Supplemental Material – Nürnberg et al

1) **Method - EMSA**
2) **Figures S1 – 8**
3) **Tables S1 – 3**
4) **HaemGen Consortium Members**

An additional file is provided separately in excel format containing list of 1,285 potentially MEIS1 regulated genes (**Supplemental File 2**)

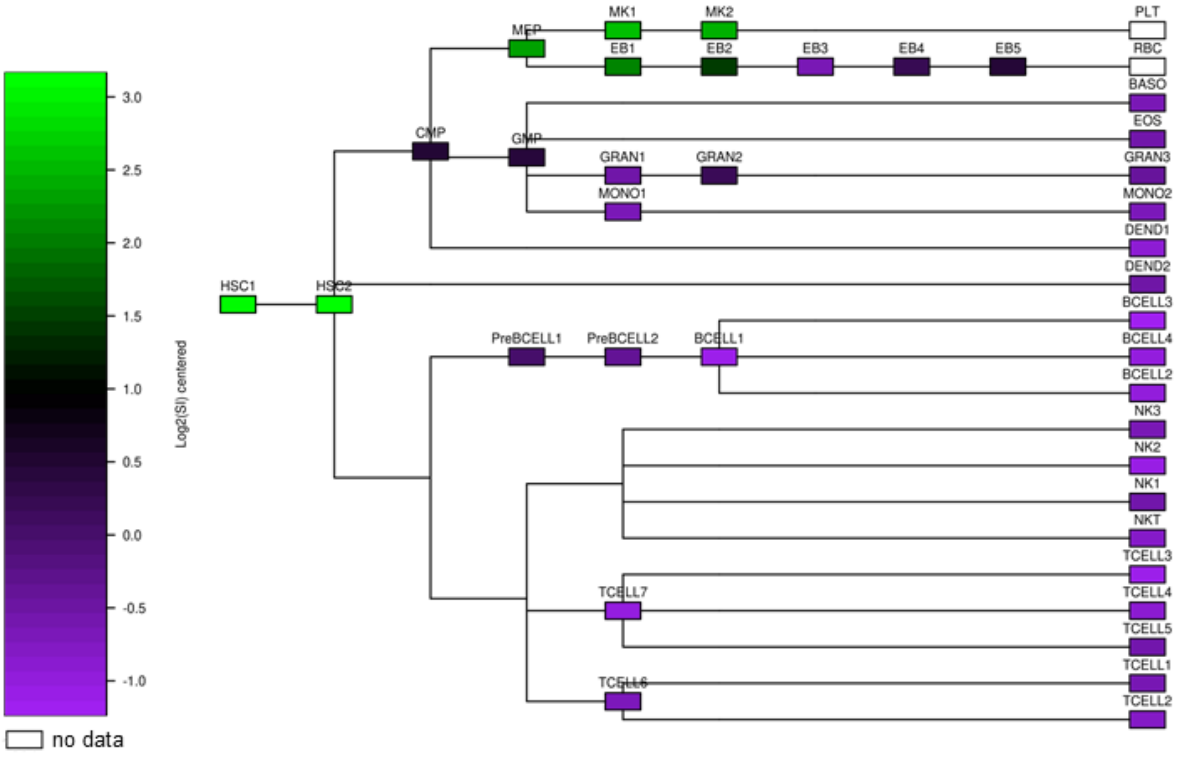
Electrophoretic mobility shift assays (EMSAs)

EMSAs with nuclear extracts from CHRF-288-11 cells were performed as previously described[2]. Briefly, nuclear extracts were prepared with the NE-PER Nuclear and Cytoplasmic Extraction Reagents (Thermo Fisher Scientific). Oligonucleotides were designed based on the genomic sequence surrounding rs2038479; the SNP position is shown in bold: 5'-biotin- ACTGC-TATTT-TCATT-TTAT**[C/A]**GATG-GAATA-CTTTG-AAG. Competitor probes were prepared without biotin tags. All oligonucleotides were ordered from Sigma-Aldrich. We performed gel mobility shift assays with the LightShift Chemiluminescent EMSA Kit (Thermo Fisher Scientific) according to the manufacturer's protocol.

Figure S1:

Expression profile of *MEIS1* during hematopoiesis

(based on microarray data from Novershtern et al. Cell 2011 (PMID: 21241896))



BCELL: B Cell
BASO: Basophil Granulocyte
CMP: Common Myeloid Progenitor
DEND: Dendritic Cells
EB: Erythroblast
EOS: Eosinophil Granulocyte
GMP: Granulocyte-Monocyte Progenitor
GRAN: Granulocyte
HSC: Haematopoietic Stem Cell
MEP: Megakaryocyte-Erythrocyte Progenitor
MK: Megakaryocyte
MONO: Monocyte
NK: Natural Killer Cell
PLT: Platelet
PreBCELL: Pre-B Cell
RBC: Red Blood Cell
TCELL: T Cell

Figure S2:

Comparison of genome-wide expression profiles of megakaryocytic cell lines DAMI, MEG01 and CHRF 288-11 and cultured megakaryocytes (MK) and erythroblasts (EB)

(Microarray data of cultured MKs and EB from Watkins et al. Blood 2009 (PMID: 19228925) is available from ArrayExpress, accession number E-TABM-633. Microarray data sets of CHRF, DAMI and MEG01 available from ArrayExpress, accession number E-MTAB-908.

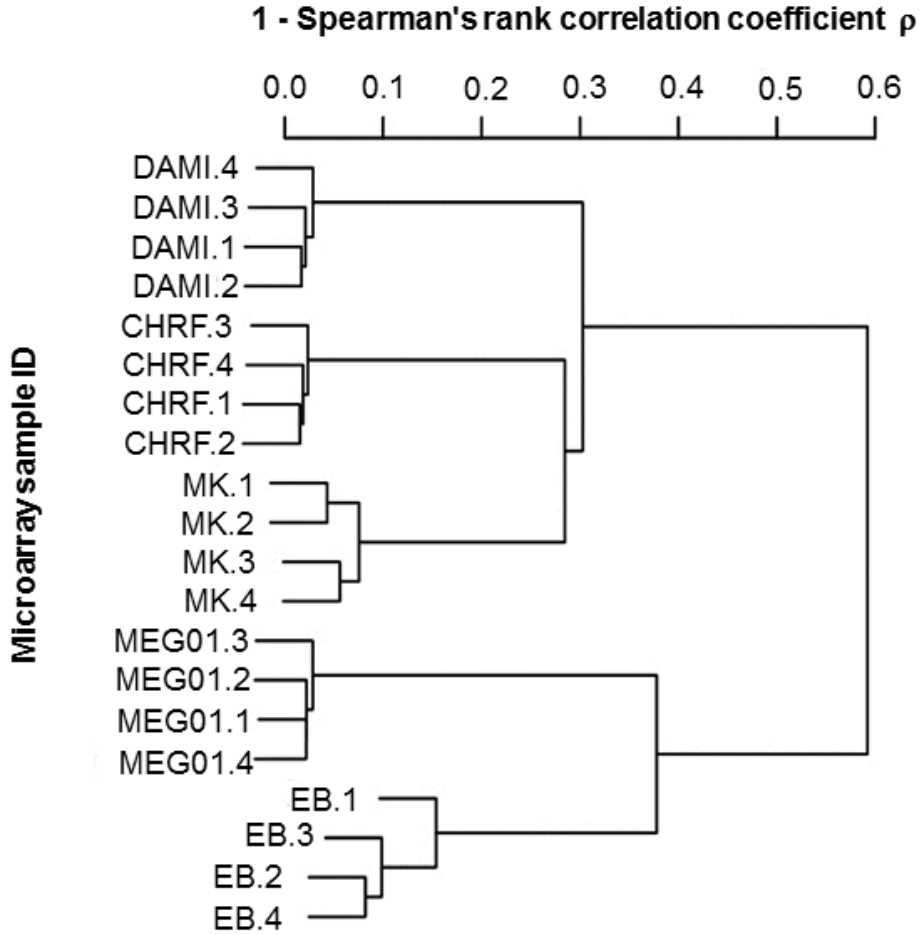


Figure S3:

