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BRIEF COMMUNICATION

Genome-wide SNP associations with rubella-specific cytokine responses in measles-mumps-rubella vaccine recipients

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Abstract Genetic polymorphisms are known to affect responses to both viral infection and vaccination. Our previous work has described genetic polymorphisms significantly associated with variations in immune response to rubella vaccine from multiple gene families with known immune function, including HLA, cytokine and cytokine receptor genes, and in genes controlling innate and adaptive immunity. In this study, we assessed cellular immune responses (IFNγ and IL-6) in a cohort of healthy younger individuals and performed genome-wide SNP analysis on these same individuals. Here, we report the first genome-wide association study focused on immune responses following rubella vaccination. Our results indicate that rs16928280 in protein tyrosine phosphatase delta (*PTPRD*) and a collection of SNPs in *ACO1* (encoding an iron regulatory protein) are associated with interindividual variations in IFNγ response to rubella virus stimulation. In contrast, we did not identify any significant genetic associations with rubella-specific IL-6 response. These genetic regions may influence rubella vaccine-induced IFNγ responses and warrant further studies in additional cohorts in order to confirm these findings.

Keywords Genome-wide association study · Polymorphism · Genetic · Cytokines · Receptor · Cytokine · Cellular · Immunity · Measles-mumps-rubella vaccine · MMR

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Introduction

Rubella vaccines were first developed in the late 1960s and early 1970s. The vaccines contain live, attenuated rubella strains (RA27/3 worldwide; TO-336 in China; Takahashi and Matsuura in Japan), and in the United States, are given as components of multivalent vaccine formulations (MMRII or MMRV) (Meyer et al. 1969; Plotkin et al. 1969). Since that time, their use has dramatically decreased the number of rubella infections and cases of congenital rubella syndrome (Reef and Plotkin 2013). The vaccines are remarkably effective; vaccine efficacy and protection rates are estimated to be >94 % (Beasley et al. 1969; Chang et al. 1970; Grayston et al. 1969; Landrigan et al. 1974), which coincide with the 2–5 % of vaccinated individuals who do not seroconvert. Among those who do respond to the vaccine, there is a large degree of variation in immune response, and we have shown that this variability is heritable, with nearly 50 % of the variance in rubella-specific antibodies following immunization being explained by genetic factors (Tan et al. 2001). Additional doses typically boost antibody titers and increase seroconversion rates (>99 %).

Both host and virus genetics have been associated with rubella virus growth in joint tissue and corresponding joint symptoms in vivo (Lund and Chantler 2000; Mitchell et al. 1998). Similarly, rubella vaccine response variability is due, in part, to differences in host genetics (Jacobson et al. 2009; Tan et al. 2001). Our lab has identified a number of genes where genetic polymorphisms are associated with vaccine response including HLA, cytokines and cytokine receptor genes, pattern recognition receptor and antiviral genes, as well as in vitamin receptor and other genes (Dhiman et al. 2007, 2010a; Haralambieva et al. 2010; Kennedy et al. 2010; Ovsyannikova et al. 2004, 2009a, b, 2010a, b, c, 2012a). These findings were the result of focused candidate gene associations studies, and indicated that genetic control of immune responses to rubella-containing vaccines are multigenic in nature (Pankratz et al.

2010), and likely involves a much larger collection of genes than originally believed.

Here, we report the first genome-wide association study conducted in a cohort of school-aged children receiving rubella-containing vaccine. While we did not identify any significant genetic associations with IL-6 response, our data indicate that rs16928280 in *PTPRD* and a collection of SNPs in *ACO1* are associated with variations in IFNγ response to rubella virus stimulation. These genetic regions may influence rubella vaccine-induced cytokine responses and warrant further testing in additional cohorts in order to replicate our findings.

Methods

Subject recruitment and demographics

The study cohort was a large population-based sample of 1,145 healthy children and older adolescents, and healthy adults (age 11 to 22 years), recruited from Olmsted County, MN. This study cohort was enrolled through three separate recruiting phases, recruited at the following various times: (1) 346 children ages 12–18, recruited in 2001–2002 (Ovsyannikova et al. 2004, 2005); (2) 440 children ages 11–18, recruited in 2006–2007 (Haralambieva et al. 2010; Ovsyannikova et al. 2010a); and (3) 388 children ages 11–22, recruited in 2008–2009 (Ovsyannikova et al. 2011, 2012c). The parents of each participant provided parental consent and medical records for 1,101 of the subjects indicated receipt of two doses of measles-mumps-rubella (MMR, Merck) vaccine. The methods described herein are similar or identical to those published for our previous studies (Dhiman et al. 2010a; Haralambieva et al. 2010; Kennedy et al. 2010; Ovsyannikova et al. 2004, 2005, 2009a, b, 2010a, b, c). The Institutional Review Boards of both the Mayo Clinic and the NHRC approved the study, which was performed in accordance with the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from each adult subject, and from the parents of all children who participated in the study.

