Otology & Neurotology
00:00–00 © 2007, Otology & Neurotology, Inc.

HLA-DRB1*1101 Allele May Be Associated With Bilateral Ménière's Disease in Southern European Population

*Jose A. Lopez-Escamez, †Jose R. Vilchez, ‡Andres Soto-Varela, ‡Sofia Santos-Perez, §Herminio Perez-Garrigues, ||Ismael Aran, and †Miguel A. Lopez-Nevot

**Otology and Neurotology Group, CTS495, Department of Surgery, Hospital de Poniente de Almería, El Ejido, Almería; †HLA Laboratory, Department of Immunology, Hospital Universitario Virgen de las Nieves, Granada; ‡Division Otoneurology, Department of Otorhinolaryngology, Hospital Clínico Universitario de Santiago de Compostela; §Division Otoneurology, Department of Otorhinolaryngology, Hospital La Fe, Valencia; and ||Department of Otorhinolaryngology, Complejo Hospitalario de Pontevedra, Pontevedra, Spain*

Objective: To analyze the associations of HLA-DRB1* and DQB1* Class II alleles in patients with bilateral Ménière's disease (MD).

Patients and Methods: Eighty patients from two ethnically defined groups with definite bilateral MD, according to the diagnostic scale of the American Academy of Otolaryngology–Head and Neck Surgery, were compared with normal controls from the same origin in a prospective multicenter study. We performed an allele-specific amplification for *HLA-DRB1** and *DQB1** genes of the major histocompatibility complex.

Results: The allele HLA-DRB1*1101 was associated with bilateral MD in the Mediterranean population (odds ratio, 3.65 [95% confidence intervals, 1.5–9.1], corrected $p = 0.029$); however, this allele was not associated in the group from Galicia (northwest of Spain). No differences were found in the distribution of alleles for the gene *HLA-DQB1** between patients and controls.

Conclusion: The allele HLA-DRB1*1101 and the allelic group HLA-DRB1*11 may determine an increased susceptibility to develop bilateral MD in a southern European population.

Key Words: Class II alleles—Controlled studies—HLA genes—Inner ear—Sensorineural hearing loss—Vertigo.

Otol Neurotol **00:**00–00, 2007.

Class II molecules of the major histocompatibility complex (MHC) present processed foreign antigens to CD4+ T cells. Class II genes are highly polymorphic, and this polymorphism in class II loci is a feature unique to MHC that determines the efficiency that CD4+ T cells recognize a specific antigen (1). The inheritance of *MHC* genes and their antigen expression may influence the susceptibility to autoimmune diseases. The best example is rheumatoid arthritis, where a conserved sequence of amino acids in the third hypervariable region of the DRβ1 chain, called shared epitope (2), has been found to be associated with both disease susceptibility and severity (3). Hence, the HLA-DRB1*04 allelic group such as *0401, *0404, *0405, and *0408, which carried the shared epitope of amino acids at position 70–74 of the DRβ1 chain, were associated with rheumatoid arthritis, whereas other HLA-DRB1*04 alleles such as *0402 or *0403 that did not carry that sequence were not associated with the disease (2). Polymorphic differences between DRβ chains may influence the immune response and determine which particular peptides are bound by HLA-DR molecules. However, the exact role of Class II molecules in the pathogenesis of autoimmune disease remains unknown.

Autoimmunity seems to be associated with the pathogenesis of some inner ear diseases (4), including rapidly progressive bilateral sensorineural hearing loss (SNHL) or autoimmune inner ear disease (5), sudden SNHL (6), and Ménière's disease (MD) (7). Early studies had determined an association between MD and the HLA Cw7 antigen in 41 British patients (8), and with the allele HLA-DRB1*1602 in a Japanese population (9),

Address correspondence and reprint requests to Jose A. López-Escámez, M.D., Ph.D., Otology and Neurotology Group CTS495, Department of Surgery, Hospital de Poniente de Almería, Ctra de Almerimar s/n, 04700 El Ejido, Almería, Spain; E-mail: jalopeze@cajamar.es

but these results were not consistent. Later studies have not confirmed these findings in Korean (10) or Spanish populations in MD (11). These varying results can be explained because of the differences in ethnic background or the criteria to define MD. Because the criteria to define MD are clinical (SNHL, vertigo, tinnitus, and aural fullness), it is possible that different causes (genetic, epigenetic, environmental) can produce the clinical phenotype of MD. This makes the selection of individuals with MD a key point to identify an allele that may increase susceptibility.

