Role of *PTPRJ* genotype in papillary thyroid carcinoma risk

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Abstract

The strong genetic predisposition to papillary thyroid carcinoma (PTC) might be due to a combination of low-penetrance susceptibility variants. Thus, the research into gene variants involved in the increase of susceptibility to PTC is a relevant field of investigation. The gene coding for the receptor-type tyrosine phosphatase *PTPRJ* has been proposed as a cancer susceptibility gene, and its role as a tumor suppressor gene is well established in thyroid carcinogenesis. In this study, we want to ascertain the role of *PTPRJ* genotype in the risk for PTC. We performed a case–control study in which we determined the *PTPRJ* genotype for the non-synonymous Gln276Pro and Asp872Glu polymorphisms by PCR amplification and sequencing. We calculated allele and genotype frequencies for the considered polymorphisms of *PTPRJ* in a total sample of 299 cases (PTC patients) and 339 controls (healthy subjects) selected from Caucasian populations. We observed a significantly higher frequency of homozygotes for the Asp872 allele in the group of PTC patients than in the control group (odds ratio = 1.61, 95% confidence interval 1.15–2.25, $P = 0.0053$). We observed a non-significant increased frequency of homozygotes for Gln276Pro polymorphism in PTC cases in two distinct Caucasian populations. Therefore, the results reported here show that the homozygous genotype for Asp872 of *PTPRJ* is associated with an increased risk to develop PTC.

Endocrine-Related Cancer (2010) 17 1001–1006

Introduction

Papillary thyroid carcinoma (PTC), a differentiated tumor arising from the follicular cells of thyroid, is the most frequent type of thyroid cancer. Although a major risk factor for PTC is the exposure to ionizing radiations (Nagataki & Nyström 2002), clear evidence of genetically inherited predisposition has also been ascertained for this tumor type (Czene *et al.* 2002).

A relevant part of the genetic predisposition of PTC is supposed to be due to low-penetrance variants in multiple cancer susceptibility genes (Adadj *et al.* 2009), but still a limited number of such variants have been clearly associated with the PTC genetic predisposition (Jazdzewski *et al.* 2008, Gudmundsson *et al.* 2009). Thus, the research of thyroid cancer susceptibility genes is a paramount issue in the

definition of the genetic component that contributes to the generation of PTC.

Mouse models are useful tools to detect cancer susceptibility genes through the positional mapping of loci associated with tumor predisposition (Demant 2003). These studies are performed by crossing mouse strains with different susceptibility to a certain type of cancer. In a study carried out to find *loci* associated with susceptibility to colon cancer in mice, the *Ptprj* gene, coding for a receptor-type tyrosine phosphatase, was found as the sole gene contained in the susceptibility colon cancer 1 (*Sccl*) locus (Ruivenkamp et al. 2002). In both mouse and human *PTPRJ* genes, there are polymorphisms that somehow could influence the gene product function. Attempts were carried out to establish a role for the human gene in the susceptibility to breast and colon cancer (Lesueur et al. 2005, Toland et al. 2008). However, no unequivocal results were obtained.

We have previously established the role of *PTPRJ* as a tumor suppressor gene in thyroid carcinogenesis. Indeed, the expression of *PTPRJ* protein is generally decreased in thyroid tumors (Trapasso et al. 2000), and loss of heterozygosity at *PTPRJ* locus is detected in 38% of the anaplastic thyroid carcinomas (Iuliano et al. 2004). Moreover, *PTPRJ* overexpression decreases the proliferation rate, suppresses the malignancy of rat and human thyroid cell lines (Trapasso et al. 2000, Iuliano et al. 2003), and it is able to dephosphorylate the product of *RET* (Iervolino et al. 2006) which is rearranged in about 20% of PTCs (Santoro et al. 1995).

In a previous study, we hypothesized a role for the Asp variant of the Asp872Glu *PTPRJ* polymorphism in the susceptibility to thyroid tumors (Iuliano et al. 2004), whereas other authors (Ruivenkamp et al. 2002) proposed the Pro allele of Gln256Pro *PTPRJ* polymorphism as important in the cancer predisposition.

Here, we report a case-control study of a clinically homogeneous panel of cases, derived from a type of thyroid tumor (PTC) that has a well-established genetic component. We determined the allele frequencies of the non-synonymous Asp872Glu and Gln256Pro polymorphisms of *PTPRJ*, obtaining results that show a possible role of the Asp872Glu polymorphism in the susceptibility of PTC.

