Association of Fcγ Receptor IIB Polymorphism with Cryptococcal Meningitis in HIV-Uninfected Chinese Patients

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Abstract

Background: As important regulators of the immune system, the human Fcγ receptors (FcγRs) have been demonstrated to play important roles in the pathogenesis of various infectious diseases. The aim of the present study was to identify the association between FCGR polymorphisms and cryptococcal meningitis.

Methodology/Principal Findings: In this case control genetic association study, we genotyped four functional polymorphisms in low-affinity FcγRs, including FCGR2A 131H/R, FCGR3A 158F/V, FCGR3B NA1/NA2, and FCGR2B 232I/T, in 117 patients with cryptococcal meningitis and 190 healthy controls by multiplex SNaPshot technology. Among the 117 patients with cryptococcal meningitis, 59 had predisposing factors. In patients with cryptococcal meningitis, the FCGR2B 232I/I genotype was over-presented (OR = 1.652, 95% CI [1.02–2.67]; P = 0.039) and the FCGR2B 232I/T genotype was under-presented (OR = 0.542, 95% CI [0.33–0.90]; P = 0.016) in comparison with control group. In cryptococcal meningitis patients without predisposing factors, FCGR2B 232I/I genotype was also more frequently detected (OR = 1.958, 95% CI [1.05–3.66]; P = 0.033), and the FCGR2B 232I/T genotype was also less frequently detected (OR = 0.467, 95% CI [0.24–0.91]; P = 0.023) than in controls. No significant difference was found among FCGR2A 131H/R, FCGR3A 158F/V, and FCGR3B NA1/NA2 genotype frequencies between patients and controls.

Conclusion/Significance: We found for the first time associations between cryptococcal meningitis and FCGR2B 232I/T genotypes, which suggested that FcγRIIB might play an important role in the central nervous system infection by Cryptococcus in HIV-uninfected individuals.

Introduction

Cryptococcal meningitis is the most common opportunistic fungal infection of the central nervous system in AIDS patients. Among HIV-uninfected patients, several predisposing factors for cryptococcal meningitis such as corticosteroid medication, solid organ transplantation and malignancy, etc, have been indentified. Yet cryptococcal infections in apparently healthy individuals are also increasingly being reported, especially from Asian data [1–3]. Our previous study has demonstrated an association between mannose-binding lectin (MBL) genetic deficiency and cryptococcal meningitis in HIV-uninfected patients [4]. However, MBL deficiency was present in only 21% of the cases, and for the remaining 79% of patients the underlying mechanism for susceptibility remained unclear.

Fc γ receptors (FcγRs) mediate a variety of immune responses after binding to IgG-opsonized pathogens or immune complexes, and therefore act as immune regulators in both autoimmune and infectious diseases [5–9]. According to their affinity to IgG, FcγRs are categorized into high-affinity and low-affinity receptors. FcγRI is the only known high-affinity receptor. Low-affinity FcγRs which include FcγRIIA, FcγRIIB, FcγRIIC, FcγRIIAIA, and FcγRIIIB, are encoded by FCGR2A, FCGR2B, FCGR2C, FCGR3A, and FCGR3B genes, respectively. FCGR polymorphisms had been associated with the susceptibility and severity of various infections. FCGR2A 131R/R had been reported to attribute to the susceptibility of meningococcal infection, community-acquired pneumonia (CAP) caused by Haemophilus influenza, and the development of severe malaria [10–12]. Another study showed that HIV-infected patients with FCGR2A 131R/R genotype progressed to a low CD4+ cell count at a faster rate, but conversely in individuals carried FCGR2A 131H/H there was an increased risk of Pneumocystis jiroveci pneumonia [14]. FCGR3A 158F/V gene polymorphism was not associated with progression of HIV infection, but predicted the risk of Kaposi’s sarcoma [14]. A study on infections during induction chemotherapy found that FCGR2A 131H/H was associated with a decreased risk of pneumonia, FCGR3B NA1/NA1 associated with infections, and FCGR3A polymorphisms not associated with infections [15]. Sadki
et al. investigated the influence of FCGR3A 158V/F and FCGR2A 131H/R polymorphisms on susceptibility to pulmonary tuberculosis in the Moroccan population but no association was found [16]. A study in East Africa found that the FCGR2B 232I/T genotype provided protectiveness for children against severe malaria [17].

