Received: 28 April 2020 | Revised: 13 July 2020 | Accepted: 4 August 2020

DOI: 10.1002/mgg3.1474

ORIGINAL ARTICLE

Molecular Genetics & Genomic Medicine Open Access WILEY

Genetic variants in *GHR* and *PLCE1* genes are associated with susceptibility to esophageal cancer

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Funding information
This study was supported by the National Natural Science Foundation of China (No. 81460284, No. 81460051, No. 31560039), Natural Science Foundation of Qinghai Provincial (No. 2015-ZJ-744), and Keypoint Research and Invention Program of Qinghai Provincial (No. 2019-SF-121).

Abstract

Background: Esophageal cancer (EC) is the leading cause of cancer-related mortality worldwide. The underlying genetic risk factors remain unclear. The association between gene growth hormone receptor (*GHR*) and phospholipase C epsilon 1 (*PLCE1*) polymorphisms and the EC risk were identified in this study.

Methods: A total of 506 EC cases and 507 controls were included in this research. Two SNPs (rs6898743 of *GHR* and rs2274223 of *PLCE1*) were selected and genotyped. The associations between gene polymorphisms and the EC risk were assessed by logistic regression analysis. The databases RegulomeDB, GTEx, and UALCAN were used for functional annotations.

Results: In the allelic frequencies analysis, the rs6898743 of *GHR* was associated with decreased susceptibility of EC (OR = 0.83, 95% CI: 0.70–1.00, $p = 0.049$), while rs2274223 of *PLCE1* was associated with increased 0.25-fold EC risk (OR = 1.25, 95% CI: 1.02–1.53, $p = 0.037$). The "GC" genotype of rs6898743 was associated with a 0.24-fold decreased risk of EC under co-dominant model (OR = 0.76, 95% CI: 0.58–0.99, $p = 0.046$), and the "GA" genotype of rs2274223 was associated with increased EC risk under co-dominant model (OR = 1.36, 95% CI: 1.04–1.77, $p = 0.023$). Using GTEx database, rs2274223 was found to be significant associated with increased *PLCE1* expression ($p = 4.1 \times 10^{-7}$) in esophagus muscularis. The UALCAN database demonstrated that the *GHR* gene was under-expressed in esophageal cancer tissues ($p = 0.017$).

Conclusion: The gene *GHR* and *PLCE1* polymorphisms are associated with EC in the general population and the results need to be verified in future.

KEYWORDS

esophageal cancer, growth hormone receptor, phospholipase C epsilon 1, single nucleotide polymorphisms

1 | BACKGROUND

Esophageal cancer (EC) is one of the most common cancers (Pennathur, Gibson, Jobe, & Luketich, 2013; Zhang, 2013) which includes esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Histologically, ESCC is the major type in Asian populations, while EAC is the dominant type in western countries (Torre et al., 2015).

Previous studies have found that environmental and genetic factors play important roles in esophageal carcinogenesis (Cheung & Liu, 2009; Hongo, Nagasaki, & Shoji, 2009). Some environmental factors, such as heavy smoking, alcohol consumption, and nutritional deficiencies are the main risk factors of EC (Chun-xia et al., 2005; Messmann, 2001; Morita et al., 2010; Siassi & Ghadirian, 2005; Sun et al., 2007; Wang et al., 2010). There is a strong tendency toward familial aggregation of EC (Guohong et al., 2010), some susceptibility loci, such as *ADHIB*, *ALDH2*, *TERT*, *NAF1*, and so on, have been exposed to be associated with the EC risk (Chenli et al., 2017; Cui et al., 2009; Y. Wu et al., 2017). However, the genetic risk factors of EC remain unclear.

Growth hormone receptor (*GHR*, OMIM 600946) is a gene that encodes a transmembrane receptor for growth hormone. Previous studies identified the GC genotype of *GHR* rs6898743 in 475 ESCC patients and 475 matched controls in Netherlands, and found a negative association between *GHR* polymorphisms and ESCC risk (Ong et al., 2014). Because of disproportionately effects of EC in different ethnicities and races (Deng et al., 2017), it is meaningful to identify whether the rs6898743 of *GHR* gene was associated with EC in Chinese Han.

