Polymorphisms in endoplasmic reticulum aminopeptidase genes are associated with cervical cancer risk in a Chinese Han population

Chuanyin Li

Chinese Academy of Medical Sciences & Peking Union Medical College Institute of medical biology

Yaheng Li

Chinese Academy of Medical Sciences & Peking Union Medical College Institute of Medical Biology

Zhiling Yan

Department of Gynaecologic Oncology The third Affiliated Hospital of Kunming Medical University

Shuying Dai

School of Basic Medical Science Kunming Medical University

Shuyuan Liu

Chinese Academy of Medical Sciences & Peking Union Medical College Institute of Medical Biology

Xia Wang

Department of gynaecologic Oncology The Third Affiliated Hospital of Kunming Medical University

Jun Wang

Department of Gynaecologic Oncology The Third Affiliated Hospital of Kunming Medical University

Xinwen Zhang

Chinese Academy of Medical Sciences & Peking Union Medical College Institute of Medical Biology

Li Shi (✉ shili.imb@gmail.com)

Chinese Academy of Medical Sciences & Peking Union Medical College Institute of Medical Biology

<https://orcid.org/0000-0001-9508-7863>

Yufeng Yao

Chinese Academy of Medical Sciences & Peking Union Medical College Institute of Medical Biology

Research article

Keywords: Endoplasmic reticulum aminopeptidase, Single nucleotide polymorphisms, Association, Susceptibility, Cervical intraepithelial neoplasia, Cervical cancer

Posted Date: January 21st, 2020

DOI: <https://doi.org/10.21203/rs.2.21433/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Version of Record: A version of this preprint was published at BMC Cancer on April 22nd, 2020. See the published version at <https://doi.org/10.1186/s12885-020-06832-2>.

Abstract

Background: antigen-processing machinery molecules play crucial roles in infectious diseases and cancers. Studies have shown that variants in endoplasmic reticulum aminopeptidase (ERAP) genes can influence the enzymatic activity of ERAP proteins and are associated with the risk of cancers. In the current study, we evaluated the influence of ERAP gene (*ERAP1* and *ERAP2*) variants on susceptibility to cervical intraepithelial neoplasia (CIN) and cervical cancer.

Methods: Six single nucleotide polymorphisms (SNPs) in *ERAP1* and 5 SNPs in *ERAP2* were selected and genotyped in 556 CIN patients, 1072 cervical cancer patients, and 1262 healthy control individuals. Candidate SNPs were genotyped using SNaPshot assay. And the association of these SNPs with CIN and cervical cancer was analysed.

Results: the results showed that allelic and genotypic frequencies of rs26653 in *ERAP1* were significantly different between cervical cancer and control groups ($P=0.001$ and 0.004). The allelic frequencies of rs27044 in *ERAP1* and rs2287988 in *ERAP2* were also significantly different between control and cervical cancer groups ($P=0.003$ and 0.004). Inheritance model analysis showed that genotypes at rs26618, rs26653, rs27044, and rs2287988 SNPs may be associated with the risk of cervical cancer ($P=0.004$, 0.001 , 0.003 , and 0.002). Additionally, haplotype analysis results showed that the *ERAP1* haplotype, rs26618T-rs26653G-rs27044C-rs30187T-rs3734016C, was associated with a lower risk of cervical cancer ($P=0.001$; OR=0.804, 95%CI:0.711-0.910). The *ERAP2* haplotypes rs2248374A-rs2549782G-rs2287988G-rs2548538A-rs1056893T might be the risk factor of cervical cancer ($P=0.009$; OR=1.592, 95%CI:1.122-2.258). Haplotype rs2248374G-rs2549782T-rs2287988A-rs2548538T-rs1056893T of *ERAP2* might be associated with lower risk of cervical cancer ($P=0.003$; OR=0.835, 95%CI:0.740-0.942).

Conclusion: Our results indicated that rs26653 and rs27044 in *ERAP1* and rs2287988 in *ERAP2* influenced susceptibility to cervical cancer.

Background

The antigen-processing machinery (APM) is composed of the proteasome, where exogenous and tumour antigens are degraded into peptides; transporters associated with antigen presentation (TAPs), which are responsible for the translocation of peptide precursors; endoplasmic reticulum aminopeptidases (ERAPs), which trim the peptides to fit major histocompatibility complex (MHC) molecules; and MHC proteins, which present antigen peptides on the cell surface (1, 2). Human ERAPs, which belong to the oxytocinase subfamily of M1 metalloproteases, are crucial molecules of the APM. In the endoplasmic reticulum lumen, ERAP1 and ERAP2 trim peptides into their final length to render them suitable for loading onto HLA class I molecules (3, 4). Recently, several studies have shown that ERAP proteins play crucial roles in autoimmune diseases (5, 6), infectious diseases (7, 8), and cancers (9, 10).

Cervical cancer is the fourth most common malignancy in women globally (11). Persistent human papillomavirus (HPV) infection confers a high risk of the initiation and development of cervical cancer (12, 13). Since the HLA class I antigen-presenting system is responsible for the presentation of foreign and cancerous antigens to the immune system, it plays a crucial role in the immune recognition and clearance of HPV and cancerous cells (14). Therefore, ERAP proteins, which are involved in the processing of viral and cancerous protein antigens, are

important for the specific immune response to HPV-infected cells and cancerous cells during the initiation and development of cervical cancer.

Studies have shown that polymorphisms in ERAP genes affect the enzymatic activity and selectivity of ERAP proteins (15-20). Moreover, when located at essential structural positions, these polymorphisms affect the conformation of ERAP proteins (19, 21, 22). This may explain the association between SNPs in ERAP genes and autoimmune and infectious diseases (23-26). Similarly, in human cancers, our previous study and other studies have reported associations between polymorphisms in ERAP genes and human cancers (27-30).

In the current study, we selected 11 SNPs located in *ERAP1* (rs26618, rs26653, rs27044, rs30187, rs3734016 and rs27037) and *ERAP2* (rs2248374, rs2549782, rs2287988, rs2548538 and rs1056893) and investigated their distribution in patients with cervical intraepithelial neoplasia (CIN) and cervical cancer and healthy individuals, to assess their association with the initiation and development of cervical cancer.

Methods

Study population

In the current study, a total of 556 patients with CIN and 1072 patients with cervical cancer were enrolled at the third Affiliated Hospital of Kunming Medical University from May 2014 to August 2018. The inclusion criteria were as follows: 1) diagnosis of CIN or cervical cancer according to *Current Diagnosis and Treatment: Obstetrics and Gynaecology* and International Federation of Gynaecology and Obstetrics (2009) guidelines; 2) no other malignancy in patients and no history of cancer or other chronic diseases in control individuals; and 3) no preoperative neoadjuvant therapies (including chemotherapy and radiotherapy). The exclusion criteria for patients were as follows: 1) a prior history of primary cancer other than cervical cancer; 2) malignant tumours other than cervical cancer; 3) currently receiving radiotherapy or chemotherapy; and 4) an unclear diagnosis. Over the same period, 1262 healthy women from a health screening project at the same hospital were enrolled as controls.

