Omics and anaesthesia: pharmacogenomics, proteomics and metabolomics

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Abstract

Variation in response to drugs used in anaesthesia is seen between individuals and it is well established that patients' genetics are a major influence. Our understanding of the role differences in the genome play, especially by identifying genetic polymorphisms of interest, is improving. This may lead to greater availability of precision anaesthesia involving drug choices and dosages tailored to individuals' genetic makeup. Furthermore, analysis of the downstream products of gene transcription, in particular of proteins and metabolic products, may allow further treatment personalisation. Prospective genetic testing is already used in specific situations but despite an improved ability to test patients and better understanding of relevant genetic polymorphisms, practical considerations remain before pharmacogenomic-, proteomic- or metabolomic-guided precision anaesthesia is likely to become routinely available. Nevertheless this point in time may be drawing closer. It is therefore important for anaesthesia practitioners to have a comprehensive understanding of the underlying science of pharmacogenomics, proteomics and metabolomics; as well as knowledge of important polymorphisms of interest with respect to anaesthetic drugs and their clinical implications.

Keywords: Anaesthesia, genetic polymorphisms, genetic testing, metabolomics, pharmacogenetics, pharmacogenomics, pharmacology, precision medicine, proteomics, single nucleotide polymorphisms

Learning objectives

After reading this article you should be able to:

- Describe the concepts of pharmacogenomics, proteomics and metabolomics
- Explain the underlying genetic science relevant to the variability in the response to drugs between individuals
- Recognise significant genetic polymorphisms relevant to commonly used anaesthetic drugs and their anticipated clinical implications
- Discuss current practice and anticipated future developments of using genetic analysis to tailor drug choices to individuals in anaesthesia

Royal College of Anaesthetists CPD Skills Framework: Scientific principles - Pharmacology and therapeutics

Introduction

Tailoring treatments to particular attributes of an individual, as opposed to offering a 'one size fits all' approach, is known as 'precision' or 'personalised' medicine. Simple examples of this in anaesthesia include age- and weight-based dosing in total intravenous anaesthesia and the use of age-related minimal alveolar concentration with inhalational anaesthesia. Since completion of the Human Genome Project[1] our ability to analyse an individual's genetic profile has improved at pace, and the prospect of broadening the use of genetic information to inform precision medicine is growing.

Rather than identifying and managing undesired effects after commencing treatment, genetics-guided precision medicine could allow them to be predicted and avoided. Similarly, it could help predict for which individuals a treatment would be particularly effective or ineffective, rather than simply judging afterwards. At present, this has only narrow applications in anaesthesia. In this article we discuss current knowledge, the underpinning basic science, and what the future may hold for using genetic information to deliver precision anaesthesia.

Background science

Pharmacogenomics, proteomics and metabolomics

It is well established that genes influence the clinical effects of drugs. Well known examples in anaesthesia include malignant hyperthermia (MH), suxamethonium apnoea and opioid-metabolising enzymes. Genetic factors influencing efficacy of drugs are not confined to these examples, they play a role in the variation of action of almost all drugs. Examining the effect of a gene on drug action is termed 'pharmacogenetics'.

If it were always the case that a single gene was responsible for the clinical efficacy of a drug, the road to precision medicine may comparatively simple, yet most cases involve many genes, each with multiple possible polymorphisms. Every time a drug interacts with a protein coded by deoxyribose nucleic acid (DNA), there is a potential for variation in response, based on the gene that protein was produced from. Therefore, predicting clinical responses to the multitude of drugs used in anaesthesia would require a profile of a large number of individual genes, or possibly, the entire genome. In contrast to pharmacogenetics which looks at individual genes, studying the effect of the genome on drug action is 'pharmacogenomics'.

Even if individual-patient genome sequencing were achieved, it could still only approximate how the drug might change the patient's physiology. A more direct assessment would be to analyse changes of the tissues of interest in terms of the proteins present or the metabolites produced due to effects of the drug, i.e. the end result of drug action. Having this information available could complement existing pharmacogenomic information to further individualise drug management. The study of the entire protein or metabolic profile of cells, tissues or entire organisms (the proteome and metabolome respectively) are termed 'proteomics' and 'metabolomics'. Proteomic and metabolomic studies combine modern techniques for biomolecular analysis such as liquid chromatography-tandem mass spectrometry, with the processing of complex bioinformatic data sets, often using machine learning techniques to deal with large volumes of data.

Except in specific individuals (for example, where there is a family history of MH) the use of genetic data to tailor delivery of anaesthetic drugs is not yet widely utilised in routine anaesthetic practice. Aside from concerns around cost,[2] our understanding of which genes (and associated polymorphisms) influence the pharmacology of various drugs *in vivo* remains incomplete. However, our knowledge in this area is ever-increasing and many important polymorphisms of significance to anaesthesia have been identified.

