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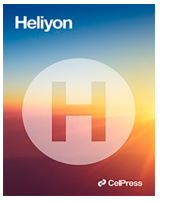

Research article

Lynch syndrome in Mexican-Mestizo families: Genotype, phenotypes, and challenges in cascade testing among relatives at risk

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ABSTRACT

Lynch syndrome (LS) is the most frequent cancer predisposition syndrome affecting the colon and rectum. A pathogenic variant (PV) disrupting one of the mismatch repair (MMR) genes is responsible for the disease. The spectrum of tumors in LS is heterogeneous and includes cancer of the colon and rectum (CRC), endometrium, ovaries, stomach, small bowel, urinary tract, bladder, pancreas, and skin. Knowledge of the phenotypic variation of patients with LS, the type and frequency of PVs, and cascade testing studies in the Latin American population is limited. The present study aims to recognize the PVs in MMR genes, describe the phenotype in Mexican-Mestizo patients and their relatives, and identify the acceptance rate of cascade testing of relatives at risk. We included 40 carriers of a MMR gene PV and 142 relatives that developed a LS-related neoplasm. Patients' clinical data, number, and type of malignancies were obtained from their medical records. Amsterdam I-II, Bethesda criteria, and PREMM5® predictive model score were estimated. Available immunohistochemistry (IHC) reports were analyzed. Relatives at risk were determined from index cases pedigrees. The distribution of MMR gene mutations among 40 probands was: *MLH1* (67.5 %), *MSH2* (22.5 %), *MSH6* (7.5 %), and *PMS2* (2.5 %). Out of the 182 LS cases, 58 % exhibited the LS phenotype before age 50. The most common tumor was CRC, followed by endometrial cancer in women and gastric cancer in males. We found a 90.0 % concordance between the IHC and germline PV. The most frequent PV in our sample was *MLH1* c.676C > T, occurring in 1/6 index cases. All probands disclosed their molecular test result to

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their family. Out of the 451 asymptomatic relatives at risk, 28.2 % underwent germline testing. Our results highlight the importance of conducting germline genetic studies in LS since it allows the establishment of appropriate cancer screening, risk-reducing measures, and genetic cascade testing among relatives at risk. Interestingly, we observed a significantly higher prevalence of the c.676C > T variant in *MLH1,* probably a singular characteristic of the Mexican-Mestizo population. New strategies to facilitate accurate communication between index cases and relatives should be implemented to improve the cascade testing acceptance rate.

1. Introduction

Colorectal cancer (CRC) is the third most frequent type of cancer worldwide, responsible for 9.4 % of total cancer deaths in 2020. Mexico has a 5-year prevalence of 21.39 per 100,000 inhabitants, and it is the second most prevalent cancer in men and fourth in women [1].

Between 5 and 10 % of CRC cases are hereditary [2]. The majority are associated with Lynch Syndrome (LS), which has an autosomal dominant inheritance pattern caused by germline pathogenic variants (PV) in DNA mismatch repair (MMR) genes: *MLH1, MSH2, MSH6,* and *PMS2.* Although not considered an MMR gene, a genomic rearrangement in *EPCAM* can lead to epigenetic silencing of *MSH2*, resulting in a similar phenotype [3,4].

In addition to having up to 80 % lifetime risk of CRC, patients with LS have a higher risk of developing other cancer such as endometrium (71 %), ovaries (38 %), stomach (37 %), urinary tract (28 %), bladder (12.8 %), small intestine (11 %), skin (<10 %), brain (8 %), pancreas (6.2 %), biliary tract (<5 %), prostate (30 %) and breast (18.6 %) [4–8]. Unlike sporadic CRC, LS-related CRC has an early presentation among ~ 44–66 years old [6,7], preference for the proximal colon (45–70 %) [9–11], and a higher frequency of synchronous and metachronous cancer (20–30 % at ten years, 44–50 % at 20 years and 66 % at 30 years from primary CRC) [4,12].

Studying asymptomatic relatives of LS cases allows appropriate cancer screening, including colonoscopies, endometrial biopsies, and risk reduction procedures, such as hysterectomies and bilateral salpingo-oophorectomies, improving clinical and economic outcomes [7,13]. Also, deficient-MMR cancers may benefit from advanced-stage immunotherapy, including PD-1 and PD-L1 inhibitors [14].

The acceptance rate of cascade testing for hereditary cancer is variable, ranging from 30.5 to 77 % [15–17]. In addition, ethnic disparities in germline testing have been reported, showing that in Hispanics and other racial minorities is less frequently done. For example, Kwon et al. found that out of 1351 men with prostate cancer who underwent germline testing, only 2 % were Hispanics in contrast with 78 % Caucasians [18]. There are no scientific reports of cascade testing in LS families in the Mexican population.

In our Institution, 37.4 % of first-time genetic consults correspond to familial cancer, half of them of hereditary CRC. Knowing the importance of early detection of LS and its phenotypical variability, this study aimed to determine the frequency and type of PVs in Mexican-Mestizo patients with LS and identify the characteristics of the neoplasms presented. In addition, we analyzed the acceptance rate of cascade testing of at-risk family members to identify and promote more effective acquiescence.

