Published in final edited form as:
Vaccine. 2008 November 18; 26(49): 6183–6188. doi:10.1016/j.vaccine.2008.06.057.

Vaccine Immunogenetics: Bedside to Bench to Population

Gregory A. Poland[a], **Inna G. Ovsyannikova**[b], and **Robert M. Jacobson**[c]

a*Mayo Vaccine Research Group, the Program in Translational Immunovirology and Biodefense, and the Departments of Medicine and Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic College of Medicine, Rochester, MN 55905, USA*

b*Mayo Vaccine Research Group, Mayo Clinic College of Medicine, Rochester, MN 55905, USA*

c*Department of Pediatric and Adolescent Medicine, Mayo Clinic College of Medicine, Rochester, MN 55905, USA*

Abstract

The immunogenetic basis for variations in immune response to vaccines in humans remains largely unknown. Many factors can contribute to the heterogeneity of vaccine-induced immune responses, including polymorphisms of immune response genes. It is important to identify those genes involved directly or indirectly in the generation of the immune response to vaccines. Our previous work with measles reveals the impact of immune response gene polymorphisms on measles vaccine-induced humoral and cellular immune responses. We demonstrate associations between genetic variation (single nucleotide polymorphisms-SNPs) in HLA class I and class II genes, cytokine, cell surface receptor, and Toll-like receptor genes and variations in immune responses to measles vaccine. Such information may provide further understanding of genetic restrictions that influence the generation of protective immune responses to vaccines, and eventually the development of new vaccines.

Keywords

genetic association; polymorphisms; HLA; cytokines; SLAM; CD46; TLR; measles vaccine

Background

Recently the Centers for Disease Control and Prevention identified ten of the greatest public health achievements and placed vaccination at the top of the list [1]. Vaccines are among the most effective and cost-effective of our public health initiatives [2]. Bunker *et al.* reported that the lifespan of a U.S. resident improved from 1900 to 1999 by 30 years with 25 of these years being due to public health interventions such as vaccines [3].

A great deal of the success with implementation of routine vaccination rests on a “one size fits all” strategy with the elimination of false contraindications and the universality of the recommendations facilitating standing orders and mass vaccination. Vaccines are the only medical intervention that we attempt to deliver to every living human on earth. With the

Address all correspondence to: Gregory A. Poland, M.D., Director, Mayo Vaccine Research Group, Director, Program in Immunovirology and Biodefense, Professor of Medicine and Infectious Diseases, Mayo Clinic College of Medicine, 611C Guggenheim Building, 200 First Street, SW, Rochester, MN 55905, (507) 284-4968, poland.gregory@mayo.edu.

advances coming from the new biology of the 21st century it is appropriate to now ask the question "how might new genetic and molecular biology information inform vaccinology practices of the future?" With the advent of whole-genome scanning and the increasing application of immunogenetic and immunogenomic approaches to vaccines, we must consider how we might advance vaccination practice with information regarding genetically-mediated individual variation in vaccine response and reactivity. Several examples are worth considering. The humoral (antibody) response to a vaccine is determined by a number of factors, including age, gender, race, the quality and quantity of vaccine antigen(s), the number of doses administered, and the route of immunization. However, a "one size fits all" approach could lead to vaccine delivery policies that may ignore future immunogenetics findings. For example, data suggest that up to 40% of the adolescent population develop protective levels of immunity (although the duration of that immunity is unclear) after one to two doses of hepatitis B vaccine (HBV) raising the question of whether everyone needs three doses of HBV. In considering issues of vaccine non-responsiveness, a good illustration is HBV, where multiple doses (6 or more) are necessary in some individuals to induce an immune response that in the majority of individuals requires only two or three doses [4]. We might similarly ask the question can we predict who will develop serious side effects after a vaccine, such as neurological complications after vaccinia or yellow fever vaccine. All of these questions expose the need for considering the application of new data emanating from genetics, immunology, molecular biology, bioinformatics, and other fields toward a more personalized or individual approach to vaccine practice.

The Immune Response Network Theory

A variety of factors impact the heterogeneity of vaccine-induced immune responses. Some of these include gender, vaccine dose, the integrity of vaccine storage and cold chain maintenance, immune system function and integrity, age, body mass index, and others. Our laboratory has been working on the "immune response network theory" [5]. The basic underlying concept of this theory states that the response to a vaccine is the cumulative result of interactions driven by a host of genes and their interactions and is, therefore, theoretically predictable. The basic genetic elements of the network include genes which activate or suppress immune responses, the dominance profile of a given gene or polymorphism, epigenetic modifications of genes, the influence of signaling genes and innate response genes, gene-gene interactions, and genes for other host response factors.

While we increasingly understand the role of genetic causes of heterogeneity and treatment effects with drugs this awareness is new in regards to our thinking with the immune response to vaccines. Spielberg [6] comments, "Just as pharmacogenetics has suggested ways of designing drugs to minimize population variability, understanding mechanisms of immunogenetic variation may lead to new vaccines designed to minimize immunogenetically based failure". So the new question that vaccinologists in the 21st century must ask is why immune responses to biologics and vaccines vary among otherwise healthy recipients and what explains this heterogeneity?

