Report of 16 kindreds and one kindred with hMLH1 germline mutation

Bo Zhao, Zhen-Jun Wang, Yu-Feng Xu, Yuan-Lian Wan, Peng Li, Yan-Ting Huang

INTRODUCTION
Hereditary nonpolyposis colorectal cancer, or Lynch syndrome, is an autosomal, dominantly inherited disease characterized by an excess of early age onset colorectal cancers. It is estimated that hereditary nonpolyposis colorectal cancer may account for 5 to 10 percent of the total colorectal cancers worldwide[2]. There are two main variants of the disorder[12-13], Lynch syndrome I, which is susceptible to colorectal carcinoma only, and the more common Lynch syndrome II, which is characterized by excessive colorectal carcinoma and malignancies of extracolonic tissue, especially the endometrium in the western world. Other tumors belong to the spectrum of this syndrome include those of the stomach, esophagus, ovaries, pancreas, and urinary tract[14-15]. HNPCC has no premonitory symptoms, and the cancer is usually found at an advanced stage at around 50 years of age.

Five causative mismatch repair genes for HNPCC (hMSH2, hMLH1, hPMS1, hPMS2, and hMSH6/GBTP) have been identified, and a germline mutation in one of them predisposes carriers to early onset cancers[5-10]. hMSH2 and hMLH1 genes contribute at least 40 and 35 percent of all HNPCC germline mutations, respectively. Mutational analysis of the two main genes not only permit diagnosis of most cancer families or patients, but also earlier detection of cancer through targeted surveillance and chemoprevention of the gene carriers.

Despite the fact that China might have the biggest HNPCC population, the disease is rare reported. And also the mismatch repair gene mutation of HNPCC families from Mainland China has not been reported. We retrospectively reviewed the clinical characteristics and treatments of 16 HNPCC kindreds registered in our hospital, and report the first hMLH1 gene mutation family in Mainland China.

MATERIALS AND METHODS
Diagnostic criteria of HNPCC family
Kindreds of independent Chinese families that included multiple patients with colorectal cancer were clinically reviewed. The strict criteria for HNPCC were the Amsterdam criteria[11]. The criteria are (1) three or more relatives with histologically verified colorectal cancer, with one of them being a first-degree relative to the other two relatives; (2) at least two successive generations were affected; (3) one or more colorectal cancer cases diagnosed under 50 years of age; and (4) familial polyposis of colon is excluded. Japanese clinical diagnostic criteria for HNPCC[12] was used for highly suspected families that did not fully meet the Amsterdam criteria. Families that met either A or B were clinically diagnosed as HNPCC. The criteria include A: a case with three or more colorectal cancers within the first-degree relatives; B: a case with two or more colorectal cancers within the first-degree relatives meeting the following criteria (1) age onset of colorectal cancers being earlier than 50 years old; (2) with right colon involvement; (3) with synchronous or metachronous multiple colorectal cancers; (4) associated with synchronous or metachronous extracolonic malignancies.

Family investigation
The diagnosis is made upon the compilation of a detailed family history. The family history of cancer was thoroughly reviewed when a...
were also found to carry the mutated gene. Two of them subsequently developed synchronous cancers and 74.6% of colorectal cancers. 34.8% of colorectal cancers were metachronous ones. Right-side colon cancers constitute 47.8% of total cancers and 74.6% of colorectal cancers. 34.8% of colorectal cancers were metachronous ones. The average age onset of colorectal cancer patients within the same period in our hospital, which is consistent with the published reports[17,18]. Colon cancers are more often right-sided, constituting 47.8% of total cancer and 74.6% of colorectal cancers, whereas in sporadic colon cancer, the opposite is true[17,18]. The next most frequently seen cancer is gastric cancer, about 10.8% in this group, well above the reported frequency in the literature[19,20]. It is interesting that gastric cancer occurred at a higher frequency and ovarian cancer at a lower frequency in our group[21,22]. More research study should be done to clarify if this is just a reflection of case selection bias or the difference is related to ethnic or geographical groups[23,24]. Endometrium is the third predisposing organ, and about 6.9% cancer is in the endometrium[25]. A small number of other cancers included pancreatic, esophageal, skin, lung, cervical, and breast cancers. There was one gastric leiomyosarcoma and glioblastoma, respectively.