Bilateral MD is an aggressive form of the disease affecting both ears that usually determines severe SNHL and chronic disequilibrium because of bilateral vestibular loss (12). The endolymphatic hydrops starts affecting one ear, which results in the second ear getting affected between 2 and 12 years after (13). Patients with bilateral involvement experience an increased disruption of daily life activities and respond poorly to therapy, resulting in a significant handicap (14).

The aim of this study was to analyze the associations of HLA DRB1* and DQB1* alleles in patients with definite bilateral MD in two different ethnically defined populations.

MATERIALS AND METHODS

Patients

Eighty patients (38 men and 42 women) with definite bilateral MD according to the diagnostic scale for MD of the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) were included in a prospective multicenter study between January 2004 and October 2006 (9). Group 1 consisted of 37 patients from the area of Galicia (northwest of Spain), and Group 2 were 43 cases from the southeast (Almeria and Granada) and east (Valencia) areas of Spain. Five hospitals recruited patients for this study: Hospital Clinico Universitario from Santiago de Compostela and Hospital de Pontevedra for Group 1, and Hospital La Fe from Valencia, Hospital Virgen de las Nieves from Granada, and Hospital de Poniente from El Ejido, Almeria included the Mediterranean cases for Group 2. The subjects' informed consent was obtained to participate in the study according to the Declaration of Helsinki, and the local institutional committees approved the study.

A complete audiologic, vestibular, and functional evaluation was performed in all patients following the AAO-HNS guidelines to define stage, class, and functional status in each patient (15). Individuals with criteria for unilateral MD or probable or possible bilateral MD according to the AAO-HNS guidelines were excluded from the study. Laboratory examinations included cytomegalovirus, Borrelia, and lues serologic tests to rule out endolymphatic hydrops secondary to these infections.

HLA Typing

Blood samples were obtained from each patient to type Class II genes. Typing was performed using low- and high-resolution techniques previously described (16). Briefly, DNA was obtained from whole peripheral blood by Qiagen protocol (Valencia, CA, USA), and HLA typing was performed for low resolution with sequence-specific oligonucleotide technique from Dynal (Oslo, Norway) using loci-specific primers. High-resolution typing was performed by a sequence-based typing kit from Applied Biosystems, and sequences were analyzed by MathTools software in an ABI PRISM 377 DNA sequencer (Applied Biosystems, Foster City, CA, USA).

Statistical Analysis

The antigen and allele frequencies were calculated on each group, and they were compared with two ethnically matched control groups from the same regions. The strength of association between bilateral MD and DRB1 and DQB1 alleles was estimated using odds ratios (ORs) and 95% confidence intervals. Levels of significance were determined using contingency tables with Fisher's exact test. Probability values (p) were corrected by multiplying the p value by the number of alleles compared (n = 29 alleles for *HLA-DRB1** gene).

RESULTS

The clinical features of both groups are shown in Table 1. Patients had been suffering for an average of 12 years (median, 10 yr) in both groups, and the distribution of age and sex was similar in both. Hearing stage was referred to the best ear, and most patients were on Stages 3 and 4 (severe to profound hearing loss). Simultaneous bilateral SNHL was found in 4 of 37 subjects in the northwestern group and in 8 of 43 subjects in the southeast group, whereas delayed hearing loss was observed in the second ear in 33 of 37 and 35 of 43 subjects, respectively. Vertigo frequency in the last 6 months was low, as expected for a long time-course (>10 yr) disease, and more than 45% of individuals did not refer spells of vertigo in the last 6 months. Impairment of daily activities was evaluated by the

