Received: 30 October 2023 | Revised: 18 December 2023 | Accepted: 26 December 2023

DOI: 10.1002/mgg3.2360

Molecular Genetics & Genomic Medicine Open Access WILEY

ORIGINAL ARTICLE

Genotype–phenotype correlations in carriers of the *PMS2* founder variant c.1831dup

Melanie Gass[1] | **Britta Seebauer**[1] | **Aline Thommen**[1] | **Alexandra Fischler**[1] | **Karl Heinimann**[1,2]

[1]Institute for Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland

[2]Research Group Human Genomics, Department of Biomedicine, University of Basel, Basel, Switzerland

Correspondence
Karl Heinimann, Institute for Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland.
Email: karl.heinimann@usb.ch

Present address
Britta Seebauer, Genetica AG, Zurich, Switzerland

Abstract

Background: Lynch syndrome represents one of the most common cancer predispositions worldwide and is caused by germline pathogenic variants (PV) in DNA mismatch repair (MMR) genes. We repeatedly identified a PV in the MMR gene *PMS2*, c.1831dup, accounting for 27% of all Swiss *PMS2* PV index patients identified. Notably, 2/18 index patients had been diagnosed with colorectal cancer (CRC) before age 30.

Methods: In this study, we investigated if this PV could (i) represent a founder variant by haplotype analysis and (ii) be associated with a more severe clinical phenotype.

Results: Haplotype analysis identified a shared common region of about 0.7 Mb/1.3 cM in 13 (81%) out of 16 index patients. Genotype–phenotype correlations, combining data from the 18 Swiss and 18 literature-derived *PMS2* c.1831dup PV index patients and comparing them to 43 Swiss index patients carrying other *PMS2* PVs, indicate that the *PMS2* c.1831dup variant may be associated with earlier (<50 y) age at CRC diagnosis (55% vs. 29%, respectively; $p = 0.047$). Notably, 30% (9/30) of cancers from c.1831dup carriers displayed atypical MMR protein expression patterns on immunohistochemistry.

Conclusion: Our results suggest that the *PMS2* c.1831dup PV represents a, probably ancient, founder mutation and is possibly associated with an earlier CRC diagnosis compared to other *PMS2* PVs.

KEYWORDS

haplotype, Lynch syndrome, *PMS2* founder variant, *PMS2* variants, *PMS2*-associated Lynch syndrome

1 | INTRODUCTION

Lynch syndrome (LS) represents one of the most common cancer predispositions known today, affecting an estimated 1 in 279 individuals (Dominguez-Valentin et al., 2020; Win et al., 2017). It is caused by heterozygous germline pathogenic variants (PV) in one of the four DNA mismatch repair (MMR) genes: *MLH1* (OMIM: *120436),

MSH2 (OMIM: *609309), *MSH6* (OMIM: *600678), and *PMS2* (OMIM: *600259). Patients have a significantly increased, gene-specific lifetime risk for several cancer types, predominantly colorectal (up to 57%) and endometrial cancer (up to 48%) and, more rarely (about 1% to 17%), other tumors like ovarian, gastric, small bowel, and urinary tract cancer (Dominguez-Valentin et al., 2020; Lynch et al., 2015). Several studies have shown that *MSH6*- and *PMS2*-associated LS display an attenuated phenotype with lower lifetime risks and a later age of first cancer diagnosis compared to *MLH1*- and *MSH2*-associated LS, resulting in gene-specific adaptations of surveillance recommendations (Bonadona et al., 2011; Broeke et al., 2018; Dominguez-Valentin et al., 2020; Jenkins et al., 2021; Seppälä et al., 2021; Ten Broeke et al., 2015). Thus, while regular colonoscopies for patients with *MLH1*- and *MSH2*-associated LS are recommended from ages 20–25 onward every 1–3 years, surveillance in patients with *MSH6*- and *PMS2*-associated LS should begin between ages 30 and 35 every 2–5 years. Depending on the individual's family history, surveillance may be initiated earlier (NCCN, 2022). In addition, the discovery that MMR status predicts the clinical benefit of immune checkpoint blockade has opened up new therapeutic possibilities and revolutionized cancer treatment. The use of anti-PD-1 immune checkpoint inhibitors for the treatment of metastatic MSI-high LS-associated cancers has demonstrated an immune-related progression-free survival rate in 67 to 78% of patients (Le et al., 2015).

Of the 2672 unique public MMR gene PVs listed in the Leiden Open Variation Database (LOVD), only 175 (approx. 6.5%) have been reported in *PMS2*, compared to 1044 (approx. 39.1%) in *MLH1*, 981 (approx. 36.7%) in *MSH2* and 472 (approx. 17.7%) in *MSH6* (https://databases.lovd.nl/shared/genes, accessed April 29th, 2023). Initially, it was thought that the majority of LS families harbor germline variants in either *MLH1* or *MSH2* (Borelli et al., 2014). More recent studies, however, estimated that the carrier frequency of *PMS2* variants might be the highest of all MMR genes (approx. 1 in 714, compared to *MSH6* = 1 in 758, *MLH1* = 1 in 1946, and *MSH2* = 1 in 2841) (Win et al., 2017). *PMS2* variants might be underreported because of technical difficulties due to masking by pseudogenes as well as reduced penetrance (S. W. Ten Broeke et al., 2015). Since 2008, five founder mutations in *PMS2* and one possible founder mutation have been reported (Clendenning et al., 2008; Grindedal et al., 2014; Li et al., 2015; Tomsic et al., 2013).

