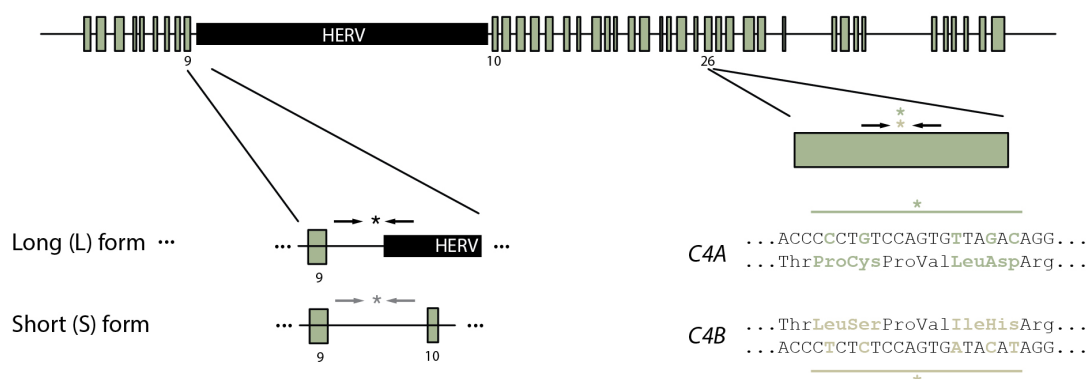
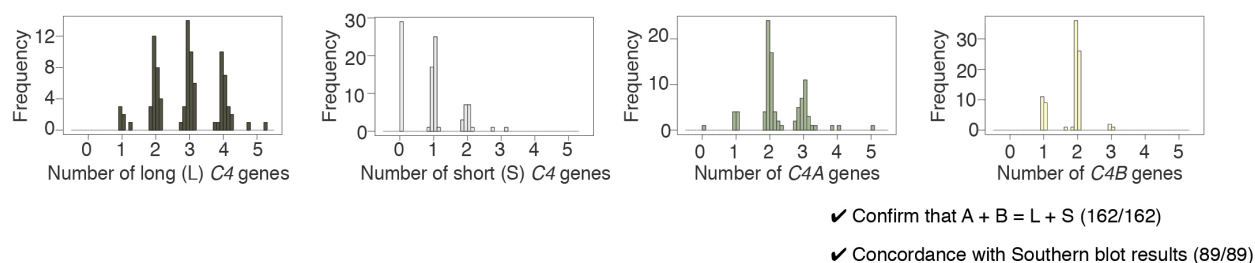


**Extended Data Figure 1**

- a** Molecular assays to measure the copy number of each *C4* gene type (A or B isotype; long or short form) in each genome sampled.



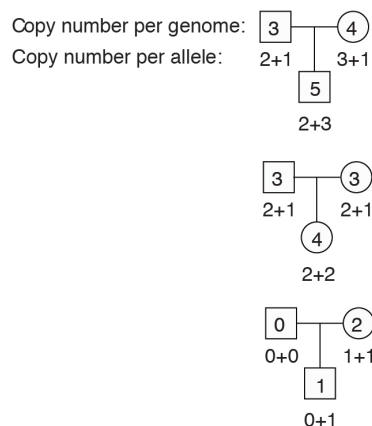
- b** Measure copy number of each *C4* gene type in 162 individuals' genomes (from HapMap).



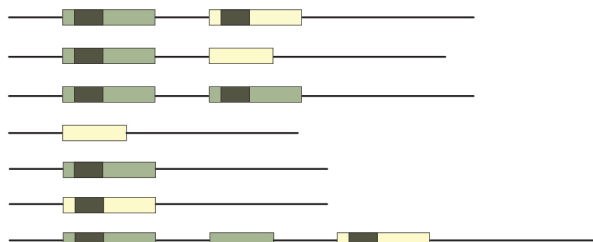
- c** Molecular assays to measure the copy number of compound structural forms of *C4* (e.g. *C4AL*).



