

Dyskeratosis congenita

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Abstract

Classical dyskeratosis congenita (DC) is a rare multisystem disorder with a prevalence estimated to 1 in 1,000,000. DC is characterized by the mucocutaneous triad of abnormal skin pigmentation, nail dystrophy and mucosal leucoplakia. A variety of other abnormalities have been reported. Bone marrow (BM) failure is the principal cause of early mortality with an additional predisposition to malignancy and fatal pulmonary complications. DC exhibits considerable clinical and genetic heterogeneity. X-linked recessive, autosomal dominant and autosomal recessive forms are recognised. The genes (DKC1 and TERC) mutated in two subtypes of DC both encode components of the telomerase complex and DC is now believed to be principally due to defective telomerase function. The identification of DKC1 mutations in patients with Hoyeraal-Hreidarsson (HH) and of TERC mutations in some patients with aplastic anaemia (AA) and myelodysplasia (MDS) have extended the range of patients who can be regarded as having DC. From a clinical perspective the link between DC and AA and in turn to defective telomerase suggests that treatments directed at correction of telomerase activity might benefit DC/AA patients who do not respond to conventional therapy. At present haemopoietic stem cell transplantation (SCT) using low intensity protocols represents the only curative option for DC patients developing BM failure.

Key-words

Aplastic anaemia (AA), dyskeratosis congenita (DC), dyskerin, Hoyeraal-Hreidarsson syndrome (HH), telomerase

Name of the disease/Included diseases

Dyskeratosis congenita is also known as Zinsser-Engman-Cole syndrome. The [Hoyeraal-Hreidarsson syndrome](#) is a severe variant of DC. Mild forms of DC can present with aplastic anaemia.

Definition

DC is an inherited disorder, which in its classical form is characterized by a triad of abnormal skin pigmentation, nail dystrophy and leucoplakia. A range of other abnormalities can be seen in a given patient. DC patients have a high predisposition to developing bone marrow (BM)

failure and malignancy. The genes (*DKC1* and *TERC*) mutated in two subtypes of DC both encode components of the telomerase complex and DC is now believed to be principally due to defective telomerase function. The identification of *DKC1* mutations in patients with HH and of *TERC* mutations in some patients with aplastic anaemia (AA)/myelodysplasia (MDS) have highlighted its considerable heterogeneity and extended the range of patients who can be regarded as having DC.

Differential diagnosis

Patients with DC have features that overlap with [Fanconi anaemia](#) (FA) and idiopathic AA. The most challenging presentation is with AA. All such patients should have chromosomal breakage analysis with mitomycin-C (MMC) or diepoxybutane (DEB) to exclude FA. If the chromosomal breakage study is normal then it is logical to proceed to *TERC* analysis. Depending on the result of this and whether the patient has somatic features of DC it is then reasonable to study the *DKC1* gene. Diagnosis of DC is relatively easy in patients who have the classical mucocutaneous features. At present diagnosis can be substantiated at the genetic level in ~ 40% (*DKC1* and *TERC*) of DC patients.

Aetiology/pathophysiology

DC is a genetically heterogeneous disorder. X-linked recessive (MIM 305000), autosomal dominant (MIM 127550) and autosomal recessive (MIM 224230) genetic subtypes are recognised. Analysis of the Dyskeratosis Congenita Registry (DCR – at Hammersmith Hospital, London) families suggests that each of the autosomal forms of DC may be genetically heterogeneous. Recent studies have shown that the genes mutated in the X-linked recessive and autosomal dominant subtypes of DC encode core components of the telomerase complex.

X-linked DC: *DKC1* and dyskerin

Initially, through linkage analysis in one large family with only affected males in more than one generation it was possible to map the gene for the X-linked form of the disease to Xq28 (Connor *et al.* 1986). The availability of genetic markers and additional X-linked families facilitated positional cloning of the gene (*DKC1*) that is mutated in X-linked DC (Knight *et al.* 1996; Knight *et al.* 1998b; Heiss *et al.* 1998; Hassock *et al.* 1999). The *DKC1* gene consists of 15 exons and spans ~15Kb within Xq28. It is transcribed into a ~ 2.5kb mRNA that is translated into a 514 aa protein. The identification of the *DKC1* gene has made available a genetic test (Knight *et al.* 1999a; Vulliamy *et al.* 1999; Knight *et al.* 2001; Heiss *et al.* 2001; Salowsky *et al.* 2002; Hiramatsu *et al.*

2002; Lin *et al.* 2002; Cossu *et al.* 2002; Wong *et al.* 2004) that can be used to confirm diagnosis in suspected cases, identify carriers and provide antenatal diagnosis in X-linked families. The majority of mutations in *DKC1* cause single acid substitutions, one of which (A353V) accounts for approximately 40% of X-linked DC cases. The phenotype in these patients with the same dyskerin mutation can vary considerably and suggests that other genetic/environmental factors influence the DC phenotype. Although the mutations are spread throughout the *DKC1* gene there are two prominent clusters involving amino acids 31-72 and 314-420, encoded in exons 3-6 and exons 9-12. This suggests that different parts of the dyskerin molecule may have different functions and warrants further studies. Based on its homologues (see below) the following domains have been identified in dyskerin: TruB (tRNA pseudouridine synthase N terminal domain) at amino acids (aa) 107-24, PUA (putative RNA-binding domain in pseudouridine synthase and Archaeosine transglycosylase) at aa 296-371 and two nuclear localisation signals at aa 11-20 and aa 446-458. In future studies it will be interesting to determine whether dyskerin mutations have different molecular consequences depending on their precise physical location within the dyskerin molecule.

The *DKC1* gene is expressed in all tissues of the body consistent with it having a “house keeping function” in the human cell. This correlates well with the multi-system phenotype of DC. The *DKC1* gene and its encoded protein, dyskerin, a nucleolar protein (Yousoufian *et al.* 1999; Heiss *et al.* 1999) are highly conserved with many homologues including in yeast (Cbf5p), rat (NAP57), drosophila (mfl) and mouse (*Dkc1*) (Jiang *et al.* 1993; Meier *et al.* 1994; Cadwell *et al.* 1997; Philips *et al.* 1998; Giordano *et al.* 1999; Ruggero *et al.* 2003). These dyskerin homologues associate with three core proteins (GAR1, NHP2 and NOP10) and form the core component of the H/ACA ribonucleoprotein particles (RNPs) (Henras *et al.* 1998). These H/ACA RNPs associate with H/ACA small nucleolar RNAs (H/ACA snoRNAs) and guide the conversion of uridine to pseudouridine (pseudouridylation) at specific sites of ribosomal RNA (rRNA). Based on studies on its homologues, dyskerin has been therefore predicted to be important in pseudouridylation of specific residues of ribosomal RNA (Tollervey & kiss 1997; Lafontaine *et al.* 1998; Watkins *et al.* 1998; Zebrarjadian *et al.* 1999; Filipowicz & Pogacic 2002; Wang and Meier 2004). This step is essential for ribosome biogenesis and it has therefore been suggested that part of the pathology in X-linked DC probably relates to

defective ribosome biogenesis (Luzzatto & Karadimitris 1998). Recent studies on the mouse dyskerin gene (*Dkc1*) (Ruggero *et al.* 2003; Mochizuki *et al.* 2004) provide additional support for this (Meier 2003). Further studies are necessary in human cells to clarify this issue.

