Supplementary Material

1. Supplementary Tables

Supplementary Table S1. Primers used for confirmation of rs111876221 genotypes in MIA/MIN-CH cohort.

Target region	Primer sequence (5' - 3')	Length (bp)	Annealing temperature (°Celsius)
SERINC5	F:TGGACAGCCCATAAGCCATC	20	65.2
	R1:GGTTGATATTCCTGTTTCTGATTGT	25	65.2
	R2: ATCCCAGTGTTCACCCAAACC	21	65.2

Supplementary Table S2: Pre-imputation data checking. The pre-imputation checking program compared markers and their frequencies to the HRC reference panel (Human Reference Consortium r1-1 2016) to check for potential issues using both location information and SNP names. Variants with no match (name or position) to the reference or failing to meet one of the above thresholds were subsequently removed in PLINK. Mitochondrial (MT), X and Y-chromosomal (XY, Y) SNPs were excluded.

Issue checked	Action performed
Chromosome and position	Updated
Non-matching alleles	Removed
XY, Y, MT SNPs	Removed
Allele frequency (AF)	Removed if AF difference > 0.2
Strand	Updated
Palindromic SNPs	Removed if MAF > 0.4
Reference allele	Updated
Variant naming	Updated

Supplementary Table S4. Characteristics of cases, tolerant and unexposed controls in the discovery cohort (MIA/MIN-CH). Tolerant controls were patients treated with metamizole for at least 28 days without agranulocytosis or neutropenia.

	Cases N=45	**Tolerant Controls N=38**	**Unexposed Controls N=153**
ANC < 500 /uL	30	-	-
Sex, male (%)	23(51)	7(45)	72(47)
Age, years (%)			
<25	10(22)	1(2.5)	27(17.5)
25-44	14(31)	6(16)	73(48)
45-64	12(27)	15(39.5)	53(34.5)
65-74	7(15.5)	9(24)	-
>74	2(4.5)	7(18)	-
BMI, median (range)	24(19-47)	28(16-39)	23(18-40)
Latency time*[a] / treatment duration[b], days	15(1-204)	25 (5197)	NA

[a] cases, [b] controls, * latency missing for 3 agranulocytosis cases and 1 neutropenia case.

ANC=lowest absolute neutrophil count, BMI=body mass index, NA=not applicable

Supplementary Table 5. Top associations of the Phase I association analysis in the MIA/MIN-CH cohort. Top genome-wide analysis results based on 195 genotyped SNPs in all 45 MIA/MIN cases vs. 191 controls (tolerant and unexposed). All results were adjusted for sex and four genetic multidimensional scaling (MDS) components. Chromosomal location is according to the Genome Reference Consortium human assembly GRCh37. CHR= chromosome, SNP=single nucleotide polymorphism, BP=base pair, MAF=minor allele frequency, OR [95%]=odds ratio with 95% confidence interval.

CHR	SNP	Alleles (minor/major)	BP	MAF cases	MAF controls	OR [95%]	P-value	Gene region
5	rs10041917	G/A	79525305	0.24	0.42	0.44 [0.25-0.76]	$3.4x10^{-3}$	*SERINC5*
5	rs7726099	G/A	79521704	0.25	0.43	0.46 [0.26-0.78]	$4.6x10^{-3}$	*SERINC5*
6	rs4148876	A/G	32796793	0.17	0.65	2.62 [1.19-5.75]	$1.6x10^{-2}$	*TAP2*
12	rs4149118	G/A	21011581	0.32	0.36	0.41 [0.19-0.86]	$1.8x10^{-2}$	*SLCO1B3*
5	rs10036776	A/G	79509974	0.21	0.33	0.49 [0.27-0.89]	$1.9x10^{-2}$	*SERINC5*
5	rs12522787	A/G	79526346	0.067	0.15	0.34 [0.13-0.90]	$3x10^{-2}$	*SERINC5*
6	rs140017767	G/T	32813576	0.022	0.0026	16.3 [1.29-205.8]	$3x10^{-2}$	*PSMB8/TAP2*
6	rs2071543	T/G	32811629	0.17	0.096	2.17 [1.05-4.47]	$3.5x10^{-2}$	*PSMB8*
6	rs3823096	T/C	3014483	0.3	0.39	0.56 [0.32-0.97]	$3.9x10^{-2}$	*NQO2*
12	rs10505871	C/T	21172053	0.25	0.38	0.50 [0.26-0.97]	$4.1x10^{-2}$	*SLCO1B7*

Supplementary Table S6. Top associations of the Phase II association analysis in the MIA/MIN-CH cohort. Top genome-wide analysis results based on 549 genotyped SNPs in all 45 MIA/MIN cases vs. 191 controls (tolerant and unexposed). All results were adjusted for sex and four genetic multidimensional scaling (MDS) components. Chromosomal location is according to the Genome Reference Consortium human assembly GRCh37. CHR= chromosome, SNP=single nucleotide polymorphism, BP=base pair, MAF=minor allele frequency, OR [95%]=odds ratio with 95% confidence interval.

