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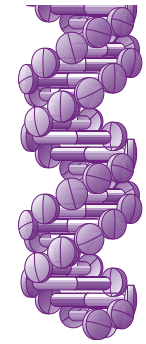
Pharmacogenomics



OCT1 genetic variants are associated with postoperative morphine-related adverse effects in children

Aim: Large interindividual variability in morphine pharmacokinetics (PK) could contribute to variability in morphine analgesia and adverse events. Respiratory depression (RD) and postoperative nausea and vomiting (PONV) are significant adverse drug response of intravenous morphine in the perioperative setting limiting its efficacy in achieving adequate surgical pain relief. OCT1 is a transporter in the liver that transports morphine from the bloodstream into hepatocytes. Earlier we reported association of genetic polymorphisms in *OCT1* with morphine PK, and lower morphine clearance in Caucasian children as compared with African–American (AA) children. The aim of this study is to identify the association between common *OCT1* genotypes affecting morphine's PK and clinically important postoperative morphine-related adverse outcomes. **Methods:** After obtaining institutional review board (IRB) approval and informed consents, 311 children ages 6–15 years, American Society of Anesthesiologists' physical status 1 or 2 scheduled for tonsillectomy who received standard anesthetic, surgical and postoperative care were recruited. Clinical data collected included postoperative pain scores, total opioid use, incidence of PONV and RD. Four nonsynonymous SNPs of the *OCT1* gene (rs12208357, rs34130495, rs72552763 and rs34059508) in each patient were genotyped using commercially available TaqMan assays. We investigated the genetic association of *OCT1* with incidences of postoperative RD and PONV. **Results:** Caucasian and AA children differed significantly in the incidence of obstructive sleep apnea ($p < 0.001$) and total morphine use ($p = 0.028$). There were incidences of prolonged post anesthesia care unit stay in 7% of Caucasian children, while no such incidences were observed for AA children ($p = 0.05$). *OCT1* polymorphism rs12208357 was associated with high incidences of PONV and PONV leading to prolonged post anesthesia care unit stay ($p < 0.05$). A significant association was also found between rs72552763 *GAT* deletion and high incidence of RD ($p = 0.007$). **Conclusion:** Children with certain *OCT1* genotypes are associated with higher risk for RD and PONV following morphine administration leading to prolonged hospital stay. The OCT1 transporters' effects on morphine's PK could explain this association.

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Morphine is a commonly used opioid to treat surgical pain in children. However, morphine has a narrow therapeutic index and large interindividual variations in clinical responses limiting its safe and effective use in children. The opioid-induced respiratory depression (RD) has potentially fatal consequences and has been reported to contribute up to 50% of postoperative respiratory failure events [1–4]. Twin studies have detected significant heritability for RD (30%) from opioids [5], which indicates that genetics may play a role in determining susceptibility to RD. In earlier work from

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our group, we reported that variants in certain genes in the morphine response pathway, namely, μ-opioid receptor (*OPRM1*), ATP-binding cassette *ABCB1* and *FAAH*, affect morphine clinical outcomes including RD in children [6–8]. The efflux of morphine glucuronides from the hepatic cell is an ATP-dependent process mediated by the ATP-binding cassette transporters including *ABCC3* [9,10]. We recently demonstrated that *ABCC3* variants contribute to variability in morphine, morphine-3-glucuronide and morphine-6-glucuronide pharmacokinetics (PK) and clinical outcomes [11,12].

In this study, we focused on *OCT1* (alternative name *SLC22A1*), the major OCT in human hepatocytes. The OCT1 transporter is responsible for uptake of drugs including morphine in liver. Earlier we reported that *OCT1* genotype variant frequency affects the morphine clearance among African–American (AA) and Caucasian children [12], and that in children with defective *OCT1* genotype, morphine clearance was less and systemic exposure was high. However, there is no report investigating relationship between *OCT1* polymorphisms and clinical outcomes related to morphine.

In this study, we hypothesized that *OCT1* variants could potentially affect serious morphine-related adverse drug reactions (ADRs) [13], namely, RD, postoperative nausea and vomiting (PONV) by altering liver transport of morphine and metabolites. The primary aim of the study was to identify associations between *OCT1*-specific polymorphisms and postoperative RD and PONV in children undergoing tonsillectomy, and RD and PONV resulting in prolonged hospital stay, as these are economically relevant outcome associated with increased healthcare costs. This is the first clinical study analyzing relationship between *OCT1* genotype and morphine-related clinical outcomes.