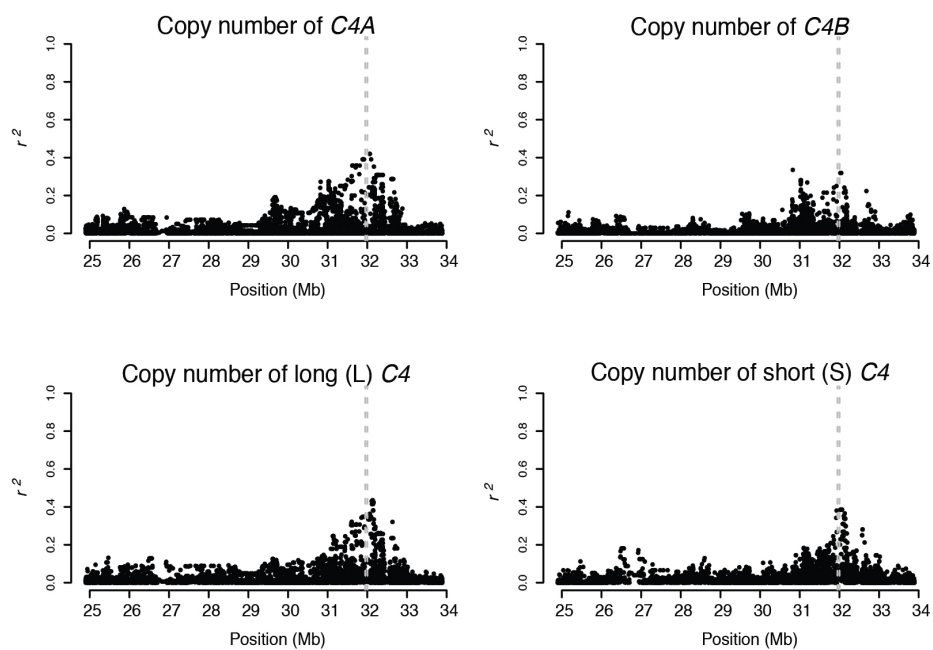
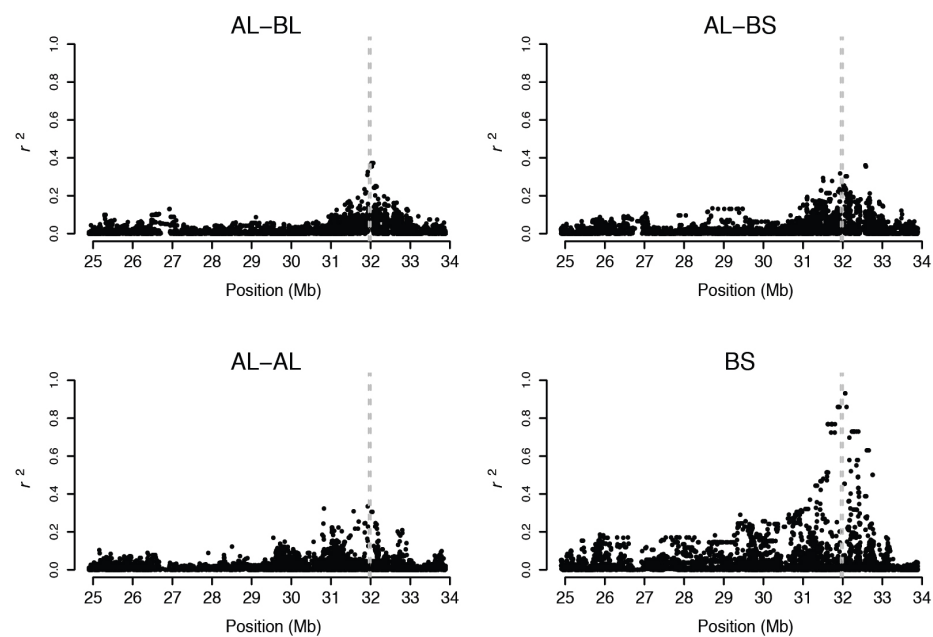
- d** Use inheritance in trios to infer copy number on shared and unshared chromosomal copies.

