EDITORIAL

Influence of Human Leukocyte Antigen-DRB1 on the Susceptibility and Severity of Rheumatoid Arthritis

Miguel A. Gonzalez-Gay, Carlos Garcia-Porrua, and Ali H. Hajeer

Background and Objectives: **All human leukocyte antigen (HLA)-DRB1 alleles associated with rheumatoid arthritis (RA) encode a conserved amino acid sequence (QKRAA, QRRAA, or RRRAA) at position 70-74 in the third hypervariable region (HVR3) of the DRβ_1 chain, which is commonly called the shared epitope (SE). Several studies, however, have associated the HLA-DRB1 gene in RA severity and progression rather than with susceptibility. Moreover, the association with disease severity and presence of the SE varies among different ethnic populations. HLA-DRB1 alleles also influence the disease onset. In this manuscript, the role of the HLA genes in RA was examined.**

Methods: **A retrospective review of the literature was conducted to analyze the influence of the HLA-class II genes on the susceptibility, severity and protection against RA.**

Results: **The HLA-DRB1*0401/*0404 genotype was associated with a higher risk for early disease onset in more severe forms in patients from the United Kingdom (UK). In northwest Spain, RA onset under 40 years is strongly associated with HLA-DRB1*0401 and *0404. In contrast, RA onset above 60 years is associated with HLA-DRB1*01. The protection against RA linked to some HLA-DRB1 alleles encoding a DERAA sequence of amino acids at position 70-74 in the HVR3 of the DRβ1 chain, and specifically aspartic acid (D) at position 70 of this chain, recently was confirmed in both UK and northwest Spanish populations. Besides HLA-class II, other genes may be implicated in RA. Polymorphism in the tumor necrosis factor (TNF) region seems to be associated with RA, even in patients without the HLA-DRB1 SE. However, other genes such as interleukin-1 (IL-1) and corticotropin-releasing hormone may play a role in susceptibility to RA.**

Conclusions: **The additive effect of various genes may account for the development of RA and its clinical severity.**

INDEX WORDS: HLA-DRB1 gene; protective alleles; shared epitope; tumor necrosis factor α.

RHEUMATOID ARTHRITIS (RA) is an autoimmune disease where both environmental and genetic factors seem to be implicated in disease susceptibility and severity. Family studies have supported a genetic influence; higher concordance of RA in monozygotic rather than in dizygotic twins has been described (1).

Human Leukocyte Antigen Association With RA

Initial studies by Stastny using mixed lymphocyte culture reactions showed an association between human leukocyte antigen (HLA)-Dw4 (HLA-DRB1*0401) and RA. Subsequent studies

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proved an association between RA and a broad serologically defined HLA-DR4 specificity (2). However, DNA sequence level studies showed that some alleles of the HLA-DRB1 gene could not be discriminated by antibodies used in tissue typing. HLA-DRB1 typing performed on DNA samples using polymerase chain reaction (PCR) based molecular methods showed that some HLA-DRB1*04 alleles, such as *0401, *0404, *0405, and *0408, were associated with RA, while other alleles, such as *0402 or *0403, were not (3). Although it became evident that HLA-DRB1*0401 and *0404 were associated with RA in Northern Europe and Western North American, studies of white patients in other populations have shown that other HLA-DR antigens also are associated with RA. For example, HLA-DR6 (DRB1*1402) was observed in Native Americans (4). HLA-DRB1*0101 and *1001 were associated with RA in Indian patients and in Mediterranean patients (3,5). These differences are more remarkable in Spain. In southern Spain, an association with HLA-DRB1*0101, *1001, and *0405 has been reported (6), whereas, in the Lugo region of northwestern Spain, the associations observed between HLA-DRB1 alleles and RA are similar to those reported in the United Kingdom (UK) (3). Thus, in that particular region of Spain, the predominant HLA association seen is with HLA-DRB1*0401, although HLA-DRB1*0404, *0405 and *0101 are all marginally increased (7).

