

Review

# Genetic Polymorphisms of DNA Repair Pathways in Sporadic Colorectal Carcinogenesis

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## Abstract

DNA repair systems play a critical role in maintaining the integrity and stability of the genome, which mainly include base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR) and double-strand break repair (DSBR). The polymorphisms in different DNA repair genes that are mainly represented by single-nucleotide polymorphisms (SNPs) can potentially modulate the individual DNA repair capacity and therefore exert an impact on individual genetic susceptibility to cancer. Sporadic colorectal cancer arises from the colorectum without known contribution from germline causes or significant family history of cancer or inflammatory bowel disease. In recent years, emerging studies have investigated the association between polymorphisms of DNA repair system genes and sporadic CRC. Here, we review recent insights into the polymorphisms of DNA repair pathway genes, not only individual gene polymorphism but also gene-gene and gene-environment interactions, in sporadic colorectal carcinogenesis.

Key words: DNA repair, polymorphism, colorectal cancer, carcinogenesis

## Introduction

DNA repair is an orchestrated system of defenses evolved to protect the genomic integrity and involved in the process preventing carcinogenesis. DNA repair systems play a critical role in maintaining the integrity and stability of the genome, which mainly include base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR) and double-strand break repair (DSBR)[1]. Interindividual differences in DNA repair capacities are important determinants of susceptibility to cancer. Cellular DNA is constantly under damage from endogenous and exogenous stimuli, leading to a dynamic cellular balance between damage and repair[2]. Defects in human DNA repair system would increase the instability of genome, and unrepaired DNA damage may thereby enhance genetic susceptibility to cancer and give rise to carcinogenesis. The polymorphisms in different DNA repair genes that are mainly

represented by single-nucleotide polymorphisms (SNPs) can potentially modulate the individual DNA repair capacity and therefore exert an impact on individual genetic susceptibility to cancer.

Colorectal cancer (CRC) is the third most common cancer in men and the second in women worldwide[3]. Among them, Sporadic colorectal cancer is the overwhelming majority, which arises from the colorectum without known contribution from germline causes or significant family history of cancer or inflammatory bowel disease[4]. In recent years, emerging studies have investigated the association between polymorphisms of DNA repair system genes and sporadic CRC. Here, we review recent insights into the polymorphisms of DNA repair pathway genes in sporadic colorectal carcinogenesis by searching different combinations of “DNA repair”, “polymorphism/variant” and “colorectal cancer/

colon cancer/rectal cancer" from Pubmed and web of science.

## BER pathway gene polymorphisms and sporadic CRC susceptibility

Base excision repair (BER) corrects small base errors which do not significantly alter the DNA helix structure. These damages mainly arise from oxidation, deamination and alkylation[5]. Upon DNA base damage, BER is initiated and four core steps are involved in this process: (1) damaged DNA base removal; (2) incision of the subsequent abasic site; (3) DNA ends processing; (4) ligation of the remaining nick in the DNA backbone[6]. From the beginning of the third step, BER diverges into two sub-pathways of short-patch(only one defective base) and long-patch (more than one defective base ) according to the number of defective bases, and each sub-pathway requires unique functional proteins[7]. OGG1 and MYH are involved in the first step of BER while APE1 and PARP1 participate in the incision of abasic site[8, 9]. Short-patch sub-pathway contains pol $\beta$ , LIG3 and XRCC1 while FEN1, PCNA and LIG1 contribute to the long-patch sub-pathway[10].

### Recognition related BER polymorphisms

#### OGG1

The *OGG1* gene located at chromosome 3p26.2, consisting of seven exons and encodes a glycosylase including 345 amino acids. OGG1 protein repairs 8-hydroxyguanine (8-oxoG), a frequently mutagenic lesion among base modification[11].

As the most common *OGG1* polymorphism, the rs1052133 polymorphism results in an amino acid substitution from serine to cysteine in codon 326 at exon 7 [12]. The GG genotype of rs1052133 polymorphism was first linked to increased CRC risk by Moreno, V. et al.'s study in Spanish population[13]. Subsequently, Canbay, E. et al. revealed in Turkish people that G allele was associated with higher risk of CRC compared with C allele[12]. And CG genotype was found to increase susceptibility to CRC according to Przybyłowska, K. et al. in Polish population[14]. However, several investigations did not demonstrate similar significance[15-23]. Additionally, one research in Taiwanese found that the CG genotype of rs1052133 polymorphism was related with increased CRC risk but no significant association was demonstrated for 11657A/G polymorphism[24]. It is worth noting that significant interaction was observed between rs1052133 polymorphism and smoking: smokers with variant homozygous GG genotype showed an increased risk of CRC[25].

#### MYH

*MYH*, also known as *MUTYH*, is mapped to chromosome 1p34.1 and encodes a glycosylase. This glycosylase initiates the BER pathway by catalyzing the removal of adenine bases of DNA which is inappropriately paired with guanine, cytosine, or 8-oxo-7,8-dihydroguanine[6].

Altogether three studies detected the role of *MYH* polymorphisms in colorectal carcinogenesis. Tao, H. et al. investigated four *MYH* SNPs of IVS1+11C>T(rs2275602), IVS6+35G>A(rs3219487), IVS10-2 A>G and 972G>C(rs3219489) for an association with altered CRC risk in Japanese[26]. They suggested that (CT+TT) genotype carriers of rs2275602 polymorphism demonstrated increased risk of CRC compared with individuals carrying CC genotype, while no significant relation was identified in the other three polymorphisms. Kasahara, M. et al. found in Japanese that dominant genetic model of rs3219489 polymorphism was associated with increased CRC risk[20]. Similar significant association was subsequently detected by Przybyłowska, K. et al. in a research based on Polish population[14].

### Incision related BER polymorphisms

#### APE1

*APE1* consists of five exons and four introns spanning 2.21 kb on chromosome 14q11.2 and encodes a protein of 317 amino acids. APE1 deletes abasic sites formed by OGG1 as well as *MUTYH* and assembles DNA polymerase  $\beta$  and DNA ligase III in BER[27].

Zhang, S. H. et al. found significant interaction of rs1760944 polymorphism with BMI: a protective effect of the T/G genotype was revealed on the development of CRC among subjects with a BMI < 25 kg/m<sup>2</sup>, although no significant association was detected between this polymorphism and CRC risk[15]. For *APE1* rs2307486 polymorphism in exon 3, carriers of AG genotype demonstrated increased risk of CRC compared with GG genotype in Polish[28]. In addition, several investigations have reported significant association between *APE1* rs1130409 G/T polymorphism and altered risk of CRC: four studies found that G allele was the risk allele[12, 15, 20, 29] while Jelonek, K. suggested that T allele significantly increased CRC risk in Polish population[30]. Another study indicated that GG genotype carriers of rs1130409 polymorphism demonstrated significantly lower *APE1* mRNA expression than TT genotype carriers, which might be an evidence for the risk role of G allele[31]. Two teams found on significant relation of rs1130409 polymorphism with CRC risk in Chinese[32] and Czech[25], respectively. Ching-Y. et

al. studied two *APE1* polymorphisms (Asp148Glu and T-656G) in Taiwanese but no significant result was found[24].

#### **PARP1**

*PARP1* gene is mapped to chromosome 1q41-q42, encoding a chromatin-associated poly (ADP-ribose) transferase which can detect single-strand breaks and contribute to BER through its interaction with the *XRCC1*[33].

One study in Singapore Chinese revealed a positive association between the *PARP1* codon 940 Lys/Arg genotype and CRC risk[22]. However, no significant relation was found between Val762Ala polymorphism and CRC risk in this study. Another study by Li, Y. et al. suggested that AlaAla genotype of Val762Ala polymorphism significantly increased CRC risk in both homozygous and recessive model in Chinese [32]. For rs8679 polymorphism in 3'UTR region, Alhadheq, A. M. et al. showed no significant association between the polymorphism and risk of CRC in Saudis population[34].

#### **End processing related BER polymorphisms**

##### **POLB**

*POLB* (DNA polymerase beta) gene is located at chromosome 8p11.2, which has 16 exons and 15 introns. Pol $\beta$  is the major DNA polymerase implicated in the initiation of both short-patch and long-patch BER[35].

Only one *POLB* SNP, rs3136797 (P242R) polymorphism, has been reported. Moreno, V. et al. investigated 28 SNPs of 15 DNA repair genes including *POLB* and indicated that *POLB* P242R polymorphism was significantly associated with a reduced risk of CRC[13]. However, the minor allele is very rare and only a few heterozygous individuals were observed, which still required future investigations to confirm.

##### **FEN1**

*FEN1* (flap structure-specific endonuclease 1), mapped to chromosome 11q12, is essential in efficient 5' flap removal during long-patch base excision repair and the maturation of Okazaki fragments in DNA replication[36].