Genetics

Pharmacogenomic variation in an individual's physiological response to a dose of a drug begins with their genome – genetic information contained within chromosomes as DNA. This consists of the nucleotide bases cytosine, guanine, adenine and thymine. Sequences of bases lie along two ribose phosphate backbone strands, creating base-pairs joined by hydrogen bonds across the strands (cytosine with guanine, adenine with thymine) producing the well-known double helix structure. Three bases in sequence create a codon, which codes for an amino acid when transcribed. Some amino acids can be coded for by multiple codons, which is why there are 64 possible codons but only 20 amino acids.

There are different ways in which the base sequence can be altered. The most common types of mutations are single nucleotide polymorphisms (SNPs)[3]; where a single base is inserted, deleted or substituted. A substitution may or may not change the amino acid (and therefore protein) produced by the involved codon due to there being more codon possibilities than amino acids. These are termed non-synonymous and synonymous mutations respectively. An insertion or deletion has more potential to change the resultant protein due to the entire sequence after the mutation being shifted forwards or backwards by one base.

Different versions of the nucleotide base sequence at a given genomic location are called alleles.[4] The commonest, or standard, variant is called the 'wild type'. When considering genetic influences on drug response, it is important to identify the specific gene alleles of interest, especially those different to the wild type. The majority of these are due to SNPs. One research approach to identity relevant SNPs is through genome-wide association studies (GWAS), where entire genomes of individuals displaying a certain trait are examined to find SNPs which occur frequently in that group.[4]

Hierarchy of the omics

There are multiple steps from DNA to protein synthesis, each of which can be a source of further inter-individual variation:

Only approximately 1.5% of an individual's DNA codes for amino acids and therefore proteins.[4] Each amino acid-coding portion within a gene is called an exon, and their entirety within the genome is the exome. The remaining genetic information does not code directly for amino acids but may be involved in regulating gene expression; these portions are called introns. As well as exons, mutations can occur in introns, which may lead to variation in the amount of protein produced.

Exons are transcribed into messenger ribonucleic acid (mRNA) via the action of RNA polymerase as an intermediate step before proteins are then translated. The primary mRNA transcript produced can be altered prior to translation, for example by 5'-end capping, splicing of out introns and 3'-end cleavage.[5] These steps are controlled by RNA-binding proteins which can have mutations of their own.

mRNA is translated into protein. Once produced, proteins can undergo further post-translational changes such as phosphorylation or glycosylation, which is another source of variation between individuals. As such, there are more proteins in the body than there are genes.[6] Therefore, to consider the effect of all proteins present in a cell or tissue, all those beyond the translational stage need consideration. At the end of cellular processes, controlled by enzymes (which are proteins), metabolites are produced. Examination of the metabolome can therefore provide information on these processes and the proteins involved, complementing proteomic data.

Each of these steps produces a hierarchy, which Lambert refers to as the 'hierarchy of the omics'[3] (Figure 1). When considering the potential for delivering precision medicine, the genome is most likely to impact clinical practice in the near future, especially as more mutations of interest are identified. However, there are already areas where proteomics and metabolomics show potential. For example, it has been found that

perioperative fasting and general anaesthesia affects over 40% of the plasma proteome.[7] Further research into the significance of this could have implications for preoperative optimisation of patients.

Other areas where proteomic analysis may be useful include pain management, disease biomarkers, central nervous system injury, myocardial injury and ischaemic preconditioning.[8] Most drugs affect metabolism in some way and therefore alter the metabolome. For example, sevoflurane has been found to affect the tricarboxylic acid cycle and glutamate metabolism.[9] Metabolomic profiling may one day allow tailoring of anaesthetic drugs to avoid undesired effects such as pain or nausea.[8]

Genetic influences on drug response

Variation in the gene coding for any protein with which drugs interact may lead to differences in clinical effects. Broadly, these can be classified into pharmacokinetic variation and pharmacodynamic variation, the latter including effects on the drug target. Pharmacokinetic variation can lead to differences in absorption, distribution, metabolism or elimination. Pharmacodynamic variation can be due to differences in ion channels, enzymes, transporters or receptors. This may impact the desired response, side effects, or produce an idiosyncratic reaction, alone or in combination. The most common genetic polymorphisms of interest to the anaesthetist are those of transport proteins, target receptors and metabolic enzymes particularly the cytochrome p450 (CYP450) system.

Sedative drugs

Propofol

Propofol produces sedation by activating gamma-aminobutyric acid (GABA) receptors, chloride ion channels which cause cell membrane hyperpolarisation and inhibition of neuronal transmission.[10] It has two main metabolic pathways. Phase I metabolism is via the CYP450 system, mainly hydroxylation via CYP2B6 but also via CYP2C9. The product is 4-hydroxypropofol, which has approximately one-third the hypnotic activity of the parent drug.[11] Phase II metabolism involves glucuronidation via uridine 5'-diphospho-glucuronosyltransferase 1A9 (UGT1A9).[11] The ratio of hydroxylation to glucuronidation varies between individuals which may account for differences in propofol sensitivity, with polymorphisms in CYP2B6 being most important.[11] This is possibly due to variable hydroxylation to 4-hydroxypropofol.[11] Polymorphisms of UGT1A9 have been found to prolong the duration of action of propofol, likely due to decreased inactivation via glucuronidation[11] (Figure 2).

