Recurrence of axial spondyloarthritis among first-degree relatives in a prospective 35-year-follow-up family study

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ABSTRACT

Objective The lifetime recurrence rate (RR) of axial spondyloarthritis (axSpA) among first-degree relatives (FDR) and the effect of proband’s gender, HLA-B27 and radiographic status is unclear. Our 35-year-follow-up family study has enabled these issues to be addressed.

Methods In 1985, 363 ankylosing spondylitis (AS) probands (members of the Swiss AS Patient Society) and 806 FDR recruited into the study, completed questionnaires regarding axSpA manifestations, underwent a physical examination and most also underwent pelvic radiography and HLA-B27 typing. At follow-up in 2018–2019, of the former participants whose current addresses could be retrieved, 162 had died and 485 (125 patients with AS plus 360 FDR) completed a postal questionnaire.

Results At follow-up, 48 of 177 HLA-B27(+) FDR had developed axSpA, an RR of 27.1% (95% CI 20.6% to 33.7%). 27/148 (18.2%) children of AS probands (modified New York (mNY) criteria) were affected versus 2/50 (4.0%) children of non-radiographic axSpA probands (p=0.0138, OR=5.36; 95% CI 1.23 to 23.40). Children of female probands were more often affected (12/22; 54.5%) than of male probands (15/78; 19.2%) (p=0.0003; OR=4.89; 95% CI 1.96 to 12.23). This increased risk applies equally to sons and daughters.

Conclusion The lifetime RR of axSpA for HLA-B27(+) FDR is substantial (27.1%), and disease severity (as defined by radiographic sacroiliitis by the mNY criteria) is an additional risk factor. Affected mothers pass on the disease significantly more often to their offspring than do affected fathers. These findings may lead to better assessment of lifetime risk for axSpA in the offspring. Moreover, investigation of this gender effect may uncover additional putative disease susceptibility factors.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Familial occurrence of axial spondyloarthritis (axSpA) is well known.
⇒ The effect of proband’s gender, HLA-B27 and axSpA radiographic status on disease recurrence among first-degree relatives (FDR) is unclear.

WHAT THIS STUDY ADDS

⇒ The lifetime recurrence rate (RR) for HLA-B27(+) FDR is substantial (27.1%).
⇒ Risk for offspring of HLA-B27(+) ankylosing spondylitis (AS) mothers is significantly higher compared with offspring of HLA-B27(+) AS fathers.
⇒ The recurrence risk of relatives of probands with AS (by modified New York criteria) is much higher than that of relatives of probands with non-radiographic axSpA.
⇒ Our findings suggest that female AS probands are genetically ‘enriched’ with disease susceptibility genes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ The substantially high lifetime RR of axSpA for FDR of AS probands necessitates greater emphasis on patient education and counselling.
⇒ There is a greater need for earlier diagnosis among FDR for better outcome due to increasing availability of more effective drugs.
⇒ It is important to further investigate this gender effect for uncovering additional putative disease susceptibility factors and for better assessment of lifetime risk for axSpA.

INTRODUCTION

Ankylosing spondylitis (AS) occurs worldwide; its prevalence in northern Europe approaches 0.5%, and 85%–95% of these patients possess HLA-B27 versus approximately 8% of the general population. Twin studies have shown concordance rates of 25%–75% in monozygotic versus 4%–15% in dizygotic twins. The reported recurrence rate (RR) for the first-degree relatives (FDR) of patients with AS has ranged between 4% and 11%.

Familial occurrence of axial spondyloarthritis (axSpA) among first-degree relatives (FDR) is unclear. Our 35-year-follow-up family study has enabled these issues to be addressed.
FDR of HLA-B27 (+) AS probands versus 1.3% for HLAGA- B27 (+) adults in the general population. Higher prevalence of disease among men than women is seen in clinical practice, and men and women may differ in the likelihood of passing on the disease to their children. The relationship of the disease RR to age of the FDR, or to the proband’s gender and disease severity is insufficiently known, and the published reports are conflicting. We address these issues in our nationwide Swiss AS family study with a 35-years follow-up.

METHODS
We assessed the RR of AS among FDR by gender of the index case (proband) considering their HLA-B27 status and the proband’s disease classification (as reflected by the presence of radiographic sacroilitis). RR implies the proportion of FDR who develop the disease (occurrence); it does not mean exacerbation after remission.

Initial phase of the study (1985–1986)
In 1985, all members of the Swiss AS Patient Society were invited to participate together with their spouses and FDR, irrespective of health status. The study was performed in centres spread all over Switzerland after ethical approval from the University Hospital of Bern and informed consents were obtained from the participants.

Altogether, 1178 persons consented to participate, completed questionnaires on disease manifestations and underwent physical examination of their axial and peripheral joints by a rheumatologist. Blood samples were drawn for HLA typing and peripheral blood nucleated cells (PBNC) were stored. Consenting non-pregnant participants aged ≥18 underwent pelvic radiography unless a recent radiograph was available. All 1081 pelvic radiographs of 360 probands and 713 FDR and 8 spouses were assessed two times, blind to participants’ clinical and HLA-B27 status, by each of four experienced readers, that is, eight (sometimes nine) blinded readings for each sacroiliac (SI) joint. This could be performed only once for 46% of the 360 radiographs of the probands and 3% of 713 radiographs of the FDR because these radiographs were only available on-site at the time of participant’s physical examination in the local hospital. Overall, 17.2% of 1081 radiographs were read once, 0.4% 2–4 times, 3.2% 5–7 times and 79.2% 8–9 times.

