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Title: NEW TERT VARIANT IN A FAMILY WITH APLASTIC ANEMIA

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Background:

TERT gene, the most frequently mutated gene in patients with telomere biology disorders (telomeropathies), encode telomerase reverse transcriptase enzyme. Heterozygous variants in the *TERT* gene impair telomerase activity by haploinsufficiency and pathogenic variants are associated with bone marrow failure syndrome and acute myeloid leukemia predisposition. *TERT* variants show incomplete penetrance and can also be found in asymptomatic family members. Some patients with telomeropathies present with severe symptoms at early age, and in other diseases may appear later in life like aplastic anemia, pulmonary or hepatic fibrosis. Affected families may show anticipation that may result in more severe forms of the disease in succeeding generations. Due to the rarity of the disease and the small number of clinical trials, telomeropathies are often unrecognized and misdiagnosed.

Aims:

To report a novel variant in *TERT* gene in familial hematopoietic disorder.

Methods:

Next Generation Sequencing of DNA isolated from peripheral blood of a patient (older sister) with clinical diagnosis of aplastic anemia, using TruSight One MiSeq platform (Illumina®) and segregation sequencing analysis of patient's mother and younger sister.

Results:

We analyzed all three family members presented with a similar clinical appearance and hematology findings (moderate megaloblastic pancytopenia). Mother was diagnosed at age 14, but reevaluated before delivery in 2001 as hypoplastic MDS and trisomy 8 in karyotype with marked thrombocytopenia, being stable for years. Two daughters, both diagnosed as familiar aplastic anemia with normal karyotype, without elements of Fanconi anemia, at age of 13 and 14 yrs, also with profound thrombocytopenia without severe bleeding episodes. Moreover, lung and liver fibrosis were excluded. We identified a novel missense heterozygous variant c.2605G>A p.(Asp869Asn) in *TERT* gene in all three family members. This variant results in replacement of aspartic amino acid on 869 position in TERT enzyme polypeptide chain by asparagine. According to ACMG classification, detected variant is characterized as likely pathogenic, class 2. This variant is very rare and was detected in gnomAD exomes and gnomAD genomes data bases. It is located in highly conserved protein region and is very likely to disrupt the function of the enzyme.

Summary/Conclusion:

As patients with telomeropathies often have a history of macrocytosis and mild to moderate thrombocytopenia, that can be wrongly diagnosed as immune-mediated thrombocytopenia, myelodysplastic syndrome or moderate aplastic anemia, our findings indicate that *TERT* rare variants pass under-recognized in these patients. Therefore, this report emphasizes the importance for routine deep genetics screening for *TERT* rare variants in patients with family history of cytopenia, different bone marrow failure syndromes and aplastic anemia, regardless the age or clinical presentation. This investigation is able to identify clinically inapparent telomere biology disorder and improve outcomes through forehand diagnosis setting, genetic counseling and the precise therapy considerations especially stem cell grafting.

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