ARTHRITIS & RHEUMATISM
Vol. 48, No. 7, July 2003, pp 1930–1938
DOI 10.1002/art.11059
© 2003, American College of Rheumatology

Role of the Fcγ Receptor IIA Polymorphism in the Antiphospholipid Syndrome

An International Meta-Analysis

Fotini B. Karassa,[1] Marc Bijl,[2] Kevin A. Davies,[3] Cees G. M. Kallenberg,[2] Munther A. Khamashta,[4] Karin Manger,[5] Marc Michel,[6] Jean-Charles Piette,[7] Jane E. Salmon,[8] Yeong Wook Song,[9] Naoyuki Tsuchiya,[10] Dae-Hyun Yoo,[11] and John P. A. Ioannidis[12]

Objective. **To assess the impact of the *FcγRIIA-R/H131* polymorphism on the risk for antiphospholipid syndrome (APS), both primary and secondary to systemic lupus erythematosus (SLE).**

Methods. **This international meta-analysis combined data from 9 research teams. *FcγRIIA-R/H131* genotypes were determined in 481 APS cases (206 with primary APS), 1,420 SLE controls, and 1,655 disease-free controls. Data were combined using fixed-effects and random-effects models.**

Results. **Compared with disease-free controls, the *RR* genotype was enriched in the entire group of APS cases (odds ratio [OR] 1.65, 95% confidence interval [95% CI] 1.28–2.14); this was driven mostly by patients with secondary APS (OR 1.95, 95% CI 1.45–2.63). The excess of *RR* homozygotes but not heterozygotes among APS patients suggested a recessive mode of inheritance, rather than the additive model seen for SLE susceptibility, where *RR* conferred greatest risk, and *RH* intermediate risk, for SLE. This probably reflected the additional influence of another opposing genetic effect of *HH* homozygosity on APS predisposition (OR 0.72 for *RH* versus *HH*, 95% CI 0.55–0.96). Among SLE patients, those with APS were more frequently *HH* homozygotes than heterozygotes (OR 0.56 for *RH* versus *HH*, 95% CI 0.39–0.81). *HH* homozygosity also tended to predominate in primary APS compared with secondary APS (OR 0.50 for *RR* versus *HH*, 95% CI 0.25–0.99 by fixed-effects model). There was no significant between-study heterogeneity for any of these effects.**

Conclusion. **The *FcγRIIA-R/H131* polymorphism is an important determinant of predisposition to APS, with different influences on SLE and APS susceptibility per se.**

The presence of antibodies in blood (lupus anticoagulant or anticardiolipin antibodies [aCL]) that recognize phospholipids, phospholipid-binding proteins, or both has been associated with a thrombophilic disorder, the antiphospholipid syndrome (APS) (1,2). This syndrome is characterized by recurrent vascular thromboses involving the venous, arterial, and placental circulation and may occur alone (primary APS) or in conjunction with other autoimmune disease (secondary APS) (1–3). Several mechanisms have been proposed for explaining the procoagulant state of APS (2). According to one hypothesis (4), antiphospholipid antibody (aPL) binding to protein–phospholipid complexes on platelets, endothelial cells, or other cells may result in their activation via crosslinking of Fcγ receptors of type IIa (FcγRIIa)

[1]Fotini B. Karassa, MD: University of Ioannina School of Medicine, Ioannina, Greece; [2]Marc Bijl, MD, PhD, Cees G. M. Kallenberg, MD, PhD: University Hospital Groningen, Groningen, The Netherlands; [3]Kevin A. Davies MD, FRCP: Imperial College School of Medicine, Hammersmith Hospital, London, UK, and Brighton and Sussex Medical School, Falmer, Sussex, UK; [4]Munther A. Khamashta, MD: The Rayne Institute, St. Thomas' Hospital, London, UK; [5]Karin Manger, MD: University of Erlangen–Nuremberg, Erlangen, Germany; [6]Marc Michel, MD: Unité INSERM U25, Faculté de Médecine Necker, Paris, France; [7]Jean-Charles Piette, MD: Hôpital Pitié Salpêtrière, Paris, France; [8]Jane E. Salmon, MD: Hospital for Special Surgery, and New York Hospital, Cornell Medical Center, New York, New York; [9]Yeong Wook Song, MD: Seoul National University Hospital, Seoul, South Korea; [10]Naoyuki Tsuchiya, MD, PhD: University of Tokyo Graduate School of Medicine, Tokyo, Japan; [11]Dae-Hyun Yoo, MD, PhD: Hospital for Rheumatic Diseases, Hanyang University, Seoul, South Korea; [12]John P. A. Ioannidis, MD: Tufts–New England Medical Center, Boston, Massachusetts, and University of Ioannina School of Medicine, and Foundation for Research and Technology–Hellas, Ioannina, Greece.

Address correspondence and reprint requests to John P. A. Ioannidis, MD, Chairman, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina 45110, Greece. E-mail: jioannid@cc.uoi.gr.

Submitted for publication December 10, 2002; accepted in revised form March 24, 2003.

(5,6). This activation may induce a prothrombotic phenotype (4). If this hypothesis is true, *FcγRIIA* function may regulate APS pathogenesis.

FcγRIIa is widely expressed on hematopoietic cells, including neutrophils and mononuclear phagocytes. This isoform is the only FcγR expressed on platelets and endothelial cells (7). A common functional polymorphism of the *FcγRIIA* gene plays a particular role in the expression of IgG2-mediated antibody responses. The 2 allelic forms of *FcγRIIA* differ by a single amino acid at residue 131 (histidine or arginine). The *H131* allele is essential for handling IgG2 immune complexes (8). This polymorphism has been proposed to be influential in a variety of autoimmune diseases (7). The low-binding *R131* allele imparts a significant risk for systemic lupus erythematosus (SLE) (9). Binding to the *H131* variant can initiate more pronounced monocyte, platelet, and endothelial cell activation in the context of an IgG2 immune response, inducing a prothrombotic phenotype. Since autoimmune disease–associated aCL show IgG2 predominance (10,11), one might expect an enrichment of the *H131* allele in APS patients (11). However, the data are not yet conclusive (12,13). Besides, in patients with APS secondary to SLE, this anticipated selection of the *H131* allele may not be evident, given the overrepresentation of the *RR* genotype in SLE (9). Thus, the role of the *FcγRIIA-R/H131* polymorphism in APS is still unclear.