Immunogenetic Determinants of Vaccine Response

Genetic influences can occur via polymorphisms of a variety of genes involved directly or indirectly in the generation of the immune response. This can include membrane-based viral receptors, innate toll-like receptors (TLRs), signaling molecules, cytokine genes, cytokine receptor genes, human leukocyte antigen (HLA) genes, immunoglobulin Gm and Km allotypes, vitamin A and D receptor genes as well as many others. In addition, it is important to consider the mechanisms for such polymorphism driven effects. These can include differential viral or antigen binding and processing, differential expression/presentation of

antigenic peptides, a differential range of presented peptides (genetic restriction), altered secretion patterns, for example of cytokines, altered transcription of important genes such as signaling molecules and gene products, altered binding of virus or antigens by membrane-based receptors, and differential receptor function, expression, and affinities as well as others.

The Measles Example

A useful model for further examining this issue of the immunogenetics of vaccine responses has been examined by our laboratory in regards to live measles virus vaccine. Interestingly measles was thought to be well controlled and on its way to eradication in the late 1980's in the US. However, beginning in 1989 a measles resurgence occurred which lasted until 1991 and led to an estimated 55,000 documented cases, > 11,000 hospitalizations, approximately 155 deaths, and direct medical expenses which exceeded $150 million dollars [7]. Our laboratory noticed that depending on the year examined 20% - 40% of these children had received one or more doses of measles vaccine, raising the specter of vaccine failure at a rate that was unanticipated. Thus our laboratory decided to use live measles vaccine as an immunogenetic probe of variations of immune responses for the following reasons [8]:

- It is the most transmissible human virus known
- Measles is a monotypic virus
- High immune response heritability [9]
- Little in the way of natural disease and hence immune markers could be ascribed to vaccine
- Outside the US measles caused significant morbidity and mortality and hence is of high public health importance
- After polio, measles is the "next" virus being considered for elimination or eradication
- Measles virus is increasingly being used as a backbone vector for delivery of other agents, for example in oncolytic vaccines [10,11]

The Role of Twin Studies

An important method in which to study genetic causes of variations in vaccine response is through the use of twin studies. Twin studies provide the ability to separate genetic and environmental factors and to explore the contribution of genetic factors related to variability and immune response. In particular, twin studies allow the determination of the proportion of variation attributed to specific genes and this enables the concept of heritability which is defined as the ratio of genetic variance to total variance [12]. In one of our early studies, we examined 120 healthy twin pairs who had received one to two doses of measles-mumps-rubella-II (MMR-II) vaccine. Among this cohort, 45 of these twin pairs where monozygotic and the remainder dizygotic [9]. We examined the heritability of immune responses to MMR-II and found that the heritability for measles was almost 90% ($p<0.0001$) whereas the heritability for mumps and rubella was much lower at 39% and 46%, respectively. These findings clearly pointed to the conclusion that much of the measles vaccine-induced immune response was genetically determined, providing the rationale for more in-depth studies of candidate genes and their association to measles vaccine-induced immune responses.

HLA Gene Polymorphisms

Given the finding of very high heritability of immune responses to measles vaccine, our laboratory embarked on a series of studies designed to answer questions such as how important are immune response gene polymorphisms in the immune response to measles vaccine, and

what is the role of gene homozygosity and of more than one dose? We also were interested in whether our answers would be generalizable across other viral vaccines and if so might we be able to identify new immunogenetic mechanisms that would explain some vaccine response enigmas. In one of our first studies we examined 900 healthy Rochester school children from both private and public schools and from all socioeconomic strata. This was a convenience sample of children who had been immunized with one dose of MMR-II vaccine and for which there was medical record documentation of immunization. There had been no circulating measles in the community since 1980, the earliest year of birth for any member of the study cohort and hence detectable antibody was due to vaccine and not infection. We performed virus-specific enzyme immunoassay (EIA)-based IgG antibody testing and molecular HLA typing, and discovered that were that 10% of the subjects were seronegative; we also noted that the seronegatives and serohyperpositives clustered among related family members who were immunized in different years [8,9]. This observation prompted the question of why in this cohort of apparently healthy children all of whom received the same vaccine did we see extremes of the biologic continuum in terms of antibody response (i.e. 10% seronegative and 10% serohyperpositive)? We reasoned that these findings might be genetically determined, and hypothesized that subjects who developed low or high antibody response after measles vaccination may have genetically determined differences in their immune response to measles virus that led to either lower levels or higher levels of antibody response.

We begin our studies examining the influence of HLA gene polymorphisms including the HLA class I A, B, and C genes and the class II DR, DQ, and DP genes on the short arm of human chromosome 6 (6p21.3). HLA genes encode proteins expressed on antigen-presenting cells and are the machinery by which endogenous and exogenous naturally processed measles virus peptides are presented to T helper cells. We hypothesized that variations in antibody response would be determined by genetic polymorphisms of the HLA genes and sought to relate antibody response to specific HLA alleles, to HLA homozygosity, and to class I and II haplotypes. We did not find any significant association with HLA-A genes, but found significant associations with HLA-B ($p=0.016$) and HLA-C ($p=0.0007$) class I loci [13]. HLA allelic associations with measles vaccine-induced humoral and cellular immunity for non-responders and hyper-responders are shown in Table 1. For example, low measles antibody levels are associated with class I HLA-B*8, B*13, B*44, and class II HLA-DRB1*03 and DQA1*0201 alleles, whereas HLA-B*7, DQA1*0104, and DPA1*0202 alleles are associated with high antibody levels following measles vaccine [14–16]. We also examined class I HLA supertypes, which are based on a shared sequence motif in the peptide-binding pockets of HLA molecules, for measles vaccine non-responders and for hyper-responders. The HLA supertypes with the strongest associations with lower measles antibody levels included B44 and B58 (global p-value=0.01). In contrast, the B7 supertype was associated with higher measles-specific antibody levels [17].

