Supplementary Materials for "Genome-wide association study identifies variants in the MHC class I, *IL10*, and *IL23R/IL12RB2* regions associated with Behçet's disease"

Elaine F. Remmers, Fulya Cosan, Yohei Kirino, Michael J. Ombrello, Neslihan Abaci, Colleen Satorius, Julie M. Le, Barbara Yang, Benjamin D. Korman, Aris Cakiris, Oznur Aglar, Zeliha Emrence, Hulya Azakli, Duran Ustek, Ilknur Tugal-Tutkun, Gulsen Akman-Demir, Wei Chen, Christopher I. Amos, Michael B. Dizon, Afet Akdag Kose, Gulsevim Azizlerli, Burak Erer, Oliver J. Brand, Virginia G. Kaklamani, Phedon Kaklamanis, Eldad Ben-Chetrit, Miles Stanford, Farida Fortune, Marwen Ghabra, William E. R. Ollier, Young-Hun Cho, Dongsik Bang, John O'Shea, Graham R. Wallace, Massimo Gadina, Daniel L. Kastner, and Ahmet Gül

**Supplementary Table 1: Demographic and clinical characteristics of the GWAS patients with Behçet's disease (n=1215).**

| Characteristic | Frequency |
|---|---|
| Male / Female, n (%) | 664/551 (54.7/45.3) |
| Mean age ± SD (range) | 39.3 ± 12.1 (13-79) |
| Recurrent oral ulcers (%) | 100.0 |
| Genital ulcers (%) | 72.7 |
| Folliculitis (%) | 77.9 |
| Erythema nodosum (%) | 50.6 |
| Pathergy reaction (n=1020) (%) | 80.3 |
| Uveitis (%) | 35.4 |
| Vascular involvement (%) | 25.2 |
| Neurologic involvement (%) | 9.0 |
| Intestinal involvement (%) | 1.0 |
| Positive family history (%) | 18.6 |