A previous study by Meletiadis et al. investigated FCGR polymorphisms in patients with cryptococcosis, and found that FCGR2A 131R/R and FCGR3A 158V/V were over-presented, and FCGR3B NA2/NA2 was under-presented in patients with cryptococcosis [10]. The purpose of this study was to investigate FCGR polymorphisms in our series of patients to further verify the association between FCGR and cryptococcal meningitis.

**Results**

**Demographic Characteristics**

A total of 117 HIV-uninfected patients with cryptococcal meningitis were included. Subjects from both the patient and control groups were of Chinese Han ethnicity. Clinical information and predisposing factors of the patients are summarized in Table 1. Of the 190 healthy control subjects, 111 were male (58.4%). The median age of the control subjects was 44 years (range, 12–79 years).

| Characteristics                  | N (%)/median (range) |
|----------------------------------|----------------------|
| Male                             | 74 (63.2)            |
| Age (years)                      | 45 (14–78)           |
| Confirmed cases                  | 101 (86.3)           |
| Probable cases                   | 16 (13.7)            |
| Predisposing factors*            | 59 (50.4)            |
| Autoimmune diseases              | 18 (15.4)            |
| Diabetes mellitus                | 13 (11.1)            |
| Liver cirrhosis                  | 6 (5.1)              |
| Chronic kidney diseases          | 5 (4.3)              |
| Solid malignancies               | 2 (1.7)              |
| Kidney transplantation           | 2 (1.7)              |
| Corticosteroidsb                 | 21 (17.9)            |
| Immunosuppression^               | 12 (10.3)            |
| Idiopathic CD4^+ T lymphocytopena| 13 (11.1)            |
| Severe cryptococcal meningitis^   | 35 (29.9)            |
| Disturbance of consciousness     | 31 (26.5)            |
| Cerebral herniation              | 9 (7.7)              |
| Death                            | 5 (4.3)              |

*NOTE: *Predisposing factors including immunocompromising diseases (liver cirrhosis, chronic kidney diseases, autoimmune diseases, malignancies, solid organ transplantation, diabetes mellitus), and corticosteroid or immunosuppressive medications, and idiopathic CD4^+ T lymphocytopenia. Some patients had more than one predisposing factor.

Genotype Distribution

Two samples failed genotyping of FCGR3A and 2 samples failed in genotyping of FCGR2B. Allele distributions of the tested FCGR genes in the control group were in Hardy-Weinberg equilibrium. The frequencies of FCGR2A, FCGR3A, FCGR3B and FCGR2B genotypes were shown in Table 2. An association was found between FCGR2B 232I/T genotypes and cryptococcal meningitis based on dominant and over-dominant model. The FCGR2B 232I/T genotype was over-presented (OR = 1.652, 95% CI [1.02–2.67]; P = 0.039) and the FCGR2B 232I/T genotype was under-presented (OR = 0.542, 95% CI [0.33–0.90]; P = 0.016) in patients with cryptococcal meningitis in comparison with controls. No significant difference was found in the distribution of FCGR2A 131H/R, FCGR3A 158F/V and FCGR3B NA1/NA2 genotypes.

We further compared the genotype distribution of FCGR2A, FCGR3A, FCGR3B and FCGR2B between the 50 patients without predisposing condition and controls. Similar to results from the overall patient group, associations were also found between FCGR2B 232I/T genotypes and cryptococcal meningitis based on dominant and over-dominant model. Specifically, FCGR2B 232I/T genotype was more frequently detected (OR = 1.958, 95% CI [1.05–3.66]; P = 0.033), and FCGR2B 232I/T genotype was also less frequently detected (OR = 0.467, 95% CI [0.24–0.91]; P = 0.023) in patients without predisposing factor than in controls. For the genotype distribution of other polymorphisms (FCGR2A 131H/R, FCGR3A 158F/V and FCGR3B NA1/NA2), there was also no significant difference between patients and controls.