GREAT analysis of enrichement of 13,842 MEIS1 binding peaks near annotated protein coding genes

A) Absolute distance to transcription start site (TSS)
B) Distance to TSS relative to gene orientation
C) Number of associated genes per region

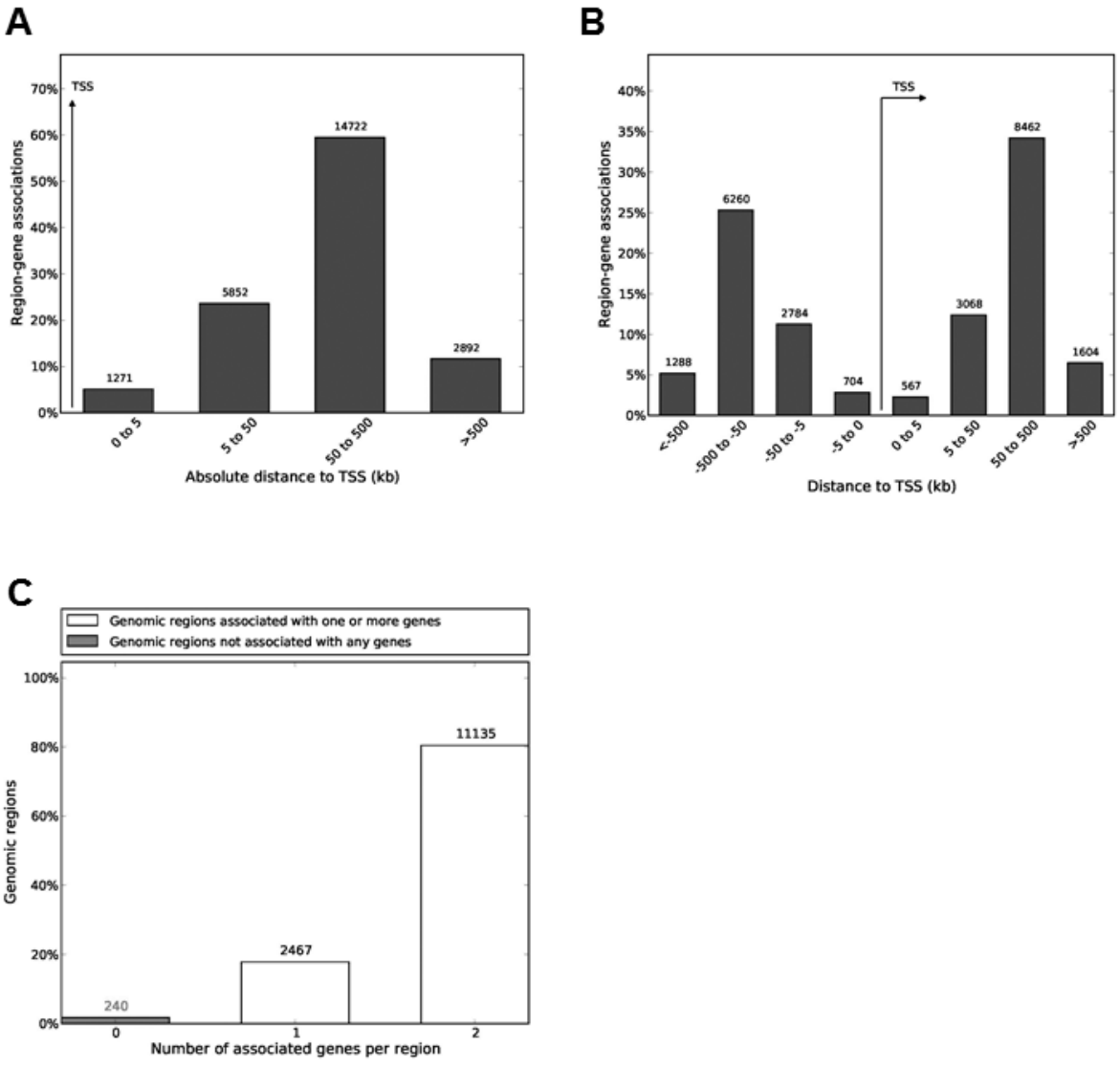
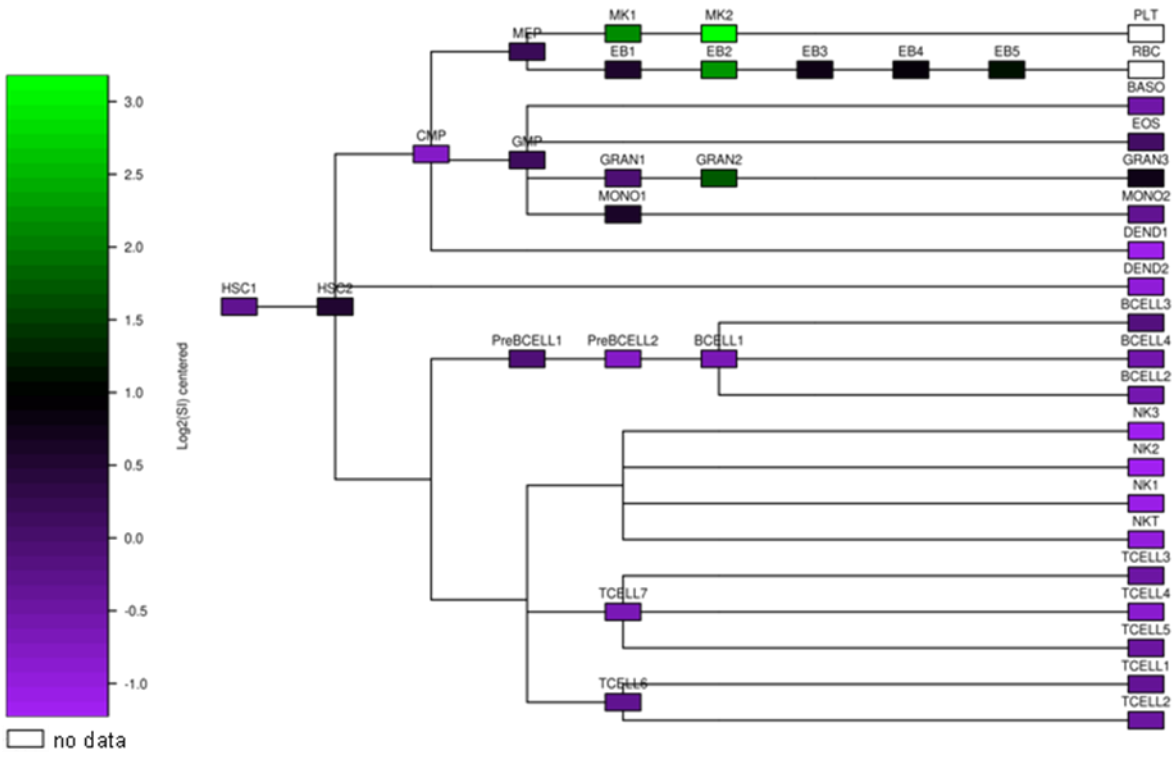


Figure S4:

Expression profile of *DNM3* during hematopoiesis

(based on microarray data from Novershtern et al. Cell 2011 (PMID: 21241896))