TABLE 1. *Clinical features of patients with bilateral MD*

	Southest Spanish group (n = 43)	Northwest Spanish group (n = 37)
Age (mean ± SD [median])	56.1 ± 9.4 (57)	57.1 ± 12.3 (61)
Sex (n [%])		
Women	22 (52.4)	20 (54)
Men	21 (47.6)	17 (46)
Time course, yr (mean ± SD [median])	11.9 ± 8.8 (10)	12.2 ± 10.6 (10)
Stage (hearing loss; n [%])		
1 (<25 dB)	0	0
2 (26–40 dB)	4 (9.3)	5 (13.5)
3 (41–70 dB)	21 (48.8)	26 (70.3)
4 (>70 dB)	18 (41.8)	6 (16.2)
Class (vertigo frequency in last 6 mo; n [%])		
A (score, 0)	20 (46.5)	17 (45.9)
B (score, 1–40)	15 (34.8)	14 (37.8)
C (score, 41–80)	5 (11.6)	3 (8.1)
D (score, 81–120)	2 (4.6)	0
E (score, >120)	1 (2.3)	3 (8.1)
Functional level		
1	12 (27.9)	7 (18.9)
2	5 (11.6)	18 (48.6)
3	5 (11.6)	4 (10.8)
4	3 (6.9)	6 (16.2)
5	6 (13.9)	2 (5)
6	3 (6.9)	0
Unknown	9 (20.9)	0

functional disability scale of the AAO-HNS. Nineteen patients (23.7%) did not report any effect of MD symptoms on their daily activities, but MD interfered in the activities of most individuals. Nine patients were not able to select a sentence that defined his or her condition in Group 2.

The allelic frequencies of *HLA-DRB1** and *DQB1** genes in patients with bilateral MD and each control group are shown in Tables 2 and 3. The allele HLA-DRB1*1101 was associated with bilateral MD in the Mediterranean population (OR = 3.65 [95% confidence interval, 1.5–9.1], corrected $p = 0.029$); in addition, the allelic group HLA-DRB1*11 was more frequently found in this group (OR = 3.30 [95% confidence interval, 1.5–7.8], corrected $p = 0.012$). However, this allele was not associated in the group from Galicia (OR = 1.27; $p > 0.05$). No differences were found in the distribution of alleles for the gene *HLA-DQB1** between patients and controls.

The allelic group HLA-DRB1*11 was not associated with simultaneous or delayed hearing loss in bilateral MD (OR = 0.24 [95% confidence interval, 0.01–2.42], $p = 0.23$). Moreover, this allele was not associated with sex, age, duration of disease, hearing stage, number of vertigo spells, or functional level (all $p > 0.05$).

DISCUSSION

Our data indicate that there is a significant association between the allele HLA-DRB1*1101 and bilateral MD in a Mediterranean population from Spain. The allele DRB1*1101 was found in 19% of patients and 6% of controls in our study, suggesting that a significant number of patients with bilateral MD can have an immune

