

Prevalence and Distribution of Autoimmune Diseases in 368 Rheumatoid Arthritis Families

LAËTITIA MICHOU, ANNE-CHRISTINE RAT, SANDRA LASBLEIZ, THOMAS BARDIN, and FRANÇOIS CORNÉLIS

ABSTRACT. *Objective.* To investigate whether frequency of rheumatoid arthritis (RA) and/or other autoimmune (AI) disorders was increased in RA French Caucasian families among the first- (FDR) and second-degree relatives (SDR), and to test whether the presence of AI disease family history identified a specific RA subset.

Methods. We conducted telephone interviews to obtain histories of AI diseases among the FDR and SDR of 368 RA probands, belonging either to trio or affected sib-pair (ASP) families. All the AI diagnoses were confirmed by the physician of the affected relative.

Results. Probands of the ASP families were characterized by older age at RA onset, longer disease duration, and larger family size versus trio families. In the trio families, the prevalence of AI diseases was 6.05% (4.76%–7.57%) in FDR and 2.40% (1.85%–3.06%) in SDR. In ASP families, the prevalence of AI diseases was, respectively, 10.24% (8.68%–11.97%) and 1.79% (1.41%–2.25%). The most frequent AI diseases among relatives were RA, thyroid AI diseases, and vitiligo. In trio families, a proband with a mean age of RA onset < 30 years was associated with AI disease prevalence in the relatives, and male gender was associated with prevalence of RA among the FDR.

Conclusion. The prevalence of AI diseases is increased, particularly among FDR, in French RA families, and some characteristics of the RA proband seem to be associated with prevalence of AI diseases in families. (First Release Mar 15 2008; J Rheumatol 2008;35:790–6)

Key Indexing Terms:

RHEUMATOID ARTHRITIS
AUTOIMMUNE DISEASES

FAMILIAL AGGREGATION
PREVALENCE

Rheumatoid arthritis (RA) is a common autoimmune (AI) disease, characterized by a chronic systemic inflammation affecting mainly the peripheral joints. The pathophysiology of RA is multifactorial, involving both genetic and environmental factors. Familial aggregation of RA is relatively common, and was previously associated either with proband characteristics such as disease severity^{1,2} and gender^{3–6}, or with a proband's family characteristics such as sibship size^{3,7,8}. Familial clustering of other AI diseases, which has also been reported in RA families, involves in addition to RA familial cases AI thyroid diseases (i.e., Hashimoto's thyroiditis and Graves' disease) and type 1 diabetes^{9–11}. A sim-

ilar observation of AI disease familial clustering was reported in families with probands affected by AI disorders such as multiple sclerosis¹², juvenile RA¹³, systemic lupus erythematosus (SLE)¹⁴, and idiopathic inflammatory myopathy¹⁵.

We investigated whether the frequency of RA and/or other AI disorders, known to be associated with RA, was increased in RA French Caucasian families among the first- (FDR) and second-degree relatives (SDR), and tested whether presence of AI disease family history identified a specific RA subset.

MATERIALS AND METHODS

Patients and families. About 10 years ago 384 RA families were recruited for participation in a genetic study on RA in France. The 200 trio families each comprised one RA patient (the proband) and both parents; and the 184 affected sibling-pair (ASP) families comprised one RA patient (the proband) and at least one affected sibling. The 4 grandparents of the probands were required to be European Caucasian. The following proband characteristics were collected: sex, date of birth, year when RA began, presence of rheumatoid factor (defined by at least one positive test result for latex, Waaler-Rose, or nephelometry), presence of erosions, nodules, secondary Sjögren's syndrome, extraarticular manifestations of RA (vasculitis), other AI diseases, and presence of at least one prosthesis or arthrodesis. RA was defined by the 1987 American College of Rheumatology (formerly, the American Rheumatism Association) criteria¹⁶, confirmed by 2 rheumatologists (SL, Dr. P. Fritz). All individuals provided informed written consent, and the study was approved by the Hospital Bicêtre ethics committee (Kremlin-Bicêtre, Assistance Publique-Hôpitaux de Paris).

Telephone interviews. Each proband was interviewed by telephone to get

From GenHotel-EA 3886, University Evry-Paris 7 Medical School, Member of the AutoCure European Consortium, Evry-Genopole;

EA 4003, Centre d'Epidémiologie Clinique, CEC-Inserm CIE6, Service d'épidémiologie et évaluation cliniques, CHU Nancy, Nancy; and Unité de Génétique Clinique, Hôpital Lariboisière, Assistance Publique-Hôpitaux de Paris, Paris, France.

