

# Esophageal Cancer Cases

Quiz Questions:

Relationship between proto-oncogene and oncogene?

Examples:

Ras

HER2/neu

MYC

## **Tumor Suppressor Genes**

### **FAP Prophylactic Surgery**

- Total proctocolectomy with ileoal pouch
- Total colectomy with ileorectal anastomosis
- Proctocolectomy with end ileostomy

### **Lynch Syndrome Prophylactic Surgery**

- No role for prophylactic colon surgery
- Prophylactic hysterectomy with BSO

## **BRCA 1/2 Prophylactic Surgery**

- Bilateral mastectomy reduces lifetime risk 90%
- Surveillance is a reasonable option
  - Yearly mammogram
  - Yearly breast MRI

## **BRAC 1/2 Prophylactic Surgery**

- Prophylactic BOS age 35-40 or after childbearing
- Reduces risk of ovarian cancer 80%
- Surveillance not as effective
  - Transvaginal ultrasound
  - CA-125 screening

## **MEN 2A/2B or FMTC Prophylactic surgery**

- Timing of thyroidectomy depends upon risk category
- Highest risk: Thyroidectomy within first year of life
- High risk: Thyroidectomy by age 5 or if calcitonin elevated
- Moderate risk: surveillance starting age 5
  - physical exam
  - neck ultrasound
  - serum calcitonin

## **FAP**

Median age of dx 39

- Duodenal and ampullary tumors
- Gastric polyps
- Thyroid tumors
- Desmoid tumors

## **FAP screening**

Colonoscopy age 10-12 EGD for duodenal polyps at age 20-30  
CT 1-3 years after colectomy and q5 yers in those with family  
hx of desmoids

## **Lynch**

Amdterdam Criteria

(Bethesda Criteria)

Mean age dx colon cancer 44-61 Predominant right side colon  
cancer Lifetime penetrance 82%

## **Lynch Other Cancers**

- Endometrial
- Stomach
- Ovarian
- Urinary tract
- Biliary Tract
- Small bowel
- CNS

## **Lynch Screening**

Colonoscopy q1-2 years staring age 20-25

Women with Lymch have 25-60% lifetime risk of endometrial  
cancer 45-12% lifetime risk of ovarian cancer Male: 1.2% risk  
of breast cancer (0.1% in general populations)

## MMR and MSI

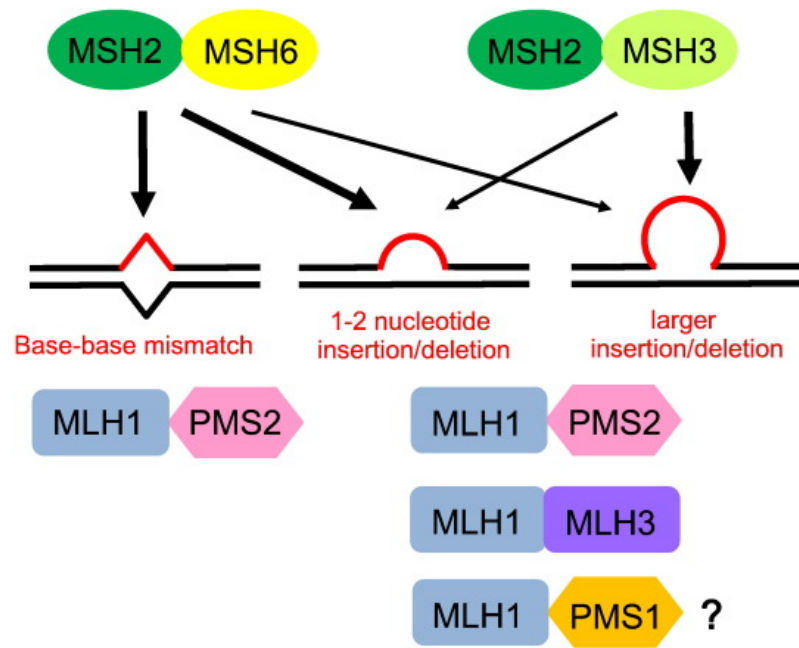
Greater than 90% of LS tumors are MSI-high (MSI-H) and/or lack expression of at least one of the MMR proteins by IHC. Ten percent to 15% of sporadic colon cancers exhibit abnormal IHC and are MSI-H most often due to abnormal methylation of the MLH1 gene promoter, rather than due to LS. Mutant BRAF V600E is found in many sporadic MSI-H CRCs and is rarely found in LS-related CRCs. There are some tumors that will have MLH1 methylation but lack a BRAF PV.

