

**Supplementary Table 3. Hierarchical modeling of associations between MC1R variants and BCC risk with three different tau<sup>2</sup> values**

| tau <sup>2</sup> = 0.025 |                                      | Val60Leu | Val92Met | Arg151Cys | Ile155Thr | Arg160Trp | Arg163Gln | Asp294His |
|--------------------------|--------------------------------------|----------|----------|-----------|-----------|-----------|-----------|-----------|
| OR                       | Equal weighted model                 | 1.43     | 1.27     | 1.72      | 1.35      | 1.54      | 1.65      | 1.49      |
| lower                    |                                      | 1.08     | 0.95     | 1.27      | 0.93      | 1.13      | 1.19      | 1.03      |
| upper                    |                                      | 1.90     | 1.70     | 2.31      | 1.97      | 2.09      | 2.29      | 2.13      |
| beta                     |                                      | 0.36     | 0.24     | 0.54      | 0.30      | 0.43      | 0.50      | 0.40      |
| se                       |                                      | 0.14     | 0.15     | 0.15      | 0.19      | 0.16      | 0.17      | 0.19      |
| OR                       | Model based on MC1R antibody binding | 1.43     | 1.22     | 1.78      | 1.48      | 1.60      | 1.62      | 1.36      |
| lower                    |                                      | 1.08     | 0.89     | 1.29      | 0.93      | 1.15      | 1.16      | 0.86      |
| upper                    |                                      | 1.90     | 1.68     | 2.45      | 2.38      | 2.22      | 2.26      | 2.15      |
| beta                     |                                      | 0.36     | 0.20     | 0.58      | 0.39      | 0.47      | 0.48      | 0.30      |
| se                       |                                      | 0.14     | 0.16     | 0.16      | 0.24      | 0.17      | 0.17      | 0.24      |
| OR                       | Model based on MSH ligand binding    | 1.43     | 1.27     | 1.72      | 1.37      | 1.54      | 1.65      | 1.48      |
| lower                    |                                      | 1.08     | 0.93     | 1.26      | 0.76      | 1.12      | 1.18      | 0.94      |
| upper                    |                                      | 1.90     | 1.73     | 2.34      | 2.47      | 2.13      | 2.30      | 2.32      |
| beta                     |                                      | 0.36     | 0.24     | 0.54      | 0.31      | 0.43      | 0.50      | 0.39      |
| se                       |                                      | 0.14     | 0.16     | 0.16      | 0.30      | 0.16      | 0.17      | 0.23      |
| OR                       | Model based on cAMP response to MSH  | 1.44     | 1.23     | 1.78      | 1.31      | 1.59      | 1.53      | 1.62      |
| lower                    |                                      | 1.09     | 0.90     | 1.30      | 0.88      | 1.15      | 1.02      | 1.04      |
| upper                    |                                      | 1.91     | 1.67     | 2.43      | 1.93      | 2.18      | 2.28      | 2.53      |
| beta                     |                                      | 0.36     | 0.21     | 0.57      | 0.27      | 0.46      | 0.42      | 0.49      |
| se                       |                                      | 0.14     | 0.16     | 0.16      | 0.20      | 0.16      | 0.21      | 0.23      |
| OR                       | Model based on kinetics - Ki-a-MSH   | 1.53     | 1.07     | 1.89      | 1.23      | 1.65      | 1.59      | 1.35      |
| lower                    |                                      | 1.14     | 0.75     | 1.38      | 0.83      | 1.21      | 1.14      | 0.92      |
| upper                    |                                      | 2.04     | 1.53     | 2.59      | 1.82      | 2.27      | 2.22      | 1.98      |
| beta                     |                                      | 0.42     | 0.07     | 0.64      | 0.20      | 0.50      | 0.47      | 0.30      |
| se                       |                                      | 0.15     | 0.18     | 0.16      | 0.20      | 0.16      | 0.17      | 0.19      |
| OR                       | Model based on kinetics - Ki-NDP     | 1.30     | 1.19     | 2.01      | 1.38      | 1.61      | 1.78      | 1.21      |
| lower                    |                                      | 0.96     | 0.88     | 1.43      | 0.94      | 1.18      | 1.27      | 0.78      |
| upper                    |                                      | 1.76     | 1.61     | 2.85      | 2.01      | 2.19      | 2.50      | 1.86      |
| beta                     |                                      | 0.27     | 0.17     | 0.70      | 0.32      | 0.47      | 0.58      | 0.19      |
| se                       |                                      | 0.15     | 0.16     | 0.18      | 0.19      | 0.16      | 0.17      | 0.22      |
