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EGFR, *SMAD7*, and *TGFBR2* Polymorphisms Are Associated with Colorectal Cancer in Patients with Lynch Syndrome

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Abstract. *Background/Aim: Epidermal growth factor receptor (EGFR), mothers against decapentaplegic homolog 7 (SMAD7) and transforming growth factor betta (TGFB) are crucial for colorectal cancer (CRC) tumorigenesis. This study investigated whether polymorphisms in EGFR, SMAD7, and TGFB are associated with CRC risk in patients with Lynch syndrome. Materials and Methods: Genotyping was performed using Sequenom iPLEX MassArray. Association between genetic polymorphisms and CRC was assessed using a weighted Cox proportional hazard model. Results: Patients carrying the AA genotype of EGFR rs2227983 had a significantly higher CRC risk than those carrying the G allele (HR=2.55, 95% CI=1.25-5.17). The dominant model of SMAD7 rs12953717 (CT + TT genotypes) significantly increased CRC risk (HR=2.17, 95% CI=1.12-4.16) when compared to the wild-type CC genotype. Similarly, the GG genotype of TGFBR2 rs6785358 significantly increased the risk of CRC (HR=21.1, 95% CI=5.06-88.1) compared to the AA genotype. Conclusion: EGFR, SMAD7, and TGFBR2 are associated with CRC risk in patients with Lynch syndrome.*

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Lynch syndrome is a cancer predisposition disorder caused by a germline mutation in one of the mismatch repair (MMR) genes (1). MMR genes encode proteins that prevent both mutation and cancer development (2). Loss of function in MMR proteins usually results in error-prone DNA replication and microsatellite instability (MSI) (3). Approximately 1 in 3,140 individuals harbors a germline mutation in *MLH1* or *MSH2* and are at a higher risk of colorectal cancer (CRC) and other cancers than the general population (4, 5). Moreover, these patients exhibit an earlier onset of CRC and other cancers compared to the general population (6, 7).

Lichtenstein *et al*. estimated that 35% of inherited genetic factors are associated with CRC susceptibility (8). One of these genetic factors is the transforming growth factor beta (*TGFB*), whose mutations have been identified in colorectal tumors with MSI (9), a feature of Lynch syndrome. The TGFB signaling pathway is mediated *via* the TGFB receptor (TGFBR) or mothers against decapentaplegic homolog 7 (SMAD7) (9). Epidermal growth factor receptor (EGFR) inhibits *TGFB* signaling pathway through SMAD7 (10). Studies have reported that single nucleotide polymorphisms (SNPs) in *EGFR*, *SMAD7*, and *TGFB* are associated with cancer predisposition (11-13). More specifically, EGFR is involved in angiogenesis, metastasis, tumor invasion, and survival; TGFB plays a crucial role in cell proliferation, differentiation, and apoptosis, whereas SMAD7 is an

inhibitor of TGFB and other SMAD family members (14-16). Prior studies have indicated that *TGFBR2* rs3087465, *EGFR* rs2227983, and *SMAD7* rs12953717 SNPs are associated with CRC risk (17-20). By contrast, other studies have found non-significant associations between *EGFR* rs2227983, *SMAD7* rs2337104, and *SMAD7* rs12953717 SNPs and CRC (21-23).

CRC is a heterogeneous disease caused by numerous biological interactions of different signaling pathways. Therefore, as part of an initiative to identify genetic factors associated with CRC susceptibility in patients with Lynch syndrome, this study investigated whether *EGFR* rs2227983, *SMAD7* (rs12953717 and rs2337104), *TGFB1* (rs1800468 and rs1800489), *TGFBR1* rs334354, and *TGFBR2* (rs3087465 and rs6785358) SNPs are associated with CRC susceptibility in patients with Lynch syndrome in Taiwan.

Materials and Methods

Study population. Using the Amsterdam II criteria, patients suspected of harboring a germline mutation in MMR genes were recruited from seven hospitals located throughout Taiwan. These patients were enrolled into the Amsterdam criteria family registry as described by our previous studies (24-26). A total of 1,014 probands and their relatives were recruited from 135 hereditary nonpolyposis colorectal cancer (HNPCC) families (patients that meet the Amsterdam criteria, but are not genetically tested for germline mutations). The protocol of this study was approved by the Taipei Medical University Institutional Review Board and also the Taiwan National Health Research Institute.

