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Review

# Pharmacogenetics and anaesthetic drugs: Implications for perioperative practice

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## HIGHLIGHTS

- Pharmacogenetic variations in anaesthetic drugs affect enzymes, transport proteins and drug receptors.
- Genotyping may provide more clues as to aetiology of conditions related to usage of anaesthetic drugs e.g. propofol infusion syndrome.
- Improved and more economical molecular technology will lead to increase in quantity of pharmacogenetic data.

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## ABSTRACT

Pharmacogenetics seeks to elucidate the variations in individual's genetic sequences in order to better understand the differences seen in pharmacokinetics, drug metabolism, and efficacy between patients. This area of research is rapidly accelerating, aided by the use of novel and more economical molecular technologies. A substantial evidence base is being generated with the hopes that in the future it may be used to generate personalised treatment regimens in order to improve patient comfort and safety and reduce incidences of morbidity and mortality. Anaesthetics is an area of particular interest in this field, with previous research leading to better informed practice, specifically with regards to pseudocholinesterase deficiency and malignant hyperthermia. In this review, recent pharmacogenetic data pertaining to anaesthetic drugs will be presented and possible future applications and implications for practice will be discussed.



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## 1. Introduction

The publication of the human genome in its entirety in 2003 signalled a new dawn in the quest for a greater and more complete understanding of the variations which govern genes and the proteins which they express. Much of the promise and potentials of the human genome project remains to be developed and seen, however, as medical science enters the post-genomic era, accompanied by ever greater advances in rapid DNA sequencing technologies, it is anticipated that the knowledge gained from the human genome project will be instrumental in advancing developments in pharmacogenetics and personalised medicine [1].

Pharmacogenetics and pharmacogenomics are terms which are often used interchangeably in medical literature, however, they are distinct entities [2]. Pharmacogenetics refers to the study of variability in an individual's response to a drug due to heritable factors [3]. Much of the research in this field has been evaluating the association of single nucleotide polymorphisms with how individuals metabolise drugs. Pharmacogenomics is a more recent, broader term which may be regarded as the application of pharmacogenetics to the whole genome and across populations [4], encompassing proposed outcomes such as generating drug–response profiles unique to each individual based on their genetic make-up [5], examining the effect of drugs on gene expression [6,7], and the eventual utilisation of genomic principles in the development and trialling of new drugs [8] (See Table 1).

## 2. Epidemiology of perioperative care and complications

Globally, it is estimated that 234 million surgical procedures are carried out annually. It is thought that 7 million patients experience harm, and 1 million die each year post-operatively worldwide [9]. It is furthermore estimated that up to 50% of this harm is avoidable [10]. The 2012 European Surgical Outcomes Survey examined mortality rates across 28 European countries and found that in the UK cohort there was a 3.6% mortality rate following non-cardiac surgery (n = 10,630) [11]. More recently, the 2014 National Audit Project Activity Survey included 15,460 patients who received general anaesthesia. Of this cohort, nine patients died, representing a 0.06% intraoperative mortality rate [12]. It should be noted that surgical mortality rates have fallen in recent decades, and this is due, in part, to an improvement in anaesthesia related factors and safety [13].

One prospective study which examined the most common complications encountered in the post-anaesthesia care unit found that of the 18,473 patients studied, 9.8% experienced post-operative nausea and vomiting, 6.9% required upper airway support, and 2.7% had hypotension which required pharmacological intervention [14]. The results from the most recent Royal College of Anaesthetists audit on accidental awareness during general anaesthesia reveal that the annual prevalence of this condition is approximately 1/15,000, sequelae of which include distress and long term psychological harm [15]. Whilst it is encouraging that mortality rates are decreasing, anaesthesia related morbidity and mortality is still prevalent, and pharmacogenomic factors are implicated in this [16].

## 3. The molecular basis of interindividual variation in pharmacogenetics

The elimination of a drug from the body involves two processes: metabolism and excretion. Metabolism occurs in two stages: catabolic phase I reactions (e.g. hydrolysis, oxidation) and anabolic phase II reactions (e.g. addition of a glucorynyl or methyl group to the metabolite to polarise it). Excretion primarily occurs via the kidneys, hepatobiliary system, or lungs.

