Paula Jorge, University of Porto, Portugal.

FMR1 gene premutations have been implicated in fragile X-associated primary ovarian insufficiency. Recent reports have suggested the association of a low FMR1 gene CGG repeat length (CGGs<26) with ovarian dysfunction, however this finding is still under discussion. We speculate that the AGG interspersions may be the key to those conflicting results. We developed a mathematical model that combines the AGG interspersion number and pattern, as well as the FMR1 gene repeat length, named allelic score. By using this model, a different perspective of FMR1 gene analysis is provided with a particular impact on female carriers. This new complexity-based categorization of the *FMR1* alleles is being used among females at reproductive age: potentially fertile and infertile females. Aiming to determine whether FMR1 allelic score relates with Xchromosome inactivation (XCI) pattern in idiopathic infertile females, we evaluated the XCI pattern - resorting to the methylation status of AR locus (HUMARA) after Hhal digestion, in both cohorts. Although exploratory, our study suggests an association with allelic score in infertile females carrying a low FMR1 gene CGG repeat length. This led us to speculate that this may result from a protective FMR1-related effect or an unknown X-chromosome linked anomaly that likely correlates with infertility.

References:

Rodrigues B, Vale-Fernandes E, Maia N, Santos F, Marques I, Santos R, Nogueira AJA, Jorge P. Development and Validation of a Mathematical Model to Predict the Complexity of *FMR1* Allele Combinations. Front Genet. 2020 Nov 13;11:557147. doi: 10.3389/fgene.2020.557147. PMID: 33281866; PMCID: PMC7691586.

Jorge P, Garcia E, Gonçalves A, Marques I, Maia N, Rodrigues B, Santos H, Fonseca J, Soares G, Correia C, Reis-Lima M, Cirigliano V, Santos R. Classical fragile-X phenotype in a female infant disclosed by comprehensive genomic studies. BMC Med Genet. 2018 May 10;19(1):74. doi: 10.1186/s12881-018-0589-6. PMID: 29747568; PMCID: PMC5946481.

Jorge P, Oliveira B, Marques I, Santos R. Development and validation of a multiplex-PCR assay for X-linked intellectual disability. BMC Med Genet. 2013 Aug 5;14:80. doi: 10.1186/1471-2350-14-80. PMID: 23914978; PMCID: PMC3751858.