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FcγRIIa and FcγRIIIb polymorphisms were not associated with meningococcal disease in Western Norway

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SUMMARY

Fcγ-receptor (FcγR) polymorphisms have been associated with acquisition and severity of invasive meningococcal disease. We studied FcγR polymorphisms in a population with a high incidence of meningococcal disease. Fifty meningococcal disease patients aged 14–60 years, with bacteriologically confirmed disease and without detected complement deficiency, together with 100 healthy adult controls were included in the study. Clinical and bacteriological data were collected prior to FcγRIIa and FcγRIIIb genotyping, which was performed by polymerase chain reaction. The distribution of the FcγRIIa and FcγRIIIb allotypes and their allele frequencies were not significantly different amongst the patients and the controls. The combination FcγRIIa-R/R and FcγRIIIb-Na2/Na2 was less common among patients than controls (OR = 0·11, Fisher's exact $P = 0{\cdot}05$). No significant association was found between the two FcγRs and severity of disease, meningococcal serogroup, age groups or gender. In contrast to previous findings, our study indicates that in Norwegian teenagers and adults, the FcγRIIa and FcγRIIIb allotypes are not decisive for the acquisition or for the severity of meningococcal disease.

INTRODUCTION

Phagocytosis is one of the cornerstones in the complex human host defence against meningococcal invasion. The Fc-regions of immunoglobulin G (IgG) molecules bind opsonized meningococci to their receptors (FcγR) on phagocytes, thereby inducing phagocytosis and killing of the bacteria [1–3]. Various subtypes of FcγRs bind IgG subclasses with different affinity, which may hamper phagocytosis, thereby increasing host susceptibility to infection.

Polymorphisms of FcγRIIa and FcγRIIIb have been shown to influence the phagocytosis of bacteria, including meningococci [4–7]. One reason may be the higher affinity of FcγRIIa for IgG2 for the allotype containing histidine (FcγRIIa-H131) than for the allotype containing arginine (FcγRIIa-R131) [8]. Furthermore, individuals homozygous for the Fcγ-RIIIb allotype Neutrophil antigen 1 (FcγRIIIb-Na1), appear to exhibit more efficient phagocytosis of bacteria than individuals homozygous for the FcγRIIIb allotype Na2 (FcγRIIIb-Na2) [9, 10]. A predominance of FcγR-R131/R131 and FcγR-Na2/Na2 has been found in patients with meningococcal disease in The Netherlands and in Russia [11–13].

Since 1983 the incidence of meningococcal disease has varied between 5 and 10 per 10^5 population per year in Western Norway, but with a decline in recent years. In a local outbreak in Nordhordland, north of Bergen, the incidence rose to 22 per 10^5 population per year [14]. The aim of this study was to examine whether the high incidence, or the severity of meningococcal disease in Western Norway was associated with genetic factors, such as FcγRIIa and FcγRIIIb polymorphisms. The study population comprised teenage and

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adult meningococcal disease patients without detected complement deficiencies, together with healthy controls.

MATERIALS AND METHODS

Patients and controls

Fifty meningococcal disease patients (25 males and 25 females, aged 14–60 years) were included in the study (Table 1). All the participants were Norwegian Caucasians living in the city of Bergen or the surrounding areas of Western Norway. Controls were healthy adults with no history of meningococcal disease. They were not matched by age or sex to the patients but were drawn from the same geographical area.

In the patients, meningococcal disease was bacteriologically confirmed by cultures from blood and/or cerebrospinal fluid (CSF) in all except one, whose disease was confirmed by PCR of CSF (Table 1, patient no. 41). Thirty of the patients had serogroup B disease and 20 serogroup C disease. Sera from all patients had normal complement-mediated lytic activity when tested by a standard assay (CH50). Mannose-binding lectin (MBL) was not examined. Due to lack of EDTA blood samples from fatal cases, only one such patient was included (Table 1, patient no. 32).

The patients had been classified into four disease categories according to the clinical manifestations within 3 h of admission to Haukeland University Hospital, Bergen (Table 1) [15]. The disease categories were: (1) meningitis ($\geqslant$100 cells/μl CSF or back rigidity) with no hypotension or ecchymoses; (2) septicaemia with hypotension (blood pressure $\leqslant$100 mmHg) and/or ecchymoses, but with no signs of meningitis; (3) as (2), but with signs of meningitis, and (4) septicaemia with or without signs of meningitis, but with no hypotension or ecchymoses.

