

FcεRIα gene –18483A>C polymorphism affects transcriptional activity through YY1 binding

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Abstract Three frequent genetic polymorphisms in the human high-affinity IgE receptor α -subunit (Fc ϵ RI α) were shown to be associated with allergic disorders and/or total serum IgE levels in allergic patients. Two of these were previously demonstrated to affect Fc ϵ RI α expression while the third –18483A>C (rs2494262) has not yet been subjected to functional studies. We hypothesized that the –18483A>C variant affects transcriptional activity of the Fc ϵ RI α distal promoter in monocytes in which Fc ϵ RI α transcription is driven through that regulatory region.

Indeed, we confirmed preferential binding of the YY1 transcription factor to the –18483C allele, resulting in lower transcriptional activity when compared with the –18483A allele.

Keywords Fc ϵ RI α · Monocytes · Polymorphism · YY1 · *FCER1A*

Considering the crucial role of the human high-affinity IgE receptor (Fc ϵ RI; Zhang et al. 2007), it is not surprising that

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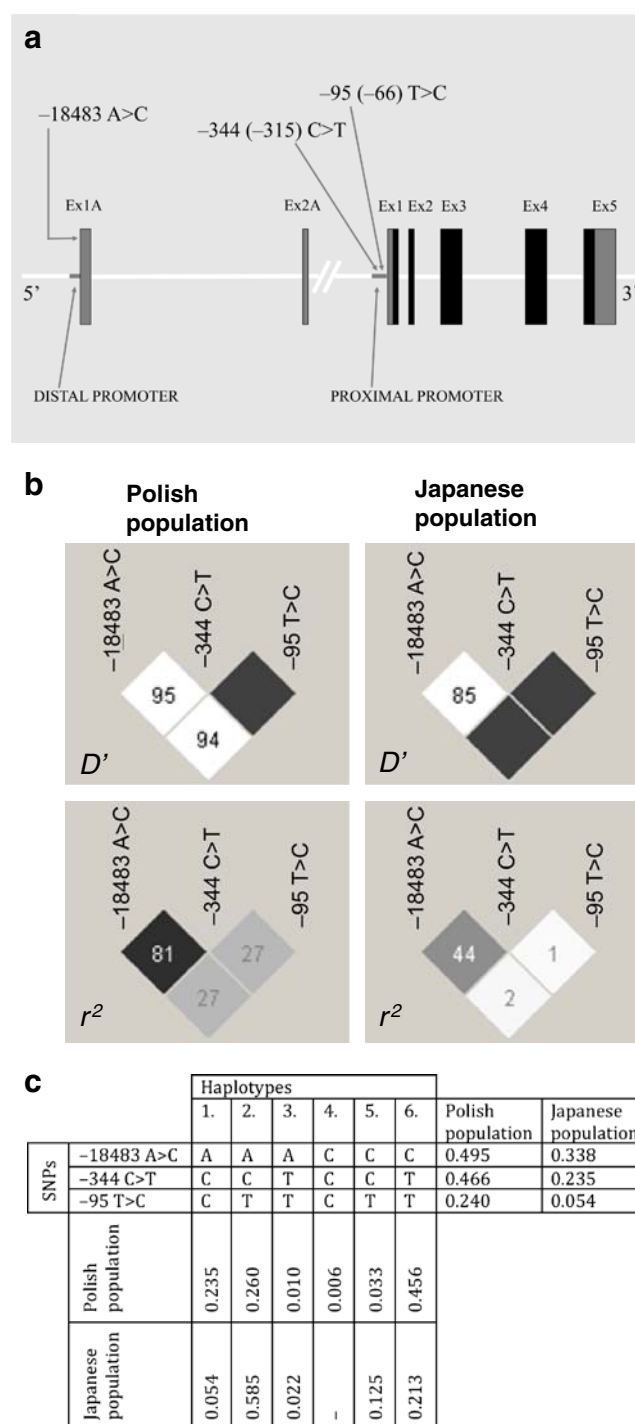
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Fig. 1 Human high-affinity IgE receptor α -subunit (*FcεRIα*) gene – 18483A>C, –344C>T, and –95T>C polymorphisms. **a** Coverage of *FcεRIα* gene by the three polymorphisms. **b** Linkage disequilibrium data between the three *FcεRIα* polymorphisms in Poles ($n=104$) and Japanese ($n=102$). D' values are plotted on the results of four game test (cutoff value=0.0). D' is expressed as a percentage of maximal value (1.0). Squares without numbers correspond to $D'=1.0$. White boxes indicate four possible two-marker haplotypes, whereas black boxes correspond to $\leq$ three pairwise gametes. On the r^2 value plot, numbers represent r^2 values expressed as a percentage of maximal value (1.0). Squares without numbers correspond to $r^2=1.0$. Shading represents r^2 magnitude with a black-to-white gradient reflecting higher-to-lower r^2 values. **c** Three *FcεRIα* polymorphisms and their haplotypes in Poles ($n=104$) and Japanese ($n=102$). Minor allele frequencies of polymorphisms and proportions of haplotypes are given. SNP denotes single-nucleotide polymorphism

