

Genetic factors underlying the risk of bortezomib induced peripheral neuropathy in multiple myeloma patients

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Online Supplementary Table S1. Demographic and clinical characteristics of MM cases and controls restricted to bortezomib treated patients in the IFM 2005-01 trial.

| | Discovery set IFM 2005-01 Included in SNP analyses (n=238) | | Validation set HOVON-65/GMMG-HD4 Not included in SNP analyses (n=229) | | Included in SNP analyses (n=183) | | P value | Czech Republic dataset Included in SNP analyses (n=48) | |
|------------------------------|---------------------------------------------------------------------|-----|--------------------------------------------------------------------------------|-----|-------------------------------------|-----|---------|--------------------------------------------------------------|-----|
| Age | | | | | | | | | |
| Median (years) | 57 | | 57 | | 57 | | 0.62 | nd | |
| Range (years) | 35-68 | | 31-65 | | 32-65 | | | nd | |
| Sex | n. | | n. | | n. | | | n. | |
| M | 132 | 61% | 144 | 63% | 109 | 60% | 0.54 | 27 | 56% |
| F | 85 | 39% | 85 | 37% | 74 | 40% | | 17 | 35% |
| nd | | | | | | | | 4 | 8% |
| ISS | | | 90 | | 82 | | 0.25 | 22 | |
| I | nd | | 73 | 32% | 46 | 25% | | 7 | 15% |
| II | nd | | 48 | 21% | 32 | 17% | | 7 | 15% |
| III | nd | | 18 | 8% | 23 | 13% | | 12 | 25% |
| nd | nd | | | | | | | | |
| M protein heavy chain | | | | | | | | | |
| IgA | 59 | 25% | 54 | 24% | 35 | 19% | 0.45 | 12 | 25% |
| IgG | 129 | 54% | 130 | 57% | 119 | 65% | | 29 | 60% |
| IgD | 6 | 3% | 4 | 2% | 2 | 1% | | 0 | 0% |
| LCD | 0 | 0% | 36 | 16% | 24 | 13% | | 3 | 6% |
| nd | 44 | 18% | 5 | 2% | 3 | 2% | | 4 | 8% |
| M protein light chain | | | | | | | | | |
| Kappa | 148 | 62% | 148 | 65% | 122 | 67% | 0.78 | 27 | 56% |
| Lambda | 71 | 30% | 76 | 33% | 59 | 32% | | 17 | 35% |
| nd | 19 | 8% | 5 | 2% | 2 | 1% | | 4 | 8% |
| BiPN grade | | | | | | | | | |
| 0 | 139 | 58% | 122 | 53% | 80 | 44% | 0.36 | 20 | 42% |
| 1 | 27 | 11% | 54 | 24% | 52 | 28% | | 10 | 21% |
| 2 | 57 | 24% | 29 | 13% | 26 | 14% | | 13 | 27% |
| 3 | 11 | 5% | 16 | 7% | 19 | 10% | | 5 | 10% |
| 4 | 4 | 2% | 8 | 3% | 6 | 3% | | 0 | 0% |

LCD indicates light chain disease; ISS: International Staging System; BiPN: bortezomib induced peripheral neuropathy; nd: not determined.

Online Supplementary Table S2. Power analysis (c2 test) in the discovery set. Indicated are the lowest possible OR to detect (upper;lower) at several levels of *P* and MAF. Number of alleles: 476; number of SNPs: 2,149.

| MAF | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 |
|----------------------|-----------|-----------|-----------|-----------|-----------|
| OR (<i>P</i> =0.01) | 8.57;0.12 | 3.67;0.27 | 2.83;0.35 | 2.54;0.39 | 2.45;0.41 |
| OR (<i>P</i> =0.05) | 8.59;0.12 | 3.23;0.31 | 2.58;0.39 | 2.36;0.42 | 2.28;0.44 |
| OR (<i>P</i> =0.10) | 7.28;0.14 | 3.07;0.33 | 2.48;0.40 | 2.28;0.44 | 2.21;0.45 |
| OR (<i>P</i> =0.25) | 6.00;0.17 | 2.86;0.35 | 2.35;0.43 | 2.18;0.46 | 2.12;0.47 |

OR: Odds Ratio; MAF: minor allele frequency.

Online Supplementary Table S3. Power analysis (one-sided test for ORs) in the validation set. Indicated are the lowest possible OR to detect (upper;lower) at several levels of *P* and MAF. Number of alleles: 462; number of SNPs: 51.

| MAF | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 |
|----------------------|-----------|-----------|-----------|-----------|-----------|
| OR (<i>P</i> =0.01) | 3.49;0.29 | 2.41;0.42 | 2.12;0.47 | 2.02;0.50 | 2.00;0.50 |
| OR (<i>P</i> =0.05) | 2.93;0.34 | 2.15;0.47 | 1.92;0.52 | 1.85;0.54 | 1.84;0.55 |
| OR (<i>P</i> =0.10) | 2.66;0.38 | 2.03;0.49 | 1.84;0.54 | 1.77;0.56 | 1.75;0.57 |
| OR (<i>P</i> =0.25) | 2.40;0.42 | 1.88;0.53 | 1.73;0.58 | 1.67;0.60 | 1.66;0.60 |

OR: Odds Ratio; MAF: minor allele frequency.

