Article published online: 2024-09-27

THIEME OPEN ACCESS

Original Article

Biallelic Mismatch Repair Deficiency in Children and Adolescents: A Review of Published and Unpublished Data from India—Need for an Indian Consortium

Gazel Sainulabdin[1] Purva Kanvinde[2] Ritika Khurana[2] Sangeeta Mudaliar[2] Vasudeva Bhat K.[3] Anju Shukla[4] V. P. Krishnan[1] Yamini Krishnan[1]

[1] Department of Pediatric Hematology Oncology and Bone Marrow Transplantation, MVR Cancer Centre and Research Institute, Kozhikode, Kerala, India
[2] Department of Pediatric Hematology Oncology, Bai Jerbai Wadia Hospital for Children, Mumbai, Maharashtra, India
[3] Department of Pediatric Hematology Oncology, Kasturba Medical College, Manipal, Karnataka, India
[4] Department of Medical Genetics, Kasturba Medical College, Manipal, Karnataka, India

Address for correspondence Yamini Krishnan, MD, DCH, DM, Department of Pediatric Hematology, Oncology and Bone Marrow Transplantation, MVR Cancer Centre and Research Institute, Calicut, Kerala, 673601, India (e-mail: dryamini@mvrccri.co).

Ind J Med Paediatr Oncol

Abstract

Introduction Biallelic mismatch repair deficiency or constitutional mismatch repair deficiency (CMMRD) is a rare and aggressive pediatric cancer predisposition syndrome that occurs as a result of homozygous (biallelic) pathogenic variants in mismatch repair genes. The primary malignancies that occur in CMMRD are mainly hematological and brain malignancies. Most published data are from the western populations and the Middle East. Data from India are limited to case reports. We performed an analysis to determine the prevalence of CMMRD in the Indian population.

Materials and Methods All children aged less than 18 years with a diagnosis of CMMRD from various centers in India were included. CMMRD confirmed using genetic, molecular, and clinical criteria by an international consensus was included in the analysis. Literature search and data submitted by individual centers were reviewed.

Results The analysis revealed that 22 children had genetically confirmed CMMRD. The median age of the cohort was 6.5 years, with a male predominance (male:female, 2:1). The classical phenotype of café-au-lait macules was observed in 72.7 % of subjects. The most common pathological variant was found in the *PMS2* gene, which accounted for 77.3 % of children. Hematological malignancy (T cell acute lymphoblastic leukemia) was the most common primary malignancy in our study that occurred at a median age of 5 years (interquartile range 4–6 years) followed by brain tumors. The age at initial presentation for CMMRD with mutations in *MSH2*, *MSH6*, and *PMS2* was 5.4, 4, and 7.5 years, respectively.

Keywords
- CMMRD
- India
- childhood and adolescence
- genetic testing

DOI https://doi.org/10.1055/s-0044-1790202.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Conclusion The diagnosis of CMMRD requires a high index of suspicion for the early diagnosis, management, surveillance, counseling, and testing of family members. The awareness about CMMRD in clinicians is important so that diagnosis is made early, and a second malignancy is detected and treated early. The need for an Indian consortium to determine the actual burden of the disease, genetic characteristics, and course of illness in our country has been emphasized.

Introduction

Biallelic mismatch repair deficiency (BMMRD) or constitutional mismatch repair deficiency (CMMRD) is a rare childhood cancer predisposition syndrome with an autosomal recessive inheritance.[1] While Lynch syndrome (LS) is associated with heterozygous (monoallelic) germline pathogenic variant in one of the mismatch repair (MMR) genes, CMMRD occurs because of homozygous (biallelic) pathogenic variant in these genes.[2] Primary malignancies that occur in LS are usually of colorectal and endometrial origin. In addition to hematological and central nervous system (CNS) malignancies, colorectal malignancies are well-known and frequent in CMMRD.[3]

Most of the published data are from the western population, as well as from the Middle East. In 2024, the findings of the study with a large cohort of more than 200 patients with CMMRD, led by the International Replication Repair Deficiency Consortium (IRRDC), was published by Ercan et al.[1] Data from India were limited to case reports. We performed a literature search to determine the prevalence of CMMRD in the Indian population.

Patients and Methods

An online literature search was done to obtain published data on pediatric CMMRD cases from India. Various centers across India were contacted for data on unpublished and confirmed CMMRD cases. Only pathogenic variant-proven CMMRD cases in children from India were included in this study.

Study Design

Retrospective study: Sample size – 22 children with CMMRD.

Primary and Secondary Outcome

The primary objective was to find the clinical presentation, type of cancer, and age of onset of primary and secondary malignancy and progression of the disease. The most common malignancy was hematological malignancy with a median age of 6.5 years (interquartile range [IQR] 4–9years) at presentation and the second most common malignancy was brain tumors at a median age of 11.5 years (IQR 8–15 years) with parental consanguinity a vital pointer toward diagnosis.

The secondary objective was to find the severity of illness and survival associated with each MMR gene and its pathological variant. Children with pathogenic variants in *MSH2* and *MSH6* tend to have an earlier onset of malignancy. *PMS2* pathogenic variants were the most common and children with *MSH2* or *MLH1* had severe disease. The incidence of pathogenic variants in *MLH1* and *MSH2* were much less than the incidence of pathogenic variants of *PMS2* and *MSH6*.

