Poster abstracts
Resumos de posters

P-01

INVESTIGATION OF X-CHROMOSOME INACTIVATION PATTERNS – A VALUABLE TOOL IN GENETIC DIAGNOSIS

Ana Gonçalves[1], Paula Jorge[1,2], Rosário Santos[1]

[1] Unidade de Genética Molecular, Centro de Genética Médica Doutor Jacinto Magalhães, Centro Hospitalar do Porto E.P.E., Porto, Portugal;

[2] Unidade Multidisciplinar de Investigação Biomédica, ICBAS-UP

ana.goncalves@chporto.min-saude.pt

To overcome the gene dosage differences between males and females, one of the X-chromosomes is epigenetically silenced in the early embryogenic process of the female foetus. The choice of which one remains active in each cell is thought to be a random process, resulting, in most cases, in a uniform X-chromosome inactivation (XCI) pattern of cells. However, studies in large cohorts of phenotipically unaffected females indicate that about 8.8% exhibit skewed profiles (>80:20). Although this skewed ratio has no clinical significance in unaffected females, it may explain disease manifestation in otherwise non-affected carries of recessive X-linked conditions. As suggested by several authors, the assessment of XCI patterns can be very useful in confirming the diagnosis of disorders involving the X-chromosome, in female patients. In our laboratory, we apply the HUMARA assay to determine the pattern of XCI. This widely used method is based on the analysis of DNA methylation and number of CAG tandem repeats at the Human Androgen Receptor (*AR*) gene locus. The *AR* gene's highly polymorphic CAG repeat enables distinction between maternal and paternal X-chromosomes, while the close proximity of cleavage sites for methylation-sensitive restriction enzymes allows the discrimination of the inactive and active X-chromosome. The work presented demonstrates the importance of performing XCI studies and determining their impact in both the clinical and the laboratory context. Several examples will be described including manifesting carriers of X-linked recessive disorders; female carriers of translocations involving the X-chromosome, carriers of newly described variants of undetermined pathogenicity and female carriers with a suspected family history of X-linked disorders associated with unilateral XCI (where no sample is available from the affected male or where no mutation has been identified). Our results corroborate previous studies and show that methylation status in the *AR* locus is a reliable method to study XCI, therefore illustrating the confidence of this approach. Nevertheless, interpretation of XCI results should be done with caution: XCI can only be ascertained in the specimen being analyzed and may not reflect the XCI patterns in other tissues; it is an age-dependent phenomenon (since skewing increases with age); in some cases, the locus under study may not be in linkage desequilibrium with the *AR* locus; other genetic factors are known to play an important role in XCI process; symptomatic females may also have other factors contributing to their phenotype.