Informed consent was obtained from all patients and genetic analyses were performed in all patients who met the Amsterdam criteria. Of the 1014 HNPCC patients who met the Amsterdam II criteria, 303 were identified as harboring *MLH1* or *MSH2* germline mutation; the details of these are available in our previous studies (25, 26). Forty-one of these 303 patients were excluded because their SNPs results were unavailable. We also excluded two patients who harbored mutations in both *MLH1* and *MSH2*. Eventually, 260 patients with germline mutations were recruited from 62 Lynch syndrome families.

Data collection. Clinical data from all patients were collected by nurses using a structured questionnaire, which included sociodemographic factors, medical, and family histories of cancer, as described by our previous studies (25, 26). Patients with Lynch syndrome were biennially followed-up for their recent cancer diagnoses. CRC and other cancer diagnoses were confirmed by cancer registry reports, pathology reports, medical reports, and death certificates.

Genotyping analyses. Sequenom iPLEX MassArray (Sequenom, San Diego, CA, USA) was used to genotype *EGFR*, *SMAD7*, and *TGFB* as described by our prior studies (25, 26). DNA sample of 10 ng was added to a polymerase chain reaction (PCR) mix containing Qiagen HotStarTaq (Qiagen, Valencia, CA, USA). PCR was performed according to Sequenom protocols and primers used in this study were obtained from Integrated DNA Technologies (Coralville, IA, USA). Assays were designed by MassARRAY Assay Design, Version 3.1. For quality control, 10% of randomly selected samples were repeated yielding a reproducibility of 100%.

Statistical analysis. Frequency distribution of all genotypes was examined for conformance to the Hardy-Weinberg equilibrium (HWE). Chi-squared goodness-of-fit test with one degree freedom was used to compare the differences between the observed and expected genotype frequencies of all the SNPs. Time at risk was considered to begin at birth and end at cancer diagnoses, death, or loss to follow-up. Patients who did not receive a diagnosis of CRC were censored at the date of their last known contact or in February 2012.

Since germline mutation carriers were recruited using non-probability sampling methods, to minimize for this nonrandom ascertainment, probability sampling weights were calculated and applied to each germline mutation carrier as previously described (27). Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between *EGFR, SMAD7*, and *TGFB* SNPs and CRC development were calculated in three genetic models (codominant, dominant, and recessive) using a weighted Cox proportional hazard model. The multivariable hazard model was used to adjust for the potential confounding factors including sex, MMR genes, year of birth, and regular colonoscopy. Furthermore, we adjusted for family and cluster correlations of these patients by using a robust sandwich covariance model, as described by a previous study (28).

For haplotype analysis, PHASE version 2.1 was used to construct haplotypes from genotypes of *SMAD7* and *TGFBR2* SNPs as described by Stephens *et al*. (29). PHASE is a Bayesian method for haplotyping population genotype data. The most frequent haplotype was used for comparison with other haplotypes. All tests were 2-sided and statistical significance was set at <0.05. All data analyses were performed by using SAS Version 9.4 for Windows.

Results

Genotype frequency distributions of *EGFR*, *SMAD7*, and *TGFB* SNPs are presented in Table I. All the SNPs, with the exception of *TGFB1* rs1800468, conformed to HWE genotypic proportions. Because *TGFB1* rs1800468 violated HWE, it was excluded from further analysis. Approximately 46.2% of participants harbored the heterozygous GA genotype of *EFGR* rs2227983. Moreover, 51.5% and 94.2% of participants harbored the wild-type homozygous genotypes of *SMAD7* rs12953717 and rs2337104, respectively. Similarly, 51.8% and 49.8% of participants harbored the heterozygous genotypes of *TGFB1* rs1800469 and *TGFBR1* rs334354, respectively. More than 70% of germline mutation carriers in this study harbored the wild-type alleles of *TGFBR2* rs3087465 and rs6785358.