CHR	SNP	Alleles (minor/major)	BP	MAF cases	MAF controls	OR [95%]	P-value	Gene region
5	rs10041917	G/A	79525305	0.24	0.42	0.41 [0.24-0.71]	$1.7x10^{-3}$	*SERINC5*
5	rs7726099	G/A	79521704	0.25	0.43	0.42 [0.24-0.73]	$2.2x10^{-3}$	*SERINC5*
5	rs10036776	A/G	79509974	0.21	0.33	0.47 [0.25-0.85]	$1.3x10^{-2}$	*SERINC5*
5	rs12522787	A/G	79526346	0.066	0.15	0.35 [0.14-0.86]	$2.3x10^{-2}$	*SERINC5*
5	rs6895353	G/A	79514675	0.49	0.36	1.70 [1.07-2.71]	$2.3x10^{-2}$	*SERINC5*
12	rs10505871	C/T	21172053	0.25	0.38	0.50 [0.27-0.92]	$2.7x10^{-2}$	*SLCO1B7*
6	rs4148876	A/G	32796793	0.17	0.065	2.41 [1.10-5.26]	$2.7x10^{-2}$	*TAP2*
17	rs11652446	C/A	72533076	0.42	0.34	1.84 [1.05-3.22]	$3.1x10^{-2}$	*CD300C*
6	rs140017767	G/T	32813576	0.022	0.0026	15.17 [1.22-187.74]	$3.4x10^{-2}$	*PSMB8/TAP1*
6	rs2071543	T/G	32811629	0.17	0.097	2.16 [1.04-4.49]	$3.8x10^{-2}$	*PSMB8*

Supplementary Table S7. Top associations of the Phase I association analysis in the MIA-CH cohort. Top genome-wide analysis results based on 195 genotyped SNPs in 30 MIA cases vs. 191 controls (tolerant and unexposed). All results were adjusted for sex and four genetic multidimensional scaling (MDS) components. Chromosomal location is according to the Genome Reference Consortium human assembly GRCh37. CHR= chromosome, SNP=single nucleotide polymorphism, BP=base pair, MAF=minor allele frequency, OR [95%]=odds ratio with 95% confidence interval.

CHR	SNP	Alleles (minor/major)	BP	MAF cases	MAF controls	OR [95%]	P-value	Gene region
5	rs10041917	G/A	79525305	0.22	0.43	0.35 [0.18-0.70]	$2.7x10^{-3}$	*SERINC5*
5	rs7726099	G/A	79521704	0.23	0.43	0.38 [0.19-0.74]	$4.5x10^{-3}$	*SERINC5*
6	rs2228391	C/T	32797773	0.033	0.0026	377.7 [5.93-24028]	$5.1x10^{-3}$	*TAP2*
6	rs4148876	A/G	32796793	0.18	0.065	3.06 [1.37-6.83]	$6.1x10^{-3}$	*TAP2*
5	rs6895353	G/A	79514675	0.55	0.36	2.07 [1.18-3.62]	$1.1x10^{-2}$	*SERINC5*
5	rs10075871	C/T	79497415	0.63	0.45	2.05 [1.15-3.62]	$1.4x10^{-2}$	*SERINC5*
6	rs1044043	A/C	32793981	0.32	0.19	1.86 [1.03-3.35]	$3.8x10^{-2}$	*TAP2*
5	rs4704627	T/C	79488191	0.18	0.33	0.48 [0.23-0.96]	$3.9x10^{-2}$	*SERINC5*
6	rs17136117	G/A	3010337	0.033	0.0052	9.7 [1.09-86.35]	$4.2x10^{-2}$	*NQO2*
5	rs13355369	T/C	79518278	0.58	0.44	1.79 [1.01-3.15]	$4.4x10^{-2}$	*SERINC5*

Supplementary Table S8. Top associations of the Phase II association analysis in the MIA-CH cohort. Top genome-wide analysis results based on 549 genotyped SNPs in 30 MIA cases vs. 191 controls (tolerant and unexposed). All results were adjusted for sex and four genetic multidimensional scaling (MDS) components. Chromosomal location is according to the Genome Reference Consortium human assembly GRCh37. CHR= chromosome, SNP=single nucleotide polymorphism, BP=base pair, MAF=minor allele frequency, OR [95%]=odds ratio with 95% confidence interval.

