Literature strategy

PubMed:

#1 (2p15[All Fields] OR rs10865331[All Fields])

#2 ((“spondylitis”[MeSH Terms] OR “spondylitis”[All Fields]) OR (“spondylitis, ankylosing”[MeSH Terms] OR (“spondylitis”[All Fields] AND “ankylosing”[All Fields]) OR “ankylosing spondylitis”[All Fields] OR (“ankylosing”[All Fields] AND “spondylitis”[All Fields])) OR SpA[All Fields] OR (“spondylarthritis”[MeSH Terms] OR “spondylarthritis”[All Fields]) OR (“spondylarthropathies”[MeSH Terms] OR “spondylarthropathies”[All Fields]) OR (“spondylarthropathies”[MeSH Terms] OR “spondylarthropathies”[All Fields] OR “spondyloarthropathy”[All Fields]) OR (“sacroiliitis”[MeSH Terms] OR “sacroiliitis”[All Fields]) OR (“spondylitis, ankylosing”[MeSH Terms] OR (“spondylitis”[All Fields] AND “ankylosing”[All Fields]) OR “ankylosing spondylitis”[All Fields] OR (“bechterew”[All Fields] AND “disease”[All Fields]) OR “bechterew disease”[All Fields]) OR (“spondylitis, ankylosing”[MeSH Terms] OR (“spondylitis”[All Fields] AND “ankylosing”[All Fields]) OR “ankylosing spondylitis”[All Fields] OR (“marie”[All Fields] AND “struempell”[All Fields] AND “disease”[All Fields]) OR “marie struempell disease”[All Fields]) OR axSpA[All Fields])

#3 #1 AND #2

Embase:

#1 (2p15 OR rs10865331)

#2 (‘spondylitis’/exp OR spondylitis OR ‘spondylitis, ankylosing’/exp OR ‘spondylitis, ankylosing’ OR ‘ankylosing spondylitis’/exp OR ‘ankylosing spondylitis’ OR (‘ankylosing’ AND (‘spondylitis’/exp OR ‘spondylitis’)) OR ‘spa’/exp OR spa OR ‘spondylarthropathies’/exp OR spondylarthropathies OR ‘sacroiliitis’/exp OR ‘sacroiliitis’ OR (‘bechterew’ AND (‘disease’/exp OR ‘disease’)) OR ‘bechterew disease’/exp OR ‘bechterew disease’ OR (‘marie’ AND ‘struempell’ AND (‘disease’/exp OR ‘disease’)) OR ‘marie struempell disease’ OR axspa)

#3 #1 AND #2

Other databases:

#1 (2p15 OR rs10865331)

#2 (spondylitis OR (“spondylitis, ankylosing” OR “ankylosing spondylitis” OR (“ankylosing” AND “spondylitis”)) OR SpA OR spondylarthropathies OR sacroiliitis OR ((“bechterew” AND “disease”) OR “bechterew disease”) OR (“marie” AND “struempell” AND “disease”) OR “marie struempell disease”) OR axSpA)

#3 #1 AND #2

Supplementary Table S1. Results of subgroup analysis.