| OR                       | Model based on hair color            | 1.37     | 1.19     | 1.79      | 1.36      | 1.68      | 1.58      | 1.73      |
| lower                    |                                      | 1.02     | 0.87     | 1.32      | 0.93      | 1.20      | 1.13      | 1.11      |
| upper                    |                                      | 1.84     | 1.63     | 2.43      | 1.98      | 2.36      | 2.21      | 2.72      |
| beta                     |                                      | 0.32     | 0.17     | 0.58      | 0.31      | 0.52      | 0.46      | 0.55      |
| se                       |                                      | 0.15     | 0.16     | 0.16      | 0.19      | 0.17      | 0.17      | 0.23      |
| OR                       | Model based on skin color            | 1.41     | 1.22     | 1.81      | 1.31      | 1.58      | 1.52      | 1.73      |
| lower                    |                                      | 1.07     | 0.90     | 1.31      | 0.90      | 1.16      | 1.04      | 1.05      |
| upper                    |                                      | 1.88     | 1.66     | 2.49      | 1.93      | 2.16      | 2.22      | 2.87      |
| beta                     |                                      | 0.35     | 0.20     | 0.59      | 0.27      | 0.46      | 0.42      | 0.55      |
| se                       |                                      | 0.14     | 0.16     | 0.16      | 0.20      | 0.16      | 0.19      | 0.26      |
| OR                       | Model based on tanning ability       | 1.42     | 1.25     | 1.76      | 1.37      | 1.55      | 1.58      | 1.64      |
| lower                    |                                      | 1.07     | 0.92     | 1.28      | 0.94      | 1.14      | 1.09      | 0.95      |
| upper                    |                                      | 1.88     | 1.69     | 2.43      | 2.01      | 2.10      | 2.30      | 2.82      |
| beta                     |                                      | 0.35     | 0.22     | 0.57      | 0.32      | 0.44      | 0.46      | 0.49      |
| se                       |                                      | 0.15     | 0.16     | 0.16      | 0.19      | 0.16      | 0.19      | 0.28      |

tau^2 = 0.10

|       |                                      | Val60Leu | Val92Met | Arg151Cys | Ile155Thr | Arg160Trp | Arg163Gln | Asp294His |
|-------|--------------------------------------|----------|----------|-----------|-----------|-----------|-----------|-----------|
| OR    | Equal weighted model                 | 1.40     | 1.13     | 1.90      | 1.11      | 1.57      | 1.85      | 1.47      |
| lower |                                      | 1.02     | 0.80     | 1.34      | 0.62      | 1.09      | 1.23      | 0.87      |
| upper |                                      | 1.92     | 1.59     | 2.68      | 1.98      | 2.25      | 2.78      | 2.47      |
| beta  |                                      | 0.34     | 0.12     | 0.64      | 0.10      | 0.45      | 0.62      | 0.38      |
| se    |                                      | 0.16     | 0.18     | 0.18      | 0.30      | 0.18      | 0.21      | 0.27      |
| OR    | Model based on MC1R antibody binding | 1.40     | 1.12     | 1.90      | 1.13      | 1.57      | 1.85      | 1.45      |
| lower |                                      | 1.02     | 0.79     | 1.34      | 0.58      | 1.09      | 1.23      | 0.81      |
| upper |                                      | 1.92     | 1.60     | 2.70      | 2.17      | 2.27      | 2.78      | 2.60      |
| beta  |                                      | 0.34     | 0.11     | 0.64      | 0.12      | 0.45      | 0.62      | 0.37      |
| se    |                                      | 0.16     | 0.18     | 0.18      | 0.34      | 0.19      | 0.21      | 0.30      |
| OR    | Model based on MSH ligand binding    | 1.40     | 1.14     | 1.88      | 1.00      | 1.55      | 1.87      | 1.55      |
| lower |                                      | 1.02     | 0.80     | 1.32      | 0.47      | 1.07      | 1.24      | 0.87      |
| upper |                                      | 1.92     | 1.62     | 2.66      | 2.15      | 2.23      | 2.80      | 2.74      |
| beta  |                                      | 0.34     | 0.13     | 0.63      | 0.00      | 0.44      | 0.62      | 0.44      |
| se    |                                      | 0.16     | 0.18     | 0.18      | 0.39      | 0.19      | 0.21      | 0.29      |
| OR    | Model based on cAMP response to MSH  | 1.40     | 1.11     | 1.92      | 1.08      | 1.58      | 1.79      | 1.55      |
| lower |                                      | 1.02     | 0.78     | 1.35      | 0.60      | 1.10      | 1.15      | 0.87      |
| upper |                                      | 1.93     | 1.58     | 2.72      | 1.96      | 2.28      | 2.78      | 2.74      |
