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Constitutional Mismatch Repair Deficiency: Scoping Review of a Cancer-Predisposition Syndrome With Distinctive Cutaneous Findings

Kristie Mar[1] | Kimia Ameri[1] | Joseph M. Lam[2,3]

[1]Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada | [2]Department of Paediatrics, University of British Columbia, Vancouver, British Columbia, Canada | [3]Department of Dermatology and Skin Science, University of British Columbia, Vancouver, British Columbia, Canada

Correspondence: Joseph M. Lam (joseph.lam@ubc.ca)

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ABSTRACT

Constitutional mismatch repair deficiency (CMMRD) is a rare but severe hereditary cancer predisposition syndrome caused by biallelic pathogenic variants in one of the mismatch repair genes (*MLH1, MSH2, MSH6*, or *PMS2*). The condition mainly presents in childhood, with cancers primarily affecting the hematological, brain, and gastrointestinal systems, along with cutaneous features typical of neurofibromatosis type 1. This scoping review aims to explore the clinical characteristics of CMMRD. A systematic search of medical databases resulted in the inclusion of 127 articles. *PMS2* is the most affected gene, followed by *MSH6, MLH1*, and *MSH2*. Blood and brain malignancies occur in early childhood for all genetic variants, with the age of onset progressively decreasing from *PMS2* to *MSH6*, to *MLH1* and *MSH2*. Gastrointestinal tumors typically present in late adolescence in individuals with *PMS2* variants, at slightly younger ages in those with *MSH6* variants, and are rarely reported in *MLH1* and *MSH2* cases. Patients with CMMRD present with café-au-lait macules that are fewer in number and larger than in patients with neurofibromatosis type 1. Additional dermatological findings include hypopigmented patches and intertriginous freckling. *PMS2* and *MSH6* pathogenic variants are linked to the broadest spectrum of cutaneous manifestations, including vascular tumors, various nevi, and pilomatricomas. Despite its rarity and diverse clinical manifestations, advancements in diagnostic criteria, genetic testing, and surveillance protocols have significantly improved survival rates and cancer management in CMMRD patients.

1 | Introduction

Constitutional mismatch repair deficiency (CMMRD) is a rare but severe hereditary cancer predisposition syndrome caused by biallelic pathogenic variants in one of the mismatch repair (MMR) genes: *MLH1*, *MSH2*, *MSH6*, or *PMS2* [1]. The first case of CMMRD was reported in 1999 and described five children born to consanguineous parents [2]. By 2016, nearly 200 cases had been reported [3].

While CMMRD typically manifests in childhood, cases have also been reported in adulthood [3]. The primary cancers linked to this condition are hematological, neurological, and gastrointestinal cancers [2, 3]. However, other malignancies, like endometrioid adenocarcinoma and undifferentiated carcinoma of the parotid, also occur [4, 5]. Several cutaneous features, such as café-au-lait macules (CALMs), hypopigmented macules or patches, and multiple pilomatricomas, have been found in patients with CMMRD and can aid in diagnosis [1, 3, 6].

Due to its rarity and diverse presentation, CMMRD often goes undiagnosed, and awareness of the condition is limited [3, 7]. Early detection is crucial, as it allows for surveillance that can extend the duration of life and can enable early testing in family members [3, 8].

The aim of this scoping review is to explore genotype–phenotype variations, family history, diagnostic methods, treatment, and surveillance for patients with CMMRD.

2 | Methods

2.1 | Protocol and Design

This scoping review adhered to the Preferred Reporting Items of Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) guidelines [9]. The protocol was registered with Open Science Framework.

2.2 | Search Strategy

A database search was conducted through PubMed, Ovid MEDLINE, Ovid Embase, and Cochrane using a search strategy on July 8, 2024. Date, geographical, and language restrictions were not applied. Search strategies were modified according to search engine requirements (Table S1).

Studies were eligible if they met our predetermined population, intervention, comparator, outcome, and study design (PICOS) framework criteria (Table S2).