2. Patient data and methods

We included patients referred to Genetic or Oncogenetic clinics of the National Institute of Medical Sciences and Nutrition, a tertiary medical center in Mexico City, from January 2003 to June 2022, having a positive molecular test for germline PV in the MMR genes. Tests were carried out in our Institution, private laboratories, or as research projects (research board review control number: HEM-1900), using next generation sequencing and/or multiplex ligation-dependent probe amplification of MMR genes. The Human Genome Variation Society (HGVS) guidelines [19] were used to describe the MMR variants. Exclusively, classes 5 (pathogenic) or 4 (likely pathogenic) were included. In addition, the International Society of Gastrointestinal Hereditary Tumors (InSIGHT) database, the Universal Mutation Database (UMD), the Human Gene Mutation Database (HGMD) and ClinVar databases were assessed to know if the variant was already reported or considered novel. The American College of Medical Genetics (ACMG) criteria was used for the novel variants to determine their pathogenicity [19]. Additionally, we included family members of patients with a confirmatory molecular test that developed a neoplasm under the LS spectrum.

Patients' clinical data, such as sex, age at diagnosis, number and type of neoplasms, and risk-reduction strategies, was obtained from their medical records. We classified cases according to whether or not they met Amsterdam I-II and Bethesda criteria. PREMM5 ® predictive model score was also calculated, and when available, an immunohistochemical report (IHC) report was reviewed.

First, second, and third-degree relatives at risk, who were over 18 years of age, were accounted for within index cases' pedigrees and grouped into those with a molecular test (referring to target mutation with Sanger sequencing) and those without it. Data about disclosure to relatives at risk and reasons for declination of cascade testing were obtained by direct interrogation of index cases, either person-to-person or by telephone call.

We used the Chi-square and Fisher's exact tests for categorical variables and the U Mann-Whitney test for numerical variables analyses. Statistical analyses were conducted using the IBM SPSS Statistics for Macintosh, version 25.0 (IBM Corp., Armonk, NY, USA). A p-value <0.05 was considered statistically significant.

3. Results

A total of 40 probands and 142 relatives with LS were studied. Table 1 shows the characteristics of the cohort. Out of the 40 families, 27 had a PV in *MLH1* (67.5 %), 9 in *MSH2* (22.5 %), 3 in *MSH6* (7.5 %), and 1 in *PMS2* (2.5 %). Of the complete cohort, including probands and relatives, the majority were men (56.0 %), and 58.2 % were diagnosed with cancer before age 50, with a median age of 46 (range 19–78). One-hundred forty-five patients had only one tumor (79.7 %), while thirty-seven had more than one (20.3 %). The most common second neoplasm was CRC in 17/37 instances (45.9 %); in 13/17 cases (76.5 %), it was synchronous or metachronous.

Fig. 1 shows the primary site of 225 neoplasms in the 182 individuals studied, grouped by sex. IHC staining was available for 40 LS patients, presenting a 90.0 % concordance with the germline PV. The four discordant IHC stains belonged to patients with the following PVs in *MLH1*: c.350C > T, c.588+5G > A, c.676C > T, and c.1943C > T. In all of them, the four proteins were present.

Retrospectively, Amsterdam I and II criteria and Bethesda guidelines were fulfilled in 40.0 %, 70 %, and 97.5 % of cases, respectively. Those with a PV in gene *MLH1* fulfilled Amsterdam I criteria more frequently than those with a PV in gene *MSH2* (51.9 % against 22.2 %), in contrast with Amsterdam II criteria which was similar between both groups (74.1 % and 77.8 %, respectively). Probands with PV in gene *MSH6* did not meet either criterion (0 %, 0/3). The PREMM5® score showed significant interindividual variation, with values ranging between 2.0 and >50 %. The median score was lower in those with a PV in gene *MLH1* (28.3 %) than in gene *MSH2* (36.7 %). Two patients (5.0 %) didn't reach the score recommended for genetic testing, with a score of 2.0 % and 2.4 % each. (Table 2).

Table 3 lists the types of PVs identified. Point mutations were observed in 90 % of the cases, while the remaining 10 % were carriers of large genomic rearrangements (LGR). The distribution of the 26 point mutations was as follows: nonsense (26.9 %), frameshift (26.9 %), splicing site (23.1 %), missense (19.2 %) and a codon deletion (3.9 %). Six of the 28 different PVs observed were recurrent in our sample. In the *MLH1* gene, recurrent PVs were c.676C > T (p.Arg226*), deletion of exons 2 and 3, c.588+5G > A, c.258delG (p.Gln86Hisfs*6), and c.2218dupA (p.Ile740Asnfs*6) (Fig. 2A). The first was observed in seven unrelated families, the deletion of exons 2–3 in three families, and the rest in two families each. In *MSH2*, the variant c.70C > T (p.Gln24*) was found in two unrelated families (Fig. 2B). No phenotypic differences were identified between point mutations and LGR. We observed three novel PVs not previously reported, *MLH1* c.258delG, *MSH2* c.1663A > T, and *MSH6* c.3934_3935insGGAG.

We could not reach four index cases to interrogate the status of family testing. Of the 36 patients we could contact, all disclosed the molecular test result to at least one relative (100 %, 36/36). The reasons for disclosing results to relatives and the perceived reasons for relatives' refusal of testing are present in Supplementary Fig. 1. In two families (2/36) all adult relatives at risk received molecular testing. We identified 451 asymptomatic relatives at risk, of whom 127 underwent germline testing (28.2 %). Out of these 127 relatives with the molecular test, 29.9 % (38/127) are asymptomatic carriers of a PV, 44.1 % (56/127) have a negative result and in 26 % (33/127) results are pending (Fig. 3).

