Genome-wide association analysis identifies novel associations in uterine fibroids.

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Introduction

Uterine leiomyoma, commonly known as uterine fibroids, are benign tumors derived from smooth muscle and fibrous tissue in the uterus, and are the leading cause of hysterectomy in the United States. The lifetime risk for a woman to develop fibroids has been estimated to be as high as 25%. Fibroids tend to grow under the influence of estrogen. The underlying causes of uterine fibroids are not well understood, but it is suggested by twin studies that approximately 55% of the variation in susceptibility to fibroids is genetic.

Methods

To investigate the genetic factors underlying uterine fibroids, we conducted a genome-wide association study (GWAS) of 4,121 cases and 12,252 controls of unrelated European ancestry individuals who have self-reported information on uterine fibroids from the 23andMe participant cohort. Samples were genotyped and imputed against 1000 Genomes reference haplotypes, a total of 8,058,452 SNPs met quality control criteria. Uterine fibroids cases were defined as having said yes to the following question: "Have you ever been diagnosed with uterine fibroids?" The following table shows demographics of individuals included in the GWAS.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-30</td>
<td>110</td>
<td>1,817</td>
</tr>
<tr>
<td>30-45</td>
<td>534</td>
<td>2,840</td>
</tr>
<tr>
<td>45-60</td>
<td>1,779</td>
<td>3,661</td>
</tr>
</tbody>
</table>

GWAS findings:

To evaluate how multiple genes in the same pathway may contribute to uterine fibroids we compared results from three pathway GWAS approaches: MAGENTA [6], ALIGATOR [7], and VEGAS [8]. Rather then focusing on a few top GWAS genes with the strongest evidence of disease association, by considering multiple contributing factors together, we potentially can improve the power to detect causal pathways and disease mechanisms.

GWAS pathway analyses:

We used a gene set of canonical pathways from the Molecular Signatures Database (MSigDB) containing 1320 gene sets compiled by domain experts [9].

Table 1. Demographics statistic for uterine fibroids phenotype.

| Regression analyses were conducted in a set of responders, controlling for age, and population structure: |
| Uterine fibroids = age + pc.0 + pc.1 + pc.2 + pc.3 + pc.4 + genotype |

Results

GWAS findings:

We report one novel genome-wide association and four suggestive associations. The most significant finding is the variant in apoptosis regulating nuclear envelope (1 SYNE1) gene (rs12484776: odds ratio=1.3, p-value=8.8 x 10⁻⁴⁶), which has been shown to promote smooth muscle cells proliferation in transgenic rabbits [3] and in patients with leiomyoma [9].

Using the high-confidence protein-protein interaction database (HPRD), we identified 36 significant protein-protein interactions. Among pathways identified as significant by MAGENTA and ALIGATOR are the ETS transcription factor pathway and cytokine Th1 Th2 pathway. Cytokine Th1/Th2 regulation is very promising.

Acknowledgments

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References