Evaluating the ovarian cancer gonadotropin hypothesis: A candidate gene study

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Invasive epithelial ovarian cancer (ovarian cancer) is a hormone-related disease with a strong genetic basis. However, none of its high-penetrance susceptibility genes and GWAS-identified variants to date are known to be involved in hormonal pathways. Given the hypothesized etiologic role of gonadotropins, an assessment of how variability in genes involved in the gonadotropin signaling pathway impacts disease risk is warranted.

Methods. Genetic data from 41 ovarian cancer study sites were pooled and unconditional logistic regression was used to evaluate whether any of the 2185 SNPs from 11 gonadotropin signaling pathway genes was associated with ovarian cancer risk. A burden test using the admixture likelihood (AML) method was also used to evaluate gene-level associations.

Results. We did not find any genome-wide significant associations between individual SNPs and ovarian cancer risk. However, there was some suggestion of gene-level associations for four gonadotropin signaling pathway genes: INHBB (p = 0.045, mucinous), LHCGR (p = 0.046, high-grade serous), GNRH (p = 0.041, high-grade serous), and FSHB (p = 0.036, overall invasive). There was also suggestive evidence for INHA (p = 0.060, overall invasive).

Conclusions. Ovarian cancer studies have limited sample numbers, thus fewer genome-wide susceptibility alleles, with only modest associations, have been identified relative to breast and prostate cancers. We have evaluated the majority of ovarian cancer studies with biological samples, to our knowledge, leaving no opportunity for replication. Using both our understanding of biology and powerful gene-level tests, we have identified four putative ovarian cancer loci near INHBB, LHCGR, GNRH, and FSHB that warrant a second look if larger sample sizes and denser genotype chips become available.

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Gene and SNP selection

Eleven gonadotropin signaling pathway genes were evaluated in our analyses: ACVR1, ACVR2, C2A, FSHB, FSHR, GNRH, GNRRH, INHA, INHBA, INHB, and LHCGR. SNPs found within each gene as well as SNPs within 25 kb upstream and downstream of each gene were assessed. Only SNPs with an imputation \( r^2 \geq 0.5 \) and a minor allele frequency (MAF) \( \geq 0.05 \) were considered in the analyses. Hence, our final analyses included 2185 SNPs.

Statistical analysis

The program LAMP was used to assign intercontinental ancestry based on genotype frequencies in European, Asian, and African populations [21]. Participants with 90% or more European ancestry were classified as European. To adjust for ancestry within the European population, a principal components analysis (PCA) was performed within our subjects using a set of 37,000 unlinked markers as well as an in-house program written in C++ that used the Intel MKL library for eigenvectors (http://cge.medschl.cam.ac.uk/software/pccalc).

Coverage referred to the total proportion of genetic variation being captured for each gene at an \( r^2 \geq 0.8 \). It was determined by calculating the pairwise \( r^2 \) between the SNPs we had genotypes for (with an imputation \( r^2 \geq 0.5 \) and a MAF \( \geq 0.05 \)) and all of the 1000 Genomes SNPs in each gene that had a MAF \( \geq 0.05 \).

Unconditional logistic regression was used to assess the association between each SNP in the gonadotropin signaling pathway genes and ovarian cancer risk. All analyses took into consideration study set and adjusted for population substructure by including the first five PCA eigenvalues in the model. This was done for all invasive ovarian cancer as well as for the four ovarian cancer histological subtypes (high-grade serous, mucinous, endometrioid, clear cell). Per-allele log odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. All reported \( p \)-values were two-sided.

Because we were interested in identifying whether or not individual genes (versus the individual SNPs) were associated with ovarian cancer risk, a burden test was performed using the admixture likelihood (AML) method [22] to determine whether overall genetic variation in each gonadotropin signaling gene was associated with disease risk after accounting for the correlation between the SNPs in each gene.

The AML method postulates that within a set of SNPs, a given proportion \( \alpha \) is associated with the outcome, and the effect size of each associated SNP will fall on a non-central \( \chi^2 \) distribution with non-centrality parameter \( \eta \). The \( \eta \) parameter is a measure closely related to that SNP’s contribution to the genetic variance of the outcome variable. The AML method estimates values for \( \alpha \) and \( \eta \) using a pseudo-maximum likelihood method. Due to a lack of independence among our SNPs, it is not possible to assess the significance of the estimated parameters by a simple likelihood ratio test so the AML method was used to assess significance by simulation instead.

