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Association between 1p13.3 genomic markers and coronary artery disease: a meta-analysis involving patients and controls

J. Guo[1,2], Y.X. Luo[1,2], L.X. Tao[1] and X.H. Guo[1,2]

[1]School of Public Health, Capital Medical University, Youanmen, Beijing, China
[2]Beijing Municipal Key Laboratory of Clinical Epidemiology, Youanmen, Beijing, China

Corresponding author: X.H. Guo
E-mail: guojin85827501@163.com

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ABSTRACT. Recently, genome-wide association studies on cardiovascular disease identified a series of associated single nucleotide polymorphisms in an intergenic region of chromosome 1p13.3. We investigated the association of this locus with cardiovascular disease in 13 case-control studies and undertook a meta-analysis for effect size, heterogeneity, publication bias, and strength of evidence. English and Chinese language articles were screened for the association of 1p13.3 single nucleotide polymorphisms with coronary heart/artery disease or myocardial infarction as primary outcomes. The included articles provided race, numbers of participants, and the data necessary to compute an odds ratio. Articles were excluded if other outcomes were reported or 1p13.3 single nucleotide polymorphisms were not included. Thirty-five articles were initially identified and 12 were eventually included in the meta-analysis. rs599839 and rs646776, representing the 1p13.3 locus, were genotyped in 13 case-control studies involving a total of 17,766 patients and 20,272 controls. For rs599839 (11 data sets), using a random-effect model, the summary odds ratio was 1.17 (95% con-

fidence interval = 1.07-1.28, P = 0.0001). For rs646776 (4 data sets), using a fixed-effects model, the summary odds ratio was 1.13 (95% confidence interval = 1.06-1.21, P = 0.0001). This broad replication provided unprecedented evidence for an association between genetic variants at chromosome 1p13.3 and the risk of cardiovascular disease.

Key words: 1p13.3; Coronary artery disease; Genetic variants; Meta-analysis

INTRODUCTION

Cardiovascular disease (CVD) is the main cause of death and disability-adjusted life years worldwide, with increasing incidence and prevalence in low- and middle-income countries (Teo et al., 2009). By 2020, over 80% of global CVD cases will be located in these countries, with the largest burden occurring in the two largest countries, China and India, as they rapidly urbanise (Teo et al., 2009). Non-modifiable risk factors include increasing age, male gender, and heredity. Modifiable risk factors include smoking, hypertension, dyslipidemia, obesity, physical inactivity, and diabetes (Hobbs, 2004; van Wyk et al., 2005; Palomaki et al., 2010). Recently, biomarkers (e.g., C-reactive protein) have been integrated with traditional risk factors to predict CVD events, and molecular markers hold further promise (Wang et al., 2006).

In 2007, genome-wide association studies (GWASs) identified a series of single nucleotide polymorphisms (SNPs) associated with CVD in an intergenic region of chromosome 9p21, near the *CDKN2A* and *CDKN2B* genes (Helgadottir et al., 2007; McPherson et al., 2007). The second most replicated region for risk of coronary artery disease (CAD) is located near 1p13.3. A variant within or near the 1p13.3 region is associated with lower risk of both CAD and myocardial infarction (MI) (Wellcome Trust Case Control Consortium, 2007; Samani et al., 2007; Myocardial Infarction Genetics (MIGen) Consortium et al., 2009; Aulchenko et al., 2009; Muendlein et al., 2009; Ellis et al., 2011) primarily through its association with low-density lipoprotein (LDL) and cholesterol serum levels (Kathiresan et al., 2008a,b; Samani et al., 2008; Sandhu et al., 2008; Willer et al., 2008; Karvanen et al., 2009); lower levels of LDL, LDL triglycerides, and ApoB; and an increased radius of LDL particles (Aulchenko et al., 2009; Linsel-Nitschke et al., 2010; Kleber et al., 2010). Two leading SNPs mapping at this locus, rs646776T/C and rs599839A/G, explain 1% of the genetic variation in circulating LDL cholesterol (LDL-C) levels and rare alleles are linked to reduced LDL-C levels (Willer et al., 2009).