The associations of *EGFR, SMAD7*, and *TGFB* SNPs with CRC risk are presented in Table II. After adjustment for potential confounding factors, hazard ratio (HR) showed that the variant homozygous AA genotype of *EGFR* rs2227983 was significantly associated with an increased risk of CRC in the recessive model compared with the wild-type G allele (HR=2.55, 95% CI=1.25-5.17). The codominant (HR=2.30, 95% CI=1.15-4.58) and dominant (HR=2.17, 95% CI=1.12-4.16) models of the *SMAD7* rs12953717 SNP were

Table I. *Frequency distributions of EGFR, SMAD7, and TGFB polymorphisms in patients with Lynch syndrome.*

Gene	SNP	Wild allele (%)	Heterozygous (%)	Variant allele (%)	Nucleotide	MAF	HWE	MAF CHB†
EGFR	rs2227983	GG (23.4)	GA (46.2)	AA (30.4)	c.1562G>A	A=0.5346	0.242	A=0.4612
SMAD7	rs12953717	CC (51.5)	CT (40.8)	TT (7.7)	g.48927559C>T	T=0.2807	0.878	T=0.2331
SMAD7	rs2337104	TT (94.2)	TC (5.4)	CC (0.4)	g.48936582T>C	C=0.0557	0.116	C=0.0341
TGFB1	rs1800468	CC (64.2)	CT (35.8)	TT (0)	c.3480C>T	T=0.1788	**0.001**	T=0.0049
TGFB1	rs1800469	CC (22.3)	CT (51.8)	TT (25.9)	c.29C>T	T=0.5176	0.559	T=0.4419
TGFBR1	rs334354	GG (29.7)	GA (49.8)	AA (20.5)	c.1255+24G>A	A=0.4536	0.938	A=0.4612
TGFBR2	rs3087465	GG (70.4)	GA (26.1)	AA (3.5)	c.-1216A>G	A=0.1653	0.369	A=0.1748
TGFBR2	rs6785358	AA (79.2)	AG (18.9)	GG (1.9)	c.3779A>G	G=0.1135	0.308	G=0.1553

EGFR, Epidermal growth factor receptor; *SMAD7*, mothers against decapentaplegic homolog 7; *TGFB*, transforming growth factor beta; SNP, single nucleotide polymorphism; MAF, minor allele frequency; CHB, Han Chinese in Beijing; HWE, Hardy-Weinberg equilibrium. †Allele frequency from other studies in Han Chinese population. Statistically significant results are shown in bold.

significantly associated with an increased risk of CRC. In addition, the variant homozygous CC genotype of *SMAD7* rs2337104 was significantly associated with CRC risk (HR=5.21, 95% CI=2.31-11.7) compared with the wild-type T allele. Similarly, the variant homozygous GG genotype of *TGFBR2* rs6785358 was significantly associated with an increased risk of CRC compared with the homozygous wild-type A allele (HR=21.1, 95% CI=5.06-88.1).

Furthermore, the association between the haplotypes of *SMAD7* and *TGFBR2* SNPs and CRC risk was assessed in germline mutation carriers (Table III). Linkage disequilibrium of rs3087465 and rs6785358 was D'=0.62 for *TGFBR2*. However, rs12953717 and rs2337104 were in linkage equilibrium for *SMAD7*. The TT haplotype of *SMAD7* SNPs was significantly associated with CRC risk (HR=2.18, 95% CI=1.13-4.19) compared to the most frequent CT haplotype. However, haplotypes of TGFBR2 were not associated with CRC risk. Table IV presents the combined effect of risk genotypes of *EGFR* rs2227983, *SMAD7* rs12953717, and *TGFBR2* rs6785358 on CRC risk, in patients with Lynch syndrome. Patients who harbored at least one risk genotype had higher CRC risk (HR=2.94, 95% CI=1.39-6.21 for patients with one risk genotype; HR=4.89, 95% CI=2.10-11.3 for patients with two risk genotypes) than those without risk genotypes.

Discussion

The present study revealed that *EGFR* rs2227983, *SMAD7* rs12953717, and *TGFBR2* rs6785358 SNPs are associated with CRC susceptibility in germline mutation carriers. Haplotype analysis revealed that the TT haplotype of *SMAD7* SNPs was associated with an increased CRC risk compared to the most frequent CT haplotype. Moreover, the presence of at least one risk genotype significantly increased CRC risk.

