Contribution of genetics to hematopoietic stem cell mobilization: a genome-wide association study of 564 healthy donors mobilized with granulocyte colony-stimulating factor

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Abstract

Hematopoietic stem and progenitor cells (HSPC) from mobilized blood are the preferred graft source for allogeneic and autologous stem cell transplantation. The efficiency of CD34$^+$ cell mobilization with granulocyte colony-stimulating factor (G-CSF) varies significantly between individuals, but is reproducible across mobilization cycles within an individual, suggesting a genetic component, a hypothesis that has been previously investigated by testing for candidate single-nucleotide polymorphisms (SNP) associations. As the genetic determinants of HSPC mobilization have not been analyzed on the genomic scale so far, we performed a genome-wide association study (GWAS) in a German population of 564 healthy G-CSF mobilized allogeneic stem cell donors. None of the association between about 5 million variants and the primary outcome investigated (CD34$^+$ cell frequency in peripheral blood) reached genome-wide significance. Focused analysis of 11 variants previously shown to be associated with basal CD34$^+$ cell levels confirmed an association of *CXCR4*-rs11688530 (A>G) and *ARHGAP45*-rs36084354 (A>G) with higher CD34$^+$ frequency in G-CSF mobilized healthy donors showing an explained variance (Var_{ex}) of 1.07% (P=0.004) and 0.86% (P=0.01), respectively. Demographic analysis revealed an association of peripheral blood CD34$^+$ cell frequency with sex (Var_{ex}=8.1%) and body mass index (Var_{ex}=7.2%) that exceeded the contribution of single variants. The current study is the first GWAS in mobilized stem cell donors and had a statistical power of 80% to detect single nucleotide polymorphism with Var_{ex} of ≥6.7% at genome-wide significance. The study results exclude a monogenetic cause of population G-CSF responsiveness and support the view that polygenetic risk scores are required as predictors.

Introduction

Hematopoietic stem-cell transplantation (HSCT) is essential in the treatment of blood disorders.[1] The number of autologous and allogenic HSCT is constantly growing with more than 48,000 transplantations in 2019 comprising 41% allogeneic donations.[2,3] Hematopoietic stem cells are most frequently collected by leukapheresis from peripheral blood after treatment of the donor with granulocyte colony-stimulating factor (G-CSF), a process

called "mobilization".[4-8] Since mobilization with G-CSF fails for up to 10% of healthy donors and up to 40% of patients, insufficient stem cell collection is not a rare event and leads to delays of treatment and increased costs.[9-11]

Previous studies have shown that basal peripheral blood CD34$^+$ cell levels in healthy individuals remain relatively stable over days, weeks, and longer periods of time such as 18 months.[12] While mobilization response varies considerably between individuals,[13,14] comparison of two mobilization rounds of the same individual with months to years in between showed a strong positive correlation of peripheral blood CD34$^+$ cell yields, explaining more than 50% of variance in well-powered studies.[15,16] In a study of 639 ethnically diverse allogeneic donors, peripheral blood CD34$^+$ cell concentrations after G-CSF treatment were significantly lower in white individuals compared to Africans, Hispanics, and Asian donors[17] suggesting a contribution of genetics to stem cell mobilization. In addition, the mobilization efficiency is influenced by demographic and life-style factors: male sex, higher body mass index (BMI), higher lymphocyte counts, and higher platelet counts are associated with better mobilization, while higher age and tobacco smoking are associated with worse mobilization in healthy donors.[18-22]

