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IL-18 polymorphisms (-137C/G and -607A/C) are not associated with tuberculosis

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Abstract

Many studies have demonstrated that (IL-18) polymorphisms (including -137C/G and -607A/C) are correlated with the risk of tuberculosis. However, the meaning of this finding remains a matter of debate. In this study, electronic databases, including PubMed, EMBASE, Web of Science, Google Scholar and CNKI, were systemically queried to identify relevant studies. Subsequently, odds ratios and corresponding 95% confidence intervals were analysed. Our data indicated that the IL-18 -137C/G polymorphism was not related to tuberculosis susceptibility (GG vs. AA odds ratio = 0.71, 95% confidence interval 0.43–1.17; GA vs. AA: odds ratio =0.80, 95% confidence interval 0.57–1.13; dominant model: odds ratio = 0.78, 95% confidence interval 0.56–1.08; recessive model: odds ratio = 0.76, 95% confidence interval 0.46–1.25). Similarly, there was no association between the IL-18 -607A/C polymorphism and tuberculosis susceptibility (AA vs. CC: odds ratio = 1.25, 95% confidence interval 0.87–1.79; CA vs. CC: odds ratio = 1.10, 95% confidence interval 0.93–1.29; dominant model: odds ratio = 1.13, 95% confidence interval 0.90–1.41; recessive model: odds ratios=1.17, 95% confidence interval 0.90–1.53). No association was found in the subgroup analysis based on the Hardy–Weinberg equilibrium. In addition, there was no publication bias. The two IL-18 gene polymorphisms (-137C/G and -607A/C) were not markedly correlated with tuberculosis susceptibility. Well-designed studies with more subjects will be required for further validation of these results.

Keywords

IL-18, tuberculosis, meta-analysis

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Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (MTB), which has been recognised as the main reason leading to single-infection source-related death in the world.[1] However, the precise aetiology and pathogenesis of TB is still uncertain. TB progresses for numerous reasons such as environmental factors and a variety of other risk factors, including malnutrition, infection by HIV, immune depressive therapy and diabetes mellitus.[2] While there are an estimated two billion cases of MTB, only 5–10% of these patients will progress to active disease,[3] indicating the potentially crucial role of host genetic factors in the susceptibility to TB.

Cytokines are important for host susceptibility and TB progression. IL-18 is one of the IL-1 family members, which represents a vital pro-inflammatory cytokine with a crucial role in the inflammatory cascade.[4] IL-18 is released by various cells, including monocytes, activated macrophages and Kupffer cells.[5] High serum IL-18 levels are also detected in TB patients.[6] Prior research supports that IL-18 may exert a crucial role against MTB infection in the host, as well as immunity to TB.[7]

The IL-18 gene, located on chromosome 11q22.2–q22.3, consists of six exons and five introns.[8] Numerous polymorphisms in the IL-18 gene promoter

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region have also been reported. In recent years, attention has been paid to such polymorphisms, especially the -137C/G(rs187238) and -607A/C(rs1946518) polymorphisms of the IL-18 gene promoter. It has been recognised that IL-18 polymorphisms of the IL-18 gene promoter are correlated with numerous disorders, including asthma,[9] type 1 diabetes[10] and viral diseases.[11]

Many studies have examined the relationship between IL-18 polymorphisms and susceptibility to TB. Nonetheless, no consistent conclusions have been reached, and single research may be of less capable of determining combined effects. Moreover, some research is restricted further due to the sample size, thereby being less powerful in examining potential effects. The current meta-analysis was therefore carried out by combining qualified studies to assess the genetic influences of IL-18 -137C/G and -607A/C polymorphisms on susceptibility to TB.

Materials and methods

Literature search and inclusion criteria

Electronic databases, including PubMed, EMBASE, Web of Science, Google Scholar and the Chinese National Knowledge Infrastructure (CNKI), were systemically searched from inception to 1 February 2019 in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses framework, with no restrictions of language, time period or sample size. The keywords 'interleukin 18/IL 18', '-137C/G', '-607A/C', 'tuberculosis' and 'polymorphism' were used in the searches. Furthermore, a manual search was carried out on the references listed in each retrieved item, so that no relevant papers were missed.