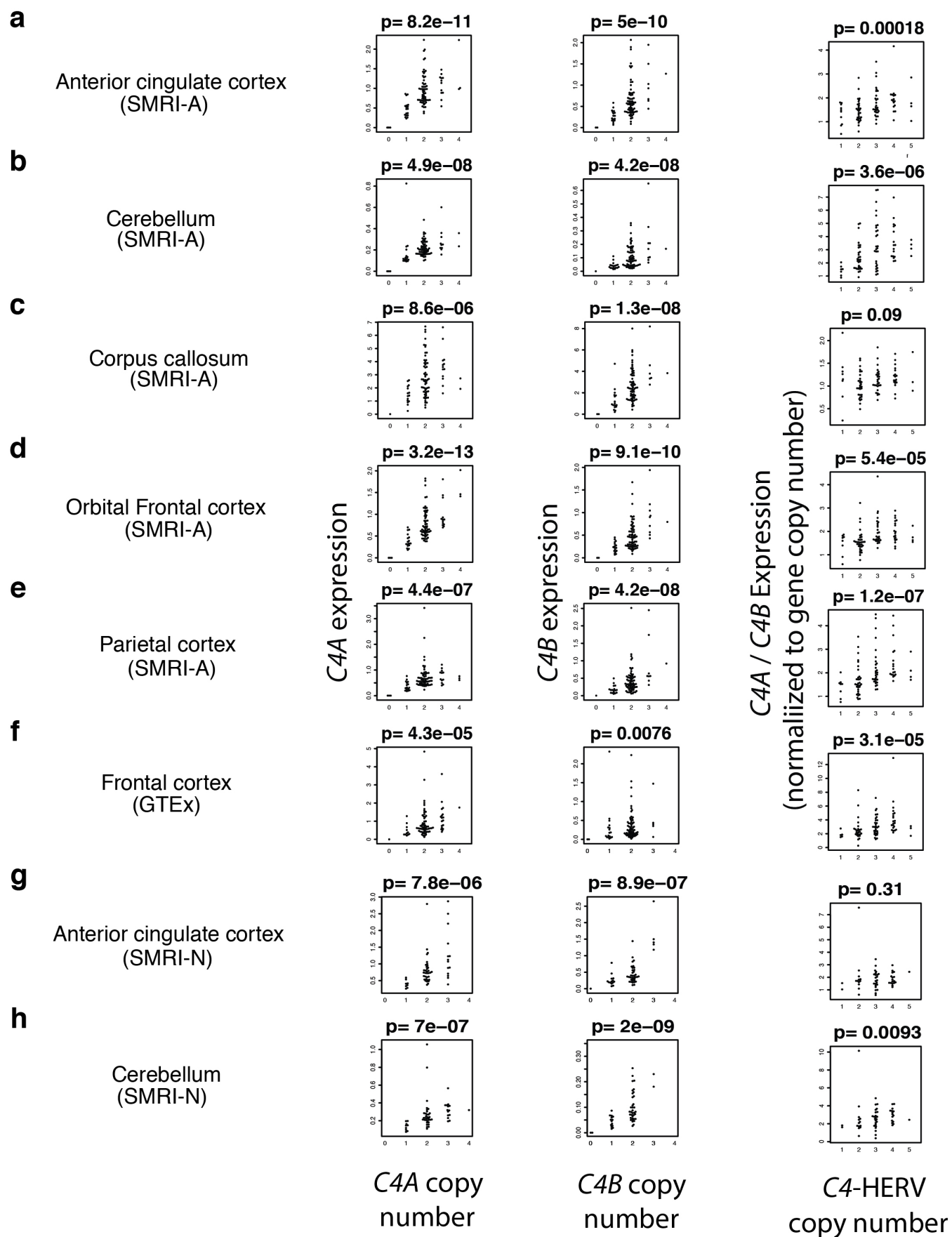


- e** Infer the *C4* gene contents of the founder chromosomes in each trio. Where possible, use existing sequence data to also infer gene order.



