Genetics in Young Onset CRC

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Trends in CRC Incidence by Age

Increasing
By 1.5%/year

1 in 10 CRCs

ACS Guidelines: Begin CRC screening at age 45

Colorectal Cancer Screening for Average-Risk Adults: 2018 Guideline Update From the American Cancer Society

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Case 1

Prostate Ca
Age 80

Colon Ca
Age 36

Stomach Ca
Age 70
Epidemiology of CRC (ca. 1996)

- Sporadic (65%–85%)
- Familial (10%–30%)
- Rare syndromes (<0.1%)
- Lynch Syndrome (2-3%)
- Familial adenomatous polyposis (FAP) (1%)
Germline Mutations in CRC (2017)

N=1,058 CRC patients tested with multigene panels

Yurgelun M et al JCO 2017

1 in 10 have germline mutations

No germline mutation 90.1%

High-penetrance mutations* 5.2%

Moderate-penetrance mutations 4.7%

Lynch syndrome (3.1%)
- MLH1 (n = 13)†
- MSH2 (n = 7)
- MSH6 (n = 6)
- PMS2 (n = 7)

Adenomatous polyposis (0.8%)
- APC (n = 5)
- Biallelic MUTYH (n = 3)

BRCA1/2 (1.0%)
- BRCA1 (n = 3)
- BRCA2 (n = 8)†

Other high-penetrance mutations (0.4%)
- PALB2 (n = 2)
- CDKN2A (n = 1)
- TP53 (n = 1)

Other moderate-penetrance mutations (1.5%)
- ATM (n = 10)
- BARD1 (n = 1)
- BRIP1 (n = 3)
- NBN (n = 2)

Moderate-penetrance mutations (3.2%)
- Monoallelic MUTYH (n = 18)‡
- APC*1307K (n = 14)‡
- CHEK2 (n = 2)
CRC Risk Assessment

• Age

• Personal hx
  – Colorectal neoplasia
  – Inflammatory bowel disease

• Family history of CRC
Case 1

Prostate Ca
Age 80

Colon Ca
Age 36

Stomach Ca
Age 70

mismatch repair= proficient
Case 1

Prostate Ca
Age 80

Colon Ca
Age 36

Mismatch repair proficient
Germline pathogenic variant in PMS2

Stomach Ca
Age 70
Genetic Predisposition to Cancer

• Germline (heritable) variants in dozens of “cancer” genes

• Population prevalence
  – 1 in 300 for high penetrance (Lynch Syndrome)
  – 1 in 100 for moderate penetrance ($\text{MUTYH, CHEK2, ATM}$)

• Variable disease penetrance and expressivity

Image © Ralph A. Clevenger
### Characteristics of Patients with Young Onset Colorectal Cancer (N=430)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (N=430)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
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<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>213 (49.5%)</td>
</tr>
<tr>
<td>Male</td>
<td>217 (50.5%)</td>
</tr>
<tr>
<td><strong>Mean age dx (range)</strong></td>
<td>40.0 (16-49)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>318 (74.0%)</td>
</tr>
<tr>
<td>Non-White</td>
<td>31 (13.9%)</td>
</tr>
<tr>
<td><strong>MSI-Status</strong></td>
<td></td>
</tr>
<tr>
<td>MSI-H</td>
<td>41 (9.5%)</td>
</tr>
<tr>
<td>MSS</td>
<td>163 (37.9%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>226 (52.6%)</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td></td>
</tr>
<tr>
<td>FDR with CRC</td>
<td>111 (25.8%)</td>
</tr>
<tr>
<td><strong>Tumor stage</strong></td>
<td></td>
</tr>
<tr>
<td>0-I</td>
<td>54 (12.6%)</td>
</tr>
<tr>
<td>II</td>
<td>43 (10.0%)</td>
</tr>
<tr>
<td>III-IV</td>
<td>183 (42.6%)</td>
</tr>
<tr>
<td><strong>CRC Site</strong></td>
<td></td>
</tr>
<tr>
<td>Right colon</td>
<td>115 (26.7%)</td>
</tr>
<tr>
<td>Left colon</td>
<td>182 (42.3%)</td>
</tr>
<tr>
<td>Rectum</td>
<td>72 (16.7%)</td>
</tr>
<tr>
<td>Not specified</td>
<td>61 (14.2%)</td>
</tr>
</tbody>
</table>

CRC dx age<50
N=430

*Stoffel et al, Gastro 2018*
CRC

Assess for MMR Deficiency

MSI/IHC

MMR Proficient (85%)

