Combined analysis of three whole genome linkage scans for Ankylosing Spondylitis


Objective. Ankylosing spondylitis (AS) is a debilitating chronic inflammatory condition with a high degree of familiality (λs = 82) and heritability (≈90%) that primarily affects spinal and sacroiliac joints. Whole genome scans for linkage to AS phenotypes have been conducted, although results have been inconsistent between studies and all have had modest sample sizes. One potential solution to these issues is to combine data from multiple studies in a retrospective meta-analysis.

Methods. The International Genetics of Ankylosing Spondylitis Consortium combined data from three whole genome linkage scans for AS (n = 3744 subjects) to determine chromosomal markers that show evidence of linkage with disease. Linkage markers typed in different centres were integrated into a consensus map to facilitate effective data pooling. We performed a weighted meta-analysis to combine the linkage results, and compared them with the three individual scans and a combined pooled scan.

Results. In addition to the expected region surrounding the HLA-B27 gene on chromosome 6, we determined that several marker regions showed significant evidence of linkage with disease status. Regions on chromosome 10q and 16q achieved ‘suggestive’ evidence of linkage, and regions on chromosomes 1q, 3q, 5q, 6q, 9q, 17q and 19q showed at least nominal linkage in two or more scans and in the weighted meta-analysis. Regions previously associated with AS on chromosome 2q (the IL-1 gene cluster) and 22q (CYP2D6) exhibited nominal linkage in the meta-analysis, providing further statistical support for their involvement in susceptibility to AS.

Conclusion. These findings provide a useful guide for future studies aiming to identify the genes involved in this highly heritable condition.

Key words: Ankylosing Spondylitis, genome scans, meta-analysis.

Ankylosing spondylitis (AS) is a chronic, inflammatory arthropathy that primarily affects the spinal joints and sacroiliac joints, causing symptoms of pain and stiffness, and progressive fusion of involved joints. Peripheral arthritis and/or uveitis (inflammation of the eye) complicates approximately 40–50% of cases; less common extra-articular manifestations include enthesitis, aortitis and pneumonitis. Associations between AS and psoriasis and inflammatory bowel disease are well described. AS has an estimated prevalence of 1/1000 to 4/1000 in white populations [1, 2].

Genetic factors have long been implicated in AS, with recognition of association with the HLA-B27 gene over 30 yrs ago [3, 4]. Whilst over 90% of AS patients carry the gene, only approximately 1–6% of the general population HLA-B27 carriers develop AS [1, 2]. Twin and family studies suggest that this can be explained by the additional involvement of several other genes [5, 6]. There is evidence that other genes lying within the major histocompatibility complex (MHC) [7], interleukin-1 gene cluster [8–11], and the gene CYP2D6 influence susceptibility to AS [12, 13], but clearly a substantial proportion of the non-B27 heritability of AS is as yet unexplained.

The International Genetics of Ankylosing Spondylitis (GAS) Consortium was established in 2003 as an international effort to define the candidate regions and genes for AS with greater precision and reliability than can be achieved by smaller individual studies. We have gathered the results of three separate whole genome scans for AS and examined them for evidence of linkage with disease. These are the ‘Oxford’ [14], Groupe Français d’Étude Génétique des Spondyloarthopathies (GFEGS) [15], and North American Spondyloarthritides Consortium (NASC) datasets [16]. The ‘Oxford’ cohort consists of two subsets, the findings of a genomewide scan on the first of which was first reported in 1998 [17], and the second in 2001 [14]. The two sets were pooled for the current study. These datasets represent all currently published genome-wide linkage data in AS. Whilst a previous meta-analysis has been reported in AS, it did not use the original linkage data as we have here, but analysed only data found in figures and tables from previous linkage screens, did not take into account the differences in phenotype definition in the different datasets, nor was able to identify and correct marker position and order errors in the original datasets [18].

In addition to examining studies individually, we examined a combined dataset of the three studies pooled together giving each dataset equal weighting (referred to as the ‘pooled’ analysis), and compared this with a weighted meta-analysis of the three studies to explore the overall combined effect across the studies (referred to as the ‘weighted’ meta-analysis). This weighted meta-analysis takes into account the differences in size, marker density and linkage information content extracted by each screen. The use of meta-analysis techniques should improve on the power of the individual datasets, allowing us to examine in finer detail the genetic effects across three independent populations.

