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Mutation spectrum in South American Lynch syndrome families

Mev Dominguez-Valentin1,2*, Mef Nilbert1,2, Patrik Wernhoff3, Francisco López-Köstner4, Carlos Vaccaro5, Carlos Sarroca6, Edenir Ines Palmero7, Alejandro Giraldo8, Patricia Ashton-Prolla9, Karin Alvarez4, Alejandra Ferro5, Florencia Neffa6, Junea Caris7, Dirce M Carraro10 and Benedito M Rossi11

Abstract

Background: Genetic counselling and testing for Lynch syndrome have recently been introduced in several South American countries, though yet not available in the public health care system.

Methods: We compiled data from publications and hereditary cancer registries to characterize the Lynch syndrome mutation spectrum in South America. In total, data from 267 families that fulfilled the Amsterdam criteria and/or the Bethesda guidelines from Argentina, Brazil, Chile, Colombia and Uruguay were included.

Results: Disease-predisposing mutations were identified in 37% of the families and affected MLH1 in 60% and MSH2 in 40%. Half of the mutations have not previously been reported and potential founder effects were identified in Brazil and in Colombia.

Conclusion: The South American Lynch syndrome mutation spectrum includes multiple new mutations, identifies potential founder effects and is useful for future development of genetic testing in this continent.

Keywords: Lynch syndrome, MLH1, MSH2, South America, Mutation

Background

Since the initial reports on disease-predisposing mutations in the mismatch-repair (MMR) genes MLH1 [MIM:120436], MSH2 [MIM:609309] and MSH6 [MIM:600678] in the early 1990’ies, a large number of studies have contributed to the establishment of the molecular map of Lynch syndrome with over 3,072 unique genetic MMR gene variants identified. These data are predominantly based on studies from North America, Europe and Asia. The mutations affect MLH1 in 42%, MSH2 in 33%, MSH6 in 18% and PMS2 in 8% [1]. Nonsense mutations, frameshift mutations and missense mutations predominate, whereas large genomic rearrangements and splice-site variants constitute <10% of the alterations [1].

The South American population is ethnically mixed from American Indian and European ancestors. In Uruguay and Argentina, European ancestry predominates. In Brazil, significant African and American Indians roots apply. In Chile, Colombia, Peru and Bolivia, Spanish colonist and American Indian ancestry influence the populations [2,3]. Mutation screening in South American families suspected of Lynch syndrome has identified disease-predisposing germline mutations in MLH1 and MSH2 in 16-45% of families that fulfill the Amsterdam criteria and/or the Bethesda guidelines [2-7]. Hereditary colorectal cancer registries have been established in Argentina, Brazil, Uruguay and Chile with the aim to collect and share data on the MMR gene mutation spectrum, identify potential founder mutations, interpret the role of unclassified genetic variants and to study cancer risks in the South American Lynch syndrome population. We used published data and unpublished register data to describe the mutation spectrum in South American Lynch syndrome families.

Methods

Ethics statement

All patients provided an informed consent for inclusion into the South American registers during genetic
counseling sessions and is in compliance with the Helsinki Declaration.

**Patient selection**
Families that fulfilled the Amsterdam criteria [8,9] and/or the Bethesda guidelines [10] were selected from the hereditary cancer registries at the Hospital Italiano (Buenos Aires, Argentina), the Hospital de las Fuerzas Armadas (Montevideo, Uruguay), the Clinica Los Condes (Santiago, Chile), the Barretos Cancer Hospital (Barretos, Brazil) and from two databases in Colombia and in Southeastern Brazil (Figure 1, Table 1) [2,3,5,11]. Patients were informed about their inclusion into the registries, which generally contained data on family history, age at onset and results of genetic testing.

**Disease-predisposing mutations**
Methods to assess MMR status, e.g. microsatellite instability analysis and MMR protein staining, varied between the countries and were excluded from the present study since these data were incomplete. Molecular diagnosis was generally based on direct sequencing of \( MLH1 \) and \( MSH2 \). Chilean and Brazilian families were also analyzed for large genomic rearrangements using the multiplex ligation-dependent probe amplification (MLPA) method (performed using the SALSA kit P003, MRC-Holland, Amsterdam, Netherlands).