**Supplementary Table 2: SNPs with allelic Chi-squared P value < 0.0001 for association with Behçet's disease.**

| SNP ID | Chromosome | Position | Gene symbol | Gene ID | Odds Ratio | 95% CI | Chi-Squared P |
|---|---|---|---|---|---|---|---|
| rs1495966 | 1 | 67525941 | IL23R | Interleukin 23 receptor | 1.26 | (1.12 - 1.40) | 6.09E-05 |
| rs1495965 | 1 | 67526096 | IL23R | Interleukin 23 receptor | 1.25 | (1.12 - 1.40) | 6.99E-05 |
| rs924080 | 1 | 67532728 | IL23R | Interleukin 23 receptor | 1.31 | (1.17 - 1.47) | 5.35E-06 |
| rs3024490 | 1 | 205011934 | IL10 | Interleukin 10 | 1.36 | (1.21 - 1.53) | 2.22E-07 |
| rs4851526 | 2 | 101984802 | IL1R2 | Interleukin 1 receptor, type II | 1.28 | (1.14 - 1.44) | 4.39E-05 |
| rs7572482 | 2 | 191723317 | STAT4 | Signal transducer and activator of transcription 4 | 1.27 | (1.13 - 1.42) | 3.18E-05 |
| rs9798281 | 2 | 239385071 | HDAC4 | Histone deacetylase 4 | 1.49 | (1.23 - 1.81) | 3.87E-05 |
| rs2291897 | 3 | 33394426 | FBXL2 | F-box and leucine-rich repeat protein 2 | 1.39 | (1.19 - 1.61) | 1.82E-05 |
| rs1807844 | 3 | 33447941 | UBP1 | Upstream binding protein 1 | 1.36 | (1.17 - 1.57) | 5.56E-05 |
| rs1357540 | 3 | 33454986 | UBP1 | Upstream binding protein 1 | 1.38 | (1.19 - 1.60) | 2.69E-05 |
| rs12487660 | 3 | 33567576 | CLASP2 | CLIP-associating protein 2 | 1.32 | (1.16 - 1.51) | 2.70E-05 |
| rs12639224 | 3 | 45891226 | LZTFL1 | Leucine zipper transcription factor-like 1 | 1.27 | (1.13 - 1.44) | 7.43E-05 |
| rs2133660 | 3 | 46006961 | FYCO1 | FYVE and coiled-coil domain containing 1 | 1.27 | (1.13 - 1.43) | 8.02E-05 |
| rs10510749 | 3 | 46155420 | CCR1 | Chemokine (C-C motif) receptor 1 | 1.43 | (1.20 - 1.69) | 4.22E-05 |
| rs7631551 | 3 | 46161314 | CCR1 | Chemokine (C-C motif) receptor 1 | 1.40 | (1.18 - 1.66) | 7.95E-05 |
| rs9990343 | 3 | 46314816 | CCR3 | Chemokine (C-C motif) receptor 3 | 1.29 | (1.15 - 1.46) | 2.76E-05 |
| rs10510933 | 3 | 65123661 | MAGI1 | Membrane ass'd guanylate kinase, WW and PDZ domain containing 1 | 1.32 | (1.16 - 1.51) | 3.46E-05 |
| rs9819066 | 3 | 71605800 | FOXP1 | Forkhead box P1 isoform 1 | 1.31 | (1.17 - 1.46) | 4.55E-06 |
| rs9828629 | 3 | 71613036 | FOXP1 | Forkhead box P1 isoform 1 | 1.30 | (1.16 - 1.45) | 8.89E-06 |
| rs6549392 | 3 | 71621386 | FOXP1 | Forkhead box P1 isoform 1 | 1.29 | (1.15 - 1.46) | 2.33E-05 |
| rs11720523 | 3 | 71627860 | FOXP1 | Forkhead box P1 isoform 1 | 1.29 | (1.15 - 1.45) | 2.09E-05 |
| rs6779258 | 3 | 71632329 | FOXP1 | Forkhead box P1 isoform 1 | 1.30 | (1.16 - 1.46) | 1.11E-05 |
| rs11720121 | 3 | 71677948 | FOXP1 | Forkhead box P1 isoform 1 | 1.30 | (1.15 - 1.46) | 1.28E-05 |
| rs6549400 | 3 | 71689156 | FOXP1 | Forkhead box P1 isoform 1 | 1.30 | (1.16 - 1.47) | 8.46E-06 |
| rs10460943 | 3 | 71754996 | FOXP1 | Forkhead box P1 isoform 1 | 1.37 | (1.17 - 1.60) | 7.33E-05 |
| rs10049211 | 3 | 72597366 | RYBP | RING1 and YY1 binding protein | 1.30 | (1.16 - 1.46) | 5.35E-06 |
| rs11128275 | 3 | 72598650 | RYBP | RING1 and YY1 binding protein | 1.26 | (1.13 - 1.41) | 3.80E-05 |
| rs11718322 | 3 | 123192776 | ILDR1 | Immunoglobulin-like domain containing receptor 1 | 1.26 | (1.12 - 1.42) | 8.23E-05 |
| rs10513355 | 3 | 150734049 | WWTR1 | WW domain containing transcription regulator 1 | 1.49 | (1.23 - 1.80) | 4.66E-05 |
| rs17810546 | 3 | 161147744 | IL12A | Interleukin 12 alpha | 1.63 | (1.30 - 2.03) | 1.49E-05 |
| rs6441306 | 3 | 161434972 | LOC401097 | LOC401097 | 1.27 | (1.13 - 1.42) | 3.52E-05 |
| rs7634425 | 3 | 184503286 | MCF2L2 | Rho family guanine-nucleotide exchange factor | 1.31 | (1.15 - 1.49) | 2.97E-05 |
| rs936551 | 4 | 811490 | CPLX1 | Complexin-1 | 1.36 | (1.22 - 1.53) | 5.29E-08 |
| rs1495714 | 4 | 177074783 | GPM6A | Glycoprotein M6A isoform 1 | 1.29 | (1.15 - 1.44) | 1.93E-05 |
| rs4690647 | 4 | 177109914 | GPM6A | Glycoprotein M6A isoform 1 | 1.29 | (1.15 - 1.44) | 1.13E-05 |
| rs563624 | 5 | 6574837 | UBE2QL1 | Ubiquitin-conjugating enzyme E2Q family-like 1 | 1.26 | (1.12 - 1.41) | 6.12E-05 |
| rs4865879 | 5 | 54196102 | ESM1 | Endothelial cell-specific molecule 1 | 1.25 | (1.12 - 1.40) | 6.81E-05 |
| rs10940434 | 5 | 54210663 | ESM1 | Endothelial cell-specific molecule 1 | 1.27 | (1.13 - 1.42) | 3.27E-05 |
| rs11167821 | 5 | 142954837 | NR3C1 | Nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor) | 1.37 | (1.17 - 1.61) | 7.98E-05 |
| rs7731137 | 5 | 153985847 | LARP1 | La ribonucleoprotein domain family, member 1 | 1.26 | (1.12 - 1.42) | 9.50E-05 |
| rs11962776 | 6 | 15368132 | JARID2 | Jumonji, AT rich interactive domain 2 | 1.67 | (1.30 - 2.13) | 3.94E-05 |
| rs4896243 | 6 | 137556483 | IFNGR1 | Interferon gamma receptor 1 precursor | 1.27 | (1.14 - 1.42) | 2.67E-05 |
| rs10486156 | 7 | 7315158 | COL28A1 | Collagen, type XXVIII precursor | 1.40 | (1.21 - 1.61) | 3.69E-06 |

