First-degree Relatives of Patients with Rheumatoid Arthritis Exhibit High Prevalence of Joint Symptoms

Irene Smolik, David B. Robinson, Charles N. Bernstein, and Hani S. El-Gabalawy

ABSTRACT. ***Objective.*** The preclinical period of rheumatoid arthritis (RA) is characterized by the presence of autoantibodies such as anticitrullinated protein antibodies (ACPA) and rheumatoid factor (RF). Little is known about the joint symptom profile preceding onset of RA, and whether symptoms are associated with RA autoantibodies. Because first-degree relatives (FDR) of North American Native (NAN) RA probands exhibit multiple risk factors for development of future RA, we investigated the prevalence of joint symptoms in this high-risk population.

Methods. We studied 306 FDR of NAN patients with RA, 323 NAN controls (NC), and 293 white controls (WC) having no family history of autoimmune diseases. Study subjects completed a questionnaire that asked whether they had pain, swelling, or morning stiffness in their hand joints, or in other joints. Serum samples were gathered at the same time and tested for the presence of ACPA, RF, and high-sensitivity C-reactive protein levels.

Results. In all cases, FDR were significantly more likely to report experiencing joint symptoms compared to the 2 control groups. FDR also exhibited a significantly higher prevalence of RA autoantibodies than the control groups. There were modest trends for joint symptoms to associate with RA autoantibodies, and individuals who were both ACPA-positive and RF-positive had the highest prevalence of joint symptoms.

Conclusion. FDR of NAN patients with RA have a higher prevalence of joint symptoms compared to individuals with no family history of autoimmune disease. This finding is only partially explained by a high prevalence of RA autoantibodies in the FDR. (First Release March 15 2013; J Rheumatol 2013;40:818–24; doi:10.3899/jrheum.121016)

Key Indexing Terms:
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Rheumatoid arthritis (RA) is an autoimmune inflammatory disease that primarily targets synovial joints. Retrospective analysis of serum samples from cohorts of individuals who ultimately developed RA have shown RA autoantibodies such as rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA) develop months to years prior to the onset of clinically evident synovitis[1,2,3]. As a result, there has been increasing interest in identifying individuals at risk for future development of RA, with the hope of intervening to prevent the onset of disease.

Many North American Native (NAN) populations are known to have a high prevalence of RA, with a young age of onset, and frequent multicase families[4,5,6]. We have studied NAN populations in central Canada and have shown high background rates of RA-predisposing HLA-DRB1 alleles and other predisposing genetic factors, as well as a high prevalence of ACPA and RF in healthy first-degree relatives (FDR) of patients with RA[4,7,8,9]. These findings suggest that FDR of patients with RA represent a high-risk cohort for future development of RA, and that careful assessment of their clinical and biomarker profile may provide an opportunity to understand events that precede the onset of this disease.

Although the spectrum of clinical symptomatology associated with established RA is widely recognized, little is known about the symptoms that precede the onset of detectable synovitis, often referred to as "arthralgia." To understand this symptomatology, we investigated the prevalence of specific joint symptoms in unaffected FDR of NAN patients with RA and the relation, if any, to known risk factors for development of RA, particularly the presence of detectable RA autoantibodies. Our findings indicate that joint symptoms are highly prevalent in the FDR, although their association with RA serum biomarkers is inconsistent.

MATERIALS AND METHODS

Study subjects. Cree/Ojibway (NAN) patients with RA were recruited from clinic populations in a city (Winnipeg, Manitoba) and 2 rural locations (Norway House and St. Theresa Point, Manitoba). All NAN study subjects

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had at least 3 of 4 grandparents of NAN ethnic background by self-report. Details of this population have been reported[7,8,9,10,11]. Patients with RA were asked to approach their FDR regarding study participation. Individuals who were 18 years of age or older and who were willing to participate in the study were enrolled at rheumatology and community health clinics in their respective areas. No other specific selection criteria were applied, and all participants were told that the study aimed to understand the risk factors of RA development, and to detect the disease at an early stage.

