

SUPPLEMENTARY DATA

Supplementary Table 1. Meta-analysis results for SNPs associated with IL-1RA in the discovery cohorts.

| MarkerName | Chr | Position (HG18) | Gene | Minor (Coded) Allele | Major Allele | Mean MAF | Discovery | | | |
|------------------|----------|------------------|------------------------------|----------------------|--------------|-------------|-------------|---------------|--------------|-----------------|
| | | | | | | | N | Effect | SE | P |
| rs4251961 | 2 | 113590938 | <i>IL1RN</i> | C | T | 0.32 | 9092 | -0.078 | 0.006 | 2.19E-34 |
| rs6759676 | 2 | 113552819 | closest <i>IL1F10</i> | C | T | 0.44 | 9131 | 0.063 | 0.006 | 6.12E-27 |
| rs10186133 | 2 | 113553415 | closest <i>IL1F10</i> | G | T | 0.42 | 9126 | 0.060 | 0.006 | 4.52E-24 |
| rs315949 | 2 | 113609245 | closest <i>IL1RN</i> | A | G | 0.37 | 5306 | -0.070 | 0.008 | 2.80E-19 |
| rs6731551 | 2 | 113561024 | closest <i>IL1F10</i> | C | T | 0.47 | 9133 | -0.052 | 0.006 | 1.20E-18 |
| rs10199363 | 2 | 113557262 | closest <i>IL1F10</i> | G | A | 0.18 | 9134 | 0.065 | 0.008 | 1.31E-16 |
| rs315921 | 2 | 113588522 | closest <i>IL1RN</i> | A | G | 0.17 | 9096 | 0.065 | 0.008 | 4.89E-16 |
| rs6761276 | 2 | 113548783 | <i>IL1F10</i> | T | C | 0.43 | 5310 | 0.061 | 0.008 | 1.13E-15 |
| rs315920 | 2 | 113589489 | closest <i>IL1RN</i> | T | C | 0.19 | 9095 | 0.059 | 0.008 | 1.26E-14 |
| rs10176274 | 2 | 113557046 | closest <i>IL1F10</i> | G | C | 0.34 | 3209 | -0.085 | 0.012 | 6.37E-13 |
| rs10188292 | 2 | 113556914 | closest <i>IL1F10</i> | T | A | 0.34 | 3209 | -0.085 | 0.012 | 6.37E-13 |
| rs6743171 | 2 | 113556529 | closest <i>IL1F10</i> | C | G | 0.34 | 3209 | -0.085 | 0.012 | 6.37E-13 |
| rs13398728 | 2 | 113558977 | closest <i>IL1F10</i> | C | T | 0.34 | 3209 | -0.085 | 0.012 | 6.37E-13 |
| rs13410964 | 2 | 113559754 | closest <i>IL1F10</i> | A | G | 0.34 | 3209 | -0.085 | 0.012 | 6.37E-13 |
| rs6722922 | 2 | 113557986 | closest <i>IL1F10</i> | T | C | 0.34 | 3209 | -0.085 | 0.012 | 6.37E-13 |
| rs6750559 | 2 | 113558003 | closest <i>IL1F10</i> | A | G | 0.34 | 3209 | -0.085 | 0.012 | 6.37E-13 |
| rs4496335 | 2 | 113560946 | closest <i>IL1F10</i> | T | C | 0.34 | 3209 | -0.085 | 0.012 | 6.37E-13 |
| rs6741180 | 2 | 113560855 | closest <i>IL1F10</i> | A | G | 0.34 | 3209 | -0.085 | 0.012 | 6.37E-13 |
| rs12328766 | 2 | 113563209 | closest <i>IL1F10</i> | G | A | 0.34 | 3209 | -0.085 | 0.012 | 6.38E-13 |
| rs12329129 | 2 | 113563478 | closest <i>IL1F10</i> | A | G | 0.34 | 3209 | -0.085 | 0.012 | 6.38E-13 |
| rs12328368 | 2 | 113563615 | closest <i>IL1F10</i> | G | C | 0.34 | 3209 | -0.085 | 0.012 | 6.38E-13 |
| rs6730516 | 2 | 113565432 | closest <i>IL1RN</i> | T | C | 0.34 | 3209 | -0.085 | 0.012 | 6.44E-13 |
| rs1446510 | 2 | 113567988 | closest <i>IL1RN</i> | T | C | 0.34 | 3209 | -0.085 | 0.012 | 6.47E-13 |
| rs1446509 | 2 | 113567630 | closest <i>IL1RN</i> | T | A | 0.34 | 3209 | -0.085 | 0.012 | 6.47E-13 |
| rs6738239 | 2 | 113567263 | closest <i>IL1RN</i> | A | C | 0.34 | 3209 | -0.085 | 0.012 | 6.47E-13 |
| rs13409360 | 2 | 113554573 | closest <i>IL1F10</i> | A | G | 0.34 | 3209 | -0.084 | 0.012 | 7.78E-13 |
| rs6734238 | 2 | 113557501 | closest <i>IL1F10</i> | G | A | 0.34 | 3209 | -0.084 | 0.012 | 1.06E-12 |

