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RESEARCH LETTERS

HLA Heterozygosity Influences Colorectal Cancer Risk and Survival Outcome

The diversity of HLAs is critical for effective immune responses against pathogens and cancer. HLA class I molecules present endogenous antigens to eliminate infected or cancerous cells, while HLA class II molecules present exogenous antigens to helper $CD4^+$ T cells, stimulating antibody production. Polymorphisms in HLA genes, particularly in the peptide-binding cleft, create diverse antigen-binding affinities, suggesting evolutionary selection pressure to maintain diversity as a defense against pathogen adaptation.[1] One mechanism by which HLA diversity is maintained is through heterozygote advantage,[2] where individuals with 2 different alleles at a genetic locus have higher fitness compared with those with 2 identical alleles. Particular attention has been focused on the role of HLA heterozygote advantage in colorectal cancer (CRC).[3–5] Our prior study of 5406 patients with CRC and 4635 controls found that HLA class I and/or II alleles may be associated with higher tumor-infiltrating lymphocytes and reduced risk of CRC.[4] Here, we expand on this work by analyzing 183,626 participants (84,907 CRC cases and 98,689 controls) from the International Colorectal Cancer GWAS Collaborative, including the United States, Europe, and Australia; United Kingdom and Europe; and Asia (Supplementary Table 1). HLA class I and class II alleles were imputed from germline genotype data, and the number of heterozygous genotypes at HLA class I (*A*, *B*, *C*) and HLA class II (*DPB1*, *DQB1*, *DRB1*) loci were quantified. Logistic regression estimated the risk of CRC, and Cox proportional hazards regression assessed overall survival (OS) and CRC-specific survival (CS) in 20,332 CRC cases (Supplementary Methods). To account for multiple hypothesis testing, we applied a Bonferroni correction, adjusting the statistical significance threshold to $P < .0063$ (.05/8 independent tests).

Our meta-analysis demonstrated that HLA heterozygosity is associated with significantly reduced CRC risk and longer survival. Compared with individuals with 0 or 1 heterozygous alleles across HLA class I and class II loci, those with 2–5 heterozygotes had a 10% reduced odds of CRC (odds ratio [OR], 0.90; $P = .004$), and those with all heterozygous genotypes at class I and class II loci were at lower odds of CRC (OR, 0.89; $P = .002$) (Figure 1*A*). For HLA class I, individuals who carried 2 or 3 heterozygous genotypes were at 10% lower risk of CRC (2 heterozygotes: OR, 0.89; $P = .003$; 3 heterozygotes: OR, 0.91; $P = .004$) (Supplementary Table 2). Among 20,322 CRC cases, a higher number of heterozygous genotypes was associated with better OS in a dose–response relationship ($P_{trend} = .008$ for class II, $P_{trend} = .029$ for class I/II combined) (Supplementary Table 3). Interestingly, early stage (I and II) CRC cases with all 6 heterozygous loci exhibited a 41% lower risk of dying from CRC (hazard ratio, 0.59; $P = .025$) (Figure 1*B*). However, this was not observed in patients with locally advanced or metastatic disease. Although our primary finding for CRC risk remained statistically significant after multiple testing correction, the survival analysis *P* values (.008−.025) did not meet this stringent threshold, but are still strongly suggestive of an association.

These findings are consistent with the hypothesis that HLA heterozygosity enhances immune surveillance by means of presenting a broader antigenic peptide repertoire to T cells. Prior studies revealed the complementary roles of HLA class I and II genotypes on the oncogenic mutational landscape and immunoediting during tumor development,[6,7] influencing both $CD8^+$ and $CD4^+$ T-cell responses. Our work explores the less-studied impact of germline HLA heterozygosity, which is distinct from the common somatic loss of heterozygosity. Analyzing germline HLA zygosity rather than individual alleles offers a key advantage in a multi-ethnic study, allowing examination of HLA variability across ancestry groups without the complexity of comparing highly population-specific alleles. Our prior analysis found an association between HLA class I and II heterozygosity and higher levels of tumor-infiltrating lymphocytes,[4] suggesting a mechanistic role in CRC development. Furthermore, a study of esophagogastric adenocarcinoma demonstrated that germline HLA class I homozygosity reduced immunogenic peptide repertoires,[8] supporting HLA heterozygote advantage in enhancing immune surveillance against cancer.

