Dyskeratosis Congenita, X-linked: *DKC1* Gene Sequencing

**Test Code:** SV  
**Turnaround time:** 4 weeks  
**CPT Codes:** 81479 x1

### Condition Description

Dyskeratosis congenita (DKC) is a bone-marrow failure syndrome characterized by:

- early onset of cutaneous hyperpigmentation  
- nail dystrophy  
- hyperkeratotic palms  
- hypotrichosis  
- continuous lacrimation due to atresia of the lacrimal ducts  
- poor dentition  
- oral leukoplakia

Other symptoms include:

- thrombocytopenia  
- anemia  
- testicular atrophy  
- Hodgkin disease  
- pancreatic adenocarcinoma  
- deafness

Reports on various families with individuals with the condition also include features such as:

- prenatal and postnatal growth retardation  
- mental retardation  
- elevated immunoglobulin levels  
- gastrointestinal hemorrhage from mucosal ulcerations  
- intracranial calcifications  
- nutmeg-like cirrhosis of the liver

Bone marrow failure has been reported in approximately 50% of cases of DKC, and in some patients symptoms related to aplastic anemia may precede the diagnosis of DKC. In 70% of cases, pancytopenia is the cause of death. Males are affected in a pattern consistent with X-linked recessive inheritance. Variability in the age of onset, severity of bone marrow failure, and range of congenital abnormalities has been observed. Mutations in the *DKC1* gene (Xq28) have been shown to cause DKC.

Mutations in *DKC1* also cause Hoyeraal-Hreidarsson syndrome (HHS), which is a more severe form of dyskeratosis congenita. Hoyeraal-Hreidarsson syndrome is a multisystem disorder affecting males and is characterized by:

- aplastic anemia  
- immunodeficiency  
- microcephaly  
- cerebellar hypoplasia  
- growth retardation

HHS may be a severe form of DKC in which affected individuals pass away before characteristic mucocutaneous features develop.

The protein product of the *DKC1* gene, dyskerin, is associated with small nucleolar RNA46 and with human telomerase RNA. The pathology of DKC is consistent with compromised telomerase function leading to a defect in telomere maintenance, which may limit the proliferative capacity of human somatic cells in epithelia and blood. Most mutations causing dyskeratosis congenita are missense mutations, although noncoding mutations have been described. In one study, mutations in the *DKC1* gene were detected in 21 of 37 families with dyskeratosis congenital. In another study, sequence variations were detected in 10 of 25 families. In a third study, four mutations were identified in five males with presumed X-linked dyskeratosis congenita.

For patients with suspected X-linked dyskeratosis congenita, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

Please [click here](https://www.omim.org) for the OMIM summary on this condition.

### Genes

**DKC1**

### Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of X-linked dyskeratosis congenita.
Carrier testing in adult females with a family history of X-linked dyskeratosis congenita.

Methodology

PCR amplification of 15 exons contained in the \textit{DKC1} gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions or other regulatory elements, and will not detect large deletions.

Detection

Clinical Sensitivity:
In one study, mutations in the \textit{DKC1} gene were detected in 21 of 37 families with dyskeratosis congenital. In another study, sequence variations were detected in 10 of 25 families. In a third study, four mutations were identified in five males with presumed X-linked dyskeratosis congenita.

Mutations in the promoter region, some mutations in the introns or other regulatory elements, and large deletions will not be detected by this analysis.

Analytical Sensitivity: \textasciitilde 99%.

Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Specimen Requirements

Submit only 1 of the following specimen types

\* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene\textsuperscript{TM} Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

Special Instructions

Please submit copies of diagnostic biochemical test results along with the sample, if appropriate. Contact the laboratory if further information is needed. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

Related Tests

- \textbf{X-Linked Dyskeratosis Congenita: DKC1 Gene Deletion/Duplication (SW)} is available for those individuals in whom sequence analysis is negative.
- \textbf{X-Linked Mental Retardation: 64-Gene Deletion/Duplication (OL)}
- \textbf{Known Mutation Analysis (KM)} is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.