Frequent intronic SNP in human estrogen receptor *ESR1* influences brain mRNA expression and behavioral disorders

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**Supplemental Data**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Location** | **position** | **dbSNP rs#** | **MAF** | **Bone/Joint** | **Cancer** | **Cardio** | **CNS** | **Infection** | **Fertility** | **References** |
| 5' near gene | 152009638 | rs2941740  | 0.34 | X |   |   |   |   |   | ([1](#_ENREF_1)) |
| upstream Intron | 152089768 | rs2485209  | 0.41 | X |   |   |   |   |   | ([2](#_ENREF_2)) |
| upstream Intron | 152119119 | rs2881766  | 0.41 |   |   | X |   |   |   | ([3](#_ENREF_3)) |
| upstream Intron | 152121442 | rs11964281  | 0.05 |   |   | X |   |   |   | ([4](#_ENREF_4)) |
| upstream Intron | 152125231 | rs34535804  | 0.19  |   |   |   | X |   |   | ([5](#_ENREF_5)) |
| upstream Intron | 152127664 | TA repeat | 0.43 |  |  |  | X |  |  | ([6](#_ENREF_6)) |
| Exon1 | 152129077 | rs2077647 | 0.43 | X | X |  | X | X |   | ([7-11](#_ENREF_7)) |
| Exon1 | 152129308 | rs746432  | 0.05 |   |   |   | X |   |   | ([10](#_ENREF_10)) |
| Intron1 | 152130918 | rs532010  | 0.38 |   |   |   | X |   |   | ([10](#_ENREF_10)) |
| Intron1 | 152140042 | rs3844508  | 0.27 |   |   |   | X |   |   | ([12](#_ENREF_12)) |
| Intron1 | 152161066 | rs9397448  | 0.41 | X |   |   |  |   |   | ([13](#_ENREF_13)) |
| Intron1 | 152162317 | rs9322331  | 0.17 |  |   | X |   |   |   | ([14](#_ENREF_14)) |
| Intron1 | 152163334 | rs8179176  | 0.45  |   |   |   | X |   |   | ([15](#_ENREF_15)) |
| Intron1 | 152163335 | rs2234693 | 0.44 | X | X | X | X | X |  | ([7](#_ENREF_7), [8](#_ENREF_8), [11](#_ENREF_11), [13](#_ENREF_13), [16-27](#_ENREF_16)) |
| Intron1 | 152163381 | rs9340799 | 0.26 | X | X | X | X | X |  | ([7](#_ENREF_7), [14-17](#_ENREF_14), [20-27](#_ENREF_20)) |
| Intron2 | 152200430 | rs9322336  | 0.23 |   | X |   |   |   |   | ([28](#_ENREF_28)) |
| Intron2 | 152201624 | rs9340844  | 0.03 |   |   | X |   |   |   | ([29](#_ENREF_29)) |
| Intron3 | 152203104 | rs6557170  | 0.26 |   |   |   | X |   |   | ([30](#_ENREF_30)) |
| Intron3 | 152208722 | rs1913474  | 0.28 |   |   | X |   |   |   | ([31](#_ENREF_31)) |
| Intron3 | 152229850 | rs2347867  | 0.44 |   |   | X |   |   |   | ([32](#_ENREF_32)) |
| Intron3 | 152236879 | rs9397453  | 0.04 |   |   | X |   |   |   | ([29](#_ENREF_29)) |
| Intron3 | 152241150 | rs988328  | 0.22 |   |   | X |   |   |   | ([3](#_ENREF_3)) |
| Intron3 | 152247152 | rs9397456  | 0.26 |   |   | X |   |   |   | ([33](#_ENREF_33)) |
| Intron3 | 152260642 | rs9371562  | 0.03 |   |   | X |   |   |   | ([29](#_ENREF_29)) |
| Exon4 | 152265522 | rs1801132 | 0.26 | X |  | X |  | X |   | ([7](#_ENREF_7), [31](#_ENREF_31), [34](#_ENREF_34)) |
| Intron4 | 152265659 | rs9397459  | 0.04 |   |   | X |   |   |   | ([29](#_ENREF_29)) |
| Intron4 | 152270672 | rs3020314  | 0.43 | X | X | X |   |   |   | ([33-35](#_ENREF_33)) |
| Intron4 | 152278741 | rs3020317  | 0.29 |   |   | X |   |   |   | ([31](#_ENREF_31), [33](#_ENREF_33)) |
| Intron4 | 152283279 | rs1884051  | 0.43 |  X |   |  |   |   |   | ([34](#_ENREF_34)) |
| Intron4 | 152285687 | rs2982694  | 0.18 |   |   | X |   |   |   | ([36](#_ENREF_36)) |
| Intron4 | 152286625 | \*rs985694  | 0.25 |  |   | X |   |   |   | ([31](#_ENREF_31), [33](#_ENREF_33)) |
| Intron4 | 152291366 | rs1884052  | 0.18 | X |   |  |   |   |   | ([37](#_ENREF_37)) |
| Intron4 | 152295613 | rs9383951  | 0.07 |  |   | X |   |   |   | ([29](#_ENREF_29)) |
| Intron4 | 152297100 | \*rs2179922  | 0.15 | X |   |   |   |   |   | ([38](#_ENREF_38)) |
| Intron4 | 152302578 | rs726281  | 0.50 |   |   |   | X |   |   | ([39](#_ENREF_39)) |
| Intron4 | 152303437 | rs728524  | 0.12 |   |   |   | X |   |   | ([15](#_ENREF_15)) |
| Intron4 | 152304596 | \*rs932477  | 0.20 |   |   | X |   |   |   | ([31](#_ENREF_31)) |
| **Intron4** | **152307706** | **rs2144025**  | **0.33** |  | **X** |  |  |  |  | **(**[**40**](#_ENREF_40)**)** |
| Intron4 | 152317140 | rs7757956  | 0.14 |  |   | X |   |   |   | ([31](#_ENREF_31)) |
| Intron4 | 152322885 | rs722208  | 0.41 |   | X |   |   |   |   | ([41](#_ENREF_41)) |
| Intron4 | 152323192 | rs722207  | 0.38 |   |   |   | X |   |   | ([42](#_ENREF_42)) |
| Intron4 | 152326197 | rs6905370  | 0.41 |   | X |  |   |   |  | ([43](#_ENREF_43)) |
| Intron4 | 152328616 | rs1569788  | 0.41 |   |   | X |   |   | X | ([4](#_ENREF_4), [44](#_ENREF_44)) |
| Intron4 | 152330673 | rs9340958  | 0.07 |   |   |   |   |   | X | ([45](#_ENREF_45)) |
| Intron5 | 152333945 | rs9340978  | 0.05 |   |   |   |   |   | X | ([45](#_ENREF_45)) |
| Intron5 | 152371190 | rs3020368  | 0.09 |   |   | X |   |   |   | ([31](#_ENREF_31)) |
| Intron5 | 152376524 | \*rs6932902  | 0.23 |   |   |   |   |   | X | ([46](#_ENREF_46)) |
| Intron5 | 152380515 | \*rs9397080  | 0.24 |   | X |   |   |   |   | ([47](#_ENREF_47)) |
| Intron6 | 152382311 | \*rs2273206  | 0.24 |   |   |   | X |   |   | ([48](#_ENREF_48)) |
| Intron6 | 152382325 | rs2273207  | 0.15 |   |   |   | X |   |   | ([48](#_ENREF_48)) |
| Intron6 | 152382382 | rs2207396 | 0.23 |  |  | X |  | X | X | ([7](#_ENREF_7), [45](#_ENREF_45), [49](#_ENREF_49)) |
| Intron6 | 152382420 | \*rs974276  | 0.24 |   |   |   | X |   |   | ([42](#_ENREF_42)) |
| Intron6 | 152389968 | rs3020375  | 0.49 |   |   |   |   |   | X | ([50](#_ENREF_50)) |
| Intron6 | 152396036 | rs7766585  | 0.23 |   | X |   |   |   |   | ([51](#_ENREF_51)) |
| Intron7 | 152418575 | rs3778099  | 0.19 | X |   |   |   |   |   | ([37](#_ENREF_37)) |
| Exon8 | 152420095 | rs2228480  | 0.18 |   |   | X |   |   |   | ([52](#_ENREF_52)) |
| 3'UTR | 152421130 | rs3798577 | 0.44 |  |  |  | X |   |   | ([39](#_ENREF_39), [53](#_ENREF_53)) |
| 3'UTR | 152421854 | rs3798758  | 0.13 |   |   | X |   |   |   | ([52](#_ENREF_52)) |
| 3'UTR | 152422335 | rs2747648  | 0.01 |   |   |   | X |   |   | ([54](#_ENREF_54)) |
| 3'UTR | 152423905 | rs1062577  | 0.14 |   | X |   |   |   |   | ([55](#_ENREF_55)) |