Our analysis revealed a dose–response relationship between HLA heterozygosity and improved OS, but not CS. This suggests that HLA heterozygosity may influence OS through mechanisms beyond exclusively cancer-specific mortality. We found that patients with early-stage CRC and greater HLA class I and II heterozygosity exhibited significantly better CS, likely because increased HLA diversity allows the immune system to recognize and respond to a wider range of tumor antigens, especially when tumor burden is low. Conversely, advanced-stage CRC patients did not experience such benefit, possibly due to factors like somatic HLA loss, immune exhaustion, or reduced tumor infiltration. Notably, a different trend was observed in the Asian cohort, where HLA class I heterozygosity was associated with worse OS and CS. This finding may be influenced by the small sample size and variability in HLA allele frequencies specific to the Asian population. The Asian cohort's limitation of including only male

Abbreviations used in this paper: CRC, colorectal cancer; CS, colorectal cancer–specific survival; OR, odds ratio; OS, overall survival.

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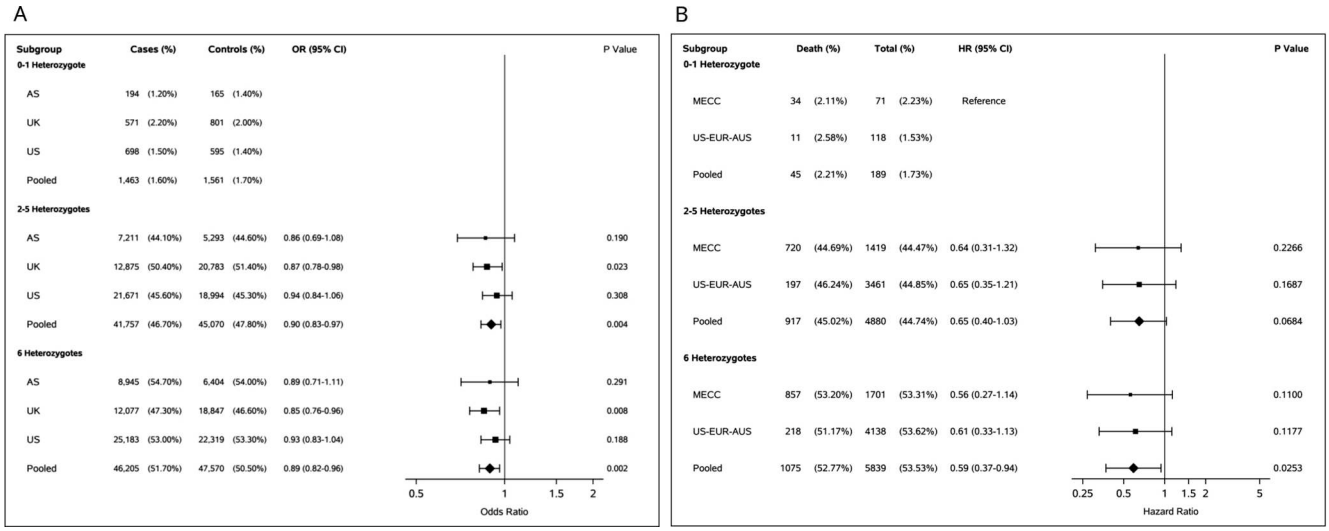

Figure 1. Associations between HLA class I and II heterozygosity and CRC risk and outcome. (*A*) HLA class I and II heterozygosity and CRC risk. (*B*) HLA class I and II heterozygosity and CRC-specific survival in patients with stage I and II disease. AS, Asia-based consortium; UK-EUR, United Kingdom and Europe-based consortium; US-EUR-AUS, United States, Europe, and Australia-based Consortium.

patients may further contribute to these differences. However, we cannot rule out that this observation is due to chance.

Despite robust statistical power, our study has limitations. Our findings, primarily from individuals of European and Asian ancestry, have limited generalizability. The lack of comprehensive treatment information, including immunotherapy, precluded analysis of the effect of HLA heterozygosity on treatment responses. Incomplete survival information for some data sets, especially the Asia-based consortium, may also give rise to potential bias. A higher proportion of stage I/II cases also constrained our stage-specific results, highlighting the need for larger samples of advanced-stage patients to better understand the influence of HLA heterozygosity on outcomes.