2.3 | Article Selection

Article selection and review were completed in two stages. Articles were first imported into Covidence, an online systematic review software (http://www.covidence.org/). Two reviewers (K.M. and K.A.) independently reviewed the title and abstract of all articles after duplicates were removed. Studies were excluded at full-text screening if they did not follow the predetermined PICOS criteria. Any conflicts between reviewers were resolved by discussion.

2.4 | Data Extraction

Data extraction was completed by two reviewers (K.M. and K.A.) in duplicate on a standardized extraction form. Data were extracted using a predetermined data form including the publication year, country, study design, age at diagnosis, sex, genotype, systemic and cutaneous features, family history, diagnostic techniques, surveillance protocols, and treatments.

2.5 | Data Synthesis

The included studies were independently coded by the two researchers based on seven themes: (1) pediatric/adult, (2) genotype, (3) clinical characteristics, (4) family history, (5) diagnosis, (6) interventions, and (7) ethics. Studies could be assigned to multiple themes. Studies including cutaneous features underwent quantitative extraction to determine the proportion of patients, pooled mean size, pooled mean number of lesions, distribution, and location.

3 | Results

The primary search yielded 1095 articles, from which 443 were duplicates. 249 articles remained for full-text review after the title and abstract screen. 193 articles were selected for data extraction, and 127 were ultimately included.

3.1 | Genotype–Phenotype Correlation

The most common gene affected in CMMRD was *PMS2*, followed by *MSH6*, *MLH1*, and *MSH2* [1]. Tumor onset typically occurred at a median age of 7 to 12.5 years [2, 10]. The course of the disease varied depending on the pathogenic variant, with *PMS2*-associated malignancies presenting later at an average age of 15 years (range 3–33), *MSH6* at 8 years (range 6–18), *MLH1* at 6 years (range 2–6), and *MSH2* at 3 years (range 1–3) [1, 2, 11].

The 3 types of cancers with comparable incidence rates observed across all pathogenic variants were hematological malignancies, brain tumors, and gastrointestinal tumors [1, 2, 12]. In addition, 10% of all patients had "other non-classic tumors", such as sarcoma, breast cancer, and Wilms' tumor, along with benign tumors like hepatic adenoma, leiomyoma, and meningioma [10].

Mortality correlated with the gene pathogenic variant [1, 2, 11]. In a study of 31 patients between 1999 and 2014, mortality was highest with *MLH1* and *MSH2* at 100%, followed by *MSH6* at 83%, and *PMS2* at 56% [1, 2, 11]. The median age of death was 6 years for *MLH1*, 9 years for *MSH2*, 13 years for *MSH6*, and 20 years for *PMS2* [2].

3.1.1 | PMS2

3.1.1.1 | Systemic Features. *PMS2* pathogenic variants were present in 56% to 60% of all CMMRD cases and were typically associated with a later onset of clinical manifestations [10, 11]. Wimmer et al. reported that 57% of *PMS2* patients developed brain cancers and 64% developed gastrointestinal cancers, compared to less than 30% of patients with *MLH1* and *MSH2* mutations [11]. The mean age of onset for the first tumor was typically around 15 years [1]. The disease course for *PMS2* was more benign than for other variants, which may be due to the lower penetrance of *PMS2* pathogenic variants [1, 11].

In children, the first malignancies typically involved hematological cancers, such as T-cell acute lymphoblastic leukemia (T-cell ALL), which can appear as early as age 3 (Figure 1) [1]. Brain tumors, often glioblastomas or gliomas, tended to develop at around 9 years [1, 11]. Gastrointestinal tumors, including colorectal cancer (CRC) and polyps, usually emerged between

