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ORIGINAL ARTICLE

A constitutional variant in the transcription factor *EP300* strongly influences the clinical outcome of patients submitted to allo-SCT

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An adequate response of the innate immune system after allo-SCT is crucial for the clinical outcome of patients submitted to this procedure. *EP300* is one of the key genes of the innate immune system (IIS). We evaluated the influence of gene variant A>G rs20551 in *EP300* in donor and/or recipient on clinical results after HLA-identical sibling allo-SCT. Patients with AA gene variant had a lower relapse incidence (31 vs 48%, $P=0.025$; odds ratio (OR) = 1.6, $P=0.05$), attained better disease-free survival (AA: 53% vs AG + GG: 24%, $P=0.001$; OR = 1.8, $P=0.01$), and better OS (AA: 53% vs AG + GG: 34%, $P=0.001$; OR = 1.9, $P=0.007$). This beneficial association was more evident when AA gene variant was present in both donor and patient. In healthy individuals, AA gene variant was associated with lower IL2 production after a mitogenic stimuli, higher CD4+ cell response after CMV infection, and higher expression of innate immune genes (*IRF-3* and *MIF)*, cell cycle genes (*AURKB, CCNA*2 and *CCNB1*), lymphocyte survival genes (*NFAT5* and *SLC38A2*), and with a lower expression of *P53* compared with recessive GG gene variant. These findings suggest a beneficial effect of the AA gene variant in rs20551 on clinical outcome after allo-SCT.

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INTRODUCTION

Allo-SCT is increasingly used for treating patients with hematological malignancies. Despite considerable progress in the management of infections, in more stringent criteria for HLA compatibility, in the use of new immunosuppressive drugs and in tailored conditioning regimens, allo-SCT is still associated with a considerable morbidity and mortality.[1] Owing to biological reactions leading to GVHD, to GVL and to immune defense against infections, the cells of the innate immune system are crucial in the success of allo-SCT.[2]

HLA compatibility remains the central means of selecting donor and patient pairs. However, an increasing number of studies show the importance of non-HLA genetic characteristics that influence individual responses to infection and to malignant cells. Thus, we and others have previously shown that variants of genes of the innate immune system, such as *IL-6,*[3] *IL-1*,[4] *NLRP2* and *NLRP3*,[5] *NOD2/CARD15*,[6,7] *MBL,*[8] TLRs,[9–13] *TGF-ß*[14] and *MIF* [15] may influence the clinical outcome of allo-SCT. No single study has analyzed the clinical impact of gene variants in *EP300,* despite the fact that it is one of the key regulators of the innate immune system. EP300 acts as a transcriptional coactivator, which possesses intrinsic histone acetyltransferase activity. *EP300* is also involved in controlling viral infection by interacting with *IRF-3* to activate IFN transcription, and also has an important role in hematopoietic stem cell proliferation and differentiation.[16,17]

Owing to the importance of *EP300* in the regulation of the innate immune response and in the cell proliferation, we aimed in this study to examine–in both donor and recipient–the most prevalent single nucleotide polymorphism (SNP) in *EP300* (rs20551) with HLA-identical allo-SCT clinical outcome, and the functional impact of this variant on the inflammatory response.

PATIENTS AND METHODS

Patients

Patients were selected retrospectively. All patients fulfilling the following criteria were included in this study: adult patients diagnosed with a hematological malignancy that underwent HLA-identical sibling allo-SCT. A total of 198 adult patients were included. In all, 99 transplants were performed in the Hematology Department of the Hospital Virgen del Rocío, Seville, between September 1996 and April 2008; the other 99 transplants were performed in the Hematology Department of the Hospital Clinic, Barcelona, between February 1997 and February 2007. All donor and recipient pairs were Caucasians from Spain. Main characteristics of the patients and the transplants are summarized in Table 1. The corresponding local Ethics Committees provided institutional review board approval for this study, and informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