**Extended Data Figure 2**

**a****b****Extended Data Figure 3**

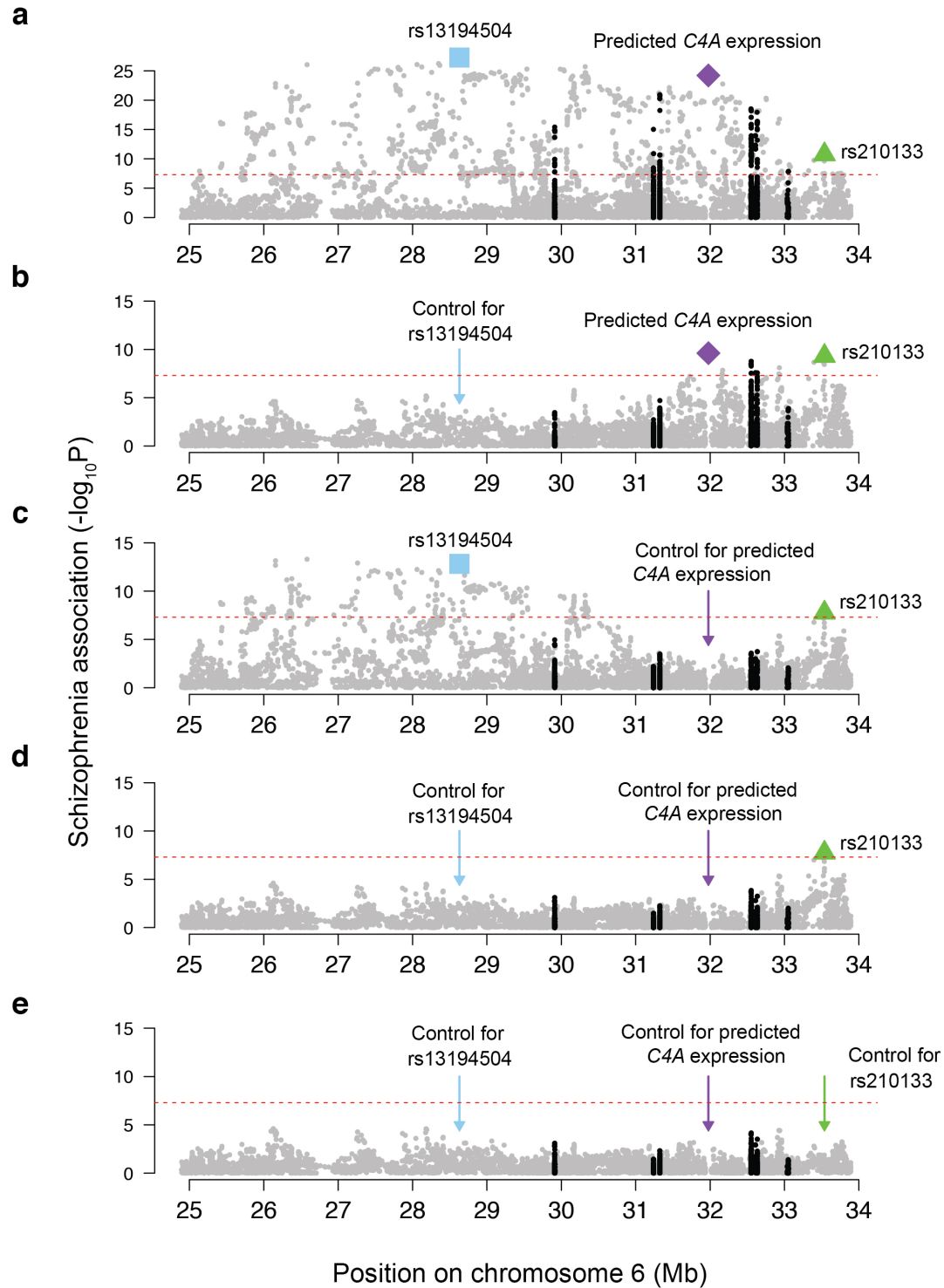


**Extended Data Figure 4**



|  | Association of SCZ with this<br>variant (unconditioned analysis) |          |           | Association of SCZ with this<br>variant (joint analysis with<br>predicted <i>C4A</i> expression as a<br>covariate) |          |           | Association of SCZ with<br>genetically predicted <i>C4A</i><br>expression (joint analysis with<br>this variant as a covariate) |          |           |
|--|--|----------|-----------|--|----------|-----------|--|----------|-----------|
|  | <u>p</u>   | <u>β</u> | <u>SE</u> | <u>p</u>   | <u>β</u> | <u>SE</u> | <u>p</u>   | <u>β</u> | <u>SE</u> |
| <b>Expression predictors (derived from <i>post mortem</i> brain RNA analysis)</b>      |  |          |           |  |          |           |  |          |           |
| <i>C4A</i> expression (genetic<br>prediction from <i>C4</i> structure)                 | 3.60E-24   | 0.247    | 0.024     | NA   | NA       | NA        | NA   | NA       | NA        |
| <i>C4B</i> expression (genetic<br>prediction from <i>C4</i> structure)                 | 2.31E-07   | -0.092   | 0.018     | 0.71   | 0.008    | 0.021     | 2.35E-18   | 0.253    | 0.029     |
| <b>Copy number of <i>C4</i> structural features</b>                                    |  |          |           |  |          |           |  |          |           |
| <i>C4A</i> genes   | 6.31E-19   | 0.112    | 0.013     | 0.45   | -0.023   | 0.030     | 6.54E-07   | 0.287    | 0.058     |
| <i>C4B</i> genes   | 1.45E-04   | -0.066   | 0.017     | 0.63   | 0.009    | 0.019     | 4.58E-21   | 0.252    | 0.027     |
| Long <i>C4</i> genes (with HERV)   | 7.09E-23   | 0.084    | 0.009     | 0.17   | 0.029    | 0.021     | 4.89E-03   | 0.170    | 0.060     |
| Short <i>C4</i> genes (no HERV)  | 3.94E-14   | -0.085   | 0.011     | 0.32   | -0.015   | 0.015     | 7.38E-12   | 0.225    | 0.033     |
| Total <i>C4</i> copy number**  | 9.41E-15   | 0.123    | 0.016     | 1.00   | 0.000    | 0.025     | 5.40E-11   | 0.247    | 0.038     |
| <b>Specific <i>C4</i> locus structures (haplotypes of one or more <i>C4</i> genes)</b> |  |          |           |  |          |           |  |          |           |