Inclusion Criteria

All children less than 18 years with a diagnosis of CMMRD from various centers in India were included. CMMRD confirmed using clinical, genetic, and molecular criteria by an international consensus was included in the analysis. Data collected from published as well as unpublished data provided by centers treating children with malignancies were considered the full study cohort. The initial literature search was executed by searching the PubMed, Cochrane Library, and Web of Science databases for studies in the English language. The search words were "CMMRD, BMMRD" restricted to "India" and then limited to "childhood" and "adolescence."

Exclusion Criteria

Duplicate publications and cases with no confirmatory genetic study were excluded.

Data Abstraction

Two investigators reviewed all the studies that were obtained and confirmed that they fulfill the inclusion criteria. Duplicate publications were excluded from analysis. Patients who had no confirmatory diagnosis of CMMRD based on molecular studies were excluded. The studies selected for data collection are included in ►**Annexure 1**.

All subject data submitted by individual centers were also reviewed for eligibility for entry into the analysis. An overview of this study is given in ►**Fig. 1**.

Analysis

The median values, IQR, and percentages were calculated from the data.

Various clinical parameters such as age at diagnosis, gender, types of first and second malignancies, consanguinity and other affected family members, and their molecular profiles were analyzed. All patients were also given a score as per the scoring system to determine germline testing eligibility for CMMRD (►**Supp. Table S1**).

Ethics

The Institutional Ethics Committee had granted approval for this retrospective study (Institutional Ethics Committee, MVR Cancer Centre & Research Institute, Kerala, India).

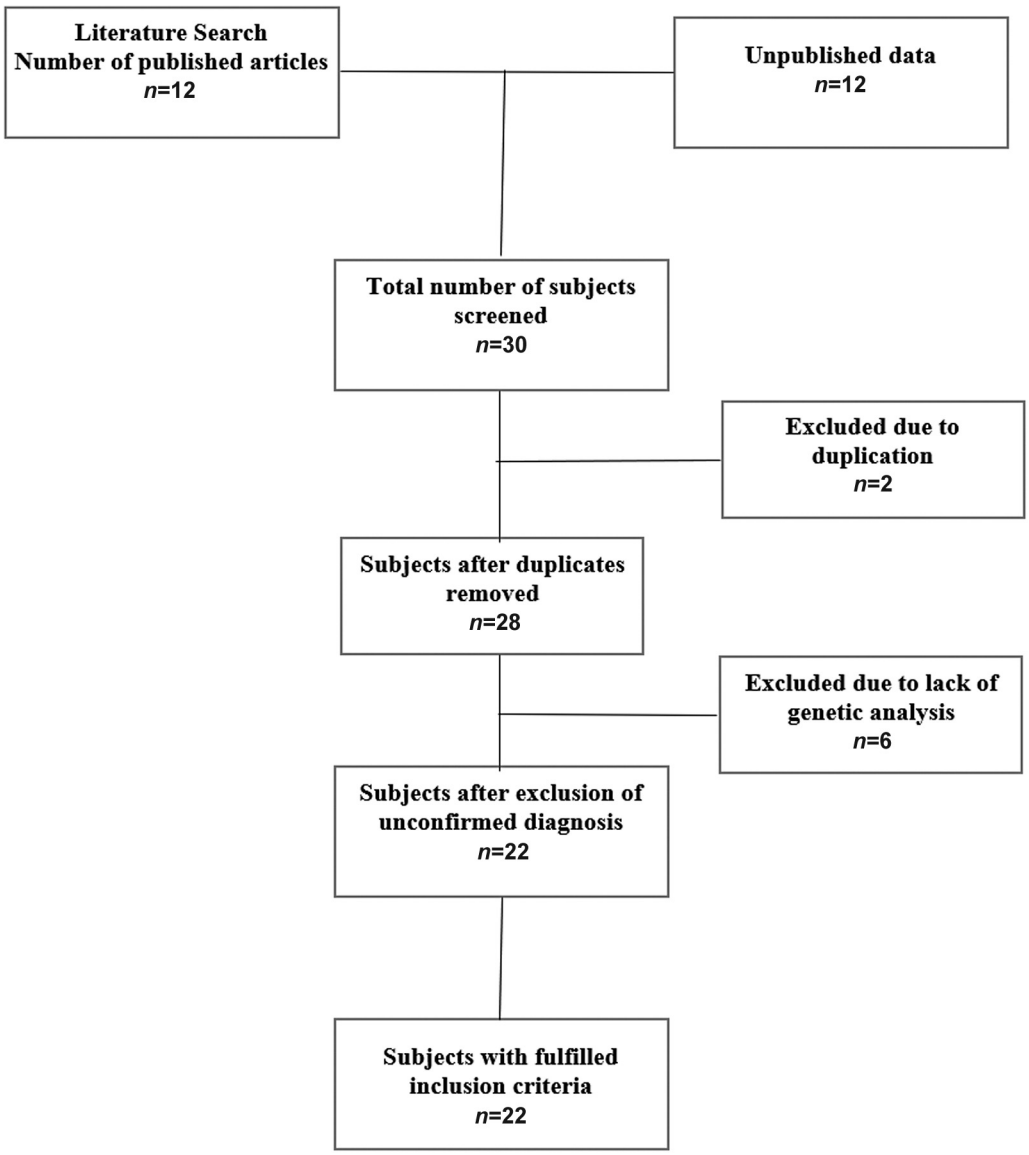

Fig. 1 Study overview of constitutional mismatch repair deficiency subjects included in the analysis.