Two breast and two lung cancers in our small group of patients are worthy of particular comment. Controversy exists whether these two kinds of cancers belong to the spectrum of HNPCC[26]. In China, breast and lung cancers are much less prevalent than those in the western world, and it is interesting that the incidence of these two cancers among those families is far above the average level in China. One breast cancer occurred in the index patients of a Lynch syndrome II kindred (Figure 1) that received sequence analysis in this study. The patient developed ascending colon cancer at 37 years of age, breast cancer at 38, rectum cancer at 52, descending colon cancer at 57. The patient developed ascending colon cancer at 37 years of age, breast cancer at 38, rectum cancer at 52, descending colon cancer at 57. The possibility of a sporadic breast cancer in this patient is small. The patient developed ascending colon cancer at 37 years of age, breast cancer at 38, rectum cancer at 52, descending colon cancer at 57. The possibility of a sporadic breast cancer in this patient is small. The patient developed ascending colon cancer at 37 years of age, breast cancer at 38, rectum cancer at 52, descending colon cancer at 57. The possibility of a sporadic breast cancer in this patient is small. The patient developed ascending colon cancer at 37 years of age, breast cancer at 38, rectum cancer at 52, descending colon cancer at 57.
Another cardinal features of the HNPPC in this group and in the medical literature is the occurrence of metachronous colorectal cancer. In our group, 39.5% colorectal cancer patients developed metachronous colorectal cancer within ten years after their initial colorectal cancer resection. But in contrast to the literature, none of the patients were found to have synchronous colorectal cancers. Although it is quite possible that small benign adenomas were not recorded or missed during the colonoscopic or barium examination, but the possibility of missing a cancer is quite small. The reason for the lack of synchronous cancer remains unclear.

81.6% of our patients received routine radical resection. Among colorectal patients who received routine segmental resection, 39.5% developed metachronous colorectal cancer, and needed re-operations. After segmental resection, a multiple primary cancer patient developed ascending colon cancer twelve years later, gastric cancer eighteen years later, and transverse colon cancer nineteen years later, and descending colon cancer twenty eight years later after the first operation. Therefore, the most eligible choice is subtotal or total colectomy with ileorectal anastomosis or with ileopouch anal anastomosis. But the possibility of missing a cancer is quite small. The reason for the occurrence of metachronous colorectal cancer is around 45 years, but Rodriguez-Bigas showed HNPCC gene carrier is unknown. The median age at diagnosis of the most eligible choice is subtotal or total colectomy with ileorectal anastomosis or with ileopouch anal anastomosis. A short term follow-up of the patients showed good life quality. In literature, different views exist regarding prophylactic colectomy for gene carriers of HNPPC. Firstly, not all carriers of the germline hMSH2 and hMLH1 gene mutations develop colorectal cancer; Vanes et al reported that up to 60 years of age, 92% of the carriers developed colorectal cancers in affected families. Secondly, complications even mortality occurred around 8% and 1% respectively in these operations. The timing of prophylactic operation in an HNPPC gene carrier is unknown. The median age at diagnosis of colorectal cancer is around 45 years, but Rodriguez-Bigas showed that 27% of their patients were diagnosed before 39 years and 88% by 69 years of age. Other uncertainties include: the psychologic impact of the invasive procedure on body image and sexuality in young adult carriers.

Colonoscopy remains the most important surveillant measure in revealing synchronous and metachronous cancers or polyps in the medical literature. In three phenotypical normal family members, the Mutation Database (HGMD) (uwcm.web.cf.ac.uk/uwcm/mg/hgmdo.html), searched for genetic abnormalities in the family. We made a search in the Human Gene Mutation Database (HGMD) (uwcm.web.cf.ac.uk/uwcm/mg/hgmdo.html), and found this to be a new mutation previously unreported in the medical literature. In three phenotypical normal family members, the same mutated gene was found in the genome. Two of them subsequently received colonoscopy examinations, and one was found to have an adenoma of 2cm which was resected endoscopically. These carriers are now needed an intensive follow-up regime.