SNP selection and genotyping

Six SNPs located in *ERAP1* and 5 SNPs located in *ERAP2* were selected in the current study. The details of the selected SNPs are displayed in Supplementary Table 1. Venous blood samples were collected for the extraction of genomic DNA, using the QIAamp Blood Mini Kit (Qiagen NV, Venlo, Netherlands). Genotyping of the 11 SNPs was performed using the SNaPshot SNP assay (Thermo Fisher Scientific, Waltham, MA, USA), and results were analysed using GeneMapper TM 4.0 software (Applied Biosystems, Foster City, CA, USA). For quality control, 5% of samples from the case and control groups were genotyped twice with unique analysis serial numbers and the reproducibility was found to be 100%.

Statistical analysis

Hardy-Weinberg equilibrium (HWE) was evaluated to determine the representativeness of the study population. The differences in age among the CIN, cervical cancer, and control groups were analysed using a one-way ANOVA, with a least significant difference test for multiple comparison correction. Allelic and genotypic frequencies of these SNPs were compared between different groups using a Chi-square test and odds ratios (ORs) with associated 95% confidence intervals (CIs) were calculated. Additionally, linkage disequilibrium (LD) was calculated and a D' value greater than 0.80 was considered to indicate LD. The haplotypes among these SNPs were analysed

using SHEsis software (31, 32). Subsequently, the distribution of the haplotypes between different groups was compared using a Chi-square test. Additionally, inheritance analysis was performed using SNPstats software, to identify the relationship between genotypes at these SNPs and cervical cancer (33). In the inheritance analysis, four inheritance models (codominant, dominant, recessive, and log-additive) were analysed. Simultaneously, Akaike information criterion (AIC) and Bayesian information criterion (BIC) values were calculated to determine the inheritance model with the best fit, i.e. the model with the smallest AIC and BIC values (33). Bonferroni correction was performed for multiple comparisons, after which the statistical significance threshold was set at $P < 0.005$ (0.05/11).

Results

Characteristics of the subjects Table 1 shows the clinical data of the subjects in the present study. There was no significant difference in age among the control, CIN, and cervical cancer groups ($P > 0.05$, $F = 1.438$), as evaluated by one-way ANOVA. In the CIN group, there were 65 patients with low-grade CIN (I/II) and 491 patients with high-grade CIN (III). In the cervical cancer group, there were 151 patients with adenocarcinoma, 903 patients with squamous cell carcinoma, and 18 patients with other pathological types. Association of the eleven SNPs with CIN and cervical cancer All 11 SNPs were in HWE in the control group ($P > 0.05$). The allelic and genotypic frequencies of these SNPs are presented in Tables 2 and 3. The results showed that the allelic and genotypic frequencies of rs26618 ($P = 0.021$ and 0.016 , respectively), rs26653 ($P = 0.001$ and 0.004), rs27044 ($P = 0.003$ and 0.012) and rs30187 ($P = 0.008$ and 0.020) in ERAP1 and rs2248374 ($P = 0.014$ and 0.020) and rs2287988 ($P = 0.004$ and 0.007) in ERAP2 were significantly different between cervical cancer and control groups. Additionally, the allelic and genotypic distributions of rs2248374 ($P = 0.015$ and 0.041 , respectively) and rs2287988 ($P = 0.014$ and 0.039) in ERAP2 were significantly different between CIN and cervical cancer groups. However, after Bonferroni correction, only rs26653, rs27044, and rs2287988 were associated with cervical cancer risk ($P < 0.005$). The results indicated that, in ERAP1, the G allele of rs26653 may be associated with a lower risk of cervical cancer compared with C allele (OR = 0.829; 95% CI: 0.738-0.930) and the G allele of rs27044 may be a risk factor for the development of cervical cancer (OR = 1.193, 95% CI: 1.062-1.340). Moreover, the A allele of rs2287988 in ERAP2 may be associated with a lower risk of cervical cancer (OR = 0.843, 95% CI: 0.751-0.946). There were no SNPs in ERAP1 or ERAP2 that exhibited a significantly different distribution between the CIN and control groups or between the CIN and cervical cancer groups ($P > 0.005$). Inheritance model analysis To evaluate the genotypic association of the 11 SNPs with CIN and cervical cancer, inheritance analysis was performed among cervical cancer, CIN, and control groups (Table 4, Table 5, and Supplementary Tables 2-5). The CC genotype of rs26618 was a risk factor for cervical cancer, compared with TT-CT genotype ($P = 0.004$; OR = 1.53, 95%CI: 1.14-2.05) in the recessive model (the best-fit inheritance model for the comparison between control and cervical cancer groups). The 2GG+CG genotype of rs26653 was associated with a lower risk of cervical cancer compared with the CC genotype ($P = 0.001$, OR = 0.82; 95% CI: 0.73-0.93) in the log-additive model (the best-fit inheritance model for the comparison between control and cervical cancer groups). The 2CC+CG genotype of rs27044 may be a protective factor against the development of cervical cancer compared with the GG genotype ($P = 0.003$, OR = 0.84; 95% CI: 0.75-0.94) in the log-additive model (the best-fit inheritance model for the comparison between control and cervical cancer groups) and the GG+GA genotype of rs2287988 may be a risk factor for cervical cancer compared with the AA genotype ($P = 0.002$, OR = 1.33; 95% CI: 1.11-1.60) in the dominant model (the best fit inheritance model for the comparison between control and cervical cancer groups). LD and haplotype analysis of SNPs in ERAP1 and ERAP2 The results of LD analysis showed that rs26618, rs26653, rs27044, rs30187, and rs3734016 in ERAP1 and rs2248374, rs2549782, rs2287988, rs2548538, and rs1056893 in ERAP2 were in LD ($D' > 0.80$). Subsequently, we constructed

the haplotypes, rs26618-rs26653-rs27044-rs30187-rs3734016 and rs2248374-rs2549782-rs2287988-rs2548538-rs1056893. The distribution of these haplotypes (with a frequency of more than 3%) was compared in a pairwise manner among the cervical cancer, CIN, and control groups (Tables 6 and 7). The ERAP1 haplotype, rs26618T-rs26653G-rs27044C-rs30187T-rs3734016C, was associated with a lower risk of cervical cancer ($P = 0.001$; OR = 0.804, 95% CI: 0.711-0.910). The distribution of haplotypes rs2248374A-rs2549782G-rs2287988G-rs2548538A-rs1056893T and rs2248374G-rs2549782T-rs2287988A-rs2548538T-rs1056893T in ERAP2 were significantly different in the control ($P = 0.009$ and 0.003 , respectively) and CIN ($P = 0.006$ and 0.009) groups compared with the cervical cancer group. The results indicated that rs2248374A-rs2549782G-rs2287988G-rs2548538A-rs1056893T may be associated with a higher risk of cervical cancer (OR = 1.592, 95% CI: 1.122-2.258) and the progression from CIN to cervical cancer (OR = 2.000, 95% CI: 1.215-3.292). Moreover, rs2248374G-rs2549782T-rs2287988A-rs2548538T-rs1056893T may be associated with a lower risk of cervical cancer (OR = 0.835, 95% CI: 0.740-0.942) and the progression from CIN to cervical cancer (OR = 0.817, 95% CI: 0.702-0.951).