Over the past 10 years, we have recurrently encountered a specific pathogenic sequence variant in the *PMS2* gene, c.1831dup, predicted to result in a frameshift, p.(Ile611AsnfsTer2), and nonsense-mediated decay (ClinVar Variation ID: 91317; LOVD DB-ID: PMS2_000091), accounting for 27% (19 out of 71) of all Swiss *PMS2* PV index patients identified during this time period at our institute. Of note, two Swiss c.1831dup carriers had been diagnosed with colorectal cancer before the age of 30 years, namely at 18 and 29 years. Therefore, in this study, we investigated whether the *PMS2* PV c.1831dup could (a) represent a founder mutation and (b) display a more severe clinical phenotype, such as younger age at diagnosis, by combining 18 Swiss and 18 literature-derived c.1831dup index patients and comparing them to 43 Swiss index patients carrying other *PMS2* PVs.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

The study was conducted with the approval of the "Ethikkommission Nordwest- und Zentralschweiz" (EK258/05).

2.2 | Swiss *PMS2* PV carriers

We retrospectively reviewed the medical records of index patients who were referred to our Medical Genetics clinic at the University Hospital Basel because of suspected LS between January 2011 and December 2021 to identify carriers of pathogenic or likely pathogenic *PMS2* variants (class 4 or 5 according to the guidelines of the American College of Medical Genetics and Genomics (Richards et al., 2015), further abbreviated as "PV"). From a total of 346 Swiss index patients harboring a germline MMR PV (102 [29.5%] in *MSH2*, 100 [28.9%] in *MLH1*, 73 [21.1%] in *MSH6*) 71 (20.5%) patients were found to carry a *PMS2* PV (Figure 1). For 61 (86%) *PMS2* index patients, detailed clinical information was available to include them in the study. Clinical (age, sex, cancer site, tumor location, ethnicity) and histopathological data (immunohistochemistry, microsatellite stability) as well as family history were retrieved.

2.3 | Literature-derived *PMS2* c.1831dup PV carriers

We next performed a systematic literature search in PubMed to identify other index patients carrying the *PMS2* c.1831dup variant (Reference Sequence NM_000535.7) until December 2021 using the following search terms: "PMS2 c.1831dup," "PMS2 c.1831dupA," "PMS2 c.1831insA," "PMS2 c.1831_1832insA," "PMS2 c.1828insA," "PMS2 p.Ile611fs," "PMS2 p.I611fs," "PMS2

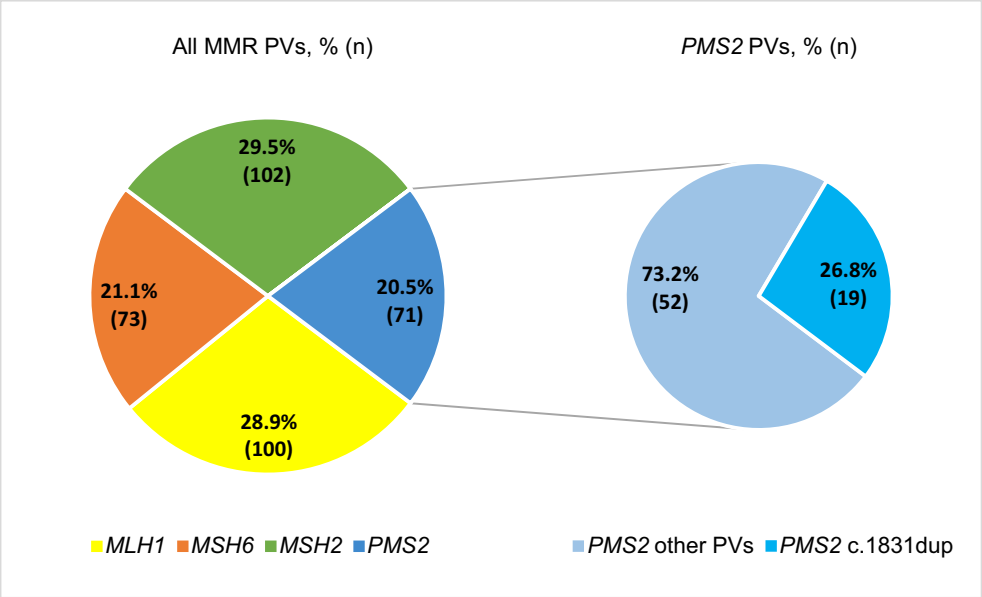

FIGURE 1 Pathogenic and likely pathogenic DNA mismatch repair variants identified at the Institute of Medical Genetics and Pathology, University Hospital Basel, between 2011 and 2021. MMR, DNA mismatch repair; PVs, pathogenic/likely pathogenic variants.

founder mutation," and "Lynch syndrome PMS2 mutations." Thirty-one patients were thus identified. Thirteen patients for whom the age at diagnosis and/or cancer site were unknown were excluded, leaving 18 (58%) patients from the literature.

2.4 | Haplotype analysis

Haplotype analysis was performed in all Swiss index patients carrying the *PMS2* c.1831dup PV from whom DNA was available. Five short tandem repeat markers (STR markers: D7S517, D7S2487, D7S2201, D7S481, D7S641) and six single nucleotide polymorphisms (SNPs; dbSNP: rs1802683, rs10000, rs2228006, rs1805321, rs1805319, rs62456182) surrounding the c.1831dup PV of the *PMS2* gene on chromosome 7p22.1 were used. STR markers were selected on the basis of the ABI PRISM® Linkage Mapping Set (LMS-MD10) and previously reported *PMS2* haplotype analyses (Clendenning et al., 2008; Tomsic et al., 2013). STR markers and SNPs span a genomic region of approx. 4.2 Mb across the *PMS2* locus (Table 1).

2.5 | Statistical methods

Statistical comparison of patients' features, encompassing phenotypic characteristics and molecular status, was done using Chi-square and Fisher's exact tests for categorical variables (e.g., gender, presence of symptoms), or Student's *t* test for continuous variables (e.g., age at diagnosis), with all of the probabilities reported as two-tailed *p* values, considering $p < 0.05$ to be statistically significant. All calculations were done in either Microsoft Excel 2016 or Stat View v.4.5 (Abacus Concepts).