**Discussion**

The distribution of FCGR polymorphisms has been reported to exhibit substantial inter-ethnic variation. According to our population, frequencies of FCGR2A 131R/R, FCGR3B NA2/NA2, and FCGR2B 232I/T in all subjects were 16%, 11%, and 7% respectively, similar to those reported among other Asian populations (which ranged 9–14%, 11–21%, and 5–11%) [19–26]. Frequencies of these genotypes in Caucasian population were reported to be 19–34%, 38–43%, and 1–3% [18,23,27–30], which were different from our data. There seems no marked difference in the distribution of FCGR3A 158F/V genotypes between the Asian and Caucasian populations [18,21,23,31,32].

The four polymorphisms of low-affinity receptors genotyped in our study have each been demonstrated to affect functions of their encoded receptors. In FCGR2A, the G>A SNP at amino acid position 131 results in a histidine (H) to arginine (R) change (FCGR2A 131H/R), resulting in reduced affinity of the corresponding receptor to IgG2 [33,34]. The T>G SNP at position 158 of FCGR3A causes a phenylalanine (F) to valine (V) substitution (FCGR3A 158F/V) and FCGR3A 158F/V encoded receptors show higher affinity to IgG1 and IgG3 [35,36]. In the FCGR3B gene, five nucleotides (141,147,227,277 and 349) are combined to form two main haplotypes termed NA1 and NA2, and receptor encoded by FCGR3B NA1 haplotype binds to IgG1 and IgG3 more easily [37]. Finally, FCGR2B 232I/T causes an isoleucine (I) to threonine (T) substitution in the transmembrane domain [22,38] and receptors encoded by FCGR2B 232I/T are unable to interact with activating receptors [39].

Although FCGR polymorphisms have been demonstrated to be associated with susceptibility and severity of numerous infections, there has only been one previous genetic association study on the relationship of FCGR genotypes and cryptococcosis [18]. Meletiadis and colleagues genotyped FCGR2A 131H/R, FCGR3A 158F/V and FCGR3B NA1/NA2 in 103 cryptococcosis patients and 395
healthy controls. They found that in patients with cryptococcosis, FCGR2A 131R/R and FCGR3A 158V/V were over-presented (P-values were 0.04 and 0.04), while FCGR3B NA2/NA2 was under-presented (P-value was 0.04).

In our study, we found for the first time that cryptococcal meningitis was associated with the FCGR2B 232I/T genotypes, which was not reported in Meteidiats' study. As the only known inhibitory FcγR, FcγRIIB has an immunoreceptor tyrosine-based inhibitory motif (ITIM) in its cytoplasmic domain, and thus it plays an important role in regulating the immune system [40]. FCGR2B 232I/T is located in the transmembrane domain, and the FcγRIIB receptors encoded by FCGR2B 232T are unable to interact with activating receptors and exert inhibitory activity [38]. Published data have suggested the mutation genotype FCGR2B 232T/T to be a susceptible genotype for systemic lupus erythematosus [17,22,32], and this genotype also provided protective effect for severe malaria in East African children [17]. The role of FcγRIIB in cryptococcal infection is still not very clear. Like the activatory FcγRs, FcγRIIB can also recognize the major component of the capsule of C. neoformans, glucuronoxylomannan (GXM). In a previous study by Monari et al., the immunosuppressive effect of GXM was demonstrated to be dependent on FcγRIIB, based on the evidences that FcγRIIB blockade inhibits GXM-induced IL-10 production and induces TNF-α secretion, and that the addition of monoclonal antibody to GXM reverses GXM-induced immunosuppression by shifting recognition from FcγRIIB to FcγRIIA [41]. Another study subsequently demonstrated that GXM triggered NO-induced macrophage apoptosis, which was dependent on FcγRII [42]. These data support that FcγRIIB plays a critical role in the pathogenesis of cryptococcal infection. In our study, it is the FCGR2B 232I/T heterozygote instead of the minor homozygote 232T/T that is under-presented in patient group. One study on children with idiopathic thrombocytopenia (ITP) also showed a similar pattern, that the FCGR2B 232I/T was less frequently detected in acute ITP in comparison with chronic ITP [27]. The reason for the heterozygotes 232I/T rather than 232T/T under-presenting in our cases in our study were diagnosed with cryptococcal meningitis, while some patients from Meletiadis' study was Caucasian in Meletiadis' study. Secondly, all the cases in our study were diagnosed with cryptococcal meningitis, while some patients from Meletiadis' study were of Chinese Han ethnicity, while the majority of subjects in Meteidiats' study were Caucasians (60%). As a matter of fact, the FCGR3A 158V allele was significantly increased only in patients who were Caucasian in Meletiadis' study. Unlike results from Meletiadis' study, no association among FCGR2A 131H/R, FCGR3A 158V/F, FCGR3B NA2/NA2 and cryptococcal meningitis was found in our study. The cause for discrepant results may be multifactorial. One was the ethnic differences between the two studies. Subjects in our study were of Chinese Han ethnicity, while the majority of subjects in Meletiadis' study were Caucasians (60%). As a matter of fact, the FCGR3A 158V allele was significantly increased only in patients who were Caucasian in Meletiadis' study. Secondly, all the cases in our study were diagnosed with cryptococcal meningitis, while some patients from Meletiadis' study were cryptococcosis without central nervous system involvement.
Furthermore, both studies had relatively small sample sizes, which could be underpowered to generate positive results.