Using the largest data set of HLA genotypes from patients with CRC across multiple continents, we unveiled the important relationship between germline HLA diversity and both CRC risk and prognosis. Our findings demonstrate that increased HLA heterozygosity is associated with reduced CRC risk and potentially better clinical outcomes, particularly in early-stage patients. These results highlight potential for incorporating HLA diversity into polygenic risk scores and prognostic models to improve CRC risk prediction and prognostication. Future research should focus on understanding the mechanisms by which HLA diversity influences CRC development and progression to inform the targeted immunoprevention and immunotherapies that leverage this diversity to improve CRC outcomes.

YA-YU TSAI
Genomic Sciences and System Biology
Cleveland Clinic
Cleveland, Ohio

CLAIRE E. THOMAS
Public Health Sciences Division
Fred Hutchinson Cancer Center
Seattle, Washington

PHILIP J. LAW
Division of Genetics and Epidemiology
The Institute of Cancer Research
London, United Kingdom

ZHISHAN CHEN
Division of Epidemiology
Department of Medicine
Vanderbilt-Ingram Cancer Center
Vanderbilt Epidemiology Center
Vanderbilt University Medical Center
Nashville, Tennessee

STEPHEN B. GRUBER
Department of Medical Oncology and Therapeutics Research and Center for Precision Medicine
City of Hope National Medical Center
Duarte, California

STEPHANIE L. SCHMIT
Genomic Sciences and System Biology
Cleveland Clinic
Cleveland, Ohio, *and*
Department of Molecular Medicine
Cleveland Clinic Lerner College of Medicine
Case Western Reserve University School of Medicine
Cleveland, Ohio

INTERNATIONAL COLORECTAL CANCER GWAS COLLABORATIVE

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2025.10.020.

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Correspondence
Address correspondence to: Stephanie L. Schmit, PhD, MPH, Genomic Sciences and System Biology, Cleveland Clinic, 9500 Euclid Avenue/NE 50, Cleveland, Ohio 44195. e-mail: schmits3@ccf.org.

