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Original Article

Significant relationship of combined ACP_1/PTPN22 genotype variants with the growth of uterine leiomyomas

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ABSTRACT

Objective: To analyze the interaction between ACP_1 and PTPN22 concerning their effects on the growth of the tumor. In previous paper we have shown (i) that ACP_1*B/*B genotype of ACP_1 is negatively associated with the growth of leiomyomas and (ii) that there is a negative association of *C/*C genotype of PTPN22 with tumor growth.

Materials and methods: Two hundred and three White women from the population of Rome with symptomatic leiomyomas were recruited in the University of Rome Tor Vergata. All subjects gave consent for the participation in the study that was approved by the Council of Department. ACP_1 and PTPN22 genotypes were determined by DNA analysis.

Results: The proportion of women with small leiomyomas decreases with the decrease of the number of protective factors and it is 37.2% in women carrying the joint genotype ACP_1*B/*B-PTPN22 *C/*C (two protective factors) and 0% in women carrying no protective factors. Three way contingency table analysis by a log linear model has shown no evidence of epistatic interaction between the two genetic systems but a highly significant cooperative effect on the dimension of leiomyomas. There is a highly significant negative correlation between the number of protective factors and the dimension of leiomyomas with a minimum (cm 4.74) in women carrying the joint genotype ACP_1*B/B-PTPN22 *C/*C and a maximum (cm 7.25) in women carrying no protective factors.

Conclusion: The present study suggests a cooperative interaction between ACP_1 and PTPN22 concerning their effects on the growth of uterine leiomyomas. The determination of the genotype of the two systems may help to evaluate the risk of clinical manifestations of this common benign tumor.

Introduction

Uterine leiomyoma is a benign neoplasm composed of smooth muscle and connective tissue resulting from somatic mutation of one single neoplastic cell. The neoplasm is very common and become “clinically apparent” in about 30% of women. Age, ethnicity, multiparity, obesity are predisposing factors; estrogens and growth factors have also an important role [1].

The Acid Phosphatase locus 1 encoding a cytosolic Low Molecular Weight Protein Tyrosine Phosphatase (cLMWPTP) has three codominant alleles *A,*B,*C and six genotypes. The enzyme is present in all the tissues and it is composed by two isoforms called fast (f) and slow (s). ACP1 is able to dephosphorylate Platelet Derived Grow Factor Receptors [2,3].

PDGF is involved in the development of leiomyomas and we have reported [4] that ACP1*B/*B genotype that shows a high f isoform concentration and it is able to dephosphorylate PDGF receptors is negatively associated with the growth of leiomyomas [5].

PTPN22 (Protein Tyrosine Phosphatase Non Receptor Type 22) encodes for Lyp, a lymphoid specific phosphatase that has a key role in the regulation of T cell receptor signaling. The W620 variant (*T allele) is associated with immune disorders [6]. This variant is probably a gain of function [7] and the number of T regs shows an inverse relationship with the level of Lyp [7].

Wegienka [8] has put forward the hypothesis of a chronically inflammatory origin of this tumor in which a central role is played by the depression of regulatory T cell (T reg) important for the inhibition of inflammation and maintenance of self tolerance. We have recently reported a positive association of *C/*T genotype of PTPN22 with tumor growth in young women [9]. The *T allele that

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Table 1
f and s isoform concentrations in relation to ACP_1 genotype.

Total quantity of f (μg/ml RBC)		Total quantity of s (μg/ml RBC)	
*B/*B	16.4	*C/*C	20.6
*A/*B	12.0	*A/*C	12.7
*B/*C	11.3	*B/*C	12.1
*A/*A	7.9	*B/*B	3.9
*A/*C	7.5	*A/*B	3.4
*C/*C	5.7	*A/*A	3.3

The quantities of enzyme are given per ml of packed red cells.

encodes W620 PTPN22 variant increasing the inhibition of TCR signaling could affect the function of regulatory T cell [6–10].

Our observation on PTPN22 supports the hypothesis of Wegienka; therefore it seems that at least two different mechanisms contribute to the growth of leiomyomas and to their clinically manifestation. The hypothesis of different mechanism is also supported by the observation that the association of leiomyomas dimension with PTPN22 is dependent on the age of women, while the association between leiomyomas dimension and ACP_1 does not show significant difference in relation to women age.

In the present paper we have analyzed the interaction between ACP_1 and PTPN22 concerning their effects on the growth of the tumor.

Material and methods

Two hundred and three White women from the population of Rome with symptomatic leiomyomas were recruited in the University Hospital of Rome Tor Vergata. Leiomyomas cases were enrolled following pathological diagnosis performed on hysterectomy or myomectomy surgical specimen. All subjects gave consent for the participation to the study that was approved by the Council of Department.

ACP_1 and PTPN22 genotypes were determined by DNA analysis as previously described [5,9]. ACP_1 shows six genotypes with activity decreasing in the order *C/*C>*C/*B>*C/*A ≥*B/*B >*B/*A>*A/*A. The proportion of f and s isoforms for each genotype is shown in Table 1. PTPN22 polymorphism has two alleles: *C1858 (encoding the R620 variant), simply called *C and *T1858 (encoding the W620 variant) simply called *T and has three genotypes, CC, CT and TT. The TT genotype is very rare.

The main diameter of tumors was considered for the comparison between the joint ACP_1/PTPN22 genotypes. Two hundred and three leiomyomas were examined.

Chi-square of independence, correlation analysis and variance analysis for difference between means were carried out using SPSS programs [11]. Three way contingency table analyses was performed by a log-linear model [12].

Eta (η) is a measure of the strength of the relationship between two variables. Eta squared (η^2) indicates the proportion of variance of the dependent variable explained by the independent variable.