Whether there exists a correlation between basal and mobilized peripheral blood CD34$^+$ cell levels is discussed controversially. While smaller studies of autologous and allogeneic donors reported an explained variance (Var_{ex}) of up to 50% and more,[23-25] the Var_{ex} was smaller than 10% in a large German study including 198 allogeneic stem cell donors.[14] Two existing genome-wide association studies (GWAS) of peripheral blood CD34$^+$ cells in unmobilized individuals analyzed the CD34$^+$ cell frequency as the primary investigated variable due to skewed distribution of CD34$^+$ cell concentration in the population. In the GWAS of Cohen *et al.*[26] heritability analysis revealed a substantial contribution of 54% to the variance of CD34$^+$ cell frequency by a comparison of 516 sibling pairs with 277 spousal pairs.[26] The recently published first large-scale GWAS of Lopez de Lapuente Portilla *et al.* including 13,167 individuals identified an association of 11 variants with steady-state CD34$^+$ cell frequency at genome-wide significance level ($P<5.0x10^{-8}$).[27]

So far, the role of genetics for successful stem cell mobilization by G-CSF has been analyzed only for selected genes but not on the genomic level.[18,28-31] Therefore, we carried out a GWAS in a German study cohort including 564 healthy allogeneic stem cell donors. We sought to identify variants associated with the CD34$^+$ cell frequency after G-CSF mobilization and to combine them into a genetic risk score to predict the mobilization success.

Methods

Study cohort and phenotype variables

A total of 612 healthy volunteer individuals eligible for G-CSF mobilized allogeneic stem cell donation were recruited in the study at the Department of Cellular Therapeutics and Cell Processing of the German Red Cross Blood Center (Frankfurt, Germany). The study was approved by the ethics committee of Johann Wolfgang Goethe University School of Medicine (permit #190/12). Donors were subjected to G-CSF induced stem cell mobilization as described, receiving 7.5-10 μg/kg bodyweight per day in two divided doses every 12 hours for a total of nine doses in preparation for stem cell donation.[13,14]

Peripheral blood CD34$^+$ and CD45$^+$ cell concentrations were measured 2-3 h after the ninth dose of G-CSF prior to apheresis, using commercial single-platform flow cytometry assays.[32] DNA was isolated from pseudonymized left-over blood samples using an automated DNA purification system (Maxwell® RSC Blood DNA Kit, Promega, Madison, WI, USA) or manually with a spin-column-based kit (DNeasy Blood & Tissue Kit, Qiagen, Hilden, Germany). DNA quantity and quality were determined fluorescence-based using Qubit® 2.0 Fluorometer (Invitrogen, Carlsbad, CA, USA) or by an electrophoresis-based system (Agilent Genomic DNA ScreenTape® and 2200 TapeStation System®, Agilent Technologies, Waldbronn, Germany). Clinical data were extracted from our stem cell donor data base.

The phenotype variables analyzed in our study were: (i) CD34$^+$ cell frequency defined as ratio of CD34$^+$ and CD45$^+$ concentrations and (ii) a binary variable describing either clinically sufficient (≥30 CD34$^+$ cells/μL) or insufficient (<30 CD34$^+$ cells/μL) stem cell mobilization. The threshold for distinguishing between sufficient and insufficient stem cell mobilization represents the tenth percentile in our database of more than 2,800 healthy donors mobilized with G-CSF in our institution (*Online Supplementary Figure S1A*) and defines a clinical value at which a sufficient graft can usually be obtained. Additionally, we analyzed donor age, sex, and BMI.

Genotyping and quality control

Blood samples were genotyped at the Helmholtz Zentrum München (München, Germany) using the Illumina Infinium Global Screening Array version 3 comprising 654,027 markers and detecting variants with a minor allele frequency of >1% in the population. Quality control and data analysis were performed using PLINK v2.[33] Samples filtering and subsequent variant filtering were performed to result in a high-quality data set. Variants not covered by the genotyping array were imputed using TOPMed v1.6.6[34-36] resulting in a total of 17,199,566 typed or imputed variants with a strong correlation (R^2≥0.8). For further details see the *Online Supplementary Appendix*.

Genome-wide association analysis

The association of CD34$^+$ cell frequency with each variant was analyzed by fitting multivariate linear models using PLINK. Herein, the CD34$^+$ cell content was the dependent

variable, while variant status as well as sex, age, BMI and the first ten principal components of the variant data were included as independent variables. Genome-wide significance was defined by $P<5.0\times10^{-8}$ (for details see the *Online Supplementary Appendix*).