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The International Colorectal Cancer GWAS Collaborative includes Jeroen R Huyghe,[1] Hang Yin,[1,2] Ceres Fernandez-Rozadilla,[3,4,5] Minta Thomas,[1] Li Hsu.[1,6] Demetrius Albanes,[7] Elizabeth L. Barry,[8] Sonja I. Berndt,[7] Stéphane Bézieau,[9] D. Timothy Bishop,[10] Hermann Brenner,[11,12] Daniel D. Buchanan,[13,14,15] Andrew T. Chan,[16,17,18,19,20] Marcia Cruz-Correa,[21,22,23] Jane C. Figueiredo,[24] Manuela Gago-Dominguez,[25] Robert C. Grant,[26] Andrea Gsur,[27] Marc J. Gunter,[28,29] Jochen Hampe,[30] Michael Hoffmeister,[11] Mark A. Jenkins,[31,32] Temitope O. Keku,[33] Loic Le Marchand,[34] Flavio Lebjkowicz,[35] Heinz-Josef Lenz,[36] Li Li,[37,38] Annika Lindblom,[39,40] Robert J. MacInnis,[41,42] Marilena Melas,[43] Aaron L. Meyers,[44,45,46] Kenneth Offit,[47,48,49] Shuji Ogino,[19,20,50,51] Rish K. Pai,[52] Rachel Pearlman,[53] Andrew J. Pellatt,[54] Elizabeth A. Platz,[55,56] Chenxu Qu,[43] Robert E. Schoen,[57] Cornelia M. Ulrich,[58] Caroline Y. Um,[59] Franzel J. B. van Duijnhoven,[60] Bethany Van Guelpen,[61,62] Veronika Vymetalkova,[63,64] Christopher P. Walker,[65] Emily White,[1,66] Alicja Wolk,[67] Michael O. Woods,[68] Anna H. Wu,[69] Amanda Phipps,[1,66] Gad Rennert,[70] Victor Moreno,[71,72,73,74] Malcolm G. Dunlop,[75] Ian Tomlinson,[76] Ulrike Peters,[1,68] Wei Zheng,[77] and Richard Houlston[78]; from the [1]Public Health Sciences Division, Fred Hutchinson Cancer Center, Seattle, Washington; [2]Institute for Public Health Genetics, University of Washington, Seattle, Washington; [3]Cancer Predisposition and Biomarkers Laboratory, Instituto de Investigacion Sanitaria de Santiago, Santiago de Compostela, Spain; [4]Genomic Medicine Group, University of Santiago de Compostela, Santiago de Compostela, Spain; [5]Galician Public Foundation for Genomic Medicine, Santiago de Compostela, Spain; [6]Department of Biostatistics, School of Public Health, University of Washington, Seattle, Washington; [7]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; [8]Department of Epidemiology, Geisel School of Medicine at Dartmouth, Hanover, New Hampshire; [9]Service de Génétique Médicale, Centre Hospitalier Universitaire Nantes, Nantes, France; [10]Leeds Institute of Medical Research, University of Leeds, Leeds, United Kingdom; [11]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Heidelberg, Germany; [12]German Cancer Consortium, German Cancer Research Center, Heidelberg, Germany; [13]Colorectal Oncogenomics Group, Department of Clinical Pathology, Melbourne Medical School, The University of Melbourne, Parkville, Victoria, Australia; [14]Genomic Medicine and Family Cancer Clinic, The Royal Melbourne Hospital, Parkville, Victoria, Australia; [15]University of Melbourne Centre for Cancer Research, Victorian Comprehensive Cancer Centre, Parkville, Victoria, Australia; [16]Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; [17]Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [18]Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; [19]Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts; [20]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Harvard University, Boston, Massachusetts; [21]Comprehensive Cancer Center, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico; [22]Pan American Center for Oncology Trials, San Juan, Puerto Rico; [23]Johns Hopkins University, School of Medicine, Baltimore, Maryland;[24]Cedars-Sinai Cancer Institute, Los Angeles, California; [25]Fundación Gallega de Instituto de Investigación de Santiago , Grupo de Genética y Epidemiología del Cáncer, Complejo Hospitalario University Santiago, Sergas, Spain; [26]Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada; [27]Center for Cancer Research, Medical University of Vienna, Vienna, Austria; [28]Cancer Epidemiology and Prevention Research Unit, School of Public Health, Imperial College, London, United Kingdom; [29]Nutrition and Metabolism Branch, International Agency for Research on Cancer, Lyon, France; [30]Department of Medicine I, University Hospital Dresden, Technische Universität Dresden, Dresden, Germany; [31]University of Melbourne Centre for Cancer Research, Victorian Comprehensive Cancer Centre, Parkville, Victoria, Australia;[32]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, Victoria, Australia; [33]Center for Gastrointestinal Biology and Disease, University of North Carolina, Chapel Hill, North Carolina; [34]University of Hawaii Cancer Center, Honolulu, Hawaii; [35]Department of Community Medicine and Epidemiology, Carmel Medical Center, Haifa, Israel;[36]Department of Medicine, University of Southern California, Los Angeles, California; [37]Department of Family Medicine, University of Virginia, Charlottesville, Virginia; [38]University of Virginia Comprehensive Cancer, University of Virginia, Charlottesville, Virginia; [39]Department of Clinical Genetics and Genomics, Karolinska University Hospital, Stockholm, Sweden; [40]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; [41]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Victoria, Australia; [42]Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, Victoria, Australia; [43]Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, California; [44]Centre for Genomic Cancer Medicine, Victorian Comprehensive Cancer Centre, University of Melbourne, Victoria, Australia; [45]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Victoria, Australia; [46]Colorectal Oncogenomics Group, Department of Clinical Pathology, Melbourne Medical School, University of Melbourne, Victoria, Australia; [47]Clinical Genetics Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York; [48]Department of Medicine, Weill Cornell Medical College, New York, New York; [49]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts; [50]Program in Molecular Pathological Epidemiology, Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [51]Institute of Science Tokyo, Tokyo, Japan; [52]Department of Laboratory Medicine and Pathology, Mayo Clinic Arizona, Scottsdale, Arizona; [53]Division of Human Genetics, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, Ohio; [54]Intermountain Health, Salt Lake City, Utah; [55]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; [56]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland; [57]Departments of Medicine and Epidemiology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; [58]Huntsman Cancer Institute and Department of Population Health Sciences, University of Utah, Salt Lake City, Utah; [59]Department of Population Science, American Cancer Society, Atlanta, Georgia; [60]Division of Human Nutrition and Health, Wageningen University and Research, Wageningen, The Netherlands; [61]Department of Diagnostics and Intervention, Oncology Unit, Umeå University, Umeå, Sweden; [62]Wallenberg Centre for Molecular Medicine, Umeå University, Umeå, Sweden; [63]Department of Molecular Biology of Cancer, Institute of Experimental Medicine of the Czech Academy of Sciences, Prague, Czech Republic; [64]Institute of Biology and Medical Genetics, First Faculty of Medicine, Charles University, Prague, Czech Republic; [65]Department of Medical Oncology and Therapeutics Research and Center for Precision Medicine, City of Hope National Medical Center, Duarte, California; [66]Department of Epidemiology, University of Washington School of Public Health, Seattle, Washington; [67]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [68]Memorial University of Newfoundland, Division of Biomedical Sciences, St John's, Newfoundland and Labrador, Canada; [69]Population and Public Health Sciences, University of Southern California, Los Angeles, California; [70]B. Rappaport Faculty of Medicine, Technion and the Association for Promotion of Research in Precision Medicine, Haifa, Israel; [71]Catalan Institute of Oncology, Hospitalet de Llobregat, Barcelona, Spain; [72]Oncobell Program, Bellvitge Biomedical Research Institute, Hospitalet de Llobregat, Barcelona, Spain; [73]Consortium for Biomedical Research in Epidemiology and Public Health, Spain; [74]Department of Clinical Sciences, Faculty of Medicine and Health Sciences and Universitat de Barcelona Institute of Complex Systems, University of Barcelona, Barcelona, Spain; [75]Colon Cancer Genetics Group, Cancer Research UK Scotland Centre, Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, United Kingdom; [76]Department of Oncology, University of Oxford, Oxford, United Kingdom; [77]Division of Epidemiology, Department of