Phospholipase C epsilon 1 (*PLCE1*, OMIM 608414) is a gene that encodes phospholipase, which is important in second messenger generation. *PLCE1* also plays a crucial role in cell growth, differentiation, and oncogenesis. Related studies on *PLCE1* variants were performed in the Asian population, and the results indicated that *PLCE1* rs2274223 polymorphism was associated with an increased risk of ESCC (G. Li et al., 2020; Xue, Zhu, Wang, He, & Zheng, 2015). Due to differences in lifestyle, we ascertained to explore the association of *PLCE1* and the EC risk in the population of Han in northwest China, and find out whether genetic polymorphisms of *PLCE1* differ between regions and races.

Based on the above findings, we conducted this association analysis between the *GHR* and *PLCE1* gene polymorphisms with the EC risk to further explore the role of these SNPs in northwest China. This study provided a theoretical basis for revealing the functional SNP involved in the occurrence of EC and its possible biological mechanism.

2 | MATERIAL AND METHODS

2.1 | Ethical compliance

The study was approved by the ethics committee of the Medical College of Qinghai University.

2.2 | Study participants

A total of 506 EC patients and 507 controls were recruited. The cases were recently diagnosed with EC at the Shaanxi Provincial Cancer Hospital. The patients were diagnosed by at least two senior pathologists. Controls were selected from the health checkup center of the Tangdu Hospital. The information of gender, age, lymph node metastasis, and tumor node metastasis (TNM) staging were collected from the participants. This study is in accordance with the tenets of the

TABLE 1 Characteristics of cases and controls in the study

Variables	Case ($n = 506$)	Control ($n = 507$)	p
Gender			0.403
Male	374	375	
Female	132	132	
Age			0.985
<64	237	266	
≥64	269	241	
Mean ±SD	63.96 ± 9.26	63.51 ± 7.76	
Body mass index			
<24	418		
≥24	72		
Tobacco smoking status			
Yes	233		
No	267		
Alcohol consumption status			
Yes	119		
No	345		
Lymph node metastasis			
Positive	174		
Negative	181		
Clinical stages			
III-IV	141		
I-II	225		

Abbreviation: SD, standard deviation.

Declaration of Helsinki and all participants signed the informed consent.

2.3 | SNP selection and genotyping

We selected rs6898743 in *GHR* (NG_011688.2) and rs2274223 in *PLCE1* (NG_015799.1) from the 1000 Genomes Project data (http://www.internationalgenome.org/) to analysis with minor allele frequency (MAF) >5%. DNA extraction from whole-blood samples and DNA concentration were conducted based on the related literature report (Geng et al., 2015). MassARRAY Nanodispenser (Agena Bioscience, San Diego, CA, USA) was used to design primers (Jin et al., 2015). The sequences of primers were listed in Table S1. Genotyping was measured by MassARRAY platform (Agena Bioscience, San Diego, CA, USA) with a standard protocol. Data processing and analysis were performed by Agena Bioscience TYPER 4.0.

2.4 | Statistical analysis

Microsoft Excel, the SPSS 16.0 (SPSS, Chicago, IL, USA), and PLINK 1.07 software were used to perform statistical analyses. Hardy–Weinberg equilibrium (HWE) was performed using a Pearson chi-squared test. The logistic regression analysis was used to calculate the odds ratios (OR) and 95% confidence interval (95% CI) (Bland & Altman, 2000). Then, we analyzed the association between different

TABLE 2 Allele frequencies in cases and controls and SNPs function annotation in RegulomeDB

SNP	Gene	Chromosome	Position	Alleles A/B	MAF		*p*-HWE	ORs (95% CI)	*p*	RegulomeDB Score
					Case	Control				
rs6898743	*GHR*	5	42602390	G/C	0.356	0.398	0.853	0.83 (0.70–1.00)	0.049*	No Data
rs2274223	*PLCE1*	10	94306584	G/A	0.258	0.218	0.120	1.25 (1.02–1.53)	0.037*	3a

Abbreviations: 3a, Transcription factor binding + any motif + DNase peak; 95% CI, 95% confidence interval; *GHR* (NG_011688.2), growth hormone receptor; HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency; OR, odds ratio; *PLCE1* (NG_015799.1), phospholipase C epsilon 1; SNP, single-nucleotide polymorphism.

