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ORIGINAL RESEARCH

GABRA1 and *GABRB2* Polymorphisms are Associated with Propofol Susceptibility

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Purpose: To explore the effect of gene polymorphisms of propofol $GABA_A$ receptor and metabolic enzyme on drug susceptibility during the induction period of general anesthesia.

Patients and Methods: A total of 294 female patients aged 18–55 years, ASA I–II, who underwent hysteroscopy with intravenous general anesthesia, were included in the study. Anesthesia was induced by continuous intravenous infusion of propofol at 40 $mg \cdot kg^{-1} \cdot h^{-1}$. Infusion of propofol was ended when both the Modified Observer's Assessment of Awareness/Sedation scale (MOAA/S scale) decreased to 1 and the BIS index decreased to 60. The time when the MOAA/S scale decreased to 1 and the time when BIS index decreased to 60 was recorded to assess the susceptibility to the sedation effect. The maximum decreased percentage in mean arterial pressure (MAP) within 5 minutes was recorded to assess the susceptibility of cardiovascular response. Venous blood of each patient was collected to identify the presence of genetic variants in the *GABRA1, GABRA2, GABRB2, GABRB3, GABRG2, CYP2B6*, and *UGT1A9* genes using the Sequenom MassARRAY® platform.

Results: After receiving propofol infusion, carriers of polymorphic *GABRA1* rs4263535 G allele required significantly less time for BIS decreased to 60, while carriers of polymorphic *GABRB2* rs3816596 T allele required significantly more time for BIS decreased to 60, carriers of polymorphic *GABRA1* rs1157122 C allele and carriers of polymorphic *GABRB2* rs76774144 T allele had a significantly less change in MAP.

Conclusion: *GABRB2* rs3816596 and *GABRA1* rs4263535 polymorphisms are associated with susceptibility to the sedation effect of propofol. *GABRA1* rs1157122 and *GABRB2* rs76774144 polymorphisms are associated with the degree of drop in blood pressure after propofol infusion.

Keywords: pharmacogenomics, drug susceptibility, $GABA_A$ receptor, *CYP2B6*, *UGT1A9*

Introduction

Propofol is an intravenous anesthetic that is frequently used for induction of general anesthesia, maintenance of general anesthesia, sedation in the intensive care unit (ICU), and various painless treatments due to its advantages of rapid onset, rapid awakening, and low incidence of postoperative nausea and vomiting.[1]

Despite the numerous advantages, propofol can still carry some side effects. Frequent adverse reactions are pain on injection, hypotension, and respiratory depression.[2] In addition, the drug effect of propofol varies with different individuals, even when administered by the same standard.[3] Deep anesthesia will excessively suppress the stress response, leading to severe hypotension and even disrupting the perfusion of vital organs, while inadequate depth of anesthesia will lead to an increased incidence of intraoperative awareness. Therefore, it is important to individualize the medication and give patients the most proper dose to maintain an appropriate depth of anesthesia.

Propofol is mainly metabolized in the liver.[4] Seventy percent of propofol bound to uridine diphosphate glucuronosyltransferase 1A9 (UGT1A9) and transform into propofol glucuronide, 29% of propofol is transformed into propofol-4-hydroxypropophol by CYP2B6 and CYP2C9, in which CYP2B6 plays a primary role and CYP2C9 a secondary role.[5]

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Propofol exerts its sedation effect mainly through activating the $GABA_A$ receptor (GABAAR), thereby enhancing the interaction between $GABA_A$ and GABAAR.[6]

Pharmacogenomics focuses on the relationship between genetic factors and drug response variability.[7] Single nucleotide polymorphism (SNP) refers to a DNA sequence polymorphism caused by a single nucleotide variation that has a prevalence of more than 1% in the population.[8] Pharmacogenomics studies often concern the SNPs related to the pharmacodynamic and pharmacokinetic of certain drugs.

Identifying SNPs associated with drug response can help reduce adverse drug reactions, particularly important in patients with poor general conditions.[9] For instance, genotype-guided treatment can optimize the dosage of antithrombotic drugs and thus reduce the risk of bleeding complications.[10] However, the application of pharmacogenomics in anesthetics is currently limited.[11] Therefore, exploring potential SNPs associated with propofol susceptibility is necessary to achieve precision and personalized medicine during the perioperative period.

This study aims to explore the association between gene polymorphisms (*CYP2B6, UGT1A9, GABRA1, GABRA2, GABRB2, GABRB3*, and *GABRG2*) and propofol susceptibility.

