*HLA-B\*38:02:01* Predicts Carbimazole/Methimazole-Induced Agranulocytosis

Supplementary Info

Supplementary Figure 1. PCA of subjects included in the GWAS.



Supplementary Figure 2. QQ plot of the GWAS of ATD-induced agranulocytosis.



Supplementary Figure 3. The prevalence of HLA-B\*38:02:01 in different geographical regions (data from the Allele Frequency Net Database: http://www.allelefrequencies.net/).



The allele frequency of HLA-B\*38:02:01 was estimated to be 4% in Chinese, 5.7% in Indonesian, 2% in Thai, and 0% in South Korean, Bulgarian, and Moroccan.

Supplementary Figure 4. The prevalence of HLA-B\*38:02 in different geographical regions (data from the Allele Frequency Net Database: http://www.allelefrequencies.net/).



Supplementary table 1. Characteristics of CMZ/MMI-induced agranulocytosis patients.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ID | Sex | Age | ATD use | Cumulative dosage | Course of treatment | Days of onset of agranulocytosis | Concomitant medications | Allergy/co-morbidity | ANC\* |
| ATD01 | F | 22 | CMZ | 960mg | First | 48 | Nil | Nil | 0 |
| ATD02 | F | 35 | CMZ | 630mg | First | 21 | Propranolol | Nil | 0.03 |
| ATD03 | F | 46 | CMZ | 1650mg | First | 55 | Propranolol; Aspirin | Atrial Fibrillation | 0 |
| ATD04 | F | 67 | CMZ | 1020mg | First | 34 | Warfarin; Digoxin; Metoprolol; Ramipril; Furosemide | Congestive heart failure; Atrial Fibrillation; Hypertension | 0 |
| ATD05 | F | 23 | CMZ | 560mg | First | 28 | Nil | Tonsillitis | 0 |
| ATD08 | F | 58 | CMZ | 1080mg | First | 36 | Propranolol | Allergic to tetracycline (Rash); Beta thalassemia trait | 0 |
| ATD09 | F | 42 | CMZ | 1340mg | First | 53 | Nil | Nil | <0.1 |
| ATD11 | F | 50 | CMZ | 600mg | First | 33 | Propranolol | Nil | 0 |
| ATD12 | F | 45 | CMZ | 900mg | First | 30 | Nil | Allergic to PTU (Angioedema) | 0.05 |
| ATD14 | F | 35 | CMZ | Unclear | First | 26 | Nil | Nil | 0 |
| ATD15 | F | 50 | CMZ | Unclear | First | 12 | Nil | Asthma; allergic to seafood | 0 |
| ATD17 | F | 42 | CMZ | 2460mg | First | 41 | Propranolol | Nil | 0.01 |
| ATD19 | M | 36 | CMZ | 1130mg | First | 42 | Nil | Nil | 0.05 |
| ATD20 | F | 41 | CMZ | 960mg | First | 32 | Propranolol | Suspected skin rash with an anti-inflammatory drug | 0 |
| ATD23 | F | 37 | CMZ | Unclear | First | <30 | Nil | Nil | 0.5 |
| ATD24 | F | 56 | CMZ | 150mg | First | 5 | Nil | Nil | 0 |
| ATD26 | F | 31 | CMZ | 525mg | First | 35 | Propranolol | Nil | 0.1 |
| ATD27 | M | 54 | CMZ | 2790mg | First | 62 | Propranolol | Nil | <0.5 |
| ATD18 | F | 43 | MMI | Unclear | First | 19 | Propranolol; Lorazepam | Skin Allergy to Cefuroxime and Co-trimoxazole | 0.1 |

\*ANC: Absolute neutrophil count (unit: x 10-9/L)