Until now, only one study by Liu L. et al. detected -69G>A and 4150G>T polymorphisms of *FEN1* in cancers of digestive tract including hepatocellular carcinoma, esophageal cancer, gastric cancer and colorectal cancer (126 cases) in Chinese population[37]. However, the results suggested no significant relation of these two variants with CRC risk.

#### **Ligation related BER polymorphisms**

##### **XRCC1**

*XRCC1* gene, located at chromosome 19q13.2, has 17 exons and 16 introns. The protein encoded by this gene works as a scaffolding protein and interacts with *PARP1*, *OGG1* and *APE1* to facilitate the processes of BER[15].

A number of studies have suggested that rs1799782 C/T in exon 6 of *XRCC1* gene could increase CRC risk: Nissar, S. et al.[38] and Li, Y. et al.[32] found CT genotype was related with increased CRC risk in Kashmiri and Chinese population, respectively; The TT genotype was also found to increase CRC risk by two studies[38, 39]. In addition, rs1799782 polymorphism demonstrated significant interaction with smoking: (CT+TT) genotype smokers had 1.6 folds increased risk of CRC[22]. For *XRCC1* IVS2-216G>A polymorphism, only one research by Berndt, S. I. et al. revealed that AA genotype was the protective genotype[29]. Although four studies have investigated *XRCC1* rs25489 A/G polymorphism of exon 9 in Japanese[40], American[18], Norwegian[41] and Korean[42], no significant association was indicated. In addition, significant interaction was observed between GG genotype of rs25489 polymorphism and alcohol drinking to increase the risk of CRC [40]. Another most frequently studied polymorphism was 25487 A/G, which is located at exon 10 and changes amino acid from Arg to Gln. Many studies have found significant relation between this polymorphism and increased CRC risk in AG vs. GG model[42-45] and AA vs. GG model[14, 30, 40, 44-46]. But other two studies observed that AG genotype[47] and AA genotype[48] of rs25487 polymorphism can decrease the risk of CRC. Some other researches failed to find significant relation between rs25487 and CRC risk in multiple population[15, 18-20, 22, 25, 32, 41, 49-56]. It is worth noting that three studies have found significant interactions of rs25487 polymorphism with smoking[15] and drinking[46, 54]: A allele carriers of rs25487 showed interaction with alcohol intake to decrease risk of CRC but AG genotype of rs25487 interacts with smoking to increase the CRC risk.

#### **NER pathway gene polymorphisms and sporadic CRC susceptibility**

As an essential and versatile system, NER monitors and repairs several types of DNA damage which involves UV-induced cyclobutane pyrimidine dimers, DNA crosslinks and bulky adducts[57]. Transcription coupled NER (TC-NER) and global genome NER (GG-NER) are two NER sub-pathways while the only difference between them is the way of

DNA damage recognition[58]. NER consists of four steps: damage recognition, damage demarcation and unwinding, damage incision and new strand ligation. Each step requires indispensable functional proteins, and over 30 factors participate in this precise process[59]. XPA and XPC participate in the first step of NER while XPD together with RPA2 and GTF2H1 play an important role in the damage demarcation and unwinding. Damage incision mainly involves three core proteins of ERCC1, XPF and XPG[60].

## DNA damage recognition related NER polymorphisms

### XPA

XPA, located at 9q22.33, contains 10 exons and encodes a zinc finger protein which participates in DNA damage recognition of NER. Interacting with DNA and a number of NER proteins, XPA assembles the NER incision complex to the domain where DNA damage occurs[61].

**Table 1.** Significant association of BER pathway gene polymorphisms with sporadic CRC susceptibility.

Variables	Location	Author	Year	Population	Case	Control	Genotypes	OR(95%CI)	Interaction		
XRCC1 rs1799782	19q13.2 Exon 6	Dai, Q.	2015	Chinese	438	438	CT vs. CC	1.19(0.90-1.57)	N.A.		
							TT vs. CC	<b>1.43(1.20-2.24)</b>	N.A.		
		Nissar, S.	2015	Kashmiri	100	100	CT vs. CC	<b>2.01(1.03-3.94)</b>	N.A.		
							TT vs. CC	<b>5.2(1.42-19.5)</b>	N.A.		
		Li, Y.	2013	Chinese	451	631	CT vs. CC	<b>1.45(1.11-1.89)</b>	N.A.		
							TT vs. CC	1.48(0.91-2.39)			
		(CT+TT) vs. CC						<b>1.45(1.12-1.88)</b>			
			Stern, M. C.	2007	Chinese	310	1176	CT vs. CC	0.9(0.7-1.2)	<b>Interaction with smoking</b>	
		TT vs. CC						0.8(0.5-1.3)			
		rs1001581	Intron 2	Berndt, S. I.	2007	American	767	773	AA vs. GG	0.74(0.55-0.99)	None with smoking, alcohol
		rs25489	Exon 9	Yin, G.	2012	Japanese	685	778	AG vs. GG	0.88(0.66-1.17)	<b>Interaction with alcohol drinking</b>
									AA vs. GG	3.07(0.80-11.79)	
		rs25487	Exon 10	Zhang, S. H.	2014	Chinese	247	300	AG vs. GG	0.74 (0.52-1.07)	<b>Interaction with smoking</b>
AA vs. GG	1.06 (0.58-1.93)										
Poomphakwaen	2014			Thai	230	230	AG vs. GG	1.28(0.86-1.90)	<b>Interaction with smoking and drinking</b>		
							AA vs. GG	<b>4.96(1.90-12.95)</b>			
Przybylowska	2013			Polish	182	245	AG vs. GG	1.31(0.81-2.20)	N.A.		
							AA vs. GG	<b>2.03(1.23-3.97)</b>			
Procopciuc	2013			Romanian	150	162	AG vs. GG	<b>1.75(1.09-2.82)</b>	N.A.		
							AA vs. GG	<b>3.49(1.55-8.02)</b>			
Yin, G.	2012			Japanese	685	778	AG vs. GG	1.13(0.91-1.41)	None with alcohol drinking		
							AA vs. GG	<b>1.57(1.01-2.42)</b>			
Zhao, Y.	2012			Chinese	485	970	AG vs. GG	<b>1.33(1.02-1.68)</b>	N.A.		
							AA vs. GG	<b>2.47(1.63-3.50)</b>			
Wang, J.	2010			Indian	302	291	AG vs. GG	1.41(0.99-2.03)	<b>Interaction with drinking</b>		
							AA vs. GG	1.20(0.71-2.03)			
Jelonek, K.	2010	Polish	113	153	A allele vs. G allele	<b>1.51(1.07-2.15)</b>	N.A.				
Stern, M. C.	2005	American	753	799	AG vs. GG	1.1(0.9-1.3)	N.A.				
					AA vs. GG	<b>0.7(0.5-1.0)</b>					
Hong, Y. C.	2005	Korean	209	209	AG vs. GG	<b>2.18(1.23-3.88)</b>	N.A.				
					AA vs. GG	1.03(0.31-3.67)					
(AG+AA) vs. GG						<b>2.00(1.15-3.47)</b>					
	Krupa, R.	2004	Polish	51	100	AG vs. GG	<b>0.73(0.55-0.95)</b>	N.A.			
AA vs. GG						1.13(0.85-2.34)					
Abdel-Rahman	2000	Egyptian	48	48	AG vs. GG	<b>3.92(1.40-11.20)</b>	N.A.				
					AA vs. GG	4.20(0.63-34.90)					
OGG1 rs1052133	3p26.2 Exon 7	Zhang, S. H.	2014	Chinese	247	300	CG vs. CC	0.86(0.53-1.40)	None with smoking, alcohol or BMI		
							GG vs. CC	0.91(0.56-1.50)			
		Przybylowska	2013	Polish	182	245	CG vs. CC	<b>1.83(1.21-2.70)</b>	N.A.		
							GG vs. CC	1.04(0.23-4.81)			
		Canbay, E.	2011	Turkish	79	247	G allele vs. C allele	<b>2.77(1.40-5.48)</b>	N.A.		
		Pardini, B.	2008	Czech	532	532	CG vs. CC	0.91(0.70-1.18)	<b>Interaction with smoking</b>		
							GG vs. CC	1.43(0.79-2.59)			
		(CG+GG) vs. CC						0.96(0.75-1.23)			
			Moreno, V.	2006	Spanish	377	329	GG vs. CC	<b>2.31(1.05-5.09)</b>	N.A.	
		Hansen, R.	2005	Norwegian	166	397	CG vs. CC	0.56(0.32-0.97)	N.A.		
							GG vs. CC	0.57(0.17-1.83)			
		Ching-Yu Lai	2016	Taiwanese	727	736	CG vs. CC	<b>1.51 (1.11-2.05)</b>			
GG vs. CC	1.23 (0.90-1.69)										

