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Perioperative Genomics

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Abstract

Since the completion of the Human Genome Project 10 years ago, the world has witnessed an incredible progress in human genetics and genomics.¹ This progress was largely driven by the availability of better, faster and cheaper sequencing technology.² While it took more than 10 years and more than 1 billion dollars to complete the Human Genome Project,³⁻⁵ an individual in the year 2011 can have his whole genome sequenced within a week for less than \$30,000. With cheaper and faster sequencing came a wealth of novel discoveries which makes it timely to review how these newly found insights into the human genome are relevant for perioperative medicine. This review summarizes the basics of genetic inheritance, the human genome and modern sequencing methods, as well as genetic variation and how this knowledge may be applied to patient care and research in the perioperative setting.

Keywords

Genetics; Genomics; Pharmacogenomics; Single nucleotide polymorphism; next-generation sequencing; Human Genome Project

The Human Genome

In its simplest form, the human genome can be viewed as a contiguous stretch of DNA, a very long one that is. Approximately 3 billion (3×10^9) DNA molecules (nucleotides) linked together build a human genome. Only four bases (A - adenosine; C - cytosine; G - guanine; T - thymine) paired with their respective complimentary partner base (A-T and G-C) form the famous DNA double helix and encode the entire genetic information of a human being. Each human being has its own genome sequence that makes him or her genetically unique. Each cell in an individual human contains an identical copy of this unique genome sequence in its nucleus. Our genome is organized into 23 chromosomes (22 autosomes and two sex chromosomes - XX for females and XY for males). In fact all of our cells (except for certain germ-line cells) have a diploid genome which means we have a pair of each chromosome (46 chromosomes total). Simplistically speaking, one copy comes from the mother and one copy from the father (this is a crude generalization as both copies undergo extensive exchange of genetic material in a process called recombination during the union of egg and sperm, but it makes the point).

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Conflicts of Interest

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Our genome, however, is not simply a linear stretch of DNA. The cell nucleus where the DNA resides harbors the tightly compacted DNA which is wrapped around histones, organized in chromosomes and packed in a large globule.⁶ It is of note that one other cellular structure has its own genome, the mitochondrion.⁷ Derived from bacteria billions of years ago, mitochondria still have their own genome which closely resembles a typical circular genome of bacteria and contains 37 genes within 16,000 bases pairs.

Previously it was assumed that most of our genome sequence would consist of genes which were then translated into proteins (the “central dogma of molecular biology”). This is not the case. Only 1.5% of the 3 billion base pairs in our genome code for genes! Another 3.5% of the sequence is evolutionarily highly conserved, but lie outside of genes. The vast majority (95%) of our genome, however, is neither in coding regions nor conserved. Until recently, this part of the genome was referred to as “junk DNA”. Full of seemingly random DNA sequence, junk DNA was thought to have no functional role for the cell and organism. As we know now, this could not be farther from the truth.⁸ While it is true that some DNA stretches are indeed junk, the majority of non-coding DNA is quite important for the regulation of when and how genes are expressed.

What is a gene?

When we speak of a gene, we typically mean a stretch of DNA that encodes for a single protein, for instance a subunit of an ion channel. While it is true that in a prokaryote genome, for example in bacteria, one gene is encoded by a single stretch or block of DNA, this is not the case in human, and in fact any vertebrate organism. Vertebrate genes are much more complicated and typically consist of several non-contiguous building blocks - called exons - that are subsequently joined in a process called splicing. The long stretches of DNA in between the building blocks - called introns - are not made into protein and not transcribed into messenger RNA (mRNA).

Why did evolution favour the development of the complex splicing process for all eukaryotes, including humans? The answer lies in the regulation of gene expression. Until the Human Genome Project was completed, estimates about the number of human genes typically ranged between 50,000 and 100,000. As it turns out, the human genome has only 22,000 genes.⁹ The rice genome has 46,000 genes, the nematode *C. elegans* about 19,000 and *E. coli* 4,400 genes. How can a much more complex organism as is the human body with its 100 trillion (10^{14}) cells have only five times as many genes as *E. coli*? This is where splicing comes in. When a gene consists of several exons, it is possible to modify which exons get spliced together, a process called *alternative splicing*. With alternative splicing hundreds or thousands of different splice variants and gene products are possible from a single gene. Therefore alternative splicing is one of the main drivers of gene product (protein) diversity.