CHR	SNP	Alleles (minor/major)	BP	MAF cases	MAF controls	OR [95%]	P-value	Gene region
5	rs10041917	G/A	79525305	0.22	0.43	0.35 [0.18-0.70]	$2.7x10^{-3}$	*SERINC5*
5	rs7726099	G/A	79521704	0.23	0.43	0.38 [0.19-0.74]	$4.5x10^{-3}$	*SERINC5*
6	rs2228391	C/T	32797773	0.033	0.0026	377.7 [5.93-24028]	$5.1x10^{-3}$	*TAP2*
6	rs4148876	A/G	32796793	0.18	0.065	3.06 [1.37-6.83]	$6.1x10^{-3}$	*TAP2*
6	rs6911119	T/C	160090193	0.05	0.0078	13.1 [1.99-86.4]	$7.3x10^{-3}$	*SOD2*
5	rs6895353	G/A	79514675	0.55	0.36	2.07 [1.18-3.62]	$1.1x10^{-2}$	*SERINC5*
5	rs10075871	C/T	79497415	0.63	0.45	2.05 [1.15-3.62]	$1.4x10^{-2}$	*SERINC5*
8	rs10103029	G/A	18267338	0.033	0.17	0.17 [0.039-0.72]	$1.6x10^{-2}$	*NAT2*
12	rs10841856	C/T	8692843	0.27	0.44	0.47 [0.25-0.87]	$1.7x10^{-2}$	*CLEC4E*
1	rs6588432	G/A	53081321	0.3	0.17	2.25 [1.14-4.42]	$1.9x10^{-2}$	*GPX7*

Supplementary Table S9. Top associations of the genome-wide association analysis in the MIA/MIN-CH cohort. Top genome-wide analysis results based on 304,704 genotyped SNPs in all 45 MIA/MIN cases vs. 191 controls (tolerant and unexposed). All results were adjusted for sex and four genetic multidimensional scaling (MDS) components. Chromosomal location is according to the Genome Reference Consortium human assembly GRCh37. CHR= chromosome, SNP=single nucleotide polymorphism, BP=base pair, MAF=minor allele frequency, OR [95%]=odds ratio with 95% confidence interval

CHR	SNP	Alleles (minor/major)	BP	MAF cases	MAF controls	OR [95%]	P-value	Gene region
6	rs191786	C/T	82497480	0.19	0.44	0.24 [0.13-0.45]	$8.6x10^{-6}$	-
6	rs9366076	T/C	167373708	0.4	0.17	3.57 [2.03-6.27]	$9.7x10^{-6}$	-
9	rs7865838	G/A	73109347	0.53	0.30	3.42 [1.97-5.94]	$1.1x10^{-5}$	*LOC101927086*
7	rs17152230	C/T	105506737	0.2	0.057	5.54 [2.54-12.03]	$1.5x10^{-5}$	*ATXN7L1*
3	rs79233583	A/G	86052689	0.12	0.021	10 [3.46-29.04]	$2.1x10^{-5}$	*CADM2*
9	rs957252	C/A	26059028	0.71	0.43	3.15 [1.85-3.4]	$2.4x10^{-5}$	-
16	rs6497573	G/A	22141042	0.47	0.24	2.88 [1.75-4.73]	$2.9x10^{-5}$	*VWA3A*
4	rs7667461	A/G	111622134	0.29	0.12	3.97 [2.08-7.61]	$3x10^{-5}$	-
6	rs162297	G/A	167455139	0.45	0.23	3.20 [1.84-5.55]	$3.4x10^{-5}$	*FGFR1OP*
6	rs194635	C/T	82521957	0.57	0.34	3.1 [1.81-5.28]	$3.5x10^{-5}$	-