It has been shown that dyskerin and the other three proteins (GAR1, NHP2 and NPO10) that form the core of the RNPs also associate with the RNA component of telomerase (*TERC*) (Pogacic *et al.* 2000; Dez *et al.* 2001), which too contains a H/ACA consensus sequence (Mitchell *et al.* 1999a; Mitchell *et al.* 1999b). Together with telomerase reverse transcriptase (TERT), *TERC* forms the core of the active telomerase complex, which is important in the maintenance of telomeres (McEachern *et al.* 2000; de Lange 2002; Chen and Greider 2004). Mitchell *et al.* (1999b) found that in one fibroblast and four lymphoblast cell lines from patients with X-linked DC the level of *TERC* was reduced while no significant defect in rRNA processing or site-specific pseudouridylation was detected. Furthermore, telomere lengths in the lymphoblast lines were shorter than expected for age-matched normal individuals. Similar results have recently been obtained for the peripheral blood mononuclear cells of one X-linked DC patient (Wong *et al.* 2004). Telomerase activity, induced by overexpression of TERT in the X-linked DC fibroblast cell line, was shown to be reduced compared to similarly treated lines from DC carriers (Mitchell *et al.* 1999b). However, in the peripheral blood mononuclear cells from five X-linked DC patients telomerase activity seems to vary over a similar range to that seen in five normal controls (Vulliamy *et al.* 2001a). It has also been shown that telomeres are shorter in blood cells from patients with autosomal forms of DC (Vulliamy *et al.* 2001a). The combination of these findings suggested that DC might be principally a disease of telomere maintenance. Further clarification has come from the elucidation of the genetic basis of autosomal dominant DC (see below).

Autosomal Dominant DC: *TERC* and DC pathophysiology

Linkage analysis in one large DC family showed that the gene for autosomal dominant DC is on chromosome 3q, in the same area where the gene for *TERC* had been previously mapped. This led to *TERC* mutation analysis in this and other DC families and the demonstration that autosomal dominant DC is due to mutations in the *TERC* gene (Vulliamy *et al.* 2001b). *TERC* is a 451 nucleotide RNA. *TERC* consists of four structural domains: the pseudoknot domain, CR4-CR5 domain, the H/ACA domain and the

CR7 domain. Structure function analysis reveals that the pseudoknot and CR4-CR5 domains (together with TERT) are required for the catalytic function while the H/ACA and CR7 domains for *TERC* RNA accumulation.

Mutations in *TERC* have been found in several of the *TERC* domains. The functional consequences of these mutations and their effect on telomerase activity (either in a cell free system or after introduction of mutant *TERC* into W138VA13 cells not expressing telomerase) and/or on the structure of telomerase RNA (e.g. using NMR spectroscopy) have been studied. Collectively, these functional studies (Comolli *et al.* 2002; Theimer *et al.* 2003a; Theimer *et al.* 2003b; Fu *et al.* 2003; Ly *et al.* 2003, Ren *et al.* 2003; Marrone *et al.* 2004) have demonstrated that *TERC* mutations seen in AD-DC patients result in reduced telomerase activity either through impaired RNA accumulation/stability (found to be the case for the following mutations: deletion from nucleotide 378 and 408 C->G) or a catalytic defect (found to be the case for the following mutations: 72C->G, 96-97 del CT, 107/108 GC->AG, and 110-113 del GACT). Furthermore, experiments reconstituting telomerase with both normal and mutant *TERC* molecules showed no evidence for a dominant negative effect. Instead the data suggests that the *TERC* mutations act via haplo-insufficiency (Fu & Collins 2003; Marrone *et al.* 2004). Additionally, it has been established for some of these mutations that are located within the conserved stem cell structure (e.g. 72C->G; 107-108 GC->AG, 408 C->G), that it is their effect on the secondary structure rather than the primary sequence that determines the functional consequences (Comolli *et al.* 2002; Ly *et al.* 2003; Marrone *et al.* 2004). Analysis of these disease causing *TERC* mutations has thus provided important confirmatory data on the different functional *TERC* domains.

Since the *DKC1* encoded protein dyskerin and *TERC* are both components of the telomerase complex and all DC patients have very short telomeres, it is currently believed that DC arises principally from an abnormality in telomerase activity (Marciniak & Guarente 2001). This telomerase deficiency results in accelerated telomere shortening in DC cells (Mitchell *et al.* 1999; Vulliamy *et al.* 2001; Wong *et al.* 2004) and is associated with increased loss of cells (Montanaro *et al.* 2002) particularly from tissues which need constant renewal, such as the haemopoietic and dermatological systems that bear the brunt of DC. Evidence for a haemopoietic stem/progenitor cell defect in DC has been established in several studies (Colvin *et al.* 1984; Friedland *et al.* 1985; Alter *et al.* 1992; Marsh *et al.* 1992; Marley *et al.* 1999) and is

therefore consistent with a basic defect in telomerase.

The effect of mutation of one allele of human telomerase RNA in families with autosomal dominant DC can be compared with the effect on laboratory mice of knocking out both alleles of the gene coding for telomerase RNA (*Terc*). Such mice showed no significant abnormalities in early generations but later generations (beyond 4th generation) showed progressive telomere shortening and a variety of defects including reduced proliferative capacity of haematopoietic cells (Blasco *et al.* 1997; Lee *et al.* 1998; Rudolph *et al.* 1999; Artandi *et al.* 2000). Heterozygous mice (*Terc*^{+/-}) appear asymptomatic but they do have difficulty in elongating their telomeres in inter-species crosses (Hathcock *et al.* 2002).

It is interesting to note that the autosomal dominant DC families show an earlier age of onset and a greater number of disease features in succeeding generations. This increase in severity of the disease (anticipation) in successive generations has been associated with progressive telomere shortening (Vulliamy *et al.* 2004), as is the case in the *Terc*^{-/-} mice. Both DC patients and *Terc*^{-/-} mice also have an increased incidence of cancer. It is likely that in both cases the increased incidence of malignancy is caused by chromosome instability, which in turn is a result of critically, shortened telomeres. Indeed end-to-end chromosome fusions have been observed in both *Terc*^{-/-} mice (Artandi *et al.* 2000) and in DC patients (Scappaticci *et al.* 1989; Dokal *et al.* 1992; Kehrer *et al.* 1992; Demiroglu *et al.* 1997).

