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ORIGINAL ARTICLE

The first steps towards the era of personalised vaccinology: predicting adverse reactions

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Until now, the occurrence of adverse reactions among individuals inoculated with identical vaccines has been ascribed to unpredictable stochastic processes. Recent advances in pharmacogenomics indicate that some features of host response to immunisation are influenced by genetic traits, henceforth predictable. The ability to predict the adverse reaction to vaccination would represent an important step towards the development of personalised vaccinology and could enhance public confidence in the safety of vaccines. Herein, we have reviewed all the available information on the association between genetic variants and the risk for healthy subjects to develop adverse reactions.

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INTRODUCTION

Adverse reactions following vaccinations represent a significant source of concerns among health authorities, physicians and the general population.[1–3] Those concerns are driven by the risks of adverse reactions, rare but in some cases severe, and lead to the risk of failure of immunisation programmes owing to unmotivated alarms on vaccine safety.[4]

Until now, the occurrence of adverse reactions among individuals inoculated with identical vaccines has been ascribed to unpredictable stochastic processes.[5–7] Recently, new genetic technologies and twin studies indicated that some features of host response to infection or immunisation are influenced by genetic traits, henceforth predictable.[6,7]

One of the first observations on the variable susceptibility to post vaccine adverse reaction was made by Black *et al.* in 1971.[8] They observed that febrile reactions to measles vaccine were more frequent among American Indians than Caucasian children,[8] suggesting the presence of genetic basis for that difference. Subsequent studies highlighted that different levels of cytokines were related to adverse reaction onset.[9,10] Although attractive, analyses of cytokine levels are difficult to implement owing to often suboptimal sampling times and difficulty to establish appropriate ranges making them an unpractical predictive factor.[6]

Pharmacogenomics holds a promise for advancing personalised medicine and bringing advances in genomics to the clinical arena, and when genetic associations are found these may radically eliminate adverse reactions. For instance, testing for HLA-B*5701 before initiating abacavir has eliminated hypersensitivity reactions to the drug.[11]

The ability to predict adverse reactions to vaccination would represent an important step towards the development of personalised vaccinology and could enhance public confidence in the safety of vaccines, which is of a paramount importance for the success of ongoing immunisation programmes.

Herein, we have reviewed all the available information on the association between genetic variants and the risk for healthy subjects to develop adverse reactions and provide an up to date definition of the recognised genetic risk factors. These data provide also an indication towards further research directions.

MATERIALS AND METHODS

We carried out a PubMed search up to 2014 using the terms 'Vaccine' OR 'Vaccination' OR 'Vaccinology' AND 'Personalised' OR 'Genetic' OR 'Pharmacogenetic' OR 'Sex' OR 'HLA'. We considered studies that included case reports and series, case–control studies, post-marketing surveillance programmes and published analyses by the VAERS (Vaccine Adverse Event Reporting System), a US-based national vaccine safety surveillance programme. We carried out an initial screening by reading each abstract to identify the articles meeting the inclusion criteria, which were conclusively assessed after a thorough analysis of their content. The retrieved studies were then read in their entirety to assess their appropriateness. Citations from each of the included articles were examined in order to identify any other published study potentially meeting the inclusion criteria. We limited the research to articles written in English.

RESULTS

Genetic variability and vaccine safety

In Table 1 we summarise the most important studies suggesting a genetic predisposition to the onset of adverse reaction after vaccination. One of the first studies aimed at assessing this correlation was conducted by Mitchell *et al.*,[12] which examined the HLA-DR Class II associations with Rubella vaccine-induced joint manifestations. They conducted the analysis on 283 white women receiving either the RA27/3 rubella vaccine or placebo to determine a possible correlation between specific HLA-DR haplotype and the

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Table 1. Genetic association studies reporting positive findings

Study	*Year*	*No of patients*	*Age*	*Race/ethnicity*	*Vaccine*	*AEFI*	*Gene*	*Variant*	*OR; 95% CI*
Mitchell *et al.*[12]	1998	283	18–41 years	European (58%); Oriental (24%); Indian (12%); other (6%)	Live attenuated RA27/3	Joint manifestations	HLA-DR1–10		
								DR2	4.8; 1.2–18.8
								DR5	7.5; 1.5–37.5
Stanley *et al.*[13]	2007	346	43 years (s.d. = 14)	White (95%); other (5%)	Smallpox	Fever	IL1A		
								Haplotype 1[b]	0.62[a]
								Haplotype 3[b]	1.7[a]
							IL1B		
								Haplotype 7[b]	4.87[a]
								Haplotype 8[b]	4.83[a]
							IL1R1		
								Haplotype 10[b]	1.47[a]
							IL18		
								Haplotype 1[b]	0.59[a]
								Haplotype 9[b]	1.83[a]
								Haplotype 10[b]	5.53[a]
Reif *et al.*[14] (first cohort)	2008	85	23.2 years (s.d. = 3.9)	White (99%); other (1%)	Smallpox	Systemic AE	MTHFR		
								1801133	2.3; 1.1–5.2
							IRF1		
								9282736	3.2; 1.1–9.8
								839	3.2; 1.1–9.8
							IL4		
								Haplotype TCA[c]	2.4; 1.0–5.7
Reif *et al.*[14] (second cohort)	2008	46	24.2 years (s.d. = 3.8)	White (96%); other (4%)	Smallpox	Systemic AE	MTHFR		
								1801133	4.1; 1.4–11.4
							IRF1		
								9282736	3.0; 1.1–8.3
								839	3.0; 1.1–8.3
							IL4		
								Haplotype TCA[c]	3.8; 1.0–14.4