TABLE 2. *HLA-DRB1 genotype frequencies in patients with bilateral MD*

Allele		Group 1 (n = 37)	Controls for group 1 (n = 145)	OR	Group 2 (n = 43)	Controls for group 2 (n = 105)	OR
DRB1*01	0101	3 (4.0)	—	—	4 (5.0)	11 (6.2)	0.82
	0102[a]	3 (4.0)	—	—	5 (6.2)	3 (1.7)	3.97
	0103	1 (1.3)	—	—	0 (0.0)	1 (0.6)	0.00
	01	7 (9.5)	23 (8.4)	1.14	9 (11.2)	15 (8.5)	1.43
DRB1*15	1501[b]	9 (12.1)	—	—	2 (2.5)	17 (9.6)	0.25
	1502	1 (1.3)	—	—	0 (0.0)	2 (1.1)	0.00
	15	10 (13.5)	—	—	4 (5.0)	19 (10.7)	0.46
DRB1*16	1601	4 (5.4)	—	—	1 (1.2)	6 (3.4)	0.38
	1602	1 (1.3)	—	—	0 (0.0)	1 (0.6)	0.00
	16	5 (6.7)	—	—	3 (3.7)	7 (3.9)	0.98
	15 or 16	15 (20.3)	38 (13.9)	1.57	7 (8.7)	26 (14.7)	0.58
DRB1*03	0301	8 (10.8)	29 (10.6)	1.02	7 (8.7)	30 (16.9)	0.49
DRB1*04	0401	3 (4.0)	15 (5.5)	0.73	1 (1.2)	3 (1.7)	0.75
	0402	0 (0.0)	3 (1.1)	0.00	2 (2.5)	1 (0.6)	4.47
	0403[c]	3 (4.0)	2 (0.7)	5.73	1 (1.2)	13 (7.3)	0.17
	0404	0 (0.0)	6 (2.2)	0.00	2 (2.5)	3 (1.7)	1.52
	0405	1 (1.3)	5 (1.8)	0.73	1 (1.2)	0 (0.0)	—
	0407	1 (1.3)	1 (0.4)	3.73	0 (0.0)	2 (1.1)	0.00
	04	8 (10.8)	38 (13.9)	0.75	7 (8.7)	22 (12.4)	0.70
DRB1*11	1101[d]	8 (10.8)	—	—	15 (18.7)	11 (6.2)	3.65
	1102	1 (1.3)	—	—	1 (1.2)	3 (1.7)	0.75
	1103	2 (2.7)	—	—	0 (0.0)	2 (1.1)	0.00
	11[d]	11 (14.9)	33 (12.1)	1.27	19 (23.7)	16 (9.0)	3.30
DRB1*12	1201	1 (1.3)	0 (0.0)	—	0 (0.0)	2 (1.1)	0.00
DRB1*13	1301	2 (2.6)	—	—	5 (6.2)	14 (7.9)	0.81
	1302	2 (2.6)	—	—	5 (6.2)	12 (6.8)	0.96
	1303	0 (0.0)	—	—	1 (1.2)	0 (0.0)	—
	1305	1 (1.3)	—	—	0 (0.0)	0 (0.0)	—
	13[e]	5 (6.7)	51 (18.7)	0.32	11 (13.7)	26 (14.7)	0.97
DRB1*14	1401	0 (0.0)	0 (0.0)	—	2 (2.5)	5 (2.8)	0.91
	1402	1 (1.3)	0 (0.0)	—	0 (0.0)	0 (0.0)	—
	1404	0 (0.0)	0 (0.0)	—	1 (1.2)	0 (0.0)	—
DRB1*07	0701	13 (17.6)	39 (14.3)	1.28	14 (17.5)	32 (18.1)	1.01
DRB1*08	0801	3 (4.0)	11 (4.0)	1.01	0 (0.0)	0 (0.0)	—
DRB1*09	0901	0 (0.0)	5 (1.8)	0.00	0 (0.0)	0 (0.0)	—
DRB1*10	1001	2 (2.6)	6 (2.2)	1.24	0 (0.0)	3 (1.7)	0.00

Values shown represent number of alleles found, with percentages in parentheses.

[a]DRB1*0102 Group 2, OR = 3.97 (0.8–21.9), uncorrected $p = 0.06$.

[b]DRB1*1501 Group 2, OR = 0.25 (0.0–1.2), uncorrected $p = 0.05$, corrected $p = 1.45$, not significant.

[c]DRB1*0403 Group 1, OR = 5.73 (0.8–50.0), uncorrected $p = 0.06$; Group 2, OR = 0.17 (0.0–1.2), uncorrected $p = 0.04$, corrected $p = 1.16$, not significant.

[d]DRB1*1101 Group 2, OR= 3.65 (1.5–9.1), uncorrected $p = 0.001$, corrected $p = 0.029$, significant; the *DR11* gene was more frequent in Group 2, OR = 3.30 (1.5–7.8), uncorrected $p = 0.0009$, corrected $p = 0.012$, significant.

[e]DRB1*13 Group 1, OR = 0.32 (0.1–0.9), uncorrected $p = 0.02$, corrected $p = 0.26$, not significant.