Criteria for inclusion and exclusion

The inclusion criteria of papers used in the current meta-analysis were: (a) relevant case-control study of TB cases and normal subjects, (b) articles investigating the relationships between IL-18 -137C/G and -607A/C polymorphisms and susceptibility to TB and (c) research containing sufficient genotype information. Exclusion criteria were: (a) non-case-control studies; (b) case reports, reviews or meta-analyses; and (c) studies with insufficient original data.

Information extraction

The following information was collected: the surname of the first author, the publication date, country, ethnicity, numbers of cases and controls, the genotype frequencies of IL-18 polymorphisms and deviation from the Hardy–Weinberg equilibrium (HWE) in the control group.

Statistical analysis

First, the HWE test was performed on all individual studies in the control group using the chi-square test. Subsequently, the relationships between IL-18 -137C/G and -607A/C polymorphisms and TB susceptibility were estimated by calculating the combined odds ratio (OR), as well as the related 95% confidence intervals (CIs). Meanwhile, potential heterogeneities among the enrolled studies were examined using the I^2 test. Typically, an I^2 of $> 50\%$ suggests the presence of heterogeneity in an enrolled study. So, the random-effects model was adopted in this meta-analysis. Furthermore, subgroup analysis stratified by HWE was also carried out. To assess result stability, a sensitivity test was also conducted by excluding one study at a time from the combined analysis in order to determine the impact of each study on the overall ORs. Finally, publication bias was assessed through funnel plot analysis. The meta package of R v3.33 (R Foundation for Statistical Computing, Vienna, Austria) was used in this meta-analysis.

Results

Characteristics of included studies

As shown in Figure 1, 508 studies were identified in which the relationships between IL-18 -137C/G and -607A/C polymorphism and TB susceptibility could be explored. Finally, six case-control studies satisfied the preset inclusion standards.[12–17] The characteristics of all the studies are shown in Tables 1 and 2.

Results of meta-analysis

For the IL-18 -137C/G polymorphism, a total of 970 patients and 1775 controls were identified. No association between -137C/G polymorphism and the susceptibility to TB was found (GG vs. AA: OR = 0.71, 95% CI 0.43–1.17; GA vs. AA: OR = 0.80, 95% CI 0.57–1.13; dominant model: OR = 0.78, 95% CI 0.56–1.08; recessive model: OR = 0.76, 95% CI 0.46–1.25; Table 3). For the IL-18 -607A/C polymorphism, a total of 813 patients and 990 controls were considered. The combined results indicated that the -607A/C polymorphism did not result in a higher TB risk (AA vs. CC: OR = 1.25, 95% CI 0.87–1.79; CA vs. CC: OR = 1.10, 95% CI 0.93–1.29; dominant model: OR = 1.13, 95% CI 0.90–1.41; recessive model: OR = 1.17, 95% CI 0.90–1.53; Table 4). Furthermore, a subgroup analysis was performed, and when the non-HWE studies were eliminated, the results did not change, indicating

