Constitutional mismatch repair deficiency and childhood leukemia/lymphoma – report on a novel biallelic *MSH6* mutation

Tim Ripperger,[1] Carmela Beger,[1] Nils Rahner,[2] Karl W. Sykora,[3] Clemens L. Bockmeyer,[4] Ulrich Lehmann,[4] Hans H. Kreipe,[4] and Brigitte Schlegelberger[1]

[1]Institute of Cell and Molecular Pathology, Hannover Medical School, Hannover; [2]Institute of Human Genetics, University of Bonn, Bonn; [3]Department of Pediatric Hematology/Oncology, Hannover Medical School, Hannover, and [4]Institute of Pathology, Hannover Medical School, Hannover, Germany

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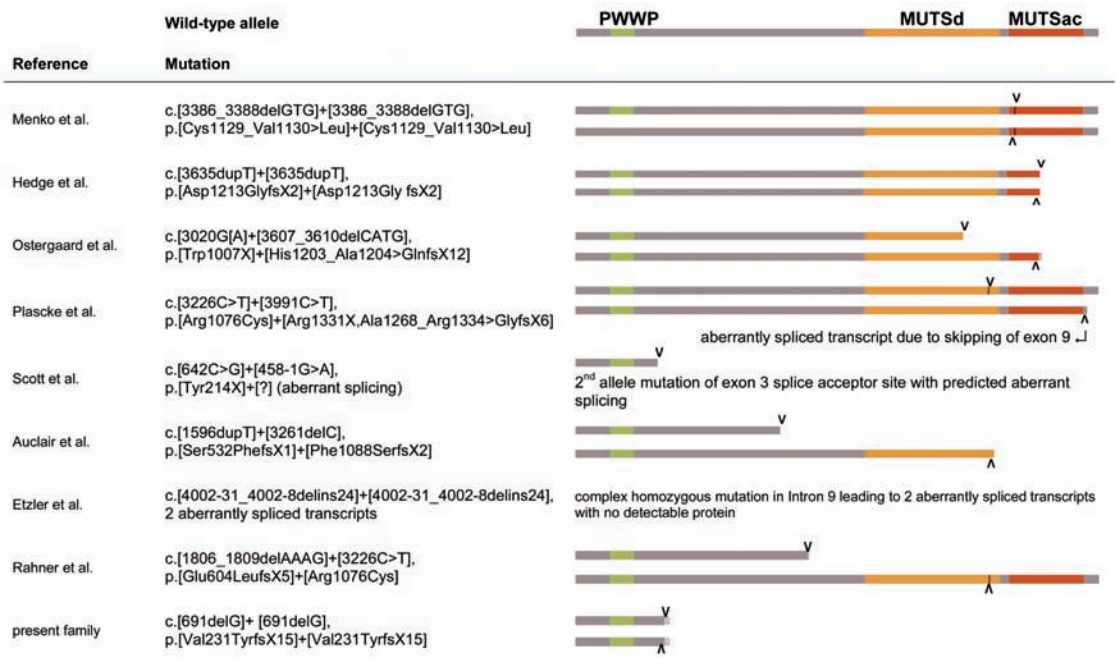
Online Supplementary Table S1. Families with constitutional mismatch repair deficiency (CMMRD) and at least one affected relative with a hematologic malignancy.

