

13 An Overview of The Genetic Basis For Variations in The Immune Response to Vaccines

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An understanding of the role of immunogenetics on vaccine response is crucial in the rational design and development of the next generation of vaccines for the 21st century. Clinically relevant adverse immunologic consequences (i.e., primary vaccine failure) can result for significant portions of the population because of genetic variation. The implications of this concept may mean that some current vaccines may fail to accomplish universal immunity because of the genetic restriction to antibody response. The vaccines of the future may take advantage of this growing knowledge base to attain higher levels of vaccine response. Importantly, it appears possible to use reverse immunogenetics to "reverse" engineer vaccines with the goal of defining vaccine peptide antigens (degenerate or otherwise) that can be universally presented to T cells, and hence stimulate the development of immunity. In this talk, I will provide an overview of the evidence for significant interactions between antibody response to a vaccine, and specific class I and II HLA genes, as well as Gm/Km allotypes.

14 Genetic Polymorphisms and Vaccine Immunity
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GM and KM allotypes, the antigenic determinants of γ chains and κ -type light chains, respectively, are inherited as autosomal codominant genes according to Mendelian laws. Linkage disequilibrium in the GM system is almost absolute and the determinants are transmitted as a group called haplotypes. Each major race has a distinct array of haplotypes. The striking qualitative and quantitative differences in the distribution of these determinants among different races raise questions concerning the nature of the evolutionary selective mechanism that maintains this variation. Associations between Ig allotypes and specific antibody responses could be a selective force for the maintenance of various haplotypes and their frequencies. Numerous studies by us and others have reported significant associations between certain GM and KM allotypes and immune responsiveness to various antigens, including Meningococcus A, B, and C, *Haemophilus influenzae* type b, type III group B streptococcal antigen, and pneumococcal polysaccharides. For some immune responses, the unlinked GM (chromosome 14) and KM (chromosome 2) genes have been shown to act epistatically. Possible ways in which constant region allotypes could contribute to the antibody specificity determined by the variable region include the following: certain alleles coding for allotypes may be in linkage disequilibrium with those coding for idiotypes. Alternatively, folding of the constant domain carrying a particular allotype may result in a slightly different tertiary structure in the variable region.

15 Genetic control of the immunological response to capsular polysaccharides (CPS) of *Streptococcus pneumoniae* (Spn).
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Using an assay for IgG to CPS of Spn, in which cross-reactive antibody to cell wall polysaccharide is removed by adsorption, we discovered that some individuals respond to antigenic challenge with CPS whereas others do not. Human responses to antigenic challenge with proteins are under tight genetic control, and it seemed reasonable to assume that the same was true for polysaccharides, although remarkably little had been reported on this subject. Our initial studies of nuclear families suggested a familial pattern. We therefore studied 61 members of an ethnically homogeneous (Ashkenazic Jewish) extended family and 72 unrelated white adult controls. IgG to 10 representative CPS was measured after vaccination with 23-valent pneumococcal vaccine. 11% of controls and 23% of family members responded to ≤ 5 of 10 CPS; 53% and 41% of the two groups responded to all 10 CPS. Segregation analysis revealed that capacity to respond was inherited in mixed codominant fashion. IgG responses were greater in controls with Gm(23)+ allotype, but not in the Ashkenazic family. HLA type was not associated with responsiveness. Repeated vaccination with early conjugate vaccines did not stimulate responses in nonresponders, but octavalent diphtheria-toxoid conjugate vaccine stimulated high levels of antibody to most CPS in 5 of 8 such persons. Protein conjugate vaccines may overcome the genetic incapacity to respond to CPS; an ideal conjugate vaccine would stimulate responses to all CPS in all subjects.

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