Discussion

The immune system is activated by MHC-peptide complexes, after which it eliminates infected and cancerous cells in various ways. The APM plays crucial roles in the initiation and development of various human diseases. As components of the APM, ERAP1 and ERAP2 are important determinants of the repertoire of peptides ultimately presented by HLA class I molecules (34-37). Our previous study showed that four polymorphisms in *ERAP1* are associated with non-small cell lung cancer in a Chinese population (27). In the current study, we selected six SNPs in *ERAP1* and five SNPs in *ERAP2*, and investigated their distribution in CIN patients, cervical cancer patients, and healthy individuals. Our results showed that rs26618, rs26653, and rs27044 in *ERAP1* and rs2287988 in *ERAP2* may be associated with cervical cancer risk.

The SNP, rs26618, in *ERAP1* leads to an amino acid substitution (I276M) and the current study showed that the CC genotype of this SNP may be associated with an increased risk of cervical cancer (OR = 1.53; 95% CI: 1.14-2.05) compared with TT-CT genotypes. In 2016, Guasp et al. reported that I276M (rs26618) may affect the peptidome of ERAP1 by destroying peptides with p2 Ala, unless the p1 amino acid was resistant to ERAP1 trimming (38), which indicated that rs26618 may be associated with cervical cancer. However, in a Netherlands population, Mehta et al. reported no association between rs26618 and cervical carcinoma. This inconsistency may be due to the different sample sizes used. The sample size used by Mehta et al. was 251, while 2890 individuals were enrolled in the current study.

In 2007, Mehta et al. reported that the C allele of rs26653 in *ERAP1* was associated with a higher cervical cancer risk in a Netherlands population (28). In the current study, the G allele (OR = 0.829; 95% CI: 0.738-0.930), compared to the C allele, and the 2GG+CG genotype, compared to the CC genotype (OR = 0.82; 95% CI: 0.73-0.93) of rs26653, were associated with lower cervical cancer risk. In 2014, Stratikos et al. and Alvarez-Navarro et al. reported that rs26653, which is a non-synonymous variant resulting in a P127R substitution, may be associated with ERAP expression (39, 40), and this substitution may also affect the enzymatic activity of ERAP1 in the editing of tumour antigen peptides. This finding may explain the association between rs26653 and cervical cancer risk; however, the mechanisms need to be determined in functional studies.

In 2007, Mehta et al. also found that rs27044 in *ERAP1* was associated with cervical cancer risk. In the current study, rs27044 was found to be associated with cervical cancer risk ($P = 0.003$). The G allele of rs27044 (Q730) was found to be a risk factor for the progression from CIN to cervical cancer (OR = 1.193, 95% CI: 1.062-1.340),

which was consistent with the results of Mehta's study (28). The SNP, rs27044, another non-synonymous variant, leads to a Q730E substitution in the IV catalysis domain of ERAP1 (21) and may change the substrate length preferences of ERAP1 (40). Thus, rs27044 may play a role in cervical cancer by affecting ERAP1 function.

In the current study, we found an association between rs2287988 in *ERAP2*, which is responsible for a synonymous variant (Q563Q), and cervical cancer. The A allele may be associated with a lower risk of cervical cancer ($P = 0.004$; OR = 0.843, 95% CI: 0.751-0.946). Moreover, the GG-GA genotype was associated with an increased risk of cervical cancer ($P = 0.002$; OR = 1.33, 95% CI: 1.11-1.60). However, association studies of this SNP are rare. Previous studies have found that ERAP2 haplotypes containing rs2287988 affect ERAP2 splicing and expression (41, 42). Thus, additional association studies in different populations are necessary to investigate the role of this variant during the initiation and development of cervical cancer.

ERAPs are markedly polymorphic and *ERAP* haplotypes whose protein products differ at multiple amino acids may affect peptide editing by ERAPs (17, 18, 43, 44). In the current study, we also analysed haplotypes of *ERAP* SNPs in LD. The results showed that the *ERAP1* haplotype, rs26618T-rs26653G-rs27044C-rs30187T-rs3734016C and the *ERAP2* haplotypes, rs2248374G-rs2549782T-rs2287988A-rs2548538T-rs1056893T and rs2248374A-rs2549782G-rs2287988G-rs2548538A-rs1056893T may be associated with cervical cancer risk. These results indicated that SNPs in polymorphic genes may have combinatorial effects on disease susceptibility.

Conclusion

Recent studies have shown that variants in human genes may affect gene expression (45-47). In addition, SNPs in ERAP genes have been shown to affect the function of ERAPs by changing their peptidome or enzymatic activity (17, 18, 38). In cervical cancer, ERAP1 and ERAP2 proteins have been reported to be highly variable, ranging from low to high expression levels (48-50). Although there are inconsistencies among these studies, it is clear that the dysregulated expression of ERAP proteins, which may be induced by *ERAP* gene SNPs (47, 51), is associated with cervical cancer risk. In the current study, we investigated the association of SNPs in ERAP genes (11 SNPs located in ERAP1 and ERAP2) with CIN (the initiation of cervical cancer) and cervical cancer (the development of cervical cancer). Our results showed that genetic variants in *ERAP1* and *ERAP2* may be associated with CIN and cervical cancer. Moreover, our results showed that variants in key antigen-processing genes affect the initiation and development of cervical cancer, a virus- and inflammation-induced cancer.

Abbreviations

Endoplasmic reticulum aminopeptidase: ERAP; Single nucleotide polymorphisms: SNPs; Antigen-processing machinery: APM; Transporters associated with antigen presentation: TAPs; Major histocompatibility complex: MHC; Human papillomavirus: HPV; Hardy-Weinberg equilibrium: HWE; Odds ratios: ORs; Cervical intraepithelial neoplasia: CIN; confidence intervals: CIs; Linkage disequilibrium: LD; Akaike information criterion: AIC; Bayesian information criterion: BIC.

Declarations

Ethics approval and consent to participate

The current study was approved by the Institutional Review Boards of the No. 3 Affiliated Hospitals of Kunming Medical University and was performed in accordance with the principles of the Declaration of Helsinki. All individuals enrolled in this study provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The data generated during the current study are available to any scientist wishing to use them for non-commercial purpose from the corresponding author on reasonable request. However, the clinical data are not available, because we did not obtain the permission from participants to release these privacy data.

Competing interests

The authors declare that they have no competing interests.

Funding

The current study was supported by grant from the National Natural Science Foundation of China (81573206), Yunnan Applied Basic Research Projects (2016FA034), The PUMC Youth Fund (3332019111), Special Funds for High-level Healthy Talents of Yunnan Province (D-201669 and L-201615), CAMS Innovation Fund for Medical Sciences (2016-I2M-2-001), Yunnan Provincial Science and Technology Department (2019HC0060), Association Foundation Program of Yunnan Provincial Science and Technology Department and Kunming Medical University (2017FR467-077 and 2017FE467-012). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Authors' contributions

LS and YFY designed the current study; CYL and YHL finished the main part of experiment and data analysis of the current study; ZLY and SYD finished the sample clinical diagnose and collection; XW and JW were responsible for the collection of venous blood; SYL and XWZ participated in the genomic DNA extraction; CYL and YHL drafted the manuscript; LS and YFY revised the manuscript. And all authors have read and approved the manuscript.

