
**INSTRUCTIONS FOR LETTERS TO THE EDITOR**

**Editorial comment in the form of a Letter to the Editor is invited. The length of a letter should not exceed 800 words, with a maximum of 10 references and no more than 2 figures or tables; and no subdivision for an abstract, methods, or results. Letters should have no more than 4 authors. Financial associations or other possible conflicts of interest should be disclosed.**

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## Usefulness of Enzyme-Linked Immunosorbent Assay (Elispot) Compared to Tuberculin Skin Testing for Latent Tuberculosis Screening in Rheumatic Patients Scheduled for Anti-Tumor Necrosis Factor Treatment. Addendum

*To the Editor:*

We would add an addendum to our report that appears in this issue of *The Journal*[1]. Important new information on the same topic comes from 2 recent publications[2,3].

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## Early Spondyloarthritis in an HLA-B27-positive Monozygotic Twin Pair: A Highly Concordant Onset, Sites of Involvement, and Disease Course

*To the Editor:*

Susceptibility to ankylosing spondylitis (AS) and the related spondyloarthropathies (SpA) is determined by a strong polygenetic predisposition interacting with as-yet unknown environmental factors. HLA-B27 is one of the major disease susceptibility genes, and studies of HLA-B27-positive twins have shown a concordance rate of 63% among monozygotic versus 24% in dizygotic twin pairs[1-5]. Making an early diagnosis of AS and related SpA is often challenging, and there are no validated diagnostic criteria[6-10]. Magnetic resonance imaging (MRI) is the imaging method of choice for early detection and assessment of inflammatory lesions in the axial skeleton prior to the development of structural damage seen on standard radiographs[11].

We describe HLA-B27-positive monozygotic Caucasian twin brothers who had experienced the onset of undifferentiated spondyloarthritis at 23 years of age only 10 months apart, and with almost identical clinical manifestations: stiffness of the neck and dactylitis of a toe in the left foot, followed by right-side sacroiliitis. The twins were living far apart in 2 different cities.

Twin A developed neck stiffness (that resolved within a few weeks) and dactylitis of the fourth toe of his left foot (that lasted about 6 months), fol-

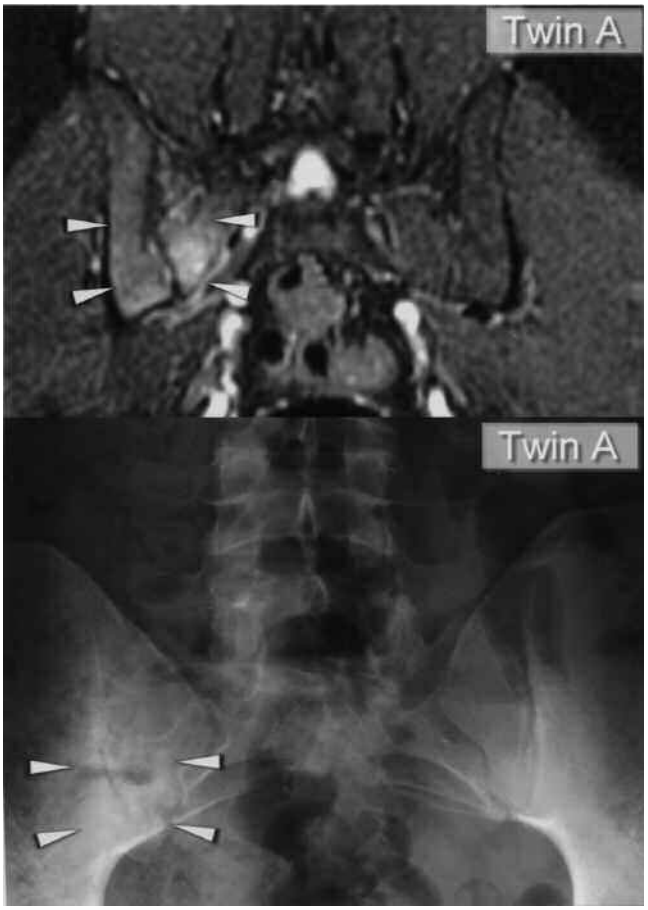


*Figure 1.* Conventional MRI (STIR sequence; performed 9 months after onset of relapsing back pain; top) and standard radiograph (performed 12 months after onset of back pain; bottom) of the pelvis in Twin A. MRI displays acute inflammatory changes of the right sacroiliac joint, and the radiograph shows advanced chronic inflammatory lesions of the right sacroiliac joint.

lowed 4 weeks later by recurrent right buttock pain with frequent flares. His buttock pain and subsequent plantar fasciitis in his left foot showed symptomatic response to treatment with indomethacin. An MRI [short-tau inversion recovery (STIR) sequence] performed 9 months after the onset of right-side buttock pain showed inflammatory lesions of the distal (cartilaginous) part of the right sacroiliac joint and the adjacent sacral and iliac bones (Figure 1, top). He was found to have HLA-B27. A standard pelvic radiograph at 12 months after the onset of buttock pain displayed right-side grade 3 sacroiliitis (Figure 1, bottom). A whole-body MRI was performed during a period of low disease activity a month later because of the patient's academic interest. It confirmed the presence of chronic inflammatory changes in the right sacroiliac joint (Figure 2A). There was no active inflammatory lesion in the entire spine, the anterior chest wall, and the shoulder and pelvic girdles (Figure 3A).