Although most tested relatives were women (59.1 %), there was no statistical difference between sexes (OR 1.43, CI (0.91–2.25), $p = 0.125$). Relatives who received the molecular test were younger than the group without it (median age 38 versus 42, $p < 0.027$). First-degree relatives were also more likely to receive the molecular test in comparison to second or third-degree relatives (OR 2.89, CI (1.89–4.41), $p < 0.00001$).

4. Discussion

This work contributes to the genotype and phenotype characterization of LS in Mexico and highlights the importance of conducting

Table 1
General characteristics of index cases (n = 40) and relatives (n = 142) with Lynch Syndrome.

	MLH1		*MSH2*		*MSH6*		*PMS2*		Total	
	n	%	n	%	n	%	n	%	n	%
Population										
Index cases	27		9		3		1		40	
Relatives	103		33		3		3		142	
Sex										
Male	80	61.5	19	45.2	3	50.0	0	–	102	56.0
Female	50	38.5	23	54.8	3	50.0	4	100.0	80	44.0
Age at diagnosis										
<50 years	74	56.9	27	64.3	4	66.7	3	25.0	106	58.2
≥50 years	56	43.1	15	35.7	2	33.3	1	75.0	76	41.8
Years at diagnosis										
Median	46		45		30		62		46	
Min-max	19–77		19–78		23–65		45–70		19–78	
Number of tumors										
1 tumor	105	80.8	31	73.8	5	83.3	4	100.0	145	79.7
2 tumors	20	15.4	11	26.2	1	16.7	0	–	32	17.6
3 tumors	4	3.1	0	–	0	–	0	–	4	2.2
4 tumors	1	0.8	0	–	0	–	0	–	1	0.5

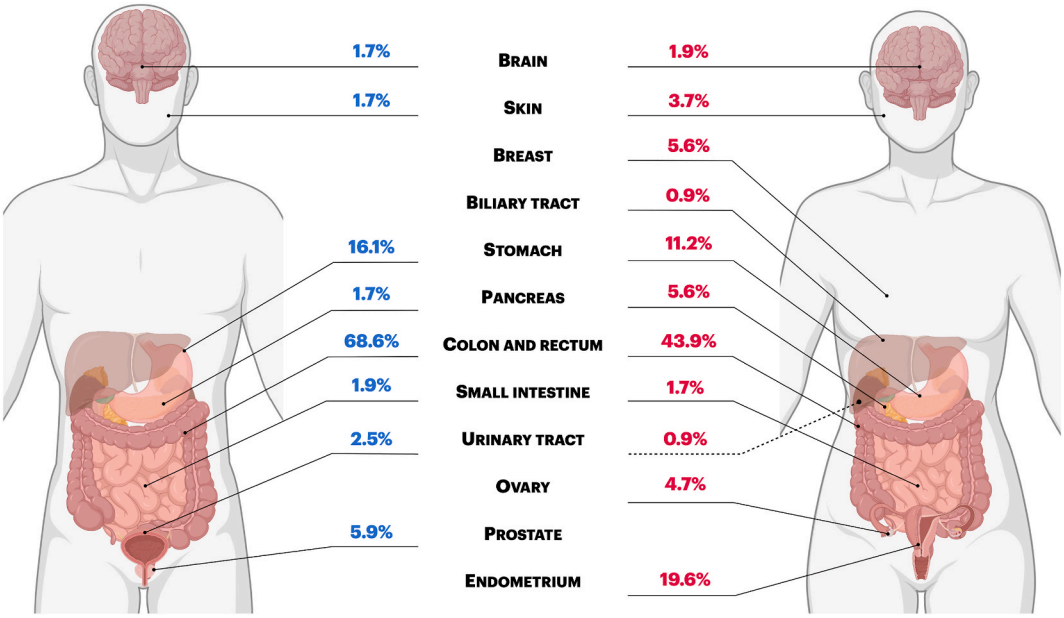

Fig. 1. Distribution of neoplasms observed in 102 male and 80 female patients with Lynch Syndrome. Created with BioRender.com.

Table 2
Frequency of index cases with Lynch Syndrome that fulfilled Amsterdam and Bethesda criteria and their PREMM5® score.

	MLH1		*MSH2*		*MSH6*		*PMS2*		Total	
	n	%	n	%	n	%	n	%	n	%
Index cases	27		9		3		1		40	
Amsterdam I										
Fulfilled	14	51.9	2	22.2	0	–	0	–	16	40.0
Not fulfilled	13	48.1	7	77.8	3	100.0	1	100.0	24	60.0
Amsterdam II										
Fulfilled	20	74.1	7	77.8	0	–	1	100.0	28	70.0
Not fulfilled	7	25.9	2	22.2	3	100.0	0	–	12	30.0
Bethesda										
Fulfilled	26	96.3	9	100.0	3	100.0	1	100.0	39	97.5
Not fulfilled	1	3.7	0	–	0	–	0	–	1	2.5
PREMM5® score										
Median	28.3 %		36.7 %		3.7 %		2.4 %		30.7 %	
Min-Max	4.6–50.0 %		4.5–50.0 %		2.0–21.0 %		2.4 %		2.0–50.0 %	

molecular genetic studies in LS since it allows the establishment of appropriate cancer screening, risk-reducing measures, and genetic cascade testing on relatives at risk.

