

Association of APOA5 rs662799 Variation with Metabolic Syndrome among Adults from Diverse Geo-climatic Setup of West Bengal, India: A Cross-sectional Study

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Abstract

Background: Apolipoprotein A5 (APOA5) plays an important role in triglyceride-rich lipoprotein metabolism, and the rs662799 (–1131T>C) polymorphism has been associated with dyslipidemia and metabolic syndrome (MetS) in several populations. However, evidence regarding this association remains inconsistent across ethnic and environmental settings. This study investigated the association between APOA5 rs662799 variation and MetS among adults from diverse geo-climatic setup of West Bengal, India.

Methods: A community-based cross-sectional study was conducted among adults aged ≥ 21 years residing in five geo-climatic setup of West Bengal: Hill, Plateau, Plain, Delta, and Coastal. APOA5 rs662799 was genotyped by PCR followed by Sanger sequencing in a subset of 155 participants. Genotypes were recorded as GG, AG, and AA according to the reference-strand orientation. MetS was defined using modified NCEP-ATP III criteria. Genotype and allele frequencies, Hardy–Weinberg equilibrium, and associations between genotype and MetS were assessed using appropriate statistical methods.

Results: Among the 155 participants, AG was the most frequent genotype (45.16%), followed by GG (36.13%) and AA (18.71%). The overall G- and A-allele frequencies were 58.71% and 41.29%, respectively. Genotype distributions varied across geo-climatic settings but showed no significant departure from Hardy–Weinberg equilibrium. Overall, APOA5 rs662799 genotype was not significantly associated with MetS (OR=0.82, 95% CI: 0.42–1.58; logistic-regression $p=0.21$). A nominally significant association was observed in the Coastal subgroup ($p=0.03$); however, the corresponding confidence interval was wide (OR=0.44, 95% CI: 0.03–5.41), indicating substantial uncertainty.

Conclusion: In this study population, APOA5 rs662799 was not significantly associated with MetS at the overall population level. The observed variation across geo-climatic setup and the exploratory Coastal finding warrant further investigation in larger studies incorporating lipid traits, lifestyle factors, and potential gene–environment interactions.

Keywords: APOA5 rs662799, metabolic syndrome, genetic polymorphism, geo-climatic variation, India.

Introduction

Metabolic syndrome (MetS) is a complex, multifactorial condition characterized by the clustering of cardiometabolic abnormalities, including central obesity, elevated blood pressure, impaired glucose regulation, hypertriglyceridemia, and reduced high-density lipoprotein cholesterol (HDL-C). These abnormalities substantially increase the risk of type 2 diabetes mellitus and cardiovascular disease. Although lifestyle factors such as physical inactivity, obesity, and dietary changes contribute to MetS, increasing evidence indicates that genetic variation also influences lipid metabolism, insulin resistance, adiposity, and susceptibility to MetS. Thus, MetS is best understood as the result of interactions among genetic, metabolic, behavioural, and environmental factors. Among the metabolic abnormalities associated with MetS, disturbances in triglyceride (TG) metabolism are particularly important. Elevated circulating TG concentrations reflect abnormalities in triglyceride-rich lipoprotein metabolism and frequently occur together with reduced HDL-C and other features of atherogenic dyslipidemia. Plasma TG levels are regulated by several apolipoproteins, lipoprotein lipase (LPL), hepatic very-low-density lipoprotein (VLDL) production, and pathways involved in lipoprotein clearance. Genetic variation in these pathways can therefore influence lipid phenotype and metabolic disease susceptibility (Pennacchio et al., 2002; Guardiola & Ribalta, 2017).

Apolipoprotein A5 (APOA5), identified in 2001 near the APOA1/C3/A4 gene cluster on chromosome 11q23, has emerged as an important genetic regulator of TG metabolism. Experimental studies demonstrated a strong relationship between APOA5 expression and plasma TG concentrations: transgenic mice expressing human APOA5 showed markedly reduced TG levels, whereas disruption of the gene resulted in substantially increased concentrations. Human genetic studies similarly demonstrated associations between APOA5 variation and plasma TG levels (Pennacchio et al., 2001). APOA5 encodes apolipoprotein A-V (apoA-V), a low-abundance apolipoprotein synthesized predominantly in the liver. Despite its low plasma concentration, apoA-V substantially influences triglyceride-rich lipoprotein metabolism, including their hydrolysis and clearance through pathways involving lipoprotein lipase. APOA5 may also affect hepatic lipid handling, intracellular TG storage, and the production and metabolism of chylomicrons and VLDL particles (Forte et al., 2015; May-Zhang et al., 2022).

