P2-534

The study of heterosubtypic antibody responses against influenza A viruses elicited by seasonal vaccination using a pseudotype neutralisation assay

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Background: The study of heterosubtypic antibody responses directed against influenza A haemagglutinins in human populations is an important facet of pandemic preparedness. The evaluation of the ability of vaccines to increase heterosubtypic antibody responses to confer broad protection against different influenza subtypes is one approach to this. Classic serological assays, such as haemagglutination inhibition and microneutralisation, have demonstrated low sensitivity for the detection of cross-neutralising antibodies, especially those directed against epitopes in the haemagglutinin HA2 stalk region. For this reason there is a need for new assay formulations that are able to detect and quantify these heterosubtypic antibody responses. Influenza pseudotypes represent safe tools to study the neutralising antibody response since they are replication-defective viruses and they harbour on their envelope only the haemagglutinin that is the major target of this response. Materials and Methods: We have generated a panel of group 2 influenza A pseudotypes (H3 A/Udorn/307/1972, H4 A/duck/Czechoslovakia/1956, H7 A/chicken/Italy/1082/1999, H10 A/chicken/Germany/N49, H14 A/mallard/Astrakhan/263/1982, H15 A/shearwater/West Australia/2576/1979) and we have used them as surrogate antigens in neutralisation assays to study the presence and magnitude of heterosubtypic neutralising antibody responses in human sera collected before and after the 2007-2008 seasonal influenza vaccination. Results: In the human sera tested, neutralising antibody responses are detected against not only human influenza viruses, but also against influenza pseudotypes harbouring avian haemagglutinins belonging to group 2 viruses. After seasonal vaccination, the pseudotype neutralisation assays detect variation in the neutralising antibody titres against avian influenza pseudotypes. Conclusions: The increased sensitivity of the pseudotype neutralisation assay performed using a panel of influenza A pseudotypes permits the detection of heterosubtypic antibody responses before and after seasonal influenza vaccination. This has implications for the development of pandemic preparedness plans at the population level.

P2-536

Host genetic factors as determinants of immunologic and adverse responses on influenza vaccination in humans

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Background: Seasonal influenza epidemics cause a great burden of illnesses, hospitalizations, and deaths worldwide. Although influenza vaccination has generally been regarded as safe and effective in preventing influenza infection, some people do develop poor immune responses or occasional serious adverse events on receiving the vaccination. Little is known about how host genetic determinants are affecting responses to influenza vaccination in humans. Materials and Methods: We used a genetic association study with a candidate gene approach based on a randomized placebo-controlled trial on influenza vaccination to examine the role of host genetic variation on immune

Return to Table of Contents

response and adverse reaction to influenza vaccine in humans. In the trial, 915 children aged 6-15 years were randomized to receive either an inactivated trivalent seasonal influenza vaccine (TIV) (Vaxigrip, Sanofi Pasteur) or placebo in phases from 2009 to 2010. Vaccine response was defined by a post-vaccination antibody titer of 1:40 or ≥ 4-fold rise in all TIV components. An adverse vaccine responder was defined by an aggregated symptom score ≥ 2 on day 1 post-vaccination, based on 10 symptoms each on a scale of 0 (absent), 1 (mild), 2 (moderate, or 3 (severe), thus having at least 2 mild or 1 moderate symptoms. All participants kept a daily symptom dairy. Whole blood samples from 535 participants receiving TIV were collected for genetic analysis in this study. DNA was extracted and genotyped for single nucleotide polymorphisms for IL-1B-511G>A (rs16944), IL-6-5843A/G (rs1818879), IL-8-251T/A (rs4073), IL-10-082A/G (rs1800896), -819T/C (rs1800871), -592A/C (rs1800872), MBL-2-5232G>A (rs1800451), 221C/G (rs7096206), -34C>T (rs5030737), -550G>C (rs11003125), MxA-88G/T (rs2071430), OSA1-347A/G (rs2660), RIG1 G/C (rs9695310), TLR3-1377T/G (rs3755290), -7G/T (rs3775296), TLR4 G/A (rs5030718), Asp299Gly (rs4986790), TLR7 Gln11Leu (rs179008), 1817G/T (rs5741880), TLR8-129G/C (rs3764879), Met1Val (rs3764880), and (rs11003131)G/T. Logistic regression models were used to evaluate the relationship of polymorphisms with various outcomes and to compute the ORs and 95% confidence interval (CIs) in relation to vaccination response and adverse vaccination reaction. The heterozygous and homozygous variant genotypes were analyzed both as a nominal and an ordinal variable as consisting, respectively, of one and two variant alleles and compared with the wild-type homozygous genotype. The heterozygous genotype was also grouped with either of the two homozygous genotypes to analyze in a dominant or recessive model. Two-sided *P* values are reported and $P \leq .05$ was considered to indicate statistical significance. Results: Among 535 subjects receiving TIV, 295 were classified as vaccine responders. Polymorphisms IL-6 rs1818879 G mutation in an ordinal model (OR = 1.56, CI = 1.054-2.31), AG (OR = 1.667, CI = 1.109-2.504), and combined AG/GG (OR = 1.637, CI = 1.093-2.454) in a dominant model were associated with increased odds of response. TLR7 rs5741880 GT (OR = 0.161, CI = 0.046-0.566), combined GT/TT (OR = 0.371, CI = 0.159-0.866) in a dominant model, and TLR3 rs3755290 GG (OR = 0.572, CI = 0.335-0.976) in a recessive model compared with GT/TT were associated with lower odds of response. No serious vaccine response, including anaphylaxis or shock, was reported by any recipient. With a symptom score ≥ 2, 26.1% were classified as adverse responders for TIV. IL-6 rs1818879 AG (OR = 1.833, CI = 1.14-2.945) and combined AG/GG (OR = 1.778, CI = 1.108-2.854) were associated with a higher risk, while CCL1 rs2282691 AT (OR = 0.578, CI = 0.347-0.963) was associated with a lower risk of adverse response. All these effects of polymorphisms in relation to vaccination response are compatible with the current understanding regarding the role played by those genes in either the pathogenesis or immunological response to influenza infection. Conclusions: Our findings suggest the potential role of host genetic variation and identified genetic determinants that affect the immunological and adverse responses to seasonal influenza vaccination in humans. These findings may help to explain the great variability in protection achieved by influenza vaccination.

Return to Table of Contents

P2-537

Immunogenicity and reactogenicity of a quadrivalent influenza vaccine administered intramuscularly to children 6 to 35 months of age in 2012-2013: day 56 results of a randomised, double-blind, controlled, multi-centre, multi-country, clinical trial (NCT01711736)

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Background: Influenza has a high attack rate in infants and young children. Vaccines containing both lineages of influenza B (Yamagata and Victoria), in addition to H3N2 and H1N1 antigens, may improve the protection of this vulnerable population. Materials and Methods: Children 6 to 35 months