| BS   | 2.29E-19   | -0.171   | 0.019     | 0.16   | -0.045   | 0.032     | 1.10E-06   | 0.200    | 0.041     |
| AL-BS  | 0.03   | -0.027   | 0.013     | 0.62   | 0.007    | 0.013     | 3.39E-23   | 0.250    | 0.025     |
| AL-BL  | 6.16E-07   | 0.058    | 0.012     | 0.41   | 0.011    | 0.013     | 6.34E-19   | 0.238    | 0.027     |
| AL-AL  | 2.09E-06   | 0.093    | 0.020     | 0.56   | -0.013   | 0.023     | 2.49E-19   | 0.256    | 0.028     |
| <b>Combinations of <i>C4</i> locus structure and flanking SNP haplotype</b>            |  |          |           |  |          |           |  |          |           |
| AL-BS-4  | 0.21   | -0.027   | 0.022     | 0.95   | -0.002   | 0.022     | 7.99E-24   | 0.247    | 0.025     |
| AL-BS-2  | 0.35   | -0.031   | 0.033     | 0.80   | -0.008   | 0.033     | 5.45E-24   | 0.247    | 0.024     |
| AL-BS-3  | 0.34   | -0.028   | 0.029     | 0.91   | -0.003   | 0.030     | 5.69E-24   | 0.247    | 0.024     |
| AL-BS-5  | 0.07   | 0.053    | 0.029     | 0.01   | 0.077    | 0.029     | 5.73E-25   | 0.252    | 0.024     |
| AL-BS-1  | 0.04   | -0.064   | 0.031     | 0.19   | -0.040   | 0.031     | 1.32E-23   | 0.245    | 0.024     |
| AL-BS-other  | 0.30   | -0.023   | 0.022     | 0.92   | 0.002    | 0.023     | 6.19E-24   | 0.247    | 0.025     |
| AL-BL-2  | 0.03   | 0.036    | 0.017     | 0.77   | 0.005    | 0.017     | 3.52E-23   | 0.246    | 0.025     |
| AL-BL-3  | 2.15E-03   | 0.042    | 0.014     | 0.55   | 0.008    | 0.014     | 3.28E-22   | 0.243    | 0.025     |
| AL-BL-1  | 0.35   | 0.032    | 0.034     | 0.92   | 0.003    | 0.035     | 5.55E-24   | 0.247    | 0.024     |
| AL-BL-other  | 0.23   | 0.029    | 0.024     | 0.95   | 0.002    | 0.024     | 7.37E-24   | 0.247    | 0.025     |
| AL-AL-1  | 0.01   | 0.074    | 0.028     | 0.38   | -0.026   | 0.029     | 9.42E-23   | 0.255    | 0.026     |
| AL-AL-2  | 3.33E-04   | 0.097    | 0.027     | 0.94   | -0.002   | 0.029     | 2.31E-21   | 0.248    | 0.026     |
| <b>Alternative hypotheses</b>  |  |          |           |  |          |           |  |          |           |
| C4B nulls (for whom total<br>C4B copy number = 0) *                                    | 0.36   | 0.061    | 0.066     |  |          |           |  |          |           |