TABLE 3. *HLA-DQB1 genotype frequencies in patients with bilateral MD*

Allele		Group 1 (n = 37)	Controls for group 1 (n = 145)	OR	Group 2 (n = 25)	Controls for group 2 (n = 105)	OR
DQB1*02	0201	9 (12.1)	—	—	5 (10.0)	—	—
	0202	9 (12.1)	—	—	6 (12.0)	—	—
	02	18 (24.3)	58 (21.9)	1.15	11 (22.0)	58 (29.7)	0.67
DQB1*03	0301	17 (22.9)	50 (18.9)	1.28	13 (26.0)	38 (19.5)	1.45
	0302	4 (5.4)	21 (7.9)	0.66	7 (14.0)	16 (8.2)	1.83
	0303	3 (4.0)	9 (3.4)	1.20	1 (2.0)	1 (0.5)	3.77
	0304	0 (0.0)	1 (0.3)	0.00	0 (0.0)	0 (0.0)	—
	0305	1 (1.3)	0 (0.0)	—	0 (0.0)	0 (0.0)	—
	03	25 (33.8)	81 (30.6)	1.16	21 (42.0)	55 (28.2)	1.84
DQB1*04	0402	4 (5.4)	13 (4.9)	1.11	0 (0.0)	0 (0.0)	—
DQB1*05	0501	10 (13.5)	34 (12.8)	1.06	6 (12.0)	23 (0.1)	1.02
	0502	5 (6.7)	7 (2.6)	2.67	1 (2.0)	8 (4.1)	0.48
	0503	0 (0.0)	11 (4.1)	0.00	3 (6.0)	6 (3.1)	2.02
	05	15 (20.3)	52 (19.6)	1.04	10 (20.0)	37 (18.9)	1.07
DQB1*06	0601	1 (1.3)	0 (0.0)	—	0 (0.0)	4 (2.0)	0.00
	0602	10 (13.5)	26 (9.8)	1.44	2 (4.0)	18 (9.2)	0.41
	0603	1 (1.3)	15 (5.7)	0.23	4 (8.0)	14 (7.1)	1.13
	0604	1 (1.3)	6 (2.3)	0.59	2 (4.0)	9 (7.2)	0.86
	0609	1 (1.3)	4 (1.5)	0.89	0 (0.0)	0 (0.0)	—
	06	14 (18.9)	61 (23.0)	0.78	8 (16.0)	45 (23.1)	0.63

Values shown represent number of alleles found, with percentages in parentheses.

basis. Unfortunately, this association was not found in the population from Galicia when they were compared with ethnically matched controls. HLA-DQB1 alleles in bilateral MD did not differ from controls in both populations. These varying results according to ethnic background suggest that MHC alleles may not be a significant factor associated with the pathogenesis of MD, but only a genetic marker in linkage disequilibrium, with one of the genes responsible for the disease.

Immunogenetic studies in patients with sensorineural hearing disorders have suggested a role for the MHC-encoded genes in disease pathogenesis (17). Allelic specificities of Class II genes have been found to be associated with progressive SNHL (18) and sudden SNHL (6).

The cause of MD is likely to be multifactorial, genetic predisposition being one of the factors (19). A pro51-to-ser mutation in the *COCH* gene, located in chromosome 14q12-q13, in one large Belgian and two small Dutch families with autosomal dominant nonsyndromic progressive SNHL associated with vestibular dysfunction (DFNA9) was related to familiar MD (20). More than 25% of carriers of this mutation showed episodes of vertigo, tinnitus, aural fullness, and SNHL, consistent with the criteria for MD. However, later studies demonstrated that patients with sporadic MD do not carry mutations in the *COCH* gene (21,22).

The finding of elevated levels of circulating immune complexes in many patients with MD, especially in the active phase, has supported the hypothesis of autoimmunity in MD (23,24). Immunohistochemical studies have demonstrated deposits of C3 and C1q in the membranous labyrinth located at the basal membrane, subepithelial connective tissue, vestibular ganglion, and endolymphatic sac of patients with MD (25). It seems that immune injury may be induced in the inner ear at sites where immune complexes are deposited in the vessels. Therefore, if deposits of immune complexes in the endolymphatic sac impair its resorptive function, this can result in endolymphatic hydrops.