Human population studies have consistently demonstrated the importance of APOA5 variation in determining lipid phenotype. Several APOA5 haplotypes have been associated with increased plasma TG concentrations, and subsequent research has established APOA5 as one of the major genetic determinants of TG levels (Pennacchio et al., 2002). A review of APOA5 genetics further concluded that the gene has one of the strongest known effects on TG metabolism and that its variants may contribute to hypertriglyceridemia and an atherogenic lipoprotein profile, particularly in individuals with increased cardiometabolic risk (Guardiola & Ribalta, 2017). Among the common APOA5 variants, the -1131T>C polymorphism (rs662799) has been extensively studied. Located in the promoter region of APOA5, this variant has been associated particularly with increased plasma TG and reduced HDL-C. Since hypertriglyceridemia and low HDL-C are important components of MetS, rs662799 represents a candidate variant for investigating the genetic basis of the syndrome. Its biological relevance is further

supported by studies linking APOA5 variation with TG-rich lipoprotein metabolism (Song et al., 2013; Xu et al., 2013).

Population-based studies have demonstrated associations between rs662799 and lipid traits. In populations from Hong Kong and Guangzhou, individuals carrying the C allele had higher TG concentrations than TT homozygotes, with the association remaining after consideration of demographic and metabolic characteristics (Wang et al., 2011). Associations with MetS have also been reported in different ethnic populations. Xu et al. (2013), in a Chinese case-control study and meta-analysis involving 51,868 participants, found that carriers of the -1131C allele had higher TG, total cholesterol, and LDL-C and lower HDL-C than TT homozygotes. The C allele was also associated with increased odds of MetS, although the magnitude of association differed among ethnic groups. Similarly, in Korean subjects, the APOA5 -1131T>C polymorphism was associated with serum TG and HDL-C levels, and C-allele carriers had higher odds of MetS after adjustment for age and sex (Song et al., 2013). These findings suggest that the relationship between APOA5 and MetS may be mediated substantially through its effects on TG metabolism (Wang et al., 2011; Xu et al., 2013; Song et al., 2013).

However, the association between rs662799 and MetS has not been consistent across populations. Studies of dyslipidemic adults and obese Caucasian adults found no significant association between the variant and overall MetS prevalence, although the C allele was associated with higher TG concentrations and, in some cases, differences in HDL-C. Such findings suggest that APOA5 variation may have a more readily detectable effect on individual lipid traits, particularly TG, than on the heterogeneous composite phenotype of MetS. Differences in age, sex, ethnicity, dietary patterns, obesity, physical activity, socioeconomic conditions, and other environmental exposures may further modify genetic associations. Recent evidence supports continued investigation of APOA5 in relation to MetS. A systematic review and meta-analysis published in 2024, including more than 20 studies, reported an overall association between APOA5 rs662799 and MetS, with approximately 1.4-fold higher odds under the dominant genetic model. However, substantial heterogeneity was observed among studies, highlighting the potential influence of population characteristics and study conditions (Mozafari et al., 2024). Population-specific studies are therefore warranted, particularly in regions characterized by substantial geographical, dietary, and environmental diversity.

West Bengal, India, comprises diverse geo-climatic settings, including hill, plateau, plain, delta, and coastal regions, which differ in topography, climate, occupation, food availability, lifestyle, and healthcare access. These differences may influence metabolic risk and interact with underlying genetic susceptibility. Within this broader context, investigation of APOA5 rs662799 provides an opportunity to examine whether variation in a biologically relevant lipid-metabolism gene is associated with MetS across geographically distinct adult populations. The present study therefore investigates the association of APOA5 rs662799 with MetS among adults from different geo-climatic settings of West Bengal, India. Sanger sequencing was used to identify the rs662799 variant, and genotype and allele distributions were examined across the Hill, Plateau, Plain, Delta, and Coastal settings.

