Title: HOXA11 regulates expression of oxytocin receptor in uterosacral ligaments.

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Background:
Uterosacral ligaments (USL) are the main supportive structures of the uterus, and upper vagina. They are attenuated in women with pelvic organ prolapse (POP), however, the mechanism of USL attenuation is unknown. Previously, we have shown that expression of a homeobox gene, HOXA11, is critical in the development of USL in mice and is decreased in the USL of women with POP. We have also noted fewer smooth muscle cells in USL of women with POP, suggesting that smooth muscle cells in USL may play a pivotal role in pelvic floor support. Additionally, we have shown that and that murine USL express the oxytocin receptor (OXTR), and that knockdown of HoxA11 in mouse USL leads to decreased expression of some smooth muscle contractile proteins. Since oxytocin is a well known regulator of smooth muscle contractility, we hypothesized that HoxA11 regulates expression of OXTR and would therefore be decreased in the USL of women with POP.

Methods:
Specimens were collected from 10 women undergoing hysterectomy for POP and 10 women with normal support undergoing hysterectomy for benign gynecologic indications. RNA was extracted and real time PCR was performed. Nulliparous 12 week old C57BL/6 mice were transfected with short hairpin RNA targeted to HoxA11 (knockdown;KD) and control vector. USL were harvested at 48 and 72h after injection (n=6 per group). RNA expression of HOXA11 and OXTR were evaluated using qPCR. One way ANOVA was performed.

Results:
OXTR expression was confirmed in human USL and was decreased by 8-fold in women with POP compared to women with normal pelvic support. In mice, Hoxa11 expression decreased by 20% 48h after KD and by 50% at 72h after compared to controls. In the KD mice, the OXTR expression was decreased by 20% at 48h and 40% at 72h compared to control USL.

Conclusion:
OXTR is expressed in both human and mouse USL. Women with POP have significantly decreased OXTR expression compared to women with normal pelvic support. The finding of decreased OXTR expression following HoxA11 KD suggests that HOXA11 influences OXTR expression in USL. HOXA11 may serve as a key regulator in the loss of smooth muscle contractility and the development of POP in women.

Keyword 1: uterosacral ligament
Keyword 2: oxytocin receptor
Keyword 3: HOXA11