Shared Epitope Hypothesis

Most HLA-DRB1 associations with RA have in common a conserved sequence of amino acids at position 70-74 in the third hypervariable region (HVR3) of the DRβ1 chain. This subsequently led to the formulation of the shared epitope (SE) hypothesis, which proposes that all RA-associated HLA-DRB1 alleles (DRB1*0101, *0102, *0401, *0404, *0405, *0408, *1001, *1402) share a conserved motif of amino acid residues (QKRAA/QRRAA/RRRAA) in the HVR3 of the DRB1 molecule (8,9) (Table 1). This remains a working hypothesis although it does not explain all that is known about RA susceptibility (10).

Table 1: Epitope Encoded by the Third Hypervariable Region of RA-Associated Alleles

	Amino Acid Position				
HLA-DRB1* **Allele**	**70**	**71**	**72**	**73**	**74**
*0101	Q	R	R	A	A
*0102	Q	R	R	A	A
*0401	Q	K	R	A	A
*0404	Q	R	R	A	A
*0405	Q	R	R	A	A
*0408	Q	R	R	A	A
*1001	R	R	R	A	A
*1402	Q	R	R	A	A

Are HLA-DRB1 Shared Epitope Alleles Associated With Disease Severity Rather Than Susceptibility?

Several studies have indicated that the influence of HLA-DRB1 molecules on RA is due to effects on disease severity and progression rather than susceptibility. This was initially reported by investigators in the UK for HLA-DR4 and appeared to be related to the extent of bone erosions (11-13). However, the association with disease severity varies among different ethnic populations. Thus, a well-defined association exists between severe disease outcome and presence of the SE, particularly in populations from northern Europe and North America (11-18). This observation also has been reported by del Rincón and Escalante (19) in Mexican Americans carrying the SE sequence. Likewise, in the Lugo region of northwest Spain, erosive disease was associated with carriage of the SE, particularly HLA-DRB1*0101 and DRB1*04, whereas rheumatoid factor positivity was associated mainly with DRB1*0401 (7). However, in patients with RA from Southern Spain the rheumatoid SE was not predictive for radiological severity after a mean follow-up period of 9 years (20). Moreover, HLA-DR4 is not a severity marker in

Abbreviations	
CRH	Corticotropin-releasing hormone
HLA	Human leukocyte antigen
IL	Interleukin
RA	Rheumatoid arthritis
SE	Shared epitope
HVR3	Third hypervariable region
TNF	Tumor necrosis factor

Greek patients with RA (21). In the present issue of Seminars in Arthritis and Rheumatism, Ioannidis et al confirm the lack of association between HLA-DRB1*0401 and RA susceptibility in Greek patients. However, these authors support the role of SE alleles, mainly due to HLA-DRB1*01 and to a lesser extent to DRB1*1001, as disease markers of disease severity manifested by higher Larsen scores in the hands and feet of SE positive patients (22). Of note, in unselected series of uniformly treated patients with RA from northwestern Spain, those patients who required treatment with cyclosporine A because of severe disease were significantly more likely to carry an SE allele than patients not requiring such treatment (23). The choice of cyclosporine A treatment because of clinical severity and partial response to methotrexate was not associated with a positive rheumatoid factor, and it was primarily associated with patients carrying DRB1*0401. These data provide further evidence for an association between the SE and the development of severe disease that is likely to require aggressive drug therapy (23). Thus, the genetic differences between Lugo and Southern Spain and Greece may help explain the variability in RA severity among different populations.

