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Ovarian cancer of endometrioid type as part of the *MSH6* gene mutation phenotype

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Abstract The *MSH6* gene is one of the DNA mismatch repair genes involved in development of inherited cancers, predominantly of the colorectum and endometrium. Herein we describe the first Polish *MSH6* family and the pathological and clinical data about the ovarian cancer diagnosed in the proband. Our results and reports by others indicate that, besides colorectal and endometrial cancer, the late-onset endometrioid type of ovarian cancer can be a feature of families with *MSH6* germline mutations.

Key words *MSH6* · Endometrioid type · Ovarian cancer · Endometrial cancer · Colon cancer · Germline mutation

Introduction

The *MSH6* gene, along with *MLH1*, *MSH2*, *PMS2*, *MLH3*, and *EXO1*, belongs to a group of DNA mismatch repair genes, which, when mutated, cause development of inherited cancers mainly in the colon, rectum, and endometrium (Kurzawski et al. 2002; Debniak et al. 2000; Nicolaides et al. 1994; Wu et al. 2001a; Wu et al. 2001b; Akiyama et al. 1997).

The *MSH6* gene has been mapped on chromosome 2 (2p15–16) and is transcribed as a 4245-bp mRNA encoding a 153-kDa protein of 1360 amino acids. This MSH6 protein contains two domains that allow interaction with the *MSH2* protein. Biochemical studies indicate that the *MSH2–MSH6* complex recognizes base–base mispairs and small insertion–deletion loops (Guerrette et al. 1998; Acharya et al. 1996).

Studies of affected individuals with *MSH6* germline mutations indicate that the clinical phenotype is often different from phenotypes observed in classical hereditary nonpolyposis colorectal cancer (HNPCC), which is caused by mutations in the *MLH1* and *MSH2* genes (Akiyama et al. 1997). Generally, *MSH6* families are characterized by later age of onset of the disease, and cancers of affected individuals exhibit low levels of instability mostly at mononucleotide repeats (Wijnen et al. 1999).

Pedigrees of *MSH6* families present a predominance of colorectal and endometrial cancers, as do *MSH2/MLH1* families. Carriers of *MSH2/MLH1* and *MSH6* mutations can also be affected by malignancies at different sites including the ovary. In *MSH2/MLH1* mutation carriers, most ovarian tumours are serous and endometrioid carcinomas, usually well or moderately differentiated, and diagnosed at an early age of ~43 years (Watson et al. 2001). Histological data concerning ovarian cancer in *MSH6* mutation carriers has been reported in one case only (Wagner et al. 2001). We now report pathological and clinical data concerning an additional case of ovarian cancer in an *MSH6* family.

Subjects and methods

The pedigree of the *MSH6* family is presented in Fig. 1. The proband (III-3), a 49-year-old woman with bilateral endometrioid ovarian cancer, had a positive family history of cancers. Her father died of colon cancer at the age of 83 years and her paternal grandmother died of endometrial cancer at the age of 69 years. Endometrial cancer was diagnosed at the age of 57 years in her cousin, who is at present 68 years old. Initial molecular analyses were performed on proband III-3. DNA was extracted from peripheral blood, and sequencing of all coding fragments of the *MSH2* and *MLH1* genes did not reveal mutation. The proband DNA was then analyzed for *MSH6* changes.

In exon 5 of the *MSH6* gene, we identified a frameshift mutation 3311–3312 delTT, which creates a termination codon at 1106 and removes the carboxy-terminal *MSH2* interaction region and the nucleotide binding region (Guerrette et al. 1998).