**Table A**: *ESR1* variants identified in candidate associations studies of various clinical phenotypes. Phenotypes were grouped into six categories: Bone/Joint, Cancer, Cardio, CNS, Infection, and Fertility. Bone/Joint includes but is not limited to bone density, body height, osteoarthritis, and rheumatoid arthritis. Cardio includes but is not limited to blood pressure, type II diabetes, lipid, and artery phenotypes. Cancer is defined as any cancer or cancer treatment. CNS is defined as any behavioral or developmental brain disorder. “\*” defines SNPs with D’>0.5 with rs2144025, with details provided in Supplemental Table 7. Position is location within the reference sequence GRCh37.p10. MAF is defined by the 1000 Genomes project. For variants with multiple associations, not every older citation is included in the table.

| snpID | Position | Phenotype | Pvalue | GWAS PMID |
| --- | --- | --- | --- | --- |
| rs45918598 | 151943639 | Bone mineral density | 4.90E-10 | 19801982 |
| rs10872676 | 151943977 | Bone mineral density | 4.40E-10 | 19801982 |
| rs9383936 | 151944614 | Breast size | 2.20E-09 | 22747683 |
| rs7776340\* | 151945666 | Bone mineral density | 4.40E-13 | 22504420 |
| rs12665607 | 151946629 | Breast size | 1.30E-09 | 22747683 |
| rs7751941\* | 151946658 | Bone mineral density | 2.00E-24 | 22504420 |
| rs6917575 | 151947539 | Breast size | 1.40E-09 | 22747683 |
| rs6901351 | 151947736 | Breast size | 2.30E-09 | 22747683 |
| rs74295874 | 151947757 | Breast size | 1.20E-09 | 22747683 |
| rs2046211\* | 151948284 | Transmission distortion | 5.90E-16 | 22377632 |
| rs2046210\* | 151948366 | Breast cancer | 3.60E-39 | 22383897 |
| rs6557161 | 151950235 | Breast size | 9.20E-09 | 22747683 |
| rs7774781 | 151950723 | Breast size | 1.70E-09 | 22747683 |
| rs9397435 | 151951220 | Breast size | 1.10E-09 | 22747683 |
| rs9397436 | 151952002 | Breast size | 8.50E-11 | 22747683 |
| rs9397437 | 151952332 | Breast size | 1.90E-10 | 22747683 |
| rs58343273 | 151953180 | Breast size | 3.40E-10 | 22747683 |
| rs9383590 | 151953765 | Breast size | 3.70E-10 | 22747683 |
| rs9397068 | 151953859 | Breast size | 4.80E-10 | 22747683 |
| rs6900157\* | 151954127 | Bone mineral density | 2.20E-09 | 19079262 |
| rs60954078 | 151955914 | Breast size | 2.50E-10 | 22747683 |
| rs9383937 | 151957119 | Breast size | 2.70E-10 | 22747683 |
| rs12173562 | 151957570 | Breast size | 3.50E-10 | 22747683 |
| rs12173570 | 151957714 | Breast size | 5.60E-11 | 22747683 |
| rs6930633 | 151958091 | Bone mineral density | 8.90E-11 | 23074152 |
| rs6912323 | 151958612 | Breast size | 6.00E-10 | 22747683 |
| rs17081533 | 151958815 | Breast size | 5.00E-10 | 22747683 |
| rs852003 | 151962202 | Bone mineral density | 2.60E-15 | 22504420 |
| rs77275268 | 151969198 | Breast size | 6.30E-10 | 22747683 |
| rs9371545 | 151969740 | Breast size | 9.30E-10 | 22747683 |
| rs712219 | 151978439 | Bone mineral density | 7.90E-09 | 18445777 |
| rs3020331\* | 152008780 | Bone mineral density | 3.10E-11 | 18445777 |
| rs3020332\* | 152008924 | Bone mineral density | 2.80E-09 | 19801982 |
| rs2941741\* | 152008982 | Bone mineral density | 2.20E-10 | 19801982 |
| rs2941740\* | 152009638 | Bone mineral density | 2.00E-10 | 20096396 |
| rs3020333\* | 152010254 | Bone mineral density | 2.90E-10 | 19801982 |
| rs2982573\* | 152010534 | Bone mineral density | 2.40E-10 | 19801982 |
| rs2982571\* | 152012739 | Bone mineral density | 3.90E-10 | 19801982 |
| rs3020334\* | 152012956 | Bone mineral density | 3.50E-10 | 19801982 |
| rs3020335\* | 152013223 | Bone mineral density | 4.80E-10 | 19801982 |
| rs2982570\* | 152013748 | Bone mineral density | 4.80E-10 | 19801982 |
| rs851982\* | 152024985 | Bone mineral density | 7.20E-12 | 18445777 |
| rs2982562 | 152052601 | Bone mineral density | 5.80E-09 | 19801982 |
| rs2982561 | 152052652 | Bone mineral density | 8.90E-09 | 19801982 |
| snpID | Position | Phenotype | Pvalue | GWAS PMID |
| rs3020343 | 152054363 | Bone mineral density | 4.80E-09 | 19801982 |
| rs2982560 | 152055606 | Bone mineral density | 4.30E-09 | 19801982 |
| rs2982558 | 152056146 | Bone mineral density | 7.00E-09 | 19801982 |
| rs2982557 | 152056369 | Bone mineral density | 3.10E-09 | 19801982 |
| rs2982556 | 152056842 | Bone mineral density | 5.00E-09 | 19801982 |
| rs2982554 | 152058010 | Bone mineral density | 4.80E-09 | 19801982 |
| rs3020349 | 152058268 | Bone mineral density | 5.50E-09 | 19801982 |
| rs3020300 | 152058844 | Bone mineral density | 8.00E-09 | 19801982 |
| rs2982552 | 152059563 | Bone mineral density | 1.50E-09 | 19801982 |
| rs2982551 | 152061210 | Bone mineral density | 2.10E-09 | 19801982 |
| rs3020301 | 152061579 | Bone mineral density | 2.00E-09 | 19801982 |
| rs1415194 | 152063998 | Bone mineral density | 5.00E-10 | 19801982 |
| rs1999807 | 152064199 | Bone mineral density | 5.20E-10 | 19801982 |
| rs3020304 | 152064464 | Bone mineral density | 1.70E-09 | 19801982 |
| rs3020306 | 152065886 | Bone mineral density | 4.80E-10 | 19801982 |
| rs3020307 | 152067244 | Bone mineral density | 5.40E-10 | 19801982 |
| rs1856057 | 152067869 | Bone mineral density | 3.30E-10 | 19801982 |
| rs1999805\* | 152068364 | Bone mineral density | 3.40E-10 | 19801982 |
| rs3020308 | 152068685 | Bone mineral density | 3.70E-10 | 19801982 |
| rs2982575 | 152069791 | Bone mineral density | 8.00E-10 | 19801982 |
| rs2152750 | 152070145 | Bone mineral density | 3.20E-10 | 19801982 |
| rs2982567 | 152075487 | Bone mineral density | 2.90E-10 | 19801982 |
| rs11155811 | 152077846 | Bone mineral density | 7.40E-10 | 19801982 |
| rs1124674 | 152080735 | Bone mineral density | 1.00E-10 | 19801982 |
| rs2504071 | 152084862 | Bone mineral density | 1.50E-10 | 19801982 |
| rs1890010 | 152085275 | Bone mineral density | 9.50E-09 | 19801982 |
| rs2504069 | 152085517 | Bone mineral density | 9.50E-09 | 19801982 |
| rs2504063\* | 152090707 | Bone mineral density | 6.10E-11 | 20096396 |
| rs1415193 | 152092638 | Bone mineral density | 3.50E-09 | 19801982 |
| rs543650\* | 152110943 | Height | 1.20E-17 | 20881960 |
| rs488133\* | 152125444 | Height | 1.20E-10 | 21194676 |
| rs827423 | 152156197 | Height | 3.40E-09 | 20881960 |
| rs827421 | 152157122 | Height | 3.00E-09 | 20881960 |
| rs3853250 | 152159900 | Height | 6.40E-09 | 20881960 |
| rs9397448 | 152161066 | Height | 7.30E-09 | 20881960 |
| rs4870056 | 152162227 | Height | 2.90E-09 | 20881960 |
| rs2234693 | 152163335 | Height | 9.40E-09 | 20881960 |
| rs7739085 | 152164548 | Height | 5.00E-09 | 20881960 |
| rs9322332 | 152166801 | Height | 4.40E-09 | 20881960 |
| rs9479130 | 152168456 | Height | 3.40E-09 | 20881960 |
| rs2982694 | 152285687 | Sudden cardiac arrest | 3.90E-12 | 21658281 |
| rs9340996 | 152342788 | Lipid level measurements | 2.90E-11 | 23063622 |
| rs3020418 | 152345162 | Height | 7.10E-09 | 20881960 |
| rs2982712 | 152358179 | Anthropometric traits | 3.70E-10 | 23563607 |