Materials and Methods

Study Participants

From October 2020 to January 2021, 294 Chinese Han female patients who underwent hysteroscopy under general anesthesia were recruited. Every patient met the following criteria: 1) ASA I–II; 2) age 18–55 years; 3) body mass index (BMI) 18–28 kg/m^2. Patients were excluded if they met one of these exclusion criteria: 1) abnormal liver and kidney function; 2) severe cardiopulmonary disease or hemodynamic instability; 3) pregnant; 4) mental disease; 5) allergy to propofol; 6) history of drug abuse. Our study was registered with the Chinese Clinical Trial Registry under registration number ChiCTR2000039432 (https://www.chictr.org.cn/index.aspx). The study was approved by the ethics committee of The Third Xiangya Hospital of Central South University (registration number: Fast I 20032). Written informed consent was signed by each patient. This study was conducted in accordance with the Declaration of Helsinki.

Treatments

Patients did not receive pre-operative medication. Non-invasive blood pressure (NIBP), electrocardiogram (ECG), pulse oxygen saturation (SPO_2), and BIS index were routinely monitored. Propofol was administered 40 $mg \cdot kg^{-1} \cdot h^{-1}$ through the infusion pump. This pumping method provides adequate discrimination of individual dose requirements of propofol and possibly enables propofol to mix entirely in the central pharmacokinetic compartment.[12] Infusion of propofol was ended when both MOAA/S scale decreased to 1 and BIS index decreased to 60. Blood pressure was monitored every minute for 5 minutes. The observation was ended after 5 minutes, and surgical operations were subsequently performed.

Assessment of Propofol Susceptibility

The time when the MOAA/S scale (score 5=patient responds rapidly to normal-sized tone calls to names; 4=patient responds dully to normal-sized tone calls to names; 3=patient responds only to loud or repeated name calls; 2=patient responds only to gentle shaking of the body; 1=patient does not respond to gentle shaking of the body and responds only to painful stimulation) decreased to 1 and the time when BIS index decreased to 60 were recorded to assess the susceptibility to the sedation susceptibility to propofol. The baseline mean arterial pressure (MAP) was recorded, and the maximal percentage decrease in MAP within 5 minutes was recorded to assess the susceptibility of cardiovascular response.

SNP Selection

We conducted an extensive literature study related to the metabolic pathways and receptor proteins of propofol. SNPs with minor allele frequencies (MAF) greater than 0.05 in Chinese Han nationality were screened through the Ensembl database (https://www.ensembl.org/). In total, 22 SNPs located in 7 different genes were selected (Table 1). Two of the

Table 1 Selected Genes and Polymorphisms

Symbol	Gene	SNP ID	Alleles	MAF	HWE p value
GABRA1	Gamma-aminobutyric acid A receptor, alpha 1	rs10068980	A/G	0.38	0.582
		rs1157122	C/T	0.31	0.319
		rs11576001	A/G	0.42	0.822
		rs4263535	A/G	0.45	0.268
		rs77332276	A/G	0.35	<0.001*
		rs78446575	A/G	0.37	<0.001*
GABRA2	Gamma-aminobutyric acid A receptor, alpha 2	rs11503014	C/G	0.06	0.500
		rs279827	A/G	0.43	0.204
		rs6856130	A/G	0.25	0.831
GABRB2	Gamma-aminobutyric acid A receptor, beta 2	rs3811996	C/T	0.25	0.927
		rs6556547	None		
		rs76774144	C/T	0.11	0.935
		rs3816596	C/T	0.35	0.488
GABRB3	Gamma-aminobutyric acid A receptor, beta 3	rs8179186	A/G	0.28	0.904
		rs8179184	C/T	0.29	0.840
		rs20317	C/G	0.30	0.702
GABRG2	Gamma-aminobutyric acid A receptor, gamma 2	rs211035	A/G	0.21	0.805
CYP2B6	Cytochrome P4502B6	rs3745274	G/T	0.18	0.974
		rs2279343	A/G	0.27	0.981
UGT1A9	Uridine diphosphate glucuronyltransferase 1A9	rs2741049	C/T	0.49	0.895
		rs3832043	T_9/T_{10}	0.50	0.842
		rs13418420	C/T	0.47	0.984

Notes: *p<0.001, Indicating that *GABRA1* rs77332276 and *GABRA1* rs78446575 did not follow the Hardy–Weinberg equilibrium.
Abbreviations: MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium.

investigated genes are involved in propofol pharmacokinetics (*CYP2B6* and *UGT1A9*). Five genes participate in the anesthetic mechanism of propofol (*GABRA1, GABRA2, GABRB2, GABRB3*, and *GABRG2*).