*$p < 0.05$ indicates statistical significance.

TABLE 3 Logistic regression analysis on the association between the SNPs and EC risk

SNP	Gene	Model	Genotype	Case	Control	Adjustment analysis	
						OR (95% CI)	*p*
rs6898743	*GHR*	Co-dominant	CC	215	182	1.00	
			GC	222	246	0.76 (0.58–0.99)	0.046*
			GG	69	79	0.73 (0.50–1.07)	0.109
		Dominant	CC	215	182	1.00	
			GC+GG	291	325	0.75 (0.59–0.97)	0.029*
		Recessive	CC+GC	437	428	1.00	
			GG	69	79	0.85 (0.60–1.21)	0.367
		Log-additive	—	—	—	0.83 (0.70–1.00)	0.045*
rs2274223	*PLCE1*	Co-dominant	AA	279	316	1.00	
			GA	193	161	1.36 (1.04–1.77)	0.023*
			GG	34	30	1.30 (0.77–2.17)	0.326
		Dominant	AA	279	316	1.00	
			GA+GG	227	191	1.35 (1.05–1.73)	0.019*
		Recessive	AA+GA	472	477	1.00	
			GG	34	30	1.16 (0.70–1.92)	0.577
		Log-additive	—	—	—	1.24 (1.01–1.52)	0.036*

Abbreviations: 95% CI, 95% confidence interval; *GHR* (NG_011688.2), growth hormone receptor; OR, odds ratio, *PLCE1* (NG_015799.1), phospholipase C epsilon 1; SNP, single-nucleotide polymorphism.

*$p < 0.05$ indicates statistical significance.

TABLE 4 Stratification analysis on the association between SNPs and EC risk

		SNP: rs6898743				SNP: rs2274223			
Stratification	**Model**	**Genotype**	**Case/ Control**	**OR (95% CI)**	***p***	**Genotype**	**Case/ Control**	**OR (95% CI)**	***p***
Male	Co-dominant	CC	162/143	1.00		AA	205/235	1.00	
		GC	164/176	0.82 (0.60–1.12)	0.216	GA	141/122	1.33 (0.98–1.80)	0.070
		GG	48/56	0.75 (0.48–1.18)	0.214	GG	28/18	1.80 (0.96–3.35)	0.064
	Dominant	CC	162/143	1.00		AA	205/235	1.00	
		GC+GG	212/232	0.81 (0.60–1.08)	0.147	GA+GG	169/140	1.39 (1.04–1.86)	0.028*
	Recessive	CC+GC	326/319	1.00		AA+GA	371/357	1.00	
		GG	48/56	0.84 (0.55–1.27)	0.396	GG	28/18	1.62 (0.88–2.98)	0.124
	Log-additive	—	—	0.86 (0.69–1.06)	0.144			1.33 (1.05–1.69)	0.017*
Female	Co-dominant	CC	53/39	1.00		AA	74/81	1.00	
		GC	58/70	0.59 (0.34–1.02)	0.059	GA	52/39	1.45 (0.86–2.45)	1.160
		GG	21/23	0.66 (0.32–1.36)	0.258	GG	6/12	0.55 (1.20–1.56)	0.263
	Dominant	CC	53/39	1.00		AA	74/81	1.00	
		GC+GG	79/93	0.61 (0.36–1.02)	0.058	GA+GG	58/51	1.24 (0.76–2.03)	0.385
	Recessive	CC+GC	111/109	1.00		AA+GA	126/120	1.00	
		GG	21/23	0.89 (0.47–1.71)	0.736	GG	6/12	0.48 (0.18–1.33)	0.160
	Log-additive	—	—	0.77 (0.54–1.09)	0.140			1.02 (0.69–1.51)	0.913
Age < 64	Co-dominant	CC	101/102	1.00		AA	132/166	1.00	
		GC	106/125	0.86 (0.58–1.25)	0.424	GA	88/83	1.30 (0.89–1.91)	0.174
		GG	30/39	0.85 (0.49–1.49)	0.574	GG	17/17	1.21 (0.59–2.48)	0.613
	Dominant	CC	101/102	1.00		AA	132/166	1.00	
		GC+GG	136/164	0.85 (0.60–1.23)	0.395	GA+GG	105/100	1.29 (0.90–1.85)	0.172
	Recessive	CC+GC	207/227	1.00		AA+GA	220249	1.00	
		GG	30/39	0.93 (0.55–1.56)	0.771	GG	17/17	1.09 (0.54–2.22)	0.805
	Log-additive	—	—	0.90 (0.70–1.17)	0.449			1.19 (0.89–1.59)	0.237
Age ≥ 64	Co-dominant	CC	114/80	1.00		AA	147/150	1.00	
		GC	116/121	0.65 (0.44–0.96)	0.028*	GA	105/78	1.40 (0.96–2.04)	0.077
		GG	39/40	0.69 (0.41–1.17)	0.170	GG	17/13	1.40 (0.65–2.99)	0.389
	Dominant	CC	114/80	1.00		AA	147/150	1.00	
		GC+GG	155/161	0.66 (0.46–0.95)	0.025*	GA+GG	122/91	1.40 (0.98–2.00)	0.065
	Recessive	CC+GC	230/201	1.00		AA+GA	252/228	1.00	