**Mutation nomenclature**
Mutation nomenclature was in accordance with the Human Genome Variation Society (HGVS) guidelines [12]. Mutations in the \( MLH1 \) or \( MSH2 \) genes were considered deleterious if they: a) were classified as pathogenic in LOVD database; b) introduced a premature stop codon in the protein sequence (nonsense or frameshift mutation); c) occurred at donor or acceptor splice sites; or d) represented whole-exon deletions or duplications. All identified mutations were correlated to the MMR Gene Unclassified Variants Database (www.mmruv.info), the Mismatch Repair Genes Variant Database (http://www.med.mun.

**Table 1 Summary of register data from MMR South American Lynch syndrome families**

| South American Institutions | Total number of patients/families | MMR mutation carriers | % of MMR mutation carriers | Mean age at CRC diagnosis | Mean age at endometrial cancer diagnosis |
|----------------------------|----------------------------------|-----------------------|----------------------------|---------------------------|-----------------------------------------|
| Hospital Italiano (Buenos Aires, Argentina) | 28 | 14 | 50.0 | 44.3 (SD 6.2) | 46.3 (SD 5.5) |
| Hospital de las Fuerzas Armadas (Montevideo, Uruguay) | 25 | 7 | 28.0 | 35.1 (SD 7.6) | 41.5 (SD 8.3) |
| Clinica Las Condes* (Santiago, Chile) | 50 | 20 | 40.0 | 35.7 (SD 10.7) | 41.1 (SD 8.8) |
| Barretos Cancer Hospital* (Barretos, Brazil) | 23 | 15 | 65.2 | 39.4 (SD 13.8) | 49.8 (SD 5.3) |
| Colombia | 13 | 8 | 61.5 | NA | NA |
| Southeastern Brazil* | 128 | 35 | 27.3 | 42.3 (SD 11.4) | 48.8 (SD 2.4) |
| Total | 267 | 99 | 37.1 | | |

*MLPA analysis included, †Valentin et al. 2011 [3] and Rossi et al. 2002 [5], ‡Giraldo et al. 2005 [2] and Alonso-Espinaco et al. 2011 [11], NA Information not available, MMR mismatch-repair genes, SD standard deviation, CRC colorectal cancer.
Table 2 Spectrum of alterations in South American Lynch syndrome families