The sacroilitis score ranged from 0 (normal) to 4 (ankylosis) for each SI joint assessment by a reader as per the modified New York (mNY) scoring system. Scores for a single SI joint were added and divided by the number of assessments (range 1–9). Scores below bilateral grade 2.0 were considered not fulfilling the mNY criteria, as did unilateral below grade 3.0 sacroilitis. Interobserver and intraobserver reliability were assessed by evaluating a subset of 243 pelvic films. Observers read films two times in sets of 40–50 radiographs. The interval between both readings was ≥7 days.

In this paper, the term axial spondyloarthritis (axSpA) comprises the full spectrum of disease, that is, both AS by mNY and non-radiographic axSpA (nr-axSpA). In 1986, participants received their study results.

Follow-up study (2018–2019)
In January 2018, the ethics committee of the Swiss Kanton Bern approved the follow-up study (#2017–00536). The former participants were asked to complete a 157-item postal questionnaire on features of axSpA that particularly dealt with symptoms at lumbar and gluteal region, thoracic spine and anterior part of the chest. Questions also addressed symptoms suggesting episodes of acute anterior uveitis. Apart from current or past axSpA manifestations, it was questioned whether between 1986 and 2019, a diagnosis of AS or axSpA was established by a Swiss rheumatologist and, if so, whether diagnostic imaging has been performed. The most decisive step to perform the follow-up study was to find out whether the former participants were still alive and, if so, to trace their current postal addresses. Starting in April 2018, up to five mailings to many Swiss city or village administrations were sent to obtain information dealing with current address of the former study participants and any deaths (including year of death).

In the spring of 2019, altogether 791 letters providing detailed information about the follow-up study were sent to updated, supposedly correct, addresses. Participants who provided written informed consent were mailed the questionnaire, and a reminder was sent to those who did not return the questionnaire. The data from all 485 questionnaires (of consenting participants) that had been returned by December 2019 were coded and anonymously stored in an Excel database for further analysis.

Ascertainment of diagnosis
The diagnosis AS in the initial study (1985–1986) is based on both the clinical findings and the evaluation of the—blindly read—pelvic radiograph described above. Probands and FDR were considered to have AS if they met the mNY criteria. Those with a clinical diagnosis of axSpA but not meeting the mNY criteria were deemed to have nr-axSpA. For the follow-up (2018–2019) study, we labelled all new patients found during the follow-up study as having axSpA (they have either radiographic axSpA (AS) or nr-axSpA) because recent SI joint images of all those reportedly diagnosed to have AS by their rheumatologists were not available for us to review.

Polygenic risk score
From the PBNC samples, stored since 1985, PRS were calculated for 124 male and 24 female AS (mNY) probands. Genotyping was performed using the Illumina Core-Exome single-nucleotide polymorphism (SNP) microarray, as previously reported. Briefly, the PRS is a numeric summary score that reflects an individual’s
estimated genetic predisposition for a given trait and can be used as a predictor or diagnostic biomarker for the disease of interest (here axSpA).

**Statistical analysis**
Counts were compared by \( \chi^2 \) testing, and the results are expressed as p values. ORs were calculated together with 95% CI.

**RESULTS**

**Initial phase of the study (1985–1986)**
Altogether 1178 persons (630 men (53.5%) and 548 women (46.5%) participated in the family study: 363 AS