(Continues)

TABLE 4 (Continued)

Stratification	Model	SNP: rs6898743				SNP: rs2274223			
		Genotype	Case/Control	OR (95% CI)	*p*	Genotype	Case/Control	OR (95% CI)	*p*
		GG	39/40	0.88 (0.54–1.42)	0.591	GG	17/13	1.23 (0.58–2.60)	0.591
	Log-additive	—	—	0.79 (0.61–1.02)	0.065			1.29 (0.96–1.73)	0.087
Lymph node metastasis	Co-dominant	CC	81/67	1.00		AA	96/97	1.00	
		GC	66/92	0.57 (0.36–0.90)	0.015*	GA	66/72	0.94 (0.60–1.45)	0.768
		GG	27/22	0.98 (0.51–1.89)	0.961	GG	12/12	1.04 (0.45–2.45)	0.920
	Dominant	CC	81/67	1.00		AA	96/97	1.00	
		GC+GG	93/114	0.65 (0.42–1.00)	0.048*	GA+GG	78/84	0.95 (0.63–1.45)	0.816
	Recessive	CC+GC	147/159	1.00		AA+GA	162/169	1.00	
		GG	27/22	1.32 (0.72–2.42)	0.374	GG	12/12	1.07 (0.47–2.47)	0.867
	Log-additive			0.86 (0.64–1.17)	0.335			0.98 (0.70–1.37)	0.905
Tumor stage	Co-dominant	CC	61/91	1.00		AA	71/128	1.00	
		GC	61/103	0.87 (0.55–1.38)	0.563	GA	60/83	1.32 (0.85–2.06)	0.217
		GG	19/31	0.92 (0.48–1.78)	0.808	GG	10/14	1.25 (0.53–2.98)	0.609
	Dominant	CC	61/91	1.00		AA	71/128	1.00	
		GC+GG	80/134	0.88 (0.58–1.36)	0.577	GA+GG	70/97	1.31 (0.86–2.01)	0.210
	Recessive	CC+GC	122/194	1.00		AA+GA	131/211	1.00	
		GG	19/31	0.99 (0.53–1.83)	0.969	GG	10/14	1.11 (0.48–2.59)	0.802
	Log-additive			0.94 (0.69–1.28)	0.676			1.21 (0.86–1.70)	0.266

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism.

*$p < 0.05$ indicates statistical significance.

TABLE 5 Association between *PLCE1* gene expression and its SNP associated with EC