Selection of genetic variant in *EP300*

Criteria for SNP selection was as follows: (1) being located either at 3′-untranslated region or 5′-untranslated region regions or at coding regions being associated with an amino-acid change, (2) frequency of the

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Table 1. Patient characteristics and clinical outcomes

N	*198*
Age at transplant (median and range):	
Patient	41 (16–66)
Donor	40 (15–69)
Gender (*n* and % of males)	90 (45)
Female donor with male recipient: *n* (%)	45 (23)
Underlying disease (n and %):	
Acute leukemias and myelodysplastic syndromes	117 (59)
CML and other myeloproliferative neoplasms	27 (14)
Lymphoproliferative neoplasms	54 (27)
Advanced phase of disease, *n* (%)	92 (47)
Source of HSC (n and %):	
Peripheral blood	197 (99.5)
BM	1 (0.5)
Conditioning (n and %):	
Myeloablative	142 (72)
Reduced intensity conditioning	54 (27)
CD34+cells infused/kg, median (range)	5.5 (1.3–21)
Clinical outcome	
TRM	22%
Relapse	41%
DFS	38%
OS	47%

Abbreviations: HSC = hemopoietic stem cells; DFS = disease-free survival. Clinical outcome values represent cumulative incidence values for TRM and relapse, *P* of DFS and OS.

less frequent homozygous allele >10% in Caucasians, and (3) associated with a functional change of the gene or involved in the pathogenesis of diseases. Based on these criteria, rs20551 in *EP300* was selected for the study. This gene variant (A>G) is located in the coding sequence in exon 15, in the chromosomal region 22q13.2, and codes for a missense change (I>V).

Genotyping

Genomic DNA from whole blood samples from patients and donors was isolated before transplant using a QIAmp DNABlood Mini Kit (QIAGEN, Hilden, Germany), following the manufacturer's instructions and stored at −20 °C. Patient samples were obtained at the time of diagnosis and donor samples were obtained previous to hematopoietic progenitor cells collection. Allelic variants were genotyped using the TaqMan SNP Genotyping Assay (Applied Biosystems, Foster City, CA, USA). The specific primers and FAM- and VIC dye-labelled probes (Foster city, CA, USA) used were designed by the Applied Biosystems assay-on-demand service. Reactions were performed as previously reported.[18]

Data analysis

Four clinical end points were considered: TRM, relapse, disease-free survival (DFS) and OS. TRM and relapse were analyzed using the Fine and Gray test. The cumulative incidence was computed with the *cmprsk* package for R 2.9.2 software (Vienna, Austria).[19] For TRM the competing event was relapse, and for relapse the competing event was death in remission. DFS and OS were obtained by the Kaplan-Meier method and compared using the log-rank test. *P* values were two-sided and significance was considered with a *P* value ⩽0.05. Variables included in the univariate analysis were donor and patient genotype for rs20551 gene variant in *EP300*, performing the analysis first in the three different genotype groups for the SNP (AA vs AG vs GG), and afterwards in two groups according to the presence or absence in homozygosis of the homozygous dominant gene variant in rs20551 (AA vs AG + GG); patient age (45 years was the cut-off value considered), relation donor/patient gender (female donor into male recipient vs others), phase of the disease (early vs advanced) and type of conditioning (myeloablative vs reduced intensity) were also included in the univariate analysis. Multivariate analysis was performed adding the SNP and incorporating to the model those clinical variables with a *P* value ⩽0.2 in the univariate analysis. Multivariate analysis of OS and DFS was performed using Cox regression with forward method and Wald statistic by SPSS 15.0 software (Chicago, IL, USA). Multivariate analysis of TRM and relapse was performed using the sub-distribution regression model of Fine and Gray with the *cmprsk* package for R 2.9.2 software. The proportional hazard assumption was tested for each variable by graphical methods according to Andersen and Klein.[20] Analysis of Hardy-Weinberg equilibrium was analyzed by Fisher's exact test.