Ten months after the onset of symptoms in Twin A, his monozygotic twin brother (Twin B) also developed neck stiffness and associated dactylitis that affected the second toe of his left foot, and MRI showed flexor tenosynovitis with synovitis of metatarsophalangeal joint of that toe. As in Twin A, there was no history of psoriasis or inflammatory bowel disease and no gastrointestinal or genitourinary symptoms. He was also found to possess HLA-B27. Dactylitis persisted despite treatment with naproxen, and 4 months later, even though he did not complain of clinically relevant buttock or low back pain, a standard pelvic radiograph was performed because of his twin brother's diagnosis of spondyloarthritis. The radiograph showed bilateral grade 1 sacroiliitis (equivocal structural changes). Four months later, when he had just begun to notice morning stiffness of his lumbar spine without back pain, a whole-body MRI (performed on the same day as in Twin A, and on the same MRI machine) showed acute inflammatory lesions of both the iliac and the sacral sides in the distal part of the right sacroiliac joint (Figure 2B). As in Twin A, there were no active inflammatory lesions in the spine, the anterior chest wall, and the shoulder girdle, but it is of interest that both twins showed remarkably identical early lumbar degenerative disc lesions at L3/L4 and L4/L5, with annulus fibrosus tear (Figure 3).

The MR signal alterations observed in the distal part of the asymptomatic right sacroiliac joint in Twin B may represent a very early sign of as-yet subclinical but evolving sacroiliitis. Previous studies have shown that early sacroiliitis starts in the distal portion of the sacroiliac joints[12,13]. Twin

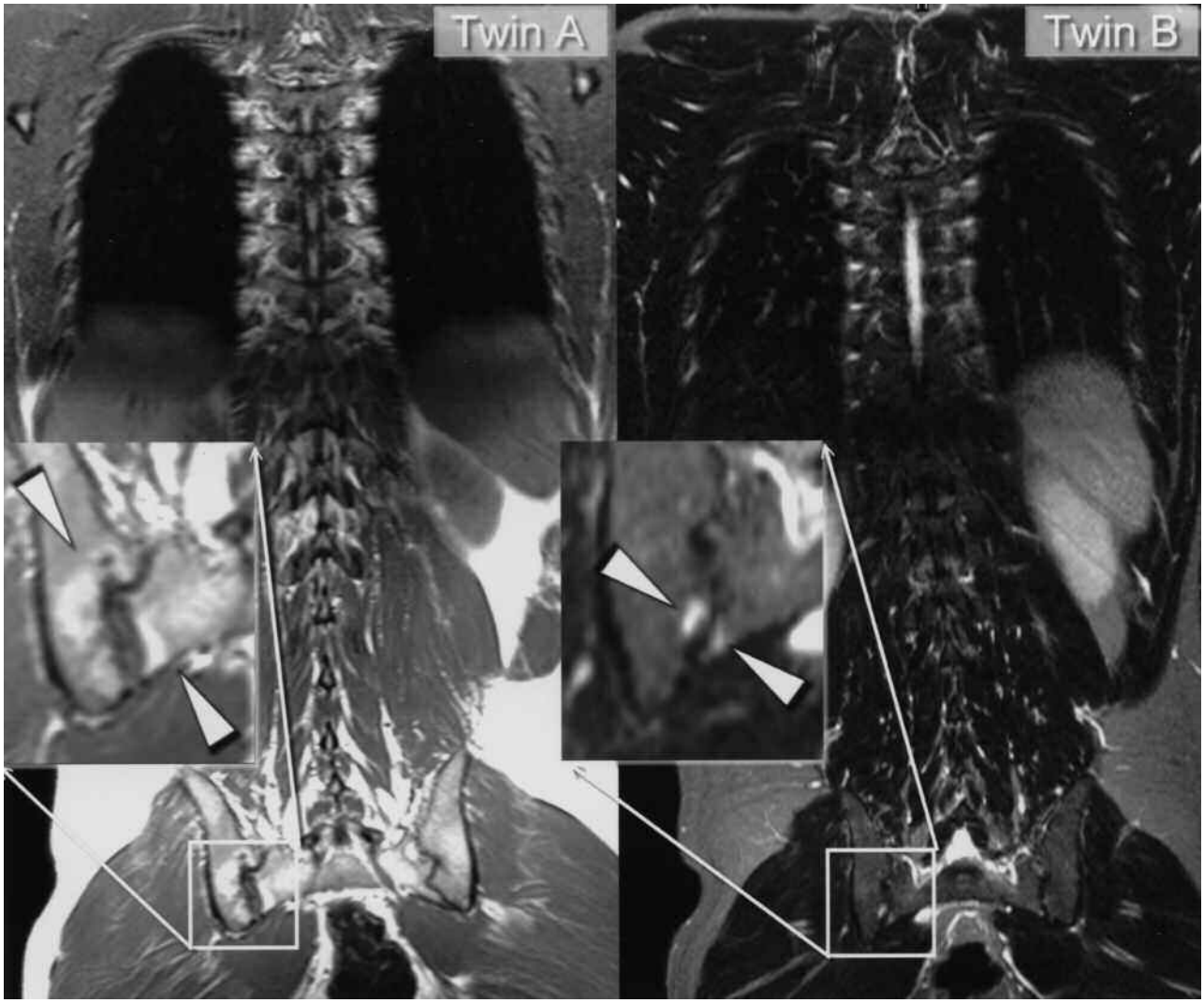


*Figure 2.* Coronal whole-body MRI performed on the same day in both twins at age 25 (left: Twin A, T1-weighted image; right: Twin B, STIR sequence). Insert shows magnification of the right sacroiliac joint; left (Twin A): 13 months after onset of right-side buttock pain, T1-weighted sequences show chronic inflammatory changes of the right sacroiliac joint with erosions, sclerosing joint margins, and fatty replacement of subchondral bone marrow on both sides. Right (Twin B): a few weeks after onset of lumbar morning stiffness, subtle acute inflammatory lesions on STIR sequences are present in the distal cartilaginous part of the right sacroiliac joint (both in the iliac and sacral side of the joint).

