GENETIC TESTING AND MOLECULAR BIOMARKERS
Volume 16, Number 4, 2012

Pp. 229–233
DOI: 10.1089/gtmb.2011.0216

MCP-1 and *CCR2* Gene Variants and the Risk for Osteoporosis and Osteopenia

Hakan Eraltan,[1] Canan Cacina,[2] Ozlem Timirci Kahraman,[2] Ozlem Kurt,[3] Hulya Yilmaz Aydogan,[2] Mehmet Uyar,[4] Ayşe Can,[3] and Bedia Cakmakoğlu[2]

Aim: In this study, we investigated whether monocyte chemotactic protein 1 (*MCP-1*) and CC chemokine receptor 2 (*CCR2*) gene polymorphisms account for an increased risk of osteoporosis or osteopenia. *Methods:* Three hundred three postmenopausal women, 80 osteoporotic, 123 osteopenic, and 100 unrelated age-matched healthy controls, were included in the study. Genotyping of *MCP-1* A2518G and *CCR2* V64I gene polymorphisms were detected by PCR-RFLP. *Results:* We, for the first time, demonstrated the positive association of *MCP-1* GG, *CCR2* Val/Ile, and *CCR2* Val+ genotype with osteoporosis risk. However, *CCR2* Ile/Ile genotype frequencies were high in the control group compared with those of the patients with osteoporosis and osteopenia. Haplotype analysis confirmed the association of *MCP-1/CCR2* gene variants with osteopenia and revealed that the frequency of *MCP-1* A:*CCR2* Val haplotype was significantly higher in patients when compared with controls. *Conclusions:* In conclusion, our findings have suggested that *MCP-1* and *CCR2* gene variants were risk factors for osteoporosis and osteopenia.

Introduction

Osteoporosis is a systemic skeletal disease in which loss of bone mass and the microarchitectural deterioration of bone tissue leads to fragility fractures (Zajickova and Zofkova, 2003; Raisz, 2005). Enhanced bone resorption may be related with osteoclastogenesis from precursor cells, enhanced fusion and activation of osteoclasts, and prolonged lifespan due to an inhibition of osteoclast apoptosis (Manolagas, 2000; Teitelbaum, 2000). There are multiple mechanisms that play roles in the regulation of bone remodeling, and these involve not only the osteoblastic and osteoclastic cell lineages but also other marrow cells, in addition to the interaction of systemic hormones, local cytokines, growth factors, and transcription factors (Raisz, 2005). They are speculated as candidates for involvement in bone loss in different types of inflammatory diseases through the recruitment of osteoclast precursors but their potential effects in osteoclast recruitment, development, or function are not well understood (Choi *et al.*, 2000; Yu *et al.*, 2004). Osteoblasts have also been shown as a source of chemokines in bones (Yu *et al.*, 2004). Chemokines, particularly of two major (CXC, CC) families, are essential signals for the trafficking and localization of circulating hematopoietic cells. Monocyte chemotactic protein 1 (MCP-1, CCL2 or SCYA2) is the most investigated CCL chemokine family member (Van Coillie *et al.*, 1999). It is expressed by various types of cells which include fibroblasts, endothelial cells (Yu and Graves, 1995), and osteoblasts (Simonet *et al.*, 1997) and exhibits chemoattractant activity toward osteoclasts. It has been reported that an *A2518G* polymorphism in the regulatory region of the *MCP-1* gene affects MCP-1 expression in response to inflammatory stimuli (Rovin *et al.*, 1999). The cellular influence of MCP-1 is mediated by the CC chemokine receptor 2 (CCR2), a G-coupled receptor (Rollins, 1997). A 190 G/A single-nucleotide polymorphism (SNP) in the *CCR2* gene, located on chromosome 3p21-p24, is the most researched *CCR2* SNP in exon 1 (Murphy *et al.*, 2000).This mutation results in the substitution of valine by isoleucine (V64I) in the transmembrane region of the protein (Attar *et al.*, 2010). In light of this information, our aim in this study was to investigate some possible associations between *MCP-1* A2518G and *CCR2* V64I gene polymorphisms and the risk for osteoporosis.

