資料4. Clinical Management and Tumor Surveillance Recommendations of Inherited Mismatch Repair Deficiency in Childhoodのレビューワーク

CCR PEDIATRIC ONCOLOGY SERIES

Clinical Management and Tumor Surveillance Recommendations of Inherited Mismatch Repair Deficiency in Childhood

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Introduction

- DNA replication is a highly conserved and controlled process during the cell cycle.
- Inherited heterozygous mutations in the MMR genes result in a cancer condition termed Lynch syndrome.
- In contrast, biallelic germline mutations in the MMR genes result in a distinct phenotypically defined constitutional mismatch repair deficiency syndrome (CMMRD).
- Children with CMMRD are affected by a large variety of malignant neoplasms, and most do not reach adulthood. CMMRD is a devastating and penetrant cancer predisposition syndrome, and urgent interventions are needed.

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Introduction

- The median age of onset of the first tumor is 7.5 years, with a wide range observed (0.4–39;ref. 11).
- The spectrum of tumors in CMMRD is expanding and is distinct from those of LS.
- The most common are malignant brain tumors, followed by gastrointestinal and hematologic malignancies.
- The median ages at diagnosis of hematologic malignancies and brain tumors have been estimated to be 6.6 and 10.3 years, respectively.

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Introduction

■ CNS

- Most brain tumors are malignant gliomas, although low-grade lesions have been observed.
- The morphologic features of these gliomas include large, multinucleated giant cells with clumped nuclei and cells with many smaller, eccentrically placed nuclei mimicking pleomorphic xanthroastrocytomas.
- Central nervous system (CNS) embryonal tumors and medulloblastomas have also been reported (11, 14).

Introduction

■ Hematopoietic malignancies

- The most commonly observed hematopoietic malignancies are non-Hodgkin lymphomas (NHL) and, in particular, T-lymphoblastic NHL.
- T-cell acute lymphoblastic leukemia (T-ALL) and acute myeloid leukemia have also been reported (11, 15).

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Introduction

■ LS-associated malignancies

- Patients with CMMRD also develop LS-associated malignancies, the vast majority being colorectal carcinoma, although cancers of the small bowel, endometrium, ovary, and urinary tract have also been seen.
- Remarkably, a large proportion of CMMRD patients develop multiple synchronous adenomas ranging from a few up to >100 polyps, mimicking attenuated familial adenomatous polyposis.
- All patients will have polyposis by the third decade of life

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Introduction

■ Other cancers

- Furthermore, recent data reveal a large variety of other cancers and multi-organ involvement. These include childhood sarcomas such as osteosarcoma and rhabdomyosarcoma (12), other childhood cancers such as neuroblastoma (横紋筋肉腫) and Wilms tumor, and genitourinary（泌尿生殖器）cancers usually seen in adults with LS.
- These tumors occur even in the first decade of life, although sarcomas and genitourinary cancers are also observed in the second decade.

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Introduction

■ Lifetime risk, consanguinity (血縁者)

- Overall, most patients will be affected during childhood (11, 12), and the median survival after diagnosis of the primary tumor is less than 30 months (12)
- A high rate of consanguinity is observed especially among homozygous cases (17), whereas in Western countries, most of the cases are associated with composite heterozygous mutation in families with no consanguinity (12).
- In contrast to family members with LS, many of the heterozygous parents will not be affected, especially among families with PMS2 or MSH6 mutations (14, 18).

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Introduction

- Nonneoplastic manifestations

- Nonneoplastic manifestations of diagnostic importance include features of NF1, in particular cafe au lait macules (CALMs), and other hyper- and hypopigmented skin alterations.
- Most children will have this feature (19).
- Other features include developmental venous anomalies, pilomatricomas (benign skin lesions that usually appear in the first two decades of life; ref. 20), agenesis of the corpus callosum (脳梁欠損), and mild immunodeficiency with decreased levels of immunoglobulins IgG2/4 and IgA, among others (11).