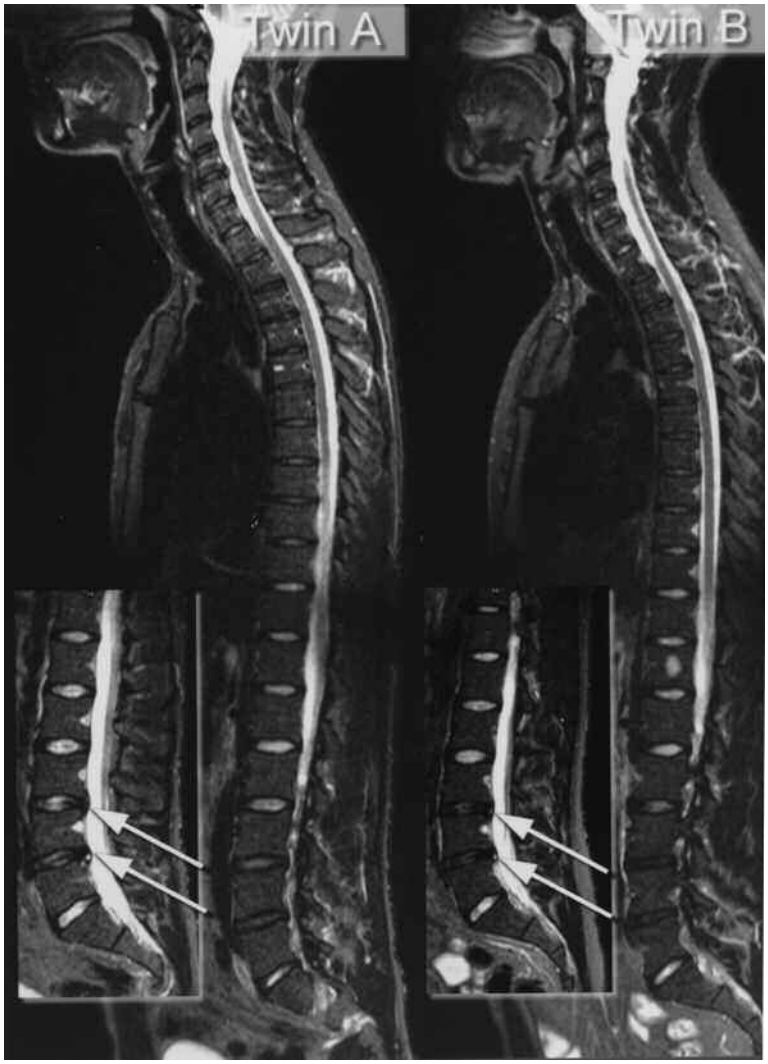


*Figure 3.* Sagittal whole-body MRI of the entire spine of Twin A (left) and Twin B (right), performed on the same day in both twins at age 25. No inflammatory lesions can be detected in the entire spine in Twin A (left) 13 months after onset of right-side sacroiliitis, and in Twin B (right) just after onset of morning stiffness of the lumbar spine. Note identical degenerative changes of the intervertebral discs in the lumbar spine at the same levels (L3/L4 and L4/L5) with additional tears of the annulus fibrosus (insert).

A showed a right-side grade 3 sacroiliitis only 12 months after onset of back pain. Possible explanations may be a rapidly progressive inflammation or a prior subclinical sacroiliitis long before back pain becomes relevant for the patients. In a study of 68 patients with inflammatory back pain of less than 2 years' duration, only 14 had radiographic sacroiliitis that fulfilled the modified New York classification criteria for AS[14].

Recent progress in MR technology (new coil designs, multichannel technology, and parallel image acquisition) has led to a new technique of whole-body MRI that provides T1-weighted spin-echo and STIR images in the coronal and sagittal planes in just 30 minutes, including patient positioning, and its spatial resolution equals that of the standard MRI[15]. It is a promising new tool to help diagnose SpA early (within 4 months after symptom onset in the case of Twin B), and for comprehensive assessment of inflammatory lesions in the entire axial skeleton, including the chest wall and hip and shoulder girdles. There is a need to develop standards in reporting the observed inflammatory signal alterations, including their sensitivity and specificity, and to demonstrate whether they predict future radiographic structural damage[16]. These issues must be addressed before the radiographic evidence of sacroiliitis in the modified New York classification criteria for AS[17] may be replaced by an assessment by MRI.

Our case report illustrates the high clinical relevance of dactylitis in making a diagnosis of spondyloarthritis. A recent literature review focusing on various clinical features, laboratory findings, and skeletal imaging techniques that clinicians rely on to diagnose AS showed that dactylitis has a specificity of 96%[18]. In both twins, long-lasting dactylitis accompanied by relatively transitory neck pain was the first manifestation of undifferentiated spondyloarthritis.

A high degree of concordance of disease onset, sites and patterns of involvement, and the disease course in identical twins is a dramatic example of genetic influences in not only the predisposition to spondyloarthritis but also its clinical onset, clinical presentation, and phenotypic expression. Our report also highlights the potential role of the whole-body MRI in very early diagnosis of spondyloarthritis and in assessing inflammation in the entire axial skeleton.

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## Clinical Hand Osteoarthritis in Tehran: Prevalence, Signs, Symptoms, and Pattern — COPCORD Stage I, Iran Study

*To the Editor:*

In Iran coordinated efforts by the World Health Organization and the International League Against Rheumatism (ILAR) have led to a Community-Oriented Program for Control of Rheumatic Diseases (COPCORD)[1-4]. The COPCORD study comprises 3 stages. In Tehran, the first stage started in 2003, and was intended to measure the prevalence of major rheumatic disorders in the urban adult population in a study carried out by the Rheumatology Research Center, Tehran University[1].

Although many studies have reported the prevalence of hand osteoarthritis (OA) in Western countries[4-8], fewer have covered it in the East[9,10]. Epidemiological studies of OA have a dual purpose: to determine its extent, so the provision of appropriate services can be promoted as necessary; and to compare results with the information acquired in a similar fashion in Western countries.