Only eight studies have reported data on Mexican-Mestizo patients with molecularly confirmed LS [5,8,20–25] shown in Table 4. In the present study, the *MLH1* gene (67.5 %) was more frequently affected than *MSH2* (22.5 %). This differs slightly from those previously reported in the Latin American population. Rossi et al. [5] reported a PV frequency in genes *MLH1, MSH2, MSH6, PMS2,* and *EPCAM*, of 53.9, 32.4, 9.5, 3.4, and 0.8 percent, respectively. Moreover, Vaccaro et al. [22] reported a lower prevalence of PVs for genes *MLH1* and *MSH6* (46.6 % and 8.4 %, respectively) and a higher frequency of PVs in *MSH2/EPCAM* and *PMS2* (37.4 % and 7.6 %).

CRC was more frequently found in males (68.6 %) than females (43.9 %). The gynecological cancers were also prevalent in the female group: endometrial (19.6 %), breast (5.6 %), and ovarian cancer (4.7 %). The stomach was the second and third most frequently affected primary site in males and females, respectively. Pancreas was affected almost three times more in females than males. Other organs involved were skin in 6 patients (sebaceous, epidermoid, and basal cell carcinomas), brain in 4 (all glioblastoma multiforme), urinary tract in 4 (including renal, urachus, and bladder cancer), prostate cancer in 7 males and biliary tract in one female patient. When stratifying the cohort by gene affected, CRC was present in 61.9 % of the patients with a PV in the *MLH1* gene and 45.3 % in those with a PV in gene *MSH2*. Of note, one patient with a PV in *MLH1* was diagnosed with CRC at 46 years and papillary thyroid cancer at age 51, although the last one is not part of the LS spectrum.

Out of the 128 colorectal neoplasms, the exact location was confirmed in 64 tumors and the clinical stage in 54. As previously described in LS patients compared to sporadic CRC, we found a higher rate of right colon affected (62.5 %, 40/64). In addition, a higher frequency of rectal cancer and advanced disease has been described in Latin American patients [24]. However, in our sample, only 4.7

Table 3
Spectrum of pathogenic variants in Mexican Lynch Syndrome families (n = 40).

Gene	Nucleotide change	Protein change	Type	Exon	Probands	Frequency
MLH1	c.676C > T	p.Arg226*	Nonsense	8	7	17.5 %
	Exon 2–3 deletion c.(116 + 1_117–1)_(306 + 1_307–1)del	?	LGR		3	7.5 %
	c.588+5G > A	p.?	Splicing	7i	2	5.0 %
	c.258delG °	p.Gln86Hisfs*6	Frameshift	3	2	5.0 %
	c.2218dupA	p.Ile740Asnfs*6	Frameshift	19	2	5.0 %
	c.350C > T	p.Thr117Met	Missense	4	1	2.5 %
	c.884+1G > A	p.?	Splicing	10i	1	2.5 %
	c.1559-1G > A	p.?	Splicing	13i	1	2.5 %
	c.1559-1G > T	p.Leu521Lysfs*34	Splicing	13i	1	2.5 %
	c.1649T > C	p.Leu550Pro	Missense	14	1	2.5 %
	c.1731G > A	p.Ser577 =	Splicing	15	1	2.5 %
	c.1791G > A	p.Trp597*	Nonsense	16	1	2.5 %
	c.1943C > T	p.Pro638Leu	Missense	17	1	2.5 %
	c.1011dupC	p.Asn338Glnfs*24	Frameshift	11	1	2.5 %
	c.1852_1854delAAG	p.Lys618del	Frameshift	16	1	2.5 %
	c.2195_2198dupAACA	p.His733GInfs*14	Frameshift	19	1	2.5 %
MSH2	c.70C > T	p.Gln24*	Nonsense	1	2	5.0 %
	c.484G > A	p.Gly162Arg	Missense	3	1	2.5 %
	c.1216C > T	p.Arg406*	Nonsense	7	1	2.5 %
	c.1661+1G > T	p.?	Splice donor	10i	1	2.5 %
	c.1663A > T°	p.Lys555*	Nonsense	11	1	2.5 %
	c.2075G > A	p.Gly692Glu	Missense	13	1	2.5 %
	c.475delA	p.Arg159Aspsfs*15	Frameshift	3	1	2.5 %
	Exon 6 deletion c.(942 + 1_943–1)_(1076 + 1_1077–1)del		LGR		1	2.5 %
MSH6	c.2105C > G	p.Ser702*	Nonsense	4	1	2.5 %
	c.3261delC	p.Phe1088Serfs*2	Frameshift	5	1	2.5 %
	c.3934_3935insGGAG°	p.Val1312Glyfs*8	Frameshift	9	1	2.5 %
PMS2	c.1882C > T	p. Arg628*	Nonsense	11	1	2.5 %

LGR: Large genomic rearrangement. ° New variants.