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Clinical Genetics

- Inheritance

- CMMRD mode of inheritance is consistent with an autosomal recessive pattern.
- Biallelic mutations have been reported in all LS-associated MMR genes (MSH2, MLH1, MSH6, and PMS2).
- Importantly, the frequency is strikingly different than in LS.
- The most commonly involved genes are PMS2 and MSH6, whereas MSH2 and MLH1 mutations are rare

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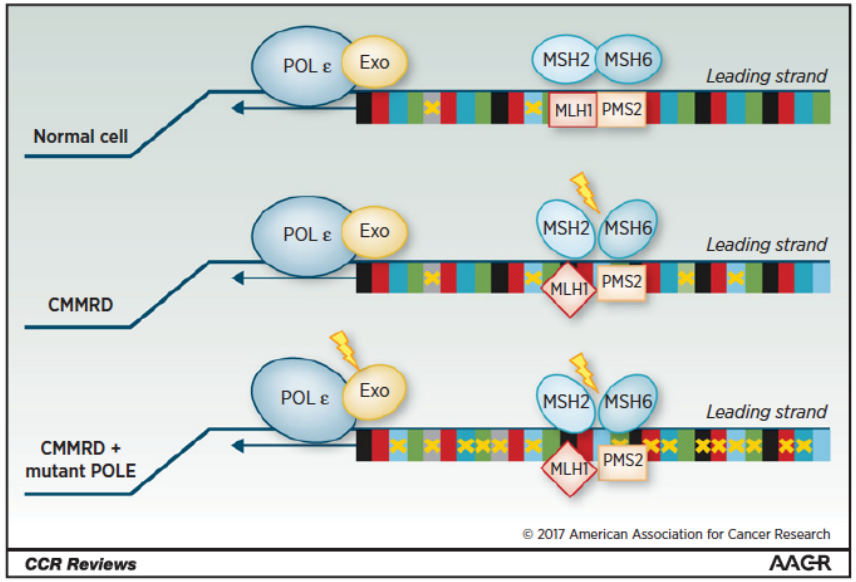
- Importantly, the frequency is strikingly different than in LS.
- The most commonly involved genes are PMS2 and MSH6, whereas MSH2 and MLH1 mutations are rarewhich might be explained by the lower penetrance and clinical severity of *PMS2* and *MSH6* heterozygous mutations on the one hand and the lethality of homozygous-null mutations in MSH2 on the other.

Diagnosis

- Protocol

- A clinical diagnostic protocol was developed by the European "Care for CMMRD (C4CMMRD)" consortium (Table 1; ref. 11).
- The scoring system is highly sensitive for CMMRD and suggests genetic counselling and testing for patients fulfilling these criteria. CMMRD should be suspected in all individuals who reach a score of three or more points.

Figure 1. A model of replication repair deficiency.



C4CMMRD scoring system for a clinical suspicion of CMMRD in cancer patients

Table 1. C4CMMRD scoring system for a clinical suspicion of CMMRD in cancer patients (11)

Indication for CMMRD testing in cancer patients	≥3 points
Malignancies/premalignancies: one is mandatory; if more than one is present in the patient, add the points	
Carcinoma from the LS spectrum[a] at age <25 years	3 points
Multiple bowel adenomas at age <25 years and absence of APC/MUTYH mutation(s) or a single high-grade dysplasia adenoma at age <25 years	3 points
WHO grade III or IV glioma at age <25 years	2 points
NHL of T-cell lineage or sPNET at age <18 years	2 points
Any malignancy at age <18 years	1 point
Additional features: optional; if more than one of the following is present, add the points	
Clinical sign of NF1 and/or ≥2 hyperpigmented and/or hypopigmented skin alterations Ø >1 cm in the patient	2 points
Diagnosis of LS in a first-degree or second-degree relative	2 points
Carcinoma from LS spectrum[a] before the age of 60 in first-degree, second-degree, or third-degree relative	1 point
A sibling with carcinoma from the LS spectrum[a], high-grade glioma, sPNET, or NHL	2 points
A sibling with any type of childhood malignancy	1 point
Multiple pilomatricomas in the patient	2 points
One pilomatricoma in the patient	1 point
Agenesis of the corpus callosum or non-therapy-induced cavernoma in the patient	1 point
Consanguineous parents	1 point
Deficiency/reduced levels of IgG2/4 and/or IgA	1 point

