

Is it all in the genes? Prof Phil Hopkins (Leeds)

Pharmacogenomics is the study of the different genes that can influence the way individuals respond to drugs. Pharmacogenetic variation in drug response was recognised prior to the characterisation of DNA by Watson and Crick in 1953 and indeed the first review in the anaesthesia literature was published in 1964 by Werner Kalow. Until the last 10-15 years, however, pharmacogenomic research was focused on single gene defects that contributed to a distinctly idiosyncratic drug response phenotype. Examples relevant to anaesthesia include acute porphyrias, malignant hyperthermia and plasma cholinesterase variants.

The continuing technological revolution in molecular genetics has broadened the potential of pharmacogenomics to include discovery of the genetic factors underlying inter-individual responses to drugs that are encompassed by the phrase "biological population variability". It is these discoveries that are necessary if the aim of "personalised medicine" is to be achieved.

In my lecture I will review current understanding of the influence of genes on pharmacokinetic and pharmacodynamic variability pertinent to anaesthesia. In doing so I will put into context research findings of studies of single polymorphic variants and provide a pragmatic perspective on how near or otherwise these findings are to clinical utility. Like any area of science or medicine, genetics has a vocabulary and unfortunately much jargon is used. I will try to avoid the latter in my lecture but below is a glossary of some of the more common terms.

A Selected Genetic Glossary

Allele. One of the variant forms of a gene at a particular locus, or location, on a chromosome. Different alleles produce variation in inherited characteristics such as hair colour or blood type. In an individual, one form of the allele (the dominant one) may be expressed more than another form (the recessive one).

Autosome. Any chromosome other than a sex chromosome. Humans have 22 pairs of autosomes.

Autosomal dominant. A pattern of Mendelian inheritance whereby an affected individual possesses one copy of a mutant allele and one normal allele. (In contrast, recessive diseases require that the individual have two copies of the mutant allele.) Individuals with autosomal dominant diseases have a 50-50 chance of passing the mutant allele and hence the disorder onto their children.

Base pair. Two bases which form a "rung of the DNA ladder." A DNA nucleotide is made of a molecule of sugar, a molecule of phosphoric acid, and a molecule called a base. The bases are the "letters" that spell out the genetic code. In DNA, the code letters are A, T, G, and C, which stand for the chemicals adenine, thymine, guanine, and cytosine, respectively. In base pairing, adenine always pairs with thymine, and guanine always pairs with cytosine.

Candidate gene. A gene, located in a chromosome region suspected of being involved in a disease, whose protein product suggests that it could be the disease gene in question.

Cloning. The process of making copies of a specific piece of DNA, usually a gene.

Codon. Three bases in a DNA or RNA sequence which specify a single amino acid.

Deletion. A particular kind of mutation: loss of a piece of DNA from a chromosome. Deletion of a gene or part of a gene can lead to a disease or abnormality.

Exon. The region of a gene that contains the code for producing the gene's protein. Each exon codes for a specific portion of the complete protein. In some species (including humans), a gene's exons are separated by long regions of DNA (called introns or sometimes "junk DNA") that have no apparent function.

Gene. The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein.

Gene expression. The process by which proteins are made from the instructions encoded in DNA.

Genetic marker. A segment of DNA with an identifiable physical location on a chromosome and whose inheritance can be followed. A marker can be a gene, or it can be some section of DNA with no known function. Because DNA segments that lie near each other on a chromosome tend to be inherited together, markers are often used as indirect ways of tracking the inheritance pattern of a gene that has not yet been identified, but whose approximate location is known.

Genome. All the DNA contained in an organism or a cell, which includes both the chromosomes within the nucleus and the DNA in mitochondria.

Genotype. The genetic identity of an individual or DNA sequence of a particular gene.

Haplotype. A way of denoting the collective genotype of a number of closely linked loci on a chromosome.

Highly conserved sequence. A DNA sequence that is very similar in several different kinds of organisms. Scientists regard these cross species similarities as evidence that a specific gene performs some basic function essential to many forms of life and that evolution has therefore conserved its structure by permitting few mutations to accumulate in it.

Homologous recombination. The exchange of pieces of DNA during the formation of eggs and sperm. Recombination allows the chromosomes to shuffle their genetic material, increasing the potential of genetic diversity. Homologous recombination is also known as crossing over

Hybridization. Base pairing of two single strands of DNA or RNA

Intron. A noncoding sequence of DNA that is initially copied into RNA but is cut out of the final RNA transcript.

Linkage. The association of genes and/or markers that lie near each other on a chromosome. Linked genes and markers tend to be inherited together.

Locus. The place on a chromosome where a specific gene is located, a kind of address for the gene.

LOD score. A statistical estimate of whether two loci are likely to lie near each other on a chromosome and are therefore likely to be inherited together. A LOD score of three or more is generally taken to indicate that the two loci are close.

mRNA. Template for protein synthesis. Each set of three bases, called codons, specifies a certain protein in the sequence of amino acids that comprise the protein. The sequence of a strand of mRNA is based on the sequence of a complementary strand of DNA (cDNA)

Microarray technology. Also known as “Gene-chip” technology, microarrays can be constructed to examine hundreds of thousands of polymorphisms across the genome or the expression pattern of anything from tens, to tens of thousands, of genes. Analysis of the vast quantities of data generated is one of the greatest challenges of bioinformatics.

Mutation. A permanent structural alteration in DNA. In most cases, DNA changes either have no effect or cause harm, but occasionally a mutation can improve an organism's chance of surviving and passing the beneficial change on to its descendants.

Nonsense mutation. A single DNA base substitution resulting in a stop codon.

Nucleotide. One of the structural components, or building blocks, of DNA and RNA. A nucleotide consists of a base (one of four chemicals: adenine, thymine, guanine, and cytosine) plus a molecule of sugar and one of phosphoric acid.

Oligo. Oligonucleotide, short sequence of single-stranded DNA or RNA. Oligos are often used as probes for detecting complementary DNA or RNA because they bind readily to their complements.

Phenotype. The observable traits or characteristics of an organism, for example hair colour, weight, or the presence or absence of a disease. Phenotypic traits are not necessarily genetic.

Polymerase chain reaction (PCR). A fast, inexpensive technique for making an unlimited number of copies of any piece of DNA. Sometimes called "molecular photocopying," PCR has had an immense impact on biology and medicine, especially genetic research.

Polymorphism. A common variation in the sequence of DNA among individuals

Probe. A piece of labelled DNA or RNA or an antibody used to detect the function of a gene.

Restriction enzymes. Enzymes that recognize a specific sequence of double-stranded DNA and cut the DNA at that site. Restriction enzymes are often referred to as molecular scissors.

Restriction fragment length polymorphism (RFLP). Genetic variations at the site where a restriction enzyme cuts a piece of DNA. Such variations affect the size of the resulting fragments. These sequences can be used as markers on physical maps and linkage maps.

Single nucleotide polymorphisms (SNPs). Common, but minute, variations that occur in human DNA at a frequency of one every 1,000 – 1,500 bases. These variations can be used to track inheritance in families. SNP is often pronounced "snip".

Transgenic. An experimentally produced organism in which DNA has been artificially introduced and incorporated into the organism's germ line, usually by injecting the foreign DNA into the nucleus of a fertilized embryo.