Null Results in Brief

Absence of Deleterious Palladin Mutations in Patients with Familial Pancreatic Cancer

Alison P. Klein,1,4 Michael Borges,1 Margaret Griffith,1 Kieran Brune,1 Seung-Mo Hong,1 Noriyuki Omura,1 Ralph H. Hruban,1,3 and Michael Goggins1,2,3

Departments of 1Pathology, 2Medicine, and 3Oncology, The Johns Hopkins University School of Medicine, and 4Department of Epidemiology, the Bloomberg School of Public Health, The Sol Goldman Pancreatic Research Center, The Johns Hopkins Medical Institutions, Baltimore, Maryland

Abstract

It has been reported that germline mutations in the palladin gene (PALLD) cause the familial aggregation of pancreatic cancer, but the evidence is weak and controversial. We sequenced the coding regions of PALLD in 48 individuals with familial pancreatic cancer. We did not find any deleterious mutations and find no evidence to implicate mutations in PALLD as a cause of familial pancreatic cancer. (Cancer Epidemiol Biomarkers Prev 2009; 18(4):1328–30)

Introduction

Brentnall et al. (1) identified a germline missense alteration (P239S) in the palladin gene (PALLD) in a familial pancreatic cancer kindred and suggested that this variant may be a cause of the familial clustering of pancreatic cancer. Members of the kindred, known as family X, develop an early onset pancreatic cancer, with pancreatic insufficiency and diabetes mellitus in an autosomal dominant fashion (2) and have significant linkage to chromosome 4q32-34, a region that includes the PALLD gene (3). Brentnall et al. (1) implicated an oncogenic function for palladin after finding overexpression of PALLD mRNA in pancreatic cancer tissues.

Since this original publication, subsequent studies have not found evidence to link palladin to familial pancreatic cancer (4-8). However, these subsequent studies including linkage analysis, analyses of the PALLD P239S variant in familial pancreatic cancer cases, and examination of pancreatic cancer palladin expression have yet to evaluate the full sequence of PALLD in patients with familial pancreatic cancer (4-8). To determine if sequence variants in PALLD could be contributing to pancreatic cancer susceptibility, we sequenced the entire coding region of PALLD in 48 individuals with familial pancreatic cancer.

Materials and Methods

Forty-eight unrelated patients with familial pancreatic cancer, defined as individuals with at least two first-degree relatives with pancreatic cancer, were selected from the National Familial Pancreatic Tumor Registry (9) for analysis. DNA was obtained from EBV-transformed lymphocyte cell lines as previously described (10). PCR of PALLD (KIAA0992 Genbank # AB023209.1) was done mainly using primers designed for the pancreatic cancer genome project (11). Sequencing of PCR products was done using the GenomeLab DTCS-Quick Start kit (Beckman-Coulter) according to the kit protocol. Products were sequenced using a CEQ 8000 GeXP Genetic Analysis System (Beckman-Coulter) and the sequence analysis was done with Sequencher v 4.1.4 (Gene Codes Corporation). Putative single nucleotide polymorphisms were evaluated by searching the single nucleotide polymorphism database at the National Center for Biotechnology Information/BLAST Web site. Over 92% of the coding region was successfully sequenced. The study was done with approval from our Institutional Review Board.

Results

No deleterious sequence variants were identified in any of the 48 patients with familial pancreatic cancer (97% confidence interval, 0-7.2%). Five single nucleotide polymorphisms were identified, only one of which changed the amino acid sequence (S236G), the same variant that was identified by Gallinger et al. (5) as a polymorphism having no association with pancreatic cancer. The prevalence of this variant (c.236 A>G) in our study sample was not significantly different (GG, 0.42; AG, 0.44; AA, 0.14) to that previously reported in controls (GG, 0.39; AG, 0.47; AA, 0.14). The remaining variants that we identified were all silent (see Table 1).
Table 1. PALLD sequence variants

<table>
<thead>
<tr>
<th>Exon</th>
<th>Nucleotide change</th>
<th>Amino acid change</th>
<th>Frequency</th>
<th>SNP database</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>c. 236 A &gt; G</td>
<td>Ser-Gly</td>
<td>GA = 0.52</td>
<td>rs62333013</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AG = 0.35</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AA = 0.13</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>c. 467 A &gt; T</td>
<td>Ala-Ala</td>
<td>AA = 0.81</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AT = 0.19</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TT = 0</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>c. 492 A &gt; G</td>
<td>Arg-Arg</td>
<td>AA = 0.90</td>
<td>rs1059444</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AG = 0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GG = 0.08</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n. 4019 G &gt; A</td>
<td>3' UTR</td>
<td>GG = 0.83</td>
<td>rs1136603</td>
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<tr>
<td>12</td>
<td></td>
<td></td>
<td>GA = 0.16</td>
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<tr>
<td></td>
<td>n. 4171 C &gt; G</td>
<td>3' UTR</td>
<td>AA = 0.02</td>
<td>rs1071738</td>
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<tr>
<td></td>
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<td>CC = 0.18</td>
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<td></td>
<td></td>
<td>CG = 0.39</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GG = 0.46</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SNP, single nucleotide polymorphism; UTR, untranslated region.

Discussion

Pancreatic cancer is a rapidly fatal disease and the fourth leading cause of cancer death in the United States (12). Therefore, considerable efforts under way to discover familial pancreatic cancer genes to help identify individuals at increased risk of developing the disease. Approximately 5% to 10% of pancreatic cancer patients report a family history of pancreatic cancer (13). Germ-line mutations in several genes including BRCA2, p16/CDKN2A, LKB1/STK11 and PARP inhibitors (26, 27).

In summary, DNA sequence analysis of the PALLD gene in familial pancreatic cancers did not identify any deleterious mutations that would support a role for PALLD as a familial pancreatic cancer susceptibility gene.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References


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