NAN controls (NC) and white controls (WC) were recruited from the same geographic areas as the patients with RA and FDR by advertisements in the local media and at health fairs. Of note, 66 of the NC subjects were recruited from an adult education school. All controls were specifically questioned about autoimmune diseases and were excluded from the study if they had a personal or family history of RA, systemic lupus erythematosus, scleroderma, polymyositis, vasculitis, spondyloarthropathies, inflammatory bowel disease, diabetes mellitus type I, or thyroid disease. As with the FDR, the controls were told that the study aimed to understand the risk factors for RA, and to detect it at an early stage. Study subjects provided informed consent in their language of choice, and all aspects of the study were approved by the Research Ethics Board of the University of Manitoba, and by the Band Councils of the individual study communities.

Study protocol and procedures. All study subjects completed the same detailed questionnaire, with assistance from a translator if necessary. Information included demographic and cultural background. The questionnaire included 6 questions that probed potential musculoskeletal and connective tissue disease symptoms (Table 1), i.e., the presence of pain, swelling, and morning stiffness, in hand joints and other joints. All FDR and controls underwent a joint examination by a rheumatologist or trained study nurse to exclude the presence of synovitis or other stigmata of inflammatory arthritis. Joints examined included the distal, proximal, and metacarpophalangeal joints of the hands, wrists, elbows, shoulders, hips, knees, ankles, and metatarsophalangeal joints, although details of the number of tender joints and their location were available only for the FDR group. As suggested in a recent European League Against Rheumatism consensus regarding studies of pre-RA[12], individuals with joint effusion or swelling that did not represent bony overgrowth were excluded. Because the significance of joint tenderness as an indicator of the presence of synovitis is less clear than that of joint swelling, individuals with joint tenderness to palpation but no evidence of swelling were included in the cohort. Further, the NAN study population was relatively young, with a mean age in the mid-30s, and no attempt was made to quantify the presence of osteoarthritis findings such as bony overgrowth in the small joints of the hands. Serum samples obtained at the time of the clinical evaluation were stored at –80°C until they were tested. Thus, the study subjects were not aware of their autoantibody status at the time the questionnaire was administered, this potentially being a source of bias. Samples were all processed according to a standard operating protocol.

Testing for ACPA and RF. Serum samples from FDR and controls were tested for the presence of second-generation ACPA (CCP2) using a standard commercial kit (Inova Diagnostics), with a cutoff of ≥ 40 units/ml being defined as positive. IgM RF was tested by nephelometry at a clinical laboratory and a cutoff of ≥ 50 IU/ml was deemed positive.

High-sensitivity C-reactive protein (hsCRP) testing. Levels of hsCRP were determined in serum samples from a subset of individuals (n = 597) using a commercial ELISA (R&D Systems) according to the manufacturer's instructions. Serum samples tested for hsCRP formed part of a previous publication regarding serum cytokine levels in this population[10]. At the time of that analysis, all the available FDR samples were tested, along with a random sampling of about 50% of the available controls. For comparisons, subjects were dichotomized into those with high (> 3.0 mg/l) and low (< 3.0 mg/l) hsCRP levels.

Statistical analysis. Nonparametric tests (chi-square) were used to analyze the prevalence of joint symptoms relative to categorical variables such as sex, urban/rural location, and grouping (FDR vs NC vs WC). Association between individual joint symptoms and continuous variables such as age and hsCRP levels was tested using nonpaired T tests. In comparing differences in the prevalence of joint symptoms between FDR and NC, the findings were further confirmed by matching individuals from these 2 groups on age, sex, and locations. Logistic regression models were used to test the independence of associations between joint symptoms and age, sex, belonging to the FDR group, and being ACPA- or RF-positive. All statistical analyses were performed on SPSS 19 software.

Table 1. Specific joint symptom questions asked of the study subjects on questionnaires. Response for each question was Yes or No.

1. Do you often have pain in the joints of your hands or fingers, now or in the past?
2. Do you often have pain in other joints, now or in the past?
3. Do you often have swelling of the joints of your hands or fingers, now or in the past?
4. Do you often have swelling in any other joints, now or in the past?
5. Do your hands feel stiff in the morning?
6. Do any of your other joints feel stiff in the morning?