Supplementary table 2. Characteristics of PTU-induced agranulocytosis patients.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ID | Sex | Age | Cumulative Dosage | Course of treatment | Days of onset of agranulocytosis | Concomitant medications | Allergy/co-morbidity | ANC\* | Remarks |
| ATD07 | F | 23 | 8100mg | Later | 27 | Propranolol; Metoprolol; Prednisolone | Nil | 0.26 | Started CMZ and developed rash and fever after 2 months, then switched to PTU for 22 months. Relapsed and resumed PTU, and developed agranulocytosis in 27 days |
| ATD10 | F | 33 | 1200mg | Later | 3 | Metoclopramide; Rabeprazole | Chronic gastritis, reflux esophagitis | 0.44 | In the first course, patient prescribed PTU for one year without agranulocytosis. Relapsed and resumed PTU, and developed agranulocytosis |
| ATD13 | F | 29 | 200mg  | First | 4 | Amoxicillin | Nil | 0.4 | Started CMZ but stopped after 2 days with unknown reason. Switched to PTU afterwards and developed agranulocytosis |
| ATD16 | F | 50 | 12000mg | Later | 60 | Propranolol | Septal defect with repair at age 19 | 0.26 | First course with CMZ without development of agranulocytosis; Agranulocytosis occurred at second course with PTU |
| ATD31 | M | 20 | 12000mg | Later | 60 | Nil | Nil | 0.1 | Reduced ANC (not reached agranulocytosis) after starting CMZ for 6 months, then switched to PTU, ANC dropped significantly, and developed agranulocytosis in 60 days |

\*ANC: Absolute neutrophil count (unit: x 10-9/L)

Supplementary table 3. Characteristics of CMZ/MMI-induced neutropenia patients.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ID | Sex | Age | ATD use | Cumulative dosage | Course of treatment | Interval | Concomitant medications | Allergy/co-morbidity | ANC\* | Remarks |
| ATD21 | M | 52 | CMZ | 120mg | First | 4 days | Nil | Nil | 0.78 |  |
| ATD29 | F | 42 | CMZ | unclear | Later | 6 days | Propranolol | Nil | 0.8 | Fourth course in CMZ, previous courses of CMZ for 5 years |
| ATD30 | F | 55 | CMZ | unclear | Later | 18 months | Aspirin; Trinitroglycerin; Metoprolol  | Ischemic heart disease | 1.4 | Third relaspe of thyrotosicosis. Previous 2 episodes treated over 20 yrs ago |

\*ANC: Absolute neutrophil count (unit: x 10-9/L)

Supplementary Table 4. Association of HLA-DRB1\*08:03 with ATD- or CMZ/MMI-induced agranulocytosis in the validation cohort.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Sample size | MAF | OR | 95% CI | P-value |
| Case | Control | Case | Control |
| ATD-induced agranulocytosis | 24 | 75 | 20.8% | 5.6% | 5.71 | (1.91-17.08) | 0.002 |
| CMZ/MMI-induced agranulocytosis | 19 | 59 | 26.3% | 5.7% | 8.73 | (2.64-28.86) | 1.1 x 10-4 |

Abbreviation: ATD, anti-thyroid drug; CMZ, carbimazole; MMI, methimazole; PTU, propylthiouracil; MAF: minor allele frequency; OR: odds ratio; CI, confidence interval.

Supplementary table 5. Characteristics of the Filipino CMZ-induced agranulocytosis patient.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ID | Sex | Age | ATD use | Cumulative dosage | Course of treatment | Interval | Concomitant medications | Allergy/co-morbidity | ANC\* | Remarks |
| ATD22 | F | 49 | CMZ | 900mg | First | 30 days | Propranolol; FeSO4 | Nil | 0.43 | Nil |

\*ANC: Absolute neutrophil count (unit: x 10-9/L)