Polymorphisms in the genes coding for GABA receptors may also affect propofol susceptibility. A study involving Chinese women found that an SNP in the $GABA_A$ receptor alpha 1 subunit (GABRA1) increased susceptibility to sedation by propofol.[12] The same study found an SNP in the beta 2 subunit lowered susceptibility.

Serotonin is a neurotransmitter in the central nervous system (CNS) acting on multiple types of 5-hydroxytryptamine receptors. Carriers of the minor allele for 5-HT2A receptors have been found to require a lower propofol dose than those with the wild type, with a 40% decrease in time of onset.[11]

As well as efficacy there appears to be genetic influence on cardiovascular response to propofol. Dominant mutations in GABRA1, GABRA2 and the muscarinic cholinergic receptor CHRM2 have all been shown to increase cardiovascular susceptability.[13]

Ketamine

Ketamine non-competitively antagonises the glutamate N-methyl-D-aspartate (NMDA) receptor. It undergoes N-demethylation to norketamine via CYP2B6 and CYP3A4. Although CYP3A4 is the predominant metabolic pathway it appears CYP2B6 polymorphisms are the main influence on action variability.[8] The

CYP2B6*6 allele reduces drug clearance, leading to higher plasma concentrations and adverse effects in chronic pain patients.[13]

Benzodiazepines

Like propofol, benzodiazepines are metabolised via cytochrome p450 and UGT enzyme pathways.[8] It was hypothesised that, due to the polymorphic nature of CYP3A4 and CYP3A5 enzymes, midazolam would exhibit phenotypic variability with the presence of different alleles. However, this has not been consistently shown in research. The allele of most significance appears CYP3A4*22 which reduces midazolam metabolism, but the effect of this on susceptibility to sedation is yet to be explored.[14]

Midazolam also acts via $GABA_A$ receptors in the CNS. One polymorphism coding for GABRA1 has been found to increase the sedative effect; rs4263535 is a A>G substitution which produces this phenotype.[13] Other polymorphisms have been found to decrease effectiveness of diazepam at the GABA receptor.[15]

Dexmedetomidine

Dexmedetomidine is a highly-selective alpha-2 adrenergic receptor agonist used for sedation and analgesia. Recently, several genes coding for proteins influencing both pharmacodynamic and pharmacokinetic mechanisms, have been proposed as affecting sedative efficacy and haemodynamic stability.[16] The most important of these appear the transporter protein ABCG2, the CYP450 enzyme CYP2D6 and subunits of both alpha-2 (ADRA2A, mutation rs1800544 in particular) and beta-2 (ADRB2) adrenergic receptors.[16]

Inhalational anaesthetic agents

Inhaled anaesthetic agents cross the alveolar-capillary membrane, enter the systemic circulation and have action in the CNS. They distribute rapidly to target tissues due to their high lipophilicity and are mostly excreted unchanged via the lungs with only a small amount metabolised. Due to these pharmacokinetic properties, their action is less subject to genetic polymorphisms in transporter proteins and metabolic enzymes. Most genetic influences on inter-individual variability are therefore pharmacodynamic, due to mutations in genes coding for the various target receptors.

While the mechanisms of action remain incompletely understood, it is thought that multiple receptor targets are involved, with the end effect of either increasing inhibitory or decreasing excitatory action.[13] These include $GABA_A$, serotonin 5-HT3, nicotinic acetylcholine, NMDA receptors, and voltage-gated cation channels.[13] An example of a relevant polymorphism is the GRIN1 gene which codes for a subunit of the NMDA receptor. Two SNPs have been found to increase the length of time to loss of consciousness upon exposure to sevoflurane.[11] Overall, it is thought unlikely that a single polymorphism of any of the genes coding for these receptors has major clinical significance, due to the apparent variety of target sites at which volatile agents act.[13]

Mutations to genes coding for subunits of the ryanodine receptor (RYR1) and dihydropyridine receptor (CACNA1S) can cause MH when a patient is exposed to inhalational agents or suxamethonium. The reaction involves hypermetabolism of skeletal muscle due to sustained activity. The relevant gene mutations are inherited in an autosomal dominant fashion.