We used the AMLcalc program (http://cge.medschl.cam.ac.uk/software/aml) to perform the burden test using 1000 simulations with the maximum proportion of associated SNPs set to 0.2 on the genotyped and imputed data and adjusting for the first five ancestry principal components. \( p \)-Values for the AML trend test are provided.

Results

The number of SNPs analyzed for each gene and the number of SNPs statistically significantly associated with invasive ovarian cancer risk (at a nominal \( p \leq 0.05 \) significance level) are presented in Table 1. Neither GNRH nor GNRRH harbored a SNP associated with overall invasive ovarian cancer at the \( p \leq 0.05 \) level (Table 1). LHCGR had the most strongly associated single SNP, rs72618637 (\( p = 0.001 \); Table 1), but FSHB showed some evidence of a gene-level association (\( p = 0.036 \); Table 1). A borderline statistically significant gene-level association between INHA and invasive ovarian cancer was also observed (\( p = 0.060 \)). However, when all SNPs across the 11 genes were considered together (“global”), no evidence of an association between genetic variation in the gonadotropin signaling pathway and invasive ovarian cancer risk was observed (\( p = 0.33 \)).

Results of the most significant association for each gene by histological subtype are presented in Tables 2A and 2B. FSHB had the most strongly associated single SNP, rs7951733 (\( p = 4.62 \times 10^{-5} \); Table 2B and Supplementary Fig. S1) across all histological subtypes, including overall invasive, and also showed suggestive evidence of a gene-level association with the invasive endometrioid subtype (\( p = 0.063 \)). In addition, while genetic variation across the 11 genes did not show evidence of a global association with any of the four histological subtypes, there was evidence of gene-level associations between LHCGR and GNRH and the invasive high-grade serous subtype (\( p = 0.046 \) and \( p = 0.041 \), respectively) as well as between INHBB and the invasive mucinous subtype (\( p = 0.045 \)). However, there was no evidence of any gene-level association with the invasive clear cell subtype.

Discussion

The gonadotropin hypothesis has been one of the leading hypotheses concerning ovarian cancer development. After evaluating this pathway, we found individual SNP associations at the \( p \leq 0.05 \) level, which is intriguing, but none was statistically significant after considerations for multiple comparisons. Rs7951733, which was an imputed SNP in our dataset (\( r^2 = 0.95 \) with a MAF = 0.08, was particularly interesting given its strong association with the endometrioid ovarian cancer subtype (\( p = 4.62 \times 10^{-5} \); Supplementary Fig. S1). It is located approximately 5 kb downstream of the FSHB gene, which encodes the beta polypeptide of FSH, a gonadotropin involved in reproduction. However, the relevance of this SNP remains uncertain.

In this case where many nominally significant associations were observed, an alternative method for evaluating whether variation in this pathway is associated with risk is needed. A standard approach would be to attempt replication. However, to our knowledge, our analysis includes the majority of ovarian cancer cases and controls available worldwide for genetic studies. Hence, we conducted burden testing using the AML approach to evaluate evidence of gene-level associations. This method did provide some evidence of gene-level associations. A total of 55 burden tests were carried out (i.e., 11 genes \times 5 types of ovarian cancer (overall invasive plus the four subtypes of ovarian cancer)), in which four significant associations (FSHB, LHCGR, GNRH, and INHBB) and one borderline significant association (INHA) were observed, compared to 2.8 expected by chance at the \( p \leq 0.05 \) level. This lends support to a possible role for genetic variation in this pathway with ovarian cancer risk.

Given that most ovarian cancer patients present at a postmenopausal stage when circulating FSH and LH levels are high and remain high due to the lack of negative feedback mechanisms by ovarian steroids, an association between chronically elevated gonadotropin levels and ovarian carcinogenesis has been suggested [23]. This is further supported by elevated gonadotropin levels in cyst and peritoneal fluid from ovarian cancer patients, although their relevance when the carcinogenesis has already occurred is uncertain [24]. Epidemiological evidence indirectly supporting the role of gonadotropins in ovarian carcinogenesis includes the well-established protective effects of pregnancies and OC use, which suppress gonadotropin secretion by the pituitary gland [25]. The gonadotropin hypothesis has also prompted substantial work on the potential risk-enhancing effects of infertility treatments, which include high-doses of gonadotropins to induce ovulation [26]. Hence, while gonadotropins alone may not reconcile all of the data pertaining to ovarian cancer etiology and progression, the evidence suggests that they are at least partly involved; it has been hypothesized that high gonadotropin levels could stimulate ovarian epithelial cells and initiate or promote tumorigenesis.
It was previously suggested that variants in FSHR (rs6165 and rs6166) may affect susceptibility of women to ovarian cancer [15–17]. However, the results from three studies that investigated this were conflicting. Our analysis of 746 SNPs in this gene included these two variants, but neither was found to be associated with risk of ovarian cancer (p = 0.46 and p = 0.45, respectively).