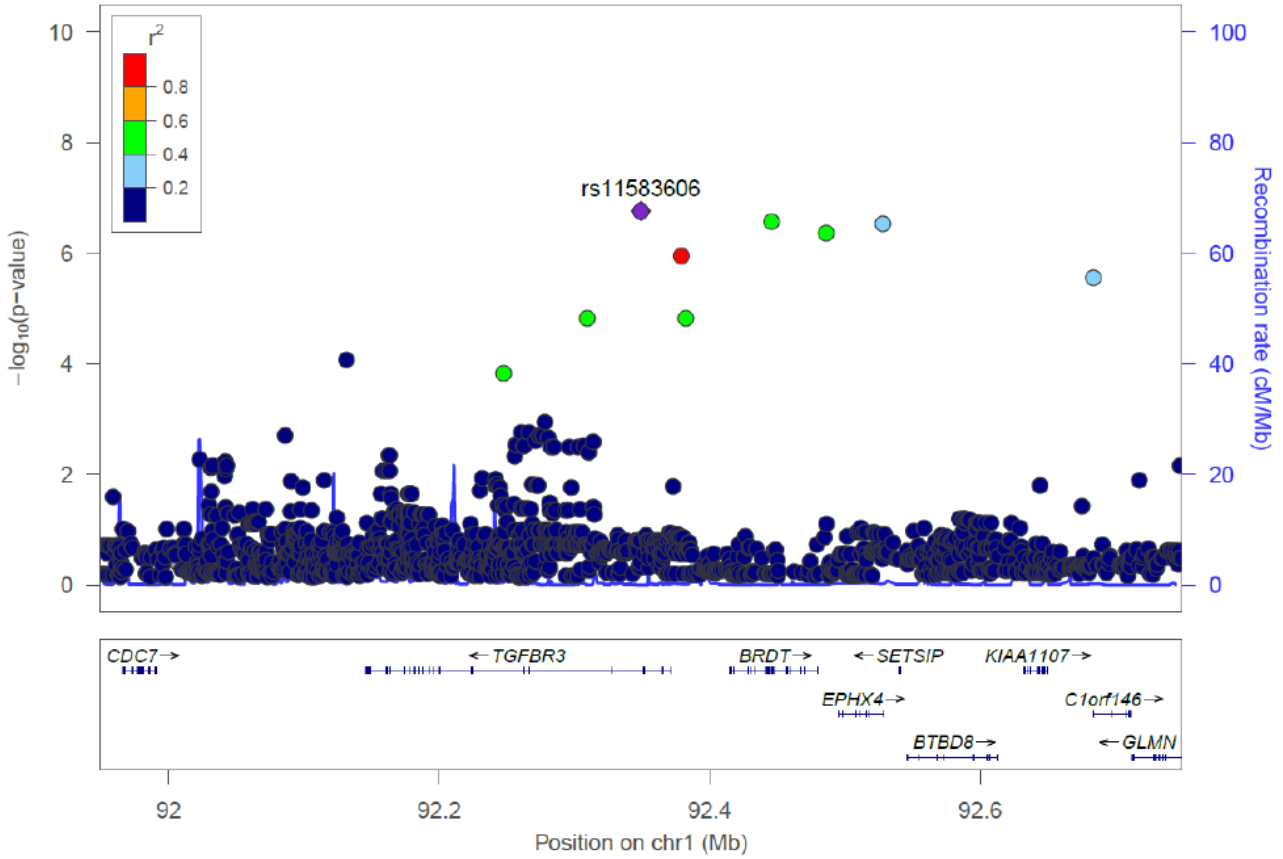
Supplementary Table S10. Top associations of the genome-wide association analysis in the MIA-CH cohort. Top genome-wide analysis results based on 304,704 genotyped SNPs in 30 MIA cases vs. 191 controls (tolerant and unexposed). All results were adjusted for sex and four genetic multidimensional scaling (MDS) components. Chromosomal location is according to the Genome Reference Consortium human assembly GRCh37. CHR= chromosome, SNP=single nucleotide polymorphism, BP=base pair, MAF=minor allele frequency, OR [95%]=odds ratio with 95% confidence interval.

CHR	SNP	Alleles (minor/major)	BP	MAF cases	MAF controls	OR [95%]	P-value	Gene region
6	rs9366076	T/C	167373708	0.46	0.17	4.81 [2.49-9.30]	$2.9x10^{-6}$	-
9	rs957252	C/A	26059028	0.78	0.43	4.73 [2.35-9.51]	$1.3x10^{-5}$	-
16	rs9937453	G/A	22155629	0.4	0.15	3.87 [2.05-7.32]	$2.9x10^{-5}$	*VWA3A*
6	rs162297	G/A	167455139	0.5	0.23	3.89 [2.05-7.37]	$3x10^{-5}$	*FGFR1OP*
4	rs11098986	A/G	129700043	0.63	0.34	3.63 [1.97-6.65]	$3.1x10^{-5}$	-
1	rs6687674	A/G	27537101	0.67	0.35	3.65 [1.98-6.73]	$3.3x10^{-5}$	-
17	rs4968887	T/C	68264545	0.5	0.23	3.57 [1.93-6.57]	$4.3x10^{-5}$	-
9	rs6475884	A/C	26121103	0.71	0.38	3.59 [1.93-6.66]	$5.2x10^{-5}$	*LOC100506422*
9	rs7865838	G/A	73109347	0.56	0.30	3.98 [2.03-7.78]	$5.3x10^{-5}$	*LOC101927086*
4	rs7667461	A/G	111622134	0.31	0.12	4.64 [2.18-9.86]	$6.3x10^{-5}$	-

