

CHRM3 rs2165870 Polymorphism Correlates with Postoperative Nausea and Vomiting Incidence and the Efficacy of Ondansetron in a Chinese Han Population

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Jiayu Wang^{1,2}

Yang Li³

Cuijuan Zheng²

Yan Sun¹

Jianping Yang¹

¹Department of Anesthesiology, The First Affiliated Hospital of Soochow University, Suzhou 215006, Jiangsu, People's Republic of China; ²Department of Anesthesiology, The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University, Huaian 223300, Jiangsu, People's Republic of China; ³Jiangsu College of Nursing, Huaian 223300, Jiangsu, People's Republic of China

Background: Previous GWAS studies have shown that there is a relationship between *M3 muscarinic acetylcholine receptor (CHRM3)* rs2165870 polymorphism and postoperative nausea and vomiting (PONV) incidence. However, no Chinese studies have addressed this issue.

Methods: To explore the relationship between *CHRM3* rs2165870 polymorphism and PONV incidence in a Chinese Han population, we enrolled 512 patients receiving elective surgery in this study. *CHRM3* rs2165870 polymorphism was genotyped using PCR-RFLP method.

Results: We found that AA genotype or A allele of *CHRM3* rs2165870 polymorphism elevated the risk of PONV (AA versus GG; OR, 2.88; 95% CI, 1.51–5.47; $P = 0.001$; A versus G; OR, 1.39; 95% CI, 1.07–1.81; $P = 0.013$). In addition, *CHRM3* rs2165870 polymorphism was related to the risk of PONV among the males, smokers, and those individuals with Apfel Score 3–4 or ASA classification 2–3. Last, we assessed the effects of *CHRM3* rs2165870 polymorphism on the treatment efficacy of ondansetron for PONV. Data uncovered that 103 of 209 patients (49.3%) showed response to ondansetron treatment for PONV. The PONV incidence was significantly higher in AA genotype carriers compared with GG genotype carriers during the first 2 h after surgery, but not from 2 to 24 h after surgery.

Conclusion: To sum up, this study reveals that *CHRM3* rs2165870 polymorphism is related to the incidence of PONV and treatment effects of ondansetron for preventing PONV in this Chinese Han population.

Keywords: postoperative nausea and vomiting, *CHRM3*, single nucleotide polymorphism, ondansetron

Introduction

Postoperative nausea and vomiting (PONV) are reported to be the most common complication after anesthesia.¹ The incidence of PONV is about 30% of overall surgical patients.² Unresolved PONV will lead to electrolyte imbalance, dehydration, pulmonary aspiration, wound dehiscence, and delayed hospital discharge.^{3,4} It may result in elongated recovery time, increased nursing care, and health care costs. Female gender, PONV or motion sickness history, non-smoking status, and post-operative opioids use are the well-established risk factors for PONV.⁵ However,

Correspondence: Jianping Yang
Email szyangjp@suda.edu.cn

individuals without exposure to these abovementioned factors may have PONV, indicating that other factors, including genetic factors, may contribute to PONV.⁶ Thus, identifying genetic markers for PONV is urgently needed.

Recently, a lot of studies have focused on the relationship between different gene polymorphisms and PONV occurrence. A recently reported systematic review and some original studies indicate that polymorphisms in genes including *hepatic cytochrome P450 (CYP2D6)*, *Opioid receptor mu 1 (OPRM1)*, *M3 muscarinic acetylcholine receptor (CHRM3)*, *5-hydroxytryptamine type 3 (5-HT)*, *DRD2*, *TACR1*, *FAAH*, *HTR3B*, and *ABCB1* were associated with PONV risk.^{6–19} Ondansetron is a 5-HT receptor antagonist, which is usually administered to prevent PONV. Ondansetron is mainly metabolized by CYP2D6 enzyme.⁷ Most of opioids exerted effects on the opioid mu-1 receptor, which is encoded by the *OPRM1* gene.⁷ *OPRM1* A118G polymorphism was a primary variant for the study of pharmacogenetics of opioid response. Kong et al performed a meta-analysis to explore the relationship between *OPRM1* gene A118G polymorphism and PONV, and found that this SNP reduced the risk of post-operative vomiting, but not pruritus, nausea, and dizziness.⁸ However, functional alleles of *CYP2D6* gene were associated with a higher occurrence of PONV.⁶ Rs2165870 polymorphism is located on promoter region of *CHRM3*. Recently, three studies investigated the association between *CHRM3* rs2165870 polymorphism and PONV risk, but with conflicting findings.^{10,11,20} A genome-wide association study (GWAS) explored the association between some loci of genes and PONV risk.²⁰ They only observed GG+AA genotype of *CHRM3* rs2165870 polymorphism was linked with PONV risk even after correcting for multiple testing.²⁰ Subsequent two studies suggested that AA or GA genotype of *CHRM3* rs2165870 polymorphism contributed to increased risk for PONV.^{10,11} To date, no studies from China have investigated the relationship between *CHRM3* rs2165870 polymorphism and PONV risk. Thus, we performed this study to evaluate the effects of *CHRM3* rs2165870 polymorphism on PONV occurrence among patients receiving elective surgery. In addition, we appraised the effects of *CHRM3* rs2165870 polymorphism on the treatment efficacy of ondansetron for preventing PONV.