BCELL: B Cell
BASO: Basophil Granulocyte
CMP: Common Myeloid Progenitor
DEND: Dendritic Cells
EB: Erythroblast
EOS: Eosinophil Granulocyte
GMP: Granulocyte-Monocyte Progenitor
GRAN: Granulocyte
HSC: Haematopoietic Stem Cell
MEP: Megakaryocyte-Erythrocyte Progenitor
MK: Megakaryocyte
MONO: Monocyte
NK: Natural Killer Cell
PLT: Platelet
PreBCELL: Pre-B Cell
RBC: Red Blood Cell
TCELL: T Cell

Figure S5:

Expression of MEIS1 and DNM3 transcript variants in different primary tissues and cell lines

(n = 3, error bars show SD, normalized on GAPDH)

A) DNM3 consensus transcript abundance
B) DNM3 alternative transcript abundance
C) Total MEIS1 abundance

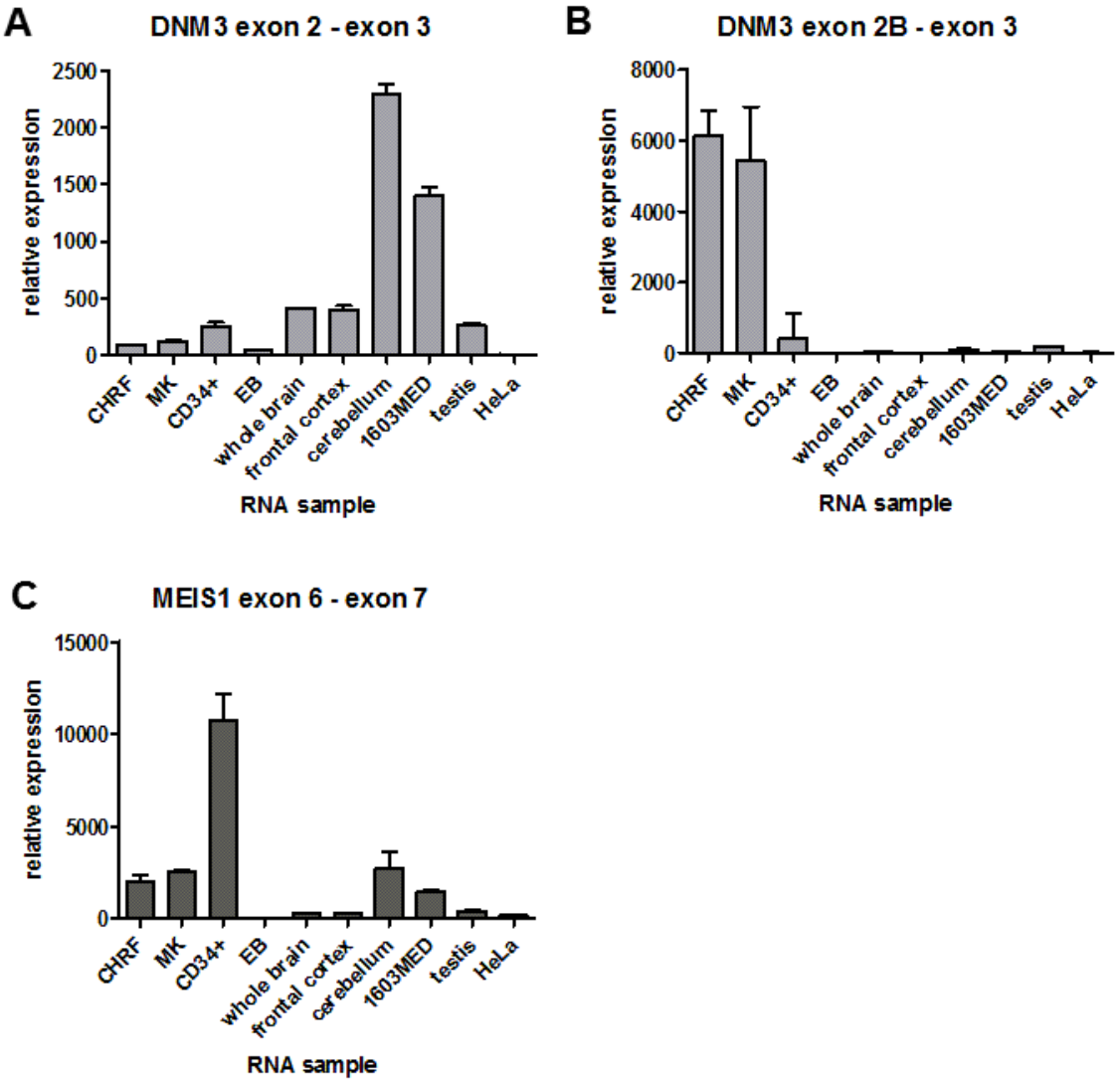


Figure S6:

Abundance of DNM3 transcript variants in 4 different MK cultures from cord blood CD34+ cells and platelets (heterozygous for rs2038479)

(n = 3, error bars show SD, normalised to GAPDH,
A-C) relative to EB = 1, D) relative to 0d Ex2-3 = 100)

A) Total DNM3 abundance
B) DNM3 consensus transcript
C) DNM3 alternative transcript
(numbers within columns represent percentage CD41+ cells)
D) Abundance of both transcript variants in platelets relative to CD34+ cells and corresponding cultured MKs at day 12

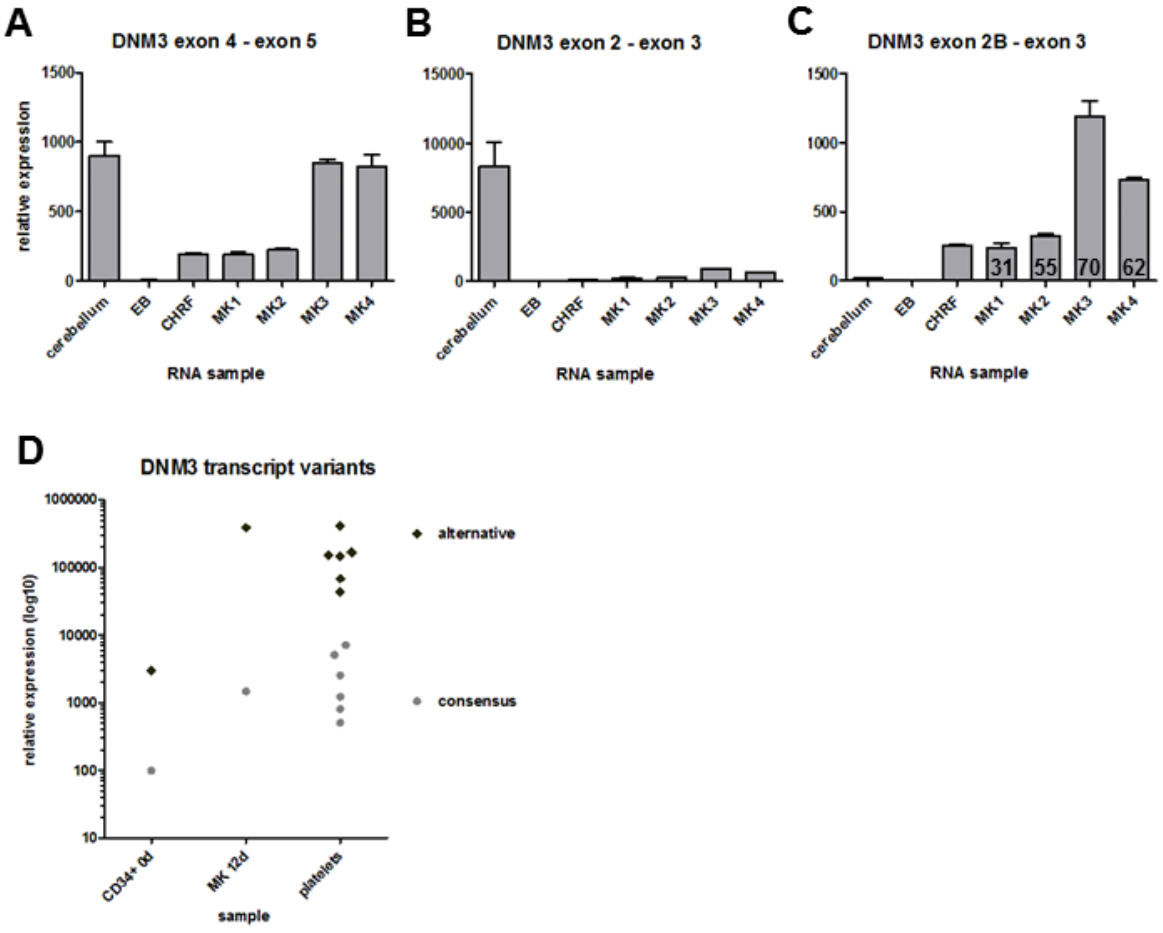


Figure S7:

Electrophoretic mobility shift assay with nuclear extract of CHRF cells and both alleles of rs2038479

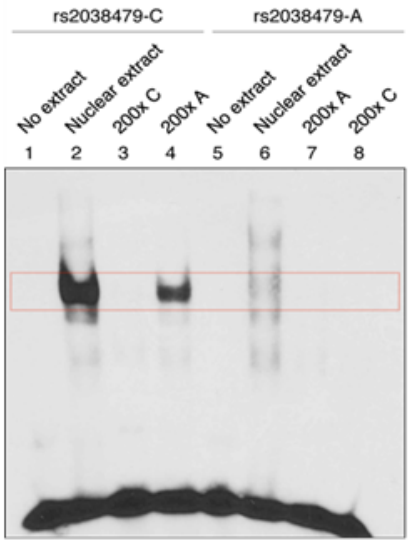


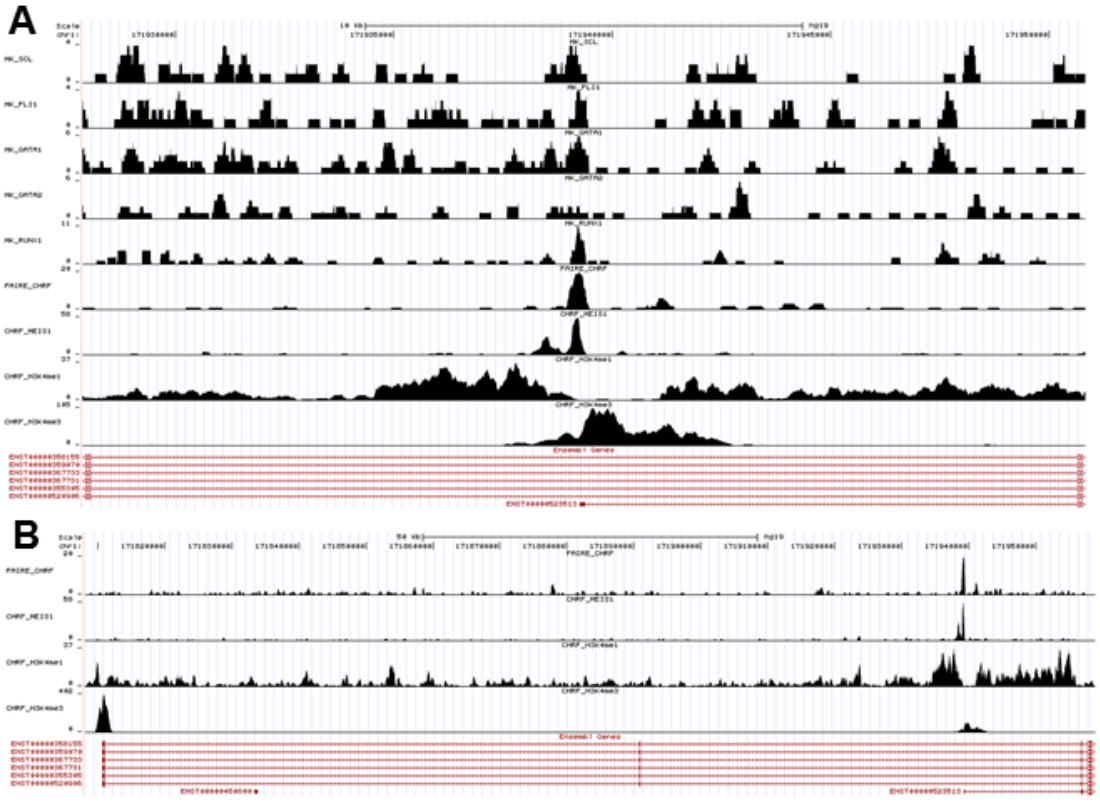
Figure S8:

Annotation of the megakaryocytic genome landscape at the *DNM3* locus

The ChIP-seq experimental results from this manuscript (lanes 6-7), non-published results on histone modifications in CHRF cells (lane 8: H3K4 monomethylation [H3K4me1] and lane 9: H3K4 trimethylation [H3K4me3]) are shown together with the ChIP-seq results (lanes 1-5) from the manuscript by Tijssen et al. (2011, Developmental Cell, 20:597-609).

A) At the MEIS1/FAIRE site at SNP rs2038479 (which marks the alternative DNM3 promoter at exon 2B) binding of the transcription factor RUNX1 is supported by a low number of reads but also low background (highest fragment count at peak of 11). The number of reads relative to the background for the other four factors does not support their binding (SCL, FLI1 and GATA1/2).

B) A snapshot of the 5' prime of the DNM3 gene at the consensus and alternative start sites. At the consensus position there is small H3K4me1 signal, strong H3K4me3 mark and no FAIRE signal, which is compatible with a canonical promoter that is repressed (see Kowalczyk MS, Hughes JR, Garrick D, et al. Mol Cell;45:447-458). At the alternative start site, H3K4me1 is high, H3K4me3 is low and FAIRE is highly suggestive of an intragenic enhancer that results in the production of multi-exon transcripts driven from this promoter.



Supplemental Tables

Table S1: TaqMan gene expression assays

Gene	Probe location	Type	Sequence	Product number
DNM3	exon2-exon3			Hs00399015_m1
DNM3	exon2B-exon3	forward primer	ATAATTTTTAAAATAATCCAATAACAAACTCAGAACTACTGAA	custom
		reverse primer	GGCGAACTTCATCAAAATCTGTAAATTTCT	
		probe	6FAM-CTCGGCATATTCTTTATTATTC-TAMRA	
DNM3	exon4-exon5			Hs00927945_m1
GAPDH				Hs99999905_m1

Table S2: 5'RACE primers and clone sequences

Primer	Sequence
465R(3)	gcttcaatctcaaggcgaac
601R(4)	ctgatctcccacaggcactt
841R(5)	gcgaagaggcaacagtttgt
CHRF1	GtTCCTTCCTTCAGCATCCTACTGCTATTTTCATTTTATAGATGGAATACTTTGAAGCACGAAAAATCATTATATCTTGNAAT AATTTTTAAAATAATCCAATAACAAACTCAGAACTACTGAAGAATAATAAAGAATATGCCGAGTTTCTACATTGCAAAGGAA AGAAATTTACAGATTTTGATGAAGTTCGCCTTGAGATTGAAGC