Acknowledgement

Our great gratitude was expressed to the participation of the patients and control subjects in current study.

References

1. Germain RN, Margulies DH. The biochemistry and cell biology of antigen processing and presentation. Annual review of immunology. 1993;11:403-50.
2. Heemels MT, Ploegh H. Generation, translocation, and presentation of MHC class I-restricted peptides. Annual review of biochemistry. 1995;64:463-91.
3. Vyas JM, Van der Veen AG, Ploegh HL. The known unknowns of antigen processing and presentation. Nature reviews Immunology. 2008;8(8):607-18.

4. Saric T, Chang SC, Hattori A, York IA, Markant S, Rock KL, et al. An IFN-gamma-induced aminopeptidase in the ER, ERAP1, trims precursors to MHC class I-presented peptides. *Nature immunology*. 2002;3(12):1169-76.
5. Pepelyayeva Y, Amalfitano A. The role of ERAP1 in autoinflammation and autoimmunity. *Human immunology*. 2019;80(5):302-9.
6. Reeves E, James E. The role of polymorphic ERAP1 in autoinflammatory disease. *Bioscience reports*. 2018;38(4).
7. Lorente E, Barriga A, Johnstone C, Mir C, Jimenez M, Lopez D. Concerted in vitro trimming of viral HLA-B27-restricted ligands by human ERAP1 and ERAP2 aminopeptidases. *PloS one*. 2013;8(11):e79596.
8. Cifaldi L, Romania P, Lorenzi S, Locatelli F, Fruci D. Role of endoplasmic reticulum aminopeptidases in health and disease: from infection to cancer. *International journal of molecular sciences*. 2012;13(7):8338-52.
9. Compagnone M, Cifaldi L, Fruci D. Regulation of ERAP1 and ERAP2 genes and their dysfunction in human cancer. *Human immunology*. 2019;80(5):318-24.
10. Stoehr CG, Buettner-Herold M, Kamphausen E, Bertz S, Hartmann A, Seliger B. Comparative expression profiling for human endoplasmic reticulum-resident aminopeptidases 1 and 2 in normal kidney versus distinct renal cell carcinoma subtypes. *International journal of clinical and experimental pathology*. 2013;6(6):998-1008.
11. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA: a cancer journal for clinicians*. 2015;65(2):87-108.
12. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*. 1999;189(1):12-9.
13. Munoz N. Human papillomavirus and cancer: the epidemiological evidence. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology*. 2000;19(1-2):1-5.
14. Delves PJ, Roitt IM. The immune system. First of two parts. *The New England journal of medicine*. 2000;343(1):37-49.
15. Birtley JR, Saridakis E, Stratikos E, Mavridis IM. The crystal structure of human endoplasmic reticulum aminopeptidase 2 reveals the atomic basis for distinct roles in antigen processing. *Biochemistry*. 2012;51(1):286-95.
16. Mpakali A, Giastas P, Mathioudakis N, Mavridis IM, Saridakis E, Stratikos E. Structural Basis for Antigenic Peptide Recognition and Processing by Endoplasmic Reticulum (ER) Aminopeptidase 2. *The Journal of biological chemistry*. 2015;290(43):26021-32.
17. Stamogiannos A, Koumantou D, Papakyriakou A, Stratikos E. Effects of polymorphic variation on the mechanism of Endoplasmic Reticulum Aminopeptidase 1. *Molecular immunology*. 2015;67(2 Pt B):426-35.
18. Evnouchidou I, Kamal RP, Seregin SS, Goto Y, Tsujimoto M, Hattori A, et al. Cutting Edge: Coding single nucleotide polymorphisms of endoplasmic reticulum aminopeptidase 1 can affect antigenic peptide generation in vitro by influencing basic enzymatic properties of the enzyme. *Journal of immunology (Baltimore, Md : 1950)*. 2011;186(4):1909-13.
19. Evnouchidou I, Birtley J, Seregin S, Papakyriakou A, Zervoudi E, Samiotaki M, et al. A common single nucleotide polymorphism in endoplasmic reticulum aminopeptidase 2 induces a specificity switch that leads to altered antigen processing. *Journal of immunology (Baltimore, Md : 1950)*. 2012;189(5):2383-92.
20. Zervoudi E, Papakyriakou A, Georgiadou D, Evnouchidou I, Gajda A, Poreba M, et al. Probing the S1 specificity pocket of the aminopeptidases that generate antigenic peptides. *The Biochemical journal*. 2011;435(2):411-

20.

21. Hattori A, Tsujimoto M. Endoplasmic reticulum aminopeptidases: biochemistry, physiology and pathology. *Journal of biochemistry*. 2013;154(3):219-28.
22. Nguyen TT, Chang SC, Evnouchidou I, York IA, Zikos C, Rock KL, et al. Structural basis for antigenic peptide precursor processing by the endoplasmic reticulum aminopeptidase ERAP1. *Nature structural & molecular biology*. 2011;18(5):604-13.
23. Wang J, Li H, Wang J, Gao X. Association between ERAP1 gene polymorphisms and ankylosing spondylitis susceptibility in Han population. *International journal of clinical and experimental pathology*. 2015;8(9):11641-6.
24. Hill LD, Hilliard DD, York TP, Srinivas S, Kusanovic JP, Gomez R, et al. Fetal ERAP2 variation is associated with preeclampsia in African Americans in a case-control study. *BMC medical genetics*. 2011;12:64.
25. Cagliani R, Riva S, Biasin M, Fumagalli M, Pozzoli U, Lo Caputo S, et al. Genetic diversity at endoplasmic reticulum aminopeptidases is maintained by balancing selection and is associated with natural resistance to HIV-1 infection. *Human molecular genetics*. 2010;19(23):4705-14.
26. Liu S, Cao D, Shen Y, Li Y, Li Y, Shi L, et al. The ERAP gene is associated with HCV chronic infection in a Chinese Han population. *Hum Immunol*. 2017;78(11-12):731-8.
27. Yao Y, Wisniewski A, Ma Q, Kowal A, Porebska I, Pawelczyk K, et al. Single Nucleotide Polymorphisms of the ERAP1 Gene and Risk of NSCLC: A Comparison of Genetically Distant Populations, Chinese and Caucasian. *Arch Immunol Ther Exp (Warsz)*. 2016;64(Suppl 1):117-22.
28. Mehta AM, Jordanova ES, van Wezel T, Uh HW, Corver WE, Kwappenberg KM, et al. Genetic variation of antigen processing machinery components and association with cervical carcinoma. *Genes, chromosomes & cancer*. 2007;46(6):577-86.
29. Mehta AM, Jordanova ES, Corver WE, van Wezel T, Uh HW, Kenter GG, et al. Single nucleotide polymorphisms in antigen processing machinery component ERAP1 significantly associate with clinical outcome in cervical carcinoma. *Genes, chromosomes & cancer*. 2009;48(5):410-8.
30. Mehta AM, Spaans VM, Mahendra NB, Osse EM, Vet JN, Purwoto G, et al. Differences in genetic variation in antigen-processing machinery components and association with cervical carcinoma risk in two Indonesian populations. *Immunogenetics*. 2015;67(5-6):267-75.
31. Li Z, Zhang Z, He Z, Tang W, Li T, Zeng Z, et al. A partition-ligation-combination-subdivision EM algorithm for haplotype inference with multiallelic markers: update of the SHEsis (<http://analysis.bio-x.cn>). *Cell Res*. 2009;19(4):519-23.
32. Shi YY, He L. SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. *Cell Res*. 2005;15(2):97-8.
33. Sole X, Guino E, Valls J, Iniesta R, Moreno V. SNPStats: a web tool for the analysis of association studies. *Bioinformatics*. 2006;22(15):1928-9.
34. Falk K, Rotzschke O. The final cut: how ERAP1 trims MHC ligands to size. *Nature immunology*. 2002;3(12):1121-2.
35. York IA, Chang SC, Saric T, Keys JA, Favreau JM, Goldberg AL, et al. The ER aminopeptidase ERAP1 enhances or limits antigen presentation by trimming epitopes to 8-9 residues. *Nature immunology*. 2002;3(12):1177-84.
36. Chang SC, Momburg F, Bhutani N, Goldberg AL. The ER aminopeptidase, ERAP1, trims precursors to lengths of MHC class I peptides by a "molecular ruler" mechanism. *Proceedings of the National Academy of Sciences of*