Polygenic scores

Polygenic scores including multiple variants were calculated from the coefficients in the linear model and the dosages of the variants in the samples (for details see the *Online Supplementary Appendix*).

Results

The study cohort included 564 stem cell donors (187 women and 377 men), which were treated with G-CSF prior to stem cell apheresis (Table 1). The median age was 32 years for the women *versus* 31 years for the men. The median BMI for female donors was 23 kg/m^2 and for male donors 25 kg/m^2.

A GWAS was performed to uncover the influence of the blood donor genotype on the mobilized stem cell yield. Peripheral blood CD34$^+$ cell frequency was the primary investigated phenotype variable, as it showed a less skewed distribution than CD34$^+$ cell concentration (*Online Supplementary Figure S1B, C*). The two variables were strongly correlated (R=0.85; *Online Supplementary Figure S1D*). Genotyping with variant arrays resulted in a total number of 1,060,834 variants after imputing and quality control. A power analysis for reaching genome-wide significance ($P<5.0\text{x}10^{-8}$) revealed a statistical power of 0.098% for a variant explaining 1% of the variance, while a statistical power of 80% can be accomplished for a variant explaining 6.7% of the variance.

Genome-wide association analysis

The association of CD34$^+$ cell frequency with the genotyped variants was analyzed using multivariate linear regression (Figure 1). None of the variants reached genome-wide significance. Using a lower significance level ($P<0.0001$) a candidate list of 602 variants of which 115 were in linkage disequilibrium

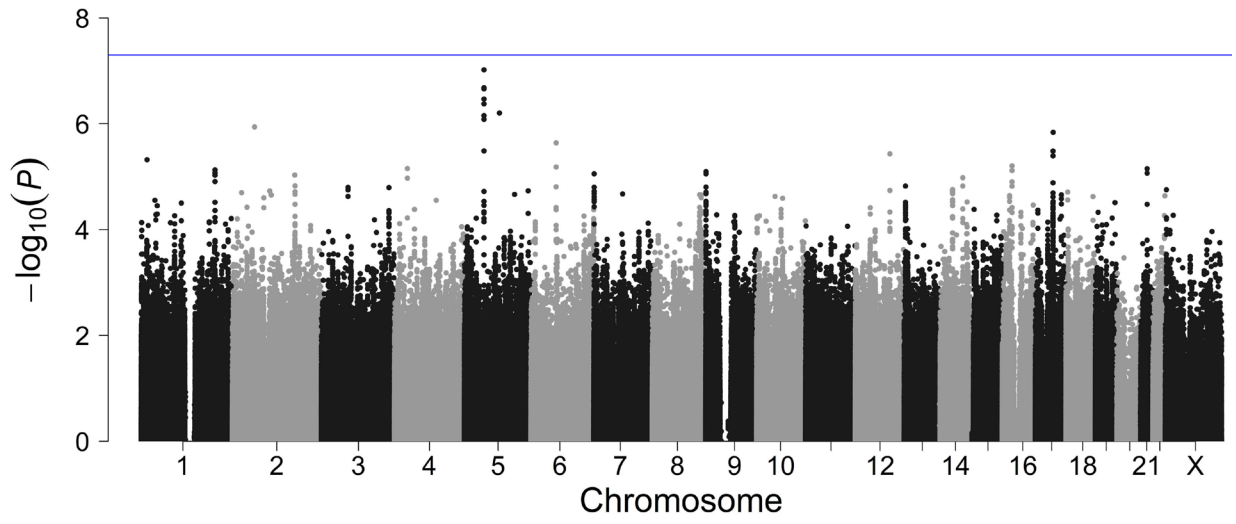

Figure 1. Association of peripheral blood CD34$^+$ cell frequency of 564 healthy granulocyte colony-stimulating factor mobilized stem cell donors with the genotyped variants. The association was analyzed using a multivariate linear model including age, sex, body mass index, and the first 10 principal components as genetic variation in the study population.

