Polymorphisms of DNA repair genes are associated with colorectal cancer in patients with Lynch syndrome

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Abstract

Background: DNA repair genes are crucial for maintaining genomic stability by preventing mutagenesis and carcinogenesis. The present retrospective cohort study aimed at investigating whether MLH1, APEX1, MUTYH, OGG1, NUDT1, XRCC5, XPA, and ERCC2 single nucleotide polymorphisms (SNPs) are associated with colorectal cancer (CRC) in Chinese population with Lynch syndrome.

Methods: From Amsterdam criteria family registry, we identified 270 patients with Lynch syndrome. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between DNA repair SNPs and CRC were calculated using a weighted Cox proportional hazard regression model.

Results: Heterozygous variants of rs1799832 in NUDT1 (HR = 2.97, 95% CI = 1.51–5.83) and rs13181 in ERCC2 (HR = 2.69, 95% CI = 1.10–6.55) were significantly associated with an increased risk of CRC compared with wild-type homozygous CC and TT genotypes, respectively. However, the variant CG + GG genotype of MUTYH rs3219489 was associated with a decreased risk of CRC (HR = 0.49, 95% CI = 0.26–0.91) compared with the homozygous CC wild-type counterparts.

Conclusion: Our findings revealed that polymorphisms of DNA repair genes that include NUDT1, ERCC2, and MUTYH are associated with CRC in patients with Lynch syndrome in Chinese population. Further studies with large sample size are needed to confirm our findings.

KEYWORDS

colorectal cancer, DNA repair, Lynch syndrome, polymorphisms, Taiwan

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1 | INTRODUCTION

Lynch syndrome is a germline mutation in mismatch repair (MMR) genes (Boland, 2005). MLH1 (OMIM: 120436), MSH2 (OMIM: 609309), MSH6 (OMIM: 600678), PMS2 (OMIM: 600259), and EPCAM (OMIM: 185535) germline mutations are responsible for Lynch syndrome (Lynch et al., 2009). More than 80% of mutation carriers have a germline mutation in MLH1 and MSH2 and are at a greater risk of colorectal cancer (CRC) than the general population (Barnetson et al., 2006). MMR genes are crucial for maintaining genomic stability by repairing mutations that occur during DNA replication in preparation for cell division (De Jong et al., 2004). Specifically, MSH2 is responsible for proofreading a newly synthesized DNA strand for mismatch base pairing, while MLH1 coordinates the activities of other genes to repair the mismatch mutations (Li, 2008). In addition to the MMR, DNA repair genes such as APEXI (OMIM: 107748), MUTYH (OMIM: 604933), OGG1 (OMIM: 601982), NUDT1 (OMIM: 600312), XRCC5 (OMIM: 194364), XPA (OMIM: 611153), and ERCC2 (OMIM: 126340) play a crucial role in repairing DNA mutations and thus preventing cancer development (Sancar, Lindsey-Boltz, Unsal-Kacmaz, & Linn, 2004).

However, DNA repair genes are polymorphic, and the single nucleotide polymorphism (SNP) of these genes is associated with cancer development (Moreno et al., 2006). Polymorphisms of MLH1, APEXI, MUTYH, OGG1, NUDT1, and XRCC5 are associated with sporadic CRC (Kim et al., 2004; Lai et al., 2016; Yang et al., 2009) and other site-specific cancers (Li et al., 2011; Savina et al., 2016; Smith et al., 2011). However, recent studies have indicated that XPA and ERCC2 SNPs are not associated with sporadic CRC (Chang et al., 2016; He, Deng, & Luo, 2015). The association between DNA repair genes and CRC in germline mutation carriers has rarely been investigated. Only three studies have investigated this association, and the results have been inconsistent (Garre et al., 2011; Reeves et al., 2012; Win et al., 2013). Of these studies, two have reported that DNA repair genes are not associated with CRC (Reeves et al., 2012; Win et al., 2013). By contrast, Garre et al. reported that OGG1, NUDT1, and MUTYH SNPs are associated with CRC risk (Garre et al., 2011). However, Garre et al. included patients with microsatellite stable-hereditary nonpolyposis colorectal cancer (MSS-HNPCC). Patients with MSS-HNPCC have lower risk of CRC and lack evidence of the MMR deficiencies that define this syndrome (Llor et al., 2005).