3 | RESULTS

Between January 2011 and December 2021, the *PMS2* c.1831dup variant was identified in 19 (27%) of 71 Swiss index patients carrying a *PMS2* PV (Figure 1). Two index patients were from the same family, leaving 18 apparently unrelated index patients for further analysis. Since the *PMS2* c.1831dup variant accounted for more than a quarter of all *PMS2* PVs, we investigated the possibility that this variant might represent a founder mutation by performing haplotype analysis in 16 patients from whom DNA was available for study.

3.1 | Haplotype analysis and geographic origin of PMS2 c.1831dup

As depicted in Table 1, out of 16 unrelated index patients, four (25%) were found to share all and nine (56%) to share 10 out of 11 markers/SNPs investigated. Thus, with STR markers D7S2478 and D7S481 constituting the respective shared 5′ and 3′ borders, the commonly shared haplotype stretch covers a region of approximately 0.69 Mb in size corresponding to approximately 1.3 cM (GRCh37/hg19; cM Estimator [https://dnapainter.com/tools/cme]). We further assessed the geographic origins of the 18 unrelated

TABLE 1 Haplotype analysis in 16 Swiss index patients carrying the *PMS2* c.1831dup pathogenic variant.

Chromosome band	**7p22.2**	**7p22.1**										**7p21.3**
Distance bp from c.1831dup	**1′528′649**	**582′350**	**396′007**	**13′515**	**13′411**	**0**	**211**	**424**	**10′416**	**12′158**	**104′618**	**2′687′194**
STR marker/ dbSNP ID	**D7S517**	**D7S2478**	**D7S2201**	**rs1802683**	**rs10000**	**rs63750250**	**rs2228006**	**rs1805321**	**rs1805319**	**rs62456182**	**D7S481**	**D7S641**
				c.2570G>C	**c.2466 T>C**	**c.1831dup**	**c.1621A>G**	**c.1408C>T**	**c.780C>G**	**c.705 + 17A>G**		
P01	250 **259**	128 **128**	260 **260**	**G** C	**T** C	WT **A**	A **G**	C **T**	C **G**	A **G**	274 **288**	92 **92**
P02	248 **259**	130 **128**	260 **260**	**G** G	**T** T	WT **A**	G **G**	T **T**	G **G**	G **G**	286 **288**	88 88
P03	255 250	128 **128**	257 **260**	**G** C	**T** C	WT **A**	A **G**	C **T**	C **G**	A **G**	280 **288**	93 **92**
P04	257 **259**	128 **128**	260 **260**	**G** C	**T** T	WT **A**	G **G**	C **T**	G **G**	A **G**	274 **288**	90 **92**
P05	250 259	128 128	257 265	**G** G	**T** C	WT **A**	G **G**	T **T**	G **G**	G **G**	288 **288**	80 **92**
P06	255 250	134 **128**	257 **260**	**G** G	**T** C	WT **A**	G **G**	T **T**	G **G**	G **G**	290 **288**	88 88
P07	253 250	128 **128**	252 **260**	**G** C	**T** C	WT **A**	G **G**	C **T**	G **G**	A **G**	280 **288**	92 **92**
P08	253 **259**	128 **128**	257 **260**	**G** C	**T** C	WT **A**	G **G**	C **T**	G **G**	A **G**	291 **288**	88 **92**
P09	255 250	128 **128**	260**260**	**G** G	**T** C	WT **A**	G **G**	C **T**	G **G**	A **G**	278 **288**	90 90
P10	255 255	134 **128**	260 **260**	**G** C	**T** C	WT **A**	G **G**	T **T**	G **G**	G **G**	291 **288**	88 90
P11	252 253	134 **128**	260 **260**	**G** G	**T** C	WT **A**	A **G**	C **T**	C **G**	A **G**	274 **288**	90 **92**
P12	248 **259**	117 **128**	260 **260**	**G** G	**T** T	WT **A**	G **G**	C **T**	G **G**	A **G**	274 **288**	90 90
P13	253 250	128 **128**	257 **260**	**G** G	**T** T	WT **A**	G **G**	C **T**	G **G**	A **G**	282 **288**	90 **92**
P14	248 **259**	130 **128**	261 **260**	**G** G	**T** T	WT **A**	G **G**	T **T**	G **G**	G **G**	278 **288**	88 88
P15	253 **259**	130 **128**	252 **260**	**G** G	**T** T	WT **A**	A **G**	C **T**	C **G**	A **G**	274 **288**	88 **92**
P16	248 252	138 128	261 261	**G** C	**T** T	WT **A**	A **G**	C **T**	G **G**	G **G**	280 289	90 90
		~0.69 Mb/1.3 cM										

Note: Reference Sequence *PMS2*: NM_000535.7. The total distance between STR markers D7S517 and D7S641 is 4.2 Mb/9.3 cM. Variant-associated haplotypes are highlighted in gray with the possible disease-associated allele marked in red. The commonly shared haplotype is shown at the bottom.

Abbreviations: bp, base pairs; cM, centimorgan; Mb, megabase; P01-P16, patient number 1 to 16; SNP, single nucleotide polymorphism; STR, short tandem repeat; WT, wild-type.

PMS2 c.1831dup index patients: 12 (63%) live in Eastern Switzerland (mainly the canton of Grisons) and six (32%) in adjacent Central Switzerland (mainly the canton of Lucerne). Thus, the geographic distance shared by 95% of *PMS2* index patients amounts to approximately 100 km. Because of the limited number of index patients, we were unable to meaningfully estimate the age of the putative founder variant. Since the commonly shared haplotype is comparatively short, it may indicate that the *PMS2* variant c.1831dup actually represents an ancient mutation (Hanein et al., 2008).