| Gene | Nucleotide | Consequence | Exon | Reported as | Country | Number of families | References |
|------|------------|-------------|------|-------------|---------|--------------------|------------|
| MLH1 | c.1-?_116 + ?del | p.M1_C39 > FfsX13 | 1 | Causal | Chile | 2 | InSIGHT |
|     | c.199G > A | p.G67R | 2 | Causal | Argentina | 1 | InSIGHT |
|     | c.211G > T | p.E71X | 3 | Causal | Brazil | 1 | InSIGHT |
|     | c.289 T > G | p.Y97D | 3 | VUS | Uruguay | 1 | InSIGHT |
|     | c.336 T > A | p.H112Q | 4 | VUS | Argentina | 1 | InSIGHT |
|     | c.350C > T | p.T177M | 4 | Causal | Uruguay | 2 | InSIGHT |
|     | c.421C > G | p.P141A | 5 | VUS | Colombia | 1 | Giraldo et al. 2005 [2] |
|     | c.503dupA | p.N168KfsX4 | 6 | Causal | Chile | 1 | InSIGHT |
|     | c.503delA⁹ | p.N168KfsX4 | 6 | Causal | Brazil | 1 | Not previously described |
|     | c.545 + 3A > G | | 6 | Causal | Brazil | 2 | InSIGHT |
|     | c.588 + 2 T > A⁵ | | 7 | Causal | Brazil | 1 | Valentín et al. 2011 [3] |
|     | c.588 + 5G > C | | 7 | Causal | Brazil | 1 | InSIGHT |
|     | c.665delA | p.N222MfsX7 | 8 | Causal | Uruguay | 2 | InSIGHT |
|     | c.676C > T | p.R226X | 8 | Causal | Argentina | 1 | InSIGHT |
|     | c.677G > A | p.R226Q | 8 | Causal | Argentina, Brazil | 3 | InSIGHT |
|     | c.677 + 5G > A | | 8 | Likely causal | Chile | 1 | French MMR network |
|     | c.779 T > G | p.L260R | 9 | Causal | Brazil | 1 | InSIGHT |
|     | c.790 + 1G > A | | 9 | Causal | Chile, Colombia | 3 | InSIGHT |
|     | c.791-6_793delgatttacGA⁶ | | 10 | Causal | Brazil | 1 | Valentín et al. 2011 [3] |
|     | c.794G > C | p.R265P | 10 | VUS | Chile | 1 | InSIGHT |
|     | c.901C > T | p.Q301X | 11 | Causal | Chile | 1 | InSIGHT |
|     | c.1013A > G⁵ | p.N338S | 11 | VUS | Brazil | 1 | InSIGHT |
|     | c.1038 + 1G > T⁸ | p.Y347FfsX13 | 11 | Causal | Chile | 1 | Wielandt et al. 2012 |
|     | c.1039-8T_1558?896Tdupa | p.I500del | 12 to 13 | Causal | Colombia | 2 | Alonso-Espinaco et al. 2011 [11] |
|     | c.1276C > T | p.Q426X | 12 | Causal | Brazil | 3 | InSIGHT |
|     | c.1459C > T | p.R487X | 13 | Causal | Brazil | 1 | InSIGHT |
|     | c.1499_1501delTCA⁴ | p.I500del | 13 | Causal | Brazil | 1 | Rossi et al. 2002 [5] |
|     | c.1558 + 1G > T | | 13 | Causal | Brazil | 1 | InSIGHT |
|     | c.1558 + 14G > A | | 13 | Causal | Brazil | 1 | InSIGHT |
|     | c.1559-2A > C | | 13 | Causal | Chile | 1 | InSIGHT |
|     | c.1559-7_1731 + ?del | p.V520_S577 > GfsX7⁹ | 14 - 15 | Causal | Chile | 1 | Wielandt et al. 2012 |
|     | c.1639_1643dup TTATA⁹ | p.L540YfsX44 | 14 | Causal | Brazil | 1 | Valentín et al. 2011 [3] |
|     | c.1690_1693delICTCA | p.L546fsX26 | 15 | Causal | Brazil | 1 | InSIGHT |
|     | c.1724G > A | p.R575K | 15 | VUS | Argentina | 1 | InSIGHT |
|     | c.1731 + 3A > T⁹ | Skipping exon 15 | 15 | Causal | Chile | 1 | Alvarez et al. 2010 [6] |
|     | c.1846delAG | p.K616del | 16 | Causal | Argentina | 1 | InSIGHT |
|     | c.1852_1853delinsGC | p.K618A | 16 | Causal | Argentina | 1 | InSIGHT |
|     | c.1852_1854delAAG | p.K618del | 16 | Causal | Argentina | 1 | InSIGHT |
|     | c.1853A > C | p.K618T | 16 | Causal | Brazil | 1 | InSIGHT |
|     | c.1853delAinsTTCTTA | p.K618IfsX4 | 16 | Causal | Brazil | 2 | Valentín et al. 2011 [3] |
| Mutation       | pmID     | Location | Status | Country(s) | Reference(s) |
|---------------|----------|----------|--------|------------|--------------|
| c.1856delGa   | 16       | Causal   | Colombia | 2          | Giraldo et al. 2005 [2] |