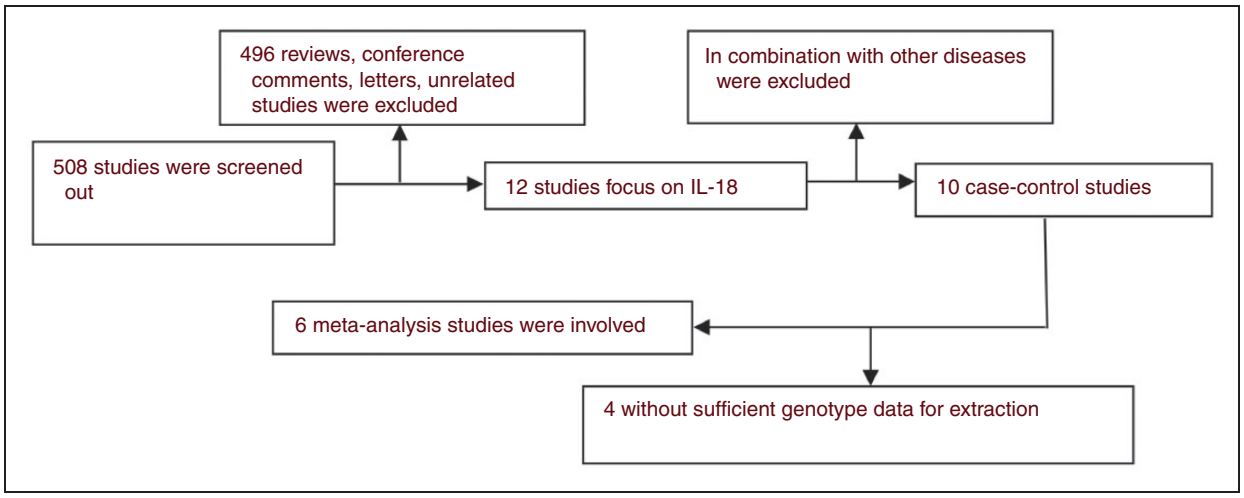

Figure 1. Flow diagram of included/excluded studies.

Table 1. Included studies of the IL-18 -137C/G polymorphism with tuberculosis.

					Polymorphism (cases/controls)			
First author	Yr	Country	Ethnicity	Cases/controls	GG	GC	CC	HWE test
Harishankar	2007	India	Asian	158/168	97/103	51/56	10/9	0.70
Liang	2009	China	Asian	200/197	154/135	37/51	9/11	0.04
Lee	2011	Korea	Asian	251/225	188/173	61/47	2/5	0.40
Zhou	2015	China	Asian	407/469	322/325	78/131	7/13	0.96

TB: tuberculosis; HWE: Hardy–Weinberg equilibrium.

Table 2. Included studies of the IL-18 -607A/C polymorphism with tuberculosis.

					Polymorphism (cases/controls)			
First author	Yr	Country	Ethnicity	Cases/controls	CC	CA	AA	HWE test
Harishankar	2007	India	Asian	165/173	75/85	71/73	19/15	0.90
Liang	2009	China	Asian	200/195	51/60	110/92	39/43	0.49
Han	2011	China	Asian	296/680	45/164	168/395	83/121	0.00
Lee	2011	Korea	Asian	240/225	62/54	113/116	65/55	0.64
Taheri	2012	Iran	Asian	174/177	74/68	80/90	20/19	0.18
Zhou	2015	China	Asian	407/469	109/124	217/247	81/98	0.22

HWE: Hardy–Weinberg equilibrium

Table 3. Summary ORs and 95% CI of the IL-18 -137C/G polymorphism with tuberculosis risk.

		GG vs. AA		GA vs. AA		Dominant model		Recessive model	
Variables	N[a]	OR (95% CI)	model	OR (95% CI)	model	OR (95% CI)	model	OR (95% CI)	model
Total	4	0.71 (0.43–1.17)	F	0.80 (0.57–1.13)	R	0.78 (0.56–1.08)	R	0.76 (0.46–1.25)	F
HWE									
Yes	3	0.71 (0.39–1.29)	F	0.87 (0.56–1.34)	R	0.85 (0.56–1.29)	R	0.75 (0.41–1.36)	F
No	1	0.72 (0.29–1.78)	/	0.64 (0.39–1.03)	/	0.59 (0.38–0.92)	/	0.80 (0.32–1.97)	/

[a]Number of comparisons.
OR: odds ratio; CI: confidence interval.

Table 4. Summary ORs and 95% CI of the IL-18 -607A/C polymorphism with tuberculosis risk.

		AA vs. CC		CA vs. CC		Dominant model		Recessive model	
Variables	N[a]	OR (95% CI)	model	OR (95% CI)	model	OR (95% CI)	model	OR (95% CI)	model
Total	6	1.25 (0.87–1.79)	R	1.10 (0.93-1.29)	F	1.13 (0.90–1.41)	R	1.17 (0.90–1.53)	R
HWE									
Yes	5	1.03 (0.81–1.31)	R	1.01 (0.84–1.21)	F	1.01 (0.85–1.21)	R	1.02 (0.83–1.25)	R
No	1	2.50 (1.62–3.85)	/	1.55 (1.06–2.26)	/	1.77 (1.23–2.55)	/	1.80 (1.31–2.48)	/

[a]Number of comparisons.

