Sex ratios and hormones in HLA related rheumatic diseases

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Abstract
The major diseases associated with HLA-B27 (Reiter’s disease, ankylosing spondylitis, acute anterior uveitis, and psoriatic arthritis) all occur much more commonly in men. Published evidence indicates that the antigen HLA-B27 is associated with high testosterone concentrations in men. Moreover, the antigen HLA-B44 exerts a protective effect on one of these diseases (psoriatic arthritis), and there are external grounds for supposing that HLA-B44 indexes an antiandrogenic process.

These data are interpreted as support for the hypothesis (first adumbrated nearly 20 years ago) that HLA antigens index unusual hormone concentrations, which in turn are causally related to the diseases.

An examination of published reports suggests that sibs of probands with ankylosing spondylitis (and perhaps Reiter’s disease) contain an excess of men, and that sibs of probands with rheumatoid arthritis contain an excess of women. These data lend further support to the hypothesis.

In 1972 Ivanyi et al reported that a genetic factor identical with or closely linked to the H-2 system in the mouse participates in the control of sex hormone metabolism. On the basis of this finding they made a remarkable prediction: ‘If the situation in histocompatibility genetics in man is analogous to that in the mouse, a great number of physiological characters and disorders may be expected to display a statistically significant association with HLA types. On the basis of the mouse model, continuous (rather than discontinuous) variation may be expected to be found in the HLA traits . . .’

Over the intervening years both parts of this prediction have been confirmed. In 1973 ankylosing spondylitis and Reiter’s disease were both shown to be closely associated with HLA-B277; other conditions (multiple sclerosis, lupus erythematosus, and various categories of arthritis) have since been shown to be less closely associated with HLA markers. In all these illnesses continuous variation in the HLA trait is apparent, as predicted.

In general, the mechanisms responsible for the associations of HLA with disease are not established, and workers have assumed that (a) the HLA antigen plays no immediate part, its locus being close to disease susceptibility genes or (b) the HLA antigen on the cell membrane interacts with other factors—for example, infectious agents, to produce disease or (c) molecular mimicry has a role in disease development.

It is interesting to consider another alternative suggested by Ivanyi’s prediction—namely, that HLA genes index endocrine abnormalities, which form necessary (but not sufficient) conditions for the disease. Several points are compatible with such a suggestion.

Firstly, there is direct evidence relating the testosterone concentrations of women6 and men5 to HLA markers; moreover, testosterone concentrations of haplotype identical brothers show greater similarity than those of haplotype non-identical brothers.6

Secondly, there are substantial heritabilities of human plasma oestrogen and testosterone concentrations in men,3 of dehydroepiandrosterone in both sexes.8

Thirdly, a considerable amount of data has been cited to support the hypothesis that the sexes of human (and other mammalian) offspring are partially controlled by the hormone concentrations of both parents at the time of conception—high concentrations of oestrogen and testosterone favouring the births of sons, and high concentrations of gonadotrophin and progesterone favouring the births of daughters.3,8-11 If this hypothesis were correct then (bearing in mind the associations of HLA markers with hormone concentrations) one might expect unusual sex ratios among the sibs and offspring of probands with HLA related diseases.

Three diseases will be discussed in this context—Reiter’s disease, ankylosing spondylitis, and rheumatoid arthritis. Ankylosing spondylitis and Reiter’s disease have a number of features in common. As mentioned above, they are both closely associated with HLA-B27, and both are much more common in men. Additionally, genitourinary infection is common in both.12 13