The cytochrome P450 (CYP) superfamily of enzymes is of particular interest when considering phase I reactions. There are 59 P450 proteins which are categorised into 18 families and 43 subfamilies, the majority of which are expressed in the smooth endoplasmic reticulum of hepatocytes, with CYP1, CY2 and CYP3 being the main families involved in human drug metabolism. Up to 80% of drug metabolism is performed by these three families of enzymes [17]. The expression, and therefore functionality of CYP proteins is influenced by a host of different factors including age, sex, disease states, and epigenetic factors [18]. CYP enzyme genes and their alleles may be affected by a variety of different mutations of which 2000 have been described [19]. Such polymorphisms include frameshift mutations, deletions, and splicing defects, all of which may affect both introns and exons, including at promoter regions of the gene, thereby having the potential to affect gene transcription. The functional effect of such polymorphisms is an increase or decrease in the activity of the gene (and thereby its enzyme) [20].

Based on the variation of functionality of proteins due to genetic polymorphisms, it is possible to classify individuals into different phenotypic classes based on enzymatic activity: poor metabolisers who demonstrate no CYP activity, intermediate metabolisers who demonstrate reduced activity, extensive metabolisers who demonstrate normal activity, and ultrarapid metabolisers who demonstrate increased activity [21]. By using this system, much of the variation in patient responses to certain opiates commonly used in anaesthetic practice e.g. codeine, tramadol, oxycodone is explained. These drugs are normally metabolised into their active, effective form by CYP2D6. However, poor metabolisers who carry two non-functional alleles for the *CYP2D6* gene will experience little analgesic effect owing to a non-functional CYP enzyme [22], whilst ultrarapid metabolisers who have three functional allele copies experience higher plasma concentrations of morphine due to CYP hyperactivity and are more prone to opiate toxicity [23]. This is one example of how existing knowledge of pharmacogenetic differences between individuals has had an impact on knowledge of pharmacokinetics and drug efficacy.

**Table 1**
Basic genetic terminology.

| | |
|---|---|
| Gene | A Section of DNA which codes for a protein |
| Genome | The entire genetic material of an organism |
| Nucleotide | A basic unit of DNA comprising an organic base, ribose sugar, and negatively charged phosphate group |
| Mutation | A change to the DNA sequence of an organism |
| Variation | Differences seen between members of the same species |
| Genotype | The genetic make-up of an organism |
| Phenotype | The physical appearance of an organism arising from its genotype |
| Polymorphism | A gene which has more than one allele allowing for phenotypic variation in a population |
| Single nucleotide polymorphism | Variation of a specific nucleotide seen in >1% of a population |
| Haplotype | A set of genetic variations which are inherited together |

**Table 2**
Pharmacogenetics of anaesthetic agents.

| Drug | Description | Gene(s) affected by polymorphism | Genetic variant | Phenotypic effect of polymorphism |
|---|---|---|---|---|
| Propofol | IV induction agent potentiating the inhibitory action of GABA at $GABA_A$ receptors | *UGT1A9* | 1887 T/G | Higher induction dose required [30] |
| | | | 331C/T | Higher levels of drug clearance |
| | | | 1818T/C | Longer time needed for loss of consciousness |
| | | *CYP2C9* | *2/*2 | Higher plasma concentration [31] |
| Isoflurane | Volatile agent used for maintenance, acts to potentiate GABA via $GABA_A$ receptors and inhibition of transmission at NDMA receptors | *RYR1* | Tyrosine 522 | Malignant hyperthermia [32] |
| Sevoflurane | Volatile agent used for induction and maintenance, acts to potentiate GABA via $GABA_A$ receptors and inhibition of transmission at NDMA receptors | *CYP2E1* | Variations in levels of enzyme expression | Renal dysfunction [33] |
| | | *RYR1* | Gly2130Arg | Malignant hyperthermia [34] |
| Ketamine | IV anaesthetic used in shocked patients and children, acts as an NMDA receptor anatagonist | *CYP2B6* | *CYP2B6*6* | Decreased enzyme binding, reduced drug clearance [35] |
| Lidocaine | Local anaesthetic acting via the blockage of sodium channels | *SCN9A* | 395N > K | Reduced efficacy [36] |
| | | *MCR1* | Melanocortin 1 receptor mutation | Decreased analgesic efficacy [37] |