We also examined measles humoral and cellular immune responses and HLA haplotypes for class I and class II genes. The haplotypes with the strongest associations with lower measles virus IgG antibody responses were A*24-C*03-B*15 ($p=0.04$), DRB1*07-DQB1*03-DPB1*04 ($p=0.001$) and DRB1*07-DQB1*02-DPB1*02 ($p=0.05$). In this study, the A*26-C*12-B*38 ($p=0.02$), DRB1*04-DQB1*03-DPB1*03 ($p=0.02$) and DRB1*03-DQB1*02-DPB1*04 ($p=0.01$) haplotypes were associated high measles-specific cellular (lymphoproliferation) immune responses (Table 1) [18]. These studies are complemented by a different study that showed associations between alleles of the DRB1, DQB1, DQA1, and DPA1 loci and IL-2, IL-10, and IL-12p40 cytokine responses to measles vaccine [19]. The immunologic significance of HLA class I and class II genes in measles vaccine-specific IFN-γ and IL-4 cytokine immune responses was also demonstrated [20,21]. Finally, we counted the number of loci (out of 7) for which each subject was homozygous. We noted that children homozygous for at least one HLA locus were almost twice as likely to be seronegative (OR

1.97, 95% CI 1.08–3.61) and children homozygous at ≥ 4 loci were 4 – 5.5 times more likely to be seronegative (95% CI; 1.22 – 25) following a single dose of measles vaccine [22]; however, we then performed an interesting study. We identified 130 children who were seronegative by EIA after one dose of MMR-II and re-immunized them with a second dose of MMR-II. We preformed IgG antibody testing six weeks later and demonstrated that 81.5% (n=106) became seropositive and 18.5% (n=24) remained seronegative [23]. We then reexamined our results among subjects who had received two doses of measles vaccine and found that except for the HLA-B*44 (B*4403) our class I and class II HLA effects were no longer detectable (Table 2), just as had been seen by others examining immune responses to repeated doses of hepatitis B vaccine [24,25]. Interestingly, individuals who were homozygous at the class II DRB1, DQA1, DPA1 and DPB1 loci had higher measles vaccine-induced IFN-γ secretion levels compared with individuals who were heterozygous for these loci. Homozygosity at increasing numbers of HLA loci (>=4) was associated with increased *in vitro* IFN-γ secretion (test for trend p-value=0.01). Thus, following two doses of live attenuated measles vaccine, we found an extinction effect, with HLA homozygosity no longer demonstrating a disadvantage for measles-specific cytokine responses [26].

Measles Virus Receptor Gene Polymorphisms

These results prompted additional studies examining immunogenetic markers of measles vaccine-induced response heterogeneity [27–29]. We started by examining gene polymorphisms in the two genes coding for the measles receptors – signaling lymphocyte activation molecule (SLAM, also known as CDw150) and membrane cofactor protein - CD46 [30,31]. SLAM and CD46 both have measles virus binding domains extending upward from the cell membrane-based receptors. We reasoned that polymorphisms in measles virus receptors could influence the immune response to live measles virus vaccination by a variety of potential mechanisms, including modified measles virus binding, altered entry, differential uptake, altered signaling, and or altered receptor expression [32]. We found a variety of statistically significant SLAM and CD46 single nucleotide polymorphisms (SNPs) associations, in some cases associated with an allele-dose relationship (global p-value for measles=0.003) (Table 3) [33]. For instance, increased representation of minor alleles for rs3796504 and rs164288 in the SLAM gene were associated with an allele dose-related four-fold decrease in measles-specific IgG antibodies. While the mechanism for this finding is unclear, we postulate that these SNPs may negatively impact the ability of measles vaccine virus to bind to its receptor, and hence prevent induction of humoral immunity. To determine whether these associations may have been due to chance we examined the specificity of genetic associations by simultaneously looking at the association between the specific SNPs found to be associated with measles immune responses and immune responses to concomitantly administered mumps and rubella vaccines. No statistically significant associations were found, further increasing our confidence in the results. Thus, the SLAM and CD46 SNP associations we observed were specific to measles vaccine-induced humoral immune response and were not found with co-administered mumps and rubella vaccine-induced immune responses [33].