Dihydropyridine receptors are voltage-sensitive L-type calcium channels and sit in the sarcolemma. Upon depolarisation e.g. by an action potential, they activate ryanodine receptors on the sarcoplasmic reticulum. This allows calcium efflux from the sarcoplasmic reticulum leading to excitation-contraction coupling. Polymorphisms of the RYR1 gene are the commonest cause of MH, accounting for approximately 70% of cases.[17] Genetic testing can be difficult due to the large gene size, locus heterogeneity (where different mutations at multiple points in the gene produce the same phenotype) and the fact that some loci have not been identified.[17] At the time of writing, 65 substitution and one deletion mutation in RYR1 have been found to be associated with MH.[18]

The CACNA1S gene codes for the α_{1S} subunit of dihydropytidine receptors and is a smaller gene than RYR1. Mutations in CACNA1S account for only 1% of MH cases. Two causative mutations have been found, both substitution SNPs.[18]

Neuromuscular blocking drugs

Neuromuscular blocking agents can be categorised as depolarising or non-depolarising. Depolarising drugs act similarly to acetylcholine (ACh) to activate the receptors, depolarising the muscle cell membrane and preventing further action. Non-depolarising drugs act as competitive antagonists.

Suxamethonium

Alongside causing MH via the mechanism described above, the other notable adverse reaction of suxamethonium is prolonged paralysis due to varying action of the butyrylcholinesterase (BChE) enzyme. This is produced in the liver, circulates in plasma and normally hydrolyses the drug within minutes to succinylmonocholine, succinic acid and choline. The BChE gene is highly polymorphic and 65 mutations have been found which can lead to prolonged neuromuscular blockade.[19] Many have been named: the Kalow variant (K) is most common with 1 in 65 people being homozygotes; activity is decreased by 30% and prolongation of paralysis is mild. Homozygotes for the fluoride-resistant (F) variant prolongs paralysis to 1–2 hours. Atypical or dibucaine-resistant (A) variant prolongs to over two hours. The silent (S) variant removes all enzyme activity leading to extremely prolonged blockade.[19] All these mutations are SNPs.

Rocuronium

Rocuronium is a non-depolarising neuromuscular blocker. A small amount is deacetylated prior to elimination and may be subject to polymorphisms in CYP450 enzymes, particularly CYP3A4.[11] The majority is excreted unchanged in bile, and the remainder in urine.[10] The genes which play the largest role in inter-individual variability code for transport proteins.

Biliary elimination depends on hepatic uptake by organic anion transporting polypeptides 1A2 (OATP1A2) and 1B1 (OATP1B1). These proteins are coded for by SLCO1A2 and 1B1 genes respectively, which are highly polymorphic.[8] They lie on the basolateral membrane of hepatocytes with a role in uptake of numerous substances,[11] which are later excreted. An SNP of SLCO1A2 reduces rocuronium clearance[13] (Figure 3). This would be hypothesised to increase duration of action. Similarly, a mutation of SLCO1B1 has been found to prolong block time due to reduced hepatic elimination and subsequent plasma accumulation.[13]

Adenosine triphosphate (ATP) binding cassettes (ABC) are found in a number of intracellular and extracellular membranes, and are also involved in substance transport.[20] One member of this group (ABCB1) codes for P-glycoprotein (P-gp) which transports various substances out of cells, including rocuronium which is moved out of hepatocytes into bile for excretion.[11] This is another highly polymorphic protein, with mutations found that shorten recovery time from neuromuscular blockade.[11]

The NE1I2 gene codes for the pregnane X receptor, which is a nuclear receptor involved in transcription regulation.[11] Examples of genes it regulates include OATP1A2, OATP1B1, P-gp and CYP3A4; all of which have implications for rocuronium elimination.[11] Recently, two mutations of NR1I2 have been found to prolong rocuronium blockade.[11]

Opioid analgesics

Many opioids are also substrates for P-gp coded by ABCB1. These transporters are found in the kidney, intestine and blood-brain barrier, as well as the liver.[21] Polymorphisms in P-gp at the blood-brain barrier are likely to influence clinical effects, where it transports substances from the CNS into the blood in an ATP-dependent manner.[22] Mutations in ABCB1 tend to reduce pump effectiveness, leading to higher opioid concentrations remaining in the brain. Morphine and fentanyl are both subject to this.[22] SNPs have been found that

lead to higher brain morphine concentrations, reduced post-operative morphine requirements, increased fentanyl-induced respiratory depression and reduced fentanyl dosing requirement.[11,21,23]

Most of the desired clinical effects of opioids come from action at the mu opioid receptor. Action at this G-protein coupled receptor inhibits adenylyl cyclase, reducing cyclic adenosine monophosphate concentrations and subsequently inhibiting neuronal activation. It is coded by the OPRM1 gene. The SNP rs1799971 is an A>G substitution which has been widely studied and the G/G genotype leads to reduced analgesia with associated higher morphine requirements.[13] Either the G/G genotype has been found to require higher doses, or the A/A require lower doses; of fentanyl, sufentanil, alfentanil, codeine and tramadol.[13,22] Over 250 SNPs of OPRM1 have been found, with one further of note being rs9384179 which leads to increased fentanyl sensitivity.[22] This is notable because it is a substitution in an intron, rather than exon.[22] It therefore does not affect the amino acid sequence but rather alters OPRM1 expression.