Online Supplementary Table S4. Incidence of peripheral neuropathy shown *per grade* in the HOVON-65/GMMG-HD4 VAD treatment arm.

| Peripheral neuropathy grade | HOVON-65/GMMG-HD4 VAD treatment arm | |
|-----------------------------|-------------------------------------|-------|
| | n. | |
| 0 | 254 | 61.6% |
| 1 | 115 | 27.9% |
| 2 | 31 | 7.5% |
| 3 | 11 | 2.7% |
| 4 | 1 | 0.2% |

VAD indicates vincristine, adriamycin and dexamethasone.

Online Supplementary Table S5. SNPs associated with BiPN (pointwise $P < 0.05$) in the validation set (HOVON-65/GMMG-HD4 and Czech Republic dataset) using a Cochran Mantel-Haenszel stratified association analysis. The genomic inflation factor λ is 1.0

| SNP | Chr | Alleles | OR | 95% CI | Pointwise P value for Cochran Mantel-Haenszel | Permutated P for Cochran Mantel-Haenszel | Gene | SNP type |
|------------|-----|---------|------|--------------|-------------------------------------------------|--------------------------------------------|----------|---------------------------------------|
| rs13321 | 9 | C > G | 1,98 | 1,28 - 3,04 | 0,002 | 0,9191 | TNC | Coding-nonsynonymous |
| rs3218634 | 3 | C > G | 3,26 | 1,39 - 7,60 | 0,003 | 0,9957 | POLQ | Coding-nonsynonymous |
| rs2252784 | 12 | G > A | 0,59 | 0,41 - 0,86 | 0,003 | 0,9998 | PTPRB | Coding-nonsynonymous |
| rs7071882 | 10 | G > T | 0,51 | 0,32 - 0,79 | 0,004 | 0,9659 | MBL2 | Intron |
| rs2280509 | 2 | C > T | 0,53 | 0,33 - 0,85 | 0,005 | 1 | FZD7 | Locus |
| rs2229113 | 11 | G > A | 1,71 | 1,16 - 2,52 | 0,006 | 1 | IL10RA | Coding-nonsynonymous |
| rs6131 | 1 | G > A | 0,55 | 0,36 - 0,84 | 0,006 | 0,9998 | SELP | Coding-nonsynonymous |
| rs11546842 | 15 | C > T | 4,33 | 1,47 - 12,78 | 0,007 | 0,9955 | POLG | Coding-nonsynonymous |
| rs7096206 | 10 | C > G | 1,83 | 1,14 - 2,92 | 0,007 | 1 | MBL2 | Locus |
| rs1540339 | 12 | G > A | 0,61 | 0,42 - 0,90 | 0,007 | 1 | VDR | Intron |
| rs11003127 | 10 | G > C | 0,53 | 0,34 - 0,83 | 0,008 | 0,9987 | MBL2 | Intron |
| rs2165810 | 10 | T > A | 0,55 | 0,36 - 0,86 | 0,009 | 1 | MBL2 | Intron |
| rs1024611 | 17 | T > C | 1,83 | 1,17 - 2,87 | 0,009 | 1 | CCL2 | Promoter |
| rs2238476 | 16 | C > T | 3,04 | 1,21 - 7,64 | 0,009 | 1 | ABCC1 | Intron,TagSNP:ABCC1 |
| rs9954562 | 18 | C > T | 0,61 | 0,42 - 0,89 | 0,010 | 1 | NFATC1 | Promoter |
| rs1799801 | 16 | T > C | 1,73 | 1,15 - 2,61 | 0,011 | 1 | ERCC4 | Coding-synonymous |
| rs3136027 | 17 | A > T | 2,27 | 1,16 - 4,45 | 0,012 | 1 | LIG3 | Intron |
| rs246218 | 16 | C > T | 0,50 | 0,29 - 0,88 | 0,012 | 1 | ABCC1 | Intron,TagSNP:ABCC1 |
| rs4151060 | 10 | G > T | 0,34 | 0,14 - 0,80 | 0,014 | 1 | BTRC | Coding-nonsynonymous |
| rs1132054 | 19 | T > C | 0,65 | 0,45 - 0,94 | 0,014 | 1 | SULT2B1 | Coding-synonymous |
| rs799917 | 17 | C > T | 0,63 | 0,43 - 0,92 | 0,014 | 1 | BRCA1 | Coding-nonsynonymous |
| rs2239704 | 6 | G > T | 0,63 | 0,43 - 0,91 | 0,014 | 1 | LTA | Untranslated |
| rs588701 | 11 | G > A | 0,61 | 0,41 - 0,91 | 0,015 | 1 | MRE11A | Intron,TagSNP:MRE11A |
| rs993568 | 1 | A > G | 0,64 | 0,44 - 0,93 | 0,016 | 1 | DPYD | Intron,TagSNP:DPYD |
| rs3739942 | 9 | A > G | 1,75 | 1,11 - 2,77 | 0,016 | 1 | KIAA1984 | Promoter |
| rs246220 | 16 | C > G | 0,49 | 0,27 - 0,89 | 0,016 | 1 | ABCC1 | Intron,TagSNP:ABCC1 |
| rs9436299 | 1 | A > C | 1,70 | 1,14 - 2,55 | 0,017 | 1 | LEPR | Intron |
| rs2976436 | 8 | C > T | 0,62 | 0,43 - 0,92 | 0,017 | 1 | NEFL | Promoter |
| rs939336 | 3 | G > A | 1,60 | 1,09 - 2,34 | 0,017 | 1 | ABCC5 | Coding-synonymous |
| rs932477 | 6 | G > A | 2,15 | 1,14 - 4,04 | 0,019 | 1 | ESR1 | Intron |
| rs1799799 | 16 | T > C | 1,65 | 1,11 - 2,46 | 0,019 | 1 | ERCC4 | Intron |
| rs246217 | 16 | C > A | 0,49 | 0,27 - 0,89 | 0,019 | 1 | ABCC1 | Intron,TagSNP:ABCC1 |
| rs1799949 | 17 | C > T | 0,62 | 0,42 - 0,93 | 0,019 | 1 | BRCA1 | Coding-synonymous,Untranslated,Intron |
| rs8058696 | 16 | C > G | 1,55 | 1,06 - 2,26 | 0,020 | 1 | ABCC6 | Coding-synonymous |
| rs2260863 | 1 | C > G | 0,61 | 0,42 - 0,91 | 0,021 | 1 | EPHX1 | Intron |
| rs1800797 | 7 | G > A | 0,63 | 0,43 - 0,92 | 0,021 | 1 | IL6 | Locus |
| rs1399291 | 1 | C > T | 0,65 | 0,45 - 0,95 | 0,021 | 1 | DPYD | Intron,TagSNP:DPYD |