Methods

Patients and Ethics Statement

This study protocol was approved by the institutional review board of Huaian No.1 People's Hospital. This

study was conducted in accordance with the Declaration of Helsinki. We used the Quanto (<http://hydra.usc.edu/gxe>) to determine the sample size before this study with the following conditions: $\alpha = 0.05$, $\beta = 0.1$, allele frequency = 0.3, power value = 0.9, and the estimated OR = 2.0; the sample sizes of case and control groups were 178 and 178, respectively. Eventually, a total of 512 patients (209 cases and 303 controls) receiving elective surgery (neurosurgery, throat and gynecological, or general surgery) with general anesthesia from the Huaian No.1 People's Hospital (ASA-physical status of 1 or 2 or 3) were recruited in this study. All participants provided written informed consent. PONV cases were patients who had nausea and vomiting from 0 to 24 h after elective surgery. Controls were patients without nausea and vomiting after elective surgery. Patients with neurological and psychiatric disorders, or a history of drug abuse were excluded. Control subjects receiving elective surgery did not have PONV. Clinical features and demographic data of these patients were collected before surgery.

Fentanyl, vecuronium bromide, midazolam, and etomidate were combined to induce the general anesthesia. All patients received a combination of inhalation and intravenous medication for maintenance of anesthesia (intravenous: propofol, 4mg/kg/hour; and inhalation: sevoflurane, 1–2 mac). The dosage of fentanyl and operation time was recorded for all patients. 0.1mg/h fentanyl was injected intravenously at 30 minutes before the end of the surgery.

In stage one, we investigated whether *CHRM3* rs2165870 polymorphism was associated the risk of PONV in a population of 512 patients. Of the 512 patients assessed to participate in this study, 209 were classified as PONV patients, 303 were classified as controls which have not incidence of PONV after elective surgery. In stage two, we explored whether the *CHRM3* rs2165870 polymorphism affect the efficacy of ondansetron (0.1 mg.kg⁻¹) to prevent PONV. Ondansetron (0.1 mg/kg) was intravenously administered at 30 minutes before the end of surgery. We noted any PONV from 0 h to 24 h after surgery. Any incidence of nausea that was recorded either in the 0–2 h or 2–24 h after the operation was presented as 'yes with' or 'no without' PONV as the responder outcome. If a patient experienced no episodes of nausea or vomiting after the administration of ondansetron, he or she was regarded as the responder to ondansetron. If a patient still experienced nausea or vomiting after the administration of ondansetron, he or she was the no-responders to ondansetron.

DNA Extraction and Genotyping

By utilizing the Puregene DNA purification kit (Gentra, Minneapolis, MN, USA), Genomic DNA extracted from 2mL of peripheral blood was obtained. The corresponding concentration and purity of the extracted DNA were measured by absorbance and running electrophoresis, respectively. The gene distribution of *CHRM3* rs2165870 polymorphism was evaluated by PCR-restriction fragment length polymorphism. The primers of the polymorphism in nucleotide extension reaction were 5'-TGCATCTGTTTACAGCCTTA-3' (forward) and 5'-TGCATCTGTTTACAGCCTTG-3' (reverse). Polymerase chain reaction (PCR) was carried out as follows: 5 min at 94 °C; 30 s at 94 °C, 35 cycles; extending for 10 min at 72 °C. The PCR products were first horizontally electrophorized on an ethidium bromide-dyed agarose gel (2% w/v) and then photographed. Ten percent of the samples were re-genotyped to ensure the genotyping accuracy, and the coincidence rate is 100%.

