

SIGNIFICANT EVIDENCE FOR A PREDISPOSITION GENE FOR PELVIC FLOOR DISORDERS ON CHROMOSOME 9

Hypothesis / aims of study

Pelvic floor disorders (PFDs), including pelvic organ prolapse (POP), stress urinary incontinence (SUI), and urge urinary incontinence (UUI) are common, multifactorial conditions with possible heritable contributions. (1,2). Linkage analysis of affected sibling pairs has been used to identify a genetic component for other common disorders such as diabetes, obesity, and Alzheimers disease. The aim of this study was to identify linkage evidence for a predisposition gene for pelvic floor disorders in a set of affected sister pairs.

Study design, materials and methods

Women who underwent surgical repair of PFDs at our University from 1996-2006 (probands) were invited to participate and provide contact information for their sisters. Sisters of probands were surveyed for surgical repair of PFDs or evidence of PFDs on standardized questionnaires (PFDI). Those sisters who were likely affected with PFDs similar to those diagnosed in probands (POP, SUI, or mixed) were seen and examined along with the probands for phenotyping (POP-Q) and for collection of a blood sample for genotyping. We used the Illumina 1 million SNP marker set to determine genotypes for 96 total women from 38 families, representing 35 sets of sisters and 3 extended pedigrees. Medical reports were obtained to confirm surgeries. A strict phenotype was used: individuals with PFDs requiring surgery or repeat surgery were defined as affected, and over 90% of individuals so defined had stage III or IV POP documented. Linkage analysis was tested by the log₁₀ of the odds for linkage, or lod score calculated using the MCLINK analysis package. We performed a parametric linkage analysis testing both dominant and recessive models for the POP phenotype.

Results

Of the 553 women contacted, 297 had surgery for POP and 256 had surgery for both SUI and POP at our University. Of these 553, 140 could not be contacted, had died, or did not respond, 94 declined or withdrew or did not have a sister who agreed to participate, and 195 had no living sisters. One hundred twenty-two probands provided information on 1 to 8 sisters per family. Sisters were identified as probably affected and were recruited for study if there was 1) evidence of moderate to severe PFDs, usually surgery for the condition 2) high homogeneity with the type of PFD in the proband and 3) in a few families, less-affected sisters were included if there was a large affected pedigree. In some cases multiple related affected siblings in different generations of the same pedigree were identified. A total of 209 women were evaluated and phenotyped with collection of blood for DNA testing. There were 75 surgically treated POP cases, of which 65% were also affected with surgically treated SUI, 35% with treated OAB, and 8% with surgically treated hernia. Significant genome-wide evidence for linkage was identified on chromosome 9q21 with a lod score of 3.41 (p=0.000037) under a recessive model.

Interpretation of results

Linkage analysis is performed to identify evidence for the chromosomal location of a phenotype observed to cluster in relatives. Lod scores greater than 1.5 are suggestive of linkage, while scores greater than 3.0 provide significant evidence for linkage. Our study provides significant evidence of linkage to chromosome 9q21. Seventeen of our pedigrees had at least nominal evidence for linkage on a by-pedigree basis at this region. Further analyses are planned for less common phenotypes of SUI, UUI, and hernia in the already genotyped families.

Concluding message

Using linkage analysis, we have presented significant evidence for a predisposition gene for PFDs on chromosome 9. This resource can be used to further localize the gene of interest. Increased understanding of the genetic predisposition for PFDs may provide insight into the pathogenesis, prevention, and intervention of these conditions.

References

1. Int Urogyn J Pelvic Floor Dysfunct 2006; 17(5):498-501
2. Obstet Gynec 2006; 108(6):1388-93

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Was informed consent obtained from the patients?	Yes