Dyskeratosis congenita

Dyskeratosis congenita (DC) is a rare, inherited multisystem disorder primarily characterized by progressive bone marrow failure and telomere dysfunction. It is considered part of the spectrum of telomere biology disorders (TBDs), where individuals have abnormally short telomeres for their age.

Epidemiology

Prevalence & Incidence

Extremely rare disease.

Estimated prevalence:

~1 in 1,000,000 individuals (exact numbers may vary slightly by region and source).

Fewer than 1,000 cases have been reported worldwide.

No clear data on annual incidence due to rarity.

Sex Distribution

Classic X-linked form (most common, DKC1 mutation):

Affects mainly males.

Females may be carriers and rarely manifest mild symptoms.

Autosomal dominant and autosomal recessive forms:

Affects both sexes equally.

Age of Onset

Most patients present in childhood or adolescence.

Some may not be diagnosed until adulthood if symptoms are mild or non-classic.

Ethnic & Geographic Distribution

Reported in all ethnic groups and geographic regions.

No particular ethnic predilection is known.

Family History

30-40% of cases: Positive family history.

~60-70%: Sporadic or de novo mutations.

Cause

DC is caused by mutations in genes involved in the maintenance and protection of telomeres, the repetitive DNA sequences at the ends of chromosomes that prevent genomic instability. Known genes associated with DC include:

DKC1 (X-linked recessive)

The dyskeratosis congenita 1 (DKC1) gene is located on the X chromosome at Xq28. Dyskerin, encoded by the DKC1 gene is associated with the formation of certain small RNAs and the telomerase activity. Inherited mutations in DKC1 inactivate the dyskerin and cause dyskeratosis congenita, which is characterized by skin defects, hematopoiesis failure, and increased susceptibility to cancer. DKC1 reportedly upregulates in several human cancers, including renal cell carcinoma and prostate cancer. Dyskerin is deregulated in B-chronic lymphocytic leukemia and breast carcinomas, but its expression and function in glioma have hardly been investigated. Hence, we were prompted to collect tissue samples and implement cell experiments. Our study reveals that DKC1 expression is significantly increased in the pathological tissues of glioma compared with that in normal tissues. The increased staining of DKC1 is related to the World Health Organization stages of tumors. DKC1 knockdown also significantly inhibits glioma cell growth by altering the expression of cell cycle-relative molecules to arrest at the G1 phase. In the transwell chamber, DKC1 knockdown glioma cells exhibit low motility. Consistent with classic oncogenic pathways, N-cadherin, HIF-1α, and MMP2 expression levels are lower compared with those of the control group. Therefore, DKC1 up-regulation in gliomas is common and necessary for extensive tumor growth. The phenotype of glioma cell lines after DKC1 downregulation suggests its use as a valuable clinical treatment strategy [1)].

The article by Miao et al. is an important contribution that opens the door to further research on DKC1 in glioma. It aligns well with the current push toward precision oncology, although more work is needed to validate its clinical and therapeutic utility.

TERT, TERC (autosomal dominant or recessive)

RTEL1, TINF2, NOP10, NHP2, and others

Classic Triad

The “classic” diagnostic triad of DC includes:

Nail dystrophy

Oral leukoplakia

Reticular skin pigmentation

These usually appear in childhood or adolescence.

Hematologic Manifestations

Bone marrow failure is the most life-threatening complication and may lead to:

Aplastic anemia

Pancytopenia

Increased risk of myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML)

Other Systemic Involvements

Pulmonary fibrosis

Liver disease (including cirrhosis, nodular regenerative hyperplasia)

Gastrointestinal telangiectasias or varices

Osteopenia/osteoporosis

Cerebrovascular anomalies (e.g., intracranial aneurysms or moyamoya)

Increased risk of cancers (especially head and neck squamous cell carcinoma)

Diagnosis

Telomere length testing (usually by flow-FISH or qPCR): patients show very short telomeres

Genetic testing to identify pathogenic variants

Bone marrow biopsy may be necessary to assess the marrow status.

Diagnosing DC is challenging based solely on the protean manifestations and multisystemic involvement. Therefore, it is urgent to identify an early feature facilitating the initial suspicion of DC.

Zhang et al. enrolled a cohort of six male children diagnosed with DC, all of whom exhibited erosions or ulcers on the tongue, while five of them did not display the complete classic triad. Strikingly, oral erosions or ulcers have never been included in any clinical diagnostic criteria for DC. Through a retrospective analysis, they further demonstrated that extensive and persistent tongue ulceration emerges as an early and practicable clinical marker, provoking suspicion of DC even in the absence of the classic triad.

The findings challenge prevailing diagnostic criteria and advocate for an expanded consideration of

tongue ulceration as a primary and indicative manifestation of DC, thereby affording a strategic advantage for early detection and intervention of this lethal disease [2].

Zhang et al. provide provocative and potentially practice-changing insight into the early detection of DC, advocating for the inclusion of tongue ulceration as a sentinel sign. While their findings are promising and warrant further investigation, the small cohort size, lack of control group, and absence of standardized criteria limit immediate clinical application. Nonetheless, this study sets the stage for larger prospective studies and a re-examination of the diagnostic criteria for DC, possibly improving survival through earlier recognition and management.

Management

Hematologic support: transfusions, growth factors

Androgens (e.g., danazol) may improve blood counts in some patients

Hematopoietic stem cell transplantation (HSCT): only curative option for marrow failure, though carries higher risks in DC patients

Surveillance and management of organ-specific complications and cancer screening

1)
Miao FA, Chu K, Chen HR, Zhang M, Shi PC, Bai J, You YP. Increased DKC1 expression in glioma and its significance in tumor cell proliferation, migration and invasion. Invest New Drugs. 2019 Dec;37(6):1177-1186. doi: 10.1007/s10637-019-00748-w. Epub 2019 Mar 7. Erratum in: Invest New Drugs. 2022 Jun;40(3):676-678. doi: 10.1007/s10637-022-01215-9. PMID: 30847721.
2)
Zhang X, Dan H, Zhou Y, Sun W, Yang W, Zeng X. Extensive and persistent tongue ulceration is an early character of dyskeratosis congenita. Orphanet J Rare Dis. 2025 Apr 21;20(1):192. doi: 10.1186/s13023-025-03721-4. PMID: 40259308.