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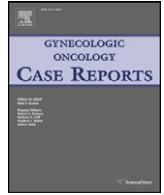
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## Case Report

## Novel *MSH2* Mutation in the First Report of a Vietnamese–American Kindred with Lynch Syndrome



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## Introduction

Although the first clinical report of hereditary colorectal cancer (CRC) was published in 1861, this patient likely had familial adenomatous polyposis (Luschka, 1861). This was followed in 1913 with Warthin's publication of a large pedigree (Family G) which included many cases of CRC in the absence of polyposis as well as uterine and gastric cancer (As, 1913). Over half a century later, Lynch et al. reported two large Midwestern kindreds from Nebraska and Michigan (Families N and M) whose constellation of malignancies was comprised of tumors similar to Family G (Lynch et al., 1966). Scrutinization of these three families (G, N and M), along with the careful study of hundreds of others that followed, helped to define the cardinal features of Lynch syndrome (LS).

LS has an autosomal dominant inheritance pattern with earlier average age (mean age 44) of CRC onset than the general population. There is increased risk of extra-colonic malignancy including the

endometrium (40–60% lifetime risk), ovary (12–15% risk), gastric, small bowel, hepatobiliary tract, pancreas, and upper uro-epithelial tract (Lynch and de la Chapelle, 2003). In 1991, an international collaborative initiative ratified the Amsterdam Criteria for diagnosing LS (Vasen et al., 1991), and in 1999 these were expanded to include extra-colonic tumors (Vasen et al., 1999). During the early 21st century, Bethesda Guidelines were developed to triage CRC patients for preliminary testing for LS (Lynch and de la Chapelle, 2003).

The first cancer susceptibility locus for LS was mapped to chromosome 2p by Peltomaki et al. in 1993 through a genome-wide search and linkage analysis in large informative families (Peltomaki et al., 1993). During that same year, a second locus was identified on chromosome 3p by Lindblom et al. (1993). LS tumors are characterized by microsatellite instability (MSI), a consequence of defective DNA replication error repair or post-synthetic DNA proofreading (Lynch and de la Chapelle, 2003). Ultimately, the first two LS genes, *MSH2* and *MLH1*, were identified on chromosomes 2p and 3p, respectively. The mismatch repair (MMR) complex also includes *MSH6*, *PMS2*, and possibly *MLH3* (Lynch and de la Chapelle, 2003).

MMR gene mutations account for 3–5% of all colorectal cancer cases, and 2–6% of all endometrial cancers (Bronner et al., 1994). Nearly 51% of women with LS present with endometrial cancer as their first primary carcinoma (Fishel et al., 1993). Because poor patient recall, cultural barriers in communication, and inadequate healthcare documentation impact the sensitivity of both the Amsterdam Criteria and Bethesda Guidelines, the Society of Gynecologic Oncology has modified the Amsterdam Criteria by including personal/familial history of uterine/ovarian cancer to improve identification of mutation carriers (Lancaster et al., 2007). “Universal screening” of tumor tissue for MSI and immunohistochemistry to detect LS-related mutations may be particularly important among endometrial cancer patients diagnosed under 55 years.

### Background on Vietnamese Immigration to the U.S.

The Fall of Saigon on April 30, 1975 ended the Vietnam War prompting three, successive, large-scale waves of Vietnamese immigration to the United States (Allen and Hiller, 1985). These were supported by President Gerald Ford, who passed the Indochina Migration and Refugee Assistance Act in 1975 (Allen and Hiller, 1985). Currently, there are approximately 1.5 million Vietnamese–Americans, with

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approximately 40% living in California (United States Census 2010; [www.census.gov](http://www.census.gov)). The largest numbers of Vietnamese outside of Vietnam reside in Orange County, California. Most are small business owners in Little Saigon (Allen and Hiller, 1985). The growth-rate of the Vietnamese population in the US was 37.9% between 2000 and 2010.