In addition to mutations to enzymes which are involved in drug elimination, another aberration which has the potential to affect human drug metabolism is mutations to transport proteins. The ATP binding cassette (ABC) family of transport proteins comprises 50 different members in humans which have been the subject of much research owing to their ubiquity, being highly expressed at the apical membranes of cells which interact most directly with xenobiotic compounds such as intestinal enterocytes, hepatocytes and the renal epithelium [24]. They are also expressed in brain capillary endothelial cells forming the blood–brain barrier.

ABCB1 (also known as p-glycoprotein and MDR1) is the most prominent example of an ABC protein. It undergoes ATP binding and subsequent hydrolysis, propagating the efflux of molecules from the cell. The *ABCB1* gene is susceptible to single nucleotide polymorphisms which may be inherited individually or as a haplotype. In 2014, He et al. conducted a study which concluded that individuals with two of these variants, the CG haplotype (C3435T and G2677T) were more likely to experience chemotherapy induced nausea and vomiting despite receiving ondansetron. The authors suggested that as the CG haplotype was associated with greater *ABCB1* expression, those individuals might have a decrease in levels of CNS accumulation of ondansetron [25], showing that variations in the genotype of transport proteins have the potential to affect drug function and patient response [26].

Drug receptors themselves also represent sources of polymorphisms which have an effect on the efficacy and pharmacodynamics properties of their drug ligands. The β2 adrenergic receptor (also known as *ADRB2*) gene is located at chromosome 5q31-32 and at least nine polymorphisms have been identified at its coding region [27]. In 2006, Smiley et al. investigated hypotension in the context of obstetric spinal anaesthesia and found that women who were homozygotes for the Gly16 or Glu27 polymorphisms required lower dosages of ephedrine to raise their systolic blood pressure [28]. In 2015, the same authors this time investigated the role of phenylephrine in counteracting hypotension seen following spinal anaesthesia for Caesarean section and found that women homozygous for Gly16 in the *ADRB2* gene also required a lower phenylephrine dose to regain adequate systolic blood pressure control (though the effect was lesser than that seen with ephedrine) [29].

Existing research has elucidated that genetic and molecular variations in drug enzymes, transport proteins and receptors have the potential to greatly affect a given drug's metabolism, rate of uptake, excretion, and ultimately its efficacy and potential for toxicity. These molecular variations represent attractive targets for future pharmacogenetic investigation and research.

## 4. Pharmacogenomics as applied to perioperative medicine

### Implications for perioperative care

The data in Tables 2 and 3 lists a selection of genetic variants in anaesthetic drugs which contribute to the differences seen in efficacy, pharmacokinetics, and side effects which patients may experience during the perioperative period. The data generated

**Table 3**
Pharmacogenetics of other perioperative medications.

| Drug | Description | Gene(s) affected by polymorphism | Genetic variant | Phenotypic effect of polymorphism |
|---|---|---|---|---|
| Fentanyl | μ-opioid receptor agonist inhibiting neurotransmission | *OPRM1* | 304 A/G | Variations in median effective dose required to achieve analgesic effect [38] |
| Suxamethonium | Depolarising neuromuscular blocker | *BChE* | 293A > G<br>1699G > A<br>695T > A | Reduced hydrolysis, increased duration of action leading to prolonged neuromuscular blockade and apnoea [39] |
| | | *RYR1* | Multiple at 19q13.1 | Malignant hyperthermia [40] |
| | | *CACNA1S* | c520C > T | Malignant hyperthermia [41] |
| Rocuronium | Non-depolarising neuromuscular blocker | *SLCO1B1*<br>*ABCB1* | rs2306283 A > G<br>rs1128503 C > T | Reduced elimination, increased duration of action and recovery time [42] |
| Ondansetron | Anti-emetic 5-HT3 receptor antagonist | *ABCB1* | 2677 TT<br>3435 TT | Increased bioavailability, reduction in PONV [43] |

from the mining of genetic sequences and variants has the potential to be applied to a number of different perioperative drugs and anaesthesia related conditions which are discussed below.

