Unknown Synergistic Effect of Digenetic Inheritance of MMR Pathogenic Mutations: Double Heterozygosity in Lynch Syndrome, A Single Case Report & Family Study

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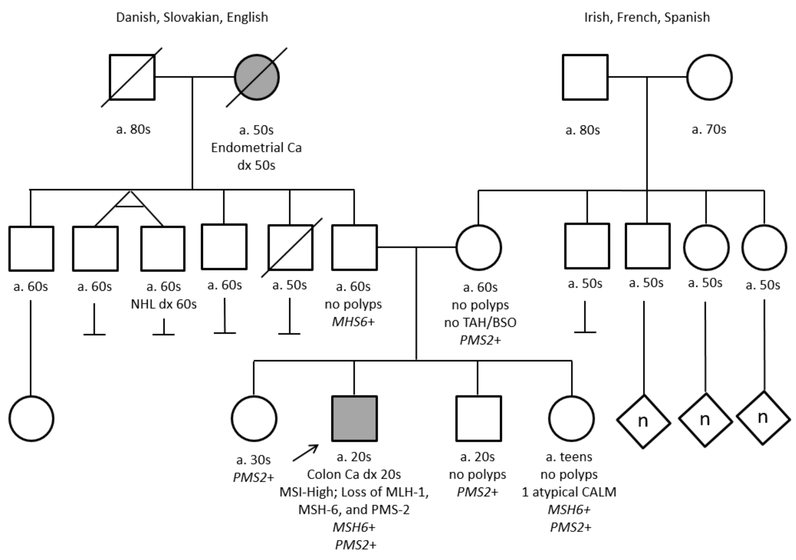
BACKGROUND

- Lynch syndrome (LS) is a well-known cause of hereditary colon cancer.
- Individuals with LS also have an increased risk of developing extracolonic cancers, which include:
  - Endometrial, stomach, ovarian, urinary tract, small bowel, brain, pancreatic, hepatobiliary, and skin.
- Pathogenic and likely pathogenic variants ("mutations") in mismatch repair (MMR) genes: *MLH1*, *MSH2*, *MSH6* and *PMS2* along with deletions of *EPCAM* have been associated with LS.[1,2]
- Biallelic mutations in MMR genes result in constitutional mismatch repair deficiency (CMMR-D) syndrome.
- CMMR-D syndrome is characterized by features similar to neurofibromatosis type 1 (NF1):
  - Café-au-lait macules, brain tumors, gastrointestinal cancers, and hematologic malignancies; occurring in childhood.[3]
- Based on limited data, current understanding of double heterozygosity for MMR mutations is that it does not cause CMMR-D but is expected to be associated with cancer risks similar to LS.[4]

CASE REPORT: CLINICAL AND FAMILY HISTORY

- A 22 year-old male presented to our clinic with locally advanced rectal adenocarcinoma.
  - The colon tumor demonstrated microsatellite instability (MSI) and loss of MLH-1, MSH-6, and PMS-2 expression with retention of MSH-2 by immunohistochemistry (IHC).
- Family history was significant for endometrial cancer in his paternal grandmother diagnosed at 52.
- The remaining family history was non-contributory (Figure 1).

FIGURE 1. PEGIDREE



CASE REPORT: GENETIC TESTING

- The patient underwent multigene panel testing. Genes evaluated include: *APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, MLH1, MRE11A,MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, POLD1, POLE, PTEN, RAD50, RAD51C, RAD51D, SMAD4, SMARCA4, STK11* and *TP53* (sequencing and deletion/duplication); *EPCAM* and *GREM1* (deletion/duplication only).
- The patient's genetic testing revealed:
  - *MSH6* pathogenic mutation: p.R482*
  - *PMS2* pathogenic mutation: EX6_8del
- The patient's nuclear family members underwent genetic testing to determine the segregation of the familial mutations (Table 1).

