**Supporting Information**

Title: Whole exome sequencing reveals genetic variants in HLA class II genes associated with transplant-free survival of indeterminate acute liver failure

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**Table S1. Genetic variants with relative risk (RR>2) and allele frequency of the 22 IND-ALF patients (AFIND-ALF>0.5)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Gene | SNP ID | Position | Mutation | Consequence | AFIND-ALF | RR |
| HLA-related |
| HLA-A | rs1143146 | chr6:29942581 | C🡪G | L10V | 0.57 | 3.70 |
| rs9260123 | chr6:29942652 | C🡪G | Intron | 0.57 | 6.48 |
| rs9260127 | chr6:29942701 | G🡪C | Intron | 0.61 | 4.56 |
| rs9256980 | chr6:29942705 | G🡪A | Intron | 0.57 | 9.52 |
| rs199474436 | chr6:29942953 | T🡪A | N90K | 0.52 | 19.73 |
| rs9256982 | chr6:29943223 | T🡪G | Intron | 0.52 | 2.05 |
| rs1136695 | chr6:29943287 | A🡪G | I121M | 0.64 | 4.21 |
| rs3173420 | chr6:29943337 | G🡪A | R138Q | 0.61 | 6.22 |
| rs3173419 | chr6:29943342 | G🡪T | D140Y | 0.55 | 42.32 |
| rs1059509 | chr6:29943377 | C🡪A | N151K | 0.57 | 13.35 |
| rs2735111 | chr6:29943761 | G🡪A | Intron | 0.57 | 9.17 |
| rs1136903 | chr6:29944503 | T🡪C | L300P | 0.66 | 2.52 |
| rs1141891 | chr6:29944591 | C🡪T | Synonymous | 0.66 | 4.11 |
| rs1655894 | chr6:29944716 | G🡪A | Intron | 0.70 | 2.35 |
| rs9260201 | chr6:29944891 | T🡪G | Intron | 0.66 | 4.88 |
| rs1137296 | chr6:29945075 | T🡪C | Synonymous | 0.64 | 5.20 |
| rs2231119 | chr6:29945079 | A🡪T | T345S | 0.64 | 5.41 |
| HLA-B | rs1050344 | chr6:31270457 | G🡪A | Synonymous | 0.64 | 46.75 |
| rs2308604 | chr6:31271074 | T🡪C | Synonymous | 0.64 | 8.56 |
| rs5006140 | chr6:31356468 | A🡪C | Intron | 0.57 | 2.48 |
| rs9266196 | chr6:31357052 | G🡪C | Intron | 0.55 | 9.33 |
| rs9266197 | chr6:31357053 | G🡪A | Intron | 0.57 | 9.96 |
| rs1050458 | chr6:31357148 | A🡪G | M4T | 0.57 | 4.36 |
| rs9266206 | chr6:31357154 | A🡪C | L2R | 0.57 | 3.95 |
| rs9266207 | chr6:31357176 | C🡪T | 5’ UTR | 0.55 | 3.42 |
| HLA-C | rs9264594 | chr6:31269271 | A🡪G | Intron | 0.64 | 2.16 |
| rs2894204 | chr6:31269284 | C🡪T | Intron | 0.64 | 3.09 |
| rs1130838 | chr6:31269347 | T🡪C | T363A | 0.64 | 6.43 |
| rs35708511 | chr6:31269385 | C🡪G | C350S | 0.64 | 10.19 |
| rs9264596 | chr6:31269453 | A🡪G | Intron | 0.64 | 32.64 |
| rs9264597 | chr6:31269456 | A🡪G | Intron | 0.64 | 40.51 |
| rs2523609 | chr6:31269478 | G🡪A | Intron | 0.61 | 77.16 |
| rs68094471 | chr6:31269546 | A🡪G | Intron | 0.64 | 138.72 |
| rs66772001 | chr6:31269556 | T🡪A | Intron | 0.64 | 187.52 |
| rs67827555 | chr6:31269576 | T🡪C | Intron | 0.64 | 321.30 |
| rs56010430 | chr6:31269628 | C🡪T | Intron | 0.64 | 509.21 |
| rs66459704 | chr6:31269660 | T🡪C | Intron | 0.64 | 952.21 |
| rs68037221 | chr6:31269672 | T🡪C | Intron | 0.64 | 11.054 |
| rs66620546 | chr6:31269686 | C🡪G | Intron | 0.59 | 822.18 |
| rs9264608 | chr6:31269883 | A🡪G | Intron | 0.64 | 5773.86 |
| rs9264609 | chr6:31269887 | C🡪T | Intron | 0.64 | 3261.30 |
| rs9264610 | chr6:31269946 | G🡪A | Intron | 0.64 | 2608.28 |
| rs2074497 | chr6:31269950 | T🡪C | Intron | 0.64 | 3166.55 |
| rs1130935 | chr6:31269990 | T🡪C | M331V | 0.64 | 4768.06 |
| rs1050105 | chr6:31269992 | G🡪A | A330V | 0.64 | 5865.75 |
| rs1050106 | chr6:31269994 | G🡪A | Synonymous | 0.64 | 4091.46 |
| rs1130947 | chr6:31269996 | T🡪C | T329A | 0.64 | 5720.66 |
| rs41540512 | chr6:31269997 | G🡪C | Synonymous | 0.64 | 7301.64 |
| HLA-C | rs41556617 | chr6:31270009 | A🡪T | Synonymous | 0.64 | 4112.73 |
| rs1050147 | chr6:31270025 | A🡪G | V319A | 0.64 | 4842.31 |
| rs1050180 | chr6:31270056 | T🡪C | M309V | 0.64 | 4136.91 |
| rs9264622 | chr6:31270099 | A🡪G | Intron | 0.64 | 2194.09 |