APS is relatively uncommon, and isolated studies regarding its genetic background are unlikely to be conclusive. Previous analyses for HLA-conferred APS susceptibility have required the combination of data from various study groups (14). The aim of the present study was to investigate the importance of *FcγRIIA* alleles for APS susceptibility in the context of an international collaborative meta-analysis. Such an approach enhances the power to detect modest, but clinically important, differences between groups and helps to avoid spurious findings due to inconsistencies of the data from different research teams.

PATIENTS AND METHODS

Eligibility criteria. The meta-analysis included study groups in which *FcγRIIA-R/H131* genotypes had been determined by molecular methods. The study groups consisted of APS patients (primary APS, APS secondary to SLE, or both) as well as disease-free control subjects and/or patients with SLE but without APS (control patients).

Participating investigators complied with the following rules to ensure consistency. The groups being compared should be racially matched. For studies of mixed racial descent, data for subjects of European, African, and Asian descent should be separated. Disease-free controls should not have APS or SLE. SLE should be defined according to the American College of Rheumatology 1982 revised criteria (15). APS should preferably be defined according to the 1999 preliminary criteria (16), but earlier alternative classification criteria were acceptable if they were clearly prespecified. Patients were classified as having secondary APS if they fulfilled criteria for both SLE and APS (15,16). Patients with primary APS should not fulfill classification criteria for SLE or any other autoimmune disease. Patients in the SLE control group should not meet criteria for definite APS (16).

Organization of the international database. Research teams worldwide working on the low-affinity FcγR and their association with autoimmune diseases were invited to contribute data, provided that their study patients met the eligibility criteria defined above. We contacted teams identified as part of a previous meta-analysis that examined the role of the *FcγRIIA-R/H131* polymorphism in SLE and lupus nephritis (9). Other potentially relevant studies were sought by searches of the Medline and EMBase databases (last search August 2002), with various combinations of key words ("antiphospholipid," "anticardiolipin," "polymorphism," "allele," "genetics," "Fc receptor," and "Fcγ receptor"). Finally, this strategy was supplemented by extensive communication with field experts.

Research teams from 9 centers (5 European, 3 Asian, and 1 American) agreed to participate. *FcγRIIA* genotype analysis was performed using polymerase chain reaction (PCR)–allele-specific oligonucleotide hybridization (8,13,17,18), PCR–restriction fragment length polymorphism (12,19), sequence-specific primer–PCR (20,21), or amplification-refractory mutation screening–PCR (22). Databases were assembled and assessed at the coordinating center (Department of Hygeine and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece). Queries were clarified through communications with the participating investigators.

Meta-analysis methods. The main analysis used 4 different comparisons: APS versus disease-free controls (with separate analyses for primary and secondary APS), secondary APS versus SLE controls, primary versus secondary APS, and SLE controls versus disease-free controls. For each comparison, the following genotype contrasts were evaluated: *RR* versus *RH* and *HH* combined; *RR* and *RH* combined versus *HH*; *RR* versus *RH*; *RH* versus *HH*; and *RR* versus *HH*. The first contrast corresponds to a net recessive genetic effect of the *R131* allele, the second contrast corresponds to a net dominant effect of this allele, and the other 3 contrasts probe into dose-response relationships. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated from each comparison and genotype contrast, since the studies typically used case–control designs.

For each comparison and genetic contrast, we estimated between-study heterogeneity using the Q statistic, which was considered significant at $P < 0.10$ (23). Study-specific data were combined using both fixed-effects (Mantel-Haenszel) (24) and random-effects (DerSimonian and Laird) (25) methods. The latter incorporate between-study heterogeneity and provide wider confidence intervals when the results of combined studies differ among themselves. In the absence of between-study heterogeneity, the two methods provide similar results. Random effects are more appropriate when between-

Table 1. Characteristics of patients with APS and control subjects included in the meta-analysis*

Research team	Ethnic descent of subjects	APS patients			Controls		*H131* allele frequency	
		All	Primary	Secondary	SLE patients	Healthy subjects	All APS patients	Healthy controls
France	European	104	87	17	63	183	0.52	0.56
Germany	European	27	–	27	100	188	0.48	0.51
Japan	Asian	13	–	13	180	303	0.81	0.81
Korea 1	Asian	4	–	4	65	64	0.50	0.63
Korea 2	Asian	33	–	33	276	197	0.67	0.67
The Netherlands	European	18	–	18	86	154	0.53	0.53
The Netherlands	Asian	2	–	2	6	–	0.75	–
UK 1	European	89	57	32	8	41	0.47	0.50
UK 2	European	82	–	82	113	283	0.36	0.45
US	African	10	3	7	257	139	0.50	0.53
US	European	99	59	40	266	103	0.51	0.50
Overall	–	481	206	275	1,420	1,655	–	–

* The 1999 preliminary classification criteria for antiphospholipid syndrome (APS) (16) were used in all studies, with the following minor prespecified exceptions: in the Korea 2 and UK 1 studies, 4 and 7 patients, respectively, were classified as having APS by fulfilling laboratory criteria and having thrombocytopenia without thrombotic events or pregnancy complications; in the US study, transient ischemic attacks were classified along with qualifying thrombotic events, and patients could also qualify for APS clinically in the presence of thrombocytopenia alone if they fulfilled laboratory criteria for APS. Except for the *H131* allele frequency, values are the number of subjects. SLE = systemic lupus erythematosus.

study heterogeneity is present, and they are used as the primary reported analysis, unless stated otherwise.

Sensitivity analyses were limited to those studies that used the preliminary classification criteria for APS (16). In a different sensitivity analysis, we also examined whether ORs would be different if the observed genotype frequencies in disease-free controls were adjusted to those expected under the assumption of Hardy-Weinberg equilibrium (26). Results were similar (data not shown).

Finally, we performed cumulative meta-analysis and recursive cumulative meta-analysis (27,28) to evaluate whether the combined OR changed over time as more data were accumulated for each comparison and contrast. Inverted funnel plots (29) were examined as diagnostics for heterogeneity related to the sample size of each study.