EGFR plays a crucial role in cell adhesion, proliferation, differentiation, and migration (14). In this study, harboring variant AA genotype of rs2227983 significantly increased CRC risk. Our findings are consistent with Lurje *et al*. (30) who reported that patients with AA genotype of rs2227983, also termed rs11543848, were associated with poor CRC outcome and shorter progression-free survival than other genotypes. In contrast, another study reported that the wild-type GG genotype of rs2227983 is associated with CRC risk (31). Moreover, patients carrying wild-type genotype have been reported to have a poorer prognosis than those carrying the variant genotype (18, 32). The rs2227983 polymorphism, an arginine-to-lysine amino acid substitution at codon 521 of the EGFR, has been shown to decrease ligand binding affinity, thus attenuating growth stimulation, tyrosine kinase activation and the induction of proto-oncogenes (33). The increased risk of CRC in patients carrying variant genotype of rs2227983 in this study is a novel finding. The mechanism for this observed association is currently unclear. However, it has been indicated that EGFR inhibits TGFB signaling pathway through SMAD7 signaling pathways (10). Disruption of TGFB signaling pathways by SMAD7 leads to various forms of tumorigenesis (34), thus increasing cancer risk. Moreover, other polymorphisms of the *EGFR*, including rs712829 and rs712830, have also been reported to be associated with CRC susceptibility (32).

In this study, patients with variant T allele of *SMAD7* rs12953717 were associated with an increased risk of CRC, corroborating previous studies (20, 35-38). In addition, a meta-analysis reported that *SMAD7* rs12953717 was associated with CRC risk (19). In contrast, a cohort study reported a non-significant association between *SMAD7* rs12953717 and CRC in germline mutation carriers (39). The non-significant results reported by Wijnen *et al*. may have been due to a lack of statistical power. SMAD7 encodes an inhibitory protein that acts as an antagonist of TGFB by

Table II. *EGFR, SMAD7, and TGFB polymorphisms and risk of CRC in patients with Lynch syndrome*.

Polymorphism	Total cohort	Person-years	CRC cases	Crude HR (95% CI)	*p*-Value	Adjusted HR (95% CI)[a]	*p*-Value
EGFR rs2227983							
Codominant model							
GG	61	2633	32	1.00		1.00	
GA	120	4973	53	0.60 (0.30-1.17)	0.135	0.49 (0.21-1.12)	0.093
AA	79	3197	35	1.79 (0.94-3.40)	0.074	1.71 (0.89-3.27)	0.102
Dominant model							
GG	61	2633	32	1.00		1.00	
GA+AA	199	8170	88	0.92 (0.52-1.59)	0.754	0.96 (0.53-1.73)	0.892
Recessive model							
GG+GA	181	7606	85	1.00		1.00	
AA	79	3197	35	**2.51 (1.26-5.00)**	**0.008**	**2.55 (1.25-5.17)**	**0.009**
SMAD7 rs12953717							
Codominant model							
CC	134	5662	67	1.00		1.00	
CT	106	4365	46	**2.17 (1.14-4.11)**	**0.017**	**2.30 (1.15-4.58)**	**0.018**
TT	20	775	7	1.50 (0.51-4.40)	0.457	1.43 (0.44-4.58)	0.544
Dominant model							
CC	134	5662	67	1.00		1.00	
CT+TT	126	5140	53	**2.06 (1.13-3.73)**	**0.017**	**2.17 (1.12-4.16)**	**0.021**
Recessive model							
CC+CT	240	10027	113	1.00		1.00	
TT	20	775	7	1.08 (0.37-3.14)	0.891	0.92 (0.28-2.93)	0.885
SMAD7 rs2337104							
Codominant model							
TT	245	10174	109	1.00		1.00	
TC	14	589	10	1.02 (0.36-2.88)	0.975	1.30 (0.48-3.51)	0.605
CC	1	39	1	**6.07 (3.15-11.6)**	**0.001**	**5.21 (2.31-11.7)**	**0.001**
Dominant model							
TT	245	10174	109	1.00		1.00	
TC+CC	15	628	11	1.07 (0.38-2.93)	0.903	1.35 (0.51-3.56)	0.541
Recessive model							
TT+TC	259	10763	119	1.00		1.00	
CC	1	39	1	**6.06 (3.19-11.5)**	**0.001**	**5.11 (2.29-11.3)**	**0.001**
TGFB1 rs1800469[b]							
Codominant model							
CC	57	2349	25	1.00		1.00	
CT	132	5526	62	1.14 (0.64-2.00)	0.651	1.15 (0.59-2.20)	0.675
TT	66	2674	29	1.45 (0.79-2.65)	0.229	1.33 (0.68-2.56)	0.401
Dominant model							
CC	57	2349	25	1.00		1.00	
CT+TT	198	8200	91	1.31 (0.73-2.35)	0.357	1.29 (0.66-2.51)	0.454
Recessive model							
CC+CT	189	7875	87	1.00		1.00	
TT	66	2674	29	1.32 (0.71-2.47)	0.375	1.20 (0.64-2.22)	0.559
TGFBR1 rs334354[c]							
Codominant model							
GG	77	3197	39	1.00		1.00	
GA	129	5318	60	0.90 (0.45-1.75)	0.752	0.92 (0.44-1.91)	0.819
AA	53	2249	20	0.93 (0.38-2.23)	0.874	1.10 (0.44-2.70)	0.832
Dominant model							
GG	77	3197	39	1.00		1.00	
GA+AA	182	7567	80	0.91 (0.47-1.77)	0.785	0.96 (0.46-1.98)	0.921
Recessive model							
GG+GA	206	8515	99	1.00		1.00	
AA	53	2249	20	1.00 (0.48-2.06)	0.999	1.17 (0.61-2.22)	0.628