Isolation of Genomic DNA

Genomic DNA was isolated from the patient's peripheral blood using the TIANamp genomic DNA kit (Tiangen Biotech (Beijing) Co. Ltd., China). The concentration and quality of DNA were detected by UV spectrophotometer and agarose gel electrophoresis.

Primers Design for Detection of the SNP Site

According to the SNP site, primers were designed by the software of Assay Design 3.1 of Sequenom Company. PCR primers and extension primers are shown in Table 2.

Table 2 The Sequences of PCR Primers and Extension Primers

rs10068980	Forward primer	5'-ACGTTGGATGAAGGTCAAGAGTAGCTGCAC-3'
	Reverse primer	5'-ACGTTGGATGCCACTGCAACTATGTCCAAG-3'
	Extension primer	5'-GGATGCAACTATGTCCAAGTTATAAG-3'
rs1157122	Forward primer	5'-ACGTTGGATGTACCATAGGAATCTCTTCAG-3'
	Reverse primer	5'-ACGTTGGATGTATCAACTAGGCACCTGCTG-3'
	Extension primer	5'-GCTTATAGTCTAAACTGAGGAT-3'
rs11576001	Forward primer	5'-ACGTTGGATGATTTGTGGGTGGAGAGCTAC-3'
	Reverse primer	5'-ACGTTGGATGAGAAGTCAGGACGAAATCCG-3'
	Extension primer	5'-GACGAAATCCGCATCTACTTT-3'
rs4263535	Forward primer	5'-ACGTTGGATGTACTGGATTCATTCTTGTC-3'
	Reverse primer	5'-ACGTTGGATGTGTAAGAAAGTAGCAGCCCC-3'
	Extension primer	5'-CCTTGCCACCAAATAAAG-3'
rs77332276	Forward primer	5'-ACGTTGGATGGCAAATTACATGTATGTGTG-3'
	Reverse primer	5'-ACGTTGGATGGATTCTCTATGAATATCAGC-3'
	Extension primer	5'-CGCTTGTAATATGTATATGCATG-3'
rs78446575	Forward primer	5'-ACGTTGGATGCAGGATACAATTGCACAGCG-3'
	Reverse primer	5'-ACGTTGGATGGAGAGAATCATAGTATAGG-3'
	Extension primer	5'-TTCCATTTCCATATACACACT-3'
rs11503014	Forward primer	5'-ACGTTGGATGGTCTCTCAATCATCAAGTCC-3'
	Reverse primer	5'-ACGTTGGATGTTCACTATCCAAGTAACCCC-3'
	Extension primer	5'-GGAGATTACTTCCTGGACT-3'
rs279827	Forward primer	5'-ACGTTGGATGACTGGTCACGTAGATGTTAG-3'
	Reverse primer	5'-ACGTTGGATGCTCTCTCCTGTGGCTCTTAT-3'
	Extension primer	5'-TCTATATTCAATCTCTTTTCTCATAT-3'
rs6856130	Forward primer	5'-ACGTTGGATGAAAAGGAAAATGTCCCCCCC-3'
	Reverse primer	5'-ACGTTGGATGTTGTGTGTTTGATCTGTCTC-3'
	Extension primer	5'-ATGTTTTATCTGAGGCGATA-3'
rs3811996	Forward primer	5'-ACGTTGGATGTAGACCCGGCCGGTGTCTG-3'
	Reverse primer	5'-ACGTTGGATGCAAGCCTGTGGAGCTACTTC-3'
	Extension primer	5'-GCCGCCTGCCGCCA-3'
rs6556547	Forward primer	5'-ACGTTGGATGAAATTGCTCACATAAAGAC-3'
	Reverse primer	5'-ACGTTGGATGTCCAAAGTTGAAACATGTC-3'
	Extension primer	5'-AGTTGAAACATGTCTTTTTTGTATC-3'

(*Continued*)

Table 2 (Continued).