Patients and methods

Study populations

There are significant differences in the disease definitions used, types of families studied, and marker sets genotyped between the
Table 1. Family compositions of genome screens employed in meta-analysis

<table>
<thead>
<tr>
<th>Families</th>
<th>GFEGS</th>
<th>AS</th>
<th>SpA</th>
<th>NASC</th>
<th>Oxford</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>27</td>
<td>84</td>
<td>232</td>
<td>197</td>
<td>488</td>
<td></td>
</tr>
<tr>
<td>Number of affected sibling pairs</td>
<td>1</td>
<td>18</td>
<td>51</td>
<td>154</td>
<td>154</td>
<td>341</td>
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<td>4</td>
<td>7</td>
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<td></td>
<td>3</td>
<td>6</td>
<td>15</td>
<td>21</td>
<td>17</td>
<td>47</td>
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<td></td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>3</td>
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<tr>
<td>More</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Sibpairs</td>
<td>46</td>
<td>139</td>
<td>245</td>
<td>251</td>
<td>589</td>
<td></td>
</tr>
<tr>
<td>Affected individuals</td>
<td>74</td>
<td>244</td>
<td>485</td>
<td>461</td>
<td>1116</td>
<td></td>
</tr>
<tr>
<td>Male (%): female (%)</td>
<td>51:49</td>
<td>50:50</td>
<td>58:42</td>
<td>66:34</td>
<td>60:40</td>
<td></td>
</tr>
</tbody>
</table>

aSpA includes all cases meeting the ESSG Criteria for Spondyloarthritis (i.e. including those also meeting the modified New York Criteria for AS).

Consensus map

A consensus map that incorporated all typed markers in each of the three datasets was constructed to pool raw genotype data across samples. This map provided a framework of markers upon which typed markers were integrated using PYGMALION [22]; markers were ordered using the deCODE recombination marker map [23].

Linkage analysis

Possible errors in the pedigree and genotype data were assessed using the RELCHECK [24], PEDCHECK [25] and MERLIN [26] programs. These analyses suggested that the maximal potential error rate in any one dataset was less than 1% of all genotypes. Our error-checking procedure resulted in the exclusion of very few families at a given marker from any of the datasets. Marker allele frequencies were estimated using the MERLIN program by maximum likelihood estimation [27].

Multipoint non-parametric linkage analysis was performed using the MERLIN v0.10.2 pedigree analysis software package [27]. $P$-values were calculated by simulation and then converted to a $-\log_{10}$ scale and plotted using JLGraph [28]. Because the dataset was simulated 10 000 times, the minimum reported $P$-value is $<10^{-4}$, and maximum $-\log_{10}(P$-value) is 4.

Pooled analysis

The three individual AS-alone datasets were combined to create a single pooled AS-alone dataset comprising all markers and families. This pooled dataset was analysed for linkage using Merlin (with the common integrated map) and empirical $P$-values calculated as previously described. A pooled SpA dataset was created by combining the markers and families from the AS alone and GFEGS-SpA datasets (i.e. all cases from the three datasets that meet the ESSG Criteria, most of whom also meet the modified New York Criteria), and analysed similarly. Because of the strong linkage between AS and markers contained in the MHC on chromosome 6 and the limits of our simulations, six markers contained in the Oxford dataset and four markers contained in the NASC dataset produced a $P$-value that was effectively zero. As this result could not be plotted on a $-\log_{10}$ scale, these markers were plotted with the arbitrary value of 10 (relative to surrounding markers). Seven markers in this same location in the both the AS-alone and SpA pooled datasets were plotted in the same manner.

Meta-analysis

We analysed each of three datasets for linkage to the genotyped markers. In order to perform a meta-analysis of the whole genome linkage scan results (for AS only affection), we then pooled linkage statistics across the datasets using a weighted combination of $z$-score approach. Given the varying information content and population sizes across the three genome scans, we chose an approach based on weighting for both information content and study size as previously described by [29].