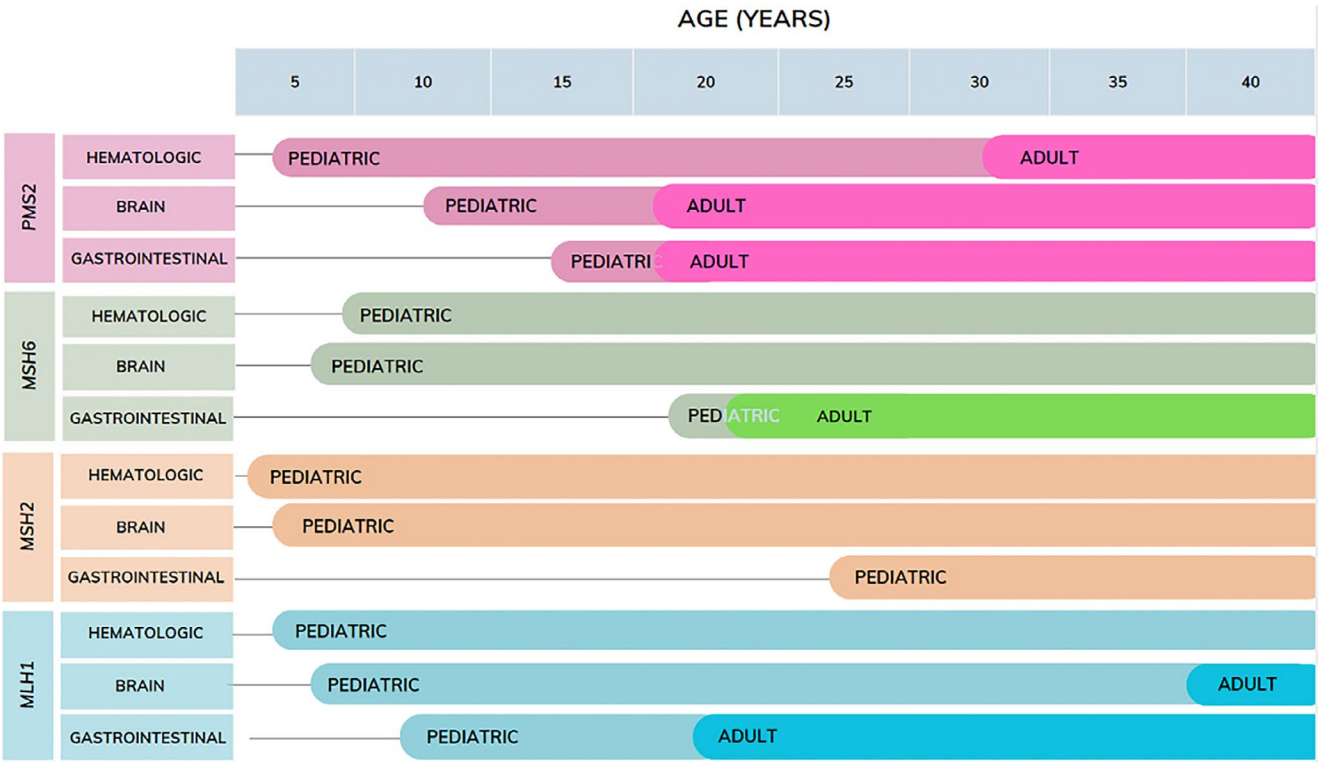

FIGURE 1 | Age of onset of first tumor.

school-age and adolescence [1, 4, 11]. Furthermore, there exist reports of children with multiple developmental venous anomalies (DVAs) [13].

In contrast, there was a predominance of gastrointestinal tumors in adults, such as CRC, colonic adenocarcinoma, and gastric adenocarcinoma, which were diagnosed in the third decade of life [1, 4, 11]. Brain tumors, including ganglioglioma, glioblastomas, anaplastic astrocytoma, and oligodendroglioma, also occurred during the third or fourth decade of life [1, 11, 14]. Hematologic malignancies, notably, acute myeloid leukemia (AML), were also seen [11]. Adults with *PMS2* also developed other types of malignancies, such as endometrioid adenocarcinoma [4].

