Correction

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Correction for "Impaired inhibitory Fcγ receptor IIB expression on B cells in chronic inflammatory demyelinating polyneuropathy," by Björn Tackenberg, Ilijas Jelčić, Anne Baerenwaldt, Wolfgang H. Oertel, Norbert Sommer, Falk Nimmerjahn, and Jan D. Lünemann, which appeared in issue 12, March 24, 2009, of *Proc Natl Acad Sci USA* (106:4788–4792; first published March 4, 2009; 10.1073/pnas.0807319106).

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Impaired inhibitory Fcγ receptor IIB expression on B cells in chronic inflammatory demyelinating polyneuropathy

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The inhibitory Fc-γ receptor FcγRIIB, expressed on myeloid and B cells, has a critical role in the balance of tolerance and autoimmunity, and is required for the antiinflammatory activity of intravenous Ig (IVIG) in various murine disease models. However, the function of FcγRIIB and its regulation by IVIG in human autoimmune diseases are less well understood. Chronic inflammatory demyelinating polyneuropathy (CIDP) is the most common treatable acquired chronic polyneuropathy, and IVIG is widely used as a first-line initial and maintenance treatment. We found that untreated patients with CIDP, compared with demographically matched healthy controls, showed consistently lower FcγRIIB expression levels on naive B cells, and failed to up-regulate or to maintain up-regulation of FcγRIIB as B cells progressed from the naive to the memory compartment. Concomitantly, the rare −386C/−120A FcγRIIB promoter polymorphism resulting in reduced promoter activity previously associated with autoimmune phenotypes was overrepresented in CIDP. Also, FcγRIIB protein expression was up-regulated on monocytes and B cells after clinically effective IVIG therapy. Thus, our results suggest that the inhibitory FcγRIIB is impaired at a critical B cell differentiation checkpoint in CIDP, and that modulating FcγRIIB expression might be a promising approach to efficiently limit antibody-mediated immunopathology in CIDP.

autoimmunity | human | immunology | Fc receptor | CIDP

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a common, although underdiagnosed, disease of the peripheral nervous system with an estimated prevalence of ≈0.5 per 100,000 children and 2 to 7 per 100,000 adults (1, 2). The clinical presentation is heterogeneous, but the most common form causes symmetrical progressive or relapsing weakness affecting proximal and distal muscles (3). Humoral immune responses are thought to have a crucial role in mediating peripheral nerve damage and represent important pharmacological targets in CIDP (2, 4). Sera and IgG antibodies from CIDP patients induce peripheral demyelination in host animals (5), can increase the permeability of the blood–nerve barrier, and impair nerve conduction in various models of peripheral neuropathies (4). Removal of humoral immune mediators by plasma exchange therapy as well as intravenous Ig (IVIG) are considered first-line treatments in patients with CIDP (6, 7).

IgG-mediated effector functions require the interaction of the Fc fragment of antibodies with their cognate cellular Fc-γ receptors (FcγR) (8). Most hematopoietic cells express both activating and inhibitory FcγR; thus, the in vivo activity of an IgG antibody results from the net effect of engaging both classes of receptors. Of the 3 classes of FcγR expressed in humans, FcγRI (CD64), FcγRII (CD32), and FcγRIII (CD16), the type II FcγRIIB (CD32B) is the only inhibitory FcγR. FcγRIIB is expressed on the cell surface of circulating B cells, on monocytes, neutrophils, as well as myeloid and plasmacytoid dendritic cells (DCs) (9). In B cells, FcγRIIB transduces an inhibitory signal upon colligation with the B cell receptor, thereby preventing B cells with low affinity or self-reactive receptors from entering the germinal center and becoming IgG positive plasma cells (8). Mice lacking FcγRIIB expression spontaneously develop autoimmune disease (10), and restoration of decreased FcγRIIB expression on activated B cells in autoimmune-susceptible mice restores immunological tolerance (8). Autoimmune prone mouse strains such as BXSB, NOD, and NZM carry a promoter polymorphism in the FcγRIIB gene, which results in decreased protein expression (11), and decreased FcγRIIB expression or nonfunctional FcγRIIB variants have been shown to be associated with the development and severity of systemic lupus erythematosus (SLE) in several human populations (8, 12). Also, this inhibitory receptor is required for antiinflammatory activity of IVIG, because disruption of this protein by genetic deletion or via blocking antibodies reverses the therapeutic effects of IVIG in various autoimmune animal models (13–16). Here, we investigated the expression profile of the inhibitory FcγRIIB on peripheral blood monocytes and B cells, its regulation after IVIG therapy, and the presence of FcγRIIB promoter polymorphisms and allelic variants, as a possible pathomechanism in patients with CIDP.