Polymerase chain reaction (PCR)

Genomic DNA was extracted from peripheral leucocytes of EDTA blood, using the QIAamp Blood Kit (Qiagen GmbH, Hilden, Germany). The amount and purity of the extracted DNA was measured by a spectrophotometer (Shimadzu Corporation, Analytical Instruments Division, Kyoto, Japan). The PCR products for both FcγRIIa and FcγRIIIb were applied onto 1·5% agarose gel, stained with ethidium bromide and visualized under UV light.

PCR of FcγRIIa

FcγRIIa allotypes were determined by a slightly modified amplification refractory mutation system–PCR (ARMS–PCR) [16]. Two PCRs were performed on each DNA sample, each producing a PCR-product of 949 base pairs (bp). The allotype-specific primers used were EC2/H131: 5′-CCA GAA TGG AAA ATC CCA GAA ATT CTC TCA-3′ and EC2/R131: 5′-CCA GAA TGG AAA ATC CCA GAA ATT CTC TCG-3′, and reverse primer TM/1: 5′-CCA TTG GTG AAG AGC TGC CCA TGC TGG GCA-3′ in both reactions. A set of primers from the TCR Vα22 gene with a PCR product of 270 bp were used as control primers and verified positive PCRs.

The 25 μl PCR reactions contained 1 × PCR buffer, 2·5 mM $MgCl_2$, 0·04 mM of each of the four dNTPs (PE Applied Biosystems, Branchburg, NJ, USA), 100 ng of TM/1 and EC2/R131 or EC2/H131, 8 ng of each of the control primers (Eurogentec, Herstal, Belgium), 1·5 units of AmpliTaq (PE Applied Biosystems), 75–100 ng genomic DNA from participants, and distilled water (dH_2O). The PCR conditions were: start: 94 °C for 3 min, then 45 cycles with denaturation: 94 °C for 45 s; annealing: 63 °C for 30 s; elongating: 72 °C for 1 min 30 s, and 1 cycle of extension: 72 °C for 7 min. All tests were run twice with control samples of the two allotypes.

PCR of FcγRIIIb

The FcγRIIIb allotypes were determined by sequence-specific primers [17]. One PCR reaction was carried out on each DNA sample, including primers of both FcγRIIIb allotypes (Na1 and Na2) in the reaction. The primers used were Na 1: 5′-CAG TGG TTT CAC AAT GTG AA-3′ and Na 2: 5′-CAA TGG TAC AGC GTG CTT-3′, and the reverse primer EC1 331–348: 5′-ATG GAC TTC TAG CTG CAC-3′, producing PCR products of 141 and 219 bp respectively. Human growth hormone (HGH) primers with a PCR product of 439 bp were used as control primers and verified positive PCRs.

The 25 μl PCRs contained 1·5 × PCR buffer, 1·0 mM $MgCl_2$, 0·04 mM of each of the four dNTPs (PE Applied Biosystems), 0·5 mM of Na1 and Na2, 1·0 mM of R, 0·125 mM of each of the control primers Hgh1 and Hgh2 (Eurogentec), 0·5 units of AmpliTaq (PE Applied Biosystems), 50–100 ng genomic DNA from the participants, and dH_2O. The PCR conditions were: start: 94 °C for 3 min, then 30 cycles with

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Table 1. *Patients with bacteriologically confirmed meningococcal disease*