**Supplementary Table 2 (continued)**

| SNP ID | Chromosome | Position | Gene symbol | Gene ID | Odds Ratio | 95% CI | Chi-Squared P |
|---|---|---|---|---|---|---|---|
| rs2709748 | 7 | 20786295 | SP8 | Sp8 transcription factor isoform 2 | 1.43 | (1.22 - 1.68) | 1.38E-05 |
| rs6967330 | 7 | 105445687 | CDH28 | Cadherin-like protein 28 precursor | 1.32 | (1.15 - 1.52) | 8.43E-05 |
| rs6986423 | 8 | 4621823 | CSMD1 | CUB and Sushi multiple domains 1 | 1.28 | (1.15 - 1.43) | 1.27E-05 |
| rs7004739 | 8 | 126397565 | NSMCE2 | Non-SMC element 2, MMS21 homolog | 1.27 | (1.14 - 1.43) | 2.14E-05 |
| rs10868677 | 9 | 89801692 | CDK20 | Cyclin-dependent kinase 20 | 1.25 | (1.12 - 1.40) | 8.79E-05 |
| rs17302884 | 9 | 118211868 | ASTN2 | Astrotactin 2 | 1.28 | (1.14 - 1.44) | 5.16E-05 |
| rs3849150 | 10 | 49779229 | WDFY4 | WDFY family member 4 | 1.34 | (1.17 - 1.54) | 2.73E-05 |
| rs1882191 | 12 | 68671590 | RAB3IP | RAB3A interacting protein | 1.31 | (1.14 - 1.49) | 7.52E-05 |
| rs7295696 | 12 | 116915710 | RFCF5 | Replication factor C (activator 1) 5 | 1.28 | (1.14 - 1.44) | 1.77E-05 |
| rs7310266 | 12 | 118582792 | PRKAB1 | Protein kinase, AMP-activated, beta 1 non-catalytic subunit | 1.28 | (1.13 - 1.44) | 5.81E-05 |
| rs3764147 | 13 | 43355925 | C13orf31 | Chromosome 13 open reading frame 31 | 1.34 | (1.18 - 1.52) | 7.36E-06 |
| rs2121037 | 13 | 43369317 | C13orf31 | Chromosome 13 open reading frame 31 | 1.32 | (1.16 - 1.52) | 4.56E-05 |
| rs8023192 | 14 | 20265311 | EDDM3A | Epididymal protein 3A | 1.26 | (1.12 - 1.41) | 9.44E-05 |
| rs4900016 | 14 | 89375413 | C14orf143 | Chromosome 14 open reading frame 143 | 1.34 | (1.17 - 1.54) | 3.53E-05 |
| rs597804 | 15 | 55888241 | GRINL1A | Glutamate R, ionotropic, N-methyl D-aspartate-like 1A | 1.29 | (1.14 - 1.45) | 5.59E-05 |
| rs11072744 | 15 | 76297874 | ACSBG1 | Acyl-CoA synthetase bubblegum family member 1 | 1.34 | (1.16 - 1.56) | 7.62E-05 |
| rs2199724 | 15 | 93036137 | MCTP2 | Multiple C2 domains, transmembrane 2 | 1.28 | (1.14 - 1.43) | 2.59E-05 |
| rs2046006 | 15 | 93038965 | MCTP2 | Multiple C2 domains, transmembrane 2 | 1.26 | (1.12 - 1.42) | 9.03E-05 |
| rs6503137 | 17 | 8506081 | CCDC42 | Coiled-coil domain containing 42 | 1.36 | (1.17 - 1.59) | 8.24E-05 |
| rs1971773 | 17 | 8574035 | CCDC42 | Coiled-coil domain containing 42 | 1.26 | (1.13 - 1.42) | 5.48E-05 |
| rs1558748 | 17 | 67578097 | SOX9 | SRY (sex determining region Y)-box 9 | 1.31 | (1.15 - 1.50) | 5.35E-05 |
| rs2285515 | 19 | 40352290 | FXYD5 | FXYD domain containing ion transport regulator 5 | 1.27 | (1.13 - 1.43) | 7.66E-05 |
| rs913678 | 20 | 48388831 | PTPN1 | Protein tyrosine phosphatase, non-receptor type 1 | 1.27 | (1.13 - 1.42) | 3.19E-05 |
| rs2187961 | 22 | 33911399 | HMGXB4 | HMG box domain containing 4 | 2.65 | (1.70 - 4.14) | 7.84E-06 |
| rs2092331 | 22 | 33961544 | HMGXB4 | HMG box domain containing 4 | 2.34 | (1.56 - 3.50) | 2.28E-05 |