Subjects and Methods

Subjects

The cohort of this study contained 303 Turkish postmenopausal women (80 osteoporotic, 123 osteopenic, and 100 healthy), 40–78 years of age, attending the Uskudar State Hospital in Istanbul between June 2009 and March 2010.

[1]Department of Physical Medicine and Rehabilitation, Azerbaijan Medical University, Baku, Azerbaijan.
[2]Department of Molecular Medicine, Institute of Experimental Medicine Research, Istanbul University, Istanbul, Turkey.
[3]Department of Biochemistry, Faculty of Pharmacy, Istanbul University, Istanbul, Turkey.
[4]Department of Physical Medicine and Rehabilitation, Uskudar State Hospital, Istanbul, Turkey.

During recruitment the WHO definitions and criteria for osteoporosis (World Health Organization Study Group, 1994) were used. The patients received a detailed, standardized questionnaire including questions regarding the osteoporosis risk factors, such as family history of osteoporosis, menopausal status and age, cigarette smoking, insufficient protein intake, alcohol consumption, medication use, and other medical conditions. Only patients with a clinical diagnosis of osteoporosis and osteopenia were recruited. The healthy group contained only individuals with normal bone mineral density (BMD). Exclusion criteria before enrollment included conditions, diseases, and/or treatments known to interfere with bone metabolism, such as malignancies, endocrinologic disorders (hypo- and hyperparathyroidism, hyperthyroidism, Cushing's syndrome), severe liver or gastroenteral diseases, skeletal diseases (Paget's disease, osteogenesis imperfecta, osteomalacia, and rheumatoid arthritis), and current pharmacological treatment with corticosteroids, anabolic androgenic steroids, estrogens, estrogen-related molecules, or anticonvulsants. Menopause was defined as amenorrhea of at least 1 year duration. The study was approved by the Local Ethical Committee of Istanbul University Medical Faculty (Protocol No. 2006/2145) and a written, informed consent was obtained from each participant prior to giving their blood sample.

BMD measurement

BMD was measured at the lumbar spine (L1–L4) and hip (femoral neck and total hip) by dual-energy X-ray absorptiometry (DXA; Lunar DPX; GE Lunar Corporation, Madison, WI).

Genotyping

Genotyping method of the *MCP-1* A2518G and *CCR2* V64I gene polymorphisms: Blood specimens were collected in tubes containing EDTA, and DNA was prepared from the leukocyte pellet by SDS lysis, ammonium acetate extraction, and ethanol precipitation (Miller *et al.*, 1988). *CCR2* V64I and *MCP-1* A2518G genotypes were determined with the PCR-RFLP method according to previously published protocols (Szalai *et al.*, 2001a; Abdi *et al.*, 2002).

Statistical analyses

Statistical analyses were performed using the SPSS software package (revision 11.5; SPSS, Inc., Chicago, IL). Differences in the distribution of *MCP-1* A2518G and *CCR2* V64I genotypes or alleles between cases and controls were tested using the χ^2 statistic. Comparisons of haplotype frequencies between the patients and the control groups were carried out using the Haploview program (Barrett *et al.*, 2005). Values of $p < 0.05$ were considered statistically significant.

Results

Characteristics of patients and healthy controls are shown in Table 1. BMI, L1-L4 BMD, femoral neck BMD, wards BMD, total BMD, and trochanter BMD were significantly different for the two study groups ($p < 0.01$).

The frequencies of *MCP-1 A2518G* and *CCR2* V64I genotypes and their respective alleles among cases and controls are shown in Table 2. There was a statistically significant difference between the controls and the patients with osteoporosis for *CCR2* V64I genotypes and ($p = 0.003$).

The control group was not in Hardy–Weinberg equilibrium for both *MCP-1* and *CCR2* genotypes ($p = 0.01$ and $p = 0.00$, respectively); patients with osteoporosis were consistent for *MCP-1* ($p = 0.79$) and *CCR2* ($p = 0.13$), and patients with osteopenia were consistent only for *MCP-1* ($p = 0.61$) but not consistent with *CCR2* genotypes ($p = 0.04$).

