

PREFERENTIAL X CHROMOSOME LOSS BUT RANDOM INACTIVATION CHARACTERIZE PRIMARY BILIARY CIRRHOSIS.

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Background and aims: Primary biliary cirrhosis (PBC) is a chronic liver autoimmune disease of unknown etiology with a striking female predominance and high concordance in monozygotic twins (1). We have recently demonstrated (1,2) an enhanced rate of X chromosome monosomy in peripheral T and B cells of affected women pointing to an X-linked haploinsufficiency. It is known that females are functional mosaics for X-linked genes, due to the random inactivation of one X chromosome (XCI). Preferential X loss or XCI might therefore unmask specific haplotypes leading to loss of tolerance.

Methods: We studied 166 women with PBC and 226 age-matched control women. (i) X loss pattern was investigated by QF-PCR of 4 X-linked short tandem repeats (STRs) in peripheral blood mononuclear cells (PBMCs) (i.e. three or more STRs with an unbalanced ratio strength). (ii) XCI status was investigated using the androgen receptor STR and (iii) the tissue specificity of the X defects was assessed comparing PBMC and buccal cells.

Results: (i) Using HUMARA STR a preferential X chromosome loss was found in 54 out of 144 PBC and in 37 out of 155 controls ($P=0.005$), by analysis of additional STRs spanning X chromosome in a subset of PBC cases, non random X loss was demonstrated in 38% of PBC cases but in none of the controls ($P=0.001$). Importantly, (ii) the frequency of women showing a skewed XCI pattern ($\geq 75\%$ or $\geq 90\%$) in PBMCs and in buccal cells was similar in all age groups, and (iii) the X chromosome defects were restricted to PBMCs.

Conclusions: X chromosome loss is preferential in women with PBC and is limited to PBMCs. Future efforts should focus on the parental origin of the monosomic X chromosome in PBC and on disease associations with genes escaping XCI.

Bibliografia:

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