SNP	Effect Size	*p*-value	Tissue
rs2274223	−0.31	2.8×10^{-13}	Cells-Transformed fibroblasts
rs2274223	0.22	6.0×10^{-11}	Skin-Sun Exposed (Lower leg)
rs2274223	0.31	7.3×10^{-11}	Heart-Left Ventricle
rs2274223	0.25	1.0×10^{-10}	Skin-Not Sun Exposed (Suprapubic)
rs2274223	0.42	1.4×10^{-9}	Adrenal Gland
rs2274223	0.19	7.2×10^{-9}	Lung
rs2274223	0.35	1.5×10^{-8}	Pituitary
rs2274223	0.20	3.9×10^{-8}	Nerve-Tibial
rs2274223	0.19	7.1×10^{-8}	Muscle-Skeletal
rs2274223	0.19	4.1×10^{-7}	Esophagus-Muscularis
rs2274223	0.32	8.7×10^{-7}	Pancreas
rs2274223	0.32	1.1×10^{-6}	Skin-Sun Exposed (Lower leg)
rs2274223	0.23	2.2×10^{-6}	Heart-Atrial Appendage
rs2274223	0.26	2.3×10^{-6}	Colon-Sigmoid
rs2274223	0.34	3.6×10^{-6}	Skin-Not Sun Exposed (Suprapublic)
rs2274223	0.23	4.0×10^{-6}	Stomach
rs2274223	0.40	6.6×10^{-6}	Spleen
rs2274223	0.37	1.1×10^{-5}	Colon-Transverse
rs2274223	0.18	1.5×10^{-5}	Colon-Transverse
rs2274223	0.14	3.2×10^{-5}	Artery-Tibial
rs2274223	0.15	4.9×10^{-5}	Adipose-Subcutaneous

Note: Using the GTEx database, the statistically significant tagSNP (rs2274223) was assessed for association with the cis-gene expression.

Abbreviations: *PLCE1* (NG_015799.1), phospholipase C epsilon 1; SNP, single nucleotide polymorphism.

genotypes and the EC risk using different genetic models stratified by gender, age, lymph node metastasis, and tumor stage, respectively.

2.5 | Bioinformatics and expression analyses

We used database RegulomeDB and Genotype-Tissue Expression (GTEx) to determine the effect of candidate gene SNPs on chromatin structure and allele-specific transcription factor binding. RegulomeDB annotates SNPs of the *Homo sapiens* genome (Boyle et al., 2012). The GTEx database provides a scientific resource to study SNPs. The online database (http://www.gtexportal.org/) was used to investigate the association between selected SNPs (rs2274223, rs6898743) and gene expression (*GHR* and *PLCE1*).

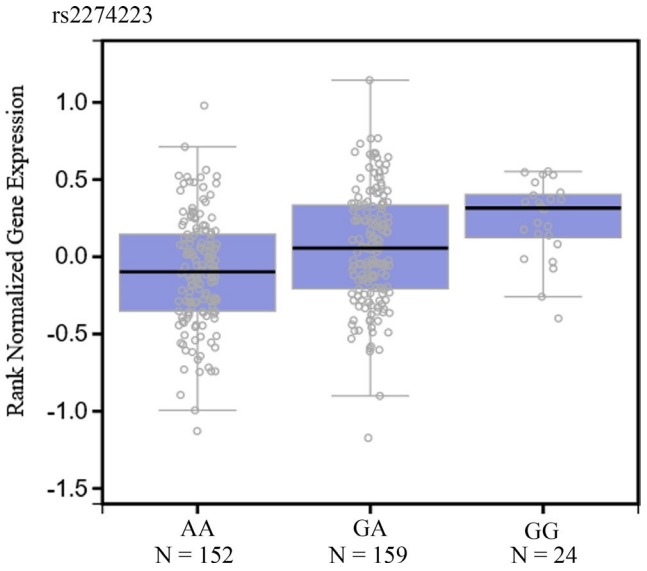

FIGURE 1 Expression of *PLCE1* (NG_015799.1) in GTEx databases: Expression quantitative trait loci (eQTL) analyses of rs2274223 with *PLCE1* mRNA expression levels in esophagus muscularis tissue

Additionally, the UALCAN database (Chandrashekar et al., 2017) was used to analyze the expression of *GHR* and *PLCE1* in EC tissues and normal tissues.

3 | RESULTS

A total of 506 cases (including 374 male and 132 female, 237 less than 64 years old and 269 greater than or equal to 64 years old) and 507 controls (including 375 male and 132 female, 266 less than 64 years old and 241 greater than or equal to 64 years old) were enrolled in our study. The gender and age were matched in this study ($p = 0.403$ and $p = 0.985$, respectively). The body mass index, tobacco smoking status, alcohol consumption status, lymph node metastasis status, and clinical stages information of cases were list in Table 1.

