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Blood 142 (2023) 5668–5669

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

509.BONE MARROW FAILURE AND CANCER PREDISPOSITION SYNDROMES: CONGENITAL

Germline Variant in *ZCCHC8* Is Associated with Pulmonary Fibrosis, Bone Marrow Failure, Liver Inflammation, Early Grey Hair and Short Telomer Length

Nikolaj Juul Nitschke, MD[1,2], *Anne Marie Jelsig, MD PhD*[3], *Mette Klarskov Andersen, MDPhD*[4], *Kirsten Grønbæk, MD DMSc*[5,6,7]

[1] Biotech Research and Innovation Centre (BRIC), Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[2] Department of Hematology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[3] Department of Clinical Genetics, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[4] Department of Clinical Genetics, Centre of Diagnostic Investigations, Copenhagen University Hospital, Copenhagen, Denmark
[5] Department of Hematology, Rigshospitalet, Copenhagen, Denmark
[6] Biotech Research and Innovation Centre, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[7] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Introduction

Telomere biology disorders (TBD) encompass rare genetic conditions that affect telomere function. TBD is associated with a wide range of symptoms, including hematologic, dermatologic, pulmonary, hepatic manifestations. Research is continuously identifying novel variants and genes causative of TBD. In a recent study, Gable et al. (2019) detected a germline missense variant in *ZCCHC8* (NM_017612.5:c.557C>T; p.(Pro186Leu)) in a single family with pulmonary fibrosis. This *ZCCHC8* variant was associated with short telomere length (TL) and pulmonary fibrosis. To the best of our knowledge, no other families or individuals have been reported to have pathogenic variants in *ZCCHC8* and TBD . However, in this abstract, we present data from a second family discovered to harbor a pathogenic variant in *ZCCHC8* and to have symptoms of TBD.

Methods

Family members provided informed consent for genetic testing and underwent trio-based whole-genome sequencing (WGS). DNA isolated from fkin-derived fibroblasts was analyzed in the proband, while DNA from whole blood was used for the parents. To measure TL, we employed Computel (Nersisyan L. et al., 2015) and compared the mean TL to a cohort of patients who also underwent WGS to estimate a relative mean TL.

Results:

The proband was a 14-year-old male who had pancytopenia and elevated ALAT levels at presentation. A bone marrow biopsy showed a hypocellular bone marrow. A liver biopsy revealed mild centrilobular, pericellular, and portal fibrosis, along with mild inflammation in the portal space, these findings were interpreted as liver regeneration following acute hepatitis. Despite thorough investigations, no explanation for the findings was found. The proband had a history of psychogenic non-epileptic seizures. When the patient was around 20 years of age his hair started to gray. At present, the proband is 23 years old and has not experienced any progression of symptoms.

Family history revealed that the proband's father and two second-degree relatives on the paternal side of the family had developed pulmonary fibrosis in the fifth and sixth decade of life as well as early grey hair. Thus, the inheritance pattern of disease related to TBD was autosomal dominant.

WGS revealed a heterozygous pathogenic variant in *ZCCHC8* (NM_017612.5c.557C>T (p.P186L)) present in the proband and the father which was absent in the mother. The variant was the same as reported by Gable et al. (2019). The variant is not present in gnomAD or COSMIC and it is the only reported pathogenic or likely pathogenic *ZCCHC8* missense variant in ClinVar to date.

Both the proband and the father exhibited short relative mean TL by Computel estimation. Subsequently, Flow-FISH analysis confirmed that the proband's telomere length was below the 1st percentile.

Conclusion

Here we present a family with a heterozygous germline variant in *ZCCHC8* and TBD including pulmonary fibrosis, pancytopenia, early graying of the hair, and liver disease. Thus, we provide strong evidence of an association between TBD and *ZCCHC8*.

Disclosures Grønbæk: *Kirsten Grønbæk received research support from Janssen and is on the advisory board of Nanexa and GSK.:* Consultancy, Research Funding.

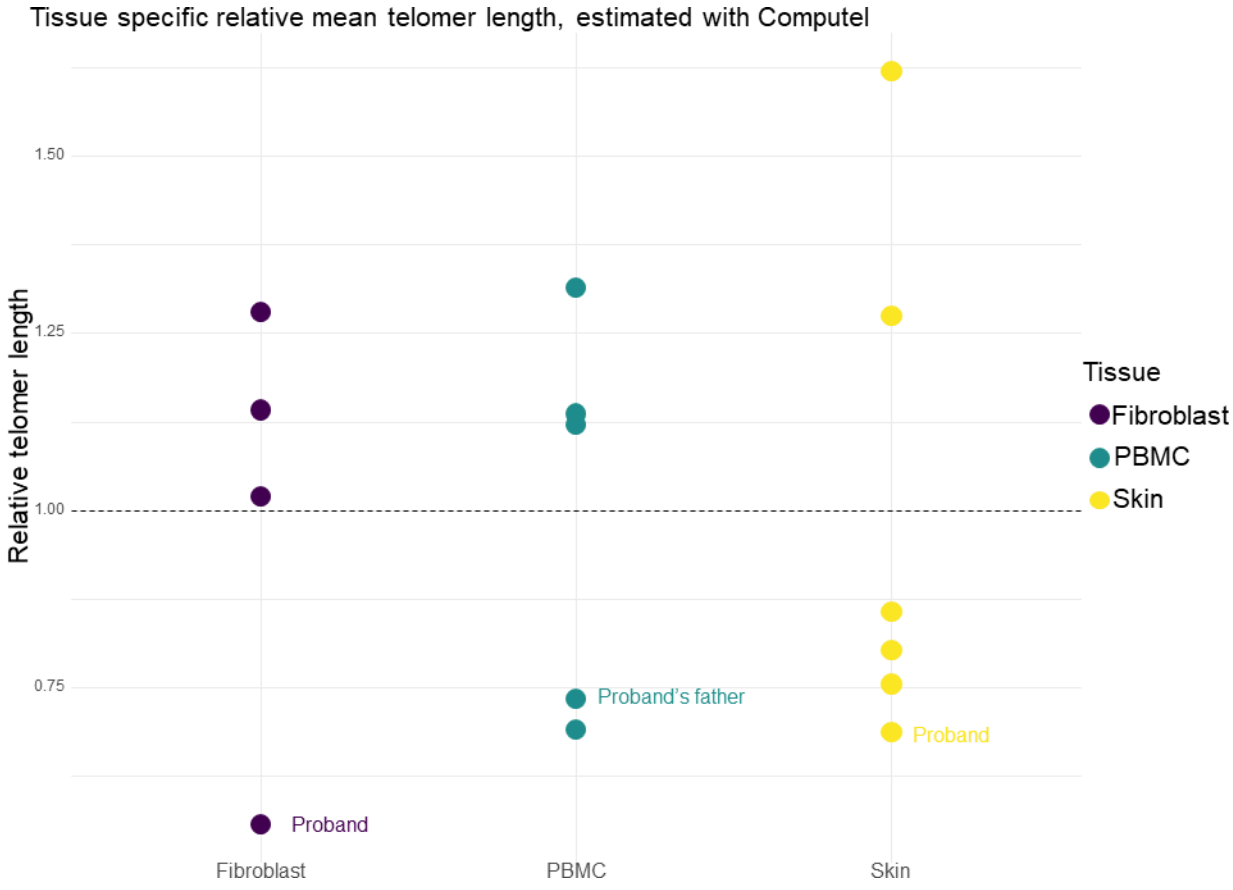

Figure 1

https://doi.org/10.1182/blood-2023-174452