Table 1. Clinical characteristics of the study cohort.

Characteristics	Female		Male	
N (%)	187 (33.16)		377 (66.84)	
	sufficient	insufficient	sufficient	insufficient
Sufficient/insufficient mobilizers, N	163	24	350	27
Median age, years	32		31	
Median BMI, kg/m^2	23		25	
	mean	SD	mean	SD
CD34$^+$ concentration, cells/μL	86.79	57.67	108.50	64.37
CD34$^+$ frequency, %	0.16	0.08	0.22	0.11

Age and body mass index (BMI) are reported as median, CD34$^+$ cell concentration and CD34$^+$ cell frequency (ratio of CD34$^+$ and CD45$^+$ cells) are reported as means with standard deviation (SD).

was compiled and further analyzed (*Online Supplementary Table S1A*). None of 16,008 investigated gene ontology categories were significantly enriched in the genes corresponding to the candidate variants (*Online Supplementary Table S1B*). To enhance sensitivity, we additionally performed an analysis restricted to the two ligand-receptor pairs CXCL12/CXCR4 and VCAM1/VLA4 (composed of ITGA4 and ITGB1), which were previously analyzed in smaller cohorts of G-CSF mobilized donors.[29,37] None of the 13 previously investigated variants reached significance after multiple testing correction (*Online Supplementary Table S2*). In particular, the variant *CXCL12*-rs1801157 (G>A) did not reach significance (β=-0.02, -0.16 to 0.11, Var_{ex}=0.02; *P*=0.75). Analysis of 17 suggestive variants (*P*<5.0x10-6) associated with steady state CD34⁺ cell frequency in an earlier GWAS by Cohen *et al.*[26] also revealed no significance