**Table B**: *ESR1* variants identified through the GRASP catalog of Genome-Wide SNP-Phenotype associations([56](#_ENREF_56)) at a p-value < 1 x 10-9. Pubmed IDs for the relevant studies are listed in the rightmost column. Variants marked with “\*” have more than one significant association, but only the strongest associations for each variant were reported.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|   | **rs851984** | **rs1285057** | **rs543650** | **rs488133** | **rs2071454** | **TA repeat** | **rs2077647** | **rs2234693** | **rs9340799** | **rs988328** | **rs1801132** | **rs3020327** | **rs3020329** | **rs2144025** |  |
| rs1285057 | **0.43** |  |  |  |  |  |  |  |  |  |  |  |  |  | rs1285057 |
| *0.07* |  |  |  |  |  |  |  |  |  |  |  |  |  |
| rs543650 | **0.16** | **0.41** |  |  |  |  |  |  |  |  |  |  |  |  | rs543650 |
| *0.01* | *0.06* |  |  |  |  |  |  |  |  |  |  |  |  |
| rs488133 | **0.17** | **0.15** | **0.93** |  |  |  |  |  |  |  |  |  |  |  | rs488133 |
| *0.01* | *0.01* | *0.66* |  |  |  |  |  |  |  |  |  |  |  |
| rs2071454 | **0.63** | **0.59** | **1.00** | **0.98** |  |  |  |  |  |  |  |  |  |  | rs2071454 |
| *0.03* | *0.08* | *0.08* | *0.06* |  |  |  |  |  |  |  |  |  |  |
| TA repeat | **0.08** | **0.41** | **0.63** | **0.75** | **0.78** |  |  |  |  |  |  |  |  |  | TA repeat |
| *0.00* | *0.08* | *0.28* | *0.30* | *0.07* |  |  |  |  |  |  |  |  |  |
| rs2077647 | **0.00** | **0.56** | **0.93** | **0.89** | **1.00** | **0.86** |  |  |  |  |  |  |  |  | rs2077647 |
| *0.00* | *0.18* | *0.50* | *0.37* | *0.14* | *0..62* |  |  |  |  |  |  |  |  |
| rs2234693 | **0.03** | **0.46** | **0.80** | **0.88** | **0.83** | **0.67** | **0.68** |  |  |  |  |  |  |  | rs2234693 |
| *0.00* | *0.13* | *0.36* | *0.34* | *0.10* | *0.36* | *0.46* |  |  |  |  |  |  |  |
| rs9340799 | **0.17** | **0.36** | **0.94** | **0.88** | **1.00** | **0.71** | **0.71** | **0.89** |  |  |  |  |  |  | rs9340799 |
| *0.01* | *0.12* | *0.31* | *0.19* | *0.08* | *0.24* | *0.30* | *0.47* |  |  |  |  |  |  |
| rs988328 | **0.14** | **0.01** | **0.10** | **0.22** | **0.29** | **0.01** | **0.04** | **0.29** | **0.33** |  |  |  |  |  | rs988328 |
| *0.01* | *0.00* | *0.00* | *0.02* | *0.07* | *0.00* | *0.00* | *0.01* | *0.01* |  |  |  |  |  |
| rs1801132 | **0.54** | **0.02** | **0.14** | **0.10** | **0.23** | **0.05** | **0.17** | **0.24** | **0.49** | **0.85** |  |  |  |  | rs1801132 |
| *0..05* | *0.00* | *0.01* | *0.01* | *0.03* | *0.00* | *0.01* | *0.02* | *0.04* | *0.44* |  |  |  |  |
| rs3020327 | **0.01** | **0.22** | **0.33** | **0.96** | **0.15** | **0.00** | **0.15** | **0.14** | **0.05** | **0.49** | **0.54** |  |  |  | rs3020327 |
| *0.00* | *0.01* | *0.01* | *0.05* | *0.02* | *0.00* | *0.00* | *0.00* | *0.00* | *0.17* | *0.13* |  |  |  |
| rs3020329 | **0.30** | **0.16** | **0.18** | **0.24** | **0.19** | **0.15** | **0.20** | **0.11** | **0.01** | **0.41** | **0.25** | **0.77** |  |  | rs3020329 |
| *0.02* | *0.02* | *0.01* | *0.01* | *0.01* | *0.01* | *0.02* | *0.00* | *0.00* | *0.08* | *0.05* | *0.20* |  |  |
| rs2144025 | **0.25** | **0.22** | **0.50** | **0.61** | **0.34** | **0.01** | **0.24** | **0.11** | **0.11** | **0.51** | **0.46** | **0.88** | **0.76** |  | rs2144025 |
| *0.01* | *0.02* | *0.03* | *0.04* | *0.07* | *0.00* | *0.01* | *0.00* | *0.00* | *0.21* | *0.17* | *0.48* | *0.33* |  |
| rs3798577 | **0.03** | **0.26** | **0.10** | **0.12** | **0.25** | **0.02** | **0.02** | **0.00** | **0.01** | **0.10** | **0.09** | **0.29** | **0.10** | **0.14** | rs3798577 |
| *0.00* | *0.04* | *0.01* | *0.01* | *0.01* | *0.00* | *0.00* | *0.00* | *0.00* | *0.00* | *0.00* | *0.01* | *0.00* | *0.00* |
|   | **rs851984** | **rs1285057** | **rs543650** | **rs488133** | **rs2071454** | **TA repeat** | **rs2077647** | **rs2234693** | **rs9340799** | **rs988328** | **rs1801132** | **rs3020327** | **rs3020329** | **rs2144025** |   |