In recent years, GWAS have provided a series of valuable data on the genetic susceptibility to CAD. Some regions are now used as predictive of incident CAD; however, whether these genetic risk regions influence disease progression in patients with CAD remains largely unknown. In fact, only a small proportion of the CAD population has been explained in Asia. For every traditional cohort or case-control study, the power to discover an association of statistical significance is low. To increase the power, we applied meta-analysis to pool data across all published and multiple unpublished articles for CAD and MI. In this study, we aimed to investigate the association between risk variants at 1p13.3 and CAD in different populations, and to describe in detail the structure and potential functioning of this region.

MATERIAL AND METHODS

Study populations

We systematically searched PubMed, Blackwell, Biosis Previews, Cochrane Library, China National Knowledge Infrastructure (CNKI), Chinese Biomedical (CBM), and Wan Fang database (China) for relevant articles published in different languages up to February 2014. We used the search term "1p13 and cardiovascular disease, coronary artery disease, acute myocardial infarction, myocardial infarction, structural heart disease or coronary atherosclerosis" in this study. Other eligible studies were identified by a series of references cited in published articles.

The inclusion criteria of this meta-analysis were as follows: a) inclusion of patients with a diagnosis that contained primary outcomes of coronary heart disease, MI, or CAD and without other related diseases; b) description of the association of SNPs in 1p13.3 polymorphisms with CAD risk; c) race and number of affected and unaffected participants reported; d) description of the genotyping method; and e) provision of genotype frequency and the odds ratio (OR) with confidence intervals (CIs) or data sufficient to compute it. If more than a single outcome was reported, the best-described phenotype was chosen. Several included articles reported consortium results with multiple independent populations. These populations were listed as separate data sets; all data were extracted independently by two reviewers according to the inclusion criteria. All the consistent datasets by reviewers were Samani et al., 2007; Huang et al., 2008; Muendlein et al., 2009; MIGen Consortium, 2009; Wang et al., 2011; Xie et al., 2011; Guo et al., 2011; Ellis et al., 2011; Gigante et al., 2012; Esparragón et al., 2012; Lee et al., 2013. Discrepancies were recorded and solved by discussion with a third reviewer. The information was extracted from all eligible studies: patients with a diagnosis of disease not related to CAD, and SNPs not in the 1p13.3 region.

Overall, we studied subjects collected in 13 different studies across Europe, Asia, and Oceania. The large majority of patients had CAD as defined by the MIGen study (N = 2967). The remaining patients had evidence of CAD based on either a revascularization procedure or anginal symptoms with a positive stress test. Details of each study are given in Table 1.

Not all researchers used the same 1p13.3 SNPs, and most articles reported results for multiple SNPs (uniquely identified by their rs number). As a proof-of-principle analysis, a number of SNPs in the 1p13.3 region with known association to CAD and MI were analyzed initially. Specifically, we examined two SNPs that were reported as lead SNPs in the first publications by the Wellcome Trust Case Control Consortium (2011) study (rs599839) and by Muendlein et al. (2009) (rs646776).

Genotyping

Different genotyping platforms were used across studies. An analysis restricted only to SNPs genotyped on all platforms would have been severely limited. For instance, the estimated overlap between the Affymetrix Genome Wide Human SNP Array 6.0 and the Illumina Human-1 mol/L chip is only about 250,000 SNPs. To allow for combined analyses across different platforms, missing SNPs were imputed for each study.

Statistical analysis

For each data set, the observed genotype frequencies in controls were compared with expected frequencies based on Hardy-Weinberg equilibrium (HWE, χ^2 test with two degrees of freedom). All P values were two-sided at the P = 0.05 level. After upload of summary data and centralized quality control, a meta-analysis across all studies was performed separately for each SNP. Depending on the heterogeneity between studies, fixed- or random-effect models were calculated, and outlying studies excluded. Summary ORs and corresponding 95%CIs were derived (by reanalysis when possible) and summarized using random-effect modeling weighted by the total variance of each data set (STATA). Subgroup differences were compared using the Q-test for heterogeneity for each covariate separately. Publication bias was examined by performing a cumulative effect analysis. Wider ranges of these summary ORs indicated the potential for publication bias.