3.2 | PMS2 genotype–phenotype comparisons

First, we compared the clinical and histopathological features of the 18 Swiss index patients with the 18 *PMS2* c.1831dup variant carriers identified from the literature search. Since the two groups were not statistically significantly different from each other (cf. Table 2), we combined the Swiss and literature-derived *PMS2* c.1831dup carriers into one group for further comparison with 43 index patients carrying other *PMS2* PVs (hereinafter referred to as the "*PMS2* control group"; Table 2).

Three (8%) index patients of the *PMS2* c.1831dup group were diagnosed with colorectal cancer (CRC) before age 35 years, two even before age 30 years. Of the 43 index patients in the *PMS2* control group, one patient (2%) had been diagnosed with CRC before age 35 years ($p = 0.3$; data not shown). CRC represented the most common tumor in both patient groups, with 83.3% (30/36) of index patients carrying *PMS2* c.1831dup and 79.1% (34/43) in the *PMS2* control group. Likewise, overall median age at diagnosis of CRC was similar, with 49 years (IQR 19.5) in the *PMS2* c.1831dup group and 52 years (IQR 8.8) in the *PMS2* control group. Splitting CRC patients into age groups, however, showed that 55% (17/31) of *PMS2* c.1831dup carriers were diagnosed before age 50 years, compared to 29% (10/34) in the *PMS2* control group (Fisher exact test: $p = 0.047$; Figure 2). Colorectal cancer site (proximal vs. distal) and site-specific median age at diagnosis did not significantly differ between the two groups.

In addition, 13 extracolonic LS associated cancers were reported: three (8.3%) endometrial, one (2.8%) ovarian, and one urinary tract cancer in the *PMS2* c.1831dup group as well as four (9.3%) endometrial, three (7%) duodenal, and one (2.3%) ovarian cancer in the *PMS2* control group.

TABLE 2 Clinical characteristics of the *PMS2* index patient groups.

	***PMS2* c.1831dup**			**Other *PMS2* PVs**
	Swiss cohort	**Literature-derived**	**Combined**	**Swiss cohort**
Number of index patients	18	18	36	43
Male, *n* (%)	8 (*44.4*)	6 (33.3)	14 (*38.9*)	25 (*58.1*)
Female, *n* (%)	10 (*55.6*)	4 (22.2)	14 (*38.9*)	18 (*41.9*)
Sex unknown, *n* (%)	0	8 (44.4)	8 (*22.2*)	0
Tumor type, *n* (%)				
Colorectal cancer	15 (*83.3*)	16 (*89*)	31 (*86.1*)	34 (*79.1*)
Endometrial cancer	2 (*11.1*)	1 (*5.5*)	3 (*8.3*)	4 (*9.3*)
Other LS-associated cancers	0	1 (*5.5*)	1 (*2.8*)	4 (*9.3*)
Other cancers	1 (*5.6*)	0	1 (*2.8*)	1 (*2.3*)
Median age at diagnosis, years (*range*)				
Colorectal cancer	51 (*18–74*)	46 (*33–77*)	49 (*18–77*)	52 (*33–75*)
Endometrial cancer	NA (*59–61*)	NA	NA (*58–61*)	NA (*43–50*)
Other LS-associated cancers	NA	NA	*NA*	NA
ACII fulfilled, *n* (%)				
Yes	3 (*16.5*)	2 (*11*)	5 (*14*)	4 (*9*)
No	12 (*67*)	5 (*28*)	17 (*47*)	33 (*77*)
Unknown	3 (*16.5*)	11 (*61*)	14 (*39*)	6 (*14*)

Note: Reference Sequence *PMS2*: NM_000535.7.

Abbreviations: ACII, Amsterdam criteria II; LS, Lynch syndrome; NA, not applicable; PV, pathogenic/likely pathogenic variants.

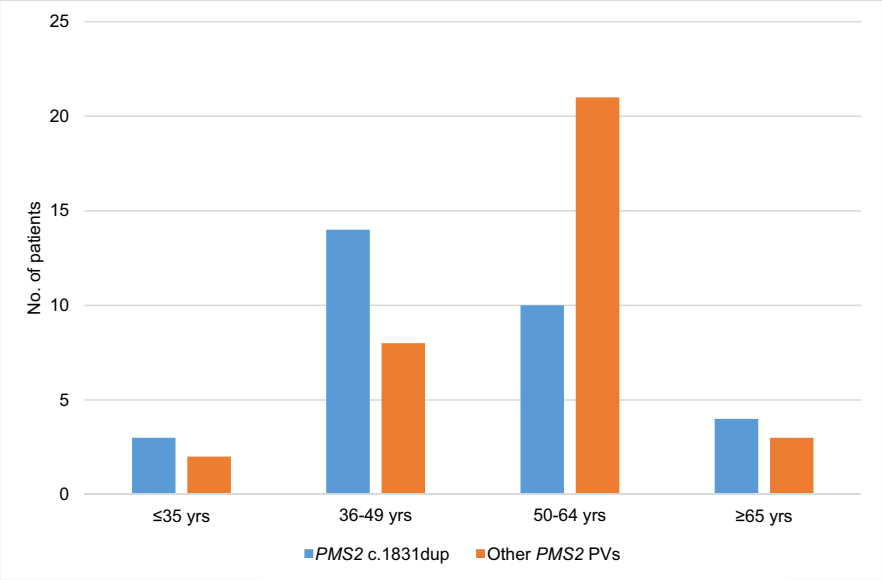

FIGURE 2 Age at colorectal cancer diagnosis in *PMS2* PV index patients. PV, pathogenic and likely pathogenic variants; yrs, years.

For 61% (22/36) of index patients carrying the c.1831dup PV and in 86% (37/43) of the *PMS2* control group, detailed family history was available. With five (14%) and four (11%) index patients, respectively, a similar minority fulfilled the Amsterdam II criteria (ACII) in each of the groups.

