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2023-05-15

Ahadova , A , Witt , J , Haupt , S , Gallon , R , Hueneburg , R , Nattermann , J , Ten Broeke , S , Bohaumilitzky , L , Hernandez-Sanchez , A , Santibanez-Koref , M , Jackson , M S , Ahtiainen , M , Pylvanainen , K , Andini , K , Grolmusz , V K , Moeslein , G , Dominguez-Valentin , M , Moller , P , Fuerst , D , Sijmons , R , Borthwick , G M , Burn , J , Mecklin , J-P , Heuveline , V , Doeberitz , M V K , Seppälä , T & Kloor , M 2023 , ' Is HLA type a possible cancer risk modifier in Lynch syndrome? ' , International Journal of Cancer , vol. 152 , no. 10 , pp. 2024-2031 . https://doi.org/10.1002/ijc.34312

http://hdl.handle.net/10138/356925
https://doi.org/10.1002/ijc.34312

Received: 15 July 2022 | Revised: 2 September 2022 | Accepted: 16 September 2022

DOI: 10.1002/ijc.34312

REVIEW

IJC INTERNATIONAL JOURNAL of CANCER

Is HLA type a possible cancer risk modifier in Lynch syndrome?

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Abbreviations: cMS, coding microsatellite; CRC, colorectal cancer; FSP, frameshift peptide; HLA, human leukocyte antigen; INDICATE, individual cancer risk by HLA type; LS, Lynch syndrome; MHC, major histocompatibility complex; MMR, mismatch repair; MSI, microsatellite instability.

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Funding information
AsCaP collaboration; Cancer Research UK Catalyst Award, Grant/Award Number: C569/A24991; CAPP3 Clinical Research Committee Late Phase Award, Grant/Award Number: A15934; Deutsche Forschungsgemeinschaft; Deutsche Krebshilfe, Grant/Award Number: 70113455; Donations against Cancer, NCT Heidelberg; Else-Kröner-Fresenius Foundation, Grant/Award Number: 2018_A44; Emil Aaltosen Säätiö; Finnish Cancer Society; Jane ja Aatos Erkon Säätiö; National Research, Development and Innovation Office, Hungary, Grant/Award Number: NKFIH-FK-21-138377; Suomen Lääketieteen Säätiö; Wilhelm Sander Foundation; Klaus Tschira Foundation, Grant/Award Number: 00.012.2021

Abstract

Lynch syndrome (LS) is the most common inherited cancer syndrome. It is inherited via a monoallelic germline variant in one of the DNA mismatch repair (MMR) genes. LS carriers have a broad 30% to 80% risk of developing various malignancies, and more precise, individual risk estimations would be of high clinical value, allowing tailored cancer prevention and surveillance. Due to MMR deficiency, LS cancers are characterized by the accumulation of frameshift mutations leading to highly immunogenic frameshift peptides (FSPs). Thus, immune surveillance is proposed to inhibit the outgrowth of MMR-deficient cell clones. Recent studies have shown that immunoediting during the evolution of MMR-deficient cancers leads to a counter-selection of highly immunogenic antigens. The immunogenicity of FSPs is dependent on the antigen presentation. One crucial factor determining antigen presentation is the HLA genotype. Hence, a LS carrier's HLA genotype plays an important role in the presentation of FSP antigens to the immune system, and may influence the likelihood of progression from precancerous lesions to cancer. To address the challenge of clarifying this possibility including diverse populations with different HLA types, we have established the INDICATE initiative (Individual cancer risk by HLA type, http://indicate-lynch.org/), an international network aiming at a systematic evaluation of the HLA genotype as a possible cancer risk modifier in LS. Here we summarize the current knowledge on the role of HLA type in cancer risk and outline future research directions to delineate possible association in the scenario of LS with genetically defined risk population and highly immunogenic tumors.