| c.1890dupa    | p.D631fsX1 | 16       | Causal  | Argentina  | 1            | Valentin et al. 2011 [3] |
| c.1897-?_1989 + ?delb | 17-19   | Causal   | Brazil   | 1          | Not previously described |
| c.1918C > T   | p.P640T  | 17       | VUS     | Colombia   | 1            | InSIGHT      |
| c.1975C > T   | p.R659X  | 17       | Causal  | Brazil     | 1            | InSIGHT      |
| c.1998G > A   | p.W666X  | 18       | Causal  | Brazil     | 1            | Rossi et al. 2012 [5] |
| c.2027 T > C  | p.L676P  | 18       | Causal  | Brazil     | 1            | InSIGHT      |
| c.2041G > A   | p.A681T  | 18       | Likely causal | Chile, Brazil, Colombia | 4 | French MMR network |
| c.2092_2093delTC | p.5698RfsX5 | 18 | Causal | Chile | 1 | Alvarez et al. 2010 [6] |
| c.2224C > T³  | p.Q742X  | 19       | Causal  | Brazil     | 1            | Valentin et al. 2011 [3] |
| c.2252,2253dupAA | p.V752KfsX26 | 19 | Causal | Brazil | 1 | InSIGHT |
| c.2104-?_2271 + ?delb | p.S702_K757del | 19 | Causal | Chile | 2 | Wielandt et al. 2012 |
| MSH2           | c.71delA² | 1        | Causal  | Brazil     | 1            | Not previously described |
| c.166G > T²   | p.E56X   | 1        | Causal  | Argentina  | 1            | InSIGHT      |
| c.174dupC²    | p.K59Q6X23 | 1        | Causal  | Brazil     | 1            | Not previously described |
| c.181C > T²   | p.Q61X   | 1        | Causal  | Uruguay    | 1            | Sarroca et al. 2003 |
| c.187delG     | p.V63fsX1 | 1        | Causal  | Brazil     | 1            | InSIGHT      |
| c.289C > T    | p.Q97X   | 2        | Causal  | Argentina  | 1            | InSIGHT      |
| c.212-?_366 + ?delb | p.A72_K122 > FfsX9 | 2 | Causal | Chile | 1 | InSIGHT |
| c.388,389delCA | p.Q130KfsX2 | 3       | Causal  | Brazil, Argentina | 2 | InSIGHT |
| c.530,531delAA² | p.E177fsX3 | 3       | Causal  | Uruguay    | 1            | Sarroca et al. 2003 |
| c.596delTG²   | 3        | Causal   | Colombia | 1          | Giraldo et al. 2005 [2] |
| c.862C > T    | p.Q287X  | 5        | Causal  | Brazil     | 1            | InSIGHT      |
| c.897 T > G   | p.Y299X  | 5        | Causal  | Brazil     | 1            | Wielandt et al. 2012 |
| c.942 + 3 A > T | p.L360KfsX16 | 7 | Causal | Argentina | 1 | InSIGHT |
| c.1077-?_1276 + ?del | p.L360KfsX16 | 7 | Causal | Argentina | 1 | InSIGHT |
| c.1147C > T   | p.R382X  | 7        | Causal  | Brazil     | 1            | InSIGHT      |
| c.1215C > A   | p.Y405X  | 7        | Causal  | Chile      | 1            | InSIGHT      |
| c.1216C > T   | p.R405X  | 7        | Causal  | Uruguay    | 1            | InSIGHT      |
| c.1294delG    | p.V417fsX21 | 7       | Causal  | Brazil     | 1            | InSIGHT      |
| c.1255C > T   | p.Q419X  | 7        | Causal  | Brazil     | 1            | InSIGHT      |
| c.1444A > T²  | p.R482X  | 9        | Causal  | Brazil     | 1            | Valentin et al. 2011 [3] |
| c.1447G > T   | p.E483X  | 9        | Causal  | Brazil     | 2            | InSIGHT      |
| c.1667del²    | p.L556X  | 11       | Causal  | Brazil     | 1            | Valentin et al. 2011 [3] |
| c.1667_1668insA² | p.T557GfsX5 | 11 | Causal | Brazil | 1 | Rossi et al. 2002 [5] |
| c.1910delA²   | p.R638fsX47 | 12       | Causal  | Argentina  | 1            | Vaccaro et al. 2007 |
| c.1967_1970dupACTT² | p.F657LfsX3 | 12 | Causal | Brazil     | 1            | Valentin et al. 2011 [3] |
ca/mmrvariants/), the French MMR network (http://www.umd.be/MMR.html) and the International Society for Gastrointestinal Hereditary Tumors (InSIGHT) (http://www.insight-group.org).

