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Argentinean Lynch syndrome registry: experience from Rosario

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Aim

There is still no national hereditary or familial cancer registers in Argentina. With the mission of improving detection, prevention and management of high risk cancer population in Rosario, with a population of 1.198.528 inhabitants, the Asociación Civil de Estudio, Tratamiento, Investigación de Enfermedades Heredo familiares de Rosario (ACETHIER) was established as a genetic reference center in 2005.

Method

Hospital Español is used to identify suspected Lynch syndrome (LS) families. The Amsterdam criteria (AMS) or Bethesda guidelines were mostly used to select cases for screening by immunohistochemistry (IHC) and/or microsatellite instability (MSI) analysis. Genetic testing was generally based on Sanger sequencing of *MLH1, MSH2, MSH6, PMS2* and/or *EPCAM*. By the advent of next generation sequencing (NGS), we are recently using 17- multigene panels including: *APC, BMPR1A, CDH1, CHEK2, MLH1, MSH2, MSH6, PMS2, MUTYH, POLD1, POLE, PTEN SMAD4, STK11, PT53*, EPCAM and GREM1(Ambry Genetics, USA). Patients are informed about their inclusion into the registry, which generally contained data on family history, clinical information, age at onset and results of DNA testing or tumour screening in the diagnosis of LS. Written informed consent was obtained from all patients during genetic counselling sessions.

Results

From our registry, 61 suspected families fulfilled AMS criteria or Bethesda guidelines. Seventeen families (28%) had MMR deficiency and underwent genetic MMR testing. *Path_ MLH1* variants was identified in 3 (21%) families, *path_ MSH2/EPCAM* variants in 11 (72%) families and *path_ PMS2* variants in 1 family (7%). LS carriers have been identified with a mean age of 37.5 years (range 18-57) and a mean of 13 follow-up years.

Conclusion

The *path_MSH2* variants are the most frequently identified in our registry and we provides support to set or improve LS genetic testing in South America. In addition, despite the small number of our registry, we described patients with a young age of onset and/or a positive family history of LS-associated cancers without an identified *path_MMR* variant, and may suggest the involvement of pathogenic variants in as yet undiscovered genes.

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Hereditary Cancer Program (ProCanHe): 21-years of experience at a referral registry in Argentina

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Aim

Registries in South America were initiated in the early 90´s with the help of Henry T. Lynch. The Programa de Cancer Hereditario (Pro.Can.He), is a multidisciplinary program established in 1996 at the Hospital Italiano, Argentina. The aim of the study is to update our 21-year experience to determine the applicability of genetic tests highlighting the most informative molecular findings in relation to Lynch syndrome mostly.

Materials and methods: Families undergoing genetic testing after genetic counselling between1996-2018 were included. Data were obtained from a prospective IRB approved database. Clinical-epidemiological and molecular variables were analysed. Genetic tests were carried out after a genetic counselling session and obtaining the informed consent of the patient.

Molecular testing

Until 2015, the search for variants was carried out by PCR and Sanger sequencing of exons and adjacent intronic regions of MLH1 and MSH2. Then, sequencing of *MLH1/MSH2/MSH6/PMS2/EPCAM* genes was performed by NGS and large rearrangements were detected by MLPA. The variants were classified according to international databases. Variants with uncertain or unreported clinical significance were analysed In-silico using the PolyPhen, SIFT and/or Human Splicing finder 3.0 software.

Results

A total of 83 families (49 fulfilled Amsterdam Criteria [AC] and 34 Bethesda Criteria [BC]) were analysed. Pathogenic variants were found in 26 out of 83 (31.3%) families, been 23 pathogenic and 3 likely pathogenic.

Splice site and large rearrangements represented 19.2% (5/26) and 11.5% (3/26) of the variants.23% (6/26) of them were originally described in this series and 1 was a founding mutation from Piedmont, Italy. Affected genes include MSH2, MLH1, MSH6 and PMS2 (12, 11, 2 and 1 cases respectively). Mutation detection rates in AC and BT families were 48.9% (N=24) and 5.9% (N=2), $p<0.01$. Among AC families, those with identified mutation had a lower median age of cancer on set and higher incidence of extra-CCR cancer than those without identified mutations. Additionally, we have also studied other genes in patients with different clinical conditions included in the registry.

We identified mutations in APC, MUTYH, BMPR1A, SMAD4, CDH1, BRCA1-2, CHEK2.

Conclusion

The multidisciplinary approach and the international collaborations allowed the correct implementation of the genetic tests. To our knowledge, this study is the first Characterization of AC families according to genetic tests in South America. This allowed the identification of AC families with different ages of onset and prevalence of extra-CRC cancers, as well as several significant variant not previously reported in international databases.

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Chilean hereditary colorectal cancer registry: experience from Clinica Las Condes

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Aim

Considering the lack of genetic studies in our country and the benefits resulting from being able to differentiate between carrier and non-carrier individuals, in 2003 we applied for grant funds offered by the Chilean government (FONDECYT). During 2004-2006, this support enabled us to implement the MSI and IHC analyses in tumors, as well as the detection of point mutations in APC, MLH1 and MSH2 genes. In 2009, with the aim of increasing the mutation detection rate, genetic studies were supplemented with deletion/duplication analysis by MLPA for APC, MLH1, MSH2 and EPCAM genes, and the identification of point mutations in MUTYH, MSH6, PMS2, STK11, PTEN, SMAD4 and BMPR1A genes. Today, we have broadened the genetic studies into gene panels (Invitae, USA), mainly in those patients whose tumor studies do not allow us to define a candidate gene or when the definition of the hereditary syndrome becomes quite difficult.

Methods

Patients are referred to the program of hereditary colorectal cancer for evaluation. Those that meet criteria are included into the registry,