Current status of Telomere Biology Disorders in Inherited Bone Marrow Failure

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Telomere biology disorders (TBDs) are a group of multi-system diseases exhibiting marked clinical and genetic heterogeneity. The recognition of these disorders came through studies on dyskeratosis congenita (DC) which is now considered to be the paradigm telomere biology disorder. DC and TBDs are characterized by variable muco-cutaneous abnormalities (abnormal skin pigmentation, nail dystrophy, leucoplakia), bone marrow failure and a predisposition to malignancy. Bone marrow failure is the principal cause of mortality and patients display features of premature aging.

Studies over the last three decades have led to significant advances with several disease genes [*DKC1* (1998), *TERC* (2001), *TERT* (2005), *NOP10* (2007), *NHP2* (2008), *TINF2* (2008), *USB1* (2010), *TCAB1* (2011), *CTC1* (2012), *RTEL1* (2013), *ACD* (2014), *PARN* (2015), *POT1* (2016), *STN1* (2016), *NAF1* (2016), *ZCCHC8* (2019), *NPM1* (2019), *MDM4* (2020), *DCLRE1B* (2022), *RPA1* (2022), *TYMS-ENOSF1* (2022), *POLA1* (2024), *RPA2* (2024), *POLA2* (2025)] having been characterized. Most of these genes have fundamental roles in telomere maintenance: they encode components that constitute the telomerase holoenzyme (TERC, TERT, DKC1, NOP10, NHP2, NAF1), telomerase trafficking (TCAB1), the shelterin complex (ACD/TPP1, POT1, TINF2), telomere replication (RTEL1, CTC1, STN1, POLA1), and are required for processing of the telomere genes (PARN). TBDs therefore, are principally diseases of defective telomere maintenance, and patients usually have very short/and or abnormal telomeres. However, many of these genes also have other functions: DKC1, NOP10, NHP2 and NAF1 are all important in ribosome biogenesis, and this may contribute to the pleiotropic nature of these disorders.

The genetic advances have also led to the association of dyskeratosis congenita with several other diseases. This includes the severe multi-system disorders Hoyeraal-Hreidarsson (1999), Revesz (2008), Coats plus (2012) syndrome, and subsets of patients with aplastic anaemia (2002), myelodysplasia (2003), leukaemia (2009), liver disease (2009) and idiopathic pulmonary fibrosis (2007). This wide spectrum of diseases ranging from syndromic dyskeratosis congenita to aplastic anaemia can now be regarded principally as disorders of defective telomere maintenance - “the telomeropathies” or “telomere biology disorders”.

In the clinic, this has translated into improvements in diagnosis (based on telomere length measurement and genetic analysis of 23 disease genes) and clinical outcomes. Patients with bone marrow failure arising primarily from defective telomere maintenance show good responses to drugs such as danazol rather than conventional immunosuppressive agents employed in idiopathic forms of aplastic anaemia. Genetic tests based on next generation sequencing are proving very helpful in diagnosing patients, particularly those with atypical presentations.

In conclusion, studies initially focusing on dyskeratosis congenita, have shown the importance of telomere maintenance in human physiology including normal haematopoieticfunction. Defective telomere maintenance arising from germline disease gene variants has subsequently been shown to be associated with a wide range of clinical phenotypes including bone marrow failure and leukaemia – “telomere biology disorders”. The treatmentof the haematological defects associated with telomere biology disorders requires careful use of danazol and related drugs. Currently, the only curative therapy for the haematological defects is low intensity fludarabine based haematopoietic stem cell transplantation. Future strategies that can correct the telomere defect may lead to promising new treatments.