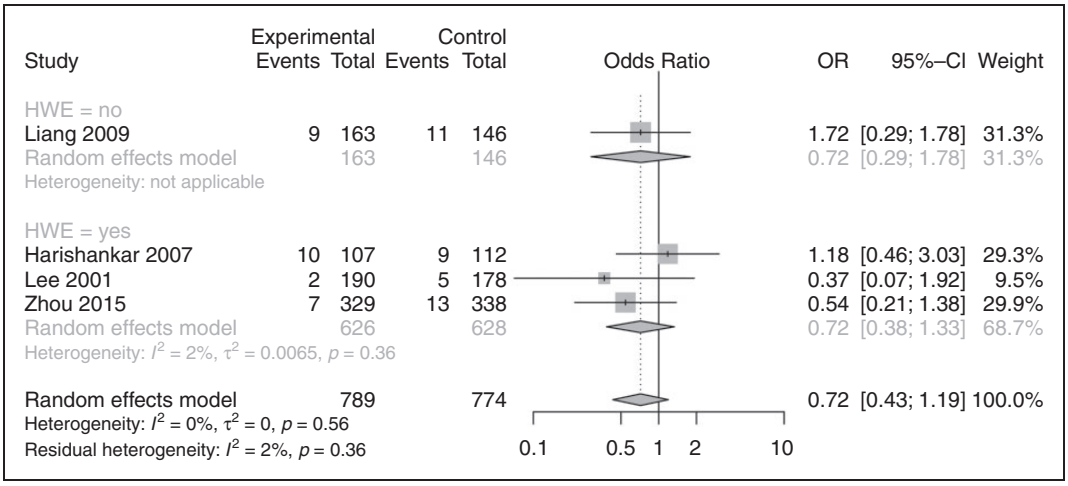

Figure 2. Forest plot for meta-analysis of the association between the IL-18 -137C/G polymorphism and tuberculosis (TB) risk under GG versus AA.

statistical significance of the meta-analysis results (Figures 2 and 3). A sensitivity analysis was performed by assessing the influence of each individual paper on the combined OR via deleting one study at a time (Figures 4 and 5). There was no single article that influenced the combined ORs, suggesting that the results are stable.

Publication bias

Potential publication bias among the enrolled studies was explored using Begg's test, and the results showed no potential publication bias (Figures 6 and 7).

Discussion

TB, one of the major infectious diseases, is still a leading public-health problem and a main cause of morbidity and mortality worldwide. Despite thorough investigation, the causes are not yet fully understood. Numerous existing studies have demonstrated that the IL-18 -137C/G and -607A/C polymorphisms are associated with TB. However, no consistent results have been obtained. Therefore, the current meta-analysis was performed to extract data from the related published or unpublished studies. Independent study results were synthesised using statistical methods by the identical research target, so as to acquire a combined quantitative conclusion. Typically, the current meta-analysis aimed to integrate similar studies to enlarge the sample size as well as the statistical power, thus obtaining more authentic results.

This meta-analysis aimed to detect an association of -137C/G and -607A/C polymorphisms of the IL-18 gene with the susceptibility to TB by including all qualifying data. To the best of our knowledge, the current meta-analysis is the first to investigate the relationships between IL-18 polymorphisms and TB. The results revealed that IL-18 -137C/G and -607A/C polymorphisms were not associated with susceptibility to TB. Probably, the non-HWE studies were associated with potential selection bias or genotyping errors, thereby leading to misleading findings. Furthermore, subgroup analysis was also be carried out to remove studies with a genotype distribution that deviated from HWE in the control group, and no altered results were detected,