Materials and Methods

Study design and study setting

The present study was based on a community-based cross-sectional investigation conducted among adults residing in five geo-climatic settings of West Bengal, India: Hill, Plateau, Plain, Delta, and Coastal regions. The study was conducted between May 2023 and January 2025. The five geo-climatic

setup were treated as separate strata to account for geographical and environmental variation. The parent study used stratified random sampling, with individuals within each stratum selected using a simple random sampling approach.

Study participants and eligibility criteria

Adults aged 21 years or older were eligible for participation. To ensure adequate long-term exposure to the environmental, lifestyle, and socio-economic characteristics of the respective geo-climatic region, participants were required to have lived in one of the five study settings for at least 15 years. Individuals with major chronic conditions that could substantially influence metabolic characteristics or physical activity were excluded. Pregnant and lactating women were also excluded because of the potential influence of pregnancy- and lactation-related metabolic changes on the measured variables. The study included 1,285 adults. Genetic analysis of APOA5 was subsequently undertaken in a selected subset of 155 participants, comprising individuals from all five geo-climatic settings. Metabolic syndrome was assessed using the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria.

Blood collection and genomic DNA extraction

For genetic analysis, 3 mL of peripheral blood was collected from each selected participant using appropriate precautions. Genomic DNA was extracted using the phenol–chloroform method.

Selection of APOA5 rs662799 polymorphism

The genetic analysis focused on the APOA5 gene, particularly the rs662799 polymorphism, commonly designated as –1131T>C and located in the promoter region of APOA5. The APOA5 rs662799 variant is conventionally reported in the literature as the –1131T>C polymorphism; however, when represented on the opposite DNA strand, the same variant is denoted as G>A. Accordingly, in the present study, genotypes were recorded as GG, AG, and AA based on the strand orientation of the reference sequence used for Sanger sequence alignment and genotype calling; these correspond to the TT, TC, and CC genotypes, respectively, when reported using the conventional –1131T>C nomenclature. APOA5 is an important regulator of triglyceride metabolism, making variation within this gene relevant to studies of dyslipidemia and MetS. The APOA5 gene is located on chromosome 11q23.3. The study targeted the genomic region encompassing rs662799 for amplification and subsequent sequence-based genotype determination.

PCR amplification of the APOA5 region

Polymerase chain reaction (PCR) was used to amplify the APOA5 genomic region containing the rs662799 polymorphic site. PCR amplification was performed using genomic DNA as the template together with sequence-specific forward and reverse primers, deoxynucleotide triphosphates (dNTPs), reaction buffer, and Taq DNA polymerase. The PCR amplification consisted of the conventional stages of denaturation, primer annealing, and extension, with cycling conditions optimized to obtain a specific amplification product encompassing the rs662799 locus.

Primer design and target sequence

Primers were designed to amplify the genomic region surrounding the APOA5 rs662799 polymorphism. The primer sequences used in the study were:

Primer	Sequence (5'–3')	Length	GC content	Approximate T _m
Forward	CGGCAAGATGGACAGTGTTC	20 nt	55%	~62°C
Reverse	GTGGCAGCAGATGAGACTGG	20 nt	60%	~64°C

The primers were designed to provide sufficient flanking sequence around the polymorphic site. Primer specificity was assessed using BLAST against the human genome to ensure that the primers targeted the intended APOA5 genomic region.

Sanger sequencing of APOA5 rs662799

Following PCR amplification, the amplified APOA5 product was purified to remove residual primers, nucleotides, and other components that could interfere with the sequencing reaction. Purified PCR products were then subjected to Sanger sequencing using the chain-termination method. Sequencing reactions were performed using the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems). The method is based on the incorporation of fluorescently labelled dideoxynucleotides during DNA synthesis. Incorporation of a dideoxynucleotide terminates extension at the corresponding nucleotide position, generating a collection of DNA fragments that can subsequently be separated and detected according to their terminal fluorescent labels. Sequencing was performed in both the forward and reverse directions to improve confidence in the sequence determination. The resulting sequencing products were analyzed by capillary electrophoresis using an Applied Biosystems 3500 Genetic Analyzer.