Fentanyl

Fentanyl is metabolised by the CYP3A4 and CYP3A5 enzymes, with no active metabolites. The CYP3A4*1G variant is associated with lower efficacy and higher dose requirement[8,11] (Figure 4). Variants of CYP3A5 are also likely to have a role in clinical variability.[8]

Codeine

Codeine is a prodrug, metabolised into morphine by O-demethylation by CYP2D6. The highly polymorphic nature of CYP2D6 is well known and numerous alleles have been identified. Depending on the alleles present individuals can be classified as either poor, intermediate, normal or ultra-rapid metabolisers.[24] As the analgesic effect of codeine depends on metabolism to morphine, a range of therapeutic response is seen. Poor metabolisers may have no analgesic effect, whereas ultra-rapid metabolisers may experience toxicity. The Clinical Pharmacogenetics Implementation Consortium lists known CYP2D6 alleles and has produced guidelines on clinical management.[24] It recommends that poor and ultra-rapid metabolisers should avoid codeine, due to lack of efficacy in the former and risk of toxicity in the latter. There have been unfortunate cases of respiratory arrest amongst newborns of breastfeeding mothers, thought to be due to ultra-rapid metabolism and subsequent high morphine concentrations in breast milk.

Local anaesthetics

Genetic variation may be a factor in reduced local anaesthetic efficacy. Voltage-gated sodium channels are the drug target, preventing action potential propagation and reducing nociception. An *in vitro* experiment found that a polymorphism in SCN9A could contribute to lidocaine resistance.[13] Further studies are required to explore any clinical significance of this mutation. The SCN5A gene coding subunit alpha 5 in the same protein may also play a role, discovered after genotyping a family with some members who exhibited local anaesthetic resistance.

Current practice and future directions

One reason to identify polymorphisms relevant to anaesthesia would be to inform tailoring of drug choices and doses in pursuit of better patient outcomes. While promising in theory, there are practical considerations to address before routine genetic profiling can bring an era of precision anaesthesia:

Which genes and relevant alleles could be tested for?

The 100,000 Genomes Project launched in 2012 and aimed to sequence 100,000 genomes, which it achieved in 2018.[25] The infrastructure built in pursuit of this has accelerated integration of genomic medicine into the National Health Service. Currently, patients are eligible to have genetic testing if they meet the criteria of having certain rare or inherited diseases or certain cancers. In some cases, whole genome

sequencing (WGS) will be performed, for example in some foetal or neonatal cases. In others, selected genes (a 'panel') will be tested. If testing were to be used for the purposes of perioperative pharmacogenomics it is likely the latter that would be used, containing selected genes and relevant alleles based on research findings; many of those discussed already in this article could be part of this panel.

Some research has already attempted to create such gene panels. Although not in the field of anaesthesia, the PREPARE trial was an international multi-centre study that used a 12-gene panel to attempt to prevent adverse reactions prior to starting therapy.[26] Although relying on patient-reported outcomes, adverse drugs events were reduced by approximately 30%. It was found to be feasible with genotyping taking 1–7 days.

Testing of specific genes linked to adverse effects is already conducted in selected cases such as MH and suxamethonium apnoea. These conditions, along with Factor V Leiden thrombophilia were examined in one study using existing genetic data, with some patients diagnosed who would otherwise not have been identified from personal and family history alone.[27] There have been calls to work towards routine genomic testing for MH-causative genes in patients undergoing elective surgery, as one component of a strategy to end deaths from the disease.[28]

Does the technology exist to provide testing at scale, which is accurate and cost-effective?

Traditionally DNA was sequenced using Sanger sequencing and this is still applied today. The technique involves denaturing genetic material to separate the two strands, then adding a primer for DNA polymerase to begin action along a portion of the DNA.[29] The reaction ends when a dideoxy-nucleotide, which is also added, is incorporated and acts as a 'full stop', preventing the reaction continuing along that strand of material. The new strands produced by DNA polymerase undergo electrophoresis, are dyed, then run through a fluorescence detector to produce a chromatogram. The original DNA can then be determined base-by-base. The advantage of Sanger sequencing is its accuracy, but it is time-consuming and inefficient for multiple genes.

Next generation sequencing methods consist of several different techniques that are faster and cheaper, with many tests able to be run in parallel. They can be thought of as lots of smaller-scale Sanger sequences running concurrently. One downside is the genetic material examined is necessarily of short length e.g. 50–700 bases. Next-generation sequencing may be the approach of choice to enable large-scale pharmacogenomics.