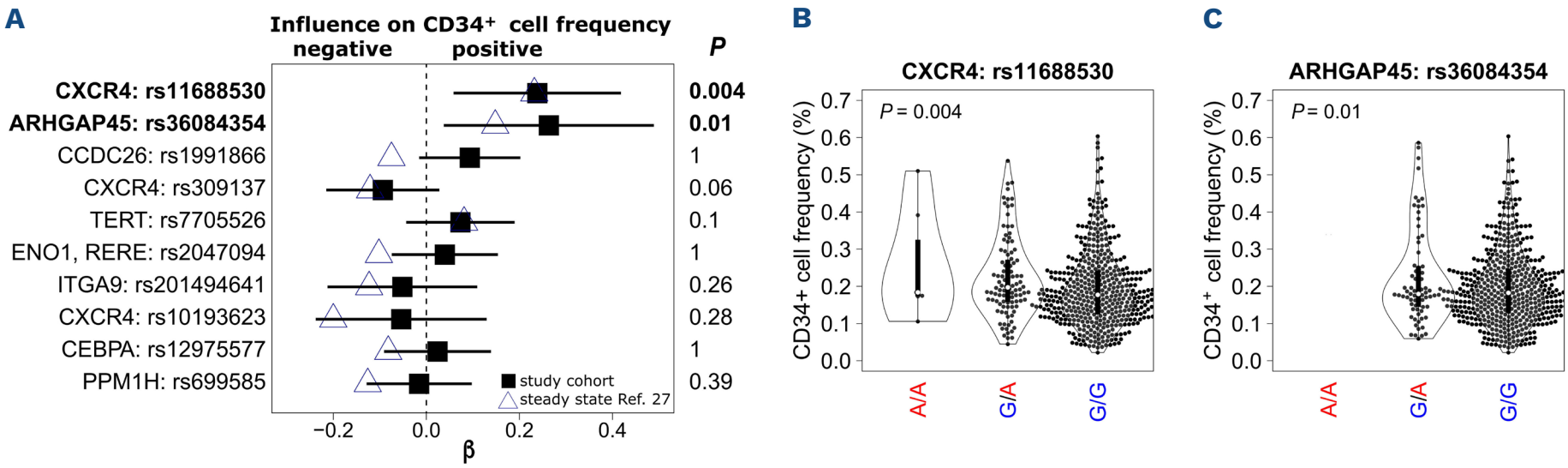

Figure 2. Comparison of the variants that correlated with the CD34⁺ cell frequency in untreated individuals in a previous study[27] with the current study population of healthy donors treated with granulocyte colony stimulating factor. (A) Comparison of the regression coefficients in the earlier investigated population (triangles) with the regression coefficients in the current study cohort (boxes) with a 95% confidence interval. Frequency of CD34⁺ cells in the current study population for the 3 genotypes of (B) rs11688530 in *CXCR4* and (C) rs36084354 in *ARHGAP45*. Alternative alleles are depicted in red, reference alleles are depicted in blue.

Table 2. Comparison of eleven variants that correlated with the CD34⁺ cell frequency in untreated individuals in a previous study[27] with the current study population of healthy donors treated with granulocyte colony stimulating factor.

Gene	rsID	Chr	CD34⁺ cell frequency, steady state (Ref 27, N=13,167)				CD34⁺ cell frequency, G-CSF mobilized (study cohort, N=564)			
			MAF %	β	Var_{ex} %	*P*	MAF %	β (95% CI)	Var_{ex} %	*P*
CXCR4	rs11688530	2	7.1	0.23	0.71	$7.9x10^{-22}$	10.5	0.24 (0.06-0.42)	1.07	0.004
ARHGAP45	rs36084354	19	8.8	0.15	0.35	$2.7x10^{-8}$	6.6	0.26 (0.04-0.49)	0.86	0.010
CCDC26	rs1991866	8	44.9	-0.08	0.28	$3.5x10^{-9}$	42.9	0.09 (-0.01 to 0.20)	0.43	1
CXCR4	rs309137	2	25.5	-0.12	0.56	$1.5x10^{-15}$	35.2	-0.09 (-0.21-0.02)	0.40	0.061
TERT	rs7705526	5	34	0.08	0.29	$1.5x10^{-9}$	37.4	0.07 (-0.04-0.19)	0.25	0.103
ENO1/RERE	rs2047094	1	49.2	-0.10	0.52	$1.3x10^{-15}$	47.6	0.04 (-0.07 to 0.15)	0.08	1
ITGA9	rs201494641	3	13	-0.12	0.34	$4.7x10^{-11}$	14.1	-0.05 (-0.21 to 0.11)	0.06	0.261
CXCR4	rs10193623	2	5.9	-0.20	0.44	$2.8x10^{-15}$	9.8	-0.05 (-0.23 to 0.13)	0.05	0.279
CEBPA	rs12975577	19	49	-0.08	0.34	$1.2x10^{-10}$	48.7	0.02 (-0.09 to 0.14)	0.03	1
PPM1H	rs699585	12	46.1	-0.13	0.79	$2.2x10^{-23}$	44.1	-0.02 (-0.13 to 0.09)	0.01	0.391
CXCR4	rs555647251	2	0.1	1.74	0.50	$1.2x10^{-11}$	0.1	NA	NA	NA

The variants *CXCR4*-rs11688530 (A>G) and *ARHGAP45*-rs36084354 (A>G) were associated with higher CD34⁺ frequency in both cohorts. G-CSF: granulocyte colony stimulating factor; Chr: chromosome; Ref.: reference; MAF: minor allele frequency; β: regression coefficient; Var_{ex}: variance explained; NA: not applicable.

in our cohort (*Online Supplementary Table S3*).

