**A few points**

**Of the 28 epistasis pairs listed in the table provided by Michael Weedon, there are 17 unique INC seq snps. All 17 display large additive effects for the cis probe in InCHIANTI. 15 of these SNPs are also present in the imputed (1000 Genomes) BSGS data. All 15 also display large additive effects for the cis probe in BSGS data.**

**These SNPs are in modest to high LD with one or both of the epistasis SNPs.**

**Do the INC seq SNPs explain more variance for the probe then the pairwise combination of epistasis SNPs? In both the InCHIANTI data and BSGS the pairwise combination explain more variance in the probe expression levels than the Inc seq SNPs (table 3). It is unclear to me why they observe no variance explained after removing the additive effects of the InC SNP (see column S in the file from Michael).**

**Another important point is the power to detect the interactions given the sample size = 450. This is particularly relevant for the genotype class sizes that must have a sufficient number of individuals to (accurately) estimate the genotype class mean expression. Looking at the file sent by Michael there is no observed interaction (based on p values) for 14/28 pairs in the in InCHIANTI data (table 1). Therefore, there is no interaction effect to remove by fitting the inc seq SNP. The reason for the lack of interaction is unknown, but it is possible that it is due to same sample size of the genotype classes (see table 2).**

**If there are low (or missing) genotype classes for these pairs in InCHIANTI then**

**Table 1** | selected columns from the file sent by Michael Weedon. The highlighted blue and yellow columns are the interaction p-values (from epiGPU) for the pair of epistatic snps before and after the additive effect of the incSeq SNP is removed. The rows highlighted orange are those that showed no initial interaction (based on p-values) in the InCHIANTI data.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Probe** | **SNP1** | **SNP1 B37 Pos** | **SNP2** | **SNP2 B37 Pos** | **incSeq** | **Interaction P** | **Interaction P** |
| ILMN\_2358626 | rs2395095 | 10:76446305 | rs10824092 | 10:75929517 | 10:75928933 | 9.1E-04 | **0.86** |
| ILMN\_2134224 | rs4284750 | 19:19810050 | rs873870 | 19:19738554 | 19:19756073 | 7.9E-03 | **0.64** |
| ILMN\_1795836 | rs9978658 | 21:48027084 | rs11701361 | 21:47764477 | 21:47703649 | 7.2E-03 | **0.43** |
| ILMN\_1761797 | rs9979356 | 21:45230974 | rs3761385 | 21:45198355 | 21:45201832 | 8.3E-07 | **0.99** |
| ILMN\_2242463 | rs7930237 | 11:88117962 | rs556895 | 11:88077479 | 11:88015717 | 5.0E-06 | **0.04** |
| ILMN\_1652333 | rs898095 | 17:80890638 | rs9892064 | 17:80827903 | 17:80678628 | 2.9E-12 | **0.43** |
| ILMN\_2410783 | rs11150847 | 17:78153130 | rs12602462 | 17:78146016 | 17:78096086 | 0.15 | **0.34** |
| ILMN\_2101920 | rs6894268 | 5:179032488 | rs4700810 | 5:178991794 | 5:178978883 | 0.53 | **0.45** |
| ILMN\_1769782 | rs1891432 | 1:203877662 | rs10900520 | 1:203780591 | 1:203747772 | 1.6E-04 | **0.52** |
| ILMN\_2313158 | rs11981513 | 7:94648239 | rs13069559 | 3:152187431 | 3:152182577 | 1.6E-02 | **0.10** |
| ILMN\_2313158 | rs16864367 | 3:152234166 | rs13079208 | 3:152116652 | 3:152182577 | 2.7E-06 | **0.16** |
| ILMN\_2313158 | rs2030926 | 6:114067127 | rs13069559 | 3:152187431 | 3:152182577 | 3.2E-02 | **0.21** |
| ILMN\_2313158 | rs218671 | 17:6604708 | rs13069559 | 3:152187431 | 3:152182577 | 0.90 | **0.79** |
| ILMN\_2313158 | rs2614467 | 14:99770138 | rs13069559 | 3:152187431 | 3:152182577 | 0.24 | **0.55** |
| ILMN\_2313158 | rs7710738 | 5:22101322 | rs13069559 | 3:152187431 | 3:152182577 | 2.3E-02 | **0.02** |
| ILMN\_2398939 | rs8092433 | 18:74747424 | rs4890876 | 18:74732087 | 18:74723459 | 0.05 | **0.28** |
| ILMN\_1710752 | rs2123758 | 8:144663661 | rs3889129 | 8:144613680 | 8:144684215 | 6.2E-06 | **0.84** |
| ILMN\_2121437 | rs7563453 | 2:232301670 | rs4973397 | 2:232291471 | 2:232320581 | 0.10 | **0.71** |
| ILMN\_1675038 | rs2839372 | 21:48063862 | rs11701058 | 21:47776382 | 21:47887791 | 2.6E-04 | **0.30** |
| ILMN\_1799381 | rs2634462 | 11:17339127 | rs6486334 | 11:17015557 | 11:17230389 | 0.37 | **0.17** |
| ILMN\_1786426 | rs807491 | 19:36268923 | rs7254601 | 19:36147315 | 19:36234489 | 2.9E-06 | **0.41** |
| ILMN\_1786426 | rs8106959 | 19:36219525 | rs1843357 | 8:13822381 | 19:36234489 | 0.44 | **0.73** |
| ILMN\_1786426 | rs8106959 | 19:36219525 | rs2351458 | 4:113317583 | 19:36234489 | 0.30 | **0.46** |
| ILMN\_1786426 | rs8106959 | 19:36219525 | rs6718480 | 2:233879066 | 19:36234489 | 0.44 | **0.69** |
| ILMN\_1786426 | rs8106959 | 19:36219525 | rs6926382 | 6:161683974 | 19:36234489 | 0.23 | **0.53** |
| ILMN\_1786426 | rs8106959 | 19:36219525 | rs914940 | 1:242889492 | 19:36234489 | 0.62 | **0.71** |
| ILMN\_1786426 | rs8106959 | 19:36219525 | rs9509428 | 13:21473952 | 19:36234489 | 0.09 | **0.39** |
| ILMN\_1743646 | rs1264226 | 19:46063167 | rs2276470 | 19:45974668 | 19:46033382 | 0.81 | **0.56** |

