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ORIGINAL ARTICLE

Spectrum of mismatch repair gene mutations and clinical presentation of Hispanic individuals with Lynch syndrome

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Lynch syndrome (LS), the most common hereditary colorectal cancer syndrome, is caused by mismatch repair (MMR) gene mutations. However, data about MMR mutations in Hispanics are limited. This study aims to describe the spectrum of MMR mutations in Hispanics with LS and explore ancestral origins. This case series involved an IRB-approved retrospective chart review of self-identified Hispanic patients (n = 397) seen for genetic cancer risk assessment at four collaborating academic institutions in California, Texas, and Puerto Rico who were evaluated by MMR genotyping and/or tumor analysis. A literature review was conducted for all mutations identified. Of those who underwent clinical genetic testing (n = 176), 71 had MMR gene mutations. Nine mutations were observed more than once. One third (3/9) of recurrent mutations and two additional mutations (seen only once) were previously reported in Spain, confirming the influence of Spanish ancestry on MMR mutations in Hispanic populations. The recurrent mutations identified (n = 9) included both previously reported mutations as well as unique mutations not in the literature. This is the largest report of Hispanic MMR mutations in North America; however, a larger sample and haplotype analyses are needed to better understand recurrent MMR mutations in Hispanic populations.

Keywords MMR mutations, Lynch syndrome, Hispanics, MLH1, MSH2, MSH6, PMS2, colon cancer

Introduction

Individuals of Hispanic or Latino ancestry represent the largest and fastest growing ethnic minority group in the United States (1). More than 50 million Americans self-identify as Hispanic or Latino, accounting for 16% of the population (2). It is projected that 30% of the total U.S. population will identify as Hispanic by 2050. There is great heterogeneity among individuals identifying as Hispanic. The term is used in aggregate for individuals of Mexican, Central and South American, Caribbean, or Spanish ancestry. The underlying population varies greatly not only by country of origin, but also by cultural identity. As the population continues to grow, along with the corresponding cancer burden, it is increasingly important to expand our understanding of cancer risk factors and etiologies in the Hispanic population.

Colorectal cancer is the second most commonly diagnosed cancer in Hispanics and endometrial cancer is the most common gynecologic cancer in Hispanic women (3). While most colorectal and endometrial cancers are not associated

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with inherited cancer syndromes, it is estimated that approximately 3–5% are attributable to Lynch syndrome (LS) or hereditary non-polyposis colorectal cancer (HNPCC) (OMIM#120435). LS is caused by mutations in *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*. The range of lifetime cancer risks faced by individuals with LS is 40–80% for colorectal cancer, 15–60% for endometrial cancer, 11–24% for ovarian cancer, and 3–13% for gastric cancer, all of which are substantially elevated over the general population (4–9). Despite these elevated risks, appropriate cancer screening and risk-reducing interventions can substantially decrease the probability of developing cancer and increase the chance of a favorable prognosis for those who develop cancer (10,11).

LS has been reported worldwide, occurring in individuals of all ethnic and racial backgrounds (12–18). However, data are limited about the mutations associated with LS in Hispanics, as the majority of the extant literature has been focused on non-Hispanic individuals of European ancestry. A large body of literature on Spanish LS cohorts exists (14,19–22), but the literature outside of Spain has been limited to just a few South American studies and one in the Caribbean (23–28). While data from Hispanic *BRCA1/2* cohorts demonstrate that Spanish ancestral ties are manifested through specific recurrent mutations, there are other common mutations that are likely Amerindian in origin (29). We hypothesized that this may also be true in LS. In order to better understand the spectrum of mutations associated with LS in Hispanics in the US and Puerto Rico, a collaborative clinic-based cohort was assembled from four institutions.

Materials and methods

Our sample was ascertained from four centers serving Hispanic populations.

