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To the editor:

Exome sequencing identifies an *MLL3* gene germ line mutation in a pedigree of colorectal cancer and acute myeloid leukemia

Recently, the frequently mutated gene *MLL3* was found to be related to the pathogenesis of hepatocellular carcinoma (HCC), fluke-associated cholangiocarcinoma, gastric cancer, and transitional carcinoma of the bladder,[1-4] raising the possibility that the *MLL3* gene and its encoded chromatin remodeling protein MLL3 are etiologically related to cancers. We performed exome sequencing for 4 patients in a multigenerational pedigree with colorectal cancers and acute myeloid leukemia (AML) and identified an insertion mutation in the *MLL3* gene on chromosome 7, producing a frame shift leading to a premature truncation at codon 827. To our knowledge, it was the first germ line MLL3 mutation found in a cancer pedigree. Because MLL3 is an enzyme for histone methylation, pharmacologic intervention may be possible.

Of the 4 patients we analyzed in this multigenerational pedigree (Figure 1), II-1 was diagnosed with rectal cancer at age 43 and still alive at age 56; II-3 was diagnosed with colon cancer at age 59 and still alive at age 67; III-2 was diagnosed with AML-M2 at age 40 and still alive at age 45 in complete remission state; and III-3 was diagnosed with AML-M1 at age 43 and died at age 43. All subjects gave informed consent, and the protocol was approved by the Committee on Studies Involving Human Beings at Tianjin Medical University and Southwest Hospital of Third Military Medical University. Genomic DNA was extracted from whole blood samples; exome sequencing was carried out for these 4 patients, respectively. A heterozygous insertion mutation in the *MLL3* gene on chromosome 7 (151,945,071 bp, ins T; Human Genome

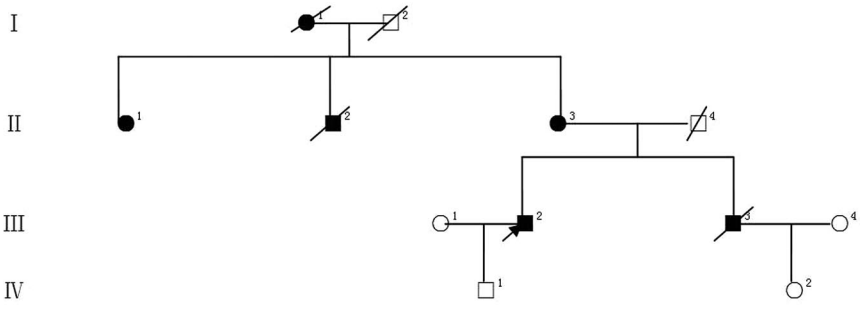

Figure 1. A Chinese pedigree with colorectal cancers and acute myeloid leukemia. Solid symbols indicate affected individuals. Open symbols indicate unaffected individuals. The arrow indicates the proband, and slashes indicate deceased persons. I-1, lung cancer. II-1, rectal cancer. II-2, rectal cancer. II-3, colon cancer. III-2 and III-3, acute myeloid leukemia, M2 and M1.

assembly GRCh37/hg19, genome.ucsc.edu) was identified in both the colorectal patients and the AML patients. The insertion, which started at codon 817 in exon 14, results in a frame shift mutation of *MLL3*, leading to a premature stop codon "TAA" at codon 827.

MLL3, which belongs to the human TRX/MLL family, is an important mammalian H3K4 methyltransferase. Down-regulation of MLL3 promoted cell proliferation in HCC cell lines.[1] Homozygous *MLL3*$^{-}$ knockout mice display tumors in the innermost layer of ureter cells.[5] These results suggest that MLL3 is a tumor suppressor.

Mechanistically, the MLL3 protein can selectively recognize H3K4me and affect the mechanistic readout of histone tail modifications.[6] In addition, ASCOM-MLL3 has a redundant but crucial role in transactivation of p53 and participates in DNA-damage-induced expression of p53-targeted genes.[5] In addition, nuclear-receptor-mediated downstream gene expression was regulated by MLL3.[7]

Because MLL3 is an enzyme, pharmacologic intervention may be possible. Drugs targeting this molecule may be effective in both colorectal and AML with *MLL3* mutation. The restoration of balance between histone methylation and demethylation may facilitate current tumor therapy.

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To the editor:

Low adhesion receptor levels on circulating platelets in patients with lymphoproliferative diseases before receiving Navitoclax (ABT-263)

Leukemia cells express high levels of Bcl-2[1] and BH3 mimetics that antagonize the prosurvival function of Bcl-2 and related proteins, thereby inducing apoptosis, are useful treatments for patients with chemotherapy-refractory leukemia.[2] BH3 mimetics such as ABT-737 and ABT-263 also inhibit Bcl-xL and trigger acute thrombocytopenia in dogs,[3] mice,[4] and humans.[5] In preclinical studies, they induced a rapid thrombocytopathy associated with shedding of GPVI and GPIbα ectodomains, platelet-specific adhesion receptors. This results in a loss of platelet adhesive function after ABT-263 treatment of human platelets in vitro or mice in vivo.[6] The pretreatment platelet count and bleeding risk are important clinical parameters when considering BH3 mimetics as treatment options in refractory chronic lymphocytic leukemia (CLL).[5]

We evaluated platelet receptor levels in citrated platelet-rich plasma (PRP) samples from patients before and after receiving ABT-263 by flow cytometry using phycoerythrin-conjugated anti-GPIbα (AK2), anti-GPVI (1G5), anti-CD9, or anti-αIIbβ3 (CD41a) monoclonal antibodies. We compared data from 5 patients with lymphoproliferative diseases refractory to standard therapies who received ABT-263,[5,7] with data obtained from 15 healthy donors or 7 patients with immunothrombocytopenia (ITP; chronic