Contribution of polymorphism in codon 72 of TP53 gene to laryngeal cancer in Polish patients

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SUMMARY

The amino acid substitution Arg72Pro in the TP53 protein has an impact on the biochemical and biological activity of this protein, and is associated with several types of cancers. However, the Arg72Pro polymorphism exhibits inconsistent contribution as a risk factor in various cancer types. Therefore, using PCR-RFLPs, we investigated the distribution of Arg72Pro genotypes and alleles in patients with laryngeal cancer (n = 123) and controls (n = 300) in Poland. We observed that patients with the Pro/Pro and Arg/Pro TP53 genotypes displayed a 1.755-fold increased risk of laryngeal cancer (95% CI = 1.149–2.680, P = 0.0099). However, we did not find a significant increase in laryngeal cancer risk for the homozygous Pro/Pro TP53 genotype OR = 2.093 (95% CI = 1.046–4.192, P = 0.0530). This result suggests that the TP53Pro variant may contribute to the risk of laryngeal cancer development in Polish patients.

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Introduction

Cancers of the upper respiratory and digestive tracts have a particularly high incidence in Eastern Europe. The exact aetiology and the mechanisms of progression of these malignant disorders are still unclear. Laryngeal cancer develops most often in middle-aged or older men. It has been reported that smoking and alcohol consumption are major risk factors for developing this type of cancer.

Susceptibility to laryngeal cancer also depends on genetic and epigenetic factors that may alter the expression of oncogenes, tumour suppressor genes, and genes encoding enzymes involved in carcinogen metabolism.

The TP53 gene is often mutated or exhibits variability of gene product expression in malignant cells. The TP53 protein plays an essential function in cell cycle regulation, DNA repair, maintenance of genomic integrity, and apoptosis. The wild-type TP53 gene displays polymorphism at codon 72 with a single nucleotide alteration that results in the substitution of proline for arginine (Arg72Pro). The Arg72Pro substitution is located in a proline-rich region of the TP53 protein, where the 72Pro amino acid is part of five PXXP motifs considered to be an Src homology 3 binding domain of SH3. This TP53 protein region is involved in TP53-mediated growth inhibition and apoptosis but has no effect on cell cycle arrest.

The amino acid substitution Arg72Pro in the TP53 protein has an impact on the biochemical and biological activity of this protein, and is associated with several types of cancers. Studies on the TP53 codon 72 polymorphism have been carried out in humans for cancers of the colon, brain, lung, prostate, oesophagus, head and neck, and have demonstrated its inconsistent contribution. Therefore, we investigated the distribution of Arg72Pro genotypes and alleles in patients with laryngeal cancer (n = 123) and controls (n = 300) in Poland.

Patients and methods

Patients and controls

The patient group was composed of 123 patients (men only) with histologically confirmed squamous cell carcinoma of the larynx treated between April 1999 and May 2001 in the Clinic of Otolaryngology and Laryngological Oncology, Poznań University of Medical Sciences in Poznań, Poland (Table 1). The control group consisted of 300 unrelated healthy blood donors (men only) selected randomly and matched by age to patients (Table 1). All subjects were Caucasian and from the same region of Poland. The protocol of the study was approved by the Local Ethical Committee.
The Odds ratio was calculated for patients. Values (95% CI) were calculated. A p and controls. Moreover, the Odds Ratio and 95% Confidence Interval from HWE. The Fisher’s exact test was applied to examine differences in genotypic and allelic distribution between patients and controls, and reached 34% and 24% in these groups, respectively (Table 2). We observed that patients with the Pro/Pro and Arg/Pro TP53 genotypes displayed a 1.755-fold increased risk of laryngeal cancer (95% CI = 1.149–2.680, P = 0.0099). However, we did not find a significant risk for the homozygous Pro/Pro TP53 genotype OR = 2.093 (95% CI = 1.046–4.192, P = 0.0530) (Table 2). We did not observe a significant association between clinical characteristics of laryngeal cancer patients and prevalence of alleles or genotypes for Arg72Pro TP53 polymorphism.