Methods

Study design & setting

This study was designed as a genotype-blinded, prospective clinical observational study, conducted in children undergoing outpatient adenotonsillectomy. This study was registered with the Clinical Trials website, NCT01140724 and approved by the Cincinnati Children's Hospital Medical Center's institutional review board. The written informed consent was obtained from parents and when appropriate assent was collected from children prior to enrollment. The clinical care team was blinded to genotype of patients.

Participants & standard anesthetic procedures

The surgery-specific standard perioperative care, including standardized surgical, anesthetic and postoperative care was provided to all patients. The exclusion criteria were non-English speaking parents or child, hepatic or renal diseases, allergy to morphine, developmental delay or preoperative pain necessitating analgesics administration.

Children scheduled for adenotonsillectomy for recurrent tonsillitis, adenotonsillar hypertrophy or obstructive sleep apnea (OSA), 6–15 years of age and with a physical status one or two of American Society of Anesthesiologists, were enrolled for the study on surgery day. Children were categorized to OSA group if any of the following criteria were met: history of snoring plus respiratory pauses during sleep lasting more than 10 s or daytime drowsiness with history of sleep-disordered breathing, or positive response to at least eight of the 22 questions in the pediatric sleep questionnaire [14,15]. Anesthesia was induced with administration of sevoflurane followed by a propofol (2 mg/kg) bolus to achieve anesthesia and facilitate endotracheal intubation. Sevoflurane was

Table 1. Demographic characteristics and morphine use.

Characteristics	White (n = 262)	Black (n = 49)	p-value
Age (years); median (IQR)	8.36 (6.93–10.73)	8.44 (7.13–10.39)	0.95
Weight (kg); median (IQR)	31.55 (25.20–43.60)	32.90 (25.30–51.40)	0.31
BMI z scores; median (IQR)	0.51 (-0.28–21.58)	0.71 (-0.01–01.90)	0.10
Intraoperative morphine requirement (mg/kg); median (IQR)	0.19 (0.17–10.22)	0.19 (0.15–10.20)	0.15
Total morphine requirement (mg/kg); median (IQR)	0.24 (0.20–20.29)	0.27 (0.20–20.34)	0.028*
Sex, male; n (%)	134 (51)	21 (43)	0.35
OSA; n (%)	109 (42)	35 (71)	<0.001*

Age, weight, BMI z score, intraoperative and total morphine requirement are compared between white and black using Wilcoxon rank sum tests; sex and OSA are shown as frequencies and proportions, and compared using Fisher's exact tests. BMI z scores were calculated using CDC growth charts.
*$p < 0.05$.
IQR: Interquartile range; OSA: Obstructive sleep apnea.

Table 2. Morphine-related adverse drug response in children.

Adverse drug response	White (n = 262)	Black (n = 49)	p-value
RD; n (%)	70 (27)	17 (35)	0.30
Prolonged PACU stay due to RD; n (%)	25 (10)	5 (10)	0.80
PONV; n (%)	45 (17)	5 (10)	0.29
Prolonged PACU stay due to PONV; n (%)	19 (7)	0 (0)	0.05

Adverse drug responses are compared using Fisher's exact tests.
PACU: Post anesthesia care unit; PONV: Postoperative nausea and vomiting; RD: Respiratory depression.

administered to sustain anesthesia in absence of neuromuscular blocking agent. Standard perioperative care and one intraoperative intravenous morphine bolus dose of 0.2 mg/kg was provided to patient. However, OSA group children were administered with a morphine dose of 0.1 mg/kg. Additionally, all patients received ondansetron (0.1 mg/kg) and dexamethasone (0.1 mg/kg) intraoperatively as prophylactic measure. Significant postoperative pain characterized by facial expression, leg movement, activity, cry and consolability pain score ≥4/10 (25) was alleviated in the post anesthesia care unit (PACU) by administering morphine rescue doses (0.05 mg/kg increments). Duration of PACU stay (time to achieve PACU discharge readiness) was defined as time spent in PACU to reach discharge criteria. A patient not achieving PACU discharge criteria in 90 min following tonsillectomy was identified as prolonged PACU stay patient.