Statistical methods

All statistical analyses were addressed by SPSS 22.0 (SPSS Inc., Chicago, USA). All variables were calculated by Chi-square (χ^2) tests or Student's t-tests. HWE test among control group was assessed using a χ^2 test. To estimate the statistical power of our study design, we implemented a comprehensive power analysis using Genetic Power Calculator 33. The crude or adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were evaluated by use of logistic regression analysis. Stratified analyses by gender, age, alcohol, smoking, history of PONV, history of motion sickness, Apfel Score, and ASA classification were conducted. If a *P* value < 0.05, it was considered statistically significant.

Results

Study Population

Table 1 contains the demographic data and clinical features of the patients. No significant differences were observed about all characteristics of these patients among different genotype carriers, except for the history of PONV. GG genotype carriers showed higher incidence of history of PONV compared with other genotypes. Other characteristics of these patients are summarized in Table 1. In addition, data indicated that 209 of 512 patients (40.8%) had PONV (Supplemental Table 1). The percentage of PONV patients with each genotype were 39.2% (GG), 45.9% (GA), 14.9% (AA), respectively (see Table 2).

PONV Risk and *CHRM3* Rs2165870 Polymorphism

The distribution of alleles and genotypes of the *CHRM3* rs2165870 polymorphism are shown in Table 2 ($P_{HWE} = 0.107$). Obviously, 209 of 512 patients (40.8%) were classified as cases, 303 of 512 patients (59.2%) were classified as controls. Data showed that AA genotype was related to an elevated risk of PONV risk (AA versus GG; OR, 2.88; 95% CI, 1.51–5.47; *P* = 0.001). Even after adjusting the gender and age, this association was still significant (*P* < 0.05). In addition, A allele of *CHRM3* rs2165870 polymorphism increased the risk of PONV in the allelic model (A versus G; OR, 1.39; 95% CI, 1.07–1.81; *P* = 0.013).

Next, we investigated the association of demographic and clinical characteristics with genotypes of rs2165870 polymorphism (Table 3). Data revealed that *CHRM3* rs2165870 polymorphism correlated with the risk of PONV among the males, smokers, and those individuals with Apfel Score 3–4 or ASA classification 2–3. In addition, we explored the effects of the types of surgeries on PONV; overall, the types of surgeries had no significant effects on PONV (Supplemental Table 2).

Association of *CHRM3* Rs2165870 Polymorphism with the Treatment Efficacy of Ondansetron for PONV

Last, we evaluated the association of *CHRM3* rs2165870 polymorphism with the efficacy of ondansetron for PONV (Table 4). The incidence of PONV was recorded among different genotypes in *CHRM3* rs2165870 polymorphism. One hundred three of 209 patients (49.3%) showed a response to ondansetron treatment. The PONV incidence was higher in AA genotype carriers compared with GG genotype carriers during the first 2 h after surgery. We did not obtain significant differences regarding the incidence of PONV for different genotypes of rs2165870 polymorphism from 2 to 24 h after surgery.

Discussion

The incidence of PONV depended on anesthetic, surgical, risk factors for patients, and genetic factors. The pharmacogenomics of PONV are poorly understood. Actually, studies on the effects of genetic factors were limited up to date. In addition, the sample size of enrolled patients in these studies was not large, which resulted in low statistical power. Among investigated genes, *ABCB1*,^{19,21}

Table I Demographics and Risk Factors for Postoperative Nausea and Vomiting Stratified for *CHRM3* Rs2165870 Genotypes

