Improving Vaccine Safety Through a Better Understanding of Vaccine Adverse Events

To the Editor—"I am worried that my child will get this serious side effect if she is vaccinated" is a common concern raised by parents of infants and toddlers. Since vaccines are generally very safe, many of these concerns can be assuaged. However, a few vaccinated children will experience serious adverse events. While current vaccines are of major public health benefit, history has taught us that even the slightest concern over a serious adverse event, perceived or real, has the inherent capacity to compromise public confidence in the specific vaccine and vaccination in general [1]. Thus, we should strive to pursue avenues of research that could improve vaccine safety even further.

How do we acquire this knowledge? While there are examples of epidemiologic studies identifying risk factors for adverse events [2, 3], effort should be put into expanding substantially on these findings and translating them to clinically useful risk scores. Additionally, it has been suggested that genetic factors could influence the propensity for developing adverse events [4]. Indeed, preliminary work supports this concept, with 2 candidate-gene studies reporting associations between variants in certain immune system genes and adverse events such as fever following smallpox vaccination [5, 6].

We recently conducted a genome-wide association study to investigate genetic determinants of febrile seizures that occur following measles, mumps, rubella (MMR) vaccination [7]. Between 3 and 16 excess cases of febrile seizures per 10 000 children can be attributed to MMR, representing one of the most common serious adverse events following vaccination overall. As compared with controls without febrile seizures, 2 genetic loci that harbor innate immunity genes *IFI44L* and *CD46* were associated with MMR-related febrile seizures at the genome-wide significance level. *IFI44L* is an interferon-stimulated gene known to be upregulated by viral infection including measles. *CD46* encodes a membrane protein that has several functions including a confirmed action as a cellular receptor for measles virus. The loci encompassing *IFI44L* and *CD46* were associated specifically with MMR-related febrile seizures; ie, significant associations were observed vs controls as well as vs febrile seizures unrelated to MMR vaccination (Table 1). An additional 4 genetic loci were significantly associated with febrile seizures overall, including *ANO3*, *SCN1A*, *SCN2A*, and a locus related to magnesium regulation, pointing to the importance of altered ion channel function in seizure susceptibility.

While much work remains to elucidate how the interaction between these genes and their products and the MMR vaccine could lead to fever and febrile seizures, the results provide firm evidence that

Table 1. Genetic Variants Distinctly Associated With Febrile Seizures Following Measles, Mumps, Rubella Vaccination

Chromosome/Single Nucleotide Polymorphism/Gene	Odds Ratio (95%); *P* Value[a,b]		Known or Possible Function of Gene and Gene Product; Known Associations.
	vs Controls	vs Cases of Febrile Seizures not Related to Measles, Mumps, Rubella Vaccination	
1/rs273259/IFI44L	1.41 (1.28–1.55); $P = 5.9 \times 10^{-12}$	1.42 (1.27–1.59); $P = 1.2 \times 10^{-9}$	Belongs to the group of interferon-stimulated genes; induced by viral infection, including measles; known antiviral effects against hepatitis C virus
1/rs1318653/CD46	1.43 (1.28–1.59); $P = 9.6 \times 10^{-11}$	1.48 (1.30–1.67); $P = 1.6 \times 10^{-9}$	Membrane protein that is part of the complement system; induces proliferation and differentiation of regulatory T cells; acts as a cellular receptor for measles virus, primarily vaccine-strain virus; another variant in gene, highly correlated with rs1318653, associated with humoral and cellular immunity to measles

[a] Odds ratios and *P* values from discovery and replication datasets combined.

[b] Genome-wide significance level set at $P < 1.25 \times 10^{-8}$.

there are genetic determinants of vaccine adverse events. Further, they open up novel avenues toward personalized medicine in vaccinology, a field that has focused on the population level alone. For instance, we envision a clinical future where genetic information as well as data regarding other biomarkers are integrated with clinical variables to derive individualized risk scores that predict adverse events. Additionally, the ability to design new vaccines that are completely free from adverse events will come from knowledge of the mechanisms of adverse events with currently available vaccines.

Note

Potential conflicts of interest. All authors: No reported conflicts.

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