Patient no.	Age	Sex	Culture	Serogroup	Category*	FcγRIIa†	FcγRIIIb†	FcγRIIa/FcγRIIIb†
1	18	F	CSF	B	1	H/H	Na1/Na1	H/Na1
2	16	M	Blood	C	2	R/R	Na2/Na2	R/Na2
3	26	F	CSF	B	1	H/R	Na2/Na2	HR/Na2
4	14	F	Blood	C	2	R/R	Na1/Na1	R/Na1
5	21	M	Blood/CSF	B	4	R/R	Na1/Na2	R/Na1&2
6	17	F	CSF	B	1	H/R	Na1/Na2	HR/Na1&2
7	18	F	Blood	C	4	H/R	Na2/Na2	HR/Na2
8	50	M	Blood/CSF	B	4	R/R	Na1/Na2	R/Na1&2
9	45	M	CSF	B	1	H/R	Na1/Na2	HR/Na1&2
10	16	M	Blood	B	4	H/R	Na2/Na2	HR/Na2
11	45	M	CSF	C	3	H/H	Na2/Na2	H/Na2
12	18	M	CSF	C	1	R/R	Na1/Na2	R/Na1&2
13	15	M	CSF	C	1	H/R	Na1/Na2	HR/Na1&2
14	16	M	Blood	C	4	H/R	Na1/Na2	HR/Na1&2
15	16	F	Blood	C	3	H/R	Na1/Na2	HR/Na1&2
16	18	F	Blood	C	2	R/R	Na1/Na2	R/Na1&2
17	15	M	Blood	B	4	H/R	Na2/Na2	HR/Na2
18	18	M	Blood	B	4	H/R	Na1/Na2	HR/Na1&2
19	29	M	Blood/CSF	C	4	H/R	Na1/Na2	HR/Na1&2
20	20	M	Blood	B	3	H/R	Na1/Na2	HR/Na1&2
21	47	F	Blood	C	2	H/H	Na1/Na2	H/Na1&2
22	18	M	Blood	C	3	H/R	Na1/Na2	HR/Na1&2
23	48	M	CSF	B	1	H/R	Na2/Na2	HR/Na2
24	18	F	Blood/CSF	B	2	H/R	Na1/Na2	HR/Na1&2
25	54	F	Blood	C	4	R/R	Na1/Na1	R/Na1
26	26	M	CSF	C	1	H/R	Na2/Na2	HR/Na2
27	18	F	CSF	B	3	H/R	Na1/Na1	HR/Na1
28	49	M	Blood	B	4	R/R	Na1/Na2	R/Na1&2
29	19	F	Blood/CSF	B	2	H/R	Na2/Na2	HR/Na2
30	60	F	CSF	B	3	H/R	Na2/Na2	HR/Na2
31	20	F	CSF	B	1	H/R	Na2/Na2	HR/Na2
32	46	M	Blood/CSF	B	2	H/H	Na1/Na1	H/Na1
33	18	M	CSF	B	1	H/R	Na1/Na2	HR/Na1&2
34	19	M	CSF	C	1	R/R	Na1/Na2	R/Na1&2
35	55	F	Blood	C	2	R/R	Na1/Na2	R/Na1&2
36	14	M	Blood	B	4	H/H	Na1/Na1	H/Na1
37	15	F	Blood	C	2	H/R	Na1/Na1	HR/Na1
38	17	F	CSF	B	1	R/R	Na2/Na2	R/Na2
39	38	M	Blood	C	4	H/H	Na1/Na1	H/Na1
40	16	F	Blood/CSF	B	2	H/R	Na1/Na2	HR/Na1&2
41	24	F	CSF	B‡	1	H/R	Na1/Na2	HR/Na1&2
42	15	F	CSF	B	1	R/R	Na2/Na2	R/Na2
43	16	M	Blood	B	4	H/H	Na1/Na2	H/Na1&2
44	47	F	CSF	B	1	H/R	Na1/Na1	HR/Na1
45	15	F	Blood	B	2	H/R	Na2/Na2	HR/Na2
46	23	F	Blood/CSF	B	2	H/H	Na1/Na2	H/Na1&2
47	26	F	Blood/CSF	C	4	H/R	Na1/Na2	HR/Na1&2
48	18	M	CSF	B	1	R/R	Na1/Na2	R/Na1&2
49	15	F	Blood/CSF	C	4	R/R	Na1/Na2	R/Na1&2
50	19	M	Blood/CSF	B	4	R/R	Na1/Na2	R/Na1&2

* Disease categories: see Material and Methods.

† FcγR polymorphisms: H, FcγRIIa-H131; R, FcγRIIa-R131; Na1, FcγRIIIb-Na1; Na2, FcγRIIIb-Na2.

‡ Serogroup confirmed by PCR of CSF.