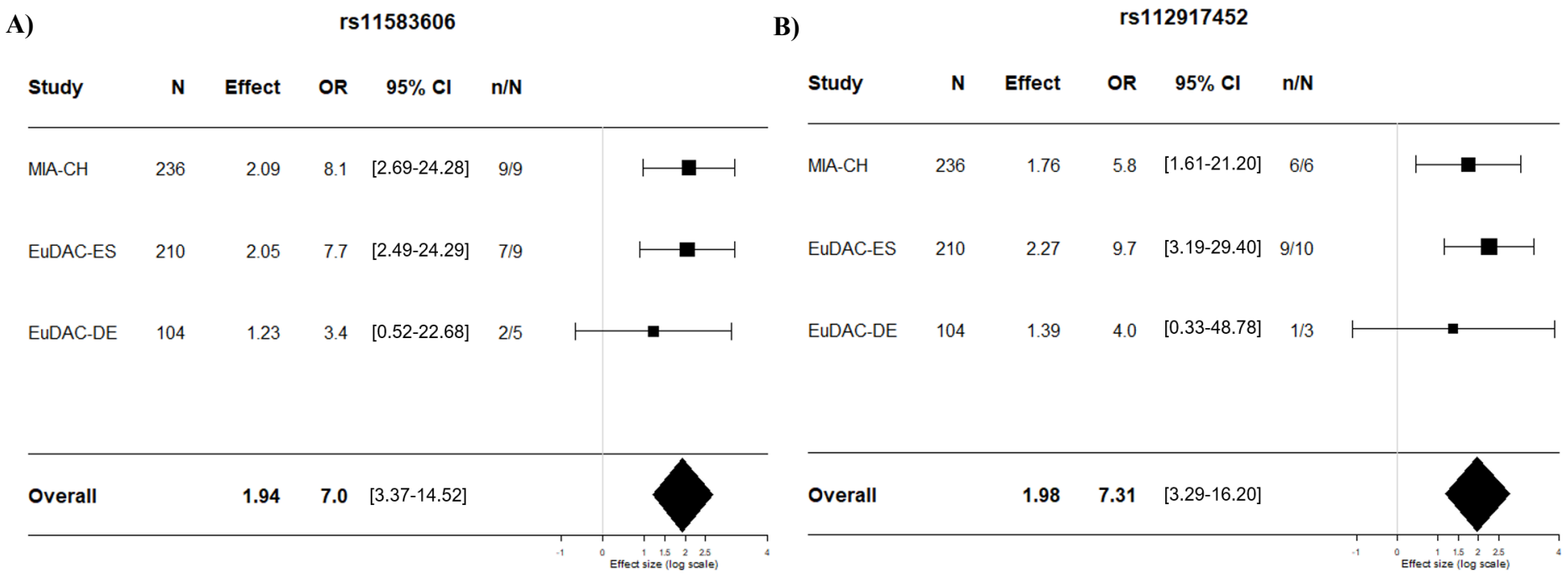
Supplementary Table S11. Replication of association signals from MIA/MIN-CH and MIA-CH analyses in the EuDAC cohorts.
*imputed genotype; **imputed very poorly (RSQ=0.00024); NA, not available

Cohort	CHR	Alleles (minor/major)	BP	MAF cases	MAF controls	OR [95%]	P-value	Gene region
EuDAC-ES	5	G/A	79525305	0.53	0.41	1.0 [0.54-1.85]	0.98	*SERINC5*
EuDAC-DE	5	G/A	79525305	0.41	0.50	0.70 [0.25-1.99]	0.511	*SERINC5*
EuDAC-ES	6	C/T	82497480	0.38	0.41	0.86 [0.48-1.55]	0.63	*TENT5A*
EuDAC-DE	6	C/T	82497480	0.29	0.30	0.94 [0.33-2.72]	0.92	*TENT5A*
EuDAC-ES	1	G/A	53081321	0.17*	0.12*	1.52 [0.71-3.26]	0.28	*GPX7*
EuDAC-DE	1	G/A	53081321	0.12	0.14	0.69 [0.16-3.01]	0.63	*GPX7*
EuDAC-ES	6	C/T	32797773	0	0	NA	NA	*TAP2*
EuDAC-DE	6	C/T	32797773	NA**	NA**	NA	NA	*TAP2*
EuDAC-ES	6	A/G	32796793	0.069	0.055	1.15[0.33-3.94]	0.68	*TAP2*
EuDAC-DE	6	A/G	32796793	0.125*	0.098*	1.51 [0.38-5.92]	0.55	*TAP2*
EuDAC-ES	6	T/C	167373708	0.29*	0.24*	1.36 [0.69-2.66	0.36	*RNASET2*
EuDAC-DE	6	T/C	167373708	0.25	0.23	1.39 [0.45-4.36]	0.56	*RNASET2*