Functional studies

Inflammatory response and CMV response. To find out whether the presence of this variant influenced the degree of inflammatory response, four mL of peripheral blood were collected in tubes precoated with PHA and CMV peptides (Cellestis Limited, Australia) from 180 blood donors. Blood samples were incubated for 24 h at 37 °C. After incubation, serum was collected to analyze the expression of Th1/Th2 cytokines (IL2, IL4, IL5, IL10 and IFNγ) and of other cytokines involved in the inflammatory and antitumour response (IL12, IL13, IL15 and IL17). All cytokines were measured with luminex system with the kits Human Th1/Th2 5-Plex panel and Human Cytokine II 5-Plex Panel, (Invitrogen, Life Technologies, Camarillo, CA, USA), according to manufacturer details.

To measure specific IFNγ production by CD4+ cells, CD8+ cells and natural killer cells after CVM exposure by flow cytometry, PBMC were obtained from 3 mL of heparinized whole blood from 120 blood donors by density gradient separation on ficoll-Hypaque. A total of 10^6 PBMC were stimulated with pp65 and IE-1 CMV peptides (JPT Peptide Technologies GmbH, Berlin, Germany) at a concentration of 1 μg/mL of each peptide for 6 h at 37 °C; cells were lysed, permeabilized and stained for intracellular detection of IFNγ production by CD8+ cells and by CD4+ cells using BD Biosciences FastImmune γ2a FITC/γ1 PE/CD8 PerCP-Cy5.5/CD3 APC and BD Biosciences FastImmune γ2a FITC/γ1 PE/CD4 PerCP-Cy5.5/CD3 APC (BD Biosciences, San Jose, CA, USA), respectively for the detection of IFNγ-producing CD8+ cells and IFNγ-producing CD4+ cells, following manufacturer details. CD69 was used as the activation marker. IFNγ-producing natural killer cells were selected gating the lymphocyte population and selecting the CD3-CD56+ population; on that gate IFNγ+ cells were selected. Natural killer cells were further subdivided into two populations on the basis of brightness for CD56, and presence or absence of CD16 and CD25. Monoclonal antibodies used were CD3-APCCy7, CD56-PE, IFNγ-APC, CD56-PE, CD16-FITC; all of them were from Beckton Dickinson (San Jose, CA, USA). A BD Biosciences FACSCanto II flow cytometer was used for all the flow cytometry analysis.

RNA isolation and gene expression analysis. An additional analysis was performed in 56 blood donors to find out whether the presence of that particular SNP influenced mRNA expression of genes involved in the inflammatory response (*HAMP*, *IRF-3*, *MIF* and *PTX3*), cell cycle (*AURKB*, *CCNA2*, *CCNB1* and *CCND3*), lymphocyte survival under osmotic stress conditions (*NFAT5, SLC38A2* and *SLC6A6*) and *P53*. RNA isolation was performed as previously described.[18] Real-time RT-PCR analysis for all the genes but *P53* was carried out using the 7900HT Fast Real-Time PCR System (Applied Biosystems). For *P53*, real time RT-PCR reactions were done in a 25-mL volume containing complementary DNA generated from 10 ng of original RNA template, 300 nM each of specific forward and reverse primers (p53Fw: 5′-GCCCACTTCACCGTACTAACC-3′ and p53Rv: 5′-GCCCAA CTGTAGAAACTACCA-3′) and 12.5 mL of iQ-SYBR Green Supermix (Bio-Rad, Hercules, CA, USA). Real-time PCR analysis was carried out using an iCycler (Bio-Rad). The amplification protocol used was as follows: initial denaturation and enzyme activation for 3 min 30 s at 95 °C, followed by 40 cycles of 95 °C for 15 s, optimal annealing temperature of 68 °C for 15 s and elongation at 72 °C for 30 s. Each assay was done in quadruplicate. Normalization of complementary DNA was performed with the housekeeping gene for 18 s. TLDA data were obtained with RealTime StatMiner