Materials and methods

Subjects and DNA extraction

A total of 299 cases of patients with PTC and 339 healthy controls were eligible for this study. All the cases and controls are Caucasians and came from Europe. Among them, there was a group of subjects

from Finland (84 cases and 96 controls), while the other subjects were from France and Italy. Diagnosis of PTC was established by an expert pathologist with the analysis of hematoxylin-eosin-stained slides. Normal human thyroid tissues adjacent to PTC tumors were obtained from surgical specimens and immediately frozen in liquid nitrogen or fixed. Thyroid tissues were collected at the Laboratoire d'Histologie et de Cytologie, Centre Hospitalier (Lyon Sud, France) and the Laboratoire d'Anatomie Pathologique, Hospital de L'Antiquaille (Lyon, France).

Written informed consent was obtained from all participants. The study protocol was approved by the ethics committees of the Centre Hospitalier Lyon Sud and the University Federico II, Napoli, and conducted in accordance with the principles of the Declaration of Helsinki as revised in 2000. DNA was extracted from normal thyroid tissues of cancer patients and from blood samples of control subjects by a commercial kit (Promega).

Genotyping

Determination of *PTPRJ* genotype was performed by PCR and subsequent sequence analysis of PCR products with the same protocol precisely described in a previous study (Iuliano et al. 2004). PCR was performed with specific oligonucleotides for amplification of exon 5 and exon 13 of *PTPRJ*, where A1176C (SNP ID: rs1566734) and C2965G (SNP ID: rs4752904) polymorphisms of *PTPRJ* are located. These polymorphisms result in the non-synonymous Gln276Pro and Asp872Glu variations. In some cases, the analysis of both polymorphisms was not possible because the quantity of DNA was not sufficient.

Statistical analysis

To test the deviation from Hardy-Weinberg equilibrium in the genotype distributions of the control populations, χ^2 and Freeman-Halton (an extension of Fisher exact test for 3×2 contingency tables) tests were used, depending on which was more appropriate.

Allele and genotype frequencies in cases and controls were compared by χ^2 , Fisher, and Freeman-Halton tests. A *P* value of 0.05 was considered statistically significant.

Estimation of relative risk was done calculating odds ratio (OR) with the corresponding 95% confidence interval (CI) by using multiple logistic regression.

Linkage disequilibrium values and genotype data about the *PTPRJ* polymorphisms analyzed were obtained from the public database of the International HapMap project (www.hapmap.org).

Results

Analysis of Gln276Pro polymorphism

To examine the role of *PTPRJ* in the susceptibility to PTC, we analyzed the non-synonymous Gln276Pro and Asp872Glu polymorphisms. To investigate the Gln276Pro polymorphism, we first analyzed the sequence of exon 5 of *PTPRJ* in 156 patients with PTC and in 299 healthy subjects. However, in this analysis, the frequency of 276Pro allele observed in the subgroup of 96 Finnish healthy individuals (15/192, 0.08) was significantly lower than that found in the group of other Caucasian control subjects (98/406, 0.24; $\chi^2=22.375$, $P=2.2 \times 10^{-6}$). Consequently, in the subsequent analyses, we considered separately the Finnish group from other Caucasians in order to eliminate any source of bias. We found a frequency for the 276Pro allele of 0.12 (15/122) in the group of PTC patients from Finland and of 0.21 (39/190) in the group of other Caucasian patients. The differences between these frequencies and those of their respective control groups were not statistically significant ($\chi^2=1.753$, $P=0.19$ in Finnish population; $\chi^2=0.954$, $P=0.33$ in other Caucasians). The distributions of *PTPRJ* genotype frequencies for the Gln276Pro polymorphism in the groups of patients and controls analyzed are shown in Table 1. Genotype frequencies in the control groups were in Hardy–Weinberg equilibrium ($P=0.84$ for Finnish Caucasians and $P=0.97$ for other Caucasians, Freeman–Halton test, and χ^2 test respectively), and genotype distributions between PTC cases and controls of the two populations were not significantly different ($P=0.20$ for Finnish Caucasians and $P=0.16$ for other Caucasians, Freeman–Halton test, and χ^2 test respectively). However, we observed a higher non-significant frequency of 276Pro homozygotes in the group of PTC sporadic cases than in the control group in both populations considered (Finnish Caucasians: 3.3 vs 0%, $P=0.15$, Fisher's test; non-Finnish Caucasians: 7.4 vs 5.4%, $P=0.51$, χ^2 test).