The objective of our study was to use the COPCORD data to generate greater evidence on the prevalence of hand OA in a general population.

Following the COPCORD principle, a random sample of inhabitants from 50 districts in Tehran were invited to participate, in compliance with our study design, as described[1]. We achieved a 75% response rate and our trained interviewers were able to complete a COPCORD Core Questionnaire on 10,291 participants. Participants who complained of any musculoskeletal symptoms (including pain or any extraarticular manifestation of rheumatic disease) underwent a complete physical examination the same day (known as the fast-track COPCORD model[3]). Blood samples and radiographs were taken when necessary.

The overall survey included questions on major rheumatic disorders, including OA. For the present study, we used the data with respect to hand OA, querying for hand pain during the previous 7 days and also for swelling, tenderness, or morning stiffness of hand joints. If they currently had a musculoskeletal complaint or any extraarticular manifestation of rheumatic disease, participants underwent a complete physical examination (n = 4685). The signs of OA in all hand and wrist joints were recorded. Clinical finger OA was defined as the presence of one of these signs: i.e., local palpable nodules [including Heberden's nodes, Bouchard's nodes, and squaring of first carpometacarpal joint (CMC1)], pain or tenderness, swelling, bony enlargement, or a combination of them at that site. Pain, tenderness, and deformity of metacarpophalangeal joints were defined as finger OA when rheumatoid arthritis was ruled out. Clinical hand OA was identified as positive if at least one joint was defined as having finger OA.

The Stata and SPSS programs were used for all analyses. Associations of hand OA and age/sex were investigated by t-tests and chi-square tests. There was an interrater agreement of 0.96 for screening the participants through the COPCORD Core Questionnaire and reporting them as participants who needed to be examined; and the kappa coefficient was 0.919.

We evaluated a total of 10,291 participants, 52.6% women, with a mean

*Table 1.* Baseline characteristics of the study population.

| Characteristics | Total Population, N = 10,291 (%) | People with Hand OA, N = 303 (%) |
|---|---|---|
| Female | 52.6 | 78.2* |
| Age, yrs, mean ± SD | 37.1 ± 16.3 | 63.9* ± 12.1 |
| Any hand complaint during the last 7 days (pain, tenderness, swelling), % | 9.4 | 55 |
| Pain | 8.8 | 50.4 |
| Swelling | 3.2 | 22.4 |
| Stiffness | 4.7 | 33.0 |
| Tenderness | 4.3 | 30.4 |
| Any wrist complaint during the last 7 days (pain, tenderness, swelling), % | 10.1 | 43.5 |
| Pain | 9.7 | 42.2 |
| Swelling | 2.6 | 15.2 |
| Stiffness | 3.8 | 21.2 |
| Tenderness | 5.0 | 24.1 |

* Significant difference.
Hand/wrist complaint in either right or left side.

age of 37.1 years (Table 1). In total, hand OA was present in 303 participants (2.66%; 95% CI 2.1–3.2).

Few of the participants aged under 40 years had hand OA (n = 4). The prevalence of hand OA in people aged 40–50 years was 2.2%, rising with age to 8.4% in people aged 50–60 years, and to 15.5% in those age 60–70 years. The highest prevalence of hand OA, 22.5%, was found in people aged > 70 years. Differentiation by gender showed that women had more hand OA than men (4.46% vs 1.35%, respectively).

Prevalence of all hand symptoms was higher in people with hand OA than in the total study population (Table 1). In people with hand OA, over 79% of distal interphalangeal (DIP) joints showed at least one of the signs on examination, while 41% of proximal interphalangeal (PIP) joints showed at least one of the signs. CMC1 was the third most common site (34%) showing at least one of the signs on examination.

Figure 1 presents the prevalence of different hand signs for each group of hand joints. The most frequent sign in the DIP and PIP joint groups was bony enlargement, followed by tenderness. Although pain upon movement was the next most common sign in PIP joints, this sign had unfortunately been omitted from the examination sheets for DIP joints, and had not been measured. The most frequent signs for the CMC1 were bony enlargement, tenderness, pain on movement, functional limitation, and deformity, respectively.