KEYWORDS
cancer immunoediting, HLA genotype, immune surveillance, Lynch syndrome, personalized cancer risk

1 | BACKGROUND

Lynch syndrome (LS) is the most common inherited cancer syndrome.[1,2] LS carriers are predisposed to developing malignancies, most commonly in the colorectum and endometrium.[3] Other typical LS spectrum tumors include cancers of the stomach, biliary tract, pancreas, small bowel, ovaries, brain and urinary tract, as well as sebaceous skin tumors.[4] As LS tumors often manifest at a younger age compared with the general population, LS carriers require more stringent cancer surveillance strategies to reduce morbidity and mortality by removal of precancerous neoplasia. Thus, LS carriers are offered regular colorectal cancer (CRC) surveillance by colonoscopy as well as prophylactic hysterectomy to prevent endometrial cancer.[5,6] Moreover, in the international CAPP2 clinical trial, daily aspirin intake has been shown to halve the risk of CRC and other common LS-associated cancers in LS carriers.[7,8] However, the lifetime risk of developing cancer varies widely between LS individuals within a family and between LS families, ranging from 30% to 80%,[9,10] and several factors, including both genetic and environmental aspects have been proposed as risk modifiers.[11,12] Such a broad risk range hampers the application of personalized cancer prevention strategies. More precise cancer risk estimates would allow cancer surveillance and prevention strategies to be tailored according to the LS carrier's personal cancer risk, thereby enabling more stringent strategies in high-risk individuals and helping to avoid unnecessary medical procedures in low-risk individuals.[13]

On the molecular level, LS is caused by a monoallelic germline variant in one of the DNA mismatch repair (MMR) genes.[14] Upon inactivation of the remaining allele by a second somatic hit, the affected cell becomes MMR-deficient. The MMR system is one of the essential tools ensuring genomic stability, specifically by correcting base mismatches and short insertion-deletion loops caused by polymerase slippage during DNA replication.[15] A deficiency of MMR function leads to the accumulation of small insertion/deletions, which occur particularly often at microsatellites, short tandem repeat DNA sequences, and results in the molecular phenotype of microsatellite instability (MSI).[16,17] Whereas mutations at microsatellites in non-coding genomic regions are unlikely to have functional consequences, insertions/deletions in coding microsatellites (cMS) can cause a shift in

the translational reading frames of genes (frameshift mutations) and early stop codons. cMS frameshift mutations can lead to the inactivation of tumor suppressor genes, and therefore drive tumorigenesis.[18-20] In addition, translation of frameshifts can generate frameshift peptides (FSPs)[21] that contain a completely new sequence of amino acids, giving rise to several novel epitopes previously unknown to the immune system. For this reason, FSPs are considered highly immunogenic.

2 | IMMUNOGENICITY OF MSI CANCERS

After the initiation of an expanding clone, the development of MSI cancers follows the principles of Darwinian evolution, where mutations providing cells with growth advantage persist in the cell population, whereas neutral mutations and those associated with a growth-repressing effect are less frequently observed.[22] This process results in the accumulation of recurrent cMS mutations during MSI tumor evolution, which are shared among tumors from different patients.[23,24] Shared mutations give rise to a shared, predictable repertoire of FSP neoantigens,[21,25] such as growth-promoting *TGFBR2* mutations shared by more than 90% of MSI CRCs.[26] The unique MSI-driven carcinogenic process, coupling acquisition of tumor-promoting mutations with the generation of highly immunogenic tumor antigens, explains why LS cancers rank among the most immunogenic of human cancers.[27] The strong immunogenicity of tumor antigens is evidenced by several observations. First, LS-associated tumors are commonly densely infiltrated by immune cells,[28-31] a feature which has been shown to correlate with a good prognosis.[32,33] Second, like sporadic MMR-deficient cancers, LS tumors respond well to immune checkpoint blockade therapy.[34-36] Importantly, a strong immune response against FSP neoantigens can be found systemically as well as locally in healthy LS carriers without tumor manifestation.[37-39] The presence of immune responses against neoantigens associated with driver mutations known to occur early during MMR-deficient cancer evolution suggests the elimination of pre-cancerous lesions by the immune system.[40-42] A crucial role of the immune system in controlling tumor outgrowth in LS is supported by the observation of rapid development of multiple skin tumors in LS carriers upon immune suppression[43] and spontaneous elimination of MMR-deficient tumor cells and pre-cancerous lesions.[44-46] Taken together, existing evidence suggests that immune surveillance by the adaptive immune system influences tumor risk in LS.