FcεRI α-subunit (*FcεRIα*) gene variability was recently studied in the context of allergies and allergic disorders. *FcεRIα* –344(–315)¹ C>T (rs2427827) polymorphism was found to be associated with aspirin-induced urticaria (Bae et al. 2007) and with total serum IgE levels in different groups of allergic subjects (Shikanai et al. 2002; Potaczek et al. 2006, 2007a, 2007b; Bae et al. 2007). Its close genomic neighbor, *FcεRIα* proximal promoter –95(–66)¹ T>C (rs2251746) polymorphism, was shown to be associated with atopic dermatitis (Hasegawa et al. 2003b). Both of these frequent polymorphisms were demonstrated to strongly affect *FcεRIα* expression in mast cells and/or basophils in an additive manner (Hasegawa et al. 2003b; Bae et al. 2007; Kanada et al. 2008), thus providing a partial mechanistic background for the genetic associations described above. In addition, the frequent –18483A>C (rs2494262) polymorphism was also found to be associated with total serum IgE levels in allergic subjects (Potaczek et al. 2007a, 2007b); however, no functional studies on that genetic variant have been conducted to date. Here, we report the results of functional analysis of *FcεRIα* –18483A>C polymorphism.

The *FcεRIα* gene is composed of five coding exons, spanning about 6 kbp, directly preceded by the proximal promoter while two additional untranslated exons (1A and 2A) are localized further upstream (about 12 and 18 kbp, respectively; Nishiyama et al. 2001) and are under transcriptional regulation of the distal promoter (Hasegawa et al. 2003a; Fig. 1a). In contrast to basophils and/or mast cells, in which the proximal promoter strongly works with the GATA-1/PU.1 transcription factor-dependent activating mechanism, in monocytes, transcription of *FcεRIα* is also driven by the distal promoter (Hasegawa et al. 2003a). Hence, in monocytes, any potential effects of –18483A>C



single-nucleotide polymorphism (SNP) on *FcεRIα* expression through the distal promoter would not be easily masked by strong activity of the proximal promoter and the potent effects of –95T>C and/or –344C>T proximal promoter polymorphisms (Hasegawa et al. 2003b; Bae et al. 2007; Kanada et al. 2008).

Coverage of the *FcεRIα* gene by the –18483A>C, –344C>T, and –95T>C polymorphisms is shown in Fig. 1a. Linkage disequilibrium (LD) data between *FcεRIα*

¹ Polymorphisms in the present study are numbered according to the translation start site; –95T>C and –344C>T polymorphisms were also numbered according to the *FcεRIα* gene proximal promoter transcription start site as –66T>C and –315C>T, respectively (Hasegawa et al. 2003b; Kanada et al. 2008).