In eight (44%) out of 18 Swiss families belonging to the *PMS2* c.1831dup group, LS-associated cancers were reported: The most common cancers among these relatives were colorectal and endometrial, followed by gastric, pancreatic, urinary tract, and duodenal cancers. Four of these relatives were diagnosed with more than one cancer. Besides LS-associated cancers, the most frequent cancer diagnosis was breast cancer, observed in seven (39%) families. In one family fulfilling the ACII criteria, the sister of the index patient (P03) was diagnosed with brain cancer at approximately age 6 years and died at age 7 years.

Detailed results about tumor microsatellite instability (MSI) analysis and MMR protein expression by immunohistochemistry (IHC) are depicted in Table S1. MSI status and IHC profiles were available for 42% (15/36) and 83% (30/36) of *PMS2* c.1831dup variant carriers, respectively. Notably, while 93% (14/15) of tumors displayed a high microsatellite instability phenotype, 30% (9/30), that is 7/20 colorectal and 2/3 endometrial cancers, showed atypical IHC results: In addition to the expected, isolated loss of PMS2 expression, the atypical profiles included loss of MLH1, MSH2, and/or MSH6; seven (78%) of them exhibited high microsatellite instability. In index patients of the *PMS2* control group, the IHC profile, available for 81% (35/43) of patients, 17% (6/35) of tumors showed an atypical MMR protein expression pattern ($p = 0.25$).

4 | DISCUSSION

With 27%, the *PMS2* c.1831dup variant represents the most frequent *PMS2* PV identified in our Swiss LS cohort. Investigating the possibility of a founder variant, 13 (81%) out of 16 unrelated index patients were found to share a common haplotype spanning 0.7 Mb and corresponding to 1.3 cM, indicating that this variant probably arose from an ancient common ancestor and represents, to the best of our knowledge, the first MMR gene founder variant described in Switzerland. Geographically, 95% of the Swiss *PMS2* c.1831dup variant carriers cluster in the Eastern and Central parts of Switzerland. Among the literature-derived patients with this variant, 10 (56%) were identified at other European institutions, namely in France (Wang et al., 2020) and the Netherlands (van der Klift et al., 2016). Of the remaining eight patients, only two could be clearly allocated, and these were identified in Australia (Schofield et al., 2012) and the United States (Vaughn et al., 2010). Thus, the *PMS2* c.1831dup variant is likely to represent a European founder mutation. To further determine its origin and age, a multinational haplotype analysis to incorporate variant carriers from other countries will be required.

It has been hypothesized that *PMS2*-associated LS might exhibit the highest carrier frequency of all MMR genes, a possible explanation being its attenuated phenotype compared to PVs in *MLH1* and *MSH2* (Win et al., 2017). Based on the seminal data from the Prospective Lynch Syndrome Database (PLSD; plsd.eu), the incidence of colorectal and endometrial cancer appears to be only slightly increased in young adults, but higher in older ages, and with, thus far, no demonstrable cancer increase in other organs (Dominguez-Valentin et al., 2020; Møller, 2020). Thus, assuming a higher

degree of fitness compared to other MMR genes, *PMS2* PV carriers will have higher chances of passing the PV to their offspring. On the other hand, the observed clustering of the *PMS2* c.1831dup PV in the Eastern and Central parts of Switzerland raises the possibility of patients with autosomal recessive constitutional mismatch repair deficiency syndrome (CMMRD), which might have been the case with the sister of our patient P03 who developed brain cancer at age 6 years. While the mother, a maternal half-brother, and the maternal grandfather were diagnosed with LS associated cancers, no cancers were reported on the paternal side and the father's *PMS2* carrier state undetermined.

Since 11% (2/18) of our Swiss c.1831dup index patients were diagnosed with colorectal cancer at an, for *PMS2* PV carriers, unusually young age, namely at 18 and 29 years, respectively, we wondered if the *PMS2* c.1831dup PV may be associated with a more severe clinical phenotype. For this, we performed genotype–phenotype correlations by comparing them with literature-derived *PMS2* c.1831dup index patients and Swiss index patients carrying other *PMS2* PVs. Overall, we did not identify a statistically significant difference in median age at diagnosis of CRC between the groups analyzed (49 years in patients carrying the *PMS2* c.1831dup PV and 52 years in the *PMS2* control group). This is similar to other *PMS2* cohorts analyzed where median age at CRC diagnosis was between 46.5 and 52.1 years (Goodenberger et al., 2016; Rossi et al., 2017; Rosty et al., n.d.; van der Klift et al., 2016). The wide age range observed among *PMS2* PV carriers might be explained by multigenic etiology and/or specific polygenic risk factor profiles resulting in a more severe phenotype in some patients (Goodenberger et al., 2016).

Subdivision into age groups, however, revealed a statistically significant difference with 55% of *PMS2* c.1831dup carriers being diagnosed with CRC before age 50 years, while 71% of index patients in the *PMS2* control group had been diagnosed after age 50 years (Figure 2). The youngest *PMS2* c.1831dup index patient in our cohort (P08; Table S1) was diagnosed with transverse colon cancer at age 18 years. As expected for *PMS2*-related kindreds, family history was largely uninformative, with only a second and, allegedly, a fourth-degree relative diagnosed with gastrointestinal cancer at ages 35 and 57, respectively. The second, unusually young, 29-year-old *PMS2* c.1831dup carrier (P04; Table S1) was diagnosed with cancer of the ascending colon and family history depicting only one first-degree relative being diagnosed with colon cancer at age 63 and two first-degree relatives with cancers not belonging to the LS spectrum. Interestingly, two other retrospective studies reported *PMS2* PV carriers with CRC diagnosis before age 30 (8%) (Goodenberger et al., 2016) and age 35 (9.8%) (van der Klift et al., 2016), including patients with a very early diagnosis (age range 22–80 years and 25–69 years (van der Klift et al., 2016)). These patients would have been missed with current screening recommendations for *PMS2* PV carriers. Also, other studies critically questioned the gene-specific guidelines for *PMS2* variant carriers, reporting CRC diagnosis before age 30 in approx. 8% (Goodenberger et al., 2016). Detailed family history is currently the only available tool for individualizing surveillance measures, which is in particular problematic in case of *PMS2*-associated LS as clinical criteria such as the ACII were only fulfilled in about 15% of families investigated in this study, consistent with other studies on *PMS2* PV carriers (Senter et al., 2008; Sjursen et al., 2010; Ten Broeke et al., 2015).

