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The Association of DNA Ligase 1 Rs20579 Polymorphism With Lung Cancer Risk Among Taiwanese

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Abstract. *Background/Aim: Impaired DNA repair capacity may play a critical role in genome instability and carcinogenesis. However, the impact of DNA ligase 1 (Lig1) genotypes on tumorigenesis remains unclear. This study aimed to investigate the contribution of Lig1 rs20579 genotypes to the risk of developing lung cancer, and review the related literature. Materials and Methods: Polymerase chain reaction-restriction fragment length polymorphism analysis was used to determine the genotypes of Lig1 rs20579 and evaluate their association with lung cancer risk among 358 lung cancer cases and 716 age- and sex-matched cancer-free control subjects. Results: The distribution of GG, AG, and AA genotypes for Lig1 rs20579 was 77.1%, 20.8%, and 2.1% among the controls, and 76.0%, 21.5%, and 2.5% among the lung cancer cases (p for trend=0.8686). There was no significant difference in the distribution of AG and AA genotypes between the two groups (p=0.8257 and 0.8098, respectively). Allelic frequency analysis indicated that individuals carrying the variant A allele for Lig1 rs20579 had a non-significant 1.07-fold higher risk of developing lung cancer than those carrying the wild-type G allele [95% confidence interval (CI)=0.82-1.40, p=0.6639]. Furthermore, no differential distribution of the Lig1 rs20579 genotype was found among non-smokers (p=0.9910) or smokers (p=0.9001). Conclusion: In contrast to Americans, Lig1 rs20579 genotypes do not appear to play a critical role in determining susceptibility to lung cancer among Taiwanese individuals.*

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Lung cancer accounts for more than 11% of all neoplasms and 18% of cancer-related deaths worldwide (1). Over the last few decades, lung cancer has been the most prevalent malignant tumor and the leading cause of cancer fatalities (2). Lung cancer is the top cause of cancer-related deaths in both sexes (3) and a major public health concern due to its high fatality rate (4) and the 5-year survival rate of only 17.8% (5). Globally, there were an estimated 2,206,771 new cases of lung cancer in 2020, accounting for 11.4% of all new cancer diagnoses (6). Furthermore, lung cancer had the third-highest incidence and mortality after breast and prostate

cancer in Asia in 2020 (7). Smoking is the most important risk factor for lung cancer, with 81.7% of lung cancer cases and 81.3% of lung cancer deaths linked to cigarette smoking (8). Smokers have a 20-fold higher risk of developing lung cancer than nonsmokers (9). However, the fact that 10% to 25% of lung cancer patients worldwide are non-smokers suggests that genetic factors also play a crucial role in the development of the disease (10). Although several genetic biomarkers have been identified in recent decades, there is still an urgent need to identify clinically useful markers for early detection of lung cancer (11-15).

According to Lindahl and Tubbs, each cell in the human body experiences tens of thousands of lesions daily (16, 17). If left unaddressed, these lesions can result in mutations, genome instability, and ultimately cancer. Both internal and external factors can cause DNA strand breaks, and human cells commonly utilize nucleotide excision repair (NER) and base excision repair (BER) mechanisms to remove DNA adducts and mend DNA strand breaks (18, 19). The *LIG1* gene, found on the 19q13.2-13.3 chromosome, encodes a nuclear enzyme known as ATP-dependent DNA ligase, which is crucial for linking Okazaki fragments during DNA replication and for repairing single-strand breaks (20-23). Lig1 plays a role in both NER and long-patch BER (24). Interestingly, the level of Lig1 protein has been found to be significantly higher in 29 malignant tumor samples compared to benign tissue samples from cancer patients, indicating that overexpression of Lig1 may be a common characteristic of cancer (25). This is not surprising as the expression level of Lig1 correlates with the capacity for cell proliferation, and cancer cells are known to proliferate rapidly (25, 26). Thus, it is reasonable to suggest that polymorphic variants of *Lig1* may be linked to overall genomic instability and the onset of tumorigenesis.