| rs2056048 | 1 | A > C | 0,66 | 0,45 - 0,95 | 0,021 | 1 | DPYD | Intron,TagSNP:DPYD |
| rs310831 | 12 | A > T | 2,04 | 1,08 - 3,84 | 0,023 | 1 | E2F7 | Coding-nonsynonymous |
| rs1799800 | 16 | G > A | 1,69 | 1,10 - 2,60 | 0,023 | 1 | ERCC4 | Intron |
| rs1946519 | 11 | C > A | 1,48 | 1,01 - 2,16 | 0,024 | 1 | IL18 | Locus |
| rs1042713 | 5 | G > A | 1,54 | 1,06 - 2,25 | 0,025 | 1 | ADRB2 | Coding-nonsynonymous |
| rs1501299 | 3 | C > A | 1,65 | 1,08 - 2,52 | 0,026 | 1 | ADIPOQ | Intron |
| rs1760217 | 1 | T > C | 0,62 | 0,39 - 0,97 | 0,027 | 1 | DPYD | Intron,TagSNP:DPYD |
| rs35620 | 16 | C > G | 1,87 | 1,06 - 3,28 | 0,028 | 1 | ABCC1 | Intron,TagSNP:ABCC1 |
| rs3778082 | 6 | G > A | 1,86 | 1,09 - 3,20 | 0,029 | 1 | ESR1 | Intron |
| rs11574750 | 2 | C > T | 0,39 | 0,16 - 0,94 | 0,029 | 1 | IL8RB | Coding-synonymous |
| rs1946518 | 11 | G > T | 1,45 | 0,99 - 2,11 | 0,029 | 1 | IL18 | Locus |
| rs3749442 | 3 | C > T | 0,58 | 0,35 - 0,94 | 0,029 | 1 | ABCC5 | Coding-synonymous |
| rs2976437 | 8 | A > G | 0,66 | 0,45 - 0,96 | 0,030 | 1 | NEFL | Promoter |
| rs4252596 | 17 | C > A | 1,79 | 1,03 - 3,11 | 0,030 | 1 | ERBB2 | Intron |
| rs2384937 | 16 | T > C | 1,79 | 1,05 - 3,05 | 0,031 | 1 | ABCC1 | Intron,TagSNP:ABCC1 |
| rs3793345 | 7 | T > C | 1,66 | 1,04 - 2,66 | 0,032 | 1 | IGFBP3 | Intron |
| rs7731453 | 5 | C > A | 0,54 | 0,30 - 0,97 | 0,032 | 1 | HMMR | Coding-nonsynonymous |
| rs1413228 | 1 | A > G | 2,03 | 1,08 - 3,81 | 0,032 | 1 | DPYD | Intron,TagSNP:DPYD |
| rs529948 | 6 | G > A | 1,94 | 1,03 - 3,67 | 0,032 | 1 | NFKBIE | Promoter |
| rs1051740 | 1 | T > C | 1,59 | 1,05 - 2,41 | 0,033 | 1 | EPHX1 | Coding-nonsynonymous |
| rs5742714 | 12 | G > C | 2,10 | 1,05 - 4,20 | 0,034 | 1 | IGF1 | Untranslated |
| rs532411 | 3 | C > T | 2,13 | 1,04 - 4,36 | 0,035 | 1 | POLQ | Coding-nonsynonymous |
| rs7805658 | 7 | G > A | 0,66 | 0,45 - 0,96 | 0,035 | 1 | SHFM1 | Intron,TagSNP:DSS1 |
| rs2274578 | 6 | G > C | 0,66 | 0,46 - 0,96 | 0,035 | 1 | BYSL | Locus,Untranslated |
| rs1364283 | 16 | A > C | 1,48 | 1,02 - 2,14 | 0,036 | 1 | HSD17B2 | 3' UTR |
| rs7172 | 1 | A > G | 0,60 | 0,38 - 0,97 | 0,036 | 1 | PSMB4 | Coding-synonymous |
| rs16941 | 17 | A > G | 0,65 | 0,44 - 0,96 | 0,037 | 1 | BRCA1 | Coding-nonsynonymous |
| rs1132776 | 3 | C > T | 1,52 | 1,04 - 2,21 | 0,037 | 1 | ABCC5 | Coding-synonymous |
| rs1137101 | 1 | G > A | 0,67 | 0,46 - 0,97 | 0,038 | 1 | LEPR | Coding-nonsynonymous |
| rs593818 | 19 | G > A | 0,69 | 0,47 - 1,00 | 0,038 | 1 | CYP4F12 | Coding-nonsynonymous |
| rs2214102 | 7 | G > A | 0,47 | 0,23 - 0,97 | 0,039 | 1 | ABCB1 | Untranslated |
| rs4148553 | 13 | G > A | 0,67 | 0,46 - 0,97 | 0,040 | 1 | ABCC4 | Untranslated |
| rs35604 | 16 | A > G | 1,77 | 1,02 - 3,08 | 0,040 | 1 | ABCC1 | Intron,TagSNP:ABCC1 |
| rs1045105 | 1 | C > A | 1,70 | 0,98 - 2,94 | 0,042 | 1 | CNKSRI | Coding-nonsynonymous |
| rs730566 | 3 | G > T | 1,48 | 0,97 - 2,26 | 0,042 | 1 | TREX1 | Locus |
| rs523349 | 2 | C > G | 0,67 | 0,45 - 1,00 | 0,042 | 1 | SRD5A2 | Intron |
| rs3131637 | 6 | A > T | 0,70 | 0,48 - 1,02 | 0,042 | 1 | LTA | Locus |
| rs2274407 | 13 | C > A | 2,18 | 0,99 - 4,80 | 0,043 | 1 | ABCC4 | Coding-nonsynonymous |
| rs1822017 | 3 | C > T | 1,68 | 1,03 - 2,74 | 0,043 | 1 | DCBLD2 | Coding-synonymous |
| rs7242 | 7 | T > G | 1,46 | 1,00 - 2,13 | 0,044 | 1 | SERPINE1 | Untranslated |
| rs3130618 | 6 | C > A | 0,56 | 0,32 - 0,99 | 0,044 | 1 | BAT4 | Coding-nonsynonymous |
| rs6033 | 1 | A > G | 0,42 | 0,20 - 0,91 | 0,044 | 1 | F5 | Coding-nonsynonymous |
| rs8192707 | 20 | A > G | 1,73 | 1,02 - 2,92 | 0,044 | 1 | PLCG1 | Coding-nonsynonymous |
| rs540199 | 11 | A > G | 0,67 | 0,46 - 0,99 | 0,045 | 1 | MRE11A | Intron,TagSNP:MRE11A |
| rs619824 | 10 | G > T | 0,70 | 0,48 - 1,01 | 0,045 | 1 | CYP17A1 | 3' UTR |
| rs10079641 | 5 | C > G | 0,53 | 0,29 - 0,98 | 0,046 | 1 | MSH3 | Intron |
| rs2470893 | 15 | G > A | 1,54 | 1,02 - 2,31 | 0,048 | 1 | CYP1A1 | Locus |
| rs1060915 | 17 | T > C | 0,68 | 0,46 - 1,01 | 0,049 | 1 | BRCA1 | Coding-synonymous,Untranslated |
| rs769412 | 12 | A > G | 0,45 | 0,20 - 1,03 | 0,049 | 1 | MDM2 | Coding-synonymous |
| rs2295275 | 6 | T > A | 2,40 | 1,00 - 5,75 | 0,050 | 1 | TRETF1 | Coding-nonsynonymous |