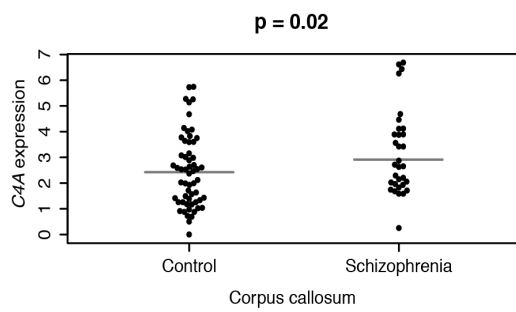
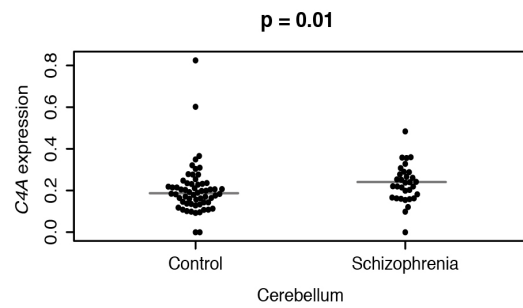
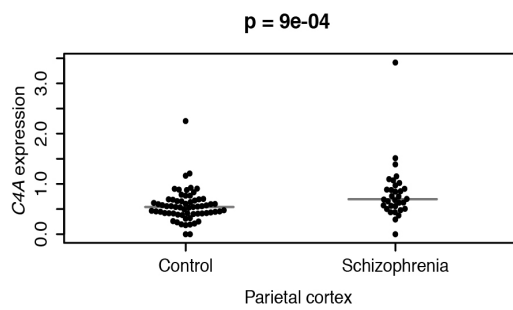
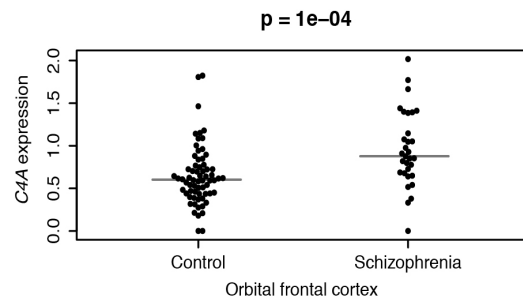
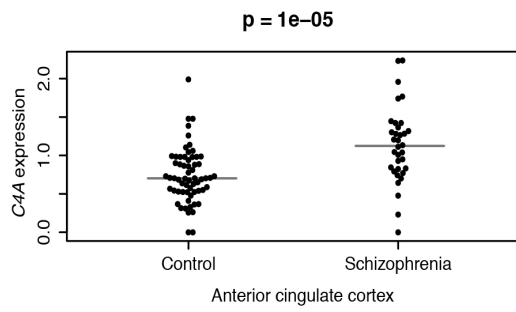
## Extended Data Figure 5