Many studies have reported the high frequency of nonspecific autoantibodies in 50 to 70% patients in MD, the antinuclear antibodies found in 37.5% cases of bilateral MD (21,26) being the most common. Moreover, different studies using Western blot immunoassay have found specific circulating autoantibodies in MD against a 68-kDa antigen from human inner ear tissue (27) and anti-HSP70 antibodies in 37% of patients with unilateral MD and in 59% of bilateral MD (28). Recently, P0 antigen, a 30-kDa protein involved in myelin folding, was suggested as a diagnostic marker for bilateral MD because immunoglobulin G autoantibodies against the P0 antigen were found in 100% (10 of 10) patients with bilateral MD (29).

Our study suggests that the inheritance of MHC Class II genes, particularly the *HLA-DRB1** gene, may influence the susceptibility to develop bilateral MD. Although early studies identified an association between the HLA-Cw7 antigen and MD (8), later series with a larger sample failed to demonstrate differences in phenotypic frequencies in Class I or II antigens (11). The *HLA-DRB1** gene is a highly polymorphic marker mainly due to diversification of the exon-2 sequences encoding the β-sheet. The allele HLA-DRB1* 1602 was found to be associated in 7.5% of Japanese in a sample of 20 individuals with MD (9), but association with this allele was not confirmed in bilateral MD in our Spanish population. In contrast, we found a significant association with DRB1*1101 in a population of bilateral disease from southeast Spain.

If allelic specificities of *HLADRB1** gene increase susceptibility to bilateral MD, the immunologic alterations found in MD can define a subset of subjects

with immunomediated inner ear disease with vestibular involvement that can potentially benefit from immunosuppressive therapy in MD.

CONCLUSION

The allele HLA-DRB1*1101 and the allelic group DRB1*11 may determine an increased susceptibility to develop bilateral MD in the southern European population.