Abbreviations: AE, adverse event; AEFI, adverse event following immunisation; CI, confidence interval; HLA, human leukocyte antigen; IL, interleukin; IRF1, interferon regulatory factor 1; OR, odds ratio. [a]Adjusted odds ratio. [b]See text. [c]IL4 risk haplotype includes rs2070874, rs2243268 and rs2243290.

onset of vaccine-induced arthralgia. The authors observed a higher frequency of DR2 and DR5 in rubella vaccine recipients with arthropathy. They concluded that certain DR2 and DR5 alleles could influence susceptibility to the development of joint manifestations following administration of the RA27/3 rubella vaccine. Notably, they also observed that the presence of DR4 along with DR1 or DR6 in an individual's immunogenic background appears to predispose to the development of post-partum arthropathy, suggesting that alleles within these DR groups influence the expression of transient autoimmunity, which might be aggravated by administration of the rubella vaccine.[12]

Stanley *et al.*[13] assessed markers predictive of the development of fever after smallpox vaccination. They identified single-nucleotide polymorphisms (SNPs) in 19 candidate genes in 346 individuals previously assessed for clinical responses to vaccination of which 176 were vaccine naïve. Subjects with a documented temperature >37.7 °C within 3–15 days after smallpox vaccination represented a case group, whereas those without documented fever after smallpox vaccination served as the control group.

The authors identified eight haplotypes in the four genes *IL1A*, *IL1B*, *IL1R1* and *IL18* that were associated with an incremented or decremented risk for the development of fever after smallpox vaccination (Table 1).[13] These haplotypes were predictive in both naïve and non-naïve subjects, whereas SNPs in *IL1R1* and *IRF1* (interferon regulatory factor 1) genes were predictive of fever only in non-naïve subjects. They also identified a haplotype in *IL4* that significantly correlated with a reduced susceptibility to fever after vaccination in the vaccine-naive individuals only.[13]

The genetic bases of the development of systemic or local adverse reaction after smallpox vaccination was evaluated also by Reif *et al.*[14] Their analysis was carried out in volunteers recruited from two independent clinical trials of the smallpox vaccine, which enrolled 85 and 45 healthy, vaccine-naïve adults, respectively.[14,15] They chose a two-stage design for the identification and replication of SNPs associated with adverse reactions: significant SNPs associated in the first study were tested on the second group of patients, who acted as the validation sample.

Subjects were evaluated at regular intervals and local and systemic adverse reactions, including oral temperature >38.3 °C, skin eruptions and enlarged or tender regional lymph nodes, were recorded. Thirty-six SNPs within 26 genes were found associated with systemic adverse events ($P \leqslant 0.05$) in the first study, an association confirmed, however, for only three of these SNPs in a replication study.[14] As highlighted in Table 1, these three SNPs included one non-synonymous SNP in the *MTHFR* (methylenetetrahydrofolate reductase) and two SNPs in the *IRF1* gene.

Interesting, Reif *et al.*[14] found a significant correlation between three SNPs in the *IL4* gene and adverse reactions in the first study; as this association was not confirmed in a second study ($P = 0.06$) the authors indicated the necessity for further confirmatory studies. Indeed they observed that there was high intragenic LD ($r^2 > 0.9$) between the tested SNPs within *IRF1* and *IL4*, suggesting the existence of additional factors that may contribute to the risk for adverse reactions.

In a subsequent analysis, Reif *et al.*[14] modelled the adverse reaction risk using 1442 genetic variables (SNPs) and 108 proteomic variables (serum cytokine concentrations) as variables using a random forest method.[16] This method represents a robust strategy suited to integrated analysis, as it represents a natural approach for studying gene–gene, gene–protein and protein–

protein interactions. The final model included the cytokines intercellular adhesion molecule-1, interleukin-10,[17] colony-stimulating factor-3 and interleukin-4.[16] The authors concluded from their model that adverse reactions after smallpox vaccination result from hyper activation of inflammatory signals, leading to excess recruitment and stimulation of monocytes in peripheral tissues.[16]

In a recent elegant analysis, Miller *et al.*[18] tried to determine the specific genetic risk factors that might have predisposed a child to develop wheezing after vaccination. The development of wheezing was associated with several common genetic variants, none of which, however, reaching the widely accepted genome-wide significance threshold.[18] Further analyses are required to confirm these results.

