Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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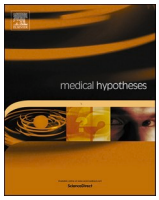

Letter to Editors

Are Dyskeratosis Congenita patients at higher risk of symptomatic COVID-19?

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ABSTRACT

Dyskeratosis Congenita (DC) is a rare and heterogeneous disease. This disorder is resulted from a defect in the telomere maintenance in stem cells. Telomerase RNA component, shelterin complex, and telomerase reverse transcriptase are mutated in this disease. Many studies have previously confirmed shorter leukocyte telomere length in DC. On the other hand, the association between telomere length and Coronavirus disease 2019 (COVID-19) indicated that people with a short telomere background mostly show more severe symptoms related to COVID-19, and the mortality rate among them increases as well. Because patients with DC have an abnormally short telomere length, in the current study, we hypothesized that they are at higher risk of developing symptomatic COVID-19 that requires further clinical care.

Dear editor

Dyskeratosis Congenita (DC) is a rare disease with a prevalence of 1 in 1/000/000 [1]. Although DC been reported in about 400 families worldwide, this complex disorder accounts for about 1% of all telomere syndromes. This congenital disorder can be inherited as Autosomal Recessive, Autosomal Dominant, and X-Link [2]. Moreover, DC is a disorder occurring in its classical form in several systems with a triad of skin abnormalities, nails, and oral leukoplakia (white spots on the inside of the mouth) or in the presence of one of the features of the triad in combination with Bone Marrow Failure (BMF) as well as two other related findings [3]. The leading cause of death in these patients is BMF; however, Pulmonary Fibrosis, cancer, and hepatic cirrhosis play a significant role in the death of these patients [4]. At the genetic level, DC is almost heterogeneous. The role of genes involved in this disease is the protection of telomere length, which in various studies was referred to as a very short telomere in these patients, which is due to a lack of protection of telomere length (Table 1) [5]. Telomere dysfunction can be resulted from the loss of telomere; for example, due to telomerase deficiency or loss, consequently leading to inappropriate activation of DNA repair pathways [6]. The reason for the decreased telomere length that generally shows its symptoms in the skin, blood, and nails, is that these tissues have a high self-renewable property. This self-renewability depends on the stem cells in these tissues. In stem cells, telomerase activity is high (telomere lengths are almost constant). Therefore, any defect in telomerase or other factors affecting telomere length will damage stem cells and impair tissue renewability [7]. Telomere shortening, as a major molecular factor, plays a significant role in the aging process. Thus, telomeres act as “clocks” determining the lifetime of the cell surface. The emergence of telomeres can lead to short-lived telomeres that cause cell aging or cellular crisis, including apoptosis, genomic instability, and shortening cell lifespan [8].

Several studies have previously shown that, due to mutations in telomere-related genes, almost all known patients with DC have short telomeres in most of their leukocyte subsets [9–11]. In December 2019, some cases of pneumonia with unknown origin were identified in Wuhan, China. Genome sequencing showed that Coronavirus disease 2019 (COVID-19) is a distinct class of viruses associated with both human severe acute respiratory syndrome and Middle East Respiratory Syndrome [12]. The disease has rapidly spread from China to other countries. In 2020, the World Health Organization declared the COVID-19 as a pandemic. The virus is a single-stranded RNA thought to be the receptor for the angiotensin-converting enzyme 2, which is a major receptor for the virus to enter the cell and then cause the infection [13]. The virus tends to target the upper respiratory tract, causing moderate to severe type of disease illness (such as colds) or severe disease (such as pneumonia). While most cases of COVID-19 are mild, the more severe form can lead to respiratory failure, septic shock, or multiple organ dysfunction [14].

According to recent findings in this regard, the researchers found an association between telomere length and COVID-19 disease severity. Vazquez et al. in their study have evaluated 89 patients with COVID-19 for telomere length and found that patients with severe type of the disease had a shorter telomere compared to patients with mild symptoms [15]. Wang et al. in a study on 6775 participants with positive test for COVID-19, have reported that individuals with shorter leukocyte telomere length had higher risk of developing adverse outcomes and hospitalization [16]. Another study found a link between telomere length and T- cell lymphopoiesis. Shorter telomeres decrease T-cell counts (lymphopenia) and increase mortality rate due to COVID-19 [17]. According to these studies, telomere length (TL) is directly related to the severe type of COVID −19 disease and we hypothesized that patients with a short telomere background (telomeropathies) like DC, mostly experience more severe symptoms of COVID −19 and they need more care. On the other hand, due to the short telomere, these patients are not able to regenerate tissue, especially the lungs, and if

Abbreviations: DC, Dyskeratosis Congenita; BMF, Bone Marrow Failure; COVID-19, Coronavirus disease 2019; TL, Telomere Length.

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Table 1
Dyskeratosis congenita genes and related disorders Online Mendelian Inheritance in Man (OMIM).

GENE/OMIM NUMBER	PROTEIN FUNCTION	DISORDERS/INHERITANCE
TERT (187270)	Reverse transcriptase in telomerase	DC (AD, AR) Leukemia-acute myeloid (AD) Pulmonary fibrosis and/or bone marrow failure (AD)
TERC (602322)	RNA template in telomerase for addition telomeric repeat	Aplastic anemia (AD) Pulmonary fibrosis idiopathic (AD) DC (AD)
DKC1 (300126)	Component of telomerase	DC (X-linked)
NOP10/ NOLA3 (606471)	Component of telomerase	DC (AR)
NHP2/NOLA2 (606470)	Component of telomerase	DC (AR)
TINF2/TIN2 (604319)	Component of shelterin	DC (AD) Revesz syndrome (AD)
TPP1/ACD (609377)	Component of shelterin	DC (AD, AR)
TCAB1 (612661)	Recruitment telomerase to Cajal body	DC (AR)
RTEL1 (608833)	Prevent the formation of the second structure in G-overhang and T-loop unwinding	DC (AD, AR) Pulmonary fibrosis and/or bone marrow failure (AD)
PARN (604212)	Degrades poly(A) tail in 3′ end TR	DC (AR) Pulmonary fibrosis and/or bone marrow failure (AD)

they get COVID-19, they are more likely to have lung fibrosis.

In conclusion, it was shown that TL plays a role in causing the severe type of COVID-19 disease. According to the performed studies, the hypothesis is that TL in patients with congenital defects in genes involved in telomere homeostasis (like DC) have shorter telomere than normal people, so they need more care because they possibly are at higher risk of developing symptomatic COVID-19.

Consent statement/Ethical approval

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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