| Table 1 | Demographic data of probands with AS, their relatives and spouses by HLA-B27 status and presence of sacroiliitis by the modified New York criteria |
|---------|-------------------------------------------------------------------------------------------------------------------------------------|
|         | Number (%) | Men (%) | Women (%) | Mean age 1985 (SD) |
| All participants | 1178 | 630 (53.5) | 548 (46.5) | 32.5 (10.3) |
| All AS probands | 363* | 249 (68.6) | 114 (31.4) | 44.0 (11.1) |
| HLA-B27 positive AS probands | 308/358 (86.0) | 219 (71.1) | 89 (28.9) | 44.0 (11.1) |
| Sacroiliitis present | 247/305 (81.0) | 185 (74.9) | 62 (25.1) | 44.6 (11.6) |
| Sacroiliitis absent | 58/305 (19.0) | 32 (55.2) | 26 (44.8) | 41.7 (8.5) |
| Pelvic X-ray not available | 3/308 (1.0) | 2 (66.7) | 1 (33.3) | 40.3 |
| HLA-B27 negative AS probands | 50/358(14.0) | 26 (52.0) | 24 (48.0) | 46.1 (11.5) |
| Sacroiliitis present | 22/50 (44.0) | 16 (72.7) | 6 (27.3) | 46.9 (10.1) |
| Sacroiliitis absent | 28/50 (56.0) | 10 (35.7) | 18 (64.3) | 45.6 (12.7) |
| All relatives | 806 | 380 (47.1) | 426 (52.9) | 27.1 (8.0) |
| Relatives of HLA-B27 positive probands | 672† | 311 (46.3) | 361 (53.7) | 26.9 (8.2) |
| HLA-B27 positive relatives | 360/668 (53.9) | 159 (44.2) | 201 (55.8) | 26.6 (8.1) |
| Sacroiliitis present | 14/308 (4.5) | 7 (50.0) | 7 (50.0) | 33.5 (8.1) |
| Sacroiliitis absent | 294/308 (95.5) | 128 (43.5) | 166 (56.5) | 28.4 (7.4) |
| No pelvic X-ray (age <18 year or pregnant) | 52/360 (14.4) | 24 (46.2) | 28 (53.8) | 14.7 (3.3) |
| HLA-B27 negative relatives | 308/668 (46.1) | 149 (48.4) | 159 (51.6) | 27.1 (8.4) |
| Sacroiliitis present | 0/278 (0) | | | |
| Sacroiliitis absent | 278/278 (100) | 133 (47.8) | 145 (52.2) | 28.3 (8.1) |
| No pelvic X-ray (age <18 year or pregnant) | 30/308 (9.7) | 16 (53.3) | 14 (46.7) | 16.0 (4.4) |
| Relatives of HLA-B27 negative probands | 94‡ | 53 (56.4) | 41 (43.6) | 26.1 (6.6) |
| HLA-B27 positive relatives | 3/92 (3.3) | 2 (66.7) | 1 (33.3) | 22.0 |
| Sacroiliitis absent | 2/2 (100) | 1 (50.0) | 1 (50.0) | 26.5 |
| No pelvic X-ray (age <18 year) | 1/3 (33.3) | 1 (100) | 0 (0) | 13.0 |
| HLA-B27 negative relatives | 89/92 (96.7) | 49 (55.1) | 40 (45.9) | 26.4 (6.5) |
| Sacroiliitis absent | 85/83 (100) | 45 (54.2) | 38 (45.8) | 27.4 (6.0) |
| No pelvic X-ray (age <18 year) | 6/89 (6.7) | 4 (66.7) | 2 (33.3) | 12.7 (1.0) |
| Relatives of probands HLA-B27 unknown | 40§ | 16 (40.0) | 24 (60.0) | 33.5 (5.2) |
| HLA-B27 positive relatives | 15/39 (38.5) | 8 (53.3) | 7 (46.7) | 34.7 (5.0) |
| Sacroiliitis absent | 14/14 (100) | 8 (57.1) | 6 (42.9) | 34.9 (5.2) |
| No pelvic X-ray (pregnant) | 1/15 (6.7) | 0 | 1 (100) | 32.0 |
| HLA-B27 negative relatives | 24/39 (61.5) | 8 (33.3) | 16 (66.7) | 32.5 (5.3) |
| Sacroiliitis absent | 22/22 (100) | 8 (36.4) | 14 (63.6) | 32.6 (5.4) |
| No pelvic X-ray (pregnant) | 2/2 (100) | 0 | 2 (100) | 31.5 |
| Spouses | 9¶ | 1 (11.1) | 8 (88.9) | 47.7 (4.7) |
| HLA-B27 negative spouses | 9/19 (100) | 1 (11.1) | 8 (88.9) | 47.7 (4.7) |
| Sacroiliitis absent | 8/8 (100) | 1 (12.5) | 7 (87.5) | 48.4 (4.6) |

Total number of pelvic radiographs 1081 (probands 360; relatives 713, spouses 8).

*HLA-B27 status unknown for five probands, including one without sacroiliitis by New York criteria.
†HLA-B27 status of four relatives unknown (no sacroiliitis: three; pelvic radiograph not available: one).
‡HLA-B27 status of two relatives unknown (both did not show sacroiliitis).
§HLA-B27 status of one relative unknown (no sacroiliitis).
¶No pelvic radiograph available for one spouse.
AS, ankylosing spondylitis.
probands, 806 FDR and 9 spouses. Table 1 and online supplemental flowcharts 1 and 2 provide their demographic data, together with radiographic results and HLA-B27 status. Considering reading of the pelvic radiographs, the interobserver and intraobserver reliability coefficients were 0.865 and 0.903, respectively.

Among the 1136 participants who could be tissue typed, 671 (59.1%) were HLA-B27(+), and among the 358 probands who could be tissue typed, 308 (86.0%) were HLA-B27(+). The mNY criteria for AS were fulfilled almost two times as often (81%) by HLA-B27(+) versus HLA-B27(−) probands (44%), indicating that at the latter group had significantly more often nr-axSpA (p=0.00001) (table 1 and online supplemental flowchart 1).

Among FDR sacroiliitis by mNY criteria was only seen in HLA-B27(+) relatives of HLA-B27(+) probands because 14/308 (4.5%) HLA-B27(+) relatives had AS, versus none of the 278 HLA-B27(−) relatives (p=0.00032) and none of the 85 relatives of HLA-B27(−) probands (p=0.0453) (table 1, online supplemental flowchart 2).