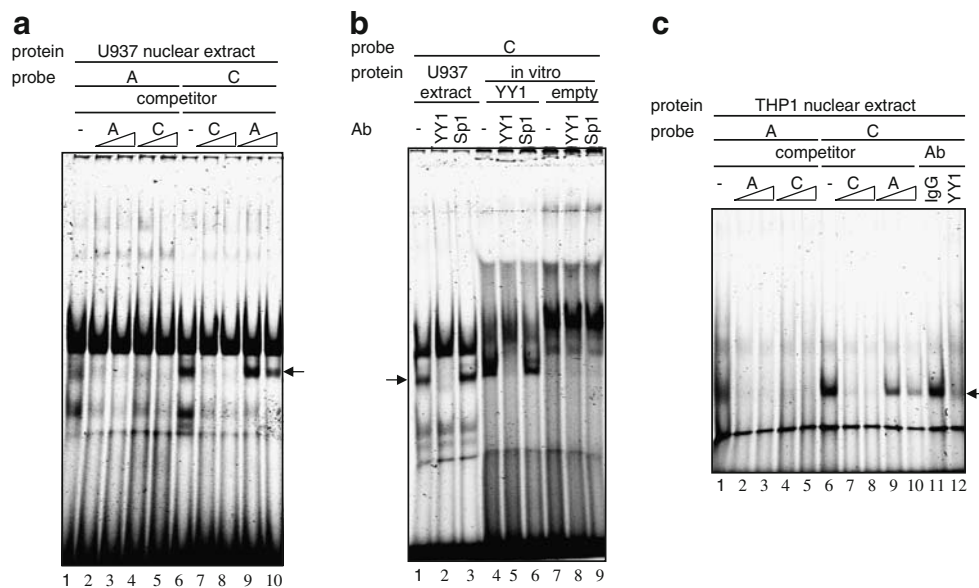


Fig. 2 Effect of human high-affinity IgE receptor α -subunit (*FcεRIα*) gene -18483A>C polymorphism on transcription factor binding on electrophoretic mobility shift assay (EMSA). **a** Effects of -18483A>C polymorphism on EMSA profile and preferential -18483C allele protein binding in U937 cells. EMSA was performed with FITC-labeled -18494/-18471 double-stranded oligonucleotide probes carrying -18483A allele (lane 1) or -18483C allele (lane 6) and nuclear extracts from U937. For competition assay, 25- or 50-fold levels of -18483A (lanes 2, 3, 9, and 10) or -18483C (lanes 4, 5, 7, and 8) competitors were used. Specific bands are indicated with by arrowheads. **b** Identification of protein preferentially binding to -18483C allele. A mixture of -18483C probe and nuclear extract from U937 was applied into wells 1–3 after addition of each antibody (Ab). Lane 1 without Ab, lane 2 with anti-YY1 Ab, lane 3 with irrelevant anti-

Sp1 (control) Ab. Specific bands are indicated by arrowheads. Binding of in vitro-translated YY1 to the -18483C probe (lanes 4–9). The -18483C probe was mixed with in vitro-translated YY1 (lanes 4–6) or with in vitro transcription/translation mixture without template cDNA (lanes 7–9). Lanes 4 and 7 without Ab, lanes 5 and 8 with anti-YY1 Ab, lanes 6 and 9 with irrelevant anti-Sp1 (control) Ab. **c** Effects of -18483A>C polymorphism on EMSA profile and preferential -18483C allele protein binding in THP-1 cells (lanes 1–10). Lanes 1–10 identical description as for the left panel, except for the usage of THP-1 nuclear extracts instead of those obtained from U937 cells. Identification of protein preferentially binding to -18483C allele in THP-1 (lanes 11 and 12). Lane 11 with IgG isotype control Ab, lane 12 with anti-YY1 Ab

-18483A>C, -344C>T, and -95T>C SNPs, estimated in representative population groups of Polish Caucasians ($n=104$) and Japanese East Asians ($n=102$), are presented Fig. 1b while the allelic frequencies and the distribution of haplotypes of the three *FcεRIα* polymorphisms are given

in Fig. 1c. In all cases, three pairwise haplotypes of -18483A>C, -344C>T, and -95T>C polymorphisms account for 97.7–100.0% of all haplotypes (Fig. 1c). In addition, all of the pairwise D' values are high, ranging from 0.85–1.0 (Fig. 1b). Therefore, it can be assumed that

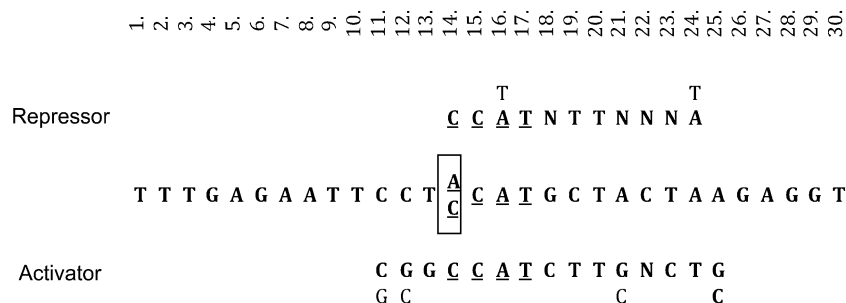


Fig. 3 Genomic neighborhood of -18483A>C polymorphism (-18470/-18499) aligned with YY1 consensus binding sequences as described by Shrivastava and Calame (1994). Nucleotides are numbered 1 to 30 for the purposes of the present figure only. If the -18483C allele is present, the sequence almost perfectly correlates with the YY1 consensus repressor binding motif (Shrivastava and Calame 1994). C in position 19 of the genomic sequence does not fit T in the consensus motif;