Statistical analysis. Analyses were conducted with the use of SPSS software, version 10.0 (SPSS, Chicago, IL) and Meta-Analyst software (Joseph Lau, Tufts–New England Medical Center, Boston, MA). *P* values are 2-tailed.

RESULTS

General characteristics. The meta-analysis included *FcγRIIA-R/H131* genotyping of 481 patients with APS (206 with primary APS, 275 with secondary APS),

Table 2. Distribution of *FcγRIIA* alleles among patients with APS and control subjects included in the meta-analysis*

Research team	Ethnic descent of subjects	*FcγRIIA-R/R131*			*FcγRIIA-R/H131*			*FcγRIIA-H/H131*		
		All APS patients	SLE controls	Healthy controls	All APS patients	SLE controls	Healthy controls	All APS patients	SLE controls	Healthy controls
France	European	26	20	33	48	28	94	30	15	56
Germany	European	10	26	50	8	39	85	9	35	53
Japan	Asian	1	7	11	3	69	95	9	104	197
Korea 1	Asian	1	8	5	2	50	37	1	7	22
Korea 2	Asian	7	47	16	8	109	99	18	120	82
The Netherlands	European	4	26	32	9	37	80	5	23	42
The Netherlands	Asian	0	2	–	1	2	–	1	2	–
UK 1	European	26	1	9	42	6	23	21	1	9
UK 2	European	40	27	90	25	71	131	17	15	62
US	European	25	66	25	47	141	53	27	59	25
US	African	4	96	33	2	120	65	4	41	41

* The distribution of *FcγRIIA* alleles among the patients with primary antiphospholipid syndrome (APS) is as follows: among the patients in France, *RR* 18, *RH* 42, and *HH* 27; among the UK 1 patients, *RR* 14, *RH* 27, and *HH* 16; among the US patients of European descent, *RR* 14, *RH* 28, and *HH* 17; and among the US patients of African descent, *RR* 2, *RH* 0, and *HH* 1. Values are the number of subjects. SLE = systemic lupus erythematosus.

Table 3. Summary ORs for the association of APS with *FcγRIIA*-specific genotypes*

Group, genotype comparison	No. of comparisons	No. of subjects	REM OR (95% CI)	FEM OR (95% CI)
All APS vs. disease-free controls				
RR vs. *RH* + *HH*	10	2,134	1.65 (1.28–2.14)	1.63 (1.25–2.11)
RR + *RH* vs. *HH*	10	2,134	0.90 (0.70–1.16)	0.90 (0.70–1.16)
RR vs. *RH*	10	1,404	1.86 (1.39–2.47)	1.83 (1.37–2.43)
RH vs. *HH*	10	1,686	0.72 (0.55–0.96)	0.72 (0.55–0.95)
RR vs. *HH*	10	1,178	1.38 (1.01–1.88)	1.37 (1.00–1.87)
Primary APS vs. disease-free controls				
RR vs. *RH* + *HH*	4	672	1.17 (0.76–1.79)	1.17 (0.76–1.78)
RR + *RH* vs. *HH*	4	672	0.87 (0.59–1.29)	0.87 (0.59–1.28)
RR vs. *RH*	4	480	1.24 (0.79–1.96)	1.26 (0.80–1.99)
RH vs. *HH*	4	524	0.81 (0.53–1.23)	0.81 (0.53–1.22)
RR vs. *HH*	4	340	1.01 (0.61–1.67)	1.01 (0.62–1.67)
Secondary APS vs. disease-free controls				
RR vs. *RH* + *HH*	10	1,928	1.95 (1.45–2.63)	1.91 (1.42–2.57)
RR + *RH* vs. *HH*	10	1,928	0.93 (0.69–1.27)	0.95 (0.70–1.28)
RR vs. *RH*	10	1,259	2.23 (1.60–3.10)	2.18 (1.56–3.03)
RH vs. *HH*	10	1,528	0.70 (0.50–0.98)	0.69 (0.50–0.97)
RR vs. *HH*	10	1,069	1.61 (1.12–2.32)	1.61 (1.12–2.32)
Secondary APS vs. SLE controls				
RR vs. *RH* + *HH*	11	1,698	1.62 (1.18–2.24)	1.60 (1.17–2.19)
RR + *RH* vs. *HH*	11	1,698	0.72 (0.52–0.99)	0.72 (0.52–0.99)
RR vs. *RH*	11	1,196	1.97 (1.37–2.87)	1.99 (1.41–2.81)
RH vs. *HH*	11	1,274	0.56 (0.39–0.81)	0.56 (0.39–0.80)
RR vs. *HH*	11	926	1.06 (0.71–1.58)	1.05 (0.71–1.55)
Primary vs. secondary APS				
RR vs. *RH* + *HH*	4	302	0.59 (0.30–1.17)	0.60 (0.35–1.04)
RR + *RH* vs. *HH*	4	302	0.64 (0.35–1.18)	0.63 (0.35–1.15)
RR vs. *RH*	4	220	0.64 (0.35–1.16)	0.66 (0.36–1.18)
RH vs. *HH*	4	221	0.73 (0.38–1.40)	0.71 (0.37–1.38)
RR vs. *HH*	4	163	0.50 (0.25–1.01)	0.50 (0.25–0.99)
SLE controls vs. disease-free controls				
RR vs. *RH* + *HH*	10	3,072	1.36 (1.02–1.82)†	1.34 (1.10–1.63)
RR + *RH* vs. *HH*	10	3,072	1.36 (1.02–1.81)‡	1.29 (1.09–1.53)
RR vs. *RH*	10	2,064	1.28 (0.92–1.78)†	1.25 (1.02–1.54)
RH vs. *HH*	10	2,442	1.28 (0.93–1.77)‡	1.21 (1.01–1.44)
RR vs. *HH*	10	1,638	1.63 (1.17–2.27)†	1.61 (1.27–2.05)

* ORs = odds ratios; APS = antiphospholipid syndrome; REM = random-effects model; 95% CI = 95% confidence interval; FEM = fixed-effects model; SLE = systemic lupus erythematosus.
† $0.01 < P < 0.10$ for heterogeneity.
‡ $P < 0.01$ for heterogeneity.

and 3,075 control subjects (1,420 with SLE and 1,655 disease-free). The primary APS patients were from 3 participating research teams, while all teams contributed secondary APS cases (Table 1). Most APS subjects were of European descent (419 of 481); 52 APS patients were of Asian descent and 10 of African descent. All but 3 patients with primary APS were of European descent.