Follow-up study (2018–2019)
The Swiss village administrations reported that among the 1178 participants of the 1985–1986 baseline study, 162 had already died (123 probands and 39 FDR), 531 former participants could not be traced or declined participation (online supplemental table 1). The remaining 485 persons (125 probands and 360 FDR) agreed to participate in the follow-up study and completed the postal questionnaire (table 2, online supplemental flowchart 3). The response rate on the invitation letter was 61.3% (485/791). Of the 1178 participants of the 1985 baseline study, 485 (41.6%) took also part in the 2018–2019 follow-up study, whereas ≥162 (13.8%) had already died.

Recurrence rate
AxSpA was present in 45 FDR; (42 of them HLA-B27(+): 17/67 (25.4%) men and 25/95 (26.3%) women); 38 of them did not have sacroilitis in 1985 (or they did not undergo pelvic radiography because they then were ≤18 years or pregnant). The remaining seven were already diagnosed in 1985 as having AS (mNY). In contrast, axSpA occurred in only 3/184 (1.6%) HLA-B27(−) FDR (table 2, online supplemental flowchart 3).

Table 3 shows the lifetime RR (with 95%CI) for the HLA-B27(+) FDR to develop axSpA. This risk increased from 4.5% in 1985 (mean age 26.64 years) to 24.6% 35 years later in 2019 (when their mean age was 60.39 years). The lifetime RR estimate for HLA-B27(+) FDR increases to 27.1% (95% CI 20.5% to 33.6%) (table 3) by including all patients with AS who, apart from the proband, had already been diagnosed to have AS at study entry in 1985.

Considering children, 27/148 (18.2%) children of AS (mNY+) probands were affected versus 2/50 (4.0%) children of nr-axSpA probands (p=0.0138, OR=5.36; 95% CI 1.23 to 23.40).

Effect of gender
For siblings of probands, the likelihood of having the disease is not influenced by gender of the family proband because 12/90 (13.3%) siblings of male probands versus 8/46 (17.4%) siblings of female probands were affected (p=NS).

However, the risk of developing axSpA among the offspring of HLA-B27(+) AS (by mNY criteria) parents is gender dependent because women probands are more likely to have at least one child also affected with axSpA than their male counterparts (p=0.02, OR=3.15; 95% CI 1.13 to 8.85) (table 4 and figure 1). Children of these women probands are significantly more often affected with axSpA than children of comparable fathers (p=0.0003 OR=4.89; 95% CI 1.96 to 12.23) (table 5). This gender effect (mothers transfer a higher risk to their offspring than fathers) applies equally to both sons and daughters of HLA-B27(+) AS (mNY+) parents (table 6). In contrast, this risk for HLA-B27(−) FDR is very low because only 3/184 (1.6%) HLA-B27(−) FDR acquired axSpA among all HLA-B27(−) FDR (of both HLA-B27(+) and HLA-B27(−) AS probands). The first of these three cases is that of a women and the HLA status of the proband is unknown because he never participated in the study. The second case is the son of an HLA-B27(−) male proband; at baseline the father (and the son) had no sacroilitis, and there is no family history of psoriasis and inflammatory bowel disease. The third case, most interestingly, is that of an HLA-B27(−) male proband; at baseline the father (and the son) had no sacroilitis, and there is no family history of psoriasis and inflammatory bowel disease. The third case, most interestingly, is that of an HLA-B27(−) male proband; at baseline the father (and the son) had no sacroilitis, and there is no family history of psoriasis and inflammatory bowel disease.

Effect of disease severity
The parent’s gender-specific risk for their offspring to get axSpA is most evident if the HLA-B27(+) AS proband meets the mNY criteria for the disease (table 6 and figure 1). Therefore, the parent’s as disease severity (considering the presence of radiographic evidence of sacroilitis to be an indicator of disease severity) enhances the risk associated with the inheritance of HLA-B27.

Gender and genetic risk score
To explore whether the observed higher parent-to-child disease recurrence for female than for male AS (mNY+) patients might be explained genetically, we compared mean PRS of 42 female HLA-B27(+) AS patients (0.418) with the mean value (0.376) of 124 male counterparts. The difference is not statistically significant.

DISCUSSION
This Swiss AS family study spanning 35 years provides four important findings.

First, HLA-B27(+) AS probands were significantly more likely to have radiographic axSpA (ie, AS) than HLA-B27(−) probands. The mean ages of both groups are comparable (table 1). In our previous study, there were no differences in age at onset, functional class, degree of deformity, pain, severity of X-ray changes or frequency of peripheral joint involvement between 63 HLA-B27(+) and 15
HLA-B27(−) AS patients, although subsequent studies have shown that HLA-B27(−) patients have later age of symptom onset and diagnosis. Therefore, taking the structural changes due to radiographic sacroiliitis as a measure of disease severity, one may extrapolate that on average HLA-B27(+) axSpA patients have more damage than HLA-B27(−) patients in the context of familial occurrence of the disease. Consistent with this, a recent study reports that HLA-B27(+) FDR contrary to HLA-B27(−) FDR having early signs or symptoms progress to clinical disease. However, once patients develop radiographic AS, the extent of spinal damage has been shown not to be influenced by HLA-B27 status.