**Table 2** | The expected genotype class sizes in InCHIANTI data. Note, this is assuming that the allele frequencies are the same as in BSGS and that in the InCHIANTI data every probe is significantly expressed in 100% of the 450 individuals. We required that all 9 genotype classes were present and that the minimum genotype class size for discovery and replication was >5. The purpose of this to accurately estimate the genotype class mean expression level.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| probe | snp1 | snp2 | aa1aa2 | aA1aa2 | AA1aa2 | aa1aA2 | aA1aA2 | AA1aA2 | aa1AA2 | aA1AA2 | AA1AA2 |
| ILMN\_2358626 | rs2395095 | rs10824092 | 6 | 12 | 35 | 12 | 23 | 69 | 14 | 28 | 84 |
| ILMN\_2134224 | rs4284750 | rs873870 | 11 | 22 | 46 | 21 | 43 | 92 | 13 | 27 | 57 |
| ILMN\_1795836 | rs9978658 | rs11701361 | 3 | 7 | 9 | 7 | 13 | 19 | 37 | 74 | 105 |
| ILMN\_1761797 | rs9979356 | rs3761385 | 2 | 4 | 26 | 4 | 8 | 53 | 10 | 21 | 130 |
| ILMN\_2242463 | rs7930237 | rs556895 | 7 | 14 | 77 | 14 | 28 | 154 | 5 | 10 | 56 |
| ILMN\_1652333 | rs898095 | rs9892064 | 20 | 39 | 21 | 39 | 79 | 41 | 37 | 73 | 38 |
| ILMN\_2410783 | rs11150847 | rs12602462 | 14 | 28 | 21 | 28 | 55 | 43 | 33 | 66 | 51 |
| ILMN\_2101920 | rs6894268 | rs4700810 | 6 | 12 | 31 | 12 | 24 | 62 | 16 | 33 | 83 |
| ILMN\_1769782 | rs1891432 | rs10900520 | 5 | 10 | 13 | 10 | 19 | 26 | 34 | 68 | 92 |
| ILMN\_2313158 | rs11981513 | rs13069559 | 3 | 6 | 3 | 6 | 11 | 6 | 78 | 156 | 81 |
| ILMN\_2313158 | rs16864367 | rs13079208 | 8 | 15 | 61 | 15 | 31 | 122 | 8 | 15 | 62 |
| ILMN\_2313158 | rs2030926 | rs13069559 | 3 | 6 | 3 | 6 | 11 | 6 | 78 | 156 | 81 |
| ILMN\_2313158 | rs218671 | rs13069559 | 2 | 4 | 4 | 4 | 8 | 8 | 58 | 116 | 104 |
| ILMN\_2313158 | rs2614467 | rs13069559 | 2 | 5 | 4 | 4 | 9 | 7 | 62 | 124 | 99 |
| ILMN\_2313158 | rs7710738 | rs13069559 | 2 | 5 | 4 | 4 | 9 | 7 | 62 | 123 | 100 |
| ILMN\_2398939 | rs8092433 | rs4890876 | 18 | 36 | 26 | 36 | 72 | 52 | 29 | 59 | 42 |
| ILMN\_1710752 | rs2123758 | rs3889129 | 7 | 14 | 27 | 14 | 28 | 53 | 21 | 41 | 78 |
| ILMN\_2121437 | rs7563453 | rs4973397 | 2 | 3 | 14 | 3 | 7 | 29 | 17 | 33 | 146 |
| ILMN\_1675038 | rs2839372 | rs11701058 | 1 | 2 | 11 | 2 | 4 | 22 | 16 | 33 | 163 |
| ILMN\_1799381 | rs2634462 | rs6486334 | 4 | 7 | 28 | 7 | 14 | 55 | 14 | 27 | 108 |
| ILMN\_1786426 | rs807491 | rs7254601 | 4 | 7 | 9 | 7 | 14 | 18 | 41 | 82 | 99 |
| ILMN\_1786426 | rs8106959 | rs1843357 | 2 | 4 | 40 | 4 | 7 | 81 | 5 | 11 | 125 |
| ILMN\_1786426 | rs8106959 | rs2351458 | 2 | 4 | 51 | 4 | 9 | 102 | 5 | 9 | 108 |
| ILMN\_1786426 | rs8106959 | rs6718480 | 2 | 5 | 54 | 5 | 10 | 109 | 5 | 9 | 103 |
| ILMN\_1786426 | rs8106959 | rs6926382 | 3 | 6 | 74 | 6 | 13 | 148 | 4 | 7 | 80 |
| ILMN\_1786426 | rs8106959 | rs914940 | 3 | 5 | 58 | 5 | 10 | 115 | 4 | 9 | 99 |
| ILMN\_1786426 | rs8106959 | rs9509428 | 3 | 7 | 76 | 7 | 13 | 153 | 3 | 7 | 78 |
| ILMN\_1743646 | rs1264226 | rs2276470 | 16 | 32 | 33 | 31 | 63 | 66 | 22 | 44 | 46 |

