Lynch Syndrome: The GYN Oncologist’s Perspective

Karen Lu, MD
Professor and Chair
Department of Gynecologic Oncology and Reproductive Medicine
Co-Medical Director
Clinical Cancer Genetics
Autosomal Dominant Inheritance

- Each child has 50% chance of inheriting the mutation
- No “skipped generations”
- Equally transmitted by either parent

```
  Non-carrier
  ∵
 ∵
  Carrier
```

```
  Non-carrier
  ∵
 ∵
  Carrier
```

```
  Non-carrier
  ∵
 ∵
  Carrier
```

```
  Non-carrier
  ∵
 ∵
  Carrier
```

```
  Non-carrier
  ∵
 ∵
  Carrier
```

```
  Non-carrier
  ∵
 ∵
  Carrier
```

```
  Non-carrier
  ∵
 ∵
  Carrier
```

```
  Non-carrier
  ∵
 ∵
  Carrier
```

```
  Non-carrier
  ∵
 ∵
  Carrier
```
Hereditary Cancer Syndromes

- Characterized by
  - Generally younger age of onset
  - More than one cancer in one patient
  - Multiple individuals in a family with cancer
Hereditary Cancer Syndromes with Endometrial Cancer

- Hereditary Non-polyposis Colorectal Cancer Syndrome (HNPCC), or Lynch Syndrome
  - Characterized by increased numbers of colon and endometrial cancers in a family
  - Germline mutation in mismatch repair gene (MLH1/MSH2/MSH6/PMS2)

- Cowden’s Syndrome
  - Characterized by intestinal hamartomas, breast cancer and endometrial cancers
  - Germline mutation in PTEN
Overview

- What is Lynch syndrome?
- What can we learn from Lynch syndrome about prevention
- Remaining challenges to consider
Historical Perspective

Aldred S. Warthin, MD, PhD
Lynch I: Autosomal dominant colon cancer only families

- Lynch II: Autosomal dominant colon cancer with endometrial, ovary, small bowel, stomach cancers

Henry T. Lynch, MD
The Human Mutator Gene Homolog MSH2 and Its Association with Hereditary Nonpolyposis Colon Cancer

Richard Fishel,* Mary Kay Lescoe,* M. R. S. Rao,§ Neal G. Copeland,† Nancy A. Jenkins,‡ Judy Garber,‡ Michael Kane,§ and Richard Kolodner§
*Department of Microbiology and Molecular Genetics
†Mary-Kay Center for Molecular Genetics
University of Vermont Medical School
Burlington, Vermont 05405
‡Mammalian Genetics Laboratory
Advanced BioScience Laboratories Basic Research Program
National Cancer Institute
Frederick Cancer Research and Development Center
Frederick, Maryland 21702
§Division of Cellular and Molecular Biology
Dana–Farber Cancer Institute
Boston, Massachusetts 02115

Summary

We have identified a human homolog of the bacterial MutS and S. cerevisiae MSH proteins, called hMSH2. Expression of hMSH2 in E. coli causes a dominant mutator phenotype, suggesting that hMSH2, like other divergent MutS homologs, interferes with the normal bacterial mismatch repair pathway. hMSH2 maps to human chromosome 2p22-21 near a locus implicated in hereditary nonpolyposis colon cancer (HNPCC). A T to C transition mutation has been detected in the -6 position of a splice acceptor site in sporadic colon tumors and in affected individuals of two small HNPCC kindreds. These data and reports indicating that S. cerevisiae msh2 mutations cause an instability of dinucleotide repeats like those associated with HNPCC suggest that hMSH2 is the HNPCC gene.

can give rise to mismatched bases (Friedberg, 1985). For example, the deamination of 5-methylcytosine creates a thymine and, therefore, a G:T mispair (Duncan and Miller, 1980). Second, misincorporation of nucleotides during DNA replication can yield mismatched base pairs and nucleotide insertions and deletions (Modrich, 1991). Finally, genetic recombination produces regions of heteroduplex DNA that may contain mismatched nucleotides when such heteroduplexes result from the pairing of two different parental DNA sequences (Holliday, 1964). Mismatched nucleotides produced by each of these mechanisms are known to be repaired by specific enzyme systems (Friedberg, 1990; Modrich, 1991).