Table 2. Clinical risk factors associated with allo-SCT clinical outcome

Allo-SCT clinical outcome	*Factor*	*AP and CI* P *value*
TRM	Phase of disease standard risk vs high risk	19% vs 27% $P = 0.2$
	Age: median: $< = 45$ years vs > 45 years	17% vs 33% $\mathbf{P = 0.02}$
	Women donors with men recipients	25% vs 22% $P = 0.9$
Relapse	Phase of disease standard risk vs high risk	37% vs 42% $P = 0.3$
	Age: median: $< = 45$ years vs > 45 years	35% vs 46% $P = 0.4$
	Women donors with men recipients	44% vs 37% $P = 0.3$
DFS	Phase of disease standard risk vs high risk	45% vs 32% $\mathbf{P = 0.01}$
	Age: median: $< = 45$ years vs > 45 years	48% vs 21% $\mathbf{P = 0.002}$
	Women donors with men recipients vs rest	32% vs 41% $P = 0.3$
OS	Phase of disease standard risk vs high risk	54% vs 38% $\mathbf{P = 0.003}$
	Age: median: $< = 45$ years vs > 45 years	58% vs 27% $\mathbf{P = 0.005}$
	Women donors with men recipients	39% vs 51% $P = 0.8$

Abbreviations: AP = actuaral probability; CI = cumulative incidence; DFS = disease-free survival. AP and CI values are shown for each factor associated with allo-SCT clinical outcome, and *P* values obtained by competing risk (for TRM and relapse) and by log rank (for DFS and OS) are shown. Significant associations are indicated in bold.

Software (Applied Biosystems). Relative mRNA expression was determined using the $2^{(-\Delta\Delta Ct)}$ method according to Livak *et al.*[2] and calibrating each SNP with the genotype showing the lowest expression values. Wilcoxon's non-parametric test was performed for comparisons between genotype groups.

RESULTS

Patient characteristics and clinical outcome after allo-SCT

Patient characteristics and main clinical outcome results are shown in Table 1. Age of the patient was associated with TRM, DFS and OS, whereas phase of the disease was associated with DFS and OS. No single clinical factor was significantly associated with relapse incidence (Table 2).

Impact of gene variant rs20551 in *EP300* on the clinical outcome after allo-SCT

The dominant homozygous gene variant AA in rs20551 in *EP300* had a beneficial impact on the allo-SCT outcome. Results were very similar when analyzed separately in the two centers (Supplementary Table 1). In the global results, when present in the patient, the dominant AA *EP300* variant was associated with a lower relapse incidence than the rest of the variants (AA: 31% vs AG: 47% vs GG: 54%, $P = 0.019$; and AA: 31% vs AG + GG: 48%, $P = 0.025$). Further, the AA gene variant was associated with a trend toward a lower TRM (AA: 17% vs AG + GG: 28%; $P = 0.1$), and impacted on a better DFS (AA: 53% vs AG + GG: 24%, $P = 0.001$) and better OS (AA: 53% vs AG + GG: 34%, $P = 0.001$) (Table 3). When present in the donor, the dominant AA gene variant was associated with a lower TRM (AA: 15% vs AG: 27% vs GG: 33%, $P = 0.039$; and AA: 15% vs AG + GG: 28%, $P = 0.05$), a higher DFS (AA: 47% vs AG + GG: 26%; $P = 0.007$) and a higher OS (AA: 51% vs AG + GG: 40%; $P = 0.02$) (Table 3). When the dominant AA gene variant was present in both donor and patient, the association with a better clinical outcome was much stronger (Figure 1). This cumulative effect was also observed for TRM incidence showing the lowest TRM in cases when the dominant AA gene variant was present in both, donor and patient. Further, the absence of the dominant AA gene variant was associated with the shortest OS (Supplementary Figure 1). At multivariate analysis, the dominant AA gene variant in *EP300* in the patient and in the donor retained its significance for DFS and OS (Table 4). Of note, when present in the patient, the AA variant retained its clinical significance for relapse, whereas its presence in donor retained its significance for TRM (Table 4).