Genetic models	Subgroup	Number of studies	Test of association				Test of heterogeneity			
			OR	95%CI	Z-value	*p*-value	Model	Chi-square	*p*-value	I^2
Subgroup of race, country and study source										
Recessive	Asian	8	1.349	1.175-1.548	4.25	<0.001	R	16.44	0.021	57.40%
	Korea	4	1.445	0.995-2.099	1.94	0.053	R	15.06	0.002	80.10%
	China	4	1.303	1.179-1.440	5.18	<0.001	F	1.14	0.768	0.00%
Dominant	Asian	8	1.565	1.313-1.865	5.00	<0.001	R	32.51	<0.001	78.50%
	Korea	4	1.899	1.341-2.689	3.61	<0.001	R	21.32	<0.001	85.90%
	China	4	1.324	1.194-1.468	5.33	<0.001	F	1.55	0.671	0.00%
Allele	Asian	8	1.347	1.213-1.496	5.57	<0.001	R	28.36	<0.001	75.30%
	Korea	4	1.486	1.174-1.881	3.29	0.001	R	21.91	<0.001	86.30%
	China	4	1.246	1.170-1.327	6.85	<0.001	F	0.93	0.817	0.00%
OR-value analysis	Asian	6	1.222	1.143-1.306	5.90	<0.001	R	14.14	0.015	64.60%
	Caucasian	5	1.317	1.269-1.368	14.47	<0.001	F	1.95	0.856	0.00%
	China	5	1.206	1.124-1.294	5.22	<0.001	R	11.80	0.019	66.10%
	TASC-WTCCC2	5	1.320	1.271-1.371	14.33	<0.001	F	1.70	0.790	0.00%
Pooled analysis	Asian	10	1.293	1.187-1.409	5.88	<0.001	R	46.96	<0.001	80.80%
	Caucasian	6	1.317	1.269-1.368	14.47	<0.001	F	1.95	0.856	0.00%
	China	7	1.207	1.140-1.278	6.49	<0.001	F	11.73	0.068	48.80%
	TASC-WTCCC2	6	1.320	1.271-1.371	14.33	<0.001	F	1.70	0.790	0.00%
	Korea	3	1.581	1.160-2.155	2.90	0.004	R	19.62	<0.001	89.80%
Subgroup of HWE										
Recessive	Yes	7	1.403	1.167-1.687	3.60	<0.001	R	17.03	0.009	64.80%
	No	2	1.314	1.129-1.528	3.54	<0.001	F	1.13	0.288	0.00%
Dominant	Yes	7	1.600	1.290-1.984	4.28	<0.001	R	30.75	<0.001	80.50%
	No	2	1.274	1.109-1.462	3.43	<0.001	F	0.16	0.692	0.00%
Allele	Yes	7	1.370	1.205-1.557	4.81	<0.001	R	26.23	<0.001	77.10%
	No	2	1.239	1.136-1.351	4.86	<0.001	F	0.54	0.461	0.00%
Subgroup of study type										
Recessive	Case-control	7	1.438	1.186-1.743	3.70	<0.001	R	17.00	0.009	64.70%
	GWAS	2	1.267	1.116-1.438	3.65	<0.001	F	0.07	0.786	0.00%
Dominant	Case-control	7	1.575	1.261-1.967	4.00	<0.001	R	31.93	<0.001	81.20%
	GWAS	2	1.343	1.135-1.588	3.44	<0.001	F	1.52	0.218	34.20%
Allele	Case-control	7	1.374	1.204-1.568	4.71	<0.001	R	26.05	<0.001	77.00%
	GWAS	2	1.242	1.214-1.470	5.27	<0.001	F	0.52	0.472	0.00%
OR-value analysis	Case-control	6	1.216	1.131-1.308	5.28	<0.001	R	12.81	0.025	61.00%
	GWAS	6	1.309	1.265-1.355	15.30	<0.001	F	2.69	0.748	0.00%
Pooled analysis	Case-control	9	1.306	1.180-1.445	5.18	<0.001	R	46.32	<0.001	82.70%
	GWAS	7	1.305	1.261-1.351	15.18	<0.001	F	4.13	0.660	0.00%

TASC-WTCCC2: The Australo-Anglo-American Spondyloarthritis Consortium (TASC), subjects are Australian, British and North American individuals of European descent. and the Wellcome Trust Case Control Consortium 2 (WTCCC2), subjects are from Australia, Great Britain and The Spondyloarthritis Research Consortium of Canada. a: Pooled analysis of primary analysis, included crude ORs and 95%CIs.

Supplementary Table S2. Outcome of reference assess (Newcastle-Ottawa Scale)

First author	Selection				Comparability		Exposure			Total scores
	Is the case definition adequate [a]?	Representat-iveness of the cases	Selection of Controls	Definition of Controls	Study controls for select the most important factor[b]	Study controls for any additional factor[c]	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate[d]	
Reveille, *et al*.	☆	-	☆	☆	-	☆	☆	☆	☆	7
Bang, *et al*.	☆	☆	☆	☆	☆	☆	☆	☆	-	8
Sanchez, *et al*.	☆	☆	☆	☆	☆	☆	☆	☆	-	8
Wang M, *et al*.	☆	☆	☆	☆	☆	☆	☆	☆	-	8
Wen, *et al*.	☆	☆	☆	☆	☆	☆	☆	☆	-	8
Wang Q, *et al*.	☆	☆	☆	☆	-	☆	☆	☆	☆	8
Jung, *et al*.	☆	☆	☆	☆	-	☆	☆	☆	☆	8
Evans, *et al*.	☆	-	☆	☆	-	☆	☆	☆	☆	7
Lin, *et al*.	☆	☆	☆	☆	-	☆	☆	☆	☆	7
Davidson, *et al*.	☆	-	☆	☆	-	☆	☆	☆	-	6
Zheng, *et al*.	☆	☆	☆	☆	-	-	☆	☆	-	6

a: Study in which patients were diagnosed by definite diagnosis criteria (1984 New York Criteria) were assigned one star.
b: Study in which both groups were demographically matched (like race, age, gender) were assigned one star.
c: Study in which both groups other factors were matched were assigned one star.
d: Study with a follow-up rate > 95% and equal non-response rate between groups was assigned one star.