Abbreviations: sPNET, supratentorial primitive neuroectodermal tumors; WHO, World Health Organization.
[a]Colorectal, endometrial, small bowel, ureter, renal pelvis, biliary tract, stomach, bladder carcinoma.

Figure 1.
A model of replication repair deficiency.

Both the internal proofreading capability of the DNA polymerases and the mismatch repair systems are key to preventing replication errors in dividing cells. Inherited mismatch repair defect or mutations in DNA polymerases lead to the gradual accumulation of mutations and, thus, increased cancer risk during adulthood. However, combination of mutations in mismatch repair and the exonuclease domains of POLE or POLD1 DNA polymerases results in an extremely rapid accumulation of mutations and onset of cancer in young children.

Table 2. 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 U/S	1 year	Q 6 months	Lymphoma	May be considered Can be alternated with WBMRI
Upper gastrointestinal endoscopy; VCE, ileocolonoscopy	4 to 6 years	Once a year	Gastrointestinal tumors	Upper and lower endoscopy, to increase once polyps are found
GYN exam, transvaginal U/S, pipelle curettage, urine cytology, dipstick	20 years	Once a year	Genitourinary cancers	As per LS guidelines

Abbreviations: GYN, gynecologic; Q, every; U/S, ultrasound; VCE, visual capsule endoscopy.

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Oncologic Surveillance for Subjects With Biallelic Mismatch Repair Gene Mutations: 10 Year Follow-Up of a Kindred

Carol A. Durno, MD,[1,2,3]* Melyssa Aronson, MS,[1] Uri Tabori, MD,[2,4] David Malkin, MD,[2,4] Steven Gallinger, MD,[1] and Helen S. L. Chan, MB, BS[2,4]

【Results】 Over the 10-year follow-up period, the screening protocol detected 15 tumors. These included three high-grade adenomatous colonic polyps and two colon cancers. In one child, MRI revealed an asymptomatic anaplastic astrocytoma which was treated by complete resection and radiation. All three cancers identified during surveillance were small and asymptomatic at diagnosis. The two sisters are currently 16 and 18 years of age with no evidence of
malignant disease.

資料

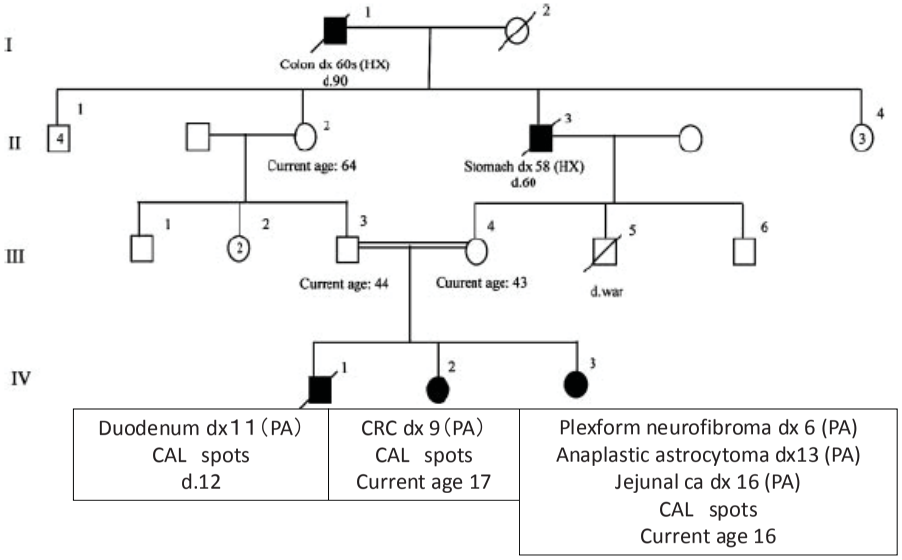

Fig. 1. Pedigree. dx, age at diagnosis;d, deceased (followed by age at death); CRC, colorectal cancer; CAL cafe´-au-lait macules; PA, cancer confirmed by pathology report.

