Tumori Colorettali Ereditari:
dall'indagine genetica alla gestione clinica

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The Fractions of Colorectal Cancer that arise in various Family Risk Settings

SPORADIC CASES
70-80%

HAMARTOMATOUS SYNDROMES
<0.1%

CASES WITH FAMILIAL RISK
10-30%

FAP
≤1%

Lynch
1-5%

SPORADIC CASES
70-80%
**Lynch Syndrome: clinical features**

- Genetic disease inherited as an autosomal dominant trait
- Frequency: 1-5% of all colorectal cancer burden
- Early age of onset, very often before 50 years of age
- Preferential proximal colonic site of tumor (from caecum to the splenic flexure)
- Synchronous and metachronous tumors (colon, other organs)
- Increased risk of cancer in endometrium, renal pelvis and urether, small bowel, ovary, stomach)
**Lynch Syndrome: genetic features**

- In early 90's genetic causes began to be uncovered
- **Mutations in Mismatch Repair (MMR) genes:** *MLH1* (3p21) or *MSH2* (2p21-22), *MSH6* (2p21), *PMS2* (7p22), *EPCAM*,
- Inactivation of the MMR system causes genomic instability, particularly evident at DNA microsatellites.
- Microsatellites are highly repeated mono- or oligonucleotides DNA sequences widespread in the genome (Microsatellite instability, MSI)
- Genomic instability is the reason why colorectal carcinogenesis is accelerated in Lynch syndrome patients.
Proteins involved in mismatch repair

Jiricny et al, Curr Opin Genet Dev 2000
Immunohistochemical expression of MMR proteins

- MSH2
- MSH6
- MLH1
- PMS2
AMSTERDAM CRITERIA II (ACII)

- At least 3 cases of Lynch-related cancers (colorectal, endometrium, small bowel, urothelium), one of them should be first-degree relative of the other two
- At least two generations should be affected
- At least one case should be diagnosed before 50 yrs

(Gastroenterology, June 1999)
Center of Hereditary Colorectal Tumors
University of Modena and Reggio Emilia

- Founded in 1984, based on a Colorectal Cancer Registry
- National Center of referral
- Belonging to the Emilia-Romagna region network of Rare Diseases (Lynch syndrome and Familial Adenomatous Polyposis)
- Research, guidelines, scientific knowledge sharing to the population
Mutated genes in the 101 Lynch families followed-up by the Center (since 1984)

<table>
<thead>
<tr>
<th>Mutated gene</th>
<th>Nº of affected families</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLH1</td>
<td>41</td>
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<tr>
<td>MSH2</td>
<td>43</td>
</tr>
<tr>
<td>MSH6</td>
<td>12</td>
</tr>
<tr>
<td>PMS2</td>
<td>3</td>
</tr>
<tr>
<td>EPCAM</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>101</td>
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</tbody>
</table>
Lynch syndrome: surveillance

- Colonoscopy starting at 25 yrs or 5 yrs before the age of earlier diagnosis in the family. Repeat every 2 years

- Gynecological ultrasound examination starting at 30 yrs or 5 years before the age of earlier diagnosis in the family. Repeat every 2 years

- Abdominal ultrasound and cytological urine analysis starting at 30 years, only if kidney tumor present in the family. Repeat every 2 years
Lynch syndrome: surgical management

• Total colectomy with ileorectal anastomosis is the surgical intervention suggested in affected mutation carriers

• Prophylactic colectomy, or histero-oophorectomy should be considered in healthy mutation carriers not willing or not able to undergo examinations
Conclusions

• Familiarity for colorectal cancer is frequent and a hereditary syndrome should be always suspected
• A nuclear pedigree should be traced and genetic tests on histological materials and, when appropriate on constitutional DNA should be offered to the proband, and, when positive, to all unaffected relatives at risk older than 18, too
• Lynch syndrome is a rare disease, and a typical case of the «research to clinical practice» approach in Internal Medicine
Microsatellite instability (mono- and dinucleotides)

BAT 26

D2S123
Diagnosis of CRC

Tumor Testing

For defective MMR by IHC

Normal proteins

Abnormal proteins

Sporadic CRC

Loss of MLH1 and PMS2

Analysis of MLH1 promoter methylation or BRAF V600E testing

Positive

Sporadic CRC

Negative

Sporadic CRC

Loss of MSH2 or MSH6 or PMS2

For MSI by PCR

MSI-high

MSI-low

No MSI

Sporadic CRC

For somatic mutations by NGS

Positive

Genetic testing of relatives

Lynch-like Syndrome (loss of MMR proteins and/or MSI)

Negative

Lynch-like Syndrome

Double somatic mutation

Genetic testing of relatives

Positive for MMR mutation = Lynch Syndrome

Negative for MMR mutation

Germline genetic testing

Sporadic CRC