Autosomal Recessive DC

The genetic basis of the autosomal recessive form(s) of DC is presently unknown. Since dyskerin and TERC have been shown to be key components of the telomerase complex other molecules associated with this complex or involved in rRNA biosynthesis would seem obvious candidates. Further studies, including linkage analysis on consanguineous AR families are on going to identify the genes mutated in autosomal recessive DC.

Implications for DC patients

The demonstration of *DKC1* and *TERC* mutations in DC families provides an accurate diagnostic test, including antenatal diagnosis, in approximately 40% of DC cases (data based on the DCR). It also provides the basis for designing the much needed new treatments. Since in any given patient DC is a single gene disorder and the cells that need to be targeted (haematopoietic stem cells) are accessible, DC is a good candidate for haematopoietic gene

therapy. Furthermore there is evidence from fibroblast culture studies and from the skewed patterns of X-chromosome inactivation seen in carriers of X-linked DC (Devriendt *et al.* 1997; Vulliamy *et al.* 1997) that cells transfected with the normal gene would have growth/survival advantage compared to the uncorrected cells. Such an advantage would also be predicted from the role of dyskerin and TERC in telomere maintenance.

Clinical description

Classical DC

Classical DC is an inherited BM failure syndrome characterized by the mucocutaneous triad of abnormal skin pigmentation, nail dystrophy and mucosal leucoplakia (Zinsser 1906; Engman 1926; Cole 1930). A variety of other (dental, gastrointestinal, genitourinary, hair greying/loss, immunological, neurological, ophthalmic, pulmonary and skeletal) somatic abnormalities have also been reported (Table 1; Sirinavin and Trowbridge 1975; Drachtman and Alter 1995; Knight *et al.* 1998; Solder *et al.* 1998; Dokal 2000). BM failure is the principal cause of early mortality with an additional predisposition to malignancy and fatal pulmonary complications (Dokal 2000).

Clinical manifestations in DC often appear during childhood although there is a wide age range. The skin pigmentation and nail changes typically appear first, usually by the age of 10 years. BM failure usually develops below the age of 20 years; 80-90% of patients will have developed BM abnormalities by the age of 30 years (Knight *et al.* 1998a; Dokal 2000). In some patients the BM abnormalities may appear before the mucocutaneous manifestations and can lead to an initial diagnosis of "idiopathic aplastic anaemia" (Do Boeck *et al.* 1981; Philips *et al.* 1992; Forni *et al.* 1993; Dokal 2000; Fogarty *et al.* 2003). There is considerable clinical variability between patients, sometimes even within the same family. Although it is difficult to make generalisations, the X-linked recessive form appears to be associated with a more severe phenotype (more abnormalities and a younger age of onset) than the autosomal dominant form; patients with autosomal dominant DC tend to have less abnormalities and a later age of onset. The mucocutaneous abnormalities in autosomal dominant DC can also be "mild" and can make diagnosis difficult. The autosomal recessive families also show considerable heterogeneity, with some patients having severe bone marrow failure by the age of 10 years, yet others having no haematological abnormalities even by the age of 40 years. The main causes of death are BM failure/immunodeficiency (~60-70%), pulmonary

complications (~10-15%) and malignancy (~5-10%) (Knight *et al* 1998a; Dokal 2000).

Table 1. Somatic abnormalities in patients with classical DC

| Abnormality | % of patients |
|--|---------------|
| <i>Classical presentation</i> | |
| Abnormal skin pigmentation | 89 |
| Nail dystrophy | 88 |
| Bone marrow failure | 85.5 |
| Leucoplakia | 78 |
| <i>Other abnormalities</i> | |
| Epiphora | 30.5 |
| Learning difficulties/developmental delay/mental retardation | 25.4 |
| Pulmonary disease | 20.3 |
| Short stature | 19.5 |
| Extensive dental caries/loss | 16.9 |
| Oesophageal stricture | 16.9 |
| Premature hair loss/greying/sparse eyelashes | 16.1 |
| Hyperhidrosis | 15.3 |
| Malignancy | 9.8 |
| Intrauterine growth retardation | 7.6 |
| Liver disease/peptic ulceration/enteropathy | 7.3 |
| Ataxia/cerebellar hypoplasia | 6.8 |
| Hypogonadism/undescended testes | 5.9 |
| Microcephaly | 5.9 |
| Urethral stricture/phimosis | 5.1 |
| Osteoporosis/aseptic necrosis/scoliosis | 5.1 |
| Deafness | 0.8 |

NB – In the future as patients identified to have DC on the basis of mutation analysis are included, these percentages are likely to change.

Atypical forms of DC

Hoyeraal-Hreidarsson syndrome

The [Hoyeraal-Hreidarsson](#) (HH) syndrome (MIM 600545) is a severe multi-system disorder that can present in the neonatal period and infancy. It is characterized by severe growth retardation, bone marrow failure, immunodeficiency and neurological abnormalities (Hoyeraal *et al.* 1970; Hreidarsson *et al.* 1988; Berthet *et al.* 1994; Aalfs *et al.* 1995; Ohga *et al.* 1995; Nespoli *et al.* 1997). The overlap of these HH features with some DC patients led to analysis of the *DKC1* gene in HH patients. These studies demonstrated that some male HH cases are a severe variant of DC where death from BM failure/immunodeficiency occurs before the appearance of the diagnostic features of DC (Knight *et al.* 1999b). It also highlighted the immunological defects that can be seen in DC, ranging from the severe “T+B-NK- severe immunodeficiency” in HH patients (Knight *et al.* 1999b; Cosu *et al.* 2002) to the more variable immunological abnormalities observed in other DC patients (Wiedemann *et al.* 1984; Rose *et al.* 1992; Solder *et al.* 1998; Dokal 2000; Knudson *et al.* 2004). Several mutations in dyskerin have now been identified in HH patients (Knight *et al.* 1999b; Yagahmai *et al.* 2000; Cosu *et al.* 2002; Sznajder *et al.* 2003).

Female cases of HH are also recognised (Mahmood *et al.* 1998; Akaboshi *et al.* 2000; DCR families) and it is likely that they represent

a severe variant of the autosomal recessive form (s) of DC, the genetic basis of which presently remains unknown.

Idiopathic aplastic anaemia and myelodysplasia

In some of the DCR families, affected members have died of severe AA before the age of 10 years and a diagnosis of DC was made subsequently, only when other members of the family survived long enough to develop the classical mucocutaneous features. If it were not for the presence of subsequent members, these would have been characterized as idiopathic AA. In addition, it has been shown that patients with AA have short telomeres compared to age matched controls (Ball *et al.* 1998; Brummendorf *et al.* 2001). These observations led to analysis of the *DKC1* and *TERC* genes in AA patients. Although the *DKC1* gene screen was found to be normal (unpublished observations), mutations in *TERC* have been found in some cases of AA (including paroxysmal nocturnal haemoglobinuria) and MDS (Vulliamy *et al.* 2002; Yamaguchi *et al.* 2003, Vulliamy *et al.* 2004; Keith *et al.* 2004). It is noteworthy that MDS patients also have short telomeres (Boulwood *et al.* 1997). Patients with *TERC* mutations who present predominantly with features of AA or MDS can be regarded as having “mild/cryptic” DC.