L. Michou, MD, PhD, GenHotel-EA 3886, University Evry-Paris 7 Medical School and Unité de Génétique Clinique, Hôpital Lariboisière; A-C. Rat, MD, EA 4003, Centre d'Epidémiologie Clinique, CEC-Inserm CIE6, Service d'épidémiologie et évaluation cliniques; S. Lasbleiz, MD; T. Bardin, MD; F. Cornélis, MD, PhD, GenHotel-EA 3886, University Evry-Paris 7 Medical School and Unité de Génétique Clinique, Hôpital Lariboisière.

Address reprint requests to Dr. L. Michou, Unité de génétique clinique, Hôpital Lariboisière, 2 rue Ambroise Paré, 75475 Paris, cedex 10, France. E-mail: laetitia.michou@lrp.aphp.fr

Accepted for publication December 25, 2007.

detailed pedigree information on FDR (i.e., parents, offspring, siblings) and SDR (i.e., grandparents, uncles, aunts, grandchildren, nephews, nieces). For each relative, we collected data on year of birth and sex, and for deceased relatives, year and cause of death. Both living and deceased relatives were considered in this study. History of the following AI diseases was determined during the interview: RA, primary Sjögren's syndrome, thyroid AI diseases (Hashimoto's thyroiditis and Graves' disease), vitiligo, pernicious anemia, type 1 diabetes, myasthenia gravis, SLE, multiple sclerosis, and other AI diseases including Crohn's disease, ulcerative colitis, celiac disease, Addison's disease, pemphigus vulgaris, and AI hepatitis.

Confirmation of AI disease diagnoses. When there was a history of AI disease for a relative, a confirmation questionnaire was sent, either via the proband or directly to the concerned relative, in order to confirm the diagnosis with the physician in charge. The AI disease onset year was also collected. When the diagnosis remained uncertain, the relative was contacted in person by telephone (LM). Medical interviews and endpoints such as use of medications were used to ascertain diagnosis. By contacting the proband, the same procedure of endpoints was used to confirm AI disease diagnoses for deceased relatives. AI diseases in the relatives were considered as "not confirmed" when the physician in charge of the patient did not confirm the diagnosis, or when the physician failed to respond to the inquiry.

Statistical analysis. For all analyses, the sibling known to have RA and who belonged to the ASP with the RA proband was excluded. RA probands and family characteristics were determined for each kind of family (compared in Table 1). All subsequent analyses were performed separately for the 2 types of families, as the genetic recruitment bias prevented us from pooling the 2 samples. We determined the number of families with at least one AI disease in the relatives and the distribution of AI diseases per family. Prevalence of AI diseases was calculated for the FDR and the SDR for all AI diseases and separately for each AI disease. The observed prevalence in the trio and ASP families was reported and contrasted with the prevalence of the different AI diseases in the general population, as no control set of families was available. The prevalences of AI diseases used were those reported for the French Caucasian population when available, or for the European Caucasian population with preference for the European country with the same latitude as that of France, to avoid bias inherent to the North-South gradient of AI disease prevalence. As our sample included adult family members of all probands, the age and sex distribution of the sample is close to that of the adult general population. All prevalence surveys referenced were standardized for age and sex, but not for ethnicity, as ethnicity

is rarely reported in Europe. Prevalences for the general population were used to calculate the familial aggregation (λ) for each AI disease in FDR and SDR. We also studied the incidence of AI diseases in relatives of trio and ASP families between the time of inclusion in the RA genetic study (i.e., from 1994 to 1998) and the year of detailed pedigree information (i.e., 2001–2002 and 2004 for trio families, and 2002–2004 for ASP families). Incidence was expressed in relative-years, one relative-year corresponding to the followup of one relative during one year. The distribution of relatives affected by an AI disease was described. Detailed familial aggregation (λ) for RA and for AI diseases was calculated in the first-degree relatives of the 2 types of family, using the following formula:

$$\lambda_{\text{relatives}} = \lambda_{\text{relatives}} / K$$

where $\lambda_{\text{relatives}}$ was prevalence for relatives in the sample and K was prevalence in the general population

The prevalence of RA in the French general population was 0.0031, 0.0011 for men and 0.0044 for women¹⁷. Prevalence data on AI diseases for the French population were not available so we used American Caucasian population prevalence rates: 0.0322 for general population, 0.0068 for men and 0.0255 for women¹⁸.