**Table C**: Linkage disequilibrium (LD) of *ESR1* SNPs in the Stanley PFC tissues. Upper values are D’ while the lower values show LD correlation R squared.



Table D: Promoter and Intron4 variants identified by targeted amplicon sequencing. The first 6 variants are in the promoter. Chi-squared p-values and ANODEV P (analysis of deviance) reflect association with AEI (ratios >2) in the 9 sequenced samples. Variants without rs numbers are listed by RefSeqGene position (pos). The RefSeqGene ID was NG\_008493.





**Table E:** Allele frequencies, location, and basic allele tests of all *ESR1* SNPs from the GAIN Bipolar Disorder data set, showing the association with number of hypomania episodes. Analyses were conducted with all subjects, and with males and females separately. rs2144025 stands out as most significant among females. Two highly significant scores among males are compromised by the low MAF in this cohort**.**





**Table F:** Association of rs2144025 and other GWAS SNPs across the *ESR1* locus with the presence of grandiose delusions in the GAIN Schizophrenia GWAS.



**Table G**: Association data for rs2144025 and other GWAS SNPs across the *ESR1* locus in the GAIN ADHD GWAS for ADHD subjects with comorbid psychological diagnoses.

| Childhood psychiatric diagnosis RSID | Position | Minor Allele Frequency | Basic allele test P | Dominant allele test P |
| --- | --- | --- | --- | --- |
| rs851972 | 151975773 | 37% | 0.9 | 0.54 |
| rs10484920 | 151979047 | 6% | 0.28 | 0.27 |
| rs9397441 | 151982315 | 10% | 0.58 | 0.61 |
| rs866457 | 151982413 | 43% | 0.47 | 0.32 |
| rs9371226 | 151986594 | 10% | 0.46 | 0.52 |
| rs1293955 | 151990954 | 26% | 0.72 | 0.92 |
| rs1293944 | 151997546 | 48% | 0.18 | 0.11 |
| rs1293940 | 151999091 | 48% | 0.18 | 0.11 |
| rs851995 | 152005534 | 49% | 0.12 | 0.11 |
| rs851993 | 152006011 | 40% | 0.2 | 0.14 |
| rs3020332 | 152008924 | 41% | 0.46 | 0.14 |
| rs2941740 | 152009638 | 39% | 0.65 | 0.27 |
| rs10214867 | 152009654 | 11% | 0.44 | 0.5 |
| rs851996 | 152016803 | 38% | 0.34 | 0.05 |
| rs851985 | 152020390 | 35% | 0.35 | 0.14 |
| rs2347637 | 152028479 | 17% | 0.42 | 0.37 |
| rs851975 | 152031303 | 21% | 0.91 | 0.76 |
| rs12525163 | 152040291 | 23% | 0.77 | 0.48 |
| rs2982565 | 152051854 | 17% | 0.6 | 0.81 |
| rs2982562 | 152052601 | 48% | 0.09 | 9.78E-03 |
| rs3020343 | 152054363 | 49% | 0.06 | 5.91E-03 |
| rs2982560 | 152055606 | 50% | 0.05 | 5.91E-03 |
| rs3020345 | 152056368 | 50% | 0.05 | 5.91E-03 |
| rs2982557 | 152056369 | 50% | 0.05 | 5.91E-03 |
| rs3020346 | 152056771 | 50% | 0.04 | 0.68 |
| rs2982556 | 152056842 | 48% | 0.08 | 6.37E-03 |
| rs2982554 | 152058010 | 47% | 0.03 | 0.54 |
| rs2982552 | 152059563 | 48% | 0.08 | 7.85E-03 |
| rs2982551 | 152061210 | 49% | 0.06 | 4.39E-03 |
| rs3020301 | 152061579 | 50% | 0.05 | 3.20E-03 |
| rs1415194 | 152063998 | 48% | 0.02 | 0.58 |
| rs1999807 | 152064199 | 48% | 0.03 | 0.62 |
| rs3020303 | 152064454 | 48% | 0.03 | 0.62 |
| rs3020304 | 152064464 | 49% | 0.06 | 2.30E-03 |
| rs3020305 | 152064487 | 48% | 0.02 | 0.58 |
| rs3020306 | 152065886 | 48% | 0.08 | 4.74E-03 |
| rs1856057 | 152067869 | 48% | 0.02 | 0.58 |