SNP: single nucleotide polymorphism; Chr: chromosome; OR: odds ratio; CI: confidence interval.

Online Supplementary Table S6. Cross validation of significantly associated SNPs in the IFM 2005-01 discovery set. A Cochran χ^2 test and a Mantel-Haenszel stratified association test were used to analyze SNP associations in the discovery set (IFM 2005-01) and the validation set (HOVON-65/GMMG-HD4 and Czech Republic samples), respectively. A one-sided test for ORs was performed to investigate cross validation of significant SNPs (pointwise $P < 0.05$) in the discovery set.

| SNP | Chr | Alleles | Gene | SNP type | One-sided test for ORs | | | IFM 2005-01 discovery set | | Pointwise P for χ^2 |
|------------|-----|---------|-----------------|-------------------------------|------------------------|-------------------------------------|-----------------------------------|---------------------------|-------------|----------------------------|
| | | | | | OR | Unadjusted P value validation set | Adjusted P value validation set | OR | 95% CI | |
| rs619824 | 10 | G > T | <i>CYP17A1</i> | 3' UTR | 0.7 | 0.03 | 0.82 | 0.64 | 0.44 - 0.93 | 0.01 |
| rs2857605 | 6 | A > G | <i>TNF</i> | Intron,TagSNP:TNF | 0.69 | 0.05 | 0.82 | 0.57 | 0.36 - 0.92 | 0.03 |
| rs6945306 | 7 | G > C | <i>STK31</i> | Coding-nonsynonymous | 1.33 | 0.08 | 0.82 | 1.71 | 1.17 - 2.52 | 0.01 |
| rs10759326 | 9 | T > G | <i>IKBKAP</i> | Coding-synonymous | 1.32 | 0.13 | 0.82 | 1.57 | 0.99 - 2.48 | 0.05 |
| rs2472299 | 15 | G > A | <i>CYP1A1</i> | Promoter | 0.8 | 0.13 | 0.82 | 0.62 | 0.42 - 0.92 | 0.02 |
| rs3136516 | 11 | A > G | <i>F2</i> | Intron | 0.82 | 0.14 | 0.82 | 0.61 | 0.42 - 0.88 | 0.01 |
| rs2074351 | 7 | G > A | <i>PON1</i> | Intron,TagSNP:PON1 | 1.22 | 0.18 | 0.82 | 1.51 | 1.01 - 2.26 | 0.05 |
| rs762551 | 15 | A > C | <i>CYP1A2</i> | Intron,TagSNP:CYP1A_cluster | 0.83 | 0.18 | 0.82 | 0.63 | 0.42 - 0.93 | 0.03 |
| rs1149901 | 10 | C > T | <i>GATA3</i> | Locus,untranslated | 1.2 | 0.2 | 0.82 | 1.62 | 1.07 - 2.45 | 0.02 |
| rs2124459 | 21 | T > C | <i>CBS</i> | Intron | 0.85 | 0.21 | 0.82 | 0.66 | 0.45 - 0.96 | 0.05 |
| rs1052637 | 2 | G > C | <i>DDX18</i> | Coding-nonsynonymous | 0.85 | 0.21 | 0.82 | 0.66 | 0.45 - 0.97 | 0.03 |
| rs854556 | 7 | C > T | <i>PON1</i> | Intron,TagSNP:PON1 | 0.85 | 0.21 | 0.82 | 0.64 | 0.44 - 0.95 | 0.03 |
| rs2227956 | 6 | T > C | <i>HSPAIL</i> | Coding-nonsynonymous | 0.84 | 0.22 | 0.82 | 0.52 | 0.3 - 0.88 | 0.02 |
| rs3733890 | 5 | G > A | <i>BHMT</i> | Coding-nonsynonymous | 0.86 | 0.23 | 0.82 | 0.66 | 0.45 - 0.98 | 0.04 |
| rs1296028 | 8 | A > G | <i>FDFT1</i> | 3' UTR | 0.86 | 0.24 | 0.82 | 0.64 | 0.42 - 0.99 | 0.05 |
| rs2228233 | 14 | C > T | <i>NFATC4</i> | Coding-synonymous | 0.9 | 0.31 | 0.82 | 0.65 | 0.43 - 0.98 | 0.05 |
| rs3758581 | 10 | G > A | <i>CYP2C19</i> | Coding-nonsynonymous | 1.19 | 0.31 | 0.82 | 2.35 | 1.12 - 4.97 | 0.05 |
| rs854555 | 7 | C > A | <i>PON1</i> | Intron,TagSNP:PON1 | 1.1 | 0.31 | 0.82 | 1.53 | 1.05 - 2.24 | 0.03 |