however, the consensus rate for T in that position is 72%, and C can be present in the YY1 binding repressor site (Shrivastava and Calame 1994). Nucleotides corresponding to the core of the YY1 binding motif are underlined (Javahery et al. 1994). Replacement of first the C in the core motif with A (position 14), corresponding to the -18483C→A substitution, leads to a 3- to 4-fold reduction in YY1 binding (Javahery et al. 1994)

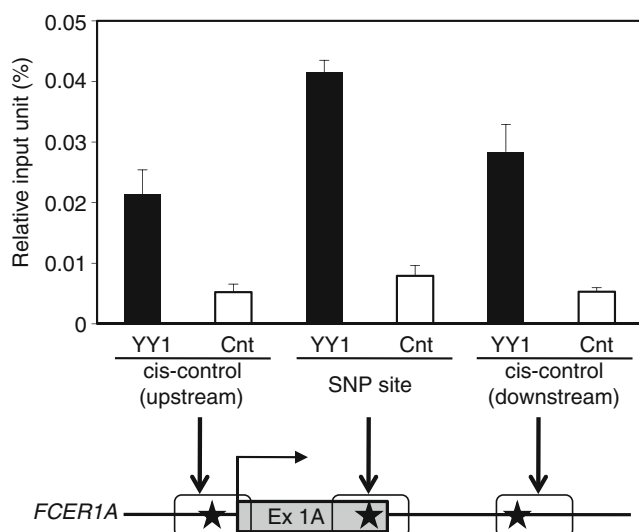


Fig. 4 In vivo binding of YY1 around the human high-affinity IgE receptor α -subunit (*FcεRIα*) gene (*FCER1A*) -18483C allele in U937 cells having the -18483CC genotype. The amount of exon 1A region (-18546/-18435) immunoprecipitated with anti-YY1 antibody (Ab) was quantitatively analyzed by chromatin immunoprecipitation assay. Two regions upstream (-18901/-18753) and downstream (-18117/-18015) were also analyzed. *Black stars* in the schematic drawing of *FCER1A* gene represent the locations of identified YY1-binding sequences in previous studies [upstream (Hasegawa et al. 2003a) and downstream (Nishiyama et al. 2001)] and in the present study (SNP). The results are expressed as means +SEM for three real-time PCRs with duplicate samples. Similar results were observed in an additional independent experiment. *Closed bars* specific YY1 Ab, *open bars* control Ab (Cnt)

there were no past pairwise recombination events (-344C>T|-95T>C in Poles and Japanese and -18483A>C|-95T>C in Japanese) or that their rates were low (-18483A>C|-344C>T in Poles and Japanese and -18483A>C|-95T>C in Poles). As a result, only four three-loci haplotypes account for 98.4% and 97.7% of all three-locus haplotypes in Poles and Japanese, respectively (Fig. 1b, c).

In most cases, high D' values are not, however, accompanied by r^2 values of a similar magnitude, which reflects the substantial pairwise differences in allelic frequencies between *FcεRIα* SNPs particularly for pairs including the -95T>C SNP in Japanese (Fig. 1b, c). One exception is the r^2 value for the -18483A>C|-344C>T pair in Poles, although this is diminished by the presence of recombinant haplotype -18483A|-344 T (1.0%), despite the pairwise difference in allelic frequencies between -18483A>C and -344C>T SNPs in that ethnic group being relatively small. Nevertheless, in both Caucasians and East Asians, the genomic relationships between the three *FcεRIα* SNPs are close as reflected by the distribution of haplotypes and high D' values.

The *FcεRIα* -18483A>C, -344C>T, and -95T>C SNPs were genotyped by the polymerase chain reaction-restriction fragment length polymorphism method, the

details of which can be found in the [Supplementary Materials](#). The structure and distribution of haplotypes were analyzed using Thesias_3.1 software (http://genecanvas.ecgene.net/uploads/Thesias_Java_interface/) (Tregouet and Garelle 2007) while measures of LD were estimated using Haploview_4.0 software (<http://www.broad.mit.edu/haploview/haploview-downloads>; Barrett et al. 2005).