In order to study the relationships between a proband's characteristics and/or those of the family and prevalence of at least one AI disease among the FDR and SDR, we performed bivariate analyses with chi-square tests for dichotomous variables and Student tests for continuous variables. Multiple logistic regression analysis included variables at the 0.1 level of significance. Another bivariate analysis was performed for the prevalence of at least one RA among the FDR. For all analyses $p < 0.05$ indicated statistical significance. Statistical analysis was performed using SAS, version 8.0 (SAS Institute Inc., 1997).

RESULTS

Six families in the trio sample were excluded from analysis because the RA proband was deceased. In the ASP sample, we excluded 8 families due to RA proband death and 2 other families, who refused to participate (Figure 1).

Characteristics of RA probands and their families. The mean age at RA onset of the ASP family probands was high-

Table 1. Characteristics of RA probands in trio families and affected sibling pair (ASP) families.

Characteristics of Probands	Trio Families, n = 194	ASP Families [†] , n = 174	p
Females, n (%)	174 (89.7)	145 (83.3)	0.07
Age at RA onset, yrs, mean ± SD	31.8 ± 9.5	42.5 ± 14.3	< 0.0001
Disease duration, yrs, mean ± SD	15.6 ± 7.5	22.6 ± 11.8	< 0.0001
Positive rheumatoid factor, n (%)	153 (78.8)	132 (75.9)	0.62
Erosions, n (%)	164 (84.5)	144 (82.7)	0.55
Nodules, n (%)	49 (25.2)	52 (29.8)	0.13
Secondary Sjögren's syndrome, n (%)	24 (12.4)	36 (20.7)	0.013
Cutaneous vasculitis, n (%)	7 (3.6)	13 (7.5)	0.10
Proband with at least one other AI disease*, n (%)	13 (6.7)	18 (10.3)	0.21
At least one prosthesis or arthrodesis, n (%)	39 (20.1)	54 (31.0)	0.016
No. first and second degree relatives per family, mean ± SD	19.6 ± 8.6	31.2 ± 11.9	< 0.0001
No. women among the first- and second-degree relatives per family, mean ± SD	9.7 ± 4.6	16.2 ± 6.1	< 0.0001

* Other autoimmune (AI) diseases: Hashimoto thyroiditis, Graves' disease, pernicious anemia, vitiligo, type 1 diabetes, and myasthenia gravis. † For all analyses, the sibling known to have RA and who belonged to the ASP with the RA proband was excluded.

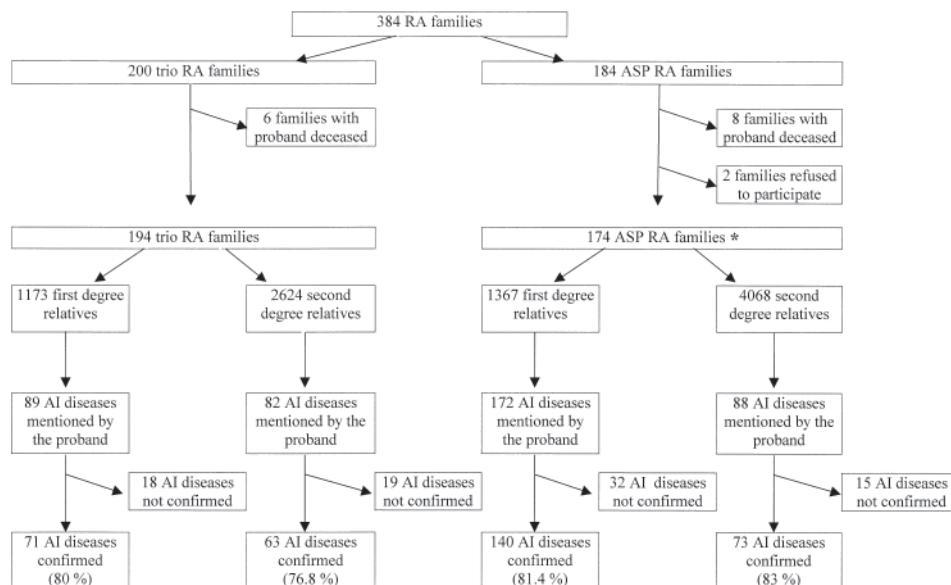


Figure 1. The design and progression of the study. ASP: affected sibling-pair; AI: autoimmune. *The sibling known to have RA and who belonged to the ASP with the RA proband was excluded.

er than in trio families (42.5 ± 14.3 yrs vs 31.8 ± 9.5 ; $p < 0.0001$) and the mean disease duration was higher (22.6 ± 11.8 yrs vs 15.6 ± 7.5 ; $p < 0.0001$). The mean number of FDR and SDR per family was also higher in the ASP families (32.2 ± 11.9 relatives vs 19.6 ± 8.6 ; $p < 0.0001$). The mean number of women among the relatives was significantly higher in ASP families versus trio families (16.9 ± 6.1 women vs 9.7 ± 4.6 ; $p < 0.0001$) but, in each sample of families, the sex ratio was 1. Interestingly, the main clinical characteristics of RA (i.e., rheumatoid factor, erosions, nodules) of the ASP and trio families' probands were similar (Table 1).