RESULTS

Demographic data. A total of 922 persons completed the study questionnaire, including 306 FDR, 323 NC, and 293 WC. The demographics of the study population are presented in Table 2. Overall, 64.7% of subjects were female, with no significant difference among the groups. FDR and NC were well matched in terms of age and place of residence, while the WC group was older than either of the 2 NAN groups (FDR 35.4 vs NC 33.6 vs WC 42.7 yrs; $p < 0.001$). Further, a greater proportion of the WC group was recruited from the urban setting (82.6% for WC vs 58.4% of NC and 53.3% of FDR; $p < 0.0001$). The WC group also had attained a significantly higher education level than both NAN groups, while the FDR group had attained a higher education level than the NC group (11.0 ±

Table 2. Demographic and serological characteristics of the study population.

Characteristic	First-degree Relatives, n = 306	NAN Controls, n = 323	White Controls, n = 293
Female, %	68.6	62.2	63.5
Age, yrs ± SD	35 ± 13*	33 ± 11	43 ± 13**
Urban, %	53.3	58.4	82.6**
Education level, yrs, mean ± SD	11.0 ± 2.7*	9.2 ± 2.1	13.8 ± 1.6**
Anti-CCP2-positive; ≥ 40 units, %	8.5 (22/258)*	3.6 (7/192)	0 (0/147)**
RF-positive; ≥ 50 units, %	33.3 (86/258)*	7.3 (14/192)	4.1 (6/147)**
RF- and anti-CCP2-positive, %	3.1 (8/258)	1.6 (3/192)	0 (0/147)**

* $p < 0.05$ FDR versus NAN controls; ** $p < 0.01$ white controls versus FDR and NAN controls. CCP: cyclic citrullinated peptide; RF: rheumatoid factor; FDR: first-degree relative; NAN: North American Native.

2.7 yrs vs 9.2 ± 2.1 yrs; p < 0.001). It should be pointed out that 66/323 (20%) of the NC group was recruited from an adult education institution where individuals were completing their high school education.

Prevalence of joint symptoms. Pain was the most common joint symptom, being reported by 40% of all individuals, while subjective swelling was the least common, being reported by 19% of individuals. There was, though, a high degree of correlation in the responses to the 6 joint symptom questions we asked (Pearson correlation coefficients ranging between 0.46 and 0.68), irrespective of demographic characteristics or study group. In other words, if a subject answered 1 question positively they were likely to answer several other questions positively. The highest correlation coefficient was detected between subjective swelling in the hands and swelling in other joint areas, and the lowest coefficients were detected between different types of symptoms, e.g., pain versus stiffness, swelling versus pain, etc. (data not shown). Data were available regarding the duration of morning stiffness for the FDR group only. In this group, 50% reported having morning stiffness, 94% of whom also reported other joint symptoms. The mean duration of morning stiffness was 61 ± 86 SD min.

The prevalence of all joint symptoms was significantly higher in females than males (56% vs 46%; p = 0.004 for the presence of any joint symptom). Further, individuals reporting any joint symptom were older than those reporting no joint symptoms (38.7 ± 13 vs 34.9 ± 12 yrs; p < 0.0001). When all study subjects (FDR, NC, and WC) were considered, there was no difference in the prevalence of joint symptoms between those living in urban and those in rural locations, although within the FDR group, the urban dwellers reported more joint symptoms than those living in rural locations (79% vs 60%; p < 0.001 for the presence of any joint symptom).

We detected striking differences between the 3 study groups when we compared the prevalence of various joint symptoms, and the FDR were significantly more likely to report joint symptoms than either the NC or the WC. Figure 1 shows the prevalence of subjective hand pain, swelling, stiffness, as well as all 3 symptoms, in the study groups, and Figure 2 shows these symptoms in other joint areas. Because of these striking differences, particularly between FDR and NC, we matched a subset of these 2 NAN groups for age and sex (N = 436) and then compared the prevalence of joint symptoms. As with the overall study population, this analysis demonstrated the same major finding, where FDR had a significantly higher prevalence of joint symptoms compared to NC (data not shown).