China's character cultural sphere, known as the sinosphere, comprises those regions of the world such as China, Taiwan, Japan, Korea, and Vietnam, where Chinese characters are found suggesting co-mingling of the cultures. Cultural immersion often parallels gene sharing. While there are many cases of LS occurring in the Chinese population, and several publications involving both Japanese and Korean families, to our knowledge, LS has not been previously reported in a Vietnamese kindred (PUBMED Medline Search).

**Case Histories: Proband Medical History**

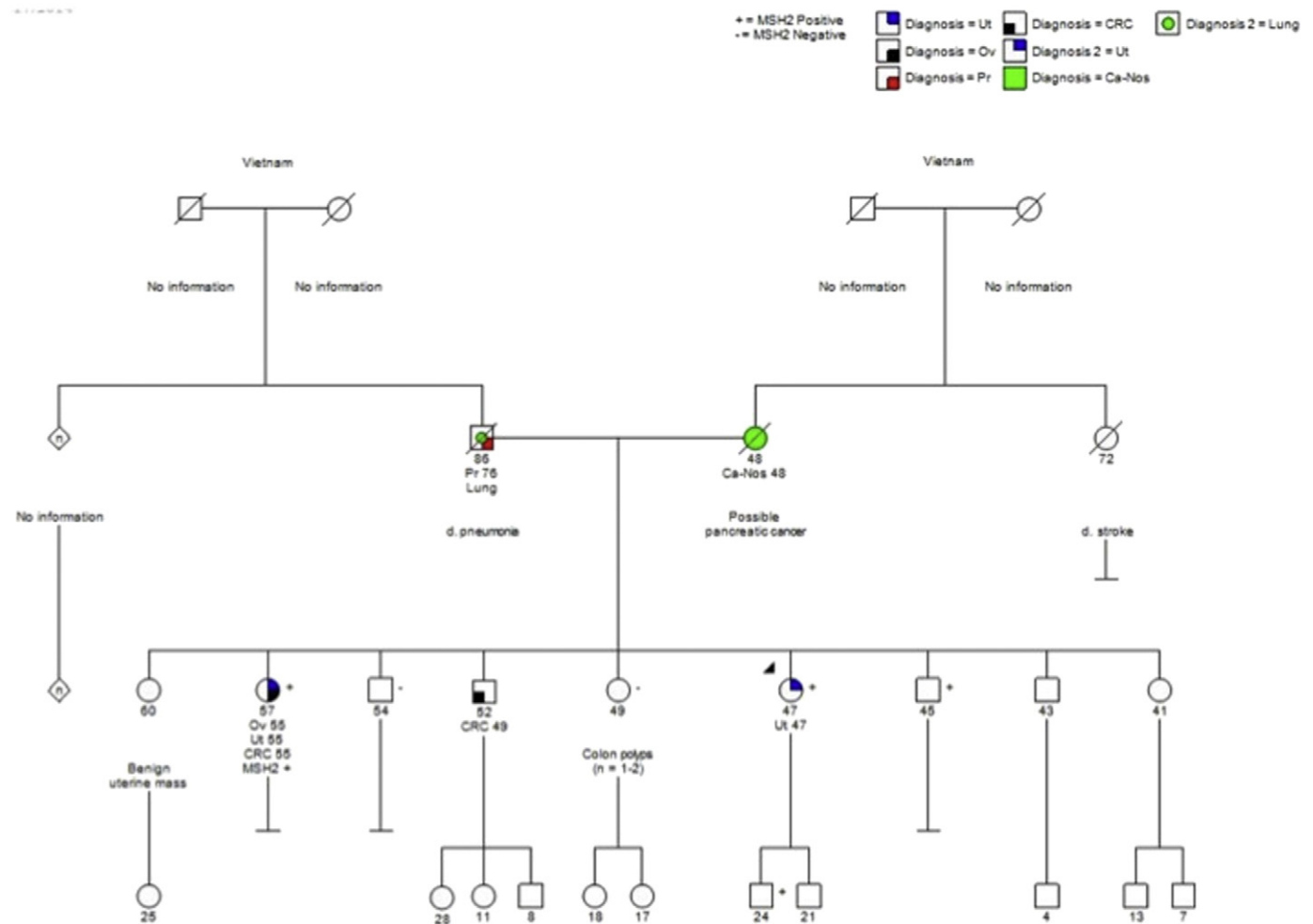
Patient #1 is a 57 year-old female who fled Vietnam in 1980. In February 2010 she was found to have an 8 cm complex right adnexal mass on ultrasound. She did not report any postmenopausal vaginal bleeding or gastrointestinal symptomatology. A pre-operative computed tomography (CT) scan demonstrated the pelvic mass and a mid-colonic lesion. The patient underwent open hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic/para-aortic lymphadenectomy and transverse colectomy with primary anastomosis. Pathology was