Approval No.: EC Ref No.: IEC2023/III/02, dated: 08/12/2023.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

We analyzed the data of 22 children with genetically confirmed CMMRD from different centers across India. Of the 22 subjects analyzed, 15 were males and 7 were females. The male:female ratio was 2:1. The median age at diagnosis of the first malignancy was 6.5 years (IQR 4–9 years). The median age at diagnosis was 7 years (IQR 4–11 years) and 6 years (IQR 4.4–9 years) for males and females, respectively. In this study, a high incidence of consanguinity was observed. Fourteen of 22 (63.6%) children were born out of a third-degree consanguineous marriage which is a high rate of consanguinity. The parents were unaffected and did not have features of LS.

Sixteen (72.7%) participants had siblings with malignancies. Upon analyzing the clinical parameters, all children had normal development and intelligence (95%), except for one child who had delayed speech development. Skin involvement in the form of café-au-lait macules (CALM) was observed in 16 children (72.7%). One child each had a hypopigmented macule, pilomatricoma, and nevus spilus, in addition to CALMs. All children had strong evidence of CMMRD according to the CMMRD diagnostic criteria as per updated international diagnostic criteria for CMMRD published by Aronson et al in 2022.

All patients were given a score according to the scoring system to determine germline testing eligibility for CMMRD, and the median score in our study was 5.5. A score of ≥ 3 requires testing for MMR gene pathogenic variant. The indications for CMMRD testing are listed in ►**Supp. Table S1**.

Table 1 Clinical parameters of children diagnosed as CMMRD

Parameter	Number (percentage)
Median age at first malignancy (range)	6.5 y (IQR 4–9 y)
Median age in males	7 y (IQR 4–11 y)
Median age in females	6 y (IQR 4.4–9 y)
Sex	
Male	15 (68.2)
Female	7 (21.8)
Consanguineous marriage	14 (63.6)
Family history	16 (72.7)
Skin findings	16 (72.7)
Normal development and intelligence	21 (95
Median age at second malignancy, $N = 8$	12 y (IQR 10–15 y
CMMRD score, mean	6
Relapse	5 (24)
Pathologic variants, genes affected	
PMS2	17 (77.2)
MSH2	4 (18.1)
MSH6	1 (4.5)
MLH1	0 (0)
Additional pathologic variants	*PMS2*
	POLE
	TP53

Abbreviations: CMMRD, constitutional mismatch repair deficiency; IQR, interquartile range.

Of all the pathogenic variants analyzed, the most common was in *PMS2*, accounting for 77.3%. *MSH2* and *MSH6* constituted 18.2 and 4.5% of the total, respectively. There were no children with *MLH1* pathogenic variant in our study. Additional pathogenic variants were detected in *PMS2* (additional second pathogenic variant), *POLE*, and *TP53* genes (►**Table 1**).

The spectrum of primary and secondary malignancies diagnosed, with the median age at diagnosis in our series, is shown in ►**Table 2**. The most common first malignancy diagnosed in our children was a hematological malignancy, accounting for 52.4% (T-acute lymphoblastic leukemia was the most common). The median age at diagnosis was 5 years (IQR 4–6 years). The second most common malignancy was brain tumor, accounting for 38.1%, and the median age at diagnosis was 10 years (IQR 7–12 years). Colorectal cancers were observed in two children, with a median age at diagnosis of 9.5 years (IQR 9–10 years). In our series, a second malignancy was seen in eight children (36.3%), and the median age of occurrence was 12 years (IQR 10–15 years). The malignancies noted were colorectal cancer, non-Hodgkin's lymphoma (NHL), astrocytoma, and sarcoma (osteosarcoma and alveolar soft part sarcoma) (►**Table 3**).

Children who developed brain tumors had a worse outcome than children who developed hematological or colorectal malignancy. Only 3 of the children with brain tumor survived to develop a second malignancy.

The ages at initial presentation for CMMRD with pathological variants in *MSH2*, *MSH6*, and *PMS2* were 5.4, 4, and 7.5 years, respectively. Children with pathological variants in *MSH2* and *MSH6* tend to have an earlier onset of malignancy. Of the 17 children with *PMS2* pathological variants, 8 (47%) developed a second malignancy at a median age of 12 years (IQR 10–15 years). None of the children with *MSH2* or *MLH6* pathological variants lived long enough to develop a second malignancy. There were no children affected with *MLH1* pathological variants in our study.

The detailed genetic characteristics of the entire cohort with detected malignancies are shown in ►**Table 4**.

Discussion

The role of MMR genes in the pathogenesis of malignancy is well known to the scientific community. LS occurs due to the heterozygous (monoallelic) germline pathological variants in the MMR genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*, and are autosomal dominantly inherited.[4] The majority of CMMRD were probably misreported as LS until the case report by Ricciardone et al, which was first published in 1999.[5] The authors identified a family with hereditary nonpolyposis

Table 2 Genes affected in the CMMRD cohort and age at presentation

Genes affected	Number of patients *N* (%)	Median age in years at first malignancy (IQR)	Median age at second malignancy in years (IQR)	Skin findings	Siblings affected
PMS2	17 (77.2)	8 (4–5)	($N = 8$) 12 (10–15)	11 (64%)	8
MSH2	4 (18.1)	10 (1–11)		4 (100%)	4
MSH6	1 (4.5)	4		1 (100%)	1
MLH1	0	0			
Total	22 (100)			15	12

Abbreviations: CMMRD, constitutional mismatch repair deficiency; IQR, interquartile range.

