Received: 19 February 2018 | Revised: 1 April 2018 | Accepted: 12 April 2018

DOI: 10.1002/ccr3.1564

CASE REPORT

WILEY Clinical Case Reports Open Access

Rare compound heterozygous mutations in gene *MSH6* cause constitutive mismatch repair deficiency syndrome

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Key Clinical Message

Few studies reported patients who harbored three kinds of primary tumors simultaneously. Here, we present a 9-year-old boy with colon carcinoma, brain medulloblastoma, and lymphoma. Genetic mutation detection was explored with next-generation sequencing, and compound heterozygous mutations in gene *MSH6* c.3103C>T p.Arg1035Ter and c.3261dupC p.Phe1088LeufsTer were discovered.

KEYWORDS

Bi-allelic mutations, CMMR-D syndrome, *MSH6*

1 | CASE REPORT

A 9-year-old boy was admitted to the Department of Neurosurgery at Beijing Children's Hospital, because of frequent headaches and intermittent blood in feces for more than half a year. A clinical routine blood examination showed low hemoglobin level (HGB 78 g/L) and high platelet count (PLT 557×10^9/L). Bone marrow examination showed active proliferation of granulocytes; polychromatic, target, and deformation erythrocytes were found (Figure 1A). Colonoscopy was performed and a $2.5 \times 2 \times 1.6$ cm adenoma was detected at the sigmoid colon, which was about 15 cm apart from the anus (Figure 1B). Brain contrast-enhanced magnetic resonance (MR) T1-weighted image (T1WI) of the cerebellar vermis was displayed in Figure 1C,D. Biopsy pathology results illustrated medulloblastoma of the cerebellar vermis and hemorrhagic necrosis, and anaplastic tumor cells were

Xue Zhang and Di Zhang contribute equally to this study.

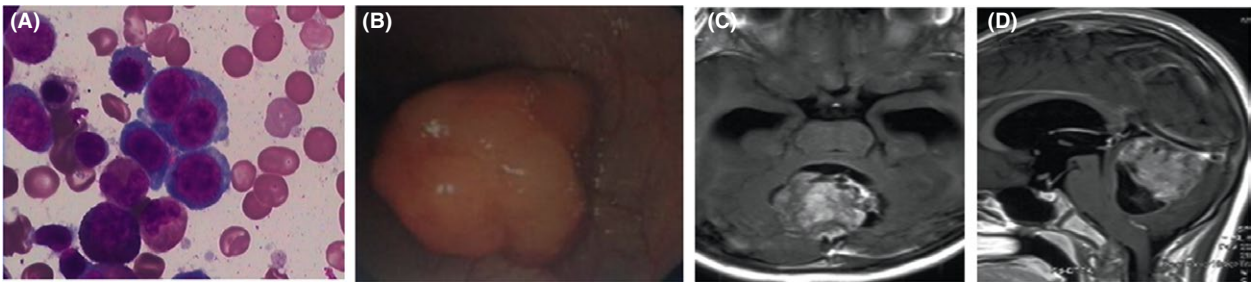

FIGURE 1 Three primary tumors in the patient. A, Cellular examination of bone marrow smears. B, Adenoma under colonoscopy detection. C&D, Enhanced MR images of cerebellum tumor in coronal and vertical planes

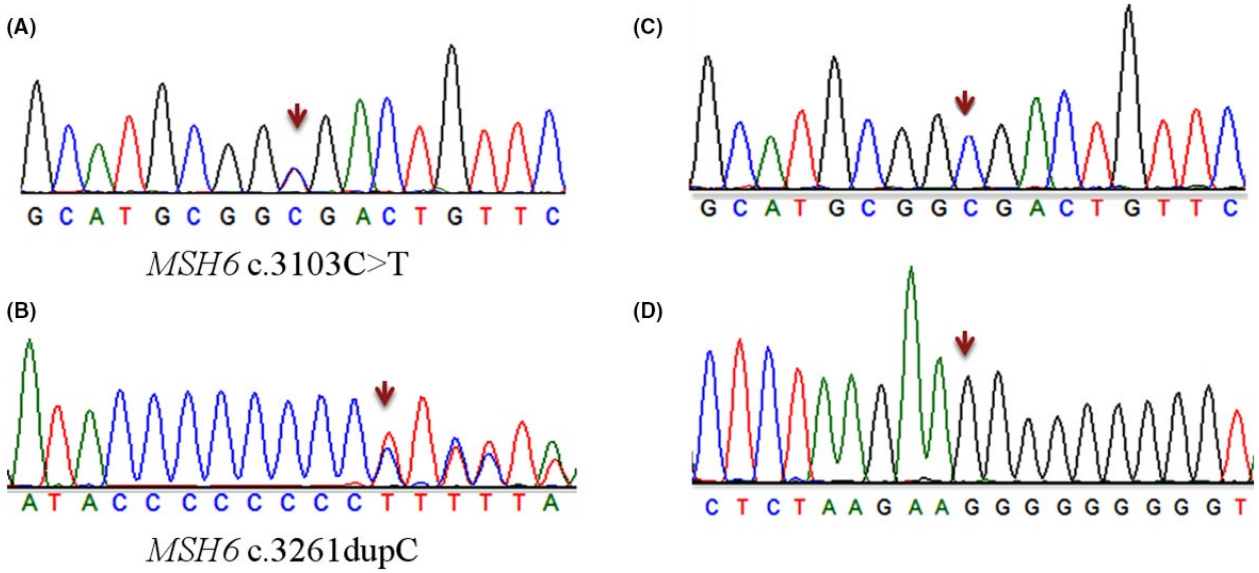

FIGURE 2 Sanger sequencing validation of the compound heterozygous mutations of gene *MSH6*. A&B, Mutations of c.3103C>T and c.3261dupC were bidirectional sequenced with Sanger sequencing after PCR with patient genome DNA. C&D, The two heterozygous mutations were transformed into the pMD18-T plasmid and sequenced with Sanger method. The result showed that the allele with c.3261dupC mutation was normal in the site of c.3103C, which implied the two mutations were bi-allelic mutations

