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PMS2 monoallelic mutation carriers: the known unknown

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Abstract

Germline mutations in *MLH1, MSH2, MSH6* and *PMS2* have been shown to cause Lynch syndrome. The penetrance for cancer and tumor spectrum has been repeatedly studied and multiple professional societies have proposed clinical management guidelines for affected

individuals. Several studies have demonstrated a reduced penetrance for monoallelic carriers of *PMS2* mutations compared to the other mismatch repair (MMR) genes, but clinical management guidelines have largely proposed the same screening recommendations for all MMR gene carriers. The authors considered whether enough evidence existed to propose new screening guidelines specific to *PMS2* mutation carriers with regard to age of onset and frequency of colonic screening. Published reports of *PMS2* germline mutations were combined with unpublished cases from the authors' research registries and clinical practices, and a discussion of potential modification of cancer screening guidelines was pursued. A total of 234 monoallelic *PMS2* mutation carriers from 170 families were included. Approximately 8% of those with CRC were diagnosed under age 30 and each of these tumors presented on the left-side of the colon. As it is currently unknown what causes the early-onset of CRC in some families with monoallelic *PMS2* germline mutations, the authors recommend against reducing cancer surveillance guidelines in families found having monoallelic *PMS2* mutations in spite of the documented reduced penetrance.

INTRODUCTION

In the mid 1990s, through a convergence of scientific observations by yeast geneticists, cancer geneticists, and clinicians, the cause of Lynch Syndrome, formerly referred to as Hereditary non-Polyposis Colon Cancer, was found to be heterozygous DNA mismatch repair (MMR) gene germline mutations [reviewed by Boland and Lynch in [1]]. Mutations in *MSH2* were reported in 1993 and mutations in *MLH1* were reported in 1994[2-5]. *PMS2* was cloned and found to be causative of Lynch syndrome in 1994 [6]. *MSH6* was added to the list in 1997[7]. Although additional genes participate in the DNA mismatch repair process, only these 4 are well established as causes of Lynch Syndrome. Over the past two decades, information on disease penetrance and spectrum accumulated and multiple professional societies and experts have issued recommendations for the management of individuals with Lynch Syndrome, generally written to encompass carriers of mutations in any of these four genes[8-10]. **(TABLE 1 and TABLE 2)**

In 1995, Hamilton et al. studied 14 families with "Turcot Syndrome" (the co-occurrence of colorectal polyposis with a primary tumor of the central nervous system)[11]. Germline *APC* mutations were found in ten families and three of the remaining four cases had evidence of a tumor DNA mismatch repair defect. Germline mutations were discovered in two, one in *MLH1* and one in *PMS2*. The *PMS2* mutation occurred in an 18 year old man with colonic adenomas, a glioblastoma at age 4 years, and café-au-lait spots. His sister had a history of rectal carcinoma. In a similarly affected, consanguineous family, Trimbath et al. identified homozygous *PMS2* mutations in affected members[12]. In 2004, De Vos et al. noted that the heterozygous family members of a homozygous case appeared to have no cancer predisposition whatsoever raising the possibility that *PMS2* predisposed to cancer only when biallelic mutations were present [13]. To underscore this possibility, De Vos et al. conducted further molecular analysis in the *PMS2* Turcot family described by Hamiliton et al. and identified a second *PMS2* mutation [13]. Analysis of *PMS2* for mutations has turned out to be far more complex than for the other MMR genes due to the existence of multiple pseudogenes[14, 15]. As a result, clinical testing for *PMS2* mutations was not available until

relatively recently, and even now there exists some uncertainty about how many mutations may be missed or miscalled due to the presence of pseudogenes[15].