The relationship between subjective joint symptoms and the presence of joint tenderness on examination was analyzed in the FDR group (n = 289). Of these FDR, 25% (71/289) had 1 or more tender joints. The mean tender joint count was 4.0 ± 4.9 in the FDR having tender joints. The joint areas most frequently found to be tender were the hands and wrists (15%), followed by ankles and feet (9%), knees (8%), shoulders (3%), elbows (2%), and hips (1%). Not unexpectedly, there was a high degree of association between having tender joints on examination and reporting subjective joint symptoms on the questionnaire (OR 8.7, 95% CI 3.3–22.5, p < 0.0001). Moreover, FDR having joint tenderness responded positively to a greater number of joint symptom questions compared to FDR with no joint tenderness (3.8 ± 2.1 vs 2.0 ± 2.1; p < 0.0001). Using a stepwise logistic regression model that incorporated all joint

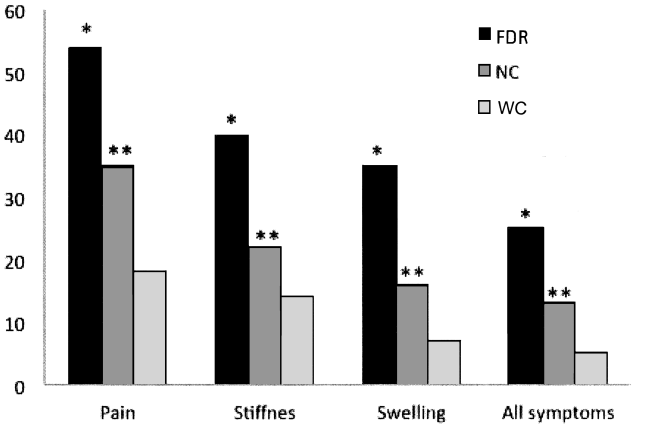

Figure 1. Prevalence of pain, swelling, stiffness, and all 3 symptoms, in the hand joints of study subjects in each group. First-degree relatives of patients with RA had significantly more symptoms than either North American native or white controls. P values are corrected by the Bonferroni method for comparing 3 groups and 4 variables. *p < 0.001 FDR versus NC versus WC. **p < 0.01 NC versus WC. FDR: first-degree relatives; NC: North American Native controls; WC: white controls.

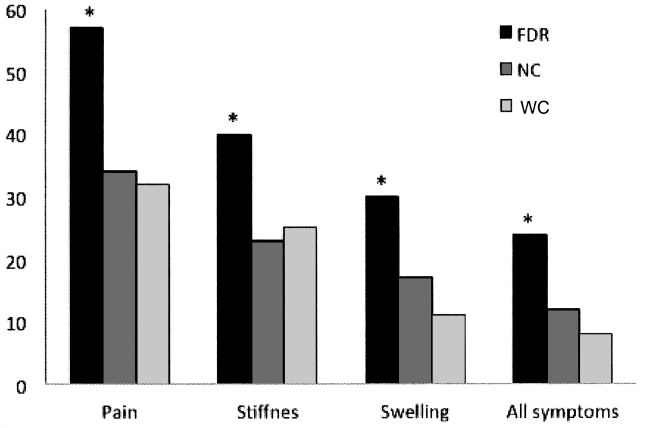

Figure 2. Prevalence of pain, swelling, stiffness, and all 3 symptoms, in joints other than the hand joints of study subjects in each group. First-degree relatives of patients with RA had significantly more symptoms than either NAN or white controls. P values are corrected by the Bonferroni method for comparing 3 groups and 4 variables. *p < 0.001 FDR versus NC or WC. FDR: first-degree relatives; NC: North American Native controls; WC: white controls.

symptom questions, we found that reports of subjective hand joint stiffness (OR 3.9, 95% CI 1.5–10, p = 0.005) and/or swelling (OR 3.0, 95% CI 1.2–7.3, p = 0.015) were the best independent predictors of having hand/wrist joint tenderness on examination. The sensitivity, specificity, positive predictive value, and negative predictive value of the hand questions for detecting objective hand/wrist tenderness were as follows: swelling (respectively, 72%, 73%, 32%, 94%), stiffness (74%, 68%, 29%, 94%), and pain (86%, 55%, 25%, 96%). Because the questions relating to other joint areas lacked sufficient specificity, we could not analyze their association with tenderness in non-hand joint areas.