In conclusion, our study suggested that FcγRIIB genetic polymorphism may contribute to the susceptibility of cryptococcal meningitis. The overall association is relatively weak, which warrants validation in larger populations.

**Ethics Statement**

This study was reviewed and approved by the Ethic Committee of Huashan Hospital, Fudan University, and informed consent was obtained from each participant.

**Materials and Methods**

**Subjects**

A total of 200 volunteers and 117 unrelated patients with proven or probably diagnosed cryptococcal meningitis who were referred to Huashan Hospital, Fudan University, China, from 2001 through 2011 were recruited for the present study. Patients who met at least one of the following criteria were considered as proven cryptococcal meningitis: (1) Isolation of *C. neoformans* from cerebrospinal fluid (CSF) by culture or positive India ink smear, and (2) compatible histopathological findings, which are 5–10 μm encapsulated yeasts observed in brain tissue. Patients who had no microbiological or pathological documentation but present with positive cryptococcal antigen titer (>1:10) in CSF and met at least one of the following criteria were regarded as probable cryptococcal meningitis: (1) abnormal laboratory tests or an increased open pressure (>200 mmH2O) of CSF, (2) abnormalities of cranial imaging (Computed Tomography or Magnetic Resonance Imaging) which could not be explained by other factors, and (3) comorbidities that compromise the host immune system. Cryptococcal antigen was determined using diluted CSF with the Antigen Detection system (Immuno-Mycologics). Patients without any of the above mentioned predisposing factors were considered as apparently healthy hosts.

**Polymorphisms Selection and Genotyping**

Four functional FCGR polymorphisms including FCGR2A 131H/R, FCGR2A 158F/V, FCGR3B NA1/NA2, and FCGR2B 232I/T were selected for genotyping after literature review of previous studies on association between FCGR polymorphisms and infectious diseases [11–17].

Venous blood was obtained by venepuncture from each subject. Genomic DNA was extracted using the QiAamp DNA kit (Qiagen, Hilden, Germany) according to manufacturer’s instructions. Genotyping of 8 SNPs in FCGRs (Table 3) was performed by multiplex SNaPshot technology using an ABI fluorescence-based assay discrimination method (Applied Biosystems, Foster city, CA, USA), which has been described in detail in previous studies [47,48]. The multiplex SNaPshot detection of single-base extended probe primers was based on fluorescence and extended length detected by capillary electrophoresis on ABI3130XL Sequencer (Applied Biosystems, Foster City, CA, USA).

