

Novel variants of unknown significance in the *PMS2* gene identified in patients with hereditary colon cancer

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Raffaella Liccardo¹
Carlo Della Ragione²
Nunzio Mitilini²
Marina De Rosa¹
Paola Izzo¹
Francesca Duraturo¹

¹Department of Molecular Medicine and Medical Biotechnologies, School of Medicine, University of Naples "Federico II", Naples, Italy; ²UOC Pathological Anatomy, AORN "A. Cardarelli", Naples, Italy

Background: Lynch syndrome is associated with genetic variants in mismatch repair (*MMR*) genes. Pathogenic variants in the *MLH1* and *MSH2* genes occur in most families in which the phenotype is highly penetrant. These testing criteria are likely to miss individuals with Lynch syndrome due to the less penetrant *MMR* genes, such as *MSH6*, *MLH3*, *MSH3*, and *PMS2*. So far, several mutations in the *PMS2* gene have been described as responsible for the clinical manifestation of Lynch syndrome. Recent data have reported that families with atypical Lynch phenotype were found to have primarily monoallelic mutations in the *PMS2* gene.

Methods: We analyzed the *PMS2* gene to detect mutations in members of 64 Lynch syndrome families by direct sequencing.

Results: We report the identification of several genetic variants in patients with LS, of which three are novel variants. The carriers of these novel variants were also carriers of other variants in *PMS2* gene and/or in other *MMR* genes.

Conclusion: Therefore, we think that these novel *PMS2* variants may act in additive manner to manifestation LS phenotype.

Keywords: Lynch syndrome, *PMS2* gene, *MMR* genes, *PMS2* variants, synergist effect of *MMR* variants

Introduction

The primary clinical manifestation of Lynch Syndrome is the development of colon cancer at an average age of 45 years; this syndrome is also characterized by an increased risk of developing extra-colonic tumors such as endometrial, ovarian, stomach, urinary, and biliary tract cancer.¹ Families affected by LS were identified using the Amsterdam Criteria (AC) and Bethesda guidelines (BG).^{2,3} Lynch syndrome (LS) testing criteria were developed based on families with cancer histories across multiple generations. LS is associated with genetic variants in DNA Mismatch Repair (*MMR*) genes and it is characterized at somatic level by high instability of microsatellite sequences (MSI).^{4,5} Pathogenic variants in the *MLH1* and *MSH2* genes occur in most families in which the phenotype is highly penetrant.^{6,7} Pathogenic variants in the less penetrant *MMR* genes, such as *MSH6*, *MLH3*, *MSH3*, and *PMS2* were also shown in LS patients.^{8–10}

The *PMS2* gene is located on chromosome 7p22 in a region spanning 16 kb and is made up of 15 exons and 862 codons.¹¹ The *PMS2* protein acts as

Correspondence: Francesca Duraturo
Department of Molecular Medicine and Medical Biotechnologies, School of Medicine, University of Naples "Federico II", Via Pansini, 5, Napoli 80131, Italy
Email francesca.duraturo@unina.it

a heterodimer together with MLH1 protein forming the MutL α complex that is associated with the MutS α complex, which primarily repairs single-nucleotide mismatches.¹² Its function is redundant with the *MLH3* gene product. Mice that have the *PMS2* gene deleted develop lymphomas and sarcomas but not gastrointestinal tumors; instead, mice lacking *PMS2* and *MLH3* develop a non-distinguishable phenotype from *MLH1* knock-out mice.¹³ Finally, it has also shown that the *PMS2* gene is also involved in the apoptotic pathway.¹⁴

So far, several mutations in the *PMS2* gene have been described as responsible for the clinical manifestation of Lynch syndrome.^{15–17} The large rearrangements in the *PMS2* gene are rarely described.^{18,19} Recent studies have demonstrated a reduced penetrance for monoallelic carriers of *PMS2* mutations compared to the other *MMR* genes.²⁰ Moreover, very often homozygous and/or biallelic point mutations in the *PMS2* gene have been reported to be responsible for Lynch phenotypes,^{21,22} as it has been also described that *PMS2* mutations together with mutations in other *MMR* genes should also be considered in patients suspected to present a Lynch syndrome with an unusual early-onset of tumors.²³

The aim of this study was to analyze the *PMS2* gene to detect mutations in members of 64 LS families. We have identified 21 variants in the *PMS2* gene; of which no variant was of certain pathogenetic significance. Most of these variants had previously been described in the literature, only three of these are novel, of which two are missense variants that could alter the functionality of the protein.