RESULTS

Literature search and databases for meta-analysis

A total of 31 articles were identified in the initial search with the medical subject heading terms. After screening the abstracts or full contents, 19 articles were excluded (8 were not related to CAD, 9 were not about SNPs in 1p13, and 2 were republished studies). Finally, 12 studies (17,766 patients and 20,272 controls) were included in this meta-analysis. Of these, 2 studies were performed in Oceania (Ellis et al., 2011), 7 in Europe and America (Samani et al., 2007; Muendlein et al., 2009; MIGen Consortium et al., 2009; Wang et al., 2011; Gigante et al., 2012; Esparragón et al., 2012), and 4 in Asia (Huang et al., 2008; Xie et al., 2011; Guo et al., 2011; Lee et al., 2013) (Figure 1 and Table 1). All genotype frequencies of studies conformed to HWE in the control groups.

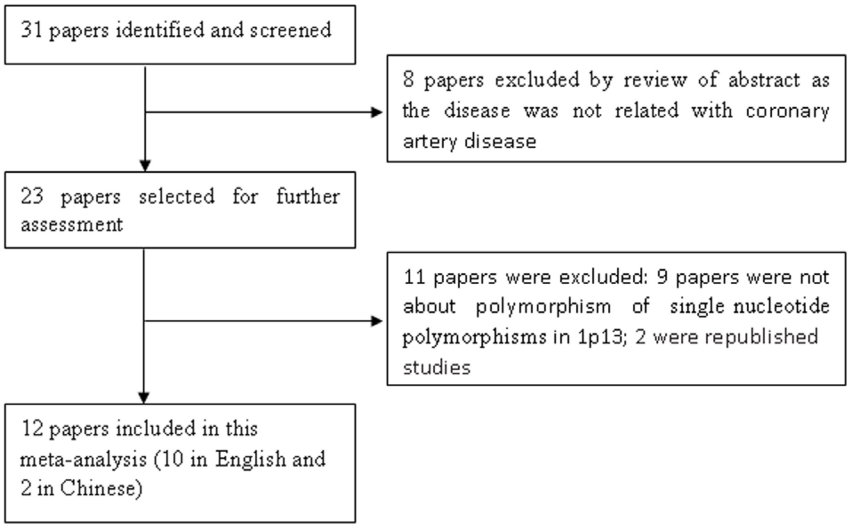

Figure 1. Paper identification and exclusion.

Table 1. Description of probands (cases/controls) in the studies included.

First author	Country	Study type	Case/controls	Male gender (Case/Controls, %)	Age (Case/Controls, years)	BMI (Case/Controls, kg/m^2)	Primary outcome	Case definition	Control definition
Ellis et al. (2011)	New Zealand	cohort study	1774/1633	66.3/70.8	62.8/66.5	26.5/27.7	Coronary disease	ECG changes, elevated levels of cardiac markers, a history of coronary disease, or ≥64 years of age in patients with diabetes mellitus or vascular disease	No personal history of overt CVD, including CAD, MI, or peripheral vascular disease
Ellis et al. (2011)	New Zealand	cohort study	858/1633	66.3/78.5	62.8/62.4	26.5/26.6	AMI	Patients who survived an AMI or were documented by coronary angiography to have at least a 70% stenosis in a major epicardial artery	No personal history of overt CVD, including CAD, MI, or peripheral vascular disease
Samani et al. (2007)	Germany	case-control study	875/1644	67.5/NA	58.1/NA	NA	MI	Patients who had MI before the age of 60 years and at least one first degree relative with premature CAD	No history of clinical CAD, stratified according to gender and age
Samani et al. (2007)	British	case-control study	1926/2938	79.3/NA	60.1/NA	NA	MI	Subjects had a history of either MI or coronary revascularization before the age of 66 years	No history of clinical CAD
Muendlein et al. (2009)	Caucasian	case-control study	934/676	77.2/52.4	65.1/62.7	27.2/27.9	CAD	Patients undergoing coronary angiography for the evaluation of suspected or established stable CAD at our institution	No history of clinical CAD
Wang et al. (2011)	USA	case-control study	1231/560	NA	NA	NA	MI	MI was diagnosed on the basis of chest pain of 30-min duration, electrocardiogram patterns consistent with patterns of AMI, and significant elevation of cardiac enzymes.	No history of clinical CAD
Gigante et al. (2012)	Swedish	case-control study	1152/1499	73.4/69.8	61.0/63.4	25.2/24.6	CAD	Cases represented 80% of hospitalized first, non-fatal MI patients	Subjects without an inquired history of CAD

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Table 1. Continued.