CHRF2	GNTGGAATACTTTGAAGCACGAAAAATCATTATATCTTGAAATAATTTTTAAAATAATCCAATAACAAACTCAGAACTACTGAAGAATAATAAAGAATATGCCGAGTTTCTACATTGCAAAGGAAAGAAATTTACAGATTTTGATGAAGTTCGCCTTGAGATTGAAGC
CHRF3	AATNCTTTGAAGCACGAAAAATCATTATATCTTGAAATAATTTTTAAAATAATCCAATAACAAACTCAGAACTGCTGAAGAATAATAAAGAATATGCCGAGTTTCTACATTGCAAAGGAANGAAATTTACAGATTTTGATGAAGTTCGCCTTGAGATTNAAG
CHRF4	GAATACTTTGAAGCACGAAAAATCATTATATCTTGAAATAATTTTTAAAATAATCCAATAACAAACTCAGAACTACTGAAGAATAATAAAGAATATGCCGAGTT
PL1	TTTTCATTTTATCGATGGAATACTTTGAAGCACGAAAAATCATTATATCTTGAAATAATTTTTAAAATAATCCAATAACAAACTCAGAACTACTGAAGAATAATAAAGAATATGCTGAGTTTCTACATTGCAAAGGAAAGAAATTTACAGATTTTGATGAAGTTCGCCTTGAGATTGAAGCAGAAACAGATCGCGTGACTGGAATGAATAAAGGCATTTCCTCCATACCCATTAATTTACGAGTCTATTCCCCACACGTGTTAAATCTAACCCTTATTGATC-TACCTGGAATAACTAAAGTGCCTGTGGGAGATCAG
PL2	TTTTCAATTTTTAAAATAATCCAATAACAAACTCAGAACTACTGAAGAATAATAAAGAATATGCTGAGTTTCTACATTGCAAAGGAAAGAAATTTACAGATTTTGATGAAGTTCGCCTTGAGATTGAAGC
PL3	TTTTCATTTTATCGATGGAATACTTTGAAGCACGAAAAATCATTATATCTTGAAATAATTTTTAAAATAATCCAATAACAAACTCAGAACTACTGAAGAATAATAAAGAATATGCTGAGTTTCTACATTGCAAAGGAAAGAAATTTACAGATTTTGATGAAGTTCGCCTTGAGATTGAAGC
MK1	CTGCATCCTACTGCTATTTTCATTTTATAGATGGAATACTTTGAAGCACGAAAAATCATTATATCTTGAAATAATTTTTAAAATAATCCAATAACAAACTCAGAACTACTGAAGAATAATAAAGAATATGCCGAGTTTCTACATTGCAAAGGAGAGAAATTTACAGATTTTGATGAAGTTCGCCTTGAGATTGAAGCA
MK2	CATTTTATAGATGGAATACTTTGAAGCACGAAAAATCATTATATCTTGAAATAATTTTTAAAATAATCCAATAACAAACTCAGAACTACTGAAGAATAGTAAAGAATATGCCGAGTTTCTACATTGCAAAGGAAAGAAATTTACAGATTTTGATGAAGTTCGCCTTGAGATTGAAGC
MK3	CATTTtaTANATGGAATACTTTGAAGCACGAAAAATCATTATATCTTGAAATAATTTTTAAAATAATCCAATAACAAACTCAGAACTACTGAAGAATAATAAAGAATATGCCGAGTTTCTACATTGCAAAGGAAAGAAATTTACAGATTTTGATGAAGTTCGCCTTGAGATTGAAGC
MK4	AGATGGAATACTTTGAAGCACGAAAAATCATTATATCTTGAAATAATTTTTAAAATAATCCAATAACAACCTCAGAACTACTGAAGAATAATAAAGAATATGCCGAGTTTCTACATTGCAAAGGAAAGAAATTTACAGATTTTGATGAAGTTCGCCTTGAGATTGAAGC
CHRF_PCR	GTTCCTTCCTTCTGCATCCTACTGCTATTTTCATTTTATAGATGGAATACTTTGAAGCACGAAAAATCATTATATCTTGAAATAATTTTTAAAATAATCCAATAACAAACTCAGAACTACTGAAGAATAATAAAGAATATGCCGAGTTTCTACATTGCAAAGGAAAGAAATTTACAGATTTTGATGAAGTTCGCCTTGAGATTGAAGCAGAAACAGATCGCGTGACTGGAATGAATAAAGGCATTT

	CCTCCATACCCATTAATTTACGAGTCTATTCCCCACACGTGTTAAATCTAACCCTTATTGATCTACCTGGAATAACTAAAGT GCCTGTGGGAGATCAGCCACCAGATATCGAGTATCAGATCAGAGAAATGATTATGCAGTTCATCACGAGGGAGAACTGTC TGATTTTAGCTGTTACTCCAGCCAACACTGATCTTGCAAACTCAGATGCGCTGAAGCTAGCTAAAGAAGTTGATCCTCAAG GTCTGAGAACCATTGGAGTTATCACCAAACTGGACCTTATGGATGAAGGAACGGATGCCAGGGATGTTCTAGAGAACAAA CTGTTGCCTCTTCGCAGGGGTTACGTGGGGGTGGTAAACAGAAGCCAGAAGGACATAGATGGGAAGAAGGACATAAAGG CAGCTATGCTGGCAGAGAGGAAGTTTTTCCTTTCCCACCCGGCTTACAGACATATCGCTGACCGAATGGGAACCCCACAC CTGCAGAAGGTCCTTAATCAGCAACTTACCAACCACATTCGGGATACCCTACCAAACTTCAGGAACAAACTACAGGGACA GTTGCTCTCCATAGAACATGAAGTAGAAGCCTACAAAAATTTCAAACCAGAAGACCCAACAAGGAAGACCAAAGCATTGCT GCAGATGGTTCAGCAATTTGCTGTGGACTTTGAGAAGAGAATTGAAGGGTCAGGGGATCAAGTAGATACCCTGGAACTCT CAGGTGGTGCTAAAATCAATCGTATTTTTCATGAACGCTTTCCTTTTGAGATAGTAAAGATGGAGTTCAATGAGAAAGAATT GCGAAGAGAAATAAGCTATGCAATCAAAAACATACATGGTATCAGGACAGGGTTGTTTACTCCAGACATGGCATTTGAAG CGATAGTCAAGAAACAGATTGTAAAGTTGAAAGGGCCTTCCTTGAAGAGTGTGGATCTGGTAATACAAGAATTAATCAACA CTGTGAAGAAGTGTACCAAAAAGCTGGCAAACTTCCCCAGACTCTGCGAGGAAACGGAAAGGATTGTTGCTAACCACATT CGTGAGCGAGAAGGGAAGACAAAGGACCAGGTATTGCTATTGATTGACATTCAAGTCTCTTACATCAACACCAACCGTGA AGACTTCATTGGCTTCGCAAATGCTCAGCAGAGGAGCAGTCAGGTTCACAAGAAAACCACAGTTGGAAATCAGGGAACCA ATCTTCCGCCTTCAAGGCAAATTGTGATTCGCAAGGGGTGGCTCACCATCAGCAACATTGGCATCATGAAAGGCGGCTCG AAGGGATACTGGTTCGTCCTTACTGCGGAAAGCTTGTCCTGGTATAAAGATGATGAGGAAAAAGAAAAGAAGTACATGCT TCCCTTGGACAACCTGAAAGTTCGGGATGTGGAAAAGAGCTTTATGTCTAGCAAGCACATCTTTGCACTCTTTAATACAGA GCAAAGGAATGTATACAAAGACTATCGCTTCCTTGAGCTGGCATGTGATTCCCAGGAGGATGTCGACAGCTGGAAGGCAT CTCTACTAAGAGCTGGGGTCTATCCTGACAAATCTGTAGCTGAAAATGATGAGAATGGACAAGCAGAAAACTTTTCCATGG ACCCACAATTGGAGAGGCAAGTGGAGACCATTCGCAACCTCGTAGACTCCTACATGTCCATTATCAACAAATGTATCCGA GATCTAATTCCAAAAACAATAATGCACCTTATGATCAATAACGTTAAAGATTTCATAAATTCCGAGCTCCTAGCACAGTTGT ATTCTTCAGAGGACCAAAATACCCTGATGGAGGAATCTGCTGAGCAGGCTCAGCGCCGGGATGAGATGCTTCGAATGTAT CAAGCACTGAAAGAAGCCCTTGGGATAATTGGGGACATCAGCACGGCCACCGTGTCCACTCCGGCACCCCCTCCAGTGG ATGACTCCTGGATACAGCACTCTCGCAGGTCACCTCCTCCAAGCCCCACAACCCAAAGGAGGCCAACACTAAGTGCTCC CCTCGCAAGGCCCACATCCGGCCGAGGACCAGCTCCTGCCATTCCCTCTCCTGGCCCCCACTCTGGGGCTCCTCCAGT CCCATTCCGTCCAGGCCCATTACCTCCTTTCCCCAGCAGCAGTGACTCCTTCGGAGCCCCTCCACAAGTTCCATCTAGGC CTACGAGGGCCCCGCCCAGTGTCCCAAGCCGGAGACCACCCCCATCACCAACTCGTCCCACTATAATCCGCCCACTAGA ATCCTCCCTGTTAGACTAA