Rubella-specific cytokine secretion

Cytokine responses to rubella virus stimulation were measured as previously described (Dhiman et al. 2010b; Ovsyannikova et al. 2009b). Briefly, 2×10^6/ml PBMCs were stimulated with the W-Therien strain of rubella virus (a gift from Dr. Teryl Frey, Georgia State University, Atlanta, GA) with optimized multiplicity of infection (MOI: IL-2, IL-6, and IFN-γ: MOI of 5. TNF-α: MOI of 0.05) and incubation times (IL-6, 24 h. IFN-γ, 48 h. IL-2 and TNF-α, 8 days). Cytokine-containing culture supernatants were stored at −80 °C until quantified using BD OptEIA™ Human ELISA kits. Absorbance levels were measured using a Molecular Devices SpectraMax 340PC.

Genome-wide SNP typing and QC

The genome-wide SNP typing protocol used for this study is essentially identical to that used in previously published reports (Kennedy et al. 2012a, b; Ovsyannikova et al. 2012b). Briefly, DNA was extracted from each subject's blood specimen using the Gentra Puregene Blood kit (Gentra Systems Inc., Minneapolis, MN) and quantified by Picogreen (Molecular Probes, Carlsbad, CA). The genome-wide SNP typing for the cohort (n=1,052) was performed using the Infinium Omni 1 M-Quad SNP array (Illumina, San Diego, CA). DNA samples underwent amplification, fragmentation, and hybridization onto each BeadChip, which were imaged on an Illumina BeadArray reader. Genotype calls based on clustering of the raw intensity data were made using BeadStudio 2 software. The resulting genotype data on SNPs were exported into SAS for analysis. Quality control checks included genotyping reproducibility, gender checks, removal of SNPs where typing failed in >1 % of subjects, removal of subjects where >1 % of SNPs failed, elimination of monomorphic SNPs, removal of duplicate samples, and a Hardy-Weinberg Equilibrium (HWE) check (SNPs with p<1e-7 were flagged as having poor genotyping quality). The genotyping success was high, with the average per-SNP call rate being 99.07 % and the average per-subject call rate being 99.07 % for this Omni1M-Quad array.

Population substructure was evaluated with EIGENSTRAT, a principal components-based assessment of genetic similarity (Price et al. 2006). We retained those subjects whose genetic background was no further than 15 % away from the predominant Caucasian cluster toward the Asian or African clusters, as identified by the two most predominant axes of genetic admixture.

Statistical analyses

Demographic and vaccination history features were summarized for the study participants with counts and percentages for nominal features and medians and interquartile ranges for numerical variables, including the outcomes of IFNγ and IL6 immune responses (summarized as the difference between the median simulated and median unstimulated observations). Linear regression models, with generalized estimating equations to account for the multiple measures obtained per subject, were used to test the associations between individual SNPs and the two cell-mediated immune response measures. In these analyses, the primary test of significance assessed the ordinal association between the genotypes of each SNP and inverse normal-transformed immune response measures while

adjusting for sex, age, and time between immunization and blood draw. We evaluated whether significance levels were inflated due to unmeasured confounding (Devlin and Roeder 1999), and adjusted the levels of significance with the estimated inflation factor. We summarized the genotype counts and the per-genotype medians and interquartile ranges of the two immune response measures for all SNPs showing suggestive associations with p values less than 1×10^{-6}.

Results

Of the original cohort, 897 subjects had usable genotyping and immune outcome data. This cohort was predominantly Caucasian (98.4 %) and, due to the lack of sufficient numbers of subjects of other race/ethnicities, we restricted our analysis to Caucasian individuals. This subset of individuals was 54.9 % male and ranged in age from 11 to 19 years old, with a median age of 15. Most of the subjects received their most recent vaccination at approximately 1 year of age (median age=10 months; interquartile range, IQR=5.0–12.0). Furthermore, the median time between second immunization with a rubella-containing vaccine and enrollment was 6.4 years (IQR=4.6–8.5 years).

Subjects had a median IFNγ response of 6.4 (IQR 1.7–19.7) pg/ml; this is indicative of a relatively weak Th1 response, which confirms an earlier report (Dhiman et al. 2010b). Despite the low levels of IFNγ produced by our subjects' PBMC samples in response to rubella virus stimulation, we identified a number of SNPs displaying significant ($p<5\times10^{-8}$) associations with IFNγ secretion (Fig. 1 and Table 1).