Since 2004, despite limitations in mutation detection technologies, multiple studies have confirmed an increased risk for cancer in heterozygous carriers of *PMS2* mutations, although penetrance for cancer is lower than for the other three MMR genes. Based on 55 families with presumably monoallelic *PMS2* mutations, Senter et al. reported risk for colorectal cancer (CRC) as 15-20% by age 70, well less than half that of *MLH1* and *MSH2* mutation carriers[16]. The study, which ascertained cases based on tumors with selective loss of expression of *PMS2* (predominantly colorectal but endometrial cases as well) found 6 cases (out of 99) with biallelic mutations, a proportion of biallelic mutation carriers that far exceeded that found in the other Lynch syndrome related genes. The six biallelic cases all demonstrated absence of PMS2 protein in the tumor tissue and adjacent normal tissue. In a 2008 review of all published cases with biallelic MMR mutations (now known as constitutional mismatch repair deficiency, CMMRD) more than half of the individuals (43/78) carried *PMS2* mutations even though heterozygous *PMS2* mutations are thought to account for only 1-15% of all individuals with Lynch Syndrome[17-21]. In Truninger et al. the isolated absence of PMS2 by IHC was found in 1.5% of >1000 consecutively collected CRC specimens from individuals undergoing surgical resection; that study showed a similar incidence of Lynch syndrome caused by mutations in *PMS2* as Lynch syndrome caused by mutations in *MSH2*[22]. Clearly the phenotype associated with mutations in *PMS2* differs in significant ways from those of *MSH2*, *MLH1*, and *MSH6*.

Historical and recent guidelines for clinical management largely combine carriers of *PMS2* mutations with all cases of Lynch syndrome[8] or propose delaying screening by 5 years [9]. The authors, all involved in the care of individuals with Lynch syndrome, formed an unfunded *ad hoc* virtual working group to collate and examine the available information on *PMS2* monoallelic mutation carriers to consider this question: “Is there adequate data to inform clinical management guidelines for individuals with *PMS2* mutations that may deviate from those formulated for individuals with mutations in the other three Lynch Syndrome genes?” A new penetrance analysis was not the objective as, like the previously published cases, the ascertainment of nearly all new unpublished cases identified came from high-risk clinics or registries. Having more families collected in such a strongly biased manner would be unlikely to provide a level of evidence needed to recommend changes in practice. This is a report of the outcomes of this working group.

METHODS

Published reports of *PMS2* germline mutation carriers were identified by searching PubMed using the terms PMS2, monoallelic MMR, Lynch Syndrome, and Hereditary Non Polyposis Colon Cancer (HNPCC). This search yielded 4,554 publications, of which 100% of relevant reports of germline monoallelic *PMS2* mutation carriers were included. Relevance for inclusion was cross-referenced by multiple authors. The references of all papers so identified were also reviewed for other eligible reports. All cases with putative monoallelic *PMS2* germline mutations were abstracted. For case reports on biallelic mutation carriers, parents were presumed to be obligate monoallelic carriers and information on their health was

included if the paper provided adequate detail (which was infrequent). A concerted effort was made to ensure that cases presented in multiple manuscripts were included only once in our series. Cases where monoallelic mutations were suspected only based on tumor studies (no germline testing) were not included. No efforts were made to contact authors of previous publications to request information not included in those papers.

In addition to published cases, all unpublished cases of individuals with reported monoallelic *PMS2* mutations known to the project's authors from their research registries or clinical practices were also collected if permitted by local institutional review boards. For all cases, both published and unpublished, the following information was collected when known: gender, last known age, specific *PMS2* mutation, site of CRC, age(s) at diagnosis of CRC, other non-CRC cancer diagnoses and ages of diagnoses, microsatellite instability (MSI) status of any tumor or non-malignant tissue testing, PMS2 loss of expression by immunohistochemistry (IHC) on any tumor or non-malignant tissue, and method of ascertainment of the individual. Family history collection was not included as it was inconsistently available and often incomplete.