Reiter’s disease. Symptoms of Reiter’s disease are commonly triggered by non-specific urethritis. This infection is powerfully associated with sexual activity: promiscuity is a well established risk factor for Reiter’s disease.14 It is not clear, however, that the infection is a necessary condition for the manifestation of the disease. So one may wonder whether Reiter’s disease and the behavioural antecedents of infection are both due to high concentrations of testosterone. If this were correct one might
expect HLA-B27 to index high concentrations of testosterone. Ollier et al.36 tabled mean testosterone concentrations of 138 healthy men and 71 men with rheumatoid arthritis by 12 HLA B markers. Out of 12 B markers the ranking of HLA-B27 was second highest in the controls and third highest in the patient sample. The combined weight of this evidence (assessed by the Haldane-Smith test37) is to suggest that—as expected—HLA-B27 is associated with high testosterone concentrations in men (p=0.05, one way). This being so, one would further expect high sex ratios (men to women) in the sibs of probands with Reiter’s disease. Table 1 gives data on this point. Although not statistically significant at a conventional level, the data nevertheless suggest an excess of men.

**Ankylosing spondylitis.** This disease is associated with genitourinary pathology typically diagnosed as ‘prostatitis’.13 The causes of this condition (or group of conditions) are diverse and only partially elucidated: some of them are venereally transmitted, however.18 19 So although the behavioural evidence for ankylosing spondylitis is weaker than that for Reiter’s disease, one would certainly suspect an association with sexual promiscuity and hence with high testosterone concentrations and thus with high sex ratios (M:F) in the families of probands with ankylosing spondylitis. Table 2 gives data on this point. There is good evidence for an excess of brothers among the sibs of probands with ankylosing spondylitis.

In none of the studies included in table 2 is it suggested that the reported numbers of brothers and sisters are the totals of sibs ever born. Instead the reported numbers comprise those living or those examined. Men have higher mortality at all ages than women and in general, men are less likely to volunteer, or make themselves available, for routine examinations. So, overall male excess exists despite these limitations.

**Rheumatoid arthritis.** Clinical rheumatoid arthritis affects more women than men. There is strong evidence of hormonal involvement in this disease, as witness the waxing and waning of symptoms associated with phases of women’s menstrual and life cycles. The hormonal associations with rheumatoid arthritis differ for the two sexes. There can be no reasonable doubt that men with rheumatoid arthritis have unusually low testosterone concentrations.31 33 In contrast, female patients seem to have normal testosterone concentrations34 35, but it has been suggested that their oestrogen concentrations are low, this being a basis for an apparent protective effect of oral contraception.36 Bearing in mind the low testosterone (in male patients) and oestrogen (in female patients) one would expect low sex ratios (M:F) in sibs of these patients. Table 3 gives the data. There certainly seems to be an excess of sisters among the sibs of probands with rheumatoid arthritis.

The three sets of data of Aaron et al.37 (shown in table 3) were compiled while probands were still young, thus largely precluding bias due to differential mortality of the sexes. The sex ratios (M:F) of the three samples show significant heterogeneity (x²=7.6, p<0.025). This suggests that (even bearing in mind possible ascertainment biases) either probands with pauciarticular juvenile rheumatoid arthritis have an excess of sisters or probands with polyarticular juvenile rheumatoid arthritis have an excess of brothers, or both. The various categories of juvenile rheumatoid arthritis have different HLA associations. I suggest that the biased sex ratios of their sibs reflect differing hormonal participation indexed by these HLA associations.

The three sets of data of Hersh et al.39 (table 3) were each assembled in order to calculate sib risks in the context of each of the three diseases: in other words, the numbers of brothers and sisters were not accumulated incidentally, but as an essential part of the research. These three sets of data also show significant heterogeneity between the sex ratios (x²=7.8, p<0.025). This suggests that one or more of the following propositions is true: (a) there is an excess of sisters among the sibs of patients with rheumatoid arthritis; (b) there is an excess of brothers among the sibs of patients with ankylosing spondylitis; (c) there is an excess of sisters among the sibs of probands with Heberden’s nodes (osteoarthritis of the finger joints).