Materials and methods

Patients and isolation of genomic DNA

Sixty-four LS patients were recruited from several hospitals in southern Italy; patients were previously established to be negative for pathogenetic mutations in other *MMR* genes including *MLH1*, *MSH2*, *MSH6*, and *MLH3* and included large rearrangements in *PMS2* gene.¹⁹ Twenty-three families with classic LS phenotype were selected by AC \geq 2 and 41 families with atypical Lynch phenotype were selected by MSI analysis as suggested BG1. Sixty samples from healthy patients collected from the Clinical Department of Laboratory Medicine of the hospital affiliated with Federico II University (Naples, Italy) were used as negative controls. The experiments

were performed on DNA extracted from peripheral blood lymphocytes. Total genomic DNA was extracted from 4 mL peripheral blood lymphocytes using a BACC2 Nucleon kit (Amersham Pharmacia Biotech, Amersham, UK). The Clinical Department of Laboratory Medicine of the hospital affiliated to Federico II University (Naples, Italy) recruited the subjects after receiving authorization from the local ethics committee “Comitato etico per le attività Biomediche Carlo Romano” of the University of Naples, Federico II (protocol no. 120/10). Once the authorization was obtained, the study received ethical approval, and participants’ informed and written consent was obtained. The experiments were performed on DNA and on cDNA extracted from peripheral blood lymphocytes.

Mutation analysis and in silico analysis

The entire coding region of the *PMS2* gene was amplified in 17 fragments, 1 for each exon and 3 overlapping fragments for exon 11, using customized primer sets, available upon request. The polymerase chain reaction (PCR) products were separated on a 1–2% agarose gel to check for unspecific amplicons. Subsequently, the PCR products were sequenced in both the forward and reverse directions using an ABI 3100 Genetic Analyzer (Applied Biosystems).

The Sorting Intolerant From Tolerant (SIFT) (<http://blocks.fhcr.org/sift/SIFT.html>) and Polymorphism Phenotyping (PolyPhen) (<http://genetics.bwh.harvard.edu/pph/>) tools were used for functional impact prediction of the novel variants, as described in our previous studies.⁶

Immunohistochemistry (IHC)

IHC was performed on a Benchmark XT automatized immunostainer (Ventana Medical Biosystems, Tucson, AZ, USA). The antibodies used were anti-MSH6, mouse monoclonal clone 44; anti-MSH2, mouse monoclonal clone G219-1129; anti-MLH1, mouse monoclonal clone M1 (Ventana); and anti-PMS2. The procedure was performed as described previously on sections of colon cancer tissues.⁹

Results

The mutation detection analysis of the *PMS2* gene, performed on samples from patients with LS, as described in the Materials and Methods section, identified 21 genetic