MCP-1 AG genotype frequencies were found low in patients with osteopenia and *MCP-1* GG genotype was high in patients with osteoporosis compared with that of the control group ($p = 0.038$, $\chi^2 = 4.31$, OR = 0.56, 95% CI: 0.32–0.97; $p = 0.042$, Fisher's exact test OR = 4.69, 95% CI: 0.94–23.28, respectively).

The frequencies of *CCR2* Val/Ile genotype and Val+ allele were high in patients with osteoporosis compared with that of the control group ($p = 0.042$, Fisher's exact test OR = 4.69, 95% CI: 0.94–23.28; $p = 0.009$, $\chi^2 = 6.89$, OR = 2.7, 95% CI: 1.26–5.76; $p = 0.015$, Fisher's exact test OR = 0.93, 95% CI: 0.88–0.98, respectively). In contrast, *CCR2* Ile/Ile genotype frequencies were high in the control group compared with the patients with osteoporosis ($p = 0.015$, Fisher's exact test OR = 0.93, 95% CI: 0.88–0.98). In patients with osteopenia, carriers of the *CCR2* Val+allele (Val/Val+Val/Ile genotype) frequency was high compared with the control group ($p = 0.045$, Fisher's exact test OR = 4.55, 95% CI: 0.92–22.43).

In addition to SNP analyses, haplotypes were evaluated for association with osteopenia and osteoporosis (Table 3). Haplotype analysis confirmed the association of *MCP-1/CCR2* gene variants with osteopenia and revealed that the frequencies of *MCP-1* A:*CCR2* Val and *MCP-1* A:*CCR2* Ile

Table 1. Clinical Characteristics of Study Participants

Parameters	*Osteopenia* (n = *123*)	*Osteoporosis* (n = *80*)	*Healthy controls* (n = *100*)	*P1*	*P2*	*P3*
Age (year)	58.32 ± 7.60	58.54 ± 5.78	56.24 ± 8.64	0.05	0.06	0.83
BMI (kg/m^2)	30.28 ± 4.79	27.84 ± 4.22	33.43 ± 4.81	0.00	0.00	0.00
Menopause age (years)	47.19 ± 4.66	46.07 ± 5.5	47.06 ± 4.29	0.88	0.36	0.14
Family history (%)	44.4	39.7	47.5	0.73	0.42	0.51
Smoking (%)	8.9	8.8	20	0.01	0.03	0.96
L1–L4 BMD (g/cm^2)	1.00 ± 0.87	0.82 ± 0.06	1.17 ± 0.11	0.00	0.00	0.00
Femoral neck BMD (g/cm^2)	0.84 ± 0.08	0.76 ± 0.09	0.96 ± 0.09	0.00	0.00	0.00
Wards BMD (g/cm^2)	0.67 ± 0.09	0.58 ± 0.10	0.81 ± 0.10	0.00	0.00	0.00
Total BMD	0.90 ± 0.08	0.81 ± 0.09	1.05 ± 0.09	0.00	0.00	0.00
Trochanter BMD (g/cm^2)	0.73 ± 0.08	0.66 ± 0.08	0.85 ± 0.01	0.00	0.00	0.00

P1, osteopenia vs. control; P2, osteoporosis vs. control; P3, osteopenia vs. osteoporosis; BMI, body mass index; BMD, bone mineral density.

TABLE 2. DISTRIBUTION OF *MCP-1* A2518G AND *CCR2* V64I GENOTYPE FREQUENCIES IN PATIENTS AND CONTROL GROUPS

Genotypes/alleles	*Osteopenia* n (%)	*Osteoporosis* n (%)	*Healthy controls* n (%)	p-*Value*
MCP-1 A2518G				
AA	78 (63.4)	38 (47.5)	51 (51.0)	0.06[a]; 0.64[b]
GG	4 (3.3)	7 (8.8)	2 (2.0)	0.56[a]; 0.042[b]
AG	41 (47.0)	35 (43.8)	47 (47.0)	0.03[a]; 0.664[b]
	p: 0.111	*p*: 0.119		
A	197 (80.0)	111 (69.37)	149 (74.5)	
G	49 (19.91)	49 (30.62)	51 (25.5)	0.15[a]; 0.28[b]
CCR2 V64I				
Val/Val	108 (87.8)	57 (71.3)	80 (80.0)	0.111[a]; 0.171[b]
Ile/Ile	2 (1.6)	0 (0)	7 (7.0)	0.045[a]; 0.015[b]
Val/Ile	13 (10.6)	23 (28.8)	13 (13.0)	0.574[a]; 0.009[b]
	p: 0.09	*p*: 0.003		
Val	229 (93.08)	137 (85.6)	173 (86.5)	
Ile	17 (6.91)	23 (14.37)	27 (13.5)	0.02[a]; 0.811[b]