Numerous single nucleotide polymorphisms (SNPs) of *Lig1* have been recorded in the National Center for Biotechnology Information website, but there is limited research on their relevance. The most prevalent SNPs of *Lig1* are rs20579, rs20580, rs20581, and rs439132, chosen because their minor allele frequencies have been identified to be greater than 5% (27). Rs20579, which involves a G to A nucleotide alteration, has been the most thoroughly studied in systematic research on DNA repair gene polymorphisms, particularly in lung cancer. The rs20580, rs20581, and rs439132 do not lead to amino acid alterations, and their functional variations are still unknown (28). In 2006, Landi *et al*. conducted research on the association of inherited DNA repair and cell cycle-related factors for early-onset lung cancer, discovering that heterozygous AG *Lig1* rs20579 carriers were at a higher risk of lung cancer (29). However, the sample size was limited, and the population studied was from Romania, Hungary, Poland, Russia, Slovakia, and the Czech Republic. The lack of homozygous variant AA carriers in the control group was noticeable, and the unfitness to the Hardy-Weinberg equilibrium was obvious (29). Chang and his colleagues discovered that although no single *Lig1* polymorphism was associated with altered lung cancer risk, the haplotype GGGAA composed of rs20581-rs156641-rs3730931-rs20579-rs439132 was linked to a decreased risk of lung cancer (30). Additionally, Lee *et al*. found that another haplotype, rs20581-rs20580-rs20579-rs439132, of *Lig1* may weakly determine the differential risk of lung cancer among US citizens (27). In 2012, Sakoda and his colleagues failed to find a positive association between AG *Lig1* rs20579 and lung cancer in a study of the contribution of NER genes to smoking-related lung cancer (31).

All previous limited studies suggested that *Lig1* rs20579 genotypes may play a critical role in determining cancer phenotypes and have clinical significance in lung cancer therapy. As a result, in this study, we aimed to conduct a hospital-based case-control study on a representative population (control:case=716:358), examine the contribution of *Lig1* rs20579, investigate the interaction of *Lig1* genotypes with smoking status on lung cancer risk, and review the related literature.

Materials and Methods

The recruitment of lung cancer and control subjects. A cohort of 358 patients with confirmed histological diagnosis of lung cancer were recruited from China Medical University Hospital, as previously described (32, 33). Exclusion criteria included a history of malignancy, chronic pulmonary diseases such as chronic obstructive pulmonary disease (COPD), pneumothorax, and asthma. The control group was selected from the Health Examination Cohort database of China Medical University Hospital, which comprised more than 15,000 individuals who consented to share their personal information. Two healthy individuals were matched to each lung cancer patient according to age (within 5 years), sex, and smoking status to minimize the impact of behavioral factors, specifically smoking. Exclusion criteria for the controls included a history of malignancy or metastasized cancer, and any genetic or familial diseases. All cases and controls were Taiwanese, and Table I provides a summary of their demographic characteristics.

Genotyping processes for Lig1 rs20579. The genomic DNA was isolated using a Qiagen kit (Qiagen, Chatsworth, CA, USA) from peripheral blood leukocytes collected from each participant within 24 h of blood withdraw (Blossom, Taipei, Taiwan), using the method previously described (34). The DNA was quantified, aliquoted as a working stock at –20˚C for genotyping and long-term stored at –80˚C. The genotyping assay for *Lig1* rs20579 was designed by the Terry Fox Cancer Research Lab, Taichung, Taiwan. The forward and reverse primers used were 5'-AATCTCCAGACGCTGCCAGA-3' and 5'-CTCTGCACAACCAATCACCT-3', respectively. Polymerase chain reaction (PCR) was performed with the following cycling conditions: an initial denaturation step at 94˚C for 5 min, followed by 35 cycles of denaturation at 94˚C for 30 s, annealing at 52˚C for 30 s, extension at 72˚C for 30 s, and a final extension step at 72˚C for 10 min. The PCR products were digested with *BsaH* I restriction enzyme and separated on a 3% agarose gel by electrophoresis at 100

Table I. *Distribution of demographic data of 358 lung cancer patients and 716 matched non-cancer controls.*