Our community-based study showed that clinical hand OA was present

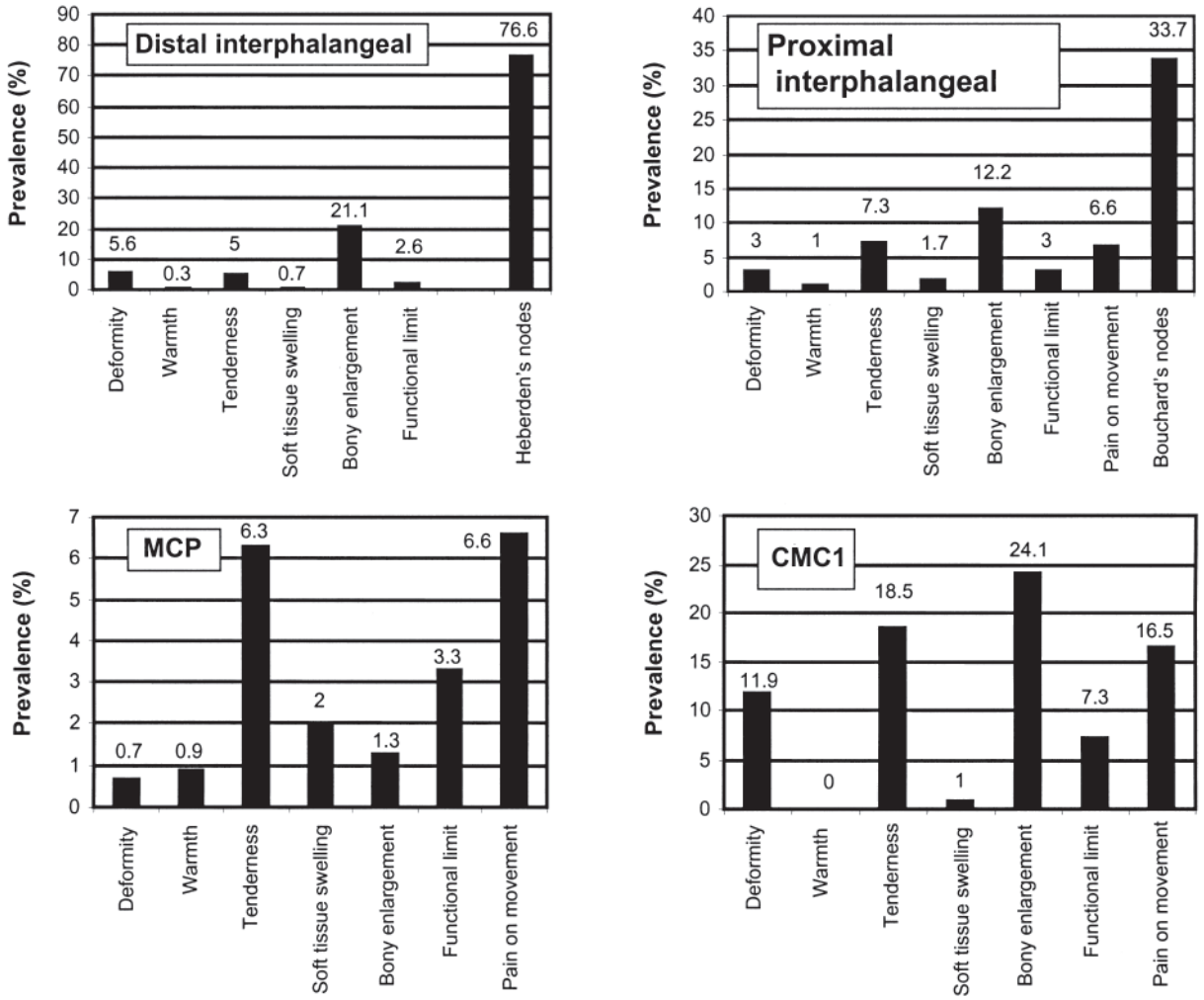


*Figure 1.* The prevalence of different hand signs for each group of hand joints. The most frequent sign in DIP and PIP joints was bony enlargement, followed by tenderness. The most frequent signs in CMC1 were bony enlargement, tenderness, pain on movement, functional limitation, and deformity. Pain on movement was not measured for DIP joints. MCP: metacarpophalangeal; CMC: carpometacarpal.

in about 2.7% of the population > 15 years of age. As in previous studies, prevalence increased with age, and was higher in women[2-5,7,9,10]. About 23% of people aged > 70 years had clinical hand OA. This supports the findings of studies in Western communities, leading us to conclude that even in those who live in the East and have an Eastern lifestyle or area of residence that is quite different, gender and aging are 2 important factors influencing hand OA[5,9,10].

To our knowledge, this is the first community-based study conducted in Iran on the epidemiology of rheumatic disorders, including clinical hand OA, in an urban population. In our view, it has 3 particular strengths. First, all physical examinations were performed by one of the rheumatology fellows. Second, the questionnaire and physical examination data sheets were reviewed by a rheumatologist, who confirmed the final diagnoses. Third, the data were collected from 50 random clusters in different socioeconomic classes in Tehran. To produce an estimate representative of the Tehran population, the survey sample was adjusted for the weight of the 1996 Tehran population survey, with districts (clusters) representing different socioeconomic classes as primary sample units. Although lack of hand radiographs prohibited comparison of radiographic hand OA with the symptomatic form, we believe that the prevalence of clinical hand OA derived from these data can be extrapolated to the general population of Tehran.

Our study adds to the evidence on the high prevalence of clinical hand OA in urban communities. It also gives a clear picture of hand signs and symptoms in an urban community. The prevalence, pattern, and relationship with age and sex of clinical hand OA in this study performed in an Eastern community resemble those found in Westerners. This prevalence calls for further attention by the appropriate services.

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## Demyelinating Disease Associated with Use of Etanercept in Patients with Seronegative Spondyloarthropathies

*To the Editor:*

Etanercept is a recombinant tumor necrosis factor-α (TNF-α) receptor immunoglobulin fusion protein. Its anti-TNF properties have gained approval for treatment of rheumatoid arthritis (RA), juvenile RA, psoriatic arthritis (PsA), Crohn's disease, and ankylosing spondylitis[1]. Etanercept binds specifically to TNF and blocks its interaction with surface TNF receptors. It inhibits binding of both TNF-α and TNF-ß to cell-surface TNF receptors, making TNF biologically inactive. Etanercept also modulates biological responses that are induced or regulated by TNF, including expression of adhesion molecules responsible for leukocyte migration, serum levels of cytokines, and serum levels of matrix metalloproteinase-3.

Data demonstrate a sustained benefit of etanercept treatment in patients with PsA, including inhibition of radiographic progression[2]. However, through clinical experience, etanercept has been linked to a potential increased risk of demyelinating disease. We describe a case series of 3 patients followed at the Carilion Clinic Rheumatology Clinic, Roanoke, Virginia, who were all diagnosed with demyelinating disease during the course of treatment with etanercept for PsA, iridocyclitis, and ankylosing spondylitis (AS). Our clinic follows 179 patients with spondyloarthritis; 81 patients (45%) are receiving TNF blockers, and 54 of them are receiving etanercept. We also follow 295 patients with RA reciving TNF blockers (36% of the RA population of the clinic). One hundred twelve patients of the 295 receive etanercept.