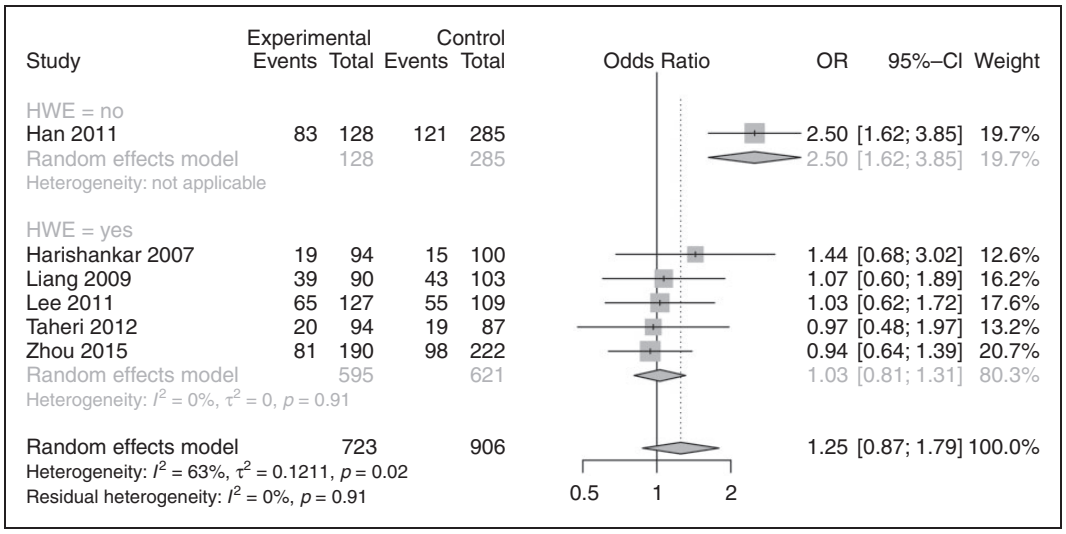

Figure 3. Forest plot for meta-analysis of the association between the IL-18 -607A/C polymorphism and TB risk under AA versus CC.

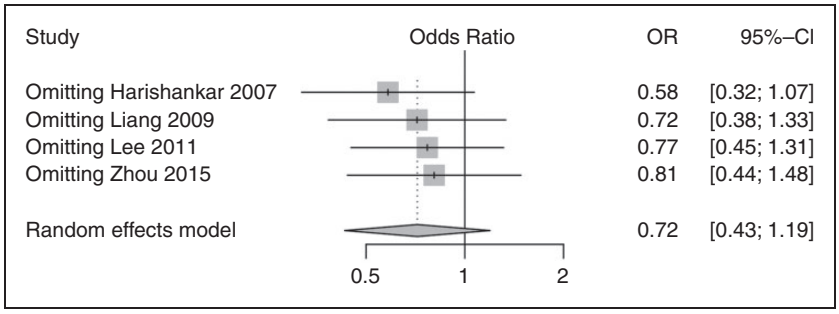

Figure 4. Subgroup analysis for meta-analysis of the association between the IL-18 -137C/G polymorphism and TB risk under GG versus AA.

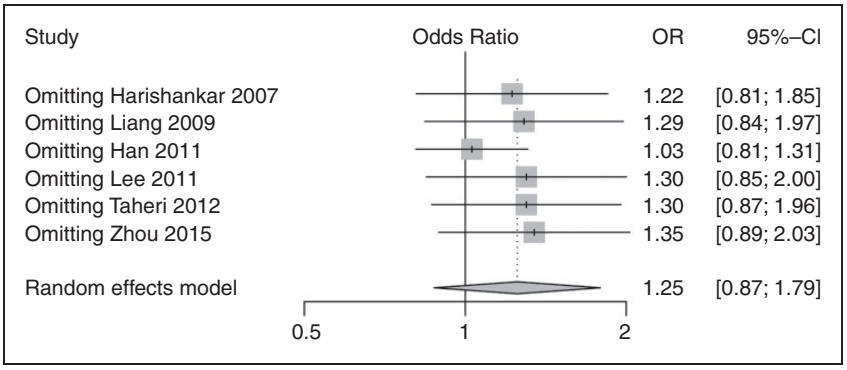

Figure 5. Subgroup analysis for meta-analysis of the association between the IL-18 -607A/C polymorphism and TB risk under AA versus CC.

indicating the result of the meta-analysis was statistically significant.