**Supplementary Table 3:** Association of GWAS SNPs within selected BD candidate genes.

| *Gene* | *Chrom* | *Position* | *Most significantly associated SNP* | *Position* | *P-value** | *Location* |
|---|---|---|---|---|---|---|
| *PTPN22*[1-2] | 1 | 114,157,963-114,215,898 | rs1217407 | 114,195,271 | 0.27 | Intronic |
| *FCRL3*[3] | 1 | 155,914,602-155,937,271 | rs7522061 | 155,935,014 | 0.00083 | Coding variant: N28D |
| *CD28*[4] | 2 | 204,279,443-204,310,802 | rs1181389 | 204,283,135 | 0.091 | Intronic |
| *CTLA4*[4-5] | 2 | 204,440,754-204,446,928 | rs10497873 | 204,470,572 | 0.013 | 3' of the gene |
| *SLC11A1*[6-7] | 2 | 218,954,996-218,969,861 | rs3731863 | 218,960,452 | 0.012 | Intronic |
| *TNFA*[8] | 6 | 31,652,271-31,654,091 | rs3093668 | 31,654,474 | 0.32 | 3' of gene |
| *IL17F*[9] | 6 | 52,209,443-52,217,257 | rs7771466 | 52,212,068 | 0.0078 | Intronic |
| *SUMO4*[10] | 6 | 149,763,188-149,763,875 | rs237012 | 149,770,891 | 0.12 | 3' of gene |
| *NOS3*[11] | 7 | 150,319,080-150,342,609 | rs2373929 | 150,345,745 | 0.33 | 3' of gene |
| *TLR4*[12] | 9 | 119,506,431-119,519,587 | rs1927906 | 119,519,936 | 0.00080 | 5' of gene |
| *MEFV*[13-14] | 16 | 3,232,029-3,246,628 | rs224218 | 3,241,898 | 0.38 | Intronic |
| *CARD15*[15] | 16 | 49,288,551-49,324,488 | rs8057341 | 49,295,481 | 0.0044 | Intronic |