The best-defined mismatch repair pathway is the Escherichia coli MutS pathway that promotes a long patch (approximately 2 kb) excision repair reaction that is dependent on the mutH, mutL, mutS, and mutU (uvrD) gene products (Modrich, 1989, 1991). The MutS pathway appears to be the most active mismatch repair pathway in E. coli and is known both to increase the fidelity of DNA replication (Ryderberg, 1979) and to act on recombination intermediates containing mispaired bases (Wagner and Meselson, 1975; Fishel et al., 1986). This system has been reconstituted in vitro and requires the MutH, MutL, MutS, and UvrD (helicase I) proteins along with DNA polymerase III holoenzyme, DNA ligase, single-stranded DNA-binding protein, and one of the single-stranded DNA exonucleases (ExoI, ExoIV, or RecJ) (Modrich, 1989, 1991; Lahue et al., 1989; Cooper et al., 1993). MutS protein binds to the mismatched nucleotides in DNA (Siu and Modrich, 1990).

MutS protein interacts with GATC sites in DNA that are hemimethylated on the adenine and is responsible for incision of the unmethylated strand (Welsh et al., 1987). Specific incision of the unmethylated strand results in increased fidelity of replication because excision repair is targeted to the newly replicated unmethylated DNA strand. MutL facilitates the interaction between MutS bound to the mismatch and MutH bound to the hemimethylated Dam site, resulting in the activation of MutH (Grilley et al., 1989). UvrD is the helicase that appears to act in conjunction with one of the single-stranded DNA-specific exonucleases to excise the unmethylated strand, leaving a scar that is repaired by the action of DNA polymerase.
Genetics of Lynch Syndrome

- Genes associated with Lynch syndrome belong to the DNA mismatch repair family
  - MLH1, MSH2, MSH6, PMS2
Lifetime risk of cancer in Lynch syndrome

![Bar chart showing lifetime risk of cancer in Lynch syndrome for ovarian, uterine, and colon cancers, comparing general population, Lynch women, and Lynch men.](chart.png)
## Risk of Endometrial and Colorectal Cancer in Women with Lynch syndrome

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Population</th>
<th>Mutation</th>
<th>Lifetime Risk Endometrial Cancer</th>
<th>Mean Age @ Dx of Endo Ca (Range)</th>
<th>Lifetime Risk Colorectal Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aarnio (1999)</td>
<td>Finland</td>
<td>MLH1, MSH2</td>
<td>60%</td>
<td></td>
<td>54%</td>
</tr>
<tr>
<td>Barrow (2009)</td>
<td>UK</td>
<td>MLH1, MSH2, MSH6</td>
<td>47%</td>
<td></td>
<td>46%</td>
</tr>
<tr>
<td>Stoffel (2009)</td>
<td>US</td>
<td>MLH1, MSH2, MSH6</td>
<td>39%</td>
<td>47</td>
<td>43%</td>
</tr>
<tr>
<td>Baglietto (2010)</td>
<td>Multiple countries</td>
<td>MSH6 only</td>
<td>26% to age 70, 44% to age 80</td>
<td>53</td>
<td>10% to age 70, 20% to age 80</td>
</tr>
</tbody>
</table>
How common is Lynch syndrome

- General population: 1/500 - 1/1000
- Endometrial cancer: 2-3%
Pathology of Lynch syndrome associated endometrial cancer (Broaddus et al, Cancer 2006)

- Compared Lynch endometrial cancers with sporadic endometrial cancers.
- Includes full spectrum of histologies, mostly endometrioid, but also papillary serous and clear cell (MSH2).

- In contrast to BRCA-associated ovarian cancers, which are almost uniformly high grade serous.
Pathology of Lynch syndrome associated endometrial cancer

(Westin et al, J Clin Onc, 2008)

- Lower uterine segment endometrial cancers, which can often be mistaken for cervix adenocarcinomas, occur more often in Lynch syndrome
- 10 of 35 (29%) had Lynch

- Similar to increased incidence of “right-sided colon cancer” in Lynch pts
Prevalence of Lynch in endometrial cancer patients under age 50

(Lu et al, J Clin Onc, 2007)

- 9/100 (9%) had Lynch syndrome mutations (7 MSH2, 1 MLH1, 1 MSH6)
- 7/9 had 1st degree relative with Lynch syndrome
- BMI for patients with Lynch: 29.2
  BMI for whole cohort: 34.4 (p=0.01)
- Similar to 9% rate (5/58) in study by Berends et al
Overview

- What is Lynch syndrome?
- What can we learn from Lynch syndrome about prevention
- Remaining challenges to consider
Chemoprevention: Possible agents

Oral Contraceptive:
- The Cancer and Steroid Hormone Study (CASH) demonstrated that use of oral contraceptives can reduce the risk of endometrial cancer by 50%.
- Endometrial proliferation is inhibited after the first few cycles of OCP use.