Second, the lifetime RR of axSpA for HLA-B27+ FDR was 4.5% in 1985 (mean age of FDR 26.64 years), and it increased to 27.1% 35 years later in 2019 (mean age 60.39 years). This figure applies for the full spectrum of axSpA (95% CI 20.5% to 33.6%) when we included all patients, apart from the proband, who had already been diagnosed to have AS by the time they entered the study.

### Table 2
Demographic data of probands and relatives participating in the Swiss AS follow-up family study by HLA-B27 status and presence of sacroiliitis by the modified New York criteria at baseline (1985)

|                          | Number (%) | Males (%) | Females (%) | Mean age 2019 (SD) |
|--------------------------|------------|-----------|-------------|--------------------|
| All participants         | 485        | 238 (49.1)| 247 (50.9)  | 64.6 (9.7)         |
| All AS probands          | 125†       | 78* (62.4)| 47† (37.6)  | 72.8 (7.3)         |
| - HLA-B27 positive AS probands | 110/123 (89.4)| 73 (66.4) | 37 (33.6)  | 72.5 (7.2)         |
| Sacroiliitis present (1985) | 79/110 (71.8)| 54 (68.4) | 25 (31.6)  |                |
| Sacroiliitis absent      | 31/110 (28.2)| 19 (61.3) | 12 (38.7)  |                |
| - HLA-B27 negative AS probands | 13/123 (10.6)| 4 (30.8)  | 9 (69.2)   | 75.5 (8.7)        |
| Sacroiliitis present (1985) | 3/13 (23.1)| 2 (66.7)  | 1 (33.3)   |                |
| Sacroiliitis absent (1985) | 10/13 (76.9)| 2 (20.0)  | 8 (80.0)   |                |
| All relatives            | 360        | 160 (44.4)| 200 (55.6)  | 61.7 (8.8)        |
| All relatives with axial SpA | 45/360 (12.5)| 18 (40.0) | 27 (60.0)  | 58.0 (8.0)        |
| HLA-B27 positive relatives | 42/45 (93.3)| 17 (40.5) | 25 (59.5)  | 57.7 (8.2)        |
| Sacroiliitis present (1985) | 7/42 (16.7)| 3 (42.9)  | 4 (57.1)   |                |
| Sacroiliitis absent (1985) | 27/42 (66.7)| 11 (40.7)| 16 (59.3)  |                |
| No pelvic X-ray available (1985) | 8/42 (19.0)| 3 (37.5)  | 5 (62.5)   |                |
| HLA-B27 negative relatives | 3/45 (6.7)| 1 (33.3)  | 2 (66.7)   | 62.0 (5.3)        |
| Sacroiliitis absent (1985) | 3/45 (100) | 1 (100)   | 2 (100)    |                |
| All healthy relatives    | 315‡       | 142 (45.1)| 173 (54.9)  | 62.2 (8.8)        |
| - Healthy relatives of HLA-B27+ AS probands | 262 | 118 (45.0) | 144 (55.0) | 62.1 (9.2)       |
| HLA-B27 positive relatives | 120/260 (46.2)| 50§ (41.7)| 70¶ (58.3) | 61.3 (8.9)       |
| HLA-B27 negative relatives | 140/260 (53.8)| 66** (47.1) | 74†† (52.9) | 62.9 (9.3)       |
| HLA-B27 unknown relatives | 2/262 (0.8)| 2‡‡ (100) | 0 (0)      | 55.5 (14.9)      |
| - Healthy relatives of HLA-B27- AS probands | 29 | 16 (55.2) | 13 (44.8)  | 60.8 (6.7)        |
| HLA-B27 positive relatives | 0/29 (0)  |           |            |                   |
| HLA-B27 negative relatives | 29/29 (100)| 16 (55.2) | 13 (44.8)  | 60.76 (6.7)       |
| - Healthy relatives of HLA-B27? AS probands | 24 | 8 (33.3)  | 16 (66.7)  | 65.3 (6.0)        |
| HLA-B27 positive relatives | 9/24 (37.5)| 4 (44.4)  | 5 (55.6)   | 68.1 (5.7)        |
| HLA-B27 negative relatives | 15/24 (62.5)| 4 (26.7)  | 11§§ (73.3)| 63.7 (5.4)        |

*Unknown HLA-B27 status of one male proband with sacroilitis.
†Unknown HLA-B27 status of one female proband with sacroilitis.
‡HLA-B27 status of 2 AS probands unknown (1 relative HLA-B27(−); 1 relative HLA-B27(+)).
§No pelvic radiograph available for five men.
¶No pelvic radiograph available for four women.
§§No pelvic radiograph available for two women.
AS, ankylosing spondylitis.
in 1985 (table 3). This 27.1% RR of the disease can be regarded to be complete (lifetime) because it is extremely uncommon to have onset of AS after age 45. This RR estimate compares well with our smaller cross-sectional Dutch family study comprising 61 HLA-B27(+) and 40 HLA-B27(−) FDR of 20 HLA-B27(+) AS probands,8 in which study 5 of 24 (21%) HLA-B27(+) FDR aged 45 years or older had AS (by mNY criteria).