Variants of uncertain significance
To establish the pathogenicity of variants of uncertain significance, web-based programs, i.e. Polyphen, MAPP-MMR, SIFT, P-mut and PON-MMR were applied to predict the effect of an amino acid substitution based on protein structural change and/or evolutionary conservation [13-17].

Statistical analysis
The statistical analyses were performed using the statistical software package IBM SPSS Statistics 20 (SPSS, Chicago, IL, USA).

Results
In total, 110 families harbored MMR gene variants, of which 99 were classified as Lynch syndrome predisposing and 11 were regarded as variants of uncertain significance. Mutations in MLH1 and MSH2 were identified in 37% (range 27-65% in the different countries/registries) of the families that fulfilled the Amsterdam criteria and/or Bethesda guidelines (Table 1). When the Amsterdam criteria were considered, the mutation detection rate was 55% (81/147), whereas 15% families that fulfilled the Bethesda guidelines had disease-predisposing mutations. The mean age at diagnosis was 35–44 years for colorectal cancer and 41–49 years for endometrial cancer in the different registries (Table 1). Pedigree information was available from 54 families and showed that among the Lynch syndrome-associated tumors, 65% were colorectal cancers (of which 43% were located in the right side of the colon), 22% endometrial cancers and 13% constituted other Lynch syndrome-associated cancer types.

Of the 99 disease-predisposing MMR gene mutations, 60% affected MLH1 and 40% affected MSH2 (Table 2). Frameshift and nonsense mutations were the most common alterations (36% and 31%, respectively), followed by splice site mutations (13%), missense mutations (12%) and large deletions (8%) (Figure 2a). Though the mutations were spread over the genes, hot-spot regions included exons 16 and 18 in MLH1 (13% of the mutations

| Table 2 Spectrum of alterations in South American Lynch syndrome families (Continued) |
|---------------------------------|---------|---------|-----------|
| c.2038C > T p.R680X             | 13      | Causal  | Chile     | 1        | InSIGHT |
| c.2046_2047delTG p.V684Dfs*14   | 13      | Causal  | Argentina | 1        | InSIGHT |
| c.2131C > T p.R711X             | 13      | Causal  | Brazil    | 1        | InSIGHT |
| c.2152C > T p.Q718X             | 13      | Causal  | Brazil    | 6        | InSIGHT |
| c.2185_2192del7insCCCT p. M729_E731delinsP729_X730 | 13 | Causal | Chile | 1 | Alvarez et al. 2010 [6] |
| c.2187G > T p.M729I             | 13      | VUS     | Brazil    | 1        | Valentin et al. 2011 [3] |
| c.2525_2526delAG p.E842VfsX3    | 15      | Causal  | Brazil    | 2        | Valentin et al. 2011 [3] |
| c.2785C > T p.R929X             | 16      | Causal  | Brazil    | 1        | Valentin et al. 2011 [3] |

*First reported, VUS variants of unclassified significance, MLH1 (MIM#120436), MSH2 (MIM#609309), pathogenicity demonstration ongoing.

![Figure 2 Spectrum of pathogenic mutations in MLH1 and MSH2 genes](http://www.hccpjournal.com/content/11/1/18)
each) and exon 13 in MSH2 (24% of the mutations each) (Figure 2b).

In total, 10 mutations identified in at least two South American families were classified as recurrent. Among these, the MSH2 c.2152C > T identified in Brazil represents an internationally hot-spot. Three founder mutations were identified in five South American families. The MLH1 c.545 + 3A > G and the MSH2 c.942 + 3A > T have been identified as founder mutations in Italy and in Newfoundland and were also identified in Brazilian families [3]. The MLH1 c.1039-8T_1558 + 896Tdup has been suggested to represent a founder mutation in Colombia [2,11]. Mutations that were unique and herein first reported in more than one family included the MLH1 c.1853delAinsTTCTT in Brazil, the MLH1 c.1856delG in Colombia and the MSH2 c.25252_2526delAG in Brazil (Table 2) (Figure 3).

In total, 11 variants of unclassified significance were identified in individuals from Argentina, Uruguay, Chile, Brazil and Colombia (Table 3) [2,3]. In silico analysis suggested that the MLH1 c.289 T > G, the MLH1 c.794G > C and the MLH1 c.1918C > T were likely disease-predisposing (Table 3).