| beta  |                                      | 0.34     | 0.11     | 0.65      | 0.08      | 0.46      | 0.58      | 0.44      |
| se    |                                      | 0.16     | 0.18     | 0.18      | 0.30      | 0.19      | 0.22      | 0.29      |
| OR    | Model based on kinetics - Ki-a-MSH   | 1.45     | 1.04     | 1.99      | 1.03      | 1.62      | 1.83      | 1.38      |
| lower |                                      | 1.05     | 0.72     | 1.40      | 0.56      | 1.13      | 1.22      | 0.81      |
| upper |                                      | 1.99     | 1.51     | 2.82      | 1.87      | 2.33      | 2.75      | 2.35      |
| beta  |                                      | 0.37     | 0.04     | 0.69      | 0.03      | 0.48      | 0.60      | 0.32      |
| se    |                                      | 0.16     | 0.19     | 0.18      | 0.30      | 0.19      | 0.21      | 0.27      |
| OR    | Model based on kinetics - Ki-NDP     | 1.36     | 1.09     | 2.03      | 1.13      | 1.59      | 1.93      | 1.28      |
| lower |                                      | 0.98     | 0.77     | 1.41      | 0.63      | 1.11      | 1.28      | 0.72      |
| upper |                                      | 1.87     | 1.55     | 2.91      | 2.01      | 2.29      | 2.91      | 2.28      |
| beta  |                                      | 0.30     | 0.09     | 0.71      | 0.12      | 0.47      | 0.66      | 0.25      |
| se    |                                      | 0.16     | 0.18     | 0.18      | 0.30      | 0.18      | 0.21      | 0.29      |
| OR    | Model based on hair color            | 1.38     | 1.10     | 1.92      | 1.11      | 1.62      | 1.81      | 1.60      |
| lower |                                      | 1.00     | 0.77     | 1.36      | 0.62      | 1.12      | 1.20      | 0.90      |
| upper |                                      | 1.90     | 1.56     | 2.72      | 1.98      | 2.34      | 2.74      | 2.85      |
| beta  |                                      | 0.32     | 0.09     | 0.65      | 0.10      | 0.48      | 0.60      | 0.47      |
| se    |                                      | 0.16     | 0.18     | 0.18      | 0.30      | 0.19      | 0.21      | 0.29      |
| OR    | Model based on skin color            | 1.40     | 1.11     | 1.93      | 1.09      | 1.58      | 1.79      | 1.60      |
| lower |                                      | 1.02     | 0.78     | 1.36      | 0.60      | 1.10      | 1.17      | 0.87      |
| upper |                                      | 1.92     | 1.57     | 2.74      | 1.96      | 2.27      | 2.75      | 2.94      |
| beta  |                                      | 0.33     | 0.10     | 0.66      | 0.08      | 0.46      | 0.58      | 0.47      |
| se    |                                      | 0.16     | 0.18     | 0.18      | 0.30      | 0.18      | 0.22      | 0.31      |
| OR    | Model based on tanning ability       | 1.40     | 1.12     | 1.91      | 1.11      | 1.57      | 1.84      | 1.51      |
| lower |                                      | 1.02     | 0.79     | 1.34      | 0.62      | 1.10      | 1.20      | 0.80      |
| upper |                                      | 1.92     | 1.59     | 2.70      | 1.99      | 2.25      | 2.81      | 2.85      |
| beta  |                                      | 0.34     | 0.11     | 0.64      | 0.11      | 0.45      | 0.61      | 0.41      |
| se    |                                      | 0.16     | 0.18     | 0.18      | 0.30      | 0.18      | 0.22      | 0.32      |

tau^2 = 0.40

|       |                                      | Val60Leu | Val92Met | Arg151Cys | Ile155Thr | Arg160Trp | Arg163Gln | Asp294His |
|-------|--------------------------------------|----------|----------|-----------|-----------|-----------|-----------|-----------|
| OR    | Equal weighted model                 | 1.39     | 1.05     | 2.00      | 0.80      | 1.58      | 2.01      | 1.45      |
| lower |                                      | 1.00     | 0.72     | 1.39      | 0.35      | 1.08      | 1.28      | 0.76      |
| upper |                                      | 1.94     | 1.53     | 2.89      | 1.85      | 2.33      | 3.15      | 2.79      |
| beta  |                                      | 0.33     | 0.05     | 0.69      | -0.22     | 0.46      | 0.70      | 0.37      |
| se    |                                      | 0.17     | 0.19     | 0.19      | 0.43      | 0.20      | 0.23      | 0.33      |
| OR    | Model based on MC1R antibody binding | 1.39     | 1.06     | 1.99      | 0.78      | 1.58      | 2.01      | 1.48      |
| lower |                                      | 1.00     | 0.73     | 1.38      | 0.32      | 1.07      | 1.29      | 0.75      |
| upper |                                      | 1.94     | 1.54     | 2.88      | 1.91      | 2.32      | 3.15      | 2.92      |