Remarkably, one-third of tumor samples from the *PMS2* c.1831dup PV carriers as well as 17% of those from the *PMS2* control group displayed an uncommon IHC pattern. Atypical MMR protein expression patterns have recently been reported in 15.2% of samples from patients with suspected LS (Pan et al., 2023). Another study evaluating patients with *PMS2* PVs identified a discordant IHC profile in 6% of their tumor samples after excluding samples with isolated PMS2 loss (van der Klift et al., 2016). When looking at MMR protein expression in CRC samples only, four out of five atypical profiles actually stemmed from tumors located in the proximal part of the colon. Unfortunately, the limited size of the study cohort precluded further meaningful subgroup analyses. Other limitations of our study are due to its retrospective design and ascertainment bias. Therefore, further research will require an international collaborative effort, ideally based on prospectively gained data as exemplified by the PLSD, to further assess the phenotype of *PMS2*-associated LS in general, and of *PMS2* c.1831dup PV carriers in particular.

In conclusion, this study represents the largest reported cohort of *PMS2*-associated LS in Switzerland. Our results suggest that the *PMS2* c.1831dup PV represents a, probably ancient, founder variant and is possibly associated with an earlier age at CRC diagnosis compared to carriers of other *PMS2* PVs. Although limited in size and restricted to index patients, the study highlights that about 10% of *PMS2* PV carriers would profit from earlier colorectal surveillance than currently recommended, in particular patients carrying the *PMS2* c.1831dup PV.

AUTHOR CONTRIBUTIONS

MG, BS, and KH contributed to the conception and design of the study. MG and BS gathered all patient information. MG performed the literature review and AT and AF performed molecular genetic analyses. The manuscript was written by MG and KH with input from all co-authors. All

authors read the manuscript and approved the submitted version.

ACKNOWLEDGMENTS

The authors thank all patients for their participation and our dedicated laboratory staff, as well as the referring physicians, for their contributions to this study, especially Prof. Hansjakob Mueller. No funding was received for conducting this study. The authors declare they have no financial interests.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

ETHICS STATEMENT

The study was conducted with the approval of the "Ethikkommission Nordwest- und Zentralschweiz" (date: 26 April 2008, approval number: EK258/05). The research was conducted in accordance with the principles embodied in the Declaration of Helsinki and in accordance with local statutory requirements. All participants gave written informed consent to participate in the study.

REFERENCES

Bonadona, V., Bonaïti, B., Olschwang, S., Grandjouan, S., Huiart, L., Longy, M., Guimbaud, R., Buecher, B., Bignon, Y.-J., Caron, O., Colas, C., Noguès, C., Lejeune-Dumoulin, S., Olivier-Faivre, L., Polycarpe-Osaer, F., Nguyen, T. D., Desseigne, F., Saurin, J.-C., Berthet, P., … French Cancer Genetics Network. (2011). Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA*, *305*(22), 2304–2310. https://doi.org/10.1001/jama.2011.743

Borelli, I., Casalis Cavalchini, G. C., Del Peschio, S., Micheletti, M., Venesio, T., Sarotto, I., Allavena, A., Delsedime, L., Barberis, M. A., Mandrile, G., Berchialla, P., Ogliara, P., Bracco, C., & Pasini, B. (2014). A founder MLH1 mutation in Lynch syndrome families from Piedmont, Italy, is associated with an increased risk of pancreatic tumours and diverse immunohistochemical patterns. *Familial Cancer*, *13*(3), 401–413. https://doi.org/10.1007/s10689-014-9726-3

Broeke, S. W. T., Klift, H. M. V., Tops, C. M. J., Aretz, S., Bernstein, I., Buchanan, D. D., Dela Chapelle, A., Capella, G., Clendenning, M., Engel, C., Gallinger, S., Garcia, E. G., Figueiredo, J. C., Haile, R., Hampel, H. L., Hopper, J. L., Hoogerbrugge, N., Doeberitz, M. V. K., Le Marchand, L., … Win, A. K. (2018). Cancer risks for PMS2-associated lynch syndrom. *Journal of Clinical Oncology*, *36*(29), 2961–2968. https://doi.org/10.1200/JCO.2018.78.4777

Clendenning, M., Senter, L., Hampel, H., Robinson, K. L., Sun, S., Buchanan, D., Walsh, M. D., Nilbert, M., Green, J., Potter, J., Lindblom, A., & de la Chapelle, A. (2008). A frame-shift mutation of PMS2 is a widespread cause of Lynch syndrome. *Journal of Medical Genetics*, *45*(6), 340–345. https://doi.org/10.1136/jmg.2007.056150

Dominguez-Valentin, M., Sampson, J. R., Seppälä, T. T., ten Broeke, S. W., Plazzer, J. P., Nakken, S., Engel, C., Aretz, S., Jenkins, M. A., Sunde, L., Bernstein, I., Capella, G., Balaguer, F., Thomas, H., Evans, D. G., Burn, J., Greenblatt, M., Hovig, E., de Vos tot Nederveen Cappel, W. H., … Møller, P. (2020). Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: Findings from the prospective Lynch syndrome database. *Genetics in Medicine*, *22*(1), 15–25. https://doi.org/10.1038/s41436-019-0596-9