Extraarticular manifestations in RA, such as rheumatoid nodules, vasculitis, and pulmonary fibrosis, usually are associated with more severe disease. Several studies have shown an association between SE alleles and extra-articular disease. Almost 2 decades ago, Ollier et al (24) suggested that the frequency of HLA-DR4 was increased in patients with nodular disease. They observed that HLA-DR4 patients constituted a subset, which exhibited features of extra-articular disease (24). HLA-DR4 also was associated with extra-articular manifestations of RA in northern Italian and French populations (25,26). In North American patients, Weyand et al (27) identified characteristic genotypes for patients with nodular disease and those who developed severe organ involvement. Both homozygosity for the HLA-DRB1*0401 allele and the presence of 2 different alleles carrying the SE accounted for an increased risk of severe extra-articular manifestations in patients from Minnesota (27). Although rheumatoid nodules were associated with heterozygosity for 2 SE alleles, homozygosity for the HLA-DRB1*401 allele was associated with major organ involvement (27). However, even though the presence of SE alleles was associated with more severe disease in patients from northwest Spain (23), the frequency of 2 different SE alleles in patients with RA with rheumatoid nodules was not different from that in patients without nodules (28). Furthermore, in Dutch patients with RA the occurrence of rheumatoid vasculitis with major organ involvement was not increased in patients carrying the HLA-DRB1*04 alleles (29).

Do Late-Onset RA and "Classic" RA Have Different HLA-DRB1 Genetic Susceptibility?*

The onset of RA usually occurs in middle age. However, disease onset may start after the age of 60 years, and these cases are defined as having a late or elderly onset (30). Of note, a subset of patients with RA with elderly onset may present with polymyalgia symptoms that may be difficult to differentiate from polymyalgia rheumatica. In this regard, few studies have examined the relationship between HLA and the age of RA onset. In the UK, Jaraquemada et al (12) observed a significantly decreased association of HLA-DR4 with increasing age of RA onset in women. More recently, MacGregor et al (31) reported that SE homozygosity and the HLA-DRB1*0401/*0404 genotype carried a substantially higher risk for early disease onset in its more severe forms, in particular in men, in UK patients RA. In northwest Spain, patients with RA with disease onset earlier than 40 years of age were associated strongly with HLA-DRB1*0401 and *0404. In contrast, patients with RA with disease onset after 60 years of age were not associated with HLA-DRB1*04 but instead were associated with HLA-DRB1*01 (32). Interestingly, the stratification of patients with late onset RA by rheumatoid factor status revealed further heterogeneity. Thus, late onset RA with positive rheumatoid factor was associated with HLA-DRB1*01, whereas late onset seronegative RA had an increased frequency of HLA-DRB1*13/*14 alleles, which also was observed in polymyalgia rheumatica (32).

RA Protective Epitope

The concept of joint protection linked to some HLA-DRB1 alleles encoding a DERAA sequence of amino acids at position 70-74 in the HVR3 of the DRβ1 chain, and specifically aspartic acid (D) at position 70 of this chain, was developed from initial observations in the mouse experimental

model of arthritis, collagen-induced arthritis. In transgenic and F1 mice, the presence of the Eb^d gene yielded a significant reduction in the incidence and severity of arthritis (33,34). As in all protective HLA-DRB1 alleles, eg, *0402, *1301, and *1302, the Eb^d gene encodes aspartic acid (D) at position 70 of the Eβd chain. Thus, the presence of this Eβ molecule, which is homologous to the human DRβ_1, induced protection in susceptible H2-A^q mice.

Zanelli et al (35) suggested that HLA-DQ genes (H-2A equivalent) might mediate the susceptibility to RA while some HLA-DRB1 alleles might mediate protection against RA. They proposed that certain HLA-DQ alleles predispose to severe RA. They also suggested that a self-peptide sequence containing DERAA from the HVR3 of the DRβ1 chain of some HLA-DRB1 alleles (DRB1*0103, *0402, *1102, *1103, *1301, and *1302) may protect against RA if it is presented by DQ molecules. In a subsequent study in Dutch and Swiss populations they found that DQA1*0301-homozygous and DQA1*0301//DQA1*0101/04-heterozygous patients were highly predisposed to RA in both populations, whereas DQA1*0101/04-homozygous subjects were not. However, DRB1 alleles carrying the motif DERAA in their HVR3 provided a protection against RA in DQA1*0101/04 but not in DQA1*0301-positive patients (36).