Our results suggest that there may be other genes involved in the gonadotropin signaling pathway that might affect risk of developing ovarian cancer and specific subtypes of ovarian cancer as well. In addition, the molecular function of such genes makes their involvement in ovarian carcinogenesis biologically plausible. GNRH is predominantly responsible for the release of the pituitary gonadotropins, FSH and LH, which makes it a likely gene to be involved in this pathway. INHBB or inhibin beta B is a subunit of inhibin, which is produced by the granulosa cells of the ovary and has been found to be a possible marker of ovarian cancer [27]. The potential association we report with the mucinous ovarian cancer subtype is interesting given case reports describing a combination of granulosa cell tumor and mucinous cystadenoma of the ovary [28,29]. It joins the alpha subunit of inhibin (INHA) to form a pituitary FSH secretion inhibitor. LHCR or luteinizing hormone/chorionicgonadotropin receptor produces a protein that acts as a receptor for two ligands: LH, which plays a role in ovulation, and chorionic gonadotropin, which is necessary for pregnancy. In addition, evidence suggests an association between genetic variability in LHCR and risk of ovarian hyperstimulation syndrome [30]. FSHB encodes the beta polypeptide of FSH, which has long been thought to play a role in ovarian carcinogenesis due to well-established protective factors that suppress its secretion [25].

Despite three genome-wide scans and multiple large-scale genotyping efforts, only 18 genome-wide significant ovarian cancer susceptibility alleles have been identified, compared to 76 in breast and 77 in prostate [unpublished results, 31]. This is largely attributable to limited sample size numbers available in each study, which emphasizes the importance of collaborative efforts, such as OCAC. In addition, because of limited numbers, new statistical methods are needed to better understand the role of genetics in ovarian cancer etiology. This study highlights one such method. By linking biology with burden testing, we were able to find some evidence of an association between the gonadotropin signaling genes GNRH, INHBB, FSHR, and LHCR and ovarian cancer risk.

None of the individual SNP associations we observed showed genome-wide significance (p = 5 × 10⁻⁸) and are thus circumstantial. However, we applied burden testing to evaluate gene-level effects as well, and although this does not allow us to identify the specific disease-associated variant, it does shed some light on potential genes to focus on in future studies. In addition, although much of the genetic data used were imputed, we restricted our analyses to only SNPs with an imputation r² ≥ 0.5 and a MAF ≥ 0.05, which is a common method used for filtering imputed data [32]. While these findings cannot be directly applied to a clinical setting, they demonstrate both a biological and genetic basis to the role of gonadotropins in ovarian carcinogenesis, which could impact how

### Table 1
Gene-level AML test and most significantly associated SNP (MAF ≥ 0.05) in each gonadotropin signaling gene for all invasive ovarian cancers.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Coverage (at imputation r² ≥ 0.8)</th>
<th>Number of SNPs</th>
<th>Number of significant SNPs (at ≤ 0.05)</th>
<th>AML burden testb</th>
<th>Most significant SNP</th>
<th>MAFa</th>
<th>Imputation r²</th>
<th>ORc</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACVR1</td>
<td>0.55</td>
<td>101</td>
<td>1</td>
<td>0.73</td>
<td>rs35160507</td>
<td>0.07</td>
<td>0.77</td>
<td>1.07</td>
<td>0.030</td>
</tr>
<tr>
<td>ACVR2</td>
<td>0.98</td>
<td>161</td>
<td>1</td>
<td>0.52</td>
<td>rs17742573</td>
<td>0.07</td>
<td>0.56</td>
<td>0.93</td>
<td>0.046</td>
</tr>
<tr>
<td>CGA</td>
<td>0.97</td>
<td>140</td>
<td>15</td>
<td>0.29</td>
<td>rs7745823</td>
<td>0.24</td>
<td>0.83</td>
<td>0.96</td>
<td>0.035</td>
</tr>
<tr>
<td>FSHR</td>
<td>0.99</td>
<td>111</td>
<td>18</td>
<td>0.036</td>
<td>rs12805742</td>
<td>0.22</td>
<td>0.94</td>
<td>1.04</td>
<td>0.018</td>
</tr>
<tr>
<td>FSHR</td>
<td>0.99</td>
<td>746</td>
<td>15</td>
<td>0.57</td>
<td>chr2:4024261D</td>
<td>0.07</td>
<td>0.70</td>
<td>0.91</td>
<td>0.007</td>
</tr>
<tr>
<td>GNRH</td>
<td>1.00</td>
<td>108</td>
<td>0</td>
<td>0.65</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>GNRHR</td>
<td>0.94</td>
<td>126</td>
<td>0</td>
<td>0.59</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>INHA</td>
<td>0.86</td>
<td>81</td>
<td>15</td>
<td>0.060</td>
<td>rs12720063</td>
<td>0.21</td>
<td>1.00</td>
<td>0.95</td>
<td>0.007</td>
</tr>
<tr>
<td>INHBB</td>
<td>1.00</td>
<td>77</td>
<td>1</td>
<td>0.80</td>
<td>rs17776182</td>
<td>0.15</td>
<td>1.00</td>
<td>0.95</td>
<td>0.010</td>
</tr>
<tr>
<td>LHCR</td>
<td>0.97</td>
<td>109</td>
<td>22</td>
<td>0.098</td>
<td>rs11900747</td>
<td>0.06</td>
<td>0.55</td>
<td>1.13</td>
<td>0.004</td>
</tr>
<tr>
<td>Global</td>
<td>–</td>
<td>2185</td>
<td>140</td>
<td>0.33</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Note: “N/A” reflects genes with no significant SNPs at p ≤ 0.05. “Global” refers to when all genes are considered.