Confirmation of variants detected in untreated blood donors

A recent large-scale GWAS including 13,167 unmobilized individuals identified 11 variants that were associated with basal CD34⁺ cell frequency.[27] Out of these, two variants could be confirmed in the present cohort of G-CSF-mobilized stem cell donors (Figure 2; Table 2). *CXCR4*-rs11688530 (A>G) located in a non-coding region and *ARHGAP45*-rs36084354 (A>G), a missense variant, were both associated with higher peripheral blood CD34⁺ cell frequency in the current study of healthy mobilized donors with P=0.004 and P=0.01, respectively. Analysis were confirmed by one-sided *t* tests. *CXCR4*-rs11688530 explained 1.07% and *ARHGAP45*-rs36084354 explained 0.86% of the variance in the current study, while the Var_{ex} for CXCR4-rs11688530 and ARHGAP45-rs36084354 were 0.71% and 0.35% in the previous study of Lopez de Lapuente Portilla *et al.*[27] The minor allele frequencies of the described variants were comparable in both study cohorts with a minor allele frequency (MAF) of 10.5% *versus* 7.1% for *CXCR4*-rs11688530 in the current study compared to the previous GWAS and a MAF of 6.6% for *ARHGAP45* in our cohort *versus* 8.8 % in the previous study.[27] In a reverse analysis of our 115 candidate variants with the lower significance level (P<0.0001) in the previous GWAS cohort no further significant variants could be detected.

Analysis of demographical factors

Association of CD34⁺ cell frequency with age, sex, and BMI was analyzed separately for each of the factors by univariate and multivariate analysis of all three parameters (Table 3). In univariate analyses, each of these factors explained 0.3%, 8.1%, and 7.2% of the variance, while explanation of the variance was 1%, 6.2%, and 6.4% in the multivariate model. In both analyses, higher BMI and being male were significantly associated with higher CD34⁺ frequency. Being younger was also significantly associated with better mobilization in the multivariate model. As BMI and sex considerably contributed to explaining the variance, we carried out ROC analysis to separate sufficient (≥30 CD34⁺ cells/μL) from insufficient (<30 CD34⁺ cells/μL) stem cell mobilizers separately in female and male donors (Figure 3A). In females, BMI separated significantly between the two groups with an area under the curve (AUC) of

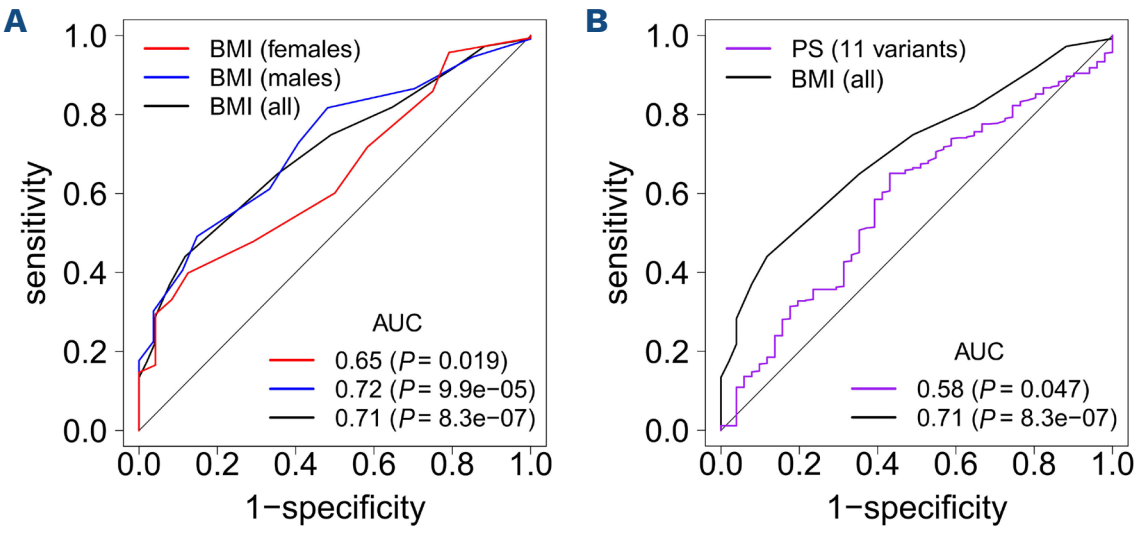

Figure 3. Separation of sufficient (≥30 CD34⁺ cells/μL) from insufficient (<30 CD34⁺ cells/μL) stem cell mobilizers. (A) Separation of the 2 groups by body mass index (BMI) separately for female and male stem cells donors. (B) Separation of the 2 groups by a polygenetic score (PS) including eleven variants that were reported before.[27] AUC: area under the curve.