Four pairs of primers for PCR amplification including 5 fragments of 587–2394 bp and 8 primers for SNaPshot extension reactions were designed by Primer3 online software (v.0.4.0) (http://frodo.wi.mit.edu/primer3/) according to the reference sequences from dbSNP (http://www.ncbi.nlm.nih.gov/SNP). There were homologous sequences between FCGRs, the specificity sequences were checked with the sequence databases using BLAST (http://www.ncbi.nlm.nih.gov/blast/blast.cgi). These sequences were also verified by SNPmasker1.1 (http://bioinfo.ibece.es/snpmasker) to make sure that the different bases were caused by SNP [49]. And each primer pair was tested for potential primer-dimer and hairpin structures using the AutoDimer software (http://www.cstl.nist.gov/biotech/strbase/AutoDimerHomepage/AutoDimerProgramHomepage.htm). The primers used in this study were listed in Table 3.

The PCR reactions were performed with 1 μL of DNA and 1 μL multiple PCR primers (the concentration was 1 μM) in a total volume of 20 μL containing 1x HotStarTaq buffer, 2.0 mM Mg2+, 0.3 mM dNTP, and 1 U HotStarTaq polymerase (Qiagen, Hilden, Germany). The cycling conditions for FCGR2A and FCGR3B were included in the control group.

**Table 3. Product size and primers of eight SNPs in FCGRs.**

| SNP ID   | Product size (bp) | PCR primer sequence | Extension primer sequence |
|----------|------------------|---------------------|---------------------------|
| FCGR2A   |                  |                     |                           |
| 131H/R   | 587              | F:TTGCTTATAGAGAATTCTCACTCCTTCA   | R:AAGCTCTGGCCCCTACTTGTT   |
| FCGR2A   |                  | F:CTCTAGATCTAATTACCTGCGG   | R:AGCCCAAAGAGAGGGATTCTG   |
| FCGR2B   |                  | F:CACATCTATAGCTGGATTAGGTACGTAA | R:CCCATATGGGGAGTTCTGGA   |
| NA1/NA2  |                  | F:TTGCTTATAGAGAATTCTCACTCCTTCA   | R:AAGCTCTGGCCCCTACTTGTT   |
| FCGR3B   |                  | F:CTCTAGATCTAATTACCTGCGG   | R:AGCCCAAAGAGAGGGATTCTG   |
| 232I/T   |                  | F:CACATCTATAGCTGGATTAGGTACGTAA | R:CCCATATGGGGAGTTCTGGA   |

Note: F indicates forward primer, R indicates reverse primer.

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FCGR3A were 95°C for 2 min, 35 cycles using 96°C for 20 s, 62°C for 2 min, and 72°C for 3 min, then 72°C for 10 min, and finally kept at 4°C. The cycling conditions for FCGR2B and FCGR3B were 95°C for 2 min, 7 cycles using 96°C for 20 s, 55°C for 2 min, and 72°C for 3 min, then 72°C for 10 min, and finally kept at 4°C. PCR products were then purified (add 1U SAP enzyme to 10μL PCR products, incubate at 37°C for 1 hour, then, inactivate at 75°C for 15 min).

The extension reaction to identify single nucleotide polymorphisms in the PCR products was performed in a total volume of 10μL containing 2μL purified PCR product, 1μL primer (the concentration was 0.8μM), 5μL SNaPShot Multiplex Kit (Applied Biosystems, Foster City, CA, USA), and 2μL ultrapure water. The cycling conditions for extension were 96°C for 1 min, 28 cycles of 96°C for 10 s, 52°C for 5 s, and 60°C for 30 s, and kept at 4°C. Then each extended product was added to 1 U shrimp alkaline phosphatase, incubated at 37°C for 1 hour, and the enzyme inactivated at 75°C for 15 min. Then, 0.5μL was added to 0.5μL Liz120 SIZE STANDARD (Applied Biosystems, Foster City, CA, USA), 9μL Hi-Di (Applied Biosystems, Foster City, CA, USA), and sequenced by ABI3130XL Sequencer (Applied Biosystems, Foster City, CA, USA). Finally, the primary data was analyzed by GeneMapper 4.0 (Applied Biosystems, Foster City, CA, USA). Genotypes were determined by the type of nucleotide presented at SNP site, which was visualized by one or two different color peaks on the figures.