TABLE II. Asymptomatic Tumors Detected During Surveillance (n = 15)

Family member	Tumor and site	Pathology	Age at diagnosis (years)
Sister IV-3	Cecum and transverse colon polyps[b] (n = 3)	Adenomatous high grade dysplasia	9
	Renal mass	Cyst	9
	Duodenal polyp	Adenomatous low grade dysplasia	10
	Brain tumor[b]	Anaplastic astrocytoma	13
	Duodenal polyp	Adenomatous low grade dysplasia	14
	Jejunal tumor	Adenocarcinoma	16
Sister IV-2[a]	Hepatic mass	Hepatic adenoma	9
	Gastric polyp	Hyperplastic	11
	Gastric polyp	Hyperplastic	12
	Ileal nodules (counted as 1 in total)	Adenomatous low grade dysplasia	14
	Duodenal polyp	Adenomatous low grade dysplasia	15
	Duodenal polyp	Adenomatous low grade dysplasia	16
	Rectal polyp	Adenomatous low grade dysplasia	16

[a]Diagnosed with adenocarcinoma of the colon prior to starting the screening protocol; [b]Underwent total colectomy and ileorectal anastomosis.

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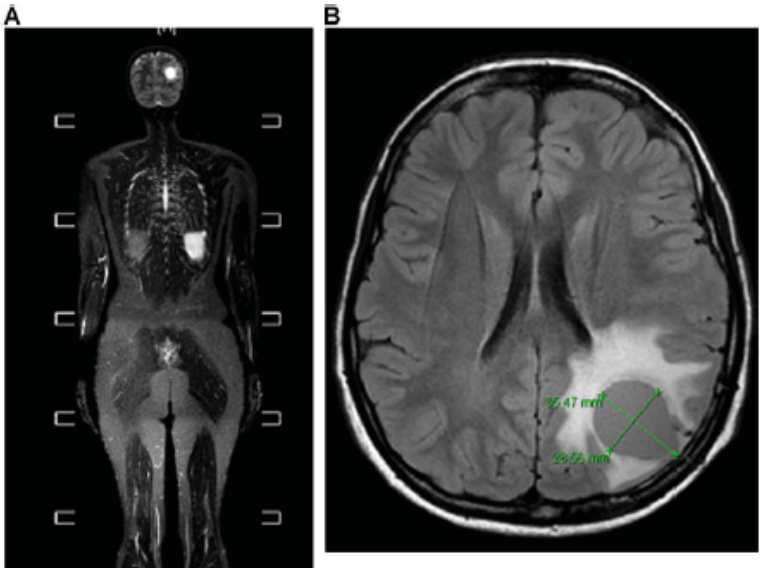

Fig. 2. Surveillance MRI reveals an asymptomatic malignant glioma.
A: Routine total body MRI reveals a small asymptomatic lesion in the left parieto-occipital lobe. B: T1 weighted MRI demonstrating the lobulated left parietal intra-axial tumor.