Variables	Location	Author	Year	Population	Case	Control	Genotypes	OR(95%CI)	Interaction
APE1	14q11.2						(CG+GG) vs. CC	1.38 (1.03-1.85)	
rs1130409	Exon 5	Zhang, S. H.	2014	Chinese	247	300	GT vs. TT	0.94(0.64-1.38)	None with smoking, alcohol or BMI
		Li, Y.	2013	Chinese	451	631	GG vs. TT	2.41(1.50-3.89)	
		Canbay, E.	2011	Turkish	79	247	GT vs. TT	1.10(0.83-1.49)	N.A.
		Jelonek, K.	2010	Polish	113	153	GG vs. TT	1.13(0.77-1.66)	N.A.
		Kasahara, M.	2008	Japanese	68	121	G allele vs. T allele	3.43(1.76-6.7)	N.A.
		Berndt, S. I.	2007	American	767	773	T allele vs. G allele	2.00(1.39-2.87)	N.A.
							(GT+GG) vs. TT	2.33(1.21-4.48)	N.A.
							GT vs. TT	1.33(1.04-1.69)	None with smoking, alcohol
							(GG+GT) vs. TT	1.27(1.01-1.60)	
rs2307486	Exon 3	Kabzinski, J.	2015	Polish	150	150	AG vs. GG	2.07(1.21-3.55)	N.A.
							AA vs. GG	1.34(0.72-2.51)	
rs1760944	Promoter	Zhang, S. H.	2014	Chinese	247	300	TG vs. TT	0.75(0.51-1.10)	<b>Interaction with BMI</b>
							GG vs. TT	0.78(0.49-1.25)	
PARP1	1q41-q42								
rs1136410	Exon 17	Li, Y.	2013	Chinese	451	631	ValAla vs. ValVal	1.19 (0.89-1.59)	N.A.
							AlaAla vs. ValVal	1.75 (1.20-2.57)	
							AlaAla vs. (ValAla+ValVal)	1.57 (1.12-2.20)	
rs3219145	Exon 21	Stern, M. C.	2007	Chinese	310	1176	(CT+CC) vs. TT	0.584(0.387-0.881)	N.A.
							LysArg vs. LysLys	1.7(1.0-3.0)	
							ArgArg vs. LysLys	7.0(0.6-84)	
MUTYH	1p34.1								
rs2275602	Intron 1	Tao, H.	2008	Japanese	685	778	(CT+TT) vs. CC	1.46(1.02-2.07)	N.A.
rs3219487	Intron 5	Tao, H.	2008	Japanese	685	778	AG vs. GG	1.14(0.88-1.49)	N.A.
							AA vs. GG	0.97(0.32-2.93)	
IVS10 -2A/G		Tao, H.	2008	Japanese	685	778	(AG+GG) vs. AA	0.67(0.39-1.14)	N.A.
rs3219489	Exon 12	Przybylowska	2013	Polish	182	245	CG vs. CC	2.69(1.47-4.94)	N.A.
							GG vs. CC	3.35(1.80-6.49)	
		Kasahara, M.	2008	Japanese	68	121	(CG+GG) vs. CC	3.53(1.44-8.70)	N.A.
		Tao, H.	2008	Japanese	685	778	CG vs. GG	0.96(0.75-1.22)	N.A.
							CC vs. GG	0.90(0.67-1.22)	
FEN1	11q12								
(-69 A/G)	Promoter	Liu, L.	2012	Chinese	126	162	AG vs. AA	1.35(0.70-2.72)	N.A.
							GG vs. AA	1.60(0.79-3.44)	
rs4246215	3'UTR	Liu, L.	2012	Chinese	126	162	GT vs. TT	1.35(0.65-2.74)	N.A.
							GG vs. TT	1.58(0.77-3.44)	
POLB	8p11.2								
rs3136797	Exon 9	Moreno, V.	2006	Spanish	377	329	(+/-) vs. (+/+)	0.23(0.05-0.99)	N.A.

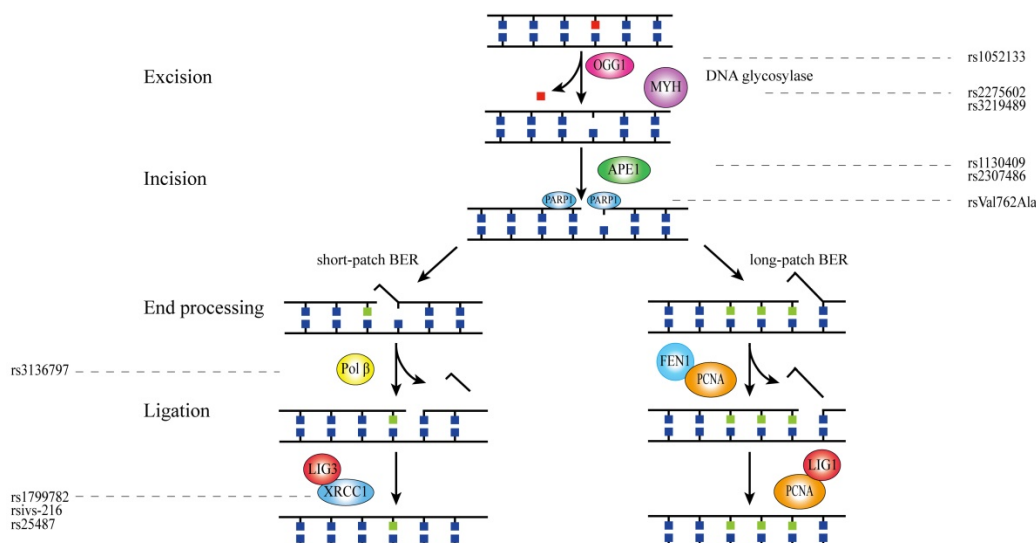


Figure 1. BER pathway gene polymorphisms and sporadic CRC susceptibility.

Only *XPA* rs1800975 polymorphism in 5'UTR has been investigated by two studies. Joshi, A. D. et al. explored 301 CRC cases and 362 controls of American population but found no significant relation of this polymorphism with CRC risk[62]. Similarly, Hansen, R. D. et al. found no significant association in 397 CRC cases and 800 controls in Denmark[63].

### **XPC**

*XPC*, mapped to chromosome 3p25.1, consists of 18 exons and is one of the eight core genes in NER system. *XPC* contributes to damage sensing as well as single-stranded DNA binding during NER process [64].

Polymorphism of rs2228001 (Lys939Gln) in exon 16 has been studied in relation with CRC susceptibility in Malaysian[65], Chinese[66, 67], Turkish[17], Czech[25] and Denmark[63]. Liu, D. et al.'s research in Chinese revealed that AC and (AC+CC) genotype of rs2228001 polymorphism were both related with increased CRC risk compared with wild-type AA genotype[66]. Ahmad Aizat, A. A. et al. found that CC genotype significantly increased the risk of CRC in Malaysian population[65]. Similar correlation was confirmed by Mucha, B. et al.'s study in Polish, which also found significant increased CRC risk of CC genotype[68]. Although no significant relation was found between rs2228001 polymorphism and CRC risk, significant interaction of this polymorphism with red meat was found to increase CRC risk by Hansen, R. D. et al.[63]. For rs2279017 A/C polymorphism at intron 11, Gil, J. et al. suggested increased CRC risk of AC genotype in Polish[69] while another study in American did not find any significant result[62]. The results of rs2228000 C/T polymorphism were still inconclusive: Sun, K. et al.'s study in Chinese[70] and Paszkowska-Szczur, K. et al.'s study in Polish[71] suggested that C allele was the risk allele. However, Steck, S. E. et al. [72] revealed that T allele was the risk allele. In addition, Rui-Xi Hua et al. did not find significant association between rs2228000 polymorphism and CRC risk[67].

### **DNA damage unwinding related NER polymorphisms**

#### ***XPD (ERCC2)***

*XPD*, located at 19q13.32, contains 24 exons and encodes a protein which participates in transcription-coupled repair of NER. *XPD* contributes to the DNA unwinding as well as the damaged DNA fragments excision[61].