The Human Genome Project not only identified the actual number of genes within our genome but equally importantly spearheaded a revolution in DNA sequencing methods. Next generation sequencing is widely seen as a “game-changer” in genomics and has delivered a trove of spectacular results just within the span of the last decade.

The genome sequencing revolution

DNA sequencing became a critical necessity after the discovery of the molecular structure of DNA by Watson and Crick in the 1950's. In 1977 Fred Sanger from the MRC in Cambridge, England, introduced the dideoxy chain-termination technique, what is now known simply as the “Sanger technique”.¹⁰ The Sanger method was an important breakthrough in DNA sequencing and led to Sanger's second Nobel Prize, but was laborious. It required many

manual steps such as pouring large agarose DNA gels, gel loading, manual data export and could sequence up to 3,000 base pairs per day. A typical gel-base sequencer could sequence a maximum of 3×96 samples per day if no problems occurred. This method was later modified to include a fluorescent dye, the basis for modern high-throughput sequencing. At the beginning of the planning of the Human Genome Project, the prospect of sequencing 3 billion base pairs was daunting given the typical throughput of a DNA sequencer. However, the introduction of automated capillary-based sequencers in the 1990's which could automatically fill and load samples and did not require gels was a huge progress and increased the throughput to 20×96 samples/day and up to 75 kilobases/run. Nevertheless, this was the state of DNA sequencing at the beginning of the Human Genome Project and still required a massive investment of time, money and effort to complete the sequencing of the 3 billion bases that comprise the human genome. It required 10 years of work and more than 1 billion dollars. Nowadays, a whole genome can be sequenced within 1 week for less than \$30,000. The goal is actually to reduce the cost of whole genome sequencing over the next few years to \$1,000 (The \$1,000 genome). How was this possible? The answer is *next-generation sequencing*.¹¹

Without going into the technical details that are quite sophisticated and differ from platform to platform, next generation sequencing achieves this enormous throughput by employing so called *massive parallel sequencing* which allows the simultaneous sequencing of millions of individual sequencing reactions on a single instrument run, for instance on a chip.² Because the sequence of the human genome is now known, it can serve as a template for the assembly of the sequence reaction readouts.

Has whole genome sequencing already entered the clinical arena? In oncology it has. Acute myeloid leukaemia has a high mortality rate and its molecular and genetic architecture was largely unknown. In 2008, researchers from Washington University in St. Louis published the first complete genome of a human cancer by comparing the whole genome from leukemic cancer cells to genotypically normal skin cells of the patients¹² and found recurring and novel mutations¹³ that could explain many cases of acute myeloid leukaemia. Oncologists are now able to use this genetic signature to make better prognoses about the aggressiveness of an individual acute myeloid leukaemia and to improve targeting the right chemotherapeutic choices to each patient.¹⁴

Genetic variation

It is a surprising fact that all humans are 99.9% identical at the DNA level, yet clearly different from each other.¹⁵ What causes this difference? Several types of genetic variation exist between individuals.^{16,17} In its simplest form, a single nucleotide can be different between two individuals. This is referred to as *single nucleotide polymorphism*, or SNP. SNPs are not only the simplest form of genetic variation but also by far the most common: it is estimated that each individual human has between 10 and 20 million SNPs. Most SNPs are common with an allele frequency in the general population of >5%. Most SNPs are also silent and do not cause any change in the protein sequence or function. If SNPs are rare and cause a disease, they are typically referred to as *mutation*. A classic example is sickle cell disease: a point mutation (SNP) in the β -globin chain of haemoglobin at position 6 results in a different haemoglobin molecule, haemoglobin S which adapts a sickle-like form under certain conditions.¹⁸ Two mutant copies are required to develop sickle cell disease (*homozygous* state). *Heterozygous* patients (only one mutated allele) - referred to as carriers - have an evolutionary advantage with substantially lower malaria infection rates compared to non-carriers.¹⁹ This benefit is also known as *heterozygote advantage*. It comes therefore as no surprise that the highest prevalence of this mutation is in regions with high malaria burden. The discovery of the molecular nature of the haemoglobin S mutation in 1949²⁰ was

heralded as a medical breakthrough as it was the first disease whose genetic and molecular cause had been solved, and it also conferred the Nobel Prize to Linus Pauling.²¹

