Androgen receptor gene polymorphism and rheumatoid arthritis in Taiwan

Sirs,

Rheumatoid arthritis (RA) is a complex and multifactorial disease which affects females more than males. The role androgens play in the pathogenesis of RA has been studied (1-4). Tissue response to androgen is determined by the androgen receptor (AR), which has the transactivation domain, the DNA-binding domain,and the ligand-binding domain. These domains are encoded by eight exons of the AR gene that span 75-90 kb of genomic DNA, located near the centromere of the X chromosome at Xq11-12 (5). Binding of the androgen-AR complex activates the expression of other genes (transactivation). This transactivation activity resides in the transactivation domain of the protein encoded by exon I, which contains a polymorphic CAG repeat sequence (6).

To the best of our knowledge, there has been only one study in the past that investigated the role androgen receptors play in the pathogenesis of RA (7). Therefore we studied the polymorphic CAG repeats of the AR gene in RA patients and normal controls in Taiwan. Clinical factors including extra-articular manifestations, joint erosion and rheumatoid factor seropositivity were also evaluated and correlated with the extent of CAG repeats.

In all, 200 patients (153 female and 47 male) with a diagnosis of RA according to the 1987 revised American College of Rheumatology criteria (8) were enrolled. In addition, 230 unrelated, healthy individuals (170 female and 60 male) served as controls. The age of the RA patients at presentation ranged from 18 to 75 (mean 49.8) years for females and from 29 to 82 (mean 57.0) years for males. The age of the controls ranged from 20 to 70 (mean 45.8) years for females and from 39 to 87 (mean 53.7) years for males. Informed consent was obtained from all the subjects who participated in this study. Nephelometry was used to detect rheumatoid factor; values ≥ 30 IU/ml were classified as positive. Serum rheumatoid factor was positive in 72% of female patients and 74% of male patients. The presence or history of extra-articular manifestations in RA was recorded (9). Radiographs of hands, wrists, and feet of patients were obtained and the presence or absence ofjoint erosion was evaluated by a radiologist and a rheumatologist.

Genomic DNA was prepared from peripheral blood using a Genomaker DNA Extractor kit, Bloosm, Taiwan). The CAG repeats in the AR gene were analyzed by polymerase chain reaction (PCR) based method. The frequency of CAG repeats between RA patients and normal healthy subjects was compared by Student's t-test. Chi-square tests were used to compare the allelic distribution of CAG repeats between two subgroups of RA patients.

Table I. Frequency distribution and mean frequency of CAG repeats of androgen receptor gene in RA patients and controls.

No. of CAG repeats	Men				Women			
	RA (47 alleles)		Control (60 alleles)		RA (306 alleles)		Control (340 alleles)	
	no.	%	no.	%	no.	%	no.	%
9	0	0.0	0	0.0	0	0.0	1	0.3
10	0	0.0	0	0.0	1	0.3	1	0.3
11	0	0.0	0	0.0	0	0.0	2	0.6
12	0	0.0	0	0.0	1	0.3	2	0.6
13	0	0.0	0	0.0	1	0.3	1	0.3
14	2	4.3	2	3.3	8	2.6	6	1.8
15	0	0.0	0	0.0	3	1.0	2	0.6
16	0	0.0	0	0.0	3	1.0	5	1.5
17	1	2.1	0	0.0	2	0.7	6	1.8
18	0	0.0	1	1.7	11	3.6	18	5.3
19	3	6.4	3	5.0	23	7.5	17	5.0
20	5	10.6	11	18.3	39	12.7	46	13.5
21	11	23.4	11	18.3	53	17.3	57	16.8
22	9	19.1	6	10.0	42	13.7	47	13.8
23	6	12.8	10	16.7	42	13.7	42	12.4
24	0	0.0	10	16.7	23	7.5	22	6.5
25	7	14.9	3	5.0	23	7.5	29	8.5
26	0	0.0	2	3.3	15	4.9	24	7.1
27	2	4.3	1	1.7	5	1.6	5	1.5
28	1	2.1	0	0.0	6	2.0	1	0.30
29	0	0.0	0	0.0	3	1.0	4	1.2
30	0	0.0	0	0.0	1	0.3	1	0.3
31	0	0.0	0	0.0	0	0.0	1	0.3
32	0	0.0	0	0.0	0	0.0	0	0.0
33	0	0.0	0	0.0	1	0.3	0	0.0
Mean ± SD	21.8 ± 2.8		21.8 ± 2.5		21.8 ± 3.1		21.6 ± 3.2	
95% CI for difference	-1.00, 1.00				-0.69, 0.29			
p-value	0.99				0.58			

