

## Expression of *HAL* in skin

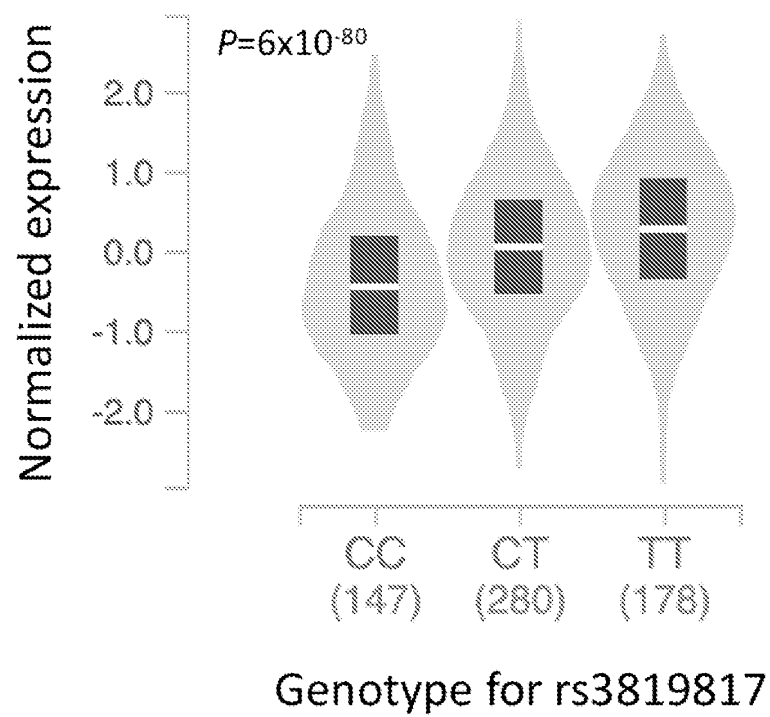


Figure 1

| Phenotype                                                                                                                                       | Study         | Effect [95% CI]       | P-value  | N cases with 0 1 2 copies of the effect allele | N controls with 0 1 2 copies of the effect allele | EAF    |
|-------------------------------------------------------------------------------------------------------------------------------------------------|---------------|-----------------------|----------|------------------------------------------------|---------------------------------------------------|--------|
| <i>Burden of rare pLOF and deleterious missense variants in HAL</i>                                                                             |               |                       |          |                                                |                                                   |        |
| Vitamin D                                                                                                                                       | UKB           | 0.116[0.099,0.132]    | 3.70E-43 | 381231 13124 27                                | NA NA NA                                          | 0.0167 |
|                                                                                                                                                 | GHS           | 0.059[0.017,0.100]    | 5.80E-03 | 54242 2039 1                                   | NA NA NA                                          | 0.0181 |
| Skin tanning                                                                                                                                    | Meta-analysis | 0.108[0.093,0.123]    | 1.80E-43 | 435473 15163 28                                | NA NA NA                                          | 0.0169 |
|                                                                                                                                                 | UKB           | 1.138[1.091,1.187]    | 2.20E-09 | 86331 13244 9                                  | 322123 10845 18                                   | 0.0167 |
| Actinic keratosis                                                                                                                               | UKB           | 1.230[1.020,1.483]    | 3.00E-02 | 2887 123 0                                     | 371288 12749 25                                   | 0.0167 |
|                                                                                                                                                 | GHS           | 1.244[1.106,1.399]    | 2.80E-04 | 9758 426 0                                     | 103672 3874 2                                     | 0.0183 |
| Non melanoma skin cancer                                                                                                                        | Meta-analysis | 1.240[1.122,1.370]    | 2.40E-05 | 12645 549 0                                    | 474960 16623 27                                   | 0.0171 |
|                                                                                                                                                 | UKB           | 1.136[1.062,1.216]    | 2.10E-04 | 26054 996 4                                    | 388311 13299 23                                   | 0.0167 |
| Melanoma skin cancer                                                                                                                            | GHS           | 1.039[0.891,1.210]    | 6.30E-01 | 5560 208 0                                     | 105832 3998 2                                     | 0.0182 |
|                                                                                                                                                 | Meta-analysis | 1.120[1.052,1.191]    | 3.40E-04 | 31614 1204 4                                   | 494143 17297 25                                   | 0.017  |
| Skin color (dark olive)                                                                                                                         | UKB           | 1.123[0.944,1.336]    | 1.90E-01 | 3863 148 0                                     | 411891 14203 27                                   | 0.0167 |
|                                                                                                                                                 | GHS           | 1.178[0.872,1.592]    | 2.90E-01 | 1203 53 0                                      | 109815 4161 3                                     | 0.0183 |
| GIWAS sentinel variant (rs10859995;C) that is in high LD with a sentinel eQTL (rs3819817;T) that increases HAL expression in skin tissue        | Meta-analysis | 1.136[0.978,1.321]    | 9.60E-02 | 5066 201 0                                     | 521706 18364 30                                   | 0.0171 |