Supplementary Table S3. Heterogeneity

Genetic models	Subgroup	Number of studies	Study removed as heterogeneity source	Percentage of removed study (%)	OR	95%CI	Z-value	P-value	Model	Chi-square	P-value	I^2
Recessive	Overall	9	Jung.a[a]	5.90%	1.308	1.203-1.423	6.26	<0.001	F	8.41	0.298	16.70%
	Asian	8	Jung.a	6.35%	1.288	1.182-1.405	5.75	<0.001	F	6.16	0.405	2.60%
	Korea	4	Jung.a	21.21%	1.219	0.931-1.595	1.44	0.15	R	4.79	0.091	58.30%
	China	4	-									
Dominant	Overall	9	Jung.a	9.00%	1.380	1.275-1.494	8.00	<0.001	F	9.26	0.235	24.40%
	Asian	8	Jung.a	9.98%	1.401	1.291-1.520	8.10	<0.001	F	7.16	0.306	16.20%
	Korea	4	Jung.a	22.85%	1.542	1.350-1.520	6.38	<0.001	F	2.55	0.280	21.50%
	China	4	-									
Allele	Overall	9	Jung.a	8.38%	1.264	1.202-1.329	9.12	<0.001	F	1.95	0.963	0.00%
	Asian	8	Jung.a	9.42%	1.265	1.201-1.332	8.89	<0.001	F	1.93	0.926	0.00%
	Korea	4	Jung.a	22.94%	1.305	1.191-1.430	5.73	<0.001	F	0.32	0.852	0.00%
	China	4	-									
OR-value analysis	Overall	12	Wang Q	17.57%	1.293	1.256-1.331	17.53	<0.001	F	6.69	0.755	0.00%
	Caucasian	6	-									
	TASC-WTCCC2	5	-									
	Asian	6	Wang Q	34.32%	1.202	1.159-1.246	10.01	<0.001	F	2.36	0.669	0.00%
	China	5	Wang Q	37.01%	1.250	1.191-1.311	9.16	<0.001	F	1.64	0.651	0.00%
Pooled analysis	Overall	16	Jung.a and Wang Q	22% and 1.16.53%	1.290	1.254-1.326	17.89	<0.001	F	8.13	0.835	0.00%
	Caucasian	6					-					
	TASC-WTCCC2	5					-					
	Asian	10	Jung.a and Wang Q	2.26% and 30.57%	1.256	1.204-1.310	10.64	<0.001	F	3.40	0.846	0.00%
	China	7	Wang Q	35.22%	1.190	1.147-1.235	9.29	<0.001	F	2.15	0.828	0.00%
	Korea	3	Jung.a	31.09%	1.326	1.195-1.471	5.32	<0.001	F	0.00	0.944	0.00%

a: Jung.a indicated the AS-GRS construction group in their study
b: Pooled analysis of all OR values, including several crude ORs and 95%CIs.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Method, Literature search and selection
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Method, Literature search and selection
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Method, Literature search and selection
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Method, Literature search and selection
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Method, Data extraction
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Method, Data extraction and Result, Data extraction and reference assessment
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Method, Reference quality assessment
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Method, Statistical analysis
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Method, Statistical analysis
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Method, Statistical analysis
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Method, Statistical analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Result, Reference search
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Result, Data extraction and reference assessment
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Result, Data extraction and reference assessment
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Result, Data extraction and reference assessment
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Result, Statistical analysis
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Result, Publication bias
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Result, Subgroup analysis, heterogeneity
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Funding

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097
For more information, visit: **www.prisma-statement.org**.

Checklist of HuGE Review
TITLE: rs10865331 in 2p15 Increases Susceptibility to Ankylosing Spondylitis: a HuGE meta-analysis.

