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CASE REPORT

MYH ASSOCIATED POLYPOSIS WITH A p.Tyr165Cys MUTATION IN A MOROCCAN PATIENT

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ABSTRACT

Recessively inherited mutations in the base excision repair gene *MYH* are related to *MYH*-associated polyposis (MAP). We report a Moroccan patient who carried the mutation p.Tyr165Cys. Genetic testing for MYH mutations should have important implications for accurate genetic counseling, and cancer surveillance for patients with colorectal cancers and their family members in Morocco.

Key words: Colorectal cancer, MYH gene, p.Tyr165 Cys mutation

INTRODUCTION

Colorectal cancer is the third most common form of cancer in males and the second most common in females [1]. Although the majority of such cases are sporadic, about a quarter of cases may involve some hereditary predisposition. A small proportion are familial, in which a very strong genetic predisposition to develop colorectal cancer is passed on within affected families. Hereditary non polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) are the most common familial forms of colorectal cancer. A small number of FAP cases involve germline mutations in the *MYH* gene, and are sub-grouped as *MYH*-associated polyposis (MAP) [1].

MYH-associated polyposis is caused by germline mutations in the base excision repair (BER) gene *MUTYH* (*MYH*) located on chromosome 1p34.3-p32.1, which contains 16 exons. The first description of an affected family was reported in 2002 [2]. The phenotype is often indistinguishable from that of an attenuated autosomal dominant FAP caused by mutations in the APC gene, but in MAP, the number of adenomas is often lower (from five to more than 100), and affected patients are often sporadic cases. Two mutational hot-spots have been identified in the *MYH* gene, p.Tyr165Cys and p.Gly382Asp [3], corresponding to approximately 90% of the mutations identified in affected Caucasians [4].

The only mutation reported in two unrelated Moroccan patients living abroad is the c.1186_1187insGG, p.Glu 396fsX42, within exon 13 [2]. We searched for these three mutations in the *MYH* gene, in a patient referred to the Department of Medical Genetics in Rabat, Morocco.

Case Report. A 53-year old man, born of non consanguineous healthy parents, was referred to our department for colorectal cancer and genetic counseling. His brothers and sisters are healthy and they never showed any digestive problems. His clinical history started with asthenia related to anemia, which was accompanied by gastric pain, intermittent abdominal colic, and on fibroscopy showed the presence of many polyps. A rectal injection of barium hydroxide in double contrast confirmed multi-

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ples polyps and showed a suspect nodule in the right colon. Pathological examination found the biopsied polyps to be adenocarcinoma of Duke. Some 80 adenomatous polyps were distributed throughout the colon.

Informed consent was obtained for DNA testing according to approved protocols. DNA was extracted from whole blood by standard methods, and the two exons 7 and 13 were amplified by polymerase chain reaction (PCR) and sequenced on an ABI PRISM™ 310 genetic analyzer (Applied Biosystems, Foster City, CA, USA) to detect the p.Tyr165Cys, p.Gly382Asp and c.1186_1187insGG MYH mutations. Any mutation was confirmed on a second independent DNA sample.

RESULTS AND DISCUSSION

The molecular analysis of the *MYH* gene in this patient showed that he carried the p.Tyr165Cys (c.494A>G) mutation in a homozygous state (Figure 1). This is the first association report between colorectal cancer and the MYH mutation p.Tyr165Cys in Morocco.

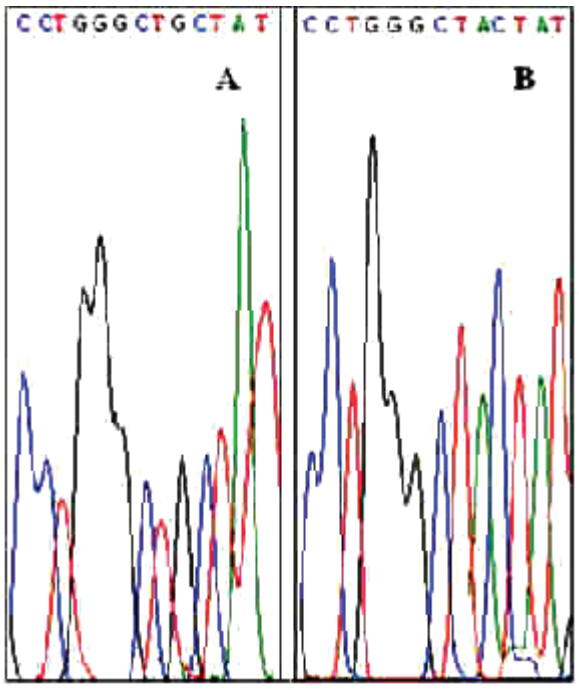

Figure 1. A.Sequence of the patient carrying the mutation c.494 A->G at a homozygous state (Y165C)
B. Normal sequence of the exon 7 of the MYH gene.

Considering the high level of consanguinity in Morocco, screening for MYH mutations should be considered in young patients presenting with sporadic colorectal cancer, even with a limited number of adenomas. A variable number of polyps (ranging from five to 100) and early onset colorectal cancer; absence of vertical transmission from parent to offspring, sporadic or multiple-case presentations within one generation, are characteristic of an autosomal recessive pattern of inheritance [5] and represent a clinical-genetic picture of MAP. This observation is similar to those described in previous studies [3,6,7] and confirms that *MYH* mutations are not frequent in the general population [8].

In Morocco, consanguineous marriage is culturally favored and is an integral part of the country's cultural and social life. The high rate of consanguinity (15.25%) explains the prevalence of autosomal recessive diseases in the country [9]. Therefore, we expect that MAP may be more common in this country than in developed countries. This consideration should be integrated in any colorectal cancer surveillance program.

In conclusion, patients with a classical or attenuated form of polyposis coli should be screened for *MYH* mutations. Identification of MYH mutations has important implications for the diagnosis, screening, genetic counseling, follow-up and therapeutic options in patients with colorectal cancer. Gene testing should identify siblings of MAP cases who are at risk and clarify the genetic status of spouses of those with biallelic mutations, so that their offspring can be counseled.

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