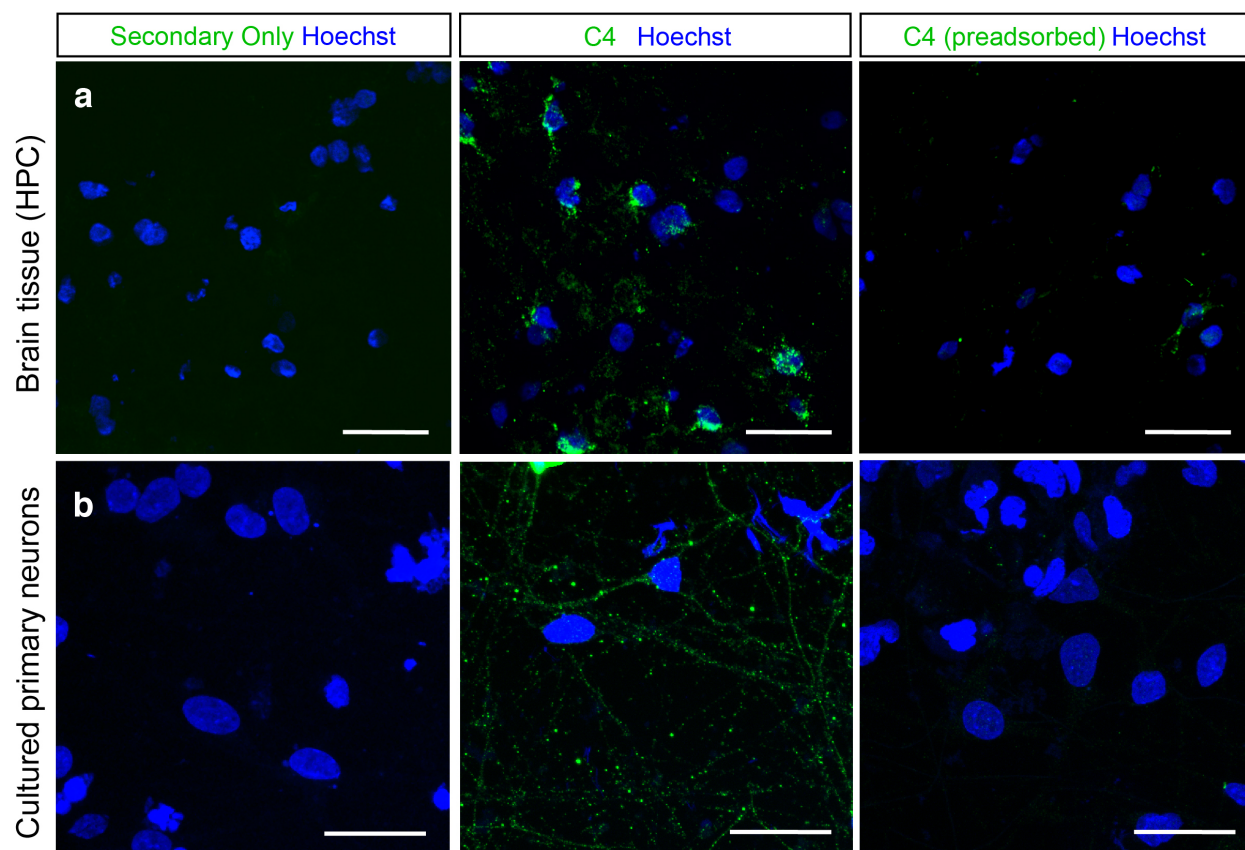
**Extended Data Figure 6**

| <u>Variants included in analysis</u> | <u>rs13194504</u> | <u>Predicted<br/>C4A<br/>expression<br/>(C4Aexp)</u> | <u>Association p-value</u> |                      |                    |
|--------------------------------------|-------------------|--|----------------------------|----------------------|--------------------|
|                                      |                   |  | <u>HLA-B*0801</u>          | <u>HLA-DRB1*0301</u> | <u>HLA-DQB1*02</u> |
| rs13194504                           | 5.50E-28          |  |                            |                      |                    |
| C4Aexp                               |                   | 3.60E-24   |                            |                      |                    |
| B*0801                               |                   |  | 1.20E-21                   |                      |                    |
| DRB1*0301                            |                   |  |                            | 6.40E-19             |                    |
| DQB1*02                              |                   |  |                            |                      | 6.25E-17           |
| rs13194504, C4Aexp                   | 8.00E-14          | 7.80E-10   |                            |                      |                    |
| rs13194504, B*0801                   | 5.75E-11          |  | 2.00E-04                   |                      |                    |
| rs13194504, DRB1*0301                | 2.89E-15          |  |                            | 6.20E-06             |                    |
| rs13194504, DQB1*02                  | 9.60E-19          |  |                            |                      | 1.82E-07           |
| rs13194504, C4Aexp, B*0801           | 6.94E-11          | 8.23E-07   | 0.96                       |                      |                    |
| rs13194504, C4Aexp, DRB1*0301        | 1.39E-12          | 2.18E-05   |                            | 0.41                 |                    |
| rs13194504, C4Aexp, DQB1*02          | 3.06E-13          | 1.03E-04   |                            |                      | 0.03               |