City of Hope (COH) cases included patients seen for genetic cancer risk assessment (GCRA) at collaborating institutions of the COH Clinical Cancer Genomics Community Research Network between 1996 and 2014. University of Southern California (USC) cases included patients who received cancer genetic services at two facilities: USC Norris Comprehensive Cancer Center and Los Angeles County + USC Medical Center, from 2007 to 2014. The University of Texas MD Anderson Cancer Center Clinical Cancer Genetics Program (MDA) maintains a comprehensive database of all patients seen for genetic counseling and genetic testing since 1999. The Puerto Rico Familiar Colorectal Cancer Registry (PURIFICAR) identifies newly diagnosed colorectal cancer cases through the Puerto Rico Cancer Registry (PRCCR).

We retrospectively collected data under IRB approved protocols at each institution (COH-#96144; USC 0S-12-4; MDA MTA#: 10334; PR #A2210207) on all probands that were of Hispanic ancestry and who were assessed for LS at their respective facilities as part of their clinical care. This assessment was defined as microsatellite instability testing (MSI) and/or immunohistochemistry (IHC) of the MMR gene protein products and/or genotyping for one or more of the MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) and *EpCAM.*

Germline genetic testing was ordered as deemed clinically indicated, based on abnormal IHC staining patterns or clinical testing criteria. Clinical criteria utilized included Amsterdam criteria, Bethesda guidelines and NCCN consensus guidelines that are annually updated (30–34). All germline genetic testing was performed at CLIA approved laboratories. The number of MMR genes analyzed varied based on the results of IHC, insurance coverage, and genes clinically available at the time of testing. Sequence alterations were classified by each CLIA-approved laboratory, based on their established variant assessment process. For consistency, all alterations were converted to the current Human Genome Variation Society and the American College of Medical Genetics and Genomics for variant nomenclature and interpretation (35,36).

A comprehensive literature review was conducted for all mutations in the cohort using PubMed, Google Scholar, the InSiGHT database, and the Mismatch Repair Genes Variant database (37,38). Ethnicity was recorded for all cases reported in the literature. When the specific ethnicity of the case was not described in a publication, the country(ies) of the authors was recorded. Descriptive statistics were performed using SPSS version 19 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0, Armonk, NY).

Results

Demographics and clinical features

Tumor studies (MSI and/or IHC) and/or genotyping of one or more of the MMR genes were performed in 397 individuals of Hispanic ancestry (Table 1 and Figure 1). Most participants reported Mexico as their country of origin (n = 124, 31.2%), followed by Puerto Rico (n = 64, 16.1%), Guatemala (n = 20, 5.0%), and El Salvador (n = 19, 4.8%). A majority of participants (n = 381, 96.0%) were diagnosed with at least one tumor, with colorectal cancer being the most common (n = 296, 74.6%). The mean age of cancer diagnosis for participants was 43.6 years.

The majority of individuals with a cancer diagnosis (n = 344, 90.2%) had MSI and/or IHC performed on their tumor. The results of these tumor studies were classified as MMR proficient if all proteins were expressed by IHC and/or the tumor was MSI stable or low. Tumors that exhibited loss of one or more of the MMR proteins by IHC or were MSI high were classified as MMR deficient. Figure 1 details these studies across the cohort, as well as subsequent germline findings.

In our multi-center cohort, 79 MMR gene sequence alterations were identified in 77 probands from unrelated Hispanic families. Seventy-one alternations were classified as pathogenic or likely pathogenic and nine as variants of unknown significance (VUS; Table 2, Appendix S1). Subsequent analyses focused on the 71 individuals with pathogenic and likely pathogenic mutations. Sixty-one had a cancer diagnosis; 66.2% had colorectal cancer, 12.7% (n = 9) had uterine cancer, 1.4% (n = 1) had gastric cancer, and 5.6% (n = 4) had other cancers (Table 1). The majority (57.7%) of the affected mutation carriers had one LS associated cancer, while 18.3% (n = 13) of individuals had two, and seven (9.9%) had three or more LS associated cancers (Table 1).

MMR gene mutations

In our cohort, 71 people were identified to have pathogenic or likely pathogenic mutations (Table 2), representing 57 distinct mutations (Appendix S1). Of these, 29 were in *MLH1*,