Table 3. Association of gene variant rs20551 in *EP300* with allo-SCT clinical outcome

TRM	*Relapse*	*DFS*	*OS*
Patient: $P = 0.1$ AA: 17% AG+GG: 28%	*Patient*: $P = 0.025$ AA: 31% AG+GG: 48%	*Patient*: $P = 0.001$ AA: 53% AG+GG: 24%	*Patient*: $P = 0.001$ AA: 53% AG+GG: 34%
Donor: $P = 0.05$ AA: 15% AG+GG: 28%	*Donor*: NS AA: 38% AG+GG: 48%	*Donor*: $P = 0.007$ AA: 47% AG+GG: 26%	*Donor*: $P = 0.02$ AA: 51% AG+GG: 40%

Abbreviations: AP = actuaral probability; CI = cumulative incidence; DFS = disease-free survival. Cumulative incidence values are shown for TRM and relapse incidence, and AP values are shown for DFS and OS. NS: correspond to *P* values > 0.1. Patient: gene variant in rs20551 present in the patient. Donor: gene variant rs20551 present in the donor.

Rs20551 in *EP300* is associated with differential inflammatory response after PHA and after CMV exposure

Functional studies showed that after PHA exposure there was a different IL2 production in serum according to gene variant rs20551 in *EP300*, showing the dominant AA gene variant and the recessive GG gene variant the lowest and the highest IL2 production, respectively (median values: AA = 1400 pg/mL, AG = 1573 pg/mL, GG = 2602 pg/mL, $P = 0.025$) (Figure 2a). None of the other cytokines analyzed presented a differential expression among the different genotypes. Furthermore, the recessive GG gene variant presented the lowest percentage of IFNγ-producing CD4+ cells in peripheral blood (PB) after CMV exposure (median values: 1.1 = AA, 1.05 = AG and 0.4 = GG). This difference was significant when comparing AA + AG vs GG ($P = 0.04$); and the significance was retained when the analysis was performed only in the blood donors who were IgG-positive for CMV ($P = 0.048$) (Figure 2b).

Rs20551 in *EP300* is associated with differential gene expression in genes involved in innate immunity and cell cycle

Rs2051 gene variant in *EP300* was associated with a differential expression in genes involved in innate immunity and in cell cycle comparing AA, AG and GG genotypes. Thus, when comparing AA with GG genotypes, AA presented a higher expression of innate immune genes (*IRF3*, 3.4-fold, $P = 0.02$; *MIF*, 6.2-fold, $P = 0.006$), cell cycle genes (*AURKB*, 5.9-fold, $P = 0.01$; *CCNA2,* 10.6-fold, $P = 0.005$; *CCNB1*, 6.4-fold, $P = 0.02$), lymphocyte survival gene (*NFAT5*, 2.8-fold, $P = 0.03$), osmotic stress genes (*SLC38A2*, 2.4-fold, $P = 0.03$) and lower expression of *P53* (4.5-fold, $P = 0.002$) than the GG genotype (Figure 3). The other genes analyzed involved in the innate immune response (*HAMP*, *PTX3*), involved in the osmotic stress (*SLC6A6*) and in cell cycle (*CCND3*), did not show a differential mRNA expression among the different genotypes.