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| | | | | | | | | | | |
|------------|---|-----------|-----------------------|---|---|------|------|--------|-------|----------|
| rs6743376 | 2 | 113548804 | <i>IL1F10</i> | C | A | 0.37 | 5303 | 0.056 | 0.008 | 2.28E-12 |
| rs315943 | 2 | 113610809 | closest <i>IL1RN</i> | G | A | 0.34 | 3209 | -0.082 | 0.012 | 2.46E-12 |
| rs13409371 | 2 | 113554616 | closest <i>IL1F10</i> | A | G | 0.40 | 3209 | -0.083 | 0.012 | 3.83E-12 |
| rs4145013 | 2 | 113547159 | <i>IL1F10</i> | G | A | 0.35 | 5306 | 0.055 | 0.008 | 5.91E-12 |
| rs7574159 | 2 | 113576232 | <i>IL1RN</i> | A | G | 0.33 | 3209 | -0.082 | 0.012 | 1.24E-11 |
| rs17207494 | 2 | 113580481 | <i>IL1RN</i> | C | A | 0.33 | 3209 | -0.082 | 0.012 | 1.34E-11 |
| rs10171849 | 2 | 113582305 | <i>IL1RN</i> | C | A | 0.33 | 3209 | -0.082 | 0.012 | 1.35E-11 |
| rs13382561 | 2 | 113580007 | <i>IL1RN</i> | G | A | 0.33 | 3209 | -0.082 | 0.012 | 1.37E-11 |
| rs13424580 | 2 | 113569035 | closest <i>IL1RN</i> | A | G | 0.33 | 3209 | -0.081 | 0.012 | 1.37E-11 |
| rs6746979 | 2 | 113570591 | closest <i>IL1RN</i> | A | T | 0.33 | 3209 | -0.081 | 0.012 | 1.38E-11 |
| rs7574427 | 2 | 113576509 | <i>IL1RN</i> | A | G | 0.33 | 3209 | -0.082 | 0.012 | 1.39E-11 |
| rs11885498 | 2 | 113616648 | closest <i>IL1RN</i> | G | A | 0.36 | 3209 | -0.078 | 0.012 | 2.53E-11 |
| rs2902452 | 2 | 113611987 | closest <i>IL1RN</i> | A | C | 0.36 | 3209 | -0.078 | 0.012 | 2.80E-11 |
| rs6754298 | 2 | 113612684 | closest <i>IL1RN</i> | A | T | 0.36 | 3209 | -0.078 | 0.012 | 2.85E-11 |
| rs1374281 | 2 | 113615260 | closest <i>IL1RN</i> | G | C | 0.36 | 3209 | -0.078 | 0.012 | 2.86E-11 |
| rs895496 | 2 | 113615496 | closest <i>IL1RN</i> | T | C | 0.36 | 3209 | -0.078 | 0.012 | 2.93E-11 |
| rs1530551 | 2 | 113534037 | <i>IL36RN</i> | T | C | 0.38 | 5307 | 0.050 | 0.008 | 1.08E-10 |
| rs380092 | 2 | 113605371 | <i>IL1RN</i> | T | A | 0.36 | 5308 | 0.052 | 0.008 | 1.13E-10 |
| rs2472188 | 2 | 113537285 | <i>IL36RN</i> | C | G | 0.38 | 5304 | 0.049 | 0.008 | 1.89E-10 |
| rs11123167 | 2 | 113623340 | closest <i>IL1RN</i> | C | G | 0.36 | 3209 | -0.074 | 0.012 | 2.82E-10 |
| rs3827763 | 2 | 113547760 | <i>IL1F10</i> | A | G | 0.30 | 5310 | 0.052 | 0.008 | 6.99E-10 |
| rs1867828 | 2 | 113485091 | closest <i>IL1F10</i> | A | G | 0.26 | 5310 | -0.052 | 0.009 | 2.27E-09 |
| rs3811050 | 2 | 113546644 | <i>IL1F10</i> | T | C | 0.18 | 5310 | -0.062 | 0.011 | 3.22E-09 |
| rs315952 | 2 | 113606775 | <i>IL1RN</i> | C | T | 0.35 | 5300 | 0.047 | 0.008 | 4.62E-09 |
| rs11678375 | 2 | 113552162 | closest <i>IL1F10</i> | T | C | 0.43 | 3209 | 0.060 | 0.011 | 2.58E-08 |
| rs13386602 | 2 | 113551291 | closest <i>IL1F10</i> | A | C | 0.43 | 3209 | 0.060 | 0.011 | 2.61E-08 |
| rs12469822 | 2 | 113547034 | <i>IL1F10</i> | G | A | 0.44 | 3209 | 0.060 | 0.011 | 3.22E-08 |