Section/topic	#	Items	Reported on section
COVER SHEET			
Title	1	Title (stating whether a meta-analysis was performed), whether new or update, contact details.	Title
ABSTRACT			
Structured summary	2	Provide a one-page structured synopsis of the issues discussed in the items below with a brief statement on each of these items. If possible, supply keywords, including the name(s) of the gene(s), the name(s) of the disease(s) or disorder(s), the word 'epidemiology' and the term 'systematic review' or 'meta-analysis'.	Abstract
INTRODUCTION			
Gene(s)	3	Identify the gene(s) being reviewed and provide a brief review of chromosome location, gene product, and function, if known.	Introduction (para.2)
Gene variants and frequency	4	List known allelic variants with effects on gene product if known. Summarize known information on the frequency of homozygosity and heterozygosity of these variants in different populations and ethnic groups. If a prevalence review exists, summarise its findings. If a prevalence review does not exist, briefly overview the available data with some key references.	Introduction (para.2, last sentence)
Disease(s) or other outcomes	5	Identify the disease(s) or other outcome(s) with which the gene(s) is/are believed to be associated. Briefly summarize the descriptive epidemiology and confirmed and suspected risk factors (including other genes). Refer to previous similar reviews, if available, and be succinct. Outline the rationale (if any) for the postulated association with the disease(s)/outcomes in the current review.	Introduction (para.1)
Objectives	6	Provide a succinct summary of the objectives of the current review	Introduction (para.3)
METHODS			
Selection criteria	7	State the gene(s), gene variant(s), disease and types of participants eligible for inclusion in the review. State the types of study (e.g., design and conduct) eligible for investigation of association. State the types of study (e.g., design and conduct), other gene(s) and environmental exposures eligible for investigation of interactions (if included in the review).	Method: Literature search and selection, study selection
Identifying studies	8	Describe the methods used to identify relevant studies and/or other sources of information. List all electronic databases searched, with details of the search strategies and the periods for which they were searched, and describe any communication with investigators.	Method: study selection
Data collection and analysis	9	Describe the methods for selection of studies, data collection (including data extraction from published reports and any attempt to retrieve unpublished or partially/selectively published data), assessment of risk of bias, methods for analysis of individual studies, methods for meta-analysis, and methods for dealing with heterogeneity and potential biases.	Method: Data extraction, Reference quality assessment, statistical analysis, Statistical analysis, subgroup analyses, heterogeneity and sensitivity analyses, publication bias
RESULTS			
Included studies	10	Include a table providing basic details of the included studies (location, date, design, types of participants (cases and controls)).	Results: Reference search, Data extraction
Quality and methodology of studies	11	Comment on the quality and methodology of studies.	Results: Reference assessment
Associations	12	Summarize the magnitude of the association between the allelic variants and the disease(s) and outcomes of interest in terms of relative, absolute, and/or attributable risks in different populations.	Results: Statistical analysis and subgroup analysis, heterogeneity, publication bias
Interactions	13	Discuss whether the allelic variants interact with other risk factors for the disease, including other genes and environmental factors. Summarize the magnitude of such interactions, whenever possible. State variables adjusted for in any adjusted analyses.	Results: Subgroup analysis
DISCUSSION			
Main findings	14	Summarise the main findings of the review and the meta-analysis	Discussion: para.1
Limitations	15	Comment succinctly on the quality of the evidence. Discuss concerns over amount of relevant information, validity of individual studies, and other biases.	Discussion: para.1,5
Biology	16	Comment on available mechanistic evidence relevant to the association.	Discussion: para.2,3
Potential public health impact and other implications of results	17	(a)Potential public health impact Summarize potential public health applications of human genome epidemiological information on the variants of the gene(s), e.g. available interventions, setting permissible exposure thresholds for individuals with specific genotypes. (b) Implications for our understanding of disease (c) Implications for research Strengths and gaps in the evidence base should be identified. Recommendations should be made to stimulate research to fill any gaps, e.g. what research might be needed to give public health consequence to the summarized genetic knowledge.	(a) Discussion: para.3 (b) Discussion: para.2,3 (c) Discussion: para.4-6
REFERENCES			
Internet sites	18	Include relevant links to various genetics databases, online resources, educational materials, consensus statements, policy statements, and support groups.	Reference 1, 32, 36, 37, 39,
POTENTIAL CONFLICTS OF INTEREST			
Potential conflicts of interest	19	Any potential conflict of interest that might influence the judgments of reviewers should be noted. If none, this should be stated explicitly.	Acknowledgments, Funding and Potential conflicts of interest