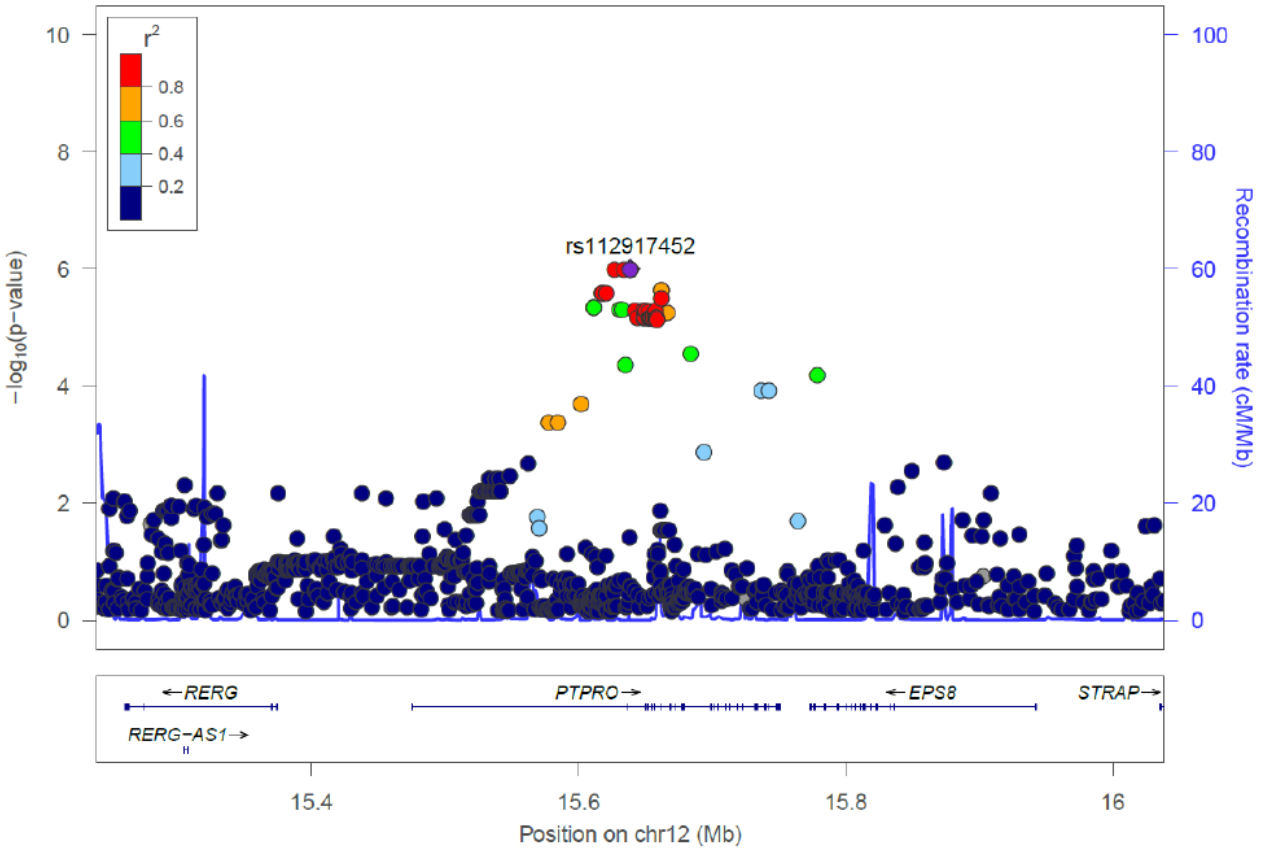
2. Supplementary Figures



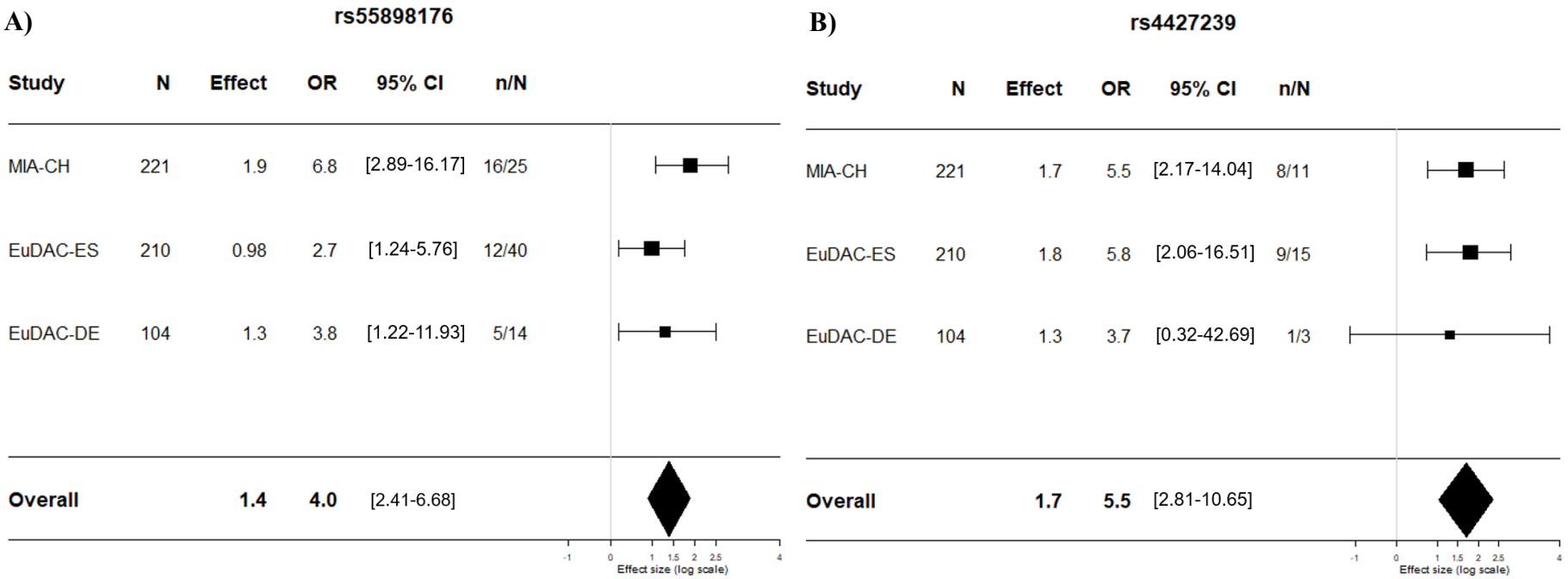
Supplementary Figure S1. Regional association plot for regions around rs11583606. Plot was produced in Locus Zoom and shows the most strongly associated SNP from the GWAS meta-analysis of all 86 cases versus 464 controls. Different colors represent the strength of the LD of each SNP with the most significant SNP represented by a diamond.



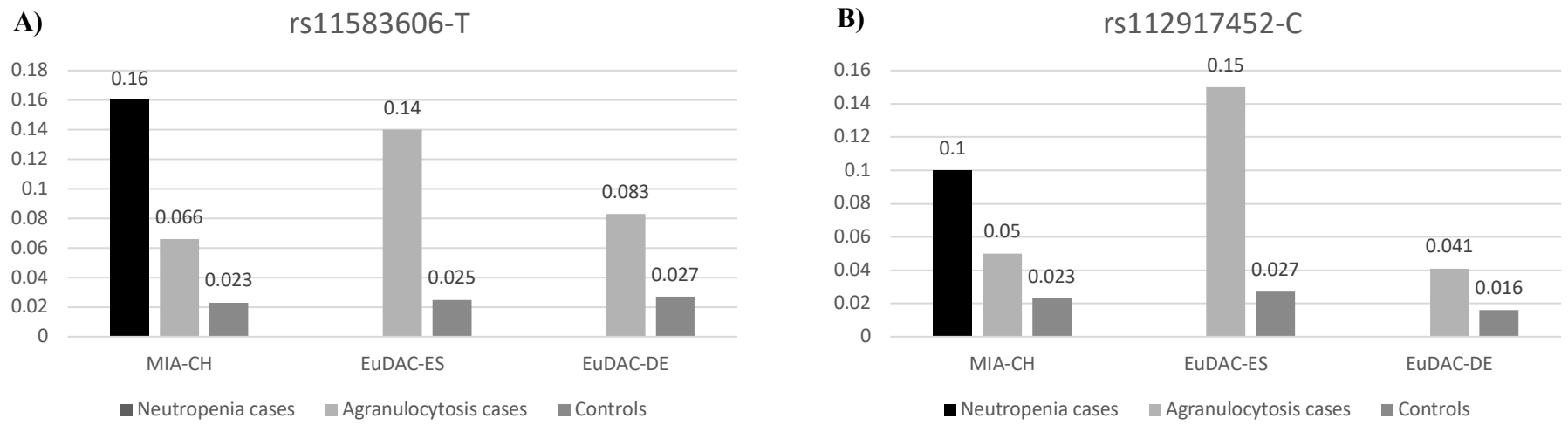
Supplementary Figure S2. Forest plot of associations with metamizole-induced agranulocytosis and neutropenia in the three independent cohorts (all cases and controls). Estimated effect sizes, odds ratio (OR) with 95% confidence intervals (CI), P-value for the independently associated rs11583606 (A) and rs112917452 (B) in 86 MIN and MIA cases and 464 controls (tolerant and unexposed). The effects are adjusted for sex and genetic multidimensional scaling (MDS) components 1-4. Numbers of patients (n) or controls (N) are given in the n/N column. N=sample size.