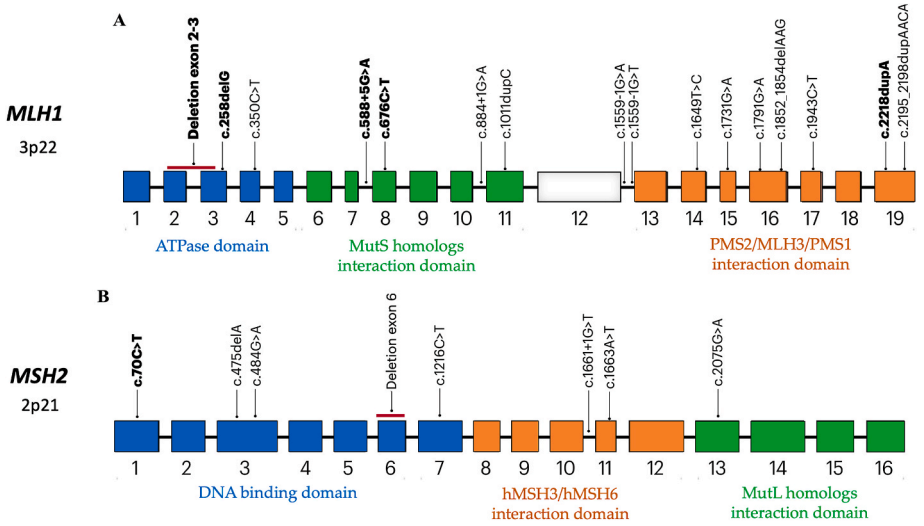

Fig. 2. Localization of pathogenic variants identified (A) *MLH1* and (B) *MSH2* genes.

% (3/64) of the cases of CRC were located in the rectum, whereas 38.9 % (21/54) were diagnosed at stages III or IV.

We found a high concordance between IHC and germline PV (90.0 %), supporting the use of IHC for universal screening of CRC. This has been recommended by several authors and institutions, especially when it is complemented with the identification of *BRAF* V600E mutation and hypermethylation of *MLH1* promoter, characteristic of sporadic CRC with loss of *MLH1* staining [7].

Two patients did not reach the recommended score for genetic testing using PREMM5 ®. One of them had a PV in *PMS2* (PREMM5 score 2.4 %) and was diagnosed with CRC at the age of 62 years. The other patient had a PV in *MSH6* and her score was 2.0 % since she presented with breast cancer, which is not considered part of the spectrum of LS neoplasms.

Interestingly, the six recurrent PVs in *MLH1* and *MSH2* identified in our sample are present in 45 % of families (18/40). The most prevalent of these is the PV in *MLH1* c.676C > T (17.5 %). The transversion of cytosine to thymine in position 676 changes arginine to a

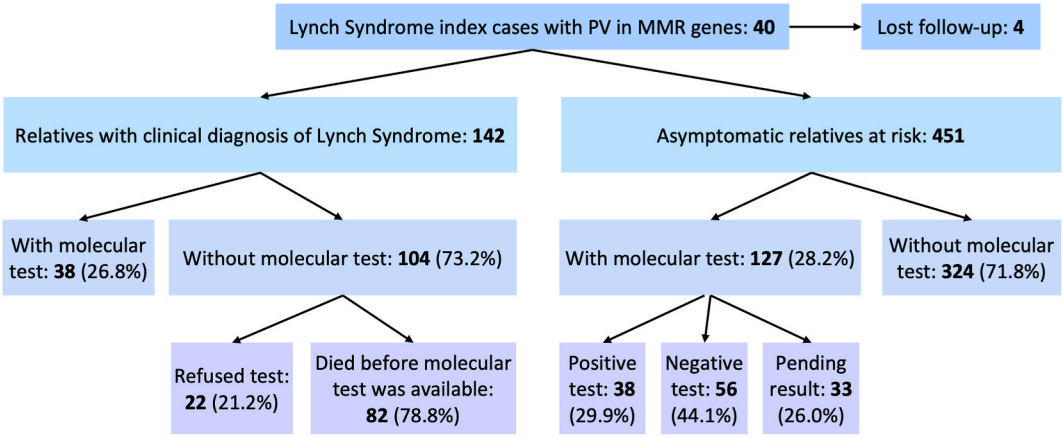

Fig. 3. Molecular status of index cases and relatives with Lynch Syndrome and asymptomatic relatives at risk.

Table 4
The frequency of genes affected in Mexican Lynch Syndrome families reported in the literature.

Study	*MLH1*		*MSH2*		*MSH6*		*PMS2*		Total
	n	%	n	%	n	%	n	%	
Vaccaro [22]	4	80.0	1	20.0	0	–	0	–	5
Ricker [21]	5	71.4	2	28.6	0	–	0	–	7
Moreno-Ortiz [20]	2	66.7	1	33.3	0	–	0	–	3
Della-Valle [23]	4	80.0	1	20.0	0	–	0	–	5
Padua-Bracho [25]	59	52.7	24	21.4	21	18.8	8	15.2	112
Current study	27	67.5	9	22.5	3	7.5	1	2.5	40
Total	101	58.7	38	22.1	27	15.7	9	5.23	172

stop codon, producing a truncated MLH1 protein. Also, the splice donor sequence is altered since nucleotide 676 is 2 base pairs from the 3' end of exon 8 [26]. This variant was first described by Moslein et al. in 1996 [27] and it was later reported in other populations from Europe, Asia, Africa, North America, and Argentina (Supplementary Table 1). It has also been reported in Mexican individuals living in the United States [11] and was found to be a recurrent variant in a previous report of LS in Mexico [25]. Fig. 4 shows that although it is distributed worldwide, the majority of index cases reported in the literature (including our sample) are of Mexican origin. In studies where the individual characteristics of the c.676C > T variant carriers were described, it was mostly associated with CRC cancer (18/21) with a median age of presentation of 40.5 years. In our sample, the 37 LS patients with *MLH1* c.676C > T variant presented 42 neoplasms, of which 28 were CRC, 4 were gastric and EC each, 2 were pancreatic and prostate cancers each, and a urachus carcinoma and sebaceous carcinoma in one patient each.