Recently, Snijders et al (37) reported a model in which a self-MHC-derived DERAA peptide modulated predisposition to autoimmune disease in humans. Interestingly, Mattey et al (38) also have shown that patients carrying a DRB1 allele with the DERAA sequence have less severe radiographic outcomes. To further investigate whether the association between RA and HLA-DRB1 is influenced by the amino acid residue encoded at position 70 (β70) of the HVR3 of the HLA-DRβ chain, our group compared the frequencies of HLA-DRB1 alleles encoding different amino acid residues at β70 between patients with RA and controls in a population from the UK, and in a population from northwest Spain (39). In both UK and northwest Spanish populations, those patients with SE+/SE- genotypes that included a SE+ allele encoding a Q residue at position 70 of the DRβ1 chain (Q^{70}) had an increased risk of developing RA. In contrast, those SE+ patients who carried an allele encoding a D residue at position 70 (D^{70}) had no increased risk. Thus, the possession of D70SE- has a dominant protective effect in SE+ patients and is more strongly protective than Q70SE-. In SE-/SE- patients, there was hierarchy of susceptibility to RA depending on the combination of alleles encoding different residues at β70. In both UK and Spanish populations, the carriage of 2 alleles encoding D^{70} was associated with the lowest risk of developing RA. Analysis of trend in both populations indicated that the strength of association of different genotypes with RA could be arranged in order (from Q^{70SE+}/Q^{70SE+} to D^{70SE-}/D^{70SE-}) according to which amino acid residues were encoded at β70 and whether or not they formed part of a SE sequence (39). Thus, not all SE+ individuals have an increased risk of developing RA, observations compatible with the hypothesis and findings of Zanelli et al (35-36).

Other Potential RA Susceptibility Genes

Besides HLA-class II, other genes may be implicated in RA. Among other potential candidates is tumor necrosis factor (TNF)-α. This proinflammatory cytokine seems to be important in destructive RA, and neutralization of this molecule with monoclonal anti-TNF antibodies is a treatment for RA (40). The TNF region is polymorphic and is located within the HLA class III region. A number of biallelic polymorphisms have been identified within the TNF locus, as well as 5 microsatellite markers (a-e) (41). Polymorphisms within the TNF region have been correlated with variations in TNF-α level and expression. Several conserved DRB1/TNF haplotypes have been identified and occur at higher frequencies in patients with RA (42). Of note, Martinez et al (43) have observed that polymorphism in the TNF region is associated with RA, even in those patients without the HLA-DRB1 SE. In patients from northwest Spain, different gene loci within the HLA-DRB1 and TNF regions were independent markers of disease susceptibility. Moreover, TNF microsatellite polymorphism was associated with the susceptibility to erosive and seropositive disease, which was independent of SE status and HLA-DRB1*04 alleles (7). In the UK, the radiographic severity of RA was associated with an interaction between the SE and the TNF a6 microsatellite polymorphism (44). Mu et al (45) also described an interaction between the SE and TNF a11 in relation to RA severity. However, in northwest Spain, the analysis of possible

interactions between HLA-DRB1 and TNF alleles showed no association with extra-articular manifestations (28).

Deighton et al (46) suggested that the contribution of genes within the major histocompatibility complex to RA only accounts for one-third to one-half of the total genetic contribution. Other potential RA susceptibility genes include interleukin (IL)-1, aromatase, corticotropin-releasing hormone (CRH), and a region on the X chromosome (47). RA is more common in women than men, especially before menopause: men may be protected by hormonal factors and require a stronger genetic component to develop disease. CRH polymorphisms have been investigated in RA. The A2B1 compound allele was protective against development of RA in Caucasoid people from England (48) and correlated with later onset of disease (48). However, in African people from South Africa, A1B1 was associated with RA (48).

In summary, RA is a polygenic disease in which different genes may be implicated in disease susceptibility and severity. The additive effect of these genes may account for the development of the disease and its clinical expression in terms of severity.