One example of how drug interactions based on genetic variations can affect clinical practice is the management of malignant hyperthermia (MH). MH is an autosomal dominant condition characterised by hypermetabolism, hypoxia, hypercapnia and hyperthermia resulting from abnormal calcium homeostasis. This is thought to be due to mutations in the ryanodine receptor gene (*RYR1*) in 70% of cases. Mutations to the CACNA1S gene are thought to be the cause in 1% of the population [44].

MH is triggered by volatile anaesthetics or suxamethonium (detailed in Table 2), so for this reason dantrolene (a skeletal muscle relaxant which inhibits calcium release from the sarcoplasmic reticulum) is now kept in theatres and recovery areas. All patients suspected of having experienced MH undergo a muscle biopsy which undergoes contracture testing by being exposed to halothane and caffeine: contraction is a positive result. Patients whose MH status is positive or equivocal can then receive medic alert bracelets and should receive MH-safe anaesthesia e.g. total intravenous anaesthesia (TIVA) in place of gaseous anaesthesia in subsequent operations. The MH mortality rate has fallen from a peak of 80%–5% [45] due to the supportive measures detailed above, particularly the use of dantrolene and effective testing.

One condition which may represent a future target for pharmacogenomic research as applied to anaesthetics is the propofol infusion syndrome (PRIS), a potentially fatal condition characterised by metabolic acidosis, rhabdomyolysis, and arrhythmias which occurs following prolonged propofol administration (>48 h) at high doses (>4 mg/kg/h) [46]. The precise aetiology of this condition is unknown, but a case report by Karakitsos et al. (2007) suggested that it may have a genetic basis and that patients who have experienced PRIS should undergo genotyping so that genetic screening might be developed [47]. If such screening is successfully developed on the basis of current and future pharmacogenomic data - with high specificity - patients could be appropriately selected for TIVA, and the incidence of PRIS could be reduced.

The prospect of generating genetic profiles which allow an individual's treatment regimen to be personalised to their specific pharmacokinetic genotype is a deeply exciting one. Individuals could be screened in order to determine their metabolic status when it comes to speed of elimination of opiate analgesics. This could lead to an improvement in therapeutic efficacy and a reduction in cases of drug toxicity, especially for medications which have a narrow therapeutic window. For example poor CYP metabolisers could be more carefully monitored for signs of toxicity or receive non-opiate analgesia if appropriate. Similarly, those with opiate receptor polymorphisms (as with fentanyl, presented in Table 3) could receive accurate drug dosages titrated to their personal capacity for drug metabolism and rate of elimination. This could lead to a reduction in the incidence of perioperative morbidity and mortality.

The recent data published in Mei et al.'s study (2015) and presented in Table 3 suggests that rocuronium's pharmacokinetics and efficacy may also be influenced by pharmacogenetic factors with a longer duration of action observed with SLCO1B1 and ABCB1 gene variants. A blood test already exists for BChE (pseudocholinesterase) deficiency which utilises dibucaine to indicate if an individual is homozygotic for the mutant alleles and thereby likely to be susceptible to prolonged blockade and apnoea in the event of suxamethonium administration; further studies into the pharmacogenomics of rocuronium might mean that similar tests could also be developed for the non-depolarising neuromuscular blockers such as rocuronium.

## 5. Concluding remarks

The cost of sequencing an individual's DNA in the clinical setting in 2015 is estimated to be approximately $3000 and declining [48]. As the prospect of sequencing a genome for $1000 or less gradually becomes feasible, it is hoped that data mining efforts can be redoubled. Whilst this has immense potential for breakthroughs in identifying novel polymorphisms, the ethical implications of pharmacogenomic research will also need to be considered, not least in determining the most optimum way of storing patient data in a safe yet accessible manner.

In conclusion, as the cost of gene sequencing technology falls and the number of genome wide association studies evaluating the effect of genetic polymorphisms on drug responses rises, there is potential that the evidence base generated from pharmacogenomic data can be translated into appropriate clinical guidelines which will complement existing anaesthetic considerations in order to deliver the best possible care to patients based on their unique genetic variations, thereby improving perioperative care and maximising patient outcomes.