Sequence analysis and genotype determination

The sequencing data were examined using Geneious Prime version 2023.2. The software was used for sequence quality assessment, base calling, sequence alignment, and identification of nucleotide variation within the amplified APOA5 region. The obtained sequences were aligned against the corresponding reference APOA5 genomic sequence. The nucleotide present at the rs662799 position was examined for each participant, and genotype assignment was made according to the sequence observed at the polymorphic site. The resulting genotypes were categorized into three groups: GG, AG, and AA. These genotype categories were subsequently used to determine genotype and allele frequencies and to investigate their relationship with MetS.

APOA5 genotype and allele frequency analysis

The distribution of APOA5 rs662799 genotypes was calculated for the complete genetic study population and separately for each geo-climatic setup. The three genotype groups (GG, AG, and AA) were expressed as frequencies and percentages. Allele frequencies were calculated from the observed genotype counts. The frequencies of the two alleles represented in the dataset were expressed as percentages for the overall sample and for each geo-climatic region. The genotype distribution was also examined for consistency with Hardy–Weinberg equilibrium (HWE). HWE was assessed separately within the geo-climatic groups and in the total genetic sample.

Statistical analysis of the association between APOA5 and MetS

Statistical analyses were performed using SPSS version 26. For the APOA5-specific analysis, genotype and allele distributions were summarized using frequencies and percentages. The association between APOA5 rs662799 genotype and MetS was examined for the overall population and separately within the five geo-climatic setup. All statistical tests were interpreted at a 95% confidence level, with $p < 0.05$ considered statistically significant.

Ethical considerations

The study received ethical approval from the Institutional Ethics Committee (IEC).

Results

Distribution of APOA5 rs662799 genotypes and alleles

A total of 155 participants were included in the APOA5 genetic analysis. The distribution of the three APOA5 rs662799 genotype groups, GG, AG, and AA was examined across the five geo-climatic settings. Overall, the AG genotype was the most frequently observed genotype, accounting for 70 participants (45.16%), followed by the GG genotype in 56 participants (36.13%) and the AA genotype in 29 participants (18.71%). At the allele level, the G allele accounted for 58.71% of the total alleles, whereas the A allele accounted for 41.29%. The genotype and allele distributions varied somewhat across the five geo-climatic settings. The Hill region had the highest proportion of the GG genotype (40%), whereas the Delta region had the highest proportion of the AG genotype (53.33%). The highest proportion of the AA genotype was observed in the Coastal region (22.58%), closely followed by the Plateau region (21.88%). The A allele frequency was highest in the Plateau region (45.31%), followed by the Coastal (43.55%) and Delta (43.33%) regions. The lowest A allele frequency was observed in the Hill region (36.67%).

Table 1: Genotypic and Allelic Distribution of APOA5 rs662799 Variant across Geo Climatic Setup

Geo-climatic setting	n	GG, n (%)	AG, n (%)	AA, n (%)	G allele (%)	A allele (%)
Hill	30	12 (40.00)	14 (46.67)	4 (13.33)	63.33	36.67
Plateau	32	10 (31.25)	15 (46.88)	7 (21.88)	54.69	45.31
Plain	32	14 (43.75)	12 (37.50)	6 (18.75)	62.50	37.50
Delta	30	9 (30.00)	16 (53.33)	5 (16.67)	56.67	43.33
Coastal	31	11 (35.48)	13 (41.94)	7 (22.58)	56.45	43.55
Total	155	56 (36.13)	70 (45.16)	29 (18.71)	58.71	41.29

The genotype distribution was also assessed for Hardy–Weinberg equilibrium. The HWE p-values were greater than 0.05 in all five geo-climatic setup, indicating no statistically significant departure from Hardy–Weinberg equilibrium in the reported dataset.