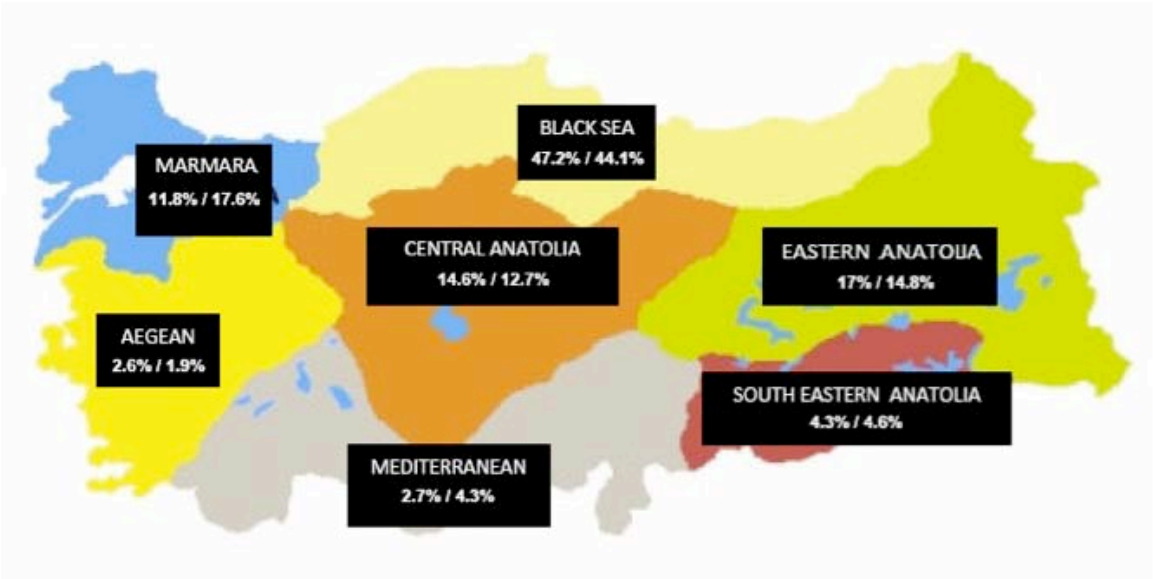
** Allelic Chi squared P-value*

References for Table


1. Baranathan, V. et al. The association of the PTPN22 620W polymorphism with Behcet's disease. *Ann Rheum Dis* **66**, 1531-3 (2007).
2. Sahin, N., Bicakcigil, M., Atagunduz, P., Direskeneli, H. & Saruhan-Direskeneli, G. PTPN22 gene polymorphism in Behcet's disease. *Tissue Antigens* **70**, 432-4 (2007).
3. Li, K. et al. Association between polymorphisms of FCRL3, a non-HLA gene, and Behcet's disease in a Chinese population with ophthalmic manifestations. *Mol Vis* **14**, 2136-42 (2008).
4. Gunesacar, R. et al. Analysis of CD28 and CTLA-4 gene polymorphisms in Turkish patients with Behcet's disease. *Int J Immunogenet* **34**, 45-9 (2007).
5. Bye, L. et al. CTLA-4 polymorphisms are not associated with ocular inflammatory disease. *Tissue Antigens* **72**, 49-53 (2008).
6. Ates, O. et al. NRAMP1 (SLC11A1) gene polymorphisms that correlate with autoimmune versus infectious disease susceptibility in tuberculosis and rheumatoid arthritis. *Int J Immunogenet* **36**, 15-9 (2009).

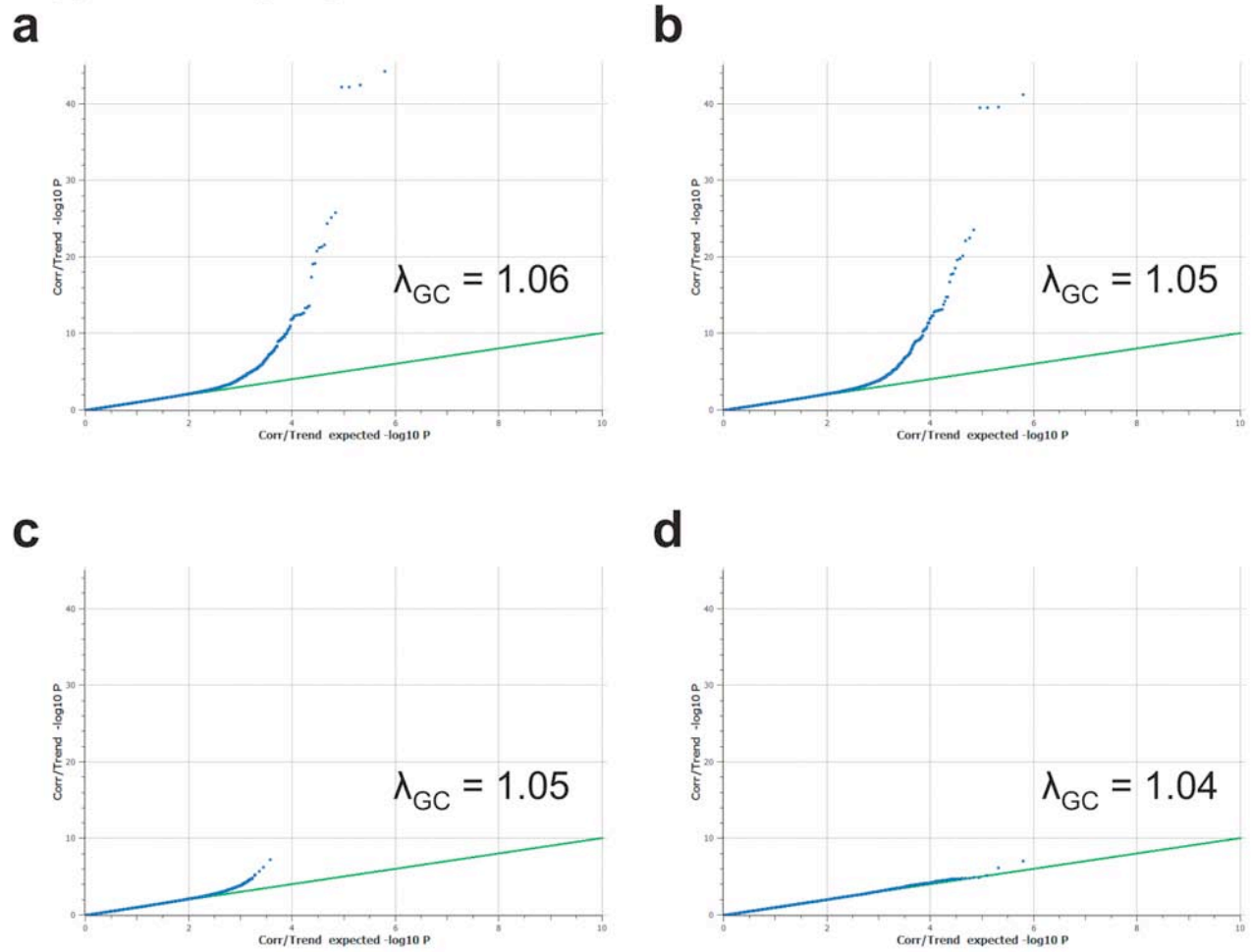