In table 3 all four samples of sibs of adult patients with rheumatoid arthritis show an

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<thead>
<tr>
<th>Table 1</th>
<th>Sexes of the sibs of probands with Reiter’s syndrome</th>
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<tbody>
<tr>
<td>Source</td>
<td>Men</td>
</tr>
<tr>
<td>Kousa et al.36</td>
<td>23</td>
</tr>
<tr>
<td>Woodrow et al.37</td>
<td>10</td>
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<tr>
<td>Totals</td>
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</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Sexes of the sibs of probands with ankylosing spondylitis</th>
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<tbody>
<tr>
<td>Source</td>
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</tr>
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<td>Lawrance (private communication)36</td>
<td>103</td>
</tr>
<tr>
<td>de Blecourt et al.38</td>
<td>200</td>
</tr>
<tr>
<td>Emery and Lawrance21</td>
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<td>Hochberg et al.21</td>
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<td>Karten et al.21</td>
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<td>O'Connell21</td>
<td>184</td>
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<tr>
<td>Romanus22</td>
<td>23</td>
</tr>
<tr>
<td>Stecher and Hersh23</td>
<td>86</td>
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<tr>
<td>Xu et al.24</td>
<td>21</td>
</tr>
<tr>
<td>Totals</td>
<td>775</td>
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</table>

*The data in Dr Lawrance’s private communication refer to the families reported in the abstract by Lawrance et al.33 The data cited here from Hochberg et al.3* relate to their families 1 and 7. The data of Romanus22 relate to the unaffected sibs of his seven affected sib pairs. The sibsex of the unaffected sibs of his other probands are apparently not available. The data of Stecher and Hersh23 are not included here, being presumed to be already contained in those of Stecher and Hersh.23

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Sexes of sibs of probands with the given disease categories</th>
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<tbody>
<tr>
<td>Source</td>
<td>Men</td>
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<tr>
<td>Aaron et al.37*</td>
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<td>228</td>
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</tbody>
</table>

*The data of Van Kerckhove et al.36 are not included here, being presumed to be included in the data of Aaron et al.37 The data of Silman (private communication) are not included here, being presumed to be already contained in those of Silman.41

In table 3 all four samples of sibs of adult patients with rheumatoid arthritis show an
Sex ratios and related correla-
tions on HLA
Reiter's disease would be elucidated.

of probands
might be
excess
hormonal
another HLA-B27 associated condition, a risk
ratio of 7:4 has been suggested.42 It is interesting
that these authors also suggest a risk ratio of
0:4—that is, a protective effect, of HLA-B44 in
disease. As noted below, bearers of the B44
antigen have been reported to have an excess of
sisters. Evidence has been cited above that
HLA-B27 indexes high androgen concentrations.
So there are two independent reasons to
suspect that B44 indexes an autoimmune
process. There seems sufficient evidence here
to warrant consideration of antianogenic drugs
in the treatment of psoriatic arthritis. More-
over, if B44 protects against Reiter's disease or
ankylosing spondylitis then perhaps those
diseases might respond to such treatment too.

Secondly, consider again the two hypotheses—
namely, those linking sex ratios to hormones,
and hormones to HLA markers. If they were
correct one might expect odd sex ratios in the
first degree relatives of carriers of some of the
antigens. The report of Van Kerckhove et al.40
supports this suggestion. These authors classi-
ﬁed probands with early onset pauciarticular juvenile rheumatoid arthritis according to
whether they were HLA-B44 positive or not and
examined the sexes of their sibs. Those probands who were positive had a significantly greater
number of sisters than those who were not.
For this reason, I suggest that B44 either
directly or indirectly indexes an autoimmune
process. As noted previously, this antigen
protects against psoriatic arthritis, possibly for
this reason.

Further research
If the above speculations seem plausible, then it
might be worth considering a number of
proposals.

Firstly, the hormonal proﬁles in HLA as-
sociated diseases should be further examined;
many of the diseases are in any case known to be
hormone related without the hormonal role
having been elucidated.

Secondly, the sex ratios of first degree relatives
of probands with these diseases should be
further examined to see if they throw light on the
hormonal status of their families. In par-
cular, it would be interesting to see more data
on the sexes of offspring and sibs of probands
with Reiter's syndrome and ankylosing
spondylitis.