Two most frequently studied *XPD* SNPs are polymorphisms of rs1799793 A/G in exon 10 and rs13181 A/C in exon 22. For rs1799793 polymorphism, Paszkowska-Szczur, K. suggested that both AG

genotype and AA genotype were associated with increased risk of CRC compared with wild-type GG genotype in Polish[71]. However, several other investigations did not find similar results in populations of Polish[73], Chinese[22, 74, 75], American[62] or Denmark[63]. Controversies still exist concerning the role of rs13181 polymorphism in relation to CRC susceptibility. Two researches indicated that CC genotype of rs13181 polymorphism was associated with increased risk of CRC compared with the AA genotype in Polish[73] and Romanian[45], respectively. However, Rezaei, H. et al. [76] and Stern, M. C. et al.[77] obtained the opposite conclusion that CC genotype was related with decreased CRC risk in American as well as Iranian. In addition, Stern, M. C. et al. found significant interaction of AC and AA genotype of rs13181 polymorphism with alcohol intake in increasing susceptibility of CRC. In addition, Gil, J. et al. found that the (AC+AA) genotype was associated with decreased CRC susceptibility in Polish[69]. Although many other studies investigated the relation between the rs13181 polymorphism and CRC risk in multiple populations[17, 22, 25, 41, 54-56, 62, 63, 74, 75, 78, 79], no significance was found. For rs3810366 polymorphism in promoter, only one team explored the association of this SNP with CRC susceptibility but observed no significance in Chinese [75].

#### ***RPA2 and GTF2H1***

*RPA2* is located at chromosome 1p35.3, encoding a subunit of the heterotrimeric complex RPA which protects single-stranded DNA from nucleases. This heterotrimeric complex binds to single-stranded DNA and contributes to the formation of nucleoprotein complex which plays a key role in DNA unwinding [80]. *GTF2H1* is mapped to chromosome 11p15.1, comprising 17 exons and 16 introns. *GTF2H1* encodes a member of core-TFIIB basal transcription factor which is involved in transcription initiation and NER pathway[81].

Naccarati, A. et al. found that GG and CG carriers of *GTF2H1* rs4596 polymorphism was associated with 0.79 fold decreased CRC risk compared with CC genotype carriers in Czechs [81]. They also observed that the GG genotype of *RPA2* rs7356 in 3'UTR region was associated with increased risk of CRC compared with AG and AA genotype. Importantly, *RPA2* protein was widely expressed in CRC and miRNA reduced *RPA2* expression by preferentially binding to variant G allele of rs7356 polymorphism. These findings partially explained the reason why rs7356 G allele was associated with decreased CRC susceptibility.

## DNA damage incision related NER polymorphisms

### ERCC1

*ERCC1*, located at 19q13.32, contains 14 exons and the protein encoded by this gene assembles XPF to form a heterodimer. The heterodimer endonuclease promotes the 5' incision in repairing DNA lesion as well as contributes to DNA recombination repair and inter-strand crosslinks repair[82].

For *ERCC1* rs2298881 A/C polymorphism in intron 1, Yang, H. et al.[83] suggested that the CC genotype was related with increased CRC risk compared with AA genotype in Chinese. They found no significant relation of rs11615 C/T polymorphism in exon 4 with CRC susceptibility in Chinese while another team obtained different result. Te-Cheng Yueh. et al.[84] found that the TT genotype of rs11615 C/T polymorphism was associated with 1.86-fold increased CRC risk compared with CC genotype in Chinese. Significant relation between AA genotype of rs3212986 A/C polymorphism in 3'UTR region and increased CRC risk was observed compared with CC genotype[74, 85] in Chinese but no significance was found in American[62]. Importantly, significant interaction was indicated in increasing risk of CRC between TT genotype of rs3212986 polymorphism and cigarette smoking[82]. Additionally, Dai, Q. et al. found that the AA genotype of rs2336219 A/G polymorphism in 3'UTR correlated with increased risk of CRC compared with wild-type GG genotype in Chinese [39]. A number of researches investigated rs11615 C/T polymorphism in CRC susceptibility but indicated no significance in Chinese and Norwegian population[74, 82-84, 86].

### XPF (ERCC4)

*XPF*, located at 16p13.12, contains 13 exons and 12 introns, spanning approximately 28.2 kb. Its encoding protein XPF forms a complex with *ERCC1*, which is responsible for the 5' incision of DNA damage repair[82].

For polymorphisms of *XPF* rs2276466 C/G in 3'UTR and rs6498486 A/C in promoter, Hou, R. et al.[82] explored their relationships with CRC risk in Chinese population but indicated no significant association. Another team[83] found no significant association between the rs2276466 C/G polymorphism and risk of CRC. Additionally, no significant association between rs1800067 polymorphism and CRC susceptibility was observed by Joshi, A. D. et al.[62] in American. The synonymous substitution of rs1799801 at exon 13 has been investigated by Kabzinski, J. et al.[87], the result of which indicated

that CT genotype correlated with decreased susceptibility of CRC compared with the CC genotype.

### XPG (ERCC5)

*XPG* is mapped to chromosome 13q33, encoding a structure-specific endonuclease XPG which is composed of 1186 amino acids. XPG contributes to the 3' incision of DNA damage and enables DNA repair complex to stabilize to the domain of damage DNA[61].

For polymorphism of *XPG* rs17655 C/G in exon 15, Du, H. et al.[88] found that the variation from G allele to C allele was associated with increased risk of CRC in Chinese. Additionally, another team observed that CG genotype of rs17655 polymorphism was related with 1.33-fold increased CRC susceptibility in Chinese compared with GG genotype[66]. In 1901 cases and 1976 controls, rs2094258, rs751402, rs2296147, rs1047768 and rs873601 polymorphisms of *ERCC1* were studied by Rui-Xi Hua et al.[89] in relation with CRC risk and most of the results demonstrated significance. In this research, they observed that four SNPs (rs2094258C/T in promoter, rs751402C/T in 5' UTR, rs1047768 C/T in exon 2 and rs873601 in 3'UTR) were associated with increased CRC risk, three of which (rs2094258, rs751402 and rs873601) also correlated with *XPG* mRNA expression. Other three studies suggested no significant association between rs17655 C/G polymorphism and risk of CRC in Chinese[70], American[62] or Czech[25]. For *XPG* 1558His/Asp polymorphism, Kabzinski, J. et al. failed to show significant association with susceptibility of CRC in Polish[73].

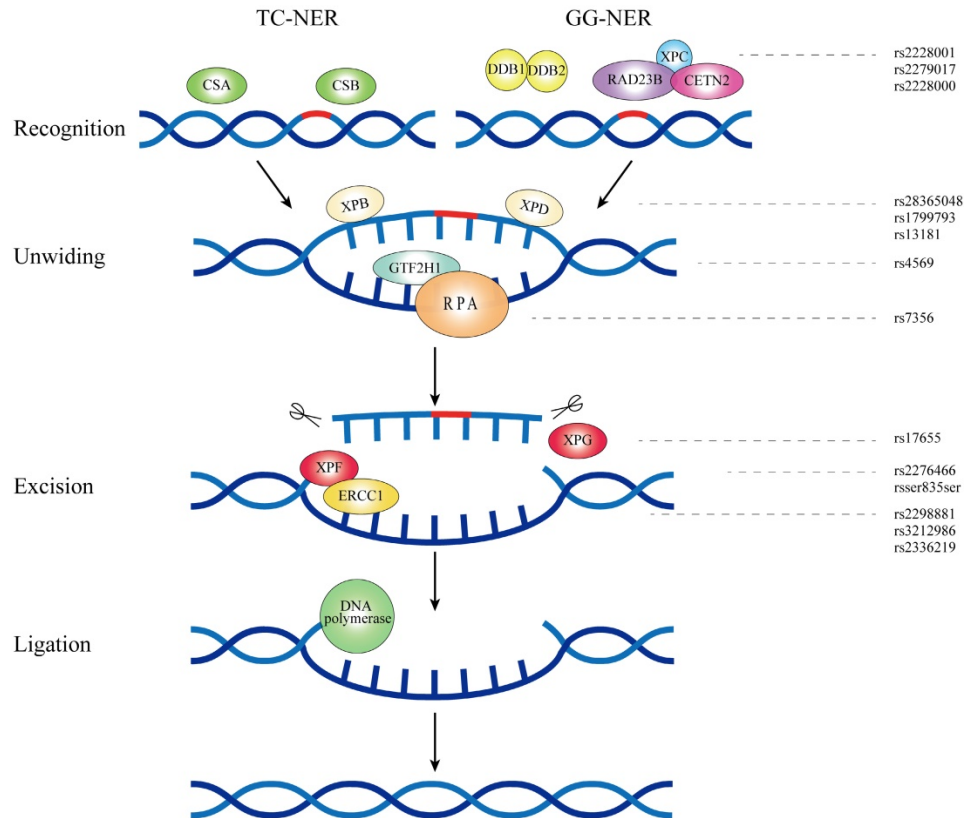
## MMR pathway gene polymorphisms and sporadic CRC susceptibility

DNA mismatch repair (MMR) is a highly conserved biological pathway that is involved in maintaining genomic stability[90]. MMR recognizes and corrects the biosynthetic errors aroused during DNA replication as well as the mispaired bases which is generated in DNA recombination or caused by oxidative DNA damage[91]. MMR decreases 100-1000 folds DNA errors and protects them from mutations during cellular proliferation[92]. Human MMR process is classified into four steps: (1) the mismatch recognition by MutS homologs (MSH2, MSH3 and MSH6) and recruitment of MutL homologs (MLH1, MLH3, PMS1 and PMS2); (2) strand discrimination to mark the erroneous DNA strand; (3) strand removal by unwinding and excision reactions (EXO1); (4) DNA-re-synthesis and ligation to complete the repair reaction[93].