Third, the likelihood for brothers and sisters of HLA-B27(+) AS probands, 8 in 24 (21%) HLA-B27(+) FDR aged 45 years or older had AS (by mNY criteria). Please, note that risk estimates shown in table 6 apply to all children of these parents and increase about twofold for the HLA-B27(+) children. It would, therefore, be about as high as 80% for HLA-B27(+) children of female AS parents and about 25% for HLA-B27(+) children of male AS parents. Since in clinical practice, AS occurs more often in men, the genetic threshold for women to develop AS might be higher (they seem to be genetically ‘enriched’ with disease susceptibility genes) and that higher genetic load increases the recurrence of disease among both their sons and daughters. This is consistent with genetic models of polygenic diseases, where it is hypothesised that risk of the disease follows a normal distribution in the population, with those carrying more than a threshold of genetic risk ultimately developing the disease26 (further discussed below).

Finally, we observed that the RR of FDR of probands with AS is much higher than those with nr-axSpA (table 6). This is consistent with studies assessing the utility of PRS in AS compared with nr-axSpA, where the ability of the PRS to discriminate between clinically unaffected chronic back pain patients and AS patients was much higher than with nr-axSpA patients, consistent with nr-axSpA being less heritable and therefore less familial.27 Indeed, the RR of axSpA in children of HLA-B27(+) nr-axSpA

### Table 3

| Study | Total number of HLA-B27(+) FDR (mean age ±SD) | Risk for all FDR to have AS (mNY+) at baseline or axSpA at follow-up (95% CI) (males+females) | Risk for all male FDR to have AS (mNY+) at baseline or axSpA at follow-up (95% CI) (males) | Risk for all female FDR to have AS (mNY+) at baseline or axSpA at follow-up (95% CI) (females) |
|-------|-----------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Baseline (1985) - Multicase families excluded | 308 (27.1±8.4) | 14/308 (4.5%) (2.2 to 6.9%) | 7/135 (5.2%) (1.5 to 8.9%) | 7/173 (4.0%) (1.1 to 6.9%) |
| Baseline (1985) - Multicase families included | 318 (27.6±8.3) | 24/318 (7.5%) (4.6 to 10.4%) | 11/139 (7.9%) (3.4 to 12.4%) | 13/179 (7.3%) (3.5 to 11.1%) |
| Follow-up 35 years later - Multicase families excluded | 171 (61.8±8.6) | 42/171 (24.6%) (18.1 to 31.0%) | 17/71 (23.9%)* (14.0 to 33.8%) | 25/100 (25.0%)* (16.5 to 33.5%) |
| Follow-up 35 years later - Multicase families included | 177 (62.1±8.5) | 48/177 (27.1%) (20.6 to 33.7%) | 19/73 (26.0%)† (15.9 to 36.1%) | 29/104 (27.9%)† (19.3 to 36.5%) |

*p = 0.87.
†p = 0.78 (no significant gender-specific difference in occurrence of axSpA among HLA-B27(+) FDR).

| Table 4 | Mothers with HLA-B27 positive AS are more likely than HLA-B27 positive fathers with AS to get at least one child with axSpA* |
|---------|-------------------------------------------------------------------------------------------------|
| Number of parents with Child with axSpA | Number of parents with no children with axSpA | Total |
| Fathers | 14 (17.9%) (95% CI: 9.4% to 26.4%) | 64 (82.1%) (95% CI: 73.6 to 90.6) | 78 (100%) |
| Mothers | 9 (40.9%) (95% CI: 19.1% to 62.6%) | 13 (59.1%) (95% CI: 38.5 to 79.6) | 22 (100%) |
| Total | 23 | 77 | 100 |
| p = 0.02 |

AS meeting the modified New York criteria.
*OR mothers/fathers 3.16 (95% CI 1.13 to 8.85)
AS, ankylosing spondylitis; axSpA, axial spondyloarthritis.
findings. This resulted in high specificity as none of the HLA-B27(−) FDR was found to have (false-positive) sacroiliitis. But in the follow-up study, the diagnosis, established by Swiss rheumatologists, was reported by the FDR. It was not possible to obtain recent radiographs or MRI of the SI joints of the ‘new’ cases, except for two of them. However, by using their responses to the questionnaire, 38/42 (90.5%) HLA-B27(+) FDR with axSpA met the ASAS classification criteria for axSpA, that is, they had either AS or nr-axSpA.30 31

The probands in our study were members of a patient society. They and their FDR volunteered to participate in the family study. A possible weakness of this kind of investigations is the potential of volunteer (selection) bias. People who have developed a certain disease might be more likely to participate in a study on their disease. FDR who had developed axSpA after the baseline study might be more inclined to participate in the follow-up study, leading to inflation of the true incidence of disease. On the other hand, studies based on registries—such as the one discussed later—are not liable to volunteer bias, but suffer from other sources of confounding factors, such as miscategorization and incomplete registration. These biases may arise, for example, when cases in a primary care setting are not referred to hospital or if there is a nationwide shortage of rheumatologists.

Our reported RR is unlikely to be a biased overestimation of the true risk. A bias would lead to a higher ratio of HLA-B27(+) FDR at the follow-up study when compared with the baseline study. The HLA-B27 status of the FDR was not known at the start of the study in 1985. However, the ratio between HLA-B27(+) FDR and HLA-B27(−) FDR of HLA-B27(+) AS probands has not changed; it was 1.17 in 1985 and 1.16 at follow-up (tables 1 and 2).