Table II. *Continued*

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Polymorphism	Total cohort	Person-years	CRC cases	Crude HR (95% CI)	*p*-Value	Adjusted HR (95% CI)[a]	*p*-Value
TGFBR2 rs3087465							
Codominant model							
GG	183	7591	77	1.00		1.00	
AG	68	2805	37	0.71 (0.34-1.43)	0.333	0.62 (0.29-1.30)	0.204
AA	9	406	6	1.63 (0.35-7.46)	0.529	2.41 (0.52-11.1)	0.258
Dominant model							
GG	183	7591	77	1.00		1.00	
AG+AA	77	3211	43	0.75 (0.37-1.48)	0.406	0.67 (0.32-1.38)	0.281
Recessive model							
GG+AG	251	10802	114	1.00		1.00	
AA	9	406	6	1.78 (0.39-8.02)	0.453	2.69 (0.60-11.9)	0.193
TGFBR2 rs6785358							
Codominant model							
AA	206	8442	90	1.00		1.00	
GA	49	2215	28	1.31 (0.69-2.46)	0.404	1.21 (0.63-2.32)	0.565
GG	5	145	2	**24.4 (6.38-93.5)**	**0.001**	**21.1 (5.06-88.1)**	**0.001**
Dominant model							
AA	206	8442	90	1.00		1.00	
GA+GG	54	2360	30	1.34 (0.71-2.52)	0.359	1.25 (0.65-2.40)	0.499
Recessive model							
AA+GA	255	10657	118	1.00		1.00	
GG	5	145	2	**23.4 (6.10-89.6)**	**0.001**	**20.4 (4.76-87.2)**	**0.001**

EGFR, Epidermal growth factor receptor; *SMAD7*, mothers against decapentaplegic homolog 7; *TGFB*, transforming growth factor beta; CRC, colorectal cancer. [a]Adjusted for sex, colonoscopy, date of birth, familial clustering, and mutated MMR gene. [b]Five patients had missing genotype data. [c]One patient had missing genotype data. Statistically significant results are shown in bold.

blocking phosphorylation of receptor-activated SMAD (40). Inhibition of TGFB results in blocking activation of downstream signaling pathways (16), which eventually lead to CRC carcinogenesis. Moreover, Broderick *et al*. showed that lower median *SMAD7* mRNA expression was associated with CRC risk among patients harboring the variant T allele (35), which support our findings.

To date, only one study has investigated the association between *SMAD7* rs2337104 and CRC (23). Akbari *et al*. reported that the TC genotype and C allele were associated with CRC risk (23), which are consistent with our findings. However, their results were not statistically significant. The rs2337104 is a T>C polymorphism occurring at intron 3 of *SMAD7*. The biological mechanism underlying the increased CRC risk among the variant C allele remains unclear, as it has rarely been investigated. Due to the low frequency of the minor C allele, our results should be interpreted with caution. Nevertheless, a haplotype analysis was performed and data revealed that the TT haplotype of rs12953717 and rs2337104 SNPs in *SMAD7* was associated with an increased CRC risk. This finding confirms that the T allele of *SMAD7* rs12953717 is a high-risk allele associated with CRC susceptibility.

To our best knowledge, this is the first study to report an association between *TGFBR2* rs6785358 and CRC. The variant GG of rs6785358 was observed to be associated with CRC risk, compared to the A allele. Our findings are consistent with other studies (41, 42); however, these studies were conducted in patients with congenital heart defects and not in patients with CRC. Li *et al*. suggested that the polymorphisms of rs6785358 result in the decreased transcriptional activity of *TGFBR2* and its low protein expression (42), thus altering the signal transduction pathways, which may explain the increased risk of CRC among individuals harboring the variant G allele.