Since germline mutation carriers have dysfunctional MMR genes and are at an increased risk of CRC, DNA repair genes are crucial for preventing mutations and cancer development. We therefore investigated whether MLH1 rs1799632, MLH1 rs11800734, APEXI rs1130409, APEXI rs1760944, MUTYH rs3219489, OGG1 rs1052133, NUDT1 rs1799832, XRCC5 rs828907, XPA rs1800975, and ERCC2 rs13181 were associated with CRC.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

Protocol of this study was performed under the approval of the Institution Review Boards of the Taiwan National Health Research Institutes and Taipei Medical University. All patients provided an informed consent for their data and biospecimens to be used by Taiwan HNPCC consortium.

2.2 | Patients

Patients suspected of HNPCC were recruited into the Amsterdam criteria family registry using the guidelines adopted from Amsterdam criteria II as previously described (Kamiza et al., 2015, 2016, 2018; Tang et al., 2009). One thousand and fourteen patients and their relatives from 135 Lynch syndrome families were recruited. Family members and relatives were recruited into the Amsterdam criteria family registry via probands.

Probands who fulfilled Amsterdam criteria were screened for germline mutation in MLH1 and MSH2. Genetic analyses were also performed to family members of probands as previously described (Kamiza et al., 2015, 2016, 2018; Tang et al., 2009). Of these probands and family members, 303 were identified as having germline mutation. Approximately, 10.2% (31) of germline mutation carriers were excluded because their DNA polymorphisms results were unavailable. In addition, two germline mutation carriers were also excluded because they had double mutation in MLH1 and MSH2. Eventually, we recruited 270 patients with Lynch syndrome.

2.3 | Data collection

Nurses were trained to conduct interviews. Clinical data from probands were collected from May 2002 onwards as previously described (Kamiza et al., 2015, 2016, 2018). In addition, patients with Lynch syndrome were interviewed using a structured questionnaire, which included demographic factors, dietary factors, lifestyle factors, medical, and family histories of cancer. All patients were followed up biennially from May 2002 to February 2012 for their recent cancer diagnosis statuses. Age at CRC and other site-specific cancer diagnoses was confirmed using medical reports, pathology reports, cancer registry reports, and death certificates.

2.4 | Genotyping of DNA repair genes

Genomic DNA from white blood cells of probands and their family members was used for genotyping MLH1 genes.
DNA repair genes included in this retrospective cohort study in Taiwan

| Gene   | dbSNP rs # | Chr | GenBank RefSeq | Protein        | Location | OMIM #   | MAF CHB |
|--------|------------|-----|----------------|----------------|----------|----------|---------|
| MLH1   | rs1799977  | 3   | NM_000249.3:c.655A>G | p.Ile219Val   | Exon 8   | 120436   | G = 0.0194 |
| MLH1   | rs1800734  | 3   | NM_000249.3:c.–93A>G | –             | Promoter | 120436   | G = 0.4320 |
| APEX1  | rs1130409  | 14  | NM_001641.3:c.444T>G | p.Asp148Glu   | Exon 5   | 107748   | G = 0.4563 |
| APEX1  | rs1760944  | 14  | NM_001641.3:c.–473T>G | –             | Promoter | 107748   | G = 0.4029 |
| MUTYH  | rs3219489  | 1   | NM_012222.2:c.1014C>G | p.Gln324His   | Exon 12  | 604933   | G = 0.4369 |
| OGG1   | rs1052133  | 3   | NM_016828.2:c.948+273C>G | p.Ser326Cys   | Exon 7   | 601982   | C = 0.4417 |
| NUDT1  | rs1799832  | 7   | NM_002452.3:c.357C>T | p.Asp119=     | Exon 5   | 600312   | T = 0.0874 |
| XRCC5  | rs828907   | 2   | NM_021141.3:c.–1428G>T | –             | Promoter | 194364   | T = 0.1942 |
| XPA    | rs1800975  | 9   | NM_000380.3:c.–4A>G   | –             | 5’UTR    | 611153   | A = 0.4634 |
| ERCC2  | rs13181    | 19  | NM_000400.3:c.2251T>G | p.Lys751Gln   | Exon 23  | 126340   | G = 0.1117 |

Chr, chromosome; RefSeq, reference sequence; OMIM#, OMIM accession numbers; MAF, minor allele frequency; CHB, Chinese Han Beijing; UTR, untranslated region.
CRC (HR = 2.69, 95% CI = 1.10–6.55) compared with wild-type homozygous TT genotype. However, the variant CG+GG genotype of MUTYH rs3219489 was associated with a decreased risk of CRC (HR = 0.49, 95% CI = 0.26–0.91) compared with the homozygous CC wild-type counterparts.