a MAF = minor allele frequency.
b AML = admixture maximum likelihood.
c OR = per allele odds ratio, taking into account study set and the first five ancestry principal components.

d MAFA Imputation r²

### Table 2A
Gene-level AML test and most significantly associated SNP (MAF ≥ 0.05) in each gonadotropin signaling gene for invasive high-grade serous and mucinous ovarian cancers.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Coverage (at r² ≥ 0.8)</th>
<th>Serous high grade (n = 6258)</th>
<th>Mucinous (n = 991)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of signif. SNPs</td>
<td>AML burden testb</td>
<td>No. of signif. SNPs</td>
</tr>
<tr>
<td>ACVR1</td>
<td>0.55</td>
<td>0.47 N/A</td>
<td>1</td>
</tr>
<tr>
<td>ACVR2</td>
<td>0.98</td>
<td>0.66 rs7870939 0.05 0.60 1.13 0.038</td>
<td>6</td>
</tr>
<tr>
<td>CGA</td>
<td>0.97</td>
<td>0.00 N/A</td>
<td>1</td>
</tr>
<tr>
<td>FSHR</td>
<td>0.99</td>
<td>0.35 rs11644731 0.21 0.99 0.05 0.049</td>
<td>37</td>
</tr>
<tr>
<td>FSHR</td>
<td>0.90</td>
<td>0.52 rs11644731 0.07 0.80 0.87 0.003</td>
<td>45</td>
</tr>
<tr>
<td>GNRH</td>
<td>1.00</td>
<td>0.012 chr2:25082375D 0.42 0.62 1.07 0.010</td>
<td>0</td>
</tr>
<tr>
<td>GNRHR</td>
<td>0.94</td>
<td>0.34 N/A</td>
<td>0</td>
</tr>
<tr>
<td>INHA</td>
<td>0.86</td>
<td>0.24 rs77120825 0.06 0.51 1.16 0.013</td>
<td>0</td>
</tr>
<tr>
<td>INHBB</td>
<td>1.00</td>
<td>0.52 rs17719440 0.08 0.98 1.11 0.008</td>
<td>0</td>
</tr>
<tr>
<td>LHCR</td>
<td>0.97</td>
<td>0.12 rs13426172 0.12 1.00 0.91 0.005</td>
<td>21</td>
</tr>
<tr>
<td>Global</td>
<td>–</td>
<td>0.154 N/A</td>
<td>137</td>
</tr>
</tbody>
</table>

Note: “N/A” reflects genes with no significant SNPs at p ≤ 0.05. “Global” refers to when all genes are considered.

a MAF = minor allele frequency.
b AML = admixture maximum likelihood.
c OR = per allele odds ratio, taking into account study set and the first five ancestry principal components.
researchers and clinicians view ovarian cancer etiology. Based on our results, the gonadotropin hypothesis would be worth re-evaluating when larger samples with denser genotyping chips become available so that there is more power with less reliance on imputation, allowing for fine mapping to be carried out.

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Conflict of interest statement

Andrew Berchuck serves on the PARP inhibitor advisory board for Astra Zeneca and Usha Menon owns shares of Abcodia Ltd., a biomarker validation company.

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