Supplementary table 6. Allele frequency of HLA-B\*38:02 (data retrieved from http://www.allelefrequencies.net/)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| # | Population | % of individuals that have the allele | Allele Frequency (in\_decimals) | Sample size |
| 1 |  Australia New South Wales Caucasian  |   | 0 | 134 |
| 2 |  Australia Yuendumu Aborigine  |   | 0 | 191 |
| 3 |  Brazil Belo Horizonte Caucasian  | 0 | 0 | 95 |
| 4 |  Brazil Mixed  |   | 0.007 | 108 |
| 5 |  China Beijing  |   | 0.008 | 67 |
| 6 |  China Beijing Shijiazhuang Tianjian Han  |   | 0.019 | 618 |
| 7 |  China Canton Han  |   | 0.07 | 264 |
| 8 |  China Guangxi Region Maonan  |   | 0.083 | 108 |
| 9 |  China Guangzhou  |   | 0.06 | 102 |
| 10 |  China Guangzhou Han  |   | 0.043 | 106 |
| 11 |  China Jiangsu Han  |   | 0.021 | 3,238 |
| 12 |  China Jiangsu Province Han  |   | 0.0192 | 334 |
| 13 |  China North Han  |   | 0 | 105 |
| 14 |  China Sichuan HIV negative  |   | 0.074 | 34 |
| 15 |  China South Han  |   | 0.071 | 284 |
| 16 |  China Southwest Dai  |   | 0.056 | 124 |
| 17 |  China Yunnan Bulang  |   | 0.03 | 116 |
| 18 |  China Yunnan Hani  |   | 0.007 | 150 |
| 19 |  China Yunnan Province Bulang  |   | 0.03 | 116 |
| 20 |  China Yunnan Province Han  |   | 0.025 | 101 |
| 21 |  China Yunnan Province Hani pop 2  |   | 0.007 | 150 |
| 22 |  Croatia  |   | 0 | 150 |
| 23 |  Cuba Caucasian  | 0 | 0 | 70 |
| 24 |  Cuba Mulatto  | 0 | 0 | 42 |
| 25 |  Czech Republic  |   | 0 | 106 |
| 26 |  Czech Republic NMDR  |   | 0.0001 | 5,099 |
| 27 |  Germany DKMS - China minority  |   | 0.0269 | 1,282 |
| 28 |  Germany DKMS - Poland minority  |   | 0 | 20,653 |
| 29 |  Germany DKMS - Portugal minority  |   | 0.0004 | 1,176 |
| 30 |  Germany DKMS - Turkey minority  |   | 0.0002 | 4,856 |
| 31 |  Germany pop 6  |   | 0.0001 | 8,862 |
| 32 |  Germany pop 8  |   | 0.0001 | 39,689 |
| 33 |  Hong Kong Chinese  | 10 | 0.054 | 569 |
| 34 |  India Khandesh Region Pawra  |   | 0 | 50 |
| 35 |  India Mumbai Maratha  |   | 0.012 | 91 |
| 36 |  India West Bhil  |   | 0.04 | 50 |
| 37 |  India West Coast Parsi  |   | 0 | 50 |
| 38 |  Indonesia Java Western  | 10.6 | 0.054 | 236 |
| 39 |  Ireland Northern  | 0 | 0 | 1,000 |
| 40 |  Italy North pop 3  | 0 | 0 | 97 |
| 41 |  Italy pop 5  |   | 0 | 975 |
| 42 |  Japan Central  |   | 0.001 | 371 |
| 43 |  Japan pop 16  |   | 0.0028 | 18,604 |
| 44 |  Japan pop 3  |   | 0.002 | 1,018 |
| 45 |  Japan pop 5  |   | 0.004 | 117 |
| 46 |  Macedonia pop 4  |   | 0.002 | 216 |
| 47 |  Malaysia Jelebu Temuan  |   | 0.042 | 25 |
| 48 |  Malaysia Kedah Baling Kensiu  |   | 0.08 | 25 |
| 49 |  Malaysia Perak Grik Jehai  |   | 0.02 | 25 |
| 50 |  Mexico Mestizo  | 0 | 0 | 41 |
| 51 |  Morocco Nador Metalsa pop 2  |   | 0 | 73 |
| 52 |  Morocco Settat Chaouya  | 0 | 0 | 98 |
| 53 |  Myanmar, Bamar  |   | 0.033 | 46 |