Characteristics	All Genotypes	GG	GA	AA	P
Total number (%)	512	219 (42.77%)	244 (47.66%)	49 (9.57%)	
Age, year	51.50±11.14	51.70±11.85	51.43±10.88	50.92±9.13	0.900
Gender, male/female	229/283	102/117	105/139	22/27	0.746
Weight, kg	62.87±6.65	63.32±6.83	62.47±6.44	62.82±6.84	0.388
Height, cm	167.0±7.73	166.40±8.24	167.50±7.42	167.10±6.84	0.306
Smoker, n	188 (36.72%)	74 (33.79%)	91 (37.30%)	23 (46.94%)	0.218
History of PONV, n	62 (12.11%)	38 (17.35%)	24 (9.84%)	0	0.001
History of motion sickness, n	55 (10.74%)	26 (11.87%)	27 (11.07%)	2 (4.08%)	0.275
Apfel Score, n					0.937
0–1	104 (20.31%)	46 (21.00%)	46 (18.85%)	12 (24.90%)	
2	180 (35.16)	75 (34.25%)	90 (36.89%)	15 (30.61%)	
3	179 (34.96%)	75 (34.25%)	87 (36.66%)	17 (34.69%)	
4	49 (9.57%)	23 (10.50%)	21 (8.60%)	5 (10.20%)	
ASA classification, n					0.611
1	131 (25.59%)	62 (28.31%)	59 (24.18%)	10 (20.41%)	
2	337 (65.82%)	141 (64.38%)	163 (66.80%)	33 (67.35%)	
3	44 (8.59%)	16 (7.31%)	22 (9.02%)	6 (12.24%)	
Elective surgery, n					0.186
neurosurgery	131 (25.6%)	54 (24.7%)	66 (27.0%)	11 (22.4%)	
throat	122 (23.8%)	63 (28.8%)	46 (18.9%)	13 (26.5%)	
gynecological	134 (26.2%)	47 (21.5%)	73 (29.9%)	14 (28.6%)	
general surgery	125 (24.4%)	55 (25.1%)	59 (24.2%)	11 (22.4%)	
Duration of operation, min	189.67±29.49	188.55±29.97	189.82±29.08	193.90±29.55	0.515
Duration of analgesia, min	236.12±34.27	235.36±33.18	235.39±34.47	243.16±37.86	0.319
Intraoperative fentanyl, ug	610.76±83.17	610.05±83.32	614.79±83.40	593.90±85.36	0.273

Note: Bold values are statistically significant ($P < 0.05$)

Abbreviations: PONV, postoperative nausea and vomiting; ASA, American Society of Anesthesiologists; cm, centimeter; kg, kilogram; mg, microgram; min, minute.

CYP2D6,^{22–24} and *OPRM1* gene were most explored genes before.^{25–27}

As for *CHRM3* gene, only three studies addressed the relationship between *CHRM3* rs2165870 polymorphism and PONV risk. Up to now, Janicki et al conducted the GWAS study, whose aims were to obtain genetic risk loci related with PONV risk.²⁰ They revealed the GG+AA genotype of *CHRM3* rs2165870 polymorphism was the only locus observed in a GWAS related with PONV risk in two independent studies.²⁰ It is of note that this GWAS only enrolled 122 surgery patients with severe PONV and 129 matched controls, which may yield false positive results. Due to the GWAS findings, Klenke et al conducted a prospective, controlled study with 454 individuals undergoing elective surgery to validate previous findings.¹¹ In addition, they found *CHRM3* rs2165870 polymorphism could predict PONV susceptibility.¹¹ They revealed that AA or GA genotype carriers showed increased risk for

PONV compared with GG genotypes. Subsequently, Klenke et al also retrospectively performed a study with 472 patients receiving elective surgery, and showed *CHRM3* rs2165870, and *KCNB2* rs349358 polymorphism increased the risk of PONV,²⁸ and they also found that AA or GA genotype of *CHRM3* rs2165870 polymorphism contributed to PONV risk. In this study, we observed that AA genotype or A allele of *CHRM3* rs2165870 polymorphism increased the risk of PONV in Chinese Han population. However, we did not observe an association between GA or GG+AA genotypes and PONV risk, which was inconsistent with abovementioned studies. Potential factors may account for these conflicting findings of these studies: 1) genetic heterogeneity in different disorders was differential; 2) clinical heterogeneity of these disorders was diverse; 3) the sample sizes were significantly different. Limited sample sizes in GWAS and the study by Klenke et al may produce the over-estimation of

Table 2 Postoperative Nausea and Vomiting (PONV) (2–6h) Occurrence to *CHRM3* Rs2165870 Genotype of Study Patients