| rs1999805 | 152068364 | 48% | 7.78E-03 | 0.36 |
| rs2982575 | 152069791 | 50% | 0.04 | 0.78 |
| rs2152750 | 152070145 | 48% | 0.02 | 0.58 |
| rs1361024 | 152070928 | 5% | 0.11 | 0.33 |
| rs1124674 | 152080735 | 43% | 0.18 | 0.51 |
| rs2504071 | 152084862 | 48% | 0.1 | 0.41 |
| rs2504069 | 152085517 | 31% | 0.27 | 0.12 |
| rs17081662 | 152086685 | 2% | 0.36 | 0.36 |
| rs2485209 | 152089768 | 49% | 0.13 | 0.97 |
| rs4870053 | 152092749 | 26% | 0.7 | 0.46 |
| rs7767143 | 152095694 | 21% | 0.5 | 0.38 |
| rs17828471 | 152097405 | 8% | 0.75 | 0.74 |
| rs17081679 | 152101823 | 6% | 0.64 | 0.63 |
| rs528529 | 152102939 | 48% | 0.67 | 0.35 |
| rs11299395 | 152106139 | 4% | 0.62 | 0.61 |
| rs17755779 | 152115403 | 2% | 0.09 | 0.09 |
| rs9478243 | 152117458 | 5% | 0.15 | 0.41 |
| rs9479117 | 152117685 | 15% | 0.39 | 0.78 |
| rs538098 | 152120869 | 3% | 0.48 | 0.47 |
| rs9478244 | 152122037 | 18% | 0.51 | 0.91 |
| rs58202367 | 152122291 | 0% | 0.68 | 0.68 |
| rs17828760 | 152123716 | 3% | 0.25 | 0.24 |
| rs6903180 | 152125231 | 3% | 0.9 | 0.89 |
| rs488133 | 152125444 | 35% | 0.9 | 0.94 |
| rs2077647 | 152129077 | 50% | 0.74 | 0.18 |
| rs576330 | 152132175 | 3% | 0.59 | 0.59 |
| rs10484922 | 152132317 | 9% | 0.92 | 0.85 |
| rs34978802 | 152132431 | 2% | 0.36 | 0.35 |
| rs73780871 | 152147597 | 0% | 0.68 | 0.68 |
| rs7759411 | 152148870 | 2% | 0.99 | 0.99 |
| rs11969288 | 152149200 | 0% | 0.68 | 0.68 |
| rs62442038 | 152149586 | 5% | 0.11 | 0.11 |
| rs12665044 | 152149872 | 12% | 0.97 | 0.97 |
| rs36120076 | 152151566 | 9% | 0.91 | 0.84 |
| rs7761133 | 152151863 | 14% | 0.98 | 0.97 |
| rs17761320 | 152151965 | 5% | 0.92 | 0.92 |
| rs6937568 | 152153964 | 1% | 0.53 | 0.53 |
| rs6902771 | 152157881 | 48% | 0.5 | 0.63 |
| rs62442039 | 152158090 | 4% | 0.55 | 0.61 |
| rs2234693 | 152163335 | 47% | 0.53 | 0.59 |
| rs9340799 | 152163381 | 38% | 0.54 | 0.85 |
| rs7774230 | 152164239 | 47% | 0.57 | 0.64 |
| rs3936674 | 152167311 | 35% | 0.6 | 0.89 |
| rs1709182 | 152175357 | 37% | 0.55 | 0.99 |
| rs827420 | 152177529 | 41% | 0.66 | 0.87 |
| rs827419 | 152177663 | 38% | 0.75 | 0.88 |
| rs9479134 | 152188995 | 2% | 0.27 | 0.27 |
| rs5880948 | 152190236 | 8% | 0.44 | 0.46 |
| rs62443560 | 152190476 | 9% | 0.69 | 0.73 |
| rs9340835 | 152199931 | 35% | 0.64 | 0.48 |
| rs9322334 | 152200041 | 24% | 0.95 | 0.89 |
| rs9322335 | 152200129 | 24% | 0.91 | 0.78 |
| rs9322336 | 152200430 | 22% | 0.9 | 0.77 |
| rs4986934 | 152201875 | 4% | 0.16 | 0.15 |
| rs11155820 | 152204210 | 27% | 0.67 | 0.95 |
| rs4870059 | 152223532 | 2% | 0.28 | 0.27 |
| rs71575914 | 152227990 | 5% | 0.01 | 0.06 |
| rs1514347 | 152229445 | 32% | 0.85 | 0.94 |
| rs12204714 | 152235339 | 44% | 0.22 | 0.28 |
| rs9322343 | 152237759 | 3% | 0.37 | 0.36 |
| rs988328 | 152241150 | 21% | 0.69 | 0.31 |
| rs9479143 | 152245465 | 38% | 0.75 | 0.29 |
| rs9397456 | 152247152 | 31% | 0.62 | 0.11 |
| rs7739274 | 152258509 | 3% | 0.79 | 0.79 |
| rs6912184 | 152260206 | 31% | 0.77 | 0.46 |
| rs4363047 | 152262834 | 31% | 0.77 | 0.46 |
| rs9340894 | 152263380 | 8% | 0.29 | 0.27 |
| rs73005959 | 152270034 | 3% | 0.19 | 0.18 |
| rs35365822 | 152270364 | 15% | 0.57 | 0.68 |
| rs3020314 | 152270672 | 42% | 0.86 | 0.41 |