Table 1 Variants identified in the PMS2 gene in our study

| Exon | Nucleotide change | Aminoacid change | Reference | Pathogenicity (www.insight-group.org) | Frequency in hereditary CRC | Frequency in healthy samples |
|------|-------------------|------------------|--------------------------------------|---------------------------------------|--|------------------------------|
| 1 | 5'UTR c.-154g>c | | Thompson et al, ¹¹ 2004 | ND | 12/64 (19%) | ND |
| | 5'UTR c.-195t>c | | Thompson et al, ¹¹ 2004 | ND | 3/64 (4.7%) | ND |
| 2 | 5'UTR c.+72c>t | p.(Ile17Val) | This study | Likely Class 1 | 12/64 (19%) | 4/60 |
| | c.52A>G | | Hendricks et al, ²⁴ 2006 | Class 2 | 1/64 (1.6%) | ND |
| | c.59G>A | p.(Arg20Gln) | Nicolaides et al, ²⁵ 1994 | Class 1 | 6/64 (9.4%) | ND |
| 3 | c.250+108a>g | | Hendricks et al, ²⁴ 2006 | ND | 7/64 (11%) | ND |
| 6 | c.705+17>g | | Thompson et al, ¹¹ 2004 | ND | 10/64 (15.8%) | ND |
| 7 | c.780C>G | p.Ser260= | Viel et al, ²⁶ 1998 | Class 1 | Heterozygous 3/64 (4.7%); Homozygous 13/64 (20%) | ND |
| 11 | c.1454C>A | p.(Thr485Lys) | Wang et al, ²⁷ 1999 | Class 1 | 4/64 (6.3%) | ND |
| | c.1621G>a | p.(Glu540Lys) | Viel et al, ²⁶ 1998 | Class 1 | 10/64 (15.8%) | ND |
| | c.1789A>T | p.(Thr596Ser) | Viel et al, ²⁶ 1998 | Class 1 | 1/64 (1.6%) | ND |
| | c.2007-4g>a | | Hendricks et al, ²⁴ 2006 | ND | 15/64 (23.4%) | ND |
| | c.2174+24c>a | | Hendricks et al, ²⁴ 2006 | ND | 6/64 (9.4%) | ND |
| 13 | c.2248G>A | p.(Gly749Ser) | This study | Likely Class 3 | 1/64 (1.6%) | 0/60 |
| | c.2253T>C | p.Phe 751= | Viel et al, ²⁶ 1998 | Class 1 | 10/64 (15.8%) | ND |
| 14 | c.2324A>G | p.(Asn774Ser) | Viel et al, ²⁶ 1998 | Class 1 | 14/64 (22.2%) | ND |
| | c.2340C>T | p.Pro780= | Hendricks et al, ²⁴ 2006 | Class 1 | 3/64 (4.7%) | ND |
| 15 | c.2380C>T | p.(Pro793Ser) | This study | Likely Class 3 | 2/64 (3.2%) | 0/60 |
| | c.2466T>C | p.Leu822= | Viel et al, ²⁴ 1998 | Class 1 | 10/64 (15.8%) | ND |
| | c.2570G>C | p.(Gly857Ala) | Viel et al, ²⁶ 1998 | Class 1 | 23/64 (36%) | ND |

Note: NCBI accession number: NM000535.

Abbreviations: ND, not done; CRC, colon rectal cancer.

variants (Table 1). These variants were shown in both families' groups (AC and BG respecting), casually. No variant of certain pathogenetic significance was identified in this study. Most variants had previously been described in the literature and reported in the *MMR* variants database of Insight Group (<https://insight-database.org/variants/>), while three were novel variants, of which two were missense variants. The two novel missense variants were analyzed using a bioinformatic tool that predicted that both these variants were likely pathogenic. These missense variants were identified in three unrelated LS families (Table 2). The genetic variant, c.2248G>A, located in exon 13 of the gene, was identified in a subject who developed right-side colon carcinoma at the age of 34 years. This variant was also identified in the father of this proband, who also developed colon cancer at 40 and in a paternal uncle who developed colon cancer at age 45. Thus, the mutation segregates with the disease in this family. Moreover, this variant was not found in the 60 healthy subjects used as negative controls. *In silico* analysis indicated that protein function was likely altered as a result of the mutation. The IHC analysis did not provide results due to paraffin-embedded tumoral tissue of poor quality. The father and son of this family were also carriers of unclassified variants in *MSH2* genes, a missense variant in exon 3, the c.573C>T (p.Pro125Ser), already reported in "Insight Variants Database" (Table 2). The second novel *PMS2* missense variant, the c.2380C>T in exon 14, was identified in two unrelated LS patients, and it was also not found in the 60 healthy subjects used as negative controls. The *in silico* analysis revealed that this variation has also a high probability of altered protein function; the IHC analysis showed normal expression of the *PMS2* protein at the somatic level, (Table 2).

Discussion

For many years, the *PMS2* gene has been considered a gene candidate for the development of cancer in Lynch Syndrome. However, to date, its role in the development of cancer in Lynch syndrome is still not well understood. It has been reported that monoallelic mutations in the *PMS2* gene are responsible for the phenotype found in families that do not fully comply with the Amsterdam criteria or who develop non-LS-related tumors.²⁰ This can be explained considering that mice lacking *PMS2* develop lymphomas and sarcomas but not gastrointestinal tumors.¹²