Cytokine and Cytokine Receptor Gene Polymorphisms

Polymorphisms in coding and noncoding regions of cytokine and cytokine receptor genes can influence many aspects of cytokine biology, for instance transcriptional activity, protein secretion, receptor binding, direct interactions with viral proteins and functional activity [34]. These observations prompted additional work involving the role of cytokine and cytokine receptor SNPs reasoning that since cytokines play an essential role in regulating viral vaccine-induced humoral and cellular immunity [35]. SNPs that alter cytokine levels or cytokine activity could also influence the outcome of immune response following measles vaccination [36]. For instance, homozygosity of CA repeats in the IFN-γ gene was found to be associated

with increased production of IFN-γ following *in vitro* stimulation with measles virus [37]. We identified a number of statistically significant associations in the IL-2, IL-10, and IL-12RB genes as well as SNP associations with secreted cytokine levels (Table 4). SNPs within the IL-2 gene were associated with high IgG antibody and high lymphoproliferative immune responses, whereas SNPs within the IL-10 and IL12R genes were associated with low antibody and lymphoproliferative responses to measles vaccination [36]. Thus, our data suggest that certain SNPs in cytokine and cytokine receptor genes may be associated with variations in immune response after measles vaccination, although a replication study is necessary to confirm this observation.

Toll-Like Receptor Polymorphisms

Since viral infections can also be initially recognized by innate receptors, such as the TLRs, we also examined the potential role of TLR polymorphisms in measles vaccine-induced immune responses. This was logical as the laboratory adapted attenuated Edmontson strain of measles virus is known to upregulate the expression of TLR3 in human dendritic cells via enhanced interferon alpha and beta (IFN-α/β) secretion [38]. Of the 10 human TLRs, 3, 7, 8 and 9 are endosomal and specialize in viral recognition. Specifically, TLR3 belongs to a family of evolutionary preserved innate immune recognition molecules and recognizes double-stranded RNA, a molecular pattern associated with viral infections [39]. Recent studies have demonstrated a MyD88-independent signaling pathway downstream of TLR3 (and TLR4) that is regulated by the adaptor molecule TRIF [40]. Measles virus nucleocapsid protein is also known to activate TLR-associated signaling molecule interferon regulatory factor-3 (IRF-3), leading to IFN production [41]. Further, wild type measles virus activates signaling through the TRL2, TLR4, and TLR7 responsive genes, and activates a TLR-responsive cytokine profile (IL-1a/β, IL-6, and IL-12) [42,43]. We examined the association between SNPs (n = 96; minor allele frequency >5%) in TLRs and their associated intracellular signaling molecules and measles-specific IgG and lymphoproliferative responses after two-doses of measles vaccine in 190 healthy individuals. We found a variety of significant SNP associations with TLRs and their associated signaling molecules that have a known role in viral immunity and variations in immunity after measles vaccination. For example, heterozygous variant for rs3775291 of the TLR3 gene was significantly associated with lower antibody response to measles vaccination (Table 5). In addition, we identified a SNP (rs5743305) in the 3'UTR of the TLR3 gene that demonstrated an association between a heterozygous variant and low measles antibody and lymphoproliferative immune responses, supporting a role for TLR3 in measles immunity [44]. This suggests a role of TLR3 in both innate and adaptive immune responses to measles immunization. We also found the minor SNP allele variant GG for rs6853 located in the 3'UTR in MyD88 that was associated with a lower measles antibody level. While it is clear that we are at an early stage in our understanding of the role of TLRs in vaccine-induced immune response outcomes, important early observations have been made and require further study. Of note, recent literature on various viral models including measles suggests that TLR immunogenetics may play a pivotal role in human disease and response to vaccination [45–47].

Summary

Through the data discussed above, we have illustrated important preliminary associations between measles vaccine immune responses and class I and class II HLA alleles, HLA supertypes and HLA haplotypes, SLAM and CD46 receptor SNPs, cytokine and cytokine receptor, TLR and MyD88 SNPs. The observation that polymorphisms in these genes modulate the humoral and cellular immune responses to measles virus vaccination is significant, but further investigations are clearly required to confirm these findings. Further we have illustrated that almost 90% of measles vaccine immune response heterogeneity was explainable

genetically. Thus, our data contribute to understanding of the immunogenetic mechanisms underlying variations in the immune response to measles vaccine. In this manner, and broadening our understanding to other vaccines, it is important to realize that understanding and defining associations between key immune response gene polymorphisms and subsequent immune response can aid in designing new vaccines, and in better understanding the immunology of viral vaccine-induced immune response variability.

These data are illustrative of the type of data that could be developed for many vaccines. In turn, such information, once further validated and confirmed, could be used to make individualized decisions regarding vaccine practice. Difficulties remain however in the study of the immunogenetics and immnogenomics of vaccine-induced immune responses. The complexity and extensive polymorphic nature of immune response genes, particularly the HLA genes, impede progress and in turn relate to statistical issues of multiple comparisons and statistical power. In addition, issues of multigenic and other gene interaction response effects such as complementation and epigenetics further complicate this type of work. Furthermore, there also appear to be gender and potential ethnic or racial differences further adding to the complexity of these studies. Finally, validation studies are essential in order to better understand the significance of gene-specific polymorphisms and to sort true-positive from false-positive associations [48].