No significant difference was observed in the frequency of CAG repeats of the AR gene when RA patients were compared with sex-matched controls (Table I). The mean CAG repeats were further compared between the following groups of patients: with extra-articular manifestations and without extra-articular manifestations; with joint erosion and without joint erosion, and rheumatoid factor seropositive and seronegative patients. Rheumatoid factor seropositive female patients had significantly higher mean CAG repeat frequency when compared with seronegative female patients (mean 22.0 ± 2.2 versus 21.1 ± 2.0, 95% CI for the difference: 0.19, 1.71, P = 0.02), data not shown. Our present study is not in concordance with a previous study which reported a lower level of CAG repeat frequency of the AR gene in younger-onset male RA patients (7). We did not find a significant difference in CAG repeats between RA patients and controls in either men or women.

The findings of this study suggest that the frequency of CAG repeats of the androgen receptor gene is not associated with the risk for rheumatoid arthritis. However, the increase of CAG repeats in rheumatoid factor seropositive female patients when compared with seronegative female patients may suggest the possible role of CAG repeat variations in the disease modification of RA, affecting its clinical severity in female RA patients. Nevertheless, the restricted subset of patients posed a limitation to this finding; therefore a causal correlation should be confirmed with more extensive studies involving a larger number of patients.

S.-F. LO[1,7], *MD, Asst. Prof.*
C.-M. HUANG[2,7], *MD, Asst. Prof.*
C.-H. TSAI[3], *MD, PhD, Prof.*
W.-C. CHEN[4,5,7], *MD, PhD, Assoc. Prof.*
C.-C. LAI[5], *PhD, Asst. Prof.*
Y. TSAI[8], *PhD, Asst. Prof.*
F.-J. TSAI[5,6,7], *MD, PhD, Prof.*

[1]Department of Physical Medicine and Rehabilitation; [2]Division of Immunology and Rheumatology, Department of Internal Medicine, China Medical University Hospital; [3]Graduate Institute of Bioinformatics, Taichung Healthcare and Management University; [4]Department of Urology, [5]Department of Medical Genetics, [6]Department of Pediatrics, China Medical University Hospital; [7]College of Chinese Medicine; [8]Graduate Institute of Chinese Medical Science, China Medical University, Taichung, Taiwan.

Address correspondence to: Prof. Fuu-Jen Tsai, MD, PhD, Department of Medical Genetics, China Medical University Hospital, No 2, Yuh Der Road, Taichung, Taiwan.
E-mail:d0704@www.cmuh.org.tw

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Systemic mast cell disease: a rare cause of osteoporosis

Sirs,

We present a case of a 53-year old woman with a history of a recent onset of weakness, widespread joint and muscle pain, iching, urticaria and lower back pain. A diagnosis of urticaria pigmentosa was performed 10 years previously by skin biopsy. After surgical menopause (49 yrs) the woman had rib fractures without major trauma; she had no anaphylactic episodes, stomach pain or diarrhoea; occasionally she suffered from diffuse iching when sunned. On examination she presented brownish pigmented skin nodules of a few centimetres in diameter, predominantly on trunk and proximal parts of legs. Darier's sign was positive and there was tenderness to finger pressure over the spinal processes of the lumbar spine. Laboratory tests were normal except for markers of bone turnover that were increased (Table I), urine and serum calcium and phosphate levels were normal. Total body scintigraphy with Tc^{99} showed increased radionuclide uptake in some areas of the skull and pelvic girdle, but radiography did not show bone lesions. Bone mineral density (BMD), (DEXA with Hologic 4500 equipment), showed rarefaction of the lumbar spine with normal femoral neck (Table I).