Results

Selective Dysregulation of FcγRIIB Expression on B Cells in CIDP. Expression of the inhibitory FcγIIB receptor was determined on circulating monocytes and B cells in untreated patients with CIDP and demographically matched healthy blood donors (Table 1). Both patients and controls were of Caucasian descent. Because previous studies showed that FcγRIIB expression changes with B cell maturation (12), $CD19^+CD27^-$ naive and $CD19^+CD27^+$ memory B cells and plasma cells were analyzed

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Table 1. Demographic and clinical characteristics of CIDP patients and controls

	CIDP $n = 23$	Controls $n = 26$
Age	56.4 ± 8.6	42.1 ± 8.6
(Years ± SD; range)	(41↔73)	(41↔65)
Duration of symptoms	1.0 ± 1.4	N/A
(Years ± SD; range)	(0↔6)	—
Male to female ratio	2.3	2.5
Fulfilling modified AAN criteria, %	23, 100	N/A
Fulfilling EFNS/PNS criteria, %	23, 100	N/A
Clinical course*	—	N/A
RR, *n*; %*	16, 70	—
PP, *n*; %†	3, 13	—
Monophasic, *n*; %	4, 17	—
CIDP subtype‡	—	N/A
CIDP, *n*; %	15, 66	—
CIDP-MGUS, *n*; %	1, 4	—
DADS, *n*; %	3, 13	—
MADSAM, *n*; %	4, 17	—
Treatment response, *n*; %§	21, 91.3	N/A

N/A, not applicable.
*Relapsing-remitting.
†Primary-progressive.
‡MGUS, monoclonal gammopathy of uncertain significance; DADS, distal acquired demyelinating sensory polyneuropathy; MADSAM, multifocal acquired demyelinating sensori-motor polyneuropathy.
§All 23 patients received immunosuppressive or immunomodulatoring treatment, i.e., IVIGs, corticosteroids, azathioprine, and/or mycophenolate mofetil after sample collection for FcγRIIB expression analysis.

separately. No statistically significant differences were detectable in either the frequencies of monocytes (mean percentage of PBMC ± SEM: 7.5 ± 1.5 for CIDP and 5.8 ± 1.0 for HD) or B cells (mean percentage of PBMC ± SEM: 9.0 ± 1.5 for CIDP and 8.5 ± 1.1 for HD) in the peripheral blood or in the distribution of $CD27^-$ (mean percentage of PBMC ± SEM: 85 ± 1.9 for CIDP and 79 ± 3.3 for HD) and $CD27^+$ (mean percentage of PBMC ± SEM: 14 ± 1.8 for CIDP and 19 ± 3.3 for HD) B lymphocytes between patients and healthy volunteers. As seen in Fig. 1*A*, the level of FcγRIIB, as reflected by the mean fluorescence intensity (MFI) staining, was equivalent on $CD14^+$ monocytes in both groups (MFI ± SEM 13.7 ± 1.5 for CIDP and 15.9 ± 2.9 for HD, $P = 0.8$). In contrast, naive and memory B cells from CIDP patients showed significantly lower surface expression of FcγRIIB compared with normal controls (naive B cells MFI ± SEM 102.4 ± 3.7 for CIDP and 132.7 ± 7.0 for HD, $P = 0.002$; memory B cells per plasma cells MFI ± SEM: 111.8 ± 5.5 for CIDP and 170.5 ± 11.5 for HD, $P = 0.0002$).