| beta  |                                      | 0.33     | 0.05     | 0.69      | -0.25     | 0.46      | 0.70      | 0.39      |
| se    |                                      | 0.17     | 0.19     | 0.19      | 0.46      | 0.20      | 0.23      | 0.35      |
| OR    | Model based on MSH ligand binding    | 1.39     | 1.06     | 1.99      | 0.70      | 1.57      | 2.02      | 1.53      |
| lower |                                      | 1.00     | 0.73     | 1.38      | 0.27      | 1.07      | 1.29      | 0.78      |
| upper |                                      | 1.94     | 1.54     | 2.87      | 1.87      | 2.31      | 3.16      | 2.98      |
| beta  |                                      | 0.33     | 0.06     | 0.69      | -0.35     | 0.45      | 0.70      | 0.42      |
| se    |                                      | 0.17     | 0.19     | 0.19      | 0.50      | 0.20      | 0.23      | 0.34      |
| OR    | Model based on cAMP response to MSH  | 1.39     | 1.05     | 2.01      | 0.79      | 1.59      | 1.98      | 1.49      |
| lower |                                      | 1.00     | 0.72     | 1.39      | 0.34      | 1.08      | 1.25      | 0.76      |
| upper |                                      | 1.94     | 1.52     | 2.90      | 1.84      | 2.34      | 3.14      | 2.93      |
| beta  |                                      | 0.33     | 0.05     | 0.70      | -0.24     | 0.46      | 0.69      | 0.40      |
| se    |                                      | 0.17     | 0.19     | 0.19      | 0.43      | 0.20      | 0.23      | 0.34      |
| OR    | Model based on kinetics - Ki-a-MSH   | 1.41     | 1.02     | 2.03      | 0.76      | 1.60      | 2.00      | 1.41      |
| lower |                                      | 1.01     | 0.70     | 1.41      | 0.32      | 1.09      | 1.28      | 0.73      |
| upper |                                      | 1.96     | 1.50     | 2.94      | 1.80      | 2.36      | 3.14      | 2.73      |
| beta  |                                      | 0.34     | 0.02     | 0.71      | -0.27     | 0.47      | 0.70      | 0.35      |
| se    |                                      | 0.17     | 0.19     | 0.19      | 0.44      | 0.20      | 0.23      | 0.34      |
| OR    | Model based on kinetics - Ki-NDP     | 1.38     | 1.04     | 2.04      | 0.81      | 1.59      | 2.04      | 1.38      |
| lower |                                      | 0.99     | 0.72     | 1.41      | 0.35      | 1.08      | 1.30      | 0.70      |
| upper |                                      | 1.93     | 1.52     | 2.96      | 1.87      | 2.34      | 3.20      | 2.72      |
| beta  |                                      | 0.32     | 0.04     | 0.71      | -0.21     | 0.46      | 0.71      | 0.32      |
| se    |                                      | 0.17     | 0.19     | 0.19      | 0.43      | 0.20      | 0.23      | 0.35      |
| OR    | Model based on hair color            | 1.39     | 1.04     | 2.01      | 0.80      | 1.60      | 2.00      | 1.51      |
| lower |                                      | 0.99     | 0.72     | 1.39      | 0.34      | 1.08      | 1.27      | 0.77      |
| upper |                                      | 1.93     | 1.52     | 2.90      | 1.85      | 2.36      | 3.13      | 2.96      |
| beta  |                                      | 0.33     | 0.04     | 0.70      | -0.23     | 0.47      | 0.69      | 0.41      |
| se    |                                      | 0.17     | 0.19     | 0.19      | 0.43      | 0.20      | 0.23      | 0.34      |
| OR    | Model based on skin color            | 1.39     | 1.05     | 2.01      | 0.79      | 1.59      | 1.99      | 1.51      |
| lower |                                      | 1.00     | 0.72     | 1.39      | 0.34      | 1.08      | 1.26      | 0.76      |
| upper |                                      | 1.94     | 1.52     | 2.90      | 1.84      | 2.34      | 3.13      | 3.00      |
| beta  |                                      | 0.33     | 0.05     | 0.70      | -0.24     | 0.46      | 0.69      | 0.41      |
| se    |                                      | 0.17     | 0.19     | 0.19      | 0.43      | 0.20      | 0.23      | 0.35      |
| OR    | Model based on tanning ability       | 1.39     | 1.05     | 2.00      | 0.80      | 1.58      | 2.01      | 1.46      |
| lower |                                      | 1.00     | 0.72     | 1.39      | 0.35      | 1.08      | 1.27      | 0.72      |
| upper |                                      | 1.94     | 1.53     | 2.89      | 1.85      | 2.33      | 3.17      | 2.94      |
| beta  |                                      | 0.33     | 0.05     | 0.69      | -0.22     | 0.46      | 0.70      | 0.38      |
| se    |                                      | 0.17     | 0.19     | 0.19      | 0.43      | 0.20      | 0.23      | 0.36      |