[a]Osteopenia vs. control.
[b]Osteoporosis vs. control.
CCR2, CC chemokine receptor 2; MCP-1, monocyte chemotactic protein.

haplotypes were significantly higher and lower, respectively, in patients when compared with controls.

Discussion

The osteoporosis candidate genes may be categorized according to the function(s) of the coded molecules, mostly included in the metabolism of bone cells (osteoblasts and osteoclasts), structure and turnover of collagen and minerals (calcium and phosphorus), and regulatory/hormonal (obviously, sex hormone) pathways. There are multiple gene polymorphisms that have been investigated in association studies with bone mass and fragility (Liu *et al.*, 2006; Ralston and Crombrugghe, 2006) but new and more effective approaches are likely to arise from a better understanding of the regulation bone cell function (Raisz, 2005). We, for the first time, demonstrated the positive association of *MCP-1* and *CCR2* gene variants with osteoporosis or osteopenia risk. In our study, the frequencies of *MCP-1* GG, *CCR2* Val/Ile, and *CCR2* Val+ genotype are more prevalent in patients with osteoporosis than in controls. On the other hand, the *CCR2* Ile/Ile genotype is more prevalent in controls than in osteoporosis and osteopenia patients In addition, haplotype analysis confirmed the association of *MCP-1*/*CCR2* gene variants with osteopenia and revealed that the frequency of *MCP-1* A:*CCR2* Val haplotype was significantly higher in patients when compared with controls.

TABLE 3. THE FREQUENCIES OF HAPLOTYPES OF *MCP-1* AND *CCR2* GENE IN STUDY GROUPS

	Frequency				
	Overall	*All patients*	*Control*	χ^2	p-*Value*
Haplotype associations in osteopenia					
MCP-1 A:*CCR2* Val	0.696	0.748	0.630	7.113	0.0077
MCP-1 G:*CCR2* Val	0.205	0.182	0.235	1.752	0.1856
MCP-1 A:*CCR2* Ile	0.080	0.052	0.115	5.594	0.018
MCP-1 G:*CCR2* Ile	0.019	0.017	0.020	0.143	0.7051
Haplotype associations in osteoporosis					
MCP-1 A:*CCR2* Val	0.607	0.579	0.630	0.96	0.3272
MCP-1 G:*CCR2* Val	0.254	0.277	0.235	0.828	0.3629
MCP-1 A:*CCR2* Ile	0.115	0.114	0.115	0.0	0.988
MCP-1 G:*CCR2* Ile	0.024	0.029	0.020	0.323	0.5695

At present, it is hard to explain by which mechanisms genotypes of chemokines result in osteoporosis or osteopenia. Nevertheless, we can make some plausible interpretations depending on the previous study findings. Inflammation can influence the balance between bone formation and resorption and patients with chronic inflammatory diseases seem to have increased risk of developing osteopenia (Hardy and Cooper, 2009). The relevance between the immune system and bone metabolism, or "osteoimmunology," involves molecular and cellular interactions between osteoblasts, osteoclasts, lymphocytes, and the monocyte–macrophage lineage (Takayanagi, 2007). The association between inflammation and bone turnover appears to depend mainly on the production of cytokines. As estrogen levels decrease at menopause, there is an increase in the production of proinflammatory cytokines; this process may contribute to increased osteoclast activity and subsequent loss of bone density (Swanberg *et al.*, 2010). However, cytokines play dual roles in bone homeostasis by different activities depending on the type of immune response (Dewhirst *et al.*, 1985; Takayanagi *et al.*, 2000; Takayanagi, 2007). Some of the studies reported that the −2518 A/G polymorphism of *MCP-1* may be related with its gene expression. Rovin *et al.* (1999) reported the over-representation of −2518 G frequency in Asian and Mexican populations compared with a Caucasian population. In results from several studies, the G allele has generally been regarded to be associated with inflammation and different types of diseases such as Kawasaki disease, coronary artery disease, asthma, and lupus nephritis (Jibiki *et al.*, 2001; Szalai *et al.*, 2001a, 2001b; Tucci *et al.*, 2004). The current study result is consistent with studies showing an increased risk of *MCP-1* GG genotype and G allele in different type of diseases.