In contrast to the relatively weak IFNγ response, this cohort had a robust, inflammatory IL-6 response, with a median production of 3,629.3 (IQR 3,095.4–4,003.8) pg/ml. Notwithstanding this robust response, we did not identify any SNPs associated with IL-6 secretion at the genome-wide level of significance set at $p<5\times10^{-8}$ (Fig. 2). Table 2 lists all SNPs associated with IL-6 secretion with p values$<1\times10^{-6}$.

Discussion

We had previously conducted a series of immunogenetic association studies with this cohort; however, those studies involved limited sets of candidate immune-related genes (HLA, cytokines and receptors, pathogen recognition receptors, antiviral, and other genes) (Dhiman et al. 2008, 2010a; Haralambieva et al. 2010; Ovsyannikova et al. 2004, 2005, 2010a, b). In this report, we conducted genome-wide SNP typing in order to perform the corresponding genetic association analyses in a manner that enabled the discovery of potentially novel associations throughout the genome.

Although our cohort displayed robust IL-6 production in response to in vitro rubella virus stimulation, we did not identify any SNPs associated with this response at the preset genome-wide level of significance. Two SNPs, rs7218761 in *DNAH9* (encoding for a dynein heavy chain subunit) and rs4140752 located near the *SLC8A1* gene (encoding a sodium/calcium ion exchanger) had p values suggestive of an effect.

In contrast to the IL-6 findings, our GWAS did reveal a number of SNPs that were significantly associated with IFNγ response to rubella virus stimulation. The most significant SNP, rs16928280, is located in *PTPRD*. *PTPRD* codes for protein tyrosine phosphatase delta, which regulates cell

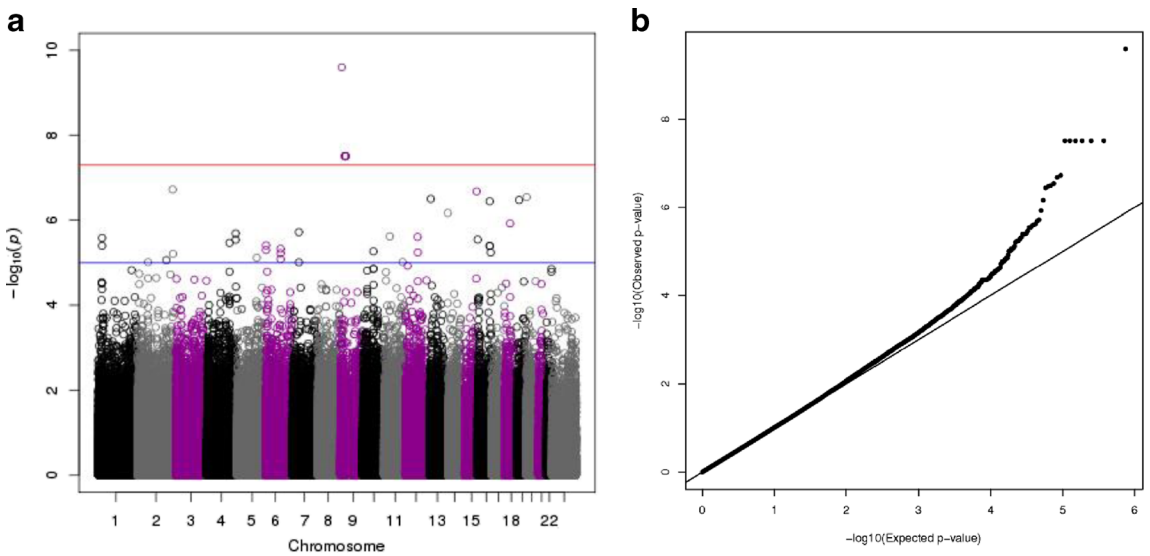

Fig. 1 Overview of SNPs associated with IFNγ response to rubella. **a** Manhattan plot and **b** QQ-plot of SNPs demonstrating significant associations with rubella-specific IFNγ production