The combined effect of having risky genotypes from MUTYH rs3219489, NUDT1 rs1799832, and ERCC2 rs13181 and risk of CRC in patients with Lynch syndrome is shown in Table 4. The HR revealed that patients with Lynch syndrome who harbored at least one risky genotype were significantly associated with an increased risk of CRC (HR = 2.15, 95% CI = 1.23–3.74, for those with one risky genotype and HR = 4.86, 95% CI = 1.69–13.9, for those with two risky genotypes) compared to those with no risky genotype.

4 | DISCUSSION

DNA repair pathway is crucial for preventing mutagenesis and carcinogenesis. APEX1, MUTYH, OGG1, NUDT1, and XRCC5 are members of base excision repair pathway and are crucial for recognizing and repairing oxidative DNA damage as well as mismatch base pairing and single strand breaks (Moreno et al., 2006). Previous studies investigating this association have reported nonsignificant findings (Reeves et al., 2012; Win et al., 2013). However, Reeves et al. suggested that failure to find an association between DNA repair SNPs and CRC does not rule out the involvement of these SNPs in modifying CRC in germline mutation carriers (Reeves et al., 2012). In the present study, MUTYH, NUDT1, and ERCC2 SNPs were associated with CRC.

MUTYH has a functional role of repairing 8-hydroxyguanine mismatches that occur as a result of adenine glycosylase activity (Slupska, Luther, Chiang, Yang, & Miller, 1999). A previous study indicated that the homozygous CC genotype of rs3219489 was associated with an increased risk of CRC when compared to the GG genotype (Picelli et al., 2010). In this study, the G allele was protective, which is in line with the findings of Picelli et al. However, a case–control study reported nonsignificant results (Garre et al., 2011). The nonsignificant results reported by Garre et al. may be due to inadequate sample size and different study population as Garre et al. included patients with MSS-HNPCC. The protective effect observed among those with G allele maybe due to its high efficiency in repairing 8-hydroxyguanine mismatches that occur during DNA replication in preparation for cell division (Yamane et al., 2003).

The present study has revealed that rs1799832 in NUDT1 was significantly associated with CRC risk, which is in line with a previous study (Garre et al., 2011). In contrast, a case–control study from Germany suggested that rs1799832 was not associated with oral cancer (Görgens et al., 2007). However, this study included only 29 patients with oral cancer. Moreover, rs1799832 deviated from HWE. NUDT1 also known as MTH1 hydrolyses 8-oxoguanine-triphosphate (8-oxo-dGTP) to 8-oxoguanine-monophosphate (8-oxo-dGMP), thus preventing incorporation of 8-oxo-dGTP into the nascent DNA strand (Nakabeppu, 2001). Rs1799832 is a C to T silent SNP occurring in exon 5 of NUDT1 (Wu et al., 1995). However, variation in this gene decreases NUDT1 enzyme activity (Maki & Sekiguchi, 1992), hence increasing the risk of CRC among those with a variant genotypes.

Previous studies in Taiwan have suggested that ERCC2 rs13181 is not associated with CRC (Chang et al., 2016; Yeh, Sung, Tang, Chang-Chieh, & Hsieh, 2005), which contrasts with our findings. In this study, ERCC2 rs13181 significantly increased the risk of CRC. The discrepancies observed may be due to different study populations. XPA and ERCC2 are members of the nucleotide excision repair pathway and are involved in repairing and removing DNA adducts (Braithwaite, Wu, & Wang, 1999). ERCC2 encodes helicase that unwinds the helix region of the damaged DNA to initiate repairing mechanism (Reardon & Sancar, 2002). Variation in ERCC2 is associated with a low DNA damage repair capacity, which leads to the accumulation of DNA adducts (Spitz et al., 2001), hence increasing the risk of CRC among those carrying the variant G allele. In addition,