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Review

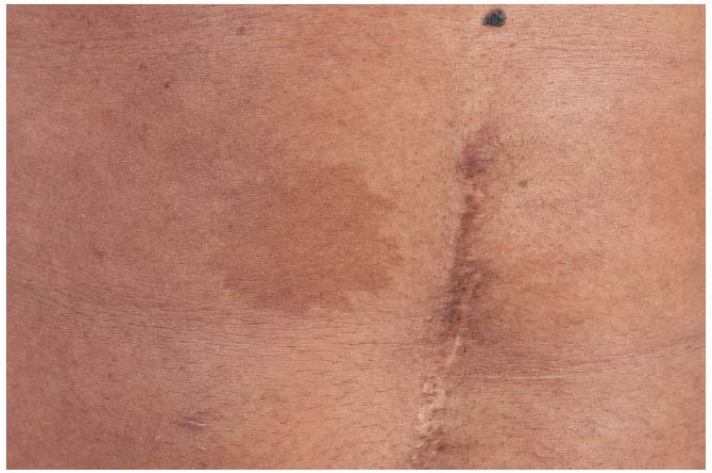
Phenotypic and genotypic characterisation of biallelic mismatch repair deficiency (BMMR-D) syndrome

Carol A. Durno[a,b,c,*], Philip M. Sherman[c], Melyssa Aronson[a], David Malkin[d], Cynthia Hawkins[e], Doua Bakry[d], Eric Bouffet[d], Steven Gallinger[a], Aaron Pollett[c], Brittany Campbell[f], Uri Tabori[d], International BMMRD Consortium

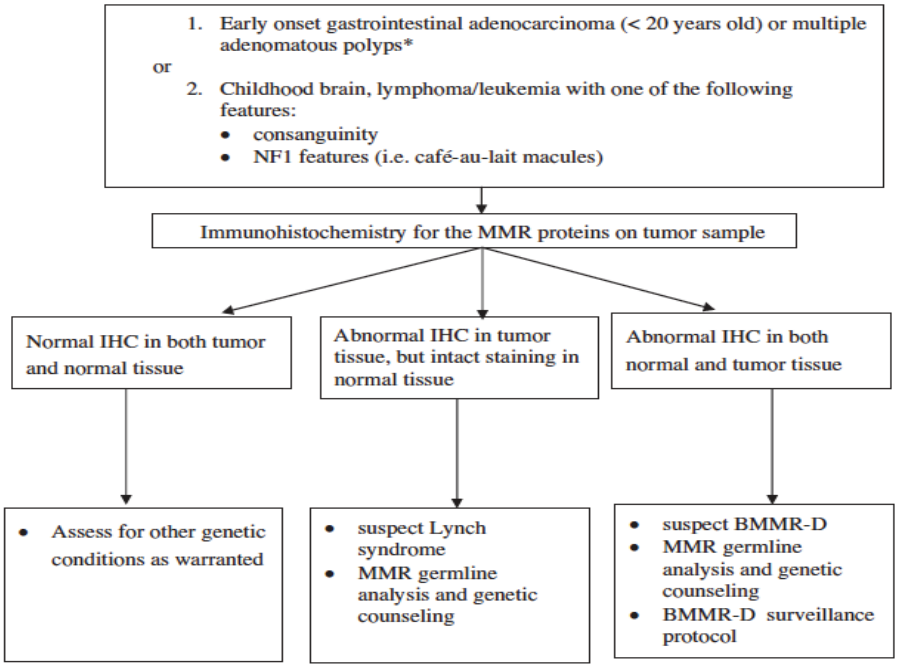
Genotype- phenotype

European Journal of Cancer (2015) 51, 977– 983

Cafe´-au-lait macules（斑点）



Cafe´-au-lait macules in an adolescent with biallelic mismatch repair deficiency (BMMR-D). Note the variation in pigmentation and irregular borders characteristic of BMMR-D.