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Arash Behrooz – sole author.

## Conflicts of interest

None.

## Guarantor

Arash Behrooz.

## Consent

N/A.

## References

[1] Francis S. Collins, Eric D. Green, Alan E. Guttmacher, Mark S. Guyer, A vision for the future of genomics research, Nature 422 (6934) (2003) 835–847.
[2] T. Ama, S. Bounmythavong, J. Blaze, M. Weismann, M.S. Marienau, W.T. Nicholson, Implications of pharmacogenomics for anesthesia providers, AANA J. 78 (5) (2010) 393–399.
[3] D.W. Nebert, Pharmacogenetics and pharmacogenomics: why is this relevant to the clinical geneticist? Clin. Genet. 56 (4) (1999) 247–258.
[4] A.K. Daly, Pharmacogenetics: A historical perspective, in: A.H. Maitland-van der Zee, A.K. Daly (Eds.), Pharmacogenetics and Individualised Therapy, John Wiley & Sons Inc, Hoboken NJ, 2012, p. 6.
[5] D.J. Morris-Rosendahl, B.L. Fiebich, The future of genetic testing for drug response, Dialogues Clin. Neurosci. 6 (1) (2004) 27–37.
[6] C. Xu, C.Y. Li, A.N. Kong, Induction of phase I, II and III drug metabolism/transport by xenobiotics, Arch. Pharm. Res. 28 (3) (2005) 249–268.
[7] T.H. Rushmore, A.N. Kong, Pharmacogenomics, regulation and signaling pathways of phase I and II drug metabolizing enzymes, Curr. Drug Metab. 3 (5) (2002) 481–490.
[8] A.R. Harper, E.J. Topol, Pharmacogenomics in clinical practice and drug development, Nat. Biotechnol. 30 (11) (2012) 1117–1124.
[9] I. Walker, I. Wilson, General Considerations, in: K.G. Allman, I.H. Wilson (Eds.), Oxford Handbook of Anaesthesia, third ed., Oxford University Press, New York, 2011, p. 4.
[10] T.G. Weiser, S.E. Regenbogen, K.D. Thompson, A.B. Haynes, S.R. Lipsitz,