Prevalence of AI diseases. In the trio families, 86 (44.3%) RA probands had at least one relative with AI disease, including 38 RA multiplex families. In the ASP families, after exclusion of the sibling known to have RA and who belonged to the ASP with the RA proband, 99 (56.9%) RA probands had at least one relative with AI disease, including 53 RA multiplex families. In the trio families, the prevalence of AI diseases among the FDR and the SDR was, respectively, 6.05% (4.76%–7.57%) and 2.40% (1.85%–3.06%) (Table 2). In the ASP families, the prevalence of AI diseases among the FDR and SDR was, respectively, 10.24% (8.68%–11.97%) and 1.79% (1.41%–2.25%) (Table 3).

In each sample, the confirmation rate of diagnosis was high, about 80%, as indicated in Figure 1. Among the 37 unconfirmed AI diseases in the trio families, 26 were due to negative physician report. In the ASP families, among the 47 unconfirmed AI diseases, 28 were due to negative physician report. The most frequent AI diseases in the trio and ASP

families were RA [2.30% (1.52%–3.33%) and 5.93% (4.73%–7.31%)], thyroid AI diseases [1.93% (1.25%–2.93%) and 2.12% (1.54%–3.03%)], and vitiligo [0.77% (0.35%–1.45%) and 0.44% (0.16%–0.95%)] among the FDR, and RA [1.33% (0.93%–1.85%) and 1.11% (0.81%–1.48%)] among the SDR. RA and SLE prevalence was higher among the FDR and SDR of each family sample than in the general population. The prevalence of thyroid AI diseases, vitiligo, myasthenia gravis, and primary Sjögren's syndrome was increased but only at the first-degree of relatedness. The FDR of ASP families also had an increased prevalence of type 1 diabetes and multiple sclerosis.

Incidence of AI diseases. During the 6 years of observation of trio families (15,938 relative-years), and the 8 years of observation of ASP families (27,223 relative-years), respectively, 21 and 41 AI diseases occurred, mostly among the FDR. The AI diseases with the greatest incidence were RA (10 cases in trio families and 22 cases in ASP families) and AI thyroid diseases (respectively, 8 and 11 cases).

Distribution of AI diseases. In the trio families, among the 62 FDR affected by at least one AI disease, 51 (82.3%) were women (51.6% being proband's mother); and among the 62 affected SDR, 44 (71.0%) were women (21.0% were maternal aunts). In the ASP families, among the 128 affected FDR, 98 (76.6%) were women (45.3% being proband's sister); and among the 71 affected SDR, 54 (76.0%) were women (22.5% being proband's niece). The percentage of siblings affected by AI diseases was increased in ASP families, with 18% of the sisters affected in ASP families versus 7.5% in the trio families and, respectively, 6.4% of the brothers affected versus 1.4%.

Table 2. Prevalence of autoimmune (AI) diseases among the first- and second-degree relatives of trio RA families versus prevalence in the general population.

Autoimmune Diseases	Trio RA Families								General Population, %
	First-Degree Relatives, n = 1173				Second-Degree Relatives, n = 2624				
	n	%	(95% CI)	λ	n	%	(95% CI)	λ	
Rheumatoid arthritis	27	2.3	(1.6–3.3)	7.4	35	1.3	(1.0–1.8)	4.2	0.31 ¹⁷
Thyroid autoimmune diseases*	23	2.0	(1.3–2.9)	1.4	18	0.7	(0.4–1.1)	0.5	1.45 ¹⁹
Vitiligo	9	0.8	(0.4–1.4)	2.1	3	0.1	(0.04–0.3)	0.3	0.38 ²⁰
Pernicious anemia	2	0.17	(0.05–0.6)	1.3	—	—	—	—	0.13 ²¹
Type 1 diabetes	1	0.1	(0.02–0.5)	0.3	3	0.1	(0.04–0.3)	0.3	0.34 ²²
Myasthenia gravis	2	0.17	(0.05–0.6)	11.3	—	—	—	—	0.015 ²³
Lupus erythematosus	2	0.17	(0.05–0.6)	6.3	1	0.04	(0.01–0.2)	1.5	0.027 ²⁴
Sjögren's syndrome	3	0.25	(0.09–0.7)	15.6	—	—	—	—	0.016 ²⁵
Multiple sclerosis	—	—	—	—	2	0.08	(0.02–0.3)	3.6	0.022 ²⁶
Other diseases [†]	2	0.17	(0.05–0.6)	—	1	0.04	(0.01–0.2)	—	—
Total	71	6.1	(4.8–7.6)	—	63	2.4	(1.9–3.1)	—	—

* Thyroid autoimmune diseases: Hashimoto thyroiditis and Graves' disease. † Other diseases: Crohn's disease, ulcerative colitis, celiac disease, Addison's disease, pemphigus vulgaris, and autoimmune hepatitis. λ : familial aggregation.