Case 1 was a 53-year-old man with a history of PsA, degenerative joint disease, dyslipidemia, and allergic rhinitis, who presented in 2001 for followup of severe PsA. He had been diagnosed 15 years before presentation. He had previously been treated with prednisone, methotrexate (MTX), and multiple nonsteroidal antiinflammatory agents, but continued to show progression of his disease. In 2002, he started taking etanercept and continued MTX, with some improvement of his symptoms. However, 6 months later he complained of numbness to his left anterior thigh, which spread to his entire left lower extremity and lower abdomen. Later he developed numbness to his right foot that was associated with mild back pain. He denied any family history of demyelinating disease. He was initially evaluated with lumbosacral spine radiographs, which showed prominent lumbar lordosis, and a diagnosis of acute sciatica, degenerative joint disease, and questionable S1 root versus pyriformis syndrome was made. He continued to have worsening back pain, with new symptoms of numbness to the left side of his face, lower extremity parasthesias, and urinary incontinence. Magnetic resonance imaging (MRI) of the thoracic spine revealed an intramedullary lesion at the C7-T1 level consistent with demyelination. Spinal fluid analysis was abnormal, with mildly elevated proteins, presence

of oligoclonal bands, and increased IgG index. Other laboratory studies were not supportive of any other etiology of his symptoms. A diagnosis of demyelinating disease was made and etanercept was discontinued. He was treated with interferon-ß (IFN-ß) 3 times weekly and given baclofen for leg cramps, with improvement of his symptoms. He had 2 subsequent flares of his multiple sclerosis (MS)-like symptoms that were treated with steroids, and he was started on IFN-ß-1a for prophylaxis of his demyelinating process in early 2004. His last flare requiring corticosteroids was in mid-2004 and his disease process has been stable since then.

Case 2 was a 42-year-old man who had a history of hyperlipidemia and PsA diagnosed 13 years before presentation in January 2004. He too had been treated previously with MTX and steroids. In addition, he had been given sulfasalazine, but continued to show progression of his disease. Nine months later, routine followup revealed worsening synovitis and he was started on etanercept. He was clinically improved taking etanercept, but 21 months later complained of headache, fatigue, and visual disturbance. This was later followed by back pain and numbness. He had no known family history of demyelinating disease. He was evaluated by a neurologist, who proceeded with investigation appropriate for MS. Laboratory studies revealed erythrocyte sedimentation rate 47 ml/h; and Lyme titer, dsDNA, antinuclear antibody, methylmalonic acid, homocysteine, and angiotensin-converting enzyme levels were all within normal limits. Cerebrospinal fluid (CSF) showed mildly increased protein and an increased IgG index. MRI of the spinal cord showed plaques at C5-C6, with subtle enhancement suggestive of MS. Etanercept was discontinued and the patient continued MTX therapy. No IFN was administered, but neurological symptoms improved with cessation of etanercept. He restarted daily steroids for PsA, but it remains poorly controlled without etanercept. In September 2007 he was given IFN by his neurologist after having a relapsing remitting course of his neurological symptoms.

Case 3 was a 51-year-old woman with a history of iron deficiency anemia and rhinosinusitis. She was HLA-B27-positive and based on the modified New York criteria fit the diagnosis of AS. Her symptoms included lower back pain and hip pain for > 3 months, morning stiffness, and iridocyclitis. A plain lumbosacral radiograph revealed she had loss of her sacroiliac joints, consistent with grade 4 sacroiliitis. She was being treated with MTX, prednisone, and nonsteroidal antiinflammatory drugs. She continued to show disease progression over a 3-year period and was started on etanercept; 18 months after initiation of etanercept she began to have paresthesias and progressive numbness of the fingertips. This was followed by numbness to the lower chest. Neurologic consultation was sought and there was a suspicion that her symptoms represented the MS-like syndrome associated with TNF-α agents. Investigations revealed an increased serum protein. CSF showed an increased immunoglobulin/albumin ratio. VDRL, Cryptococcal antigen, and India ink and Lyme studies were all negative. Thyroid-stimulating hormone and folate were within normal limits. MRI of the spine was positive for increased signal from C1–T4 with definite enhancement. MRI of the brain showed changes consistent with advanced demyelination in keeping with MS. Etanercept was discontinued in December 2006, with mild improvement in her neurological symptoms. At followup in May 2007 she continued to have abdominal numbness and pain and was scheduled to be seen again by her neurologist. To date she has not been started on a course of interferon.

The longterm safety of etanercept was compared between 597 elderly subjects (≥ 65 yrs) and 3296 younger subjects (< 65 yrs) in a metaanalysis of 22 etanercept clinical studies[3]. The analysis included 22 rheumatoid arthritis (RA), 2 psoriatic arthritis (PsA), and 2 AS studies. Eight cases of demyelinating disease were observed in subjects aged < 65 years, 6 in RA and 2 in PsA; no cases were found in patients age > 65 years. Another publication reporting data from September 1998 and June 2003 evaluated the rate of adverse events associated with the use of etanercept, infliximab, leflunomide, and MTX, in which the rate of demyelinating disorders was 29.96 per 100,000 patient-years in the etanercept patients[3]. A publication from the US Food and Drug Administration's FDA Medwatch system in December 2001 reported 20 cases of neurological disease, 18 after etanercept treatment and 2 after infliximab[4].

Cases of transverse myelitis, optic neuritis, MS, and new onset or exacerbation of seizure disorders have been observed in association with etanercept therapy. The causal relationship between these events and etanercept therapy remains unclear. The reported rate of demyelination from postmarketing experience likely underestimates the incidence of these events due to underreporting, and the total number of patients exposed to etanercept being an estimate[3]. Therefore it is difficult to state whether the rate of demyelinating disease noted in our patient population is higher than expected, with 2.5% of our patients receiving etanercept demonstrating a clinical picture in keeping with demyelinating disease.