3.1.1.2 | Cutaneous Features. CALMs were present in 71% of *PMS2* cases (Table 1). The pooled data revealed several differences from the CALMs typically found in patients with NF1. Patients with *PMS2* presented with fewer but larger CALMs (>15 mm). The pooled average number of CALMs in *PMS2* cases was 4.5, with a mean diameter of 89 mm, with some as large as 200 mm (Figure 2). These patches were primarily on the trunk and extremities. Atypical CALMs were also frequently reported. For example, one case detailed a large CALM over the neck, chest, and arm [15], while another noted CALMs with irregular edges and foci of hypopigmentation within areas of hyperpigmentation [4]. In addition, hypopigmented macules or patches were observed in 26% of *PMS2* patients, usually 1–2 in number, ranging from 5 to 10 mm in diameter and nearly always on the trunk [16]. Freckling was present in 25% of *PMS2* variants, predominantly found in the axillae, and to a lesser extent, the inguinal region (Figure 3).

Pilomatricomas were reported in 3% of *PMS2* cases, with a single case involving a pilomatrix carcinoma. Neurofibromas, both plexiform and cutaneous, were also reported in 3% of *PMS2* patients. Other findings included hyperpigmentation (6%), which was described as irregular and distinct from café-au-lait macules (CALMs) in one case. In addition, 2 cases were reported for each of the following: melanocytic nevi (2%), sebaceous adenomas or carcinomas (2%), vascular malformations or tumors (2%), and lentigines (2%). There were individual cases of squamous cell carcinoma, lichen planus, and dermoid cyst, among others.

3.1.2 | MSH6

3.1.2.1 | Systemic Features. The incidence of *MSH6* pathogenic variants was 28% among patients with CMMRD [10], with the median age of onset for the first tumor at 8 years (range 1–17) [17]. The time between the first tumor and death was typically 0.6 years [1]. Out of 38 individuals affected with the *MSH6* variant, 19 had one malignancy, 13 had two, and 7 had more than two [17]. The majority of cases involved brain tumors, with an average age of onset of 5 years [18], followed by equal proportions of hematological and gastrointestinal tumors, with an average age of onset of 8 and 19 years, respectively [18].

In children with *MSH6* pathogenic variants, brain tumors were most commonly glioblastoma multiforme, high-grade gliomas, and, less frequently, medulloblastoma [17–20]. Hematological malignancies were often non-Hodgkin lymphoma (NHL) of T-cell lineage, particularly T-cell ALL [21–23], with reports of Burkitt lymphoma and AML [18, 19]. Gastrointestinal malignancies typically included colonic adenocarcinoma [17, 19]. In addition, there have been reports of multiple DVAs in children [13]. Among adults with *MSH6* pathogenic variants, colonic

TABLE 1 | Skin findings reported for each genotype.

Gene	Number of patients reporting skin findings	Skin finding	Proportion (%)	Pooled mean number of lesions	Pooled mean size (mm)	Distribution	Distribution proportion (%)	Location	Location proportion (%)
MLH1	4	CALM	100.0	2	—	—	—	—	—
		Vascular malformation/tumor	25.0		—	—	—	Legs	100.0
MSH2	3	CALM	100.0	1	—	—	—	Legs	100.0
		Hypopigmented macule/patch	100.0	1	—	—	—	Trunk	100.0
		Freckling	33.3	—	—	—	—	Axillary	100.0
MSH6	59	CALM	89.8	5.4	56.7	—	—	Arms	10.0
								Trunk	60.0
								Trunk & Extremities	30.0
		Hypopigmented macule/patch	16.9	2	—	—	—	Trunk	100.0
		Hyperpigmented macule/patch	6.8	6	10	—	—	Trunk & Extremities	100.0
		Freckling	20.3	—	—	—	—	Axillae	25.0
								Axillae & Inguinal	66.7
								Inguinal	8.3
		Nevi	10.2	40.0	3.0	—	—	Back	33.3
								Hands & Feet	33.3
								Scalp	33.3
		Neurofibroma	1.7	—	—	—	—	—	
		Vascular malformation/tumor	5.1	—	—	—	—	Trunk	100.0
		Melanosis	1.7	—	—	—	—	Eyes	100.0
		Atypical dermal melanocytosis	1.7	—	50.0	—	—	Back	100.0