Table 3 Types of malignancies and median age of onset in each type

Type of malignancy	First malignancy *N* (%)	Median age at first malignancy in years (IQR)	Second malignancy *N* (%)	Median age at second malignancy (y)
Hematological				
T-ALL	6 (27.4)	6 (4–8)		
B-ALL	3 (13.6)	4 (3.5–4.4)		
NHL	2 (9)	4	2 (25)	13
Brain tumors				
GBM/Astrocytoma	4 (18.2)	9 (5–11)	2 (25)	10.5
Medulloblastoma	3 (13,6)	11		
High-grade glioma	1 (4.6)	15		
Lynch syndrome associated				
Colorectal cancer	2 (9)	9.5	2 (25)	16
Other cancers				
ASPS			1 (12.5)	8
Osteosarcoma			1 (12.5)	12
No malignancy	1 (4.6)			
Total	22 (100)		8 (100)	

Abbreviations: ALL, acute lymphoblastic leukemia; ASPS, alveolar soft part sarcoma; GBM, glioblastoma multiforme; IQR, interquartile range; NHL, non-Hodgkin lymphoma.

Table 4 Genetic characteristic of the entire cohort with malignancies detected

Sl. no.	*PMS2*	Exon	*MSH2*	Exon	*MSH6*	Exon	Homozygous	First and second malignancies (age at diagnosis in years)
1	delC	11					Yes	T-ALL (8); GBM (12)
2	delC	11					Yes	T-ALL (6); ASPS (8)
3	double heterozygous (p. Ser815Leu and p.Gln275Gln)						Yes	CRC (9); GBM (9)
4	c.1500delC at codon 501	11					Yes	GBM (11); CRC (15)
5	c.1500delC at codon 501	11					Yes	Medulloblastoma (9); NHL (11)
6	c.2402C > T	14					Yes	GBM (9)
7	c.2402C > T	14					Yes	CRC (10)
8	c.325dupG	4					Yes	T-ALL (4); Relapse (8)
9	c.325dupG	4					Yes	T-ALL (4); NHL (15)
10	c.325dupG	4					Yes	NHL (7)
11	c.478C > T	5					Yes	GBM (4)
12			(c.221_231del)	2			Yes	GBM (5)
13			(c.221_231del)	2			Yes	High-grade glioma (15)
14	(c.2404C > T)	14					Yes	

(*Continued*)

Table 4 (*Continued*)

Sl. no.	*PMS2*	Exon	*MSH2*	Exon	*MSH6*	Exon	Homozygous	First and second malignancies (age at diagnosis in years)
15	(c.2404C > T)	14					Yes	B-ALL (4)
16					c.1670G > A	4	Yes	B-ALL (4) Relapse
17	c.128_130del	2					Yes	T-ALL (6); Osteosarcoma (12)
18	c.525_534del	5					Yes	B-ALL (3); Relapse (4)
19	c.778del	7					Yes	Medulloblastoma (12); CRC (17)
20	c.778del	7					Yes	Medulloblastoma (12)
21			c.1165C > T	7			Yes	T-ALL (11 mo)
22			c.1165C > T	7			Yes	NHL (1 y)

Abbreviations: ALL, acute lymphoblastic leukemia; ASPS, alveolar soft part sarcoma; CRC, colorectal cancer; GBM, glioblastoma multiforme; NHL, non-Hodgkin lymphoma.

colorectal cancer, with three children who had hematological malignancy at a very young age and had a neurofibromatosis phenotype. Deoxyribonucleic acid analysis revealed the presence of a homozygous *MLH1* pathological variant. Since then, biallelic germline pathologic variants involving MMR genes have been described in approximately 200 patients and have been recognized as distinct cancer predisposition syndromes: constitutional or biallelic MMR deficiency (-CMMRD/BMMRD) syndrome (OMIM #276300).[6]

The IRRDC was established in 2007, and since have identified more than 100 patients from different countries across the world.[3]

A large cohort of patients with CMMRD was reported by Wimmer and Etzler in 2008, with 78 cases detected in 46 families.[7] In 2013, a European consortium was formed —"Care for CMMRD" (C4CMMRD)—which identified 146 patients from 91 families.[8,9] In 2022, latest recommendations and guidelines from the international consensus working group (IRRDC, C4CMMRD, and experts dedicated to CMMRD) for diagnosis and surveillance for individuals with CMMRD was published by Aronson et al. They established six diagnostic criteria (four criteria with strong evidence and two criteria with moderate evidence) and also outlined the surveillance and ancillary tests needed in each group (►**Supp. Table S2**). A scoring system to identify the eligibility for genetic testing was also published.[3]

In 2024, Ercan et al published a study involving more than 200 patients; the largest study led by the IRRDC.[1] The Middle East Network on Hereditary Colorectal Cancer was also established with the aim of obtaining more information on the epidemiology of hereditary colorectal cancer and CMMRD in the Middle East.[10] A position paper in 2020 highlighted the challenges of CMMRD diagnosis in low-resource settings and the need for more data given the high levels of consanguinity in this particular population.[11] In our Indian study, we identified 22 cases from 11 families.

The most common malignancies associated with CMMRD in the study by Ercan et al were CNS tumors (51%), followed by gastrointestinal (GI) malignancy (22%).[1] In our study, the most common malignancy was hematological malignancies accounting for 52.4% of all cases followed by CNS tumors (38.1%) and GI malignancies (9%). This disparity could be primarily due to the reason that the study was conducted in children less than 18 years of age, where hematological malignancy is the most common malignancy. A large population-based study is required to establish age and the type of malignancies that occur in our population.