We report that HLA-B27(+) AS mothers with AS are more likely to have axSpA than children of HLA-B27 positive fathers with AS.

Proportion of axSpA among HLA-B27 positive parents

Table 5 Children of HLA-B27 positive mothers with AS are more likely to have axSpA than children of HLA-B27 positive fathers with AS.

|                | Children with axSpA number (%) | Healthy children number (%) | Total |
|----------------|-------------------------------|-----------------------------|-------|
| AS fathers (n=78) | 15 (12.6%) (95% CI: 6.6% to 18.6%) | 104 (87.4%) | 119 (100%) |
| AS mothers (n=22) | 12 (41.4%) (95% CI: 22.7% to 60.1%) | 17 (58.6%) | 29 (100%) |
| Total            | 27                            | 121                         | 148   |

p=0.00032

AS by modified New York criteria.
OR 4.89 with 95% CI 1.96 to 12.23.
Mean number of children for fathers: 119/78=1.53.
Mean number of children for mothers: 29/22=1.32.
Mean number of axSpA children.
For mothers: 15/78=0.19 (95% CI 0.10–0.27).
Mean number of axSpA children.
For fathers: 12/22=0.55 (95% CI 0.33 to 0.77).
AS, ankylosing spondylitis; axSpA, axial spondyloarthritis.

Our reported RR is unlikely to be a biased overestimation of the true risk. A bias would lead to a higher ratio of HLA-B27(+) FDR at the follow-up study when compared with the baseline study. The HLA-B27 status of the FDR was not known at the start of the study in 1985. However, the ratio between HLA-B27(+) FDR and HLA-B27(−) FDR of HLA-B27(+) AS probands has not changed; it was 1.17 in 1985 and 1.16 at follow-up (tables 1 and 2).

We report that HLA-B27(+) AS mothers (mNY+) are ~3 times more likely to pass on the disease to sons and
Table 6  Probands New York radiographic and HLA-B27 status and proband’s gender strongly affect likelihood of axSpA among offspring

| AxSpA among offspring | Father | Mother | P value |
|-----------------------|--------|--------|---------|
| All probands          | 16/144 (11.1%) | 13/61 (21.3%)* | 2.17 (0.71 to 4.84) | 0.056 |
| HLA-B27(+) probands   | 15/132 (11.4%) | 13/42 (31.0%) | 3.50 (1.50 to 8.15) | 0.0026 |
| HLA-B27(−) probands   | 1/12 (8.3%) | 0/12 (0%) | – | 0.31 |
| New York(+) AS probands | 15/119 (12.6%) | 12/29 (41.4%) | 4.89 (1.96 to 12.23) | 0.00032 |
| New York(−) nr-axSpA probands | 1/25 (4%) | 1/25 (4%) | – | – |
| New York(+) and HLA-B27(+) AS probands | 15/119 (12.6%) | 12/29 (41.4%) | 4.89 (1.96 to 12.23) | 0.00032 |
| New York(−) and HLA-B27(−) AS probands | – | – | – | – |
| New York(−) and HLA-B27(+) nr-axSpA probands | 0/13 (0%) | 1/13 (7.7%) | – | 0.31 |
| New York(−) and HLA-B27(−) nr-axSpA probands | 1/12 (8.3%) | 0/12 (0%) | – | 0.31 |

Table 7  Recurrence rate of axSpA among siblings and children in three studies

| Relatives of male probands | First-degree relatives | # AxSpA/total Swiss study | # AxSpA/total Swedish study | # AxSpA/total UK study |
|---------------------------|------------------------|--------------------------|---------------------------|----------------------|
| Sibs                      | 12/90 (13.3%)          | 447/12576 (3.6%)         | 243/3177 (7.7%)           | 5                    |
| Children                  | 15/119 (12.6%)         | 294/15293 (1.9%)         | 48/772 (6.2%)             | 3                    |
| Sons                      | 5/53 (9.4%)            | 194/7817 (2.5%)          | 35/396 (8.8%)             | 6                    |
| Daughters                 | 10/66 (15.2%)          | 100/7476 (1.3%)          | 13/376 (3.5%)             | 8                    |

| Relatives of female probands | # AxSpA/total Swiss study | # AxSpA/total Swedish study | # AxSpA/total UK study |
|------------------------------|---------------------------|---------------------------|----------------------|
| Sibs                         | 8/46 (17.4%)              | 236/6576 (3.6%)           | 142/1286 (11.0%)      | 5                    |
| Children                     | 12/29 (41.4%)             | 204/8547 (2.4%)           | 40/375 (10.7%)        | 3                    |
| Sons                         | 4/11 (36.4%)              | 104/4358 (2.4%)           | 23/185 (12.4%)        | 8                    |
| Daughters                    | 8/18 (44.4%)              | 100/4189 (2.4%)           | 17/190 (8.9%)         | 8                    |
| Criteria for probands       |                           |                           |                       |                      |
| HLA-B27 status of probands  |                           |                           |                       |                      |
| Age of children              |                           |                           |                       |                      |
| New York 100% HLA-B27 +100% HLA-B27 unknown all >45 years | New York estimated >50% HLA-B27 unknown non-specified | New York 100% HLA-B27 estimated 92% all >30 years |