Variants that passed the discovery P value threshold of 5.0×10^{-8} are shown. The two most significantly associated independent SNPs from the discovery meta-analysis (marked in bold) were then taken forward for replication.

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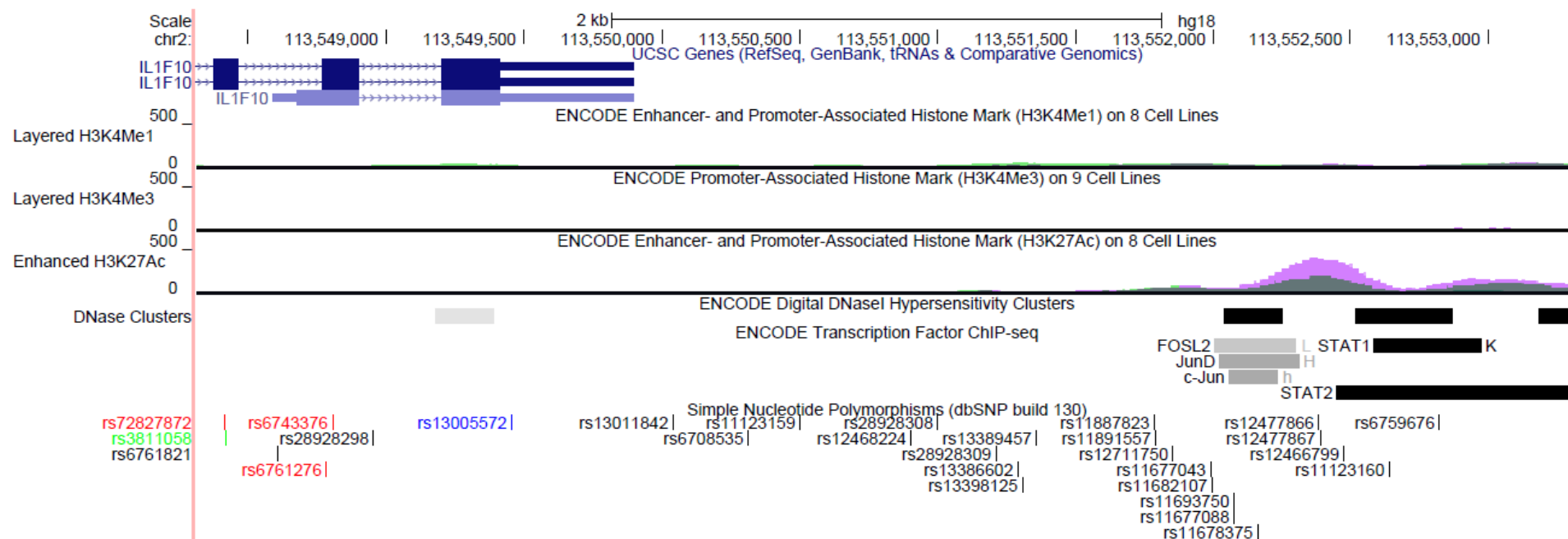
Supplementary Table 2. Replication and combined meta-analysis results for the SNPs independently associated with circulating IL-1RA levels with YFS included in analyses.