rs76774144	Forward primer	5'-ACGTTGGATGAAGAGGCGGGAAGAGTAGAC-3'
	Reverse primer	5'-ACGTTGGATGATTTGAGCTCTGGCCTTTCC-3'
	Extension primer	5'-TCCAGTTCTTCACCCA-3'
rs3816596	Forward primer	5'-ACGTTGGATGTTCCTTCGGACGGCCTTGTG-3'
	Reverse primer	5'-ACGTTGGATGCAAAAGAAGTCTTCCCTCCG-3'
	Extension primer	5'-TGAGGTGCTACGAGT-3'
rs8179186	Forward primer	5'-ACGTTGGATGCACTGTGGACGCCTGTGAT-3'
	Reverse primer	5'-ACGTTGGATGTCGACATGGTTTCCGAAGTC-3'
	Extension primer	5'-GATGGTGAGTGCCCGC-3'
rs8179184	Forward primer	5'-ACGTTGGATGCCATTCATTAAGTCCTGGAA-3'
	Reverse primer	5'-ACGTTGGATGCCTACTTGTAGCCAACTAAC-3'
	Extension primer	5'-CTTCTTGTGTTCTGTAGACTTCTT-3'
rs20317	Forward primer	5'-ACGTTGGATGAAGACGGGTCAGGCGGGAAA-3'
	Reverse primer	5'-ACGTTGGATGTAACCTGCTGGGATCCGCTC-3'
	Extension primer	5'-CCTCCGAGCAGCCAAAC-3'
rs211035	Forward primer	5'-ACGTTGGATGGATCACACCACTGCACATTC-3'
	Reverse primer	5'-ACGTTGGATGCACATTCTCTGCCTCATATC-3'
	Extension primer	5'-ACAGGGTCTCGTTCT-3'
rs3745274	Forward primer	5'-ACGTTGGATGTGATCTTGGTAGTGGAATCG-3'
	Reverse primer	5'-ACGTTGGATGTGATGTTCCCCAGGCACTTC-3'
	Extension primer	5'-CACCTTCCTCTTCCA-3'
rs2279343	Forward primer	5'-ACGTTGGATGCCCTAGGCAAACCTCACCA-3'
	Reverse primer	5'-ACGTTGGATGCCTCCCTTTCCCTATTCTC-3'
	Extension primer	5'-TTTCCCCCAGCGCCCCCA-3'
rs2741049	Forward primer	5'-ACGTTGGATGCCCAGAGGAAATGGTCTTAG-3'
	Reverse primer	5'-ACGTTGGATGGTCCAGCCCAATACTAGATT-3'
	Extension primer	5'-TTAACAAAATAGGTGTGAGAATTT-3'
rs3832043	Forward primer	5'-ACGTTGGATGTATCTCAGCAAAAGCTACTC-3'
	Reverse primer	5'-ACGTTGGATGTAGAGGGCGTGTTTTTATCC-3'
	Extension primer	5'-TGTTTTTATCCTTTCATAAAAAAAAA-3'
rs13418420	Forward primer	5'-ACGTTGGATGAGCCTACTGTGCACTAGAAG-3'
	Reverse primer	5'-ACGTTGGATGTTTCTTTTCTCTAGCTGAC-3'
	Extension primer	5'-TTCTCTAGCTGACTTCATT-3'

Table 3 Clinical Characteristics of 294 Patients

Characteristics	x±SD
Age (years)	32.17±5.24
Body height (cm)	158.98±4.32
Body weight (kg)	54.03±5.84
Body mass index (kg/m^2)	21.37±2.13
The time MOAA/S scale decreased to 1 (s)	164.81±31.17
The time BIS index decreased to 60 (s)	177.90±33.51
Maximal percentage decrease in MAP (%)	23.58±5.67

SNP Genotyping

DNA template containing SNP sites was amplified by PCR, using shrimp alkaline phosphatase to neutralize unincorporated dNTPs in amplification products, and then a single base extension was carried out. After being purified by resin, the extended products were transferred onto a SpectroCHIP by the MassARRAY nano dispenser. The SpectroCHIP was then analyzed by the MassARRAY analyzer compact. The mass spectrum peaks were detected by MassARRAY Typer 4.0 software, and the genotypes of target sites were interpreted according to the mass spectrum peaks.

Statistical Analysis

SPSS 25.0 statistical software was used for statistical analysis. Pearson χ^2 test was adopted to assess Hardy–Weinberg equilibrium (HWE). The genotypes of each tested SNP were divided into two groups: 1) homozygotes of the major alleles and 2) combination of homozygotes and heterozygotes of the minor allele. As the sedation effect data did not follow a normal distribution, the results were presented in a median with an interquartile. Analysis of sedation effects between every two groups was performed by Mann–Whitney *U*-test. As the maximal percentage decrease in MAP followed a normal distribution, the results were presented as a mean value with standard deviation. Analysis of maximal percentage decrease in MAP between every two groups was performed by independent sample *t*-test. P values lower than 0.05 were considered statistically significant.