TABLE 1. GENETIC TEST RESULTS FOR PATIENT'S AT-RISK FAMILY MEMBERS

Family Member	Pathogenic Mutation Detected
Father	*MSH6* p.R482*
Mother	*PMS2* EX6_8del
Older sister	*PMS2* EX6_8del
Younger brother	*PMS2* EX6_8del
Adolescent sister	*MSH6* p.R482*, *PMS2* EX6_8del

CASE REPORT: MUTATION DETAILS

MSH6* pathogenic mutation: p.R482

- Amino acid substitution from an arginine to a stop codon.
- Previously reported in the literature in families with LS:
  - Detected in a family that met Amsterdam II criteria and showed moderate segregation with disease.[5]
  - Identified in four Danish Lynch syndrome families.[6]

***PMS2* pathogenic mutation: EX6_8del**

- Gross deletion spans coding exons 6 through 8 in the *PMS2* gene.
- Previously reported in the literature in individuals concerning for LS and CMMR-D:
  - Detected in an individual diagnosed with a large colonic adenoma at age 30; tissue demonstrated isolated loss of PMS-2 staining on IHC.[7]
  - Observed in a child with CMMR-D in conjunction with a *PMS2* splice site mutation; there was no reported family history of cancer.[3]

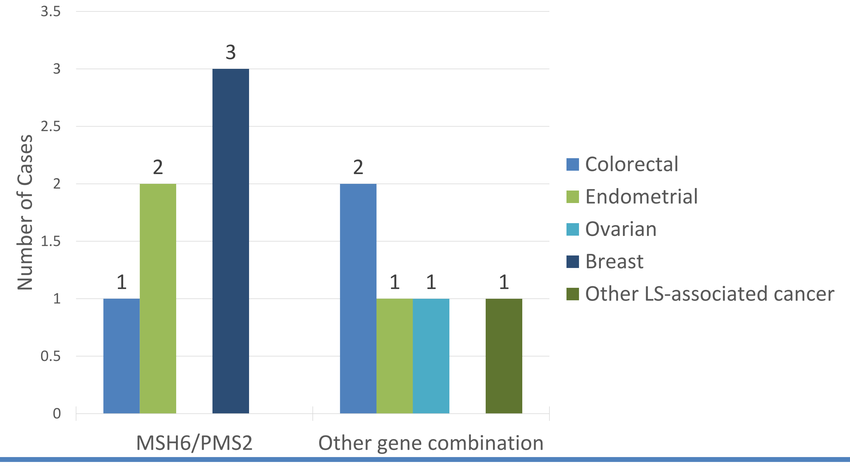
METHODS

- Genetic test results were reviewed for individuals who were tested for two or more MMR genes from a single clinical diagnostic laboratory.
- Medical and family histories obtained from test requisition forms were reviewed to assess the clinical phenotype of LS double heterozygotes.
- The cohort consisted of over 75,000 cases tested between July 2009 and March 2016.

RESULTS

- Seven double heterozygotes from six families were identified (0.009%).
- 6/7 probands had a diagnosis of at least one LS-related cancer (Figure 2).
  - The remaining proband had a diagnosis of breast cancer only.
- 4/7 probands were *MSH6/PMS2* double heterozygotes.
  - The remaining three probands were heterozygous for a moderate-risk gene (*MSH6* or *PMS2*) and a high-risk gene (*MLH1*, *MSH2*, or *EPCAM*).
- All seven probands had first-degree or second-degree relatives with colorectal or endometrial cancer. There were no reports of any childhood onset cancers in any of these families.

FIGURE 2. PROBAND CANCER HISTORIES BY GENE COMBINATION



CONCLUSION

- In a cohort of over 75,000 cases tested for two or more MMR genes at a clinical diagnostic laboratory, seven LS double heterozygotes were identified.
- In the identified cases, the clinical histories were suggestive of LS; none of the histories showed classic features of CMMR-D syndrome.
- There are few case reports of LS double heterozygotes published in the literature.
- Due to this rarity, the interactive effect of harboring mutations in two different MMR genes is unknown and the relative cancer risk cannot be predicted.
- Further studies are needed exploring the functional impact of double heterozygous MMR mutations to help clarify lifetime cancer risks and appropriate management for these patients.

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