These findings show that in some cases of AA/MDS the primary defect is in the maintenance of telomeres and this has

implications for the management of patients failing conventional therapies such as immunosuppressive therapy. They also highlight the clinical and genetic heterogeneity of DC and a possible rationale for screening the DC genes in uncharacterised patients (e.g. unexplained pulmonary or liver disease) who have clinical features that overlap with DC.

Diagnostic methods

The diagnosis of DC is relatively easy when all the classical mucocutaneous features are present. However the age at which these features develop is very variable and some patients may initially present with non-cutaneous features of DC, which makes diagnosis based on clinical criteria very difficult. For example, some patients may present with aplastic anemia as their first presentation as highlighted above. Since the genes mutated in the X-linked recessive (*DKC1*) and autosomal dominant (*TERC*) DC sub-types are now known it is possible to substantiate the diagnosis in a significant proportion of DC patients. It is appropriate to screen for the *DKC1* gene if patients are male and have 2 out of the following: abnormal skin pigmentation, nail dystrophy, leucoplakia, BM failure. The situation regarding the *TERC* screen is different for two reasons. Firstly we already know that a sub-group of patients with AA have mutations in *TERC*. Secondly, screen for *TERC* is relatively easy. Therefore it is reasonable to undertake analysis of the *TERC* gene in all patients presenting with aplastic anemia. There is as yet no easy universal functional test for DC. In patients with presenting with AA it is also important to undertake chromosomal breakage analysis for FA.

Epidemiology

The precise incidence/prevalence of DC is unknown. It has been observed in many racial subtypes and it is estimated that the prevalence of DC is approximately 1 per 1000000 persons. The DCR at the Hammersmith Hospital (London, UK) has information on 340 patients of all races and distinguishes DC into X-linked recessive (MIM 305000), autosomal dominant (MIM 127550) and autosomal recessive (MIM 224230) subtypes.

Genetic counselling

Identification of a mutation in either the *DKC1* or *TERC* gene facilitates accurate genetic counselling. Counselling should adhere to standards established for all genetic disorders.

Antenatal diagnosis

In families where mutation in the *DKC1* or *TERC* gene has been characterized antenatal diagnosis is possible.

Management including treatment

DC is a multi-system disorder and may require the input of many sub-specialists. It is advisable that DC patients should avoid exposure to sunlight (use barrier creams). They should also avoid smoking and alcohol if possible as the livers and lungs of DC patients are more susceptible to damage. Use of moisturising creams to prevent damage to skin and good oral hygiene are also important.

Bone marrow failure/immunodeficiency is the principal cause of premature mortality in DC patients. Oxymetholone (an anabolic steroid) can produce an improvement in haemopoietic function in many patients (approximately 60%) for a variable period of time (Smith *et al.* 1979; Dokal unpublished data). Successful responses to hematopoietic growth factors such as GM-CSF, G-CSF and erythropoietin have also been reported (Russo *et al.* 1990; Alter *et al.* 1997; Erduran *et al.* 2003) although usually these are transient. The main current treatment for severe BM failure is allogeneic haemopoietic stem cell transplantation (SCT) and there is some experience using both sibling and alternative stem cell donors (Berthou *et al.* 1991; Dokal *et al.* 1992; Langston *et al.* 1996; Yabe *et al.* 1997; Rocha *et al.* 1998; Ghavamzadeh *et al.* 1999; Lau *et al.* 1999). Unfortunately because of early and late fatal pulmonary/vascular complications following SCT, the results of allogeneic SCT have been less successful. The presence of pulmonary disease in a significant proportion of DC patients (Table 1, Paul *et al.* 1992; Verra *et al.* 1992; Knight *et al.* 1998; Safa *et al.* 2001; Kilic *et al.* 2003) explains the high incidence of fatal pulmonary complications in the setting of SCT. It also highlights the need to avoid agents, which are associated with pulmonary toxicity (such as busulphan and radiotherapy). Since BM failure is the main cause of premature death in DC patients and SCT is currently the only curative option for the BM failure, SCT should continue to be performed on selected patients. The best candidates for SCT are patients with no pre-existing pulmonary disease and who have sibling donors. SCT using fludarabine-based reduced-intensity conditioning regimens, which avoid busulphan and radiotherapy, appears to be giving encouraging results (Cossu *et al.* 2002; Nobili *et al.* 2002; Dror *et al.* 2003; Gungor *et al.* 2003). For patients lacking compatible SCT donors there is a great need to develop new treatment strategies.

It is also important to monitor the pulmonary system and to screen for malignancies, as these are the other important causes of mortality.

Unresolved questions

Many aspects of DC remain unresolved. These include some of the following:

1. What are the functions of dyskerin? Does it have a role in pseudouridylation in addition to telomere maintenance?
2. What are the relative contributions of defective telomere maintenance and ribosomal biogenesis in the pathophysiology of DC, particularly X-linked DC?
3. What is the genetic/molecular basis of autosomal recessive DC?
4. What is the proportion of idiopathic AA that is due to defects in DC genes?
5. What is the best conditioning regimen for DC patients undergoing SCT?
6. Will it be possible to develop new treatment strategies based on correction of the telomerase defect?

References

Aalfs C.M., van den Berg H., Barth P.G., and Hennekam R.C.M. 1995. The Hoyeraal-Hreidarsson syndrome: the fourth case of a separate entity with prenatal growth retardation, progressive pancytopenia and cerebellar hypoplasia. *Eur J Pediatr* 154: 304-308.

Akaboshi S., Yoshimura M, Hara T., Kageyama H., Nishikwa K., Kawakami T, Leshima A., and Takeshita K. 2000. A case of Hoyeraal-Hreidarsson syndrome: Delayed myelination and hypoplasia of corpus callosum are other important signs. *Neuropediatrics* 31: 141-144.

Alter B.P., Knobloch M.E., He L., Gillio A.P., O'Reilly R.J., Reilly L.K., and Weinberg, R.S. 1992. Effect of stem cell factor on in vitro erythropoiesis in patients with bone marrow failure syndromes. *Blood* 80: 3000-3008.

Alter B.P., Gardner E.H., and Hall, R.E. 1997. Treatment of dyskeratosis congenita with granulocyte macrophage colony-stimulating factor and erythropoietin. *Br J Haematol* 97: 309-311.

Artandi S.E., Chang S., Lee S.L. *et al.* 2000. Telomere dysfunction promotes non-reciprocal translocations and epithelial cancers in mice. *Nature* 406: 641-645.