| Marker name | Chr | Position (HG18) | Gene | Minor (coded) allele | Major allele | Mean MAF | Replication | | | | I^2 (%) | Meta-analysis model |
|-------------|-----|-----------------|-----------------------|----------------------|--------------|----------|-------------|--------|-------|----------|-----------|---------------------|
| | | | | | | | <i>N</i> | Effect | SE | <i>P</i> | | |
| rs4251961 | 2 | 113590938 | <i>IL1RN</i> | C | T | 0.32 | 6802 | -0.064 | 0.027 | 0.016 | 90.74 | RE |
| rs6759676 | 2 | 113552819 | closest <i>IL1F10</i> | C | T | 0.44 | 6802 | 0.073 | 0.034 | 0.031 | 94.94 | RE |

| Marker name | Chr | Position (HG18) | Gene | Minor (coded) allele | Major allele | Mean MAF | Combined | | | | I^2 (%) | Meta-analysis model |
|-------------|-----|-----------------|-----------------------|----------------------|--------------|----------|----------|--------|-------|----------|-----------|---------------------|
| | | | | | | | <i>N</i> | Effect | SE | <i>P</i> | | |
| rs4251961 | 2 | 113590938 | <i>IL1RN</i> | C | T | 0.32 | 15894 | -0.077 | 0.012 | 9.46E-11 | 79.72 | RE |
| rs6759676 | 2 | 113552819 | closest <i>IL1F10</i> | C | T | 0.44 | 15933 | 0.068 | 0.013 | 9.14E-08 | 84.69 | RE |