| rs67298404 | chr6:31270154 | CAGA🡪C | Intron | 0.64 | 30661.29 |
| rs9264623 | chr6:31270173 | T🡪C | Intron | 0.61 | 204.74 |
| rs9264624 | chr6:31270178 | T🡪G | Intron | 0.61 | 220.09 |
| rs9264625 | chr6:31270183 | G🡪C | Intron | 0.59 | 217.90 |
| rs9264626 | chr6:31270185 | T🡪C | Intron | 0.59 | 215.66 |
| rs9264627 | chr6:31270186 | G🡪A | Intron | 0.59 | 216.27 |
| rs9264628 | chr6:31270194 | C🡪T | Intron | 0.59 | 203.85 |
| rs9264629 | chr6:31270198 | T🡪C | Intron | 0.59 | 183.78 |
| rs2308628 | chr6:31270214 | G🡪T | S297R | 0.59 | 151.92 |
| rs1131015 | chr6:31270233 | T🡪G | Q291P | 0.55 | 5017.97 |
| rs2308622 | chr6:31270252 | T🡪C | M285V | 0.59 | 199.12 |
| rs1050317 | chr6:31270358 | G🡪A | Synonymous | 0.64 | 21.85 |
| rs1050320 | chr6:31270361 | C🡪T | Synonymous | 0.64 | 21.87 |
| rs1050716 | chr6:31270453 | G🡪C | L218V | 0.64 | 42.69 |
| rs1131096 | chr6:31270482 | G🡪T | P208H | 0.64 | 621.85 |
| rs9264636 | chr6:31270520 | C🡪T | Intron | 0.64 | 51.78 |
| rs9264637 | chr6:31270531 | G🡪C | Intron | 0.64 | 50.74 |
| rs9264638 | chr6:31270541 | G🡪A | Intron | 0.64 | 451.50 |
| rs9264640 | chr6:31270595 | C🡪G | Intron | 0.64 | 30.08 |
| rs9264642 | chr6:31270713 | T🡪C | Intron | 0.57 | 24.29 |
| rs9264643 | chr6:31270715 | C🡪A | Intron | 0.64 | 17.83 |
| rs9264645 | chr6:31270747 | G🡪A | Intron | 0.64 | 56.58 |
| rs9264646 | chr6:31270758 | T🡪C | Intron | 0.64 | 110.32 |
| rs9264647 | chr6:31270836 | A🡪G | Intron | 0.61 | 93.33 |
| rs9264651 | chr6:31270951 | G🡪C | Intron | 0.64 | 66.27 |
| rs17884428 | chr6:31270982 | C🡪T | Intron | 0.55 | 39.81 |
| rs9264652 | chr6:31270985 | T🡪C | Intron | 0.64 | 40.72 |
| rs9264653 | chr6:31271037 | T🡪C | Intron | 0.52 | 40.37 |
| rs1050366 | chr6:31271180 | A🡪C | L171W | 0.59 | 8.43 |
| rs9264663 | chr6:31271428 | C🡪T | Intron | 0.64 | 9.29 |
| rs9264664 | chr6:31271450 | C🡪T | Intron | 0.64 | 7.00 |
| rs66565287 | chr6:31271493 | GATCCA🡪G | Intron | 0.64 | 4.07 |
| rs9264665 | chr6:31271502 | T🡪C | Intron | 0.64 | 3.80 |
| rs9264668 | chr6:31271845 | C🡪A | D33Y | 0.57 | 6.26 |
| rs9264669 | chr6:31271904 | A🡪T | Intron | 0.57 | 4.01 |
| HLA-DQA1 | rs3187964 | chr6:32637430 | C🡪G | 5’ UTR | 0.57 | 2.49 |
| rs1047989 | chr6:32637480 | C🡪A | L8M | 0.55 | 4.76 |
| rs9272441 | chr6:32637603 | T🡪G | Intron | 0.55 | 4.27 |
| rs9272442 | chr6:32637623 | C🡪T | Intron | 0.55 | 4.51 |
| rs707950 | chr6:32642096 | G🡪C | Q152H | 0.61 | 2.56 |
| rs9272756 | chr6:32642270 | T🡪C | Intron | 0.57 | 3.44 |
| rs34843907 | chr6:32642282 | T🡪G | Intron | 0.57 | 4.48 |
| rs9272858 | chr6:32642941 | C🡪T | Intron | 0.55 | 2.50 |
| HLA-DRB1 | rs9281872 | chr6:32584091 | G🡪GC | Intron | 0.52 | 4.83 |
| *Others* |
| CDK11A | rs77869096 | chr1:1713611 | C🡪T | Intron | 0.73 | 3.12 |
| CDK11A | rs33938712 | chr1:1714399 | CA🡪C | Intron | 0.80 | 8.44 |
| CDK11A | rs61777494 | chr1:1722599 | G🡪A | Intron | 0.77 | 2.32 |
| ANKRD36 | rs33971912 | chr2:97151827 | C🡪CT | Intron | 1.00 | 2.00 |
| FRMD1 | rs71004185 | chr6:168075852 | CGTGTCCACATTTCCGGTGCCCGGTGTCCACATTTCCGGCGTCCCGTGTCCACATTTCCGGTGCCCG🡪C | Intron | 0.75 | 40.93 |
| GTF2IRD2 | rs142434912 | chr7:74797024 | G🡪T | Q830K | 1.00 | 2.45 |
| RSPH10B | rs369329751 | chr7:5966800 | G🡪A | Intron | 0.70 | 47.48 |
| DENND2B | - | chr11:8718092 | A🡪AG | - | 0.55 | 14.55 |
| FAIM2 | rs1248263 | chr12:49877589 | G🡪T | Intron | 0.66 | 2.27 |
| P2RX2 | rs55726692 | chr12:132620863 | AGCCTGGGACTGACCCGGGCTCTCGAGGGGCCTCTCGTGTGCCCTTGTGACCCCCTTCCCTG🡪A | Intron | 0.70 | 3.12 |
| TCF25 | rs143440936 | chr16:89907369 | CTCCCAGT🡪C | Intron | 0.61 | 2.69 |
| ZNF28 | rs9917046 | chr19:52799646 | G🡪C | Non-coding | 0.86 | 8.84 |
| ZNF28 | rs9917044 | chr19:52799689 | C🡪T | Stop lost | 0.86 | 14.27 |



