**Supplemental Table 1**. Target therapeutic ranges for tacrolimus trough levels by organ type

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Time post-transplant | Heart | Liver | Lung | Kidney |
| 0-3 months | 10-12 μg/L | 12-15 μg/L | 15-18 μg/L | 10-12 μg/L |
| 3-6 months | 8-10 μg/L | 6-8 μg/L | 12-15 μg/L | 8-10 μg/L |
| 6-12 months | 6-8 μg/L | 5-6 μg/L | 10-12 μg/L | 6-8 μg/L |

**Supplemental Table 2**. SNPs significantly associated with tacrolimus levels adjusted for clinical co-variates

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SNP | Gene | Chr | Discovery cohort (n=455) | | |  |  | SNP validation cohort (n=213) | Organ type significant at p<0.05 |
|  |  |  | MAF | Minor Allele | β | s.e | p | p |  |
| **rs776746\*** | *CYP3A5* | 7 | 0.152 | T | -1.742 | 0.244 | 9.71E-13 | 5.97E-08 | heart, liver, kidney |
| rs4646457 | *CYP3A5, ZSCAN25* | 7 | 0.16 | C | -1.699 | 0.241 | 1.88E-12 | 1.36E-07 |  |
| rs10242455 | *CYP3A5, ZSCAN25* | 7 | 0.155 | G | -1.701 | 0.244 | 3.44E-12 | 1.56E-07 |  |
| rs15524 | *CYP3A5* | 7 | 0.152 | G | -1.526 | 0.239 | 1.67E-10 | 2.02E-06 |  |
| rs6465750 | *ZSCAN25, CYP3A5* | 7 | 0.138 | T | -1.55 | 0.246 | 2.83E-10 | 3.72E-07 |  |
| rs1859690 | ZSCAN25 | 7 | 0.145 | G | -1.49 | 0.239 | 4.66E-10 | 9.16E-07 |  |
| **rs2257401** | *CYP3A7, CYP3A7-CYP3AP1* | 7 | 0.148 | C | -1.312 | 0.253 | 2.10E-07 | 9.43E-05 | heart, liver, kidney |
| **rs2242480** | *CYP3A4* | 7 | 0.18 | T | -0.91 | 0.202 | 6.49E-06 | 6.93E-03 | heart, kidney |
| **rs12333983\*** | *CYP3A4, CYP3A7* | 7 | 0.193 | A | -0.924 | 0.206 | 7.38E-06 | 2.15E-06 | heart, kidney |
| rs2687086 | *CYP3A5, CYP3A7, CYP3A7-CYP3AP1* | 7 | 0.167 | C | -1.184 | 0.22 | 7.54E-08 | 4.26E-07 |  |
| rs3735451 | *CYP3A4* | 7 | 0.194 | C | -0.98 | 0.208 | 2.43E-06 | 3.03E-06 |  |
| rs6945984 | *CYP3A4, CYP3A7* | 7 | 0.192 | C | -0.97 | 0.208 | 3.15E-06 | 1.65E-06 |  |
| **rs17161780** | *CYP3A5, ZSCAN25* | 7 | 0.071 | A | -1.702 | 0.33 | 2.45E-07 | 8.45E-03 | heart, kidney |
| rs115435341 | *ZSCAN25* | 7 | 0.067 | T | -1.765 | 0.339 | 1.97E-07 | 1.23E-01 |  |
| **rs4646450** | *CYP3A5* | 7 | 0.234 | A | -1.165 | 0.214 | 5.00E-08 | 1.79E-04 | heart, kidney |
| **rs11762273** | *ARPC1B, ARPC1A* | 7 | 0.222 | G | -1.023 | 0.225 | 5.52E-06 | 5.92E-05 | heart, kidney |
| rs6962772 | *ZNF789* | 7 | 0.229 | G | -1.016 | 0.206 | 7.71E-07 | 1.36E-03 |  |
| rs3137 | *ZKSCAN5* | 7 | 0.226 | A | -1.041 | 0.213 | 9.99E-07 | 3.29E-03 |  |
| **rs72816873** | *VPS35, ORC6* | 16 | 0.08 | C | 1.528 | 0.296 | 2.42E-07 | 6.90E-01 | heart, liver |
| **rs6519705** | *MN1, LINC01422* | 22 | 0.356 | T | -0.817 | 0.162 | 4.64E-07 | 2.67E-01 | heart, liver |
| **rs12957142\*** | *KC6, LOC101927900* | 18 | 0.255 | A | 0.936 | 0.187 | 5.31E-07 | 7.85E-01 | heart, liver, kidney |
| **rs17161692** | *ARPC1A* | 7 | 0.108 | T | -1.275 | 0.264 | 1.35E-06 | 2.41E-04 | heart, kidney |
| **rs35154575** | *ZC3H13, SIAH3* | 13 | 0.097 | T | 1.292 | 0.271 | 1.95E-06 | 8.66E-01 | heart, liver |
| **rs28608208** | *MYH16* | 7 | 0.224 | G | -0.999 | 0.22 | 5.87E-06 | 6.52E-02 | heart, kidney |
| **rs4646458** | *CYP3A5, ZSCAN25* | 7 | 0.092 | G | -1.341 | 0.296 | 6.04E-06 | 1.95E-02 | heart, kidney |

SNPs in LD are indicated in 4 colors (orange, green, blue and yellow); Bold = independent or non-redundant SNPs; \*indicates SNPs selected by machine learning and linear regression models for association with dose-adjusted T1 levels

SNP, single-nucleotide polymorphisms; MAF, minor allele frequency; Chr, chromosome; s.e, standard error; β, coefficient

**Supplemental Figure 1:** Proportion oftacrolimus levels with concomitant CYP3A4 inhibitor use at six post-transplant (tx) time points in heart (red), liver (blue) lung (green)and kidney (purple),



**Supplemental Figure 2**: Principal Component Analysis plot for ethnicity showing distribution of ancestry markers plotted against HapMap3 population. African (red), American (blue), European (green), East Asian (magenta), South Asian (yellow) and study population (grey)

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**Supplemental Figure 3**: Linkage disequilibrium (LD) plot showing SNPs in LD clustered in 4 haplotype blocks in black, blue, red and green.