Ball S.E., Gibson F.M., Rizzo S. Tooze J.A., Marsh J.C., and Gordon-Smith E.C. 1998. Progressive telomere shortening in aplastic anemia. *Blood* 91 (10): 3582-3592.

Berthet F., Caduff R., Schaad U.B., Roten H., Tuchschmid P., Boltshauser E., and Seger R.A. 1994. A syndrome of primary combined immunodeficiency with microcephaly, cerebellar hypoplasia, growth failure and progressive pancytopenia. *Eur J Pediatr* 153: 333-33

Berthou C., Devergie A., D'Agay M.F., Sonsino E., Scrobohaci M.L., Loirat C., and Gluckman, E. 1991. Late vascular complications after bone marrow transplantation for dyskeratosis congenita. *Br J Haematol* 79: 335-336.

Blasco M. A., Lee H.W., Hande M.P., Samper E., Lansdorp P.M., DePinho R.A., and Greider C.W. 1997. Telomere shortening and tumor formation by mouse cells lacking telomerase RNA. *Cell* 91 (1): 25-34.

Boulwood J., Fidler C., Kusec R., Rack K., Elliott P.J., Atoyebi O., Chapman R., Oscier D.G., and Wainscoat J.S. 1997. Telomere length in myelodysplastic syndromes. *Am J Hematol* 56 (4): 266-271.

Brummendorf T.H., Maciejewski J.P., Mak J., Young N.S., and Lansdorp P.M. 2001. Telomere length in leukocyte subpopulations of patients with aplastic anemia. *Blood* 97 (4): 895-900.

Cadwell C., Yoon H.J., Zebarjadian Y., and Carbon J. 1997. The yeast nucleolar protein Cbf5p is involved in rRNA biosynthesis and interacts genetically with the RNA polymerase I transcription factor RRN3. *Mol Cell Biol* 17: 6175-6183.

Chen J.L., and Greider C.W. 2004. Telomerase RNA structure and function: implications for dyskeratosis congenita. *Trends Biochem Sci* 29: 183-192.

Cole H.N., Rauschkolb J.C., and Toomey J. 1930. Dyskeratosis congenita with pigmentation, dystrophia unguis and leukokeratosis oris. *Arch Dermatol Syph* 21: 71-95.

Colvin B.T., Baker H., Hibbin, J.A., Gordon-Smith E.C., and Gordon M.Y. 1984. Haemopoietic progenitor cells in dyskeratosis congenita. *Br J Haematol* 56: 513-515.

Comolli L.R., Smirnov I., Xu L., Blackburn E.H., and James T.L. 2002. A molecular switch underlies a human telomerase disease. *Proc Natl Acad Sci U.S.A* 99: 16998-17003.

Connor, J.M., Gatherer, D., Gray F.C., Pirrit, L.A. & Affara, N.A. (1986) Assignment of the gene for dyskeratosis congenita to Xq28. *Hum Genet* 72: 348-351.

Cossu F., Vulliamy T.J., Marrone A., Badiali M., Cao A., and Dokal I. 2002. A novel *DKC1* mutation, severe combined immunodeficiency (T+B-NK- SCID) and bone marrow transplantation in an infant with Hoyeraal-Hreidarsson syndrome. *Br J Haematol* 119: 765-768.

De Boeck K., Degreef H., Verwilghen R, Corbeel L., and Casteels-Van Daele M. 1981. Thrombocytopenia: first symptom in a patient with dyskeratosis congenita. *Pediatrics* 67: 898-903.

de Lange T. 2002. Protection of mammalian telomeres. *Oncogene* 21: 532-540.

- Demiroglu H.**, Alikasifoglu M., and Dundar S. 1997. Dyskeratosis congenita with an unusual chromosomal abnormality. *Br J Haematol* 97: 243-244.
- Devriendt K.**, Matthijs G., Legius E., Schollen E., Blockmans D., van Geet C., Degreef H., Cassiman J.-J., and Fryns J.P. 1997. Skewed X-chromosome inactivation in female carriers of dyskeratosis congenita. *Am J Hum Genet* 60: 581-587.
- Dez C.**, Henras A., Faucon B., Lafontaine D.L.J., Caizergues-Ferrer M., and Henry Y. 2001. Stable expression in yeast of the mature form of human telomerase RNA depends on its association with the box H/ACA small nucleolar RNP proteins Cbf5p, Nhp2p and Nop10p. *Nucleic Acids Res* 29: 598-603.
- Dokal I.**, Bungey J., Williamson P., Oscier D., Hows J., and Luzzatto L. (1992) Dyskeratosis congenita fibroblasts are abnormal and have unbalanced chromosomal rearrangements. *Blood* 80: 3090-3096.
- Dokal I.** 2000. Dyskeratosis congenita in all its forms. *Br J Haematol* 110: 768-779.
- Dokal I.**, and Vulliamy T. 2003. Dyskeratosis congenita: its link to telomerase and aplastic anaemia. *Blood Rev* 17: 217-225.
- Drachtman R.A.**, and Alter B.P. 1995. Dyskeratosis congenita. *Dermatol Clin* 13: 33-39.
- Dror Y.**, Freedman M.H., Leaker M., Verbeek J., Armstrong C.A., Saunders F.E., and Doyle J.J. 2003. Low-intensity hematopoietic stem-cell transplantation across human leucocyte antigen barriers in dyskeratosis congenita. *Bone Marrow Transplant* 31: 847-850.
- Engman M.F.** 1926. A unique case of reticular pigmentation of the skin with atrophy. *Arch Dermatol Syph* 13: 685-687.
- Erduran E.**, Hacisalihoglu S., and Ozoran Y. 2003. Treatment of dyskeratosis congenita with granulocyte-macrophage colony stimulating factor and erythropoietin. *J Pediatr Hematol Oncol* 4: 333-335.
- Filipowicz W.**, and Pogacic V. 2002. Biogenesis of small nucleolar ribonucleoproteins. *Curr Opin Cell Biol* 14: 319-327.
- Fogarty P.F.**, Yamaguchi H., Wiestner A., Baerlocher G.B., Sloand E., Zeng W.S., Read E.J., Lansdorp P.M., and Young N.S. 2003. Late presentation of dyskeratosis congenita as apparently acquired aplastic anaemia due to mutations in telomerase RNA. *Lancet* 362: 1628-1630.
- Forni G.L.**, Melevendi C., Jappelli S., and Rasore-Quartino A. 1993. Dyskeratosis congenita: Unusual presenting features within a kindred. *Paediatr Hematol Oncol* 10: 145-149.
- Friedland M.**, Lutton J.D., Spitzer R., and Levere R.D. 1985. Dyskeratosis congenita with hypoplastic anemia: a stem cell defect. *Am J Hematol* 20: 85-87.
- Fu D.**, and Collins K. 2003. Distinct biogenesis pathways for human telomerase RNA and H/ACA small nucleolar RNAs. *Mol Cell* 11: 1361-1372.
- Ghavamzadeh A.**, Alimoghadam K., Nasser P., Jahani M., Khodabandeh A. & Ghahremani G. 1999. Correction of bone marrow failure in dyskeratosis congenita by bone marrow transplantation. *Bone Marrow Transplant*, 23: 299-301.
- Giordano E.**, Peluso I., Senger S., and Furia M. 1999. minify, a Drosophila gene required for ribosome biogenesis. *J Cell Biol* 144: 1123-1133.
- Gungor T.**, Corbacioglu S., Storb R., and Seger R.A. 2003. Nonmyeloablative allogeneic hematopoietic stem cell transplantation for treatment of dyskeratosis congenita. *Bone Marrow Transplant* 31: 407-410.
- Hassock S.**, Vetrie D., and Giannelli, F. 1999. Mapping and characterization of X-linked dyskeratosis congenita (DKC) gene. *Genomics* 55: 21-27.
- Hathcock K.S.**, Hemann M.T., Opperman K.K., Strong M.A., Greider C.W., and Hodes R.J. 2002. Haploinsufficiency of mTR results in defects in telomere elongation. *Proc Natl Acad Sci U.S.A* 99: 3591-3596.
- Heiss N.S.**, Knight S.W., Vulliamy T.J., Klauck S.M., Wiemann S., Mason P.J., Poustka A., and Dokal I. 1998. X-linked dyskeratosis congenita is caused by mutations in a highly conserved gene with putative nucleolar functions. *Nat Genet* 19: 32-38.
- Heiss N.S.**, Girod A., Saowsky R., Wiemann S., Pepperkok R., and Poustka A. 1999. Dyskerin localises to the nucleolus and its mislocalisation is unlikely to play a role in the pathogenesis of dyskeratosis congenita. *Human Mol Genet* 8: 2515-2524.
- Heiss N.S.**, Megarbane A., Klauck S.M., Kreuz F.R., Makhoul E., Majewski F., and Poustka A. 2001. One novel and two recurrent missense *DKC1* mutations in patients with dyskeratosis congenita (DKC). *Genet Couns* 12: 129-136.
- Henras A.**, Henry Y., Bousquet-Antonelli C., Noaillac-Depeyre J., Gelugne J.P., and Caizergues-Ferrer, . 1998. Nhp2p and Nop10p are essential for the function of H/ACA snoRNPs. *EMBO J* 17: 7078-7090.
- Hiramatsu H.**, Fujii T., Kitoh T., Sawada M., Osaka M., Koami K., Irino T., Miyajima T., Ito M., Sugiyama T., and Okuno T. 2002. A novel missense mutation in the *DKC1* gene in a Japanese family with X-linked dyskeratosis congenita. *Pediatr Hematol Oncol* 19: 413-419.
- Hoyeraal H.M.**, Lamvik J., and Moe P.J. 1970. Congenital hypoplastic thrombocytopenia and