Results

Genotyping Results

In this study, 22 SNPs in 294 individuals were genotyped. The genotype distributions of the 22 selected SNPs are shown in Table 1. No useful results were obtained from testing on *GABRB2* rs6556547. Except for *GABRA1* rs77332276 and *GABRA1* rs78446575, the frequencies of all other polymorphisms followed the Hardy–Weinberg equilibrium (HWE).

Propofol Susceptibility Results

Detailed information about the clinical characteristics of 294 included patients is given in Table 3. According to our result, after propofol infusion, the time MOAA/S scale decreased to 1 varied from 100 seconds to 300 seconds (3.0-fold), the time BIS index decreased to 60 varied from 115 seconds to 300 seconds (2.6-fold), and the maximal percentage decreased in MAP within 5 minutes varied from 7.51% to 38.98% (5.2-fold), indicating that propofol susceptibility varied from individuals.

Correlation Between Genotype and Propofol Susceptibility

The time MOAA/S scale decreased to 1 (s), the time BIS index decreased to 60 (s), and the maximal percentage decrease in MAP (%) were recorded to assess propofol susceptibility.

Table 4 SNPs with Detected Significant Differences in Propofol Susceptibility

Genotype/Alleles	Patients (n)	The Time MOAA/S Scale Decreased to 1 (s)	The Time BIS Index Decreased to 60 (s)	Maximal Percentage Decrease in MAP (%)
GABRA1 rs1157122				
TT	143	160.00(145.00–183.50)	175.00(156.50–200.00)	24.51±5.81
CT+CC	148	160.00(145.00–170.00)	173.50(155.00–188.00)	22.74±5.45#
GABRA1 rs4263535				
AA	94	160.00(145.00–180.00)	180.00(160.00–200.00)	24.37±5.92
AG+GG	198	160.00(142.75–178.00)	172.50(150.25–190.75)*	23.21±5.55
GABRB2 rs3816596				
CC	117	157.00(145.00–175.00)	170.00(150.00–188.00)	24.36±5.92
CT+TT	175	160.00(145.00–180.00)	180.00(158.00–199.00) *	23.06±5.46
GABRB2 rs76774144				
CC	233	160.00(145.00–176.50)	173.00(155.00–190.50)	23.95±5.69
CT+TT	59	163.00(140.00–187.00)	180.00(154.00–203.00)	22.25±5.46#

Notes: *p<0.05 (Mann–Whitney *U*-test), #p<0.05 (independent sample *t*-test).

Excluding the two SNPs that did not follow Hardy–Weinberg's equilibrium law (*GABRA1* rs77332276 and *GABRA1* rs78446575) and the SNP with no genotype result (*GABRB2* rs6556547), the remaining 19 SNPs were continued to be analyzed.

Based on genotypes of each SNP, patients were divided into two groups: 1) homozygotes of the major alleles and 2) combination of homozygotes and heterozygotes of the minor allele. Propofol susceptibility was compared between two groups of each SNP. There were significant differences in the time BIS index decreased to 60 between two groups of *GABRA1* rs4263535 (AA group vs AG+GG group) and *GABRB2* rs3816596 (CC group vs CT+TT group) (Table 4). In addition, there were significant differences in the percentage of maximal decrease in MAP between two groups of *GABRA1* rs1157122 (TT group vs CT+CC group) and *GABRB2* rs76774144 (CC group vs CT+TT group) (Table 4). The remaining 15 SNPs showed no significant difference in propofol susceptibility (Table 5).

Comparison of Clinical Characteristics Between Groups

To eliminate the effect of clinical features of the patients, we further analyzed the clinical characteristics (age, height, weight, and BMI) between different genotype groups of significant SNPs (Table 6). No statistical differences were shown in the general clinical characteristics between the groups.

GABRA1 rs4263535 and *GABRB2* rs3816596 are Associated with Sedation Effect of Propofol

In our study, carriers of polymorphic *GABRA1* rs4263535 G allele required significantly less time for BIS decreased to 60 (180.00 [160.00–200.00] vs 172.50 [150.25–190.75], $Z = -1.984$, $p = 0.047$) (Table 4). The results indicate that G carriers of *GABRA1* rs4263535 are more susceptible to the sedation effect of propofol.