Table S3: Luciferase assay cloning primers and construct inserts

Name	Sequence
conprom xhoI for	ctcgagactccaacaggcctgccacc
conprom bglII rev	agatctgcctatctccgcgacgcc
altprom xhoI for	ggccctcgagtatccccattttacatagaggaaac
altprom gblII rev	agatctttcttcagtagttctgagtttgttattg
random construct	AAACTTGACCTGGAAATTAAAAAGATACTTTTTATGGAATTGGACAACGCATTAACGCAACGAATCTACATTATAAC GTGTATAGTAAAAACAAAATTGCTGACGACAAAAGCGACATTGAAATCTGTTTATTGTTATTTGCGAAAAACATCCG TTTACAAGGCGGATATTGATTGACACGATTTTATAGAAGGTTAGGGGAATAGATTAAATTAAATAGCTTAAAAATGT TATATCTGGGATTAAAGTGTAGTAAACTATAATTAACGGAGACGGTTTTAAGACAGAAATTTACAAAATCAAACGAG GTCATTACAACAATTATTTTTGATGATTTAGGCGTACAATGTCTTAAAGAATATTTAAAAAAAAAGCATTCCTTGTTG CCTAGAATTACTTAC
alternative promoter major	CTATCCCCATTTTACATAGAGGAAACTGAGGCACAGAGAAGTTACAGTTTACCCAGAACAGTCAGGGTTGTTTGGA GTATTAACATGAAATAATGTGTGTGACTAAAAGCTTGGTGTGTAGTACAGCAGATTCTCAGTCATTTTTAATTTACTC TAAGGGTCAAGAGTTAGTAAATATAGAAGTCCATGTGACTTTGGGGCTTTCATTGGGCAAAACCACAAGTTTTGGC GGAAACAGATAAAGATAAGCACTTATTCTTATTTGGCATAGATAGTTCCTTCCTTCTGCATCCTACTGCTATTTTCAT TTTATAGATGGAATACTTTGAAGCACGAAAAATCATTATATCTTGAAATAATTTTTAAAATAATCCAATAACAAACTCA GAACTACTGAAGAA
alternative promoter minor	CTATCCCCATTTTACATAGAGGAAACTGAGGCACAGAGAAGTTACAGTTTACCCAGAACAGTCAGGGTTGTTTGGA GTATTAACATGAAATAATGTGTGTGACTAAAAGCTTGGTGTGTAGTACAGCAGATTCTCAGTCATTTTTAATTTACTC TAAGGGTCAAGAGTTAGTAAATATAGAAGTCCATGTGACTTTGGGGCTTTCATTGGGCAAAACCACAAGTTTTGGC GGAAACAGATAAAGATAAGCACTTATTCTTATTTGGCATAGATAGTTCCTTCCTTCTGCATCCTACTGCTATTTTCAT TTTATCGATGGAATACTTTGAAGCACGAAAAATCATTATATCTTGAAATAATTTTTAAAATAATCCAATAACAAACTCA GAACTACTGAAGAA

consensus promoter	AGACTCCAACAGGCCTGCCACCCTGGGAGGAGTCATCGCGGATTCTGGAGAAGGGCGTGACAGAGGAGATTTCC TTTCGGGAAGTGTAGTCTGGCAGCGGTGCCCCGGTGGTGGCGGCGGCGGTGCTGCTGTTGCTGGTGATCGTGT GGTGGTGTTAGCGGCGATAGTGCTTTCCACTGGGCTTTGGCTTGGTAGCCGCTGAAAGAGAACAACGCTGCCGC TGCTGCTGATTTCATGCCATTTCCTGACCCGGCGCTGTAACTTGGCCTCTGAGCCTTGGCCACAGAACGCAGAGG CCGTGGCATCTGGCCGCAGCTGGGCTGCAGTGCGTGCGCGCCTGGCCTGGTGGTCCGATGGGAAGCCCGGGGG CGGGGCAGCCGCGGGGCGGGGGCGGGGCGTCGCGGAGATAGGCA

HaemGen Consortium

The HaemGen Consortium granted pre-publication access to the results of their genome-wide association meta-analysis study in about 67,000 individuals for platelet volume and count, which identified the 68 independent genetic loci that are associated with either or both traits at genome-wide significance. It consists of the following members:

Christian Gieger[1*], Aparna Radhakrishnan[2,3*], Ana Cvejic[2,3*], Weihong Tang[4*], Eleonora Porcu[5*], Giorgio Pistis[6*], Jovana Serbanovic-Canic[2,3*], Ulrich Elling[7], Alison H. Goodall[8,9], Yann Labrune[10], Lorna M. Lopez[11,12], Reedik Mägi[13,28], Stuart Meacham[2,3], Yukinori Okada[14,15], Nicola Pirastu[16,17], Rossella Sorice[18], Alexander Teumer[19], Katrin Voss[2], Weihua Zhang[20], Ramiro Ramirez-Solis[3], Joshua C. Bis[21], David Ellinghaus[22], Martin Gögele[23], Jouke-Jan Hottenga[24], Claudia Langenberg[25],Peter Kovacs[26], Paul F. O'Reilly[27], So-Youn Shin[3,28], Tõnu Esko[29,30,31], Jaana Hartiala[32,33], Stavroula Kanoni[3,34], Federico Murgia[35], Afshin Parsa[36], Jonathan Stephens[2], Pim van der Harst[37], C. Ellen van der Schoot[38], Hooman Allayee[32,33],Antony Attwood[2,3], Beverley Balkau[39,40], François Bastardot[41], Saonli Basu[42], Sebastian E. Baumeister[43], Ginevra Biino[35,44,45], Lorenzo Bomba[46], Amélie Bonnefond[10], François Cambien[47], John C. Chambers[20], Francesco Cucca[5], Pio D'Adamo[16,17], Gail Davies[12], Rudolf A. de Boer[37], Eco J. C. de Geus[24], Angela Döring[48,49], Paul Elliott[20,50], Jeanette Erdmann[51,102], David M. Evans[52], Mario Falchi[53], Wei Feng[42], Aaron R. Folsom[4], Ian H. Frazer[54], Quince D. Gibson[36], Nicole L. Glazer[55], Chris Hammond[28], Anna-Liisa Hartikainen[56], Susan R. Heckbert[57,58], Christian Hengstenberg[59], Micha Hersch[60], Thomas Illig[61], Ruth J. F. Loos[25], Jennifer Jolley[2], Kay Tee Khaw[62,63], Brigitte Kühnel[1], Marie-Christine Kyrtsonis[64], Vasiliki Lagou[65], Heather Lloyd-Jones[2], Thomas Lumley[66], Massimo Mangino[28], Andrea Maschio[5], Irene Mateo Leach[37], Barbara McKnight[66], Yasin Memari[3,28], Braxton D. Mitchell[36], Grant W. Montgomery[67], Yusuke Nakamura[68], Matthias Nauck[69], Gerjan Navis[70], Ute Nöthlings[71,72], Ilja M. Nolte[73], David J. Porteous[11,74], Anneli Pouta[56,75], Peter P. Pramstaller[23], Janne Pullat[29], Susan M. Ring[52], Jerome I. Rotter[76], Daniela Ruggiero[18], Aimo Ruokonen[77], Cinzia Sala[6], Nilesh J. Samani[8,9], Jennifer Sambrook[2,78], David Schlessinger[79], Stefan Schreiber[21], Heribert Schunkert[50,101], James Scott[79], Nicholas L. Smith[56,57,80], Harold Snieder[72], John M. Starr[11,82], Michael Stumvoll[83], Atsushi Takahashi[14], W. H. Wilson Tang[84,85], Kent Taylor[76], Albert Tenesa[86,87], Swee Lay Thein[88], Anke Tönjes[83], Manuela Uda[5], Sheila Ulivi[16], Dirk J. van Veldhuisen[37], Peter M. Visscher[11,67], Uwe Völker[19], H.-Erich Wichmann[48,89], Kerri L. Wiggins[21], Gonneke Willemsen[24], Tsun-Po Yang[3], Jing Hua Zhao[25], Paavo Zitting[90], John R. Bradley[78], George V. Dedoussis[34], Paolo Gasparini[16,17], Stanley L. Hazen[84], Andres Metspalu[29,30,31], Mario Pirastu[35,44], Alan R. Shuldiner[36,91], L. Joost van Pelt[92], Jaap-Jan Zwaginga[93], Dorret I.Boomsma[24], Ian J. Deary[11,12], Andre Franke[22], Philippe Froguel[10,53], Santhi K. Ganesh[94], Marjo-Riitta Jarvelin[27,95,96], Nicholas G. Martin[67], Christa Meisinger[49], Bruce M. Psaty[58,97], Timothy D. Spector[28], Nicholas J. Wareham[25], Jan-Willem N. Akkerman[98], Marina Ciullo[18], Panos Deloukas[3], Andreas Greinacher[99], Steve Jupe[100], Naoyuki Kamatani[14], Jyoti Khadake[100], Jaspal S. Kooner[80], Josef Penninger[7], Inga Prokopenko[65], Derek Stemple[3], Daniela Toniolo[6,45], Lorenz Wernisch[101], Serena Sanna[5*], Andrew A. Hicks[23*], Augusto Rendon[2,101*], Manuel A. Ferreira [67*], Willem H. Ouwehand [2,3,78*] & Nicole Soranzo[3*]

[1]Institute of Genetic Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Ingolstädter Landstr.1, 85764 Neuherberg, Germany. [2]Department

of Haematology, University of Cambridge & NHS Blood and Transplant, Cambridge CB2 0PT, UK. [3]Wellcome Trust Sanger Institute, Hinxton, Cambridge, CB10 1HH/1SA, UK. [4]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota 55455-0354, USA. [5]Istituto di Ricerca Genetica e Biomedica, Consiglio Nazionale delle Ricerche, c/o Cittadella Universitaria di Monserrato, Monserrato, Cagliari 09042, Italy. [6]San Raffaele Scientific Institute, Via Olgettina 58, 20132 Milano, Italy. [7]IMBA, Institute of Molecular Biotechnology of the Austrian Academy of Sciences, 1030 Vienna, Austria. [8]Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Groby Road, Leicester LE3 9QP, UK. [9]Leicester NIHR Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester LE3 9QP, UK. [10]CNRS-UMR-8199, Institut de Biologie de Lille, 1 Rue du Professor Calmette, BP245, 59019 Lille Cedex, France. [11]Centre for Cognitive Ageing and Cognitive Epidemiology, 7 George Square, The University of Edinburgh, Edinburgh EH8 9JZ, UK. [12]Department of Psychology, The University of Edinburgh, 7 George Square, Edinburgh EH8 9JZ, UK. [13]Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford OX3 7BN, UK. [14]Laboratory for Statistical Analysis, RIKEN Center for Genomic Medicine, Institute of Physical and Chemical Research, 1-7-22 Suehiro-cho, Tsurumi-ku, Yokohama, Kanagawa 230-0045, Japan. [15]Department of Allergy and Rheumatology, Graduate School of Medicine, University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, 113-8654, Japan. [16]Institute for Maternal and Child Health, IRCCS-Burlo Garofolo, University of Trieste, via dell‚ÄôIstria 65, 34137 Trieste, Italy. [17]University of Trieste, Piazzale Europa 1, 34127 Trieste, Italy. [18]Institute of Genetics and Biophysics A. Buzzati-Traverso, CNR, Via P. Castellino, 8031 Naples, Italy. [19]Interfaculty Institute for Genetics and Functional Genomics, Ernst-Moritz-Arndt-University Greifswald, 17487 Greifswald, Germany. [20]Department of Epidemiology and Biostatistics, School of Public Health, Faculty of Medicine, St Mary,s Campus, London W2 1PG, UK. [21]Department of Medicine, University of Washington, 1959 Northeast Pacific Street, Seattle, Washington 98195-0001, USA. [22]Institute of Clinical Molecular Biology, Christian-Albrechts-University, 24105 Kiel, Germany. [23]Centre for Biomedicine, European Academy Bozen/Bolzano, Viale Druso 1, 39100 Bolzano, Italy. [24]Department of Biological Psychology, VU University Amsterdam, De Boelelaan 1105, 1081 HV Amsterdam, The Netherlands. [25]MRC Epidemiology Unit, Institute of Metabolic Science, Addenbrooke,s Hospital, Box285, CambridgeCB20QQ,UK. [26]Interdisciplinary Centre for Clinical Research, University of Leipzig, Inselstr. 22, 04103 Leipzig, Germany. [27]Department of Epidemiology and Biostatistics, Imperial College London, London W2 1PG, UK. [28]Department of Twin Research and Genetic Epidemiology, King,s College London, London SE1 7EH, UK. [29]Estonian Genome Center, University of Tartu, Tiigi 61b, 50410 Tartu, Estonia. [30]Estonian Biocenter, Riia 23b, 51010, Tartu, Estonia. [31]Institute of Molecular and Cell Biology, University of Tartu, Tartu, Estonia. [32]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California 90089-9075, USA. [33]Institute for Genetic Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California 90089-9075, USA. [34]Department of Nutrition-Dietetics, Harokopio University, Athens 17671, Greece. [35]Institute of Population Genetics, National Council of Research, 07100 Sassari, Italy. [36]University of Maryland School of Medicine, 655 West Baltimore Street, Baltimore, Maryland 21201-1559, USA. [37]Department of Cardiology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands. [38]Department of Experimental Immunohaematology, Sanquin Research, Plesmanlaan 125, 1066 CX Amsterdam, The Netherlands and Landsteiner Laboratory, Academic Medical Centre, University of Amsterdam, Meibergdreef 9, 1105 AZ