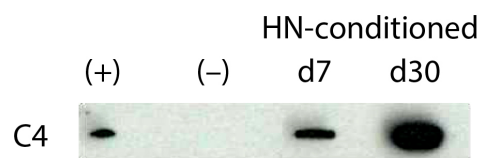
## Extended Data Figure 7



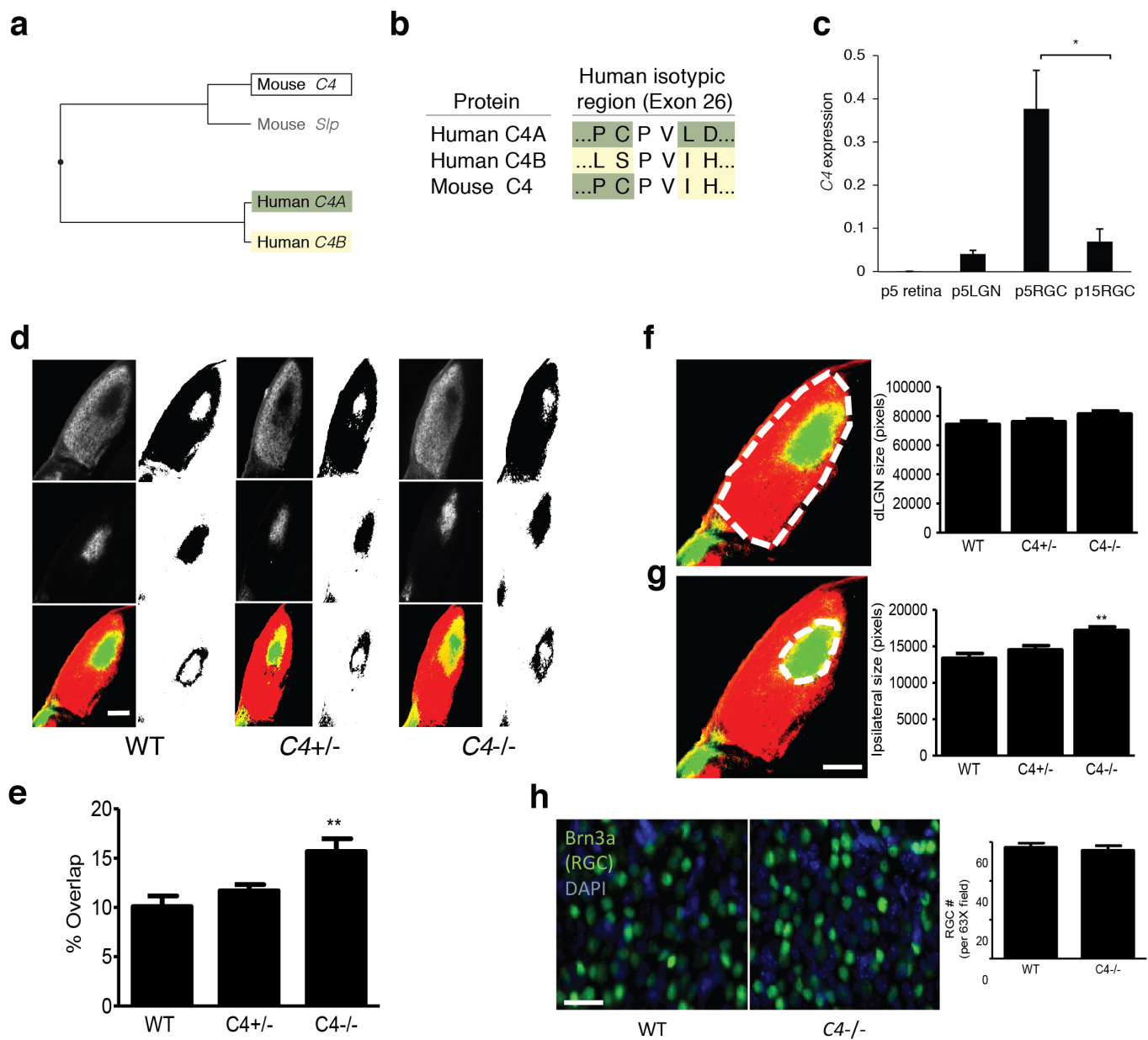
**Extended Data Figure 8**



**C**



**Extended Data Figure 9**



**Extended Data Figure 10**