cerebral malformations in two brothers. *Acta Paediatrica Scandinavia* 59: 185-191.

Hreidarsson S., Kristjansson K., Johannesson G., and Johannesson J.H. 1988. A syndrome of progressive pancytopenia with microcephaly, cerebellar hypoplasia and growth failure. *Acta Paediatrica Scandinavia* 77: 773-775.

Jiang, W., Middleton, K., Yoon H.J., Fouquet C. and Carbon J. 1993. An essential yeast protein, CBF5p, binds in vitro to centromeres and microtubules. *Mol Cell Biol* 13, 4884-4893.

Kehrer H., Krone W., Schindler, D., Kaufmann, R., and Schrezenmeier H. 1992. Cytogenetic studies of skin fibroblast cultures from a karyotypically normal female with dyskeratosis congenita. *Clin Genet* 41: 129-134.

Keith W.N., Vulliamy T., Zhao J., Ar C., Erzik C., Bisland A., Ulku B., Marrone A., Mason P.J., Bessler M., Serakinci N., and Dokal I. 2004. A mutation in a functional Sp1 binding site of the telomerase RNA gene (*hTERC*) promoter in a patient with paroxysmal nocturnal haemoglobinuria. *BMC Blood Disorders* 4: 3-11.

Kilic S., Kose H., and Ozturk H. 2003. Pulmonary involvement in patient dyskeratosis congenita. *Pediatr Int* 45: 740-742.

Knight S.W., Vulliamy T., Forni G.L., Oscier D., Mason P.J., and Dokal I. 1996. Fine mapping of the dyskeratosis congenita locus in Xq28. *J Med Genet* 33: 993-995.

Knight S., Vulliamy T., Copplestone A., Gluckman E., Mason P., and Dokal I. 1998a. Dyskeratosis Congenita (DC) Registry: identification of new features of DC. *Br J Haematol* 103: 990-996.

Knight S.W., Vulliamy T.J., Heiss N.S., Matthijs G., Devriendt K., Connor J.M., D'Urso M., Poustka A., Mason P.J., and Dokal, I. 1998b. 1.4 Mb candidate gene region for X-linked dyskeratosis congenita defined by combined haplotype and X-chromosome inactivation analysis. *J Med Genet* 35: 993-996

Knight S.W., Heiss N.S., Vulliamy T.J., Aalfs C.M., McMahon C., Richmond P., Jones A., Hennekam R.C., Poustka A., Mason P.J., and Dokal I. 1999a. Unexplained aplastic anaemia, immunodeficiency, and cerebellar hypoplasia (Hoyeraal-Hreidarsson syndrome) due to mutations in the dyskeratosis congenita gene, *DKC1*. *Br J Haematol* 107: 335-339.

Knight S.W., Heiss N.S., Vulliamy T.J., Greschner S., Stavrides G., Pai G.S., Lestringant G., Varma N., Mason P.J., Dokal I., and Poustka A. 1999b. X-linked dyskeratosis congenita is predominantly caused by missense mutations in the *DKC1* gene. *Am J Hum Genet* 65: 50-58.

Knight S.W., Vulliamy T.J., Morgan B., Devriendt K., Mason P.J., and Dokal I. 2001. Identification of novel *DKC1* mutations in

patients with dyskeratosis congenita: implications for pathophysiology and diagnosis. *Hum Genet* 108: 299-303.

Knudson M., Kulkarni S., Ballas Z., Bessler M., and Goldman F. 2004. Association of immune abnormalities with telomere shortening in autosomal dominant dyskeratosis congenita. *Blood*. (Epub ahead of print).

Lafontaine D.L., Bousquet-Antonelli C., and Henry Y. 1998. The box H+ACA snoRNAs carry Cbf5p, the putative pseudouridine synthase. *Genes Dev* 12: 527-537.

Langston A.A., Sanders J.E., Deeg H.J., Crawford S.W., Anasetti C., Sullivan K.M., Flowers M.E.D., and Storb R. 1996. Allogeneic marrow transplantation for aplastic anaemia associated with dyskeratosis congenita. *Br J Haematol* 92: 758-765.