| rs9640663 | 7 | A > G | <i>PTPN12</i> | Coding-nonsynonymous | 0.91 | 0.32 | 0.82 | 0.67 | 0.46 - 0.98 | 0.04 |
| rs121 | 7 | A > G | <i>OSBPL3</i> | Intron,TAG | 1.08 | 0.34 | 0.82 | 1.61 | 1.11 - 2.32 | 0.01 |
| rs2239330 | 16 | C > T | <i>ABCC1</i> | Coding-synonymous | 0.92 | 0.35 | 0.82 | 0.59 | 0.39 - 0.9 | 0.01 |
| rs878201 | 1 | G > A | - | Intergenic | 1.07 | 0.37 | 0.82 | 1.54 | 1.04 - 2.29 | 0.02 |
| rs2007231 | 1 | T > C | <i>NRAS</i> | Intron | 0.94 | 0.37 | 0.82 | 0.66 | 0.44 - 0.97 | 0.04 |
| rs3759217 | 12 | C > T | <i>CDKN1B</i> | Locus | 1.08 | 0.39 | 0.83 | 2.76 | 1.58 - 4.84 | < 0.001 |
| rs440454 | 6 | C > T | <i>RDBP</i> | Locus,Intron | 0.95 | 0.41 | 0.83 | 0.62 | 0.39 - 0.97 | 0.03 |
| rs3212254 | 14 | C > A | <i>PARP1</i> | Intron | 1.04 | 0.46 | 0.83 | 2.12 | 1.04 - 4.31 | 0.04 |
| rs2686184 | 8 | G > A | <i>BLM</i> | Intron | 1.01 | 0.48 | 0.83 | 1.72 | 1.19 - 2.49 | 0.01 |
| rs6768093 | 3 | T > A | <i>ATR</i> | Locus | 0.99 | 0.49 | 0.83 | 0.66 | 0.45 - 0.96 | 0.04 |
| rs7169 | 1 | T > C | <i>SLCO1A2</i> | Untranslated,intron | 1 | 0.5 | 0.83 | 1.65 | 1.14 - 2.39 | 0.01 |
| rs584589 | 17 | A > G | <i>UGT2B7</i> | Locus | 1 | 0.51 | 0.83 | 2.01 | 1.16 - 3.47 | 0.01 |
| rs3776432 | 5 | G > A | <i>PROCR</i> | Coding-nonsynonymous | 0.99 | 0.51 | 0.83 | 1.52 | 1.04 - 2.24 | 0.03 |
| rs1641536 | 17 | G > A | <i>SHBG</i> | 3' UTR | 1.01 | 0.52 | 0.83 | 0.43 | 0.22 - 0.86 | 0.02 |
| rs2033178 | 12 | C > T | <i>IGF1</i> | Intron | 0.93 | 0.58 | 0.90 | 2.42 | 1.23 - 4.74 | 0.01 |
| rs4148949 | 10 | C > T | <i>CHST3</i> | Untranslated | 1.05 | 0.61 | 0.92 | 0.6 | 0.41 - 0.88 | 0.01 |
| rs1002153 | 1 | T > C | <i>PARP1</i> | Intron | 1.1 | 0.65 | 0.94 | 0.56 | 0.33 - 0.95 | 0.03 |
| rs1805405 | 1 | C > A | <i>PARP1</i> | Intron | 1.11 | 0.66 | 0.94 | 0.56 | 0.33 - 0.95 | 0.03 |
| rs2231142 | 4 | C > A | <i>ABCG2</i> | Coding-nonsynonymous | 0.83 | 0.71 | 0.95 | 2.12 | 1.04 - 4.31 | 0.04 |
| rs11466155 | 17 | C > T | <i>NGFR</i> | Coding-synonymous | 0.89 | 0.71 | 0.95 | 1.87 | 1.25 - 2.8 | 0 |
| rs4799055 | 18 | G > T | <i>NFATC1</i> | Intron | 0.87 | 0.77 | 0.98 | 1.61 | 1.1 - 2.35 | 0.03 |
| rs228851 | 20 | G > T | <i>NFATC2</i> | Intron | 1.16 | 0.79 | 0.98 | 0.59 | 0.41 - 0.86 | 0.01 |
| rs1050152 | 5 | C > T | <i>SLC22A4</i> | Coding-nonsynonymous | 1.18 | 0.81 | 0.98 | 0.68 | 0.47 - 0.99 | 0.04 |
| rs9885672 | 6 | T > C | <i>KIAA0274</i> | Coding-nonsynonymous | 0.78 | 0.82 | 0.98 | 1.86 | 1.08 - 3.21 | 0.02 |
| rs1801105 | 2 | C > T | <i>HNMT</i> | Coding-nonsynonymous | 0.74 | 0.85 | 0.98 | 1.95 | 1.06 - 3.6 | 0.04 |
| rs2228088 | 6 | G > T | <i>TNF</i> | Coding-synonymous, TagSNP:TNF | 1.43 | 0.87 | 0.98 | 0.56 | 0.36 - 0.87 | 0.01 |
| rs3817074 | 19 | C > T | <i>BAX</i> | Intron | 0.67 | 0.9 | 0.98 | 1.95 | 1.06 - 3.6 | 0.03 |
| rs1405655 | 19 | T > C | <i>NR1H2</i> | Intron | 0.76 | 0.92 | 0.98 | 1.56 | 1.05 - 2.32 | 0.04 |