Table 1 SNPs associated with variations in IFNγ response to rubella

SNP ID[a]	Chr[b]	Gene[c]	Rochester Cohort				*p* value[g]
			MAF[d]	Genotype	N[e]	Median (IQR)[f]	
rs16928280	9	PTPRD	0.01	GG	819	6.4 (1.6, 20.8)	2.55E-10
				GA	19	1.8 (−5.4, 10.1)	
				AA	0		
rs10813374	9	LOC100288436/ACO1	0.01	GG	822	6.4 (1.5, 20.5)	3.10E-08
				GA	16	2.7 (0.7, 5.7)	
				AA	0		
rs10969943	9	LOC100288436/ACO1	0.01	AA	822	6.4 (1.5, 20.5)	3.10E-08
				AG	16	2.7 (0.7, 5.7)	
				GG	0		
rs10969948	9	LOC100288436/ACO1	0.01	AA	822	6.4 (1.5, 20.5)	3.10E-08
				AC	16	2.7 (0.7, 5.7)	
				CC	0		
rs10969950	9	LOC100288436/ACO1	0.01	GG	822	6.4 (1.5, 20.5)	3.10E-08
				GA	16	2.7 (0.7, 5.7)	
				AA	0		
rs12235303	9	LOC100288436/ACO1	0.01	AA	822	6.4 (1.5, 20.5)	3.10E-08
				AG	16	2.7 (0.7, 5.7)	
				GG	0		
rs2375090	9	LOC100288436/ACO1	0.01	AA	822	6.4 (1.5, 20.5)	3.10E-08
				AG	16	2.7 (0.7, 5.7)	
				GG	0		
rs1430246	2	SLC4A3/EPHA4	0.051	GG	753	6.8 (1.8, 21.8)	1.89E-07
				GA	83	2.6 (−1.6, 7.0)	
				AA	1	6.5 (6.5, 6.5)	
rs9806400	15	LOC145820/NR2F2	0.018	GG	808	6.4 (1.6, 20.9)	2.09E-07
				GA	28	1.8 (−1.6, 7.5)	
				AA	1	0.3 (0.3, 0.3)	
rs6112821	20	PDYN/STK35	0.014	AA	815	6.5 (1.6, 20.9)	2.85E-07
				AG	22	2.1 (−1.6, 3.7)	
				GG	1	4.6 (4.6, 4.6)	
rs3736995	13	CDK8	0.023	CC	799	6.5 (1.7, 20.8)	3.15E-07
				CA	38	1.7 (−1.2, 10.4)	
				AC	1	−1.5 (−1.5, −1.5)	
kgp4580976	19	IL27RA	0.013	AA	817	6.4 (1.6, 20.8)	3.33E-07
				AG	21	1.6 (−0.7, 5.4)	
				GG	0		
rs1982955	16	CNTNAP4/MON1B	0.022	GG	800	6.4 (2.9, 20.9)	3.58E-07
				GA	38	2.9 (−0.3, 8.4)	
				AA	0		
rs1243704	14	RNASE10/RNASE9	0.012	AA	817	6.4 (1.6, 20.8)	6.82E-07
				AG	21	0.3 (−3.1, 3.1)	
				GG	0		

SNPs showing significant association with IFNg secretion

[a] rs SNP identification number

[b] Chromosomal location

[c] Gene or genetic region containing the indicated SNP

[d] Minor allele frequency

[e] Number of subjects with a given genotype

[f] Median outcome measurement for each genotype group. Results are expressed as picograms per milliliter. The interquartile range (*IQR*) is shown in parentheses

[g] *p* values were adjusted for demographic and clinical variables as well as inflation of significance described in the section "Methods"