Two examples from perioperative medicine and pain therapy may help to illustrate how single nucleotide polymorphisms can substantially reduce enzyme activity and influence clinical outcomes. The cytochrome P450 (CYP) enzyme is the major drug metabolizing enzyme in the human liver²² and its 2D6 subtype (CYP2D6) is responsible for the metabolism of more than 25% of all clinically used drugs.²³⁻²⁵ CYP2D6 metabolizes most opioid analgesics. Approximately 5% of the population has two non-functional alleles in CYP2D6 which results in a “poor metabolizer” phenotype.²⁶ Poor metabolizers are unable to process CYP2D6-dependent substrates. Most commonly the poor metabolizer status is caused by SNP within the CYP2D6 gene which renders the enzyme non-functional. The consequences for the patient can be significant: a case was recently published where a 5 year old child died of a fatal hydrocodone overdose due to poor CYP2D6 metabolizer status which resulted in a toxic hydrocodone blood concentration.²⁷

Another example is from our own work: It is well known that nitrous oxide inactivates vitamin B₁₂ which consequently reduces the ability of the cell to provide ubiquitously required methyl-groups from the folate cycle.²⁸⁻³⁰ It turns out that approximately 10-15% of the population is homozygous for the C677T single nucleotide polymorphism in the *MTHFR* gene which reduces the MTHFR enzyme activity to 20-30%.³¹⁻³³ The *MTHFR* gene is the core enzyme in the folate cycle and a reduced function leads to a limited methyl-group availability and causes elevated plasma homocysteine levels. In our study we could show that patients with the *MTHFR* 677TT polymorphism had a significantly higher risk to develop abnormal plasma homocysteine levels after nitrous oxide anaesthesia compared to wild-type patients, confirming the so-called double-hit hypothesis.³⁴

It has become clear that SNPs can be both, a rare mutation that directly causes a disease and a common polymorphism that is shared among a major fraction of the population. As seen in the case of sickle cell disease, a single point mutation is enough to cause the disease. But what is the genetic contribution to our common diseases such as hypertension, diabetes, and coronary artery disease? It is clear that many of these common diseases have a strong familial clustering or genetic component. Consequently, many geneticists reasoned that a combination of several common SNPs may be associated with disease risk - the *common disease-common variant* hypothesis.³⁵⁻³⁷ To investigate this popular hypothesis, geneticists developed a method that allowed them to interrogate initially 500,000 (now 2 million) SNPs on a single chip.³⁸ These microarrays were the technical basis for *genome-wide association studies* (GWAS) that were designed to identify the common genetic variants predisposing individuals to common diseases.³⁹ The cost of a single chip was on the order of \$1,000 and since GWAS required very large sample sizes to mitigate the multiple-comparison problem, these studies were very expensive. Nevertheless, more than 200 GWAS have been published so far. Some GWAS had spectacular successes - but most GWAS could only identify few of the potentially causal gene variants. In genetic terms, they could only explain a small fraction of the genetic variance, which is known in genetic circles as the “missing heritability problem”.⁴⁰

A great success, however, was the identification of the causative variant responsible for the statin-induced myopathy. After the wide-spread introduction of HMG-CoA reductase inhibitors, commonly better known as statins, reports trickled in that several patients developed rhabdomyolysis, acute kidney failure and death.⁴¹ This adverse drug reaction was clearly serious, but also rare. The fact that the SEARCH trial⁴² had collected buffy-coat samples among its 12,000 participants randomized to either 80mg simvastatin or 20 mg simvastatin, allowed the investigators to perform a genetic analysis of the 85 patients with

statin-induced myopathy and comparing them to control patients. The GWAS identified a single strong genetic association with a SNP within the *SLCO1B1* gene which encodes an anion transport protein responsible for hepatic uptake of statins.⁴³ This variant alone was responsible for more than 60% of all cases of myopathy. Patients heterozygous for this variant (having one mutated allele of the gene) had a 4.5-fold higher risk to develop myopathy and patients homozygous (both alleles mutated) had a 17-fold increased risk. This was a remarkable success story given the small sample size and the results should serve as the basis for prospectively identifying patients at high risk for statin-induced myopathy.