## DNA Mismatch Repair Proteins



## DNA Mismatch Repair Proteins

MLH1 PMS1 MSH6 MSH2 MSH5



## DNA Mismatch Repair Proteins



## Mismatch Repair Proteins in Lynch Syndrome

Lynch Syndrome can be caused by loss of expression of:

- MLH1
- PMS1
- MSH6
- MSH2
- MSH5

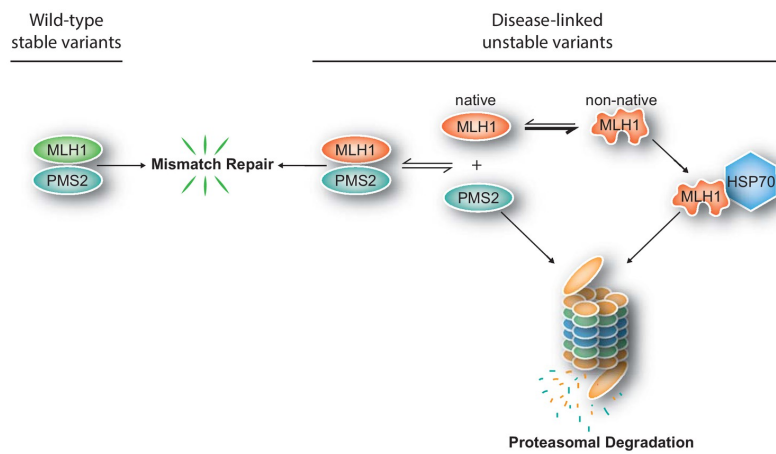
## MLH1 and PMS Dimer in Mismatch Repair

wild-type MLH1 and PMS2 form a stable heterodimer



## MLH1 and PMS Dimer in Mismatch Repair

Mutant MLH1 fails to form a stable heterodimer



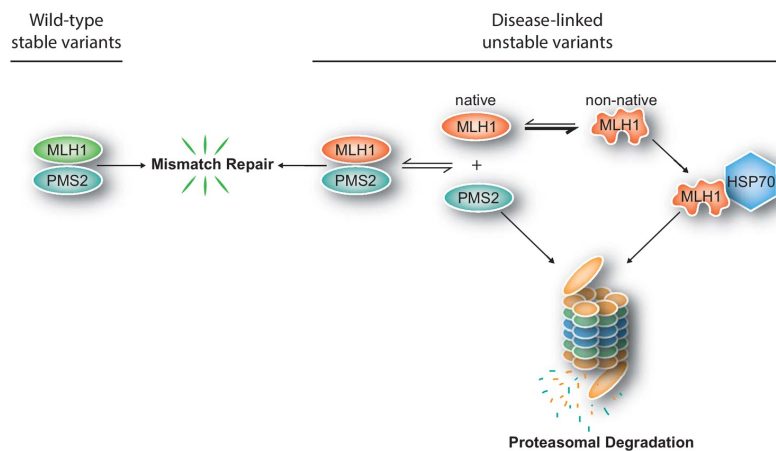
## MLH1 and PMS Dimer in Mismatch Repair

Mutant MLH1 fails to form a stable heterodimer → PMS2 is degraded



## MLH1 and PMS Dimer in Mismatch Repair

If MLH1 is mutated → PMS2 protein is *not* detected



## Colon Polyposis: >10 adenomatous polyps

- Classical FAP
- Attenuated FAP (AFAP)
- MUTYH-associated polyposis (MAP)
- Colonic adenomatous polyposis of unknown etiology (CPUE)



## **Colon Polyposis: >4 hamartomatous polyps**

- Puetz-Jaghers
- Juvenile Polyposis Syndrome
- Cowden Syndrome/PTEN Hamartoma Tumor Syndrome

## **Serrated Colon Polyps**

5 serrated polyps/lesions proximal to the rectum, all being 5 mm in size, with 2 being 10 mm in size OR >20 serrated polyps/lesions of any size distributed throughout the large bowel, with 5 being proximal to the rectum

## **Muir-Torre Syndrome**

Muir-Torre syndrome refers to individuals with LS who have LS-associated skin findings of sebaceous adenomas/carcinomas or keratoacanthomas.