**Table 3 |** proportion of variance explained by the epistasis and inc seq SNPs. For the InCHIANTI data this is calculated by; R2/(1-R) ~ df \* chisq(df) / N. with df=1 or 8 depending on the model and chisq calculated from the reported p-values.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| probe | var% bsgs snp1 InCHIANTI | var% bsgs snp2 InCHIANTI | | var% inc snp InCHIANTI | var% epiGPU 8DF InCHIANTI | var%inc snp in bsgs | var% epiGPU 8DF bsgs |
| ILMN\_2358626 | 12.34 | 2.88 | | 24.77 | 62.8 | 15.366 | 48.866 |
| ILMN\_2134224 | 2.91 | 1.24 | | 19.37 | 36.27 | / | 46.83 |
| ILMN\_1795836 | 3.5 | 0.04 | | 18.19 | 35.32 | 36.634 | 47.301 |
| ILMN\_1761797 | 0.96 | 1.49 | | 15.43 | 41.2 | 21.206 | 48.456 |
| ILMN\_2242463 | 9.12 | 0.82 | | 10.09 | 57.81 | 5.465 | 51.311 |
| ILMN\_1652333 | 0.92 | 0.11 | | 26.56 | 51.45 | / | 50.719 |
| ILMN\_2410783 | 0.15 | 0.96 | | 5.9 | 17.92 | 13.667 | 46.902 |
| ILMN\_2101920 | 1.73 | 0.62 | | 3.09 | 18.42 | 19.71 | 48.268 |
| ILMN\_1769782 | 3.38 | 1.15 | | 11.6 | 43.64 | 44.233 | 59.606 |
| ILMN\_2313158 | 0.46 | 3.78 | | 12.66 | 36.2 | 19.968 | 58.403 |
| ILMN\_2313158 | 1.87 | 0.43 | | 12.66 | 43.31 | 19.968 | 58.566 |
| ILMN\_2313158 | 0.16 | 3.78 | | 12.66 | 36.2 | 19.968 | 58.288 |
| ILMN\_2313158 | 0 | 3.78 | | 12.66 | 31.41 | 19.968 | 59.029 |
| ILMN\_2313158 | 0.19 | 3.78 | | 12.66 | 31.41 | 19.968 | 58.011 |
| ILMN\_2313158 | 0.02 | 3.78 | | 12.66 | 35.65 | 19.968 | 58.87 |
| ILMN\_2398939 | 0.65 | 1.55 | | 7.76 | 23.76 | 20.232 | 48.044 |
| ILMN\_1710752 | 20.29 | 1.1 | | 30.56 | 73.8 | 37.386 | 66.063 |
| ILMN\_2121437 | 0.8 | 0.11 | | 3.23 | 17.92 | 6.923 | 46.786 |
| ILMN\_1675038 | 0.02 | 11.3 | | 18.62 | 58 | 5.299 | 47.712 |
| ILMN\_1799381 | 3.92 | 1.87 | | 30.62 | 36.64 | 25.123 | 47.244 |
| ILMN\_1786426 | 4.7 | 17.46 | | 34 | 72.34 | 47.119 | 74.265 |
| ILMN\_1786426 | 29.16 | 0.01 | | 34 | 77.1 | 47.119 | 73.819 |
| ILMN\_1786426 | 29.16 | 0.92 | | 34 | 77.52 | 47.119 | 74.342 |
| ILMN\_1786426 | 29.16 | | 0.32 | 34 | 77.42 | 47.119 | 74.488 |
| ILMN\_1786426 | 29.16 | | 0.45 | 34 | 77.91 | 47.119 | 73.864 |
| ILMN\_1786426 | 29.16 | | 0 | 34 | 77.51 | 47.119 | 73.997 |
| ILMN\_1786426 | 29.16 | | 0.17 | 34 | 77.52 | 47.119 | 74.979 |
| ILMN\_1743646 | 0.42 | | 1.84 | 13.31 | 17 | 49.341 | 56.315 |