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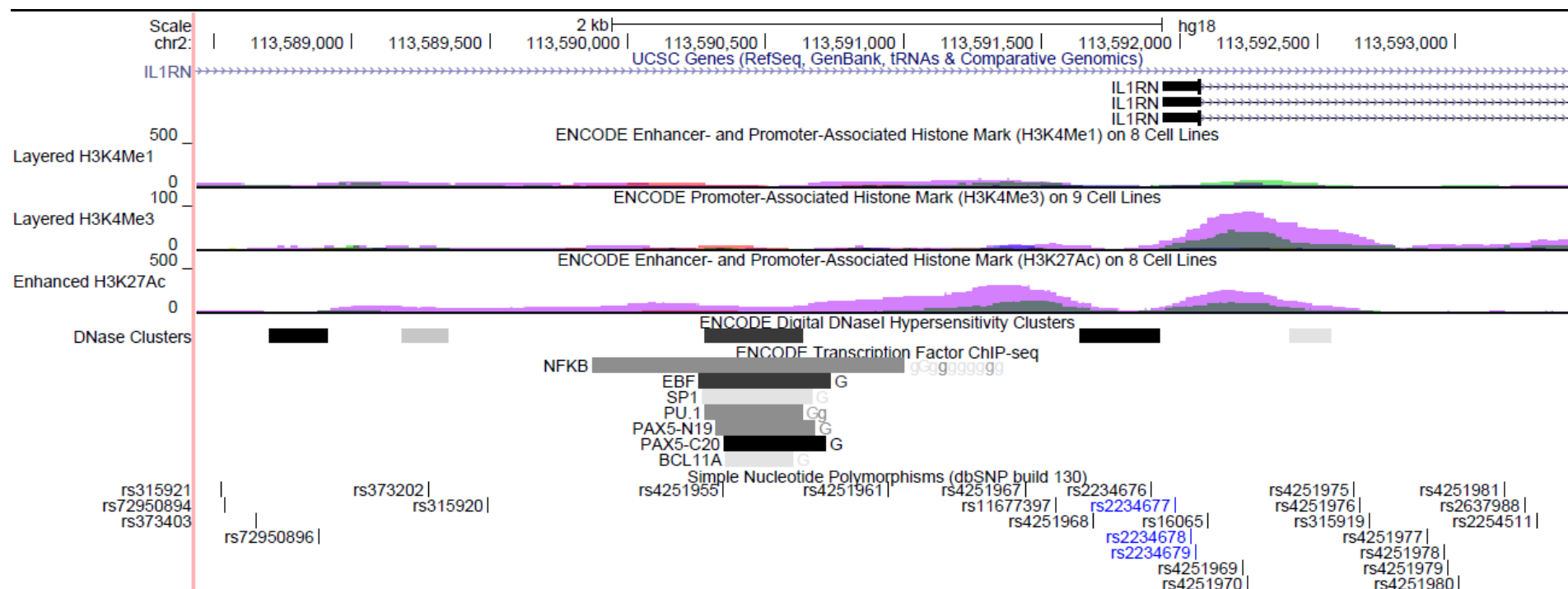
Supplementary Figure 1. In silico functional analysis for rs6759676.



A snapshot of the UCSC Genome Browser shows that rs6759676 falls within an region enriched for H3K27Ac histone acetylation (often found near active regulatory elements) in epidermal keratinocytes cells (pink peak) and human mammary epithelial cells (grey peak); within a DNase hypersensitive region (characteristic of open chromatin regions) in multiple cell lines; and also within STAT transcription factor binding sites.

SUPPLEMENTARY DATA

Supplementary Figure 2. In silico functional analysis for rs4251961.