**Table 2.** Significant association of NER pathway gene polymorphisms with sporadic CRC susceptibility.

Variables	Location	Author	Year	Population	Case	Control	Genotypes	OR(95%CI)	Interaction
XPC	3p25.1								
rs2228001	Exon 16	Ahmad Aizat	2013	Malaysian	255	255	AC vs. AA	1.27(0.87-1.84)	N.A.
							CC vs. AA	<b>1.88(1.08-3.28)</b>	
		Liu, D.	2012	Chinese	1028	1085	AC vs. AA	<b>1.40(1.16-1.69)</b>	N.A.
							CC vs. AA	0.98(0.84-1.13)	
							(AC+CC) vs. AA	<b>1.31(1.10-1.56)</b>	
		Hansen, R. D.	2007	Dane	397	800	AC vs. AA	1.08(0.83-1.42)	<b>Interaction with red meat</b>
							CC vs. AA	1.16(0.77-1.77)	
		Mucha, B.	2018	Polish	221	270	AC vs. AA	1.07(0.65-1.76)	N.A.
							CC vs. AA	<b>1.82(1.08-3.06)</b>	
rs2279017	Intron 11	Gil, J.	2012	Polish	133	100	AC vs. CC	<b>2.07(1.14-3.78)</b>	N.A.
rs2228000	Exon 9	Sun, K.	2015	Chinese	890	910	CT vs. TT	1.06(0.87-1.30)	N.A.
							CC vs. TT	<b>2.19(1.60-3.01)</b>	
		Paszowska	2015	Polish	758	1841	CT vs. CC	<b>0.59(0.49-0.72)</b>	N.A.
							TT vs. CC	<b>0.29(0.20-0.41)</b>	
		Steck, S. E.	2014	African American	244	331	CT vs. CC	<b>1.7(1.1-2.6)</b>	N.A.
rs1799793	Exon 10	Paszowska	2015	Polish	758	1841	AG vs. GG	<b>1.92(1.41-2.62)</b>	N.A.
							AA vs. GG	<b>6.92(4.61-10.36)</b>	
rs13181	Exon 22	Kabzinski, J.	2015	Polish	235	240	AC vs. AA	0.60(0.35-1.02)	N.A.
							CC vs. AA	<b>14(6.31-31.05)</b>	
		Rezaei, H.	2013	Iranian	88	88	AC vs. AA	1.33(0.68-2.62)	N.A.
							CC vs. AA	<b>0.10(0.03-0.30)</b>	
		Procopciuc	2013	Romanian	150	162	AC vs. AA	1.49(0.91-2.44)	N.A.
							CC vs. AA	<b>3.02(1.15-8.25)</b>	
		Gil, J.	2012	Polish	133	100	(AC+CC) vs. AA	<b>0.45(0.22-0.91)</b>	N.A.
		Stern, M. C.	2006	American	753	799	AC vs. AA	1.0(0.8-1.2)	<b>Interaction with smoking or drinking</b>
							CC vs. AA	<b>0.7(0.4-1.0)</b>	
XPF(ERCC4)	16p13.12								
Ser835Ser	Exon 15	Kabzinski, J.	2015	Polish	146	149	CT vs. CC	<b>0.57(0.34-0.98)</b>	N.A.
							TT vs. CC	1.12(0.60-2.07)	
XPG(ERCC5)	13q33								
rs17655	Exon 15	Sun, K.	2015	Chinese	890	910	CG vs. GG	1.01(0.80-1.26)	N.A.
							CC vs. GG	1.12(0.85-1.47)	
		Du, H.	2014	Chinese	878	884	CG vs. GG	<b>1.41(1.15-1.74)</b>	N.A.
							CC vs. GG	<b>1.34(1.00-1.79)</b>	
							(CG+CC) vs. GG	<b>1.40(1.15-1.70)</b>	
		Liu, D.	2012	Chinese	1028	1085	CG vs. GG	<b>1.33(1.09-1.63)</b>	N.A.
							CC vs. GG	0.93(0.81-1.06)	
							(CG+CC) vs. GG	1.20(0.99-1.46)	
rs2094258	Promoter	Rui-Xi Hua	2016	Chinese	1901	1976	CT vs. CC	<b>1.17(1.01-1.36)</b>	
							TT vs. CC	<b>1.49(1.18-1.89)</b>	
rs751402	5'UTR	Rui-Xi Hua	2016	Chinese	1901	1976	CT vs. CC	<b>0.82(0.70-0.96)</b>	
							TT vs. CC	<b>0.69(0.55-0.86)</b>	
rs1047768	Exon 2	Rui-Xi Hua	2016	Chinese	1901	1976	TC vs. TT	1.00(0.86-1.16)	
							CC vs. TT	<b>1.33(1.01-1.75)</b>	
rs873601	3'UTR	Rui-Xi Hua	2016	Chinese	1901	1976	AG vs. GG	<b>1.18(1.00-1.40)</b>	
							AA vs. GG	<b>1.41(1.15-1.72)</b>	
ERCC1	19q13.32								
rs2298881	Intron 1	Yang, H.	2015	Chinese	279	316	AC vs. AA	1.37(0.91-1.92)	N.A.
							CC vs. AA	<b>2.68(1.47-4.75)</b>	
		Hou, R.	2014	Chinese	204	204	AC vs. AA	1.08(0.71-1.74)	N.A.
							CC vs. AA	1.45(0.64-3.46)	
rs11615	Exon 4	Te-Cheng Y.	2017	Chinese	362	362	CT vs. CC	1.06 (0.77-1.46)	
							TT vs. CC	<b>1.86 (1.20-2.87)</b>	
rs3212986	3'UTR	Ni, M.	2014	Chinese	213	240	AC vs. CC	1.47(0.99-2.18)	None with smoking or drinking
							AA vs. CC	<b>2.50(1.10-5.70)</b>	
		Hou, R.	2014	Chinese	204	204	GT vs. GG	1.26(0.81-2.03)	<b>Interaction with smoking</b>
							TT vs. GG	1.93(0.96-3.94)	
		Zhang, Q.	2018	Chinese	200	200	AC vs. CC	1.20(0.79-1.81)	N.A.
							AA vs. CC	<b>2.53(1.14-5.60)</b>	
rs2336219	3'UTR	Dai, Q.	2015	Chinese	438	438	AG vs. GG	1.34(0.88-1.77)	N.A.
							AA vs. GG	<b>1.46(1.14-2.43)</b>	
RPA2	1p35.3								
rs7356	3'UTR	Naccarati	2012	Czech	1098	1469	GG vs. (AG+AA)	<b>1.33(1.01-1.75)</b>	N.A.
GTF2H1	11p15.1								
rs4596	3'UTR	Naccarati	2012	Czech	1098	1469	(CG+GG) vs. CC	<b>0.79(0.64-0.99)</b>	N.A.





**Figure 2.** NER pathway gene polymorphisms and sporadic CRC susceptibility.

## MutS homologs related MMR polymorphisms

### MSH2

*MSH2* is located at chromosome 2p21-p16.3, consisting of 21 exons and 20 introns. *MSH2* participates in the formation of two heterodimeric complexes of MutS $\alpha$  and MutS $\beta$  which are involved in insertion-deletion loops in DSB[94].

In Chinese population, Li, G. et al.[95] found that CT genotype of *MSH2* IVS15-214 polymorphism was associated with decreased risk of CRC compared with TT genotype. They observed that the AG genotype of IVS11+107 polymorphism were related with decreased CRC susceptibility compared with AA genotype. Importantly, significant gene-environment interactions were detected of both C allele of IVS15-214 polymorphism and GG genotype of IVS11+107 polymorphism with cereals intake in decreasing CRC susceptibility. In addition, TT genotype of rs1981928 polymorphism was correlated with 0.78 fold reduced CRC risk in English[96]. For rs4987188 polymorphism, several researches showed no significant association with CRC risk in American[62], Canadian[97] or Polish[98]. No significant relationship was observed of another two SNPs of -118 T/C[99] and IVS12-6 T/C[97] polymorphisms with CRC risk in Canadian population.