Characteristics	Controls (n=716)			Patients (n=358)			*p*-Value[a]
	n	%	Mean (SD)	n	%	Mean (SD)	
Age (years)			64.8 (6.8)			64.0 (6.9)	0.5871
Sex							
Male	488	68.1%		254	70.9%		
Female	228	31.9%		104	29.1%		0.3642
Smoking status							
Ever smokers	563	78.6%		293	81.8%		
Non-smokers	153	21.4%		65	18.2%		0.2282
Histology							
Adenocarcinoma				218	60.9%		
SCC				106	29.6%		
Other				34	9.5%		

[a]Based on Chi-square test with Yates' correction. SCC: Squamous cell carcinoma; SD: standard deviation.

volts for 25 min. The *Lig1* rs20579 genotypes were then identified based on the following pattern: A/A with a single 402-bp band, A/G with 402, 303, and 99 bp bands, and G/G with 303 and 99 bp bands.

Statistical methodology. The age distribution of the case and control groups was compared using Student's *t*-test. The Hardy-Weinberg equilibrium among the different *Lig1* rs20579 genotypes in 716 cancer-free controls was assessed using the goodness-of-fit chi-square test. Pearson's chi-square method was used to compare the distributions of *Lig1* rs20579 genotypes among subgroups and to perform stratification analysis to assess the interaction between *Lig1* rs20579 genotypes and smoking status. Logistic regression analysis was used to estimate the odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) to determine the associations between *Lig1* rs20579 genotypes and lung cancer risk. *p*-Value less than 0.05 was considered to indicate statistically significant differences.

Results

Table I displays the frequency distributions of age, sex, and smoking status for 358 patients with lung cancer and their 716 matched non-cancer healthy controls. The table also presents the histology of the patients with lung cancer. The healthy controls were recruited using frequency matching based on age, sex, and smoking status, and there were no significant differences in the distribution of these factors between the two groups (all $p>0.05$). It should be noted that the high percentage of smokers (78.6%) in the control group was due to the frequency matching strategy and may not represent the entire Taiwanese population. Adenocarcinoma was the most common histological type, accounting for 60.9% (218/358) of lung cancer cases, followed by squamous cell carcinoma (29.6%, 106/358) and other types (9.5%, 34/358).

Table II displays the genotypic frequency distributions of *Lig1* rs20579 among the 716 non-cancer controls and the 358 lung cancer patients. First, the genotypic frequencies of *Lig1* rs20579 among control subjects were found to be in Hardy-Weinberg equilibrium ($p=0.1927$, Table II). Second, the genotypic frequencies of *Lig1* rs20579 were found not to be differently distributed between the lung cancer and healthy control groups (p for trend=0.8686, Table II). Specifically, the variant AG and AA genotypes of *Lig1* rs20579 were both not associated with elevated lung cancer risks (OR=1.05 and 1.22, 95%CI=0.77-1.43 and 0.53-2.82, $p=0.8257$ and 0.8098, respectively; Table II). Third, the recessive model for carrier comparison showed a non-significant 1.21-fold increase in lung cancer risk for the carriers of the *Lig1* rs20579 AA genotype compared to those with either GG or AG genotypes (95%CI=0.52-2.78, $p=0.8267$, Table II). As for the dominant model, there was no significantly elevated lung cancer risk for the carriers of the AG or AA genotypes of *Lig1* rs20579 compared to those carrying GG genotypes (OR=1.06, 95%CI=0.79-1.43, $p=0.7400$, Table II).

To validate the findings in Table II, the analysis of allelic frequency distribution for *Lig1* rs20579 was performed, and the results are presented in Table III. The results further support the notion that *Lig1* rs20579 genotype is not associated with lung cancer risk, as the proportion of the variant A allele was found to be 13.3% among the lung cancer cases and 12.5% for the cancer-free controls (OR=1.07, 95%CI=0.82-1.40, $p=0.6639$).

We have performed a stratification analysis to investigate the joint effects of the inherited *Lig1* rs20579 genotype and personal cigarette smoking habits on lung cancer risk. The data showed that there was no significant genetic-environmental interaction among non-smokers or smokers (both p for trend>0.05) (Table IV). The results remained at a non-significant level after adjusting for age, sex, and alcohol drinking status (Table IV).

