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Letter to the Editor

Polymorphism of the extrapituitary prolactin promoter and systemic sclerosis

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Abstract:

Extrapituitary prolactin (PRL) production is regulated by the alternative promoter which contains functional single nucleotide polymorphism -1149 G/T (rs1341239). G allele of this SNP leads to higher mRNA PRL synthesis in lymphocytes. Polymyositis (PM) and systemic sclerosis (SSc) has been associated with increased serum PRL levels and lymphocytes of patients with SSc produce more PRL mRNA. In our association study we tested 75 patients with SSc, 115 patients with polymyositis/dermatomyositis and 123 healthy individuals for -1149 G/T SNP of the extrapituitary PRL promoter. PCR RFLP methodology for allele detection and χ^2 test with Bonferroni correction for statistical evaluation was used in this study. The genotype and allele distribution did not show any variances in groups of PM, DM

and SSc patients compared to healthy individuals. However, we found a significant inverse association between TT genotype in SSc patients with disease onset above 45 years compared to individuals with SSc and diseases onset prior 45 years (P corrected = 0.02; OR = 0.13; CI (95%): 0.02 - 0.69) and healthy subjects (P corrected=0.04; OR 0.2; CI (95%) 0.04-0.82). TT genotype of the -1149G/T SNP of the extrapituitary PRL promoter decreased a risk for SSc development in older age. Further investigation of the PRL role in SSc pathogenesis is necessary.

Sirs,

Increased serum prolactin (PRL) levels have been demonstrated in several autoimmune diseases including polymyositis (PM) and systemic sclerosis (SSc) (1, 2, 3). PRL is produced by the lactotrophs of the pituitary gland, but the immune cells can produce PRL as well, and PRL acts as a cytokine with role in B, T and dendritic cells maturation (1). Czuwara-Ladykowska et al. demonstrated higher PRL mRNA synthesis in lymphocytes from patients suffering from SSc than in healthy individuals (4). Multiple promoters regulate *PRL* gene transcription. Unlike the pituitary production controlled by the pituitary promoter under the influence of transcriptional factor Pit-1, the extrapituitary (including that by immune cells) PRL secretion is regulated by the Pit-1 independent alternative promoter located 5.840 bp distal to the start of the PRL transcriptional site (5). This extrapituitary promoter contains functional single nucleotide polymorphism (SNP) -1149 G/T (rs1341239) in the GATA sequence; G allele leads to higher PRL mRNA in lymphocytes synthesis (6). GG genotype has been associated with systemic lupus erythematosus (SLE) (6,7), while TT genotype was identified as protective for non-Hodgkin and follicular lymphoma and rheumatoid arthritis development (8,9).

In this study we looked for distribution of allele and genotype of the -1149 G/T SNP of the extrapituitary PRL promoter in 75 patients with SSc (average age 61.4), in 47 subjects with PM (average age 57.8) and in 68 DM patients (average age 58.3), and in 123 healthy Czech individuals (blood donors and medical students, average age 39.7). SSc and PM/DM patients met classification criteria for these illnesses (10,11). PCR-RFLP methodology was used for -1149G/T SNP detection (7). Briefly, we amplified 137 bp region of the PRL extrapituitary promoter and for restriction used ApoI endonuclease. We determined genotypes: the homozygote TT characterized by 120 bp + 17 bp, the homozygote GG by 85 bp + 35 bp + 17 bp, and the heterozygote GT by 120 bp + 85 bp + 35 bp + 17 bp DNA fragments. Results were evaluated by χ^2 test with Bonferroni correction. Control group was in Hardy-Weinberg equilibrium.

The genotype and allele distribution did not show any significant differences in groups of PM, DM and SSc patients compared to healthy individuals (Table I) and we detected neither gender distribution differences (data not shown) nor correlation with specific clinical or serological manifestation of these diseases (lung fibrosis, type of scleroderma, antiScl-70 and antiJo-1 positivity) (Table I). However, we found a significant inverse association between TT genotype in SSc patients with disease onset above 45 years compared to individuals with SSc and diseases onset prior 45 years ($2/47 = 4.1\%$ versus $6/18 = 25\%$,

respectively; P corrected = 0.02; OR = 0.13; CI (95%): 0.02 - 0.69). Similar results were obtained when compared TT genotype in patients with SSc onset after the age of 45 and healthy subjects (P corrected=0.04; OR 0.2; CI (95%) 0.04-0.82), see Table I.