consistent with 3 synchronous lesions: FIGO stage IA grade 1 endometrial carcinoma, FIGO IC clear cell ovarian carcinoma, and stage I adenocarcinoma of the colon. She received adjuvant platinum- plus taxane-based intravenous chemotherapy.

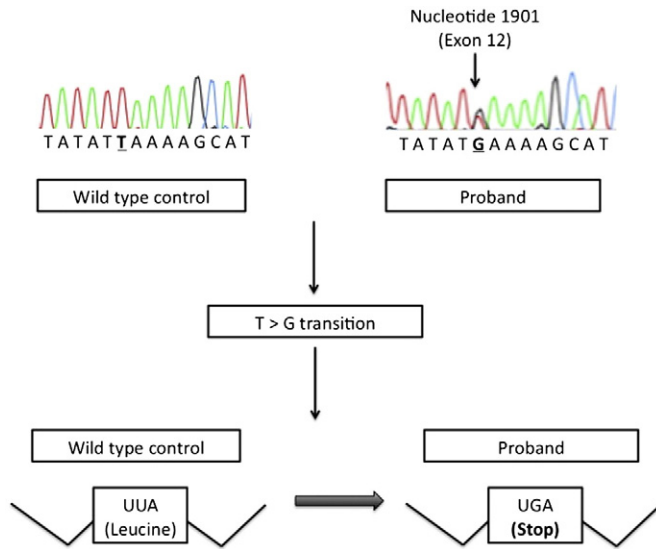
In October 2012, the proband's sister Patient #2 reported menorrhagia and was diagnosed with grade 2 endometrioid adenocarcinoma. She was referred to the same Gynecologic Oncologist that cared for her sister and provided a more detailed family history (colon cancer in her brother (age 49) and maternal pancreatic cancer (deceased age 48)). She underwent a robotic hysterectomy with bilateral salpingo-oophorectomy and lymphadenectomy. Final pathology revealed a FIGO stage IA, grade 2 endometrioid adenocarcinoma with no lymphovascular space invasion. IHC screening of the tumor for MLH1, MSH2, MSH6, and PMS2 was positive for LS. Both sisters and their brother were referred for genetic counseling.

**Case Histories: Vietnamese–American Kindred**

A comprehensive family pedigree was created (Fig. 1) which demonstrated 9 cases of carcinoma occurring over 3 generations. The proband (subject III–II) had 8 siblings, and of these, 2 had a diagnosis of carcinoma (including her sister, subject III–VI, described above). Independent genetic testing confirmed an *MSH2* mutation (L634X (1901T > G) in the proband, her sister, and additional unaffected brother (III–VII) (Fig. 2).



**Fig. 1.** Vietnamese–American kindred family pedigree. A total of 9 cases of carcinoma, occurring over 3 generations were identified. Subject III–II had synchronous ovarian, uterine and colon cancer. Subject III–VI had uterine cancer. Subject III–IV was diagnosed with colon cancer but has not had genetic testing. Three unaffected family members have been tested and one (III–VII) carries the deleterious *MSH2* mutation. Lastly, subject IV–VI elected to proceed with genetic counseling and testing at age 24 and was confirmed to carry the same *MSH2* deleterious mutation.



