Unraveling an Association between Hypodontia and Epithelial Ovarian Cancer

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OUTLINE

HYPODONTIA

HYPODONTIA

Defined as the developmental absence of one or more teeth as well as variations in size, shape, rate of dental development and eruption time.

Hypodontia is the agenesis of 6 or less teeth.
Oligodontia is the agenesis of 6 or more teeth.
Anodontia is the agenesis of all teeth.

2.6-11.3% reported prevalence worldwide.
Women are affected more than males at a ratio of 3:2.
Both genetic and environmental explanations for hypodontia have been reported.

HYPODONTIA & CANCER

• Over 300 genes are involved in odontogenesis including MSX1, PAX9, and AXIN2
• Genes involved in dental development also have roles in other organs of the body
• Mutation in several genes governing tooth development have already been associated with cancer
• Mutations in AXIN2 cause familial tooth agenesis and predispose to colorectal cancer
• AXIN2 gene is highly expressed in ovarian tissue so may play a role in epithelial ovarian cancer (EOC)
• Reduced expression of PAX9 can lead to hypodontia and has been correlated with increased malignancy of dysplastic and cancerous esophageal epithelium
• RUNX transcription factor family (RUNX1, 2, and 3) are involved in odontogenesis and has been the most targeted genes in acute myeloid leukemia and acute lymphoblastic leukemia
• RUNX2 is amplified in various cancers including osteosarcoma and may play a role in breast and prostate cancer

WHAT IS OVARIAN CANCER?

OVARIAN CANCER

Ovarian cancer is a gynecological cancer that begin in the ovaries.

Although ovarian cancer only ranks 8th in most common cancer in women...

...it is the 5th leading cause of cancer death in women.

• Mainly affects women over the age of 40
• Symptoms include:
  • Vaginal bleeding
  • Pain or pressure in pelvic region or abdominal area
  • Back pain
  • Bloating
  • Change in bathroom habits
• Increased risk of EOC is correlated with:
  • Family history of ovarian cancer
  • Increasing age
  • History of breast, uterine, or colorectal cancer
  • Infertility
  • Endometriosis

**Research**

**Hypodontia as a risk marker for epithelial ovarian cancer**

A case-control study

**Purpose**

- Compare prevalence rates of hypodontia among epithelial ovarian cancer (EOC) subjects and control subjects
- Explore the possible genetic association between the two phenotypes

**Findings**

- Prevalence of hypodontia was 20% for EOC subjects (p < .001)
- Reported family hx of hypodontia and ovarian cancer was higher in EOC subjects
- EOC subjects were 8.1 times more likely to have hypodontia than women without EOC

**Ovarian Cancer in the Literature**

**Gene Selection:**

Locus 8q24

- Previous genome wide association study (GWAS) identified a ovarian cancer susceptibility loci at 9q22 and found a 20% reduction in risk with each copy of the minor alleles
- Most recent GWAS identified two new susceptibility loci for ovarian cancer
  - 2q31 (p = 3.8 x 10^-10): rs2072590
  - 8q24 (p = 8.0 x 10^-15): rs10088218, rs1519682 and rs10098821
- SNPs at these two loci showed strong support for an association with ovarian cancer with p-values < 0.001.
- At locus 8q24, minor allele (A) of SNP rs10088218 was associated with a decreased risk for ovarian cancer


**Materials and Methods**

**Subject Population**

- 110 Caucasian subjects were recruited from the orthodontic clinic at the University of Kentucky College of Dentistry
  - 67 females, 43 males
- Subjects were classified into two research groups:
  - Controls: patients without hypodontia
  - Subjects: patients with hypodontia

**Saliva Collection**

- 2-4 mm of saliva was collected from all study participants
- Oragene-DNA Collection Kits (DNA Genotek Inc., Ottawa, Ontario, Canada)
- Preservatives in container will preserve DNA for 5+ years

**DNA Isolation**

- Genomic DNA extracted and resuspended in 10 mM Tris-HCl, 1 mM EDTA pH 8.0, and stored at 20°C
- DNA isolated and purified via ethanol precipitation
- DNA concentrations measured on the NanoDrop-1000 spectrophotometer (Thermo Fischer Scientific, Wilmington, DE)

**Taqman® Gene Assay Kits**

- Analysis of all SNPs were performed on the genomic DNA utilizing Taqman® Genotyping Assay Kits on Roche LightCycler 480®
- Following RT-PCR amplification, each SNP allele was identified using allele specific probes
  - VIC or FAM fluorescence
- Analyze SNP rs10088218

**Null Hypothesis (H₀)**

SNP rs10088218 is NOT associated with hypodontia.

**Alternative Hypothesis (H₁)**

SNP rs10088218 is associated with hypodontia.
**Statistical Methods**

- The Chi-Square ($\chi^2$) Analysis
  - Used to evaluate the potential association of each SNP with hypodontia
  - Co-dominant mode on inheritance was utilized for potential association
  - Significance set at an alpha of 5% ($p<0.05$)

\[ X^2 = \sum \frac{(O - E)^2}{E} \]

**MATERIALS AND METHODS**

**Statistical Methods**

- Genotyping of SNP rs10088218 was completed in all 30 subjects with NMT and 80 controls.
- No deviation from HWE was observed in either the controls or the entire cohort.
- SNP rs10088218 was significantly associated with the presence of hypodontia in 25 individuals versus 80 controls ($p=0.019$) with an odds ratio (OR) of 11.51 (95% confidence interval (CI) 1.49-88.98) under an additive mode of inheritance (MOI).
- SNP rs10088218 was also significantly associated with the presence of hypodontia in 30 individuals versus 80 controls ($p=0.021$; OR=4.37 95%CI: 1.25-15.35) under an additive MOI.

**RESULTS**

**SNP rs10088218**

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of individuals within the group with a given genotype (% of the total group)</th>
<th>SNP (95% Confidence Interval)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypodontia Subjects Only (n=25)</td>
<td>G (96.0)</td>
<td>A (4.0)</td>
<td>0</td>
</tr>
<tr>
<td>Controls (n=80)</td>
<td>54 (67.5)</td>
<td>23 (28.75)</td>
<td>3 (3.75)</td>
</tr>
<tr>
<td>Hypodontia and Oligodontia Subjects (n=30)</td>
<td>G (90.0)</td>
<td>A (10.0)</td>
<td>0</td>
</tr>
<tr>
<td>Controls (n=80)</td>
<td>54 (67.5)</td>
<td>23 (28.75)</td>
<td>3 (3.75)</td>
</tr>
</tbody>
</table>

- Hypodontia patients are 11.5x more likely to be homozygous for the G allele than controls
- Odds ratio reduces with addition of oligodontia patients

**Frequency of Missing Teeth**

- Same as previously reported
- Maxillary lateral incisor was the most commonly missing tooth
- The next most commonly missing tooth type included the mandibular second premolars followed by maxillary second premolars
- Females affected more than males at a ratio of 3:1

**DISCUSSION & CONCLUSIONS**

**Conclusions**

- Hypodontic teeth reported in this study are consistent with those previously reported missing in women diagnosed with EOC and hypodontia
- The null hypothesis was rejected
- SNP rs10088218 is significantly associated with the occurrence of hypodontia ($p=0.019$)

**REFERENCES**

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