### MSH3

*MSH3*, also known as *DUP*, *FAP4* and *MRP1*, is located at 5q14.1 and consists of 24 exons. *MSH3* cooperates with *MSH2* to form a heterodimer MutS $\alpha$  which binds to a mismatch and activates the MMR pathway[93].

Only one study by Koessler, T. et al.[96] explored the association between *MSH3* rs1979005 C/T polymorphism and CRC risk and found that the TT genotype was associated with decreased risk of CRC compared with CC genotype in English. They observed that the GG genotype of rs26279 A/G polymorphism in exon 23 correlated with 1.31 folds increased risk of CRC compared with wild-type AA genotype.

### MSH6

*MSH6* is mapped to chromosome 2p16.3 and encodes a MutS family protein which contributes to the mismatched nucleotides recognition before repair. Together with *MSH2*, *MSH6* forms a mismatch recognition heterodimer complex which adjusts the function of MMR by exchanging ATP and ADP when DNA mismatches are bound and divided[94].

For *MSH6* rs1042821 G/A polymorphism in exon 1, significant association was found of the AG

genotype with increased CRC risk compared with GG genotype in Polish [100] but another team failed to observe significance in mixed population [101]. However, Tulupova, E. et al. found that GA and AA genotype of the same rs1042821 polymorphism in promoter correlated with decreased CRC susceptibility compared with GG genotype in Czech population, the reason of which might be that rs1042821 played different roles in variant transcripts. They also observed that T-allele carriers of *MSH6* rs3136228 polymorphism in promoter were associated with increased risk of CRC in Czechs compared with carriers of GG genotype [102]. For *MSH6* -159C/T promoter polymorphism, Mrkonjic, M. et al. showed no significance in Canadians [99].

### MutL homologs related MMR polymorphisms

#### *MLH1* and *PMS2*

*MLH1*, located at 3p22.2, contains 21 exons and *PMS2* is mapped to 7p22.1, consisting of 16 exons and 15 introns. *MLH1* and *PMS2* form a MutL-alpha heterodimer which manages the activity of endonuclease involved in mismatches recognition and loops insertion or deletion [103]. In addition, MutL-alpha heterodimer also plays a key role in mismatched DNA removal [103].

For *MLH1* rs1800734 A/G polymorphism in promoter, A allele was found to significantly reduce the risk of CRC compared with G allele in Polish [98], Spanish [104] and Mexican population [51]. However, Nizam, Z. M. suggested that AG genotype was associated with 3.71 folds increased CRC risk compared with GG genotype in Malaysian [105]. Other two researches also investigated the relation of rs1800734 polymorphism with CRC risk but no significance was shown in American [101] and Canadian [97]. For *MLH1* rs1799977 polymorphism in exon 8, Nejda, N. et al. observed that both AG and GG genotype were associated with increased risk of CRC compared with AA genotype in Spanish [106]. But other teams failed to find significance in Mexican [51], American [62, 101] or Canadians [97]. Only Raptis, S. et al. studied *MLH1* IVS14-19A>G polymorphism but did not obtain significant result [97]. Although H.X. Peng et al. studied the relation of *V384D*, *R217C* and rs1799977 polymorphisms with CRC risk, the samples of each genotypes were insufficient to draw reliable conclusion [107]. For *PMS2* rs63750451 polymorphism in exon 9, one team explored its relation with CRC risk but show no significance in Polish [100].

### DNA nicking related MMR polymorphisms

#### *EXO1*

*EXO1*, mapped to 1q42-q43, consists of 17 exons

and encodes a protein with 5' to 3' exonuclease activity and RNase H activity, which participates in DNA nicking of MMR. Additionally, *EXO1* is the only known active nuclease in human cells MMR [93].

For *EXO1* rs9350 polymorphism in exon 14, Haghghi, M. M. et al. found that CT genotype was associated with 0.17-fold decreased CRC susceptibility compared with CC genotype in Iranian [108]. Another team observed that C allele of rs9350 significantly increased the risk of CRC compared with T allele in American [109]. Importantly, they showed a significant interaction between C allele of rs9350 polymorphism and cigarette smoking in increasing CRC risk.

### DSBR pathway gene polymorphisms and sporadic CRC susceptibility

DNA double-strand breaks (DSBs) are highly toxic lesions which result in genetic instability [110]. To preserve genome integrity, a number of DSBR reactions exist in organisms, of which non-homologous end-joining (NHEJ) and homologous recombination (HR) are the two most widely used systems [111]. NHEJ is regarded as an error-prone manner and utilizes limited or no homologous DNA for end joining. Bound to the damaged DNA ends to initiate NHEJ, the Ku70/80 heterodimer recruits and triggers the DNA-dependent protein kinase catalytic subunit (DNA-PKcs) which facilitates the downstream repair processes. Then, scaffold proteins XRCC4 and XLF move to the defect domain and combine with DNA Ligase 4 for repairing the lesions [111, 112]. In contrast, HR is largely error free and requires extensive homology for the repair of DNA DSBs. After the recognition of DSBs in HR, the resection of DSBs is completed by the MRE11/RAD50/NBS1 complex which then generates a 3' ssDNA overhang. *BRCA2*, *RAD51* as well as *RAD51* paralogous (*Rad51C*, *Rad51D*, *XRCC2*, *XRCC3*) bind to the ssDNA tails and form a presynaptic filament. Subsequently, the formation of D loop in strand invasion is initialized and DSBs were repaired by structure-specific nucleases [113].

### Homologous recombination (HR)

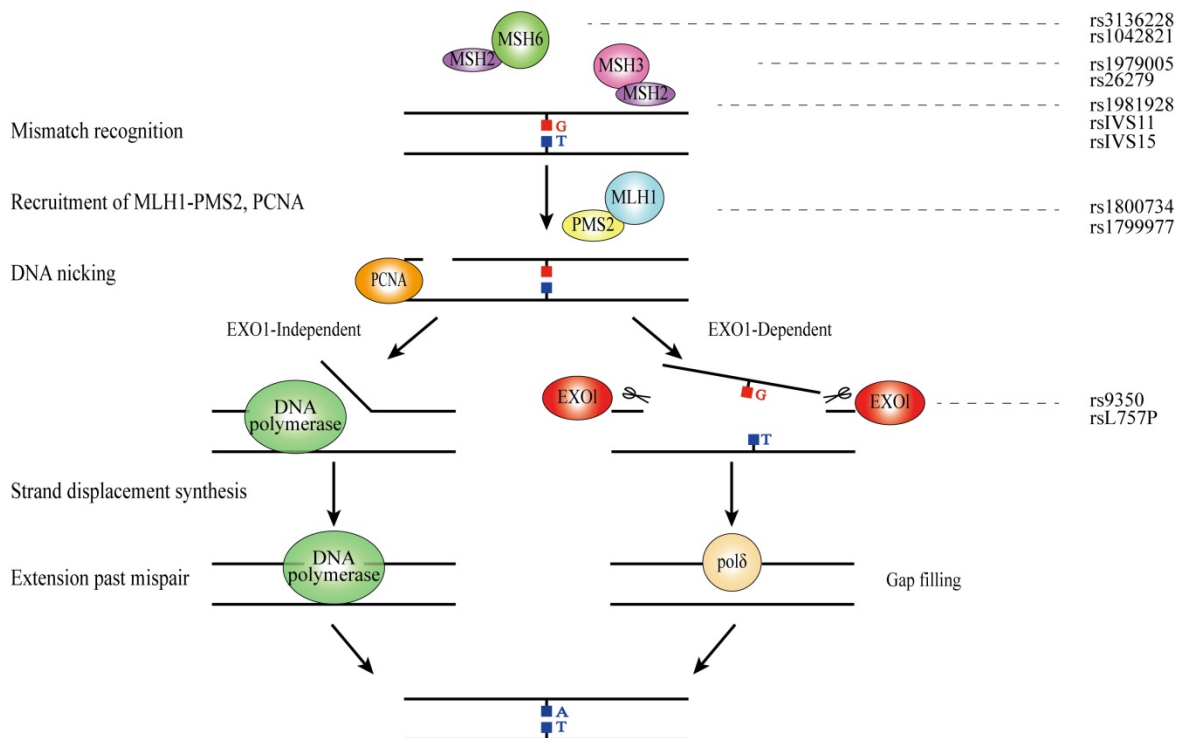
#### End resection related DSBR polymorphisms

##### *MRE11* and *NBS1*

*MRE11*, located at chromosome 11q21, contains 22 exons and encodes a protein with 3' to 5' exonuclease and endonuclease activity. *NBS1* is mapped to 8q21.3 and consists of 19 exons and 18 introns. Together with *MRE11* and *RAD50*, *NBS1* forms a complex involved in DNA ends resection, which generates 3' single-stranded tails in HR [114].

