**Supplemental Table S2: Association between *DPYD* variants and individual grade>3 AEs**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Grade>3 AE** | **c.483+18 G>A** | | | | **c.680+139 G>A** | | | | **c.1129-5923 C>G\*** | | | | **HapB3\*\*** | | |
| **GG AE/total** | **GA AE/total** | **AA**  **AE/total** | ***p*-value1** | **GG**  **AE/total** | **GA**  **AE/total** | **AA**  **AE/total** | ***p*-value1** | **CC**  **AE/total** | **CG**  **AE/total** | **GG**  **AE/total** | ***p*-value1** | **WT AE/total** | **Carrier AE/total** | ***p*-value2** |
| **5FU-AEs**  **(n=638)** | 609/1877  (32.5%) | 28/75  (37.3%) | 1/1  (100%) | 0.2358 | 495/1541  (32.1%) | 131/383  (34.2%) | 12/29  (41.4%) | 0.2433 | 606/1875  (32.3%) | 31/77  (40.3%) | 1/1  (100%) | 0.0821 | 609/1878  (32.4%) | 29/75  (38.7%) | 0.2586 |
| Diarrhea  (n=245) | 235/1877 (12.5%) | 10/75 (13.3%) | 0/1  (0%) | 0.9061 | 187/1541 (12.1%) | 54/383  (14.1%) | 4/29  (13.8%) | 0.3131 | 234/1875 (12.5%) | 11/77 (14.3%) | 0/1  (0%) | 0.7092 | 235/1878 (12.5%) | 10/75 (13.3%) | 0.8584 |
| Neutropenia (n=201) | 186/1877 (9.9%) | 15/75 (20.0%) | 0/1  (0%) | **0.0075** | 141/1541 (9.2%) | 55/383  (14.4%) | 5/29  (17.2%) | **0.0012** | 184/1875 (9.8%) | 17/77 (22.1%) | 0/1  (0%) | **0.0009** | 186/1878 (9.9%) | 15/75 (20.0%) | **0.0100** |
| Pain  (n=105) | 102/1877 (5.4%) | 3/75  (4.0%) | 0/1  (0%) | 0.5621 | 84/1541 (5.5%) | 20/383  (5.2%) | 1/29  (3.4%) | 0.7045 | 102/1875 (5.4%) | 3/77  (3.9%) | 0/1  (0%) | 0.5307 | 102/1878 (5.4%) | 3/75  (4.0%) | 0.7953 |
| Fatigue  (n=101) | 99/1877 (5.3%) | 2/75  (2.7%) | 0/1  (0%) | 0.3045 | 82/1541 (5.3%) | 18/383  (4.7%) | 1/29  (3.4%) | 0.5260 | 99/1875 (5.3%) | 2/77  (2.6%) | 0/1  (0%) | 0.2857 | 99/1878 (5.3%) | 2/75  (2.7%) | 0.4311 |
| Nausea / Vomiting (n=91) | 88/1877 (4.7%) | 2/75  (2.7%) | 1/1  (100%) | 0.8225 | 73/1541 (4.7%) | 16/383  (4.2%) | 2/29  (6.9%) | 0.8964 | 88/1875 (4.7%) | 2/77  (2.6%) | 1/1  (100%) | 0.8638 | 88/1878 (4.7%) | 3/75  (4.0%) | 1.0000 |
| Stomatitis / Mucositis (n=81) | 78/1877 (4.2%) | 3/75  (4.0%) | 0/1  (0%) | 0.9113 | 74/1541 (4.8%) | 7/383  (1.8%) | 0/29  (0%) | **0.0046** | 78/1875 (4.2%) | 3/77  (3.9%) | 0/1  (0%) | 0.8751 | 78/1878 (4.2%) | 3/75  (4.0%) | 1.0000 |
| Dehydration (n=45) | 42/1877 (2.2%) | 3/75  (4.0%) | 0/1  (0%) | 0.3486 | 36/1541 (2.3%) | 8/383  (2.1%) | 1/29  (3.4%) | 0.9571 | 42/1875 (2.2%) | 3/77  (3.9%) | 0/1  (0%) | 0.3727 | 42/1878 (2.2%) | 3/75  (4.0%) | 0.2478 |
| Leucopenia (n=32) | 30/1877 (1.6%) | 2/75  (2.7%) | 0/1  (0%) | 0.5046 | 24/1541 (1.6%) | 8/383  (2.1%) | 0/29  (0%) | 0.7603 | 30/1875 (1.6%) | 2/77  (2.6%) | 0/1  (0%) | 0.5286 | 30/1878 (1.6%) | 2/75  (2.7%) | 0.3499 |

1Armitage Trend Test 2Fisher Exact

\* Complete linkage was observed between c.1129-5923 C>G, c.1236 G>A, and c.959-51 T>C therefore only c.1129-5923 C>G is displayed.

\*\* HapB3 consists of patients carrying at least one minor allele for all four hapB3 variants (c.483+18 G>A, c.680+139 G>A, c.959-51 T>C, and c.1236 G>A). Incidence of hapB3 carriers is identical with or without the inclusion of the deep intronic variant c.1129-5923 C>G.