Putative miRNAs regulators of *HMGA2* in Uterine Leiomyomas and its association with *MED12* mutation

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BACKGROUND: Uterine Leiomyomas (UL) are the most common mesenchymal benign tumors. The main indication to treat these patients is the hysterectomy, implying in a significant public health problem. The more significant symptoms include infertility, abnormal bleeding and pregnancy complications. Rearrangements of 12q15 and 6q21, 7q deletion, *HMGA2* overexpression (10% of cases) and *MED12* mutations (48 to 92% of cases) have been reported as recurrent genomic alterations.

HYPOTHESIS: The overexpression of *HMGA2* is regulated by miRNAs and *MED12* mutations and *HMGA2* alterations are critical events in UL.

METHODS: Eighty-five fresh frozen UL and 20 adjacent normal myometrium (MM) were obtained from 54 patients submitted to hysterectomy. All samples were evaluated by Sanger sequencing to detect *MED12* mutation (exon 2). Quantitative real time RT-PCR was applied to evaluate the expression levels of miRs (miR-let7a, miR-21, miR-26a, miR-26b, miR-197 and miR-143 using RNU44, RNU48 and U47 as endogenous control) and *HMGA2* expression (*RPLP0* and *GUSB* as reference).

RESULTS: We detected 40% (34/85) of samples with *MED12* mutation. A significant overexpression ($p<0.001$) of *HMGA2* was detected in UL in comparison with matched MM, including a set of samples (five) with the presence of *MED12* mutation. Three miRNAs predicted to regulate *HMGA2* were found as significantly downregulated ($p< 0.001$): miR-let7a, miR-26a, and miR-26b.

CONCLUSION: The *MED12* and *HMGA2* aberrations revealed to be events not mutually exclusive in a subgroup of cases. These data suggest that these pathways can contribute to the UL development. The mechanism involved in *HMGA2* deregulation could be associated with three miRNAs described as predicted to regulate this gene.