Since CRC is caused by numerous biological interactions of different signaling pathways, we evaluated the joint effect of harboring risk genotype on CRC risk. Our results revealed that carrying at least one risk genotype in *EGFR* rs2227983, *SMAD7* rs12953717, and *TGFBR2* rs6785358 significantly increased CRC risk. In addition to the significance of individual SNPs, genetic combination of relevant SNPs may contribute to CRC susceptibility, as demonstrated in this retrospective cohort study.

However, this study was limited by the inability to test other MMR genes including *MSH6, PMS2*, and *EPCAM*.

Table III. *Haplotypes of SMAD7 and TGFBR2 and CRC risk in patients with Lynch syndrome.*

Haplotypes	Allele n (%)	Crude HR (95% CI)	*p*-Value	Adjusted HR (95% CI)[a]	*p*-Value
SMAD7[b]					
C/T	358 (69.3)	1.00		1.00	
T/T	146 (27.8)	**2.07 (1.13-3.76)**	**0.017**	**2.18 (1.13-4.19)**	**0.019**
C/C	16 (2.9)	1.25 (0.41-3.70)	0.694	1.65 (0.54-4.85)	0.384
T/C	0 (0)	–	–	–	–
TGFBR2[c]					
G/A	387 (73.6)	1.00		1.00	
A/G	60 (10.7)	1.13 (0.56-2.25)	0.731	0.94 (0.38-2.26)	0.884
A/A	50 (10.4)	0.63 (0.28-1.41)	0.267	0.55 (0.24-1.26)	0.159
G/G	23 (5.3)	0.61 (0.22-1.59)	0.311	0.49 (0.18-1.34)	0.168

SMAD7, Mothers against decapentaplegic homolog 7; *TGFBR2*, transforming growth factor beta receptor type 2; CRC, colorectal cancer. [a]Adjusted for sex, colonoscopy, date of birth, familial clustering, and a mutated MMR gene. [b]Haplotypes of rs12953717 and rs2337104. [c]Haplotypes of rs3087465 and rs6785358. Statistically significant results are shown in bold.

Table IV. *Combined effect of EGFR rs2227983, SMAD7 rs12953717, and TGFBR2 rs6785358 polymorphisms and risk of CRC in patients with Lynch syndrome.*

Risk genotype[a]	Total cohort	Person-years	CRC cases	Crude HR (95% CI)	*p*-Value	Adjusted HR (95% CI)[b]	*p*-Value
0	92	3986	48	1.00		1.00	
1	127	5185	54	2.49 (1.21-5.07)	**0.012**	**2.94 (1.39-6.21)**	**0.004**
2	40	1597	18	4.34 (1.88-9.97)	**0.001**	**4.89 (2.10-11.3)**	**0.001**

EGFR, Epidermal growth factor receptor; *SMAD7*, mothers against decapentaplegic homolog 7; *TGFBR2*, transforming growth factor beta receptor type 2; CRC, colorectal cancer. [a]Risk genotypes included *EGFR* rs2227983 AA, *SMAD7* rs12953717 CT+TT, and *TGFBR2* rs6785358 GG genotypes. [b]Adjusted for sex, colonoscopy, date of birth, familial clustering, and a mutated MMR gene. Statistically significant results are shown in bold.

Some patients were not willing to be followed-up; hence, some cancer cases were not recorded. In addition, the associations of *EGFR, SMAD7*, and *TGFB* SNPs with CRC could not be compared in patients without Lynch syndrome. The main strengths of this study are that all patients included were confirmed to have germline mutation in *MLH1* or *MSH2*. Statistical methods that correctly adjust for ascertainment bias were used; thus, our results are comparable to others. Moreover, all cancer diagnoses were confirmed histologically.

In conclusion, *EGFR* rs2227983, *SMAD7* rs12953717, and *TGFBR2* rs6785358 SNPs are associated with CRC risk in Chinese patients with Lynch syndrome. Moreover, harboring at least one risk genotype of *EGFR* rs2227983, *SMAD7* rs12953717, and *TGFBR2* rs6785358 significantly increases the risk of CRC in patients with Lynch syndrome.

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