- the United States of America. 2005;102(47):17107-12.
37. Saveanu L, Carroll O, Lindo V, Del Val M, Lopez D, Lepelletier Y, et al. Concerted peptide trimming by human ERAP1 and ERAP2 aminopeptidase complexes in the endoplasmic reticulum. *Nature immunology*. 2005;6(7):689-97.
 38. Guasp P, Alvarez-Navarro C, Gomez-Molina P, Martin-Esteban A, Marcilla M, Barnea E, et al. The Peptidome of Behcet's Disease-Associated HLA-B*51:01 Includes Two Subpeptidomes Differentially Shaped by Endoplasmic Reticulum Aminopeptidase 1. *Arthritis & rheumatology (Hoboken, NJ)*. 2016;68(2):505-15.
 39. Stratikos E, Stamogiannos A, Zervoudi E, Fruci D. A role for naturally occurring alleles of endoplasmic reticulum aminopeptidases in tumor immunity and cancer pre-disposition. *Frontiers in oncology*. 2014;4:363.
 40. Alvarez-Navarro C, Lopez de Castro JA. ERAP1 structure, function and pathogenetic role in ankylosing spondylitis and other MHC-associated diseases. *Mol Immunol*. 2014;57(1):12-21.
 41. Andres AM, Dennis MY, Kretzschmar WW, Cannons JL, Lee-Lin SQ, Hurle B, et al. Balancing selection maintains a form of ERAP2 that undergoes nonsense-mediated decay and affects antigen presentation. *PLoS genetics*. 2010;6(10):e1001157.
 42. Vanhille DL, Hill LD, Hilliard DD, Lee ED, Teves ME, Srinivas S, et al. A Novel ERAP2 Haplotype Structure in a Chilean Population: Implications for ERAP2 Protein Expression and Preeclampsia Risk. *Molecular genetics & genomic medicine*. 2013;1(2):98-107.
 43. Goto Y, Hattori A, Ishii Y, Tsujimoto M. Reduced activity of the hypertension-associated Lys528Arg mutant of human adipocyte-derived leucine aminopeptidase (A-LAP)/ER-aminopeptidase-1. *FEBS letters*. 2006;580(7):1833-8.
 44. Kochan G, Krojer T, Harvey D, Fischer R, Chen L, Vollmar M, et al. Crystal structures of the endoplasmic reticulum aminopeptidase-1 (ERAP1) reveal the molecular basis for N-terminal peptide trimming. *Proceedings of the National Academy of Sciences of the United States of America*. 2011;108(19):7745-50.
 45. Dixon AL, Liang L, Moffatt MF, Chen W, Heath S, Wong KC, et al. A genome-wide association study of global gene expression. *Nature genetics*. 2007;39(10):1202-7.
 46. Harvey D, Pointon JJ, Evans DM, Karaderi T, Farrar C, Appleton LH, et al. Investigating the genetic association between ERAP1 and ankylosing spondylitis. *Human molecular genetics*. 2009;18(21):4204-12.
 47. Hanson AL, Cuddihy T, Haynes K, Loo D, Morton CJ, Oppermann U, et al. Genetic Variants in ERAP1 and ERAP2 Associated With Immune-Mediated Diseases Influence Protein Expression and the Isoform Profile. *Arthritis & rheumatology (Hoboken, NJ)*. 2018;70(2):255-65.
 48. Mehta AM, Jordanova ES, Kenter GG, Ferrone S, Fleuren GJ. Association of antigen processing machinery and HLA class I defects with clinicopathological outcome in cervical carcinoma. *Cancer immunology, immunotherapy : CII*. 2008;57(2):197-206.
 49. Uhlen M, Fagerberg L, Hallstrom BM, Lindskog C, Oksvold P, Mardinoglu A, et al. Proteomics. Tissue-based map of the human proteome. *Science (New York, NY)*. 2015;347(6220):1260419.
 50. Steinbach A, Winter J, Reuschenbach M, Blatnik R, Klevenz A, Bertrand M, et al. ERAP1 overexpression in HPV-induced malignancies: A possible novel immune evasion mechanism. *Oncoimmunology*. 2017;6(7):e1336594.
 51. Costantino F, Talpin A, Evnouchidou I, Kadi A, Leboime A, Said-Nahal R, et al. ERAP1 Gene Expression Is Influenced by Nonsynonymous Polymorphisms Associated With Predisposition to Spondyloarthritis. *Arthritis & rheumatology (Hoboken, NJ)*. 2015;67(6):1525-34.

Tables

Table 1. Characteristics of the subjects enrolled in the current study.