For quality control, a random sample of 5% of the cases and controls was genotyped twice by different researchers, with a reproducibility of 100%. The minor allele counts were compared with database (http://www.ncbi.nlm.nih.gov/projects/SNP/), and the data were matched well. Genotyping was performed blind to group status.

Statistical Analysis

Dominant, over-dominant, recessive, and allelic models were applied for the analysis of genotype distribution. Hardy-Weinberg equilibrium, differences in gene polymorphism distributions between patients and controls were analyzed with 2×2 χ² tests or Fisher’s exact test where appropriate. P-values, odds ratios (ORs) and 95% confidence intervals (CIs) were obtained by SPSS 16.0 for Windows (SPSS, Inc, Chicago, IL). P-values <0.05 were considered statistically significant.

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Author Contributions

Conceived and designed the experiments: X-PH J-QW L-PZ X-HW. Performed the experiments: X-PH XW. Analyzed the data: X-PH J-QW XW L-PZ. Contributed reagents/materials/analysis tools: BX R-YW X-HW. Conceived and designed the experiments: X-PH J-QW L-PZ X-HW. Performed the experiments: X-PH XW. Analyzed the data: X-PH J-QW XW L-PZ. Contributed reagents/materials/analysis tools: BX R-YW X-HW. Conceived and designed the experiments: X-PH J-QW L-PZ X-HW. Performed the experiments: X-PH XW. Analyzed the data: X-PH J-QW XW L-PZ. Contributed reagents/materials/analysis tools: BX R-YW X-HW. Conceived and designed the experiments: X-PH J-QW L-PZ X-HW. Performed the experiments: X-PH XW. Analyzed the data: X-PH J-QW XW L-PZ. Contributed reagents/materials/analysis tools: BX R-YW X-HW. Conceived and designed the experiments: X-PH J-QW L-PZ X-HW. Performed the experiments: X-PH XW. Analyzed the data: X-PH J-QW XW L-PZ. Contributed reagents/materials/analysis tools: BX R-YW X-HW. Conceived and designed the experiments: X-PH J-QW L-PZ X-HW. Performed the experiments: X-PH XW. Analyzed the data: X-PH J-QW XW L-PZ. Contributed reagents/materials/analysis tools: BX R-YW X-HW. Conceived and designed the experiments: X-PH J-QW L-PZ X-HW. Performed the experiments: X-PH XW. Analyzed the data: X-PH J-QW XW L-PZ. Contributed reagents/materials/analysis tools: BX R-YW X-HW.
disease in newly diagnosed idiopathic thrombocytopenia in childhood: results of a prospective study. Br J Haematol 127: 561–567.

28. Hessner MJ, Curtis BR, Endean DJ, Aster RH (1996) Determination of neutrophil antigen gene frequencies in five ethnic groups by polymerase chain reaction with sequence-specific primers. Transfusion 36: 895–899.

29. Magnusson V, Zucar R, Oldenberg J, Sturfelt G, Tuedesso L, et al. (2004) Polymorphisms of the Fc gamma receptor type IIb gene are not associated with systemic lupus erythematosus in the Swedish population. Arthritis Rheum 50: 1348–1350.

30. van Schie RC, Wilson ME (2000) Evaluation of human FcγRIIA (CD32) and FcγRIIIB (CD16) polymorphisms in Caucasians and African-Americans using salivaary DNA. Clin Diagn Lab Immunol 7: 676–681.

31. Kyogoku C, Tsuchiya N, Matsuta K, Tokunaga K (2002) Studies on the association of Fc gamma receptor IIA, IIB, IIIA and IIIB polymorphisms with rheumatoid arthritis in the Japanese: evidence for a genetic interaction between HLA-DRB1 and FCGR3A. Genes Immun 3: 408–409.