7. Kim, S.K. et al. SLC11A1 gene polymorphisms in Korean patients with Behcet's disease. *Scand J Rheumatol* **35**, 398-401 (2006).
8. Park, K., Kim, N., Nam, J., Bang, D. & Lee, E.S. Association of TNFA promoter region haplotype in Behcet's Disease. *J Korean Med Sci* **21**, 596-601 (2006).
9. Jang, W.C. et al. Interleukin-17F gene polymorphisms in Korean patients with Behcet's disease. *Rheumatol Int* **29**, 173-8 (2008).
10. Hou, S. et al. SUMO4 gene polymorphisms in Chinese Han patients with Behcet's disease. *Clin Immunol* **129**, 170-5 (2008).
11. Karasneh, J.A. et al. Polymorphisms in the endothelial nitric oxide synthase gene are associated with Behcet's disease. *Rheumatology (Oxford)* **44**, 614-7 (2005).
12. Horie, Y. et al. Association of TLR4 polymorphisms with Behcet's disease in a Korean population. *Rheumatology (Oxford)* **48**, 638-42 (2009).
13. Ayesh, S. et al. Molecular analysis of MEFV gene mutations among Palestinian patients with Behcet's disease. *Scand J Rheumatol* **37**, 370-4 (2008).
14. Touitou, I. et al. MEFV mutations in Behcet's disease. *Hum Mutat* **16**, 271-2 (2000).
15. Ahmad, T. et al. CARD15 polymorphisms in Behcet's disease. *Scand J Rheumatol* **34**, 233-7 (2005).