Table 3. Prevalence of autoimmune diseases among the first- and second-degree relatives of affected sibling pair (ASP) RA families versus prevalence in the general population.

Autoimmune Diseases	ASP RA Families [†]							General Population, %	
	First-Degree Relatives, n = 1367				Second-Degree Relatives, n = 4068				
	n	%	(95% CI)	λ	n	%	(95% CI)		λ
Rheumatoid arthritis	81	5.9	(4.8–7.3)	19.0	45	1.1	(0.8–1.5)	3.5	0.31 ¹⁷
Thyroid autoimmune diseases*	29	2.1	(1.5–3.0)	1.4	8	0.2	(0.1–0.4)	0.1	1.45 ¹⁹
Vitiligo	6	0.44	(0.2–0.9)	1.1	3	0.07	(0.03–0.2)	0.2	0.38 ²⁰
Pernicious anemia	—	—	—	—	2	0.05	(0.01–0.2)	0.4	0.13 ²¹
Type 1 diabetes	6	0.44	(0.2–0.9)	1.3	8	0.2	(0.1–0.4)	0.6	0.34 ²²
Myasthenia gravis	1	0.07	(0.01–0.4)	4.6	—	—	—	—	0.015 ²³
Lupus erythematosus	5	0.36	(0.2–0.8)	3.3	2	0.05	(0.01–0.2)	1.8	0.027 ²⁴
Sjögren's syndrome	5	0.36	(0.2–0.8)	22.5	—	—	—	—	0.016 ²⁵
Multiple sclerosis	4	0.29	(0.1–0.7)	13.2	1	0.02	(0–0.1)	0.9	0.022 ²⁶
Other diseases ^{††}	3	0.22	(0.07–0.6)	—	4	0.1	(0.04–0.2)	—	—
Total	140	10.2	(8.7–12.0)	—	73	1.8	(1.4–2.2)	—	—

* Thyroid autoimmune diseases: Hashimoto thyroiditis and Graves' disease. † For all analyses, the sibling known to have RA and who belonged to the ASP with the RA proband was excluded. †† Other diseases: Crohn's disease, ulcerative colitis, celiac disease, Addison's disease, pemphigus vulgaris, and autoimmune hepatitis. λ : familial aggregation.

Familial aggregation of RA and AI diseases. Familial aggregation of RA in trio families and in ASP families was higher at the first degree of relatedness (respectively, $\lambda = 7.4$ and $\lambda = 19.0$) than at the second (respectively, $\lambda = 4.2$ and $\lambda = 3.5$). In trio families, the familial aggregation of RA and AI diseases for the parents was stronger than for the siblings, whereas in the ASP families, the familial aggregation was stronger for the siblings, even in the absence of the affected sibling who belonged to the affected sibling-pair. In ASP families, we also observed a familial aggregation of RA and AI diseases for the RA proband's offspring (Table 4).

Bivariate and multivariate analysis. In trio families, the prevalence of AI diseases among the FDR and SDR was associated with a younger age at RA onset for the proband

(29.5 ± 8.7 yrs in the families with at least one AI disease among the relatives vs 33.6 ± 9.7 ; $p = 0.0027$). A proband less than 30 years of age at RA onset increased the risk of having at least one relative with an AI disease by 1.90 (1.07–3.39). In the second bivariate analysis performed in trio families, the prevalence of RA among the FDR was associated with a proband of male gender [6 (30%) male probands had at least one RA in their FDR vs 20 (11.5%) female probands; $p = 0.03$]. In multivariate analysis, being a male with RA increased the risk by 3.22 (1.09–9.50) to have a relative with RA.

In ASP families, no significant association was observed between probands' characteristics and AI disease prevalence. The prevalence of RA among FDR was associated, in

Table 4. Familial aggregation of RA and autoimmune (AI) diseases in first-degree relatives of trio and affected sibling-pair (ASP) families. To determine the familial aggregation (λ) of RA and AI diseases in the first-degree relatives, we used RA prevalence in the French general population of 0.0011 for men and 0.0044 for women¹⁷ and AI disease prevalence in the US Caucasian population of 0.0068 for men and 0.0255 for women¹⁸.