Table 1 Genotype distribution of Gln276Pro. No significant results were obtained applying recessive or overdominant models

	Gln/Gln (n (%))	Gln/Pro (n (%))	Pro/Pro (n (%))
Finnish Caucasians			
Controls (n=96)	81 (84.4)	15 (15.6)	0 (0)
PTC patients (n=61)	48 (78.7)	11 (18.0)	2 (3.3)
Non-Finnish Caucasians			
Controls (n=203)	116 (57.1)	76 (37.4)	11 (5.4)
PTC patients (n=95)	63 (66.3)	25 (26.3)	7 (7.4)

Analysis of Asp872Glu polymorphism

We first performed the analysis of Asp872Glu polymorphism by sequencing of exon 13 of *PTPRJ* in the same groups of cases and controls investigated for the Gln276Pro polymorphism. In this case, we found a non-significant difference in the distribution of genotypic frequencies of control subjects between Finnish Caucasians and other Caucasians ($\chi^2=4.631$, $P=0.099$) and after pooling the two Caucasian populations a significant difference between PTC sporadic cases and controls ($\chi^2=8.104$, $P=0.017$). Thus, for the study of Asp872Glu polymorphism, we decided to expand the groups analyzed, adding more cases and controls.

We finally analyzed *PTPRJ* Asp872Glu polymorphism in a panel of 299 Caucasian PTC patients and in a control group of 339 Caucasian subjects. We found a frequency for the Asp allele of 0.589 (352/598) in the group of PTC cases and 0.538 (365/678) in the control group. This difference was not statistically significant ($\chi^2=3.263$, $P=0.07$).

The distribution of genotype frequencies for Asp872Glu polymorphism in the samples analyzed is shown in Table 2. The frequencies in the control group did not show significant deviation from those expected under Hardy–Weinberg equilibrium ($\chi^2=1.872$, $P=0.39$) and did not differ significantly ($\chi^2=2.701$, $P=0.26$) from those found in a sample of 60 subjects taken from a Caucasian population (ss48421211, HapMap Project: www.hapmap.org). Genotype distributions between PTC cases and controls were significantly different ($\chi^2=8.971$, $P=0.011$). We observed a significantly higher frequency of homozygotes for the Asp872 allele in the sample of PTC patients than in the control group ($\chi^2=7.778$, $P=0.0053$). A recessive model in which the Asp872 allele was responsible for the susceptibility to PTC (OR=1.61, 95% CI 1.15–2.25) could account for this difference, while a dominant model for the Asp872 allele of increased susceptibility to PTC was unlikely because it did not reach statistical significance ($\chi^2=0.007$, $P=0.93$; OR=1.02, 95% CI 0.69–1.50). However, we also found a significantly higher frequency of Asp872Glu heterozygotes in the control group than that of PTC patients ($\chi^2=7.124$, $P=0.0076$). Therefore, the genotype distribution was also compatible with an overdominant model in which heterozygous carriers had a reduced risk (OR=0.65, 95% CI 0.48–0.89) to get PTC compared with subjects homozygous for whichever allele.

Table 2 Genotype distribution of Asp872Glu. Significant results were obtained applying different models in the comparisons between papillary thyroid carcinoma (PTC) and controls

	Asp/Asp (n (%))	Asp/Glu (n (%))	Glu/Glu (n (%))
Controls (n=339)	92 (27.1)	181 (53.4)	66 (19.5)
PTC patients (n=299)	112 (37.5)	128 (42.8)	59 (19.7)

Recessive model: Asp/Asp versus Asp/Glu plus Glu/Glu; OR=1.61, 95% CI 1.15–2.25, *P*=0.0053. Overdominant model: Asp/Glu versus Asp/Asp plus Glu/Glu; OR=0.65, 95% CI 0.48–0.89, *P*=0.0076.