Recent years have seen a rapid expansion in commercial genome testing, marketed for purposes of determining ancestry or informing clinical care. There have been cases when commercially obtained genetic information has been used in anaesthesia to tailor drug choice based on CYP450 and other metabolic enzyme genotype.[30] However, there are concerns about the quality of 'direct-to-consumer' testing due to lack of standardisation, risks of false positives/negatives, and lack of analysis for known alleles of clinical relevance.[31]

The cost of producing the first 'draft' genome by the Human Genome Project was estimated at $300 million.[32] Recently a target of $1000 per WGS has been set, and the current cost appears not far off.[32] As discussed, for the purposes of perioperative pharmacogenetics WGS is likely to be unnecessary and a panel of selected genes of interest tested for instead. The cost of testing a panel of 46 genes for solid tumour analysis was estimated to be £339 in 2017,[33] and would likely cost less now. As scale increases and technology improves, costs should continue to fall. Nevertheless, it is not known whether the benefits would justify the costs, as an economic analysis relevant to anaesthesia has not yet been conducted.

How should genetic information be stored within medical records and presented to clinicians?

PharmGKB is a database managed by Stanford University which allows clinicians to input known genotypes and receive prescribing advice, although it does not contain all genes which may be of interest to anaesthesia providers.[34] It integrates recommendations from the Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group and is a useful resource if genetic information is available for a patient.

The ImPreSS trial is currently underway and due to complete in 2027.[35] Patients are tested pre-operatively for a panel of genes of pharmacogenetic relevance. In one arm the information is available to anaesthesia providers and in the other it is not. The information is presented in a secure web-based portal which compares patients' genotype against a database of drugs, with each given a 'traffic light' rating to inform the clinician about safety and efficacy. In the pilot study for this trial, 71 operative events were examined, with the portal accessed in 41 of these (58%). Feedback suggested the information was easy to access and interpret, but noted a significant barrier was forgetting to access it as part of standard clinical workflow.[36] It is likely that a platform such as this would be required so pharmacogenetic information could be clinically useful, as expecting clinicians to remember a large number of alleles and their implications would pose significant challenge.

In the PREPARE study participants were given a card with information on their genotype relevant to commonly prescribed drugs.[26] It also contained a personal QR code which providers could scan to gain access to a platform offering patient-specific prescribing advice. This allowed patients to have ownership of access to their own records, providing reassurance where there may be concerns about privacy and third-party use of genetic information.

Does using pharmacogenetic data in clinical practice improve outcomes?

If there is no 'real world' benefit to using pharmacogenetic data, then the topic of pharmacogenomics loses relevance in clinical practice. Is there convincing evidence we should be moving towards pharmacogenetic-guided medicine at all, including in anaesthesia? Around 95% of the population carry at least one genetic variant of discordance to at least one drug, with there being ten drugs of relevance to the average patient.[37] It therefore follows that using information from pre-treatment pharmacogenetic screening to guide drug choices could be beneficial.

There are already cases of this being successfully implemented in other areas of medicine, where single genes of interest are examined. For example, there is strong evidence that those who carry one of the 'loss of function' alleles of the CYP2C19 gene involved in the metabolism of clopidogrel, show increased risk of recurrent cerebrovascular events.[38] In the UK, national guidance therefore recommends CYP2C19 genotyping prior to commencing clopidogrel after stroke or transient ischaemic attack.[39] Another example is genotyping of the DPYD gene to look for deficiency in dihydropyrimidine dehydrogenase, for which it codes. This enzyme is responsible for the breakdown of some chemotherapeutic agents including 5-fluorouracil, capecitabine and tegafur.[40] Dihydropyrimidine dehydrogenase deficiency can lead to toxicity and DPYD testing is therefore recommended in all patients prior to starting therapy.[40]

It is more difficult to determine differences in outcome from utilising prospectively-tested gene panels. One systematic review and meta-analysis examining pharmacogenetic-guided pathways, consisting mostly of studies utilising gene-panels, found that for those in primary care hospital admissions were halved.[37] The researchers acknowledged that several trials which would add to our knowledge in this area were underway at their time of writing, including PREPARE, which as noted above showed a substantial reduction in adverse drug reactions.[26]

In summary, current use of pharmacogenetic data to improve outcomes shows promise in other fields. The results of the ImPreSS study will be particular interest to anaesthetists as it appears to be the most comprehensive examination of applied pharmacogenomics in this setting. Overall, the direction of travel is towards increased integration of this information into clinical practice, especially as costs decrease and testing infrastructure improves. Clinicians will need to familiarise themselves with significant genetic variants of relevance to common anaesthetic drugs, understanding of the underpinning science and how these relate to practice.