Table I. Values of the parameters examined before and after neridronate therapy.

	BMD L1-L4 g/cm^2	T score L1-L4	BMD femoral neck (g/cm^2)	T score femoral	PYR	D-PYR	u NTX	AP
Before therapy	0.770	-2.5	0.991	0.4	45	9.8	59	285
After therapy	0.824	-2.0	1.013	0.6	32	6.7	38	120

u NTx: urine crosslinked N telopeptides of type I collagen (nM BCE/mM Creatinine) (normal female range 3-51) competitive inhibition enzyme linked immunosorbent assay; PYR: urine pyridinoline (nM/mM creatine) (normal female range 16-37) competitive enzyme immunoassay; DPYR: urine deoxipyridinoline (nM/mM creatine) (normal female range 3.0-7.4) competitive enzyme immuno assay; AP: alkaline phosphatase (UI) (normal range 0-270).

A bone marrow biopsy taken from the iliac crest was compatible with medullary mastocytosis : paraosteal and centromedullary sites showed rounded cell aggregates formed of lymphocytes (CD3 positive), plasma cells (CD79 positive), eosinophils and histiocytes, abundant mast cells with metachromatic cytoplasmic granules in a fine reticulin network; the megakaryocytic and eythropoietic lines were normally represented.

According to the above data the diagnosis of systemic mast cell disease was performed (1-4). The patient was treated with neridronate: 25 mg i.m./month for 6 months; skin lesions were managed with ketotifen (10 mg/die). Ten months later BMD was increased and markers of bone turnover returned into normal ranges (Table I).

Our patient has clearly been affected for years by systemic form of mast cell disease, not by cutaneous mastocytosis: indeed, bone marrow biopsy showed mastocytosis bone localization. Mast cells infiltrating bone marrow release several substances affecting bone metabolism that seem to be related to the extent and the severity of the disease (5, 6).

Radiological lesions occur in 60-80% of cases of systemic mast cell disease; generally bone lesions are widespread: osteosclerotic lesions predominate in the axial skeleton and are sometimes present in the long bones; generalised rarefaction with vertebral fractures occurs in 16% of cases (6, 7). Several cases of osteoporosis secondary to mastocytosis have been reported without skin manifestations or other extraosseous symptoms associable with systemic mast cell disease (3, 6, 8)

There is still no specific treatment for systemic mast cell disease. Ketotifen, inhibiting histamine release, acts on the pathogenetic mechanism of mastocytosis and would therefore affect bone remodelling without altering bone mineral density. Bisphosphonates, inhibiting bone resorption, could potentially be useful in management of systemic mast cell disease, although few data are available in the literature; however, clodronate and pamidronate might have positive effects on bone mineral density and bone pain (9). Owing to high levels of bone resorption markers we prescribed to our patient intramuscular neridronate 25 mg/-month for 6 months. Neridronate is a third generation bisphosphonate with high antiresorptive activity whose main indication is treatment of osteogenesis imperfecta but also used in management of post-menopausal osteoporosis.

In our patient, the increase in bone mineral density and the normalization of bone turnover markers after 6 months of neridronate therapy can be related to the strong antiresorptive effects of this drug and suggests that neridronate could be an effective treatment for osteoporosis caused by systemic mast cell disease.

E. CACACE, *MD*
G. SALIS, *MD*
V. RUGGIERO, *BS*
G. PERPIGNANO, *MD*

Rheumatology Unit, Department of Internal Medicine, University General Hospital, Cagliari, Italy.

Address correspondence to: Enrico Cacace MD, Cattedra di Reumatologia I, Policlinico Universitario, SS 554 Bivio Sestu, Monserrato, 09100 Cagliari, Italy.
E-mail: cacace@pacs.unica.it

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