All patients informed their families about the molecular study result. We found that although in 31/36 of the families, at least one relative at risk agreed to the molecular test, the general rate of test uptake was 28.2 % (127/451). Previous studies have shown that women are more likely to agree to germline testing [28], however, this was not the case in our cohort. Nevertheless, consistent with other studies, first-degree relatives were more likely to perform the molecular test in comparison to second or third-degree relatives [15,16,28].

When asking probands for the reasons why some relatives at risk have not performed the molecular test, the two most common answers were that some of them do not perceive their own risk and that they have fear (Supplementary Fig. 1). This is probably because most of them did not have direct contact with a clinical geneticist for appropriate counseling and relied solely on the proband's capacity to communicate the information. In addition, the average Mexican family size is considerably larger than what is normally seen in other western countries. In our sample, the average number of relatives at risk was 14.8 per index case, of which 23.9 % (142/593) developed cancer. This is a potential challenge for the index case when asked to provide the information to all relatives at risk. Another frequent answer was economic limitations since the molecular test was not free of charge in the early stages of the study. For example, in a study by Márquez-Rodas, the acceptance rate for hereditary cancer was >95 % due to proper genetic counseling, but also full coverage of expenses with the Madrid health system [29].

To date, we have diagnosed 38 presymptomatic relatives with positive test results who began appropriate cancer screening. In addition, 13 patients with LS and 2 asymptomatic carriers from our sample underwent risk-reduction procedures. Also, as important, we identified 54 relatives with a negative test result, which translates to resource savings for the patient, the family, and the Institution, since these individuals do not require the strict long-term follow-up of those patients with a PV in MMR genes.

Our study had some limitations. Although to our knowledge this is one of the largest cohorts of exclusively Mexican-Mestizo LS patients that has been published, we only had three probands with PV in *MSH6*, one in *PMS2,* and none in *EPCAM;* therefore, genotype-

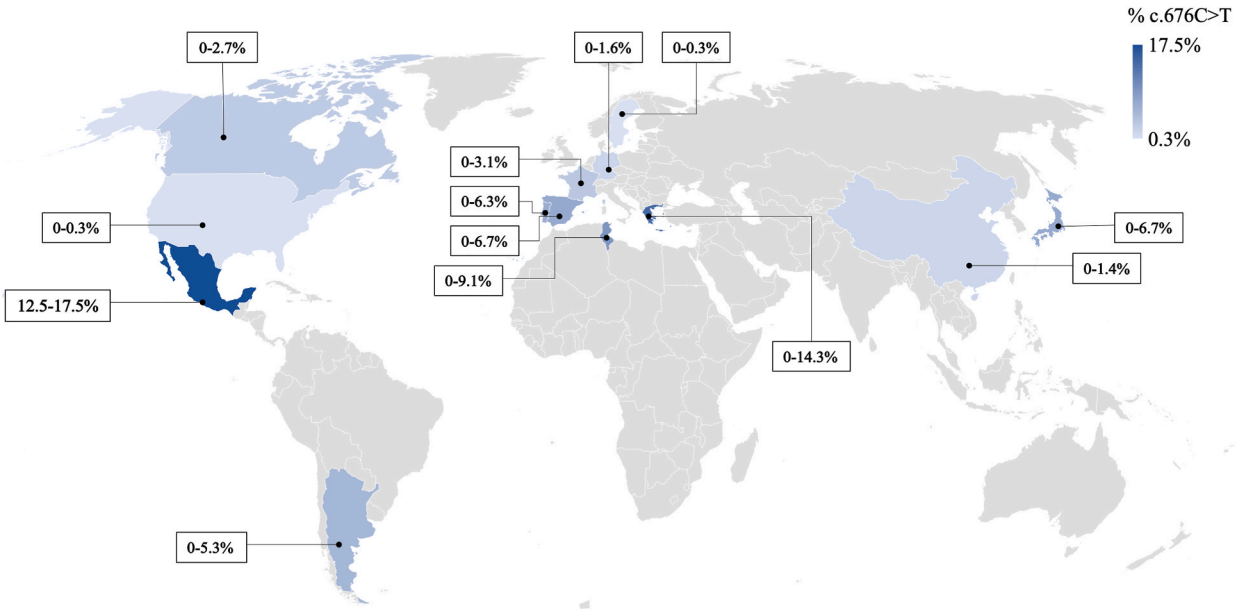

Fig. 4. Lynch Syndrome Index cases with *MLH1* c.676C > T variant reported worldwide per country. Greece's 14.3 % corresponds to 1 out of 7 patients with the c.676C > T PV. Tunisia's 9.1 % corresponds to 1 out of 9 patients with the c.676C > T PV.

phenotype correlations could not be made. In addition, pathology reports and IHC reports were not available in all patients. The fulfillment of Amsterdam and Bethesda criteria, the calculated PREMM5® score, and the identification of relatives at risk relied on the accuracy of the reported family history by the patient or the clinician in the medical record. We tried to corroborate missing data directly with the patient but it was not always feasible.