Associations between joint symptoms and RA immune-inflammatory biomarkers. Because it has been shown that individuals who are seropositive for ACPA and/or RF are at increased risk for development of future RA, we investigated whether there was an association between the presence of joint symptoms and RA autoantibodies in our study populations. These data are shown in Table 3 and indicate weak, albeit consistent, trends for a higher prevalence of joint symptoms in seropositive individuals. There was no difference in the presence or duration of morning stiffness in the 32% of FDR who were either RF-positive or anti-CCP-positive, or both, and the rest of the FDR group. Of note, the small number of double-positive individuals (RF- and ACPA-positive), 8 of whom were FDR and 3 NC, demonstrated a significantly higher prevalence of joint symptoms compared to all other study subjects (91% vs 54%, respectively; p = 0.01). The double-positive group also tended to have higher prevalence of any joint symptom compared to all other FDR (91% vs 67%; p = 0.09), although only 2 of these individuals also had joint tenderness on examination. Of note, in the autoantibody-positive FDR (RF- or ACPA-positive) for whom we had complete tender joint counts available (n = 97), the negative predictive value of reporting no joint symptoms for having no joint tenderness on examination was 97%, and indeed was found to be > 85% for each of the individual questions. This indicates that a negative response to the questions used in the questionnaire was highly effective in ruling out objective joint tenderness in seropositive individuals.

Because it has been shown that the imminent onset of RA is preceded by an increase in the levels of multiple cytokines and inflammatory indicators such as CRP[13,14,15], we also sought to determine whether the presence of joint symptoms was associated with higher levels of hsCRP. Data regarding levels of hsCRP were available for 597/922 (65%) of the overall study population. This included 84% of FDR, 60% of NC, and 50% of WC. As we have previously demonstrated[10], the FDR had significantly higher hsCRP levels than both control groups (4.9 ± 4.7 mg/l vs 1.8 ± 1.8 mg/l; p < 0.0001). The analysis of hsCRP levels relative to the presence of joint symptoms demonstrated that across the entire study population, individuals with joint symptoms had significantly higher hsCRP levels than those with no joint symptoms (3.7 ± 4.0 mg/l vs 2.6 ± 3.2 mg/l; p < 0.0001). This was also the case when comparing hsCRP levels according to each individual self-reported joint symptom (data not shown).

Because the FDR group had substantially higher hsCRP levels, as well as a higher prevalence of joint symptoms and RA autoantibodies, we sought to determine whether there was an association between joint symptoms and hsCRP in this subgroup alone. These analyses demonstrated no significant differences in hsCRP levels between FDR with and those without any joint symptoms, with similar results being

Table 3. Association between joint symptoms and RA autoantibodies in the study groups. Data are percentages.

	Hand Joints			Other Joints		
	Pain	Swelling	Stiffness	Pain	Swelling	Stiffness
First-degree relatives						
RF+, n = 84	50	41	39	54	34	45
RF–, n = 171	52	30	37	56	24	34
ACPA+, n = 22	50	41	41	64	50	50
ACPA–, n = 233	52	33	39	55	25	37
Controls						
RF+, n = 20	42	21	40*	50	20	30
RF–, n = 338	27	10	16	33	15	25
ACPA+, n = 7	33	14	29	43	14	29
ACPA–, n = 329	28	11	17	34	15	25
All						
ACPA+ and RF+, n = 11	73	55*	66*	82*	64**	64
All others, n = 593	37	20	25	42	19	29

All comparisons are between autoantibody-positives (RF+, or ACPA+, or both) and all other individuals in that group. * p < 0.05, ** p < 0.01 after Bonferroni correction for 6 comparisons in each analysis (e.g., RF+ vs RF–). RA: rheumatoid arthritis; RF: rheumatoid factor; ACPA: anticitrullinated protein antibodies.

observed for each individual joint symptom (data not shown). Moreover, the hsCRP levels of FDR having a combination of RA autoantibodies (RF or ACPA) and joint symptoms (n = 66) were not significantly different from all other FDR. In the control groups, there was also no difference in the hsCRP between those with and without joint symptoms. Together, these data indicate that the association between joint symptoms and hsCRP seen in the overall study population (FDR and controls) is likely explained by the high prevalence of both these features in the FDR.