First-degree Relatives	Trio RA Families, n = 194				ASP RA Families, n = 174*			
	RA Prevalence, % (95% CI)	λ RA	AI Disease Prevalence, % (95% CI)	λ AI Diseases	RA Prevalence, % (95% CI)	λ RA	AI Disease Prevalence, % (95% CI)	λ AI Diseases
Mothers	8.8 (5.5–13.6)	20	17.0 (12.4–22.9)	6.6	12.1 (8.0–17.7)	27.5	14.9 (10.4–21.0)	5.8
Fathers	2.1 (0.8–5.2)	19	3.6 (1.8–7.3)	5.3	2.3 (0.9–5.8)	20.9	3.4 (1.6–7.3)	5
Sisters	2.3 (1.0–5.4)	5.2	10.8 (7.3–15.7)	4.2	11.4 (8.4–15.3)	25.9	19.7 (15.8–24.4)	7.7
Brothers	0.4 (0.1–2.5)	4.1	1.4 (0.5–3.9)	2.1	4.0 (2.3–6.9)	36.6	6.4 (4.1–9.7)	9.4
Daughters	0	0	1.7 (0.6–4.9)	0.6	2.5 (1.1–5.8)	5.7	9.7 (6.3–14.6)	3.8
Sons	0	0	1.1 (0.3–4.1)	1.6	0.5 (0.1–2.8)	4.5	2.5 (1.1–5.7)	3.7

* For all analyses, the sibling known to have RA and who belonged to the ASP with the RA proband was excluded.

ASP families, with a higher mean number of relatives (8.7 ± 2.8 when at least one FDR in the family had RA vs 7.4 ± 2.8 ; $p = 0.0058$) and a higher mean number of women in the FDR (5.5 ± 2.0 women vs 4.5 ± 1.9 ; $p = 0.0029$).

DISCUSSION

We investigated whether frequency of RA and/or other AI disorders was increased in French Caucasian RA families and evaluated their distribution.

ASP family probands were characterized by older age of RA onset, longer disease duration, and larger family size than those of trio families, but the main clinical characteristics of RA in the 2 samples were similar. The overall prevalence of AI diseases in FDR was 6.05% (4.76%–7.57%) in trio families and 10.24% [8.68%–11.97%] in ASP families, and, respectively, 2.40% (1.85%–3.06%) and 1.79% (1.41%–2.25%) in the SDR. The most frequent AI diseases were RA, thyroid AI diseases, and vitiligo in the FDR, and RA in the SDR. We observed a familial aggregation for RA and AI diseases in the FDR that was stronger for RA, particularly for the ASP family siblings. The higher estimate of occurrence of RA within the ASP families in comparison with the trio families may be largely explained by the difference in ascertainment. In trio families, a proband with RA onset before age 30 years was associated with prevalence of AI diseases in relatives, and a male gender with the prevalence of RA among FDR.

The differences in the probands' clinical characteristics can be explained by the genetic criteria of recruitment: in trio families, both parents are alive, which leads to younger proband selection. The prevalence of AI diseases in our study was particularly high in FDR but rapidly decreased to about 2% in SDR, the prevalence of autoimmunity in the general population being evaluated in the American population at 3.2%¹⁸. Indeed, we observed a strong familial aggregation for RA and AI diseases in FDR. In SDR, familial aggregation was weaker, especially in the ASP families, in whom the familial aggregation for RA was 19.0 in the FDR and 3.5 in SDR. The absence of familial aggregation for RA

in offspring in trio families can be explained by the young age of the offspring at the time of construction of the pedigrees, RA being a late-onset disorder. AI diseases are also known to increase with age, which can explain why prevalence of AI diseases in the sibship of the ASP families was higher than in the trio families, the mean age of the siblings in the ASP being about 60 years versus 45 years in the trio families.

As described in the literature, we observed familial clustering of RA, AI thyroid diseases, vitiligo, and SLE^{9–11}. Surprisingly, the prevalence of type 1 diabetes was increased only in the ASP family FDR. The RA familial aggregation in the siblings (λ s) has been reported by several authors but remains uncertain, ranging from 2 to 10²⁷. Here, we observed a λ for RA at 4.5 in trio families and 25.2 in ASP families, although the λ s in the ASP families is underestimated (the RA sibling belonging to the sib-pair was excluded from analysis). This high familial aggregation value could be explained by the low prevalence of RA in the French population (0.31%) in comparison with RA prevalence as generally cited of 0.8%–1%²⁸. The familial aggregation of RA but not of AI diseases in the SDR may be explained by a bias of AI disease underreporting, the probands being more aware of the RA symptoms than those of other AI diseases. This observation may also result from an overestimation of the AI disease prevalence in the general population, the prevalence in the population being of paramount importance for calculation of familial aggregation¹⁴. We observed an association between prevalence of RA in FDR and male gender of the proband in the trio families that was also reported in 3 American studies^{4–6}.