| rs7745370 | 152274260 | 16% | 0.46 | 0.54 |
| rs3020393 | 152278885 | 23% | 0.65 | 0.48 |
| rs3003921 | 152279514 | 27% | 0.61 | 0.34 |
| rs3020396 | 152279878 | 41% | 0.95 | 0.65 |
| rs1884051 | 152283279 | 41% | 0.99 | 0.6 |
| rs985192 | 152283478 | 26% | 0.66 | 0.38 |
| rs3003925 | 152284458 | 25% | 0.32 | 0.31 |
| rs6557177 | 152284821 | 17% | 0.38 | 0.4 |
| rs985694 | 152286625 | 23% | 0.4 | 0.25 |
| rs9340917 | 152287224 | 2% | 0.7 | 0.7 |
| rs1884049 | 152287367 | 23% | 0.4 | 0.25 |
| rs3020318 | 152289770 | 40% | 0.94 | 0.65 |
| rs73009815 | 152298397 | 2% | 0.32 | 0.31 |
| rs726281 | 152302578 | 31% | 0.13 | 0.08 |
| rs728524 | 152303437 | 2% | 0.17 | 0.17 |
| rs9397463 | 152304328 | 14% | 0.71 | 0.79 |
| rs926777 | 152305047 | 28% | 0.22 | 0.09 |
| rs9371236 | 152306346 | 2% | 0.85 | 0.85 |
| rs3020407 | 152307261 | 35% | 0.18 | 0.06 |
| **rs2144025** | **152307706** | **16%** | **6.20E-03** | **8.96E-04** |
| rs7743290 | 152309132 | 30% | 6.68E-03 | 0.07 |
| rs9340944 | 152313718 | 17% | 0.77 | 0.98 |
| rs722208 | 152322885 | 34% | 2.05E-03 | 0.05 |
| rs13216134 | 152328484 | 13% | 4.43E-05 | 3.64E-05 |
| rs9340955 | 152330201 | 2% | 0.1 | 0.09 |
| rs9340978 | 152333945 | 10% | 0.84 | 0.83 |
| rs9340994 | 152342713 | 8% | 0.16 | 0.18 |
| rs73009834 | 152344346 | 4% | 0.08 | 0.07 |
| rs2982701 | 152347010 | 33% | 0.04 | 0.16 |
| rs9478265 | 152348901 | 6% | 0.37 | 0.35 |
| rs926778 | 152355782 | 32% | 0.02 | 0.12 |
| rs2982712 | 152358179 | 45% | 0.05 | 0.52 |
| rs3020434 | 152358940 | 18% | 0.79 | 0.87 |
| rs2982720 | 152360650 | 38% | 6.58E-03 | 0.14 |
| rs3020368 | 152371190 | 13% | 0.2 | 0.18 |
| rs6913408 | 152378112 | 3% | 0.22 | 0.24 |
| rs9322354 | 152382014 | 14% | 7.05E-04 | 4.96E-04 |
| rs9341019 | 152382688 | 2% | 0.99 | 0.99 |
| rs72993651 | 152385568 | 3% | 0.37 | 0.36 |
| rs73781083 | 152388479 | 3% | 0.25 | 0.27 |
| rs9479193 | 152394779 | 14% | 4.83E-04 | 3.32E-04 |
| rs2747645 | 152396352 | 4% | 0.15 | 0.14 |
| rs2982896 | 152399493 | 23% | 0.8 | 0.61 |
| rs66465244 | 152407061 | 11% | 9.45E-06 | 9.60E-06 |
| rs3778092 | 152408273 | 11% | 9.45E-06 | 9.60E-06 |
| rs2982900 | 152414992 | 10% | 0.54 | 0.57 |
| rs9341056 | 152417142 | 3% | 0.79 | 0.79 |
| rs9341062 | 152419079 | 4% | 0.56 | 0.55 |
| rs3798577 | 152421130 | 46% | 0.27 | 0.53 |
| rs3798758 | 152421854 | 4% | 0.27 | 0.26 |
| rs2747648 | 152422335 | 5% | 0.97 | 0.84 |
| rs9341077 | 152423128 | 5% | 0.58 | 0.57 |
| rs9341086 | 152424534 | 4% | 0.27 | 0.26 |
| rs910416 | 152432902 | 49% | 0.42 | 0.9 |
| rs34133739 | 152434278 | 48% | 0.27 | 0.57 |
| rs73781642 | 152436453 | 3% | 0.48 | 0.47 |
| rs7450824 | 152438103 | 18% | 0.59 | 0.41 |
| rs2813549 | 152441239 | 21% | 0.89 | 0.87 |
| rs11970277 | 152441660 | 3% | 0.48 | 0.47 |
| rs2813554 | 152442338 | 24% | 0.91 | 0.79 |
| rs2250122 | 152443468 | 26% | 0.16 | 0.19 |
| rs2295190 | 152443744 | 9% | 0.3 | 0.3 |
| rs9383964 | 152444815 | 8% | 0.14 | 0.12 |
| rs2747654 | 152447099 | 24% | 0.91 | 0.79 |
| rs2747655 | 152447321 | 21% | 0.96 | 0.96 |
| rs9397486 | 152449900 | 34% | 0.44 | 0.44 |
| rs2459111 | 152450470 | 29% | 0.27 | 0.22 |
| rs6925149 | 152452759 | 5% | 0.2 | 0.19 |