3 | ROLE OF HLA MOLECULES IN CANCER IMMUNE SURVEILLANCE

Surveillance by the adaptive immune system depends on the presentation of antigens by host cells, which requires intracellular processing and binding to HLA (Human Leukocyte Antigen) molecules on the cell surface. The HLA system was discovered in 1958 through reports from three research groups, all describing antibodies in human sera which reacted against leucocytes from certain individuals.[47-49] Thus, the antigens on human leucocytes were shown to be polymorphic across the human population.[50] Exposure to viral pathogens has generally been suggested as a major driving force behind the high diversity of HLA alleles conferring advantage to humans in protection against viruses.[51] In its current form, the HLA system (also called Major Histocompatibility Complex, MHC) has two major functions. First, HLA molecules themselves serve as "identity cards" thereby allowing the immune system to distinguish between self and non-self cells. In this capacity, the HLA system plays a crucial role in organ transplantation by determining graft rejection.[52,53] Second, the HLA system is responsible for the presentation of exogenous and endogenous cellular antigens, and therefore for eliciting antigen-specific immune responses.[54] Whereas exogenous antigens are usually presented by HLA class II molecules, endogenous antigens, such as those arising during cancer evolution, are commonly presented by HLA class I molecules. HLA class I molecules interact with CD8-positive T cells, which are considered the most powerful mediators of anti-tumor immune responses. In the following we will therefore focus on the HLA class I system.

During antigen processing, proteins are digested into peptides that assemble in a complex with an HLA molecule, which is then presented on the cell surface to immune cells.[54,55] The molecular structure of the HLA peptide-binding groove determines the type of peptides that are able to assemble with a certain HLA molecule.[56-58] This means that the immune system only recognizes the antigens that can bind to the patient's HLA molecules and are therefore presented on the cell surface. Conversely, it remains "blind" to those that cannot assemble with available HLA molecules (Figure 1). Thus, an individual's HLA genotype is one of the most important factors determining the binding of epitopes during antigen presentation and immune recognition of tumor antigens. Clinically, it is also one of the determinants of the success of immunotherapy approaches aiming to reactivate the existing HLA-mediated anti-tumor immune response, such as immune checkpoint blockade.[59,60]

4 | COMPOSITION OF AN INDIVIDUAL'S HLA GENOTYPE

HLA class I molecules are heterodimers, consisting of a heavy chain, and a light chain, Beta-2-Microglobulin (B2M). Whereas B2M is highly conserved across human populations, HLA class I heavy chain-encoding genes are very diverse between different humans and different populations.[61] The antigen-binding groove of each HLA allele has its own shape and chemical properties. Therefore, different HLA molecules fit a specific antigen to varying degrees. Genes encoding HLA class I heavy chains are located on chromosome 6.[62] There are three classical HLA class I genes, encoded by the HLA-A, HLA-B and HLA-C loci. As an individual has two parental alleles of each HLA locus, a person possesses a defined set of up to 6 classic HLA class I alleles (Figure 2). Using machine learning-based tools for peptide binding prediction, such as NetMHCpan 4.1,[63] one can theoretically predict which antigens will be recognized by, and which antigens will "fly under the radar" of, the immune system of an individual with a