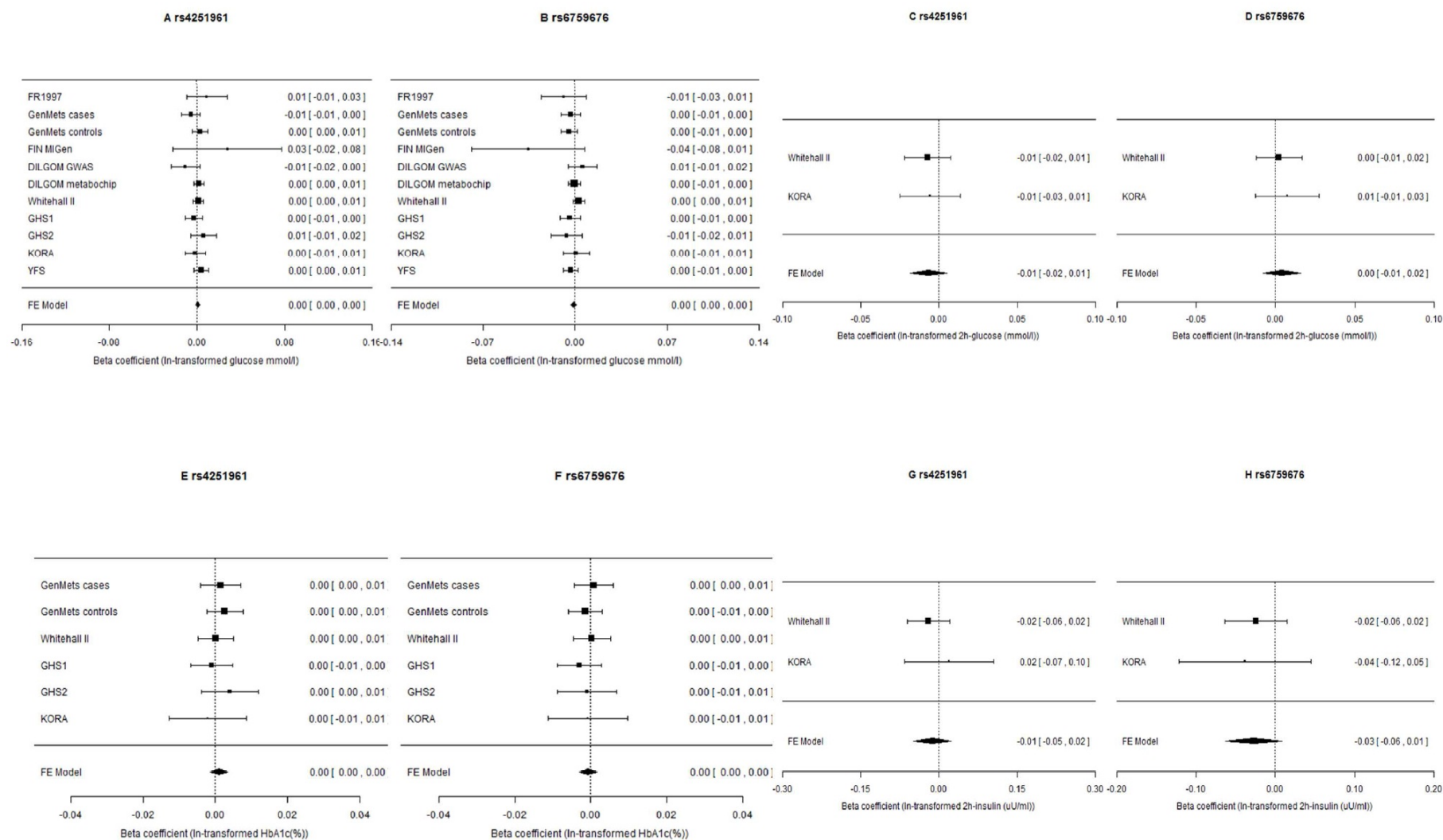


A snapshot of the UCSC Genome Browser shows that rs4251961 falls within a region enriched for the H3K27Ac histone acetylation mark (often found near active regulatory elements) in epidermal keratinocytes cells (pink peak) and human mammary epithelial cells (grey peak) (Supplementary Figure 2), upstream of the IL1RN gene. It is very close to regions enriched for transcription factor binding and DNase hypersensitivity, indicative of open chromatin.

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Supplementary Figure 3. Association of rs4251961 and rs6759676 with circulating fasting glucose, 2-hr glucose, HbA1c and 2-hr insulin in individual studies included in the discovery and replication analysis.

A, B: fasting glucose; C, D: 2-hr glucose; E, F: HbA1c; G, H: 2-hr insulin.
All analyses were adjusted for age, sex, BMI, waist-to-hip ratio and smoking.



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Supplementary Figure 4. Association of rs4251961 and rs6759676 with circulating IL-1RA levels in individual discovery and replication studies while YFS is included in the replication analysis.

All analyses were adjusted for age, sex, BMI, waist-to-hip ratio and smoking.

