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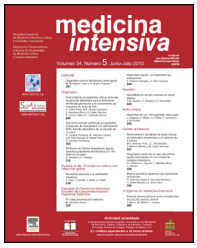

REVIEW

Community acquired pneumonia: Genetic variants influencing systemic inflammation☆

J.M. Ferrer Agüero[a], S. Millán[b,c], F. Rodríguez de Castro[d,e], I. Martín-Loeches[b,c], J. Solé Violán[a,c,*]

[a] *Servicio de Medicina Intensiva, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain*
[b] *Centro de Cuidados Intensivos, Corporación Sanitaria Universitaria Parc Taulí, Hospital Universitario de Sabadell, Universidad Autónoma de Barcelona, Sabadell, Barcelona, Spain*
[c] *Centro de Investigaciones Biomédicas en Red de Enfermedades Respiratorias (CIBERES), Sabadell, Barcelona, Spain*
[d] *Servicio de Neumología, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain*
[e] *Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain*

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Abstract The inflammatory response depends on several factors, including pathogenicity and duration of the stimulus, and also on the balance between the inflammatory and antiinflammatory response. Several studies have presented evidence of the importance of genetic factors in severe infections. The innate immune response prevents the invasion and spread of pathogens during the first few hours after infection. Each of the different processes involved in innate immunity may be affected by genetic polymorphisms, which can result in susceptibility or resistance to infection. The results obtained in the different studies do not irrefutably prove the role or function of a gene in the pathogenesis of respiratory infections. However, they can generate new hypotheses, suggest new candidate genes based on their role in the inflammatory response, and constitute a first step in understanding the underlying genetic factors.

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* Corresponding author.
E-mail address: jsolvio@gobiernodecanarias.org (J. Solé Violán).

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PALABRAS CLAVE
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Susceptibilidad a sepsis

Neumonía adquirida en la comunidad: variantes génicas implicadas en la inflamación sistémica

Resumen La respuesta inflamatoria del huésped viene determinada por la virulencia del microorganismo, la duración del estímulo y el equilibrio entre la respuesta inflamatoria y la antiinflamatoria. Diversos estudios han mostrado la importancia de la genética en las infecciones graves. La respuesta inmune innata es el mecanismo que impide la invasión y propagación de microorganismos durante las primeras horas tras la infección. Cada uno de los procesos implicados en la respuesta innata puede alterarse por polimorfismos de los genes implicados, pudiendo esto resultar en una mayor susceptibilidad o resistencia a la infección. Los resultados obtenidos en los diferentes estudios genéticos no prueban de forma irrefutable el papel o la función de un gen en la patogénesis de la infección respiratoria. Sin embargo, permiten generar nuevas hipótesis, indican nuevos genes candidatos en base a su papel en la respuesta inflamatoria y proporcionan el primer paso en la comprensión de los factores genéticos subyacentes.

Introduction

The genetic variability among individuals could explain why community-acquired pneumonia (CAP) can manifest as a serious illness in some people and as a relatively mild disorder in others. Sorensen et al.[1] published a study on the causes of premature death in 1000 families with children adopted at an early age, and found that if the biological parents of these children had died as a result of infection before 50 years of age, the offspring had a relative risk of death due to infection of 5.81. In contrast, death of the adopting parents because of infection did not imply an increased risk of death due to infection in the adopted child. Thus, the susceptibility and response to infection appear to have a strong genetic influence.

In some diseases, the mutation of a single gene is necessary and sufficient to produce the clinical phenotype and cause the illness. These rare monogenic diseases are often associated to recurrent bacterial infections, and are detected in childhood.

However, most phenotypical traits of common diseases are determined by many genes that collaborate in different loci and lack the simple (or Mendelian) hereditary pattern that characterizes monogenic disorders. These complex or polygenic diseases are the result of the combination of different genetic and environmental factors, and include conditions as frequent as diabetes, hypertension, arteriosclerosis and susceptibility to infection. Such disorders exhibit a non-Mendelian hereditary pattern.

The incidence of infectious diseases indicates that the genetic variants associated to these processes must be relatively frequent (a polymorphism), rather than rare mutations. A genetic polymorphism is a region of the human genome (HG) that varies among different individuals in a given population. This allelic variant must affect a significant portion of the normal population (generally over 1%), and may involve the substitution of a single nucleotide (single nucleotide polymorphism, SNP) or affect the number of nucleotide simple sequence repeats (microsatellites), which account for over 50% of the HG.[2,3] The so-called single nucleotide polymorphisms (SNPs) are the most important and frequent form of variation in the HG (Table 1; Fig. 1).

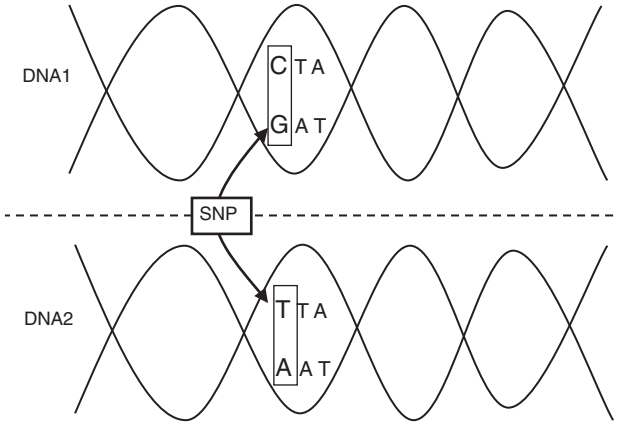

Figure 1 Single nucleotide polymorphisms (SNPs). Variations in DNA sequences corresponding to a single nucleotide (A, T, C or G) in the genome. Molecule DNA1 differs from molecule DNA2 by a single base pair (C/T polymorphism).
SNP: single nucleotide polymorphism.

Those polymorphisms that modify the sequence of amino acids encoded for by a gene or those bases located in its regulator region are the forms with the greatest probability of producing functional repercussions.[2,3]

Identification of genes implicated in innate defense against infection

The innate immune system represents the first line of defense against the invasion and spread of pathogens in the first hours following infection. As a first step, the host must recognize the invading pathogen and induce its elimination through either complement-mediated lysis or phagocytosis. In turn, an inflammatory response must be triggered, and finally an antiinflammatory response is required in order to restore the homeostatic balance. Each of these processes can be affected by polymorphisms of the implicated genes, and which can produce susceptibility or resistance to infection. It also must be taken into account that although different genes within one same chromosome can determine