Goodenberger, M. L., Thomas, B. C., Riegert-Johnson, D., Boland, C. R., Plon, S. E., Clendenning, M., Win, A. K., Senter, L., Lipkin, S. M., Stadler, Z. K., Macrae, F. A., Lynch, H. T., Weitzel, J. N., De La Chapelle, A., Syngal, S., Lynch, P., Parry, S., Jenkins, M. A., Gallinger, S., … Lindor, N. M. (2016). PMS2 monoallelic mutation carriers: The known unknown. *Genetics in medicine*, *18*(1), 13–19. https://doi.org/10.1038/gim.2015.27

Grindedal, E. M., Aarset, H., Bjørnevoll, I., Røyset, E., Mæhle, L., Stormorken, A., Heramb, C., Medvik, H., Møller, P., & Sjursen, W. (2014). The Norwegian PMS2 founder mutation c.989-1G>T shows high penetrance of microsatellite instable cancers with normal immunohistochemistry. *Hereditary Cancer in Clinical Practice*, *12*(1), 1–7. https://doi.org/10.1186/1897-4287-12-12

Hanein, S., Perrault, I., Gerber, S., Delphin, N., Benezra, D., Shalev, S., Carmi, R., Feingold, J., Dufier, J. L., Munnich, A., Kaplan, J., Rozet, J. M., & Jeanpierre, M. (2008). Population history and infrequent mutations: How old is a rare mutation? GUCY2D as a worked example. *European Journal of Human Genetics*, *16*(1), 115–123. https://doi.org/10.1038/sj.ejhg.5201905

Jenkins, M. A., Macrae, F. A., Möslem, G., Haile, R. W., Database, C, Jeanette, G., Lee, G., Templeton, A. S., Contributing, D., Kiwamu, G., Aksoy, S., Alonso, A., Alvarez, K., Amor, D. J., Ankathil, R., Brunet, J., Buchanan, D. D., Bucksch, K., Buecher, B., … Pearlman, R. (2021). Variation in the risk of colorectal cancer for lynch syndrome: A retrospective family cohort study. *Lancet Oncology*, *22*(7), 1014–1022. https://doi.org/10.1016/S1470-2045(21)00189-3.Variation

Le, D. T., Uram, J. N., Wang, H., Bartlett, B. R., Kemberling, H., Eyring, A. D., Skora, A. D., Luber, B. S., Azad, N. S., Laheru, D., Biedrzycki, B., Donehower, R. C., Zaheer, A., Fisher, G. A., Crocenzi, T. S., Lee, J. J., Duffy, S. M., Goldberg, R. M., de la Chapelle, A., … Diaz, L. A. (2015). PD-1 blockade in tumors with mismatch-repair deficiency. *New England Journal of Medicine*, *372*(26), 2509–2520. https://doi.org/10.1056/nejmoa1500596

Li, L., Hamel, N., Baker, K., McGuffin, M. J., Couillard, M., Gologan, A., Marcus, V. A., Chodirker, B., Chudley, A., Stefanovici, C., Durandy, A., Hegele, R. A., Feng, B. J., Goldgar, D. E., Zhu, J., De Rosa, M., Gruber, S. B., Wimmer, K., Young, B., … Foulkes, W. D. (2015). A homozygous PMS2 founder mutation with an attenuated constitutional mismatch repair deficiency phenotype. *Journal of Medical Genetics*, *52*(5), 348–352. https://doi.org/10.1136/jmedgenet-2014-102934

Lynch, H. T., Snyder, C. L., Shaw, T. G., Heinen, C. D., & Hitchins, M. P. (2015). Milestones in Lynch: 1985–2015. *Nature Reviews*, *15*, 181–194.

Møller, P. (2020). The prospective Lynch syndrome database reports enable evidence-based personal precision health care. *Hereditary Cancer in Clinical Practice*, *18*(1), 1–7. https://doi.org/10.1186/s13053-020-0138-0

NCCN. (2022). Genetic/familial high-risk assessment: Colorectal. NCCN Guidelines Recommendations, Version 2. https://www.nccn.org/guidelines/guidelines-detail?category=2&id=1436

Pan, S., Cox, H., Willmott, J., Mundt, E., Gorringe, H., Landon, M., Bowles, K. R., Coffee, B., Roa, B. B., & Mancini-DiNardo, D. (2023). Discordance between germline genetic findings and abnormal tumor immunohistochemistry staining of mismatch repair proteins in individuals with suspected Lynch syndrome. *Frontiers in Oncology*, *13*, 1–9. https://doi.org/10.3389/fonc.2023.1069467

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W. W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., & Rehm, H. L. (2015). Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in Medicine*, *17*(5), 405–424. https://doi.org/10.1038/gim.2015.30

Rossi, B. M., Palmero, E. I., López-Kostner, F., Sarroca, C., Vaccaro, C. A., Spirandelli, F., Ashton-Prolla, P., Rodriguez, Y., de Campos Reis Galvão, H., Reis, R. M., Escremim de Paula, A., Capochin Romagnolo, L. G., Alvarez, K., Della Valle, A., Neffa, F., Kalfayan, P. G., Spirandelli, E., Chialina, S., Gutiérrez Angulo, M., … Dominguez-Valentin, M. (2017). A survey of the clinicopathological and molecular characteristics of patients with suspected Lynch syndrome in Latin America. *BMC Cancer*, *17*(1), 1–26. https://doi.org/10.1186/s12885-017-3599-4

Rosty, C., Clendenning, M., Walsh, M. D., Eriksen, S. V., Southey, M. C., Winship, I. M., Macrae, F. A., Boussioutas, A., Poplawski, N. K., Parry, S., Arnold, J., Young, J. P., Casey, G., Haile, R. W., Gallinger, S., Le Marchand, L., Newcomb, P. A., Potter, J. D., DeRycke, M., … Buchanan, D. D. (n.d.). Germline mutations in PMS2 and MLH1 in individuals with solitary loss of PMS2 expression in colorectal carcinomas from the colon cancer family registry cohort on behalf of the colon cancer family registry cohort. https://doi.org/10.1136/bmjopen-2015