REFERENCES

1. Silman AJ, MacGregor AJ, Thomson W, Holligan S, Carthy D, Farhan A, et al. Twin concordance rates for rheumatoid arthritis: Results from a nationwide study. Br J Rheumatol 1993;32:903-7.
2. Stastny P. Association of the B-cell alloantigen DRw4 with rheumatoid arthritis. N Engl J Med 1978;298:869-71.
3. Ollier W, Thomson W. Population genetics of rheumatoid arthritis. Rheum Dis Clin North Am 1992;18:741-59.
4. Willkens RF, Nepom GT, Marks CR, Nettles JW, Nepom BS. Association of HLA-Dw16 with rheumatoid arthritis in Yakima Indians. Further evidence for the "shared epitope" hypothesis. Arthritis Rheum 1991; 34:43-7.
5. Ollier WE, Stephens C, Awad J, Carthy D, Gupta A, Perry D, et al. Is rheumatoid arthritis in Indians associated with HLA antigens sharing a DR beta 1 epitope? Ann Rheum Dis 1991; 50:295-7.
6. Yelamos J, Garcia-Lozano JR, Moreno I, Aguilera I, Gonzalez MF, Garcia A, et al. Association of HLA-DR4-Dw15 (DRB1*0405) and DR10 with rheumatoid arthritis in a Spanish population. Arthritis Rheum 1993;36:811-4.
7. Hajeer AH, Dababneh A, Makki RF, Thomson W, Poulton K, Gonzalez-Gay MA, et al. Different gene loci within the HLA-DR and TNF regions are independently associated with susceptibility and severity in Spanish rheumatoid arthritis patients. Tissue Antigens 2000;55:319-25.
8. Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis Rheum 1987;30:1205-13.
9. Winchester R, Dwyer E, Rose S. The genetic basis of rheumatoid arthritis. The shared epitope hypothesis. Rheum Dis Clin North Am 1992;18:761-83.
10. Ollier WER, Hajeer AH. Does the HLA-DRB1 shared epitope really contribute that much to the development or severity of rheumatoid arthritis? In: Controversies in Rheumatology, Isenberg DA, Tucker LB, eds. London, Martin Dunitz 2000; 1-12.
11. Young A, Jaraquemada D, Awad J, Festenstein H, Corbett M, Hay FC, et al. Association of HLA-DR4/Dw4 and DR2/Dw2 with radiologic changes in a prospective study of patients with rheumatoid arthritis. Preferential relationship with HLA-Dw rather than HLA-DR specificities. Arthritis Rheum 1984;27:20-5.
12. Jaraquemada D, Ollier W, Awad J, Young A, Silman A, Roitt IM, et al. HLA and rheumatoid arthritis: A combined analysis of 440 British patients. Ann Rheum Dis 1986;45:627-36.
13. Jaraquemada D, Ollier W, Awad J, Young A, Festenstein H. HLA and rheumatoid arthritis: Susceptibility or severity? Dis Markers 1986;4:43-53.
14. Weyand CM, Hicock KC, Conn DL, Goronzy JJ. The influence of HLA-DRB1 genes on disease severity in rheumatoid arthritis. Ann Intern Med 1992;117:801-6.
15. Moreno I, Valenzuela A, Garcia A, Yelamos J, Sanchez B, Hernanz W. Association of the shared epitope with radiological severity of rheumatoid arthritis. J Rheumatol 1996;23: 6-9.
16. Wagner U, Kaltenhauser S, Sauer H, Arnold S, Seidel W, Hantzchel H, et al. HLA markers and prediction of clinical course and outcome in rheumatoid arthritis. Arthritis Rheum 1997;40:341-51.
17. Toussirot E, Auge B, Tiberghien P, Chabod J, Cedoz JP, Wendling D. HLA-DRB1 alleles and shared amino acid sequences in disease susceptibility and severity in patients from eastern France with rheumatoid arthritis. J Rheumatol 1999;26: 1446-51.
18. Meyer JM, Evans TI, Small RE, Redford TW, Han J, Singh R, et al. HLA-DRB1 genotype influences risk for severity of rheumatoid arthritis. J Rheumatol 1999;26:1024-34.
19. Del Rincón I, Escalante A. HLA-DRB1 alleles associated with susceptibility or resistance to rheumatoid arthritis, articular deformities, and disability in Mexican Americans. Arthritis Rheum 1999; 42:1329-38.
20. Valenzuela-Castaño A, García-López A, Pérez-Vilches D, Rodríguez-Pérez R, González-Escribano MF, Núñez-Roldán A. The predictive value of the HLA shared epitope for severity of radiological joint damage in patients with rheumatoid arthritis. A 10 year observational prospective study. J Rheumatol 2000;27:571-4.
21. Boki A, Drosos AA, Tzioufas AG, Lanchbury JS, Panayi GC, Moutsopoulos HM. Examination of HLA-DR4 as a severity marker for rheumatoid arthritis in Greek patients. Ann Rheum Dis 1993;52:517-9.
22. Ioannidis JPA, Tarassi K, Papadopoulos IA, Voulgari PV, Boki KA, Papasteriades CA, et al. Shared epitope and rheumatoid arthritis: Disease associations in Greece and meta-