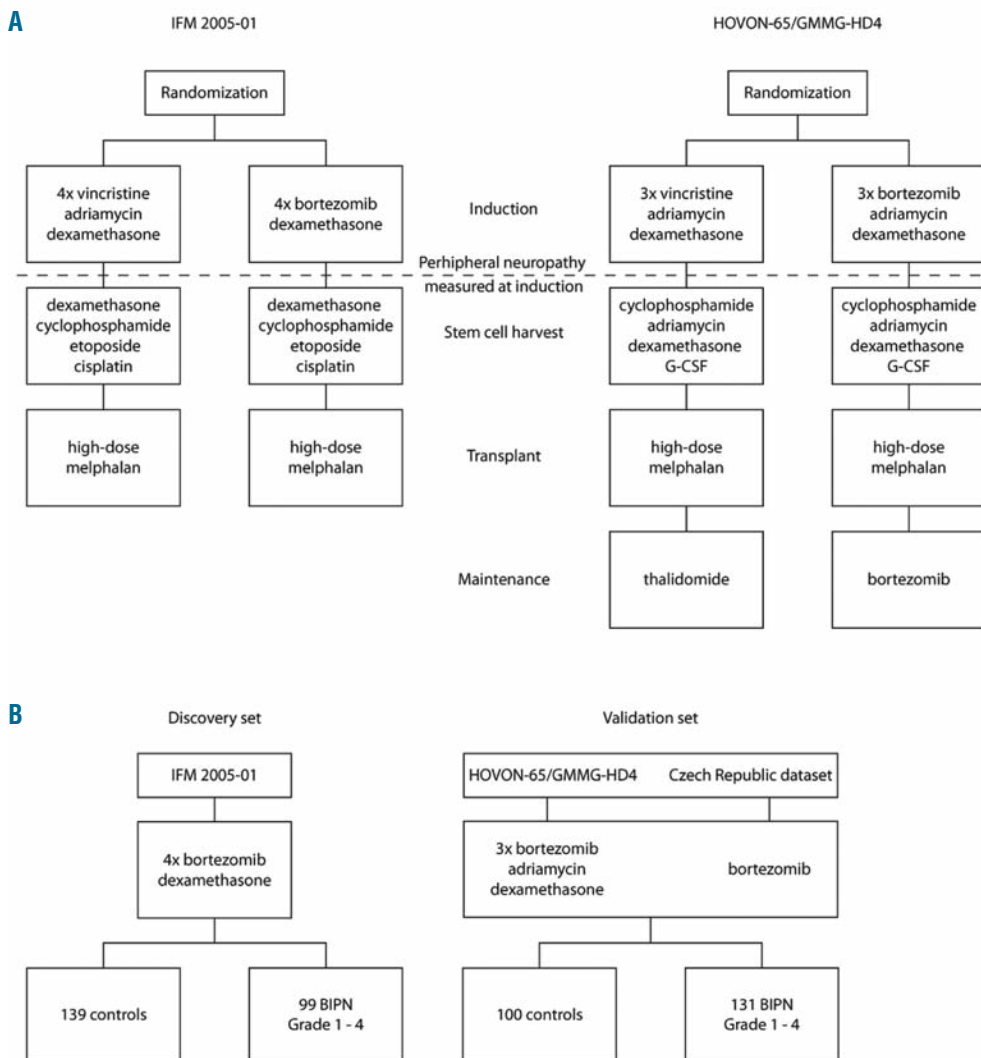
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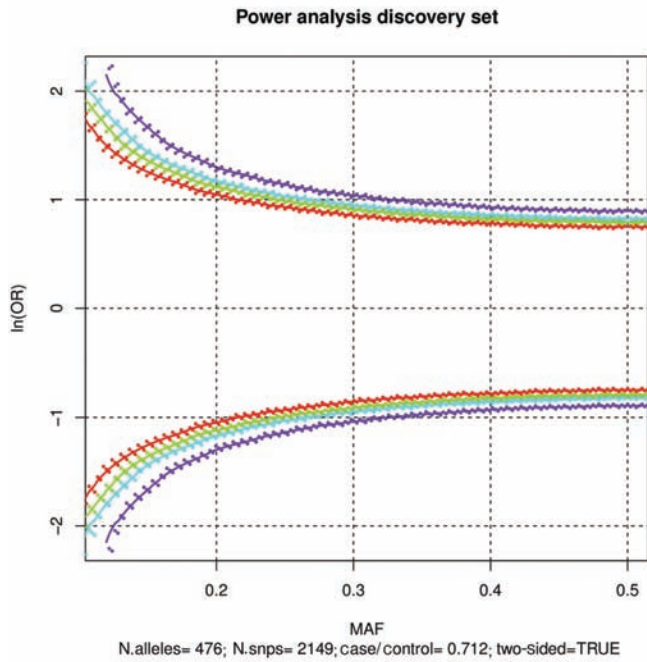
| | | | | | | | | | | |
|-----------|----|-------|---------------|----------------------|------|------|------|------|-------------|------|
| rs2973015 | 5 | A > G | <i>GHR</i> | Intron | 1.34 | 0.94 | 0.98 | 0.63 | 0.44 - 0.91 | 0.02 |
| rs504122 | 13 | C > T | <i>HNMT</i> | Intron,TagSNP:HNMT | 1.34 | 0.94 | 0.98 | 0.63 | 0.43 - 0.93 | 0.02 |
| rs163078 | 2 | C > T | <i>CYP1B1</i> | Intron,TagSNP:CYP1B1 | 1.38 | 0.94 | 0.98 | 0.63 | 0.43 - 0.92 | 0.03 |
| rs2976437 | 8 | A > G | <i>NEFL</i> | Promoter | 0.66 | 0.99 | 0.99 | 1.63 | 1.13 - 2.37 | 0.01 |
| rs6033 | 1 | A > G | <i>F5</i> | Coding-nonsynonymous | 0.42 | 0.99 | 0.99 | 2.53 | 1.3 - 4.94 | 0.01 |