Thirdly, the normal proﬁles associated with
HLA markers should be directly investigated
further. In particular, attempts should be made to
correlate major histocompatibility complex
class II antigens with hormone concentrations.
Moreover, if, as suggested above, hormones
mediate between the antigens and the diseases
for which they are markers then presumably the
antigens would correlate more strongly with the
hormones than with the diseases. In particular,
one would like to see further work on hormone
concentrations of HLA-B27 carriers. Do hor-
monal proﬁles discriminate between diseased
and non-diseased HLA-B27 subjects, and
between those with the various B27 related
diseases?

Fourthly, it would be interesting to know
whether in man, as in the mouse and pig (34)
tests size is related to HLA markers. If this
were so it would provide impetus for the research
here suggested.

Fifthly, it would be interesting to know
whether (consistent with the suggestion that
hormones play a central part in these diseases) men
with ankylosing spondylitis or Reiter's disease
are taller than other men, on the
average.

Finally, a comparison of the data of Ollier et al.12 with those of Gerencer et al.13 (on the
associations of HLA markers with testosterone
concentrations in respectively men and women)
suggests that although HLA-B27 indexes high
testosterone in men, it does not do so in women. If this is correct then one would expect that
HLA-B27 would not serve as a marker (or so powerful a marker) for these
diseases in women. The point could readily be
tested.

I am grateful to Drs J S Lawrence (of Manchester) and A J Silman (now of the University of Manchester) for providing the data
cited in tables 1 and 3.

1 Iveni P, Hampel R, Starka L, Mickova M. Genetic association
between H-2 gene and testosterone metabolism in mice. Nature
NeuroBiology 1972; 230: 281–2
1973; ii: 996–8
3 Schwimmbek P L, Oldstone M B A. Molecular mimicry
between human leukocyte antigen B 27 and khelesia:
85 (supp 6A): 51–3
4 Gerencer M, Tuic M, Kerhin-Bekliaic V, Kastelan A. An
association between serum testosterone level and HLA
5 Ollier W, Spectot T, Silman A, et al. Are certain HLA
haplotypes responsible for low testosterone levels in males?
Dis Markers 1989; 7: 159–35
6 Spectot T D, Ollier W E R, Perry L A, Silman A J. Evidence for
similarity in testosterone levels in haplotype identical
7 Mickle A W, Bishop D T, Stingham J D, West D W. Quantitating genetic and nongenetic factors that determine
plasma sex steroid variation in normal male twins. Metab-
olism 1986; 35: 1090–5
8 Reiter J I, Wong F L, Liffrak E T, Parker L N. A genetic
component to the variation of dehydroepiandrosterone
sulfate. Metabolism 1985; 34: 731–40
9 James W H. The human sex ratio. Part 2: a hypothesis and a
program of research. Hum Biol 1987; 59: 873–900
10 James W H. Parental hormone levels and mammalian sex
11 James W H. The hypothesized hormonal control of human
sex ratio at birth—an update. J Theor Biol 1990; 143:
555–64
12 Romanus R. Pelvo-spondylitis ossiflicans in the male
(ankylosing spondylitis, Morbus Bechterew—Marie–
Strümpell) and genitourinary infection. Acta Med Scand
1953; (suppl 280): 1–368
13 Calin A, Reiter's disease. In: Calin A, ed. Spondylarthro-
14 Conoir G W. The course of Reiter's syndrome. BMJ 1958; i:
1086–90
15 Haldane J B S, Smith C A B. A simple exact test for birth
16 Kousa M, Lassar A, Karvenon J, Tähtikari A, Aho K,
Family study of Reiter's disease and HLA B 27 distrib-
17 Woodrow J C, Treanor B, Usher N. The HL-A system in
Reiter's syndrome. Tissue Antigens 1974; 4: 533–40

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