It was shown that polymorphisms in the *CCR2* gene that alter macrophage recruitment have been reported to influence a number of diseases including AIDS (Doms and Peiper, 1997), multiple sclerosis (Miyagishi *et al.*, 2003), breast cancer (Zafiropoulos *et al.*, 2004), carotid atherosclerosis (Nyquist

et al., 2009), and renal transplant rejection (Omrani *et al.*, 2008). It has been speculated that its distribution is strongly dependent on ethnicity (Smith *et al.*, 1997; Anzala *et al.*, 1998; Struyf *et al.*, 2000; Lewandowska *et al.*, 2002). The *CCR2* (V64I) mutation leads to the substitution of valine by isoleucine in the transmembrane region of the protein. Data on the effect of this SNP on the expression of CCR2 are controversial (Nakayama *et al.*, 2004; Navratilova, 2006).

In conclusion, our study has suggested that *MCP-1* polymorphism may increase the transcription of MCP-1 by increasing association of MCP-1 with its receptor, leading to the elevated biological activity of the MCP-1/CCR2 system. The increased activity of this system may contribute to inducing osteoclast activity and subsequent loss of bone density. However, further studies are required to evaluate the association of the MCP-1/CCR2 system with osteoporosis.

Disclosure Statement

No competing financial interests exist.

References

Abdi R, Tran TB, Sahagun-Ruiz A, *et al.* (2002) Chemokine receptor polymorphism and risk of acute rejection in human renal transplantation. J Am Soc Nephrol 13:754–758.

Anzala AO, Ball TB, Rostron T, *et al.* (1998) CCR2-64I allele and genotype association with delayed AIDS progression in African women. University of Nairobi Collaboration for HIV Research. Lancet 351:1632–1633.

Attar R, Agachan B, Kuran SB, *et al.* (2010) Association of CCL2 and CCR2 gene variants with endometrial cancer in Turkish women. In Vivo 24:243–248.

Barrett JC, Fry B, Maller J, Daly MJ (2005) Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 21:263–265.

Choi SJ, Cruz JC, Craig F, *et al.* (2000) Macrophage inflammatory protein 1-alpha is a potential osteoclast stimulatory factor in multiple myeloma. Blood 96:671–675.

Dewhirst FE, Stashenko PP, Mole JE, Tsurumachi T (1985) Purification and partial sequence of human osteoclast-activating factor: identity with interleukin 1 beta. J Immunol 135:2562–2568.

Doms RW, Peiper SC (1997) Unwelcomed guests with master keys: how HIV uses chemokine receptors for cellular entry. Virology 235:179–190.

Hardy R, Cooper MS (2009) Bone loss in inflammatory disorders. J Endocrinol 201:309–320.

Jibiki T, Terai M, Shima M, *et al.* (2001) Monocyte chemoattractant protein 1 gene regulatory region polymorphism and serum levels of monocyte chemoattractant protein 1 in Japanese patients with Kawasaki disease. Arthritis Rheum 44:2211–2222.

Lewandowska M, Franciszkiewicz K, Prokop J, *et al.* (2002) Distribution of two HIV-1-resistant polymorphisms (SDF1-3'A and CCR2-64I alleles) in the Polish population. J Hum Genet 47:585–589.

Liu YJ, Shen H, Xiao P, *et al.* (2006) Molecular genetic studies of gene identification for osteoporosis: a 2004 update. J Bone Miner Res 21:1511–1535.

Manolagas SC (2000) Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. Endocr Rev 21:115–137.

Miller SA, Dykes DD, Polesky HF (1988). Simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 16:1215.

Miyagishi R, Niino M, Fukazawa T, *et al.* (2003) C-C chemokine receptor 2 gene polymorphism in Japanese patients with multiple sclerosis. J Neuroimmunol 145:135–138.