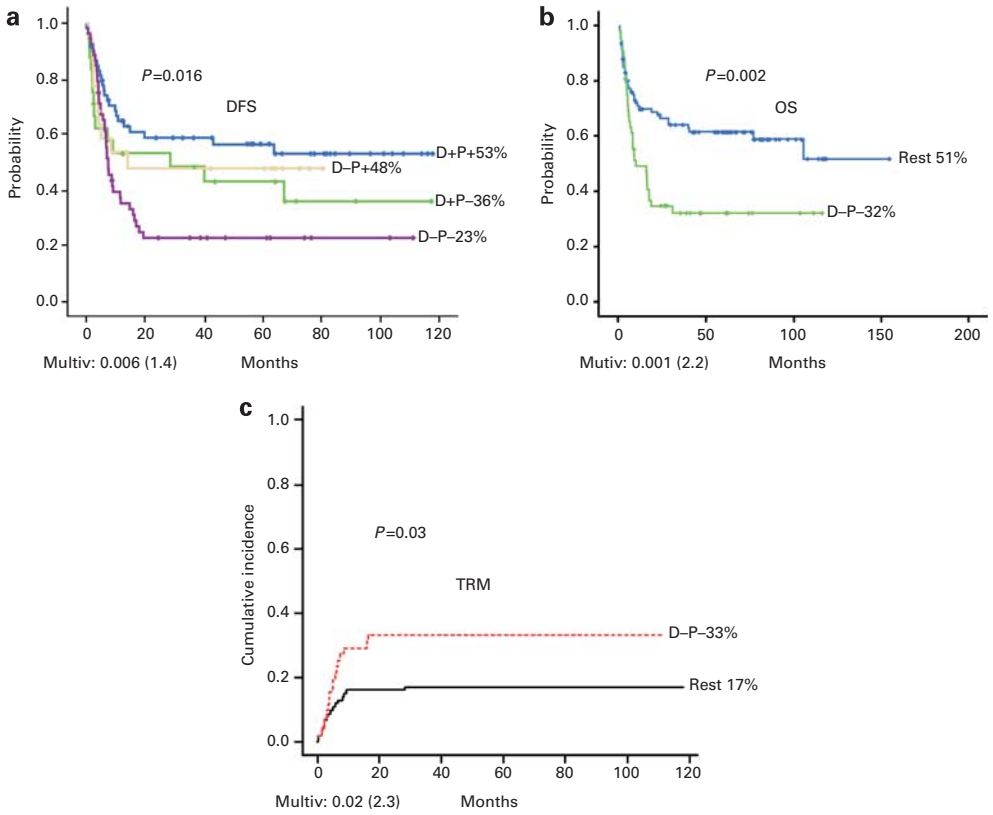

Figure 1. Clinical outcomes according to the presence or absence of the dominant gene variant AA in rs20551 in *EP300*. (**a**) Actuarial probability of disease-free survival (DFS) according to the presence (+) or absence (−) of the dominant gene variant AA in rs20551 in *EP300* in patient (P) or in donor (D). (**b**) Actuarial probability of OS; and (**c**) Cumulative incidence of TRM according to the absence (−) of the dominant gene variant AA in rs20551 in *EP300* in patient (P) and in donor (D) with respect to the other possibilities (Rest). Multiv: *P* values and OR (odds ratio) obtained at multivariate analysis adding phase of disease and age.

Table 4. Multivariate analysis

Outcome	*Variable*	*OR (P value) [95% CI]*
TRM	AA rs20551 in *EP300* (D)	**0.44 (0.024)** (0.2–0.85)
	Phase of disease	1.6 (0.15) (1.06–4.3)
	Age	**1.97 (0.049)** (1.07–4.2)
Relapse	AA rs20551 in *EP300* (P)	**0.57 (0.028)** (03–0.8)
	Phase of disease	1.26 (0.3) (0.9–2.4)
DFS	AA rs20551 in *EP300* (P)	**0.57 (0.006)** (0.4–0.9)
	Phase of disease	**1.5 (0.03)** (1.01–2.2)
	Age	**1.6 (0.02)** (1.1–2.4)
	AA rs20551 in *EP300* (D)	**0.53 (0.002)** (0.35–0.8)
	Phase of disease	**1.8 (0.004)** (1.2–2.7)
	Age	1.4 (0.07) (0.9–2.2)
OS	AA rs20551 in *EP300* (P)	**0.6 (0.008)** (0.4–0.9)
	Phase of disease	**1.6 (0.03)** (1.1–2.5)
	Age	**1.6 (0.04)** (1.1–2.4)
	AA rs20551 in *EP300* (D)	**0.5 (0.006)** (0.3–0.8)
	Phase of disease	**2.05 (0.002)** (1.3–3.2)
	Age	1.4 (0.1) (0.9–2.3)