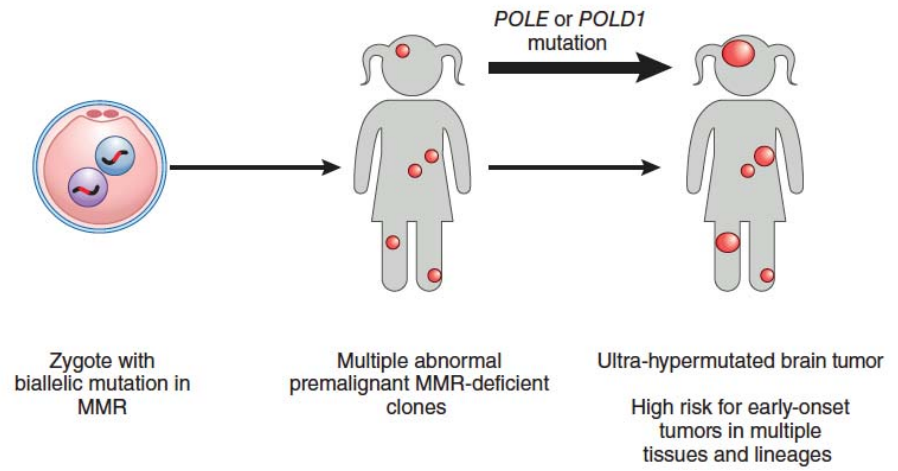


Figure 1 Mutation accumulation and cancer development in patients with bMMRD. Patients with bMMRD inherit deleterious variants in both copies of an MMR gene. Somatic mutations (rate indicated by arrow width) result in high risk for diverse cancers beginning in childhood. Malignant brain tumors have mutations of proofreading DNA polymerases, leading to mutation burdens among the highest ever documented.

Avalanching mutations in biallelic mismatch repair deficiency syndrome

Joshua J Waterfall & Paul S Meltzer

Tumors from pediatric patients generally contain relatively few somatic mutations. A new study reports a striking exception in individuals in whom biallelic germline deficiency for mismatch repair is compounded by somatic loss of function in DNA proofreading polymerases, resulting in 'ultra-hypermutated' malignant brain tumors.

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CONSENSUS GUIDELINES

Recommendations on Surveillance and Management of Biallelic Mismatch Repair Deficiency (BMMRD) Syndrome: A Consensus Statement by the US Multi-Society Task Force on Colorectal Cancer

Carol Dumo,[1] C. Richard Boland,[2] Shlomi Cohen,[3] Jason A. Dominitz,[4,5] Frank M. Giardiello,[6] David A. Johnson,[7] Tonya Kaltenbach,[8] T. R. Levin,[9] David Lieberman,[10] Douglas J. Robertson,[11,12] and Douglas K. Rex[13]

米国4学会合同声明

- Gastroenterology **152**(6): 1605-1614.
- Am J Gastroenterol **112**(5): 682-690.Volume 85, No. 5 : 2017
- Gastrointest Endosc **85**(5): 873-882.
- J Pediatr Gastroenterol Nutr **64**(5): 836-843.

Table 2 . Clinical and Laboratory Features to Raise Suspicion for Possible BMMRD

- ✓ Child or young adult with a Lynch syndrome cancer (colorectal, small bowel, ureter, endometrial, and so forth)
- ✓ Child or young adult with colonic adenomatous polyposis not explained by a known polyposis syndrome mutation (familial adenomatous polyposis, *MUTYH*-associated polyposis)
- ✓ Any child or young adult with cancer plus parental consanguinity, cafe au-lait macules, or features of neurofibromatosis, not explained by other confirmed germline mutation (ie, neurofibromatosis)
- ✓ Any cancer with abnormal immunohistochemistry for the DNA-MMR proteins in normal and tumor tissue
- ✓ History of brain cancer, lymphoma, or leukemia without history of radiation
- ✓ Any child or adult with hypermutated tumor

Table 1 . Estimated Penetrance and Age of Onset of Neoplasms in BMMRD （一部改訂）

Organ	Estimated penetrance, %	Age at diagnosis, median (range), y
Small-bowel adenomas	50	12 (10–20)
Colorectal adenomas	>90	9 (6–15)
Small-bowel cancer	10	28 (11–42)
Colorectal cancer	70	16 (8–48)
Low-grade brain tumors	Unknown	Unknown
High-grade brain tumors	70	9 (2–40)
Lymphoma	10–40	5 (0.4–30)
Leukemia	10–40	8 (2–21)
Endometrial cancer	<10	(19–44)
Urinary tract cancer	<10	(10–22)