We speculated that the *FcεRIα* -18483A>C polymorphism affects the transcriptional activity of the distal promoter localized immediately upstream (Nishiyama et al. 2001; Hasegawa et al. 2003a). To verify our hypothesis, we examined the potential of the -18483A>C polymorphism to affect the binding of transcription factors using electrophoretic mobility shift assay (EMSA) as described previously (Kanada et al. 2008; Fig. 2). Oligonucleotides, antibodies, and basic vectors used in the present study are shown in [Supplementary Materials](#).

EMSA conducted using nuclear extracts from human monocytic U937 cells with competitive oligonucleotides showed preferential binding of nuclear protein(s) to the -18483C allele (Fig. 2a). Thus, we analyzed the sequence surrounding the -18483C allele and noted that it almost perfectly matched the YY1 binding consensus repressive motif while its homology to the consensus YY1 activating site was comparatively low (Shrivastava and Calame 1994; Fig. 3). Indeed, subsequent EMSA with specific antibodies confirmed that the transcription factor binding to -18483C allele was YY1 (Fig. 2b), which was further confirmed using in vitro translated YY1 protein (Fig. 2b) obtained as described previously (Hasegawa et al. 2003a; Kanada et al. 2008). Similar results were obtained using nuclear extracts from human monocytic THP-1 cells (Fig. 2c).

In order to confirm YY1 binding in vivo, we performed chromatin immunoprecipitation (ChIP) assay as described previously (Wang et al. 2008). ChIP assay was conducted using U937 cells confirmed by direct sequencing (Potaczek et al. 2008) to possess -18483CC (Fig. 4). Significantly larger amounts of chromosomal DNA around -18483 were immunoprecipitated by YY1 antibody (Ab) as compared with control Ab, which demonstrated the occurrence of YY1 binding around the -18483C allele in vivo (Fig. 4, center). Although two *cis*-control regions at ~350 bp upstream (Fig. 4, left) and downstream (Fig. 4, right) exhibited significant binding with YY1, possibly due to the presence of YY1-bindable sequences (marked with stars; Nishiyama et al. 2001; Hasegawa et al. 2003a), the SNP site showed the highest amount, thus suggesting that detection of the SNP site was not dependent on YY1 binding to the YY1 sequences in the distal promoter and in intron 1A. One cannot, however, exclude the possibility that some of the SNP site detection was derived from the fragments containing binding motifs in the distal promoter or intron 1A.