ACKNOWLEDGMENT

We appreciate the invaluable technical assistance and great help of Dr. Ding-fang Bu from Experimental Center of our hospital.

REFERENCES

1 Lynch HT, Smyrk T, Lynch J. An update of HNPPC (Lynch syndrome). Cancer Genet Cytogenet 1997;95:84-99
2 Stephenson BM, Finan PJ, Gascoyne J, Garbett F, Murday VA, Bishop DT. Frequency of familial colorectal cancer. Br J Surg 1991;78:1162-1166
3 Vanes HF, Offerhaus GJ, den Hartog Jager FC, Menko FH, Nagengast FM, Griffioen G, van Hogezand RB, Heintz AP. The tumor spectrum in hereditary non-polyposis colorectal cancer: a study of 24 kindreds in the Netherlands. Int J Cancer 1990;46:31-34
4 Watson P, Lynch HT. OMIM. Extracolonic cancer in hereditary nonpolyposis colorectal cancer. Cancer 1993;71:677-685
5 Fisher R, Lescoe MK, Rao MR, Copeland NC, Jen J, Parsons RB, Peltomaki P, Sistonen P, Aaltonen LA. Mutations of a mutI homolog in hereditary nonpolyposis colorectal cancer. Cell 1993;75:1215-1225
6 Beijnen CE, Baker SM, Morrison PT, Warren G, Smith LH, Lescoe MK, Kane M, Earabino C, Lipford J, Lindblom A. Mutation in the DNA mismatch repair gene hMLH1 is associated with hereditary non-polyposis colon cancer. Nature 1994;36:258-261
7 Papadopoulos N, Nicolaides NC, Wei YF, Ruben SM, Carter KC, Rosen CA, Haselting WA. Fleischmann RD, Fraser CM, Adams MD. Mutation of a mut II homolog in hereditary colorectal cancer. Science 1994;264:1625-1629
8 Nicolaides NC, Papadopoulos N, Liu B, Wei YF, Carter KC, Ruben SM, Rosen CA, Haselting WA, Fleischmann RD, Fraser CM. Mutations of two FM3 homologues in hereditary nonpolyposis colon cancer. Nat Genet 1995;12:392-396
9 Vanes HF, Mecklin JP, Khan PM, Lynch HT. The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPPC). Dis Colon Rectum 1991;34:424-425
10 Baba S. Hereditary nonpolyposis colorectal cancer: an update. Dis Colon Rectum 1997;40:886-95
11 Weber TK, Conlon W, Petrelli NJ, Rodriguez-Bigas M, Kritz B, Pazik JF, Farrell C, O’Malley L, Oshamim M, Admo M, Anderson G, Stoler D, Yandell D. Genomic DNA-based hMSH2 and hMLH1 mutation screening in 32 Eastern United States hereditary nonpolyposis colorectal cancer pedigrees. Cancer Res 1997;57:3798-3803
12 Ponz de Leon M. Prevalence of hereditary nonpolyposis colorectal carcinoma (HNPPC). Ann Med 1994:26:209-214
13 Marra G, Boland CR. Hereditary nonpolyposis colorectal cancer: the syndrome, the genes, and historical perspectives. J Natl Cancer Inst 1995;87:1114-1125
14 Lynch HT, Richardson JD, Amin M, Lynch F, Cavalleri RJ, Bronson E, Fusaro RM. Variable gastrointestinal and urological cancers in a Lynch syndrome II kindred. Dis Colon Rectum 1991;34:891-895
15 Mecklin JP, Jarvinen HJ. Clinical features of colorectal carcinoma in cancer family syndrome. Dis Colon Rectum 1986:29:160-164
16 Fitzgibbons RJ Jr, Lynch HT, Stanislav GV, Watson PA, Lanspa SJ, Marcus JN, Smyrk T, Kriegl MD, Lynch JF. Recognition and treatment of patients with hereditary nonpolyposis colon cancer (Lynch syndromes I and II). Ann Surg 1987:206:289-295
17 Green SE, Bradburn DM, Varma JS, Burn J. Hereditary non-polyposis colorectal cancer. Int J Colorectal Dis 1998:13:3-12
18 Lin KM, Shashidharan M, Ternent CA, Thorson AG, Blatchford GJ, Christensen MA, Lanspa SJ, Lemon SJ, Watson P, Lynch HT. Colorectal and extracolonic cancer variations in MLH1/MSH2 hereditary nonpolyposis colorectal cancer kindreds and the general population. Dis Colon Rectum 1998;41:428-433
19 D’Emilia JC, Rodriguez-Bigas MA, Petrelli NJ. The clinical and genetic manifestations of hereditary nonpolyposis colorectal carcinoma. Am J Surg 1995;169:368-372
20 Watson P, Lynch HT. OMIM, Related Articles. Extracolonic cancer in hereditary nonpolyposis colorectal cancer. Cancer 1993;71:677-685
21 Froggatt NJ, Joyce IA, Gayne R, Garbett D, Evans R, Ponder BA, Barton DE, Maher ER. A frequent hMSH2 mutation in hereditary non-polyposis colon cancer syndrome. Lancet 1995;345:727
22 Peltohakki P, Vanes HF. Mutations predisposing to hereditary nonpolyposis colorectal cancer: database and results of a collaborative study. The International Collaborative Group on Hereditary NonPolyposis Colorectal Cancer. Gastroenterology 1997;113:1146-1158
23 Itoh H, Houlston RS, Harocopos C, Slack J. Risk of cancer death in first-degree relatives of patients with hereditary non-polyposis cancer syndrome (Lynch type II): a study of 130 kindreds in the United Kingdom. Br Med J 1990;77:1367-1370
24 Nelson CL, Sellers TA, Rich SS, Potter JD, McGovern PG, Kushi LH. Familial clustering of colon, breast, uterine, and ovarian cancers as assessed by family history. Genet Epidemiol 1993:10:235-244
25 Rensing J, Barrett J, Waterman P, Lynch HT. Motor molecular genetic evidence of the occurrence of breast cancer as an integral tumor in patients with the hereditary nonpolyposis colorectal cancer syndrome. Cancer www.wjgnet.com
28 Lynch HT, Lanspa SJ, Boman BM, Smyrk T, Watson P, Lynch JF, Lynch PM, Cristofaro G, Bufo P, Tauro AV. Hereditary nonpolyposis colorectal cancer—Lynch syndromes I and II. *Gastroenterol Clin North Am* 1988;17:679-712

