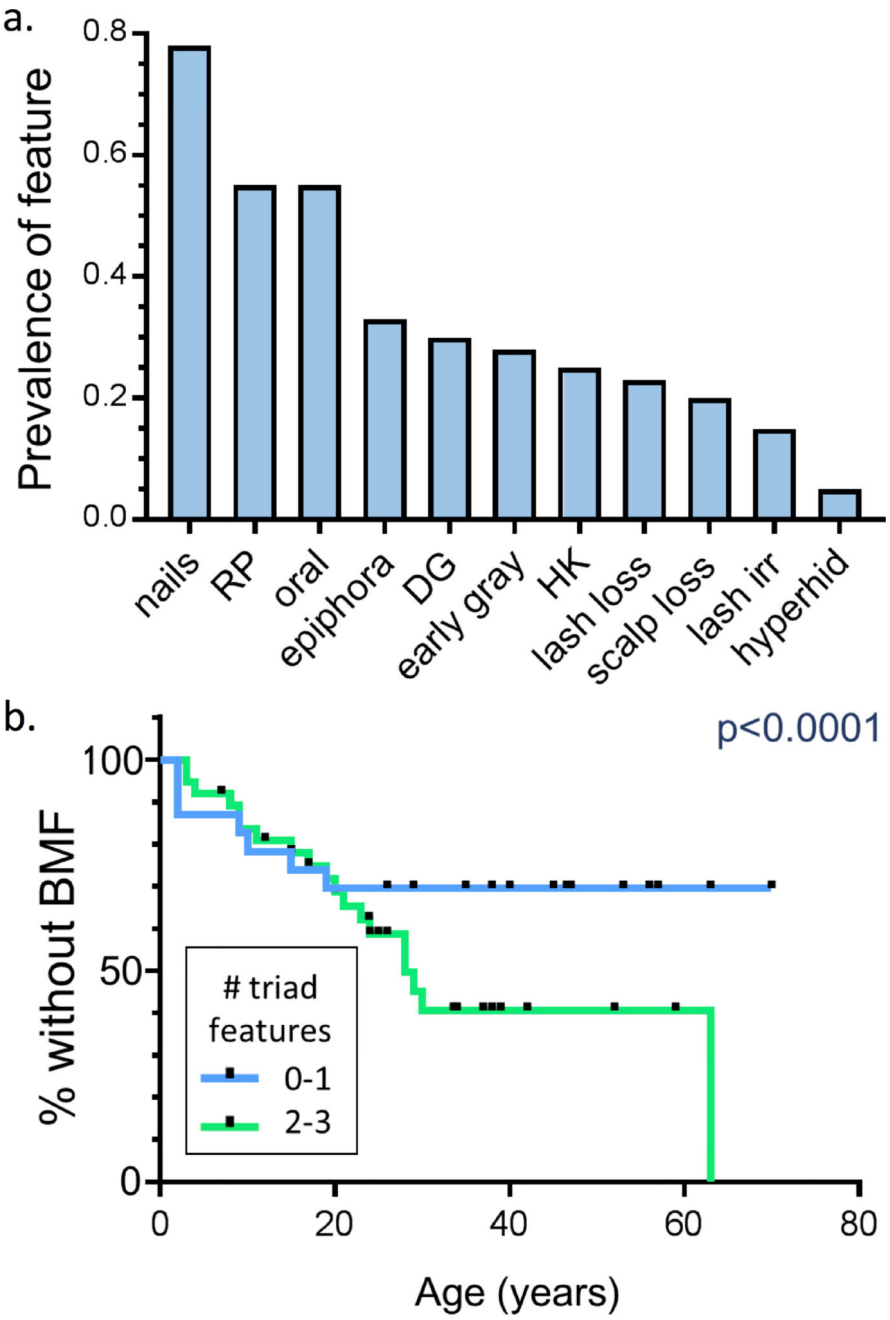

Figure 1. Dyskeratosis Congenita

a: Prevalence of mucocutaneous findings in 60 patients. Nails= nail dystrophy, RP= reticulate pigmentation, oral= leukoplakia or oral SCC, early gray= graying of the hair before age 30, HK= hyperkeratosis of the palms and/or soles, lash loss= thinning or sparseness of the eyelashes, DG= dermatoglyphic changes, scalp loss= premature hair thinning or balding of the scalp, lash irr= blepharitis or irritation due to lash regrowth, hyperhid= hyperhidrosis. **b: The number of DC clinical triad features is associated with moderate to severe bone marrow failure**. Kaplan Meier curves for development of moderate to severe BMF among patients with 0–1 (blue) or 2–3 (green) DC clinical triad

features. BMF was defined as peripheral blood counts below the normal for age. Black notches indicate time points at which patients were censored. P values for Kaplan Meier curves were calculated with Cox regressions. Statistical analysis was performed with Stata Statistical Software (Release 14, StataCorp LP)

Table I

Patient demographics and results

Characteristics (%)	**Total (n=60)**	**XLR/AR (n=23)**	***TINF2* (n=14)**	**Non-*TINF2* AD (n=23)**
Age (yrs)				
Median	23	32	17	15
Range	1–69	1–46	2–31	1–69
Age group (yrs)				
0–9 (n=14)	14 (23)	6 (26)	6 (43)	2 (9)
10–19 (n=14)	14 (23)	10 (43)	1 (7)	3 (13)
20–29 (n=14)	14 (23)	5 (22)	6 (43)	3 (13)
30–39 (n=7)	7 (12)	1 (4)	1 (7)	5 (22)
40–49 (n=6)	6 (10)	1 (4)	0	5 (22)
50+ (n=6)	6 (10)	0	0	5 (22)
DC gene				
TINF2	14 (23)	-	14 (100)	-
RTEL1	12 (20)	6 (26)	-	6 (26)
DKC1	11 (18)	11 (48)	-	-
TERT	10 (17)	1 (4)	-	9 (39)
TERC	8 (13)	-	-	8 (35)
PARN	3 (5)	3 (13)	-	-
ACD	1 (2)	1 (4)	-	-
WRAP53	1 (2)	1 (4)	-	-
CTC1	0	0	-	-
NHP2	0	0	-	-
NOP10	0	0	-	-
Sex				
Male	44 (73)	20 (87)	12 (86)	12 (52)
Female	16 (27)	3 (13)	2 (14)	11 (48)
# Triad features				
0/3	6 (10)	0	0	6 (26)
1/3	17 (28)	6 (26)	2 (14)	9 (39)
2/3	15 (25)	6 (26)	4 (29)	5 (22)
3/3	22 (37)	11 (48)	8 (57)	3 (13)
# Total features				
0–2	23 (38)	7 (30)	3 (21)	13 (57)
3–5	21 (35)	7 (30)	4 (29)	10 (43)
6–9	16 (27)	9 (39)	7 (50)	0

XLR:X-linked recessive inheritance, pathogenic variants in *DKC1*. AR: autosomal recessive, pathogenic variants in *RTEL1, PARN, ACD, TERT*, and *WRAP53*. AD: autosomal dominant, pathogenic variants in *TERT, TERC*, and *RTEL1*. Parenthesis indicate percent of total with specified inheritance pattern (%).