Medicine, Vanderbilt-Ingram Cancer Center, Vanderbilt Epidemiology Center, Vanderbilt University Medical Center, Nashville, Tennessee; and [78]Division of Genetics and Epidemiology, Institute of Cancer Research, London, United Kingdom.

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CrediT Authorship Contributions

Ya-Yu Tsai, PhD, MS (Conceptualization: Lead; Data curation: Supporting; Formal analysis: Lead; Methodology: Lead; Project administration: Lead; Writing – original draft: Lead; Writing – review & editing: Lead)

Claire E. Thomas, PhD, MPH (Conceptualization: Lead; Formal analysis: Equal; Methodology: Equal; Writing – review & editing: Supporting)

Philip J. Law, PhD (Formal analysis: Equal; Writing – review & editing: Supporting)

Zhishan Chen, PhD (Formal analysis: Equal; Writing – review & editing: Supporting)

Stephen B. Gruber, MD, PhD (Conceptualization: Lead; Data curation: Supporting; Formal analysis: Supporting; Funding acquisition: Lead; Methodology: Lead; Project administration: Lead; Resources: Lead; Supervision: Supporting; Writing – review & editing: Supporting)

Stephanie L. Schmit, PhD, MPH (Conceptualization: Lead; Data curation: Supporting; Formal analysis: Supporting; Methodology: Lead; Project administration: Lead; Resources: Supporting; Supervision: Lead; Writing – review & editing: Lead)

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Data Availability

Summary statistics for the full set of Asian and European genome-wide association studies are available through the GWAS catalog (GCST90129505). Individual-level genotype data are available via dbGaP (phs001415.v1.p1, phs001315.v1.p1, phs001078.v1.p1, phs001903.v1.p1, phs001856.v1.p1, and phs001045.v1.p1 for CCFR, CORECT, CORSA_2 and GECCO), the European Genome-Phenome Archive (accession numbers EGAS00001005412 for NSCCG, EGAS00001005421 for COIN), UK Biobank (http://www.ukbiobank.ac.uk), and THL Biobank (for Finnish data). Access to the remaining individual-level data require application through oversight committees or specific contacts, as detailed for CCFR (www.coloncfr/collaboration.org), QUASAR2, SCOT, CORGI (LP1), Scotland Phase 1, Scotland Phase 2, SOCCS, DACHS, Croatia (access.crc.gwas.data@outlook.com), CORSA_1 (gecco@fredhutch.org), Generation Scotland controls (access@generationscotland.org), and Asian cohorts (Aichi1, Aichi2, Korea and Shanghai cohorts; see https://swhs-smhs.app.vumc.org/ or contact Dr. Zheng at wei.zheng@vanderbilt.edu). Germline genotype data are available in dbGAP for the MECC study (https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001045.v1.p1; https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001856.v1.p1; https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001903.v1.p1).