Results

Table 2 shows the relationship between the dimension of leiomyomas in quartiles and the number of protective factors. The proportion of women with small leiomyomas decreases with the decrease of the number of protective factors and it is 37.2% in women carrying the joint genotype ACP_1*B/*B-PTPN22 *C/*C (two protective factors) and 0% in women carrying no protective factors (Fig. 1). Conversely the proportion of women with large leiomyomas increases with the decrease of the number of protective factors and it is 24.4% in women carrying the joint ACP_1 *B/*B- PTPN22 *C/*C and 37.2% in women carrying no protective factors. Three way contingency table analysis by a log linear model has shown no evidence of epistatic interaction between the two genetic systems concerning their effects on leiomyomas dimension but a highly significant cooperative effect of LYP and ACP_1 on the dimension of leiomyomas. The effect of ACP1, however, is much more marked as compared to the effect of LYP.

Table 2
The relationship between the dimension of leiomyomas in quartiles and the number of protective factors (ACP_1*B/*B and *C/*C genotype of PTPN22).

Number of factors	Joint ACP_1-PTPN22 genotype	Quartile of leiomyomas dimension			Total n°
		1st Q	2nd Q and 3rd Q	4th Q	
2	ACP_1*B/*B PTPN22 *C/*C	37.2%	38.5%	24.4%	78
1	ACP_1*B/*B PTPN22 *T carrier	14.3%	57.1%	28.6%	7
1	Other ACP_1 genotypes PTPN22 *C/*C	15.7%	51.0%	33.3%	102
0	Other ACP_1 genotypes PTPN22 *T carrier	0.0%	62.5%	37.5%	16

Chi square test of independence p = 0.008.
Correlation with the number of protective factors p = 0.001.
Three way contingency table analysis by a log linear model: Interaction between ACP_1-PTPN22 on leiomyomas quartile p = 0.600. Independence of quartile from ACP_1 and PTPN22 p = 0.002.
There is a correlation between the number of factors and the dimension of leiomyomas measured in quartiles. The smaller leiomyomas (1st quartile) are more represented in presence of two protective factors and viceversa the greatest leiomyomas (4th quartile) are more represented in absence of protective factors.

Table 3 shows the mean dimension of leiomyomas in centimeters of the main diameter in relation to the number of protective factors (ACP_1 *B/*B and PTPN22 °C/°C genotypes). There is a highly significant negative correlation between the number of protective factors and dimension of leiomyomas with a minimum (cm 4.74) in women carrying the joint genotype ACP_1*B/B-PTPN22 *C/*C and a maximum (cm 7.25) in women carrying no protective factors.

The correlation between the number of protective factors and the dimension of leiomyomas is stronger in women aging less than 36 years ($\eta^2 = 0.295$) than in older women ($\eta^2 = 0.049$).

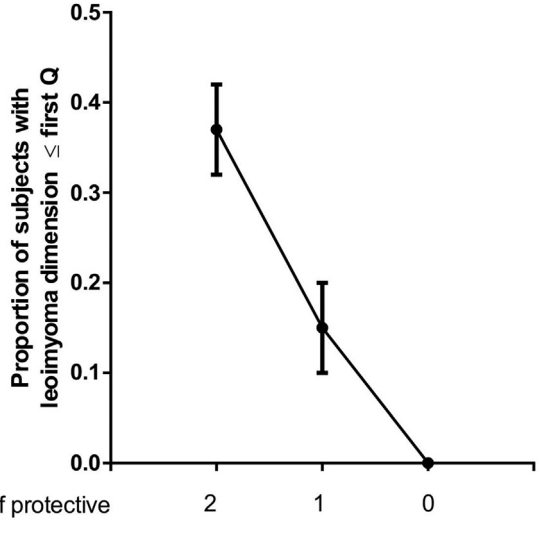

Fig. 1. The relationship between the proportion of subjects showing the dimension of leiomyomas ≤ first quartile and the number of protective factors (ACP_1*B/*B and PTPN22 *C/*C).

Table 3
Mean dimension of leiomyomas in centimeters of the main diameter in relation to number of protective factors (ACP1 *B/*B and PTPN22 *C/*C genotypes).

Number of protective factors	Joint ACP1-PTPN22 genotype	Dimension of leiomyoma (cm)		
		Mean	S.E.	Total n°
2	ACP_1*B/*B PTPN22 *C/*C	4.74	0.266	78
1	ACP_1*B/*B PTPN22 *T carrier	5.43	0.972	7
1	Other ACP_1 genotypes PTPN22 *C/*C	5.86	0.248	102
0	Other ACP_1 genotypes PTPN22 *T carrier	7.25	0.844	16

Significance of difference between groups $p = 0.001$.
Correlation with the number of protective factors $p = 0.000$.
The significance of difference has been calculated by variance analysis.

Discussion

Our analysis supports the hypothesis of independent mechanism of action of ACP_1 and PTPN22 concerning their effects on the growth of leiomyomas. It is likely that PTPN22 acts through immune mechanism while ACP_1 through a metabolic mechanism involving PDGF. However the possibility of an action of ACP_1 through immunological mechanism due to its influence on ZAP 70 tyrosine kinase activity cannot be excluded at present [13]. Further studies would clarify the mechanism of action.

It is interesting to note that in females aging less than 36 years the combination of the two genetic factors explains about 30% of leiomyomas dimension variance pointing to an important role of these factors in the growth of leiomyomas.

From a practical point of view, the determination of the genotypes of the two systems may help to evaluate the risk of severe clinical manifestations of this common benign tumor.

Conflict of interest

None.

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