The Swiss and UK studies comprise probands of AS patient societies, whereas the Swedish study is based on national registers.  
*OR: Ratio of odds of children with axSpA from mother with AS and odds of children with axSpA from father with AS.  
1p=0.00032; 2p=0.0162; 3p=0.00791; 4p=0.00000; 5p=0.00026; 6p=0.00197; 7p=0.00003.  
8p=0.0193; 9p=0.00726.  
AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; nr-axSpA, non-radiographic axial spondyloarthritis.

daughters than HLA-B27(+) fathers, suggesting a higher genetic load among females AS probands (table 7). Our results are supported by a British family study of 4400 AS patients seen at an AS hospital and/or members of the British national patient society (National Ankylosing Spondylitis Society) and a Swedish nationwide registry-based family study. All show that risk for children to develop axSpA is greatest if the parent is woman. Furthermore, the British and Swedish studies also show that significantly more sons than daughters of AS fathers...
develop the disease. In Sweden, mothers as compared with fathers had more frequently an affected daughter.\textsuperscript{18}

The British study also assessed the effect of disease onset below age 21 in female probands on their offspring; 5/16 (38\%) children developed axSpA, in contrast to 3/39 (8\%) children of fathers.\textsuperscript{17} These findings are in line with our results (41.4\% for children of mothers vs 12.6\% children of fathers). They also reported a higher rate of affected sibs if the proband is women; numbers in our study might have been too small to show such an effect.

The prevalence of AS among the FDR in the Swedish study ranged between 2.1\% and 3.6\%, contrasting with a 4\%–11\% prevalence observed in European countries,\textsuperscript{14} and it was 0.07\%–0.19\% among Swedish controls (comparing well with the 0.1\%–0.4\% figure from the literature).\textsuperscript{1,8}

The disease RR for the offspring of HLA-B27(+) mNY +AS mothers is higher compared with male probands, but PRS of the female probands while 11\% higher than the PRS of male probands is not statistically significantly increased. What about a possible explicatory role of the X-chromosome and (by definition maternal) mitochondrial DNA? Since in clinical practice, AS occurs more often in men, the genetic threshold for women to develop AS might be higher (they seem to be genetically ‘enriched’ with disease susceptibility genes), and that higher genetic load increases the RR among both their sons and daughters. This is consistent with genetic models of polygenic diseases, where it is hypothesised that risk of the disease follows a normal distribution in the population, with those carrying more than a threshold of genetic risk ultimately developing the disease.\textsuperscript{26} At this point, the actual genes involved in the difference in genetic risk between genders are not clear, as we have discussed elsewhere.\textsuperscript{32}

Differences in recurrence of disease in offspring patients in highly heritable conditions like AS could potentially occur where there are significant X-chromosomal or mitochondrial encoded susceptibility variants involved. The PRS employed here only uses autosomal SNPs and does not include X-chromosome markers. Substantial X-chromosome involvement would lead to female children of male AS patients being more likely to develop AS; evidence to date suggests that the converse is true.\textsuperscript{17} Linkage studies have excluded major genetic effects on the X-chromosome in AS,\textsuperscript{33} association studies of the X-chromosome are in progress. Mitochondrial genetic diseases are transmitted from affected mothers rather than affected fathers, consistent with our observation of increased risk in offspring of affected mothers. However, the gender ratio of affected children in offspring of mothers with mitochondrial diseases is typically equal, which is not consistent with the known gender bias in AS. Therefore, neither X-chromosome nor mitochondrial genetic variation are likely to be the dominant explanatory factor of the gender bias in AS in the general population along with the difference in RR of offspring of affected parents, whereas differences in the required genetic threshold to develop the disease can explain both these features of AS. Currently, one can only speculate about possible drivers of gender-related different thresholds, for example, epigenetic, hormonal or other environmental factors. Further studies comparing genetic associations in male and female AS patients will be required to investigate whether the threshold model is correct.

Finally, a family study with follow-up 35 years later is challenging. Some lessons learnt are provided in online supplemental table 2.

In summary, the lifetime RR of axSpA for HLA-B27(+) FDR is substantial: 27.1\% (95\% CI 20.6\% to 33.7\%). HLA-B27(+) female AS probands are significantly more likely to pass on the disease to sons and daughters than the HLA-B27(+) male AS probands. The risk increases twofold if the child inherits the HLA-B27 allele from the affected parent. Genetic susceptibility threshold for women to develop radiographic axSpA seems higher than for men, and it enables women to transmit the disease susceptibility to a higher proportion of their offspring. Independent of HLA-B27, offspring of patients with m-axSpA is not at increased risk of axSpA. These findings are also relevant for patient education and counselling. It is important to further investigate this gender effect for uncovering putative additional disease susceptibility factors and for better assessment of lifetime risk for axSpA. Finally, to honour our teachers, long before the HLA-B27 era, studies had already reported an increased risk of disease for offspring of female AS patients.\textsuperscript{34,35}

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