

## SIGNIFICANT LINKAGE EVIDENCE FOR PELVIC ORGAN PROLAPSE ON CHROMOSOME 10Q26

### Hypothesis / aims of study

It has been established by us and others that genetic factors contribute to the risk of pelvic organ prolapse (POP). Our original POP Genetic Resource focused on identifying sibs, who in most cases were treated surgically. Our Genetic Resource has been expanded to include larger extended pedigrees with elevated risk of POP; some of the cases in these pedigrees may not have received treatment for POP. The objective of this study is to present genome-wide linkage results for pedigrees with women who report *at least bothersome* symptoms of POP. Compared to our original linkage report of *strictly defined POP cases based on surgical treatment*, we hypothesized that this more moderate definition of POP might increase power to detect additional linkage regions of interest.

### Study design, materials and methods

We assessed linkage evidence in 53 pedigrees with at least two women per pedigree who reported at least bothersome symptoms of POP. Bothersome symptoms were defined based on standardized symptom questions (Pelvic floor distress inventory PFDI, responses moderately or quite bothered), pelvic examination, and/or review of treatment records. The pedigrees ranged in size from 2 to 17 genotyped and affected individuals (n=243 total genotyped subjects of whom 164 were affected); three of the pedigrees had 20 or more genotyped individuals. Genotype data were obtained from Illumina HumanHap550, 610Q, the Human1M-Duo, or the Human Omni1-Quad platforms. We identified a set of single nucleotide polymorphism (SNP) markers common to all platforms and used this as our marker set. This set of markers was further pruned to derive a set of SNPs from which those in high linkage disequilibrium were eliminated. Parametric linkage analysis using a general dominant and recessive model was performed using the Markov Chain, Monte Carlo linkage analysis method, MCLINK. Results are reported as heterogeneity logarithm of odds scores (HLODs), where suggestive evidence is a score of 1.86 or higher and significant evidence is a score of 3.3 or higher.

### Results

There were 38 affected individuals with only bothersome POP symptoms, 87 subjects who had been surgically treated, and 39 subjects who required repeat surgical intervention. Significant genome-wide linkage evidence was found on chromosome 10q24-26 with a maximum HLOD score of 3.59 under a recessive model. There were 24 pedigrees (45.2%) that had at least nominal linkage evidence ( $p < 0.05$ ) in this region. Other regions of suggestive linkage evidence included 1q42 (HLOD maximum 2.27), 9p22 (HLOD maximum 1.96), 17q24 (HLOD maximum 2.06) and 19q13 (HLOD maximum 1.89).

### Interpretation of results

While the etiology of this common condition is unknown, this study provides increasing evidence that POP is a heritable condition, and less strict criteria in phenotyping cases has identified additional linkage regions. Further study should focus on narrowing down these linkage regions to identify genes that contribute to POP.

### Concluding message

These results provide additional evidence that genetic factors contribute to POP, and suggest chromosome arm 10q24-26 as a region of special interest.

### Disclosures

**Funding:** Eunice Kennedy Shriver National Institute of Child Health and Human Development **Clinical Trial:** No **Subjects:** HUMAN **Ethics Committee:** University of Utah Institutional Review Board **Helsinki:** Yes **Informed Consent:** Yes