Abbreviations: D = donor; DFS = disease-free survival; P = patient. Multivariate analysis was performed for AA gene variant in rs20551 in *EP300* and adding those clinical variables associated with the allo-SCT clinical outcome with a p value < 0.2. Significant associations are indicated in bold.

DISCUSSION

We report that the dominant AA gene variant in rs20551 in *EP300* influences favorably the clinical outcome of adult patients with hematological malignancies who underwent HLA-identical sibling allo-SCT. The clinical impact of this gene variant was more pronounced when it was present in the patient, and to a lesser extent when it was present in the donor. Moreover, this gene variant in the patient had more influence on the relapse incidence, whereas when it was present in the donor it impacted more on the TRM. Results from the multivariate analyses suggest that the AA gene variant in rs20551 in *EP300* had, with respect to other clinical variables, the highest independent impact on clinical outcomes. In a study conducted in healthy individuals to explore the functional relevance of this gene variant, we found that the AA gene variant and the GG gene variant presented opposite effects after an inflammatory response and in the cell cycle, showing that AA gene variant had a lower IL2 production, higher percentage of IFNγ-producing CD4+ cells in PB after CMV exposure, a higher expression of genes involved in innate immune response, cell cycle, lymphocyte survival and a lower expression of *P53*.

EP300 has a critical role in biological process involved in tumorigenesis.[17,21] Thus, gene mutations that modify the structure of EP300 appear in several types of cancer.[21–23] *EP300* and CBP (CREB-binding protein) give rise to the transcriptional coactivator P300/CBP. Mutations in this complex in hematological malignancies have been described very recently, showing that about 39% of diffused large B-cell lymphoma and 41% of follicular lymphoma cases display genomic deletions and/or somatic mutations that remove or inactivate the histone and non-histone acetyltransferases coding domain of CBP and EP300.[24] Recently, rs20551 gene variant in *EP300* has been associated with childhood ALL.[25] P300/CBP during cell cycle acetylates and degradates cyclin A, allowing mitosis progression.[26] *EP300* also has a critical role in the

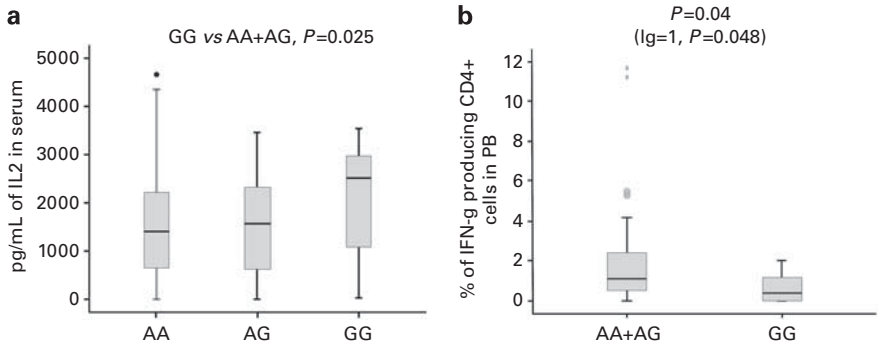

Figure 2. Inflammatory response after PHA and CMV stimulation according to the different gene variants in blood donors. (**a**) IL2 production in serum after PHA exposure in peripheral blood in 180 blood donors. *P* value obtained corresponds to comparison between GG and AA + AG. (**b**). Percentage of IFNγ-producing CD4 + cells in peripheral blood after CMV stimulation of PBMCs in 120 blood donors. *P* value obtained corresponds to comparison between GG and AA + AG, and Ig = 1 corresponds to *P* value obtained when the analysis was performed with donors who were IgG-positive for CMV. AA, AG and GG correspond to dominant, heterozygous and recessive gene variant in rs20551 in *EP300*, respectively.