Once collection of the entire list of cases and associated data were completed, the table was circulated to the working group for consideration. An on-line discussion was conducted via e-mail with the specific question being whether there was sufficient evidence to suggest that a modification of standard Lynch Syndrome cancer screening guidelines[9, 10] was indicated for carriers of monoallelic *PMS2* mutations. Discussion was moderated and recorded by the lead and senior authors. At various points in the process, summaries of the viewpoints previously expressed were provided back to the work group in order to facilitate continued discussion. On-going discussion was pursued until all viewpoints were expressed and consensus on the conclusion as articulated in this manuscript was achieved. Throughout the discussion, all participants were invited to provide feedback on the collected data and all authors participated, at minimum by giving their agreement to the conclusion that was finally formed.

RESULTS

Table S1, Table S2, and Table S3 show details regarding the 234 monoallelic *PMS2* mutation carriers from 170 families that were included in the final dataset: 129 carriers were from previously published reports and 105 from previously unreported cases. This included 90 men, 101 women, and 43 with sex not specified.

Most individuals had been diagnosed with CRC (n = 159, 68%) with a mean age of first CRC diagnosis of 48 years (range 22 – 80; age at diagnosis not available on 4 individuals). **(TABLE S1)** The percentage of 155 identifiable carriers that developed CRC at age in the 20s, 30s, 40s, 50s, and 60s or above is 8%(n=12), 20% (n=31), 31% (n=49), 22% (n=34), and 19% (n=29), respectively. Fifteen carriers had either synchronous or metachronous CRCs.

Table 3 shows the distribution of CRCs by colorectal subsite. None of the CRCs diagnosed under the age of 30 years (0 out of 9) were located in the ascending colon or cecum

compared with 57% (57 out of 100) diagnosed over the age of 30 years ($p < 0.001$). In those under age 30, 78% of the CRCs were in the left colon (within the splenic flexure, descending, sigmoid, rectosigmoid junction, or rectum). In *PMS2* carriers with colon cancer in their 30s to 80s, the percentage in the left colon ranged from 21% to 60%. Following these observations, previously published cases of biallelic MMR mutation carriers[16, 23] were reviewed for the CRC site and are also shown in **TABLE 3**. In these cases, the majority of the reported colorectal cancer was in the left colon.

Of individuals with non-CRC tumors **(TABLE S1 and TABLE S2)**, there were 32 women, 9 men and 5 cases with sex not reported. The most common cancer after CRC was uterine cancer (n=20) with average age at diagnosis of 54.5 years (range 30 - 80). Three cases of ovarian cancer and two cases of primary peritoneal cancer were reported with average age at diagnosis of 53 years. Other cancers reported included cancers of the breast, duodenum and small intestine, stomach, urinary tract, brain and central nervous system.

Tumor IHC results were known for 110 cases (IHC was performed on not only CRC, but also other tumor types plus a large adenoma in one case), with all showing isolated loss of PMS2, except one individual whose CRC showed loss of both MSH6 and PMS2 (rechecked and confirmed). MSI status was known for 51 of the cases; 50 were MSI-H and one case of a rectal adenocarcinoma with isolated loss of PMS2 by IHC was microsatellite stable.

Seventy-six of the *PMS2* mutation carriers had no history of CRC **(TABLE S2 and TABLE S3)**. The average last known age was 48 (range 18 to 78, median age of 47). Of these, 32 were abstracted from previously published reports, and 44 were from the coauthors' previously unpublished clinical practice and research experiences.

Approximately 97 e-mail correspondences were sent amongst the group during the process, with an average of three e-mails sent from each member of the working group. After the cases were compiled and distributed to the group, an eventual consensus was formed by the group: there does not exist enough evidence to modify standard Lynch syndrome cancer screening guidelines for carriers of monoallelic *PMS2* mutations as determined by current molecular testing methods.