The median age of onset of malignancies was younger in our study (6.5 years) than in other studies (Ercan et al, 8.9 years).[1] The typical age of onset is the first decade for hematological and brain malignancies, and the second or third decade for LS-associated malignancies. According to data from C4MMRD, NHL was the most common hematological malignancy, mainly the T-lymphoblastic type, followed by acute lymphoblastic leukemia (ALL) and acute myeloid leukemia.[9] The high incidence of T-cell lymphoma suggests an inefficient immunoglobulin class switch and subclinical immune deficiency.[5] Among malignant brain tumors, glioblastoma and high-grade astrocytic tumors constitute the majority, followed by medulloblastoma and supratentorial primitive neuroectodermal tumors.[3,9] Among the LS-associated tumors, GI malignancies are the most common; endometrial and urinary tract/bladder malignancies being less frequently reported.[3] Childhood-onset colorectal cancer with a mean age of 16.4 years at diagnosis is the most common GI malignancy, followed by that of the small intestine.[12] Other embryonal tumors such as neuroblastoma, Wilms tumor, and rhabdomyosarcoma have also been reported.[3] In our analysis, although ALL was the most common malignancy, the mean age at diagnosis was younger than that in other studies described in the literature.[1,9] A similar trend was

observed with the mean age of patients with colorectal malignancy also.

Children with CMMRD have a phenotype characteristic of this condition. The most common clinical finding is the presence of CALM. These hyperpigmented macules have more diffuse irregular borders and have hypopigmented areas within, when compared to the CALMs observed in patients with neurofibromatosis 1 (NF1).[13,14] Lisch nodules, axillary freckling, and plexiform neurofibroma seen more commonly in NF1 are rarely observed in CMMRD.[1,3], Developmental abnormalities of the brain, such as agenesis of the corpus callosum and venous and vascular anomalies, are among the described clinical findings.[3] In our analysis, all children with *MSH6* and *MLH2* pathogenic variants had skin findings in the form of CALMs. In children with *PMS2* pathogenic variants, 64% had CALMs. Pilomatricoma and nevus spilus were also seen in 2 children with *PMS2* pathogenic variants. The other benign tumors described are polyps of the stomach, small and large intestines, and hepatic adenoma.[9]

The overall incidence of CALMs was 72.7% as against 89% in the study by Ercan et al.[1] Almost 10 to 25% of children with CMMRD can present without skin involvement. A high index of suspicion is required in children who present without CALMs, for early diagnosis especially in a setting of consanguinity and occurrence of second malignancy.

The most common gene affected was *PMS2*, accounting for 77.3% (as against 60% in Aronson et al[3] and 65% in Ercan et al) [1]. *MSH2* and *MSH6* constitutes 18.2% (as against 10–20% by Aronson et al and 5% by Ercan et al) and 4.5% (as against 20–30% by Aronson et al and 26% by Ercan et al) of the total, respectively.[1,3]

A history of parental consanguinity is the most important clue that might allow the physician to suspect CMMRD, especially in a child presenting with a malignant brain tumor, hematological malignancies, or childhood-onset GI cancer.[13] Results from communities with high rates of consanguinity suggest a high incidence of CMMRD.[13,15] Our study also found high rates of consanguinity (63% as against 54% in study by Ercan et al and 39–45% by Aronson et al).[1,3]

National Family Health Survey from India suggests that the prevalence of consanguinity is high in certain communities, especially in South India, and only a nationwide study on CMMRD can provide a clearer picture of the situation in India.[15] Most parents of the affected children are asymptomatic and do not have a history of malignancy, even though they are heterozygous carriers of the disease. This is probably because malignancies associated with LS usually develop during the fourth decade of life. In addition, owing to the low penetrance of *PMS2* (the most common MMR pathogenic variant), clinical evidence of LS in family may be absent.[1]

Once a pathogenic variant is identified, the pathogenic nature of the variant has to be determined from the available genetic databases. Biallelic pathogenic variants in the MMR genes *PMS2*, *MLH1*, *MSH6*, and *MSH2* are responsible for the development of CMMRD, with *PMS2* and *MSH6* being the most common. In the IRRDC cohort of 201 patients, 65% carried the *PMS2* pathogenic variants and the rest carried the *MSH6* and *MLH1*/*MSH2* bialleles.[1] This observation is in contrast to LS, in which the majority of patients carry heterozygous *MLH1* or *MSH2* mutations.

In our analysis, *PMS2* was the most common mutation identified. No child was found to have pathogenic variants in *MLH1*. This could be either due to, less testing for CMMRD or because *MLH1* mutations are rare in India. Or it could be that the disease was so severe that the affected proband did not survive long enough to undergo genetic testing. None of the children in our study had a synchronous malignancy. All the children who developed a second malignancy ($n = 8$) had it only beyond 6 months from first diagnosis (metachronous).

CMMRD is the most penetrant and aggressive pediatric cancer predisposition syndromes and patients can develop another malignancy every 2 years and *MLH1* and *MSH2* genes were found to be more aggressive.[1]

In the literature, it has been observed that primary hematological malignancies were infrequent or absent in the *MLH1* or *MSH2* pathological variant group compared to GI and brain tumors that were seen with all the MMR genes.[1] In our cohort of four children who had *MSH 2* mutation, two children who presented early (11 months and 1 year; exon 2 mutation) had hematological malignancy and two children who had late presentation had brain tumors (glioblastoma multiforme at 5 years and glioma at 15 years; exon 7 mutation). None of these four children survived the first malignancy. In the study by Ercan et al, hematological malignancy was absent in MLH1 or MSH2 pathogenic variants; and no survivors were found in cohort with MSH2 pathogenic variants.[1] Only one child had an *MSH6* mutation and developed B-cell ALL at 4 years of age. In our cohort, only children with *PMS2* mutations survived the first malignancy and developed a second malignancy. The presence of additional mutations in genes such as *POLE1* was observed in our analysis, which has also been described previously.[1]

Though genetic testing is the gold standard for diagnosing CMMRD, testing challenges can arise due to pseudogenes and frequent gene conversion in *PMS2*; the most frequently affected gene with the highest incidence of variants of uncertain significance. These challenges for interpretation of the results can be overcome by specialized assays and also by following the scoring system to know the eligibility for genetic testing and the diagnostic criteria for CMMRD.