No clinical trials have been performed evaluating etanercept therapy in patients with MS. However, other TNF-α antagonists administered to patients with MS have been associated with increases in disease activity. The exacerbation of MS appeared to occur as a result of neutralization of TNF-α rather than lymphotoxin. In addition, TNF-α antagonists cannot penetrate the blood-brain barrier to neutralize CNS TNF demyelination. This association has been seen with infliximab, in which clinical studies have demonstrated an increase in disease activity with MRI evidence of worsening disease[5]. One report on demyelination occurring during anti-TNF therapy showed that the time interval from receiving the drug to the presentation of symptoms was on average 2–6 months for those with PsA, but had an even wider range in patients with RA, from 1 dose of the medication to 10 months[6]. Interestingly, some of our cases showed a much longer time lag. Data from Amgen reported cases in which the interval between introduction of etanercept and neurologic complaints was 9–17 months. No case of demyelinating disease was observed in patients older than age 65 years[3].

Our case series emphasizes that the neurologic deficits from etanercept occurred in an unpredictable manner when viewed in relation to the initiation of the drug. Also, a wide spectrum of deficits appeared to be associated with etanercept. Our 3 patients had no personal or family history of MS, which favors the postulate of de novo occurrence of these neurologic deficits with use of TNF-α antagonist. We concur with recommendations that patients be diligently screened using a comprehensive history and neurological examination before starting TNF-α antagonists such as etanercept, and that the physician remain vigilant for symptoms of development of demyelinating disease when seeing patients for routine followup during treatment with these agents. All cases of new-onset demyelination should be identified to determine what if any risk factors they might share[7]. It would also seem reasonable to avoid the use of anti-TNF-α agents in patients with established demyelinating disease and to immediately discontinue therapy and pursue diagnostic tests in any patient with suspected demyelination[8]. Current guidelines are to avoid the use of anti-TNF drugs in individuals with a history of MS or demyelinating disease. However, although the overall number of individuals with new-onset demyelinating events undergoing anti-TNF therapy appears to be small, these episodes can be clinically silent, making it difficult to assess the actual numbers of affected individuals[7]. This emphasizes the need to establish registries of patients receiving these agents; these registries should include a comparison cohort of patients not receiving biological treatments. It will likely be many years before definitive answers are available[9].

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## Recovery from Multiple Cranial Nerve Palsy of Wegener's Granulomatosis with Infliximab

*To the Editor:*

Wegener's granulomatosis (WG)-related intracranial involvement is classified into 3 forms: contiguous invasion of granuloma from extracranial sites, remote intracranial granuloma, and central nervous system vasculitis[1,2]. We describe a case of WG in which the extension of granuloma from extracranial sites of the skull base resulted in refractory multiple cranial nerve palsy that was dramatically resolved by infliximab therapy.

A 42-year-old man had developed bilateral hearing loss and facial nerve palsy since November 2004. Pulmonary nodules were observed and partial resection of the left upper lobe was performed, with a pathological finding of necrotizing vasculitis with granulomatous formation. Otitis media, facial nerve palsy, hearing loss, and swallowing disturbance become apparent, and he was referred to our hospital in June 2005. On admission, neurological examinations revealed peripheral cranial palsies of bilateral trigeminal, facial, vagal, and hypoglossal nerves. Other cranial nerves, pyramidal tract, and extrapyramidal tract were not involved. In audiometry, the right hearing level was scaled out and the left was 111.3 dB. The C-reactive protein (CRP) level had increased to 7.95 mg/dl, but proteinase 3 antineutrophil cytoplasmic autoantibodies [PR3-ANCA (PR3-ANCA kit; Euro–Diagnostica AB, Malmö, Sweden)] were negative. T1-weighted magnetic resonance imaging (MRI) of the brain with gadolinium-diethylenetriamine (Gd-DPTA) infusion showed a remarkably enhanced lesion from the skull base. According to the international classification criteria[3], he was diagnosed as having WG complicated with intracranial granuloma formation, extending from the skull base.

He was treated with oral prednisolone (PSL; 60 mg/day) and cyclophosphamide (CYC; 100 mg/day) for 2 months. CRP improved slightly from 7.95 mg/dl to 4.87 mg/dl; however, neither cranial nerve palsy nor abnormal MRI lesion changed with treatment (Figure 1A). Moreover, manic-depressive psychosis, probably due to corticosteroid therapy, had appeared, leading to reduction of PSL dosage from 60 to 30 mg/day at 2 months. Considering the therapeutic time course, this patient appeared to have WG that was difficult to cure by standard therapy. A protocol for therapy with infliximab was approved by the Institutional Review Board of Nagasaki University, and scheduled according to the same sequential regime used in rheumatoid arthritis in Japan (3 mg/kg), with continuation of CYC and PSL.

After the second infusion at 6 weeks, CRP diminished to 0.08 mg/dl and the Birmingham Vasculitis Activity Score (BVAS)[4] fell from 22 to 4. Swallowing disturbance as well as trigeminal and facial nerve palsy gradually improved. In nerve conduction velocity studies, the amplitude of the facial nerves also improved: improvement was found in the right orbicularis oculi muscle (from 0 to 200 μV), left orbicularis oculi muscle (from 500 to 920 μV), left nasalis muscle (from 270 to 1610 μV), and left orbicularis oris muscle (from 104 to 540 μV) at 14 weeks after the third infusion. The right auditory disorder did not resolve, but the left hearing level improved from 111.3 dB to 45.0 dB. Pulmonary nodules also disappeared. MRI detection of the enhancement area at proximate infliximab infusion (Figure 1A) was significantly reduced compared with 14 weeks (Figure 1B) and 80 weeks (Figure 1C). Remission (BVAS 0) was achieved at 14 weeks. Infliximab infusion was continued every 8 weeks up to 78 weeks (11 infusions), when PSL was tapered from 30 to 5 mg/day. CYC dosage reached 10 g, then was switched to azathioprine. BVAS remained 0 at 78 weeks, and then infliximab was discontinued. Remission still remained at 102 weeks.