Clinical outcome measures

To measure clinical outcome, opioid-related ADR, clinical RD and refractory PONV were recorded for each patient in the PACU for the tonsillectomy cohort. Clinical RD was defined as a persistent (longer than 1 min) oxygen desaturation less than 90% or a respiratory rate less than eight breaths per minute or oxygen desaturation less than 94% in addition to respiratory rate less than ten per minute requiring supplemental oxygen to maintain SpO2 more than 94% in the absence of clinically obvious upper airway obstruction [16]. PONV is defined as occurrence of emesis or requirement of antiemetic administration due to self-reported experience of nausea. Standard criteria to be met for PACU discharge were: level of consciousness arousable or awake, airway patent with adequate air exchange, core temperature ≥36.3°C, acceptable pain level, hemodynamically stable and surgical site without any bleeding or complications. More than 90 min stay in PACU due to RD or PONV were termed as prolonged RD and prolonged PONV, respectively [16]. The sum of morphine (mg/kg) administered intraoperatively and during postoperative period at PACU was termed as 'total morphine dose.'

Genotyping

In operating room, patients were anesthetized and intravenous catheter placed from which blood sample was collected for genotyping. Blood cell DNA was isolated by standard DNA extraction method and stored at -20°C for further use. Using TaqMan allelic discrimination system assays (Life Technologies and Applied Biosystems, CA, USA), genotypes were determined for rs12208357 (Arg61Cys), rs34130495 (Gly401Ser), rs34059508 (Gly465Arg) and rs72552763 (deletion of Met420) in the *OCT1* gene; all the polymorphisms are known to be responsible for diminished or lost transporter activity of OCT1 [17].

Analysis of genetic association with RD, prolonged RD, PONV & prolonged PONV

Before conducting analyses, quality of the data was checked. The patient characteristics were examined and compared between AA and Caucasian children. Continuous variables including patient age, weight, BMI z score, intraoperative and total morphine requirement were presented as median and interquartile range and compared using Wilcoxon rank sum tests, while categorical variables including sex, OSA, RD, prolonged PACU stay due to RD (prolonged RD), PONV and prolonged PACU stay due to PONV (prolonged PONV) were represented as frequencies and proportions, and compared using Fisher's exact test. The properties of the SNPs were examined in AA and Caucasian children, respectively, and Hardy–Weinberg equilibrium (HWE) was tested.

Genetic association was examined using logistic regression, in which additive, dominant or recessive genetic effects were assessed. Prior to evaluation of each of the *OCT1* variants using the logistic models, the effects of covariables were tested, including race, age, sex, OSA, BMI z score and total morphine dose. To select the best fitting model, log likelihood, Akaike and Bayesian information criterion were compared; covariables that significantly improved model fitting ($p < 0.05$) were retained for subsequent genetic analyses. Race effects were specifically tested,

especially for prolonged PACU stay due to PONV which showed racial difference. We found that including race in the model did not change the conclusion on any of the genetic associations. Therefore, in the final model, for RD and prolonged RD, total morphine dose and BMI z scores were included; for prolonged PONV, sex and OSA were included, while for PONV, no covariables were included.

The analyses were performed using SAS software, version 9.4 (SAS Institute, NC, USA), except for the properties of the SNPs and HWE which were examined using JMP Genomics software, version 8.0 JMP Genomics (SAS Institute). We used p-value ≤0.05 to indicate the statistical significance.

Results

Demographics & clinical characteristics

Demographic characteristics including age, weight, BMI z scores and intraoperative morphine requirement and sex were comparable in self-identified as Caucasian or AA children. Compared with Caucasian children, AA children had higher proportion of OSA ($p < 0.001$), and showed a greater need of total morphine ($p = 0.028$; Table 1).

AA children tended to have higher incidence of RD and lower incidence of PONV, but no statistical significance was reached (Table 2). Incidence of RD resulting in prolonged recovery room stay (prolonged RD) was comparable in both races. Marginally significant difference was observed in PONV resulting in prolonged recovery room stay ($p = 0.05$) with incidence of 7% in Caucasian children and no PONV in AA children.

As shown in Table 3, two of the SNPs had minor allele frequency (MAF) less than 0.05. The rs34059508 may deviate from HWE; after checking and verifying the genotypes, we included this SNP for analysis. The linkage between the *OCT1* SNPs is shown in Table 4.

Genetic association with clinical outcomes

The genetic association of the *OCT1* SNPs with each of the ADR is shown in Table 5. Nominal association of rs12208357 with PONV ($p = 0.038$) and PONV resulting in prolonged PACU stay ($p = 0.024$) were detected using additive models. For both PONV and PONV resulting in prolonged PACU stay, the T allele was the risk allele and was associated with increased odds by 2.2-fold (95% CI: 1.1–4.4) for PONV and by 3.3-fold (95% CI: 1.2–8.6) for PONV resulting in prolonged recovery room stay, respectively.