Table II. *Distribution of Lig1 rs20579 genotypes among the 358 patients with lung cancer and non-cancer 716 controls.*

Genotypes	Controls, N	%	Patients, N	%	OR (95%CI)	*p*-Value[a]
rs20579						
GG	552	77.1	272	76.0	1.00 (Reference)	
AG	149	20.8	77	21.5	1.05 (0.77-1.43)	0.8257
AA	15	2.1	9	2.5	1.22 (0.53-2.82)	0.8098
p_{trend}						0.8686
p_{HWE}						0.1927
Carrier comparison						
GG+AG	701	97.9	349	97.5	1.00 (Reference)	
AA	15	2.1	9	2.5	1.21 (0.52-2.78)	0.8267
GG	552	77.1	272	76.0	1.00 (Reference)	
AG+AA	164	22.9	86	24.0	1.06 (0.79-1.43)	0.7400

N: Number; OR: odds ratio; CI: confidence interval; [a]Based on Chi-square with Yate's correction test; p_{HWE}: whether the frequencies in controls are consistent with Hardy-Weinberg Equilibrium.

Table III. *Distribution of Lig1 rs20579 allelic frequencies among the 358 patients with lung cancer and the non-cancer 716 controls.*

Allele	Controls, N	%	Patients, N	%	OR (95%CI)	*p*-Value[a]
rs20579						
G	1,253	87.5%	621	86.7%	1.00 (Reference)	
A	179	12.5%	95	13.3%	1.07 (0.82-1.40)	0.6639

N: Number; OR: odds ratio; CI: confidence interval; [a]Based on Chi-square with Yate's correction test.

Table IV. *Distribution of Lig1 rs20579 genotypes among 358 patients with lung cancer and 716 controls after stratification by smoking. status.*

Genotype	Non-smokers, N		OR (95% CI)[a]	aOR (95% CI)[b]	*p*-Value	Smokers, N		OR (95%CI)[a]	aOR (95%CI)[b]	*p*-Value
	Controls	Cases				Controls	Cases			
GG	125	53	1.00 (ref)	1.00 (ref)		427	219	1.00 (ref)	1.00 (ref)	
AG	26	11	1.00 (0.46-2.17)	1.06 (0.48-1.88)	0.9956	123	66	1.04 (0.74-1.47)	1.02 (0.71-1.33)	0.8628
AA	2	1	1.18 (0.10-13.29)	1.11 (0.09-11.76)	0.8937	13	8	1.20 (0.49-2.94)	1.09 (0.47-2.46)	0.8688
Total	153	65				563	293			
p_{trend}					0.9910					0.9001

N: Number; OR: odds ratio; CI: confidence interval; [a]Based on Chi-square with Yate's correction test; [b]Based on Chi-square with Yate's correction test after adjustment of age and sex.

Discussion

Lig1, responsible for the joining of Okazaki fragments during DNA synthesis on the lagging strand and the completion of DNA excision repair, has been implicated in the development of cancer (35-37). However, despite working in conjunction with other replication proteins, the specific mechanisms by which Lig1 contributes to base excision repair (BER) and nucleotide excision repair (NER) have yet to be fully investigated (38). From a genomic perspective, the potential contribution of the *Lig1* genotype to the risk of lung cancer has not been previously reported. Therefore, we have taken the initiative to examine the *Lig1* rs20579 genotype among Taiwanese individuals and validate any potential association between the *Lig1* rs20579 genotype and lung cancer risk in an East Asian population.