## **BRCA 1/2**

BRCA1: 87% lifetime risk of breast cancer and 40-60% risk of ovarian cancer

BRCA2: 80% lifetime breast cancer and 15-27% ovarian cancer  
- Elevated risk of prostate, pancreas, melanoma

Male carriers of BRCA2: 8.9% lifetime risk of breast cancer

## **BRCA risk factors:**

- Breast cancer dx before age 40
- Bilateral breast cancer
- Breast and ovarian cancer
- 2 family members with breast cancer < age 50
- Family history of breast and ovarian
- Family history of male breast cancer

## **Attenuated FAP**

~30 polyps 70% penetrance by age 80 - mean age at dx 50-55

## **Li-Fraumeni**

Mutation of TP53 tumor suppressor gene

- Breast cancer 90% by age 50
- Sarcoma
- Leukemia
- Brain tumors
- Adrenocortical carcinoma

## **Breast cancer in Li-Fraumeni**

Mastectomy favored to avoid radiation therapy

Bilateral prophylactic mastectomy recommended

## **p16 = CDKN2A mutation**

- Increased risk of melanoma
  - Familial Atypical Multiple Mole Melanoma (FAMMM)
  - Familial Atypical Multiple Mole-Pancreatic Carcinoma (FAMMMPC)
- Melanoma penetrance 58-92% by 80
- Pancreatic cancer penetrance 17% by age 75

## **FAMMM**

- Malignant melanoma in one or more first degree or second-degree relatives
- High total body nevus count
- Nevi with certain features on microscopy

Genetic testing not performed as only 50% of FAMMM harbor a mutation in CDKN2A

## Neurofibromatosis 1

Mutation in NF1 tumor suppressor gene

- Multiple neurofibromas
- Cafe au lait spots
- Lisch nodules (hamartoma of the iris)

Risk of - NPNST - Pheochromocytoma - Astrocytoma - Leukemia

## NF1 diagnosis

Two or more of the following 6 criteria:

- Six or more café-au-lait macules
- Two or more neurofibromas or one plexiform neurofibroma
- Axillary or inguinal freckling
- Optic glioma
- Two or more Lisch nodules
- Characteristic osseous lesions
- A first degree relative with NF1

## Neurofibromatosis 2

NF2 gene

- Multiple neurofibromas
- Cafe au lait spots
- Bilateral vestibular schwannomas
- CNS tumors

Most affected develop bilateral schwannomas by age 30 with average age of death 26

Annual surveillance MRI starting age 10-12 and hearing evaluation

## **PTEN**

Cowden Syndrome Mutation in *PTEN* tumor suppressor gene

- Mucocutaneous facial lesions
- Macrocephaly
- Bilateral breast cancer
- Thyroid and endometrial tumors
- Hamartomatous polyposis of the GI tract

## **MEN1**

- Mutation of MENIN tumor suppressor
- Parathyroid
- Pituitary
- Pancreatic islet cells

Hyperparathyroidism usually first presentation Most common pancreatic tumor is non-functional

Dx by 2/3 of following:

- Parathyroid adenoma/hyperplasia
- Pancreatic islet cell tumors
- Pituitary tumors

## **MEN1 screening**

Surveillance with serum prolactin, IGF-1, fasting glucose and insulin starting age 5 Calcium, chormogranin A, pancrea polypeptide glucagon AP age 8 Serum gastrin starting age 20 Brain MRI starting age 5 Abdominal CT/MRI starting age 20

## **MEN1 surgical treatment**

Parathyroidectomy 3.5 gland or 4 glands with autotransplantation

Pancreatic tumor resection if >2cm

Pituitary tumors resected via transsphenoidal

## **MEN2 Family of Syndromes**

- RET proto-oncogene
- Medullary thyroid cancer in almost 100%
- MEN2A
  - pheochromocytoma in 50%
  - Parathyroid hyperplasia in 20-30%

-MEN2B - pheochromocytoma in 50% - Megacolon - Marfanoid habitus - Ganglioneuromas - Mucosal neuromas

## **MEN 2 Prophylactic surgery**

Prophylactic total thyroidectomy

Testing for pheochromocytoma prior with adrenalectomy

Monitor calcitonin and CEA after thyroidectomy

## Orientation Handbook



## References