The C4CMMRD consortium has devised criteria for indications for genetic testing among suspected patients using a point-based system.[3] The main criteria used were type of malignancy and age at presentation, such as LS spectrum tumors or multiple bowel adenomas, grade III or IV glioma, and NHL of T-cell lineage or primitive neuroendocrine tumor, in both children and young adults. The additional features considered were NF1 signs, developmental brain abnormalities, and the family history in siblings or first-degree relatives (►**Table 1**). Aronson et al in the year 2022 defined two newer hallmark malignanciesin CMMRD: (1) glioma or CNS embryonal tumors < 18 years and (2) GI adenocarcinoma < 18 years. Only 11 to 15.6% cases presented beyond 18 years of age. The first consensus for diagnostic criteria for CMMRD (members of the IRRDC and the C4CMMRD consortia) laid down six diagnostic criteria

and recommendations for surveillance and genetic counseling of the family.[3]

CMMRD diagnostic criteria are presented in ►**Supp. Table S2**.[3]

Definitive genetic diagnosis has an important role in tumor surveillance, family testing, and further treatment. In addition to genetic testing, use of ancillary testing like microsatellite instability (MSI) in tissue and MMR immunohistochemistry (IHC) showing loss of MMR protein expression can help diagnose CMMRD. IHC from normal tissue was found to have more than 90% sensitivity and specificity in diagnosing CMMRD. Another assay named ex vivo MSI (ev MSI) MSI is considered to be 100% sensitive and 100% specific. Similarly, next-generation sequencing-based MSI is also highly sensitive and specific for CMMRD. These ancillary tests can help when facing atypical cases with diagnostic challenges.[3]

Low-pass genomic instability characterization assay for CMMRD was found to be more sensitive tool than MSI, IHC, and tumor mutational burden and it was able to distinguish CMMRD from other cancer predisposition syndromes. It is useful for diagnosis as well as surveillance of individuals with CMMRD.[16]

Cascade testing (genetic counseling and testing) of family members, especially siblings, is the most important goal, as it helps for early detection and treatment of disease at an early stage.[17]

In the IRRDC study it was found that patients who underwent surveillance had better outcome and surveillance was the single most important confounding factor in the MLH1/MSH2 group (40% survival against 0% survival). The first consensus for diagnostic criteria for CMMRD (members of the IRRDC and the C4CMMRD consortia) has laid down recommendations for surveillance and genetic counseling of the family (►**Table 5**).[1,17,18]

Apart from the conventional treatment modalities for childhood malignancies, multiple studies have found that treatment with immune checkpoint inhibitors like nivolumab and ipilimumab greatly improved survival in advanced metastatic and recurrent cancers, especially in brain tumors (especially high-grade glioma). Combined modality of reirradiation and synergistic immune agents have helped in hypermutant high-grade glioma even after progression of disease.[18–22]

The limitation of our study was that the data were a combined analysis of published and unpublished data from individual centers. This might not be helpful in determining the nationwide prevalence of CMMRD. A more structured analysis with clinical diagnostic criteria, ancillary testing, and genetic testing of all children and family members who satisfy the CMMRD criteria might be ideal. The financial implications of the same are the most important restrictive factors in a low-resource country such as ours. In our analysis, despite the patient having a high CMMRD score, a substantial number of patients did not undergo genetic testing. Genetic analysis was not performed in a centralized laboratory as in IRRDC cohort, but at multiple centers across India.

Conclusion

CMMRD is an aggressive pediatric cancer predisposition disease that can have rapid fatal outcome if not diagnosed early and treated. It needs a high index of suspicion for early diagnosis, more so in a setting of consanguinity. The awareness regarding surveillance and cascade testing for early detection of malignancies in the affected child and siblings at the earliest to ascertain the gene involved is to be emphasized. The probability and risk of a child developing second malignancy in a life time is overwhelming in terms of social, psychological, and financial aspects. The biggest limitation is financial burden as we live in low- to middle-income country where testing and treatment are costly. The genes commonly affected are different in our study cohort and disease characteristics too are different. We need a large population-based study to ascertain if the findings represent the genetic characteristics of Indian population. The authors would like to reemphasize the need for a national policy for management and an Indian consortium on CMMRD.

Table 5 Surveillance protocol for patients with CMMRD

Examination	Start age	Frequency	Tumors	Comment
MRI brain	At diagnosis	Q 6 months	Brain tumors	Should not be replaced with WBMRI
WBMRI	6 years	Once a year	All tumors	Should not replace dedicated CNS imaging
CBC	1 year	Q 6 months	Leukemia	May be considered
Abdominal ultrasound	1 year	Q 6 months	Lymphoma	May be considered
Upper gastrointestinal endoscopy; video capsule endoscopy, ileocolonoscopy	4 to 6 years	Once a year	Gastrointestinal tumors	Upper and lower endoscopy, to increase once polyps are found
Gynecological exam, transvaginal ultrasound, pipelle curettage, urine cytology, dipstick	20 years	Once a year	Genitourinary cancers	As per Lynch syndrome guidelines

Abbreviations: CBC, complete blood count; CMMRD, constitutional mismatch repair deficiency; CNS, central nervous system; MRI, magnetic resonance imaging; WBMRI, whole body MRI scan.