(Continues)

TABLE 1 | (Continued)

Gene	Number of patients reporting skin findings	Skin finding	Proportion (%)	Pooled mean number of lesions	Pooled mean size (mm)	Distribution	Distribution proportion (%)	Location	Location proportion (%)
PMS2	119	CALM	71.4	4.5	89.0	Generalized	50.0	Extremities	11.1
						Unilateral	50.0	Legs	22.2
								Trunk	55.6
								Trunk & Extremities	11.1
		Hypopigmented macule/patch	26.0	2.0	7.5	Generalized	100.0	Trunk	33.3
								Trunk & Extremities	66.7
		Hyperpigmented macule/patch	5.9	—	—	—	—	Trunk	25.0
								Trunk & Extremities	75.0
		Freckling	13.4	—	—	—	—	Axillae	57.1
								Axillary & Groin	14.3
								Groin	14.3
								Trunk	14.3
		Pilomatricoma	2.5	—	—	—	—	—	
		SCC	0.8	—	—	—	—	—	
		Nevi	1.7	—	—	—	—	Trunk	100.0
		Neurofibroma	3.4	—	—	—	—	Face	100.0
		Sebaceous adenoma/ carcinoma	1.7	—	—	—	—	—	—
		Vascular malformation/tumor	1.6	—	—	—	—	—	—
		Ash leaf spot		5	30	—	—	—	—
		Lichen planus	0.8	—	—	—	—	Legs	100.0

(Continues)

TABLE 1 | (Continued)

Gene	Number of patients reporting skin findings	Skin finding	Proportion (%)	Pooled mean number of lesions	Pooled mean size (mm)	Distribution	Distribution proportion (%)	Location	Location proportion (%)
		Dermoid cyst	0.8	—	—	—	—	Trunk	100.0
		Melanosis	0.8	—	—	—	—	Trunk	100.0
		Lentigines	1.7	100	—	—	—	—	
		Telangiectasia	0.8	—	—	—	—	Axillary & Groin	100.0
		Pilomatrix carcinoma	0.8	—	—	—	—	—	—

polyps and colorectal cancer were commonly observed, often presenting in the second decade of life [23–25].

3.1.2.2 | Cutaneous Features. CALMs were present in 90% of the 59 *MSH6* cases that documented cutaneous features. The average number of CALMs was 5.4, with a pooled mean diameter of 57 mm, ranging as high as 110 mm. These macules were primarily located on the trunk, followed by the extremities. Hypopigmented macules or patches were observed in 17% of *MSH6* patients, usually few in number, and located on the trunk. Freckling was present in 20% of patients, commonly in the axillae and inguinal region. Other skin findings included hyperpigmentation (7%) and a variety of nevi (10%), such as Spitz nevi, congenital melanocytic nevi, eruptive melanocytic nevi, and a single "nevus-like lesion". Less frequent findings included vascular features, such as capillary malformations and hemangiomas (5%). There was a single report of extensive atypical dermal melanocytosis with irregular outlines, as well as neurofibromas—though it is unclear whether these were cutaneous or plexiform—and ocular melanosis.

3.1.3 | MSH2

3.1.3.1 | Systemic Features. The incidence of *MSH2* pathogenic variants was 6% of patients with CMMRD [10], with the median age of onset for the first tumor of 2.9 years [1]. The median time between the first tumor and death was approximately 0.6 years [1]. *MSH2* pathogenic variants were associated with a more severe phenotype and a lower chance of survival [5].

Brain tumors such as glioblastoma and high-grade gliomas typically presented in early childhood (between 3 and 12 years of age) [1, 26]. Hematological malignancies, like T-cell ALL, were reported as early as 1 year of life [1]. Gastrointestinal tumors were less common, though there was a case report of rectal cancer diagnosed at 24 years of age [26].

3.1.3.2 | Cutaneous Features. CALMs and hypopigmentation were present in all *MSH2* cases with reported cutaneous findings. One case described axillae freckling. There was no documentation of other cutaneous features, such as hypopigmented macules, vascular tumors or malformations, and pilomatricomas.

