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Great Ormond Street Hospital for Children



NHS Trust

Genetics in ITU

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Fundamental Knowledge:

List of topics relevant to PIC that will have been covered in membership examinations.

They will not be repeated here.

- Function of cells; genes and their expression
- Syndrome associations and chromosome anomalies; complex syndrome disorders involving a multidisciplinary input

Information for Year 1 ITU Training (basic):

Year 1 ITU curriculum

- Basics of genetic influences in the response to critical illness

Curriculum Notes for Year 1:

Genetics is the study of single genes and their effects.

Monogenetic diseases are conditions in which single known gene defects correlate directly with clinical severity (Sickle cell disease, haemophilia etc.). These represent only a very small part of the genetic influence on clinical disease.

Genomics is the study of the functions and interactions of all the genes in the genome.

The relationship between base-pair code and functional protein is highly complex with approximately 30,000 genes producing more than 100,000 proteins resulting from intermediate steps including 'alternative splicing'.

The majority of disease processes that are familiar to intensive care doctors are influenced by mutation in genes responsible for key mediators e.g. in systemic inflammation. Examples of key references are given below.

Recent reviews of the field and the influences on critical care medicine:

- Guttmacher AE, Collins FS. Genomic medicine – a primer. N Engl J Med 2002; 347(19): 1512-1520.

Effects of single gene polymorphisms on Sepsis:

Review:

- Lin MT, Albertson TE. Genomic polymorphisms in sepsis. Crit Care Med 2004; 32:569-579.

Originals

- Harding,D.; Baines,P.B.; Brull,D.; Vassiliou,V.; Ellis,I.; Hart,A.; Thomson,A.P.; Humphries,S.E.; Montgomery,H.E. Severity of meningococcal disease in children and the angiotensin-converting enzyme insertion/deletion polymorphism. Am J Respir Crit Care Med.2002;165(8):1103-1106

- Haralambous, E.; Hibberd, M.L.; Hermans, P.W.; Ninis, N.; Nadel, S.; Levin, M. Role of functional plasminogen-activator-inhibitor-1 4G/5G promoter polymorphism in susceptibility, severity, and outcome of meningococcal disease in Caucasian children. *Crit Care Med.* 2003; 31(12): 2788-2793.

Effects of MBL polymorphisms:

- Garred, P.; Strom, J.; Quist, L.; Taaning, E.; Madsen, H.O. Association of mannose-binding lectin polymorphisms with sepsis and fatal outcome, in patients with systemic inflammatory response syndrome. *J Infect Dis.* 2003; 188:1394-1403
- Fidler, K.J.; Wilson, P.; Davies, J.C.; Turner, M.W.; Peters, M.J.; Klein, N.J. Increased incidence and severity of the systemic inflammatory response syndrome in patients deficient in mannose-binding lectin. *Intensive Care Med* 2004; 30:1438-1445

Information for Year 2 ITU Training (advanced):

Year 2 ITU curriculum

- Current research into the genetic influences on the response to critical illness: e.g. ACE, MBL, IL-6 polymorphisms
- New genetics

Curriculum Notes for Year 2:

Examples of single nucleotide polymorphisms and their relationship to systemic inflammation are provided in the year 1 reading. These kinds of gene-phenotype association studies have been produced in huge numbers. They are prone to a number of biases, including a high risk of selection bias (following analyses of multiple genes throwing up chance associations) and publication biases.

They are also highly likely to be very sensitive to the inclusion criteria applied – especially in complex processes like septic shock. For example; a genotype associated with low mannose binding levels (MBL) seems to increase the risk of infection - e.g. with meningococcal disease. However the severity of this episode of infection is probably dominated by the impact of other genes – including the Plasminogen Activator Inhibitor –1. The relationship between MBL and risk of infection is therefore very different than between MBL and risk of severity. Many studies are weakened by vague inclusion criteria or other sources of variability such as the ethnicity of the patient group.

Many recent reviews have highlighted the difficulties and limitation innate in gene-phenotype association studies. Some examples are provided:

- AS Slutsky, R James Genetics of critical illness: Methodological issues *Critical Care Medicine*: Volume 30(10) October 2002 pp 2382-2383
- Functional genomics of critical illness and injury T. Philip Chung, J M. Laramie, M Province, J. Perren Cobb, *Crit Care Med* 2002 Vol. 30, No. 1 (Suppl.)

Mendelain Randomisation.

This term has been widely used recent to describe using the random nature of distribution of genotypes to determine the impact of that mediator in complex diseases. This may be a key tool in dissecting very complex multiple mediator pathways such as sepsis.

- Aroon Hingorani, Steve Humphries. Nature's randomised trials *Lancet* 2005; 366, 1906-8
- David Clayton, Paul M McKeigue. Epidemiological methods for studying genes and environmental factors in complex diseases *Lancet* 2001; 358: 1356–60 *Lancet* 2005; 366:1906-1908

New genetics.

Some studies have now started to screen multiple genes and attempt to distil multiple complex associations into clinically useful tools. Something similar must be the aim for septic shock.

- R Liu, X Wang, et al. The Prognostic Role of a Gene Signature from Tumorigenic Breast-Cancer Cells. N Engl J Med 2007;356:217-26.

Recent **further** sources of variability in the inheritance and expression of genes has been identified. The numbers of copies of genes may vary, as may the structure of the supporting molecules. In the future association studies will need to assess the impact of these new sources of variability.

- RG. Gosden, and AP. Feinberg Genetics and Epigenetics — Nature's Pen-and-Pencil Set. N Engl J Med 2007;356(7);731-3
- K Christensen, and JC. Murray, What Genome-wide Association Studies Can Do for Medicine N Engl J Med 2007; 356;(11), 1094-7

Other sources of information:

Websites.

<http://www.emedicine.com>

<http://www.nlm.nih.gov/nlmhome.html>