Models	Genotype	Case ^a (n = 209)	Control ^b (n = 303)	OR (95% CI)	P-value	*OR (95% CI)	*P-value
		(n, %)	(n, %)				
rs2165870							
Co-dominant	GG	82 (39.2%)	137 (45.2%)	1.00 (reference)	-	1.00(reference)	-
Heterozygote	GA	96 (45.9%)	148 (48.8%)	0.92 (0.63–1.34)	0.675	0.83(0.51–1.19)	0.586
Homozygote	AA	31 (14.9%)	18 (5.9%)	2.88 (1.51–5.47)	0.001	2.79(1.46–5.61)	0.002
Dominant	GG	82 (39.2%)	137 (45.2%)	1.00 (reference)	-	1.00(reference)	-
	GA+AA	127 (60.8%)	166 (54.8%)	0.78 (0.55–1.12)	0.179	0.69(0.53–1.05)	0.158
Recessive	GG+GA	178 (85.1%)	285 (94.1%)	1.00 (reference)	-	1.00(reference)	-
	AA	31 (14.9%)	18 (5.9%)	2.76 (1.50–5.08)	0.001	2.66(1.43–5.01)	0.001
Allele	G	260 (62.2%)	422 (59.6%)	1.00 (reference)	-	1.00(reference)	-
	A	158 (37.8%)	184 (30.4%)	1.39 (1.07–1.81)	0.013		

Notes: Bold values are statistically significant ($P < 0.05$). ^aCases were PONV patients who had nausea and vomiting after elective surgery; ^bControls were patients without nausea and vomiting after elective surgery; *Adjustment for age, sex, smoking status, PONV risk, and motion sickness.

effect size; and 4) differences in inclusion criteria of patients should be considered. Subgroup analysis obtained that *CHRM3* rs2165870 polymorphism was related to increased risk of PONV in the groups of males, smokers, patients with higher Apfel Score and ASA classification.

Although some risk factors, surgical treatment, and perioperative drugs determine the patient's risk for PONV, identifying the patient's genetic genotypes was useful for selecting appropriate medications to prevent PONV during the perioperation. In this study, we found

Table 3 Stratified Analyses Between *CHRM3* Rs2165870 Polymorphism and the Risk of PONV

Characteristics	Genotype Distributions			
<i>CHRM3</i> rs2165870, n	GG (n = 82)	GA (n = 96)	AA (n = 31)	GA+AA (n = 127)
Age				
≥60/<60	27/55	20/76	7/24	27/100
OR (95% CI); P-value	1.00 (reference)	0.54 (0.27–1.05); 0.068	0.59 (0.23–1.55); 0.285	0.55 (0.29–1.03); 0.060
Gender				
male/female	32/50	58/38	12/19	70/57
OR (95% CI); P-value	1.00 (reference)	2.39 (1.30–4.36); 0.004	0.99 (0.42–2.30); 0.976	1.92 (1.09–3.38); 0.023
Smoking				
Yes/No	28/54	31/65	17/14	48/79
OR (95% CI); P-value	1.00 (reference)	0.92 (0.49–1.72); 0.793	2.34 (1.00–5.44); 0.045	1.17 (0.66–2.09); 0.592
History of PONV				
Yes/No	11/71	11/85	0/31	11/116
OR (95% CI); P-value	1.00 (reference)	0.84 (0.34–2.04); 0.693	1.16 (1.06–1.26); 0.033	0.61 (0.25–1.49); 0.274
History of motion sickness				
Yes/No	13/69	16/80	1/30	11/137
OR (95% CI); P-value	1.00 (reference)	1.06 (0.48–2.36); 0.884	0.18 (0.02–1.41); 0.107	0.43 (0.18–1.00); 0.069
Apfel Score				
3–4/02	25/57	52/44	14/17	66/61
OR (95% CI); P-value	1.00 (reference)	2.70 (1.45–5.00); 0.001	1.88 (0.80–4.39); 0.143	2.47 (1.37–4.43); 0.002
ASA classification				
2–3/1	54/28	82/14	26/5	103/24
OR (95% CI); P-value	1.00 (reference)	3.04 (1.47–6.29); 0.002	2.70 (0.93–7.79); 0.060	2.23 (1.18–4.21); 0.013

Note: Bold values are statistically significant ($P < 0.05$).

