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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Dyskeratosis congenita

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Dyskeratosis congenita (Zinsser–Engman–Cole syndrome).[1–9]

1.2 OMIM# of the disease

Three modes of inheritance:
X-linked recessive (OMIM # 305000)
Autosomal dominant (OMIM # 127550)
Autosomal recessive (OMIM # 224230)

1.3 Name of the analysed genes or DNA/chromosome segments

DKC1 X-linked recessive (~30% of dyskeratosis congenita)
TERC Autosomal dominant (~5–10% of dyskeratosis congenita)
TERT Autosomal dominant and autosomal recessive (~5–10% of dyskeratosis congenita)
NOP10 Autosomal recessive (<1% of dyskeratosis congenita)
NHP2 Autosomal recessive (<1% of dyskeratosis congenita)
TINF2 Autosomal dominant (~15% of dyskeratosis congenita)
C16orf57 Autosomal recessive (~2% of dyskeratosis congenita)

1.4 OMIM# of the gene(s)

DKC1 OMIM # 305000
TERC OMIM # 127550
TERT OMIM # 127550 and OMIM # 224230
NOP10 OMIM # 224230
NHP2 OMIM # 224230
TINF2 OMIM # 127550
C160rf57 OMIM # 224230

1.5 Mutational spectrum

DKC1 Mainly missense mutations, >50 different mutations reported.
TERC Heterozygous mutations—point mutations, small and large deletions, >40 different mutations reported.
TERT Heterozygous and biallelic mutations. Mainly missense mutations, >50 different mutations reported.
NOP10 One homozygous missense mutation.
NHP2 Biallelic mutations reported in two families.
TINF2 Mainly missense mutations, >20 different mutations reported.
C16orf57 Homozygous or biallelic frameshift, nonsense or splice site mutations; 10 different mutations reported.

1.6 Analytical methods

PCR amplification of genomic DNA fragment(s) of *DC* genes (*DKC1*, *TERC*, *TERT*, *NOP10*, *NHP2*, *TINF2*, *C16orf57*) followed by denaturing HPLC and/or direct DNA sequence analysis.

1.7 Analytical validation

Sequencing of the appropriate DNA fragment.

1.8 Estimated frequency of the disease (incidence at birth ('birth prevalence') or population prevalence)

1 in 1 000 000 (approximate)

1.9 If applicable, prevalence in the ethnic group of investigated person

1 in 1 000 000 (approximate)

1.10 Diagnostic setting

	Yes	No
A. (Differential) diagnostics	☒	☐
B. Predictive Testing	☒	☐
C. Risk assessment in relatives	☒	☐
D. Prenatal	☒	☐

Comment: Dyskeratosis congenita (DC) is an inherited bone-marrow failure syndrome exhibiting considerable clinical and genetic heterogeneity. In its classical form, DC is characterised by a muco-cutaneous triad of abnormal skin pigmentation, nail dystrophy and mucosal leucoplakia. A given patient may also have a variety of other somatic features and there is an increased risk of malignancy. X-linked recessive, autosomal dominant (AD) and autosomal recessive (AR) forms of DC are recognised. The gene mutated in X-linked DC (*DKC1*) encodes a highly conserved nucleolar protein called dyskerin. Dyskerin associates with the H/ACA class of small nucleolar RNAs in small nucleolar ribonucleoprotein particles (snoRNPs), which are important in guiding the conversion of uracil to pseudouracil during the maturation of ribosomal RNA. Dyskerin also associates with the RNA component of telomerase (*TERC*) where it is important in stabilising the telomerase complex, which is critical in the maintenance of telomeres. Heterozygous mutations in *TERC* and *TERT* (telomerase reverse transcriptase) have been found in patients with AD-DC and in some patients with aplastic anaemia (AA), myelodysplasia (MDS) and pulmonary fibrosis. A subset of patients with the multi-system disorder Hoyeraal–Hreidarsson (HH) syndrome, have been found to have *DKC1* mutations. It has also been established that AR-DC is genetically heterogeneous with three characterised subtypes due to biallelic mutations in *NHP2*, *NOP10* and *TERT*. One AD-DC subtype was recently found to be due to mutations in *TINF2*, which

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encodes a component of the shelterin complex that protects telomeres and controls access to the telomere. Collectively, these findings have demonstrated that classical DC, HH, a subset of AA, MDS/AML and pulmonary fibrosis are principally due to defects in telomere maintenance and cells from these patients have short telomeres. Equally it has become clear that the spectrum of patients who can now be considered to have DC has expanded considerably. This does raise the issue as to what should now be called DC. Very recently some AR-DC families have been found to have homozygous mutations in the *C16orf57* gene and normal length telomeres; the function of its encoded protein is presently unknown.