In addition, carriers of polymorphic *GABRB2* rs3816596 T allele required significantly more time for BIS decreased to 60 (170.00[150.00–188.00] vs 180.00[158.00–199.00], $Z = -2.212$, $p = 0.027$) (Table 4). The results indicate that T carriers of *GABRB2* rs3816596 are less susceptible to the sedation effect of propofol.

Table 5 SNPs with No Significant Difference in Propofol Susceptibility

Genotype/Alleles	Patients (n)	The Time MOAA/S Scale Decreased to 1 (s)	The Time BIS Index Decreased to 60 (s)	Maximal Percentage Decrease in MAP (%)
GABRA1 rs10068980				
GG	117	158.00(142.00–180.00)	175.00(158.00–200.00)	24.30±5.82
AG+AA	175	160.00(145.00–177.00)	174.00(155.00–190.50)	23.12±5.56
GABRA1 rs11576001				
AA	101	160.00(145.00–182.00)	178.00(158.00–200.00)	24.28±5.89
AG+GG	191	160.00(145.00–177.00)	173.00(153.00–188.00)	23.22±5.56
GABRA2 rs11503014				
CC	262	160.00(145.00–178.25)	173.50(155.00–192.00)	23.33±5.63
CG+GG	31	165.00(140.00–190.00)	185.00(144.00–200.00)	25.43±5.76
GABRA2 rs279827				
GG	99	159.00(145.00–180.50)	170.00(155.00–190.25)	24.14±5.24
AG+AA	182	160.00(145.00–180.00)	175.00(154.00–198.00)	23.35±5.91
GABRA2 rs6856130				
AA	164	160.00(145.00–175.00)	173.00(155.00–191.00)	23.65±5.27
AG+GG	129	160.00(145.00–180.00)	175.00(158.00–196.50)	23.47±6.21
GABRB2 rs3811996				
TT	163	160.00(145.00–180.00)	173.00(151.50–190.00)	23.93±5.80
CT+CC	129	160.00(145.00–179.00)	180.00(158.00–200.00)	23.06±5.49
GABRB3 rs8179186				
GG	145	160.00(145.00–180.00)	172.50(155.00–192.25)	24.01±5.69
AG+AA	139	158.00(140.00–179.25)	175.00(155.00–198.50)	23.12±5.67
GABRB3 rs8179184				
CC	140	160.00(145.00–180.00)	175.00(155.00–192.50)	24.07±5.70
CT+TT	143	160.00(141.50–180.00)	175.00(157.25–198.50)	23.03±5.67
GABRB3 rs20317				
GG	140	160.00(145.00–180.00)	175.00(155.00–193.50)	24.09±5.73
CG+CC	151	158.00(141.50–179.25)	175.00(157.25–193.50)	23.13±5.63
GABRG2 rs211035				
GG	184	160.00(145.00–179.25)	175.00(158.00–192.00)	23.34±5.89
AG+AA	109	160.00(142.00–180.00)	174.00(153.00–196.00)	23.97±5.30
CYP2B6 rs3745274				
GG	193	160.00(145.00–175.00)	175.00(155.00–192.00)	23.25±5.62
GT+TT	94	160.00(145.00–185.00)	175.00(151.00–200.00)	24.24±5.55

(*Continued*)

Table 5 (Continued).

Genotype/Alleles	Patients (n)	The Time MOAA/S Scale Decreased to 1 (s)	The Time BIS Index Decreased to 60 (s)	Maximal Percentage Decrease in MAP (%)
CYP2B6 rs2279343				
AA	151	160.00(145.00–175.00)	174.50(155.00–192.00)	23.02±5.65
AG+GG	134	158.00(141.00–182.00)	175.00(155.00–194.50)	24.14±5.65
UGT1A9 rs2741049				
TT	75	159.00(150.00–179.25)	177.50(159.75–200.00)	23.59±5.34
CT+CC	211	160.00(142.25–180.00)	172.00(152.25–191.00)	23.51±5.87
UGT1A9 rs3832043				
$T_{10}T_{10}$	76	158.00(150.00–179.00)	178.00(159.00–200.00)	23.87±5.24
T_9T_{10}+T_9T_9	214	160.00(145.00–180.00)	172.00(153.00–191.00)	23.45±5.87
UGT1A9 rs13418420				
TT	79	157.50(140.00–182.75)	170.00(150.00–188.00)	22.99±5.44
CT+CC	205	160.00(145.00–180.00)	175.00(157.75–195.00)	23.72±5.68