**Table 3.** Significant association of MMR pathway gene polymorphisms with sporadic CRC susceptibility.

Variables	Location	Author	Year	Population	Case	Control	Genotypes	OR(95%CI)	Interaction
MLH1 rs1800734	3p22.2 Promoter	Nizam	2013	Malaysian	52	104	AG vs. GG AA vs. GG	<b>3.71(1.42-9.74)</b> 2.36(0.88-6.31)	N.A.
		Michal Mik	2017	Polish	144	151	AG vs. AA GG vs. AA	1.09 (0.58-2.05) <b>2.07 (1.11-3.83)</b>	
		Martinez	2013	Spanish	183	236	AG vs. GG AA vs. GG	<b>0.58(0.39-0.86)</b> 1.16(0.35-3.91)	N.A.
		Muniz	2012	Mexican	108	120	AG vs. GG AA vs. GG	0.66(0.37-1.17) <b>0.32(0.13-0.79)</b>	N.A.
rs1799977	Exon 8	Nejda, N.	2009	Spanish	140	125	AG vs. AA GG vs. AA	<b>2.55(1.48-4.39)</b> <b>2.48(1.20-5.11)</b>	N.A.
V384D		H.X. Peng	2016	Chinese	156	311	AA AT TT	0.03 (0-0.24) <b>28.18 (3.81-∞)</b> ∞ (0-∞)	
MSH2 IVS15-214T>C	2p21-p16.3	Li, G.	2015	Chinese	451	630	CT vs. TT CC vs. TT	<b>0.62(0.46-0.83)</b> 0.89(0.62-1.26)	<b>Interaction for cereals</b>
IVS11+107A>G		Li, G.	2015	Chinese	451	630	AG vs. AA GG vs. AA	<b>0.61(0.42-0.88)</b> 0.76(0.52-1.10)	<b>Interaction for cereals</b>
rs1981928	Intron 7	Koessler, T.	2008	English	2299	2284	AT vs. AA TT vs. AA	1.05(0.93-1.18) <b>0.78(0.62-0.99)</b>	N.A.
MSH3 rs1979005	5q14.1 Intron 20	Koessler, T.	2008	English	2299	2284	CT vs. CC TT vs. CC	0.90(0.76-1.06) <b>0.41(0.18-0.94)</b>	N.A.
rs26279	Exon 23	Koessler, T.	2008	English	2299	2284	AG vs. AA GG vs. AA	1.04(0.92-1.17) <b>1.31(1.05-1.62)</b>	N.A.
MSH6 rs1042821	2p16.3 Exon 1	Piotr Zelga	2017	Polish	200	200	AG vs. GG AA vs. GG	<b>1.69 (1.1-2.61)</b> 2.08 (0.52-8.42)	
rs3136228	Promoter	Tulupova	2008	Czech	614	614	(GT+TT) vs. GG	<b>1.29(1.02-1.62)</b>	N.A.
rs1042821	Promoter	Tulupova	2008	Czech	614	614	(GA+AA) vs. GG	<b>0.76(0.60-0.98)</b>	N.A.
EXO1 rs9350	1q42-q43 Exon 14	Haghighi	2010	Iranian	90	98	CT vs. CC TT vs. CC	<b>0.17(0.03-0.82)</b> 0.69(0.37-1.28)	N.A.
		Gao, Y.	2011	American	1338	1503	C allele vs. T allele	<b>1.30(1.11-1.51)</b>	<b>Interaction with smoking</b>



**Figure 3.** MMR pathway gene polymorphisms and sporadic CRC susceptibility.

Naccarati, A. et al. found that CC genotype of *MRE11* rs2155209 polymorphism was associated with decreased risk of CRC compared with TT genotype in Italian[115]. However, they did not find significant relation between CT genotype of *NBS1* rs14448 polymorphism and CRC risk. For *NBS1* rs2735383 polymorphism, Li, J. T. et al. observed that CC genotype correlated with increased CRC susceptibility compared with GG genotype in Chinese[116]. In addition, no significant association was found of *NBS1* rs1805794 polymorphism in exon 5 with CRC susceptibility in Czech population[25].

### Strand invasion and exchange related DSBR polymorphisms

#### *XRCC2*

*XRCC2* is located at chromosome 7q36.1 and comprises three exons and two introns. *XRCC2* protein improves the activity of *RAD51* which is involved in strand invasion and exchange reactions in HR[117].

Li, X. B. et al. demonstrated significant association of *XRCC2* rs718282 polymorphism with increased CRC risk in Chinese but no significance was found for rs3218384 polymorphism[117]. For *XRCC2* rs3218499 polymorphism, Curtin, K. observed that CC genotype correlated with increased CRC risk compared with CG and GG genotypes in the mixed population of English and American[118]. Additionally, two researches failed to find significant relationship between rs3218536 polymorphism in exon 3 and CRC susceptibility in Polish [119] and American[120].

#### *XRCC3*

*XRCC3*, also known as *CMM6*, is located at chromosome 14q32.3 and contains 10 exons. *XRCC3* encodes a member of Rad51-related proteins which function in the maintenance of chromosome stability and initiation of homologous sequence strand invasion[121].

Controversial results were found for the association between *XRCC3* rs861539 C/T polymorphism and CRC risk. Zhao, Y. et al. observed that T allele was a risk factor for CRC in Chinese[44] but C allele indicated higher CRC risk according to Mort, R. et al.'s study in English[122]. Other two teams suggested that CT genotype was related with increased CRC risk compared with CC genotype in Kashmirian[123] and Chinese[121], respectively. However, Mucha, B. et al. suggested that CT genotype significantly decreased CRC risk in Polish[124]. Krupa, R. et al. found that CT genotype significantly decreased risk of CRC but TT genotype correlated with increased susceptibility of CRC in Polish[48]. In addition, some other researches failed to indicate significant association of rs861539 polymorphism

with CRC risk in Algerian[78], Polish[119], Indian[54], Czech[25], Chinese[55], Norwegian[41] or American [47, 120]. For rs1799794 and rs1799796 polymorphisms of *XRCC3*, no significant relation was observed in American[120].

#### *RAD51*

*RAD51*, located at chromosome 15q15.1, contains 14 exons and encodes *RAD51* which interacts with *BRCA1* and *BRCA2* in response to the DNA damage in DSBR. *RAD51* also cooperates with *RAD51* paralogues to handle the strand transfer of DNA in HR[112].

For *RAD51* rs1801320 polymorphism, Krupa, R. et al. found that CC genotype was related with decreased CRC risk compared with GG genotype in Polish[119] but another team obtained an opposite conclusion in the same population[125]. Nissar, S. et al. suggested that CG genotype was a risk genotype of CRC in Kashmiri[126]. No significant association was found in Yazdanpanahi, N. et al.'s study of *RAD51* rs1801320 polymorphism in Iranian[127]. One research investigated the relationship between *RAD51* 172G/T polymorphism and CRC risk in Polish but no significance was found[125]. Mucha, B. et al. indicated that AG genotype of rs5030789 promoter polymorphism was associated with increased CRC susceptibility [128] but no significant association was observed for rs2619679 [128] or rs1801320 polymorphism[129].

#### *RAD52*

*RAD52* is located at chromosome 12p13.33 and contains 17 exons and 16 introns. *RAD52* works as a mediator alone in HR or interacts with *RAD51* to participate in the strand invasion and exchange in human cells[112].