Murphy PM, Baggiolini M, Charo IF, *et al.* (2000) International union of pharmacology. XXII.Nomenclature for chemokine receptors. Pharmacol Rev 52:145–176.

Nakayama EE, Tanaka Y, Nagai Y, *et al.* (2004) A CCR2-V64I polymorphism affects stability of CCR2A isoform. AIDS 18:729–738.

Navratilova Z (2006) Polymorphisms in CCL2&CCL5 chemokines/chemokine receptors genes and their association with diseases. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 150:191–204.

Nyquist PA, Winkler CA, McKenzie LM, *et al.* (2009) Single nucleotide polymorphisms in monocyte chemoattractant protein-1 and its receptor act synergistically to increase the risk of carotid atherosclerosis. Cerebrovasc Dis 28:124–130.

Omrani MD, Mokhtari MR, Tagizadae A, *et al.* (2008) Association of CCR5-59029 A/G and CCR2-V64I variants with renal allograft survival. Iran J Immunol 5:201–206.

Raisz LG (2005) Pathogenesis of osteoporosis: concepts, conflicts, and prospects. J Clin Invest 115:3318–3325.

Ralston SH, de Crombrugghe B (2006) Genetic regulation of bone mass and susceptibility to osteoporosis. Genes Dev 20:2492–2506.

Rollins BJ (1997) Chemokines. Blood 90:909–928.

Rovin BH, Lu L, Saxena R (1999) A novel polymorphism in the MCP-1 gene regulatory region that influences MCP-1 expression. Biochem Biophys Res Commun 259:344–348.

Simonet WS, Lacey DL, Dunstan CR, *et al.* (1997) Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. Cell 89:309–319.

Smith MW, Dean M, Carrington M, *et al.* (1997) Contrasting genetic influence of CCR2 and CCR5 variants on HIV-1 infection and disease progression. Hemophilia Growth and Development Study (HGDS), Multicenter AIDS Cohort Study (MACS), Multicenter Hemophilia Cohort Study (MHCS), San Francisco City Cohort (SFCC), ALIVE Study. Science 277:959–965.

Struyf F, Thoelen I, Charlier N, *et al.* (2000) Prevalence of CCR5 and CCR2 HIV-coreceptor gene polymorphisms in Belgium. Hum Hered 50:304–307.

Swanberg M, McGuigan F, Ivaska KK, *et al.* (2010) Polymorphisms in the macrophage migration inhibitory factor gene and bone loss in postmenopausal women. Bone 47:424–429.

Szalai C, Duba J, Prohászka Z, *et al.* (2001a). Involvement of polymorphisms in the chemokine system in the susceptibility for coronary artery disease (CAD). Coincidence of elevated Lp(a) and MCP-1 −2518G/G genotype in CAD patients. Atherosclerosis 158:233–239.

Szalai C, Kozma GT, Nagy A, *et al.* (2001b) Polymorphism in the gene regulatory region of MCP-1 is associated with asthma susceptibility and severity. J Allergy ClinImmunol 108:375–381.

Takayanagi H (2007) Osteoimmunology: shared mechanisms and crosstalk between the immune and bone systems. Nat Rev Immunol 7:292–304.

Takayanagi H, Ogasawara K, Hida S, *et al.* (2000) T-cell-mediated regulation of osteoclastogenesis by signalling cross-talk between RANKL and IFN-gamma. Nature 408:600–605.

Teitelbaum SL (2000) Bone resorption by osteoclasts. Science 289:1504–1508.

Tucci M, Barnes EV, Sobel ES, *et al.* (2004) Strong association of a functional polymorphism in the monocyte chemoattractant

protein 1 promoter gene with lupus nephritis. Arthritis Rheum 50:1842–1849.

Van Coillie E, Van Damme J, Opdenakker G (1999) The MCP/eotaxin subfamily of CC chemokines. Cytokine Growth Factor Rev 10:61–86.

World Health Organization Study Group (1994) Assessement of fracture risk and its application to screening for postmenopausal osteoporosis. Geneva. World Health Organ Tech Rep Ser 843:1–129.

Yu X, Graves DT (1995) Fibroblasts, mononuclear phagocytes, and endothelial cells express monocyte chemoattractant protein-1 (MCP-1) in inflamed human gingiva. J Periodontol 66:80–88.