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Table 2. *FcγRIIa allotypes and allele frequencies in patients and healthy controls*

		FcγRIIa allotypes*			Allele frequency	
	No.	H/H	H/R	R/R	H	R
Patients	50	8 (16%)	27 (54%)	15 (30%)	0·43	0·57
Controls	100	21 (21%)	46 (46%)	33 (33%)	0·44	0·56

* See notes to Table 1.

Table 3. *FcγIIIb allotypes and allele frequencies in patients and healthy controls*

		FcγRIIIb allotypes*			Allele frequency	
	No.	Na1/Na1	Na1/Na2	Na2/Na2	Na1	Na2
Patients	50	9 (18%)	27 (54%)	14 (28%)	0·45	0·55
Controls	100	12 (12%)	46 (46%)	42 (42%)	0·35	0·65

* See notes to Table 1.

denaturation: 94 °C for 1 min 30 s; annealing: 57 °C for 2 min 30 s; elongating: 72 °C for 1 min 30 s, and 1 cycle of extension: 72 °C for 7 min. All tests were run twice, with control samples of the two allotypes.

Statistical methods

The Statistical Package for Social Sciences (SPSS) was used to process the data. Odds ratios (OR) with confidence intervals (95% CI) were calculated, and the χ^2 test and Fisher's exact test were applied to compare the distribution of the different FcγRIIa and FcγRIIIb genotypes and allele frequencies between the patients and the controls, and between different subgroups of the patients. P values $<0{\cdot}05$ were considered significant.

RESULTS

Patients and controls

The genotypes and allele frequencies of the FcγRIIa of the patients and the controls are shown in Table 2. Eight (16%) patients and 21 (21%) controls were homozygous for FcγRIIa-H131, 15 (30%) patients and 33 (33%) controls were homozygous for FcγRIIa-R131, and 27 (54%) patients and 46 (46%) controls were heterozygous. The distribution of the FcγRIIa genotypes was not significantly different for the patients and the controls ($\chi^2=0{\cdot}96$, $P=0{\cdot}62$), and the allele frequencies were approximately equal for the two groups.

The genotypes and allele frequencies of the FcγRIIIb are shown in Table 3. Nine (18%) patients and 12 (12%) controls were homozygous for FcγRIIIb-Na1, and 14 (28%) patients and 42 (42%) controls were homozygous for FcγRIIIb-Na2, and 27 (54%) patients and 46 (46%) controls were heterozygous. The distribution of the FcγRIIIb genotypes was not significantly different for patients and controls ($\chi^2=3$, $P=0{\cdot}22$). The FcγRIIIb-Na2 allele was less common among patients than controls, but this was not significantly different (OR = 0·66, 95% CI = 0·39–1·1, $\chi^2=2{\cdot}8$, $P=0{\cdot}09$).

When genotypes of FcγRIIa and FcγRIIIb were combined, the FcγRIIa-R/R and FcγRIIIb-Na2/Na2 combination was less common among the patients than the controls (OR = 0·11 and Fisher's exact $P=0{\cdot}05$) (Table 4). However, numbers were small and only 6 individuals (4 patients and 2 controls) had the combination FcγRIIa-H/H and FcγRIIIb-Na1/Na1.

Disease category, strain, age and sex

The allele frequencies of FcγRIIa and FcγRIIIb for the different disease categories are shown in Table 5. The highest case fatality rate was in patients with disease category 2, i.e. patients with septicaemia with hypotension and/or ecchymoses, but with no signs of meningitis [15]. We compared this group of severely ill patients with the remaining patients, to seek any association between severity of meningococcal disease and particular FcγRIIa and FcγRIIIb allele frequencies. The FcγRIIa-R131 allele frequencies were

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Table 4. *The combined genotypes of FcγRIIa and FcγRIIIb in patients and controls*

		FcγRIIa and FcγRIIIb*		
	No.	H/H&Na1/Na1	H/R&Na1/Na2	R/R&Na2/Na2
Patients	50	4	14	3
Controls	100	2	18	15

* See notes to Table 1.