Among study limitations, the families studied here were recruited for a genetic study, and our results cannot be generalized to all RA seen in clinical practice. The probability of diagnosing RA or AI disease in the family of an RA patient is higher because RA patients are aware of the symptoms and are better informed. We thus added confirmation of AI disease diagnosis by a physician to minimize this bias. Conversely, we cannot exclude an underreporting bias, par-

ticularly among the SDR, as we did not specifically call relatives with a negative history to confirm absence of AI disorder. Because we considered absence of physician confirmation to indicate “not confirmed” as though the physician in charge of the patient denied the diagnosis, we may have introduced misclassification, which could represent a conservative bias. Although we collected information in 3797 relatives in trio families and 5435 relatives in ASP families, we also cannot exclude that those samples might not have been large enough to determine the percentage estimate among the less common AI disorders. Indeed, for a prevalence of a specific disease of 0.01% or less, no case is expected to be detected in a sample of 5000 persons except by chance. Finally, a bias of sibship size may be possible in the ASP families (i.e., the larger the sibship, the greater the chance of AI diseases). However, this bias was controversial in the literature^{29,30}.

Because the frequency of AI diseases among the relatives was increased, we can hypothesize that different AI phenotypes may share common susceptibility genes, which may act as risk factors for autoimmunity, as suggested by recent reports on CTLA4³¹ and PTPN22 genes³². However, while shared familial genetic factors are the most likely cause of AI disease aggregation in RA families, we must keep in mind that shared environmental factors can also explain such familial clustering.

The association of proband characteristics with AI disease prevalence among relatives would be useful for targeting families who are more at risk for AI diseases. Our results on the distribution of AI diseases in relatives should also be of great interest for genetic counselling in those RA families, but our results need to be replicated in independent studies.

The prevalence of autoimmune diseases was increased, particularly among first-degree relatives, in French RA families, and some characteristics of the RA proband seemed to be associated with the prevalence of family autoimmune diseases.

ACKNOWLEDGMENT

The authors are grateful to the patients, their families, and to the physicians who allowed us to confirm the AI disease diagnoses in relatives; and to Dr. Pierre Fritz for reviewing clinical data.