Table 6 Clinical Characteristics of Each Genotype Group of *GABRA1* rs1157122, *GABRA1* rs4263535, *GABRB2* rs3816596, and *GABRB2* rs76774144

Genotype/ Alleles	Patients (n)	Mean Age (years)	Mean Height (cm)	Mean Weight (kg)	Mean BMI (kg/m^2)
GABRA1 rs1157122					
TT	143	32.58±5.30	159.02±4.31	54.07±5.74	21.38±2.07
CT+CC	148	31.80±5.19	158.95±4.29	54.07±5.91	21.40±2.19
GABRA1 rs4263535					
AA	94	32.21±5.32	159.20±4.32	53.72±5.67	21.19±2.05
AG+GG	198	32.11±5.22	158.90±4.31	54.17±5.84	21.45±2.14
GABRB2 rs3816596					
CC	117	32.37±4.95	158.54±4.75	53.92±5.82	21.45±2.05
CT+TT	175	32.06±5.45	159.27±3.94	54.10±5.78	21.33±2.18
GABRB2 rs76774144					
CC	233	32.15±5.10	158.85±4.34	54.24±5.87	21.49±2.10
CT+TT	59	32.22±5.88	159.66±4.14	53.45±5.60	20.97±2.18

Abbreviation: BMI, body mass index.

GABRA1 rs1157122 and *GABRB2* rs76774144 are Associated with Percentage of Maximal Decrease in MAP After Propofol Infusion

Since the dose of propofol can affect the degree of drop in blood pressure, analyses of the total dose of propofol between two genotype groups of *GABRA1* rs1157122 and *GABRB2* rs76774144 are necessary. The results showed no statistical difference in dose between two groups (p>0.05) (Table 7).

Table 7 Dose of Propofol of Each Genotype Group of *GABRA1* rs1157122 and *GABRB2* rs76774144

Genotype/Alleles	Patients (n)	Dose at MOAA/S Scale Reached 1 (mg)	Dose at BIS Index Reached 1 (mg)
GABRA1 rs1157122			
TT	143	99.12±17.21	107.52±19.80
CT+CC	148	97.88±18.28	105.64±20.66
GABRB2 rs76774144			
CC	233	98.46±17.26	106.36±20.08
CT+TT	59	98.37±19.65	107.20±20.84

Carriers of polymorphic *GABRA1* rs1157122 C allele had a less change in MAP within 5 minutes after receiving propofol infusion ([24.51%±5.81]% vs [22.74%±5.45%], t = −2.569, p = 0.011) (Table 4). Likewise, carriers of polymorphic *GABRB2* rs76774144 T allele had a less change of MAP within 5 minutes after receiving propofol infusion ([23.95%±5.69%] vs [22.25%±5.46%], t = 1.992, p = 0.047) (Table 4).

Discussion

Precision dosing aims to provide individualized dosing regimens based on the variability of the patient's response to the drug, which is particularly relevant in the case of drugs with a narrow therapeutic window and severe side effects.[13] With the development of pharmacogenomics, researchers have revealed that genetic factors can affect an individual's sensitivity to drugs.[14] SNPs on metabolic enzyme genes and receptor protein genes of drugs widely present in the human genome.[15] However, only a minority of SNPs were significantly associated with drug effects. Thus, identifying SNPs that have an enormous impact on the pharmacodynamics or pharmacokinetics of drugs is significant.

The precise control of the anesthetics dose helps achieve precision medicine during the perioperative period.[16] Adjusting the depth of anesthesia is an essential portion of the perioperative period, as anesthetic depth influences the outcome of patients.[17] Propofol is one of the most frequently used intravenous general anesthetics, but the drug effect varies among individuals.[3] A previous study has reported that ethnicity affects the required dose of propofol,[18] indicating genetic factors as a cause of variation in propofol susceptibility. There remain numerous SNPs that are associated with propofol susceptibility to be explored.

We examined the drug effects of propofol in 294 Chinese female patients during the induction period of general anesthesia. The sedation susceptibility to propofol (The time MOAA/S scale decreased to 1 and the time BIS index decreased to 60) and MAP decrease were recorded. Twenty-two SNPs were genotyped for each patient. The result showed that both the sedation effect and decrease of MAP vary from individuals during the induction period of anesthesia.

