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Phenotypic Diversity of Lynch Syndrome and the Role of NGS in Its Molecular Characterization

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Introduction

Lynch syndrome (LS) is the most common cancer predisposition syndrome caused by pathogenic variants in mismatch repair genes (MMR PV), with a variable tumor spectrum. Diagnostic and treatment strategies for non-LS spectrum tumors remain suboptimal.

This study aimed to characterize the phenotypic features of LS patients in relation to MMR PV, as well as MSI.

Methods

MMR gene analysis was performed for patients with LS-associated tumors based on the results of routine testing (MSI/dMMR) using Sanger sequencing/NGS. For measuring MSI in non-LS spectrum (non-LSS) tumors, MSI-score was calculated using validated NGS-test (Solo-test Driver, OncoAtlas, Russia). Clinical data were extracted from medical records.

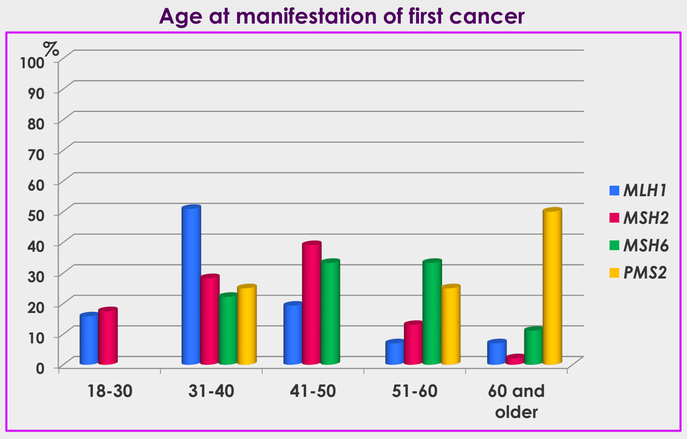
Results

MMR PV were identified in 119 patients:

- 57 in *MLH1* (47.9%)
- 47 in *MSH2* (39.5%)
- 9 in *MSH6* (7.6%)
- 4 in *PMS2* (3.4%)

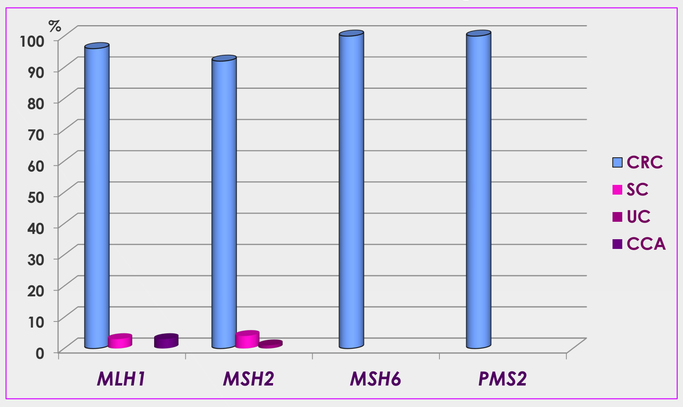
The mean age at diagnosis was 39.9 years for *MLH1*, 40.7 for *MSH2*, 49 for *MSH6*, and 55.7 for *PMS2* carriers

Age at manifestation of first cancer

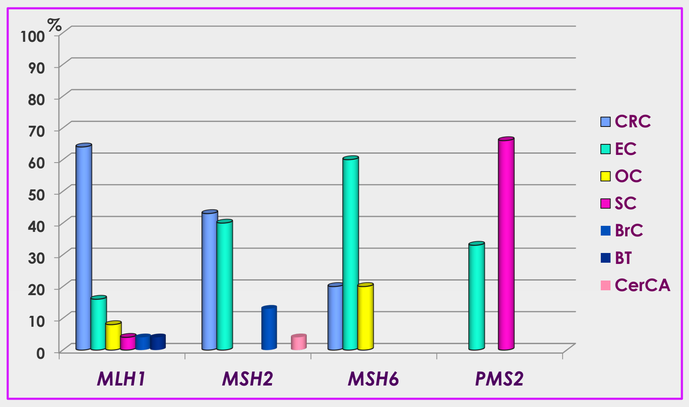


Colorectal cancer (CRC) was the most common initial diagnosis in *MLH1/MSH2* carriers; carriers of *MLH1* PV had uterine, ovarian, gastric, breast, meningioma, cholangiocarcinoma; *MSH2* – ovarian, gastric, breast, ureter, cervical tumors. However, gynecological cancers were the most common first diagnosis in women with *MSH2* PVs.