REFERENCES

- Deighton CM, Roberts DF, Walker DJ. Effect of disease severity on rheumatoid arthritis concordance in same sexed siblings. *Ann Rheum Dis* 1992;51:943-5.
- Weyand CM, Schmidt D, Wagner U, Goronzy JJ. The influence of sex on the phenotype of rheumatoid arthritis. *Arthritis Rheum* 1998;41:817-22.
- Deighton CM, Wentzel J, Cavanagh G, Roberts DF, Walker DJ. Contribution of inherited factors to rheumatoid arthritis. *Ann Rheum Dis* 1992;51:182-5.
- Lynn AH, Kwok CK, Venglish CM, Aston CE, Chakravarti A. Genetic epidemiology of rheumatoid arthritis. *Am J Hum Genet* 1995;57:150-9.
- Wolfe K, Kleinheksel SM, Khan MA. Prevalence of familial prevalence in patients with rheumatoid arthritis. *Br J Rheumatol* 1988;27 Suppl 2:150-2.
- Kwok CK, Venglish C, Lynn AH, Whitley DM, Young E, Chakravarti A. Age, sex, and the familial risk of rheumatoid arthritis. *Am J Epidemiol* 1996;144:15-24.
- Deighton CM, Walker DJ. What factors distinguish probands from multicase rheumatoid arthritis same sex sibships from sporadic disease? *J Rheumatol* 1992;19:237-41.
- Barrera P, Radstake TRDJ, Albers JMC, Van Riel PLCM, Van de Putte LBA for the European Consortium on Rheumatoid Arthritis Families (ECRAF). Familial aggregation of rheumatoid arthritis in The Netherlands: a cross-sectional hospital-based survey. *Rheumatology Oxford* 1999;38:415-22.
- Torfs CP, King MC, Huey B, Malmgren J, Grumet FC. Genetic interrelationship between insulin-dependent diabetes mellitus, the autoimmune thyroid diseases, and rheumatoid arthritis. *Am J Hum Genet* 1986;38:170-87.
- Lin JP, Cash JM, Doyle SZ, et al. Familial clustering of rheumatoid arthritis with other autoimmune diseases. *Hum Genet* 1998;103:475-82.
- Taneja V, Singh RR, Malaviya AN, Anand C, Mehra NK. Prevalence of autoimmune diseases and relationship of autoantibody expression with HLA phenotypes in multicase rheumatoid arthritis families. *Scand J Rheumatol* 1993;22:152-7.
- Broadley SA, Deans J, Sawcer SJ, Clayton D, Compston DAS. Autoimmune disease in first-degree relatives of patients with multiple sclerosis. A UK survey. *Brain* 2000;123:1102-11.
- Prahalad S, Shear ES, Thompson SD, Giannini EH, Glass DN. Increased prevalence of familial autoimmunity in simplex and multiplex families with juvenile rheumatoid arthritis. *Arthritis Rheum* 2002;46:1851-6.
- Alarcon-Segovia D, Alarcon-Riquelme ME, Cardiel MH, et al. Familial aggregation of systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune diseases in 1177 lupus patients from the GLADEL cohort. *Arthritis Rheum* 2005;52:1138-47.
- Ginn LR, Lin JP, Plotz PH, et al. Familial autoimmunity in pedigrees of idiopathic inflammatory myopathy patients suggests common genetic risk factors for many autoimmune diseases. *Arthritis Rheum* 1998;41:400-5.
- Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-24.
- Guillemin F, Saraux A, Guggenbuhl P, et al. Prevalence of rheumatoid arthritis in France — 2001. *Ann Rheum Dis* 2005;64:1427-30.
- Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin Immunol Immunopathol* 1997;84:223-43.
- Tunbridge WM, Evered DC, Hall R, et al. The spectrum of thyroid disease in a community: the Whickham survey. *Clin Endocrinol Oxford* 1977;7:481-93.
- Howitz J, Brodthagen H, Schwartz M, Thomsen K. Prevalence of vitiligo. *Arch Dermatol* 1977;113:47-52.
- Scott E. Prevalence of pernicious anemia in Great Britain. *J Coll Gen Pract* 1960;3:80-4.
- Gatling W, Budd S, Walters D, Mullee MA, Goddard JR, Hill RD. Evidence of an increasing prevalence of diagnosed diabetes mellitus in the Poole area from 1983 to 1996. *Diabet Med* 1998;15:1015-21.
- Robertson NP, Deans J, Compston DAS. Myasthenia gravis: a population based epidemiological study in Cambridgeshire, England. *J Neurol Neurosurg Psychiatry* 1998;65:492-6.
- Johnson AE, Gordon C, Palmer RG, Bacon PA. The prevalence and

- incidence of systemic lupus erythematosus in Birmingham, England. *Arthritis Rheum* 1995;38:551-8.
25. Thomas E, Hay EM, Hajeer A, Silman AJ. Sjögren's syndrome: a community-based study of prevalence and impact. *Br J Rheumatol* 1998;37:1069-76.
 26. Moreau T, Manceau E, Lucas B, Lemesle M, Urbinelli R, Giroud M. Incidence of multiple sclerosis in Dijon, France: a population-based ascertainment. *Neurol Res* 2000;22:156-9.
 27. Gregersen PK. Genetics of rheumatoid arthritis: confronting complexity. *Arthritis Research* 1999;1:37-44.
 28. Silman AJ. Rheumatoid arthritis. In: Silman AJ, Hochberg MC, editors. *Epidemiology of the rheumatic diseases*. Oxford: Oxford University Press; 1993:7-68.
 29. Ueda H, Howson JM, Esposito L, et al. Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. *Nature* 2003;423:506-11.
 30. Barrera P, Radstake TRDJ, Albers JMC, van Riel PLCM, van de Putte LBA for the European Consortium on Rheumatoid Arthritis Families (ECRAF). Familial aggregation of rheumatoid arthritis in The Netherlands: a cross-sectional hospital-based survey. *Rheumatology Oxford* 1999;38:415-22.
 31. Jawaheer D, Lum RF, Amos CI, Gregersen PK, Criswell LA. Clustering of disease features within 512 multicase rheumatoid arthritis families. *Arthritis Rheum* 2004;50:736-41.
 32. Criswell LA, Pfeiffer KA, Lum RF, et al. Analysis of families in the Multiple Autoimmune Disease Genetics Consortium (MADGC) collection: the PTPN22 620W allele associated with multiple autoimmune phenotype. *Am J Hum Genet* 2005;76:561-71.