Lau Y.L., Ha S.Y., Chan C.F., Lee A.C.W., Liang R.H.S., and Yuen H.L. 1999. Bone marrow transplant for dyskeratosis congenita. *Br J Haematol* 105: 571.

Lee H.W., Blasco M.A., Gottlieb G.J. *et al.* 1998. Essential role of mouse telomerase in highly proliferative organs. *Nature* 392: 569-574.

Lin J.H., Lee J.Y., Tsao C.J., and Chao S.C. 2002. *DKC1* gene mutation in a Taiwanese kindred with X-linked dyskeratosis congenita. *Kaohsiung J Med Sci* 18: 573-577.

Luzzatto L., and Karadimitris A. 1998. Dyskeratosis and ribosomal rebellion. *Nat Genet* 19: 6-7.

Ly H., Blackburn E.H., and Parslow T.G. 2003. Comprehensive structure-function analysis of the core domain of human telomerase RNA. *Mol Cell Biol* 23: 6849-6856.

Mahmood F., King M.D., Smyth O.P., and Farrell M.A. 1998. Familial cerebellar hypoplasia and pancytopenia without chromosomal breakages. *Neuropediatrics* 29: 302-306.

Marciniak R., and Guarente L. 2001. Testing telomerase. *Nature* 413: 370-373.

Marley S.B., Lewis J.L., Davidson R.J., Roberts I.A.G., Dokal I., Goldman J.M., and Gordon M.Y. 1999. Evidence of a continuous decline in haemopoietic function from birth: application to evaluating bone marrow failure in children. *Br J Haematol* 106: 162-166.

Marrone A., Stevens D., Vulliamy T., Dokal I., and Mason P.J. 2004. Heterozygous telomerase RNA mutations found in dyskeratosis congenita and aplastic anaemia reduce telomerase activity via haploinsufficiency. *Blood*. (Epub ahead of print).

Marsh C.W., Will A.J., Hows J.H, Sartori P., Derbyshire P., Williamson P.J., Oscier D.G., Dexter T.M., and Testa N.G. 1992. "Stem cell" origin of the hematopoietic defect in dyskeratosis congenita. *Blood* 79: 3138-3144.

- McEachern** M.J., Krauskopf A., and Blackburn E.H. Telomeres and their control. 2000. *Annu Rev Genet* 34: 331-358.
- Meier** U.T., and Blobel G. 1994. NAP57, a mammalian nucleolar protein with a putative homolog in yeast and bacteria. *J Cell Biol* 127: 1505-1514.
- Meier** U.T. 2003. Dissecting dyskeratosis. *Nat Genet* 33: 116-117.
- Mitchell** J.R., Cheng J., and Collins K. 1999a. A box H/ACA small nucleolar RNA-like domain at the human telomerase RNA 3' end. *Mol Cell Biol* 19: 567-576.
- Mitchell** J.R., Wood E., and Collins K. 1999b. A telomerase component is defective in the human disease dyskeratosis congenita. *Nature* 402: 551-555.
- Mochizuki** Y., He J., Kulkarni S., Bessler M., and Mason P.J. 2004. Mouse dyskerin mutations affect accumulation of telomerase RNA and small nucleolar RNA, telomerase activity, and ribosomal RNA processing. *Proc Natl Acad Sci U.S.A* 101: 10756-10761.
- Montanaro** L., Chillo A., Treme D., Pession A., Gouoni M., Tazzari P.L., and Derenzini M. 2002. Increased mortality rate and not impaired ribosomal biogenesis is responsible for proliferation defect in dyskeratosis congenita cell lines. *J Invest Dermatol* 118: 193-198.
- Nespoli** L., Lascari C., Maccario R., Nosetti L., Broggi U., Locatelli F., Binda S., Gaudio, F., Casalone R., and Bosi, F. 1997. The Hoyeraal-Hreidarsson syndrome: the presentation of the seventh case. *Eur J Pediatr* 156: 818-820.
- Ni** J., Tien A.L., and Fournier, M.J. 1997. Small nucleolar RNAs direct site-specific synthesis of pseudouridine in ribosomal RNA. *Cell* 89: 565-573.
- Nobili** B., Rossi G., De Stefano P., Zecca M, Giorgiani G., Canazzio A., and Locatelli F. 2002. Successful umbilical cord blood transplantation in a child with dyskeratosis congenita after a fludarabine-based reduced-intensity conditioning regimen. *Br J Haematol* 119: 573-574.
- Ohga** S., Kai T., Honda K., Nakayama H., Inamitsu T., and Ueda K. 1997. What are the essential symptoms in the Hoyeraal-Hreidarsson syndrome? *Eur J Pediatr* 156: 80-81.
- Paul** S.R. Perez-Atayde A., and Williams D.A. 1992. Interstitial pulmonary disease associated with dyskeratosis congenita. *Am J Pediatr Hematol/Oncol* 14:89-92.
- Philips** R.J., Judge M., Webb D., and Harper J.I. 1992. Dyskeratosis congenita: delay in diagnosis and successful treatment of pancytopenia by bone marrow transplantation. *Br J Dermatol* 127: 278-280.
- Philips** B., Billin A.N., Cadwell C., Buchholz R., Erickson C., Merriam J.R., Carbon J., and Poole S.J. 1998. The Nop60B gene of *Drosophila* encodes an essential nucleolar protein that functions in yeast. *Mol Gen Genet* 260: 20-29.
- Pogacic** V., Dragon F., and Filipowicz W. 2000. Human H/ACA small nucleolar RNPs and telomerase share evolutionarily conserved proteins NHP2 and NOP10. *Mol Cell Biol* 20: 9028-9040.
- Ren** X., Gavory G., Li H., Ying L., Klenerman D., and Balasubramanian S. 2003. Identification of a new RNA:RNA interaction site for human telomerase RNA (hTR): structural implications for hTR accumulation and a dyskeratosis congenita point mutation. *Nucleic Acids Res* 31: 6509-6515.
- Rocha** V., Devergie A., Socie G., Ribaud P., Esperou H., Parquet N., and Gluckman E. Unusual complications after bone marrow transplantation for dyskeratosis congenita. *Br J Haematol* 103: 243-248.
- Rose** C., and Kern W.V. 1992. Another case of *Pneumocystis carinii* pneumonia in a patient with dyskeratosis congenita (Zinsser-Cole-Engman syndrome)[letter]. *Clinical Infectious Diseases* 15: 1056-1057.
- Rudolph** K.L., Chang S., Lee H.W., Blasco M., Gottlieb G.J., Greider C., and DePinho R.A. 1999. Longevity, stress response, and cancer in aging telomerase-deficient mice. *Cell* 96: 701-712.
- Ruggero** D., Grisendi S., Piazza F., Rego E., Mari F., Rao P.H., Cordon-Cardo C., and Pandolfi P.P. 2003. Dyskeratosis congenita and cancer in mice deficient in ribosomal RNA modification. *Science* 299: 259-262.
- Russo** C.L., Glader B.E., Israel R.J., and Galasso F. 1990. Treatment of neutropenia associated with dyskeratosis congenita with granulocyte-macrophage colony-stimulating factor. *Lancet* 336: 751-752.
- Safa** W.F., Lestringant G.G., and Frossard P.M. 2001. X-linked dyskeratosis congenita: restrictive pulmonary disease and a novel mutation. *Thorax* 56: 891-894.
- Scappaticci** S., Fraccaro M., and Cerimele, D. 1989. Chromosomal abnormalities in dyskeratosis congenita. *Am J Med Genet* 34: 609-610.
- Salowsky** R., Heiss N.S., Benner A., Wittig R., and Poustka A. 2002. Basal transcription activity of the dyskeratosis congenita gene is mediated by Sp1 and Sp3 and a patient mutation in a Sp1 binding site is associated with decreased promoter activity. *Gene* 293: 9-19.
- Scappaticci** S., Fraccaro M., and Cerimele D. 1989. Chromosomal abnormalities in dyskeratosis congenita. *Am J Med Genet* 34: 609-610.
- Sirinavin** C., and Trowbridge A. 1975. Dyskeratosis congenita: clinical features and