Three of the research teams used criteria (11,30,31) other than the preliminary criteria for the classification of APS. Apart from the essential clinical features of vascular thrombosis and complications of pregnancy (16), the alternative criteria allowed patients with thrombocytopenia (in 3 studies) or transient ischemic attacks (in 1 study) to be classified as having APS if they also had aCL or lupus anticoagulant. The distribution of genotypes (Table 2) in all disease-free control groups was in accordance with Hardy-Weinberg equilibrium (all $P > 0.10$).

Meta-analysis findings (Table 3). *APS patients versus disease-free controls.* The APS patient group had an enrichment of the homozygous state for the low-binding allele, with an OR for APS being 1.65 in *RR* homozygous patients compared with both other genotypes combined ($P < 0.001$; no significant between-study heterogeneity) (Figure 1A). Evaluation of specific genotype contrasts showed that the genetic relationship was complex. The presence of *RR* increased APS risk as compared with *RH*, and less so as compared with *HH*, although the 95% CIs overlapped. The presence of *RH* significantly decreased the risk for APS as compared with *HH* (Figure 1B).

The primary APS patients did not differ significantly from the disease-free controls in any genotype

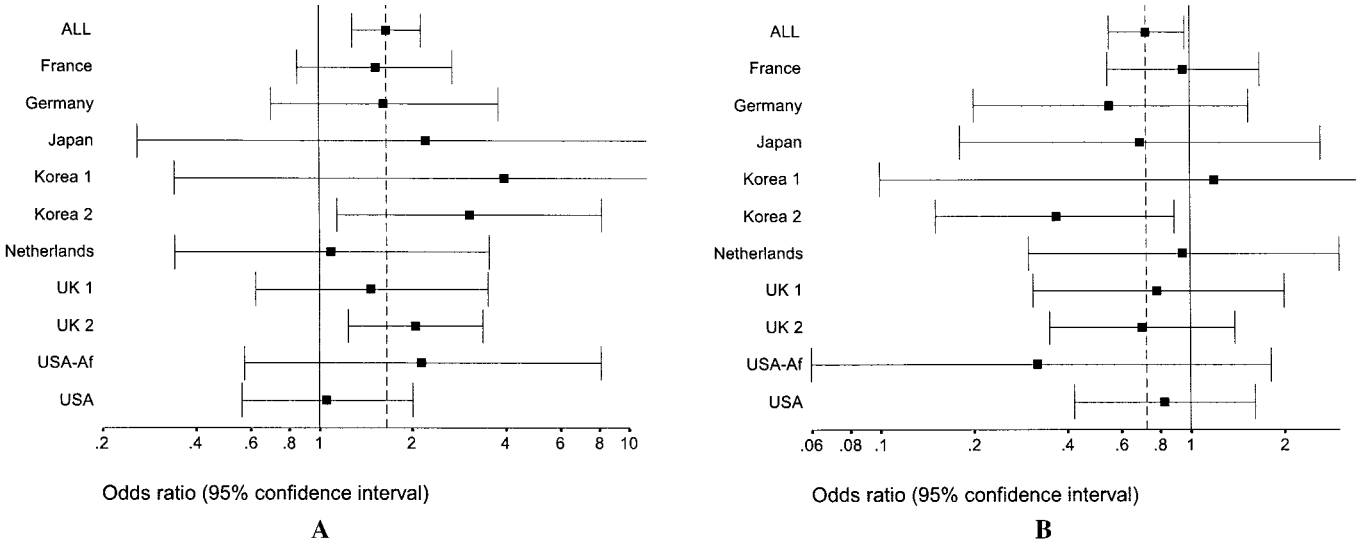

Figure 1. Meta-analysis for the effects of *FcγRIIa-R/H131* polymorphism on the risk of antiphospholipid syndrome (APS), comparing APS patients with disease-free control subjects. **A,** *RR* versus *RH* + *HH*. **B,** *RH* versus *HH*. Comparisons from individual study teams that participated in this meta-analysis are shown. Subjects from 6 study teams in France, Germany, The Netherlands, UK 1, UK 2 and US were of European descent. Three more centers (2 in Korea and 1 in Japan) provided data for subjects of Asian descent. These analyses also included data from subjects of African (Af) descent contributed by the US center. For each comparison, a point estimate of the odds ratio (OR) and the accompanying 95% confidence interval are presented. Also shown is the summary OR estimate (ALL) according to random effects calculations (broken vertical line). Solid vertical line corresponds to no association (an OR of 1).

contrast, but modest associations could have been missed due to limited data. Conversely, as compared with disease-free controls, secondary APS patients had an overrepresentation of the *RR* genotype relative to both of the other genotypes combined (OR 1.95) (Figure 2) or relative to each of the other genotypes separately (OR 2.23 versus *RH* and OR 1.61 versus *HH*). Again, *HH* homozygous SLE patients were at greater risk of developing APS compared with *RH* heterozygotes.

Secondary APS patients versus SLE controls. Among lupus patients, both homozygous states contributed to APS susceptibility. In particular, *RR* homozygotes were more prone to developing APS. A maximum effect was seen when *RR* homozygotes were contrasted with *RH* heterozygotes (OR 1.97). Likewise, the *HH* genotype was associated with a trend toward an increased predisposition to APS, particularly when contrasted with *RH* heterozygosity (Figure 3).

Primary APS patients versus secondary APS patients. The *HH* genotype tended to be more common in patients with primary APS than in those with secondary APS. There was formal statistical significance with fixed-effects modeling when *HH* was contrasted against *RR* in particular, and there was no significant between-study heterogeneity for any genotype contrast.