Nonetheless, based on work such as what we have discussed above we envision a new “vaccinomics” era of personalized “predictive vaccinology” in the future [5,49] whereby we might:

- Abandon a one-size (and dose) –fits-all vaccine approach for all vaccines and all persons
- Predict the likelihood of a significant adverse event to a vaccine [50]
- Decide the number of doses likely to be needed to induce a sufficient response to a vaccine
- Design and develop new vaccines and studies to prove their efficacy and safety in such a way as to begin to use them in an individualized manner [51]
- Identify approaches to vaccination for individuals and groups (based on age, gender, race, other) based on genetic predilections to vaccine response and reactivity

The issue of racial and ethnic differences in vaccine response is important, but inadequately studied. For example, early on it was demonstrated that American Indian and Alaskan native populations had decreased humoral immune responses to Haemophilus influenzae type b and pneumococcal vaccines [52–54]. Similarly, native Amazon basin tribes demonstrated greater reactivity to measles vaccine [55]. These early studies provide hints of what could be genetically-mediated variations in vaccine responses that if better clarified could inform vaccinology practice. Such advances could require variations in dose and schedule if not substrate of vaccine. Further understanding of the genetic variation in vaccine response may drive an individualization of vaccination for groups and individuals at high risk for vaccine failure or vaccine adverse effects.

All of this must be balanced with the sobering thoughts of William Roper, MD, the Director of the CDC from 1990 to 1993, who noted that despite the great public health success of vaccination, the costs of routine vaccination remained a significant barrier to obtaining recommended vaccines for persons who were uninsured or underinsured [2,56]. Cost is important for any public health strategy and must be balanced with potential gains. While immunogenetics can further our understanding of vaccination, it is clear that for any widespread adoption of personalized vaccinology, much data remains to be developed, costs for genetic

testing must be orders of magnitude less expensive than it is currently, and high throughput technologies along with bioinformatics approaches that are easily accessible must be in place. Should this occur, and driven by potential discoveries such as whether one is at risk for an adverse outcome of a given infection – and hence whether vaccination would be cost-effective, as well as data on adverse side effects and dosing; a new era in vaccine practice may well evolve.

Acknowledgments

We thank the many subjects and Mayo Vaccine Research Group staff who have participated in our studies. We thank Cheri A. Hart for her editorial assistance. In addition we acknowledge support from the National Institutes of Health grants AI 33144 and AI 48793 for this work.

References

1. Centers for Disease Control and Prevention. Ten Great Public Health Achievements - United States, 1900–1999. MMWR 1999 April;48(No 12):241–264. [PubMed: 10220250]
2. CDC's 60th anniversary: director's perspective--William L. Roper, M.D., M.P.H., 1990–1993. MMWR Morb Mortal Wkly Rep 2007;56(18):448–452. [PubMed: 17495792]
3. Bunker JP, Frazier HS, Mosteller F. Improving health: measuring effects of medical care. Milbank Q 1994;72(2):225–258. [PubMed: 8007898]
4. Alper CA, Kruskall MS, Marcus-Bagley D, et al. Genetic prediction of nonresponse to hepatitis B vaccine. N.Engl.J.Med 1989;321:708–712. [PubMed: 2528067]
5. Poland GA, Ovsyannikova IG, Jacobson RM, Smith DI. Heterogeneity in vaccine immune response: The role of immunogenetics and the emerging field of vaccinomics. Clin.Pharmacol.Ther 2007;82(6): 653–664. [PubMed: 17971814]
6. Spielberg SP. Therapeutics and toxicology. Curr.Opin.Pediatr 1998;10:201–202. [PubMed: 9608900]
7. Poland GA, Jacobson RM. Failure to reach the goal of measles elimination. Apparent paradox of measles infections in immunized persons. Arch.Intern.Med 1994;154:1815–1820. [PubMed: 8053748]
8. Poland GA. Variability in immune response to pathogens: using measles vaccine to probe immunogenetic determinants of response. Am.J.Hum.Genet 1998;62:215–220. [PubMed: 9463343]
9. Tan P-L, Jacobson RM, Poland GA, Jacobsen SJ, Pankratz SV. Twin studies of immunogenicity - determining the genetic contribution to vaccine failure. Vaccine 2001;19:2434–2439. [PubMed: 11257374]
10. Grote D, Russell SJ, Cornu TI, et al. Live attenuated measles virus induces regression of human lymphoma xenografts in immunodeficient mice. Blood 2001;97:3746–3754. [PubMed: 11389012]
11. Peng KW, Frenzke M, Myers R, et al. Biodistribution of oncolytic measles virus after intraperitoneal administration into Ifnar-CD46Ge transgenic mice. Hum.Gene Ther 2003;14(16):1565–1577. [PubMed: 14577918]
12. Jacobson RM, Ovsyannikova IG, Targonski PV, Poland GA. Studies of twins in vaccinology. Vaccine 2007;25(16):3160–3164. [PubMed: 17284336]
13. Poland GA, Jacobson RM. The genetic basis for variation in antibody response to vaccines. Curr.Opin.Pediatr 1998;Vol.10:208–215. [PubMed: 9608902]
14. Jacobson RM, Poland GA, Vierkant RA, et al. The association of class I HLA alleles and antibody levels following a single dose of measles vaccine. Hum.Immunol 2003;64(1):103–109. [PubMed: 12507820]
15. Poland GA, Ovsyannikova IG, Jacobson RM, et al. Identification of an association between HLA class II alleles and low antibody levels after measles immunization. Vaccine 2001;20(3–4):430–438. [PubMed: 11672906]
16. Ovsyannikova IG, Jacobson RM, Vierkant RA, Pankratz SV, Jacobsen SJ, Poland GA. Associations between human leukocyte antigen (HLA) alleles and very high levels of measles antibody following vaccination. Vaccine 2004;22:1914–1920. [PubMed: 15121303]