Table 2 listed the basic characteristics of SNPs, and all SNPs in the control group satisfied HWE. The rs6898743 of *GHR* was correlated with EC risk reduction through the Pearson chi-squared test (OR = 0.83, 95% CI: 0.70–1.00, $p = 0.049$), while the rs2274223 of *PLCE1* was associated with EC risk increased 0.25-fold (OR = 1.25, 95% CI: 1.02–1.53, $p = 0.037$). Predicted by RegulomeDB database, there was no data about SNP rs6898743 function annotation, but rs2274223 is evaluated as 3a and is classified as "transcription factor binding + any motif + DNase peak."

We used the logistic regression test to analyze the associations between the SNPs and EC risk in different genetic models. As shown in Table 3, we found that the "GC" genotype

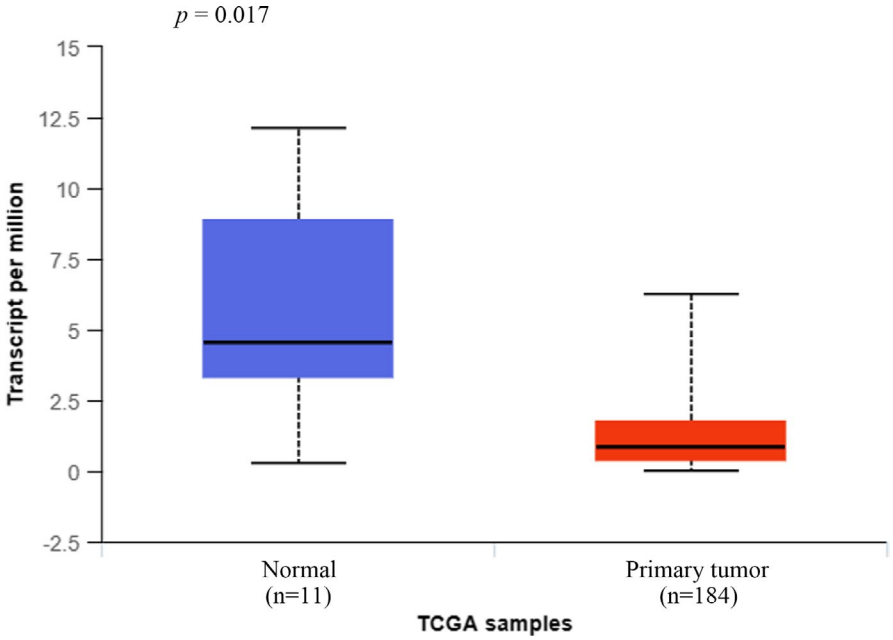

FIGURE 2 Expression of *GHR* (NG_011688.2) in human tissue databases: *GHR* gene expression is downregulated in esophagus cancer tissues ($n = 184$) compared with normal tissues ($n = 11$)

of rs6898743 was associated with a reduced EC risk under co-dominant (OR = 0.76, 95% CI: 0.58–0.99, $p = 0.046$), dominant (OR = 0.75, 95% CI: 0.59–0.97, $p = 0.029$), and log-additive models (OR = 0.83, 95% CI: 0.70–1.00, $p = 0.045$). In addition, there was a 1.36-fold increased risk of EC for individuals with GA genotype of rs2274223 compared with homozygous wild-type individuals under co-dominant model (OR = 1.36, 95% CI: 1.04–1.77, $p = 0.023$) and 1.35-fold increased risk of EC under dominant (OR = 1.35, 95% CI: 1.05–1.73, $p = 0.019$) and log-additive models (OR = 1.24, 95% CI: 1.01–1.52, $p = 0.036$) after adjustment for gender and age.

We further conducted the stratified analysis on gender, age, lymph node metastasis and tumor stage, and the results of the effects of SNPs on EC were listed in Table 4. Under the gender stratified analysis, there was the associations between rs2274223 and the increased risk of EC among males under dominant (OR = 1.39, 95% CI: 1.04–1.86, $p = 0.028$) model and log-additive model (OR = 1.33, 95% CI: 1.05–1.69, $p = 0.017$). In the age stratified analysis, there was the associations between rs6898743 and the decreased risk of EC among patients greater than or equal to 64 years old under co-dominant (OR = 0.65, 95% CI: 0.44–0.96, $p = 0.028$) and dominant models (OR = 0.66, 95% CI: 0.46–0.95, $p = 0.025$). For rs6898743, GC+GG genotype carriers were less likely to have regional lymph node metastasis (OR = 0.65, 95% CI: 0.42–1.00, $p = 0.048$) than CC genotype carriers under dominant model. However, there was no association between rs2274223 and the risk of EC in the lymph node metastasis stratified analysis. The results also showed no association between rs6898743 and rs2274223 and the risk of EC in the tumor stage stratified analysis.