SLE controls versus disease-free controls. SLE controls had an enrichment of the *R131* allele compared with disease-free controls. *RR* homozygotes were at greater risk of developing SLE compared with *RH*

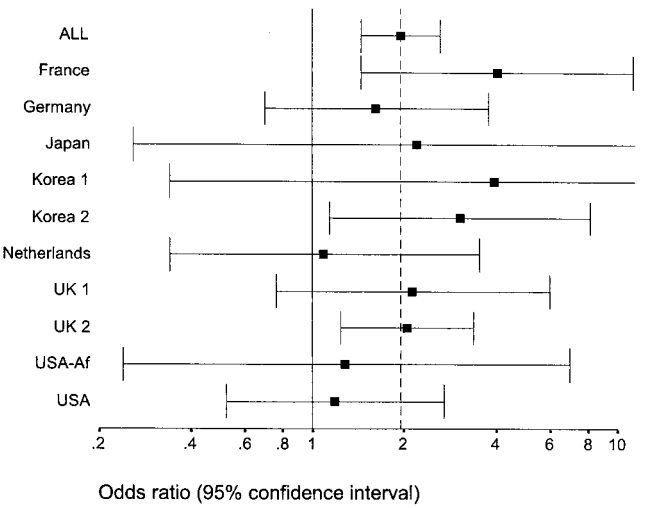

Figure 2. Meta-analysis for the effects of the *RR* genotype versus the *RH* + *HH* genotypes on the risk of APS secondary to systemic lupus erythematosus, comparing secondary APS patients with disease-free controls. See Figure 1 for explanations of the ethnic descent of the subjects and the presentation of the data.

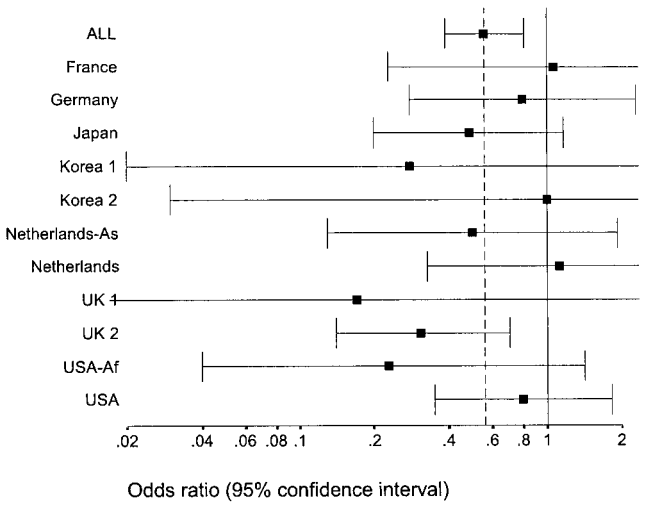

Figure 3. Meta-analysis for the effects of the *RH* genotype versus the *HH* genotype on the risk of APS secondary to systemic lupus erythematosus, comparing secondary APS patients with SLE patient controls. Data for the Asian (As) subjects provided by The Netherlands center were also included in this analysis; see Figure 1 for explanations of the ethnic descent of the subjects and the presentation of the data.

heterozygotes (OR 1.28). A maximum effect was seen when *RR* homozygotes were contrasted with *HH* homozygotes (OR 1.63), while the OR for *RH* versus *HH* was 1.28. Even though significant between-study heterogeneity was detected in these comparisons, the results are consistent with the previously described dose-response effect of the *R131* allele in SLE susceptibility (9).

Sensitivity analysis findings. When we excluded studies that did not use the 1999 preliminary criteria for the classification of APS, the results were similar. The random effects OR estimate for the risk of developing APS was 1.74 in *RR* homozygous subjects compared with both of the other genotypes combined (95% CI 1.26–2.41; no significant between-study heterogeneity). There was still an enrichment of the *RR* genotype in secondary APS patients as compared with disease-free controls (OR 2.04 for *RR* versus other genotypes combined, 95% CI 1.42–2.95; no significant heterogeneity). Among SLE patients, the homozygous *HH* genotype also conferred a greater risk of developing APS than did *RH* heterozygosity (OR 0.57 for *RH* versus *HH*, 95% CI 0.35–0.93; no significant heterogeneity).

Other bias diagnostics. There was no evidence that the strength of the observed associations was different in early studies versus those published recently. In particular, the effect of the *R131* allele seemed to become clearer over time for both the total APS group and the group with APS secondary to SLE, while the effect of the high-binding allele had been steady all along (data not shown). Similarly, inverted-funnel plots showed no evidence of bias differentiating the magnitude of the observed effects in the key comparisons between small and large studies (data not shown).

DISCUSSION

This international meta-analysis suggests a complex genetic background underlying the relationship between the *FcγRIIA-R/H131* polymorphism and APS. A significant increase in *RR* homozygosity was documented in the whole group of APS patients. This selection was most striking in patients with APS secondary to SLE. The *R131* allele seemed to confer risk for APS under a recessive model, whereas the effect of *R131* on susceptibility to SLE has been found to have a dose-response character (9). This difference may be explained by the fact that among lupus patients, those who have APS also have an overrepresentation of homozygosity for the high-binding *H131* allele. This may be even more prominent in primary APS, but data on primary APS comparisons were too limited to be definitive. As a result of these composite genetic influences, when the whole group of APS patients was contrasted against disease-free controls, there was a selection of the *HH* genotype as compared with the *RH* genotype. Thus, the meta-analysis results suggest that the observed genetic profile may be a composite of 2 different and opposing influences with regard to APS susceptibility.

Recent evidence suggests an effect of FcγR as potential initiators of thrombosis. This complication seems to be a consequence of platelet activation initiated when platelet FcγRIIa are crosslinked by antibodies (5,32). Since the interaction of IgG2-containing antibodies with FcγRIIa is allotype-dependent (8), it has been hypothesized that the high-binding *H131* allele would be overrepresented among subjects with antibody-mediated thrombosis (11,33). The hypothesis has also been investigated in heparin-induced thrombocytopenia, another syndrome with similar immune-mediated thrombosis, but no consistent relationship between the *H131* allele and this syndrome was shown (34).

The results of this meta-analysis may help to explain discrepancies among findings of previous studies of *FcγRIIA-R/H131* in APS (11–13). *HH* homozygosity increases the risk of APS relative to *RH* heterozygosity. However, the effect of *HH* homozygosity for susceptibility to APS is overwhelmed by the larger effect of *RR* homozygosity for susceptibility to SLE in general (9),

especially among patients with secondary APS. The *R131* allele may confer risk for SLE through deficient handling of IgG2-containing immune complexes by the mononuclear phagocyte system, leading to their tissue deposition and to accelerated organ damage (7).