When recessive genetic effects were assumed, genetic associations were also detected between rs12208357 and the two PONV outcomes ($p = 0.027$; $p = 0.016$). As in our cohort, only one TT genotype was identified, a recessive genetic effect of rs12208357 cannot be ruled out.

The *OCT1* SNP rs72552763 showed a clear dominant genetic effect on RD ($p = 0.007$), in which homozygous minor allele carriers showed high odds of RD compared with major allele carriers (Odds ratio [OR]: 9.5; 95% CI: 1.7–54.1; Table 5). No other genetic associations were detected.

Discussion

Interindividual variability in adverse effects with intravenous morphine has been well characterized. In this prospective study of 311 children undergoing tonsillectomy, we found associations between nonsynonymous polymorphisms in the *OCT1* gene and morphine-induced postoperative adverse outcomes, PONV, PONV leading to prolonged PACU stay and RD.

We previously reported that *OCT1* genotype influences morphine PK and clearance. Morphine concentration was fitted to a two-compartment model and in population pharmacokinetic analysis, bodyweight and homozygous *OCT1* genotype were identified as covariates influencing morphine clearance [12]. Allometrically scaled morphine clearance in homozygotes of loss of function variants was significantly less (20%) than wild-type and heterozygotes ($p < 0.05$) [12].

Human OCT1, though expressed in many organs, is primarily expressed in the liver. Hepatic OCT1

Table 3. Minor allele and minor allele frequency of the *OCT1* polymorphisms.

OCT1 SNPs	Location†	Putative function†	White		Black		All	
			MAF	p-value	MAF	p-value	MAF	p-value
rs12208357	160543148	Missense	T (0.09)	0.40	T (0.01)	0.94	T (0.08)	0.50
rs34130495	160560824	Missense	A (0.03)	0.05	A (0)	–	A (0.02)	0.71
rs72552763	160560883–160560885	In-frame deletion	Del (0.17)	0.70	Del (0.05)	0.71	Del (0.15)	0.86
rs34059508	160575837	Missense	A (0.02)	0.70	A (0.01)	0.94	A (0.02)	0.03

p-values were generated using the Hardy–Weinberg equilibrium.
†Annotated based on Human Genome version 19.
Del: Deletion.

Table 4. Linkage between *OCT1* polymorphisms.

OCT1 SNPs	rs12208357		rs34130495		rs72552763	
	|D'|	R^2	|D'|	R^2	|D'|	R^2
rs34130495	1	0.002	–	–	–	–
rs72552763	0.826	0.010	0.785	0.002	–	–
rs34059508	1	0.002	1	0.000	1	0.118

Linkage was presented as absolute D' and R^2 estimated using JMP Genomics, 8.0.

plays a fundamental role in the cellular uptake, elimination and ultimately clearance of various cationic substrates including other important agents. We had previously reported that morphine's clearance was decreased in homozygotes of loss-of-function *OCT1* variants [18]. In addition, *in vitro* and adult human volunteer studies by Tzvetkov *et al.* support the role of hepatic OCT1 on morphine's PK and PD [19]. Hence, hepatic OCT1 expression is most likely contributor for observed PD patterns.

Active OCT1 expression results in greater uptake of drug in liver, high clearance and low levels in plasma. However, there is no report on contribution of different SNPs of *OCT1* on clinical outcomes/adverse effects of morphine. Four loss of function *OCT1* variants have been reported before: Arg61Cys (rs12208357), Cys88Arg (rs55918055), Gly401Ser (rs34130495) and Gly465Arg (rs34059508), and change of Met420 (rs72552763) amino acids [20,21]. Tzvetkov *et al.* [19] showed *in vitro* studies that morphine uptake was increased up to fourfold in HEK293 cells overexpressing human OCT1. The increase was concentration-dependent and followed Michaelis–Menten kinetics, and that OCT1-mediated morphine uptake was abolished by common loss-of-function polymorphisms in the *OCT1* gene; the authors also showed that in concordance with their *in vitro* data, morphine plasma concentrations in healthy volunteers were significantly dependent on *OCT1* polymorphisms [19]. In addition, Kerb *et al.* [22] showed that *hOCT1* wild-type and *hOCT1* mutations were expressed in *Xenopus* oocytes and were analyzed for OCT1 activity by measuring uptake of tritium-labeled 1-methyl-4-phenylpyridinium (MPP); the rs12208357 mutation resulted in 70% decrease in ^{3}H-MPP uptake, while rs55918055 or rs34130495 mutation resulted in more than 98% reduction in ^{3}H-MPP uptake. In another study of *OCT1* polymorphisms in Caucasian males by Tzvetkov *et al.*, carriers of alleles of rs12208357, rs34130495, rs72552763 or rs34059508 exhibited significantly lower metformin renal clearance ($p = 0.04$) [20]. The homozygotes of these *OCT1* SNPs have negligible OCT1 activity (9% of Caucasian population) [19]. The heterozygotes have only one functional *OCT1* allele and constitute about 40% of Caucasian population [19]. In case of loss of OCT1 function, there is reduced uptake of drugs in liver as also reported for tramadol and metformin [23,24]. Our findings (e.g., association between rs72552763 G*AT* deletion and high incidence of RD) are similar and to supportive of previously published associations between loss of function OCT1 and morphine and other drug effects. In addition, as we reported, race is a very important factor in determining total morphine dose required. Hence, information about race should be utilized while personalizing morphine's dose for a patient.