Yu X, Huang Y, Collin-Osdoby P, Osdoby P (2004) CCR1 chemokines promote the chemotactic recruitment, RANKL development, and motility of osteoclasts and are induced by inflammatory cytokines in osteoblasts. J Bone Miner Res 19:2065–2077.

Zafiropoulos A, Crikas N, Passam AM, Spandidos DA (2004) Significant involvement of CCR2-64I and CXCL12-3a in the development of sporadic breast cancer. J Med Genet 41:e59.

Zajickova K, Zofkova I (2003) Osteoporosis: genetic analysis of multifactorial disease. Endocr Regul 37:31–44.

Address correspondence to:
Bedia Cakmakoğlu, Ph.D.
Department of Molecular Medicine
Institute of Experimental Medicine Research
Istanbul University
Vakif Gureba cad, Capa
Istanbul 34093
Turkey

E-mail: bedia@istanbul.edu.tr

Master Journal List JOURNAL LIST

Search terms: *GENETIC TESTING AND MOLECULAR BIOMARKERS
Total journals found: 1

A3a6

1. GENETIC TESTING AND MOLECULAR BIOMARKERS
Monthly
ISSN: 1945-0265
E-ISSN: 1945-0257
MARY ANN LIEBERT, INC, 140 HUGUENOT STREET, 3RD FL, NEW ROCHELLE, USA, NY, 10801

1. Science Citation Index Expanded
2. Current Contents - Clinical Medicine
3. Current Contents - Life Sciences
4. BIOSIS Previews

Genetic Testing and Molecular Biomarkers

ISSN: 1945-0265

MARY ANN LIEBERT, INC
140 HUGUENOT STREET, 3RD FL, NEW ROCHELLE, NY 10801
USA

Go to Journal Table of Contents **Go to Ulrich's**

Titles
ISO: Genet. Test. Mol. Biomark.
JCR Abbrev: GENET TEST MOL BIOMA

View TitleChanges

Categories
GENETICS & HEREDITY - SCIE

Languages
English

12 Issues/Year;

Key Indicators

Year	Total Cites Graph	Journal Impact Factor Graph	Impact Factor Without Journal Self Cites Graph	5 Year Impact Factor Graph	Immediacy Index Graph	Citable Items Graph	Cited Half-Life Graph	Citing Half-Life Graph	Eigenfacto Score Graph	Article Influence Score Graph	% Articles in Citable Items Graph	Normalizec Eigenfacto Graph	Average JIF Percentile Graph
2017	1,289	1.181	1.140	1.199	0.180	111	4.8	7.1	0.00...	0.286	98.20	0.35...	14.327
2016	1,234	1.263	1.211	1.197	0.175	126	4.2	7.0	0.00...	0.284	99.21	0.37...	17.066
2015	1,156	1.297	1.261	1.248	0.317	123	3.6	6.8	0.00...	0.328	99.19	0.45...	14.759
2014	1,118	1.464	1.416	1.336	0.266	128	2.8	7.1	0.00...	0.335	99.22	0.48...	21.257
2013	830	1.147	1.088	1.179	0.331	151	2.6	7.4	0.00...	0.313	98.01	0.37...	13.636
2012	607	1.444	1.187	1.345	0.228	250	2.3	7.8	0.00...	0.305	98.80	Not...	20.186
2011	324	1.110	1.022	1.110	0.193	145	2.1	7.4	0.00...	0.324	99.31	Not...	16.772
2010	135	0.879	0.780	0.879	0.136	132	1.4	7.5	0.00...	0.250	98.48	Not...	13.782
2009	12	Not A...	Not A...	Not...	0.091	132	Not...	7.1	0	Not...	96.21	Not...	1.027

Source Data

Rank

Cited Journal Data

Citing Journal Data

Box Plot

Journal Relationships

Journal Source Data

	Citable Items			Other (O)	Percentage (C/(C + O))
	Articles	Reviews	Combined (C)		
Number in JCR Year 201...	109	2	111	13	89%
Number of References (B)	3,490	111	3,601	108	97%
Ratio (B/A)	32.0	55.5	32.4	8.3	

null