First author	Country	Study type	Case/Controls	Male gender (Case/Controls, %)	Age (Case/Controls, years)	BMI (Case/Controls, kg/m^2)	Primary outcome	Case definition	Control definition
Esparragón et al. (2012)	Canary/Spanish	case-control study	281/307	77.9/73.3	55.9/54.6	27.3/27.3	CAD	An individual with a diagnosis of MI or unstable angina pectoris, as well as evidence of CAD by coronary angiography	An individual who had not suffered CVD
MIGen Consortium et al. (2009)	USA, Sweden Finland, Spain, Italy	case-control study	2967/3075	NA	NA	NA	MI	Early-onset MI (in men ≤50 years old or women ≤60 years old)	Age- and gender-matched controls free of MI
Xie et al. (2011)	China	case-control study	2335/1078	66.9/50.8	65.4/60.4	24.5/24.6	Coronary atherosclerosis	Coronary atherosclerosis include: CAD and its main complication MI.	No history of clinical CAD
Huang et al. (2008)	China	case-control study	303/312	58.4/57.4	52.9/54.4	23.2/22.9	CAD	Coronary artery disease	No history of clinical CAD
Lee et al. (2013)	Korea	case-control study	2123/3591	NA	NA	NA	CAD	Atherosclerosis include: CAD	No history of clinical CAD
Guo et al. (2011)	China	case-control study	1148/1185	72.1/71.3	59.4/60.4	25.0/24.4	AMI	Patients admitted to hospital with first incident AMI were enrolled within 24 h of onset of symptoms	free from CAD

NA = not available; CAD = coronary artery disease; AMI = acute myocardial infarction; MI = myocardial infarction; CVD = cardiovascular disease.

Quantitative synthesis

The results of all the populations for our proof-of-principle analysis are shown in Figures 2 and 3. For rs599839 (11 data sets), heterogeneity was checked separately using the Q statistic (Q = 32.4; I^2 = 69.2%; P < 0.001). Therefore, a random-effect model was used, and the summary OR was 1.17 (95%CI = 1.07-1.28, P = 0.0001). For rs646776 (4 data sets), heterogeneity was checked separately using the Q statistic (Q = 7.4; I^2 = 59.5%; P = 0.060). For this analysis, a fixed-effect model was used; the summary OR was 1.13 (95%CI = 1.06-1.21, P = 0.0001).

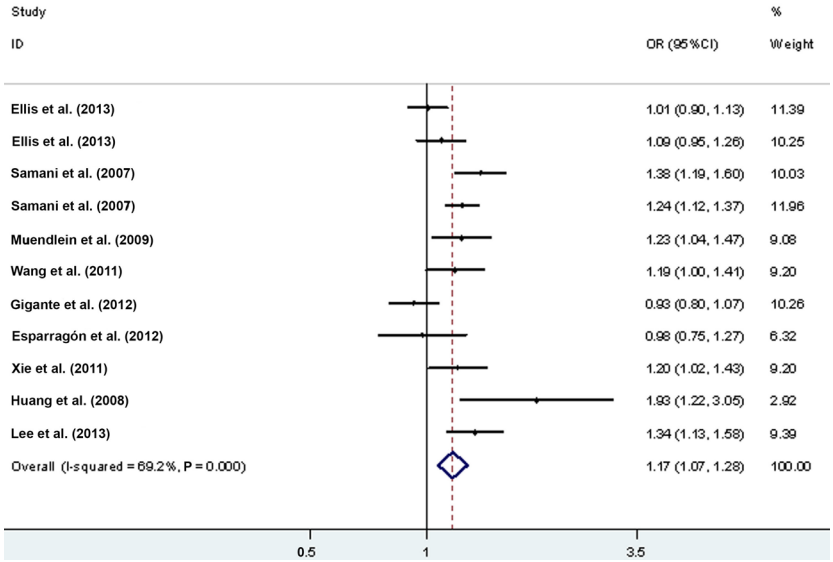

Figure 2. Forest plots for single nucleotide polymorphism rs599839 (risk allele = A); the random effect model was calculated. Heterogeneity between the studies is indicated by I^2. CI = confidence interval; OR = odds ratio.