Using the GTEx database, the SNP rs2274223 was found to be associated with the cis-gene expression. Moreover, the SNP of *PLCE1* was identified as cis-eQTLs in different tissues (Table 5). We compared the expression of *PLCE1* among individuals with different genotypes and found that the risk allele of rs2274223 (Figure 1) was associated with increased *PLCE1* expression ($p = 4.1 \times 10^{-7}$) in esophagus muscularis tissues. Using the UALCAN database, the *GHR* gene was detected to be under-expressed in EC tissues ($p = 0.017$) (Figure 2).

4 | DISCUSSION

In this study, we tested two SNPs of two candidate genes *GHR* and *PLCE1* in 1013 subjects. We found that genetic variant rs6898743 in *GHR* was significantly associated with a decreased risk of EC, while rs2274223 in *PLCE1* was associated with an increasing EC risk. Based on the GTEx portal, we found that the risk allele of rs2274223 was associated with increased expression of *PLCE1* in esophagus muscularis samples. Additionally, the UALCAN database demonstrated that the *GHR* gene was under-expressed in EC tissues.

As a transmembrane receptor for growth hormone, the *GHR* gene has been studied on obesity in Korean (Yang, 2016), and rs6898743 showed a significant association with obesity. In addition, this SNP also has an influence on tumor. McElholm et al. (2010) analyzed 102 SNPs in the Insulin-like growth factor (IGF) axis and characterized the genetic variant rs6898743 of *GHR* gene, which appeared to be associated with EAC, in an Irish population-based case control study. Ong et al. (2014) found the GC genotype of rs6898743 of *GHR* gene was negatively associated

with ESCC in a Dutch case-control study. In this research, we investigated the association between the genetic variant rs6898743 of *GHR* gene and the EC risk in a Chinese case control population, and we concluded a positive result in accordance with McElholm et al. The possible molecular mechanism is that IGF pathway is involved in the development of EC, but it still requires independent verification of our findings.

A genome-wide association study of Chinese subjects was conducted for gastric adenocarcinoma and ESCC, and Abnet et al. found rs2274223 of *PLCE1* was related with gastric cancer ($p = 8.40 \times 10^{-9}$) and ESCC ($p = 3.85 \times 10^{-9}$) (Abnet et al., 2010). The studies have reported that *PLCE1* has an oncogenic role in skin and intestinal carcinogenesis (Bai et al., 2004; Li, Edamatsu, Kitazawa, Kitazawa, & Kataoka, 2009), as well as in head and neck squamous cell carcinoma progression (Bunney, Baxendale, & Katan, 2009). Furthermore, our research results also validate the research on the risk factors of EC conducted by Wang and Wu et al (Wang et al., 2010; Wu et al., 2011). Besides, in the stratification analysis on age and gender, we also found that rs2274223 acted as a risk factor of EC in males under dominant and additive models with *p*-values of 0.028 and 0.017, respectively.

However, the limited number of the selected SNPs in genes *GHE* and *PLCE1* is one of the restrictions in this study. Besides, the molecular mechanisms involved in regulating the EC risk has not been investigated. Therefore, the results need to be verified and future studies are needed to reveal the potential molecular mechanism of the *GHE* and *PLCE1* involved in EC.

5 | CONCLUSIONS

The variants rs6898743 of *GHR* and rs2274223 of *PLCE1* are associated with the EC risk and rs2274223 may influence the *PLCE1* gene expression in Chinese population.

ACKNOWLEDGMENTS

We like to thank all participators in this study.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

RW prepared the manuscript; LNS, DRZ, GPS, and QFL collected and analyzed the collection; YLZ designed the study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Wang R, Si L, Zhu D, Shen G, Long Q, Zhao Y. Genetic variants in *GHR* and *PLCE1* genes are associated with susceptibility to esophageal cancer. *Mol Genet Genomic Med*. 2020;8:e1474. https://doi.org/10.1002/mgg3.1474