In this study, all variants identified in the *PMS2* gene are unclassified, including also the novel variants. Bioinformatics studies have shown that two novel missense variants may be detrimental to the functionality of the protein. In particular, c.2248G>A, identified in exon 13 of the *PMS2* gene, was found to segregate with the disease in the AC family and all family members' carrier of this variant developed colon cancer. Our previous investigations showed that the index case of this family and his father were also carriers of a missense variant in the *MSH2* gene, already described in literature as benign variant. Unfortunately, it was not possible to analyze the other affected family members because didn't available. The MSI analysis performed on tumoral colon tissue of the index case showed a high MSI status (data not shown). Instead, the IHC investigations did not provide reliable results due to poor quality of the paraffin-embedded tumor tissue from the index case; therefore, we have not been able to escape a deficiency of MMR proteins at the somatic level associated with other causes, such as hypermethylation of the *MLH1* promoter.¹ Thus, we speculated that likely these two variants identified in this family may act as low-risk alleles that together determine the deficiency of MMR system, as shown by high MSI status on tumoral DNA of index case. Also the other missense variant identified in this study, the c.2380C>T, in exon 14 of the *PMS2* gene was found in two unrelated patients that both showed high MSI status on tumoral colon tissues (data not shown) but a poor one significant family history of LS-related cancers. However, the IHC analysis performed on colon cancer tissue of both index cases (07/6 and 00/12) showed normal expression of MMR proteins, MLH1, MSH2, MSH6, and *PMS2* (Table 2). This last data does not contrast with the result of the MSI rather it reinforces our hypothesis, first formulated; indeed, a missense mutation is predicted to alter the functionality of the protein but not its production. Moreover, also these two patients were carriers of other variants in *MMR* gene. In particular, the carrier 07/6 showed in addition to novel missense variant also a high numbers of other variants in *PMS2* gene (Figure 1) and a variant in *MLH3* gene (Table 2). Also, the carrier 00/12 showed two variants in *PMS2* (included the novel variant) and one variant in *MLH3* gene. Previously, literature data showed that the monoallelic mutations in the *PMS2* gene are likely compatible with a more attenuated Lynch phenotype or a low-penetrance²⁰ and, thus in the case of a classical phenotype,

Table 2 Lynch syndrome patients carrier of novel PMS2 variants identified in this study

| ID | MMR genes variants | Microsatellite instability | Immunohistochemistry | Clinical phenotype | Family history |
|-----------|---|----------------------------|--|-------------------------------|---|
| 05/ 7 | MSH2: ex3c.573C>T (p. Pro125Ser) PMS2: ex7c.780C>G+/+ [p. Ser260=] ex13c.2248G>A (p. Gly749Ser) ^a ex13c.2253T>C [p.Phe751=] ex14c.2324A>G (p. Asn774Ser) | MSI-H | MSH2: +/+ MSH6: ND MLH1: ND PMS2: ND | Right-colon cancer at age 44. | Father affected by colon cancer at age 36 and 49 years, PMS2 and MSH2 MUT+; paternal uncle died of colon cancer at age 60, PMS2 MUT+; paternal uncle died of lung cancer at age 60 years and his son affected by three right colon adenoma at age 42. |
| 00/ 12 | MLH3: ex1-13c.2896T>C (p.Ser965Pro) PMS2: ex14c.2324A>G (p. Asn774Ser) ex14c.2380C>T (p. Pro793Ser) ^a | MSI-H | MSH2: +/+ MSH6: +/+ MLH1: +/+ PMS2: +/+ | Right-colon cancer at age 64. | Father affected by colon cancer at age 63; paternal aunt died of breast cancer at age 40; sister died of lung cancer at age 63. |
| 07/ 6 | MLH1: IVS1+9C>G+/+; MLH3: ex1-13c.2896T>C (p.Ser965Pro) PMS2: ex2c.59G>A (p. Arg20Gln) ex6c.705+17a>g, ex7c.780C>G +/+[p. Ser260=] ex12c.2007-7c>t, ex12c.2007-4g>a, ex13c.2253T>C [p.Phe751=] ex14c.2380C>T (p. Pro793Ser) ^a ex15c.2466T>C [p.Leu822=] | MSI-H | MSH2: +/+ MSH6: +/+ MLH1: +/+ PMS2: +/+ | Right-colon cancer at age 59. | Parents who died in old age, not affected by neoplastic disease; two maternal aunts died of colon cancer at age 55 and 80, respectively. |

Note: ^aNovel variant.

Abbreviations: ID, identification number; patient: ND, not done; +/+, homozygous variant; Mut+, carrier mutation; MSI-H, high microsatellite instability; IHC, immunohistochemistry.