The reduction in FcγRIIB expression was stronger in the $CD19^+CD27^+$ memory compared with $CD19^+CD27^-$ naive B cell compartment due to a failure of CIDP patients to up-regulate or to maintain up-regulation of FcγRIIB as B cells become memory cells or as a consequence of deregulated apoptotic elimination of $Fc\gamma RIIB^{low}$ vs. $Fc\gamma RIIB^{high}$ cells in CIDP. Whereas all healthy controls showed significantly increased levels of FcγRIIB on memory compared with naive B cells ($P < 0.02$), only 14 out of 23 CIDP patients showed higher FcγRIIB expression levels on memory B cells (Fig. 1*B*) with no statistically significant differences between both B cell compartments. Thus, although the basal level of FcγRIIB expression is unchanged on myeloid cells, naive and memory B cells show decreased expression levels in untreated patients with CIDP.

Induction of FcγRIIB Expression in Memory B Cells in CIDP Patients Responding to IVIG Therapy. IVIG is widely used as a first-line initial and maintenance treatment for CIDP. Several prospective placebo-controlled clinical trials consistently demonstrated that administration of IVIG improves neurologic disability (17–19), and provides long-term benefits to patients with CIDP (7). IVIG is thought to act through several pathways, including complement inactivation and neutralization of idiotypic antibodies (6). Studies in various mouse autoimmune models provided solid evidence that the antiinflammatory activity of IVIG crucially depends on the presence and up-regulation of FcγRIIB (14, 17, 19). Therefore, we determined FcγRIIB expression levels on circulating monocytes and B cells in treatment-naive CIDP patients before and 2–3 weeks after IVIG administration (2-g/kg body weight over 5 days). All patients responded to IVIG treatment as defined by an improvement of disability within 4 weeks after IVIG therapy (2, 20). Compared with baseline levels, IVIG led to a significant up-regulation of FcγRIIB expression on naive B cells in 12/12 patients ($P < 0.0001$), and on memory B cells in 11/12 patients ($P < 0.0001$) (Fig. 2). FcγRIIB expression levels were also induced on monocytes in 9/12 patients ($P < 0.03$)

