

Correspondence

To the editor:

Development of Hodgkin lymphoma in homozygotic triplets with constitutional deletion in *MKL1*

First-degree relatives of patients with Hodgkin lymphoma (HL) have a threefold to fourfold increased risk of developing HL, which is stronger when the proband is <40 years at diagnosis, in males and in siblings. Monozygotic twins carry an even higher risk than first-degree relatives.^{1,2} It is currently not known whether (or how) extrinsic factors interact with genetic predisposition though a susceptibility gene on chromosome 4 has been suggested.^{3,4} We herein report, to our knowledge, the first cases of HL in 2 male homozygotic triplets occurring in middle adulthood and with a 23-year interval. The first triplet was diagnosed in 1985 at age 40 with stage IIIA HL of Epstein-Barr virus (EBV)-positive mixed cellularity subtype. He remains in first complete remission after mustargen, oncovin, procarbazine, prednisone/adriamycin, bleomycin, vinblastine, and dacarbazine chemotherapy. The second triplet developed stage IIIB HL in 2008 at the age of 63. His tumor was also EBV-positive but of nodular sclerosis (NS) subtype. A complete and lasting remission was achieved following adriamycin, bleomycin, vinblastine and dacarbazine chemotherapy.

Considering the epidemiology of the different HL subtypes in developed countries, with mixed cellularity and NS predominantly arising in older and younger patients, respectively, the reciprocal presentation in these patients is somewhat unusual. Similarly, the detection of EBV also in the tumor cells of the NS tumor is not a typical feature of this entity.⁵ The third triplet is free from lymphoma. A 5-generation pedigree revealed a tonsillar cancer in the mother (at 67 years) and a breast cancer at 63 years in the aunt. No other malignancy or immunodeficiency was found. Homozygosity of the triplets was established with quantitative fluorescent polymerase chain reaction of 22 polymorphic markers from chromosome 13,18, 21, and X and Y. Microarray comparative genomic hybridization and multiplex ligation-dependent probe amplification of all triplets showed a 15- to 31-kb deletion of chromosome 22, with deletion of the first intron of the *megakaryoblastic leukemia 1* gene (*MKL1*). *MKL1* functions as a coactivator of serum response factor, which among other biological processes is involved in cell survival and apoptosis.⁶ *MKL1* has not been reported to be involved in lymphomagenesis. The significance of the deletion of intron 1 of *MKL1* in the triplets is unclear. Due to the fact that the deletion is located in an untranslated part of the gene, the mutation is not predicted to affect the translated amino acid sequence and, thus, likely does not affect its function. On the other hand, highly conserved nucleotides of the intron are deleted, which might affect transcription and posttranscriptional processing of the RNA, and in this way affect the function of *MKL1*.

In summary, we report the first constitutional mutation of *MKL1* in homozygotic triplets of whom 2 so far have developed HL. The deletion may represent an accidental finding, but potentially it could have contributed to the pathogenesis of HL.

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Contribution: M.B. took care of the patients/triplets, organized investigations and wrote the manuscript; U.A.N. and J.S. assisted in immunological and other investigations; J.S., M.B., and E.B. completed the pedigree; A.P. made histological examinations including EBV analyses; and E.B. performed genetic analyses. All authors contributed in interpretation of data and preparation of the final manuscript.

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