CYP2B6 is a hepatic cytochrome P450 enzyme with exceptionally high inter-individual variability.[19] CYP2B6 plays an important role in the metabolism of propofol, participating in the hydroxylation process.[20] *CYP2B6* rs3745274 (c.516G>T) and rs2279343 (c.785A>G) are two missense mutations that occur in exons. Several studies have demonstrated that *CYP2B6* rs3745274 affects the metabolic rate of propofol and influences the total propofol dose during the perioperative period.[21–25] *CYP2B6* rs2279343 has also been reported to affect the metabolism of propofol.[26] In contrast, some studies have reported that *CYP2B6* rs3745274 contributes little to the variation of drug effects of propofol.[3,27–30] Our current results suggest that *CYP2B6* rs3745274 and rs2279343 do not influence propofol susceptibility during the induction period of anesthesia.

UGT1A9 is involved in the glucuronidation process in propofol metabolism.[31] *UGT1A9* c.98T>C[30] and *UGT1A9* –440C>T[32] have been reported to be associated with the required dose of propofol. *UGT1A9* rs2741049 (I399C> T) is a high-frequency mutation that occurs in an intron and increases glucuronidation activity.[33] rs13418420 (−1818T > C) and rs3832043 (−118 > insT, T9 > T10) locate near to the 5' end of gene *UGT1A9*, which may affect the transcription of

UGT1A9 mRNA. However, our results suggest that none of the three *UGT1A9* SNPs examined were associated with propofol drug sensitivity during anesthesia induction.

Although some SNPs in *CYP2B6* and *UGT1A9* have been reported to be potential impact factors of propofol susceptibility in some previous studies, none of the metabolic enzyme SNPs detected in our study is significantly associated with anesthetic sensitivity. This may be attributed to the experimental design. Since the observation duration was limited to the anesthetic induction period, the SNPs are challenging to influence the effects of the function of metabolic enzymes significantly.

$GABA_A$ receptor plays a vital role in the anesthetic effects of propofol and is composed of a very broad species of subunits.[34] Most GABAARs are composed of two α1 subunits, two β2 subunits, and one γ2 subunit.[35] The research on the influence of SNPs of $GABA_A$ receptor genes in propofol susceptibility is currently scarce. According to Zhong et al, *GABRA1* rs2279020 is associated with sedation susceptibility to propofol.[36] In our study, 17 SNPs in $GABA_A$ receptors (*GABRA1, GABRA2, GABRB2, GABRB3*, and *GABRG2*) were investigated. In conclusion, our results show that *GABRA1* rs4263535 and *GABRB2* rs381659 significantly correlate with the individual variation of the propofol sedation effect.

Hypotension is one of the most frequent adverse effects of propofol, which may cause inadequate perfusion of vital organs, leading to serious complications.[37] Zhong et al first explored the relationship between SNPs of $GABA_A$ receptor genes and hypotension after propofol infusion. Their results indicated that *GABRA1* rs2279020 and *GABRA2* rs11503014 influence the cardiovascular response after propofol infusion.[36] Contrary to their previous research, our results did not show the correlation between *GABRA2* rs11503014 and the degree of MAP decrease. However, our results still show the same trend (*GABRA2* rs11503014 - CC vs CG+GG = [23.33±5.63] vs [25.43±5.76], $p = 0.053$). This insignificant result may be attributed to the insufficient of patients included. Nevertheless, our present study showed that *GABRA1* rs115712 and *GABRB2* rs76774144 impacted the degree of MAP decrease after propofol infusion. It has been reported that $GABA_A$ plays an essential role in regulating the cardiovascular system and sympathetic activity by affecting the hypothalamic paraventricular nucleus (PVN) and rostral ventrolateral medulla (RVLM).[38] The SNPs of the $GABA_A$ receptor may influence the sympathetic activity regulated by $GABA_A$ and thus affects the degree of blood pressure decrease after propofol infusion.

Limitations

The sample size of this study was relatively small, and the observations in this study were limited to the induction period of anesthesia rather than the entire perioperative period. Additional studies are required with more participants and more extended observation for drug response.

Conclusion

This study suggests that *GABRA1* rs4263535 and *GABRB2* rs3816596 are associated with susceptibility to the sedation effect of propofol. In addition, *GABRA1* rs1157122 and *GABRB2* rs76774144 polymorphisms are associated with the degree of drop in blood pressure after propofol infusion.

Data Sharing Statement

Individual deidentified participant data used to support the results of this study are available from the corresponding author based on reasonable demand. Data will be available within 1 year of publication.

Disclosure

The authors report no conflicts of interest in this work.

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