**Supplementary Figure 1**



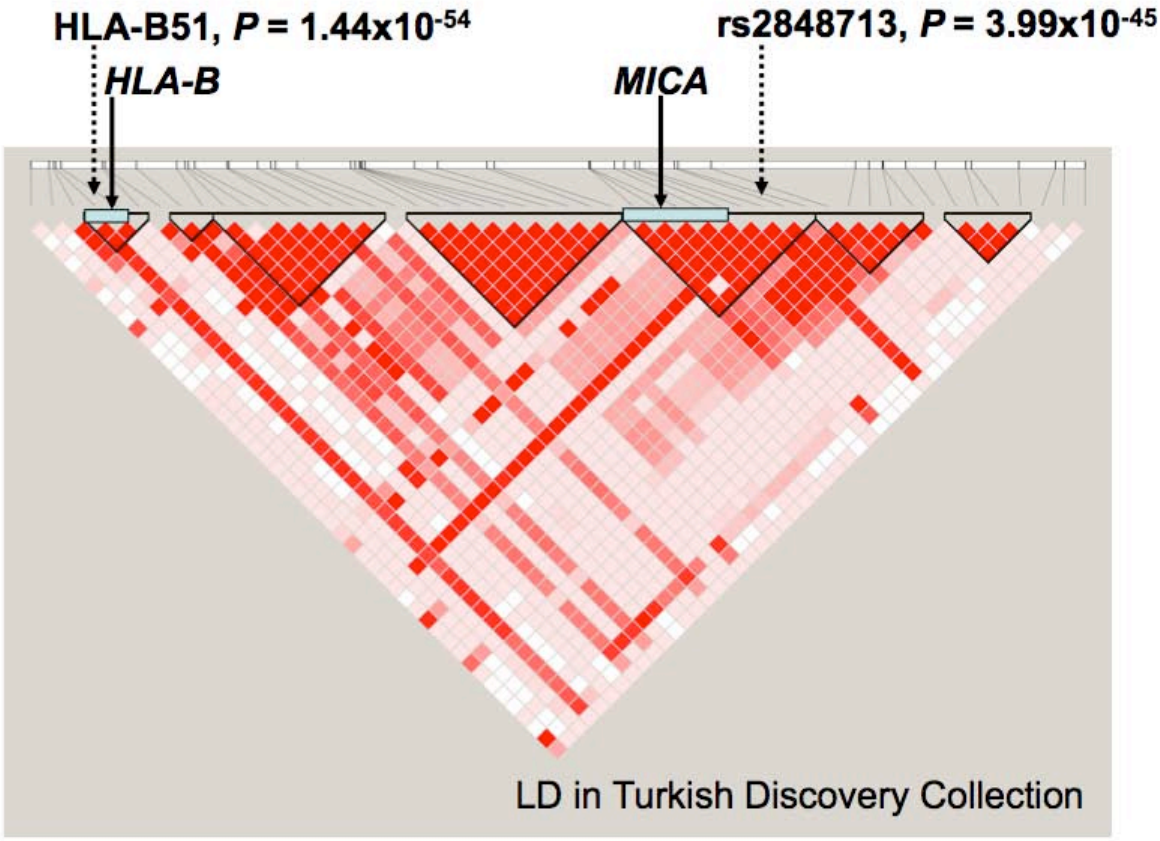

**Supplementary Figure 1:** The familial birth place origins of BD cases and controls. Comparison of the distribution of Turkish region of origin for cases and controls genotyped in this study (% cases/% controls).