This study contributes to the LS genotype and phenotype characterization of the Mexican population and further supports the important representation of the c.676C > T variant in *MLH1*. Although LS index cases understand the importance of cascade testing after appropriate genetic counseling, new strategies to facilitate accurate communication between index cases and relatives at risk should be implemented to improve the cascade testing acceptance rate. Several strategies have demonstrated success in previous research, including pretest genetic counseling provided directly to at-risk relatives by a geneticist, informative letters or flyers outlining the implications of cascade genetic studies, financial assistance programs, regular follow-up by health-care professionals and psychological support after receiving the results, could be further investigated in subsequent studies [13,28,30,31].

Ethics statement

This work was approved by the Ethics Committee and Ethics on Research Committee of Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (HEM-1900).

Informed consent statement

Informed consent was obtained from all individual participants included in the study.

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CRediT authorship contribution statement

Pamela Rivero-García: Writing – original draft, Methodology, Data curation, Conceptualization. **Yanin Chavarri-Guerra:** Writing – review & editing, Project administration, Investigation. **José Luis Rodríguez Olivares:** Writing – review & editing, Methodology, Investigation. **Jeffrey N. Weitzel:** Writing – review & editing, Validation, Funding acquisition, Formal analysis, Conceptualization. **Josef Herzog:** Writing – review & editing, Software, Resources, Formal analysis, Data curation. **Fernando Candanedo-González:** Supervision, Methodology, Investigation. **Javier Ríos-Valencia:** Resources, Methodology, Investigation. **Osvaldo M. Mutchinick:** Writing – review & editing, Visualization, Formal analysis. **Jazmín Arteaga-Vázquez:** Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31855.