	Cervical cancer	CIN	Control	<i>F</i>	<i>P</i> value
N	1072	556	1262		
Age	47.81±10.21	47.42±9.37	48.28±9.60	1.438	0.238
Pathological types					
SCC	903				
AC	151				
Others	18				
Stages of CIN					
Low degrade of CIN (I/II)		65			
High Degrade of CIN (III)		491			

Table 2. The allelic and genotypic distribution among control, CIN and cervical cancer groups of SNPs in ERAP1 gene

SNPs	Control	CIN	Cervical cancer	Control vs Cervical cancer		Control vs CIN		CIN vs Cervical cancer	
				<i>P</i> value	OR[95%CI]	<i>P</i> -value	OR[95%CI]	<i>P</i> value	OR[95%CI]
rs26618									
C	672(0.266)	327(0.294)	636(0.297)	0.021	1.162[1.023-	0.083	1.148[0.982-	0.879	1.012[0.863-
T	1852(0.734)	785(0.706)	1508(0.703)		1.321]		1.342]		1.187]
C/C	88(0.070)	56(0.101)	110(0.103)	0.016		0.076		0.989	
C/T	496(0.393)	215(0.387)	416(0.388)						
T/T	678(0.537)	285(0.513)	546(0.509)						
rs26653									
G	1297(0.514)	538(0.484)	1001(0.467)	0.001	0.829[0.738-	0.095	0.887[0.770-	0.359	0.934[0.808-
C	1227(0.486)	574(0.516)	1143(0.533)		0.930]		1.021]		1.080]
G/G	316(0.250)	124(0.223)	228(0.213)	0.004		0.224		0.591	
G/C	665(0.527)	290(0.522)	545(0.508)						
C/C	281(0.223)	142(0.255)	299(0.223)						
rs27044									
G	1350(0.535)	611(0.549)	1240(0.578)	0.003	1.193[1.062-	0.416	1.061[0.920-	0.114	1.125[0.972-
C	1174(0.465)	501(0.451)	904(0.422)		1.340]		1.222]		1.301]
G/G	362(0.287)	175(0.315)	360(0.336)	0.012		0.454		0.196	
G/C	626(0.496)	261(0.469)	520(0.485)						
C/C	274(0.217)	120(0.216)	192(0.179)						
rs30187									
C	1317(0.522)	589(0.530)	1203(0.561)	0.008	1.170[1.042-	0.678	1.030[0.895-	0.087	1.135[0.982-
T	1205(0.478)	523(0.470)	941(0.439)		1.313]		1.187]		1.313]
C/C	343(0.272)	169(0.304)	347(0.324)	0.020		0.151		0.134	
C/T	631(0.500)	251(0.451)	509(0.475)						
T/T	287(0.228)	136(0.245)	216(0.201)						
rs3734016									
C	2159(0.855)	947(0.852)	1801(0.840)	0.145	0.888[0.756-	0.767	0.970[0.795-	0.387	0.915[0.748-
T	365(0.145)	165(0.148)	343(0.160)		1.041]		1.184]		1.119]
C/C	921(0.730)	404(0.727)	752(0.701)	0.318		0.832		0.500	
C/T	317(0.251)	139(0.250)	297(0.277)						
T/T	24(0.019)	13(0.023)	23(0.021)						
rs27037									
G	1372(0.544)	592(0.532)	1092(0.509)	0.020	0.872[0.777-	0.532	0.956[0.830-	0.212	0.912[0.789-
T	1152(0.456)	520(0.468)	1052(0.491)		0.978]		1.101]		1.054]
G/G	359(0.284)	161(0.290)	283(0.264)	0.020		0.323		0.462	
G/T	654(0.518)	270(0.486)	526(0.491)						
T/T	249(0.197)	125(0.225)	263(0.245)						

Note: The statistical significant threshold was set at $P < 0.005$ after Bonferroni correction.

Table 3. The allelic and genotypic distribution among control, CIN and cervical cancer groups of SNPs in ERAP2 gene

SNPs	Control	CIN	Cervical cancer	Control vs Cervical cancer		Control vs CIN		CIN vs Cervical cancer	
				P Value	OR[95%CI]	P Value	OR[95%CI]	P Value	OR[95%CI]
rs2248374									
A	1128(0.447)	487(0.438)	1035(0.483)	0.014	1.155[1.029-	0.616	0.964[0.837-	0.015	1.198[1.035-
G	1396(0.553)	625(0.562)	1109(0.517)		1.296]		1.116]		1.386]
A/A	248(0.197)	100(0.180)	232(0.216)	0.020		0.690		0.041	
A/G	632(0.501)	287(0.516)	571(0.533)						
G/G	382(0.303)	169(0.304)	269(0.251)						
rs2549782									
G	1106(0.438)	484(0.435)	998(0.465)	0.062	1.117[0.995-	0.869	0.988[0.857-	0.100	1.130[0.977-
T	1418(0.562)	628(0.565)	1146(0.535)		1.253]		1.139]		1.307]
G/G	239(0.189)	101(0.182)	217(0.202)	0.089		0.906		0.214	
G/T	628(0.498)	282(0.507)	564(0.526)						
T/T	395(0.313)	173(0.311)	291(0.271)						
rs2287988									
A	1407(0.557)	623(0.560)	1104(0.515)	0.004	0.843[0.751-	0.875	1.011[0.877-	0.014	0.833[0.720-
G	1117(0.443)	489(0.440)	1040(0.485)		0.946]		1.166]		0.964]
A/A	387(0.307)	167(0.300)	267(0.249)	0.007		0.743		0.039	
A/G	633(0.502)	289(0.520)	570(0.532)						
G/G	242(0.192)	100(0.180)	235(0.219)						
rs2548538									
A	1063(0.421)	474(0.426)	959(0.447)	0.073	1.112[0.990-	0.774	1.021[0.885-	0.252	1.089[0.941-
T	1461(0.579)	638(0.574)	1185(0.553)		1.249]		1.178]		1.261]
A/A	240(0.190)	107(0.192)	224(0.209)	0.197		0.948		0.524	
A/T	583(0.462)	260(0.468)	511(0.477)						
T/T	439(0.348)	189(0.340)	337(0.314)						
rs1056983									
C	1062(0.421)	465(0.418)	919(0.429)	0.587	1.033[0.919-	0.884	0.989[0.858-	0.567	1.044[0.901-
T	1462(0.579)	647(0.582)	1225(0.571)		1.160]		1.141]		1.209]
C/C	239(0.189)	104(0.187)	207(0.193)	0.830		0.990		0.831	
C/T	584(0.463)	257(0.462)	505(0.471)						
T/T	439(0.348)	195(0.351)	360(0.348)						

Note: The statistical significant threshold was set at $P < 0.005$ after Bonferroni correction.