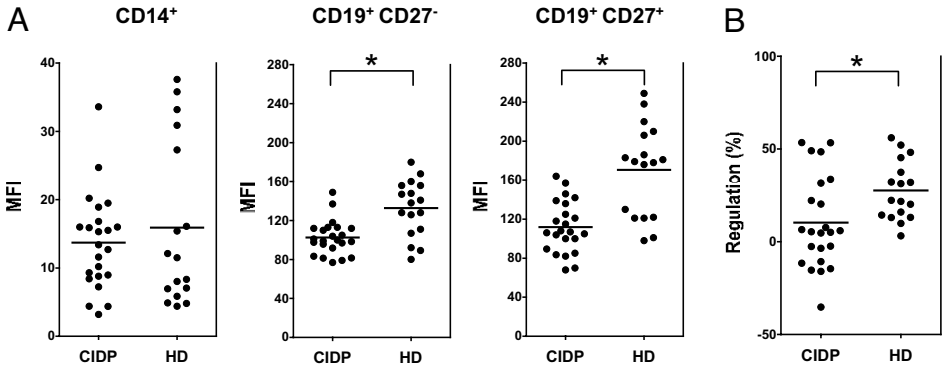

Fig. 1. Decreased level of FcγRIIB expression on B cells in CIDP. PBMCs were stained with monoclonal antibodies specific for CD14, CD19, and CD27, and FcγRIIB compared with an isotype matched control antibody. (*A*) Shown are MFI of FcγRIIB expression levels on monocytes ($CD14^+$), naive B cells ($CD19^+CD27^-$), and memory B cells ($CD19^+CD27^+$) in 23 untreated patients with CIDP and 17 age-matched healthy blood donors after subtracting the MFI from the control antibody. Horizontal lines indicate mean expression values within 1 group. The asterisk indicates a significant difference between 2 groups. There is no difference in FcγRIIB expression on monocytes, but there is decreased expression of FcγRIIB on both naive ($P < 0.002$; Mann–Whitney *U* test) and memory ($P < 0.0002$; Mann–Whitney *U* test) B cell compartments in untreated patients with CIDP. (*B*) Shown are percentage changes in FcγRIIB expression in memory compared with naive B cells in patients with CIDP. In contrast to patients with CIDP, healthy donors show an increase of FcγRIIB expression as B cells progressed from the naive to the memory compartment ($P < 0.02$; Mann–Whitney *U* test).

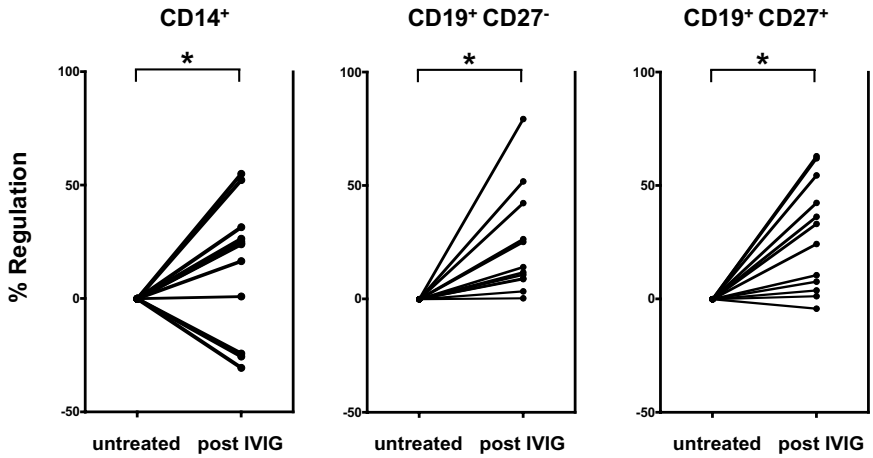

Fig. 2. Up-regulation of FcγRIIB expression in CIDP patients responding to IVIG treatment. FcγRIIB expression was determined in samples taken before and 1–3 weeks after IVIG therapy (2 g/kg body weight) in 12 previously untreated patients with CIDP. Shown are IVIG-induced changes in FcγRIIB expression compared with baseline levels. Clinically effective IVIG therapy led to significant changes in FcγRIIB expression levels in monocytes ($P < 0.03$; Mann Whitney U test), naive B cells ($P < 0.0001$; Mann Whitney U test), and memory B cells ($P < 0.0001$; Mann Whitney U test) in patients with CIDP. Dots represent expression values before and after treatment connected by lines for individual patients, the asterisk indicates a significant difference.

after IVIG therapy. These data indicate that the impaired expression of the inhibitory FcγRIIB in CIDP can, at least partially, be restored by clinically effective IVIG treatment.

Increased Frequency of the −386C/−120A FcγRIIB Promotor Variant in CIDP. To gain an insight into the possible mechanism of dysregulated FcγRIIB expression, we next investigated whether CIDP patients show increased frequencies of functionally relevant SNPs in the FcγRIIB promoter that have previously been associated with autoimmune phenotypes, i.e., SLE (9, 21–23). These polymorphisms are located at −386 or −120 base pairs upstream of the first exon of FcγRIIB and form 2 distinct haplotypes (Fig. 3*A*). The majority of the Caucasian healthy population (> 90%) carries a guanine residue at position −386 (−386G) and a thymidine residue at position −120 (−120T), whereas <10% carry the −386C/−120A variant (21). However, the latter haplotype is overrepresented in Caucasian patients with SLE (14.4% in SLE patients vs. 9.4% in controls according to ref. 21), and SLE patients homozygous for this allelic variant show reduced FcγRIIB surface expression levels on activated B cells (23). An additional nonsynonymous polymorphism in the transmembrane domain of FcγRIIB, in which an isoleucine residue in the transmembrane domain is replaced by a threonine residue (I232T), is also enriched in SLE patients from Asian populations (24), and might also be overrepresented in Caucasian patients with SLE.