Patient Consent
The written consent of caregivers for publication has been obtained.

Ethical Issues
None.

Institutional Ethics Committee Approval Obtained
IEC2023/III/2.

Funding
None.

Conflict of Interest
None declared.

Acknowledgment
None.

References

1 Ercan AB, Aronson M, Fernandez NR, et al. Clinical and biological landscape of constitutional mismatch-repair deficiency syndrome: an International Replication Repair Deficiency Consortium cohort study. Lancet Oncol 2024;25(05):668–682
2 Wimmer K, Kratz CP. Constitutional mismatch repair-deficiency syndrome. Haematologica 2010;95(05):699–701
3 Aronson M, Colas C, Shuen A, et al. Diagnostic criteria for constitutional mismatch repair deficiency (CMMRD): recommendations from the international consensus working group. J Med Genet 2022;59(04):318–327
4 Abedalthagafi M. Constitutional mismatch repair-deficiency: current problems and emerging therapeutic strategies. Oncotarget 2018;9(83):35458–35469
5 Ricciardone MD, Ozçelik T, Cevher B, et al. Human MLH1 deficiency predisposes to hematological malignancy and neurofibromatosis type 1. Cancer Res 1999;59(02):290–293
6 Durno CA, Sherman PM, Aronson M, et al; International BMMRD Consortium. Phenotypic and genotypic characterisation of biallelic mismatch repair deficiency (BMMR-D) syndrome. Eur J Cancer 2015;51(08):977–983
7 Wimmer K, Etzler J. Constitutional mismatch repair-deficiency syndrome: have we so far seen only the tip of an iceberg? Hum Genet 2008;124(02):105–122
8 Wimmer K, Kratz CP, Vasen HF, et al; EU-Consortium Care for CMMRD (C4CMMRD) Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). J Med Genet 2014;51(06):355–365
9 Suerink M, Wimmer K, Brugieres L, et al. Report of the fifth meeting of the European Consortium 'Care for CMMRD' (C4CMMRD), Leiden, The Netherlands, July 6th 2019. Fam Cancer 2021;20(01):67–73
10 Ghorbanoghli Z, Jabari C, Sweidan W, et al. A new hereditary colorectal cancer network in the Middle East and eastern Mediterranean countries to improve care for high-risk families. Fam Cancer 2018;17(02):209–212[published correction appears in Fam Cancer. 2017 Jul 27;]
11 Kebudi R, Amayiri N, Abedalthagafi M, et al; International RRD Consortium on Low-Resource Settings Panel. Position paper: challenges and specific strategies for constitutional mismatch repair deficiency syndrome in low-resource settings. Pediatr Blood Cancer 2020;67(08):e28309
12 Khdair-Ahmad O, Al Husaini M, Ghunaimat S, et al. Constitutional mismatch repair deficiency in children with colorectal carcinoma: a Jordanian center experience. Pediatr Hematol Oncol 2021;6(01):18–21
13 Amayiri N, Tabori U, Campbell B, et al; BMMRD Consortium. High frequency of mismatch repair deficiency among pediatric high grade gliomas in Jordan. Int J Cancer 2016;138(02):380–385
14 Özyörük D, Cabı EÜ, Taçyıldız N, et al. Cancer and constitutional mismatch repair deficiency syndrome due to homozygous MSH 6 mutation in children with Café au Lait Spots and review of literature. Turk J Pediatr 2021;63(05):893–902
15 Sharma SK, Kalam MA, Ghosh S, Roy S. Prevalence and determinants of consanguineous marriage and its types in India: evidence from the National Family Health Survey, 2015-2016. J Biosoc Sci 2021;53(04):566–576
16 Chung J, Negm L, Bianchi V, et al; International Replication Repair Deficiency Consortium. Genomic microsatellite signatures identify germline mismatch repair deficiency and risk of cancer onset. J Clin Oncol 2023;41(04):766–777
17 Durno C, Ercan AB, Bianchi V, et al. Survival benefit for individuals with constitutional mismatch repair deficiency undergoing surveillance. J Clin Oncol 2021;39(25):2779–2790
18 Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357(6349):409–413
19 Henderson JJ, Das A, Morgenstern DA, et al. Immune checkpoint inhibition as single therapy for synchronous cancers exhibiting hypermutation: an IRRDC study. JCO Precis Oncol 2022;6:e2100286
20 Palova H, Das A, Pokorna P, et al. Precision immuno-oncology approach for four malignant tumors in siblings with constitutional mismatch repair deficiency syndrome. NPJ Precis Oncol 2024;8(01):110
21 Das A, Sudhaman S, Morgenstern D, et al. Genomic predictors of response to PD-1 inhibition in children with germline DNA replication repair deficiency. Nat Med 2022;28(01):125–135
22 Das A, Fernandez NR, Levine A, et al. Combined immunotherapy improves outcome for replication-repair-deficient (RRD) high-grade glioma failing anti-PD-1 monotherapy: a report from the International RRD Consortium. Cancer Discov 2024;14(02):258–273

