

# Chapter 1

## Introduction

### An Introduction to the Second Edition of the Telomere Biology Disorders Diagnosis and Management Guidelines

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It is with both great pride and humility that I introduce you to the second edition of the Telomere Biology Disorders Diagnosis and Management Guidelines. The pride stems from watching Team Telomere grow from the fledgling group known as Dyskeratosis Congenita Outreach to a global advocacy, education, and outreach organization. My humility as an editor of the second edition and a telomere biology disorder researcher comes from the recognition that our discoveries of the clinical manifestations and genetic causes of these disorders are just the beginning.

Dyskeratosis congenita (DC) was first described between 1906 and 1910 [1]. The initial reports suggested X-linked recessive inheritance since only males were affected. However, the first female case was published in 1963, and we now know that both males and females can be affected with DC [2]. A slight male predominance remains due to pathogenic variants (mutations) in the dyskerin (*DKC1*) gene located on the X chromosome. Dr. Inderjeet Dokal's research group identified mutations in *DKC1* as the cause of X-linked DC in 1998 [3]. Basic science studies showed that *DKC1* mutations led to abnormal dyskerin protein, very short telomeres, and low levels of telomerase in

patient cells [4]. These studies were the very first to link telomere biology to inherited disease.

Subsequent studies included sequencing genes encoding components of the telomerase enzyme complex in families with DC and the development of leukocyte telomere length measurement by flow cytometry with fluorescent *in situ* hybridization (flow FISH) as the diagnostic test for DC [5-9]. Telomere length, instead of complex clinical manifestations, was key to the discovery of mutations in *TINF2* as a cause of DC [10]. Around the same time, researchers also found mutations in telomere biology genes in families with apparently isolated pulmonary fibrosis [11, 12]. The 2003 completion of the first draft DNA sequence of the human genome led to a genomic revolution, making it possible and affordable to effectively and efficiently identify the genetic causes of many disorders. Pathogenic variants (*i.e.*, germline mutations) in at least 15 different telomere biology genes have since been identified and associated with a spectrum of manifestations, from very early childhood to adult-onset illnesses associated with telomeres ranging from significantly less than the 1<sup>st</sup> percentile to the 10<sup>th</sup> percentile for age [13, 14].

These breakthroughs over the last decade led to a growing appreciation of the clinical spectrum of illnesses now called the telomere biology disorders (TBDs). Some people have childhood onset of bone marrow failure, physical manifestations, and many other complications due to X-linked or autosomal recessive pathogenic variants, whereas others may not manifest a TBD until they develop pulmonary fibrosis in middle age. Telomere lengths are also associated with the mode of inheritance and clinical manifestations [7, 15-17]. Connecting these rare disorders through biology helps ensure that a breakthrough, for example, in pulmonary fibrosis due to a heterozygous pathogenic *TERT* variant could also potentially benefit a patient with DC due to biallelic pathogenic *TERT* variants.

These clinical care guidelines are the result of a multi-disciplinary international collaboration between clinicians and scientists united by the goal of improving the lives

of people with TBDs. The clinical management recommendations are based on expert opinions of the chapter authors, reviewers, and editors. While there are ongoing hematopoietic cell transplantation and danazol treatment trials, there are currently no evidence-based TBD-specific clinical management guidelines. It is very important that the care of each person affected by a TBD be multi-disciplinary and specifically tailored to their needs.

So, what is in a name and especially in a long name, Telomere Biology Disorder, with an abbreviation – TBD – that can mean other things (to be determined)? It comes down to their root cause: abnormalities in telomere biology resulting in a spectrum of overlapping illnesses. Understanding the causes and complications of TBDs is the first step. Collaboration between research, clinical, and patient communities will ensure there are many future next steps aimed at improving the lives of all those affected by TBDs.

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