The following categories of individuals can be considered to have DC:

(1) Those with all three (abnormal skin pigmentation, nail dystrophy and leucoplakia) muco-cutaneous features.
(2) Individuals with one out of three mucocutaneous features, +bone-marrow failure, +2 other somatic features of DC.
(3) Those presenting with AA or MDS or pulmonary fibrosis associated with a pathogenic telomerase mutation.
(4) Individuals having four or more of features of the Hoyeraal–Hreidarsson syndrome (growth retardation, developmental delay, microcephaly, bone-marrow failure, immunodeficiency and cerebellar hypoplasia).
(5) Individuals with two or more features seen in DC associated with very short telomeres (<1st centile).

NB: it is noteworthy that 'classical DC' often presents as a multisystem disorder in the paediatric age group whereas adult patients presenting with one or more feature of DC display a very variable phenotype and the associated telomerase mutations are usually acting as risk factors. DC and related disorders thus represent a very wide clinical and genetic spectrum.

2. TEST CHARACTERISTICS

	Genotype or disease		A: True positives B: False posities	C: False negatives D: True negatives
	Present	Absent		
Test				
Posititve	A	B	Sensitivity:	A/(A+C)
			Specificity:	D/(D+B)
Negative	C	D	Positive predictive value:	A/(A+B)
			Negative predictive value:	D/(C+D)

2.1 Analytical sensitivity (proportion of positive tests if the genotype is present)
Not determined; probably >95%.

2.2 Analytical specificity (proportion of negative tests if the genotype is not present)
Difficult to comment on as the genetic basis is currently only known for ~50% of DC patients.

2.3 Clinical sensitivity
(proportion of positive tests if the disease is present)
The clinical sensitivity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if a quantification can only be made case by case.

As features of the disease develop progressively with time, individuals with pathogenic mutations may not have any/all clinical features at time of analysis. The age of onset and range of clinical features is very variable.

2.4 Clinical specificity
(proportion of negative tests if the disease is not present)
The clinical specificity can be dependent on variable factors such as age or family history. In such cases, a general statement should be given, even if a quantification can only be made case by case.

As the genetic diagnosis can only be substantiated in about 50% of cases at present, not finding a mutation in one of the seven known DC genes does not definitively exclude the diagnosis of DC.

2.5 Positive clinical predictive value
(life time risk to develop the disease if the test is positive)
This is high (>90%) for *DKC1* and *TINF2* mutations, but difficult to be precise for *TERC* and *TERT* mutations, as these are sometimes seen as risk factors for the development of disease.

2.6 Negative clinical predictive value
(probability not to develop the disease if the test is negative)
Assume an increased risk based on family history for a non-affected person. Allelic and locus heterogeneity may need to be considered.

Index case in that family had been tested:

Index case in that family had not been tested:

As highlighted previously, as the genetic basis is only known in about 50% of DC cases, not finding a mutation in one of the seven known DC genes does not exclude the possibility of developing DC. It is also important to note that some mutations (particularly in the *TERT* gene) are not associated with disease in all individuals carrying the mutation, suggesting the mutation is more a risk factor for the development of disease.

3. CLINICAL UTILITY

3.1 (Differential) diagnosis: the tested person is clinically affected
(To be answered if in 1.10 'A' was marked)

3.1.1 Can a diagnosis be made other than through a genetic test?

No	☐ (Continue with 3.1.4)	
Yes	☒	
	Clinically	☒
	Imaging	☐
	Endoscopy	☐
	Biochemistry	☐
	Electrophysiology	☐
	Other (please describe)	☒Through identification of very short telomere length in leukocytes (<1st centile) using flow-fluorescence *in situ* hybridization or quantitative PCR

3.1.2 Describe the burden of alternative diagnostic methods to the patient
In patients with classical features (eg presence of muco-cutaneous triad) clinical diagnosis is possible. However as there is considerable variation in the onset and severity of clinical features, diagnosis exclusively based on clinical features is both difficult and unreliable. This is further highlighted by some of the 'cryptic' presentations of DC (eg, aplastic anaemia); in such cases it is the finding of a pathogenic mutation in one of the *DC* genes that helps in clinching the diagnosis of DC.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?

Clinical diagnosis is dependent on clinical expertise. A delay in diagnosis can lead to inappropriate and inadequate management. This may in some cases lead to increased morbidity and mortality.

