

## The Association of Symptomatic uterine Leiomyomas With P53 Codon 72 Polymorphism: A Confirmation Study in the Italian Population

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### ABSTRACT

**AIM:** To confirm the excess of \*Pro/\*Pro genotype of p53 codon 72 polymorphism in uterine leiomyomas as compared to controls observed in the population of Freiburg.

**METHODS:** 205 women admitted to the Hospital for leiomyomas requiring surgical intervention and 258 controls were studied in the population of Rome. p53 codon 72 genotype was determined by DNA analysis.

**RESULTS:** An excess of \*Pro/\*Pro genotype (21.9%) in women with leiomyomas as compared to controls (7.4%) is observed in Rome: such association is identical to that observed in Freiburg.

**CONCLUSION:** The present study confirms the association between p53 codon 72 with uterine leiomyomas reported in the population of Freiburg. Determination of the genotype of this system could help to identify women with high risk of severe clinical manifestation of uterine leiomyomas.

**Key words:** p53 codon 72; Leiomyomas; Genetic polymorphism

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### INTRODUCTION

An increase of \*Pro/\*Pro genotype of p53 codon 72 in uterine leiomyomas compared to controls has been observed by Denschlag et al in Freiburg population<sup>[1]</sup>. In the present note we report our observations in a sample of women from the population of Rome admitted to Hospital with diagnosis of leiomyomas requiring surgical intervention. Comparison between Roma and Freiburg samples is reported: in particular the deviation of observed p53 codon 72 genotype frequencies from Hardy-Weinberg (HW) expectation has been analyzed.

The genetic polymorphism of p53 codon 72 results in the inclusion of arginine or proline in the amino acid sequence of the protein. This has relevant effects on the function of p53: arginine variant is a stronger apoptosis inducer while proline variant is a stronger transcription activator<sup>[2]</sup>.

### MATERIALS AND METHODS

We have studied prospectively 205 women with leiomyomas requiring surgical intervention and 258 women of comparable age without clinical manifestations of leiomyomas. In the control group no ultrasound or imaging procedures were performed. The mean age ( $\pm$  SD) of patients was 34.74 years ( $\pm$  6.46). The proportion of patients who had at least one newborn was 28.6%. 15.5% women showed a minimal-mild lesion and 84.5% a moderate-severe lesion. All women were from the White population of Rome and had been considered also in previous studies<sup>[3,4]</sup>. Verbal informed consent was obtained by these patients to participate to the study that was approved by the Council of the Department. The collection of the data has been performed a few years ago before the establishment of the Ethical Committee. The p53 codon 72 genotype was determined by DNA analysis on blood samples as previously described<sup>[5]</sup>, Chi square test of independence was performed using SPSS programs<sup>[6]</sup>.

## RESULTS

Table 1 shows the distribution of p53 codon 72 genotypes in women with uterine leiomyomas and in controls. Compared to controls in women with leiomyomas there is a highly significant increase of the proportion of \*Pro/\*Pro genotype and a decrease of that of other genotypes. Odds Ratio is 3.538; 95% CI = 1.930-6.533 in the population of Rome, very similar to that observed in Freiburg (OR = 3.84).

In table 2 we have compared the observed with the expected frequencies of p53 codon 72 genotypes assuming H.W. equilibrium in the sample of Rome and in that of Freiburg. In the controls there is no difference between observed and expected proportions assuming H.W. equilibrium neither in Rome nor in Freiburg. In women with leiomyomas, on the contrary, both in Rome and in Freiburg there are significant differences between observed and expected proportions with a strong increase of observed \*Pro/\*Pro genotype compared to H.W. expected proportion.

In our sample of women with leiomyomas no statistical significant association has been observed between p53 codon 72 genotype and women age and number, dimension and localization of the tumor.

## DISCUSSION

The excess of \*Pro/\*Pro genotype in women with tumor observed in Freiburg is confirmed in the population of Rome. In both populations there is a statistically significant deviation from H.W. expectation women with leiomyomas but not in controls. This may suggest technical error in genotype determination. However, the similarity of the pattern in two independent studies makes unlike this possibility. It is likely that the higher proportion of \*Pro/\*Pro genotype with respect to H.W. expectation reflects a higher susceptibility of this genotype to severe clinical manifestations of the tumor.