SNP: single nucleotide polymorphism; Chr: chromosome; OR: Odds Ratio; CI: confidence interval; N/A: not applicable.

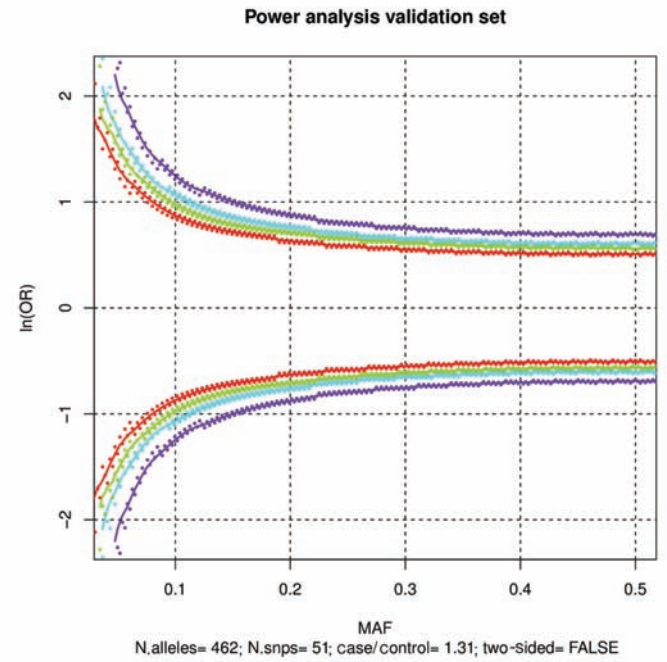
Online Supplementary Figure S1. Schematic representation of MM patient treatment and numbers. (A) Schematic representation of IFM 2005-01 and HOVON-65/GMMG-HD4 treatment. (B) BiPN case and control comparisons used in SNP analysis for discovery and validation set. G-CSF indicates granulocyte colony-stimulating factor.



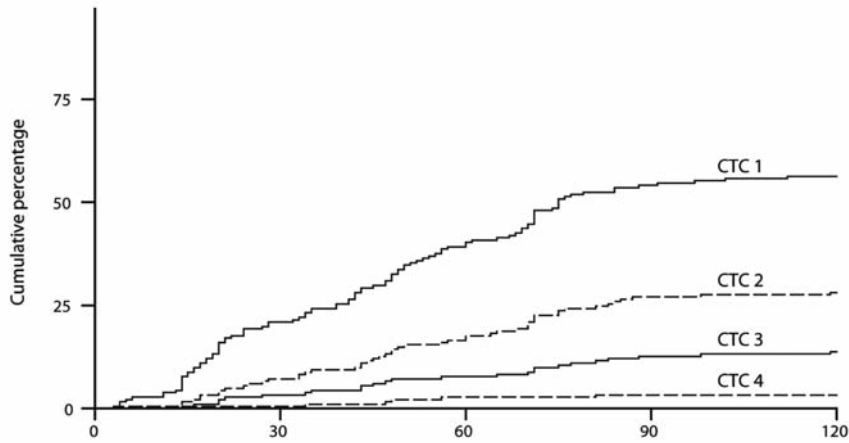
Online Supplementary Figure S2. Power analysis in the discovery set. At several P levels; dark blue: $P=0.01$; light blue: $P=0.05$; green: $P=0.1$; red: $P=0.25$.



