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Potential association between the functional variant RS2043556 in MIR605 gene and development of multiple primary tumors in TP53 P.ARG337HIS mutation carriers

Igor Araujo Vieira, Isabel Cristina Bandeira da Silva, Larissa Brussa Reis, Tiago Finger Andreis, Edenir Inez Palmero, Karina Miranda Santiago, Maria Isabel Waddington Achatz, Patricia Ashton-Prolla - HCPA

Li-Fraumeni and Li-Fraumeni-like syndromes (LFS/LFL) are cancer predisposition syndromes associated with TP53 germline mutations and characterized by high risk for multiple early-onset cancers. In Southern and Southeastern Brazil, a founder germline mutation located in the oligomerization domain of the TP53 gene and with incomplete penetrance, c.1010G>A (p.Arg337His), has been detected in many families showing a predisposition to at least some of the cancers of the LFS/LFL spectrum. Recently, the functional variant rs2043556 (A>G), located in MIR605 gene, was identified as a novel genetic modifier of the LFS phenotype in families with classical hotspot TP53 mutations (DNA binding domain mutations). Indeed, miR-605 is a component in the p53 regulatory network, being transcriptionally activated by p53 and post-transcriptionally repressing Mdm2 (a well-known negative regulator of p53 expression levels and activity). Here, we determined the frequency and explored possible effects of the SNP rs2043556 on clinical manifestations of Brazilian individuals carrying TP53 p.Arg337His mutation. Genotyping was performed by allelic discrimination using TaqMan assay and statistical analyzes were conducted on SPSS V.18.0 software. Among 233 patients harboring the founder TP53 mutation, the variant G-allele was detected in 132 (56.7%), of which 23 in homozygosis (GG genotype, 9.9%). Although this SNP was associated with an earlier mean age of tumor onset in LFS patients (classic phenotype) from a Canadian population, this effect was not replicated in our cohort (P = 0.6). A possible reason for this conflicting result is because there were no LFS/LFL families with this highly-prevalent Brazilian mutation evaluated in the previous study. The MIR605 rs204356 genotype was also not associated with the tumor type diagnosed in TP53 p.Arg337His mutation carriers (P = 0.4). However, the GG genotype showed a borderline modifier effect (P = 0.049) to the manifestation of multiple primary tumors in the same group. Among these TP53 p.Arg337His and rs204356[GG]-positive patients with tumor diagnosis in multiple primary sites, a female patient developed very early-onset breast and thyroid cancers (at 23 and 25 years, respectively). To our knowledge, this is the first description of LFS/LFL patients with the variant G-allele of MIR605 rs204356 in homozygosis. Further functional studies are necessary to clarify the effects of this variant in cancer pathways. Uniterms: Li-Fraumeni Syndrome; MicroRNAs; Genetic modifiers.

P1454

Clinical and molecular characterization of women diagnosed with epithelial ovarian cancer, primary peritoneal and fallopian tube cancer in Rio Grande do Sul

Daniele Konzen, Marina Bianchi Lemieszek, Anderson Roberto dos Santos, Cristina Netto, Patricia Ashton Prolla - HCPA

Aims: To clinically characterize and to evaluate the prevalence of germline BRCA1 and BRCA2 pathogenic variants in Brazilian women diagnosed with epithelial ovarian cancer, primary peritoneal and fallopian tube cancer (OC). Material and Methods: Women diagnosed with OC, unselected for age or family history were invited to participate in the study. Clinical, surgical and family history data were obtained using a questionnaire. BRCA1 and BRCA2 genes were analyzed by NGS and MLPA. Results: Sixty women were included and 17 (28.3%) were found to carry a germline pathogenic variant, 8 in BRCA1 and 9 in BRCA2. Of these 17 pathogenic variants there were 13 different mutations and 10 were found only once in this group of women. Sixteen (94.1%) women carrying a pathogenic variant had a positive family history of tumors of the HBOC spectrum versus 58.1% of the non-carriers. Of the 17 mutation carriers, 6 (35.3%) had non-serous OC. Conclusion: In this series we identified a germline BRCA mutation in about one-third of unselected patients diagnosed with ovarian, peritoneal or fallopian tube cancers. This prevalence, increased in comparison to what has been reported previously is likely due to the high frequency of a positive family history of cancer observed in the cohort. Occurrence of germline mutations was not restricted to patients diagnosed with serous adenocarcinoma OC. It is of great importance to be able to identify woman and families at risk of developing OC, to offer genic counselling and testing. Uniterms: BRCA1/BRCA2; Câncer de ovário; Oncogenética.

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Identificação do trinucleotídeo gaa na região polimórfica do gene FXN humano

Rafael Caesar Gomes Gonçalves, Rafaella Mergener, Sandra Leistner-Segal, Jonas Alex Saute, Laura Bannach Jardim, Maria Luiza Saraiva-Pereira - HCPA

A Ataxia de Friedreich (FRDA) é a mais comum das desordens neurodegenerativas de herança autossômica recessiva, com incidência de 1:29000. A FRDA é causada pela expansão do número de repetições do trinucleotídeo GAA no íntron 1 do gene FXN ou por mutações de ponto no gene. Esse gene é localizado no braço longo do cromossomo 9 e codifica a frataxina, uma proteína de membrana mitocondrial. Ainda que as suas funções não sejam completamente entendidas, a frataxina tem função essencial na homeostase de ferro intracelular. O número de repetições GAA no gene é variável, sendo que alelos normais apresentam entre 7 e 34 repetições. Nos alelos mutantes podem ser encontrados entre 70 a 1000 ou mais repetições GAA. O objetivo desse estudo foi determinar a distribuição do tamanho da região polimórfica em uma população normal e aplicar o TP-PCR (triplet repeat primed-PCR) para detectar alelos expandidos. O DNA foi isolado de amostras de sangue periférico de indivíduos com suspeita clínica de FRDA (n=43) e de controles (n=29). A região que abrange a repetição GAA e suas regiões adjacentes foram amplificadas por PCR convencional utilizando um primer marcado com fluorescência. Para avaliação de alelos com expansão, foi utilizada a metodologia de TP-PCR. Os produtos de PCR de ambas as reações foram analisados por eletroforese capilar. Os resultados obtidos incluem a identificação de expansões em ambos os alelos de 8 indivíduos com suspeita clínica de FRDA (18,6%), confirmando o diagnóstico. Um caso apresentou apenas um alelo expandido, o qual será submetido a análises complementares. As outras 34 amostras mostraram apenas alelos dentro da faixa normal esperada. Esse estudo permitiu também o estabelecimento da distribuição alélica das repetições, sendo que cerca de 75,7% dos alelos apresentam entre 7 e 9 repetições, o que está de acordo com dados obtidos em outras regiões do mundo. O presente trabalho permite concluir que o protocolo laboratorial é capaz de identificar alelos normais e alelos expandidos, sendo possível a determinação da distribuição alélica. Além disso, o uso do protocolo estabelecido permitiu o diagnóstico correto de casos de FRDA associados com a expansão da região polimórfica do trinucleotídeo GAA. Unitermos: Ataxia; Gene FXN; Repetições nucleotídicas.