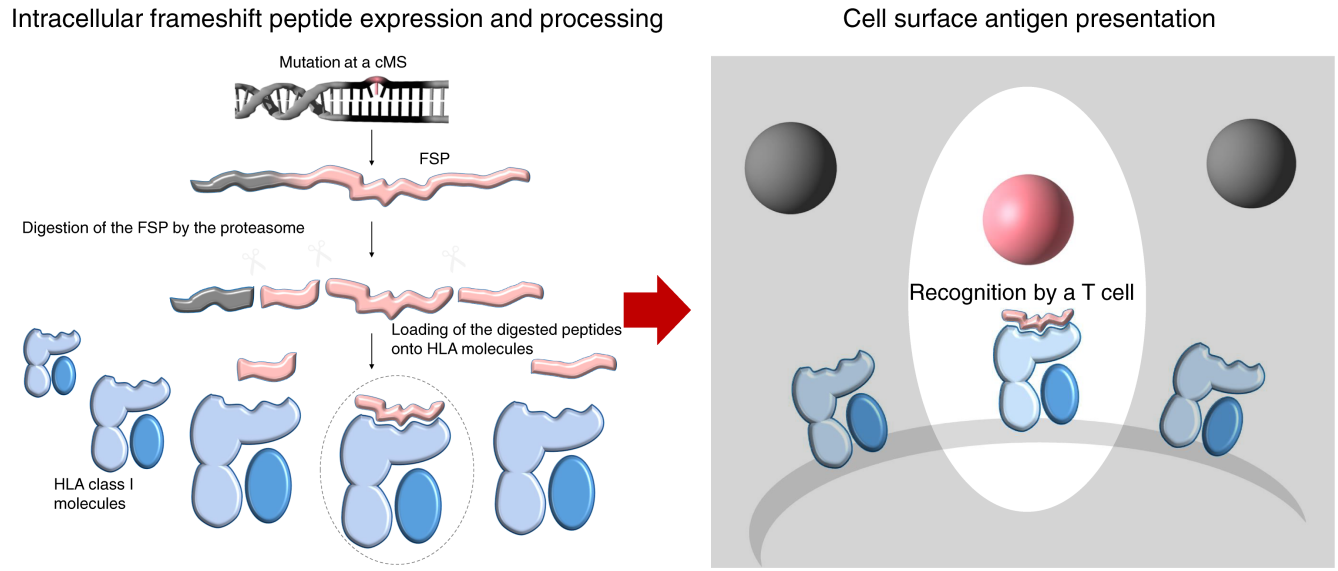

FIGURE 1 Simplified schematic illustration of the antigen presentation machinery focusing on the assembly of HLA molecules and binding of antigen-derived peptides, which serve as potential epitopes. Only peptides fitting into the peptide-binding groove are able to form a complex with the HLA molecules and are presented as epitopes to immune cells. FSP, frameshift peptide

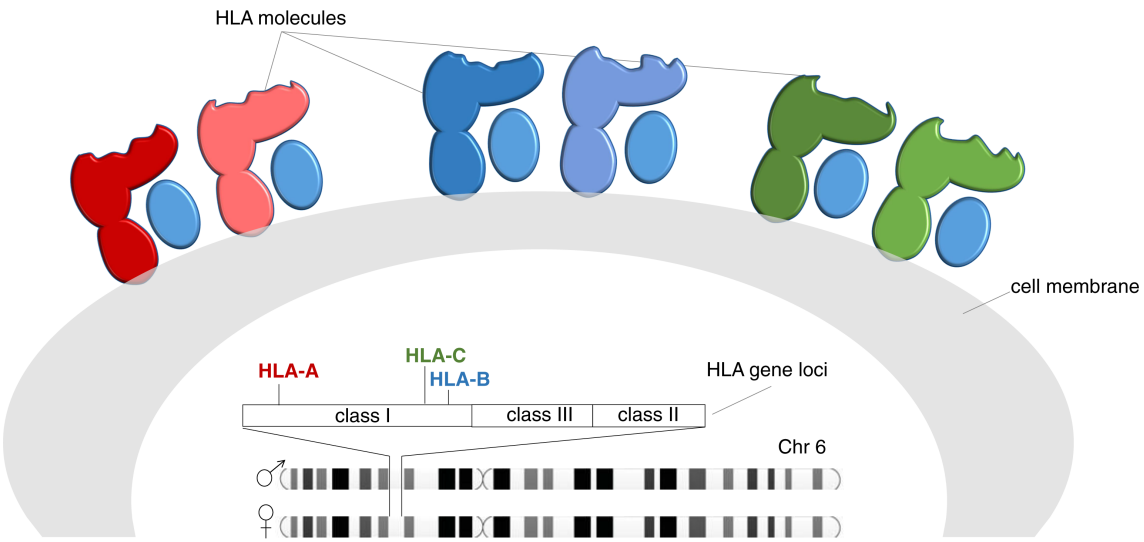

FIGURE 2 HLA class I protein-encoding region in the human genome. HLA class I proteins are encoded by three classical HLA class I gene loci HLA-A, HLA-B and HLA-C located on chromosome 6. As each locus has two alleles (maternal and paternal), a human can have up to six different HLA class I alleles and proteins resulting thereof

defined composition of HLA class I heavy chain-encoding genes (referred to in the following as HLA genotype or HLA type).