We found that none of the patients and <5% of healthy controls (1/26) tested for FcγRIIB promotor SNPs were homozygous for the rare −386C/−120A haplotype. In contrast, 43% of CIDP patients (6/14), but, again, <5% of the healthy

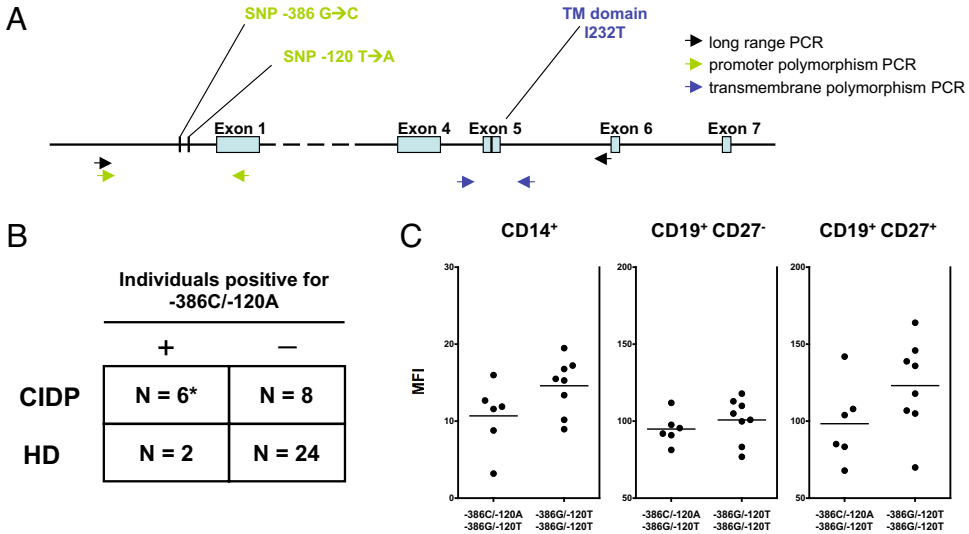

Fig. 3. Increased frequency of the −386C/−120A FcγRIIB promotor polymorphism in CIDP. (*A*) Schematic representation of the FcγRIIB gene and promoter region including the primer sites used for determination of the SNPs in the FcγRIIB promoter region and in the region encoding the transmembrane domain. (*B*) SNPs were determined in 14 patients with CIDP and 26 healthy controls. None of the patients and <5% of healthy controls (1/26) tested for FcγRIIB promoter SNPs were homozygous for the rare −386C/−120A haplotype. In contrast, 43% of CIDP patients (6/14), but <5% (1/26) of the healthy controls were heterozygous for the −386C/−120A variant (*, $P < 0.02$ for comparing −386C/−120A frequencies between patients and controls; Fisher's exact test). (*C*) FcγRIIB surface expression tended to be lower in patients heterozygous for the −386C/−120A variant ($n = 6$), but the overall difference was not statistically significant compared with patients homozygous for the 386G/−120T haplotype ($n = 8$). Horizontal lines represent mean expression values.

controls (1/26) were heterozygous for the −386C/−120A variant (Fig. 3*B*) ($P < 0.02$ for comparing −386C/−120A frequencies between patients and controls). FcγRIIB surface expression tended to be lower in patients carrying this promotor variant, although the overall difference was not statistically significant compared with patients homozygous for the 386G/−120T haplotype (Fig. 3*C*). However, the latter result is based on a limited number of patients and clearly requires further investigation in larger cohorts of patients carrying this polymorphism. We did not detect any differences in frequencies of homozygous or heterozygous I232T carriers between patients (3/14) and controls (4/26). Due to the small sample size of our study and the rarity of this polymorphism, further studies will be necessary to investigate a possible disease association of this allele. Altogether, these data suggest that heterozygous −386C/−120A carriers are overrepresented in patients with CIDP.