Table 5. *FcγRIIa and FcγRIIIb related to disease category, serogroup, age and sex*

		Allele frequency FcγRIIa*		Allele frequency FcγRIIIb*	
	No.	H	R	Na1	Na2
Patients	50	0·43	0·57	0·45	0·55
Category					
2*	12	0·46	0·54	0·50	0·50
1, 3 and 4	38	0·42	0·58	0·45	0·55
Serogroup					
B	30	0·47	0·53	0·42	0·58
C	20	0·38	0·62	0·50	0·50
Age					
<20	29	0·38	0·62	0·45	0·55
$\geqslant 20$	21	0·50	0·50	0·45	0·55
Sex					
Male	25	0·44	0·56	0·44	0·56
Female	25	0·42	0·58	0·46	0·54

* See notes to Table 1.

0·54 and 0·58 respectively for disease category 2 patients and the remaining patients, which was not significantly different ($P = 0{\cdot}75$). The FcγRIIIb-Na2 allele frequency was identical (0·54) for both groups. The patient who died (Table 1, patient no. 32) was genotyped FcγRIIa-H/H and FcγRIIIb-Na1/Na1. There were no significant differences in the allele frequencies of FcγRIIa and FcγRIIIb for the different serogroups, age groups and gender (Table 4).

DISCUSSION

In this prospective case-control study, FcγRIIa and FcγRIIIb genotyping was performed by PCR on 50 teenage and adult meningococcal disease patients and 100 healthy adult controls. The clinical and bacteriological data were collected prior to the FcγR genotyping.

The distribution of FcγRIIa and FcγRIIIb allotypes and their allele frequencies were similar for patients and the controls. This is in contrast to previous findings relating the FcγRIIa-R131 and FcγRIIIb-Na2 allotypes to impaired phagocytosis capacity and increased susceptibility to bacterial infections [18, 19]. Specific studies on patients with meningococcal disease have found a higher proportion homozygotes for FcγRIIa-R131 among patients than healthy controls [12, 13, 20]. In addition, Fijen et al. [11, 21] found an association between the FcγRIIa-R/R and FcγRIIIb-Na2/Na2 combination and meningococcal disease. Though numbers were small, this combination was less common among the patients than the controls in our study.

In a study on children, Bredius [12] found an association between FcγRIIa-R131 and fulminant meningococcal septic shock. Our study on teenagers and adults found no significant association between FcγRIIa- and FcγRIIIb polymorphisms and the severity of meningococcal disease. However, only one fatal patient was examined and he was genotyped

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FcγRIIa-H/H and FcγRIIIb-Na1/Na1. Finally, no significant association was found between the two FcγRs allotypes and the different serogroups, age groups and gender.

The reason for our findings is not clear. Previous studies on meningococcal disease patients and FcγRs have focused on children and/or patients with late complement deficiencies. Individuals with late complement deficiencies lack anti-meningococcal bactericidal activity, and are therefore more dependent on opsonophagocytosis and proper functioning FcγRs [22]. We included only patients without detected complement deficiencies since the majority of meningococcal disease patients have a normal complement system [23]. Furthermore, only teenagers and adults were included, without regard to possible differences between children and teenagers/adults concerning the role of FcγRs in host defence against meningococci.

Host defence plays a crucial role in the acquisition and the severity of meningococcal disease, involving a complement-mediated bactericidal response and an opsonophagocytic response [24]. Antibody production can be induced by vaccination, disease and/or carriage of meningococci [25, 26]. Even carriage of different meningococcal strains and other species such as *N. lactamica* may induce cross-reacting antibodies [27]. However, antibodies to meningococci vary with regard to antigen specificity, immunoglobulin class and function, some are not protective, and some may even block antigen sites on the meningococci [24]. Furthermore, acutely ill patients have low levels of anti-meningococcal opsonic antibodies [28, 29], and opsonic antibodies are needed to bind meningococci to FcγRs on phagocytes, inducing phagocytosis of meningococci. Low concentrations of opsonic antibodies in acutely ill patients suggest that the FcγR polymorphisms may be of less relative importance for the contraction and the severity of meningococcal disease.

The epidemiology of meningococcal disease is very complex. Substantial geographic variations have been documented regarding incidence rates, disease causing strains, age groups affected by disease, and distribution of FcγRs and other host genetic factors [30–33]. In this study in individuals from Western Norway, no association was found between FcγR polymorphisms and meningococcal disease in patients older than 13 years without detected complement deficiencies. FcγRIIa and FcγRIIIb polymorphisms or combinations of the two do not explain the high incidence and the severity of meningococcal disease in Western Norway.

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