5 | HLA GENOTYPE AS A POSSIBLE CANCER RISK MODIFIER

The immune system can eliminate emerging MMR-deficient cells and so shapes tumorigenesis and tumor growth by selecting less immunogenic cells. This process, called immunoediting, has been recently suggested to select for tumor cells with an antigen repertoire that is undetectable by the immune system in an HLA genotype-dependent manner, or, in a more extreme example, to lead to the outgrowth of cell clones, which have lost their antigen presentation, for example by mutation of *B2M*, the essential light chain of the HLA class I complex.[24] The major role of HLA molecules in cancer antigen presentation implies its involvement in regulating immune surveillance and thus, also its possible influence on the tumor outgrowth at the precancerous stage, thereby modifying an individual's cancer risk. Outside the field of cancer, the associations of HLA genotype with the risk of infectious diseases have been demonstrated before. For instance, the role of HLA genotype in the susceptibility to COVID-19[64,65] or individual response

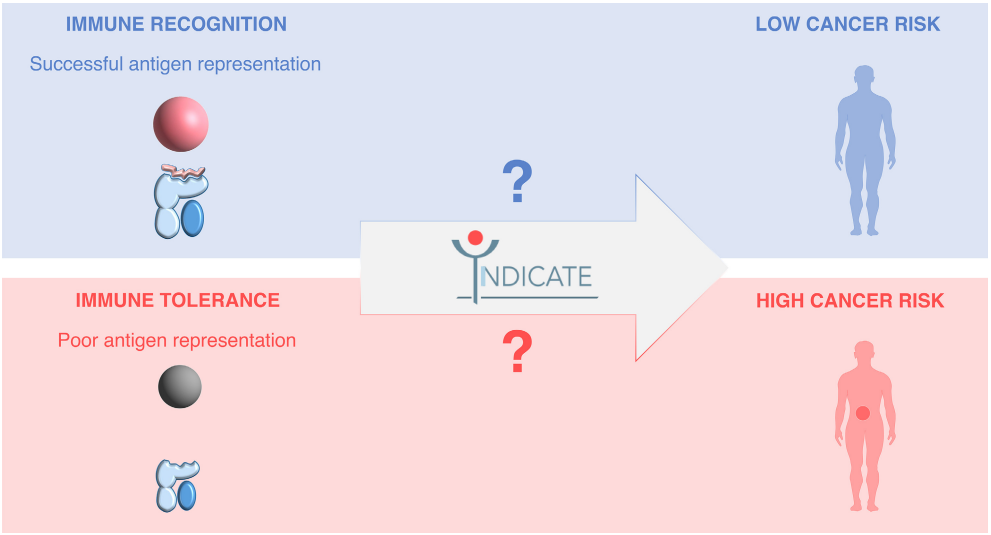

FIGURE 3 Scientific hypothesis of the INDICATE collaborative initiative. INDICATE aims to find out, whether the risk of developing a tumor in LS is associated with the HLA type of the individual, so delineating the HLA type-related cancer risk of LS carriers

to vaccination against the virus[66] has been reported. Regarding tumor diseases, to date only a few correlations have been identified so far concerning cancer susceptibility,[67-72] immune response,[73,74] therapy response,[59,60] and survival.[74] Importantly, studies analyzing potential biomarkers for response to immune checkpoint blockade identified certain HLA alleles to be associated with better or poorer therapy response and survival in tumor patients.[59,60] For example, a study analyzing response of melanoma patients to immune checkpoint blockade found extended survival in patients with HLA-B44 supertype and poor outcome in those with HLA-B62 supertype.[59] Moreover, analysis of immune checkpoint blockade therapy response among patients with different advanced tumors revealed HLA-A03 allele as a predictive biomarker of poor therapy response.[60] However, to date, findings relating to HLA genotype and cancer risk associations still are mostly related to cancers known to be induced by infectious pathogens including HPV, HBV and Helicobacter pylori. Similar data on cancers not related to a specific infectious pathogen are scarce.

Features of MSI cancer pathogenesis outlined above and the genetically defined population of LS carriers provides a unique opportunity to investigate the possible influence of HLA genotype on cancer risk in a pathogen-independent cancer type. Studying the impact of an individual's HLA type on cancer incidence and cancer mutation profile in LS, a cancer syndrome characterized by highly immunogenic MMR-deficient tumors, will deliver novel insights into the role of HLA type as a cancer risk modifier (Figure 3). Moreover, understanding the HLA genotype-tailored immune responses in LS patients may help in the design of cancer immunotherapeutic and preventive approaches, which can be applied also beyond the LS scenario.