Discussion

Our study provides evidence for a selective dysregulation of the inhibitory FcγRIIB on B cells in CIDP, the most common treatable acquired chronic polyneuropathy. Untreated patients with CIDP show lower FcγRIIB expression levels on naive B cells, and failed to up-regulate or to maintain FcγRIIB as B cells progressed from the naive to the memory compartment. Moreover, functionally relevant FcγRIIB promotor polymorphisms that were previously associated with the development or severity of SLE and lead to a decreased expression of this receptor were enriched in CIDP patients (9, 12). Moreover, we found that clinically effective IVIG treatment induces FcγRIIB expression. These data suggest that FcγRIIB may play a pivotal role in the pathogenesis of CIDP.

By using either ubiquitous or B cell specific overexpression of the inhibitory FcγRIIB, it was demonstrated that increasing the threshold for B cell activation is sufficient to ameliorate autoimmune disease in SLE prone mouse strains, such as NZM and BXSB, and in induced models of autoimmune disease such as collagen induced arthritis (CIA) (25, 26). Also, it was suggested that the antiinflammatory activity of IVIG essentially depended on the presence or up-regulation of the inhibitory FcγRIIB. Animals deficient in FcγRIIB are no longer protected by IVIG in models of immune thrombocytopenic purpura, rheumatoid arthritis, and nephrotoxic nephritis (13–16). In addition, IVIG administration resulted in an up-regulation of FcγRIIB surface expression on effector macrophages or the enhanced recruitment of FcγRIIB positive myeloid cells at the site of inflammation in vivo (13–15). Consistent with these observations, FcγRIIB was up-regulated on circulating B cells and monocytes in patients responding to IVIG treatment, indicating that IVIG might also work by increasing the FcγRIIB expression level in humans. These data suggest that FcγRIIB expression mediates immunomodulatory effects of IVIG by raising the activation threshold for B lineage and myeloid cells. Within the inflamed peripheral nerve, recruitment of FcγRIIB expressing monocytes and induction of FcγRIIB expression in resident myeloid cells might additionally contribute to the beneficial effects of IVIG, because macrophages are main local effector cells in CIDP (4, 27, 28). These data provide evidence that the observations obtained in murine model systems with respect to the mechanism of IVIG activity in vivo might be transferable to humans.

In addition to our protein expression analysis, we could show that a certain FcγRIIB promoter haplotype, for which an association with the development and severity of SLE in humans has been previously reported (21–23), was significantly enriched in CIDP patients. The −386 GC haplotype (sometimes also referred to as the 343 haplotype; see refs. 22, 23) shows a particular strong association with human SLE. Recent studies suggest that this polymorphism leads to the displacement of activating transcription factors, such as AP1, by other transcriptional regulators; thus, offering a potential explanation for the lower expression level of FcγRIIB (22). Although we did not find homozygous CIDP patients for this SNP, one functionally impaired allele of FcγRIIB might be sufficient to result in a decreased expression level or functionally impaired regulation of expression during B cell development. However, not all patients carried this promoter variant, suggesting that other additional factors might be involved in the deregulated expression of the inhibitory FcγRIIB. Also, given the low allelic frequencies of FcγRIIB polymorphisms, many patients and controls need to be analyzed to allow definite conclusions on frequencies of FcγRIIB allelic variants such as CA promoter polymorphism and their impact for FcγRIIB expression levels and B cell function in CIDP.

In conclusion, we identified a deficiency in CIDP patients in the expression of a specific inhibitory receptor known to have a role in peripheral tolerance in antigen-activated B cells. Because IVIG, which up-regulates and acts through FcγRIIB expression, is an effective first-line initial and maintenance treatment for this autoimmune disease, previously undescribed strategies specifically targeting FcγRIIB (29) might have therapeutic merit in CIDP.