N.	Gene	Mutation*	Pat.†	Malignant tumors (Age at diagnosis in years)‡	(years)§	Signs of NF1	Family history	References
1	*MLH1*	c.[676C>T]+[676C>T], p.[Arg226X]+[Arg226X]	F1 F2 M1	**Atypical CML (1)** **NHL (3.25)** **Acute leukemia (2)**	u u u	CLS, 2 dermal fibromas CLS	LSF^{AC}; consanguineous parents	Ricciardone et al.[1]
2	*MLH1*	c.[199G>T]+[199G>T], p[Gly67Trp]+[Gly67Trp]	F1 F2	**Undifferentiated NHL(2)** **AML (6)**; medulloblastoma (7)	2 -	Hemicorporal CLS, pseudoarthrosis of the tibia CLS, multiple dermal neurofibromas	LSF^{AC}; consanguineous parents	Wang et al.[2]
3	*MHS2*	c.[1662-1G>A]+[1662-1G>A], p.[Ser554_Gly587>ArgfsX11]+[Ser554_Gly587>ArgfsX11]	M1	**T-ALL(2)**; **B-cell lymphoma (8)**	a	CLS	No family history indicative of LS; no parental consanguinity, but the same ethnic, religious, and geographical background	Whiteside et al.[3,4]
4	*MSH2*	c.[1-?_1076+?del]+[454delA], p.[Met1_Arg359>IlefsX29]+[Met152CysfsX22]	F1 M1	**T mediastinal lymphoma (1.25)** Temporal glioblastoma (3)	1.25 4		No clear family history indicative of LS; paternal great uncle: astrocytoma, age 27; mother of the paternal grandfather: endometrium carcinoma, age 59; maternal great aunt: endometrium carcinoma, age 43	Bougeard et al.[5]
5	*MSH2*	c.[226C>T]+[226C>T], p.[Gln76X]+[Gln76X]	M1 M2 F1	**Mediastinal T-cell lymphoblastic NHL (2.5)**; > 20 colonic adenomas with moderate dysplasia, no evidence of malignancy (6) **T-NHL (0.42)** **T-cell lymphoblastic lymphoma (2.5)**; a cystic pulmonary mass was identified by antenatal ultrasound, its origin remains unknown	a 1.25 a	CLS and hypopigmented skin lesions CLS and hypopigmented skin lesions CLS and hypopigmented skin lesions	Finally, LSF^{AC}, but when the T-NHL was diagnosed in M1, there was no family history of LS, only the paternal grandmother had been diagnosed with CRC at age 65; consanguineous parents	Scott et al. [6]
6	*MSH6*	c.[3635dupT]+[3635dupT], p.[Asp1213GlyfsX2]+[Asp1213GlyfsX2]	M1 F1	**Lymphoblastic lymphoma (5)**; CRC (8) Glioblastoma multiforme (8)	9 10	CLS, a few small axillary freckles CLS, solitary freckle in each axilla	LSF^{RBC} (maternal great uncle: CRC, age 48); parents deny any knowledge of consanguinity	Hegde et al.[7]
7	*MSH6*	c.[3020G>A]+[3607_3610delCATG], p.[Trp1007X]+[His1203_Ala1204>GlnfsX12]	M1 F1	Pilocytic astrocytoma, grade I (9); tumor recurrence as anaplastic astrocytoma, grade III (9.5); **mediastinal T-cell lymphoma (10)** Spinal cord glioblastoma (T4-L1) (2)	10.5 3	CLS, freckles in left axilla; in basal ganglia and cerebellum, high signal changes, T2-weighted MRI CLS, axillary freckling	Maternal LSF, known *MSH6* mutation (c.3020G>A), history of cancer in the paternal family, but no clear history indicative of LS	Ostergaard et al.[8]
8	*MSH6*	c.[642C>G]+[458-1G>A], p.[Tyr214X]+[?], *aberrant splicing*	F1	Medulloblastoma (7); **AML M5 (10)**; CRC (13); numerous tubulovillous colonic adenomas with varying grades of dysplasia (13)	a	CLS, hypopigmented skin lesions, sebaceous cysts on the scalp, 2 hairy nevi	No family history indicative of LS	Scott et al.[9]
9	*MSH6*	c.[4002-31_4002-8delins24]+[4002-31_4002-8delins24], *2 aberrantly spliced transcripts*	F1 M2	Medulloblastoma (6); **MDS/AML (9)** Glioblastoma multiforme (9)	12 10.25	CLS CLS, hypopigmented skin lesions	No family history indicative of LS, maternal grandfather with stomach cancer; consanguineous parents	Etzler et al.[10]

Online Supplementary Table S1. continued.