**Fig. 2.** Sequencing studies with wild type thymine (T) to guanine (G) transition at amino acid 1901, of codon 634 in exon 12 (L634X (1901T>G)). This single site mutation results in insertion of a UGA stop codon and premature truncation of the *MSH2* protein product.

This novel homozygous T to G *MSH2* point mutation occurred in codon 634 of exon 12, and resulted in premature truncation of the *MSH2* protein, with stop codon UGA substituted for UUA, which normally codes for amino acid leucine. Subject III–IV's son (IV–VI) (age 24) underwent counseling/testing and was found to carry the same deleterious mutation. Affected family members have been advised to undergo colonoscopy every 1–2 years, upper endoscopy with extended duodenoscopy every 3–5 years, annual urinalysis, and annual physical examination.

## Discussion

The DNA MMR system plays a pivotal role in eliminating the mismatch of base–base insertions and deletions resulting from polymerase errors during DNA synthesis. The MMR genes are also involved in ensuring the fidelity of genetic recombination, and facilitating the apoptotic response to DNA damage.

Together, the MMR gene products function as heterodimers. Nearly 80% of *MSH2* is found in a complex involving *MSH2*–*MSH6*, and it functions to recognize the mismatch of base–base insertions and deletions, and can also recognize large deletions and insertions. Mutations in *MSH2* have been reported in 36% of MMR germline variants (Moline et al., 2013). While most variants are nonsense or frameshift mutations that do not yield a stable protein product, 18% of *MSH2* variants are missense variants that may affect only a single amino acid.

While truncated *MSH2* protein product has been reported previously in the *MSH2* initiation codon on chromosome 2p16, in the kindred we have described that the truncated protein is a result of a mutation more downstream in exon 12 that results in premature truncation of the protein at amino acid 634. In the absence of mutation, the *MSH2*–*MSH6* heterodimer binds to single-base mismatches or insertions via paired N-terminal mismatch binding domains, while the *MSH2*–*MSH3* binds to larger insertion/deletion loops in DNA (Peltomaki, 2003). It is not known whether the truncated *MSH2* protein resulting from our kindred's mutation will affect the binding and/or biochemical activity of the *MSH2*–*MSH6* or *MSH2*–*MSH3* heterodimers.

The truncated product lacks evolutionary domains required for *MSH6* interaction, DNA binding and ultimately excision repair (Lynch and de la Chapelle, 2003; Peltomaki, 2003). The identification of mutation carrier status is of significant clinical importance, as there are clear implications for all members of the family. Specifically, institution of appropriate

screening measures, as well as risk reducing surgery (hysterectomy and bilateral salping-oophorectomy, subtotal colectomy), where appropriate, may translate into prevention and/or early detection of LS-related cancers. Identification of non-carriers will alleviate anxiety and prevent unnecessary procedures. Lack of healthcare insurance and financial hardships related to co-pays have been the primary obstacles to comprehensive family testing.

The societal and medical implications of delayed diagnosis in the Vietnamese–American population are implicit, and implementation of appropriate screening algorithms has gained attention in recent years. It is recognized from survey-based studies conducted over the past 15 years that the Vietnamese–American population lags behind other Asian groups in general health maintenance, health-related education and cancer screening. Studies exploring adherence to mammography and cervical cancer screening describe one of the most commonly reported barriers as lack of physician/health care provider education (McPhee et al., 1997). Programs utilizing lay health care workers and media education, created and implemented in both California and Texas, have shown promise by significantly increasing the rates of receipt and maintenance of breast and cervical cancer screening tests.

This report details the identification of an *MSH2* mutation in a large Vietnamese kindred, and highlights the importance of physician and patient awareness. Moving forward, local and state-based databases will be mined in an effort to detect familial cancer trends in this population that had gone previously unrecognized. Additionally, the development of culturally sensitive community outreach and awareness programs in order to promote recognition and education will be a priority. Identification and appropriate counseling as they relate to hereditary cancer syndromes are imperative.

## Conflict of interest

None of the authors have any relevant financial conflicts of interests to disclose.

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