Flow-FISH measurement of leucocyte telomere length is currently only available as a diagnostic method in one international lab (Repeat Diagnostics, Vancouver, Canada) and is relatively expensive. It also needs further validation. Telomere length measurement should perhaps be regarded as a good screening test for DC. Individuals found to have very short telomeres should ideally go on to have genetic analysis for the DC genes.

3.1.4 Will disease management be influenced by the result of a genetic test?

No	☐	
Yes	☒	
	Therapy (please describe)	This is complicated. For the haematological defect (which is a major cause of mortality) patients with dyskeratosis congenita are more likely to respond to androgens (eg, oxymetholone) rather than to the conventional immunosuppressive (anti-thymocyte globulin and cyclosporine) therapy used in idiopathic aplastic anaemia. The diagnosis of dyskeratosis congenita will also influence the details of patient monitoring. It will also influence the drug-conditioning regimen (low intensity) in patients who become candidates for bone-marrow transplantation.
	Prognosis (please describe)	This can vary considerably from death in infancy (usually due to bone-marrow failure) to that in the seventh decade. The major causes of death relate to bone-marrow failure (~70%), cancer (~10%) and lung disease (particularly pulmonary fibrosis, ~10–20%). The bone-marrow failure develops progressively with time; up to 80% of patients will have bone-marrow failure by the age of 30 years. Cancer (haematological and non-haematological) usually develops after the third decade. The most frequent solid malignancies are head and neck squamous cell carcinomas.
	Management (please describe)	As this is a multi-system disorder it is important to monitor many systems of the body. BM failure is one of the commonest and severe complications. About 50–70% of patients will respond to androgens, but patients have to be monitored carefully for side effects. For those who do not have an efficacious response to androgens and have a compatible bone-marrow donor, haemopoietic stem cell transplantation using a low-intensity conditioning regime is an option. It is important to use low-intensity fludarabine-based conditioning regimes as conventional regimes using radiotherapy or busulphan are associated with high toxicity and poor survival. Treatment for cancer depends on the specific cancer but consideration has to be given to the underlying dyskeratosis congenita (ie, more supportive care, reduce drug doses). With regards to pulmonary disease, patients should be encouraged to avoid smoking. Medical treatment is usually difficult in severe lung disease; lung transplant may be an option in some cases. Advice on skin care (eg, use of moisturising creams) and avoidance of sunlight is important. Liver disease (cirrhosis and non-cirrhotic portal hypertension) is more common in dyskeratosis congenita patients than the normal population. Alcohol consumption should therefore be kept to a minimum and all drug administrations require close monitoring.

3.2 Predictive Setting: The tested person is clinically unaffected but carries an increased risk based on family history

(To be answered if in 1.10 'B' was marked)

3.2.1 Will the result of a genetic test influence lifestyle and prevention?

If the test result is positive (please describe):

The management plan will have an impact on lifestyle. As highlighted above it is important that patients with DC (or predicted to be at risk of developing DC based on genetic testing) avoid smoking, sunlight and keep alcohol intake to a minimum. They should also avoid occupations that expose them to hazardous chemicals.

If the test result is negative (please describe):

No specific lifestyle change necessary.

3.2.2 Which options in view of lifestyle and prevention does a person at-risk have if no genetic test has been done (please describe)?

Uncertainty will remain for the individual as to whether they need to modify their lifestyle with respect to smoking, alcohol and sun exposure.

3.3 Genetic risk assessment in family members of a diseased person

(To be answered if in 1.10 'C' was marked)

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?

Yes, if a pathogenic mutation has been identified in a DC-causing gene it is possible to offer genetic testing and appropriate counselling to all family members.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?

In some circumstances only. For example, in the case of *TINF2* mutations usually the mutation has arisen de-novo in the index case. In these families it then makes it unnecessary to test the unaffected sibs of the index case.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?

Yes. NB: there can be variability in disease expression even within families (suggesting a role of other genetic and/or environmental factors in the development of disease features). This always needs to be communicated to family members.

3.4 Prenatal diagnosis

(To be answered if in 1.10 'D' was marked)

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnosis?

Yes.

4. IF APPLICABLE, FURTHER CONSEQUENCES OF TESTING

Please assume that the result of a genetic test has no immediate medical consequences. Is there any evidence that a genetic test is nevertheless useful for the patient or his/her relatives? (Please describe).

In female carriers of X-linked DC (*DKC1*), there is usually no medical problem. However X-linked DC carriers can go on to give rise to affected boys. Carrier testing for the X-linked gene (*DKC1*) in appropriate families is therefore useful even though it has no immediate consequences for the carrier.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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