Table 3. Association of the CD34⁺ cell frequency with age, sex, and body mass index.

Variable	β (95% CI)	Var_{ex} %	*P*
Univariate model			
Age	-0.0006 (-0.0015 to 0.0003)	0.3	0.172
Sex: male *vs.* female	0.0628 (0.08-0.045)	8.1	$5.51x10^{-12}$
BMI	0.0062 (0.0044-0.0081)	7.2	$9.4x10^{-11}$
Multivariate model			
Age	-0.0010 (-0.0019 to -0.00024)	1	0.011
Sex: male *vs.* female	0.0548 (0.072-0.038)	6.2	$5.89x10^{-10}$
BMI	0.0059 (0.0041 - 0.0077)	6.4	$5.98x10^{-10}$

Analyzes were performed by univariate and multivariate linear regression. BMI: body mass index; β: regression coefficient; CI: confidence interval; Var_{ex}: explained variance.

0.65 (P=0.019). In males, an even stronger separation with AUC=0.72 (P=9.9x10^{-5}) was detected.

Polygenic scores

Sum scores were calculated by adding β values weighted for heterozygous or homozygous occurrence of the variants. First, we evaluated a polygenic score (PS) including the 11 variants that were associated with CD34$^+$ cell frequency in the cohort published before.[27] The scores were significantly associated with sufficient stem cell mobilization with AUC=0.58 (P=0.047) in a ROC analysis (Figure 3B). Second, we evaluated PS constructed from the study results and including 10, 20, 50, 100, 200, 500, and 1,000 variants to predict the sufficiency of stem cell mobilization. To this end, we trained and tested PS including the top (ranked by the P value) variants in 10-fold cross-validation. None of the seven PS was significantly associated with CD34$^+$ cell frequency or the sufficiency of stem cell mobilization (*Online Supplementary Figure S2*).

Discussion

This is the first GWAS analyzing the genetic determinants of stem cell mobilization after stimulation with G-CSF. Genetic association of stem cell mobilization has long been suspected, based on data in mice and humans showing different mobilization responses in different mouse strains and in different ethnic groups, respectively.[17,38,39] This hypothesis is supported by the high degree of individual similarity of the mobilization responses during further mobilization cycles on the one hand with a high inter-individual mobilization response with a factor of more than 100 between the poorest and best mobilizers under G-CSF on the other hand.[13-15] So far, the genetic contribution to G-CSF-induced stem cell mobilization has only been investigated by targeted genotyping, with a focus on genes playing a known role in the regulation of the hematopoietic stem cell niche.[28-31,37] Our study is the first GWAS analyzing the genetic determinants of stem cell mobilization in a cohort of 564 healthy stem cell donors. However, in our analysis the association of none of the about 5 million investigated variants reached genome-wide significance. A total of 602 variants, of which 105 were in linkage disequilibrium, reached the lower significance level of P<0.0001 (*Online Supplementary Table S1*). The list of detected variants can serve as input for future validation studies.