3.1.4 | MLH1

The incidence of *MLH1* pathogenic variants was 6% of patients with CMMRD [10], with the median age of onset for the first tumor ranging from 5.5 to 8.4 years (range 1 to 35 years) [1, 6] Hematological malignancies often appeared around 3 years of age [6], brain tumors at about 5 years [6, 27, 28], and gastrointestinal tumors between 8 and 12 years [5, 6]. *MLH1* pathogenic variants were associated with a more severe phenotype and a lower chance of survival compared to *MSH6* or *PMS2* pathogenic variants [5]. The median delay between the first tumor and death was approximately 2.1 years [1].

In terms of specific tumor types, NHL was the most common hematological subtype reported [6]. Brain tumors included

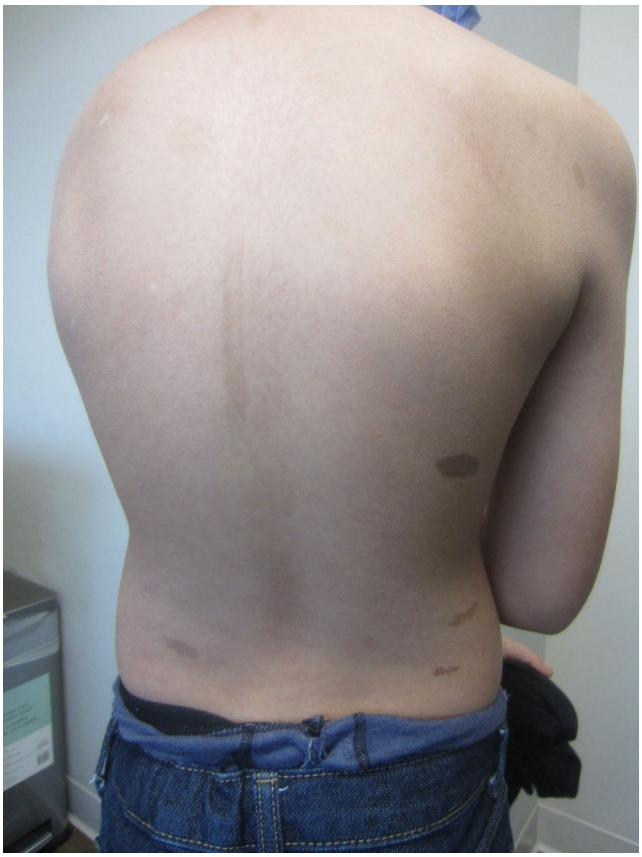

FIGURE 2 | Six café-au-lait macules larger than 5 mm in diameter over the right upper, right lower, and left lower back in an 8-year-old male with a homozygous pathogenic *PMS2* variant.

medulloblastoma, glioblastoma, and gliomas [6, 27, 28]. Gastrointestinal tumors were predominantly CRC; however, [2] duodenal cancers were also noted [5]. While exceedingly rare, carcinoma of the parotid gland and adenocarcinoma of the ampulla of Vater were seen in these patients [5]. Among the few adult cases, gastrointestinal tumors, specifically rectal adenoma and CRC, were reported between ages 18 and 58 [5, 6]. A single case of astrocytoma was reported at age 37 [5].

3.1.5 | Cutaneous Features

Only 4 cases reported cutaneous features. CALMS were present in all, with a mean number of 2 macules. One case reported a hemangioma.

3.2 | Family History

Given its autosomal recessive inheritance pattern, consanguinity is often present. Since harboring one pathogenic variant in the MMR genes leads to Lynch syndrome (LS), a family history of Lynch syndrome-related cancers such as colon cancer, endometrial cancer, and other types of cancer at a young age may be a clue to the diagnosis of CMMRD. However, most probands have no immediate family history of LS-related cancers at the time of diagnosis, as their parents may not be old enough to develop these malignancies [29]. In addition, heterozygous *PMS2* pathogenic variants have reduced penetrance, explaining why parents of probands may have no history of cancer and be in good health [30].