Amsterdam, The Netherlands. [39]Inserm, CESP Centre for research in Epidemiology and Population Health, U1018 Villejuif, 94807 France. [40]University Paris Sud 11, UMRS 1018, Villejuif, 94807 France. [41]Service de Medecine Interne, CHUV, 1011 Lausanne, Switzerland. [42]Division of Biostatistics, School of Public Health, University of Minnesota, A460 Mayo Building, mmc 303, 420 Delaware St SE, Minneapolis, Minnesota 55455,USA. [43]Institute for Community Medicine, Ernst-Moritz-Arndt-University Greifswald, 17475 Greifswald, Germany. [44]Shardna Life Sciences, Loc. Piscinamanna 09010 Pula (CA), Italy. [45]Insitutte of Molecular Genetics-CNR Via Abbiategrasso 207, 27100 Pavia, Italy. [46]Istituto di Zootecnica, Universita Cattolica del Sacro Cuore sede Piacenza, via Emilia Parmense 84, 29122 Piacenza, Italy. [47]INSERM UMRS 937, Pierre and Marie Curie University (UPMC, Paris 6) and Medical School, 91 Bd de l,Hopital, 75013 Paris, France. [48]Institute of Epidemiology I, Helmholtz Zentrum München, German Research Center for Environmental Health, Ingolstädter Landstr.1, 85764 Neuherberg, Germany. [49]Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Environmental Health, Ingolstädter Landstr.1, 85764 Neuherberg, Germany. [50]MRC-HPA Centre for Environment and Health, Imperial College London, St Mary,s Campus, Norfolk Place, London W2 1PG, UK. [51]Universität zu Lübeck, Medizinische Klinik 2, Lübeck Germany. [52]MRC Centre for Causal Analyses in Translational Epidemiology, School of Social and Community Medicine, University of Bristol, Oakfield House, Oakfield Grove, Bristol BS8 2BN, UK. [53]Department of Genomics of Common Disease, School of Public Health, Imperial College London, The Commonwealth Building, The Hammersmith Hospital, Du Cane Road, London W12 ONN, UK. [54]The University of Queensland Diamantina Institute, Princess Alexandra Hospital, Brisbane, Queensland 4102, Australia. [55]Department of Medicine, Boston University, Boston, Massachusetts 02118, USA. [56]Department of Clinical Sciences/Obstetrics and Gynecology, University of Oulu, Aapistie 7, Oulu, 90220 Finland. [57]Department of Epidemiology, University of Washington, Seattle, Washington 98195-7236, USA. [58]Group Health Research Institute, Group Health Cooperative, Seattle,Washington 98101-1448, USA. [59]Klinik und Poliklinik für Innere Medizin II, Universitätsklinikum Regensburg, 93053 Regensburg, Germany. [60]Department of Medical Genetics, University of Lausanne, and Swiss Institute of Bioinformatics, Lausanne, Switzerland. [61]Unit for Molecular Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Ingolstädter Landstr.1, 85764 Neuherberg, Germany. [62]Department of Public Health and Primary Care, Strangeways Research Laboratory, University of Cambridge, Cambridge CB1 8RN, UK. [63]Clinical Gerontology Unit, Addenbrooke,s Hospital, Hills Road, Cambridge CB2 2QQ, UK. [64]First Department of Propedeutic Internal Medicine and Hematology Department, National and Kapodistrian University of Athens Medical School, Laikon General Hospital, Athens 11727, Greece. [65]OxfordCentre for Diabetes,Endocrinology and Metabolism, University of Oxford, Oxford OX3 7LJ, UK. [66]Department of Biostatistics, University of Washington, Seattle, Washington 98195-7232, USA. [67]Genetic Epidemiology, Queensland Institute of Medical Research, The Bancroft Centre, 300 Herston Road, Herston 4006, Queensland, Australia. [68]Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, University of Tokyo, Tokyo 108-8639, Japan. [69]Institute of Clinical Chemistry and Laboratory Medicine, Ernst-Moritz-Arndt-University Greifswald, 17475 Greifswald, Germany. [70]Department of Internal Medicine, University Medical Center Groningen, University of Groningen, 9713 GZ Groningen, The Netherlands. [71]Section for Epidemiology, Institute for Experimental Medicine, Christian-Albrechts-University Kiel, 24105 Kiel, Germany. [72]Popgen Biobank, University Clinic Schleswig-Holstein, 24105 Kiel, Germany. [73]Unit of Genetic Epidemiology and Bioinformatics, Department of Epidemiology, University Medical Center Groningen,

University of Groningen, 9713 GZ Groningen, The Netherlands. [74]Medical Genetics Section, University of Edinburgh, MolecularMedicine Centre, Western General Hospital, Crewe Road South, Edinburgh EH4 2XU, UK. [75]National Institute for Health and Welfare, Aapistie 1, Oulu 90220, Finland. [76]Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California 90048, USA. [77]Institute of Diagnostics, Clinical Chemistry, University of Oulu, Box 5000Y, University of Oulu, Oulu 90014, Finland. [78]NIHR Cambridge Biomedical Research Centre, Cambridge CB2 0QQ, UK. [79]Laboratory of Genetics, National Institute on Aging, Baltimore, Maryland 21224-6825, USA. [80]Faculty of Medicine, National Heart and Lung Institute, Cardiovascular Science, Hammersmith Campus, Hammersmith Hospital, Imperial College London, London W12 0HS, UK. [81]Seattle Epidemiologic Research and Information Center of the Department of Veterans Affairs Office of Research and Development, Seattle, Washington 98108, USA. [82]Geriatric Medicine Unit, The University of Edinburgh, Royal Victoria, Craigleith Road, Edinburgh EH4 2DN, UK. [83]Department of Medicine, University of Leipzig, Liebigstr. 18, 04103 Leipzig, Germany. [84]Center for Cardiovascular Diagnostics and Prevention, Department of Cell Biology and Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio 44195, USA. [85]Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio 44195, USA. [86]Institute of Genetics and Molecular Medicine, MRC Human Genetics Unit, Edinburgh EH4 2XU, UK. [87]The Roslin Institute, Royal (Dick) School of Veterinary Studies, University of Edinburgh, Roslin Midlothian EH25 9RG, UK. [88]Department of Molecular Haematology, King,s College London, 125 Coldharbour Lane, London SE5 9NU, UK. [89]Institute ofMedical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-Universität and KlinikumGrosshadern, Marchioninistr. 15, 81377 Munich, Germany. [90]Department of Physiatrics, Lapland Central Hospital, Rovaniemi, 96101, Finland. [91]Geriatric Research and Education Clinical Center, Veterans Administration Medical Center, Baltimore, Maryland 21208, USA. [92]Department of Laboratory Medicine, University Medical Center Groningen, University of Groningen, 9713GZ, Groningen, The Netherlands. [93]Sanquin Research Leiden, Jon J. van Rood Center for Clinical Transfusion research, and the Department of Immuno-hematology and Blood Transfusion, Leiden University Medical Center, 2333 Leiden, The Netherlands. [94]Division of Cardiovascular Medicine, University of Michigan Health System, Ann Arbor, Michigan, USA. [95]Institute of Health Sciences, University of Oulu, Aapistie 7, Oulu, 90220 Finland. [96]National Institute for Health and Welfare, Biocenter Oulu, University of Oulu, Aapistie 7, Oulu, 90220 Finland. [97]Department of Medicine, Epidemiology, and Health Services, University of Washington, Seattle, Washington 98101-1448, USA. [98]Department of Clinical Chemistry and Haematology, University Medical Center Utrecht, 3584 CX Utrecht, Netherlands. [99]Institute for Immunology and Transfusion Medicine, Ernst-Moritz-Arndt-University Greifswald, 17475 Greifswald, Germany. [100]Proteomics Services, EMBL, European Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SD, UK. [101]MRC Biostatistics Unit, Institute of Public Health, University Forvie Site, Robinson Way, Cambridge CB2 0SR, UK. [102]Nordic Center of Cardiovascular Research, Lubeck, Germmany.