17. Ovsyannikova IG, Jacobson RM, Vierkant RA, Pankratz VS, Poland GA. HLA supertypes and immune responses to measles-mumps-rubella viral vaccine: Findings and implications for vaccine design. Vaccine 2007;25(16):3090–3100. [PubMed: 17280755]
18. Ovsyannikova IG, Pankratz VS, Vierkant RA, Jacobson RM, Poland GA. Human leukocyte antigen haplotypes in the genetic control of immune response to measles-mumps-rubella vaccine. J Infect Dis 2006;193(5):655–663. [PubMed: 16453260]
19. Ovsyannikova IG, Jacobson RM, Ryan JE, Vierkant RA, Pankratz VS, Poland GA. Human Leukocyte Antigen and Interleukin 2, 10 and 12p40 cytokine responses to measles: Is there evidence of the HLA effect? Cytokine 2006;36:173–179. [PubMed: 17234427]
20. Ovsyannikova IG, Ryan JE, Vierkant RA, Pankratz SV, Jacobson RM, Poland GA. Immunologic significance of HLA class I genes in measles virus-specific IFN-gamma and IL-4 cytokine immune responses. Immunogenetics 2005;57(11):828–836. [PubMed: 16331510]
21. Ovsyannikova IG, Jacobson RM, Ryan JE, et al. HLA class II alleles and measles virus-specific cytokine immune response following two doses of measles vaccine. Immunogenetics 2005;56:798–807. [PubMed: 15712014]
22. St. Sauver JL, Ovsyannikova IG, Jacobson RM, et al. Associations between human leukocyte antigen homozygosity and antibody levels to measles vaccine. J Infect Dis 2002;185(11):1545–1549. [PubMed: 12023759]
23. Poland GA, Jacobson RM, Thampy AM, et al. Measles re-immunization in children seronegative after initial immunization. JAMA 1997;277:1156–1158. [PubMed: 9087472]
24. St. Sauver JL, Dhiman N, Ovsyannikova IG, et al. Extinction of the human leukocyte antigen homozygosity effect after two doses of the measles-mumps-rubella vaccine. Hum.Immunol 2005;66:788–798. [PubMed: 16112026]
25. Kruskall MS. The major histocompatibility complex: The value of extended haplotypes in the analysis of associated immune diseases and disorders. Yale J.Biol.Med 1990;63:477–486. [PubMed: 2293506]
26. Ovsyannikova IG, Dhiman N, Jacobson RM, Vierkant RA, Pankratz VS, Poland GA. HLA homozygosity does not adversely effect measles vaccine-induced cytokine responses. Virology 2007;364(1):87–94. [PubMed: 17397893]
27. Ovsyannikova IG, Jacobson RM, Poland GA. Variation in vaccine response in normal populations. Pharmacogenomics 2004;5(4):417–427. [PubMed: 15165177]
28. Ovsyannikova IG, Dhiman N, Jacobson RM, Poland GA. Human leukocyte antigen polymorphisms: variable humoral immune responses to viral vaccines. Expert Review of Vaccines 2006;5(1):33–43. [PubMed: 16451106]
29. Poland, GA.; Ovsyannikova, IG.; Jacobson, RM.; Kaslow, RA., editors. Genetic influences on the immune response to vaccines. Oxford: Oxford University Press; 2008. Genetic Susceptibility to Infectious Diseases; p. 414-429.
30. Dorig RE, Marcil A, Chopra A, Richardson CD. The human CD46 molecule is a receptor for measles virus (Edmonston strain). Cell 1993;75(2):295–305. [PubMed: 8402913]
31. Tatsuo H, Ono N, Tanaka K, Yanagi Y. SLAM (CDw150) is a cellular receptor for measles virus. Nature 2000;406(6798):893–897. [PubMed: 10972291]
32. Dhiman N, Jacobson RM, Poland GA. Measles virus receptors: SLAM and CD46. Rev Med Virol 2004;14(4):217–229. [PubMed: 15248250]
33. Dhiman N, Cunningham JM, Jacobson RM, et al. Variations in measles vaccine-specific humoral immunity by polymorphisms in SLAM and CD46 measles virus receptors. J.Allergy Clin.Immunol 2007;120(3):666–672. [PubMed: 17560639]
34. van Deventer SJH. Cytokine and cytokine receptor polymorphisms in infectious disease. Intensive Care Med 2000;26:S98–S102. [PubMed: 10786965]
35. Biron CA. Cytokines in the generation of immune responses to, and resolution of, virus infection. Curr.Opin.Immunol 1994;6:530–538. [PubMed: 7946039]
36. Dhiman N, Ovsyannikova IG, Cunningham JM, et al. Associations between measles vaccine immunity and single nucleotide polymorphisms in cytokine and cytokine receptor genes. J Infect Dis 2007;195:21–29. [PubMed: 17152005]