analysis of Mediterranean European populations. Semin Arthritis Rheum 2002;31:361-370.

23. Gonzalez-Gay MA, Hajeer AH, Garcia-Porrua C, Dababneh A, Thomson W, Ollier WE, et al. Patients chosen for treatment with cyclosporine because of severe rheumatoid arthritis are more likely to carry HLA-DRB1 shared epitope alleles, and have earlier disease onset. J Rheumatol 2002;29: 271-5.

24. Ollier W, Venables PJW, Mumford PA, Maini RN, Awad J, Jaraquemada D, et al. HLA antigen associations with extra-articular rheumatoid arthritis. Tissue Antigens 1984;24: 279-91.

25. Salvarani C, Macchioni PL, Mantovani W, Rossi F, Veneziani M, Boiardi L, et al. Extraarticular manifestations of rheumatoid arthritis and HLA antigens in Northern Italy. J Rheumatol 1992;19:242-6.

26. Perdriger A, Chales G, Semana G, Guggenbuhl P, Meyer O, Quillivic F, et al. Role of HLA-DR-DR and DR-DQ associations in the expression of extraarticular manifestations and rheumatoid factor in rheumatoid arthritis. J Rheumatol 1997; 24:1272-6.

27. Weyand CM, Xie C, Goronzy JJ. Homozygosity for the HLA-DRB1 allele selects for extraarticular manifestations in rheumatoid arthritis. J Clin Invest 1992;89:2033-9.

28. Mattey DL, Gonzalez-Gay MA, Garcia-Porrua C, Thomson W, Hajeer HA, Ollier WER. Influence of HLA-DRB1 and TNF microsatellite polymorphisms on the expression of extraarticular manifestations in rheumatoid arthritis patients from northwest Spain. Clin Exp Rheumatol 2001;19:703-8.

29. Voskuyl AE, Hazes JMW, Schreuder GMT, Schipper RF, de Vries RPP, Breeveld FC. HLA-DRB1, DQA1, and DQB1 genotypes and risk of vasculitis in patients with rheumatoid arthritis. J Rheumatol 1997;24:852-5.

30. Healey LA. Rheumatoid arthritis in the elderly. Clin Rheum Dis 1986;12:173-9.

31. MacGregor A, Ollier W, Thomson W, Jawaheer D, Silman A. HLA-DRB1*0401/0404 genotype and rheumatoid arthritis: Increased association in men, young age at onset, and disease severity. J Rheumatol 1995;22:1032-6.

32. Gonzalez-Gay MA, Hajeer AH, Dababneh A, Makki R, Garcia-Porrua C, Thomson W, et al. Seronegative rheumatoid arthritis in elderly and polymyalgia rheumatica have similar patterns of HLA association. J Rheumatol 2001;28:122-5.

33. Gonzalez-Gay MA, Nabozny GH, Bull MJ, Zanelli E, Douhan J 3rd, Griffiths MM, et al. Protective role of major histocompatibility complex class II Ebd transgene on collagen-induced arthritis. J Exp Med 1994;180:1559-64.