Using the weighted meta-analysis approach, the $z$-scores for each of the 338 common markers across the scans were combined. These weighted $z$-scores follow a standard normal distribution ($\text{mean}=0$, S.D. = 1), from which $P$-values were determined. As with the empirical linkage results, we converted the resulting $P$-values to a $-\log_{10}$ scale for plotting using JLGraph. Three marker locations contained in chromosome 6 produced $P$-values of zero, and as described previously were assigned the value of 10 for plotting purposes.

IBD sharing by affected sibling pairs and $\lambda_{(\text{LOCUS})}$ values were determined using MapMaker/Sibs [30] weighted according to the number of affected sibling pairs available in each cohort. The contribution of each locus to the overall sibling recurrence risk was calculated assuming a sibling recurrence risk ratio of 82 [6], and multiplicative interaction between loci [31], the most likely model in AS [6].

Results

The results of the three individual whole genome linkage scans for AS are presented in Fig. 1. The results of the pooled AS-alone analysis and weighted meta-analyses are compared in Fig. 2 and Fig. 3 presents the results of the pooled AS-alone and the pooled SpA analyses. Significant results are indicated in Figs 1–3 by small $P$-values (large values on a $-\log_{10}$ scale) forming peaks over relevant markers. Note that the positioning of results within each of the figures reflect that most p-terminal markers used in each study are not located at 0 cM on the chromosomal genetic map.

Individual scans

Considering the individual scans (Fig. 1), each shows highly significant linkage to the region of chromosome 6 encoding the MHC ($P < 10^{-5}$). 'Nominal' or greater evidence of linkage
FIG. 1. Ankylosing spondylitis whole genome linkage scans. A circle indicates the marker has a \( P \)-value \(< 0.05\), a square indicates \( P \)-values \(< 0.01\), a triangle indicates \( P \)-values \(< 0.001\). Linkage with AS affection status is shown for GFEGS, Oxford and NASC datasets in red, blue and green respectively. Please note, chromosome 6 has a different \(-\log_{10} P\)-value scale.
Fig. 2. Ankylosing spondylitis weighted meta-analysis vs pooled dataset. A circle indicates the marker has a $P$-value $< 0.05$, a square indicates $P$-values $< 0.01$, a triangle indicates $P$-values $< 0.001$. Weighted meta-analysis is shown in red, while pooled linkage scan is shown in blue. Please note, chromosome 6 has a different $-\log_{10} P$-value scale.
Combined analysis of AS genome linkage scans

FIG. 3. Pooled SpA dataset vs pooled AS-alone dataset. A circle indicates the marker has a $P$-value $< 0.05$, a square indicates $P$-values $< 0.01$, a triangle indicates $P$-values $< 0.001$. Pooled SpA is shown in red, while pooled AS-alone scan is shown in blue. Please note, chromosome 6 has a different $-\log_{10} P$-value scale.
(P < 0.05) was observed for two or more scans on chromosomes 1, 3, 5, 7, 9, 10, 13, 16, 17, 19 and 22. Regions achieving at least moderate evidence of linkage (P < 0.05 in three or more individual datasets or the meta-analyses) are given in Table 2. These were observed in the GFEGS-SpA scan on chromosomes 9 (129 cM, P < 0.0003), 11 (53 cM, P = 0.003), 12 (31 cM, P = 0.002), and 17 (93 cM, P = 0.005). When considering cases of AS alone, of these linkages only the chromosome 12 linkage remained significant (P < 0.01). In the NASC dataset, moderate or greater linkage was observed on chromosome 3 (95 cM, P = 0.0002), 4 (35 cM, P = 0.007), 5 (204 cM, P = 0.007), 6q (161 cM and 172 cM, P = 0.002), 16 (50 cM, P = 0.005), and 22 (56 cM, P = 0.009). In the Oxford families, moderate or greater linkage was observed on chromosomes 1 (95 cM, P = 0.003), 2 (135 cM, P = 0.0003), 5 (166 cM, P = 0.009), 10 (127 cM, P = 0.003), 16 (101 cM, P = 3 × 10⁻⁶), and 19 (76 cM, P = 0.0003).

