Supplementary table 3 Missense variants with predicted biological consequence

Gene	Exon	Nucleotide change	Amino acid change	Previous report*	De novo mutation†	Cosegregation‡ (No of families)	No of aff gene carriers§	Phylogenetic conservation¶	Functional alteration in yeast**	Predicted gross structural alteration††
MSH2	1	1A>C	M1L				1			Initiation codon
MSH2	1	4G>A	A2T				1			Kozak consensus
MSH2	3	380A>G	N127S	Y	Y		2			DNA recognition (a)
MSH2	3	435T>G	I145M	Y		1	6			
MSH2	3	560T>G	L187S			1	3	Y (11)		
MSH2	6	989T>C	L330P				1	Y (11)		
MSH2	6	998G>A	C333Y	Y		1	2			Interdomain interaction (11)
MSH2	6	1022T>C	L341P			2	5	Y (11)		
MSH2	12	1786del3	596del	Y		1	3			
MSH2	12	1906G>C	A636P	Y		1	2			ATPase activity (11)
MSH2	13	2021G>A	G674D	Y		1	3	Y (11)	Y (17)	ATPase activity (11)
MSH2	13	2075G>T	G692V	Y	Y		1	Y (11)		Interdomain interaction (11)
MSH2	13	2087C>T	P696V			1	2	Y (11)		
MSH2	13	2089T>C	C697R	Y	*Y*		3	Y (11)		Structural integrity (11)
MSH2	14	2245G>A	D749K				1	Y (11)	Y (17)	ATPase activity (11)
MLH1	1	2T>C	M1T				1			Initiation codon
MLH1	1	83C>T	P28L	Y			1	Y (13)		ATPase activity (13)
MLH1	1	109G>A	E37K	Y			2	Y (12, 13)		
MLH1	2	121G>C	D41H				3	Y (12, 13)		
MLH1	2	199G>A	G67R	Y			1	Y (12, 13)	Y (14)	ATPase activity (13)
MLH1	3	301G>A	G101S			1	3	GFRGEAL motif (12, 13)	Y (12)	ATPase activity (13)
MLH1	4	307G>C	A103P				1	GFRGEAL motif (12, 13)		ATPase activity (13)
MLH1	4	350C>T	T117M	Y		2	5	Y (13)	Y (14, 15)	ATPase activity (13)
MLH1	8	677G>A	R226Q	Y			1	Y (13)		ATPase activity (13)
MLH1	11	976del9	326del3			1	10	Y (13)		ATPase activity (13)
MLH1	14	1595G>A	G532D		*Y*		1	Y		
MLH1	14	1612T>G	W538G		*Y*		1	Y		
MLH1	14	1616C>A	A539D			1	2	Y		
MLH1	14	1642T>G	Y548D			1	3	Y		

MLH1	14	1651del3	551del			1	3	Y	
MLH1	16	1754T>G	L585R			2	4	Y	
MLH1	16	1846del3	616del	Y		1	9		Y (16)
MLH1	19	2146G>A	V716M	Y		1	4		
MLH1	19	2223del9	742del3				1	CTH motif (12)	

*Previous report of the mutation in HNPCC families (http://archive.uwcm.ac.uk/uwcm/mg/ns/1/203983.html & 249617.html, http://www.expasy.ch/cgi-bin/niceprot.pl?P43246 & P40692). †Mutation present in the probands without familial cancer history; italic Y indicates that the mutation was absent in both parents, paternity having been verified by typing both parents and proband with eight microsatellite markers, that is, occurrence of a true new mutation. ‡Cosegregation of the mutation with the disease, as evidenced by the presence of the mutation in all affected subjects of multiplex families. §No of subjects, related or not, found to be gene carriers. ¶Translation initiation, or paralogous and orthologous phylogenetic conservation of the amino acid position, including for *MHS2* the mutS bacterial protein. **Functional impairment of the mutated gene product in yeast. ††Predicted gross alteration of the protein 3D structure upon non-conservative amino acid substitution.