Table 4. Inheritance model analysis of SNPs in ERAP1 gene between control and cervical cancer groups

SNPs	Models	Genotypes	Control	Cervical cancer	OR[95%CI]	P-value	AIC	BIC
rs26618	Condominant	T/T	677 (53.7%)	546 (50.9%)	1	0.016	3217.7	3240.7
		C/T	496 (39.3%)	416 (38.8%)	1.04[0.88-1.24]			
		C/C	88 (7%)	110 (10.3%)	1.55[1.15-2.10]			
	Dominant	T/T	677 (53.7%)	546 (50.9%)	1	0.180	3222.2	3239.5
		C/T-C/C	584 (46.3%)	526 (49.1%)	1.12[0.95-1.32]			
	Recessive	T/T-C/T	1173 (93%)	962 (89.7%)	1	0.004	3215.9	3233.1
		C/C	88 (7%)	110 (10.3%)	1.53[1.14-2.05]			
	Overdominant	T/T-C/C	765 (60.7%)	656 (61.2%)	1	0.790	3223.9	3241.2
		C/T	496 (39.3%)	416 (38.8%)	0.98[0.83-1.16]			
	Log-additive	---	---	---	1.16[1.02-1.31]	0.023	3218.9	3236.1
rs26653	Condominant	G/G	281 (22.3%)	299 (27.9%)	1	0.004	3214.8	3237.8
		C/G	665 (52.7%)	545 (50.8%)	0.77 [0.63-0.94]			
		C/C	315 (25%)	228 (21.3%)	0.68 [0.54-0.86]			
	Dominant	G/G	281 (22.3%)	299 (27.9%)	1	0.002	3214.2	3231.5
		C/G-C/C	980 (77.7%)	773 (72.1%)	0.74 [0.61-0.89]			
	Recessive	G/G-C/G	946 (75%)	844 (78.7%)	1	0.034	3219.5	3236.7
		C/C	315 (25%)	228 (21.3%)	0.81 [0.67-0.98]			
	Overdominant	G/G-C/C	596 (47.3%)	527 (49.2%)	1	0.360	3223.2	3240.4
		C/G	665 (52.7%)	545 (50.8%)	0.93 [0.79-1.09]			
	Log-additive	---	---	---	0.82 [0.73-0.93]	0.001	3213.5	3230.7
rs27044	Condominant	C/C	362 (28.7%)	360 (33.6%)	1	0.012	3217.2	3240.2
		C/G	625 (49.6%)	520 (48.5%)	0.84 (0.70-1.01)			
		G/G	274 (21.7%)	192 (17.9%)	0.71 (0.56-0.89)			
	Dominant	C/C	362 (28.7%)	360 (33.6%)	1	0.012	3217.6	3234.9
		C/G-G/G	899 (71.3%)	712 (66.4%)	0.80 (0.67-0.95)			
	Recessive	C/C-C/G	987 (78.3%)	880 (82.1%)	1	0.021	3218.7	3235.9
		G/G	274 (21.7%)	192 (17.9%)	0.79 (0.64-0.97)			
	Overdominant	C/C-G/G	636 (50.4%)	552 (51.5%)	1	0.620	3223.7	3241
		C/G	625 (49.6%)	520 (48.5%)	0.96 (0.82-1.13)			
	Log-additive	---	---	---	0.84 (0.75-0.94)	0.003	3215.2	3232.5
rs30187	Condominant	C/C	343 (27.2%)	347 (32.4%)	1	0.020	3218.2	3241.2
		C/T	631 (50%)	509 (47.5%)	0.80 (0.66-0.96)			
		T/T	287 (22.8%)	216 (20.1%)	0.74 (0.59-0.94)			
	Dominant	C/C	343 (27.2%)	347 (32.4%)	1	0.007	3216.6	3233.9
		C/T-T/T	918 (72.8%)	725 (67.6%)	0.78 (0.65-0.93)			
	Recessive	C/C-C/T	974 (77.2%)	856 (79.8%)	1	0.120	3221.6	3238.9
		T/T	287 (22.8%)	216 (20.1%)	0.86 (0.70-1.04)			
	Overdominant	C/C-T/T	630 (50%)	563 (52.5%)	1	0.220	3222.5	3239.8
		C/T	631 (50%)	509 (47.5%)	0.90 (0.77-1.06)			

rs3734016	Log-additive	---	---	---	0.86 (0.76-0.96)	0.009	3217.1	3234.3
	Condominant	C/C	920 (73%)	752 (70.2%)	1	0.330	3223.8	3246.8
		C/T	317 (25.1%)	297 (27.7%)	1.15 (0.95-1.38)			
		T/T	24 (1.9%)	23 (2.1%)	1.17 (0.65-2.09)			
	Dominant	C/C	920 (73%)	752 (70.2%)	1	0.140	3221.8	3239.0
		C/T-T/T	341 (27%)	320 (29.9%)	1.15 (0.96-1.37)			
	Recessive	C/C-C/T	1237 (98.1%)	1049 (97.8%)	1	0.690	3223.8	3241.1
		T/T	24 (1.9%)	23 (2.1%)	1.13 (0.63-2.01)			
	Overdominant	C/C-T/T	944 (74.9%)	775 (72.3%)	1	0.160	3222	3239.3
		C/T	317 (25.1%)	297 (27.7%)	1.14 (0.95-1.37)			
rs27037	Log-additive	---	---	---	1.13 (0.96-1.33)	0.150	3221.9	3239.1
	Condominant	G/G	359 (28.5%)	283 (26.4%)	1	0.020	3218.2	3241.2
		G/T	653 (51.8%)	526 (49.1%)	1.02 (0.84-1.23)			
		T/T	249 (19.8%)	263 (24.5%)	1.34 (1.06-1.69)			
	Dominant	G/G	359 (28.5%)	283 (26.4%)	1	0.280	3222.8	3240.1
		G/T-T/T	902 (71.5%)	789 (73.6%)	1.11 (0.92-1.33)			
	Recessive	G/G-G/T	1012 (80.2%)	809 (75.5%)	1	0.006	3216.2	3233.5
		T/T	249 (19.8%)	263 (24.5%)	1.32 (1.09-1.61)			
	Overdominant	G/G-T/T	608 (48.2%)	546 (50.9%)	1	0.180	3222.2	3239.4
		G/T	653 (51.8%)	526 (49.1%)	0.89 (0.76-1.05)			
	Log-additive	---	---	---	1.15 (1.02-1.29)	0.020	3218.6	3235.8

Note: The statistical significant threshold was set at $P<0.005$ after Bonferroni correction.

Table 5. Inheritance model analysis of SNPs in ERAP2 gene between control and cervical cancer groups