| TABLE 2 | Clinicopathological characteristics of patients with Lynch syndrome in Taiwan |
|---------|-----------------------------------------------|
| Variables | n = 270 | % |
| Age at diagnosis | | |
| Median (IQR)\(^a\) | 44.3 | 37.5–52.3 |
| Mean (SD) | 45.7 | 11.5 |
| Sex, n (%) | | |
| Female | 146 | 54.1 |
| Male | 124 | 45.9 |
| MMR gene mutated, n (%) | | |
| MLH1 | 190 | 70.4 |
| MSH2 | 80 | 29.6 |
| Colorectal cancer, n (%) | | |
| No | 141 | 52.2 |
| Yes | 129 | 47.8 |
| Colorectal cancer site, n (%) | | |
| Proximal colon | 110 | 85.3 |
| Distal rectal | 19 | 14.7 |

\(^a\)IQR, interquartile range; SD, standard deviation.
| DNA repair genes | Total cohort | Person years | CRC cases | Crude HR (95%CI) | p value | Adjusted HR (95%CI) | p value |
|-----------------|--------------|--------------|-----------|-----------------|---------|---------------------|---------|
| **MLH1 rs1799977** |              |              |           |                 |         |                     |         |
| AA              | 264          | 11,076       | 126       | 1.00            | 1.00    |                     |         |
| AG              | 6            | 200          | 3         | **2.54 (1.30–4.95)** | .006    | 2.17 (0.90–5.16)    | .081    |
| GG              | 0            | 0            | 0         | –               | –       | –                   | –       |
| **MLH1 rs1800734** |              |              |           |                 |         |                     |         |
| AA              | 101          | 4,432        | 50        | 1.00            | 1.00    |                     |         |
| AG              | 130          | 5,385        | 59        | 1.18 (0.62–2.21) | .614    | 1.06 (0.59–1.87)    | .852    |
| GG              | 39           | 1,459        | 20        | 1.21 (0.47–3.09) | .693    | 0.99 (0.39–2.45)    | .981    |
| AG + GG         | 169          | 6,844        | 79        | 1.18 (0.64–2.17) | .594    | 1.05 (0.60–1.82)    | .865    |
| **APEX1 rs1130409** |              |              |           |                 |         |                     |         |
| TT              | 116          | 4,949        | 61        | 1.00            | 1.00    |                     |         |
| TG              | 121          | 5,001        | 55        | 1.18 (0.67–2.06) | .335    | 1.22 (0.74–2.01)    | .432    |
| GG              | 33           | 1,327        | 13        | 0.62 (0.18–2.08) | .437    | 0.58 (0.14–2.27)    | .434    |
| TG + GG         | 154          | 6,328        | 68        | 1.08 (0.62–1.88) | .785    | 1.08 (0.64–1.82)    | .761    |
| **APEX1 rs1760944** |              |              |           |                 |         |                     |         |
| AA              | 88           | 3,644        | 39        | 1.00            | 1.00    |                     |         |
| AC              | 135          | 5,623        | 69        | 0.95 (0.52–1.72) | .855    | 0.92 (0.51–1.66)    | .791    |
| CC              | 40           | 1,675        | 16        | 0.89 (0.39–2.02) | .780    | 0.84 (0.35–1.97)    | .691    |
| AC + CC         | 175          | 7,298        | 85        | 0.90 (0.45–1.75) | .748    | 0.85 (0.43–1.66)    | .642    |
| **MUTYH rs3219489** |              |              |           |                 |         |                     |         |
| CC              | 79           | 3,212        | 35        | 1.00            | 1.00    |                     |         |
| CG              | 130          | 5,482        | 63        | 0.81 (0.43–1.52) | .514    | 0.77 (0.40–1.49)    | .441    |
| GG              | 49           | 2,045        | 21        | 0.44 (0.17–1.14) | .092    | 0.44 (0.17–1.09)    | .078    |
| CG + GG         | 179          | 7,527        | 84        | 0.69 (0.34–1.36) | .288    | **0.49 (0.26–0.91)** | **0.024** |
| **OGG1 rs1052133** |              |              |           |                 |         |                     |         |
| GG              | 101          | 4,271        | 53        | 1.00            | 1.00    |                     |         |
| GC              | 119          | 4,795        | 50        | 0.74 (0.34–1.62) | .459    | 0.95 (0.44–2.03)    | .891    |
| CC              | 50           | 2,210        | 26        | 1.76 (0.94–3.29) | .076    | 2.18 (0.99–4.79)    | .053    |
| GC + CC         | 169          | 7,005        | 76        | 1.04 (0.53–1.99) | .915    | 1.29 (0.66–2.51)    | .457    |
| **NUDT1 rs1799832** |              |              |           |                 |         |                     |         |
| CC              | 230          | 9,595        | 107       | 1.00            | 1.00    |                     |         |
| CT              | 39           | 1,661        | 22        | **2.97 (1.57–5.60)** | **.001** | **2.97 (1.51–5.83)** | **.001** |
| TT              | 1            | 20           | 0         | –               | –       | –                   | –       |
| **XRCC5 rs828907** |              |              |           |                 |         |                     |         |
| GG              | 163          | 6,635        | 78        | 1.00            | 1.00    |                     |         |
| GT              | 79           | 3,371        | 31        | 0.69 (0.33–1.42) | .316    | 0.81 (0.40–1.63)    | .559    |
| TT              | 17           | 761          | 11        | 1.47 (0.74–2.92) | .266    | 1.83 (0.79–4.22)    | .158    |
| GT + TT         | 96           | 4,132        | 41        | 0.82 (0.44–1.48) | .501    | 0.96 (0.52–1.75)    | .891    |
| **XPA rs1800975** |              |              |           |                 |         |                     |         |
| GG              | 80           | 3,499        | 46        | 1.00            | 1.00    |                     |         |
| GA              | 131          | 5,406        | 51        | 0.64 (0.29–1.39) | .263    | 0.68 (0.31–1.49)    | .341    |
| AA              | 57           | 2,286        | 30        | 1.02 (0.53–1.92) | .957    | 1.01 (0.52–1.92)    | .982    |
| GA + AA         | 188          | 7,692        | 81        | 0.77 (0.42–1.40) | .393    | 0.80 (0.43–1.46)    | .471    |