6 | INDICATE—AN INTERNATIONAL INITIATIVE TO UNRAVEL HLA GENOTYPE'S ROLE IN LS-ASSOCIATED CANCER RISK

Due to the wide variety of HLA genotypes, studying HLA type-dependent tumor risk in LS is only possible in the framework of a large international collaborative approach. To realize this endeavor, researchers from several European centers agreed to establish a network aiming to delineate HLA type-dependent changes in cancer risk in the context of LS (INDICATE, Individual cancer risk by HLA type, http://indicate-lynch.org/). Sample collection (Germany, Finland, the UK and Hungary) of tumor and peripheral blood leukocyte DNA and first feasibility analyses have been initiated.

INDICATE pursues two major objectives. First, to validate the possible HLA type-dependent immune selection process during LS tumorigenesis, individual cMS mutation spectra of tumors from LS carriers will be established and compared with the predicted HLA type-specific epitope spectra using tools such as NetMHCpan 4.1.[63] To enable this, paired formalin-fixed paraffin-embedded tumor tissue and blood samples from LS patients will be collected for tumor mutation profiling and HLA typing, respectively. This analysis will account for the presence of somatic mutations associated with a complete loss of HLA expression. Moreover, HLA allele losses shall also be accounted for in LS-associated cancers, as the frequency of somatic loss events for a specific HLA type may be indirectly indicative of its role in immune surveillance. Second, to examine the potential role of HLA type as a cancer risk modifier in LS, HLA type will be retrospectively and prospectively correlated with cancer incidence in LS carriers using anonymized clinical data collected by participating centers. Case number calculations based on 80% power and two-sided 95% confidence intervals demonstrate that an increase or decrease in the lifetime cancer risk of 18% would be detectable for common HLA alleles, such as HLA-A*02 (with a prevalence of about 40% in Caucasians, allelefrequencies.net), of 22% for HLA-A*03 (with a prevalence of about 28% in Caucasians) and of 41% for rarer HLA alleles, such as HLA-B*27 (with a prevalence of about 5% in Caucasians), in a cohort of 1000 LS carriers, using Kelsey's formula[75] (Figure 4). The international collaborative approach will enable the collection of samples covering different populations, and therefore different HLA genotypes, and enable an unprecedented analysis of the

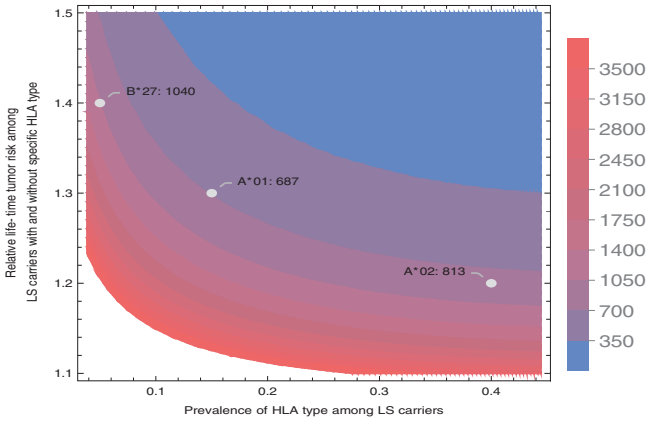

FIGURE 4 Sample size calculations for different HLA types. Using Kelsey's formula,[75] sample size calculations based on 80% power and two-sided 95% confidence intervals were performed for the comparison of patients with and without a specific HLA type. Required sample sizes (numbers according to the color legend) to detect a certain relative life time tumor risk (y-axis) among HLA-positive and HLA-negative LS carriers are illustrated for different HLA types with varying prevalence among LS carriers. Prevalences are taken from allelefrequencies.net and exemplary sample sizes are given for the HLA types A*02, A*01, B*27 with assumed increase in life-time tumor risk of 20%, 30% and 40%, respectively

influence of HLA genotype on CRC risk in the high-risk population of LS carriers, with a perspective to roll-out to other populations. This endeavor is designed as an open platform that actively invites all scientists interested in this field and willing to contribute scientifically to join the collaboration.

