Reviewer’s report

Title: Development of metachronous rectal cancers in a young man with dyskeratosis congenita: A case report

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Reviewer: Stefan Aretz

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General

The authors report on a young Japanese patient with suspected dyskeratosis congenita and early-onset (metachronous) rectal cancer where a potentially causative DKC1 germline variant was identified. This case report is of potential interest to further explore the functional relevance of specific DKC1 germline variants and the phenotypic variability associated with DKC1 variants. However, the authors should address and clarify several issues to increase the value of this study.

Specific comments

1. Beside of bone marrow failure and early-onset (metachronous) rectal cancer the patient seem to have no specific DC-related symptoms. Thus, the clinical diagnostic criteria seem not to be met and DC is just a suspected but not a clinically confirmed diagnosis. Was the patient specifically examined for other typical DC-related symptoms?

2. Were the parents and the two brothers carefully examined for specific DC-related symptoms? May there be other affected members is the maternal branch of the family?

3. Can the authors exclude that the second rectal cancer was not just a relapse of the first cancer instead of a second, independent rectal cancer? As stated, at least the third cancer with 19 years of age was a relapse, and thus, "multiple" rectal cancers (page 7, line 22) are not more than a maximum of two.
4. Usually, analysis of telomere length is part of the routine diagnostic work-up of patients suspected to have DC to identify short telomeres, e.g. by multicolor flow cytometry FISH. It is not clear to me why this examination was not done or possible.

5. Page 7, line 8: the authors stated that the DKC1 variant was confirmed to be a germline variant by analysing normal tissue. What kind of normal tissue was used? Was it clearly spatial separated from tumor tissue? Why a blood sample (leukocyte DNA) was not used?

6. The degree of evidence to classify the identified putative missense germline variant c.361A>G as being causative for the symptoms of the patient or DC, respectively, is not clear and needs further work-up. It was reported as causative in another study, but the evidence for this classification is not described and the published patients for this and another nearby putative missense variant had a different phenotype, i.e. a severe course in contrast to the mild phenotype of the patient in the present report. Thus, it is important to better describe the variant: does it fit to the known germline mutation spectrum of DC with respect to distribution of variants across the gene and mutation type (truncating, missense mutations)? Is it a conserved amino acid, can it affect splicing? Is it listed in population-based databases such as dbSNP, ExAC, genomAD, and if so, what about the frequency?

7. A first and simple way to further elucidate the functional relevance of the variant would be a segregation analysis within the family: Does one of the unaffected brothers carry the variant as well?

Minor issues

1. Page 5, line 26: "… and pathogenic germline variants have been identified …":

2. Page 6: I am not familial with the abbreviations "Rb" and "tub2". Authors might explain briefly.
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