Assess phenotype + Family history

MMR Deficient (15%)

Tumor absence of MLH1

Assess for somatic BRAF mutation

BRAF mutation and/or MLH1 promoter hypermethylation present

Referral for genetic testing for Lynch Syndrome

No family history and Personal history <10 polyps

No further testing

Personal history of >10 (20) polyps

Consider genetic referral

Family history (+) or Personal history + for other herald cancers

BRAF mutation absent (wild type) and/or absent MLH1 promoter hypermethylation

Tumor absence of MSH2, MSH6, or PMS2 (isolated)
Outcomes of **Clinical Evaluations in Young CRC**

CRC cases dx <50y, N=430

- Germline test performed, N=315
  - Positive, N=79 (18.4%)
  - Syndrome-Specific Sequencing, N=74
    - MMR (56)
      - MSH2 (25)
      - MLH1 (24)
      - MSH6 (5)
      - PMS2 (2)
    - APC (10)
    - MUTYH (7)
      - biallelic (4), monoallelic (3)
    - SMAD4 (1)
  - VUS, N=21 (4.9%)
  - Negative, N=215 (50.0%)
  - No testing, N=115

- Multigene Panel, N=5
  - BRCA1 (1)
  - CHEK2 (1)
  - MUTYH, monoallelic (1)
  - TP53 (1)
  - SMAD4 (1)

*Stoffel et al, Gastro 2018*
University of Michigan Cancer Genetics Clinic

CRC cases dx <50y, N=430

Germline test performed, N=315

Positive, N=79 (18.4%)
N=85 (19.8%)

Clinical Sequencing, N=75
- MMR (56)
  - MSH2 (25)
  - MLH1 (24)
  - MSH6 (5)
  - PMS2 (2)
- APC (10)
- MUTYH (7)
  - biallelic (4), monoallelic (3)
- SMAD4 (1)
- TP53 (1)

Clinical Multigene Panel, N=4
- BRCA1 (1)
- CHEK2 (1)
- MUTYH, monoallelic (1)
- SMAD4 (1)

VUS, N=21 (4.9%)

Negative genetic test, N=215 (50.0%)

No testing, N=115

Pathogenic mutations, N=6
- PMS2 (1)
- MSH6 (1)
- MUTYH (1)
- TP53 (1)
- POLE (1)
- APC (1)

Research NGS sequencing, N=117

1 in 5 young CRC pts had Actionable germline mutations

Stoffel et al, Gastro 2018
Germline Variants in CRC Age<50

- N=450 (Ohio population-based)
- Universal germline testing
  - Next generation sequencing
  - 25 gene panel
- 16% w/ Genetic Dx
  - Lynch Syndrome 8%
  - Polyposis 5% (APC, MUTYH, SMAD4)
  - 1 in 5 mutations found in “non CRC” genes
  - 1 in 3 did not meet criteria for the syndrome

Pearlman R JAMA Oncol 2017. 3:464-71
Why increase in Young CRC?

Can tumor phenotypes provide clues?

- Young tumors with different mutation and methylation profiles compared to older-onset
  - LINE-1 hypomethylation

Elena M. Stoffel MD MPH

Antelo M. PLoS ONE 2012
Survival in CRC Patients dx age<50 by Race

Holowatyj et al, JCO 2016
Modifiers of Cancer Risk

Genetics

Environment

Health Behaviors
Modifiers of Cancer Risk

- Genetics
- Health Behaviors
- Environment
- Diet
- Vitamin D
- Microbiome
- Inflammation
- screening
Hereditary Predisposition to CRC

- Adenomatous Polyposis
  - APC
  - MUTYH
  - POLE
  - POLD1
  - PTEN
  - SMAD4
  - BMPR1A
  - STK11

- Non-polyposis CRC
  - Lynch Syndrome
    - MLH1
    - MSH2
    - MSH6
    - PMS2
    - EPCAM
  - POLE
  - POLD1

- HAMartomatous/Mixed Polyposis CRC
  - BRCA1
  - BRCA2
  - PALB2

- Lynch Syndrome
  - MLH1
  - MSH2
  - MSH6
  - PMS2
  - EPCAM
Summary: Genetics in Young CRC

- Pathogenic germline variants in 1 in 5 (20%) CRC dx age<50
  - *Germline genetic testing for all young CRC*

- Use of multigene panels increases diagnostic yield of germline testing

- Most young onset CRCs are not associated with known highly-penetrant hereditary cancer syndromes