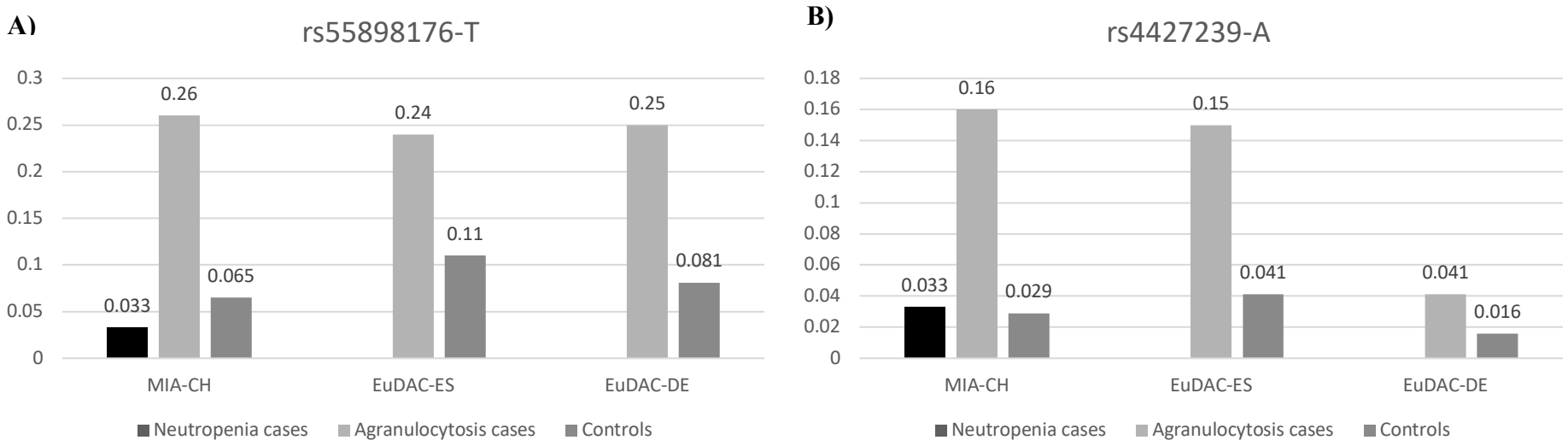
Supplementary Figure S3. Regional association plot for regions around rs112917452. Plot was produced in Locus Zoom and shows the most strongly associated SNP from the GWAS meta-analysis of all 86 cases versus 464 controls. Different colors represent the strength of the LD of each SNP with the most significant SNP represented by a diamond.



Supplementary Figure S4. Forest plot of associations with metamizole-induced agranulocytosis in the three independent cohorts (agranulocytosis cases and controls). Estimated effect sizes, odds ratio (OR) with 95% confidence intervals (CI), P-value for the independently associated rs55898176 (A) and rs4427239 (B) in 71 MIAcases and 464 controls (tolerant and unexposed). The effects are adjusted for sex and genetic multidimensional scaling (MDS) components 1-4. Numbers of patients (n) or controls (N) are given in the n/N column. N=sample size.



Supplementary Figure S5. Allele frequency distribution of the leading SNPs associated with metamizole-induced agranulocytosis and neutropenia in the three independent cohorts (all cases versus controls). The allele frequencies show the risk allele distribution of rs11583606 (A) and rs112917452 (B) in the MIN (black), MIA (light grey) and control groups (dark grey) of the MIA/MIN-CH, EuDAC-ES and EuDAC-DE cohorts.



Supplementary Figure S6. Allele frequency distribution of the leading SNPs associated with metamizole-induced agranulocytosis in the three independent cohorts (agranulocytosis cases versus controls). The allele frequencies show the risk allele distribution of rs55898176 (A) and rs4427239 (B) in the MIN (black), MIA (light grey) and control groups (dark grey) of the MIA/MIN-CH, EuDAC-ES and EuDAC-DE cohorts.