7 | SUMMARY

So far, the associations of HLA genotype and clinical tumor manifestation has been proposed only for a narrow spectrum of tumors and has focused predominantly on virus- or, generally, pathogen-induced cancer entities. However, recent studies show that response to immune-modulating therapies in highly immunogenic cancers can depend on the HLA genotype of the patient. Moreover, HLA genotype has been suggested to impact the immunoediting in MSI cancers. The latter observation points at a possible role of HLA genotype as a cancer risk modifier beyond the subset of pathogen-induced cancers. For LS carriers, who are at a particularly enhanced but broad cancer risk due to their genetic predisposition, such associations have not been analyzed systematically so far. The INDICATE collaborative initiative aims to analyze, whether the importance of HLA genotype in the anti-tumor immune response can be linked to cancer risk in LS. This analysis has the potential to deliver scientific evidence for developing novel personalized cancer risk prediction models accounting for constitutive immune factors, and allow the design of personal, risk-adapted surveillance strategies and tailored therapeutic approaches for affected individuals.

AUTHOR CONTRIBUTIONS

Conceptualization: Aysel Ahadova, Richard Gallon, Toni Seppälä, Matthias Kloor. Data curation and formal analysis: Aysel Ahadova, Johannes Witt, Saskia Haupt, Matthias Kloor. Funding Acquisition: Aysel Ahadova, Vince Kornel Grolmusz, Gillian M. Borthwick, John Burn, Jukka-Pekka Mecklin, Vincent Heuveline, Magnus von Knebel Doeberitz, Toni Seppälä, Matthias Kloor. Investigation: Aysel Ahadova, Johannes Witt, Saskia Haupt, Richard Gallon, Robert Hüneburg, Jacob Nattermann, Lena Bohaumilitzky, Alejandro Hernandez-Sanchez, Vince Kornel Grolmusz, Daniel Fürst, Jukka-Pekka Mecklin, Vincent Heuveline, Toni Seppälä, Matthias Kloor. Methodology: Aysel Ahadova, Johannes Witt, Saskia Haupt, Daniel Fürst, Matthias Kloor. Project administration: Aysel Ahadova, Matthias Kloor. Resources: Richard Gallon, Robert Hüneburg, Jacob Nattermann, Sanne ten Broeke, Mauro Santibanez-Koref, Michael S. Jackson, Maarit Ahtiainen, Kirsi Pylvänäinen, Katarina Andini, Vince Kornel Grolmusz, Gabriela Möslein, Mev Dominguez-Valentin, Pål Møller, Daniel Fürst, Rolf Sijmons, John Burn, Jukka-Pekka Mecklin, Toni Seppälä, Matthias Kloor. Software: Johannes Witt, Saskia Haupt, Vincent Heuveline. Supervision: Aysel Ahadova, Magnus von Knebel Doeberitz, Matthias Kloor. Validation: All authors. Visualization: Aysel Ahadova, Johannes Witt, Saskia Haupt, Richard Gallon, Matthias Kloor. Writing—original draft preparation: Aysel Ahadova, Johannes Witt, Saskia Haupt, Richard Gallon, Matthias Kloor. Writing—review and editing: All authors. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

ACKNOWLEDGEMENT

All contributors participating in the generation of the data discussed in this review article are gratefully acknowledged. Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

Previous studies leading to the constitution of the hypothesis have been supported by Wilhelm Sander Foundation, Deutsche Krebshilfe (German Cancer Aid, 70113455), German Research Foundation, "Donations against Cancer" program of the NCT Heidelberg. Pilot experiments were supported by the Else-Kröner-Fresenius Foundation, AsCaP collaboration and Cancer research UK Catalyst Award (Grant Number: C569/A24991), the CaPP3 Clinical Research Committee Late Phase Award (A15934), Finnish Medical Foundation, Emil Aaltonen Foundation, Finnish Cancer Society, Jane and Aatos Erkko foundation and the National Research, Development and Innovation Office (Hungary, NKFIH-FK-21-138377). Mathematical analyses were supported by the Klaus Tschira Foundation, Heidelberg, Germany in frame of the project "Mathematics in Oncology—Towards optimal prevention and treatment in patients with inherited cancer syndrome."

CONFLICT OF INTEREST

Toni Seppälä declares being CEO and co-owner of Healthfund Finland and reports consultation fees from Boehringer Ingelheim Finland and Amgen Finland. The other authors have no conflict of interest to declare.

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How to cite this article: Ahadova A, Witt J, Haupt S, et al. Is HLA type a possible cancer risk modifier in Lynch syndrome? *Int J Cancer*. 2023;152(10):2024-2031. doi:10.1002/ijc.34312