Finally, we used logistic regression models to confirm the independent effect of being an FDR on the presence of joint symptoms. For these multivariate analyses, we excluded the WC because of the substantial population differences between this group and the 2 NAN groups, particularly with respect to age and urban/rural residence. Input variables included belonging to the FDR versus the NC group, female sex, age, urban residence, hsCRP level, ACPA or RF seropositivity, and seropositivity for both ACPA and RF. Separate models were built for the presence of each joint symptom, for the presence of any joint symptom, and for the presence of hand pain, stiffness, and swelling together. We reasoned that the latter combination of hand symptoms might have the highest specificity for a preclinical RA syndrome. Table 4 shows data from 2 of these logistic models, one predicting the presence of any joint symptoms (n = 105) versus none (n = 380), and another predicting the presence of all hand symptoms (n = 75) versus all other combinations (n = 409). As shown by these models, being a FDR is an independent predictor of reporting joint symptoms, with age and urban residence also significantly increasing the odds. Female sex, seropositivity for RF or ACPA, and hsCRP levels did not contribute to these models, although being seropositive for both RA autoantibodies was associated with high OR for any joint symptom (OR 11.4, 95% CI 1.1–120, p = 0.04) and for all hand symptoms (OR 5.2, 95% CI 0.7–39, p = nonsignificant), with the wide CI due to the small number of individuals.

Table 4. Two logistic regression models for association of multiple variables with having any joint symptom and also for all hand joint symptoms. Models were tested in the NAN population only (FDR and NAN controls).

Variable	Any Joint Symptoms, n = 358/624		All Hand Symptoms, n = 115/621*	
	OR (95% CI)	p	OR (95% CI)	p
FDR	2.2 (1.4–3.6)	0.001	2.0 (1.1–3.6)	0.02
Female	0.8 (0.5–1.2)	NS	1.6 (0.9–2.8)	NS
Age	1.1 (1.0–1.1)	< 0.001	1.1 (1.0–1.1)	< 0.001
Urban	1.7 (1.1–2.6)	0.01	2.0 (1.2–3.4)	0.01
hsCRP	1.0 (0.9–1.1)	NS	1.0 (0.9–1.1)	NS
ACPA	0.5 (0.2–1.3)	NS	0.5 (0.1–2.4)	NS
RF	1.0 (0.6–1.6)	NS	1.3 (0.7–2.4)	NS
ACPA and RF	11.4 (1.1–120)	0.04	5.2 (0.7–39)	NS

* Having pain, stiffness, and swelling of hand joints. FDR: first-degree relative; NAN: North American Native; ACPA: anticitrullinated protein antibodies; RF: rheumatoid factor; hsCRP: high-sensitivity C-reactive protein; NS: nonsignificant.

DISCUSSION

We have previously reported that the Cree/Ojibway NAN population, as with several other NAN populations, has a high prevalence of RA, multicase families, and a high background frequency of predisposing HLA-DRB1 alleles[4,6,8,9,11,16]. We have also previously shown that unaffected FDR of NAN patients with RA exhibit a number of risk factors for the development of future RA including high prevalence of smoking, periodontitis, and a high prevalence of RA-associated autoantibodies[9,10,11]. Several retrospective studies of preclinical RA cohorts have demonstrated that RA-associated autoantibodies precede the onset of clinically detectable disease, and that their titers tend to rise, along with levels of multiple cytokines, prior to onset of RA[1,2,3,15,17]. Together, this suggests that the FDR of NAN patients with RA are at high risk for developing future RA, and may provide a unique opportunity to study the events that precede the onset of this disease. In the current study we demonstrate that they exhibit a high prevalence of joint symptoms along with the biological risk factors for RA development, although a direct association between the symptoms and the biomarkers was difficult to demonstrate.

In most cases of early RA, it is the presence of articular symptoms that brings individuals to the attention of healthcare providers. It is also well recognized that many of these articular symptoms, typically referred to as "arthralgia," are nonspecific, and are often not associated with detectable joint inflammation. The presence of one or more RA autoantibodies in association with arthralgia is currently regarded as the most important predictor of imminent RA, and it was shown in a Dutch study that 40% of individuals with arthralgia who were seropositive for both RF and ACPA had developed RA within a few months[18].