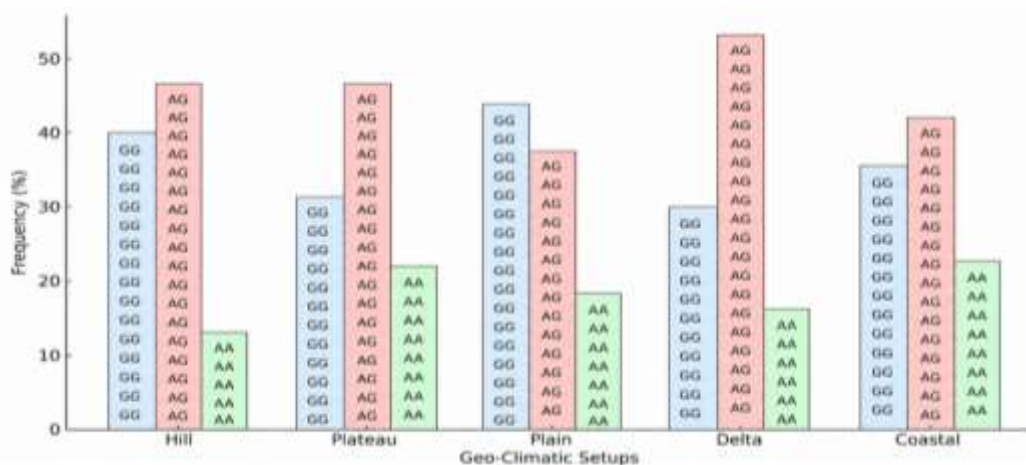


Fig.: Distribution of Genotype Frequencies (GG, AG, AA) across Geo-climatic Setup

Association between APOA5 rs662799 genotype and metabolic syndrome

The association between APOA5 rs662799 genotype and MetS was examined separately for each geo-climatic setup and for the total study population. The results are presented in Table 2. In the Hill region, the reported odds ratio was 6.00 (95% CI: 0.46–77.75), while the Kruskal–Wallis p-value was 0.51 and the logistic-regression p-value was 0.18. Although the point estimate of the odds ratio was relatively high, the confidence interval was very wide and included 1, indicating substantial statistical uncertainty. For the Plateau region, the odds ratio was 0.50 (95% CI: 0.07–3.55), with a Kruskal–Wallis p-value of 0.65 and a logistic-regression p-value of 0.45. In the Plain region, the corresponding odds ratio was 0.90 (95% CI: 0.12–6.77), with p-values of 0.82 for the Kruskal–Wallis test and 0.19 for logistic regression. In the Delta region, an odds ratio of 0.83 (95% CI: 0.09–7.67) was observed, while the Kruskal–Wallis and logistic-regression p-values were 0.82 and 0.38, respectively. In the Coastal region, the reported odds ratio was 0.44 (95% CI: 0.03–5.41). The Kruskal–Wallis p-value was 0.51, whereas the logistic-regression analysis produced a p-value of 0.03, which was statistically significant according to the predefined threshold of $p < 0.05$. For the overall study population, the odds ratio was 0.82 (95% CI: 0.42–1.58). The overall HWE p-value was 0.78, while the Kruskal–Wallis p-value was 0.63 and the logistic-regression p-value was 0.21. The overall chi-square statistic reported in the thesis was 3.92, with $p > 0.05$.

Table 2. Association of APOA5 rs662799 genotypes with metabolic syndrome across geo-climatic settings

Geo-climatic setting	n	OR	95% CI	HWE p-value	KW p-value	Logistic regression p-value	χ^2
Hill	30	6.00	0.46–77.75	0.99	0.51	0.18	3.92
Plateau	32	0.50	0.07–3.55	0.95	0.65	0.45	
Plain	32	0.90	0.12–6.77	0.52	0.82	0.19	
Delta	30	0.83	0.09–7.67	0.89	0.82	0.38	
Coastal	31	0.44	0.03–5.41	0.71	0.51	0.03*	
Total	155	0.82	0.42–1.58	0.78	0.63	0.21	

[* $p < 0.05$]

[OR = odds ratio; CI = confidence interval; HWE = Hardy–Weinberg equilibrium; KW = Kruskal–Wallis]

Overall, the APOA5 rs662799 genotype did not show a statistically significant association with MetS in the total study population based on the reported overall logistic-regression analysis ($p = 0.21$) and chi-square result ($p > 0.05$). The overall odds ratio of 0.82 had a 95% CI of 0.42–1.58, which included the null value of 1. The HWE analysis likewise showed no significant deviation from equilibrium. Among the individual geo-climatic setup, the Coastal group showed a statistically significant logistic-regression p-value ($p = 0.03$). However, the corresponding 95% CI for the reported odds ratio was wide (0.03–5.41) and included 1. The other four geo-climatic settings did not show statistically significant logistic-regression associations. Given the relatively small number of participants in each geo-climatic subgroup, the regional estimates, particularly those with wide confidence intervals, should be interpreted with caution. Thus, within the present dataset, the main finding was that APOA5 rs662799 genotype and

MetS were not significantly associated at the overall population level, although a nominally significant regression result was observed in the Coastal subgroup.