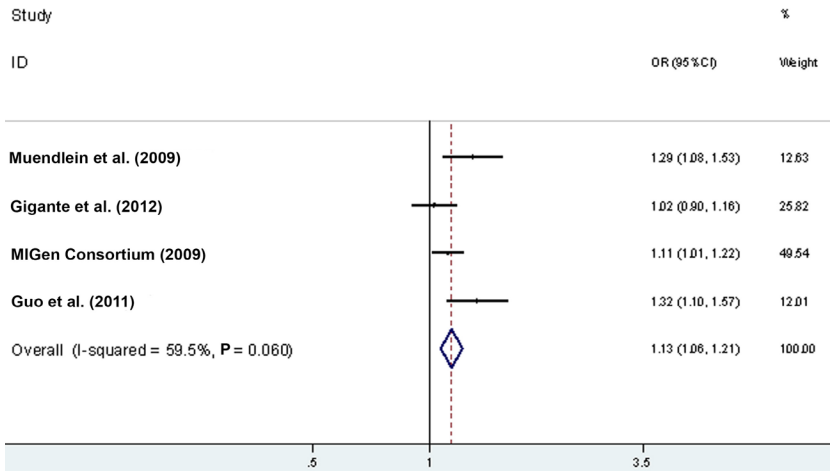

Figure 3. Forest plots for single nucleotide polymorphism rs646776 (risk allele = C); the fixed-effect model was calculated. Heterogeneity between the studies is indicated by I^2. CI = confidence interval; OR = odds ratio.

In subgroup analyses, the A allele of SNP rs599839 was also found to be significantly associated with CAD in European and Asian populations (Table 2). The ORs were significantly different between Asians (4 data sets) and other races (Europe, 7 data sets; Oceania, 2 data sets) (ORs of rs599839: 1.31, 1.16, and 1.04, respectively).

Table 2. Main results of rs599839 in the total and subgroup analysis.

Race	Total		Heterogeneity		Model	Bias in total	
	OR (95%CI)	P value	Q_x (P)	I^2		P value for Begg test	P value for Egger test
Total: A *vs* G	1.17 (1.07-1.28)	0.0001*	32.42 (0.001)	69.2%	RE	0.484	0.439
Europe: A *vs* G	1.16 (1.03-1.31)	0.0001*	10.30 (0.003)	72.3%	RE	0.573	0.550
Asia: A *vs* G	1.31 (1.17-1.47)	0.0001*	3.74 (0.154)	46.6%	FE	0.602	0.315
Oceania: A *vs* G	1.04 (0.95-1.14)	0.3900	0.77 (0.380)		FE	0.317	

FE = fixed-effect model; RE = random-effect model. *The pooled OR has a statistically significant.

Sensitivity analysis

We performed sensitivity analyses by excluding the studies that were not in HWE, and the pooled ORs were not materially altered using the recessive genetic model (data not shown), indicating that the model results were statistically robust. In the subgroup analyses, sensitivity analyses could not be performed because of the smaller sample size and lower power.

Publication bias

Begg's rank correlation and Egger's weighted regression methods were utilized to assess the publication bias in the recessive genetic model. The funnel plot is shown in Figure 4. No evidence for publication bias was found in our study.

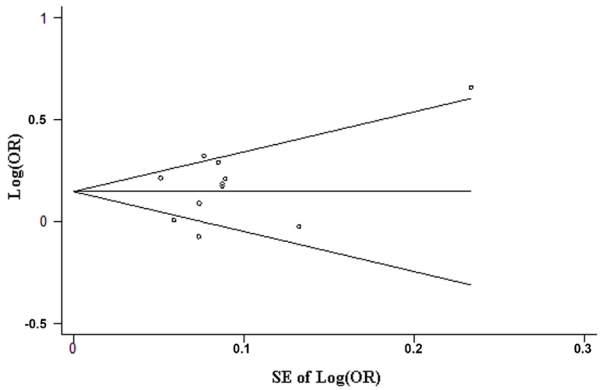

Figure 4. Funnel plot of rs599839. SE = standard error; OR = odds ratio.