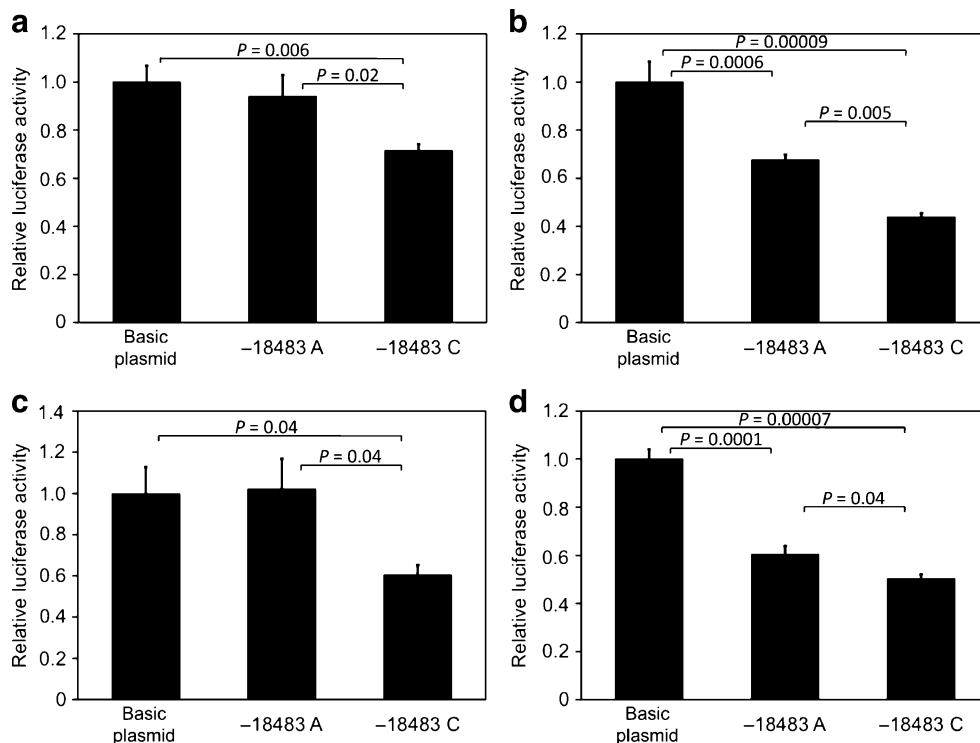


Fig. 5 Effects of *FcεRIα* gene -18483A>C polymorphism on transcriptional activity analyzed by luciferase assay using pGL4.23 [*luc2*/miniP]-based constructs in human monocytic THP-1 cells (**a**), human basophilic KU812 cells (**b**), rat basophilic RBL-2H3 cells (**c**), and mouse mastocytic PT18 cells (**d**). Triple motif CCT(A/C)CATGCTACTAAG (-18486/-18471), containing the -18483A>C polymorphism within its genomic neighborhood, was cloned upstream of the minimal promoter of pGL4.23 [*luc2*/miniP] plasmid. *Basic*

plasmid denotes the pGL4.23 [*luc2*/miniP] vector with no genomic insert. Relative luciferase activity is represented as the ratio of activity to that of the basic pGL4.23 [*luc2*/miniP] plasmid. The results are expressed as means +SEM for four (**a**), three (**d**), or two (**b**, **c**) independent experimental series conducted in triplicate. One-way ANOVA followed by post hoc Duncan's test was used for comparisons. Only significant results ($P < 0.05$) on post hoc testing are shown

Next, we examined the potential effects of -18483A>C substitution on transcriptional activity by performing luciferase reporter assay as described previously (Kanada et al. 2008; Wang et al. 2008). We used tandem repeated constructs based on the pGL4.23 [*luc2*/miniP] plasmid to evaluate the effect of this SNP on transcriptional activity. Briefly, triple motif CCT(A/C)CATGCTACTAAG (-18486/-18471), containing the -18483A>C polymorphism within its genomic neighborhood and covering in length for repressive or activator YY1 consensus binding sites (Shrivastava and Calame 1994), was *XhoI/HindIII* subcloned upstream of the minimal promoter of pGL4.23 [*luc2*/miniP] plasmid. In human monocytic THP-1 cells, the luciferase activity of the -18483C allele-specific construct was significantly lower when compared with that of both the -18483A allele-specific construct and the basic (containing no genomic insert) plasmid (Fig. 5a).

Confirmatory analyses were conducted in human basophilic KU812 cells (Fig. 5b), rat basophilic RBL-2H3 cells (Fig. 5c), and mouse mastocytic PT18 cells (Fig. 5d). In all cases, reporter activity of the -18483C allele-specific vector

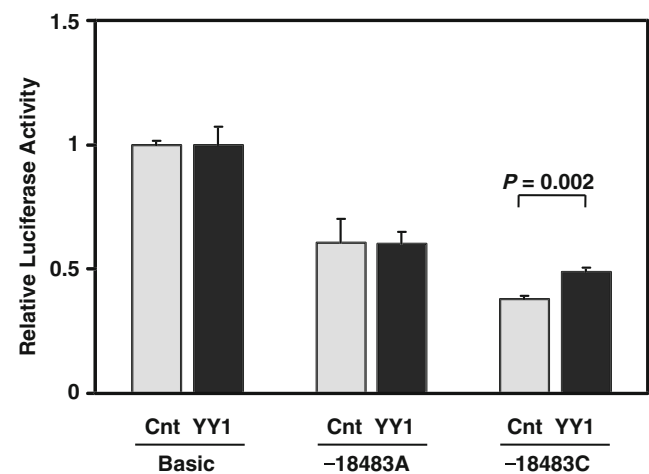


Fig. 6 Effects of YY1 siRNA on -18483C allele-mediated transcriptional suppression. Each reporter plasmid of pGL4.23-based series was introduced with YY1 siRNA or control siRNA using Nucleofector II. YY1 siRNA significantly upregulated C-allele vector-driven activity ($P < 0.005$ on unpaired Student's *t* test). Significant differences between the A-allele (Cnt) and C-allele (Cnt; $P < 0.025$ on post hoc Duncan's test) were eliminated by YY1 siRNA treatment [$P = 0.18$ between A-allele (YY1) and C-allele (YY1)]