Discussion

Completion of the human genome project has revealed more than ten million single nucleotide polymorphisms, however, the significance of most of them in health and disease states is still elusive. The TP53 gene is located at 17p13.1 and approximately 50% of human tumours carry somatic mutations in this gene.40 The TP53 tumour suppressor protein reacts to DNA-damage and/or acts as a cell cycle checkpoint failsafe resulting in anti-proliferative responses. The TP53 protein is able to initiate apoptosis, and disruption of this pathway can initiate tumour progression and therapy resistance.11

To date it has been reported that the TP53 Pro/Pro genotype or presence of the TP53Pro allele is a potential risk factor for cancers of the lung, oesophagus, stomach, breast, nasopharynx, urothelium, prostate, liver, and colon.22–34 However, in other populations, the TP53 Arg/Arg genotype or TP53Arg allele have been determined to be risk factors in cancers of the cervix, colon, breast, and larynx.35–38 Other studies have failed to confirm associations of Arg72Pro TP53 polymorphism with cancer incidence.41–44

Our data suggest that the TP53Pro allele contributes to the risk of laryngeal cancer in Polish patients. An oncogenic potential for laryngeal cancer with respect to the investigated polymorphism was observed by Gottschlich et al. who found that the Pro72Pro TP53 genotypes display a 1.755-fold increased risk of laryngeal cancer (95% CI = 1.149–2.680, P = 0.0099). However, we did not find a significant risk for the homozygous Pro/Pro TP53 genotype OR = 2.093 (95% CI = 1.046–4.192, P = 0.0530) (Table 2). We did not observe a significant association between clinical characteristics of laryngeal cancer patients and prevalence of alleles or genotypes for Arg72Pro TP53 polymorphism.


distribution of genotypes in all groups was tested for deviation from HWE. The Fisher’s exact test was applied to examine differences in genotypic and allelic distribution between patients and controls. Moreover, the Odds Ratio and 95% Confidence Intervals (95% CI) were calculated. A p value <0.05 was considered statistically significant.

Statistical analysis

The distribution of genotypes in all groups was tested for deviation from HWE. The Fisher’s exact test was applied to examine differences in genotypic and allelic distribution between patients and controls. Moreover, the Odds Ratio and 95% Confidence Intervals (95% CI) were calculated. A p value <0.05 was considered statistically significant.

Table 2

Association of the TP53 codon 72 polymorphism in patients and controls.

<table>
<thead>
<tr>
<th>n</th>
<th>Genotype distribution absolute number (frequency %)</th>
<th>Allele distribution absolute number (frequency %)</th>
<th>Odds ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53 Arg72Pro</td>
<td>Arg/Arg</td>
<td>Arg/Pro</td>
<td>Pro/Pro</td>
<td>Arg</td>
</tr>
<tr>
<td>Total 456 (82)</td>
<td>176 (59)</td>
<td>104 (53)</td>
<td>20 (42)</td>
<td>456 (76)</td>
</tr>
<tr>
<td>Cancer 162 (36)</td>
<td>123 (59)</td>
<td>76 (53)</td>
<td>16 (48)</td>
<td>123 (76)</td>
</tr>
</tbody>
</table>

The Odds ratio was calculated for patients.

a Homozygous carrying risk allele vs homozygous or heterozygous.
b Homozygous or heterozygous carrying risk allele vs homozygous.
c Fisher exact test.
The differences of impact of the Arg72Pro TP53 gene polymorphism on laryngeal and other cancers may be due to genetic heterogeneity, which may complicate the exploration of complex multigenic diseases. Various environmental factors, diet, tobacco, and alcohol intake, combined with genetic heterogeneity may also influence the Arg72Pro polymorphism's contribution to laryngeal cancer.

There are a number of distinctions between the Arg72Pro variants in their ability to bind elements to the transcriptional complex, transcription initiation, apoptosis induction, and the malignant transformation inhibition of primary cells. It has been reported that the Arg72 allele in homozygotes exhibits a 15-fold higher apoptosis-inducing ability than the Pro72 allele. However, the TP53Pro variant results in more cells arresting in the G1 cell cycle phase than does the TP53Arg protein variant. It has been suggested that the lower apoptosis-inducing properties of the TP53Pro protein variant may be due, in part, to its decreased mitochondrial allocation, which would result in decreased availability of the TP53 protein for interaction with the pro-apoptotic BAK protein. Moreover, the Arg form of TP53 was more susceptible to binding the HPV-E6 oncoprotein and subsequent degradation than the Pro form. This mechanism partially explains the possible contribution of the TP53Arg form to laryngeal or cervical malignancies associated with HPV infection, as reported by some investigators. However, our observations suggest that the TP53Pro protein variant may support laryngeal cancer development in Polish patients because of its decreased ability to induce apoptosis.

Therefore, to more precisely establish the contribution of the Arg72Pro polymorphism to laryngeal cancer incidence, further examination of the prevalence of these variants in other populations is required.

**Conflict of interest statement**

None declared.

**Acknowledgement**

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**References**

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