DISCUSSION

In a completely different context, former Secretary of Defense Donald Rumsfeld asserted: "There are known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns -- the ones we don't know we don't know[24]." The relevance of this quotation to *PMS2* is still developing, but data on *PMS2* today is sufficient only to know that there remain some very important unknowns. The convergence of several factors has made understanding the clinical implications of *PMS2* mutations elusive. The gene is difficult to sequence because of its structure and repetitive nature, so there was a long delay in clinical testing availability relative to the other MMR genes, reducing the available data from clinical labs on this gene. Multiple studies[16, 22, 25, 26] have indicated a low penetrance compared with mutations in the other Lynch Syndrome genes and our survey of

available carriers shows a large number of unaffected carriers and supports this observation. It is likely that most *PMS2* carriers are undiagnosed because they are not diagnosed with a cancer or alternatively, that affected carriers do not undergo genetic evaluation and testing due to a lack of identifiable risk factors suspicious for Lynch syndrome in their personal or family history. Universal testing for Lynch Syndrome is not being performed widely and/or has not been going on long enough to have altered the situation.

In this review, the authors examine a known unknown, “Is there adequate data to inform clinical management guidelines for individuals with monoallelic *PMS2* mutations that may deviate from those formulated for individuals with mutations in the other three Lynch Syndrome genes?” In considering our original question of appropriateness of clinical screening recommendations for *PMS2* mutation carriers, one has to balance the well-documented and accepted low penetrance (even in highly preselected cases that over-estimate penetrance) and the intermittent appearance of CRC developing in strikingly young individuals: approximately 8% of the individuals with a CRC in this review were under the age of 30. The co-author group discussed the juxtaposition of low penetrance with very young age of onset, and was unable to resolve if this was biologically incongruous or not. These properties of a genetic disorder may vary independently.

While this review did not set out to evaluate biallelic *PMS2* mutation carriers (they were actively excluded), based on this limited amount of data one speculation that surfaced was how certain one could be that a very young person with CRC might not actually have biallelic mutations in *PMS2*, or perhaps an unidentified hypomorphic allele, given the notoriously difficult molecular analysis that this gene presents. Genetic testing for *PMS2*, while still difficult, has improved in recent years and many of the published cases of *PMS2* monoallelic mutation carriers may not have had deletion and duplication analysis performed as it was not available at the time. This current data set does include one young onset case with a VUS in *PMS2* in addition to the pathogenic mutation (case #129) and another case had 4 synchronous colorectal cancers and 14 adenomas at age 26 (case #27), which is much more in keeping with the picture emerging of biallelic carriers.

IHC of non-malignant tissue has been suggested as one method to distinguish monoallelic from biallelic carriers, but there are reports of expression in some tissues even in those with known biallelic mutations so this is not a failsafe method to confirm a monoallelic mutation [27]. For the majority of instances of CRC under age 30, no information regarding IHC of non-malignant tissue was available or had not been tested in the individual. For three of the cases, the potential for a bi-allelic mutation, despite a single mutation identified by molecular analysis, was explored and for all three cases, staining of PMS2 was present in non-malignant tissue. Besides case #27, no other cases with early-onset were found to have multiple polyps. The clinical phenotype of *café au lait* macules was not reported in any of the cases described here but could have been overlooked. None of the cases of CRC under age 30 were diagnosed with a pediatric brain tumor or hematologic malignancies that would have suggested CMMRD. No colorectal cancers had occurred in the parents of the very young onset cases, arguing against particularly virulent monoallelic mutations resulting in very early onset and higher penetrance disease.

Cases of CRC diagnosed under age 30 were evaluated further to determine if there was any pattern that distinguished them from the *PMS2* mutation carriers diagnosed with cancer at older ages. One unexpected difference was that the very young onset cancers did not show the typical CRC site of Lynch Syndrome. In fact, none of the 9 cases had a right-sided tumor, whereas those diagnosed beyond age 30 showed the typical right-sided predisposition. In comparison to previously described MMR biallelic cases from Durno et al. [23] and Senter et al.[16] **(TABLE 3)**, there does appear to be a trend toward left-sided colorectal cancers in the published MMR biallelic carriers, similar to the observed under-age-30 presumed monoallelic *PMS2* carriers, though the data are limited.