## Supplementary Figure 2



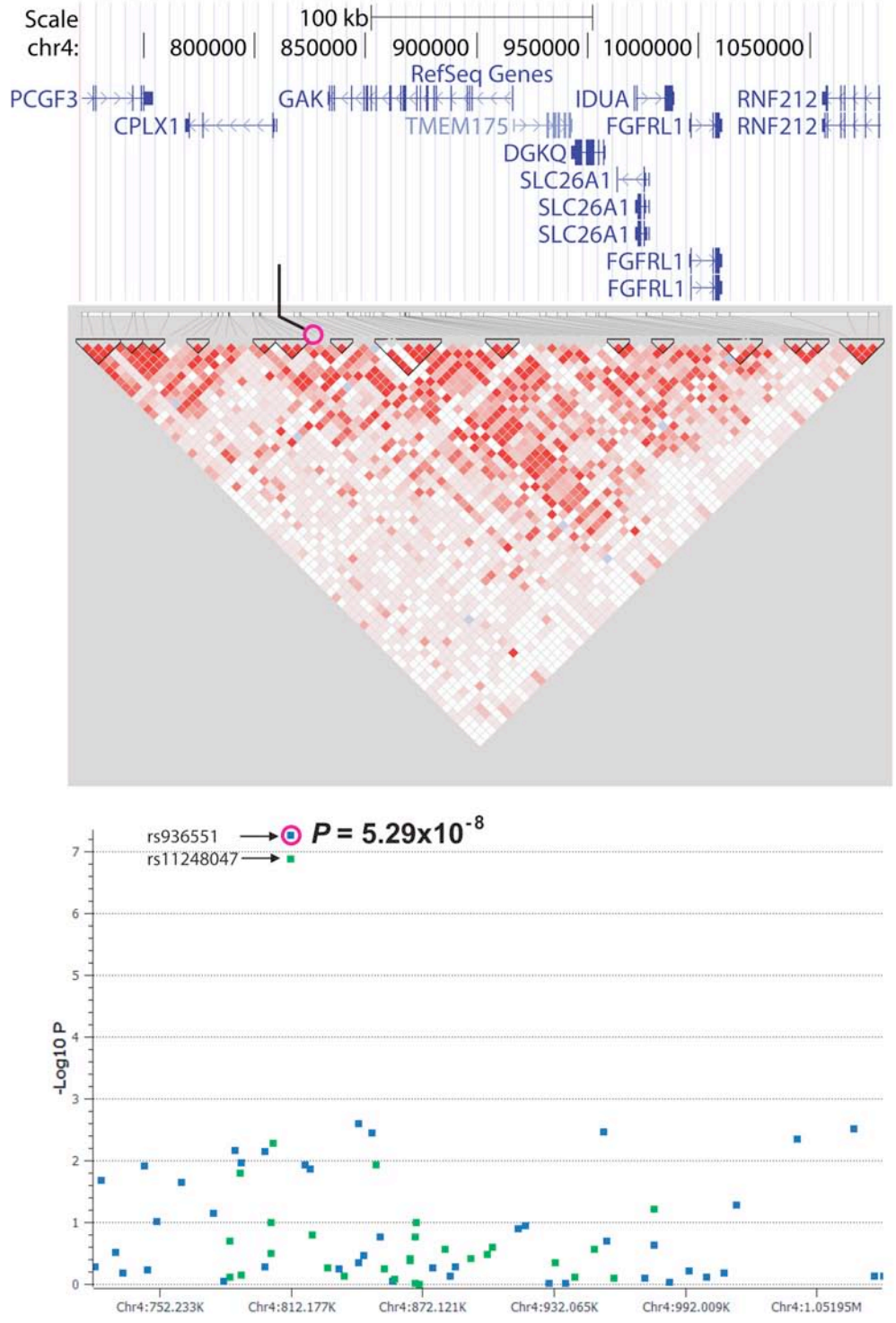

**Supplementary Figure 2:** Probability-probability plots for detection of population stratification. $\lambda_{GC}$ represents the genomic inflation factor, a measure of the deviation of the observed probabilities from the expected probabilities. **(a)** Plot of observed versus expected probabilities (Correlation/Trend Test) for 311,459 SNPs meeting quality standards ($\lambda_{GC}$ = 1.06). **(b)** Plot of observed versus expected probabilities (Correlation/Trend Test) after correction for 6 principal components ($\lambda_{GC}$ = 1.05). **(c)** Plot of observed versus expected probabilities (Correlation/Trend Test) from **(b)** after removal of MHC region SNPs. **(d)** Plot of observed versus expected probabilities (Correlation/Trend Test) determined without the disease-associated MHC region SNPs, but with correction for 6 principal components ($\lambda_{GC}$ = 1.04).

**Supplementary Figure 3**



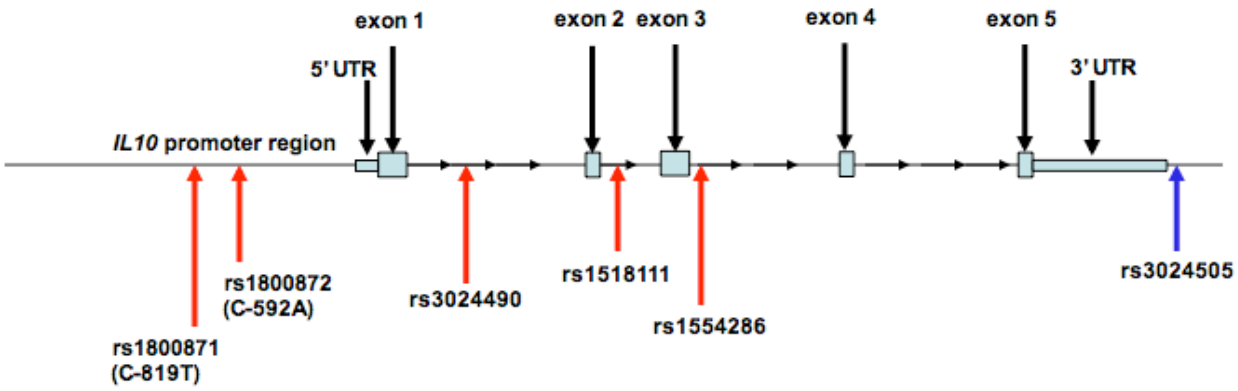

**Supplementary Figure 3:** Linkage disequilibrium structure of SNPs surrounding *HLA-B* and *MICA* in the Turkish discovery collection. The inclusion of HLA-B51 genotype as a constituent of *HLA-B* defines an extended LD haplotype which extends across several blocks of linkage disequilibrium, and includes the strongest disease-associated SNP, rs2848713 (1190 cases and 1257 controls).

## Supplementary Figure 4




**Supplementary Figure 4:** Fine-mapping of the *CPLX1* region. Regional association plot and linkage disequilibrium structure of the disease-associated region surrounding *CPLX1* showing SNPs genotyped in the genome-wide analysis (blue) and in the fine-mapping analysis (green). The LD structure of the same region is shown with red filled squares linking pairs of markers indicating the intensity of LD by intensity of fill, D'= 1 (intense red) to D' = 0 (no fill). The pink circles represent the most strongly associated marker, rs936551.

**Supplementary Figure 5**




**Supplementary Figure 5:** Locations of BD-associated *IL10* gene region SNPs. The most significant disease-associated SNP, rs1518111, which lies within the second intron, forms a disease-associated haplotype with the two promoter SNPs, rs1800871 and rs1800872, along with rs3024490 located in intron 1 (D' > 0.95, $r_2$ > 0.95 haplotype association P = 9.76 E-09). rs1554286, located in intron 3, was less strongly associated with BD. rs3024505 (blue arrow) is associated with ulcerative colitis, systemic lupus erythematosus, and type 1 diabetes, but not with BD.