was significantly lower when compared with that of both the -18483A allele-specific construct and the basic plasmid (Fig. 5b–d). In KU812 and PT18 cells, the luciferase activity of the -18483A allele-specific vector was also lower when compared with that of the basic plasmid (Fig. 5b, d). If the C allele is present in the -18483 locus, the nucleotide sequence surrounding the -18483A>C polymorphism possesses strong homology with the YY1 recognition repressor sequence (Shrivastava and Calame 1994) while replacement of C by A in the core YY1 binding motif, corresponding to replacement of the -18483C allele by the -18483A variant, results in a 3–4-fold reduction in YY1 binding (Javahery et al. 1994; Fig. 3). Therefore, YY1 binding to the -18483C allele would be expected to result in a lower transcription rate when compared with the -18483A allele. Indeed, in all four cell lines, the luciferase activity of the -18483C allele-specific vector was lower when compared with both the -18483A allele-specific and basic vectors (Fig. 5a–d).

In the case of KU812 and PT18 cells, -18483A allele-specific constructs also demonstrated lower luciferase activity when compared with the basic vector (Fig. 5b, d). This may be explained by low-affinity binding of the YY1 transcription factor to the -18483A allele, which could be also observed in EMSA (Fig. 2a, c), resulting in a repressive effect on transcriptional activity in some cells. Nevertheless, in all the cases, luciferase activity of -18483C allele-specific constructs was lower than that of -18483A allele-specific vectors (Fig. 5a–d). Although the -18483A>C polymorphism is located downstream of the distal promoter transcription start site, it would not be surprising that binding of YY1 downstream of the transcription initiation site can affect gene expression (Griffioen et al. 2000).

Finally, in order to confirm the effects of YY1 on -18483C allele-mediated transcriptional suppression, reporter assay was performed under YY1 knockdown conditions. Briefly, YY1 siRNA or control siRNA was introduced into THP-1 cells with a reporter plasmid using Nucleofector II (Amaxa, Cologne, Germany) as described previously (Maeda et al. 2006). As shown in Fig. 6, luciferase activity driven by a plasmid carrying the C allele was significantly upregulated by the introduction of YY1 siRNA, whereas the other two promoters, basic and carrying the A allele, were not affected by YY1 siRNA, thus suggesting that transcriptional suppression depending on the C allele at the -18483 locus is regulated by YY1.

YY1 was previously reported to be involved in regulation of several important allergy-related genes. Briefly, Silverman et al. (2004) demonstrated that, being associated with variant YY1 binding and thus altering transcriptional activity, the -509C>T polymorphism of transforming growth factor- β_1 was associated with asthma. Guo et al. (2001) and Mordvinov et al. (1999) showed that YY1 transcription factor regulates T cell cytokine gene expres-

sion and allergic immune responses. Finally, some members of our group demonstrated the involvement of YY1 in transcriptional regulation of Fc ϵ RI subunit expression. Briefly, variant YY1 factor binding to Fc ϵ RI β -subunit (Fc ϵ RI β) -654C>T polymorphism was shown to affect its expression (Nishiyama et al. 2004). Moreover, YY1 was demonstrated to contribute to the regulation of Fc ϵ RI α transcription through proximal and distal promoters (Nishiyama et al. 2001, 2002; Hasegawa et al. 2003a).

In summary, we demonstrated preferential binding of YY1 to the Fc ϵ RI α gene -18483C allele resulting in lower transcriptional activity. The differences in transcriptional activity between -18483C and -18483A alleles are not apparently striking, but they may potentially be of some biological importance in monocytes in which the potential effect of -18483A>C variant on the distal promoter would not be easily masked by strong activity of the proximal promoter (Hasegawa et al. 2003a) and/or potent influences of -344C>T/-95T>C polymorphisms (Hasegawa et al. 2003b; Bae et al. 2007; Kanada et al. 2008). The associations between Fc ϵ RI α polymorphism and serum IgE levels and/or allergic disorders (Shikanai et al. 2002; Hasegawa et al. 2003b; Potaczek et al. 2006, 2007a, 2007b; Bae et al. 2007) may result from haplotypic interplay between functional (Hasegawa et al. 2003b; Bae et al. 2007; Kanada et al. 2008) -344C>T, -95T>C, and -18483A>C polymorphisms. A hypothetical mechanism by which alterations in Fc ϵ RI(α) expression could affect IgE synthesis/levels remains unknown. Therefore, further functional studies focusing on this issue are necessary.

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