Overall, given the possible lack of the typical *café au lait* macules, hematologic or brain tumors phenotypes, and the trend towards left-sided colorectal cancers, this group may be qualitatively and clinically different from biallelic *PMS2* mutation carriers, yet also different from monoallelic *PMS2* mutation carriers. Beyond a possible undetected second *PMS2* mutation, another possible consideration could be the presence of a modifier of cancer risk involving another gene altogether, i.e. digenic inheritance, which might result in early cancer. In this scenario, family members who inherit just the *PMS2* mutation would have risks of monoallelic *PMS2* carriers. Family members inheriting both the modifier and the *PMS2* monoallelic mutation could be at a higher risk, more likely to develop early onset cancers, perhaps even more left colonic predisposition. Certainly this hypothesis merits additional consideration and genetic research.

One factor considered when the authors discussed screening options related to how the first case in the family presented. If this is an older onset colorectal cancer presentation with the typical minimal family history, consistent with the *PMS2* low penetrance reports, then delaying colonoscopy for gene-carrying relatives to at least age 30 seems reasonable. In this review, there were no cases of families ascertained with CRCs diagnosed over age 30 that reported a history of relatives with CRCs under age 30 (no family history data shown and available data is incomplete). Conversely, if a family presents due to a very young onset CRC, the possibility of an undetected second mutation in *PMS2*, other modifier gene or digenic inheritance could be highlighted and counseled for. Screening of the siblings, who may be at 25% risk for carrying the same *PMS2* genotype, may be advised earlier initiation of CRC screening, such as age 20. The children of the affected young person could also have digenic inheritance, if this was the mechanism, and so their risks might parallel that of the parent. These data suggest that perhaps the general rule of thumb to initiate screening 5 years younger than the youngest case in the family or by age 30, whichever is earliest, could be appropriate.

When looking at the reported age of onset of CRC there is not a bimodal distribution across the decades. The percentages of the 155 carriers who developed CRC at ages in the 20s, 30s, 40s, 50s, and 60s or above is 8%, 20%, 31%, 22%, and 19%, respectively. This may be a counter argument for the existence of a biallelic or digenic subset accounting for the very early onset cases and suggests a very broad age of onset of CRC among monoallelic *PMS2* mutation carriers.

We are thus left with the dilemma of a known unknown: what is the cause of a low penetrance disorder that sometimes appears with very early onset cancer? There is currently no convincing evidence that the very early onset PMS2-related cancers represent a different disorder from the later onset PMS2-related cancers. Review of all available data on monoallelic *PMS2* mutation carriers speaks against stepping back from the cancer surveillance guidelines that have been developed for colorectal cancer and endometrial cancer risks in Lynch Syndrome in general, in spite of well documented differences in CRC risks. These guidelines still appear to be reasonable for carriers of monoallelic *PMS2* until data emerges that changes our current understanding.

The carrier frequency of *PMS2* pathogenic mutations is unknown but may be more common than the other Lynch syndrome related genes, given the notable excess of biallelic *PMS2* cases reported to date. The possibility of a hypomorphic *PMS2* variant or involvement of another gene altogether might occur that when paired with a typical pathogenic *PMS2* mutation may cause a very early onset cancer without the clinically striking phenotype of the constitutional mismatch repair deficiency, is still entirely speculative. The phenomenon of very early onset development of cancers in PMS2 mutation carriers merits additional research. We hope to encourage ongoing prospective genetic and epidemiologic studies that might one day make known today's unknowns.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Published Cumulative Cancer Risks to Age 70 for Lynch syndrome

Cancer Site	Cancer Risks for *MLH1, MSH2*	Cancer Risks *MSH6*	Cancer Risks for *PMS2*
Colorectal	28% - 75%[28-30]	10-70%[29, 31, 32]	15%-20%[16]
Endometrium	27% - 60%[28-30]	15-71%[29, 31, 32]	15%[16]
Ovary	6% - 21%[28, 29, 33, 34]	1%[29]	increased risk
Urinary Tract	8% - 9%[28, 29, 33, 34]	<1%[29]	increased risk
Stomach	5% - 20%[28, 29, 33, 34]	<1%[29]	increased risk