Currently, the ability to specifically identify preclinical RA symptoms remains challenging, and the tools available to do this are limited. In a prospective cohort of FDR of patients with RA in a large multicenter US study, where RA was specifically excluded, Kolfenbach, *et al* describe using the Connective Tissue Disease Screening Questionnaire in their study population[19]. This questionnaire was originally designed for use in epidemiologic studies to probe the presence of symptomatology related to a spectrum of rheumatic diseases[20], and has been widely used in multiple populations, but its utility in detecting preclinical RA symptomatology has not been established. Although the questionnaire used in our study has also not been validated,

the questions are typical of what clinicians might use to explore the possibility of early RA. The questionnaire had a particular focus on the joints of the hands. Nevertheless, an important limitation in these hand questions, as posed, is that they did not specifically discriminate between the groups of small joints and the wrists. It is now established that the presence of synovitis in the wrists and the metacarpophalangeal joints carries a high degree of specificity for RA[21]. A further limitation in our questionnaire is that non-hand joints were grouped together as "other joints," and we did not have the ability to discriminate specific areas outside of the hands. We acknowledge that this is a particularly significant limitation, because the metatarsophalangeal joints have been noted to be a common site of early involvement in patients with arthralgia who develop RA[22]. Having said this, it is important to note that our studies of the clinical phenotype of RA in our NAN population suggest that large-joint involvement is quite frequent, not uncommonly in the absence of small-joint involvement[6]. Future refinements in questionnaires designed to detect symptoms that are characteristic of the preclinical stages of RA will need to integrate a higher degree of specificity for joints in multiple regions, such as the metacarpophalangeal, proximal interphalangeal, and metatarsophalangeal joint areas, with validation in patients with early RA.

Notwithstanding these limitations in methodology, the major finding in our study is that FDR of NAN patients with RA report a substantially higher prevalence of joint symptoms compared to ethnically matched controls of similar age and sex, but with no family history of autoimmunity. The reasons for this are not clear, and likely represent a complex mixture of psychosocial and biological factors. We did not specifically acquire information regarding occupation. It is certainly possible that individuals performing manual labor or repetitive work may have more joint symptoms, although it is unlikely that there were major differences in this variable in comparing NAN FDR and controls. Alternatively, it could be speculated that because of more familiarity with joint symptoms in their affected relatives, FDR may be more likely to report them than controls. Currently, we have no way of detecting this type of bias, but it can potentially explain, at least in part, the major differences in the prevalence rate of joint symptoms between FDR and controls.

Not unexpectedly, we show that the FDR have a much higher prevalence of RA autoantibodies than either the NC or WC groups, and indeed one-third of the FDR were positive for either RF or ACPA or both. None of the study subjects were aware of their autoantibody status at the time of questionnaire administration. When we examined the relationship between the presence of RA autoantibodies and joint symptoms we found weak trends for association, particularly with ACPA positivity. Of note, we did find that the small number of individuals who were double-positive for both RF and ACPA (n = 11), most of whom were FDR, had a high prevalence of joint symptoms compared to all other study subjects, although only a minority had tenderness on joint examination. This is consistent with observations in a US population of FDR of patients with RA, where individuals who were positive for IgM RF had an increased prevalence of joint tenderness and higher CRP levels than FDR who were autoantibody-negative[19]. It is likely that these double-positive individuals are nearing onset of RA, and it will be of interest to follow them longitudinally for the first evidence of clinically detectable synovitis. Based on the estimates from a Dutch population, the risk of developing RA within 2 years is estimated to be as high as 40% in individuals who report having arthralgia and who are positive for both RF and ACPA[18].

In addition to the high prevalence of autoantibodies in the FDR of NAN patients with RA compared to individuals with no family history of autoimmunity, we have also recently observed a remarkable tendency toward familial clustering of the serum cytokine profile in the NAN FDR[10]. Serum levels of multiple cytokines, chemokines, and growth factors were shown to be elevated in the FDR compared to controls. This included a wide spectrum of pro- and anti-inflammatory mediators, and is reflected in the current study by the significantly higher hsCRP levels in FDR compared to controls. Although there was a positive association between hsCRP levels and joint symptoms in the overall study population of FDR and controls, this was primarily explained by the increased prevalence of high hsCRP levels and joint symptoms in the FDR group, and an analysis within the FDR population alone failed to demonstrate any association between hsCRP levels and joint symptoms. Together, these findings point to a clustering of multiple RA risk factors in FDR of NAN patients with RA, although it is difficult to show direct associations between the various factors within this high-risk population. The predictive value of subjective joint symptoms such as pain, swelling, and stiffness for the future development of RA in the context of such high biological risk awaits the results of longitudinal followup of this, and other, prospectively followed populations. Further, it will be of considerable interest to determine whether there is similar clustering of risk factors in the FDR of non-NAN patients with RA.

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