### Pooled analysis

In addition to the very significant evidence of linkage with the 30–70 cM region of chromosome 6 containing the MHC, the pooled analysis results show markers with moderate evidence of linkage (P < 0.01) in chromosomes 3, 4, 5, 6, 10, 11, 13, 16, 17 and 22 (Table 2). Clusters of significant marker results were seen on chromosome 1 at approximately 170 cM (P < 0.05), chromosome 3 at 88–130 cM (P < 0.01) and 198 cM (P < 0.05), and with several markers across chromosome 17.

Consistent with each of the individual scans and the AS-alone weighted meta-analysis, the pooled analysis exhibited significant evidence of linkage (P < 0.00001) with the 30–90 cM region of chromosome 6 in the AS-alone and AS-SpA datasets. Clusters of significant marker results are also seen on chromosomes 1 (P < 0.01), 3 (P < 0.01), 10, 11, 12, and 13 (P < 0.01), 17 (P < 0.001), 21 (P < 0.01) and 22 (P < 0.01).

### Weighted meta-analysis

Considering the analyses of AS alone, highly significant linkage was observed with all three individual scans and with the combined analyses (P < 10⁻⁹) to the 37–75 cM region of chromosome 6, consistent for linkage with the location of the HLA-B27 marker. In the weighted AS-alone meta-analysis, the next strongest evidence of linkage was found at chromosome 16q (maximum linkage at 99 cM, P = 1.8 × 10⁻⁶). Evidence for linkage between markers in this this region with AS was seen in both the NASC and Oxford datasets (P = 0.02 at 99 cM and P = 3 × 10⁻⁵ at 101 cM, respectively). Other regions achieving moderate evidence of linkage (P < 0.01) were identified on chromosomes 3, 10 and 19. On chromosome 3, peak linkage was seen at 202 cM (P = 0.005), with support in the GFEGS, NASC and Oxford datasets (P = 0.02, 0.03 and 0.03, respectively, each at 202 cM). On chromosome 10, peak linkage was seen at 127 cM (P = 0.008), with support in the NASC and Oxford datasets (P = 0.02 at 113 cM and P = 0.003 at 127 cM, respectively). A broad region of linkage was observed on chromosome 19, the peak of which lay at 76 cM (P = 0.005), with support in the NASC and Oxford datasets, although the peaks of linkage in these studies were quite separated (P = 0.03 at 109 cM and P = 0.0003 at 76 cM, respectively).
The $\lambda_{\text{LOCUS}}$ value for chromosome 6p was 4.5, representing 34% of the familiality of AS, assuming a multiplicative interaction between loci. For chromosome 16q, the $\lambda_{\text{LOCUS}}$ value was 1.6, representing 11% of the familiality of AS.

**Previously associated regions**

Association has previously been reported between AS and the IL-1 gene cluster on chromosome 2q13 (at 126 cM), and the gene CYP2D6 on chromosome 22q13.2 (at 50 cM). Considering the IL-1 gene cluster, this region showed evidence of linkage in the Oxford dataset (135 cM, $P = 0.0003$) and in the weighted meta-analysis (135 cM, $P = 0.01$), but not in other individual datasets. The CYP2D6 region showed nominal evidence of linkage in the North American and Oxford datasets (56 cM, $P = 0.009$ and 37 cM, $P = 0.04$, respectively) and in the pooled analysis (56 cM, $P = 0.003$).

Examining heterogeneity of findings between the three studies (for AS-alone), using the 338 common markers, we found that 114 (approx. 33%) of the marker locations had substantial heterogeneity ($>50\%$) using the $\chi^2$ test [32]. 105 show substantial heterogeneity ($P < 0.1$) using Cochran’s Q test. Groups of markers showing substantial heterogeneity are discussed further in the Discussion.

**Discussion**

This study was designed to investigate the evidence for linkage to AS phenotypes in a retrospective analysis of combined genome-wide data from three separate studies. Meta-analysis can potentially improve on the power of individual genome screens to identify linkages, and help clarify the significance of linkage results where there is inconsistent replication across screens (such as [29, 33–35]). We have performed meta-analysis by both pooling results and a weighted combination of linkage statistics across studies. These two approaches each have strengths and weaknesses. Weighted meta-analysis more correctly accounts for the difference in size and information content between the different scans, but only uses markers common to the three studies ($n = 338$). The pooled analysis uses all markers available potentially increasing its power, but weights each study equally.