Table 2

Current Published Screening Guidelines for Lynch Syndrome

Cancer Site	Recommended Screening for *MLH1, MSH2*	Recommended Screening for *MSH6*	Recommended Screening for *PMS2*
Colon			
NCCN[9]	- Colonoscopy every 1-2 years, beginning at age 20 to 25 years (or 2-5y prior to earliest colon cancer in family)	- Colonoscopy every 1-2 years, beginning at age 25 to 30 years (or 2-5y prior to earliest colon cancer if it is diagnosed before age 30 years)	- Colonoscopy every 1-2 years, beginning at age 25 to 30 years (or 2-5y prior to earliest colon cancer if it is diagnosed before age 30 years)
Other recommendations:	- Colonoscopy every 1-2 years[10]	- Colonoscopy every 1-2 years[10] - Colonoscopy every 1-2 years, beginning at age 30[35]	- Colonoscopy every 1-2 years, beginning at age 30[16] - Colonoscopy every 1-2 years, beginning at age 35[35]
Endometrium and Ovary			
NCCN[9]	- Consideration of annual endometrial sampling offered annually - Consideration of transvaginal ultrasound and serum CA-125 - TAH BSO should be considered if childbearing is complete	- Consideration of annual endometrial sampling offered annually - Consideration of transvaginal ultrasound and serum CA-125 - TAH BSO should be considered if childbearing is complete	- Consideration of annual endometrial sampling offered annually - Consideration of transvaginal ultrasound and serum CA-125 - TAH BSO should be considered if childbearing is complete
Other recommendations:	- Gynecological exam, transvaginal ultrasound and endometrial sampling offered beginning at age 35 to 40 years[10] - TAH BSO should be considered[10] - Gynecological exam, transvaginal ultrasound and endometrial sampling offered beginning at age 30 to 35 years[35]	- Gynecological exam, transvaginal ultrasound and endometrial sampling offered beginning at age 35 to 40 years[10] - TAH BSO should be considered[10]	
Urinary Tract			
NCCN[9]	-Consideration of annual urinalysis, beginning at age 25 to 30 years		
Other recommendations:	- Consideration of annual urinalysis, beginning at age 30 to 35 years[35]		
Stomach			
NCCN[9]	- Consideration of EGD with extended duodenoscopy every 3-5 years, beginning at age 30 to 35 years		
Other recommendations:	- Consideration of EGD with biopsy of the gastric antrum every 2-3 years, beginning at age 30 to 35 years[35]		

Table 3

Comparison of Site of CRC in Previously Published Biallelic MMR Mutation Carriers Compared to Monoallelic *PMS2* mutation Carriers

Site of CRC	Senter et al Biallelics [16]	Durno et al Biallelics [23]	Monoallelic CRC in 20s	Monoallelic CRC in 30s	Monoallelic CRC in 40s	Monoallelic CRC in 50s	Monoallelic CRC in 60s	Monoallelic CRC in 70-80s
Cecum	0	4	0	4	7	6	4	1
Ascending	0	7	0	9	11	10	4	1
Hepatic Flexure	0	1	0	1	1	1	1	0
Transverse	0	2	2	1	7	2	0	0
Splenic Flexure	0	6	0	0	1	0	0	0
Descending	1	5	1	0	3	3	0	0
Sigmoid	1	6	3	0	4	1	7	1
Rectosigmoid Junction	0	1	1	0	0	1	0	2
Rectum, NOS	2	8	2	4	2	1	0	0
% of distal colon *	100%	65%	78%	21%	29%	24%	44%	60%

*includes splenic flexure, descending, sigmoid, rectosigmoid junction, rectum