Researchers aiming to identify the genetic basis for human height by GWAS were not so lucky.⁴⁴ Height has a very high degree of inheritance within families, but despite genotyping more than 180,000 individuals, researchers could only explain 10% of the phenotypic variation in height by the identified genetic variants.⁴⁵ Many GWAS had similarly disappointing results and many geneticists now believe that rare variants that occur in less than 5 % of the population are more likely to be causally associated with common diseases.

In perioperative medicine, one of the first GWAS recently identified several SNPs associated with postoperative nausea and vomiting.⁴⁶ Using a typical GWAS design with separate discovery and replication cohorts, Janicki et al. found one SNP in the *CHRM3* gene which codes for a unit of the muscarinic acetylcholine receptor.

Over the last decade it has become apparent that another form of genetic variation is also very common: insertions and deletions (“indel”) of stretches of DNA ranging from a kilobase (kb; 1000 bases) to several megabases (million bases) within the genome.^{47,48} This form of genetic variation is referred to as *copy number variation* (CNV). CNV is currently a very hot topic in human genetics as several diseases have been associated with CNVs, most importantly autism-spectrum disorders,^{49,50} schizophrenia⁵¹ and unexplained childhood mental retardation.⁵²

CNVs are not only relevant for causing human diseases, but also affect drug metabolism. As mentioned above, the CYP2D6 enzyme is responsible for metabolizing more than 25% of all known drugs.^{23,53,54} Approximately 5% of the population has more than 2 functional copies of the CYP2D6 gene and up to 15 copies have been described, a classic case of CNV. The consequence of this CNV in the CYP2D6 gene is the “ultra-rapid metabolizer” phenotype.²⁴ Ultra-rapid metabolizers metabolize the substrate (drug) much faster than patients with a normal CYP2D6 metabolism. This can result in lack of efficacy due to low drug plasma concentrations or, in the case of prodrugs that require CYP2D6 metabolism for conversion into the active compound, in dangerously elevated drug concentrations. In 2006, the fatal morphine poisoning of a breastfed neonate was reported whose mother was prescribed codeine.⁵⁵ Codeine is a prodrug which is converted by CYP2D6 into morphine. The mother had an ultra-rapid metabolizer phenotype which resulted in toxic morphine concentrations in the breast milk that ultimately were responsible for the fatal poisoning of the neonate.

Conclusions

The completion of the Human Genome Project ten years ago has jumpstarted an new and exciting era in human genetic research that undoubtedly will influence anaesthesiology and perioperative medicine in the future. We currently observe the first clinical applications of this new wave of genetics-based individualized diagnosis and treatment, be it in cancer therapy or to guide warfarin dosing. In perioperative medicine, promising fields for investigation comprise sepsis, pain therapy, and pharmacogenomics.

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Practice Points

- The Human Genome Project has been completed 10 years ago and has already delivered spectacular insights into the nature of our genome
- Genomewide association studies (GWAS) have revolutionized our understanding about genetic variation in the population. A GWAS was instrumental in determining the cause for statin-induced myopathy.
- Personalized medicine, the targeted diagnosis and treatment of patients according to the genetic background of the patient, has entered the clinical arena. Examples are individualized warfarin dosing and acute myeloid leukemia diagnosis.
- The recent genomics revolution was largely driven by an incredible improvement in sequencing technology. Next generation sequencing is now able to sequence an entire human genome in less than 2 weeks for only a fraction of the cost. The goal over the next years is to get to a \$1000 genome.

Research agenda

- The impact of genomics for perioperative medicine has just begun to be unraveled. Only a few researchers are active in this area and most of the pressing questions remain unanswered.
- Particularly the impact of pharmacogenomics and personalized medicine for anesthesiology and perioperative medicine cannot be overstated. Individualized drug therapy for pain management and for prevention of adverse cardiovascular outcomes after surgery such as myocardial infarction and stroke appear to be of high impact.
- Without a doubt, genetic factors play a major role in predisposition for sepsis and the clinical course of patients with sepsis. Therefore, sepsis may be a particularly fruitful field of perioperative genomics research.