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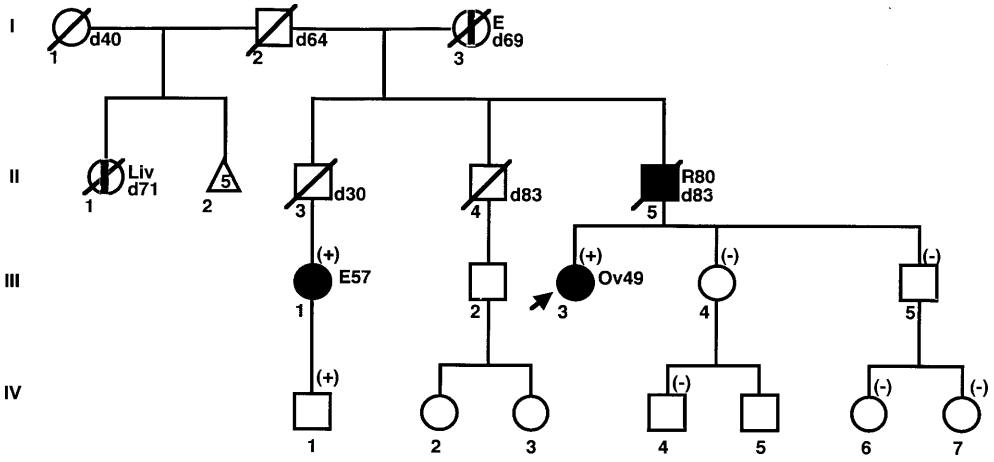

Fig. 1. Pedigree of the *MSH6* family. *E*, Endometrial cancer; *R*, rectal cancer; *Ov*, ovarian cancer; *Liv*, liver cancer. The numbers following abbreviations indicate the age at diagnosis; (+), *MSH6*-mutation positive; (−), *MSH6*-mutation negative. Arrow indicates the proband

The proband and family members were informed about the findings and were invited to be tested for the presence of the mutation. DNA testing for this mutation was performed in seven living relatives, three male relatives and five female relatives. Two relatives with a previously diagnosed HNPCC-related tumour (III-1, III-3) and one unaffected relative (IV-1) were carriers. Other relatives were negative for the *MSH6* mutation (III-4, III-5, IV-4, IV-6, IV-7). The histopathological and clinical data of the proband were independently verified. Her current age is 63 years and she was diagnosed at age 49 years as having bilateral ovarian cancers of the endometrioid type with morphological malignancy grade G1/2 and clinical stage I/II, according to the International Federation of Gynecology and Obstetrics (FIGO).

Results and discussion

This case study of histologically verified ovarian cancers in an *MSH6* carrier, as well as that previously reported (Wagner et al. 2001) are of endometrioid type. Thus, ovarian cancers of this type may be characteristic of *MSH6* mutation carriers; such cancers have also been reported as characteristic in HNPCC cases (Watson et al. 2001). A potential difference between such cancers in *MLH1/MSH2* and *MSH6* mutation carriers may be the age at diagnosis. The average age at diagnosis of ovarian cancers in *MSH6* mutation carriers is 48 years, whereas these tumors in *MSH2/MLH1* mutation carriers were diagnosed at an average age of 43 years.

Later age at diagnosis of cancers may be a major feature useful in differential diagnosis in *MSH2/MLH1* and *MSH6* families because colorectal and endometrial cancers also occur at a later age in *MSH6* mutation carriers: 53 vs 43 years and 55 vs 48.5 years, respectively. In approximately 20% of families with the *MSH6* mutation, cancers appear at ≥50 years of age, despite the fact that *MSH6* mutation analyses were performed frequently, if not consecutively, in those cases that showed Amsterdam criteria and were negative for *MSH2/MLH1* (Akiyama et al. 1997; Wu et al. 1999; Wagner et al. 2001; Wijnen et al. 1999; Kolodner et al. 1999; Miyaki et al. 1997; Plaschke et al. 2000; Huang et al. 2001; Berends et al. 2002; Plaschke et al. 2002; Verma et al. 1999).

In summary, it may be worthwhile to develop studies to assess whether later onset of endometrioid ovarian cancer is characteristic of carriers with *MSH6* constitutional mutations.

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