Supplementary information
Table S1

Mutation[a,b]	Predicted protein change	RNA group[d]	references RNA analysis[e]	Number of mutation carriers (families)	Frequency (%)
c.736_741delinsTGTGTGTGAAG	p.Pro246Cysfs*3	1	1	61 (25)	15.9
c.1882C>T	p.Arg628*	1	1	47(14)	12.3
deletion exon 11 - 15 (c.1145-1350_ *20545del)	p.?	(1)	na	23(4)	4.7
c.2192_2196del	p.Leu731Cysfs*3	1	1	18(6)	4.4
c.697C>T	p.Gln233*	1	1	13(5)	3.7
c.1831dup	p.Ile611Asnfs*2	(1)	na	10(3)	2.6
deletion exon 1 – 11[c]	p.?	(1)	na	9(1)	2.3
c.823C>T	p.Gln275*	1	2	8(2)	2.1
deletion of the whole gene	p.0	(1)	na	7(3)	1.8
c.1112_1113delinsTTTA	p.Asn371Ilefs*2	(1)	na	5(1)	1.3
c.325dup	p.Glu109Glyfs*30	1	2	5(3)	1.3
c.1079_1080del	p.Ile360Argfs*4	(1)	na	4(1)	1
c.2117delA	p.Lys706SerfsX19	1	2	4(1)	1
c.861_864del	p.Arg287Serfs*19	1	1	4(1)	1
c.903G>T (skips exon 8)	p.Tyr268*	1	3	3(1)	1
c.1145-?_c.2006-?del (deletion exon 11)[c]	p.?	(1)	na	3(1)	0.8
c.2155C>T	p.Gln719*	1	2	3(2)	0.8
c.804-60_804-59insJN866832.1	p.?	1	4	3(2)	0.8
c.1214C>A	p.Ser405*	(1)	na	2(1)	0.5
c.2156delA	p.Gln719Argfs*6	(1)	na	2(1)	0.5
c.354-1G>A	p.?	(1)	na	2(1)	0.5
c.251-2A>C	p.?	(1)	na	2(2)	0.5
c.856_857del	p.Asp286Glnfs*12	(1)	na	1(1)	0.3
c.1261C>T	p.Arg421*	(1)	na	1(1)	0.3
c.211_214delAATG	p.Asn71Aspfs*4	(1)	na	1(1)	0.3
c.658dup	p.Ser220Lysfs*29	(1)	na	1(1)	0.3
c.904_911delGTCTGCAG	p.Val302Thrfs*4	(1)	na	1(1)	0.3
c.989-?_2275+?del (deletion exon 10-13)[c]	p.?	(1)	na	1(1)	0.3
deletion exon 5 - 15[c]	p.?	(1)	na	1(1)	0.3
deletion exon 9 -11[c]	p.?	(1)	na	1(1)	0.3
c.247_250dupTTAA	p.Thr84Ilefs*9	1	2	1(1)	0.3
c.825A>G (first 22 nucleotides exon 8 spliced out)	p.Ile269Alafs*31	1	5	1(1)	0.3
c.137G>T	p.Ser46Ile	2	1	19(8)	5
c.2113G>A	p.Glu705Lys	(2)	na	11(2)	2.9
c.2444C>T	p.Ser815Leu	2	1	4(1)	1
deletion exon 5 – 7[c]	p.?	3	na	18(5)	4.7
deletion exon 14	p.?	3 (no NMD observed)	1	11(3)	2.9
c.219_220dup	p.Gly74Valfs*3	3 (partial NMD observed)	1	10(3)	2.6
c.24-12_107delinsAAAT	p.Ser8Argfs*5	3 (no NMD observed)	1	9(2)	2.3

c.989-1G>T	p.?	3 (no NMD observed)	6	9(1)	2.3
c.989-2A>G	p.Glu330_Glu381del	3 (no NMD observed)	7	8(1)	2.1
deletion exon 2[c]	p.?	3	na	7(4)	1.8
c.319C>T	p.Arg107Trp	3 (change in ratio alternative transcripts)	2	7(1)	1.8
c.2404C>T	p.Arg802*	3	na	4(2)	1
c.1144+2T>A	p.Glu330_Glu381del	3 (no NMD observed)	1	4(1)	1
deletion exon 10	p.?	3	na	3(2)	0.8
c.2174+1G>A	p.?	3 (multiple transcripts)	2	3(1)	0.8
c.1A>G	p.?	3	na	1(1)	0.3
c.989-296_1144+706del (deletion exon 10)	p.Glu330_Glu381del	3	na	1(1)	0.3
deletion exon 6 - 7	p.?	3 (multiple transcripts)	2	1(1)	0.3
c.163+2T>C	p.Ser8Argfs*5	3 (no NMD observed)	1	1(1)	0.3
deletion exon 3 - 7	p.?	3 (no NMD observed)	1	1(1)	0.3
c.2445+1G>T	p.?	3 (no NMD observed)	2	1(1)	0.3
Total				**381 (134[f])**	**100**

Table 1 mutation frequencies

[a] Except large genomic deletions, mutations were described according to the Human Genetic Variation Society approved guidelines (http://www.hgvs.org/mutnomen/) with reference to PMS2 GenBank reference sequence NM_000535.5. The large genomic rearrangements, nonsense, frame-shift, and canonical splice site mutations in this study are considered pathogenic or likely pathogenic (class 5 or 4).[1]
b To avoid interference of pseudogene sequences using long range PCR, either with cDNA or genomic DNA as template was used for detection of point mutations and small insertions and deletions.[2-5] Mutations were found using different techniques, depending on the involved diagnostic laboratory.
[c] The large deletions were mostly detected using the multiplex ligation-dependent probe amplification (MLPA) kit P008-A1 (MRC-Holland, Amsterdam, the Netherlands). This MLPA kit version lacks (reliable) probes for PMS2 exon 3, 4, 12, 13, 14 and 15. Because the exact extent of these deletions is often not characterized, they are included with an informal description.
[d] 1=no mRNA expression from mutated allele, 2=normal mRNA expression; 3=RNA expression unknown, or mRNA present but with exon(s) skipped
[e] references 1=van der Klift et al 2010[4]; 2=van der Klift, unpublished observations; 3= microattribution Mensenkamp & Ligtenberg in LOVDdb ; 4=van der Klift, 2012[6]; 5=Johannesma et al.2011[7]; 6=Sjursen et al 2009[8]; 7=Borras et al 2013[9]; na=not available
[f] the total number of families in is 134 because four families carry two different segregating mutations.

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4. van der Klift HM, Tops CM, Bik EC, et al. Quantification of sequence exchange events between PMS2 and PMS2CL provides a basis for improved mutation scanning of Lynch syndrome patients. Hum Mutat 2010;31:578-87.
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7. Johannesma PC, van der Klift HM, van Grieken NC, et al. Childhood brain tumours due to germline bi-allelic mismatch repair gene mutations. Clin Genet 2011;80:243-55.
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9. Borras E, Pineda M, Cadinanos J, et al. Refining the role of PMS2 in Lynch syndrome: germline mutational analysis improved by comprehensive assessment of variants. J Med Genet 2013;50:552-63.