29 Svendsen LB, Bulow S, Mellemgaard A. Metachronous colorectal cancer in young patients: expression of the hereditary nonpolyposis colorectal cancer syndrome? *Dis Colon Rectum* 1991;34:790-793

30 Rodriguez-Bigas MA. Prophylactic colectomy for gene carriers in hereditary nonpolyposis colorectal cancer. Has the time come? *Cancer* 1996;78:199-201

31 Lynch HT. Is there a role for prophylactic subtotal colectomy among hereditary nonpolyposis colorectal cancer germline mutation carriers? *Dis Colon Rectum* 1996;39:109-110

32 Vasen HF, Taal B, Griffioen G, Nagengast FM, Cats A, Menko FH, Oskam W, Kleibeuker JH, Offerhaus GJ, Khan PM. Clinical heterogeneity of familial colorectal cancer and its influence on screening protocols. *Gut* 1994;35:1262-1266

33 Rodriguez-Bigas MA, Lee PH, O'Malley L, Weber TK, Suh O, Anderson GR, Petrelli NJ. Establishment of a hereditary nonpolyposis colorectal cancer registry. *Dis Colon Rectum* 1996;39:649-653

34 Gaglia P, Atkin WS, Whitelaw S, Talbot IC, Williams CB, Northover JM, Hodgson SV. Variables associated with the risk of colorectal adenomas in asymptomatic patients with a family history of colorectal cancer. *Gut* 1995;36:385-390

35 Jarvinen HJ, Mecklin JP, Sistonen P. Screening reduces colorectal cancer rate in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology* 1995;108:1405-1411

Edited by Wu XN