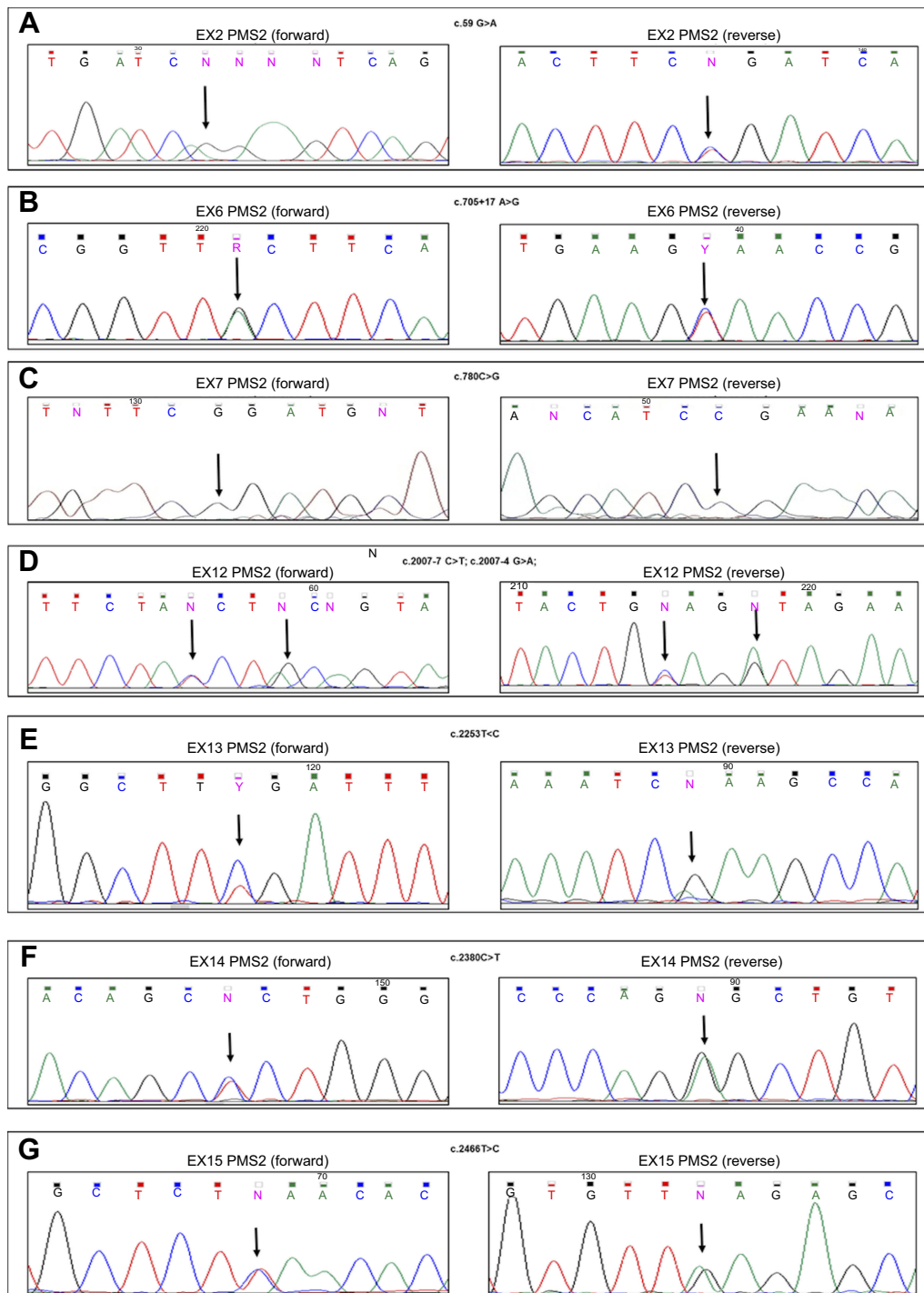


Figure 1 DNA sequencing electropherograms of the PMS2 exon 2 (A), exon 6 (B), exon 7 (C), exon 12 (D), exon 13 (E), exon 14 (F), and exon 15 (G) for the 07/6 patient sample. Arrows indicate the homozygous variant in the exon 7 (C), and the heterozygous variants in the exon 2 (A), the exon 6 (B), the exon 12 (D), the exon 13 (E), the exon 14 (F), and the exon 15 (G). Each variant is shown in the forward (left) and reverse (right) DNA sequencing analysis.

a second mutation may also be present in same *PMS2* gene or in another *MMR* genes.²³ Even if, all variants identified in this study seem unlikely to have pathogenic effects on protein function it cannot be ruled out that such variants

represent low-penetrance alleles rather than benign variants or polymorphisms. Therefore, it is possible that the synergist effect of these low-risk alleles is causing disease manifestation in our patients.

Disclosure

The authors report no conflicts of interest in this work.

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