DISCUSSION

The correlation between genetic factors and adverse reactions to vaccines has been investigated less than the one between the therapeutic responses to vaccines, for which several factors have been identified. Umlauf *et al.*[19] showed a clear association between measles-specific immune responses with gender and race, and the association between several SNPs and measles vaccine response has also been demonstrated.[20] Age, concomitant drugs and genetic variability have also been proposed to influence vaccine response.[21–23] Of importance, mechanisms at the basis of the response to vaccines may also participate in the molecular genesis of specific adverse reactions,[9,24,25] and a better understanding of vaccine response genetics may thus allow a better comprehension also of their adverse effects.

Clarifying these aspects is relevant also because in developed countries the fears of real or supposed adverse reactions still represent one of the major reasons for the failure of immunisation programmes.[2,26] These fears are fuelled by real cases in which a serious illness, whether related to the vaccine or not, occurs closely to vaccination in healthy individuals.[4,27–36]

Cases when bouts of fears of vaccination led to the recrudescence of infections were not confined to the 19th century[37,38] but extend also to recent times. In Japan in 1975 the government suspended the pertussis immunisation programme due to the death of two infants within 24 h from vaccination.[39] Four years later Japan faced the re-emergence of whopping cough and 41 persons died because of this disease.[39] Where these programmes went on unhindered, the pertussis toxin vaccine was proven to be safe.[40]

Recently, the hypothesis of correlation between the Hepatitis B vaccine and MS was brought forward.[41,42] This hypothesis, supported by the reports of temporal association between vaccine shot and MS onset, was sufficient to fuel major vaccine-safety controversies. Despite two decades of studies not finding significant evidence of a correlation between this vaccine and MS onset, the confidence in the safety of the Hepatitis B vaccine was lost. Particularly because of this controversy, the Hepatitis B immunisation programme in France largely failed and vaccine coverage remains below 25%.[41,42]

The identification of individuals who are at risk of developing a serious reaction before the vaccination would represent an impressive step forward as it would assure an increase in the safety of immunisation programmes and a decrease of the impact of vaccine refusal movement.

This result has already been seen with pharmacogenetic tests for drugs.[43] According to a study on a variant in the kinesin-like protein 6 (KIF6) gene for statins therapy, tested patients were significantly more compliant regardless of the results.[43,44] A similar collateral effect in vaccine acceptances would be of great importance for public health, as it would enhance coverage and reduce the weight of anti-vaccine movement theories.

Intriguingly, some of these studies focalised on fever and arthralgia, two relevant post-vaccination phenomena that were also included as major clinical criteria in the recently defined autoimmune/inflammatory syndrome induced by adjuvants.[31,35] Further analyses aimed at defining the relationship between genetic variants and this syndrome are of interest as they may help a better defining of such clinical entities.[4] They may also open new perspectives on the role of genetics in the response to adjuvants. This aspect is gaining relevance after the observation that the increased risk of narcolepsy after AS03-adjuvated H1N1 vaccination was most likely due to the AS03 adjuvant acting as an environmental trigger in HLA-DQB1*06:02 positive people.[45]

As reported in Table 1, most of the studies were carried out considering the smallpox vaccine,[6,9,14] for which adverse reactions such as fever are common (ranging between 15–20% of vaccinated children). The incidence of adverse reactions among vaccinated subjects represents an important limitation that should be addressed and considered in the design of these pharmacogenomics studies. Indeed, it would be difficult for most of the researchers to identify a number of cases of rare adverse vaccine reactions suitable for a large genetic analysis. As an example, we estimated recently the incidence of post-HPV vaccine ADEM to be of $0.26/10^6$ vaccinations (CI 95%: $0.16/10^6$–$0.37/10^6$).[27] Even assuming a 10-fold higher incidence because of biases such under-reporting to the surveillance databases,[28] still the retrieving of a number of case large enough would require a large scale, national or international study.

A possible solution for this problem was proposed by Davis in a recent paper on the Vaccine Journal.[46] He proposed to take advantage of the VAERS to build a repository of bio-specimens for genetic studies of vaccine adverse events. Alongside the VAERS database, other safety surveillance databases could be used for this purpose. These databases could include international databases such as the European Database of suspected adverse drug reaction reports (http://www.adrreports.eu/EN/search.html#) or nationwide active surveillance programmes on specific populations.[47]

On the basis of the data reviewed above we feel that that a correlation between vaccine adverse reactions and genetics exists and deserves further studies.

The idea of identifying the genetic variants predictive for vaccine adverse events and suitable for the introduction in clinical practice is, in our opinion, feasible as the cost of genotyping is falling rapidly and large-scale genotyping at birth is not too far off the horizon (www.aaas.org/spp/PM/ppts/Collins.pdf).

CONFLICT OF INTEREST

The authors declares no conflict of interest.

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