Localization of the first tumor for each gene, male



Localization of the first tumor for each gene, female



CRC	colorectal cancer
EC	endometrial cancer
SC	stomach cancer
OC	ovarian cancer
BrC	breast cancer
BT	brain tumor
CCA	cholangiocarcinoma
CerCA	cervical cancer
UC	ureter cancer
SBC	small bowel cancer
BladC	bladder cancer
EsC	esophageal cancer
SkC	skin cancer
PrC	prostate cancer
KidC	kidney cancer
ThyrC	thyroid cancer
Mel	melanoma
CUP	cancer of unknown primary
LG	lymphogranulomatosis
PanC	pancreatic cancer
LivC	liver cancer

Multiple primary malignancies were observed in 42% of *MLH1* (≤4 tumors), 49% of *MSH2* (≤10), 56% of *MSH6* (≤4), and 50% of *PMS2* carriers. In addition to common LS-associated tumors, pts had small bowel, esophageal, and breast cancers. In *MSH2* carriers, additional tumors included urinary tract, skin, kidney, thyroid and glioma.

Two cases of Constitutional MMR deficiency syndrome were detected:

- Patient 1: 3-year-old boy

Ds: Embryonal rhabdomyosarcoma of the skull base

Parents - healthy, sister (10 y.o.) – glioblastoma.

PMS2 PV homo: c.631C>T/c.631C>T

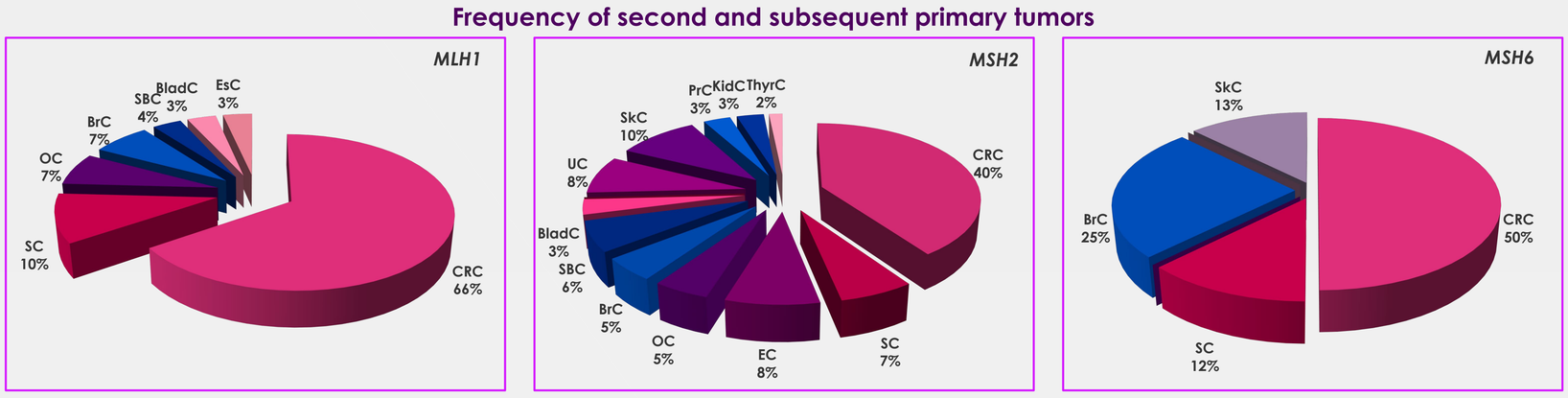
- Patient 2: 8-year-old boy

Ds: glioblastoma

Parents - healthy

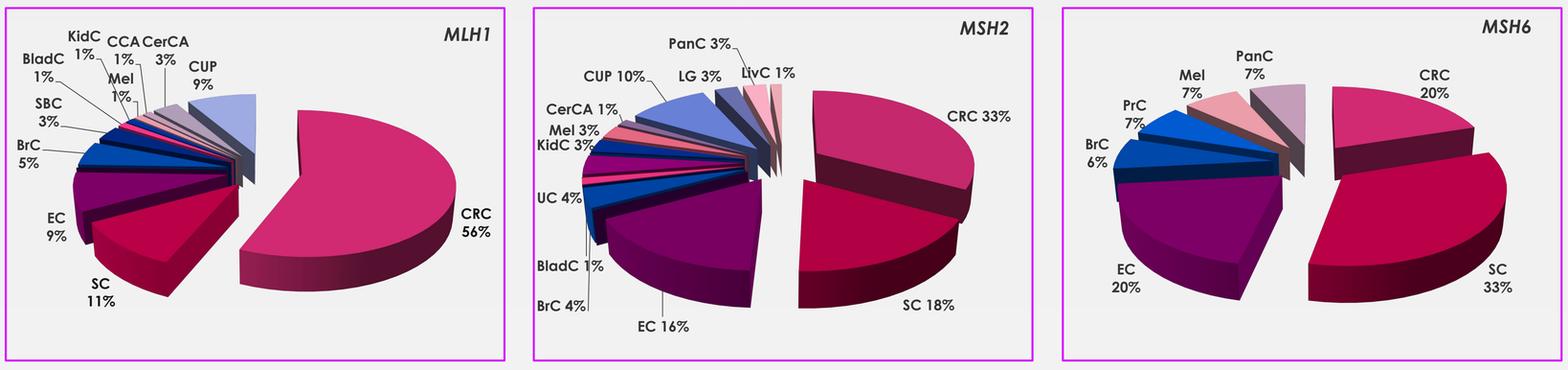
MLH1 PV: c.790+1G>A/?

