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GENETIC DETERMINANTS OF STRESS URINARY INCONTINENCE IN WOMEN

Hypothesis / aims of study

The etiology of stress urinary incontinence (SUI) in women is poorly understood, but is probably multifactorial. Twin studies (1) suggest that both genetic and environmental factors contribute to SUI. More sophisticated genetic testing includes association studies which can be performed on unrelated affected individuals, and sib-pair linkage studies which are limited to related affected individuals but have been the source of some of the most important genetic discoveries in the last decade (2). The aim of our study was to use sib-pair linkage analysis to identify possible genetic contributions to SUI.

Study design, materials and methods

As part of a large study of pelvic floor disorders, we asked women who had undergone surgery for SUI from 1997-2007 at our University Hospital to contact their sisters for possible enrolment. Most of the probands had urodynamic stress incontinence. Sisters (and other close female family members) were invited for evaluation if they had symptoms of SUI symptoms on questionnaires (PFDI) or if they had had documented surgery for SUI. Blood for DNA was collected from the probands and any affected female relative, and for the purposes of this study we defined "affected cases" as having undergone at least one surgery for SUI. Surgical records were obtained to confirm the phenotype. IRB approved consent was obtained from all subjects. We performed a genome-wide linkage analysis in 39 kindreds with 2 or more affected female relatives. Genotyping was performed using the Illumina 610Q marker set, and linkage analysis was tested by the $\log_{10}$ of the odds for linkage (LOD score) calculated using the McLINK analysis package. Because SUI is likely to be a heterogeneous condition, results are reported as the stricter heterogeneity LOD score (HLOD score); HLOD scores of 1.86 or greater are suggestive of linkage, and HLOD scores of 3.3 or greater represent significant linkage.

Results

One hundred women in 39 kindreds were included in this analysis: 25 families with 2 or more affected sisters, 5 families with affected mother-daughters, 3 families with affected aunt-nieces, one family with affected cousins, and six families with extended pedigrees. Seventy-eight women had undergone one surgery for treatment of SUI, and 22 had undergone 2 or more surgeries. Sixty-three women identified as having surgery for SUI were found also to have undergone surgery for POP at some time. Mean parity was 3.9 ± 2.4 (n=90), mean BMI was 27.7 ± 5.8 kg/m^2, and mean age at diagnosis was 47.1 ± 13.7 years (n=62.) We observed linkage peaks on five chromosomes: Chr 2q37.3 (HLOD 2.58), Chr 4q25-q28 (HLOD 2.98), Chr 8p22 (2.58), Chr 10q26.2-q26.3 (HLOD 2.36) and Chr 11p15.5 (HLOD 2.15), most under a recessive model (Figure 1).

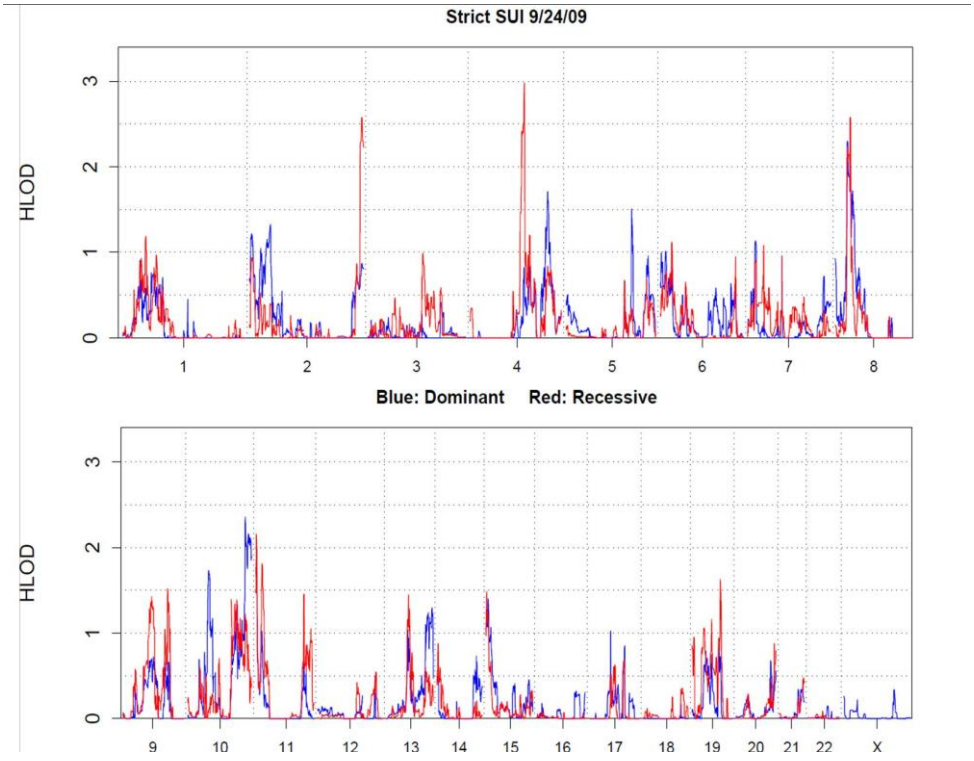

Figure 1: HLOD scores for SUI phenotype plotted by chromosome 1-22, X

Interpretation of results

With a small initial sample of related women treated surgically for SUI, we found suggestive evidence for predisposition genes on five chromosomes: 2, 4, 8,10 and 11. Previous reports of linkage in women with surgically treated POP have been found on

chromosome 9q21 (3). As we increase our sample of related SUI cases, we anticipate confirming some of these peaks as containing significant predisposition genes for SUI.

Concluding message

Using linkage analysis in related women treated surgically for SUI, we have demonstrated suggestive linkage for SUI predisposition genes in five chromosomes. This resource can be used to further localize the genes of interest. Increased understanding of the genetic predisposition for SUI and other pelvic floor disorders may provide insight into the pathogenesis, prevention, and intervention of these conditions.

References

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Was informed consent obtained from the patients?	**Yes**