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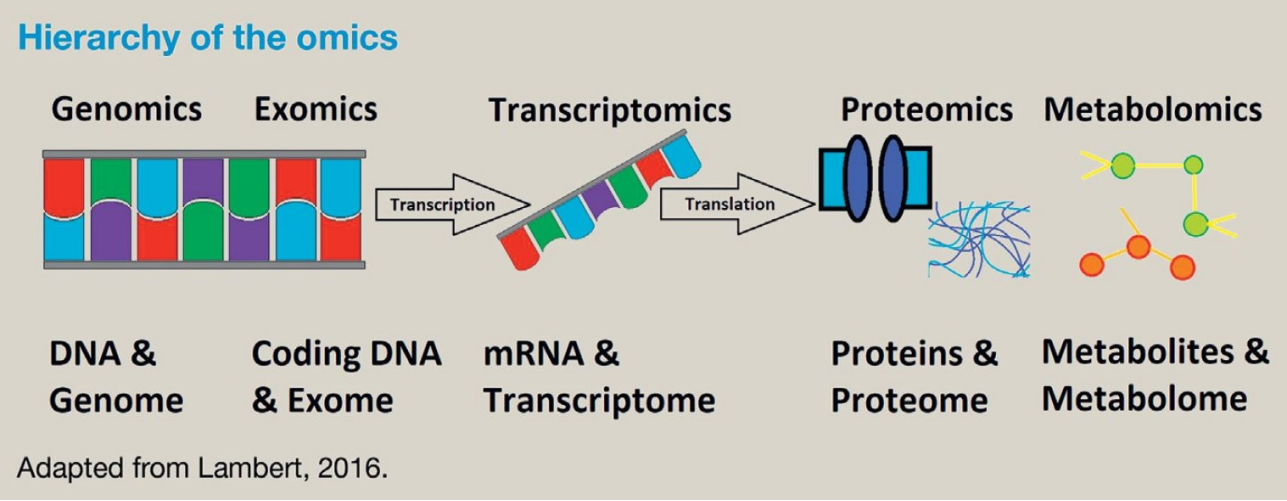

Figure 1 – Hierarchy of the omics. Adapted from Lambert, 2016.[3]

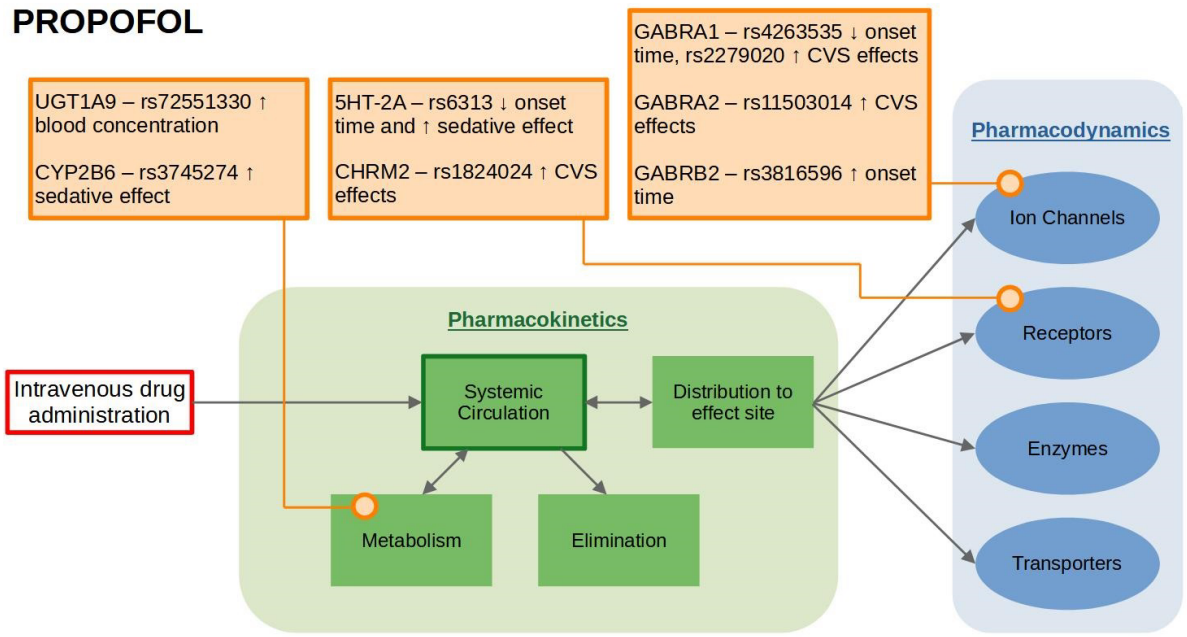

Figure 2. Notable genetic polymorphisms influencing the clinical effects of propofol. CVS, cardiovascular system.