It is not clear whether *RR* homozygosity may also confer an increased risk of primary APS per se, aside from SLE, through some common pathophysiologic link to SLE. We should caution that the classification criteria for APS and SLE are functional criteria and may not fully correspond to the subgrouping of APS and SLE based on genetic predisposition. APS is a remarkably heterogeneous syndrome with different prognostic profiles (35).

Alternative hypotheses could explain an independent effect of *RR* homozygosity on the risk of APS. For example, apoptotic cells are a major source of autoantigens, and an impairment of their physiologic clearance may promote the development of autoimmunity. Anionic phospholipids redistribute from the inner leaflet to the outer leaflet of cell membranes during apoptosis (36). This systemic exposure could enable the binding of phospholipid-binding proteins such as β_2-glycoprotein I (β_2GPI) to apoptotic cell membranes (37) and may also trigger the production of aPL antibodies (38,39). Phospholipid–β_2GPI complexes on the surface of membrane blebs are recognized by aPL antibodies (37,38, 40,41), which leads to opsonization of apoptotic cells that are then phagocytosed by FcR-positive macrophages (40,41). Considering that aPL (10,11), especially those with reactivity to β_2GPI (42,43), show IgG2-dominant distribution, such antibodies would be predicted to be poor opsonins in *RR* homozygous subjects. Defective clearance of aPL-opsonized apoptotic particles by macrophages may lead to inflammatory removal pathways (44,45), favoring an autoimmune, rather than an antiinflammatory, response to apoptotic cells. Thus, antigen processing and presentation by antigen-presenting cells (44,45) provide an antigenic stimulus for specific T and B clones, leading to further aPL antibody production that may exert procoagulant effects (2). Moreover, persistently circulating apoptotic cells could express procoagulant properties, thus supporting thrombotic events (46).

That the *RR* genotype is mostly enriched among lupus patients with APS is also consistent with this explanation, since SLE is characterized by an increased rate of activation-induced cell death (47). Increased apoptotic load with the augmented exposure of anionic phospholipids may amplify the consequences of the defective handling of apoptotic cells in lupus patients who are homozygous for the low-binding allele. Remarkably, aPL antibodies occur more frequently and earlier in SLE patients with the *RR* genotype (20,48). Furthermore, macrophages from SLE patients with sufficient expression of receptors implicated in phagocyte recognition of cells undergoing apoptosis (CD14 and CD36) exhibit defective engulfment of apoptotic cell material in vitro (49).

Patients with either primary or secondary APS have similar clinical profiles as far as thrombotic manifestations are concerned (3,50). Nevertheless, arthritis, low C4 levels, and hematologic abnormalities such as hemolytic anemia, thrombocytopenia, leukopenia, and neutropenia are more common among patients with APS secondary to SLE (3,50). The selection of the *RR* homozygous state that was demonstrated only in patients with secondary APS relative to disease-free controls could also be related to these differences, even though other factors may also play a role in the pathogenesis of these manifestations. It is noteworthy that such clinical features and serologic findings seem to be overrepresented in lupus patients with low-binding FcγR alleles (20,21). Moreover, a critical role for FcγR has been demonstrated in models of collagen-induced arthritis as well as in models of experimental cytopenias (51,52).

The relevance of the *FcγRIIA-R/H131* polymorphism for APS susceptibility should be viewed at the population level. Although the summary OR estimates suggest only a moderate genetic effect, the importance of this effect may be considerable at the population level, given the high frequency of the *RR* genotype ($\sim$25%) in populations of European descent (7). Thus, modest ORs translate to a clinically meaningful proportion of APS cases that could be attributed to *RR* homozygosity (at least 10% in populations of European descent). Empirical evidence suggests that for multigenetic diseases, the magnitude of the ORs is generally modest. Among 55 genetic associations examined in different disciplines, none had an OR exceeding 2.0, and only 13 showed a significant OR exceeding 1.5 (53).

Some limitations of this study should be discussed. First, the number of APS patients with specific clinical manifestations was too small to reliably assess the effect of the *FcγRIIA-R/H131* polymorphism on the risk of vascular thromboses or other APS-related features. Multiple comparisons and small subgroups would make such inferences impractical, even with the sample size of the meta-analysis. Second, bias is possible in a meta-analysis. However, bias diagnostics did not suggest the presence of such problems in this study. Three study

teams did not use the preliminary criteria for the classification of APS; nevertheless, similar results were obtained when data from these study teams were excluded. Last, the association of the *FcγRIIA-R/H131* polymorphism with APS could be explained by the existence of linkage disequilibrium between this gene and other candidate genes on chromosome 1 that may also be more directly relevant for the risk of specific disease manifestations (54). This would require the investigation of extended haplotypes (55,56) in the future. Genetic variants in different genes might also contribute to the pathogenesis of APS (57,58). Recognition of specific disease-associated genetic factors may expand our understanding of disease pathogenesis and may also be useful for identifying subjects at increased risk of developing APS.

ACKNOWLEDGMENTS

Other key investigators of the collaborating study teams involved in this project were as follows: Toru Fukazawa, MD, PhD (Juntendo University, Tokyo, Japan), Hiroshi Hashimoto, MD, PhD (Juntendo University, Tokyo, Japan), Elisabeth Tournier-Lasserve, MD (Faculté de Médecine Necker, Paris, France), Kwang-Taek Oh, MD (Hanyang University, Seoul, South Korea), Jan G. J. van de Winkel, PhD (Department of Immunology and Genmab, University Medical Center Utrecht, Utrecht, The Netherlands).