References

[1] World Health Organization, All cancers: globocan 2020 [internet], Available from: https://gco.iarc.fr/today, 2020.
[2] F.M. Giardiello, J.D. Brensinger, G.M. Petersen, AGA technical review on hereditary colorectal cancer and genetic testing, Gastroenterology. W.B. Saunders 121 (2001) 198–213.
[3] E. Chen, X. Xu, T. Liu, Hereditary nonpolyposis colorectal cancer, and cancer syndromes: recent basic and clinical discoveries, in: Journal of Oncology, vol. 2018, Hindawi Limited, 2018.
[4] R. Sehgal, K. Sheahan, P.R. O'Connell, A.M. Hanly, S.T. Martin, D.C. Winter, Lynch Syndrome: an updated review, Genes 5 (3) (2014) 497–507.
[5] B.M. Rossi, E.I. Palmero, F. López-Kostner, C. Sarroca, C.A. Vaccaro, F. Spirandelli, et al., A survey of the clinicopathological and molecular characteristics of patients with suspected Lynch syndrome in Latin America, BMC Cancer 17 (1) (2017 Sep 5).
[6] G. Idos, L. Valle, Lynch syndrome, in: M. Adam, H. Ardinger, R. Pagon (Eds.), GeneReviews, University of Washington, Seattle, Seattle (WA), 2004.
[7] S. Gupta, J.M. Weiss, C.A. Burke, L.M. Chen, D.C. Chung, K.M. Clayback, et al., NCCN guidelines version 1.2021 genetic/familial high-risk assessment: colorectal NCCN guidelines version 1.2021 genetic/familial high-risk assessment: colorectal NCCN guidelines index table of contents discussion NCCN guidelines panel disclosures continue [Internet], Available from: https://www.nccn.org/home/, 2021.
[8] A.Y. Sunga, C. Ricker, C.R. Espenschied, D. Castillo, M. Melas, J. Herzog, et al., The spectrum of mismatch repair gene mutations and clinical presentation of Hispanic individuals with Lynch Syndrome, Cancer Genet 213–213 (2017) 1–7.
[9] H.F. A Vasen, J. Th Wijnen, F.H. Menko, Ø.H. Jan Kleibeuker, B.G. Taal, G. Griffioen, et al., Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis, Gastroenterology 110 (1996).
[10] L. Pérez-Cabornero, M. Infante, E. Velasco, E. Lastra, C. Miner, M. Durán, Genotype-phenotype correlation in MMR mutation-positive families with Lynch syndrome, Int. J. Colorectal Dis. 28 (9) (2013 Sep) 1195–1201.
[11] J. Leclerc, C. Vermaut, M.P. Buisine, Diagnosis of lynch syndrome and strategies to distinguish lynch-related tumors from sporadic MSI/DMMR tumors, Cancers. MDPI AG 13 (2021) 1–33.
[12] S. Parry, A.K. Win, F.A. Macrae, B. Parry, L.C. Gurrin, N.M. Lindor, et al., Metachronous colorectal cancer risk for mismatch repair gene mutation carriers – the advantage of more extensive surgery, Hered. Cancer Clin. Pract. 9 (Suppl 1) (2011) O1.
[13] S.C. O'Neill, J.G. Hamilton, C.C. Conley, B.N. Peshkin, R. Sacca, G.A. McDonnell, et al., Improving our model of cascade testing for hereditary cancer risk by leveraging patient peer support: a concept report, Hered. Cancer Clin. Pract. 19 (1) (2021 Dec 1).
[14] D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, et al., PD-1 blockade in tumors with mismatch-repair deficiency, N. Engl. J. Med. 372 (26) (2015 Jun 25) 2509–2520.
[15] M. Sarki, C. Ming, M. Aceti, G. Fink, S. Aissaoui, N. Bürki, et al., Relatives from hereditary breast and ovarian cancer and lynch syndrome families forgoing genetic testing: findings from the Swiss CASCADE cohort, J. Personalized Med. 12 (10) (2022 Oct 1).
[16] E.M. Stoffel, B. Ford, R.C. Mercado, D. Punglia, W. Kohlmann, P. Conrad, et al., Sharing genetic test results in lynch syndrome: communication with close and distant relatives, Clin. Gastroenterol. Hepatol. 6 (3) (2008 Mar) 333–338.
[17] E.M. Bednar, C.C. Sun, S. Mccurdy, S.W. Vernon, Assessing relatives' readiness for hereditary cancer cascade genetic testing, Am. J. Med. Genet. (2020), https://doi.org/10.1038/s41436 [Internet].
[18] D.H.M. Kwon, H.T. Borno, H.H. Cheng, A.Y. Zhou, E.J. Small, Ethnic disparities among men with prostate cancer undergoing germline testing, Urol. Oncol.: Seminars and Original Investigations 38 (3) (2020 Mar 1) 80.e1–80.e7.
[19] S. Richards, N. Aziz, S. Bale, D. Bick, S. Das, J. Gastier-Foster, et al., Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of medical genetics and genomics and the association for molecular pathology, Genet. Med. 17 (5) (2015 May 8) 405–424.
[20] J.M. Moreno-Ortiz, M.D.L.L. Ayala-Madrigal, J.R. Corona-Rivera, M. Centeno-Flores, V. Maciel-Gutiérrez, R.A. Franco-Topete, et al., Novel mutations in MLH1 and MSH2 genes in Mexican patients with lynch syndrome, Gastroenterol Res Pract 2016 (2016).
[21] C. Ricker, N. Klipfel, G. Ault, L. Roman, D. Spicer, H.J. Lenz, Characteristics of lynch syndrome in 13 hispanic families, Hered. Cancer Clin. Pract. 8 (Suppl 1) (2010) P19.
[22] C.A. Vaccaro, F. López-Kostner, D.V. Adriana, E.I. Palmero, B.M. Rossi, M. Antelo, et al., From colorectal cancer pattern to the characterization of individuals at risk: picture for genetic research in Latin America, Int. J. Cancer 145 (2019) 318–326. Wiley-Liss Inc.
[23] A. della Valle, B.M. Rossi, E.I. Palmero, M. Antelo, C.A. Vaccaro, F. López-Kostner, et al., A snapshot of current genetic testing practice in Lynch syndrome: the results of a representative survey of 33 Latin American existing centres/registries, Eur. J. Cancer 119 (2019 Sep 1) 112–121.
[24] C.N. Ricker, D.L. Hanna, C. Peng, N.T. Nguyen, M.C. Stern, S.L. Schmit, et al., DNA mismatch repair deficiency and hereditary syndromes in Latino patients with colorectal cancer, Cancer 123 (19) (2017 Oct 1) 3732–3743.
[25] A. Padua-Bracho, J.A. Velázquez-Aragón, V. Fragoso-Ontiveros, P.M. Nuñez-Martínez, M.L. Mejía Aguayo, Y. Sánchez-Contreras, et al., A previously unrecognized molecular landscape of lynch syndrome in the Mexican population, Int J Mol Sci [Internet] 23 (19) (2022 Sep 30) 11549. Available from: https://www.mdpi.com/1422-0067/23/19/11549.
[26] S.C. Huang, J.E. Lavine, P.S. Boland, R.O. Newbury, R. Kolodner, T.T.T. Pham, et al., Germline characterization of early-aged onset of hereditary non-polyposis colorectal cancer, J. Pediatr. 138 (5) (2001) 629–635.
[27] G. Moslein, D.J. Tester, N.M. Lindor, R. Honchel, J.M. Cunningham, A.J. French, et al., Microsatellite instability and mutation analysis of hMSH2 and hMLH1 in patients with sporadic, familial and hereditary colorectal cancer, in: Human Molecular Genetics, vol. 5, Oxford University Press, 1996.

[28] R.N. Sharaf, P. Myer, C.D. Stave, L.C. Diamond, U. Ladabaum, Uptake of genetic testing by relatives of lynch syndrome probands: a systematic review, Clin. Gastroenterol. Hepatol. 11 (2013) 1093–1100.
[29] I. Márquez-Rodas, M. Lobo, C. Flores-Sanchez, M. Sanz, S. Luque, S. Lizarraga, et al., Five years of multidisciplinary care in hereditary cancer: our experience in a Spanish university hospital, Oncology (Switzerland) 92 (2) (2017 Jan 1) 68–74.
[30] N. Ishii, M. Arai, Y. Koyama, et al., Factors affecting encouragement of relatives among families with Lynch syndrome to seek medical assessment, Fam. Cancer 10 (4) (2011) 649–654, https://doi.org/10.1007/s10689-011-9462-x.
[31] R.D. Pentz, S.K. Peterson, B. Watts, et al., Hereditary nonpolyposis colorectal cancer family members' perceptions about the duty to inform and health professionals' role in disseminating genetic information, Genet. Test. 9 (3) (2005) 261–268, https://doi.org/10.1089/gte.2005.9.261.