| 54 |  Myanmar, Kayin  |   | 0.034 | 44 |
| 55 |  Netherlands Leiden  |   | 0.001 | 1,305 |
| 56 |  Oman  | 0 | 0 | 118 |
| 57 |  Philippines Ivatan  | 12 | 0.06 | 50 |
| 58 |  Romania  | 0 | 0 | 348 |
| 59 |  Singapore Chinese  | 9.4 | 0.047 | 149 |
| 60 |  Singapore Chinese Han  |   | 0.064 | 94 |
| 61 |  Singapore Javaneses  |   | 0.071 | 51 |
| 62 |  Singapore Riau Malay  |   | 0.045 | 132 |
| 63 |  Singapore Thai  |   | 0.035 | 100 |
| 64 |  South Africa Natal Zulu  | 0 | 0 | 100 |
| 65 |  South Korea pop 10  |   | 0.008 | 4,128 |
| 66 |  South Korea pop 3  |   | 0.011 | 485 |
| 67 |  Taiwan Hakka  | 7.3 | 0.036 | 55 |
| 68 |  Taiwan Han Chinese  |   | 0.033 | 504 |
| 69 |  Taiwan Minnan pop 1  | 12.7 | 0.064 | 102 |
| 70 |  Taiwan Pazeh  | 3.6 | 0.018 | 55 |
| 71 |  Taiwan pop 2  |   | 0.038 | 364 |
| 72 |  Taiwan pop 3  |   | 0.026 | 212 |
| 73 |  Taiwan Puyuma  | 2 | 0.01 | 50 |
| 74 |  Taiwan Saisiat  | 2 | 0.01 | 51 |
| 75 |  Taiwan Siraya  | 5.9 | 0.029 | 51 |
| 76 |  Taiwan Tao  | 20 | 0.11 | 50 |
| 77 |  Taiwan Tzu Chi Cord Blood Bank  |   | 0.044 | 710 |
| 78 |  USA African American  |   | 0 | 252 |
| 79 |  USA African American Bethesda  | 0 | 0 | 187 |
| 80 |  USA African American pop 4  |   | 0 | 2,411 |
| 81 |  USA African American pop 8  |   | 0 | 605 |
| 82 |  USA Alaska Yupik  |   | 0 | 252 |
| 83 |  USA Asian  |   | 0.066 | 358 |
| 84 |  USA Asian pop 2  |   | 0.0365 | 1,772 |
| 85 |  USA Caucasian Bethesda  | 0 | 0 | 307 |
| 86 |  USA Caucasian pop 2  |   | 0.002 | 265 |
| 87 |  USA European American pop 2  |   | 0 | 1,245 |
| 88 |  USA Hispanic  |   | 0 | 234 |
| 89 |  USA Hispanic pop 2  |   | 0 | 1,999 |
| 90 |  USA NMDP Alaska Native or Aleut  |   | 0.001 | 1,376 |
| 91 |  USA NMDP Caribean Black  |   | 0.001 | 33,328 |
| 92 |  USA NMDP Caribean Indian  |   | 0.001 | 14,339 |
| 93 |  USA NMDP Chinese  |   | 0.04 | 99,672 |
| 94 |  USA NMDP European Caucasian  |   | 0 | 1,242,890 |
| 95 |  USA NMDP Filipino  |   | 0.1272 | 50,614 |
| 96 |  USA NMDP Hawaiian or other Pacific Islander  |   | 0.0174 | 11,499 |
| 97 |  USA NMDP Hispanic South or Central American  |   | 0.0002 | 146,714 |
| 98 |  USA NMDP Japanese  |   | 0.0033 | 24,582 |
| 99 |  USA NMDP Korean  |   | 0.0096 | 77,584 |
| 100 |  USA NMDP Mexican or Chicano  |   | 0.0003 | 261,235 |
| 101 |  USA NMDP Middle Eastern or North Coast of Africa  |   | 0.0002 | 70,890 |
| 102 |  USA NMDP South Asian Indian  |   | 0.007 | 185,391 |
| 103 |  USA NMDP Southeast Asian  |   | 0.0151 | 27,978 |
| 104 |  USA NMDP Vietnamese  |   | 0.0584 | 43,540 |
| 105 |  USA North American Native  |   | 0 | 187 |
| 106 |  USA Philadelphia Caucasian  | 0 | 0 | 141 |
| 107 |  USA San Antonio Caucasian  |   | 0 | 222 |
| 108 |  USA South Texas Hispanic  |   | 0 | 194 |
| 109 |  Vietnam Hanoi Kinh pop 2  |   | 0.056 | 170 |
| 110 |  Wales  | 0 | 0 | 1,798 |