Annexure 1

1 Modi MB, Patel PN, Modi VM, , et al. First reported case of alveolar soft part sarcoma in constitutional mismatch repair deficiency syndrome tumor spectrum - diagnosed in one of the siblings with constitutional mismatch repair deficiency. South Asian J Cancer 2017;6(01):41–43
2 Modi M, Patel T, Trivedi P, , et al. Secondary malignancies developing after acute lymphoblastic leukemia and its treatment with constitutional mismatch repair deficiency syndrome in siblings: secondary malignancies after ALL & treatment. Natl J Integr Res Med 2018;7(02):44–51
3 Mishra AK, Achari RB, Zameer L, , et al. Germline biallelic mismatch repair deficiency in childhood glioblastoma and implications for clinical management. Neurol India 2022;70(02): 772–774
4 Paul C, Chakraborty S, Chakraborty S, Goswami K. Constitutional mismatch repair deficiency syndrome in a patient from India. Clin Case Rep 2020;8(12):2824–2826
5 Alphones S, Chatterjee U, Singh A, , et al. Immunohistochemical screening for mismatch repair protein deficiency in paediatric high-grade gliomas - institutional experience and review of literature. Childs Nerv Syst 2021;37(08):2521–2530
6 Lipsa A. Genomic Landscape of Hereditary and Early Onset Sporadic Colorectal Cancer [dissertation]. ACTREC-TMC/Homi Bhabha National Institute; 2020
7 Lipsa A, Kunduru RR, Sarin R. Comprehensive genotypic and phenotypic characterization of heterozygous versus homozygous MMR gene mutation carriers in an Indian Cohort. Eur J Hum Genet 2019;27(Suppl 1):440–441
8 Gupta A, George R, Aboobacker FN, ThamaraiSelvi B, Priscilla AJ. Pilomatricomas and café au lait macules as herald signs of constitutional mismatch repair deficiency (CMMRD) syndrome-a case report. Pediatr Dermatol 2020;37(06):1139–1141
9 Srivastava P, Husain N, Shukla S, Gupta V. Wilms tumour and colorecta adenocarcinoma an unusual concurrence. Saudi J Pathol Microbiol 2020;05(04):207–210
10 Ramachandra C, Challa VR, Shetty R. Constitutional mismatch repair deficiency syndrome: do we know it? Indian J Hum Genet 2014;20(02):192–194

Supp. Table S1 Scoring system to determine germline testing eligibility for CMMRD

	Indication for CMMRD testing	Score
	Mandatory criteria: 1 is mandatory and add if more than one criteria	
1	Carcinoma from the LS spectrum, age < 25 years	3
2	Multiple bowel adenomas at age < 25 years and absence of *APCI*/*MUTYH* mutations or a single high-grade dysplasia/adenoma at age < 25 years	3
3	WHO grade III or IV glioma at age < 25 years	2
4	NHL or T-cell lineage or sPNET at age < 18 years	2
5	Any malignancy at age < 18 years	1
	Additional features: Optional criteria: add if more than one criteria	
6	Clinical signs of NF1 and or > 2 hyper $+$/hypopigmented skin alterations > 1 cm	2
7	Diagnosis of Lynch syndrome in a first- or a second-degree relative	2
8	Carcinoma from LS spectrum in a 1st, 2nd, or 3rd degree relative < 60 years	1
9	A sibling with a malignancy from the LS spectrum, high-grade glioma, sPNET, or NHL	2
10	A sibling with any type of childhood malignancy	1
11	Multiple pilomatricomas in the patient	2
12	One pilomatricoma in the patient	1
13	Agenesis of the corpus callosum or nontherapy-induced cavernoma in the patient	1
14	Consanguineous parents	1
15	Deficiency/reduced levels of IgG 2/4 and /or IgA	1

Abbreviations: CMMRD, constitutional mismatch repair deficiency; Ig, immunoglobulin; LS, Lynch syndrome; NF1, ; NHL, non-Hodgkin lymphoma; sPNET, supratentorial primitive neuroendocrine tumor; WHO, World Health Organization.

Supp. Table S2 CMMRD diagnostic criteria

Criterion		Germline result[a] *PMS2*, *MSH6*, *MSH2*, *MLH1*	Positive ancillary testing	Clinical phenotype
Definitive diagnosis (strong evidence of CMMRD)	1	Biallelic pathogenic variants (P/P)[a], confirmed in trans	Not required unless unaffected > 25 y, then one required	Not required if under age 25 (if no malignancy over age 25, ancillary testing required)
Definitive diagnosis (strong evidence of CMMRD)	2	Biallelic P/LP or LP/LP[a] variants, confirmed in trans	One required unless unaffected by hallmark cancer, then 2 required	Hallmark CMMRD cancer diagnosis > or C4CMMRD criteria of 3 points (then 2 ancillary tests required)
Definitive diagnosis (strong evidence of CMMRD)	3	Heterozygous P or LP variant (±VUS[a] or likely benign variants)	One required	Hallmark CMMRD cancer diagnosis
Definitive diagnosis (strong evidence of CMMRD)	4	No P or LP MMR variants (including VUS/VUS)[b] or no testing available (i.e., deceased proband)	Two required	Hallmark CMMRD cancer diagnosis
Likely diagnosis (moderate evidence of CMMRD)	5	Biallelic P/LP[a] or LP/LP variants confirmed in trans	Not required	C4CMMRD criteria of 3 points
Likely diagnosis (moderate evidence of CMMRD)	6	Heterozygous P or LP variant or no testing available (i.e., deceased proband)	Two required	a. C4CMMRD criteria of 3 points b. Individual < age 18 with NF1 features (i.e., no malignancy or polyposis history) c. Malignancy under age 30

Abbreviations: CMMRD, constitutional mismatch repair deficiency; LP, likely pathogenic; MMR, mismatch repair; P, pathogenic; VUS, variant of unknown significance.
[a]Same gene on both alleles.
[b]Consanguinity supports diagnosis.