DISCUSSION

The region with strongest association with CAD after 9p21 is the *CELSR2-PSRC1-SORT1* gene cluster. The risk allele at the *CELSR2-PSRC1-SORT1* cluster has a frequency of 81% in European subjects and an additive OR of 1.19 (MIGen Consortium et al., 2009). rs646776 and

rs599839 in the 1p13.3 region have been confirmed to exhibit correlation with CAD in a large-scale analysis (Samani et al., 2007; Carrasquillo et al., 2010). Based on previous studies, evidence for the association between heart disease and chromosome 1p13.3 SNP markers exhibits strong credibility. The 1p13.3 SNP markers have been identified through GWAS and appear independent of traditional risk factors or family history (Samani et al., 2007). Our study investigated the two associated SNPs rs599839 (11 studies, OR = 1.17) and rs646776 (4 studies, OR = 1.13).

The genomic region at 1p13.3 contains four genes: proline/serine-rich coiled protein 1 (*PSRC1*), cadherin EGF LAG seven pass G-type receptor 2 (*CELSR2*), myosin-binding protein H-like (*MYBHL*), and sortilin 1 (*SORT1*). Of these, *SORT1* has emerged as the most likely candidate causal gene. *SORT1* is a transmembrane protein receptor that binds a variety of ligands and is involved in the endocytosis and degradation of lipoprotein lipase, a rate-limiting enzyme for the hydrolysis of triglycerides in lipoproteins (Nielsen et al., 1999). One recent expression analysis conducted using 400 liver samples expanded the association between the GWAS risk allele and increased LDL-C concentrations to decreases in both *SORT1* and *CELSR2* expression levels (Schadt et al., 2008). Another transcriptome analysis conducted using 176 whole blood samples suggested that functional variants at this locus might reside within the *SORT1* gene since the risk allele was associated with decreased *SORT1* expression, increased plasma LDL-C concentration, and increased CAD risk (Linsel-Nitschke et al., 2010). Because of the important role of LDL in the development of CVD, it had been assumed that increased *SORT1* expression in carriers of the G allele led to greater LDL tissue uptake, which resulted in reduced circulating LDL levels and, subsequently, a lower CAD risk (Erdmann et al., 2010).

However, as most studies have indicated only a modest reduction in LDL-C in carriers of the homozygous GG genotype of SNP rs599839, it is possible that this allele does not entirely explain the significant reduction in the risk of CAD that has been observed for this SNP. In subsequent studies, we hope to further research the 1p13.3 region *SORT1* gene and its relationship with LDL on a larger scale, to identify the exact evidence. Meanwhile, additional analyses will be required to exclude causal roles for other genes (i.e., *CELSR2* and *PSRC1*) that map closer to the strongest associations across a neighboring recombination hotspot to *SORT1*. Recently, *SORT1* has been connected to the endocytosis of ApoA-V-containing chylomicrons (Nilsson et al., 2008). The main SNP near *SORT1* gene is associated with LDL-C and ApoB, and this association is most significant in the whole genome scan. Similarly, the sampled variation at the locus as a whole is second only to variation near the *APOE* locus for explaining the variance in the lipids due to genetics (Chasman et al., 2008). In our separate data study, ApoA and ApoB were introduced into the final calibration model as covariates, and SNP rs599839 remained statistically significant. The final analysis showed that 1p13 and ApoA had a statistically significant interaction and worth further exploration.

Few studies have examined the associations between SNPs on chromosome 1p13.3 and CVD risk in Asian populations. Our research found that SNP rs599839 showed a higher association with the CVD (OR = 1.31) in Asians. Such an association with lipid concentrations has been previously reported in a Japanese and Korean population (Xie et al., 2011). An even larger-scale case-control study in the Han Chinese population should be performed to evaluate the association of rs599839 and rs646776 with CAD susceptibility and serum lipid levels. Overall, our results suggest that the region of 1p13.3 plays a role in multiple complex diseases. Further studies should focus on the identification of the underlying mechanism at this locus for CVD. In addition, the interactions between gender, smoking, and excess weight and these SNPs need to be replicated in other populations.

This broad replication provided unprecedented evidence for association between genetic variants at chromosome 1p13.3 and the risk of CAD. The SNPs rs599839 and rs646776 might serve as novel genetic markers for CAD risk.

Conflicts of interest

The authors declare no conflict of interest.

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