W.R. Berry, A.A. Gawande, An estimation of the global volume of surgery: a modelling strategy based on available data, Lancet 372 (9633) (2008) 139–144.
[11] R.M. Pearse, R.P. Moreno, P. Bauer, et al, Mortality after surgery in Europe: a 7 day cohort study, Lancet 380 (9847) (2012) 1059–1065.
[12] M.R. Sury, J.H. Palmer, T.M. Cook, J.J. Pandit, The state of UK anaesthesia: a survey of National Health Service activity in 2013, Br. J. Anaesth. 113 (4) (2014) 575–584.
[13] J.H. Schiff, A. Welker, B. Fohr, A. Henn-Beilharz, U. Bothner, H. Van Aken, A. Schleppers, H.J. Baldering, W. Heinrichs, Major incidents and complications in otherwise healthy patients undergoing elective procedures: results based on 1.37 million anaesthetic procedures, Br. J. Anaesth. 113 (1) (2014) 109–121.
[14] R. Hines, P.G. Barash, G. Watrous, T. O'Connor, Complications occurring in the postanesthesia care unit: a survey, Anesth. Analg. 74 (4) (1992) 503–509.
[15] J.J. Pandit, T.M. Cook, W.R. Jonker, E. O'Sullivan, A national survey of anaesthetists (NAP5 baseline) to estimate an annual incidence of accidental awareness during general anaesthesia in the UK, Br. J. Anaesth. 110 (4) (2013) 501–509.
[16] A. Kant, P.M. Hopkins, Adverse Drug Reactions, in: H.C. Hemmings Jr., T.D. Egan (Eds.), Pharmacology and Physiology for Anesthesia, Elsevier Saunders, Philadelphia, 2013, p. 96.
[17] J. van der Weide, J.W. Hinrichs, The influence of cytochrome P450 pharmacogenetics on disposition of common antidepressant and antipsychotic medications, Clin. Biochem. Rev. 27 (1) (2006) 17–25.
[18] U.M. Zanger, M. Schwab, Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation, Pharmacol. Ther. 138 (1) (2013) 103–141.
[19] S.C. Preissner, M.F. Hoffmann, R. Preissner, M. Dunkel, A. Gewiess, S. Preissner, Polymorphic cytochrome P450 enzymes (CYPs) and their role in personalized therapy, PLoS One 8 (12) (2013). E-Publication.
[20] V. Dolžan, Pharmacogenetics in drug metabolism: role of Phase I Enzymes, in: A.H. Maitland-van der Zee, A.K. Daly (Eds.), Pharmacogenetics and Individualised Therapy, John Wiley & Sons Inc, Hoboken NJ, 2012, p. 15.
[21] G. Umamaheswaran, D.K. Kumar, C. Adithan, Distribution of genetic polymorphisms of genes encoding drug metabolizing enzymes & drug transporters - a review with Indian perspective, Indian J. Med. Res. 139 (1) (2014) 27–65.
[22] M. Pirmohamed, Pharmacogenetics: past, present and future, Drug Discov. Today 16 (19–20) (2011) 852–861.
[23] C.F. Samer, K.I. Lorenzini, V. Rollason, Y. Daali, J.A. Desmeules, Applications of CYP450 testing in the clinical setting, Mol. Diagn Ther. 17 (3) (2013) 165–184.
[24] J. Xiong, D. Mao, L. Liu, Research progress on the role of ABC transporters in the drug resistance mechanism of intractable epilepsy, BioMed. Res. Int. 2015 (2015), http://dx.doi.org/10.1155/2015/194541.
[25] H. He, J.Y. Yin, Y.J. Xu, X. Li, Y.2 Zhang, Z.G. Liu, F. Zhou, M. Zhai, Y. Li, X.P. Li, Y. Wang, H.H. Zhou, Z.Q. Liu, Association of ABCB1 polymorphisms with the efficacy of ondansetron in chemotherapy-induced nausea and vomiting, Clin. Ther. 36 (8) (2014) 1242–1252.
[26] L. Silverton, M. Dean, K. Moitra, Variation and evolution of the ABC transporter genes ABCB1, ABCC1, ABCG2, ABCG5 and ABCG8: implication for pharmacogenetics and disease, Drug Metabol. Drug Interact. 26 (4) (2011) 169–179.
[27] A.C.Z. De Paiva, F.A. Marson, L. de, J.D. Ribeiro, C.S. Bertuzzo, Asthma: Gln27Glu and Arg16Gly polymorphisms of the beta2-adrenergic receptor gene as risk factors, Allergy Asthma Clin. Immunol. 10 (1) (2014) 8.
[28] R.M. Smiley, J.L. Blouin, M. Negron, R. Landau, beta2-adrenoceptor genotype affects vasopressor requirements during spinal anesthesia for cesarean delivery, Anesthesiology 104 (4) (2006) 644–650.
[29] L. Odekon, R. Landau, J.L. Blouin, D. Brodow, S. Wang, R.M. Smiley, The Effect of β2-Adrenoceptor Genotype on Phenylephrine Dose Administered During Spinal Anesthesia for Cesarean Delivery, Anesth. Analg. 120 (6) (2015) 1309–1316.