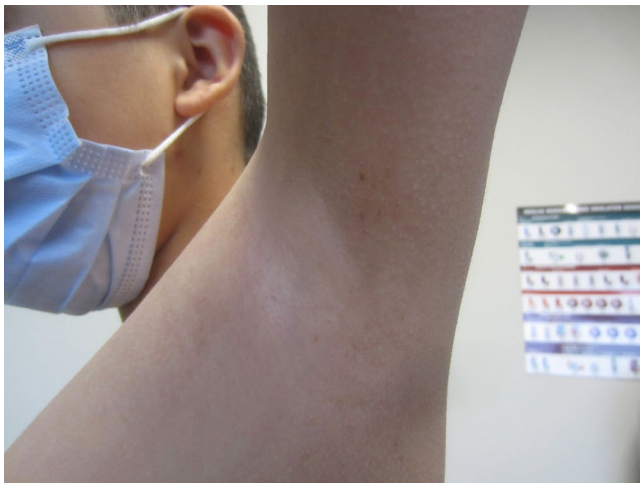

FIGURE 3 | Bilateral axillary freckling in an 8-year-old male with a homozygous pathogenic *PMS2* variant.

3.3 | Diagnostics

There are guidelines for initiating diagnostic testing of CMMRD [18]. For example, the scoring system established by the European "Care for CMMRD" (C4CMMRD) Consortium [18, 31] in 2014 assigned points based on the type and age of onset of tumors, presence of specific skin lesions, consanguinity, and family history of LS-associated cancers [18, 31]. Cutaneous features include NF1-like features, two or more hyperpigmented or hypopigmented macules greater than 1 cm in diameter, or the presence of a pilomatricoma [18, 31]. Another set of diagnostic criteria for CMMRD, created in 2021, helped streamline the diagnostic process [18, 31]. It placed more emphasis on the genetic variants present, categorizing diagnoses based on biallelic or heterozygous pathogenic/likely pathogenic variants. It also considered whether variants were confirmed "in trans" and used ancillary testing to support a diagnosis. If a patient's scoring warranted diagnostic testing (above or equal to 3), one of the first laboratory tests done was genetic testing for microsatellite instability by allelotyping or immunohistochemical analyses of MMR protein expression in removed tumor tissue [28].

3.4 | Surveillance

Early diagnosis enables surveillance and intervention strategies. This improves patient outcomes and reduces the morbidity and mortality associated with malignancies [32–35]. The International Replication Repair Deficiency Consortium (IRRDC) published a surveillance protocol in 2017 that identified about 75% of brain, gastrointestinal and other solid tumors [33, 34]. The protocol included brain magnetic resonance imaging (MRI), complete blood count, and an abdominal ultrasound (US) every 6 months, as well as a whole-body MRI, upper gastrointestinal video capsule endoscopy, ileocolonoscopy, gynecologic exam, and a trans-vaginal ultrasound once per year [33, 34]. The

IRRDC surveillance protocol has achieved a 79% 4-year survival rate following initial diagnosis, compared to a 55% survival rate with partial surveillance and 15% for those who did not receive any additional surveillance [33, 34]. The 5-year survival rate increased to 90% when the cancers were identified during the asymptomatic phase [12, 34]. Of note, the existing literature lacks sufficient evidence on the onset of specific dermatologic findings in CMMRD patients, highlighting the role of dermatologic surveillance in management. It remains unclear whether skin manifestations that appear later in life precede, coincide with, or follow the onset of malignancies, as this relationship has not been definitively established. One study reported a patient with neurofibromas and CALMs noted at the time of his cancer diagnosis at age 32. The duration of these skin findings prior to diagnosis remains unknown [36]. In a second case, where a tumor was discovered at age 8, follow-up over the next 3 years revealed the development of 2 CALMs and over 100 lentigines [37].