34. Gonzalez-Gay MA, Zanelli E, Krco CJ, Nabozny GH, Hanson J, Griffiths MM, et al. Polymorphism of the MHC class II Eb gene determines the protection against collagen-induced arthritis. Immunogenetics 1995;42:35-40.

35. Zanelli E, Gonzalez-Gay MA, David CS. Could HLA-DRB1 be the protective locus in rheumatoid arthritis? Immunol Today 1995;16:274-8.

36. Zanelli E, Huizinga TW, Guerne PA, Vischer TL, Tiercy JM, Verduyn W, et al. An extended HLA-DQ-DR haplotype rather than DRB1 alone contributes to RA predisposition. Immunogenetics 1998;48:394-401.

37. Snijders A, Elferink DG, Geluk A, van Der Zanden AL, Vos K, Schreuder GM, et al. An HLA-DRB1-derived peptide associated with protection against rheumatoid arthritis is naturally processed by human APCs. J Immunol 2001;166:4987-93.

38. Mattey DL, Hassell AB, Plant MJ, Cheung NT, Dawes PT, Jones PW, et al. The influence of HLA-DRB1 alleles encoding the DERAA amino acid motif on radiological outcome in rheumatoid arthritis. Rheumatology (Oxford). 1999;38: 1221-7.

39. Mattey DL, Dawes PT, Gonzalez-Gay MA, Garcia-Porrua C, Thomson W, Hajeer AH, et al. HLA-DRB1 alleles encoding an aspartic acid at position 70 protect against development of rheumatoid arthritis. J Rheumatol 2001;28:232-9.

40. Elliott MJ, Maini RN, Feldmann M, Lung-Fox A, Charles P, Biji H, et al. Repeated therapy with monoclonal antibody to tumor necrosis factor alpha (cA2) in patients with rheumatoid arthritis. Lancet 1994;344:1125-7.

41. Udalova IA, Nedospasov SA, Webb GC, Chaplin DD, Turestskaya RL. Highly informative typing of the human TNF locus using adjacent polymorphic markers. Genomics 1993;16: 180-6.

42. Hajeer AH, Worthington J, Silman AJ, Ollier WER. Association of tumor necrosis factor microsatellite polymorphisms with HLA-DB1*04–bearing haplotypes in rheumatoid arthritis patients. Arthritis Rheum 1996;39:1109-14.

43. Martinez A, Fernandez-Arquero M, Pascual-Salcedo D, Conejero L, Alves H, Balsa A, et al. Primary association of tumor necrosis factor-region genetic markers with susceptibility to rheumatoid arthritis. Arthritis Rheum 2000;43:1366-70.

44. Mattey DL, Hassell AB, Dawes PT, Ollier WER, Hajeer A. Interaction between tumor necrosis factor microsatellite polymorphisms and the HLA-DRB1 shared epitope in rheumatoid arthritis. Influence on disease outcome. Arthritis Rheum 1999; 42:2698-704.

45. Mu H, Chen JJ, Jiang Y, King M-C, Thomson G, Criswell LA. Tumor necrosis factor α microsatellite polymorphism is associated with rheumatoid arthritis severity through an interaction with the HLA-DRB1 shared epitope. Arthritis Rheum 1999;42:438-42.

46. Deighton CM, Walker DJ, Griffiths ID, Roberts DF. The contribution of HLA to rheumatoid arthritis. Clin Genet 1989; 36:178-82.

47. Ollier WE, Harrison B, Symmons D. What is the natural history of rheumatoid arthritis? Baillieres Best Pract Res Clin Rheumatol 2001;15:27-48.

48. Baerwald CG, Mok CC, Tickly M, Lau CS, Wordsworth BP, Ollier B, et al. Corticotropin releasing hormone (CRH) promoter polymorphisms in various ethnic groups of patients with rheumatoid arthritis. Z Rheumatol 2000;59:29-34.