Table 4 Effects of *CHRM3* Rs2165870 on the Efficacy of Ondansetron for Postoperative Nausea and Vomiting

Models	Genotype	Responder (n, %)	Non-Responder (n, %)	OR (95% CI)	P-value
First 2h		n = 103	n = 106		
Co-dominant	GG	38 (36.9%)	44 (41.5%)	1.00 (reference)	
Heterozygote	GA	42 (40.8%)	54 (50.9%)	0.90 (0.50–1.63);	0.729
Homozygote	AA	23 (22.3%)	8 (7.6%)	3.33 (1.33–8.30);	0.008
Dominant	GG	38 (36.9%)	44 (41.5%)	1.00 (reference)	
	GA+AA	65 (53.1%)	62 (58.5%)	1.21 (0.70–2.12);	0.494
Allele	G	118 (57.3%)	142 (67.0%)	1.00 (reference)	
	A	88 (42.7%)	70 (33.0%)	1.41 (1.02–2.25)	0.041
2–24h		n = 185	n = 24		
Co-dominant	GG	70 (37.8%)	12 (50.0%)	1.00 (reference)	
Heterozygote	GA	86 (46.5%)	10 (41.7%)	1.47 (0.60–3.61);	0.394
Homozygote	AA	29 (15.7%)	2 (8.3%)	2.49 (0.52–11.81);	0.391
Dominant	GG	70 (37.8%)	12 (50.0%)	1.00 (reference)	
	GA+AA	105 (62.2%)	12 (50.0%)	1.50 (0.64–3.53);	0.351
Allele	G	226 (61.1%)	34 (70.8%)	1.00 (reference)	
	A	144 (38.9%)	14 (29.2%)	1.55 (0.81–2.98)	0.190

Note: Bold values are statistically significant ($P < 0.05$).

that AA genotype or A allele carriers showed high incidence of PONV in patients with elective surgery, which promoted clinicians to use some medications for these patients to restrain the occurrence of PONV. Therefore, we utilized ondansetron to prevent PONV. Our data observed that AA genotype or A allele carriers showed response to ondansetron treatment during the first 2 h after surgery. However, the incidence of PONV between different genotype carriers showed no significant differences regarding the treatment of ondansetron from 2 to 24 h after surgery. Thus, *CHRM3* rs2165870 polymorphism may be an important marker for predicting the responsiveness for ondansetron treatment for PONV patients.

As for clinical practice, we found that AA genotype or A allele of *CHRM3* rs2165870 polymorphism elevated the risk of PONV risk in this study, suggesting that surgery patients carrying AA genotype or A allele should be taken care of PONV issue for clinicians. Thus, gene detection for surgery patients before anesthesia may be necessary in the future. In addition, the PONV incidence was significantly higher in AA genotype carriers compared with GG genotype carriers during the first 2 h after surgery, but not from 2 to 24 h after surgery, indicating that AA genotype carriers in PONV was associated with lower response to ondansetron. Maybe clinicians should use other drugs to restrain the occurrence of PONV patients carrying AA genotype.

This study had several limitations. First, the sample size was not large enough in this study, which may yield false positive results. Further studies with larger sample size are urgently needed. Second, this study only investigated *CHRM3* rs2165870 polymorphism whether other genetic variants of *CHRM3* gene contributed to the genetic PONV risk. Whether *CHRM3* rs2165870 polymorphism was in linkage disequilibrium with other SNPs should be also explored. Third, because a hospital-based case-control design, selection bias was unavoidable. Fourth, the potential mechanisms of *CHRM3* rs2165870 polymorphism affecting the incidence of PONV should be investigated. Further cell and animal experiments should be performed to explore the underlying mechanisms. Fifth, Ondansetron is mainly metabolized by CYP2D6 enzyme; however, we did not assess the impact of *CYP2D6* gene variations on ondansetron treatment for PONV patients in the Chinese population. Finally, further studies in other populations are needed to verify our findings.

In conclusion, this study indicates that *CHRM3* rs2165870 polymorphism correlates with the incidence of PONV and the treatment effects of ondansetron for preventing the occurrence of PONV in this Chinese Han population.

Data Sharing Statement

The data are available on reasonable request to the correspondence author.

Disclosure

The authors report no funding and no conflicts of interest for this work.

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