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REVIEW

Genetic predisposition in anaesthesia and critical care, science fiction or reality?

Malte Book*, Ulrike M. Stamer, Lutz E. Lehmann, Frank Stüber

University Department of Anaesthesiology and Pain Medicine, Inselspital, CH-3010 Bern, Switzerland

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SUMMARY

Considering the individual genetic background is a major undertaking in the personalization of anaesthesia and critical care medicine. Especially, functional relevant single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) are in the focus of current research. Candidate gene studies showed many positive associations of genetic variants with sepsis or perioperative disorders such as nausea and vomiting. However, these studies frequently lack adequate statistical power and the results have not been replicated. Genome-wide association studies (GWAS), apart from candidate gene studies, also failed in defining the heritability in complex diseases. The next generation sequencing method might enable whole genome sequencing with practicable conditions. Although there are still some problems to solve, it is promising to fundamentally increase the knowledge about the genetic background of complex diseases.

1. Introduction

Considerations about the individual genetic background for safe and successful anaesthesia or critical care medicine are not first line subjects for planning individualized procedures in our patients. Genetic research is widely perceived as “basic science” without impact on the single patient. Although the 2001 sepsis definition conference introduced the PIRO (Predisposition, Infection, Response, Organ dysfunction) concept. The participants identified the genetic background as an important predisposition which is relevant for clinicians.[1] Especially in the field of sepsis there is strong evidence for a heritable effect. In 1988 Sorensen and co workers presented the strong inheritance of mortality due to infection.[2] To date, particular recent genetic findings assign this as the tip of the iceberg of perioperatively relevant genetic research. Interindividual genetic differences are responsible for changes in the tramadol metabolization by the liver enzyme cytochrome P450 CYP2D6. These variations are clearly involved in the varying response to pain medication in post-operative patients.[3] Moreover, an increasing number of perioperative patients are treated with antiplatelet drugs for cardiovascular reasons. The platelet response to clopidogrel is modified by the cytochrome P450 CYP2C19. The genotype CYP2C19*2 is associated with a decreased antiplatelet effect and poorer cardiovascular outcome and a higher risk for adverse cardiovascular events, respectively.[4]

These examples highlight two important fields of perioperatively relevant genetic research focussing on the exchange of one particular base. These polymorphisms are called single nucleotide polymorphisms (SNP). However, another recently spotted type of genetic variation is much more common and might have a more functional impact: Gene copy number variations (CNV). These variations are characterized by the duplication of complete genes with all the necessary promoter and start sequences.

The aim of this review is i) to give an overview of the important types of genetic variants, ii) to highlight actual research findings relevant for anaesthesia and critical care, and iii) to provide an outlook on the future development of perioperative genetic research.

2. Genetic variation

2.1. Single nucleotide polymorphism (SNP)

This variation is defined by the exchange of one nucleotide in the DNA double strand (Fig. 1). Subsequently, there are two different alleles in the population. Individuals with two wildtype or polymorphic alleles on their homologue chromosomes are homozygous whereas individuals with one wildtype and one polymorphic allele are heterozygous.

The 1000 genomes project assembled the location, genotype frequency and haplotype structure of approximately 15 million SNPs.[5] 55% of these variants were previously unknown. Based on the fact that the human genome comprises approximately 3 billion nucleotides about 0.5% of the genome is involved in these kinds of

* Corresponding author.
E-mail address: malte.book@dkf.unibe.ch (M. Book).

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Fig. 1. T/C single nucleotide polymorphism in the upper DNA strand with consecutive change in the complementary lower DNA strand.

genetic variation. SNPs are distributed all over the human genome. The vast majority are located in noncoding regions and their functional relevance is unclear. Some 640,000 human SNPs were identified resulting in single amino acid substitution.[6] For some 21,000 (3%) of these a functional relevance and for some 27,000 (4%) a disease association was reported.[6] The overlap between these two subgroups contains about 1600 SNPs.[6] Single nucleotide polymorphisms are detectable by commercially available gene chips. The latest chips contain at most 2.3 million of the estimated 15 million human SNPs. Furthermore, these chips are limited by the over-representation of common SNPs. Alternatively, the new second generation sequencing methods are appropriate for genome-wide SNP detection.