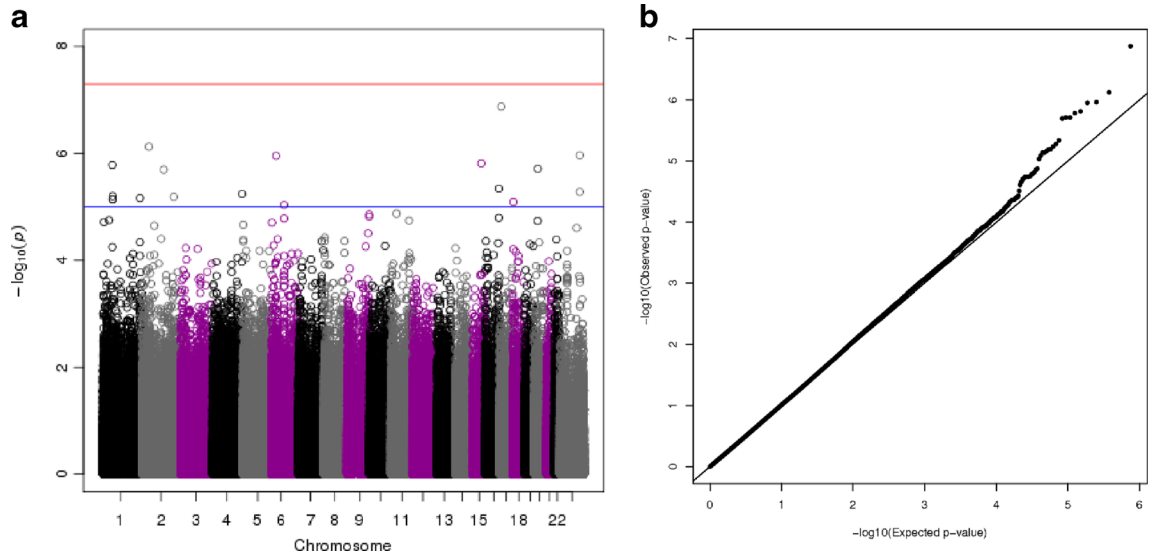

Fig. 2 Overview of SNPs associated with IL-6 response to rubella. **a** Manhattan plot and **b** QQ-plot of SNPs demonstrating significant associations with rubella-specific IL-6 production

signaling processes involved in cell growth, division, and differentiation. PTPRD has been shown to have very low levels of expression in immune cells (Arimura and Yagi 2010) and has yet to be linked to any immune function. We also identified six SNPs on chromosome 9 near the *ACO1* gene that were significantly associated with IFNγ response. ACO1 encodes for aconitase 1, an iron-binding protein involved in the conversion of citrate to isocitrate. Aconitase also binds to, and suppresses, translation of ferritin mRNA. Although regulation of iron (primarily sequestration) has been identified as an innate immune defense mechanism as far back as the 1940s (Cartwright et al. 1946), the role of iron regulation in adaptive immune function has not been studied extensively. Our results indicate that the genetic region encompassing ACO1 may be associated with cytokine responses to rubella vaccination and further investigation of this locus is warranted.

Our study is the first reported GWAS with adaptive immune responses to rubella vaccine. As such, it expands the available data regarding genetic control of rubella vaccine-induced immunity. We have identified several genetic regions for further analysis and investigation. As with many studies,

Table 2 SNPs associated with variations in IL-6 response to rubella

SNP ID[a]	Chr[b]	Gene[c]	Rochester Cohort				*p* value[g]
			MAF[d]	Genotype	*N*[e]	Median (IQR)[f]	
rs7218761	17	DNAH9	0.018	AA	824	3,625 (3,089; 4,009)	1.33E-07
				AC	30	3,514 (3,032; 3,898)	
				CC	1		
rs4140752	2	SLC8A1	0.067	AA	746	3,646 (3,121; 4,027)	7.50E-07
		LOC400950		AG	104	3,407 (3,022; 3,867)	
				GG	5	2,761 (2,441; 3,182)	

SNPs showing significant association with IL-6 secretion

[a] rs SNP identification number

[b] Chromosomal location

[c] Gene or genetic region containing the indicated SNP

[d] Minor allele frequency

[e] Number of subjects with a given genotype

[f] Median outcome measurement for each genotype group. Results expressed as picograms per milliliter. The interquartile range (*IQR*) is shown in parentheses

[g] *p* values were adjusted for demographic and clinical variables as well as inflation of significance described in the section "Methods"

ours has several limitations including the small sample size (<1,000); the fact that our observed phenotypes represent subtle variations in immune responses rather than clear cut, dichotomous outcomes; and the multigenic nature of complex biological processes, such as immunity, where each SNP likely has small effects on the phenotype in question. Our intent is to conduct replication studies in additional cohorts of rubella-vaccinated subjects, followed by fine mapping through any genetic regions where we identify replicated associations. This approach allows us to overcome many of the limitations of the current study. We set a genome-wide level of significance at $p<5\times10^{-8}$; however, evidence suggests that genetic associations not meeting this level of significance may also be real and worth pursuing (Panagiotou and Ioannidis 2012). With this in mind, additional loci will be carried forward into the replication studies in order to definitively assess whether or not they are truly associated with immune responses to rubella.

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Competing interests Dr. Poland is the chair of a Safety Evaluation Committee for novel investigational vaccine trials being conducted by Merck Research Laboratories. Dr. Poland offers consultative advice on vaccine development to Merck & Co. Inc., CSL Biotherapies, Avianax, Sanofi Pasteur, Dynavax, Novartis Vaccines and Therapeutics, PAXVAX Inc, and Emergent Biosolutions. Drs. Poland and Ovsyannikova hold patents related to vaccinia and measles peptide research. These activities have been reviewed by the Mayo Clinic Conflict of Interest Review Board and are conducted in compliance with the Mayo Clinic Conflict of Interest policies. This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and was conducted in compliance with the Mayo Clinic Conflict of Interest policies. The other authors do not have any conflicts of interest.

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