REFERENCES

1. Robinson J, Waller MJ, Parham P, et al. IMGT/HLA and IMGT/MCH: sequence databases for the study of the major histocompatibility complex. *Nucleic Acids Res* 2003;31:311–4.
2. 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.
3. Gonzalez-Gay MA, Garcia-Porrua C, Hajeer AH. Influence of human leucocyte antigen DRβ1 on the susceptibility and severity of rheumatoid arthritis. *Semin Arthritis Rheum* 2002;31:355–60.
4. McCabe BF. Autoimmune sensorineural hearing loss. *Ann Otol Rhinol Laryngol* 1979;88:585–9.
5. Harris JP, Weisman MH, Derebery JM, et al. Treatment of corticosteroids-responsive autoimmune inner ear disease with methorexate: a randomized controlled trial. *JAMA* 2003;290:1875–83.
6. Amor-Dorado JC, Paco L, Martin J, Lopez-Nevot MA, Gonzales-Gay MA. Human leukocyte antigen–DQB1 and –DRB1 associations in patients with idiopathic sudden sensorineural hearing loss from a defined population of Northwest Spain. *Acta Otolaryngol* 2005;125:1277–82.
7. Hughes GB, Kinney SE, Barna BP, Calabrese LH. Autoimmune reactivity in Ménière's disease: a preliminary report. *Laryngoscope* 1983;93:410–7.
8. Xenellis J, Morrison AW, McClowskey D, Festenstein H. HLA antigens in the pathogenesis of Ménière's disease. *J Laryngol Otol* 1986;100:21–4.
9. Koyama S, Mitsuishi Y, Bibee K, Watanabe I. HLA associations with Ménière' disease. *Acta Otolaryngol (Stockh)* 1993;113:575–8.
10. Yeo SW, Park S, Jeon E, Lee HY, Pyo CW, Ki TG. Influence of human leucocyte antigen in the pathogenesis of Ménière's disease in the South Korean population. *Acta Otolaryngol* 2002;122:851–6.
11. Lopez-Escamez JA, Lopez-Nevot A, Cortes R, Ramal L, Lopez-Nevot MA. Expression of A, B, C and DR antigens in definite Ménière disease in a Spanish population. *Eur Arch Otorhinolaryngol* 2002;259:347–50.
12. Paparella MM, Griebie MS. Bilaterality of Ménière's disease. *Acta Otolaryngol* 1984;97:233–7.
13. Salvinelli F, Trivelli M, Greco F, Silvestrini M, Fernandez E, Pallini R. Ménière's disease: is it a bilateral disease? *Eur Rev Med Pharmacol Sci* 1990;3:129–33.
14. Kodama A, Kitahara M, Kitanishi T. Clinical findings in Ménière's disease with bilateral fluctuant hearing loss. *Acta Otolryngol Suppl* 1995;519:227–9.
15. American Academy of Otolaryngology–Head and Neck Foundation, Inc. Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Ménière's disease. *Otolaryngol Head Neck Surg* 1995;113:181–5.
16. Pascual M, Nieto A, López-Nevot MA, et al. Rheumatoid arthritis in southern Spain: toward elucidation of a unifying role of the HLA class II region in disease predisposition. *Arthritis Rheum* 2001;44:307–14.
17. Bernstein JM, Shanahan TC, Schaffer FM. Further observations on the role of the MHC genes and certain hearing disorders. *Acta Otolaryngol (Stockh)* 1996;116:666–71.
18. Cao MY, Thonnard J, Deggouj N, Gersdorff M, Tomasi JP. HLA class II–associated genetic susceptibility in idiopathic progressive sensorineural hearing loss. *Ann Otol Rhinol Laryngol* 1996;105: 628–33.
19. Morrison AW, Mowbray JF, Williamson R, Sheeka S, Sodha N, Koskinen N. On genetic and environmental factors in Ménière's disease. *Am J Otol* 1994;15:35–9.
20. Fransen E, Vertreken M, Verhagen WI, et al. High prevalence of symptoms of Ménière's disease in three families with a mutation in the COCH gene. *Hum Mol Genet* 1999;8:1425–9.
21. Sanchez E, Lopez-Escamez JA, Lopez-Nevot A, Cortes R, Martin J. Absence of COCH mutations in patients with Ménière' disease. *Eur J Hum Genet* 2004;12:75–8.
22. Usami S, Takahashi K, Yuge I, et al. Mutations in the COCH gene are a frequent cause of autosomal dominant progresive cochleovestibular dysfunction, but not of Ménière's disease. *Eur J Hum Genet* 2003;11:744–8.
23. Brooks GB. Circulating immune complexes in Ménière's disease. *Arch Otolaryngol Head Neck Surg* 1986;112:536–40.
24. Derebery MJ, Rao VS, Siglock TJ, Linthicum FH, Nelson RA. Ménière's disease: an immune complex-mediated illness? *Laryngoscope* 1991;101:225–9.
25. Hausler R, Arnorld W, Schfferlic J. C3 and C1q complement deposits in the membranous labyrinth of patients with Ménière's disease. *Adv Otorhinolaryngol* 1988;42:116–22.
26. Ruckestein MJ, Prasthoffer A, Bigelow DC, Von Feldt JM, Kolasinski SL. Immunologic and serologic testing in patients with Ménière's disease. *Otol Neurotol* 2002;23:517–21.
27. Gottschlich S, Billings PB, Keithley EM, Weisman MH, Harris JP. Assessment of serum antibodies in patients with rapidly progressive sensorineural hearing loss and Ménière's disease. *Laryngoscope* 1995;105:1347–52.
28. Rauch SD, San Martin JE, Moscicki RA, Bloch KJ. Serum antibodies against heat shock protein in Ménière's disease. *Am J Otol* 1995;16:648–52.
29. Passali D, Damiani V, Mora R, Passali FM, Passali GC, Bellussi L. P0 antigen detection in sudden hearing loss and Ménière's disease: a new diagnostic marker? *Acta Otolaryngol* 2004;124:1145–8.