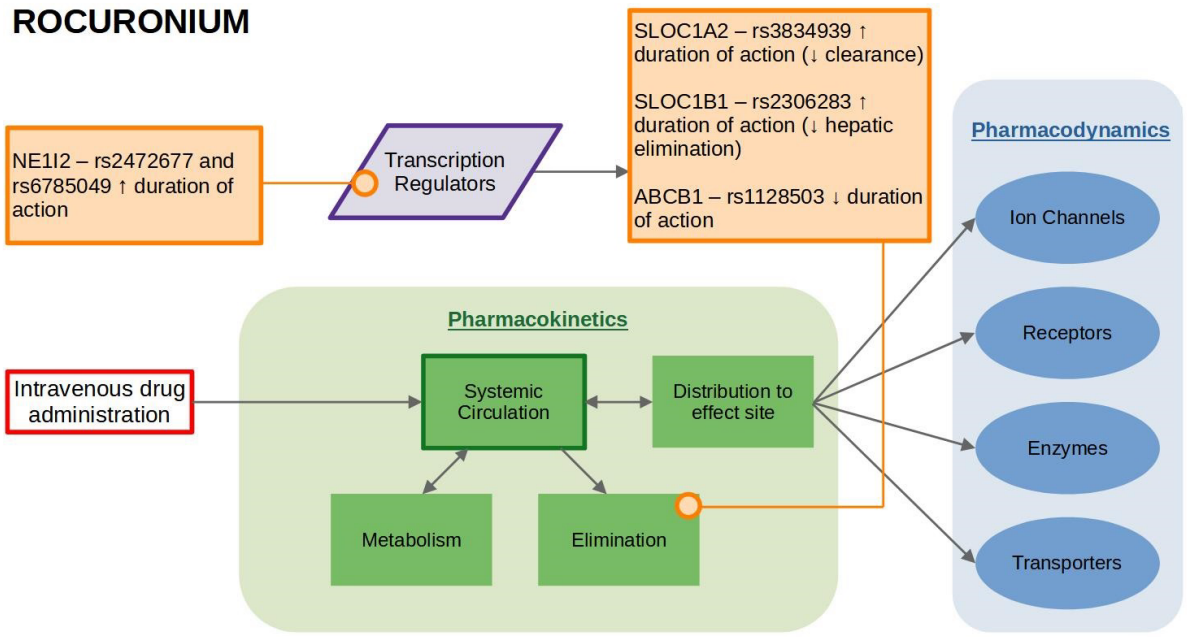

Figure 3. Notable genetic polymorphisms influencing the clinical effects of rocuronium

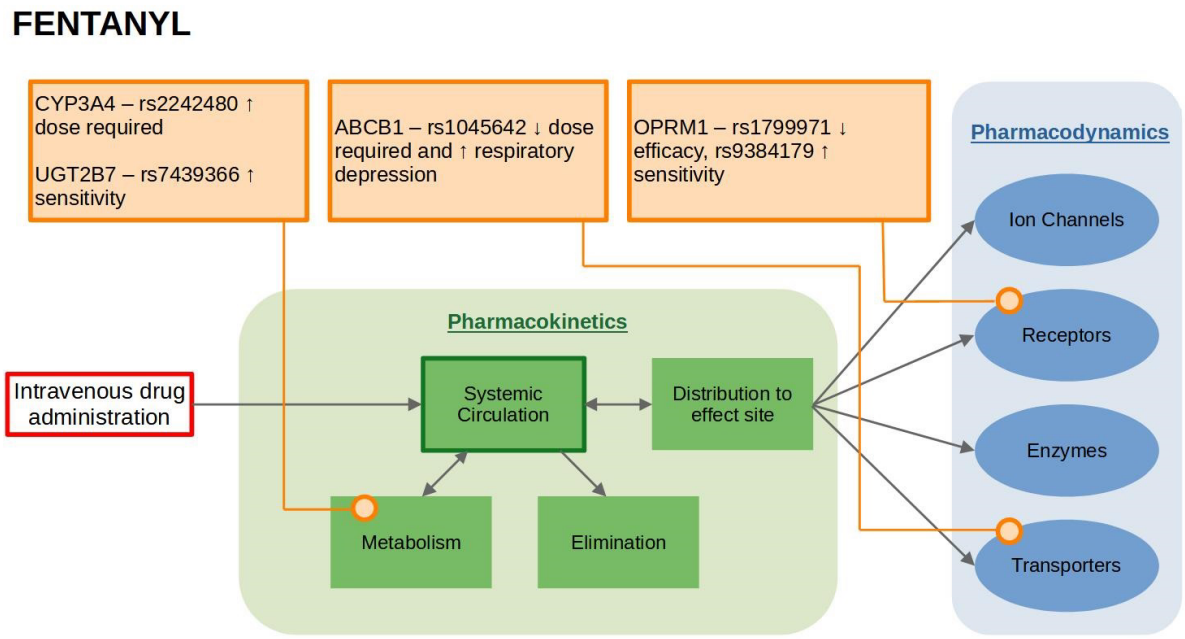

Figure 4. Notable genetic polymorphisms influencing the clinical effects of fentanyl