So far, there are only two larger GWAS, investigating the role of genetics on CD34$^+$ levels in the steady state. In a study of 1,786 unmobilized individuals, no significant association of variants with log-transformed CD34$^+$ cell frequency was detected on the genome-wide significance level (P<5.0x10^{-8}).[26] Using a lower significance level of P<5.0x10^{-6}, this study revealed 17 suggestive variants, all of them in non-coding regions. A recently published large-scale GWAS, seeking association of genetics with HSPC in blood in the steady-state included 13,167 individuals and revealed for the first time 11 variants with genome-wide significance.[27] The 11 identified variants were associated with steady-state circulating CD34$^+$ frequency among white blood cells and could explain between 0.28% and 0.71% % of the observed variability. Restricting our analysis to the set of variants discovered, a variant in *CXCR4* (rs11688530) and a variant in *ARHGAP45* (rs36084354) could be confirmed by our study cohort. Rs11688530 is located in the non-coding region of *CXCR4*, while rs36084354 is a missense variant of *ARHGAP45*, the Rho GTPase-activating protein 45. While the chemokine receptor *CXCR4* expressed on hematopoietic cells is a known regulator of the hematopoietic stem cell niche, the role of *ARHGAP45*, a human minor histocompatibility antigen, in stem cell mobilization is still unclear. Previous studies report that ARGHAP4 is involved in the regulation of endothelial integrity and hematopoietic progenitor cell engraftment in the bone marrow.[40,41] Our results support the hypothesis that a part of the genetic markers associated with stem cell frequency in the steady state are relevant for the efficiency of stem cell mobilization after treatment with G-CSF as well.

The genetic contribution of G-CSF-induced stem cell mobilization was previously investigated in smaller studies, focusing the analysis mainly on variants of the CXCL12/CXCR4 and VCAM1/VLA4 axis.[28-31,37] The variants investigated by targeted genotyping approaches were discussed controversially in terms of their contribution to stem cell mobilization and did not show an association with peripheral blood CD34$^+$ cell frequency in our larger study cohort. Potential explanations for the disconcordant results include differences in the size or ethnic population of the cohort or the inclusion of patients with altered function of the bone marrow or stem cell compartment in the analysis.

In spite of an unbiased approach using GWAS in the largest cohort of mobilized healthy donors studied to date, our analyses fail to uncover genetic variants with actionable predictive strength for G-CSF induced stem cell egress. Even the variants most strongly associated with mobilization efficiency explain only 1.1% of the 100-fold variability of G-CSF responsiveness, far less than race[17] or sex and BMI. The latter two are confirmed by our study, contributing to 8.1% and 7.2% of the observed variability, indirectly validating our cohort. In order for genetic variables to be actionable for donor selection or adjustment of mobilization strategy or to be potentially informative from a mechanistic point of view, a strong effect, definitely an effect exceeding that of sex or BMI, would be required. Our cohort is sufficiently powered to detect such effects responsible for 6.7% of the Var_{ex} or more to reach genome-wide significance. The fact that we could not reveal such effects clearly implies a polygenic nature of G-CSF responsiveness. To detect variants with lower explained variances of 1% and 0.5% respectively with a power of 80%, a cohort size of 3,935 and 7,895 samples would be required.

While clinical observation strongly suggests genetic determination of mobilization efficiency what factors these might be remains elusive. Clearly, though, no single factor, or modest-sized set of factors, can sufficiently predict mobilization efficiency or failure to support decision making with respect to donor selection, dosing of mobilizing agents, or pre-emptive addition of CXCR4 antagonists.
In summary, the results of the current study are in line with a contribution of genetics to stem cell mobilization, but at the same time suggest that the contribution of a single variant to the explanation of variance is limited. As a consequence, prediction of mobilization success is not feasible using a single variant marker and future research on the prediction of mobilization success should focus on the integration of multiple variants in polygenetic scores.

Disclosures
No conflicts of interest to disclose.

Contributions
The contributions of the authors are reported using the Contributor Role Taxonomy (CRediT). Conceptualization by MS, JB, JLB and HB. Methodology by MS, JB, A-LV and AA. Data acquisition by MS, ALdLP, BN and YPL. Data analysis by SB, IO and NP. Investigation by MS, SB and JB. Software by SB. Formal analysis by SB and JB. Visualization by SB and JB. Supervision by MS and JB. Writing of the original draft by MS, SB and JB. Writing i.e., review and editing by all authors. Funding acquisition, management and project administration by MS. All authors have critically contributed to the manuscript in accordance with the ICMJE criteria, have approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Data-sharing statement
The summary statistics of the interrogated variants in the current study can be downloaded from the GWAS Catalog at EBI (https://www.ebi.ac.uk/gwas/search?query=GCST90502916).

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