SNPs	Models	Genotypes	Control	Cervical cancer	OR[95%CI]	P-value	AIC	BIC
rs2248374	Condominant	G/G	382 (30.3%)	269 (25.1%)	1	0.020	3218.1	3241.2
		A/G	631 (50%)	571 (53.3%)	1.28 (1.06-1.56)			
		A/A	248 (19.7%)	232 (21.6%)	1.33 (1.05-1.69)			
	Dominant	G/G	382 (30.3%)	269 (25.1%)	1	0.005	3216.2	3233.5
		A/G-A/A	879 (69.7%)	803 (74.9%)	1.30 (1.08-1.56)			
	Recessive	G/G-A/G	1013 (80.3%)	840 (78.4%)	1	0.230	3222.6	3239.8
		A/A	248 (19.7%)	232 (21.6%)	1.13 (0.92-1.38)			
	Overdominant	G/G-A/A	630 (50%)	501 (46.7%)	1	0.130	3221.7	3238.9
		A/G	631 (50%)	571 (53.3%)	1.14 (0.96-1.34)			
	Log-additive	---	---	---	1.16 (1.03-1.31)	0.012	3217.7	3235.0
rs2549782	Condominant	T/T	395 (31.3%)	291 (27.1%)	1	0.088	3221.1	3244.2
		G/T	627 (49.7%)	564 (52.6%)	1.22 (1.01-1.47)			
		G/G	239 (18.9%)	217 (20.2%)	1.23 (0.97-1.56)			
	Dominant	T/T	395 (31.3%)	291 (27.1%)	1	0.028	3219.2	3236.4
		G/T-G/G	866 (68.7%)	781 (72.8%)	1.22 (1.02-1.46)			
	Recessive	T/T-G/T	1022 (81%)	855 (79.8%)	1	0.430	3223.4	3240.6
		G/G	239 (18.9%)	217 (20.2%)	1.09 (0.89-1.33)			
	Overdominant	T/T-G/G	634 (50.3%)	508 (47.4%)	1	0.170	3222.1	3239.4
		G/T	627 (49.7%)	564 (52.6%)	1.12 (0.95-1.32)			
	Log-additive	---	---	---	1.12 (1.00-1.26)	0.057	3220.4	3237.6
rs2287988	Condominant	A/A	387 (30.7%)	267 (24.9%)	1	0.007	3216.0	3239.0
		A/G	632 (50.1%)	570 (53.2%)	1.30 (1.07-1.58)			
		G/G	242 (19.2%)	235 (21.9%)	1.41 (1.11-1.78)			
	Dominant	A/A	387 (30.7%)	267 (24.9%)	1	0.002	3214.5	3231.8
		A/G-G/G	874 (69.3%)	805 (75.1%)	1.33 (1.11-1.60)			
	Recessive	A/A-A/G	1019 (80.8%)	837 (78.1%)	1	0.100	3221.3	3238.6
		G/G	242 (19.2%)	235 (21.9%)	1.18 (0.97-1.45)			
	Overdominant	A/A-G/G	629 (49.9%)	502 (46.8%)	1	0.150	3221.9	3239.2
		A/G	632 (50.1%)	570 (53.2%)	1.13 (0.96-1.33)			
	Log-additive	---	---	---	1.19 (1.06-1.34)	0.003	3215.3	3232.5
rs2548538	Condominant	T/T	439 (34.8%)	337 (31.4%)	1	0.200	3222.8	3245.8
		A/T	582 (46.1%)	511 (47.7%)	1.14 (0.95-1.37)			
		A/A	240 (19%)	224 (20.9%)	1.22 (0.96-1.53)			
	Dominant	T/T	439 (34.8%)	337 (31.4%)	1	0.089	3221.1	3238.4
		A/T-A/A	822 (65.2%)	735 (68.6%)	1.16 (0.98-1.38)			
	Recessive	T/T-A/T	1021 (81%)	848 (79.1%)	1	0.260	3222.7	3240.0
		A/A	240 (19%)	224 (20.9%)	1.12 (0.92-1.38)			
	Overdominant	T/T-A/A	679 (53.9%)	561 (52.3%)	1	0.480	3223.5	3240.8
		A/T	582 (46.1%)	511 (47.7%)	1.06 (0.90-1.25)			
	Log-additive	---	---	---	1.11 (0.99-1.24)	0.080	3220.9	3238.2
rs1056983	Condominant	T/T	439 (34.8%)	360 (33.6%)	1	0.820	3225.6	3248.6
		C/T	583 (46.2%)	505 (47.1%)	1.06 (0.88-1.27)			
		C/C	239 (18.9%)	207 (19.3%)	1.06 (0.84-1.34)			
	Dominant	T/T	439 (34.8%)	360 (33.6%)	1	0.530	3223.6	3240.9
		C/T-C/C	822 (65.2%)	712 (66.4%)	1.06 (0.89-1.25)			
	Recessive	T/T-C/T	1022 (81%)	865 (80.7%)	1	0.810	3223.9	3241.2
		C/C	239 (18.9%)	207 (19.3%)	1.03 (0.83-1.26)			
	Overdominant	T/T-C/C	678 (53.8%)	567 (52.9%)	1	0.680	3223.8	3241.1
		C/T	583 (46.2%)	505 (47.1%)	1.03 (0.88-1.22)			
	Log-additive	---	---	---	1.03 (0.92-1.16)	0.580	3223.7	3241.0

Note: The statistical significant threshold was set at $P < 0.005$ after Bonferroni correction.

Table 6. The distribution of the haplotypes constructed by SNPs in ERAP1 gene

Haplotypes	Control	CIN	Cervical cancer	Control vs Cervical cancer		Control vs CIN		CIN vs Cervical cancer	
				P-value	OR[95%CI]	P-value	OR[95%CI]	P-value	OR[95%CI]
C-C-G-C-C	646.12 (0.256)	299.22 (0.269)	556.04 (0.259)	0.041	1.151 [1.006-1.316]	0.122	1.137 [0.966-1.338]	0.890	1.012 [0.855-1.197]
T-G-G-T-C	76.43 (0.030)	37.05 (0.033)	64.76 (0.030)	0.612	1.091 [0.779-1.528]	0.486	1.153 [0.773-1.719]	0.794	0.947 [0.627-1.428]
T-G-C-T-C	1101.70 (0.437)	444.48 (0.400)	759.76 (0.354)	0.001	0.804 [0.711-0.910]	0.260	0.918 [0.791-1.065]	0.096	0.876 [0.750-1.024]
T-C-G-C-C	196.08 (0.078)	72.59 (0.065)	176.09 (0.082)	0.150	1.169 [0.945-1.447]	0.315	0.866 [0.655-1.146]	0.039	1.350 [1.015-1.795]
T-C-G-C-T	336.22 (0.133)	142.58 (0.128)	278.80 (0.130)	0.402	1.076 [0.906-1.278]	0.970	1.004 [0.813-1.241]	0.533	1.072 [0.862-1.334]

Note: The statistical significant threshold was set at $P < 0.01$ (0.05/n, n=0.05) after Bonferroni correction.

Table 7. The distribution of the haplotypes constructed by SNPs in ERAP2 gene

Haplotypes	Control	CIN	Cervical cancer	Control vs cervical cancer		Control vs CIN		CIN vs Cervical cancer	
				P-value	OR[95%CI]	P-value	OR[95%CI]	P-value	OR[95%CI]
A-G-G-A-C	953.78 (0.378)	411.75 (0.370)	784.87 (0.366)	0.219	1.080 [0.955-1.220]	0.908	0.991 [0.852-1.153]	0.336	1.079 [0.925-1.258]
A-G-G-A-T	58.71 (0.023)	20.26 (0.018)	72.44 (0.034)	0.009	1.592 [1.122-2.258]	0.053	1.837 [0.983-3.434]	0.006	2.000 [1.215-3.292]
A-G-G-T-C	61.18 (0.024)	25.61 (0.023)	71.82 (0.033)	0.018	1.513 [1.070-2.139]	0.638	1.130 [0.678-1.884]	0.055	1.560 [0.987-2.465]
G-T-A-T-T	1346.11 (0.533)	586.29 (0.527)	973.03 (0.454)	0.003	0.835 [0.740-0.942]	0.908	1.009 [0.868-1.173]	0.009	0.817 [0.702-0.951]

Note: The statistical significant threshold was set at $P < 0.013$ (0.05/n, n=4) after Bonferroni correction.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementarytables.docx](#)