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ABSTRACTS BOOK

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A SPECIFIC MLH1 GENE MUTATION IN FAMILIES FROM MENDOZA ASSOCIATED WITH LYNCH SYNDROME

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Lynch syndrome (LS) is the most common cause of hereditary colon cancer which predisposen to colorectal, endometrial, and other cancers. LS is caused by germline mutations in the mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*). The MMR system detects and corrects replication errors, maintaining the stability of the genome. Consequently defects in the MMR increase the mutation rate causes microsatellite instability (MSI) and increased cancer risk. The main objective of our study was to analyze clinical characteristics and diagnostic algorithms of two unrelated families from Mendoza, Argentina, carrying a specific mutation in *MLH1* gene. The clinical importance of these mutations and their significance in the general population were also examined. After carrying out the genealogical study, MMR proteins MLH1, MSH2, MSH6 and PMS2 were evaluated in paraffin-embedded tissue sections from colorectal tumors using Ventana Benchmark automated immunostaining. MSI analysis was performed using STRs markers (NR-21, NR-24, BAT-25, BAT-26 and Mono-27) and Illumina next-generation sequencing (NGS). Family characteristics and evidences are presented below. Family A: a male patient, 36 years old, with right-sided colon cancer and MLH1/PMS2 proteins absent by immunohistochemistry (IHC). Two sisters with colorectal cancer before 40 years of age. The father and the paternal grandmother died from colon cancer. A pathogenic mutation was localized in *MLH1* c.1890dupT(p.Asp631Ter1) by NGS. Family B: a 33-year-old male patient with right-sided colon cancer. IHC staining showed the absence of MLH1 expression. The patient also presented MSI. The mother had endometrial and colon cancer, a maternal uncle had colon cancer and papillary urothelial carcinoma, and the maternal grandfather had colon cancer. Using NGS, a mutation in *MLH1* c.1890dupT(p.Asp631Ter1) was found. Our results demonstrate the important implications of clinical and molecular algorithms to improve the efficiency of LS diagnosis, as well as the detection of asymptomatic carriers. These data allow to established guidelines for the follow-up, risk-reduction management and treatment strategies for patients found to has pathogenic mutations. In addition, our data contribute to determine frequencies of specific mutationsin the general population. The mutation of the *MLH1* gene described above is prevalent among families with LS in South America.

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CASE REPORT: HEREDITARY BREAST CANCER AND LARGE REARRANGEMENTS IN PATIENT OF ASHKENAZI ORIGIN

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Hereditary breast cancer represents 5-10% of cases of breast cancer and is mainly associated with mutations in *BRCA1* and *BRCA2* genes. Patients of ashkenazi Jewish origin have an increase in the prevalence of mutations in these genes, with 90-95% carriers of founder pathogenic mutations in BRCA1/2, while 2-4% carry another type of mutation. To date, there are no reports of large rearrangements in patients of this origin. In our experience, the frequency of mutations produced by large rearrangements is 0.0045% (9/2000). We present the case of a patient of Ashkenazi-Sephardi origin with breast cancer, carrying a pathogenic deletion in the *BRCA1* gene. Case: 37 year-old patient with breast cancer and negative hormone receptors. Her mother, of Sephardic origin, ovarian cancer was diagnosed at 60 years of age. From a sample of genomic DNA, the *BRCA1/2* genes were studied by Next Generation Sequencing (NGS) and Multiple Ligation-dependent Probe Amplification assay (MLPA) for the study of large rearrangements. The presence of pathogenic mutation was not detected by sequencing. By MLPA (probemix P002 MRC Holland®) the heterozygous deletion including exons 23 and 24 of the BRCA1 gene (c.5407-?(*1_?) Del) was detected. This mutation is reported in the reference bases as pathogenic. It is considered important to search for a rearrangement in patients of this ethnic group in our country and to study these genes in full form to establish prevention measures, risk reduction and family counseling.