**Fig. S1. The polygenic risk score (PRS) using 31 SNPs from table 2 predicts the risk for the 22 IND-ALF patients and compares them to the MELD-Na scores and ALFSG indexes.** (A) The predicted risk scaled from 0% (lowest risk) to 100% (highest risk). The patients who survived spontaneously were colored red, and patients who died or underwent LT were colored grey. The dashed line separates the IND-ALF patients (1–22) and patients with identified etiologies (23–26). (B) The receiver operating characteristic (ROC) curve shows the true positive rate (TPR) against the false positive rate (FPR) at different classification thresholds. The areas under the curve (AUC) of PRS (red), MELD-Na (blue), and ALFSG (green) are 0.96, 0.72, and 0.72, respectively.



**Fig. S2. The combination of polygenic risk score (PRS) with MELD-Na predicts the risk for the 22 IND-ALF patients and compares them to the mere MELD-Na scores and ALFSG indexes.** (A) The predicted risk scaled from 0% (lowest risk) to 100% (highest risk). The patients who survived spontaneously were colored red, and patients who died or underwent LT were colored grey. The dashed line separates the IND-ALF patients (1–22) and patients with identified etiologies (23–26). (B) The receiver operating characteristic (ROC) curve shows the true positive rate (TPR) against the false positive rate (FPR) at different classification thresholds. The areas under the curve (AUC) of PRS (red), MELD-Na (blue), and ALFSG (green) are 0.82, 0.72, and 0.72, respectively.



**Fig. S3. The combination of polygenic risk score (PRS) with ALFSG predicts the risk for the 22 IND-ALF patients and compares them to the MELD-Na scores and mere ALFSG indexes.** (A) The predicted risk scaled from 0% (lowest risk) to 100% (highest risk). The patients who survived spontaneously were colored red, and patients who died or underwent LT were colored grey. The dashed line separates the IND-ALF patients (1–22) and patients with identified etiologies (23–26). (B) The receiver operating characteristic (ROC) curve shows the true positive rate (TPR) against the false positive rate (FPR) at different classification thresholds. The areas under the curve (AUC) of PRS (red), MELD-Na (blue), and ALFSG (green) are 0.82, 0.72, and 0.72, respectively.



**Fig. S4. The combination of polygenic risk score (PRS) with MELD-Na and ALFSG predicts the risk for the 22 IND-ALF patients and compares them to the MELD-Na scores and ALFSG indexes.** (A) The predicted risk scaled from 0% (lowest risk) to 100% (highest risk). The patients who survived spontaneously were colored red, and patients who died or underwent LT were colored grey. The dashed line separates the IND-ALF patients (1–22) and patients with identified etiologies (23–26). (B) The receiver operating characteristic (ROC) curve shows the true positive rate (TPR) against the false positive rate (FPR) at different classification thresholds. The areas under the curve (AUC) of PRS (red), MELD-Na (blue), and ALFSG (green) are 0.82, 0.72, and 0.72, respectively.