We earlier studied formation of morphine metabolites, morphine-6-glucuronide and morphine-3-glucuronide along with morphine clearance [11]. The *OCT1* homozygotes had lower morphine clearance and reduced metabolite formation (~39%). We also demonstrated that significant association between *ABCC3* variants (rs729923, rs414812) and RD leading to prolonged PACU stay (prolonged RD) supported by increased formation clearance of morphine glucuronides in children with *ABCC3* rs4148412 AA and rs4973665 CC genotypes in this cohort. However, there remains some interindividual variability in morphine's clinical responses that was not explained by the *ABCC3* associations.

In current study, significant association was observed for rs12208357 with PONV ($p = 0.038$) and prolonged PONV ($p = 0.024$). This SNP is in LD with the other SNPs that were previously found to be associated with reduced morphine clearance. The rs12208357 is associated with decreased OCT1 protein expression [25]. It is hypothesized that decreased OCT1 transporter activity results in lower morphine uptake in liver, reduced morphine clearance and increased systemic morphine level. Higher plasma morphine level will lead to greater incidences of morphine-induced PONV and RD. This SNP was reported to be associated with reduced metformin transport [26], lower tough concentration of metformin in diabetic patient [27], increased C_{max} and reduced vomiting episodes following tropisetron and

ondansetron administration [28], increased tramadol plasma level and increased miosis response in pain treatment [24].

We found that another SNP rs72552763 was also found to be associated with RD (p = 0.007). This SNP was reported to be related with lower trough values of metformin in diabetic patients [27], increased plasma concentration and higher clinical efficacy of tropisetron and ondansetron administered for nausea [28], increased probability of imatinib failure in chronic myeloid leukemia [29] and higher plasma level of tramadol [24]. Both of these SNPs rs12208357 and rs72552763 have been linked to decreased uptake in European-American population [26]. However, their expression was not observed in Asian population [30]. Mainly expressed in liver, low-level expression of this transporter has been reported in other tissues such as kidney, brain, placenta, heart, lung, skeletal muscle [31,32]. In brain, weak OCT1 expression was found in endothelial cells [33] and certain regions of corpus callosum and cerebellum [34]. Further study is needed to correlate distribution of *OCT1* variants in brain regions potentially altering morphine-induced RD and PONV.

In comparison of clinical characteristics, higher proportion of OSA (p < 0.001) and greater need of total morphine (mg/kg; p = 0.028) were observed in AA group. In our previously published study, we found that morphine clearance was higher in the AA group in comparison to Caucasians, likely explained by higher MAF of loss of function variants in the Caucasians [12]. This difference in allele frequency of *OCT1* genotype may also be responsible for decreased morphine requirement among the Caucasians, and increased incidence of PONV, compared with AA. Hence, *OCT1* variants may be responsible for the observed racial differences observed in morphine's clearance and PONV.

In addition to *OCT1* variants, morphine uptake could be hampered by if coadministered with drugs such as codeine, ondansetron, verapamil, irinotecan due to drug–drug interaction [19]. Individuals with loss of function *OCT1* expression are at a greater risk of ADR, as morphine uptake in liver will be further diminished due to drug–drug interaction [19]. In this study, all children received coadministration of ondansetron intraoperatively, which could have decreased morphine's uptake.

One of the limitations of our study is that it was performed in younger children undergoing outpatient adenotonsillectomy, which is a short surgery with relatively less severe pain than major inpatient surgeries; our findings need to be reproduced in children receiving higher doses of morphine for a longer duration following major surgery as morphine is widely used to manage perioperative pain. Our results may not be applicable to races other than AA or Caucasian as we did not have adequate

Table 5. Genetic association of the *OCT1* polymorphisms with morphine-related respiratory depression and postoperative nausea and vomiting.