Discussion

In South America, disease-predisposing mutations linked to Lynch syndrome have been identified in 99 families, which corresponds to 37% of the families that fulfilled the Amsterdam criteria and/or Bethesda guidelines and underwent genetic testing. The mutation rate is high compared to prevalence rates of 28% for MLH1 and 18% for MSH2 in the Asian population, 31% and 20% in a multi-ethnic American population and 26% and 19% in European/Australian populations [18]. The mutation spectrum is predominated by MLH1 (60%) and MSH2 (40%) mutations [3,19-22], but the seemingly larger contribution than the 42% and 33% reported in the InSIGHT database could reflect failure to test for MSH6 and PMS2 mutations in most South American studies [1]. Referral bias in populations that have more recently been screened for mutations represents a potential limitation, but the strong contribution from MLH1 and MSH2 could also reflect population structure [2,4,5,7]. Frameshift mutations and nonsense mutations were the most common types of mutations, which are in agreement with findings from other populations [1,23-26], with hotspots in exons 16 and 18 of MLH1 and in exon 13 of MSH2 (Figure 2b). Exon 16 and 18 in MLH1 have been identified as a genetic hot spot also in other populations with 26% of the MLH1 mutations reported herein [3,18]. The frequent mutations in MSH2 exon 13 may be linked to the c.2152C>, which was first identified in Portuguese Lynch syndrome families. This alteration accounted for 35% (6/17) of the MSH2 mutations in the Brazilian population, which is in line with the Portuguese migration to Brazil [3,27].

Founder mutations have been identified in several populations where they significantly contribute to disease predisposition and thereby allow for directed genetic testing [28]. Two of the mutations identified in South American Lynch syndrome families have been suggested to constitute potential founder mutations in other populations, e.g. the Italian MLH1 c.545 + 3A > G and the Newfoundland MSH2 c.942 + 3A > T [3]. The Spanish founder mutations MLH1 c.306 + 5G > A and c.1865 T > A and MSH2 c.2635-3 T > C; c2635-5C > T; c.2063 T > G were, however, not observed in South American Lynch syndrome families [27-30]. In Colombia, the MSH2 c.1039-8T_1558 + 896Tdup was suggested to represent a founder mutation [2,11]. The Colombian population has a mixed ancestry with a strong influence from Spanish colonists and thereby genetically differs from previously studied populations [2,6].