37. Pravica V, Asderakis A, Perrey C, Hajeer A, Sinnott PJ, Hutchinson IV. In vitro production of IFN-gamma correlates with CA repeat polymorphism in the human IFN-gamma gene. Eur.J Immunogenet 1999;26(1):1–3. [PubMed: 10068907]
38. Tanabe M, Kurita-Taniguchi M, Takeuchi K, et al. Mechanism of up-regulation of human Toll-like receptor 3 secondary to infection of measles virus-attenuated strains. Biochem.Biophys.Res.Commun 2003;311(1):39–48. [PubMed: 14575692]
39. Heinz S, Haehnel V, Karaghiosoff M, et al. Species-specific regulation of Toll-like receptor 3 genes in men and mice. J Biol.Chem 2003;278(24):21502–21509. [PubMed: 12672806]
40. Yamamoto M, Sato S, Hemmi H, et al. Role of adaptor TRIF in the MyD88-independent toll-like receptor signaling pathway. Science 2003;301(5633):640–643. [PubMed: 12855817]
41. tenOever BR, Servant MJ, Grandvaux N, Lin R, Hiscott J. Recognition of the measles virus nucleocapsid as a mechanism of IRF-3 activation. J.Virol 2002;76(8):3659–3669. [PubMed: 11907205]
42. Bieback K, Lien E, Klagge IM, et al. Hemagglutinin protein of wild-type measles virus activates toll-like receptor 2 signaling. J.Virol 2002;76(17):8729–8736. [PubMed: 12163593]
43. Hahm B, Cho JH, Oldstone MB. Measles virus-dendritic cell interaction via SLAM inhibits innate immunity: Selective signaling through TLR4 but not other TLRs mediates suppression of IL-12 synthesis. Virology 2006;358(2):251–257. [PubMed: 17070884]
44. Dhiman N, Ovsyannikova IG, Vierkant RA, et al. Associations between SNPs in toll-like receptors and related intracellular signaling molecules and immune responses to measles vaccine: preliminary results. Vaccine 2008;26:1731–1736. [PubMed: 18325643]
45. Schroder NW, Schumann RR. Single nucleotide polymorphisms of Toll-like receptors and susceptibility to infectious disease. Lancet Infect.Dis 2005;5(3):156–164. [PubMed: 15766650]
46. Tal G, Mandelberg A, Dalal I, et al. Association between common Toll-like receptor 4 mutations and severe respiratory syncytial virus disease. J Infect Dis 2004;189(11):2057–2063. [PubMed: 15143473]
47. Hill AV. Aspects of genetic susceptibility to human infectious diseases. Annu.Rev.Genet 2006;40:469–486. [PubMed: 17094741]
48. Chanock SJ, Manolio T, Boehnke M, et al. Replicating genotype-phenotype associations. Nature 2007;447(7145):655–660. [PubMed: 17554299]
49. Poland GA. Personalized vaccines: From populations to persons. Expert Opinion on Biological Therapy. 2008(in press)
50. Stanley SL Jr, Frey SE, Taillon-Miller P, et al. The immunogenetics of smallpox vaccination. J Infect Dis 2007;196(2):212–219. [PubMed: 17570108]
51. Ovsyannikova IG, Johnson KL, Bergen HR III, Poland GA. Mass spectrometry and peptide-based vaccine development. Clin.Pharmacol.Ther 2007;82(6):644–652. [PubMed: 17971823]
52. Siber GR, Santosham M, Reid GR, et al. Impaired antibody response to *Haemophilus influenzae* type b polysaccharide and low IgG2 and IgG4 concentrations in Apache children. N.Engl.J.Med 1990;323:1387–1392. [PubMed: 2233905]
53. Ward J, Brenneman G, Letson GW, Heyward WL. The Alaska H.Influenzae Vaccine Study Group. Limited efficacy of a *Haemophilus influenzae* type b conjugate vaccine in Alaska native infants. N.Engl.J.Med 1990;323:1393–1401. [PubMed: 2233906]
54. Santosham M, Rivin B, Wolff M, et al. Prevention of *Haemophilus influenzae* type b infections in Apache and Navajo children. J.Infect.Dis 1992;165:S144–S151. [PubMed: 1588150]
55. Black FL, Hierholzer W, Woodall JP, Pinhiero F. Intensified reactions to measles vaccine in unexposed populations of American Indians. J.Infect.Dis 1971;124:306–317. [PubMed: 4947190]
56. Hinman AR, Orenstein WA, Rodewald L. Financing immunizations in the United States. Clin Infect Dis 2004;38(10):1440–1446. [PubMed: 15156483]

Table 1

Associations between HLA gene polymorphisms and humoral (IgG antibody) and cellular (lymphoproliferation) immune responses to measles vaccine