Discussion

The present study investigated the association between the APOA5 rs662799 polymorphism and metabolic syndrome (MetS) among adults from five geo-climatic setup of West Bengal, India. The study identified considerable variation in genotype and allele frequencies across the Hill, Plateau, Plain, Delta, and Coastal groups; however, no statistically significant association between rs662799 genotype and MetS was observed in the overall study population. The overall odds ratio was 0.82 (95% CI: 0.42–1.58), with a logistic-regression p-value of 0.21. These findings suggest that, within the present sample, rs662799 may not independently explain variation in MetS prevalence at the population level.

The observed genotype distribution showed that the AG genotype was the most common, followed by GG and AA, with an overall A-allele frequency of 41.29%. Although genotype and allele frequencies differed modestly between geo-climatic setup, all groups were reported to be in Hardy–Weinberg equilibrium. This supports the absence of an obvious deviation from the expected genotype distribution within the sampled populations. Nevertheless, differences in allele frequencies between geographical groups may reflect underlying population structure and warrant investigation in larger samples. The lack of a significant overall association between rs662799 and MetS is consistent with studies indicating that the effect of APOA5 variation may be more evident for individual lipid traits, particularly triglyceride concentrations, than for the composite MetS phenotype. APOA5 has a well-established role in triglyceride-rich lipoprotein metabolism, and the rs662799 variant has repeatedly been associated with variation in circulating TG levels. However, MetS encompasses several interacting components, including obesity, blood pressure, glucose metabolism, and lipid abnormalities. Therefore, an effect of APOA5 on triglyceride metabolism may not necessarily translate into a detectable association with the complete MetS phenotype.

The present findings also contrast with reports from some Asian populations in which the rs662799 C allele was associated with increased TG concentrations and higher odds of MetS. Such differences may arise from variation in genetic background, environmental exposures, dietary patterns, obesity prevalence, sample characteristics, and diagnostic criteria. Previous meta-analytic evidence has likewise suggested an association between rs662799 and MetS but has reported substantial heterogeneity among studies. Therefore, the absence of a significant association in the present West Bengal population does not necessarily contradict previous findings but emphasizes the population-specific nature of genetic associations. An interesting finding was the nominally significant logistic-regression result in the Coastal group ($p=0.03$).

However, this result should be interpreted cautiously. The Coastal subgroup consisted of only 31 participants, and the corresponding odds ratio of 0.44 had a very wide 95% confidence interval (0.03–5.41), which included the null value. The discrepancy between the p-value and confidence interval also indicates that this subgroup result requires verification of the underlying regression coding, reference genotype, and model specification before being interpreted as evidence of an association. Similarly, the Hill group produced a relatively large odds ratio (6.00), but its confidence interval was extremely wide (0.46–77.75) and the regression p-value was not statistically significant. This illustrates the substantial uncertainty associated with estimates derived from the small geo-climatic subgroups. Consequently, the regional results should be regarded as exploratory rather than definitive. The findings should also be

considered in light of several limitations. The genetic analysis included only 155 participants, resulting in limited statistical power, particularly after stratification into five geo-climatic groups. The small numbers of individuals in some genotype categories may have contributed to unstable odds-ratio estimates and wide confidence intervals. In addition, MetS is influenced by multiple genetic and environmental factors, and analysis of a single APOA5 variant cannot capture the full genetic architecture of the syndrome. Dietary intake, physical activity, adiposity, socioeconomic factors, and other lipid- and glucose-related genetic variants may also modify the relationship between APOA5 and MetS.

Conclusion

The present study found no significant association between APOA5 rs662799 genotype and metabolic syndrome in the overall study population from the different geo-climatic setup of West Bengal. Although a nominally significant association was observed in the Coastal subgroup, the small sample size and wide confidence interval warrant cautious interpretation. Overall, the findings suggest that rs662799 may not be an independent determinant of MetS in this population. Larger studies incorporating lipid profiles, lifestyle factors, and gene-environment interactions are required to further clarify the role of APOA5 variation in metabolic syndrome.

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