These findings suggest that the risk of TB may be not related to IL-18 -137C/G and -607A/C polymorphisms, or that so far, research has been insufficient to identify such an association. There are several potential explanations for the negative results. First, given that multiple genes are related to susceptibility

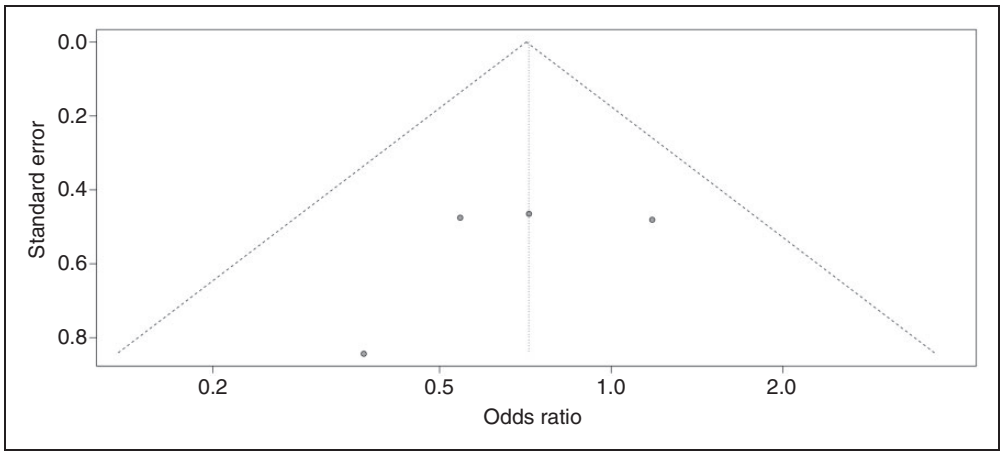

Figure 6. Begg's funnel plot analysis to detect potential publication bias for IL-18 -137C/G polymorphism under GG versus AA.

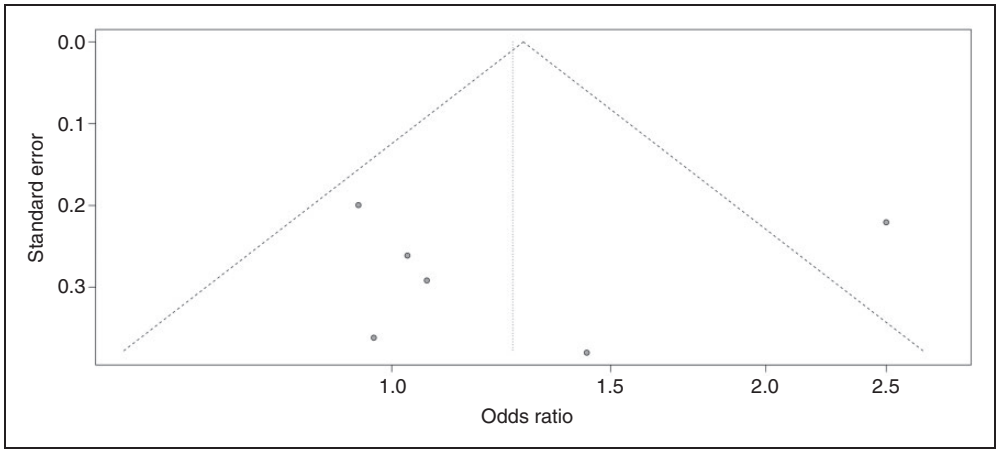

Figure 7. Begg's funnel plot analysis to detect potential publication bias for IL-18 -607A/C polymorphism under AA versus CC.

to TB, the focus should be on interactions between genes. Typically, the IL-18 -607A/C polymorphism was found may synergistically increase the risk of TB with rs5744247 and rs549908, and a previous study showed that these haplotypes (including -607A/C, rs5744247 and rs549908) in the IL-18 gene may synergistically increase the susceptibility to TB.[16] Second, the findings may also be related to the heterogeneity among the studies included in the current analysis. Heterogeneity can be derived from any variation in terms of genetic constitution and/or environmental trait among different populations, as well as the various sample selection criteria (such as age, sex and diagnostic criteria) and the varying study designs.[18] Third, the data from the studies included in the present meta-analysis were mainly from Asian subjects. Other ethnicities, including Caucasian, Africans and others, should be investigated in future studies. Finally, the effect of gene–environment interactions was not addressed due to a lack of relevant data.

Taken together, this meta-analysis indicates that the -137C/G and -607A/C polymorphisms of the IL-18 gene are not related to susceptibility to TB. Further studies are needed to clarify these findings and to address the limitations of the current research.

Declaration of conflicting interests

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