[30] M.S. Khan, E.L. Zetterlund, H. Gréen, A. Oscarsson, A.L. Zackrisson, E. Svanborg, M.L. Lindholm, H. Persson, C. Eintrei, Pharmacogenetics, plasma concentrations, clinical signs and EEG during propofol treatment, Basic Clin. Pharmacol. Toxicol. 115 (6) (2014) 565–570.
[31] M.S. Khan, E.L. Zetterlund, H. Gréen, A. Oscarsson, A.L. Zackrisson, E. Svanborg, M.L. Lindholm, H. Persson, C. Eintrei, Pharmacogenetics, plasma concentrations, clinical signs and EEG during propofol treatment, Basic Clin. Pharmacol. Toxicol. 115 (6) (2014) 565–570.
[32] M.G. Chelu, S.A. Goonasekera, W.J. Durham, W. Tang, J.D. Lueck, J. Riehl, I.N. Pessah, P. Zhang, M.B. Bhattacharjee, R.T. Dirksen, S.L. Hamilton, Heat- and anesthesia-induced malignant hyperthermia in an RyR1 knock-in mouse, FASEB J. 20 (2) (2006) 329–330.
[33] B.P. Sweeney, Do genes influence outcome from anaesthesia? Br. J. Anaesth. 90 (6) (2003) 725–727.
[34] K. Sanem Cakar Turhan, Volkan Baytaş, Yeşim Batislam, Oya Özatamer, Delayed Onset Malignant Hyperthermia after Sevoflurane, Case Rep. Anesthesiol. 2013 (2013) 3. Article ID 712710.
[35] Y. Li, J.K. Coller, M.R. Hutchinson, K. Klein, U.M. Zanger, N.J. Stanley, A.D. Abell, A.A. Somogyi, The CYP2B6*6 allele significantly alters the N-demethylation of ketamine enantiomers in vitro, Drug Metab. Dispos. 41 (6) (2013) 1264–1272.
[36] M. Cohen, S. Sadhasivam, A.A. Vinks, Pharmacogenetics in perioperative medicine, Curr. Opin. Anaesthesiol. 25 (4) (2012) 419–427.
[37] E.B. Liem, T.V. Joiner, K. Tsueda, D.I. Sessler, Increased sensitivity to thermal pain and reduced subcutaneous lidocaine efficacy in redheads, Anesthesiology 102 (3) (2005) 509–514.
[38] R. Landau, C. Kern, M.O. Columb, R.M. Smiley, J.L. Blouin, Genetic variability of the mu-opioid receptor influences intrathecal fentanyl analgesia requirements in laboring women, Pain 139 (1) (2008) 5–14.
[39] H. Delacour, S. Lushchekina, I. Mabboux, et al, Characterization of a Novel*BCHE* "Silent" Allele: Point Mutation (p.Val204Asp), in: F. Rodrigues-Lima (Ed.), Causes Loss of Activity and Prolonged Apnea with Suxamethonium, 2014. PLoS One. 9(7):e101552.
[40] R.S. Litman, H. Rosenberg, Malignant hyperthermia: update on susceptibility testing, JAMA 293 (23) (2005) 2918–2924.
[41] D. Carpenter, C. Ringrose, V. Leo, A. Morris, R.L. Robinson, P.J. Halsall, , et al.M.-A. Shaw, The role of *CACNA1S* in predisposition to malignant hyperthermia, BMC Med. Genet. 10 (2009) 104, http://dx.doi.org/10.1186/1471-2350-10-104.
[42] Y. Mei, S.-Y. Wang, Y. Li, S.-Q. Yi, C.-Y. Wang, M. Yang, K.-M. Duan, Role of SLCO1B1, ABCB1, and CHRNA1 gene polymorphisms on the efficacy of rocuronium in Chinese patients, J. Clin. Pharmacol. 55 (2015) 261–268.
[43] K. Farhat, M. Ismail, S. Ali, A.K. Pasha, Resistance to ondansetron: role of pharmacogenetics in post-operative nausea and vomiting, Egypt. J. Med. Hum. Genet. 14 (4) (2013) 331–336.
[44] H. Rosenberg, N. Sambuughin, S. Riazi, et al, Malignant Hyperthermia Susceptibility [Updated 2013 Jan 31], in: R.A. Pagon, M.P. Adam, H.H. Ardinger, et al. (Eds.), GeneReviews® [Internet], Seattle (WA): University of Washington, Seattle, 2003 Dec 19, pp. 1993–2015. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1146/.
[45] D.-C. Kim, Malignant hyperthermia, Korean J. Anesthesiol. 63 (5) (2012) 391–401.
[46] V. Fodale, E. La Monaca, Propofol infusion syndrome: an overview of a perplexing disease, Drug Saf. 31 (4) (2008) 293–303.
[47] D. Karakitsos, J. Poularas, A. Kalogeromitros, A. Karabinis, The propofol infusion syndrome treated with haemofiltration. Is there a time for genetic screening? Acta Anaesthesiol. Scand. 51 (2007) 644–645.
[48] T. Katsila, G.P. Patrinos, Whole genome sequencing in pharmacogenomics, Front. Pharmacol. 6 (2015) 61.