genetic aspects. Report of a family and review of the literature. *J Med Genet* 12: 339-354.

Smith, C.M., Ramsay N.K.C., Branda R., Nesbit M.E., and Krivit W. 1979. Response to androgens in the constitutional aplastic anemia of dyskeratosis congenita. *Pediatr Research* 13: 441.

Sznajder Y., Baumann C., David A., Journal H., Lacombe D., Perel Y., Segura J.F., Cezard J.P., Peuchmaur M., Vulliamy T., Dokal I., and Verloes A. 2003. Further delineation of the congenital form of X-linked dyskeratosis congenita (Hoyeraal-Hreidarsson syndrome). *Eur J Pediatr* 162: 863-867

Solder B., Weiss M., Jager A., and Belohradsky B.H. 1998. Dyskeratosis congenita: Multisystem disorder with special consideration of immunologic aspects. *Clin Pediatr* 19: 32-38.

Theimer C.A., Finger L.D., Trantirek L., and Feigon J. 2003a. Mutations linked to dyskeratosis congenita cause changes in the structural equilibrium in telomerase RNA. *Proc Natl Acad Sci U.S.A* 100: 449-454.

Theimer C.A., Finger L.D., and Feigon J. 2003b. YNMG tetraloop formation by a dyskeratosis congenita mutation in human telomerase RNA. *RNA* 9: 1446-1455.

Tollervey D., and Kiss T. 1997. Function and synthesis of small nucleolar RNAs. *Curr Opin Cell Biol* 9: 337-342.

Vulliamy T.J., Knight S.W., Dokal I., and Mason P.J. 1997. Skewed X-inactivation in carriers of X-linked dyskeratosis congenita. *Blood* 90: 2213-2216.

Vulliamy T.J., Knight S.W., Heiss N.S., Smith O.P., Poustka A., Dokal I., and Mason P.J. 1999. Dyskeratosis congenita caused by a 3' deletion: germline and somatic mosaicism in a female carrier. *Blood* 94: 1254-1260.

Vulliamy T.J., Knight S.W., Mason P.J., and Dokal I. 2001a. Very short telomeres in the peripheral blood of patients with X-linked and autosomal dyskeratosis congenita. *Blood Cells Mol Dis* 27: 353-357.

Vulliamy T., Marrone A., Goldman F., Dearlove A., Bessler M., Mason P.J., and Dokal I. 2001b. The RNA component of telomerase is mutated in autosomal dominant dyskeratosis congenita. *Nature* 413: 432-435.

Vulliamy T., Marrone A., Dokal I., and Mason P.J. 2002. Association between aplastic anaemia and mutations in telomerase RNA. *Lancet* 359: 2168-2170.

Vulliamy T., Marrone A., Szydlo R., Walne A., Mason P.J., and Dokal I. 2004. Disease anticipation is associated with progressive

telomere shortening in families with dyskeratosis congenita due to mutations in *TERC*. *Nat Genet* 36: 447-449.

Verra F., Kouzan S., Saiag B., Bignon J., and de-Cremoux H. 1992. Bronchoalveolar disease in dyskeratosis congenita. *Eur Resp J* 5: 497-499.

Wang C., and Meier U.T. 2004. Architecture and assembly of mammalian H/ACA small nucleolar and telomerase ribonucleoproteins. *EBMO J* 23: 1857-1867.

Watkins N.J. A., Gottschalk G., Neubauer B., Kastner P., Fabrizio M., Mann, M. & Luhrmann, R. 1998. Cbf5p, a potential pseudouridine synthase, and Nhp2p, a putative RNA-binding protein, are present together with Gar1p in all H BOX/ACA-multi snoRNPs and constitute a common bipartite structure. *RNA* 4: 1549-1568.

Wiedemann H.P., McGuire J., Dwyer J.M., Sabetta J., Gee J.B., Smith G.J., and Loke J. 1984. Progressive immune failure in dyskeratosis congenita. Report of an adult in whom *Pneumocystis carinii* and fatal disseminated candidiasis developed. *Arch Int Med* 144: 397-399.

Wong J.M.Y., Kyasa M.J., Hutchins L., and Collins K. 2004. Telomerase RNA deficiency in peripheral blood mononuclear cells in X-linked dyskeratosis congenita. *Hum Genet* 115: 448-455.

Yabe M., Yabe H., Hattori K., Morimoto T., Hinoara T., Takakura I., Shimamura K., Tang, X., and Kato S. 1997. Fatal interstitial pulmonary disease in a patient with DC after allogeneic bone marrow transplantation. *Bone Marrow Transplant* 19: 389-392.

Yaghai R., Kimyai-Asadi A., Rostamiani K., Heiss N.S., Poustka A., Eyaid W., Bodurtha J., Nousari H.C., Hamosh A., and Metzenberg A. 2000. Overlap of dyskeratosis congenita with the Hoyeraal-Hreidarsson syndrome. *J Pediatr* 136: 390-393.

Yamaguchi H., Baerlocher G.M., Lansdorp P.M., Chanock S.J., Nunez O., Sloand E., and Young N.S. 2003a. Mutations of the human telomerase RNA gene (*TERC*) in aplastic anemia and myelodysplastic syndrome. *Blood* 102: 916-918.

Youssofian H., Gharibyan V., and Qatanani M. 1999. Analysis of epitope-tagged forms of the dyskeratosis congenita protein (dyskerin): Identification of a nuclear localization signal. *Blood Cells Mol Dis* 25: 305-309.

Zinsser F. 1906. Atrophia cutis reticularis cum pigmentatione, dystrophia ungiomet leukoplakia oris. *Ikonogr Dermatol (Hyoto)* 5: 219-22