REFERENCES

1. Hughes GR. The antiphospholipid syndrome: ten years on. Lancet 1993;342:341–4.
2. Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. N Engl J Med 2002;346:752-63.
3. Cervera R, Piette J-C, Font J, Khamashta MA, Shoenfeld Y, Camps MT, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002;46:1019–27.
4. Arnout J. The pathogenesis of the antiphospholipid syndrome: a hypothesis based on parallelisms with heparin-induced thrombocytopenia. Thromb Haemost 1996;75:536–41.
5. Arvieux J, Roussel B, Pouzol P, Colomb MG. Platelet activating properties of murine monoclonal antibodies to beta 2-glycoprotein I. Thromb Haemost 1993;70:336–41.
6. Arvieux J, Jacob MC, Roussel B, Bensa JC, Colomb MG. Neutrophil activation by anti-beta 2 glycoprotein I monoclonal antibodies via Fcγ receptor II. J Leukoc Biol 1995;57:387–94.
7. Salmon JE, Pricop L. Human receptors for immunoglobulin G: key elements in the pathogenesis of rheumatic disease. Arthritis Rheum 2001;44:739–50.
8. Salmon JE, Millard S, Schachter LA, Arnett FC, Ginzler EM, Gourley MF, et al. FcγRIIA alleles are heritable risk factors for lupus nephritis in African Americans. J Clin Invest 1996;97:1348–54.
9. Karassa FB, Trikalinos TA, Ioannidis JPA, and the FcγRIIa-SLE Meta-Analysis Investigators. Role of the Fcγ receptor IIa polymorphism in susceptibility to systemic lupus erythematosus and lupus nephritis: a meta-analysis. Arthritis Rheum 2002;46:1563–71.
10. Levy RA, Gharavi AE, Sammaritano LR, Habina L, Qamar T, Lockshin MD. Characteristics of IgG antiphospholipid antibodies in patients with systemic lupus erythematosus and syphilis. J Rheumatol 1990;17:1036–41.
11. Sammaritano LR, Ng S, Sobel R, Lo SK, Simantov R, Furie R, et al. Anticardiolipin IgG subclasses: association of IgG2 with arterial and/or venous thrombosis. Arthritis Rheum 1997;40:1998–2006.
12. Atsumi T, Caliz R, Amengual O, Khamashta MA, Hughes GRV. FcγIIA H/R131 polymorphism in patients with antiphospholipid antibodies. Thromb Haemost 1998;79:924–7.
13. Michel M, Piette J-C, Roullet E, Duron F, Frances C, Nahum L, et al. The R131 low-affinity allele of the FcγRIIA receptor is associated with systemic lupus erythematosus but not with other autoimmune diseases in French Caucasians. Am J Med 2000;108:580–3.
14. Ioannidis JP, Tektonidou MG, Vlachoyiannopoulos PG, Stavropoulos-Giokas C, Spyropoulou-Vlachou M, Reveille JD, et al. HLA associations of anti-β_2 glycoprotein I response in a Greek cohort with antiphospholipid syndrome and meta-analysis of four ethnic groups. Hum Immunol 1999;60:1274–80.
15. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.
16. Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette J-C, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum 1999;42:1309–11.
17. Song YW, Han C-W, Kang S-W, Baek H-J, Lee E-B, Shin C-H, et al. Abnormal distribution of Fcγ receptor type IIa polymorphisms in Korean patients with systemic lupus erythematosus. Arthritis Rheum 1998;41:421–6.
18. Yun H, Koh H, Kim S, Chung W, Kim D, Hong K, et al. FcγRIIa/IIIa polymorphism and its association with clinical manifestations in Korean lupus patients. Lupus 2001;10:466-72.
19. Hatta Y, Tsuchiya N, Ohashi J, Matsushita M, Fujiwara K, Hagiwara K, et al. Association of Fcγ receptor IIIB, but not of Fcγ receptor IIA and IIIA polymorphisms with systemic lupus erythematosus in Japanese. Genes Immun 1999;1:53–60.
20. Manger K, Repp R, Spriewald BM, Rascu A, Geiger A, Wassmuth R, et al. Fcγ receptor IIa polymorphism in Caucasian patients with systemic lupus erythematosus: association with clinical symptoms. Arthritis Rheum 1998;41:1181–9.
21. Dijstelbloem HM, Bijl M, Fijnheer R, Scheepers RHM, Oost WW, Jansen MD, et al. Fcγ receptor polymorphisms in systemic lupus erythematosus: association with disease and in vivo clearance of immune complexes. Arthritis Rheum 2000;43:2793–800.
22. Botto M, Theodoridis E, Thompson E, Beynon H, Briggs D, Isenberg D, et al. FcγRIIa polymorphism in systemic lupus erythematosus (SLE): no association with disease. Clin Exp Immunol 1996;104:264–8.
23. Lau J, Ioannidis J, Schmid C. Quantitative synthesis in systematic reviews. Ann Intern Med 1997;127:820–6.
24. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719–48.
25. Fleiss J. The statistical basis of meta-analysis. Stat Methods Med Res 1993;2:121–45.
26. Lathrop GM. Estimating genotype relative risks. Tissue Antigens 1983;22:160–6.
27. Ioannidis JP, Contopoulos-Ioannidis DG, Lau J. Recursive cumulative meta-analysis: a diagnostic for the evolution of total randomized evidence from group and individual patient data. J Clin Epidemiol 1999;52:281–91.
28. Ioannidis J, Lau J. Evolution of treatment effects over time: empirical insight from recursive cumulative metaanalyses. Proc Natl Acad Sci U S A 2001;98:831–6.

29. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
30. Harris EN. Antiphospholipid antibodies. Br J Haematol 1990;74: 1–9.
31. Harris EN. Antiphospholipid syndrome. In: Klippel J, Dieppe P, editors. Rheumatology. St. Louis: Mosby; 1994. p. 32.1–6.
32. Anderson GP. Insights into heparin-induced thrombocytopenia. Br J Haematol 1992;80:504–8.
33. Burgess JK, Lindeman R, Chesterman CN, Chong BH. Single amino acid mutation of Fcγ receptor is associated with the development of heparin-induced thrombocytopenia. Br J Haematol 1995;91:761–6.
34. Trikalinos TA, Karassa FB, Ioannidis JPA. Meta-analysis of the association between low-affinity Fcγ receptor gene polymorphisms and hematologic and autoimmune diseases. Blood 2001;98: 1634–5.
35. Tektonidou MG, Ioannidis JP, Boki KA, Vlachoyiannopoulos PG, Moutsopoulos HM. Prognostic factors and clustering of serious clinical outcomes in antiphospholipid syndrome. QJM 2000;93: 523–30.
36. Martin SJ, Reutelingsperger CP, McGahon AJ, Rader JA, van Schie RC, LaFace DM, et al. Early redistribution of plasma membrane phosphatidylserine is a general feature of apoptosis regardless of the initiating stimulus: inhibition by overexpression of Bcl-2 and Abl. J Exp Med 1995;182:1545–56.
37. Price BE, Rauch J, Shia MA, Walsh MT, Lieberthal W, Gilligan HM, et al. Anti-phospholipid autoantibodies bind to apoptotic, but not viable, thymocytes in a β2-glycoprotein I-dependent manner. J Immunol 1996;157:2201–8.
38. Casciola-Rosen L, Rosen A, Petri M, Schlissel M. Surface blebs on apoptotic cells are sites of enhanced procoagulant activity: implications for coagulation events and antigenic spread in systemic lupus erythematosus. Proc Natl Acad Sci U S A 1996;93:1624–9.
39. Mevorach D, Zhou JL, Song X, Elkon KB. Systemic exposure to irradiated apoptotic cells induces autoantibody production. J Exp Med 1998;188:387–92.
40. Manfredi AA, Rovere P, Galati G, Heltai S, Bozzolo E, Soldini L, et al. Apoptotic cell clearance in systemic lupus erythematosus. I. Opsonization by antiphospholipid antibodies. Arthritis Rheum 1998;41:205–14.
41. Manfredi AA, Rovere P, Heltai S, Galati G, Nebbia G, Tincani A, et al. Apoptotic cell clearance in systemic lupus erythematosus. II. Role of β_2-glycoprotein I. Arthritis Rheum 1998;41:215–23.
42. Arvieux J, Roussel B, Ponard D, Colomb MG. IgG2 subclass restriction of anti-β2 glycoprotein I antibodies in autoimmune patients. Clin Exp Immunol 1994;95:310–5.
43. Amengual O, Atsumi T, Khamashta MA, Bertolaccini ML, Hughes GRV. IgG2 restriction of anti–β_2-glycoprotein I as the basis for the association between IgG2 anticardiolipin antibodies and thrombosis in the antiphospholipid syndrome: comment on the article by Sammaritano et al [letter]. Arthritis Rheum 1998; 41:1513–4.
44. Albert ML, Sauter B, Bhardwaj N. Dendritic cells acquire antigen from apoptotic cells and induce class I-restricted CTLs. Nature 1998;392:86–9.
45. Inaba K, Turley S, Yamaide F, Iyoda T, Mahnke K, Inaba M, et al. Efficient presentation of phagocytosed cellular fragments on the major histocompatibility complex class II products of dendritic cells. J Exp Med 1998;188:2163–73.
46. Bombeli T, Karsan A, Tait JF, Harlan JM. Apoptotic vascular endothelial cells become procoagulant. Blood 1997;89:2429–42.
47. Georgescu L, Vakkalanka RK, Elkon KB, Crow MK. Interleukin-10 promotes activation-induced cell death of SLE lymphocytes mediated by Fas ligand. J Clin Invest 1997;100:2622–33.
48. Manger K, Repp R, Jansen M, Geisselbrecht M, Wassmuth R, Westerdaal NA, et al. Fcγ receptor IIa, IIIa, and IIIb polymorphisms in German patients with systemic lupus erythematosus: association with clinical symptoms. Ann Rheum Dis 2002;61:786–92.
49. Herrmann M, Voll RE, Zoller OM, Hagenhofer M, Ponner BB, Kalden JR. Impaired phagocytosis of apoptotic cell material by monocyte-derived macrophages from patients with systemic lupus erythematosus. Arthritis Rheum 1998;41:1241–50.
50. Vianna JL, Khamashta MA, Ordi-Ros J, Font J, Cervera R, Lopez-Soto A, et al. Comparison of the primary and secondary antiphospholipid syndrome: a European multicenter study of 114 patients. Am J Med 1994;96:3–9.
51. Van Lent PLEM, van Vuuren AJ, Blom AB, Holthuysen AEM, van de Putte LBA, van de Winkel JGJ, et al. Role of Fc receptor γ chain in inflammation and cartilage damage during experimental antigen-induced arthritis. Arthritis Rheum 2000;43:740–52.
52. Clynes R, Ravetch JV. Cytotoxic antibodies trigger inflammation through Fc receptors. Immunity 1995;3:21–6.
53. Ioannidis JPA, Trikalinos TA, Ntzani EE, Contopoulos-Ioannidis DG. Genetic associations in large versus small studies: an empirical assessment. Lancet 2003;361:567–71.
54. Karassa FB, Trikalinos TA, Ioannidis JP, and the FcγRIIIa-SLE Meta-Analysis Investigators. The FcγRIIIA-F158 allele is a risk factor for the development of lupus nephritis: a meta-analysis. Kidney Int 2003;63:1475–82.
55. Kyogoku C, Dijstelbloem HM, Tsuchiya N, Hatta Y, Kato H, Yamaguchi A, et al. Fcγ receptor gene polymorphisms in Japanese patients with systemic lupus erythematosus: contribution of FCGR2B to genetic susceptibility. Arthritis Rheum 2002;46: 1242–54.
56. Zuñiga R, Ng S, Peterson MGE, Reveille JD, Baethge BA, Alarcón GS, et al. Low-binding alleles of Fcγ receptor types IIA and IIIA are inherited independently and are associated with systemic lupus erythematosus in Hispanic patients. Arthritis Rheum 2001;44:361–7.
57. Hirose N, Williams R, Alberts AR, Furie RA, Chartash EK, Jain RI, et al. A role for the polymorphism at position 247 of the β_2-glycoprotein I gene in the generation of anti–β_2-glycoprotein I antibodies in the antiphospholipid syndrome. Arthritis Rheum 1999;42:1655–61.
58. Tàssies D, Espinosa G, Muñoz-Rodríguez FJ, Freire C, Cervera R, Monteagudo J, et al. The 4G/5G polymorphism of the type 1 plasminogen activator inhibitor gene and thrombosis in patients with antiphospholipid syndrome. Arthritis Rheum 2000;43: 2349–58.