3.5 | Treatment

Although following surveillance protocols does improve survival rates, they do not ensure detection at a curable stage. Patients with CMMRD undergo the standard of care for their respective cancers, including surgical resection, chemotherapy, and radiation, which has been found to have outcomes similar to sporadic cancers originating in the same tissues [2, 11, 18, 38]. An emerging approach is personalized treatment for patients through incorporation of the comprehensive molecular and genetic findings in the CMMRD-tumors to utilize targeted therapies [32, 35, 39]. Moreover, acetylsalicylic acid (aspirin) has shown promise for chemoprevention against high microsatellite instability CRC, ovarian cancer, and T-cell lymphoma by inducing nitric oxide-mediated apoptosis that specifically targets unstable and mutation-prone cells [32]. A more recent approach involves the use of checkpoint inhibitors [36, 40, 41]. For example, nivolumab has found success in pediatric cases of glioblastoma as a stand-alone agent or in combination with other checkpoint inhibitors, causing clinically significant outcomes and tumor regression in patients with CMMRD [40, 42, 43].

3.6 | Comorbidities

Identifying comorbidities with CMMRD can be challenging due to the complex and varying phenotypes associated with CMMRD. Kaimakliotis et al. highlighted the challenge in diagnosing a CMMRD patient with a biallelic *PMS2* mutation with Crohn's disease, as it is a condition that had not been previously associated with CMMRD [16]. Another comorbidity of CMMRD that is often overlooked is immunodeficiency, associated with the *MSH6* variant [44].

3.7 | Ethics

Genetic testing plays a crucial role in identifying CMMRD when symptoms arise, enabling early intervention and informing family members of their potential risks [16, 45]. Offering predictive testing for CMMRD in children depends on two factors: (1) the child's age and ability to make informed decisions and (2) the potential for early, life-saving interventions [6]. Because minors are not legally able to provide full consent, parental or guardian consent is required and may be obtained without input from the child, but the child's assent should also be sought, depending on their age and developmental capacity. Ethical implications extend to family members, since the identification of a pathogenic variant may inadvertently disclose information about relatives' genetic risks [6]. This raises concerns about privacy, consent, and the potential psychological and social consequences for family members who may not have opted for genetic testing themselves but could face implications for surveillance, diagnosis, and reproductive decisions. Ultimately, asymptomatic testing of patients at risk for CMMRD appears justified due to the high implications of a positive test and the significant benefits of early detection and intervention.

3.8 | Limitations

Inherent limitations of scoping reviews include the absence of data analysis and the lack of quality assessment of the evidence. Due to the rarity of the condition, most of the included studies were case reports and case series. Furthermore, there was high heterogeneity in clinical presentations, patient populations, diagnostic techniques, and treatment that limit the ability to draw robust conclusions on the disease course and outcomes.

4 | Conclusion

This review comprehensively examines the current literature on CMMRD, focusing on genotypic-phenotypic associations, family history, diagnostic techniques, surveillance protocols, and treatments. Clues to diagnosis can be seen in dermatological features that mimic those in NF1-like CALMs and flexural freckling. Understanding the subtle differences in the presentation of CALMs can help distinguish between these conditions. A family history of cancers, especially those linked to LS, and consanguinity in a child with NF1-like features should raise suspicion for CMMRD. In addition, research highlights a genotype–phenotype correlation in CMMRD, involving tumor onset, tumor types, and the presence and types of cutaneous features, though these correlations are still being refined due to the limited number of cases for some pathogenic variants. Current screening guidelines are effective but can benefit from refinement as we learn more about the differences between genetic subtypes. Finally, while there are ethical considerations regarding the screening of asymptomatic individuals, this is a case where the benefits of early detection and intervention outweigh the concerns, making screening a justifiable approach for asymptomatic family members.

Author Contributions

Authors made significant contribution to study conception and design, data collection, analysis and interpretation of results, and draft manuscript preparation. All authors read and approved the final version.

Consent

Obtained.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

This study is a scoping review and does not involve the generation of new data. All data analyzed in this review were obtained from previously published articles, which are cited and referenced within the manuscript.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.