Discussion

In this study, we investigated the role of non-synonymous *PTPRJ* polymorphisms in cancer risk for PTCs. The possibility of a role of *PTPRJ* in the susceptibility of PTC is supported by the previous demonstration that the encoded tyrosine phosphatase can affect the oncogenic activity of mutated/rearranged forms of RET (Iervolino et al. 2006).

We studied the polymorphisms of Asp872Glu and Gln276Pro in Caucasians. Other non-synonymous polymorphisms are present in *PTPRJ*, but they are not polymorphic in Caucasian populations (Lesueur et al. 2005; www.hapmap.org) or, in the case of Arg326Gln, in complete linkage disequilibrium with Gln276Pro (Iuliano et al. 2004, Lesueur et al. 2005; www.hapmap.org).

We found a significant association between the homozygous genotype for the 872Asp allele and the susceptibility to PTC. Since the statistical significance of this association was not very strong, the possibility of a type I error cannot be discarded. In addition, we detected a significant excess of heterozygotes for the Asp872Glu polymorphism in the control group, compatible with overdominance at this locus.

Although the hypothesis of overdominance cannot be completely rejected, we believe that in our case, the excess of heterozygotes found for the Asp872Glu polymorphism in the control group can be explained by the model formulated by Lipsitch et al. (2003). This model accounts for an excess of heterozygotes in a population generated by the high frequency of a susceptibility allele with the assumption that the susceptibility caused by the disease predisposing allele is not very strong.

There is no evidence about the functional relevance of the Asp872Glu variation, except that the Asp872Glu polymorphism is located in the eighth fibronectin type III domain of the extracellular region of PTPRJ, a domain important for the correct localization of this receptor-type tyrosine phosphatase

(Iuliano et al. 2009). Another possibility, which is not experimentally explored yet, is that the nucleotide change affects the process of splicing, since it modifies a sequence potentially targeted by splicing factors.

While the genotype distributions in the Caucasian populations are quite homogenous for the Asp872Glu polymorphism, this is not true for the Gln276Pro polymorphism. We found significant differences between Finnish and non-Finnish Caucasian populations. This observation is supported by the fact that in two previous studies, the allelic frequencies of the polymorphism rs1503185 (SNP ID of Arg326Gln polymorphism), which is in complete linkage disequilibrium with Gln276Pro, resulted different in distinct Caucasian populations (Lesueur et al. 2005, Toland et al. 2008). We did not detect any significant difference between cases and controls for this polymorphism, but we found an increase of homozygotes for the 276Pro allele in both groups of PTC patients studied compared with their relative control groups. The inability to detect significant results, in this case, could be due to insufficient power of our study. In fact, in the non-Finnish Caucasian population, the power of our study to detect an OR equal to 2 and 3 for the homozygotes for 276Pro allele is 34 and 73% respectively. However, a significant association between the 276Pro variant and cancer was not observed in a thyroid study (Powell et al. 2004) and in two different colorectal studies (van Puijenbroek et al. 2005, Toland et al. 2008), even though, also in colon cancer, there is genetic and functional evidence of a role of *PTPRJ* as a tumor suppressor gene (Ruivenkamp et al. 2002, Balavenkatraman et al. 2006, Luo et al. 2006). Conversely, in a Japanese population, the variant 276Pro was associated with an increased risk of various kinds of tumors, indicating that this polymorphism of *PTPRJ* could be important in the determination of cancer risk in non-Caucasian populations (Mita et al. 2010).

The differences between the results obtained for the Gln276Pro and the Asp872Glu polymorphisms can be explained by the fact that linkage disequilibrium between the two loci is not complete.

Discrepancies among studies of *PTPRJ* susceptibility to tumors could be due to the different types of tumors analyzed. In our opinion, *PTPRJ* involvement in genetic susceptibility to cancer is possible in different tumor types with different modalities. In this context, it is noteworthy that in a genome-wide analysis, a susceptibility locus for chronic lymphocytic leukemia was identified in the 11p11 chromosomal region (Sellick et al. 2005), where the *PTPRJ* gene is located.

In conclusion, homozygous genotype of *PTPRJ* Asp872 variant is associated with an increased risk to develop PTC, and *PTPRJ* involvement in susceptibility to human cancer deserves further analyses.

Declaration of interest

The authors declare that there is no conflict of interest that would prejudice the impartiality of the research reported.

Funding

This work was supported by a grant from the Associazione Italiana Ricerca sul Cancro (AIRC).

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