|                                                                                                                                                 | UKB           | 1.071[0.939,1.222]    | 3.10E-01 | 6956 254 0                                     | 404178 13946 27                                   | 0.0168 |
| <i>GIWAS sentinel variant (rs10859995;C) that is in high LD with a sentinel eQTL (rs3819817;T) that increases HAL expression in skin tissue</i> |               |                       |          |                                                |                                                   |        |
| Vitamin D                                                                                                                                       | UKB           | -0.040[-0.044,-0.035] | 3.60E-74 | 69201 192291 132890                            | NA NA NA                                          | 0.5808 |
|                                                                                                                                                 | GHS           | -0.026[-0.037,-0.015] | 3.80E-06 | 11106 27942 17234                              | NA NA NA                                          | 0.5532 |
| Skin tanning                                                                                                                                    | Meta-analysis | -0.038[-0.042,-0.034] | 9.00E-78 | 80307 220233 150124                            | NA NA NA                                          | 0.5775 |
|                                                                                                                                                 | UKB           | 0.954[0.943,0.964]    | 8.80E-17 | 16507 44025 29052                              | 57476 162040 113470                               | 0.5811 |
| Actinic keratosis                                                                                                                               | UKB           | 0.988[0.947,1.029]    | 5.50E-01 | 436 1113 805                                   | 80368 224007 155210                               | 0.5814 |
|                                                                                                                                                 | GHS           | 0.941[0.911,0.972]    | 2.60E-04 | 2117 5035 3032                                 | 21204 53211 33133                                 | 0.5533 |
| Non melanoma skin cancer                                                                                                                        | Meta-analysis | 0.951[0.924,0.978]    | 4.90E-04 | 2553 6148 3837                                 | 101572 277218 188343                              | 0.576  |
|                                                                                                                                                 | UKB           | 0.958[0.941,0.976]    | 3.40E-06 | 4995 13075 8958                                | 69988 195779 135576                               | 0.5812 |
| Melanoma skin cancer                                                                                                                            | GHS           | 0.949[0.912,0.987]    | 9.40E-03 | 1295 2905 1829                                 | 22436 56179 34883                                 | 0.5531 |
|                                                                                                                                                 | Meta-analysis | 0.956[0.941,0.972]    | 1.10E-07 | 6290 15980 10787                               | 92424 251958 170459                               | 0.5753 |
| Skin color (dark olive)                                                                                                                         | UKB           | 0.915[0.875,0.957]    | 9.80E-05 | 773 1981 1256                                  | 74478 207523 143801                               | 0.5812 |
|                                                                                                                                                 | GHS           | 0.928[0.857,1.004]    | 6.40E-02 | 2801656 374                                    | 23311 58371 36150                                 | 0.5531 |
| Skin color (dark olive)                                                                                                                         | Meta-analysis | 0.918[0.883,0.955]    | 1.70E-05 | 1053 2637 1630                                 | 97789 265894 179951                               | 0.5754 |
|                                                                                                                                                 | UKB           | 0.971[0.939,1.005]    | 9.30E-02 | 1322 3567 2321                                 | 73177 203844 141130                               | 0.5811 |

Figure 2