Thus, genotype -1149 TT of the extrapituitary PRL promoter SNP (via reduced PRL promoter activity and consequently lower PRL levels in lymphocytes) seems to be associated with decreased risk to SSc development in older age. On the other hand, any genotype or allele differences in patients with polymyositis and dermatomyositis according to the age of manifestation onset were found (data not shown). We can assume that this polymorphism might be somewhat specific for SSc and therefore warrants further investigation of prolactin genetics and its levels during the disease course.

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Table I.

Genotype and allele distribution of the prolactin (<i>PRL</i>) extrapituitary promoter -1149 G/T SNP in the autoimmune diseases: Polymyositis (PM), Dermatomyositis (DM), Systemic Sclerosis (SSc) and healthy individuals (Controls)						
Characterization of tested groups		<i>PRL</i> extrapituitary promoter -1149 G/T SNP				
		Genotype			Allele	
		GG	GT	TT	G	T
PM	n=47	20	21			
	(%)	(42.5)	(44.7)	6 (12.8)	61 (64.9)	33 (35.1)
	P_1	ns	ns	ns	ns	ns
		37.5	56.3			
Jo-1 positive (34.0%)	% (P_2)	(ns)	(ns)	6.2 (ns)	65.6 (ns)	34.4 (ns)
CPM (4.3%)	% (P_2)	(ns)	(ns)	0 (ns)	75 (ns)	25 (ns)
DM	n=68	19	35			
	(%)	(27.9)	(51.5)	14 (20.6)	73 (53.7)	63 (46.3)
	P_1	ns	ns	ns	ns	ns
		15.5	46.1		38.5	61.5
Jo-1 positive (19.1%)	% (P_2)	(ns)	(ns)	38.4 (ns)	(0.03 ^a)	(0.03 ^b)
CDM (13.2%)	% (P_2)	(ns)	(ns)	22.2 (ns)	50 (ns)	50 (ns)
SSc	n=75	31	36			
	(%)	(41.3)	(48.0)	8 (10.7)	98 (65.3)	52 (34.7)
	P_1	ns	ns	ns	ns	ns
		51.5	42.4		72.7 (ns)	27.3 (ns)
Scl-70 positive (45.2%)	% (P_2)	(ns)	(ns)	6.1 (ns)	72.7 (ns)	27.3 (ns)
Lung Fibrosis (40.3%)	% (P_2)	(ns)	(ns)	6.9 (ns)	67.2 (ns)	32.8 (ns)
lSSc (54.6%)	% (P_2)	(ns)	(ns)	4.9 (0.03)	70.7 (ns)	29.3 (ns)
dSSc (38.6%)	% (P_2)	(ns)	(ns)	17.2 (ns)	58.7 (ns)	41.3(ns)
Onset after 45 years (65.3%)	% (P_2)	40.8 (ns)	55.1 (ns)	4.1 (0.007 ^d ;0.01 ^e)	68.3 (ns)	31.3 (ns)
Controls	n= 123	49	51	23 (18.7)	149 (60.6)	97 (39.4)
	(%)	(39.8)	(41.5)			

a) P value is defined when compare Jo-1positive DM and healthy controls. $P_c=0.06$, ns

b) P value is defined when compare Jo-1positive DM and healthy controls. $P_c=0.06$, ns

c) P value is defined when compare SSc patients with limited disease compare to controls, $P_c=0.09$,ns

d) P value is defined when compare SSc patients with disease onset before and after 45 years. $P_c=0.02$; OR 0.13; CI(95%) 0.02-0.69

e) P value is defined when compare SSc patients with disease onset after 45 years and controls.

Pc=0.04; OR 0.2; CI(95%) 0.04-0.82

Abbreviations: n: number of cases, P1: P value was determined by the χ^2 test comparing each group (PM,DM,SSc) and controls. P2: P value was determined by the χ^2 test comparing positive/negative feature and comparing each feature and controls; Pc.: P value corrected for multiple comparisons (3 detected genotypes, 2 alleles), ns - not significant, ANA: Antinuclear antibodies, Jo-1: antibodies against histidyl-tRNA synthetase, Scl-70 antibodies against DNA topoisomerase I, lSSc-limited cutaneous SSc, dSSc-diffuse cutaneous SSc, CPM: cancer associated Polymyositis, CDM: cancer associated Dermatomyositis