Schofield, L., Grieu, F., Goldblatt, J., Amanuel, B., & Iacopetta, B. (2012). A state-wide population-based program for detection of lynch syndrome based upon immunohistochemical and molecular testing of colorectal tumours. *Familial Cancer*, *11*(1), 1–6. https://doi.org/10.1007/s10689-011-9494-2

Senter, L., Clendenning, M., Sotamaa, K., Hampel, H., Green, J., Potter, J. D., Lindblom, A., Lagerstedt, K., Thibodeau, S. N., Lindor, N. M., Young, J., Winship, I., Dowty, J. G., White, D. M., Hopper, J. L., Baglietto, L., Jenkins, M. A., & de la Chapelle, A. (2008). The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. *Gastroenterology*, *135*(2), 419–428.e1. https://doi.org/10.1053/j.gastro.2008.04.026

Seppälä, T. T., Latchford, A., Negoi, I., Sampaio Soares, A., Jimenez-Rodriguez, R., Evans, D. G., Ryan, N., Crosbie, E. J., Dominguez-Valentin, M., Burn, J., Kloor, M., von Knebel Doeberitz, M., van Duijnhoven, F. J. B., Quirke, P., Sampson, J. R., Møller, P., & Möslein, G. (2021). European guidelines from the EHTG and ESCP for Lynch syndrome: An updated third edition of the Mallorca guidelines based on gene and gender. *British Journal of Surgery*, *108*(5), 484–498. https://doi.org/10.1002/bjs.11902

Sjursen, W., Haukanes, B. I., Grindedal, E. M., Aarset, H., Stormorken, A., Engebretsen, L. F., Jonsrud, C., Bjørnevoll, I., Andresen, P. A., Ariansen, S., Lavik, L. A. S., Gilde, B., Bowitz-Lothe, I. M., Mæhle, L., & Møller, P. (2010). Current clinical criteria for Lynch syndrome are not sensitive enough to identify MSH6 mutation carriers. *Journal of Medical Genetics*, *47*(9), 579–585. https://doi.org/10.1136/jmg.2010.077677

Ten Broeke, S. W., Brohet, R. M., Tops, C. M., Van Der Klift, H. M., Velthuizen, M. E., Bernstein, I., Munar, G. C., Garcia, E. G., Hoogerbrugge, N., Letteboer, T. G. W., Menko, F. H., Lindblom, A., Mensenkamp, A. R., Moller, P., Van Os, T. A., Rahner, N., Redeker, B. J. W., Sijmons, R. H., Spruijt, L., … Wijnen, J. T. (2015). Lynch syndrome caused by germline PMS2 mutations: Delineating the cancer risk. *Journal of Clinical Oncology*, *33*(4), 319–325. https://doi.org/10.1200/JCO.2014.57.8088

Tomsic, J., Senter, L., Liyanarachchi, S., Clendenning, M., Vaughn, C. P., Jenkins, M. A., Hopper, J. L., Young, J., Samowitz, W., & de la Chapelle, A. (2013). Recurrent and founder mutations in the PMS2 gene. *Clinical Genetics*, *83*(3), 238–243. https://doi.org/10.1111/j.1399-0004.2012.01898.x

van der Klift, H. M., Mensenkamp, A. R., Drost, M., Bik, E. C., Vos, Y. J., Gille, H. J. J. P., Redeker, B. E. J. W., Tiersma, Y., Zonneveld, J. B. M., García, E. G., Letteboer, T. G. W., Olderode-Berends, M. J. W., van Hest, L. P., van Os, T. A., Verhoef, S., Wagner, A., van Asperen, C. J., ten Broeke, S. W., Hes, F. J., … Tops, C. M. J. (2016). Comprehensive mutation analysis of PMS2 in a large cohort of Probands suspected of Lynch syndrome or constitutional mismatch repair deficiency syndrome. *Human Mutation*, *37*(11), 1162–1179. https://doi.org/10.1002/humu.23052

Vaughn, C. P., Robles, J., Swensen, J. J., Miller, C. E., Lyon, E., Mao, R., Bayrak-Toydemir, P., & Samowitz, W. S. (2010). Clinical analysis of PMS2: Mutation detection and avoidance of pseudogenes. *Human Mutation*, *31*(5), 588–593. https://doi.org/10.1002/humu.21230

Wang, Q., Leclerc, J., Bougeard, G., Olschwang, S., Vasseur, S., Cassinari, K., Boidin, D., Lefol, C., Naïbo, P., Frébourg, T., Buisine, M. P., & Baert-Desurmont, S. (2020). Characterisation of heterozygous PMS2 variants in French patients with Lynch syndrome. *Journal of Medical Genetics*, *57*(7), 487–499. https://doi.org/10.1136/jmedgenet-2019-106256

Win, A. K., Jenkins, M. A., Dowty, J. G., Antoniou, A. C., Lee, A., Giles, G. G., Buchanan, D. D., Clendenning, M., Rosty, C., Ahnen, D. J., Thibodeau, S. N., Casey, G., Gallinger, S., Le Marchand, L., Haile, R. W., Potter, J. D., Zheng, Y., Lindor, N. M., Newcomb, P. A., … MacInnis, R. J. (2017). Prevalence and penetrance of major genes and polygenes for colorectal cancer. *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive*

Oncology, *26*(3), 404–412. https://doi.org/10.1158/1055-9965.EPI-16-0693

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Gass, M., Seebauer, B., Thommen, A., Fischler, A., & Heinimann, K. (2024). Genotype–phenotype correlations in carriers of the *PMS2* founder variant c.1831dup. *Molecular Genetics & Genomic Medicine*, *12*, e2360. https://doi.org/10.1002/mgg3.2360