Disturbance of the equilibrium between cell proliferation and apoptosis with a prevalence of the proliferation associated with \*Pro allele and a relative deficit of apoptosis activity associated with \*Arg variant could be responsible for a more aggressive tumor resulting in manifestations of clinical relevance.

**Table 1** Distribution of p53 codon 72 genotypes in women with leiomyomas and in controls.

	*Arg/*Arg	*Arg/*Pro	*Pro/*Pro	Total n*
Women with leiomyomas	48.3%	29.8%	21.9%	205
Control women	53.9%	38.8%	7.4%	258
Chi-square test of independence	$\chi^2$	df	p	
All genotypes	20.939	2	0.00003	
*Pro/*Pro vs other genotypes	19.200	1	0.00001	
Odds Ratio analysis	O.R.	3.538		
	95% C.I.	1.930-6.533		

**Table 2** Hardy-Weinberg equilibrium analysis. Comparison between the data of Rome and those of Freiburg.

	Women with leiomyomas							
	Rome				Freiburg			
	*Arg/*Arg	*Arg/*Pro	*Pro/*Pro	Total n°	*Arg/*Arg	*Arg/*Pro	*Pro/*Pro	Total n°
N° of genotypes observed	99	61	45	205	65	40	20	125
Expected n° assuming H.W. equilibrium and gene frequencies of women with leiomyomas	81.9	95.4	27.8	205.1	57.8	54.4	12.8	125
Expected n° assuming H.W. equilibrium and gene frequencies of controls	110.0	80.3	14.7	204.7	77.4	41.9	5.7	125
	Controls							
N° of genotypes observed	139	100	19	258	158	84	12	254
Expected n° assuming H.W. equilibrium	138.5	101.1	18.4	258	157.3	85.2	11.5	254

From practical point of view, the determination of p53 codon 72 genotype may allow the identification of women with high risk of severe clinical disturbances of uterine leiomyomas.

However since, in some studies no significant association between p53 codon 72 and leiomyomas has been found<sup>[7]</sup> further studies are necessary to draw firm conclusions. In particular it would be important to study the rate of tumor growth in relation to p53 codon 72 phenotype.

## COMPETING INTERESTS

The authors declare that they have no competing interests. Author's contribution: F. Gloria-Bottini: Project development, Data analysis, Manuscript writing; M. Ammendola: Data collection, Manuscript revision; A. Pietropolli: Data collection, Laboratory analysis; A. Neri: Project development, Manuscript revision, Data analysis; A. Magrini: Project development, Manuscript writing and revision; E. Bottini: Project development, Manuscript editing, Data analysis.

## REFERENCES

- Denschlag D, Bettendorf H, Watermann D, Keck C, Tempfer C, Pietrowski D. Polymorphism of the p53 tumor suppressor gene is associated with susceptibility to uterine leiomyoma. *Fertil Steril* 2005; **84**: 162-6.
- Matlashewski GJ, Tuck S, Pim D, Lamb P, Schneider J, Crawford LV. Primary structure polymorphism at amino acid residue 72 of human p53. *Mol Cell Biol*. 1987; **7**: 961-3.
- Ammendola ML, Pietropolli A, Lista F, Saccucci P, Piccione E, Bottini E, Gloria-Bottini F. Is there an association between uterine leiomyomas and acid phosphatase locus 1 polymorphism? *Am J Obstet Gynecol*. 2009; **200**: 110.e1-5. doi: 10.1016/j.ajog.2008.07.033
- Gloria-Bottini F, Pietropolli A, Ammendola M, Saccucci P, Bottini E. (PTPN22 and uterine leiomyomas. *Eur J Obstet Gynecol Reprod Biol*. 2015; **185**: 96-8. doi: 10.1016/j.ejogrb.2014.11.043.
- Ammendola M, Gloria-Bottini F, Sesti F, Piccione E, Bottini E. Association of p53 codon 72 polymorphism with endometriosis. *Fertil Steril*. 2008; **90**: 406-8
- SPSS/PC+ Version 5.0 Chicago, IL (1992)
- Yao-Yuan Hsieh-Chi-Chen ChangFuu-Jen TsaiCheng-Chieh LinLian-Shun YehChang-Hai Tsai. Tumor necrosis factor- $\alpha$ -308 promoter and p53 codon 72 gene polymorphisms in women with leiomyomas. *Fertil Steril* 2004; **1177**-1181.