2.2. Copy number variants (CNVs)

Deletions, insertions, duplications and complex multi-site variants are termed as copy number variants. The length is defined as a DNA segment that is 1 kb or longer and presents a variable copy number in comparison with a reference genome.[7,8] The amount of DNA involved is probably higher compared with SNPs. First approximations that about 12% of the genome is involved in CNVs[9] might overestimate the CNV incidence. The average genetic variability between two humans is estimated to be some 0.2%. 0.08% at the nucleotide level (SNPs) and 0.12% at the structural level (CNVs).[10]

The defensin gene locus on chromosome 8p23.1 is a site of chromosomal rearrangement (Fig. 2). Hollox et al. reported about up to 12 gene copies per diploid genome.[11] Especially the genes of the potent innate immunity effector molecules human beta defensin 2–4 (hBD 2–4), called DEFB4, DEFB103 and DEFB104, are in the focus of interest.

The amount of the constitutive gene expression of the DEFB4 gene is associated with the gene copy number.[12] The dependency of the gene expression on the copy number is also confirmed in cytochrome P450 CYP2D6 copy number variants on chromosome 22q13.1.[13] The results indicate that the possible functional impact of such genetic variants is incommensurable with the huge number of SNPs located in noncoding and nonregulatory regions.

3. Candidate gene studies

Central proteins in the physiology or pathophysiology of biological processes were identified as candidate genes. For instance proinflammatory cytokines in the pathophysiology of sepsis were investigated as candidate genes. This approach is based on the hypothesis that genetic variants in the key molecules of sepsis are associated with the incidence, outcome or clinical course of sepsis. Other exemplary candidate genes are the cytochrome P450 enzyme system which is involved in the metabolism of various anaesthesia relevant drugs.

3.1. Critical care medicine

There are a great many positive candidate gene association studies with incidence or outcome of systemic infections. An SNP in the lipopolysaccharide binding protein (LBP) is associated with the incidence of sepsis and multiple organ dysfunction in two independent Chinese multiple trauma patient cohorts.[14] LBP is a central mediator in the acute phase of gram negative infections. The protein–LPS complex binds to the CD14 receptor and is involved in the LPS dependant monocyte response. In total 112 SNP have been identified in this gene so far. Zeng et al. investigated 9 tagging SNPs out of 51 SNP with a minor allele frequency above 0.05. One of these tagging SNPs showed the above mentioned results whereas the other 8 were not associated with the incidence of sepsis.[14] The tagging SNP concept based on a linkage disequilibrium of SNPs located in close proximity to each other which is called haplotype. Therefore, the tagging SNP allows a highly probable conclusion about the alleles of other SNPs in the haplotype.

Adamzik et al. reported on an aquaporin gene promoter SNP which is associated with a 30 day survival in patients with severe sepsis.[15] Aquaporin qualifies as a candidate gene because of its modulation of cell migration/proliferation and of the renin–angiotensin–aldosterone system.[16,17]

Human defensins are candidate genes for relevant gene copy number variants. They are effector molecules of the innate immune system. They are expressed by any epithelial tissue in the human body and by leukocytes. In the local setting their antimicrobial effects against bacteria, fungi and virus support the innate immunity

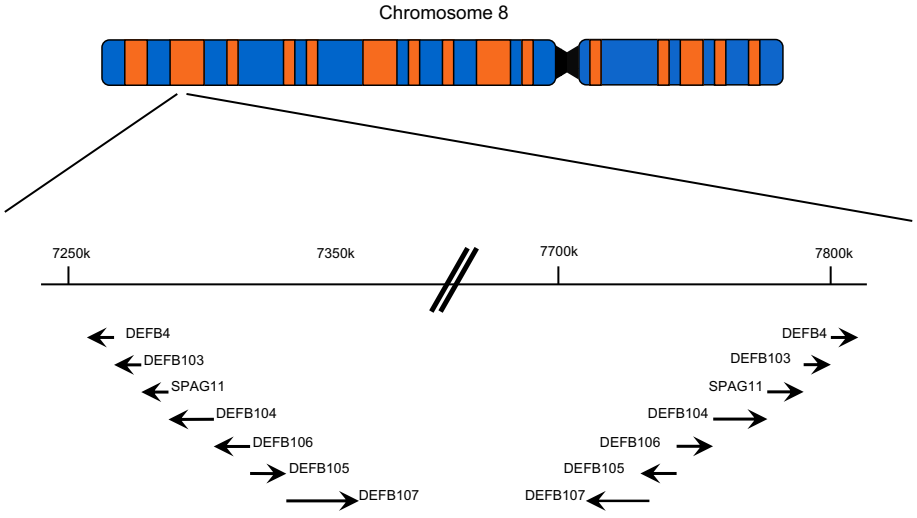

Fig. 2. Schematic arrangement of the beta defensin gene locus with one repeat between 7700 k and 7810 k.