Progesterone:
- Progesterone is used clinically as a treatment for endometrial hyperplasia.
- Hyperplasia with and without atypia can be converted to normal endometrium by treatment with progesterone.
- Mirena IUD
Study Design (N01-CN-05127)

Women, age 25-50, with documented Lynch gene mutation (n=50)

Baseline: transvaginal ultrasound and endometrial biopsy

Randomize to OCP or DepoMPA

3 months: transvaginal ultrasound and endometrial biopsy
Number of women screened for eligibility:
Cumulative numbers

<table>
<thead>
<tr>
<th>Site</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDACC</td>
<td>50</td>
<td>100</td>
<td>150</td>
<td>238</td>
<td>313</td>
<td>333</td>
</tr>
<tr>
<td>Creighton</td>
<td>47</td>
<td>98</td>
<td>173</td>
<td>182</td>
<td>212</td>
<td>220</td>
</tr>
<tr>
<td>UCSF</td>
<td>37</td>
<td>50</td>
<td>80</td>
<td>125</td>
<td>145</td>
<td>155</td>
</tr>
<tr>
<td>Cumulative Total</td>
<td>134</td>
<td>248</td>
<td>403</td>
<td>545</td>
<td>670</td>
<td>708</td>
</tr>
</tbody>
</table>
Results: Primary Endpoint Ki-67

![Boxplot showing Ki-67 levels for Depo-Provera and OCP before and after treatment.](image-url)
Results: Histology

• **Good responses**
  - 22/23 in OCP arm *
  - 20/23 in depoMPA arm

• **Poor responses**
  - 0/23 in OCP arm
  - 3/23 in depo MPA arm

* Pathologic finding in 1/23 in OCP arm: small foci of complex hyperplasia without atypia in background of atrophy
## Results: Pre- and post-tx TVS

<table>
<thead>
<tr>
<th>Endometrial thickness (mm)</th>
<th>depoMPA</th>
<th>OCP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>5.5</td>
<td>6.5</td>
<td>0.19</td>
</tr>
<tr>
<td>Range</td>
<td>2.6-10.1</td>
<td>2.0-19</td>
<td></td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4.5</td>
<td>4.5</td>
<td>0.93</td>
</tr>
<tr>
<td>Range</td>
<td>1.0-9.3</td>
<td>2.0-10.0</td>
<td></td>
</tr>
<tr>
<td><strong>Overall change</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.9</td>
<td>1.7</td>
<td>0.22</td>
</tr>
<tr>
<td>Range</td>
<td>-5.0 to 6.0</td>
<td>-1.0 to 5.0</td>
<td></td>
</tr>
</tbody>
</table>
Results: Point estimate of baseline endometrial abnormalities in asymptomatic Lynch+ women

- 2/51 women: 3.9% (95% CI: 0.5% to 13.5%) of asymptomatic pre-menopausal women with Lynch syndrome had complex atypical hyperplasia (CAH).

- While 2 cases were both CAH on EMB, subsequent hysterectomy showed endometrioid adenoCA grade 1, Stage Ia for both.
Conclusions: Clinical findings

- Confirmation of short-term ability of OCP and DepoProvera in women with Lynch syndrome
  - decrease proliferation (Ki-67)
  - induce atrophy of glands

- There is preliminary evidence to support efficacy of OCP or progestin as a chemoprevention strategy for women with Lynch syndrome
Conclusions: Clinical findings

- TVS not sensitive at detecting complex hyperplasia or early endometrial cancer in asymptomatic women with Lynch syndrome.

- Point estimate of having endometrial hyperplasia or cancer in asymptomatic women with Lynch syndrome is 4%.

- Follow-up: European study of Mirena IUD did not complete accrual.
Where do we go from here?

• Prevention: Do OCPs prevent Type 1 and Type 2 endometrial cancers
  – In Lynch syndrome?
  – In sporadic endometrial cancer?

• Prevention: Opportunity for “local” prevention

• Prevention: If OCPs are such a good preventive agent for endometrial cancer (and ovarian cancer), why don’t women know about it?