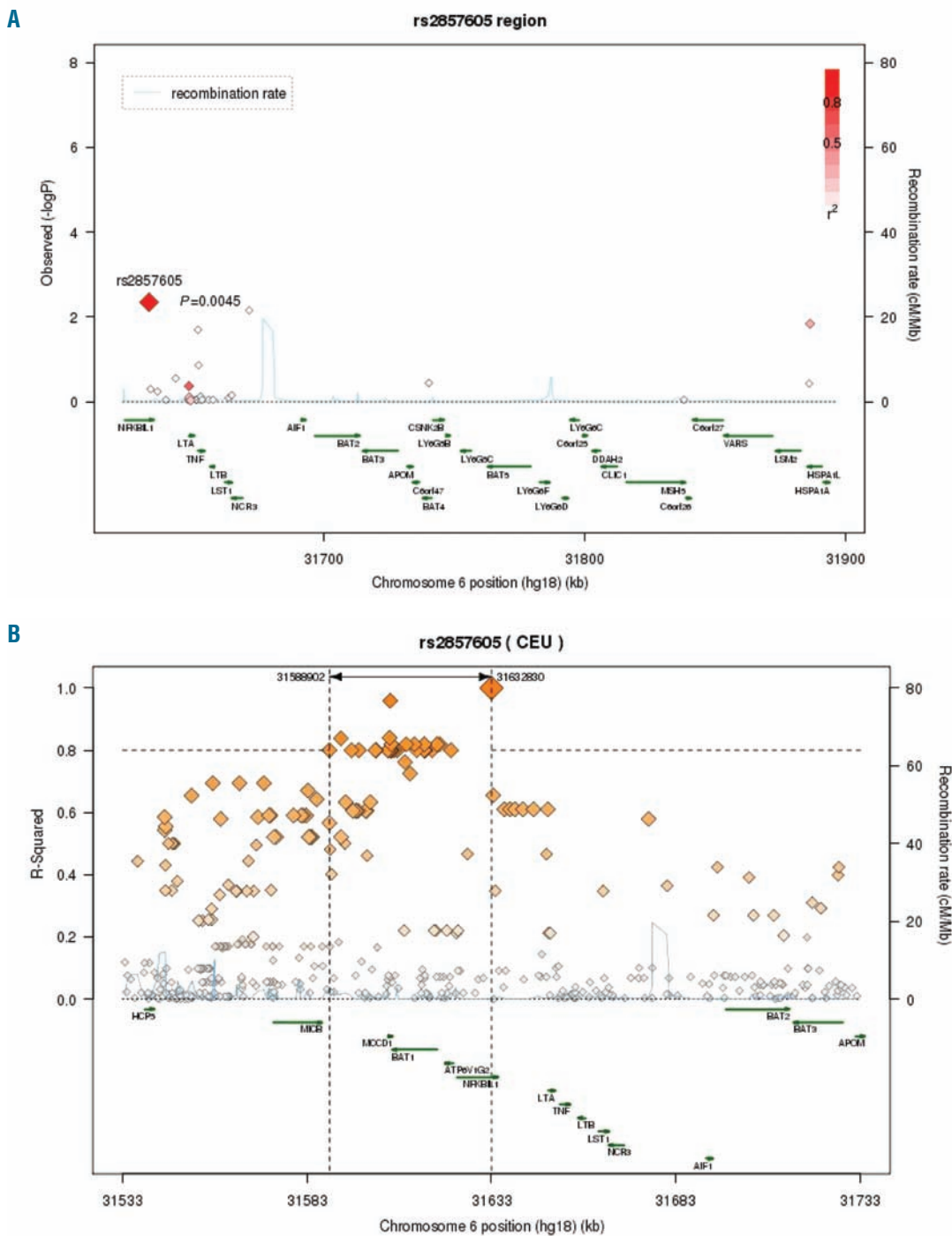
Online Supplementary Figure S3. Power analysis (one-sided test for ORs) in the validation set. At several P levels; dark blue: $P=0.01$; light blue: $P=0.05$; green: $P=0.1$; red: $P=0.25$.



Online Supplementary Figure S4. BiPN rates by time to BiPN in the HOVON-65/GMMG-HD4 trial. Cumulative percentage of MM patients from the HOVON-65/GMMG-HD4 ($n=412$) who developed grade 1 (26%), grade 2 (13%), grade 3 (9%) or grade 4 (3%) BiPN shown in time (days).



Online Supplementary Figure S5. SNP rs2857605 in TNF α region is associated with BIPN. Figures were generated using the web-based tool SNAP.³ Haploview 4.0 was used to generate the linkage disequilibrium plot. The International HapMap Project was used to calculate recombination rates. (A) Regional linkage disequilibrium plot for SNP rs2857605 in the TNF α gene region at 6p21, which is associated with BIPN. (B) SNPs genotyped across the TNF α gene region.



References

1. Johnson AD, Handsaker RE, Pulit SL, Nizzari MM, O'Donnell CJ, de Bakker PI. SNAP: a web-based tool for identification and annotation of proxy SNPs using HapMap. *Bioinformatics*. 2008;24(24):2938-9.