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GenOSept: Genetics of Sepsis and Septic Shock

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Frank Stüber introduces an EU funded project, GenOSept, which aims to unravel the genetic predisposition of sepsis and septic shock.

Introduction

The European Society of Intensive Care Medicine (ESICM) has recently signed a contract with the European Commission to conduct a large diagnostic trial funded by the EU's 6th framework programme. ESICM leads a consortium of 14 partners which conducts the project GenOSept to unravel the genetic predisposition of sepsis and septic shock. For the first time, a major genetic epidemiologic study in intensive care medicine has been granted by public European funds. This represents an outstanding opportunity to conduct cutting edge diagnostic research on a European level, for ESICM as an international scientific society to ultimately contribute to improvement of intensive care.

Genetic studies within the intensive care research community have gained considerable attention throughout the last decade. Many genotyping results in intensive care have been published to date. Most of them relate to the genetic predisposition for the development of severe sepsis or death from systemic infection. There is a major publication bias regarding genotyping results. Most of the published studies show significant positive associations between gene variants and the phenotype (i.e. severe sepsis or adverse outcomes of sepsis). These results are indeed exciting, but on the other hand, many genotyping results which do not show positive association with disease remain unpublished. Some studies appear to be statistically underpowered which is usually reflected by low numbers of patients included, prompting a high probability of beta type error. A statistically significant result ($p<0.05$) of an underpowered study may not be reproducible. Therefore, large well designed genetic epidemiologic trials are needed to provide conclusive answers to the question of the genetic predisposition for sepsis and septic shock.

Why GenOSept is Important

Morbidity and mortality of critical illness is still mainly determined by the incidence and course of sepsis and its sequelae. Evidence based efforts to improve standard care of sepsis patients are bundled in major campaigns like the surviving sepsis campaign of the Societies of Intensive Care Medicine of Europe and North America, as well as the International Sepsis Forum. In addition, new definitions and diagnostic concepts are in the process of evaluation to facilitate early diagnosis and evidence based therapies. These advances comprise the PIRO concept, which is designed to classify states of sepsis in the future. The PIRO concept's P stands for predisposition and GenOSept is designed to deliver information on patterns of genomic variation associated with predisposition in this context. Genetic predisposition for the incidence and outcome of sepsis has been recognized and suggested as a possible powerful tool for future risk stratification and even as inclusion criteria for therapeutic trials. Genomics research has, therefore, entered a new area of complex diseases of which sepsis remains the greatest challenge in acute medicine. Genomic research and genotyping in the critically ill will not stand isolated, but will be integrated in the field of functional genomics. GenOSept also contains a module which links patterns gene expression with patterns of genomic variation in corresponding genes. Genomic variants may influence the individual phenotype including gene expression levels and patterns as well as protein levels and protein structure. Genotyping techniques have advanced to high throughput methodology employing a high degree of automation; genomic microarrays for genotyping have

become technically feasible. Standards as well as quality control measures of genotyping are currently being implemented and tested in ongoing and oncoming large scale genetic epidemiologic studies in intensive care medicine, not only in Europe but also in the United States. It will be finally of major importance, also to understand the impact of genomic variants on the fate of intensive care patients of diverse ethnicity. As a possible result, future intensive care physicians may have access to readily available genetic risk patterns including pharmacogenetics of their patients which not only allows for better risk stratification, but may also help tailor individual patient care and drug therapy.

Basics of Genomic Variation

Human genotyping depicts a biochemical analysis of human DNA. DNA consists of a long chain of some 6 billion molecules, i.e. nucleotides Adenine- Cytosine- Guanine- and Thymine, carrying the genetic code (genes) for peptides and proteins, which constitute living organisms. DNA is found in the nucleus of cells where it is organized into highly specific nucleotide sequences that define each gene on the 23 chromosomes, which occur in a set of two in somatic cells (46 chromosomes) and in a single set in germline cells. An organized sequence of nucleotides that "spells out" the information necessary to construct a specific messenger called "messenger RNA", in turn, translates into a specific protein. The human genome project's results have reduced our expectation of the number of genes existing in the human DNA code from initially 100,000 to some 25,000. All human beings carry the same genes, apart from the genes coded on allosomes defining gender – the X and Y chromosomes.

In contrast to the comparable set of genes between individuals, there is considerable interindividual difference in base sequences encoding these genes. When the chromosomes of two humans are compared, their DNA sequences can be identical for hundreds of bases. But at about one in every 1,200 bases, on average, the sequences will differ. One person might have an Adenine at that location, while another person has a Guanine, or a person might have extra bases at a given location or a missing segment of DNA. Each distinct "spelling" of a chromosomal region is called an allele, and a collection of alleles in a person's chromosomes is known as a genotype. Although many "spellings" of a gene, i.e. alleles, may exist, just two of them, because of the two sets of chromosomes, form the genotype.

Differences in individual bases are the most common type of genetic variation. These genetic differences are known as single nucleotide polymorphisms, or SNPs. Approximately 10 million SNPs have been estimated to occur commonly (frequency > 1% in the population) in the human genome. Rare variants (frequency < 1%) are called "mutations". For geneticists SNPs act as markers to locate genes in DNA sequences. Say that a spelling change in a gene increases the risk of suffering from organ failure when the host is systemically infected, but researchers do not know where in our chromosomes that gene is located. They could compare the SNPs in patients who have organ failure with the SNPs of patients who do not. If a particular SNP is more common among patients with organ failure, that SNP could be used as a pointer to locate and identify the gene involved in the disease.

Goal of the Project

The goal of GenOSept is to identify patients at high risk for fatal outcome from severe sepsis based on community aquired pneumonia, fecal peritonitis, necrotizing pancreatitis and meningococcal disease by means of genetic analysis. Some 5000 patients will be recruited throughout Europe, followed up on their clinical course and will have their individual genetic variations associated with outcome parameters. Finally, a diagnostic set of genetic markers might be provided to be used for risk stratification and as determinants of genetic predisposition within the PIRO concept.

Progress of the Project

GenOSept started officially in February 2005. Many preparations for the clinical study, namely the recruitment of patients, needed to be done and are still in progress. The consortium has also developed applications to local ethics boards and these have been approved by a European ethics committee appointed by the European Commission. The ethics review process at local institutions is ongoing. A web based electronic case report form has been developed for easy online data entry. European intensive care institutions and their ICUs are welcome to participate in GenOSept; please do not hesitate to contact public@esicm.org and visit the website at www.esicm.org. ESICM is happy to refer you to national GenOSept coordinators. Start of recruitment will be the autumn/winter period of 2005.

Possible Impact on Management of Sepsis

GenOSept hopefully will contribute to further fill the PIRO concept to determine the individual predisposition of sepsis and its sequelae. There are many aspects how genetic studies ultimately can impact management of sepsis. GenOSept is one of the first large scale genetic studies in intensive care medicine to focus on identification of high risk sepsis patients.

First of all, genetic information is for a lifetime, it does not change. It can be used to stratify preoperative patients undergoing high risk surgical procedures. Special preventive measures may be taken or surgical procedures adjusted. Some high risk patients appear to have higher release of primary or secondary sepsis mediators because of their genetic predisposition. Future interventional studies in sepsis patients may stratify cohorts according to genotype. Ultimately, genotyping may help to direct specific therapeutics and resources to those who benefit. GenOSept is a first, but important step in this direction.

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