Where there is discordance between the studies this can lead to the findings from smaller studies having a disproportionate effect on pooled results.

The study confirms on a genome-wide level the ‘highly significant’ linkage ($P < 3 \times 10^{-5}$) of the region of chromosome 6 encoding the MHC, and also identifies ‘suggestive’ linkage ($P < 7.4 \times 10^{-5}$) on chromosomes 6q, 10q and 16q. Several other regions, whilst not achieving ‘suggestive’ or greater evidence of linkage, found support in two or more screens such as to suggest that it is likely that they are true positive findings.

In addition to the highly significant linkage observed on chromosome 6p around the location of HLA-B27, there are a number of other interesting marker patterns on the chromosome 6 which illustrate the advantage of the meta-analysis approach compared with comparisons of individual screens. Between 140 cM and 175 cM in the NASC linkage results in Fig. 1, there are eight markers with significant ($P < 0.01$) linkage to AS. In contrast, the Oxford and GFEGS datasets return no significant markers for this region. The pooled analysis, as expected given the fact that the NASC dataset contributes 42% of the total studied, also returns significant results for the region. The weighted meta-analysis is therefore of particular interest, given the lack of replication across this region in the remaining two studies, identifying four significant markers for linkage in this region, the most significant result being at 160.64 cM (marker name AFM269x21/DSS441, $P = 0.007$). Examining the three linkage scan results individually could have missed this linkage, as the results were not reproduced across studies, demonstrating the value of the meta-analysis method. These findings strongly support the existence of further non-MHC genes involved in susceptibility to AS on chromosome 6q.

Linkage to chromosome 16q in AS was first reported by the Oxford group in 1998 [17], with further support for this being a true positive finding coming from their further genome screen [14] and the NASC study [16]. However, no linkage was observed in this region in the GFEGS study. In the weighted meta-analysis this region is the most significant non-MHC region, achieving $P = 0.0002$, the peak lying at 99 cM. Results for chromosome 10 surrounding 124 cM were also significant in the NASC and Oxford but not the GFEGS dataset. In particular, the marker at location 127 cM (AFM331xa9/D10S597) was significant in the meta-analysis ($P = 0.004$) and the pooled analysis ($P = 0.0005$). Thus, despite the inconsistent replication of this finding in different genome screens, the meta-analysis findings suggest that these are probably true positive findings, warranting further study.

Other regions potentially containing AS genes may only fulfil less stringent statistical threshold but are worth pursuing, particularly if there is support from more than one screen. Other than the regions described earlier, nominal or greater evidence of linkage ($P < 0.05$) was observed for (two or more scans on chromosomes 1, 3, 5, 9, 13, 17, 19 and 22. Although there is clearly less certainty about these findings, there is at least a moderate probability that they contain disease-susceptibility genes.

Substantial differences were observed between the findings of the GFEGS study and those from the NASC and Oxford cohorts, the main exception being the consistent linkage to the MHC in all three screens. Potential explanations for this include the lower sample size of the GFEGS study, differences in structure of the families studied (the GFEGS cohort included a higher proportion of large pedigrees rather than affected-sibling pairs of families than the Oxford cohort), or the diagnostic scheme applied. The GFEGS–AS dataset is significantly smaller than the NASC or Oxford datasets, which likely explains the difference in the findings for that study. These differences between the scans at least partly explain the differences in finding between the pooled analysis and weighted meta-analyses.

Examining the differences between the pooled AS-alone and SpA analyses, a number of interesting patterns occur. As shown in Fig. 3, the evidence for linkage of chromosome 16q with disease is evident in the AS-alone dataset and not in the pooled SpA dataset. However, as noted previously, the GFEGS dataset is smaller than the NASC or Oxford datasets, likely explaining the difference in the pooled analysis and weighted meta-analysis findings at this region. On chromosome 21 at $\approx$40–56 cM the individual scans and the weighted meta-analysis reveal no evidence for significant linkage, while the pooled SpA analysis reveals a cluster of markers suggestive of linkage, peaking at marker D21S268 (49 cM, $P = 0.0009$). Similarly, a closer examination of markers in the 35–50 cM region of chromosome 10 also shows evidence for linkage ($P < 0.01$) with markers in the pooled SpA analysis, that do not appear in the weighted meta-analysis. These results warrant further investigation to determine whether this is a result of the combined pooled analysis composition, or reflects heterogeneity in disease definition between the pooled datasets, or some other confounding factor.