32. Siriboonrit U, Tsuchiya N, Sirikong M, Kyogoku C, Bejrachandra S, et al. (2003) Association of Fcgamma receptor Iib and IIIb polymorphisms with susceptibility to systemic lupus erythematosus in Thais. Tissue Antigens 61: 374–383.

33. Reilly AF, Norris CF, Surrey S, Bruchak FJ, Rappaport EF, et al. (1994) Genetic diversity in human Fc receptor II for immunoglobulin G: Fc gamma receptor IIA ligand-binding polymorphism. Clin Diagn Lab Immunol 1: 640–644.

34. Warmerdam PA, van de Winkel JG, Vlug A, Westerdaal NA, Capel PJ (1991) A single amino acid in the second Ig-like domain of the human Fc gamma receptor II is critical for human IgG2 binding. J Immunol 147: 1338–1343.

35. Koene HR, Kleijer M, Algra J, Roos D, von dem Borne AE, et al. (1997) Fc gamma RIIB-158V/F polymorphism influences the binding of IgG by natural killer cell Fc gamma RIIs, independently of the Fc gamma IIIA-48L/R/H phenotype. Blood 90: 1109–1114.

36. Wu J, Edberg JC, Redecha PR, Bansal V, Gurey PM, et al. (1997) A novel polymorphism of FcgammaRIIa (CD16) alters receptor function and predisposes to autoimmune disease. J Clin Invest 100: 1059–1067.

37. Bredius RG, Fijen CA, De Hass M, Kuijper EJ, Weening RS, et al. (1994) A novel polymorphism of FcgammaRIa (CD32) and Fc gamma RIIB (CD16) polymorphic forms in phagocytosis of human IgG1- and IgG3-opsonized bacteria and erythrocytes. Immunology 83: 624–630.

38. Li X, Wu J, Carter RH, Edberg C, Su K, et al. (2003) A novel polymorphism in the Fcgamma receptor IIB (CD1832) transmembrane region alters receptor signaling. Arthritis Rheum 48: 3242–3252.

39. Futo RA, Clatworthy MR, Heilbronner KR, Rosen DR, MacAry PA, et al. (2003) Loss of function of a lupus-associated FcgammaRIIb polymorphism through exclusion from lipid rafts. Nat Med 11: 1056–1058.

40. Nimmerjahn F, Vaneck JV (2008) Fcgamma receptors as regulators of immune responses. Nat Rev Immunol 8: 34–47.

41. Monari C, Koziel TR, Pagano F, Pericolini E, Perito S, et al. (2006) Microbial immune suppression mediated by direct engagement of inhibitory Fc receptor. J Immunol 177: 6842–6851.

42. Chiapello LS, Baeretti JL, Garro SP, Spesso MF, Masul DT (2008) C.f. C. neoformans glucuronoxylomannan induces macrophage apoptosis mediated by nitric oxide in a caspase-independent pathway. Int Immunol 20: 1527–1541.

43. Pappas PG, Perfect JR, Cloud GA, Larsen RA, Pankey GA, et al. (2001) Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. Clin Infect Dis 33: 690–699.

44. De Paou B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, et al. (2008) Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 46: 1813–1821.

45. Zonios DI, Falloon J, Huang CY, Chaitt D, Bennett JE (2007) Cryptococcosis and idiopathic CD4 lymphocytopenia. Medicine (Baltimore) 86: 76–92.

46. Chayakulkeeree M, Perfect JR (2006) Cryptococcosis. Infect Dis Clin North Am 20: 507–544.

47. Di Cristofaro J, Selvy M, Chiaronna J, Bally P (2010) Single PCR multiplex SNaPshot reaction for detection of eleven blood group nucleotide polymorphisms: optimization, validation, and one-year of routine clinical use. J Mol Diagn 12: 453–460.

48. Wang L, Xing Y, Zhang Y, Wang Y, Huang S, et al. (2012) Association analysis of IL-17A and IL-17F polymorphisms in Chinese Han women with breast cancer. PLoS One 7: e34400.

49. Andreson R, Puurand T, Remm M (2006) SNPmasker: automatic masking of SNPs and repeats across eukaryotic genomes. Nucleic Acids Res 34: W531–535.