RESEARCH POINTERS

Association of common genetic variant with susceptibility to invasive pneumococcal disease

Host factors influencing susceptibility to infection with *Streptococcus pneumoniae* remain incompletely understood, even though it is a major cause of infectious mortality. We report a genetic locus associated with susceptibility to invasive pneumococcal disease.

C reactive protein is an acute phase protein that may be important in the early stages of this infection.[1] It binds the C polysaccharide of the cell wall of *S pneumoniae*, activates the classical complement pathway, and in vitro promotes phagocytosis by polymorphonuclear leucocytes.[2 3] In vivo, transgenic mice with human C reactive protein have reduced bacteraemia and longer survival after infection with *S pneumoniae* than wild type controls.[2] Our case-control study compared the frequency of a dinucleotide repeat polymorphism located in an intron of the C reactive protein gene in patients with invasive pneumococcal disease and in healthy controls.[3]

Participants, methods, and results

Altogether 205 cases were recruited from three Oxfordshire hospitals (John Radcliffe, Horton, and Wycombe) as part of the enhanced active surveillance of invasive pneumococcal disease, and 345 controls were selected randomly from local blood donors and transplant donors. People who—or whose parents or grandparents—were born outside the United Kingdom were excluded, and all cases and controls were white. A case was defined as a patient in whom *S pneumoniae* had been isolated from a normally sterile site (blood, cerebrospinal fluid, or joint fluid); 23 cases were in children, the median age was 65 years, and half were male. Amplification by polymerase chain reaction (PCR) with the CA strand primer GATCTATCCCCTCACTTACG and tetrachloro-6-carboxyfluorescein labelled GT strand primer TATGAACAGAACAGTGGAGC yielded a product of 134 base pairs. The size of the fragments was analysed by using ABI 373 sequencing machines and Genescan and Genotyper software.

The overall distribution of alleles (table) differed significantly in cases and controls ($\chi^2 = 18.6$, df=9, $P < 0.05$). The most common allele, of 134 base pairs, was found more often in cases than controls (χ^2=10.57, P=0.001; odds ratio 1.52, 95% confidence interval 1.18 to 1.96). Genotypes of 134 base pairs were not different from Hardy-Weinberg equilibrium in cases and controls and, compared with people without this allele, homozygotes with 134 base pairs were at significantly increased risk of disease (odds ratio 2.21, 1.18 to 4.13; P=0.007) but heterozygotes were not (1.52, 0.83 to 2.79; P=0.14). The odds ratio for heterozygotes was almost half the effect, namely the square root of the odds ratio obtained for homozygotes, which may imply a risk linearly related to the number of alleles. The peak concentrations of C reactive protein within seven days of culture in cases with and without allele 134 were not significantly different, but variations between patients in time of sampling after infection will have reduced the power of this analysis. As variation of microsatellites is often not of direct functional importance, future studies will address the relative strengths of association and functional effects of the microsatellite allele of 134 base pairs and polymorphisms in close linkage disequilibrium with it.

Number (percentage) of alleles of C reactive protein found in cases of invasive pneumococcal disease and controls

Allele size (base pairs)	Controls (n=345)	Cases (n=205)
130	8 (1.2)	2 (0.5)
132	21 (3.0)	7 (1.7)
134	384 (55.6)	269 (65.6)*
136	22 (3.2)	10 (2.4)
138	2 (0.3)	2(0.5)
140	6 (0.9)	1 (0.25)
142	60 (8.7)	32 (7.8)
144	180 (26.1)	86 (21)
146	7 (1.0)	0
148	0	1 (0.2)
Total	690	410

*P=0.001 uncorrected, P=0.01 corrected for 10 comparisons.

Comment

The association shown in this study of a variant in the C reactive protein gene with susceptibility to invasive pneumococcal disease provides the first evidence that a common genetic variant may influence susceptibility to this major global cause of mortality and morbidity. Studies in mice have provided direct evidence of a protective role for C reactive protein against pneumococcal infection and disease.[3] Our study provides genetic evidence for a role that this highly conserved and abundant acute phase reactant has in human pneumococcal disease.

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