Figure 3 Map of South America showing the countries where Lynch syndrome families with the founder, recurrent, unique mutations and variants of unclassified significance (VUS) have been identified. The figure depicts the countries participating in the study (gray). The pie chart represents in percentage the recurrent mutations, founder mutations, unique mutations and VUS identified in the South American families. Brazil is characterized by 16% of the founder mutations, 39% of the recurrent mutations, 14% of the unique mutations and 31% of the VUS, while Colombia by 20% of the founder mutations, 20% of the unique mutations and 60% of the VUS. Chile, Argentina and Uruguay are characterized by 80%, 50% and 67% of the recurrent mutations and 20%, 50% and 33% of the VUS, respectively.
| Country | Gene | Nucleotide | Consequence | Exon | Polyphen Score | Polyphen Classification | SIFT Score | SIFT Classification | MAP_MMR Score | MAP_MMR Classification | P-mut Score | P-mut Classification | PON-MMR Score | PON-MMR Classification |
|---------|------|------------|-------------|------|----------------|-------------------------|------------|---------------------|----------------|------------------------|-------------|---------------------|----------------|---------------------|
| Uruguay | MLH1 | c.289 T > G | p.Y97D | 3    | 0.999          | Probably damaging       | 0          | Damaging            | 10.51         | Damaging               | 0.7266      | Pathological          | 0.83         | Pathogenic            |
| Argentina | MLH1 | c.336 T > A | p.H112Q | 4    | 0.03           | Damaging                | 2.430      | Neutral             |               |                        | NA          | NA                  | 0.61         | VUS                  |
| Colombia | MLH1 | c.421C > G | p.P141A | 5    | 0.329          | Benign                  | 3.15       | Borderline deleterious |               |                        | 0.4928      | Neutral              | 0.48         | VUS                  |
| Chile   | MLH1 | c.794G > C | p.R265P | 10   | 1              | Probably damaging       | 38.09      | Damaging            |               |                        | 0.7623      | Pathological          | 0.83         | Pathogenic            |
| Brazil  | MLH1 | c.1013A > G | p.N338S | 11   | 0.05           | Damaging                | 2.78       | Neutral             |               |                        | 0.2551      | Neutral              | 0.38         | VUS                  |
| Colombia | MLH1 | c.1558 + 14G > A |             | 13   | NA             | NA                      | NA         | NA                  |               |                        | NA          | NA                  | NA           | NA                  |
| Argentina | MLH1 | c.1724G > A | p.R575K | 15   | 0.001          | Benign                  | 1.490      | Neutral             |               |                        | NA          | NA                  | 0.15         | Neutral              |
| Brazil  | MLH1 | c.1853A > C | p.K618T | 16   | 0.997          | Probably damaging       | 5.11       | Damaging            |               |                        | 0.7802      | Pathological          | 0.67         | VUS                  |
| Colombia | MLH1 | c.1918C > T | p.P640T | 17   | 1              | Probably damaging       | 17.77      | Damaging            |               |                        | 0.6534      | Pathological          | 0.83         | Pathogenic            |
| Brazil  | MLH1 | c.2252_2253dupAA | p.V752Kfs*26 | 19   | NA             | NA                      | NA         | NA                  |               |                        | NA          | NA                  | NA           | NA                  |
| Brazil  | MSH2 | c.2187G > T | p.M729I | 13   | 2.293          | Probably damaging       | 21.99      | Damaging            |               |                        | 0.1988      | Neutral              | 0.71         | VUS                  |

MLH1 (MIM#120436), MSH2 (MIM#609309), NA: not applicable, VUS: variants of unclassified significance, If SIFT score <0.05 then the aminoacid (AA) substitution is predicted to affect protein function, if PolyPhen score >0.5 then the AA substitution is predicted to affect protein function, if MAPP-MMR score >4.55 then the AA substitution is predicted to affect protein function, If P-mut score > 0.5, the AA substitution is classified as pathological, if PON-MMR score >0.7615, the AA substitution is classified as pathogenic.
Conclusions

In conclusion, disease-predisposing mutations in MLH1 and MSH2 have been identified in a relatively large proportion of the South American families suspected of Lynch syndrome that have been tested. Genetic hot-spot regions, internationally recognized founder mutations and potential South American founder mutation have been recognized, which is of relevance for genetic counseling and testing that are increasingly available in South America.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

MDV, MN, BMR participated in the conception and design of the study. All authors participated in the acquisition of data, or analysis, interpretation of data and have been involved in drafting the manuscript. All authors read and approved the final manuscript.

Author details

1The Danish HNPPC Register, Clinical Research Centre, Hvidovre Hospital, Copenhagen University, Hvidovre, Denmark. 2Department of Oncology, Institute of Clinical Sciences, Lund University, Lund, Sweden. 3Department of Experimental Medical Science, Unit of Muscle Biology, Lund Transgenic Core Facility/Reproductive Immunology, Lund University, Lund, Sweden. 4Molecular Laboratory, Clínica Los Condes, Santiago, Chile. 5Hereditary Cancer Program, Hospital Italiano, Buenos Aires, Argentina. 6Hospital Fuerzas Armadas, Grupo Colaborativo Uruguay de Investigación de Afecciones Oncológicas Hereditarias (GCU), Montevideo, Uruguay. 7Department of Oncogenetics, Barretos Cancer Hospital, Barretos, Brazil. 8Facultad de Medicina de la Universidad del Sínú, Montería, Colombia. 9Department of Genetics UFGRS, Hospital de Clínicas, Porto Alegre, Brazil. 10Department of Molecular Oncogenetics, Laboratory of Genomics and Molecular Biology, AC Camargo Hospital, São Paulo, Brazil. 11Hospital Sirio Libanes, São Paulo, Brazil.

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