Comparison of pooled analysis and weighted meta-analysis results are helpful in the interpretation of chromosomal regions suggestive of linkage with AS-alone that are not replicated in the SpA datasets. Linkage observed with chromosome 10 at 127 cM in the weighted meta-analysis of AS-alone and SpA, and in the pooled AS-alone analysis, returned no significant evidence for linkage within the pooled SpA analysis. The broad region of chromosome 19 identified for linkage in the AS-alone meta-analysis was not identified at all within the SpA dataset (either in the meta-analysis or the pooled studies). Notably neither the
GFEFS-AS datasets provide evidence for linkage to this chromosome. This absence of linkage would least affect the AS-alone weighted meta-analysis. Thus, this disparity may be due to identification of marker locations specific to AS-alone rather that the more general condition of SpA, an observation warranting further study.

A closer examination of the population heterogeneity calculation across the studies reveals that the majority of markers showing substantial heterogeneity fall in regions where no significant evidence for linkage was discovered. The only major block of linkage results that overlay a large region of markers showing heterogeneity is on chromosome 12 at ~66–112 cM in the pooled SpA analysis. However, the weighted meta-analysis and pooled AS-alone analysis reveal no significant evidence for linkage in this region, suggesting that perhaps the linkage with SpA in this region may reflect population heterogeneity. Other large blocks of markers showing substantial heterogeneity are located at the q-terminal of chromosome 13 and across the entire chromosome 14, where no significant evidence for linkage was revealed in any of the analyses.

In comparison with a previously published meta-analysis [36], this study is more accurate and powerful. The previous study employed data extrapolated from published graphs and tables and did not accurately differentiate between AS and SpA, the AS families from the GFEFS screen being excluded from the AS-alone analysis. In contrast, we have used the original genotype data allowing for better genotype error checking, correction of marker maps to take into account the most recent genome maps, precise multipoint analysis rather than division into 30 cM bins, and pooled and weighted analyses. AS and SpA analysis have been presented separately. Lee et al.‘s study report only three loci achieving P < 0.01 (on chromosomes 6, 16 and 19), which were each identified in this screen. Two other regions achieved nominal levels of significance with the two statistical scores used in this study (Paurunk, Pord < 0.05, > 0.01), lying on chromosome 17p and 9q. These areas overlap with regions identified in the current study. However, the level of significance we report is generally greater than reported by Lee et al., which also did not identify several regions we report, including on chromosomes 3, 5, 10 and 13 which were present in three or more datasets or analyses (Table 2).

In conclusion, this analysis provides an important step forward for narrowing down chromosomal locations that may hold the key to discovering the genetic linkages of AS. By performing a meta-analysis, we have identified several common markers that bear further investigation. In particular, we found ‘suggestive’ linkage on chromosomes 10q and 16q, and moderate evidence of linkage (P < 0.01) on chromosomes 3, 4, 5, 6, 10, 11, 16, 17 and 22. Further, regions on chromosome 2 (the IL-1 gene cluster) and 22 (the CYP2D6) previously reported to be associated with AS, showed at least nominal evidence of linkage (P < 0.05) with AS in the meta-analysis. These findings strongly support that this disease is at least oligogenic, and provide a valuable road-map for future studies aiming to identify the genes involved in this condition.

Rheumatology key messages

- Linkage of AS and SpA with the MHC is strong, but the condition is most likely polygenic, with loci on chromosomes 1q, 3q, 5q, 6q, 9q, 10q, 16q, 17q and 19 likely to harbour additional susceptibility genes.
- Regions previously associated with AS on chromosome 2q (the IL-1 gene cluster) and 22q (CYP2D6) exhibited nominal linkage in the meta-analysis, providing further statistical support for their involvement in susceptibility to AS.

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References