Materials and Methods

Patients and Healthy Blood Donors. Twenty-three untreated patients with CIDP fulfilling both the modified AAN and the EFNS/PNS diagnostic guidelines (2, 3, 30), and 26 demographically matched healthy blood donors were included in this study (Table 1). FcγRIIB expression on circulating blood cells was determined in all patients and compared with 17 matched controls; 12 patients were followed longitudinally to investigate FcγRIIB expression expression levels before and 2–3 weeks after IVIG treatment (2-g/kg body weight). All of these patients showed a clinical response to IVIG as defined by an improvement of disability, as assessed by the modified Rankin disability scale (2, 20), within 4 weeks after IVIG treatment. FcγRIIB genotyping was performed in 14 patients and 26 healthy controls. Patients and healthy blood donors were recruited from the Department of Neurology at the Phillips University of Marburg. The study was approved by the local Institutional Review Board, and all subjects provided informed consent.

Antibodies and Flow Cytometry. The mAb 2B6 that selectively recognizes the inhibitory FcγRIIB as shown in prior studies by ELISA, surface plasmon resonance, and FACS staining of cell lines and transfectants (12) was coupled to Alexa Fluor 647. An IgG1 isotype control-APC antibody (clone MOPC-21) as well as CD14-Pacific Blue (clone M5E2), CD19-FITC (clone HIB19), CD27-PE (clone M-T271), and CD138-PerCPCy5.5 (clone MI15) antibodies were purchased from BD Bioscience. Paired prae-IVIG and post-IVIG samples from patients with CIDP were analyzed at a later time point and on a different LSR II flow cytometer than paired samples form patients and healthy donors. To display the data in a more comparable format, we analyzed and display relative changes in FcγRIIB expression in memory compared with naive B cells (Fig. 1*B*), and after IVIG treatment compared with baseline levels (Fig. 2) instead of MFI values. Peripheral blood mononuclear cells (PBMCs) were purified from whole blood by density gradient centrifugation by using Ficoll-Hypaque. 2×10^6 PBMCs were incubated with the indicated mAbs for 45 min on ice. Cells were washed twice with PBS and resuspended in 200 μL FACS buffer (0.01% sodium azide in PBS) before FACS analysis. The PBMC samples were analyzed on an LSR II flow cytometer gating on PBMC excluding cell duplets based on size and monocytes and B cells on being $CD14^+$ or $CD19^+$ cells, and within the B cell population on being $CD27^-$ and $CD27^+$ populations. FcγRIIb was expressed on $CD19^+$ $CD138^+$ plasma cells, but the low frequency of $CD138^+$ cells (< 1% of circulating B cells) precluded a thorough evaluation of FcγRIIb expression levels on plasma cells. Cell duplets were excluded based on size. Gating and calculations for precursor frequencies were performed with FlowJo (Tree Star) software.

FcγRIIB Genotyping. Due to the high sequence homology between FcγRIIB, FcγRIIA, and FcγRIIC, we used a 2 step PCR protocol to specifically amplify FcγRIIB as described before (21). Briefly, a long-range PCR was performed initially with a set of FcγRIIB specific primers and by using the Qiagen LongRange PCR Kit. The amplified 15-kb PCR product was gel-purified (Qiagen Gel purification Kit) and used as template for the nested PCR to amplify the

promoter region with primers as published before. Last, the 2-kb PCR product was sequenced to determine any polymorphisms in the promoter sequence. To analyze the allelic variant with the amino acid exchange in the transmembrane domain (I232T variant), the nested PCR was performed with a set of primers that amplified this region. The sense (5′-cctgcctgctcacaaatgta-3′) and antisense primers (5′-cactgctctccccaagac-3′) were chosen to flank the polymorphism in intron 5. As before, the resulting 750-bp PCR product was gel purified and sequenced.

Statistics. Statistical analyses were performed by using commercial software (PRISM 4, GraphPad). FcγRIIB expression levels and frequencies of circulating monocytes and B cells in MS patients and healthy donors were compared by using the nonparametric Mann–Whitney *U* rank sum test. FcγRIIB haplotype frequencies were compared by using Fisher's exact test.

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