Frequency of second and subsequent primary tumors



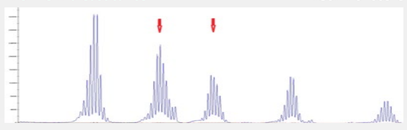
Family history of tumors was present in 92% of *MLH1/MSH2*, 67% of *MSH6*, 50% of *PMS2* cases.

Tumor incidence in relatives of I-II degree of relationship

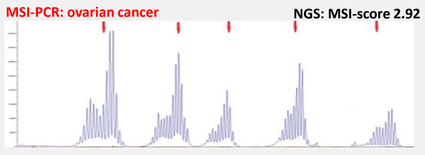


Patient, f, 46 y.o.
Diagnosis: Primary Multiple Malignant Neoplasms
43 y. - breast cancer
45 y. - ovarian cancer
BRCA1/2, ATM, CHEK2, PALB2 - wt

MSI-PCR: breast cancer NGS: MSI-score 1.40



MSI-PCR: ovarian cancer NGS: MSI-score 2.92



Family history: father - stomach cancer, bladder cancer, CRC; aunt and cousin on paternal side - stomach cancer

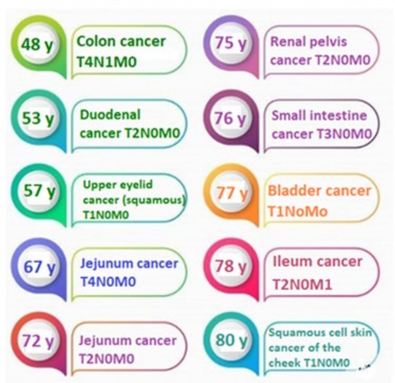
MSH2 PV: c.1288A>T (p.Lys430Ter) rs63751646)

Patient 80 y.o.

Diagnosis: Primary Multiple Malignant Neoplasms

MSH2 PV: c.2231T>G (p.Leu744Ter) rs63750403

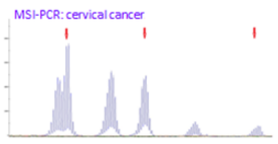
Family history - father - stomach cancer, mother - breast cancer

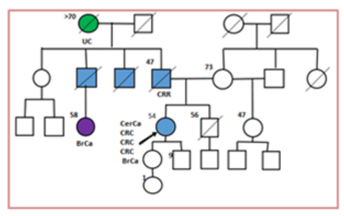


Multi-locus Inherited Neoplasia Allele Syndrome (MINAS)

47 y. - cervical cancer stage IIIB
53 y. - cancer of the cecum stage I
54 y. - luminal breast cancer B IIIC.
54 y. - sigmoid colon cancer stage I
54 y. - descending colon cancer stage I

MSI-PCR: cervical cancer





NGS: cervical cancer – **MSI,** score3.72
NGS: breast cancer – **MSS,** score 0.54

BRCA1 - c.5266dup (p.Gln1756Profs) rs80357906
MSH2 - c.1861C>T (p.Arg621Ter) rs63750508

When comparing results of NGS-based analysis of MSI between CRC and non-Lynch syndrome-associated tumors, a different pattern was observed. In CRC, MSI+ and MSS tumors could be easily distinguished, as MSI scores for MSI and MSS tumors were clustered (5.28 [95% CI, 1.64, 9.76] for MSS and 0.44, [95% CI, 0.37, 0.49], respectively, p<0.001). At the same time, in non-LSS tumors MSI scores for MSI and MSS tumors were less clustered (MSS 0.4, [95% CI, 0.29, 0.54] for MSS tumors and 3.46 [95% CI 0.62, 9.90], respectively, p<0.001)

Conclusion

Patients exhibit heterogeneous phenotypic features depending on the mutated MMR gene, with each gene demonstrating distinct organ-specific penetrance/expressivity. In non-LSS tumors, NGS-based MSI analysis may be more informative and can improve accuracy of patient stratification for LS diagnosis and immunotherapy indication.

Disclosures. All authors, including the presenting author, have no conflicts of interest to declare.