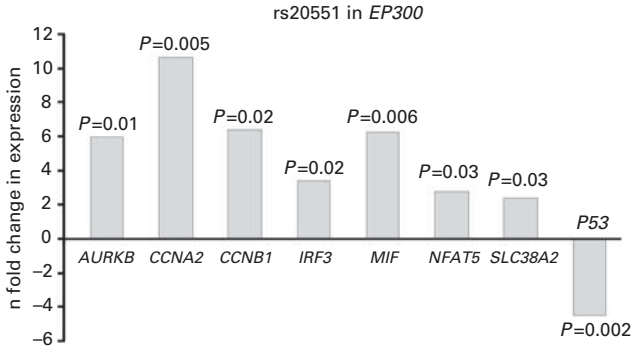

Figure 3. Real-time RT-PCR in blood donors for the different genotypes in rs20551 in *EP300*. Values represent *n*-fold increase of mRNA expression levels for all the genes indicated in the dominant AA gene variant in rs20551 in *EP300* compared with individuals carrying the recessive GG genotype.

inflammatory response.[17,21] Thus, following viral infection, IRF-3 associates with P300/CBP and translocates to the nucleus to induce IFN-β transcription.[17,27] All these important biological effects mediated by *EP300* might explain why a constitutional variant in this gene influences the clinical outcome after allo-SCT. We have found a possible functional role for this gene variant in the inflammatory response, presenting the beneficial AA gene variant and the deleterious GG gene variant in rs20551, opposite effects in the IL2 production after a mitogenic stimulus and in the CD4 response after CMV stimulation. Thus, AA gene variant had a lower inflammatory response and higher CD4 + cell response after CMV stimulation, which could explain in part the association of AA and GG gene variants with a lower and higher TRM incidence, respectively. Additionally, an abnormal interaction of AA gene variant in *EP300* with IRF-3 could lead to a higher immune response after viral infection. In this sense, this study shows that healthy individuals harboring AA gene variant, as compared with individuals harboring GG gene variant, present higher expression of innate immune genes (*IRF-3* and *MIF*) and lymphocyte survival genes (*NFAT5* and *SLC38A2*), which could explain also the impact of AA gene variant in a lower TRM incidence. Furthermore, this gene variant is associated with a significant change in the mRNA expression of key genes involved in the cell cycle. Thus, our results present that the beneficial AA gene variant compared with the deleterious GG gene variant in rs20551 has a higher mRNA expression of cell cycle genes (*CCNA2*, *CCNB1* and *AURKB*). A different interaction of EP300 with cyclin A, due to a missense change of *EP300* AA gene variant, in cells of the patient could translate into a lower cyclin-A degradation, being responsible for higher cyclin-A mRNA accumulation and the following downstream genes in the cell cycle as it is shown by a higher mRNA expression of cell cycle genes (*CCNA2*, *CCNB1* and *AURKB*), impacting in a slower cell cycle in cells of the patient. This effect could explain the association of AA gene variant in *EP300* with a lower relapse incidence when present in the patient.

The associations herein presented strongly suggest a beneficial effect of a dominant gene variant AA in rs20551 in *EP300* on the outcome of adult HLA-identical sibling allo-SCT. This effect might be explained by its influence in the inflammatory response and by its influence on mRNA expression of cell proliferation, and lymphocyte survival genes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Author contributions: AU and BM designed the study; AU obtained funding; JF, IE, MS, MR, FFA, CM, FM and RC obtained clinical data; BM, IA and AB obtained genetic data; BM performed the statistical analysis; AU and BM drafted the manuscript.

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Supplementary Information accompanies the paper on Bone Marrow Transplantation website (http://www.nature.com/bmt)