(Continues)
a recent study also indicated that G allele of rs13181 is associated with CRC (Procopciuc, Osian, & Iancu, 2017), which is in line with our findings. We also assessed the combined effects of having risky genotypes. Our results demonstrated that patients with Lynch syndrome harboring at least one risky genotype in MUTYH, NUDT1, and ERCC2 SNPs were at an increased risk of CRC compared to those without risky genotype. Our results support the evidences that CRC is a complex disease caused by complex interactions of different DNA repair pathways (Farrington et al., 2005). However, previous studies reported nonsignificant association between DNA repair genes and CRC (Reeves et al., 2012; Win et al., 2013). The nonsignificant results may be attributed to the differences in ethnicity between Han Chinese and Caucasians. Moreover, Win et al. excluded other types of colorectal polyps, which may have underestimated CRC risk if some of the polyps were malignant.

The main weaknesses of our study are our inability to test MSH6, PMS2, and EPCAM. Almost 54% of the patients were not willing to be followed up, hence, we did not record some newly developed cases. The main strengths of this retrospective cohort study are that all patients include were confirmed to have germline mutation in MLH1 and MSH2 and all cancer diagnoses were histologically confirmed.

We have demonstrated for the first time that DNA repair genes are associated with CRC in Chinese population with Lynch syndrome. Our study revealed that NUDT1 rs1799832 and ERCC2 rs13181 significantly increased the risk of CRC, whereas MUTYH rs3219489 exerted a protective effect.

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**CONFLICT OF INTEREST**

The authors declare that they have no competing interests.

**AUTHOR CONTRIBUTION**

RT, CAH, and CCY conceived and designed the experiments. JFY, WCW, HTC, CHL, LLC, and TPL performed the experiments. ABK, TPL, KYH, CAH, and CCY analyzed the data: CCY, CAH, and RT contributed reagents and analytical tools. ABK, CAH, and CCY drafted the manuscript.

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