The first finding of the current study revealed that in the Taiwanese population, the distribution of GG, AG, and AA genotypes for *Lig1* rs20579 was 77.1%, 20.8%, and 2.1%, respectively (Table II), with an A allelic frequency of 12.5% in the control group (Table III). These percentages are consistent with those reported for East Asian populations on

Table V. *Literature reported the genotypes of Lig1 rs20579 among lung cancer patients.*

First author	Year	Ethnicity	GG, AG, AA genotype # of the controls	GG, AG, AA genotype # of the cases	Highlights of the findings	Ref #
Chang	2023	Asians	552:149:15	272:77:9	No variant genotypes contributed to altered lung cancer risk (p for trend=0.8686)	Current
Sakoda	2012	Mixed Americans	1,126:312:36	583:141:18	No variant genotypes contributed to altered lung cancer risk (p for trend=0.4878)	31
Chang	2008	Latinos	217:75:7	72:36:5	No variant genotypes contributed to altered lung cancer risk (p for trend=0.1706)	30
		African Americans	137:117:26	150:92:13	AG and AA genotypes contributed to decreased lung cancer risk (p for trend=0.0341)	
Lee	2008	Mixed Americans	586:187:7	294:118:11	AA genotypes contributed to increased lung cancer risk (p for trend=0.0169)	27
Landi	2006	Mixed Europeans	245:61:0	206:73:6	AG genotypes contributed to increased lung cancer risk (p for trend=0.0078)	29

the National Center for Biotechnology Information (NCBI) website, which shows a minor allelic frequency of 13.09% based on the genotyping results of 3124 subjects (updated on 2023/05/09). The second finding demonstrated that neither the AG nor the AA genotype of Lig1 rs20579 was associated with an increased risk of lung cancer (Table II and Table III), which is consistent with other studies as summarized in Table V (27, 29-31). Our results align with the reports of Sakoda and Chang, who investigated mixed Americans and Latinos, respectively, and found no association between variant genotypes and lung cancer risk in both populations (Table V). However, Chang's study in the same publication examining African Americans found that AG and AA genotypes were associated with a decreased risk of lung cancer (30). Furthermore, Lee's and Landi's studies showed that variant AA/AG genotypes of *Lig1* rs20579 increased the risk of lung cancer in the mixed American and European populations they investigated, respectively. The frequencies of the major allele G in mixed American populations in Sakoda's and Landi's reports appeared to be slightly higher than those in the NCBI record (87.0% and 87.1% *versus* 84.2%) of genotyping results from 694 American samples. The different findings may be attributed to sampling bias and the diversity of ethnicities since Americans have multiple ethnicities. In Landi's study, the lack of homozygous variant AA carriers in the control group and the inconsistency with the Hardy-Weinberg equilibrium supported the possibility of sampling bias (29). In summary, although our study is the first to provide evidence for the contribution of *Lig1* genotype to lung cancer risk in the Asian population, all findings need to be validated.

In the scientific literature, other *Lig1* polymorphisms in combination with rs20579 have been explored for their potential impact on lung cancer risk. For example, Chang and colleagues found that the haplotype GGGAA, composed of rs20581-rs156641-rs3730931-rs20579-rs439132, was associated with a decreased risk of lung cancer (30). Lee and colleagues provided another haplotype that weakly determined the risk for lung cancer among individuals (27). We acknowledge that other SNPs of *Lig1*, either alone or in combination, may be closely associated with lung cancer susceptibility. Discovering new *Lig1* biomarkers for lung cancer can aid in precision medicine by facilitating early detection and prediction.

In conclusion, our study suggests that the *Lig1* rs20579 genotype may not be a reliable predictor of lung cancer susceptibility, regardless of smoking status. Further investigations into the association between *Lig1* genotypes and mRNA/protein expression levels, as well as BER capacity, may shed light on the underlying mechanisms of lung carcinogenesis. Such studies may pave the way for the development of novel biomarkers and targeted therapies for lung cancer.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Research Design: Chang WS, Bau DT and Hsia TC; Patient and Questionnaire Summary: Chang SM, Yang YC, Chen LH, Shen TC, Liu YF, and Hsia TC; Experimental Data Clearing and Checking: Wang YC and Chang WS; Statistical Analysis: Chen LH, Yang YC, and Chen LH; Literature Review: Chang SM, Wang YC, and Tsai CW; Manuscript Writing: Chang SM, Tsai CW, Hsia TC, Chang WS and Bau DT; Reviewing and Revising: Bau DT, Chang WS and Hsia TC.

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