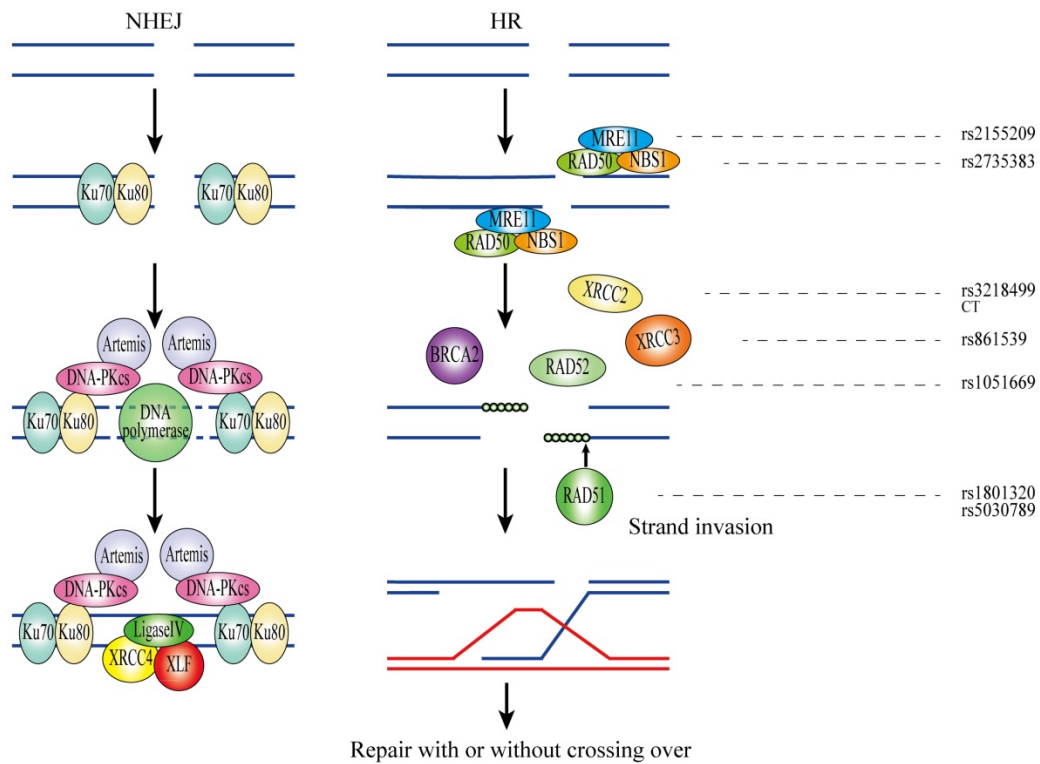
Although the relation was studied between several *RAD52* SNPs and CRC risk, only Naccarati, A. et al. found that AA genotype of *RAD52* rs1051669 polymorphism significantly increased CRC risk compared with GG genotype in Italian [130]. For rs11571378, rs7963551, rs6489769 and rs10774474 polymorphisms, no significance was found in relation with CRC susceptibility[130, 131].

### Non-homologous end-joining (NHEJ)

#### End ligation related DSBR polymorphisms

#### *XRCC4*

*XRCC4*, also known as *SSMED*, is mapped to chromosome 5q14.2 and consists of 13 exons and 12 introns. Together with *XLF*, scaffold protein *XRCC4* binds DNA ligase IV in order to seal the breaks in NHEJ[112]. Emami, N. studied the relationship of *XRCC4* rs6869366 and rs28360071 polymorphisms with CRC risk in Iranian population but demonstrated no significance[132].



**Figure 4.** DSBR pathway gene polymorphisms and sporadic CRC susceptibility.

**Table 4.** Significant association of DSBR pathway gene polymorphisms with sporadic CRC susceptibility.

Variables	Location	Author	Year	Population	Case	Control	Genotypes	OR(95%CI)	Interaction
XRCC2	7q36.1								
rs718282		Li, X. B.	2014	Chinese	246	262	(CT+TT) vs. CC	<b>1.65(1.13-2.40)</b>	N.A.
rs3218384	Promoter	Li, X. B.	2014	Chinese	246	262	(CG+CC) vs. GG	1.30(0.89-1.90)	N.A.
rs3218499	Intron 2	Curtin, K.	2009	U.K./U.S.	1252	1422	CC vs. (CG+GG)	<b>1.6(1.1-2.2)</b>	N.A.
XRCC3	14q32.3								
rs861539	Exon 7	Nissar, S.	2014	Kashmirian	120	150	CT vs. CC	<b>2.53 (1.37-4.66)</b>	N.A.
		Mucha, B.	2013	Polish	194	204	TT vs. CC	2.29(0.96-5.40)	N.A.
		Zhao, Y.	2012	Chinese	485	970	CT vs. CC	<b>1.82(1.24-2.93)</b>	N.A.
		Jin, M. J.	2005	Chinese	140	280	CT vs. CC	<b>3.25(1.42-7.42)</b>	None with smoking or drinking
		Krupa, R.	2004	Polish	51	100	CT vs. CC	<b>0.26(0.25-0.27)</b>	N.A.
							TT vs. CC	<b>9.45(8.77-11.65)</b>	
		Tranah, G. J.	2004	American	932	1282	CT vs. CC	0.95(0.78-1.16)	N.A.
							TT vs. CC	0.89(0.68-1.17)	
		Mort, R.	2003	English	246	256	C allele vs. T allele	<b>1.52(1.04-2.22)</b>	N.A.
NBS1	8q21.3								
rs2735383	3'UTR	Li, J. T.	2015	Chinese	1076	1263	CG vs. GG	1.13(0.97-1.41)	N.A.
							CC vs. GG	<b>1.68(1.31-2.13)</b>	
							CC vs. (CG+GG)	<b>1.55 (1.27-1.94)</b>	
rs14448	3'UTR	Naccarati, A.	2016	Italian	1111	1469	TC vs. TT	0.78 (0.51-1.19)	
RAD51	15q15.1								
rs1801320	5' UTR	Nissar, S.	2014	Kashmiri	100	120	CG vs. GG	<b>3.84(3.84-7.20)</b>	N.A.
							CC vs. GG	1.82(0.85-3.88)	
							(CG+CC) vs. GG	<b>3.0(1.6-5.3)</b>	
		Romanowicz	2012	Polish	320	320	CG vs. GG	0.60 (0.38-0.96)	N.A.
							CC vs. GG	<b>5.84 (3.76-9.09)</b>	
		Krupa, R.	2011	Polish	100	100	CG vs. GG	0.60(0.33-1.12)	N.A.
							CC vs. GG	<b>0.06(0.02-0.22)</b>	
rs5030789	Promoter	Mucha, B.	2015	Polish	115	118	AG vs. GG	<b>1.85(1.06-2.26)</b>	N.A.
							AA vs. GG	1.21(0.47-3.12)	
RAD52	12p13.33								
		Naccarati, A.	2016	Italian	1111	1469	GA vs. GG	1.09( 0.86-1.37)	

Variables	Location	Author	Year	Population	Case	Control	Genotypes	OR(95%CI)	Interaction
MRE11A rs2155209	11q21 3'UTR	Naccarati, A.	2016	Italian	1111	1469	AA vs.GG	<b>1.78 (1.13-2.80)</b>	N.A.
							(GA+AA) vs. GG	1.17 (0.93-1.46)	
							AA vs.(GG+GA)	<b>1.72( 1.10-2.69)</b>	
							CT vs. TT	0.94 (0.75-1.19)	
							CC vs.TT	<b>0.66 (0.45-0.96)</b>	
(TC+CC) vs TT	0.88 (0.70-1.09)								
							CC vs.(TT+TC)	<b>0.68 (0.47-0.97)</b>	

## Summary and Future Directions

Genetic polymorphisms in DNA repair genes may modulate DNA repair efficiency thereby influencing the development of sporadic CRC. In recent years, substantial progress has been made towards uncovering the genetic architecture of CRC, which offer great opportunity to benefit the understanding of sporadic CRC development. In this review, we summarized the genetic architecture of DNA repair genes involved in sporadic colorectal carcinogenesis as well as discussed the future directions of how genetic insights improve clinical surveillance, prevention and treatment strategies of sporadic CRC.

Previously, polymorphisms of BER core genes including *XRCC1*, *OGG1*, *APE1*, *PARP1*, *MUTYH* and *POLB* have been linked to altered CRC risk by multiple studies. Important genes involved in NER pathway of *XPC*, *XPD*, *XPF*, *XPG* and *ERCC1* all possess certain polymorphisms which significantly influence CRC susceptibility. For MMR system, key genes of *MLH1*, *MSH2*, *MSH3*, *MSH6* and *EXO1* demonstrated significant associations with CRC risk. As essential members of DSB repair pathway, *XRCC2*, *XRCC3*, *NBS1*, *RAD51*, *RAD52* and *MRE11A* polymorphisms showed involvement in the determination of CRC susceptibility. The observed significant associations of polymorphisms in BER, NER, MMR and DSB repair pathway core genes with sporadic CRC risk suggested an extensive implication of genetic polymorphisms of DNA repair pathways in colorectal carcinogenesis. The promising values of these polymorphisms in CRC prediction and prevention as well as their underlying mechanisms are of great importance. In addition, polymorphisms of DNA repair pathways might be applied in clinical outcomes to guide management of CRC patients. For example, *ERCC1* and *XRCC1* polymorphisms may influence the clinical outcome of colorectal cancer patients treated with mFOLFOX6 adjuvant chemotherapy[133]. Genetic polymorphisms of *MLH3* rs175057 as well as *MSH2* rs3771273, rs10188090 and rs10191478 may predict prognosis in patients with locally advanced rectal cancer who received preoperative chemoradiotherapy [134]. *XRCC3* Thr241Met polymorphism was associated with

time-to-metastasis of CRC[135]. The specific role of the summarized polymorphisms of our review in clinical application and underlying mechanisms required further studies to elucidate.

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## Competing Interests

The authors have declared that no competing interest exists.

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