HLA Gene	Variant	Effect	References
Class I allele	B*8, B*13, B*44	Decreased antibody (single dose)	[14]
Class I allele	B*7	Increased antibody (single dose)	
Class II allele	DRB1*03, DQA1*0201	Decreased antibody (single dose)	[15]
Class II allele	DRB1*08, DQA1*0104, DPA1*0202	Increased antibody (single dose)	[16]
Class I supertype	B7	Increased antibody (two doses)	[17]
Class I supertype	B44	Decreased antibody (two doses)	
Class I supertype	B58	Decreased antibody (two doses)	
Class I haplotype	A*24-C*03-B*15	Decreased antibody (two doses)	[18]
Class II haplotype	DRB1*07-DQB1*03-DPB1*04	Decreased antibody (two doses)	[18]
Class II haplotype	DRB1*07-DQB1*02-DPB1*02	Decreased antibody (two doses)	
Class II haplotype	DRB1*15/16-DQB1*06-DPB1*04	Increased antibody (two doses)	
Class I haplotype	A*26-C*12-B*38	Increased cellular (two doses)	[18]
Class II haplotype	DRB1*04-DQB1*03-DPB1*03	Increased cellular (two doses)	[18]
Class II haplotype	DRB1*03-DQB1*02-DPB1*04	Increased cellular (two doses)	

B7 supertype includes alleles *0702, *0704, *0705, *3501, *3502, *3503, *5101, *5301, *5501, *5601

B44 supertype includes alleles *3701, *4001, *4101, *4402, *4403, *4501, *4901, *5001

B58 supertype includes alleles *1516, *1517, *5701, *5702, *5801, *5802

Table 2

Extinction of HLA associations with measles IgG antibody non-response after one versus two doses of measles vaccine

No. of Measles Vaccine Doses (MMR-II)	HLA Class I Alleles	HLA Class II Alleles
1 dose	B*8, B*13, B*44	DRB1*03, DQA1*0201
2 doses	B*4403	None

Table 3

Associations between SNPs in the SLAM and CD46 genes and humoral (IgG antibody) immune response to measles vaccine

SNP ID	Location	Genotype	Median IgG Antibody (IU/L)
SLAM[1]			
rs3796504	**Thr-Pro (Ex-7)**	**GG/GT/TT**	**1589/1066/497**
rs164288	**Thr-Thr (Ex-3)**	**GG/GA/AA**	**1602/1102/497**
rs164283	Intronic	TT/TC/CC	1670/1265/1848
rs1503854	Intronic	AA/AG/GG	1619/1348/1863
rs12076998	5'UTR	TT/TC/CC	1467/1991/*
rs2025515	Intronic	GG/GT/TT	1477/1796/*
rs11265452	Intronic	AA/AG/GG	1553/1453/1924
rs11265449	Intronic	CC/CG/GG	1559/1445/1796
rs16832283	Intronic	TT/TC/CC	1553/1476/1924
CD46[2]			
rs11118580	**Intronic**	**TT/TC/CC**	**1795/1329/1072**
rs14374	Intronic	TT/TC/CC	1528/2748/197
rs11690650	Intronic	TT/TC/CC	1478/1463/3014
rs2724384	Intronic	AA/AG/GG	1563/1131/*

Thr-Threonine; Pro-Proline; Ex-exon; 5'UTR-5' untranslated region

[1] A total of 21 SNPs were tested; only those found to be statistically significant ($p \leq 0.05$) shown

[2] A total of 29 SNPs were tested; only those found to be statistically significant ($p < 0.05$) shown

* No subject in that genotype

Values in boldface demonstrate an allele-dose response relationship

Table 4

Cytokine and cytokine receptor SNP associations with humora (IgG antibody) and cellular (lymphoproliferation) immune responses to measles vaccine

Gene	SNP ID	Genotype	Phenotype
IL-2			
	Rs2069762	GG/TG/TT	$Antibody^{high}Cellular^{high}$
	Rs2069763	GG/TG/TT	$Antibody^{high}Cellular^{high}$
IL-10			
	Rs1800890	AA/TA/TT	$Antibody^{low}Cellular^{low}$
	Rs1800871*	AA/GA/GG	$Antibody^{low}Cellular^{low}$
	Rs1800872*	AA/CA/CC	$Antibody^{low}Cellular^{low}$
IL-12RB			
	Rs3790567	AA/GA/GG	$Antibody^{low}Cellular^{low}$
	rs372889	AA/AG/GG	$Antibody^{low}Cellular^{low}$

A total of 58 SNPs were tested; only those found to be statistically significant ($p<0.05$) shown

*rs1800871 and rs1800872 are in linkage disequilibrium ($r^2=1.0$)

Table 5

Associations between SNPs in toll-like receptors and associated intracellular signaling molecules and measles-vaccine humoral (IgG antibody) immune response

SNP ID	Location	Genotype	Median IgG Antibody (IU/L)
TLR3			
rs3775291	Phe412Leu	GG/GA/AA	1602/1025/2133
rs5743305*	Promoter region	AA/AT/TT	1412/1063/1670
MyD88			
rs6853	3'UTR	AA/AG/GG	1430/1583/272

Phe-Phenylalanine; Leu-Leucine; A-Adenine; C-Cytosine; G-Guanine; T-Thymine

P-values ≤0.02 are shown

MyD88-myeloid differentiation primary response gene 88; 3'UTR-3' untranslated region

*demonstrated an association between heterozygous variant AT and low measles-specific lymphoproliferative response