**Table H:** Association data for rs2144025 and other GWAS SNPs across the *ES1* locus in the eMERGE Boston Children’s Hospital study of children and adolescents with comorbid psychological diagnoses. Allele frequencies, location, and basic allele tests of *ESR1* SNPs from The Gene Partnership (TGP) - eMERGE data set, testing an association with any diagnosed psychiatric disease in Caucasian females age 9 or older.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| SNP | Proxy | Distance | RSquared | DPrime | CEU MAF | Coordinate HG18 |
| rs2144025 | rs2144025 | 0 | 1 | 1 | 0.125 | 152349399 |
| rs2144025 | rs932477 | 3110 | 0.27 | 1 | 0.033 | 152346289 |
| rs2144025 | rs2179922 | 10606 | 0.27 | 1 | 0.033 | 152338793 |
| rs2144025 | rs9397074 | 22009 | 0.27 | 1 | 0.031 | 152371408 |
| rs2144025 | rs6932902 | 68818 | 0.22 | 0.56 | 0.067 | 152418217 |
| rs2144025 | rs9397080 | 72809 | 0.22 | 0.56 | 0.067 | 152422208 |
| rs2144025 | rs2273206 | 74605 | 0.22 | 0.56 | 0.075 | 152424004 |
| rs2144025 | rs974276 | 74714 | 0.22 | 0.56 | 0.083 | 152424113 |
| rs2144025 | rs985694 | 21081 | 0.20 | 0.51 | 0.150 | 152328318 |