N.	Gene	Mutation*	Pat.†	Malignant tumors (Age at diagnosis in years)‡	(years)§	Signs of NF1	Family history	Ref.
10	*MSH6*	c.[691delG]+[691delG], p.[Val231TyrfsX15]+[Val231TyrfsX15]	F1	**mediastinal T-NHL(6)**, **T-NHL relapse (8)**, CRC (13)	a	CLS	LSF^{RBC} (paternal uncle with synchronous CRC, age 42), consanguineous parents	present case
11	*PMS2*	c.[1169_1170ins20]+[1169_1170ins20], *truncating mutation*	F1	CRC (16); ovarian neuroectodermal tumor (21); endometrial adenocarcinoma (23); brain tumor (24)	a	CLS	No family history indicative of LS, paternal grandmother: CRC, age 53; consanguineous parents	Trimbath et al.[11]
			F2	Anaplastic astrocytoma (7); 3 adenomatous colonic polyps (20)	a	CLS		
			M1	**ALL (4)**	4	CLS		
12	*PMS2*	c.[2404C>T]+[2404C>T], p.[Arg802X]+[Arg802X]	F1	**Cerebral high-grade B-cell NHL (10)**	12	CLS	No family history indicative of LS; consanguineous parents¶	De Vos et al.[12,13]
			M1	Temporoparietal PNET (8); multiple colonic polyps	a	CLS		
			F2	Frontal lobe SPNET (14)	a	CLS		
13	*PMS2*	c.[400C>T]+[2184_2185delTC], p.[Arg134X]+[Leu729GlnfsX6]	F1	CRC and 3 colorectal adenomas (11); diagnosis of phenotypic adenomatous polyposis followed by total colectomy (14); anaplastic glioma with oligodendroglial features (23)	a	CLS	No family history indicative of LS	Taylor et al.[14], Hamilton et al.[15], and De Vos et al.[12]
			M1	Glioblastoma with oligodendroglial component (4); 2 colonic adenomas and 1 hyperplastic polyp led to total colectomy in view of the affected sister (F1) (13); **large B-cell NHL of the terminal ileum at the site of ileorectal anastomosis (17)**; glioblastoma with oligodendroglial components (21)	21	CLS		
14	*PMS2*	c.[2404C>T]+[2404C>T], p.[Arg802X]+[Arg802X]	U1	**T-ALL (2)**; **T-cell lymphoma (14)**; multiple CRC(18)	a	CLS	No family history indicative of LS; consanguineous parents¶	De Vos et al.[13]
15	*PMS2*	c.[2404C>T]+[2404C>T], p.[Arg802X]+[Arg802X]	U1	Glioma (15)	16	CLS	No family history indicative of LS; consanguineous parents¶	De Vos et al.[13]
			U2	**ALL (15)**	15	CLS		
			U3	Astrocytoma (6); glioblastoma (7)	8	CLS		
16	*PMS2*	c.[2404C>T]+[2404C>T], p.[Arg802X]+[Arg802X]	U1	Giant cell glioblastoma (2)	2		No family history indicative of LS; consanguineous parents¶	De Vos et al.[13]
			U2	**T-cell NHL (3)**	3			
			U3	**ALL (6)**	7			
17	*PMS2*	c.[2404C>T]+[2404C>T], p.[Arg802X]+[Arg802X]	U1	**ALL (6)**	7	CLS	No family history indicative of LS; consanguineous parents¶	De Vos et al.[13]
18	*PMS2*	c.[812G>T]+[812G>T], p.[Gly271Val]+[Gly271Val]	F1	Sigmoid CRC (13); right-sided CRC (14); multiple colorectal polyps (14)	a	CLS, discrete axillary freckling	No family history indicative of LS; consanguineous parents	Kruger et al.[16]
			F2	**T-cell NHL (10)**; CRC (11); multiple colonic polyps (11)	a	CLS		
19	*PMS2*	c.[1306dupA]+[1306dupA], p.[Ser436LysfsX22]+[Ser436LysfsX22]	F1	**Mediastinal T-cell lymphoblastic lymphoma (6)**; CRC (16); adenomatosis polyposis (16)	a	CLS	No family history indicative of LS, no consanguinity was reported	Kratz et al.[17]
			F2	SPNET (9)	9	CLS		
20	*PMS2*	c.[614A>C]+[1A>G], p.[Gln205Pro]+[?], *5' truncation*	U1	CRC (20); duodenal cancer (41); **lymphoma (?)**	a		No family history indicative of LS, one brother and one sister with a brain tumor at age 38 and 31, respectively	Senter et al.[18]

Online Supplementary Table S1. Families with constitutional mismatch repair deficiency (CMMRD) and at least one affected relative with a hematologic malignancy. *: the description of mutations is based on the nomenclature in the review by Wimmer and Etzler[19] following the Human Genome Variation Society (HGVS) guidelines for the description of sequence variants (http://www.hgvs.org/mutnomen/) with +1 corresponding to the adenine (A) of the ATG translation start site; †: Pat., patients; F, female; M, male; U, sex not reported; numbers, personal identifier for each family; ‡: malignancies are listed following the order of diagnosis; numbers in brackets, age at diagnosis; ?, unknown age at diagnosis; hematologic malignancies are given in bold letters; §: A.d., age at death (years); u, patient deceased, but A.d. was not reported; a, patient alive at date of study report; ¶: all five families described by De Vos et al. were of Pakistani origin (Mirpur region of Northeastern Pakistan), due to marker analysis, a common ancestry seemed possible, but no consanguinity was reported by the families.[12,13] ALL: acute lymphoblastic leukemia; AML: acute myelogenous leukemia; CML: chronic myelogenous leukemia; CLS: café-au-lait spots; CRC: colorectal cancer; LS: Lynch syndrome; LSF: Lynch syndrome family; LSF^{AC}: LSF Amsterdam criteria are fulfilled; LSF^{RBC}: LSF revised Bethesda criteria are fulfilled; MDS: myelodysplastic syndrome; *MLH1*: mutL homolog 1; *MSH2*: mutS homolog 2; *MSH6*: mutS homolog 6; NF1: neurofibromatosis type 1; NHL: non-Hodgkin's lymphoma; PNET: primitive neuroectodermal tumor; *PMS2*: postmeiotic segregation increased 2; SPNET: supratentorial primitive neuroectodermal tumor.



Online Supplementary Figure S1. Biallelic germline mutations in MSH6 causing constitutional mismatch repair deficiency (CMMRD). Observed mutations in MSH6 (NM_000179) are schematically illustrated in view of functional domains (P52701, 1360 AA), i.e. PWWP (green, 90-152 AA), MUTSd (orange, 753-1102 AA, DNA binding domain of DNA mismatch repair MUTS family), and MUTSac domain (red, 1127-1321 AA, ATPase domain of DNA mismatch repair MUTS family) (http://smart.embl-heidelberg.de).7-10,20-24 V, site of mutation; |, missense alteration; patterned shading, altered reading frame.

References Supplemental Data

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