found (WHO Grade-IV, Figure S1). Abnormal density of the right lobe of liver and kidney images was found with abdomen MR, which were primarily considered to be metastatic adenocarcinoma of the liver and renal cyst (Figure S2A-D, respectively). Candidate gene mutation detection (Table S1) with next-generation sequencing illustrated compound heterozygous mutations in gene *MSH6*c.3103C>T p.Arg1035Ter and c.3261dupC p.Phe1088LeufsTer, and we validated the mutations used Sanger sequencing (Figure 2A,B). As the parental blood was unavailable, a 2.7-kb PCR product contained the two heterozygous mutations was transformed into the pMD18-T plasmid and sequenced with the Sanger method, and the allele with mutation of *MSH6* c.3261dupC was found with normal base of *MSH6* c.3103C (Figure 2C,D). And we also validated the bi-allelic mutations with PacBio long-read amplicon sequencing (Figure S3).

2 | DISCUSSION

We report a 9-year-old boy with hematologic malignancies, brain tumor, and colon carcinoma. The research was approved by duly constituted ethics committee of Peking Union Medical College Hospital. Candidate gene mutation detection illustrated compound heterozygous mutations in MMR gene of *MSH6*. This case was comprehensively diagnosed as constitutional mismatch repair deficiency (CMMR-D) syndrome, which was rarely reported in the previous studies. CMMR-D syndrome was caused by homozygous or compound heterozygous mutations in the MMR genes *MLH*, *MSH2*, *MSH6*, or *PMS2*, and rather than monoallelic germline mutations in MMR genes, CMMR-D owing to a wide tumor spectrum, including four main types of childhood tumors: central nervous system tumors, colorectal tumors and multiple intestinal

polyps, hematologic malignancies, and other malignancies like embryonic tumors or rhabdomyosarcoma,[1] and some of the patients also show signs of reminiscent of neurofibromatosis type 1, particularly multiple cafe-au-lait macules.[2] CMMR-D is in autosomal recessive inheritance; however, both of the parents refused to donate their blood and stated no family history, so we could not identify the compound heterozygous mutations of *MSH6* were de novo or inherited from the parents. However, both mutations were classified as "Pathogenic" in the ClinVar database. Single heterozygous stop gain mutation of *MSH6* c.3103C>T p.Arg1035Ter was previously described in a family with endometrial cancer and rectal cancer,[3] and also the Lynch syndrome,[4] while single frameshift heterozygous mutation of *MSH6* c.3261dupC p.Phe1088LeufsTer was previously reported in multiple kinds of tumors, including the Lynch syndrome,[5-11] colorectal cancer,[12-15] prostate cancer,[16] and endometrial cancer.[17] In addition, c.3261dupC variant has been seen in the homozygous state in several individuals from a consanguineous family with CMMR-D syndrome, and in this family, the carriers parents had not presented any tumor, but should participate the preventive program for Lynch syndrome.[18] Although there were multiple studies illustrated that both of the two mutations were pathogenic in different tumors, there was no study illustrated that what will exactly happen when these two known mutations exist in one patient simultaneously. The unique phenotypic presentation in our study further suggested the variable expressivity of CMMR-D syndrome.

MSH6 encodes protein of the DNA mismatch repair MutS family, and helps to recognize the mismatched nucleotides prior to their repair. *MSH6* protein heterodimerizes with *MSH2* to form a mismatch complex and functions as a bi-directional molecular switch, which provokes ADP-to-ATP exchange.[19] *MSH6* gene deficiency during embryonic development may influence the recognition of mismatched nucleotides, and random mismatching may cause multiple types of malignancies in different organs. The potential function of the *MSH6* gene, particularly in the phase of embryonic development, needs to be further investigated in the future.

ACKNOWLEDGMENT

We thank the patient for the blood donation and the cooperation. Chinese Academy of Medical Sciences (CAMS) Initiative for Innovative Medicine (CAMS-I2M), (Grant / Award Number: '2017-I2M-1-001') Central public welfare and Basic scientific research business expenses of Chinese Academy of Medical Sciences, (Grant / Award Number: '2015PT320017').

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

CL: wrote the manuscript and performed sequencing data analysis. HS, WY, MG, and YJ: collected the clinical information and patient blood sample. SH: conducted the plasmid experiment. XZ and DZ: designed and managed the project.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Ling C, Yang W, Sun H, et al. Rare compound heterozygous mutations in gene *MSH6* cause constitutive mismatch repair deficiency syndrome. *Clin Case Rep*. 2018;6:1448–1451. https://doi.org/10.1002/ccr3.1564