**Table I**: LD and genomic coordinates for rs2144025 and *ESR1* SNPs with clinical associations and with D’ above 0.5 from SNAP ([57](#_ENREF_57)).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PWM** | **Strand** | **Ref** | **Alt** | **Match on:**Ref: GAACAAAATGCACATTTTGTGGACCAACT**T**GTTGTTTTAGATCTATTTTTGAAAACTCAAlt: GAACAAAATGCACATTTTGTGGACCAACT**C**GTTGTTTTAGATCTATTTTTGAAAACTCA |
| SIX5\_disc4 | - | 7.4 | -4.5 | W**T**GTAGTTTT |
| Zfp105 | - | 11.9 | 7.8 | HNHW**T**KTTDWTTRHD |

**Table J:** Regulatory DNA binding motifs altered by SNP rs2144025, generated by Haploreg([58](#_ENREF_58)).

**Liver**

**Breast**

ESR1-203

ESR1-008

ESR1-202

ESR1-201

ESR1-001

ESR1-203

ESR1-008

Fig A: Expression of isoforms in brain and other tissues from the GTEx dataset.



Fig B: Absolute allelic mRNA ratios measured with rs3798577 and rs1801132 in different tissues. Subjects heterozygous for rs2144025 are designated with an asterisk. A dotted line in each graph marks the cut-off ratio (1.4) determining a finding of AEI. Allelic ratios tended to be lower in these tissues than in the Stanley cohort tissues, with only a few just exceeding 2, detected with rs1801132, comparable to allelic ratios in the control group in Fig. 1B. In the brain tissues from the Miami Dade County Brain Bank, 15%of subjects were heterozygous for rs2144025, also comparable to the control group in Fig. 1B.While AEI was detectable, it was not significantly associated with rs2144025

**ESR1-203**

**ESR1-008**

\*

\*

**Fig C:** Real-time PCR assays of ESR1 mRNA in PFC tissues from the Stanley collection. qRT-PCR was performed employing primers for *beta-actin* and the 3’UTR

(ESR1-203) and exon4 of *ESR1* mRNA, and cycle threshold differences determined(Ct).Values Shown are normalized relative levels (linear scale), mean ± SD.

 Upper panel: (\*) p=0.02, *CC versus CT* controls;; lower panel: \*: P=0.03,*CT & TT* BP *versus CT & TT* schizophrenia



Fig D: Top scoring RNA folding structure of 650 base pairs surrounding rs2144025*C>T* was conducted *in silico* using Mfold software. In each structure the position of the SNP is designated by a red arrow (“U” in the left structure and “C” in the right structure).

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