Supplementary Table 7. Power calculation of the GWAS cohort using QUANTO.

|  |  |
| --- | --- |
| OR | MAF of the risk allele |
| 0.01 | 0.03 | 0.05 | 0.1 | 0.15 | 0.2 | 0.25 | 0.3 | 0.35 | 0.4 | 0.45 |
| 2 | 0 | 0 | 0 | 0 | 0.0001 | 0.0002 | 0.0003 | 0.0004 | 0.0005 | 0.0005 | 0.0005 |
| 3 | 0 | 0.0001 | 0.0003 | 0.0027 | 0.0074 | 0.0129 | 0.0172 | 0.0194 | 0.0195 | 0.0179 | 0.0151 |
| 4 | 0 | 0.0007 | 0.0038 | 0.0282 | 0.0648 | 0.095 | 0.1115 | 0.1144 | 0.107 | 0.0929 | 0.0754 |
| 5 | 0.0001 | 0.0038 | 0.0205 | 0.1159 | 0.2134 | 0.271 | 0.2909 | 0.2832 | 0.2571 | 0.2197 | 0.1771 |
| 6 | 0.0003 | 0.0141 | 0.0663 | 0.273 | 0.4159 | 0.4777 | 0.4873 | 0.464 | 0.4187 | 0.3592 | 0.2923 |
| 7 | 0.0008 | 0.0382 | 0.1518 | 0.4592 | 0.6061 | 0.6534 | 0.6498 | 0.6153 | 0.5584 | 0.4849 | 0.4006 |
| 8 | 0.0019 | 0.0822 | 0.2717 | 0.6287 | 0.7503 | 0.779 | 0.7666 | 0.7277 | 0.6672 | 0.5879 | 0.4941 |
| 9 | 0.0041 | 0.1485 | 0.4087 | 0.759 | 0.8468 | 0.8612 | 0.845 | 0.807 | 0.7482 | 0.669 | 0.5715 |
| 10 | 0.008 | 0.2345 | 0.5432 | 0.8491 | 0.9072 | 0.9127 | 0.8962 | 0.8617 | 0.8076 | 0.7318 | 0.6347 |
| 11 | 0.0142 | 0.3333 | 0.6614 | 0.9073 | 0.9438 | 0.9445 | 0.9295 | 0.8995 | 0.851 | 0.7803 | 0.686 |
| 12 | 0.0235 | 0.4365 | 0.7569 | 0.9435 | 0.9656 | 0.9642 | 0.9513 | 0.9257 | 0.883 | 0.818 | 0.7277 |
| 13 | 0.0367 | 0.5365 | 0.8296 | 0.9656 | 0.9787 | 0.9764 | 0.9657 | 0.9442 | 0.9068 | 0.8476 | 0.762 |
| 14 | 0.0544 | 0.6276 | 0.8826 | 0.9789 | 0.9866 | 0.9842 | 0.9754 | 0.9574 | 0.9248 | 0.871 | 0.7903 |
| 15 | 0.0769 | 0.7066 | 0.92 | 0.9869 | 0.9914 | 0.9892 | 0.982 | 0.9669 | 0.9385 | 0.8897 | 0.8138 |
| 16 | 0.1044 | 0.7727 | 0.9458 | 0.9918 | 0.9944 | 0.9925 | 0.9866 | 0.974 | 0.9491 | 0.9049 | 0.8336 |
| 17 | 0.1369 | 0.8261 | 0.9634 | 0.9948 | 0.9962 | 0.9946 | 0.9899 | 0.9792 | 0.9575 | 0.9172 | 0.8504 |
| 18 | 0.1738 | 0.8684 | 0.9753 | 0.9966 | 0.9975 | 0.9961 | 0.9923 | 0.9832 | 0.9641 | 0.9275 | 0.8648 |
| 19 | 0.2147 | 0.9011 | 0.9832 | 0.9978 | 0.9982 | 0.9972 | 0.994 | 0.9863 | 0.9694 | 0.936 | 0.8771 |
| 20 | 0.2588 | 0.9261 | 0.9886 | 0.9985 | 0.9988 | 0.9979 | 0.9953 | 0.9887 | 0.9737 | 0.9432 | 0.8879 |
| 21 | 0.3052 | 0.9449 | 0.9922 | 0.999 | 0.9991 | 0.9984 | 0.9962 | 0.9906 | 0.9773 | 0.9493 | 0.8972 |
| 22 | 0.353 | 0.959 | 0.9946 | 0.9993 | 0.9994 | 0.9988 | 0.997 | 0.9921 | 0.9802 | 0.9545 | 0.9055 |

Power calculation settings: 20 cases and 775 controls; log additive model; baseline risk was set to be 0.0001.