OCT1 SNPs	Genotype (n)	RD				Prolonged stay due to RD				PONV				Prolonged stay due to PONV			
		%	p†	p‡	p§	%	p†	p‡	p§	%	p†	p‡	p§	%	p†	p‡	p§
rs12208357	C/C (264)	29	0.90	0.23	0.96	9	0.69	0.43	0.56	14	0.038	0.55	0.027	5	0.024	0.69	0.016
	C/T (46)	27				11				28				15			
	T/T (1)	0				0				0				0			
rs34130495	G/G (298)	29	0.14	0.35	0.16	10	0.54	0.54	0.60	16	0.33	0.55	0.36	6	0.81	0.82	0.77
	G/A (12)	17				8				8				8			
	A/A (1)	0				0				0				0			
rs72552763	GAT/GAT (222)	27	0.22	0.007	0.66	10	0.33	0.31	0.40	16	0.86	0.89	0.81	6	0.73	0.36	0.87
	GAT/-(82)	27				9				17				6			
	–/–(7)	71				0				14				0			
rs34059508	G/G (298)	28	0.84	–	0.84	10	0.10	–	0.10	16	0.94	–	0.94	6	0.16	–	0.16
	G/A (13)	31				0				15				0			

The proportions of ADR cases are shown by genotypes of each of the OCT1 polymorphisms. Genetic associations with RD and PONV were tested by logistic regression adjusting for significant covariables, assuming additive, dominant and recessive genetic effects.
†Additive.
‡Dominant.
§Recessive.
ADR: Adverse drug reaction; PONV: Postoperative nausea and vomiting; RD: Respiratory depression.

representations from other races such as Asian and Latino. Our findings also do not preclude other unstudied *OCT1* variants or gene–gene interactions that might play a role in affecting opioid outcomes, as we did not study them.

Understanding genetic predictors of morphine PK and adverse outcomes is the basis of the clinical application of preemptive genotyping to help determine optimum morphine dose to get desired analgesic effect and avoid adverse response. Identification of susceptible patients with loss of function *OCT1* variants would allow clinicians to choose an opioid that is not dependent on OCT1 pathway, like hydromorphone or fentanyl. This will help in reducing incidences of morphine adverse effects in patients with loss of function *OCT1* variants.

Conclusion

In conclusion, *OCT1* SNP rs12208357 is associated with higher incidences of PONV and prolonged PONV, and rs72552765 with RD. The Caucasian population, which has a lower MAF of *OCT1* variants, is more vulnerable to morphine ADRs with incidence rate of 7% for prolonged PONV, in comparison to no PONV in AA children. Caucasian population require significantly less total morphine dose and have high incidence of morphine-related adverse effects with respect to AA population. These findings in addition to our previous findings could be utilized for making guidelines for morphine administration and determine personalized dose with appropriate validations in different surgical cohorts.

Author contributions

The authors directed and had access to all the analyses and the full clinical and genetic database, wrote all drafts of the report, decided to publish the results and attest for the accuracy and completeness of the data. Specifically, S Sadhasivam, V Chidambaran and T Fukuda conceived of and designed the research. S Sadhasivam, V Chidambaran, R Balyan and T Mizuno acquired the data. S Sadhasivam, V Chidambaran, R Balyan, AA Vinks, X Zhang and LJ Martin analyzed and interpreted the data. X Zhang and LJ Martin did statistical analyses. V Chidambaran, R Balyan and S Sadhasivam drafted the initial manuscript. S Sadhasivam participated in funding and supervision. All authors made critical revisions to the report for important intellectual content.

Disclaimer

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Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Summary points

Inter-racial difference in morphine-related adverse drug reaction may be observed owing to OCT1 genotype

- Caucasians have a higher frequency of loss of function *OCT1* variants.
- African–American children had higher proportion of obstructive sleep apnea and showed a greater need of total morphine Caucasian children.
- Higher incidences of postoperative nausea and vomiting (PONV) were observed in Caucasian children despite lower morphine use than African–American children.

Genetic association between OCT1 SNPs & occurrence of adverse drug reactions

- *OCT1* SNP rs12208357 is associated with high incidences of morphine-related PONV and PONV leading to prolonged post anesthesia care unit stay.
- *OCT1* SNP rs72552765 is associated with high incidences of morphine-related respiratory depression.

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