This is a case of ANCA-negative, biopsy-proven WG with severe intracranial granulomatous involvement with multiple cranial nerve palsies. Reinhold-Keller, *et al* reported that ANCA-negative WG shows more serious CNS involvement than PR3-ANCA-positive WG[5], which is consistent with our case.

Efficacy of TNF blockage agents in WG is reviewed in several reports[6]. On the basis of high rates of adverse events, etanercept use is not recommended for WG; however, Mukhtyar and Luqmani have described an excellent effect of infliximab, demonstrating that 43 of 53 patients (81%) given infliximab experienced remission. In addition, 37 of these 53 patients (69%) had been classified as refractory cases with standard treatment[6]. Infliximab, in most cases, is administered with concurrent treatment[6]. Since the therapeutic duration of CYC and PSL is short, 2 months in this case, a delayed efficacy of CYC and PSL could become apparent after infliximab. However, high BVAS, abnormal MRI lesion, and high serum CRP concentration were still present, before infliximab, regardless of the administration of 100 mg/day CYC and PSL (at least 30 mg/day) for 2 months, and these indicators rapidly improved in 6 weeks after infliximab. We suggest these therapeutic outcomes indicate the efficacy of infliximab.

Our case is the first infliximab-induced recovery of intracranial involvement of WG. We hope this experience encourages the consideration of infliximab treatment for refractory and life-threatening WG.

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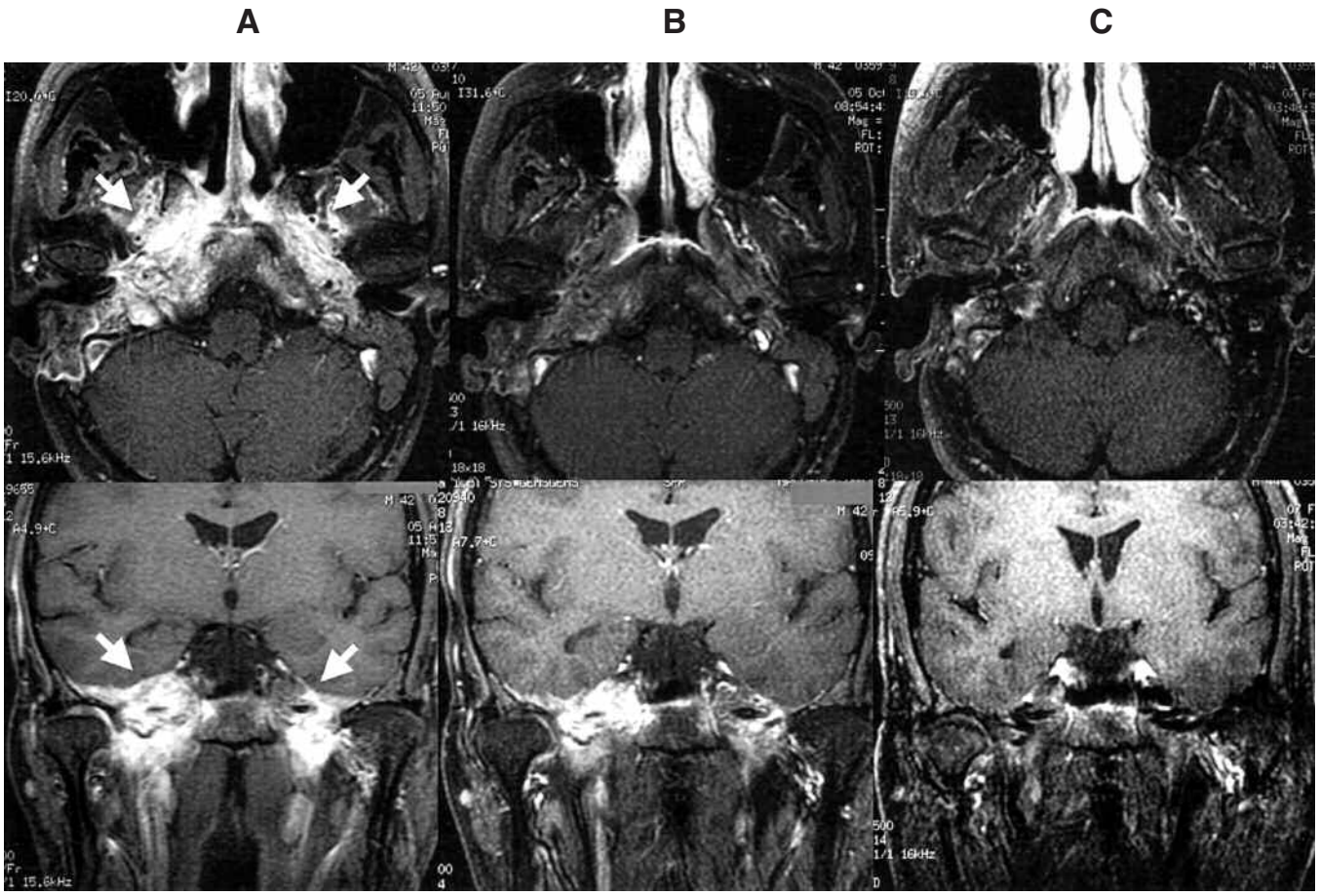


*Figure 1.* Axial and coronal T1-weighted MR images with gadolinium enhancement before infliximab injection (A) and after infliximab injection at Weeks 14 (B) and 80 (C). Abnormal MRI features were unresolved by conventional therapy (A). However, the area was reduced by infliximab therapy (B and C).

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# Correction

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The author Hyoung Doo Shin is affiliated with the Laboratory of Genomic Diversity, Department of Life Science, Sogang University, Seoul, Korea. We regret the error.