Analysis of Copy Number Variations in Brain DNA from Patients with Schizophrenia and Other Psychiatric Disorders

Supplemental Information

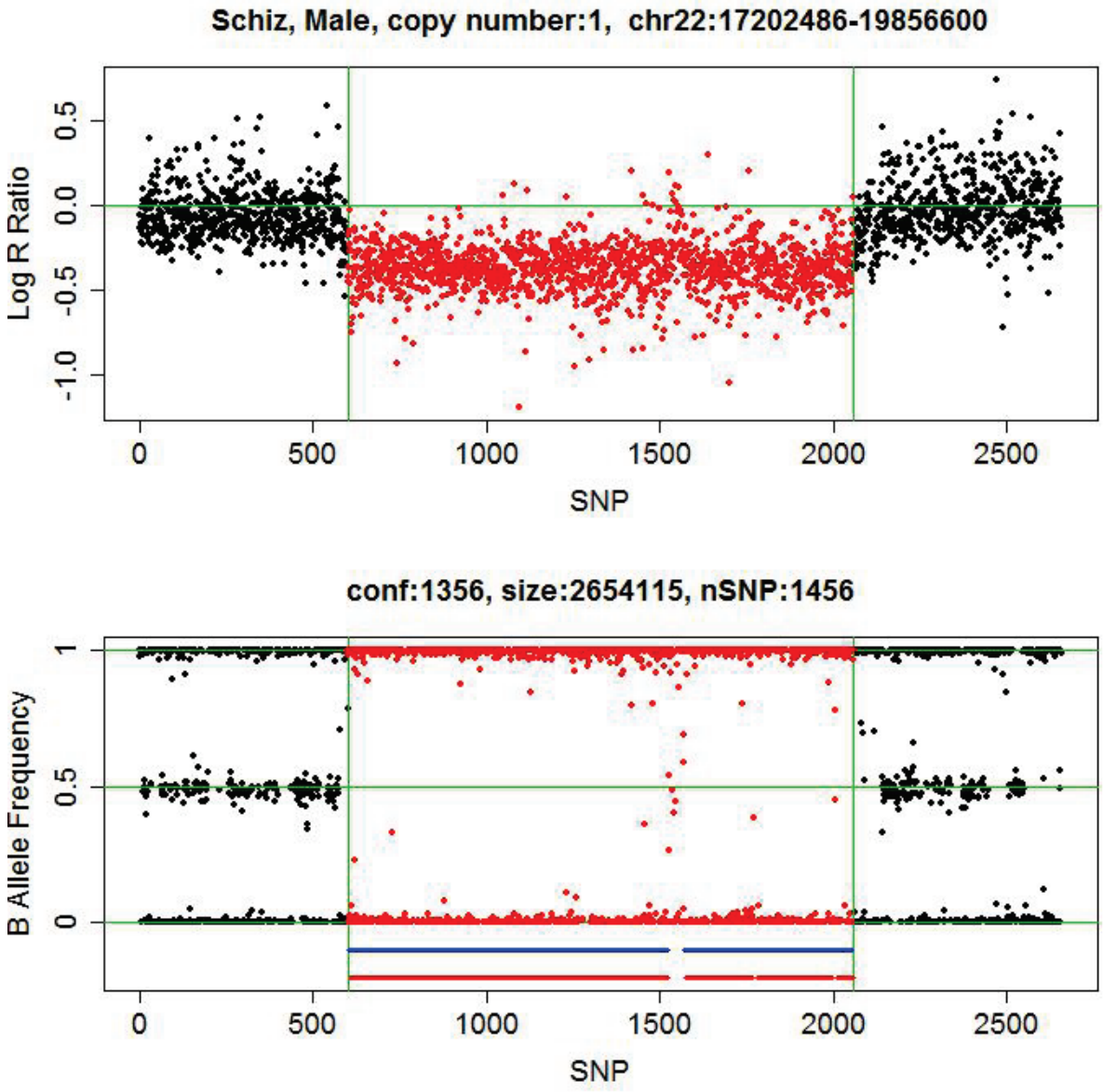

Figure S1. A 2.7 Mb deletion in 22q11 in a male patient with schizophrenia (Sample 1). The upper plot depicts Log R ratios of single nucleotide polymorphism (SNP) probe intensities. On top of the plot the diagnosis (schiz = schizophrenia), sex of the patient (male), copy number (1 = deletion) and the copy number variation (CNV) location are provided. Lower plot is the beta allele frequency plot. On top of the lower plot, a confidence interval of the CNV call, the size of the CNV and the number of SNPs in the CNV call are provided. The blue and red horizontal lines in the lower figure represent CNV locations according to *PennCNV* and *QuantiSNP*, respectively.

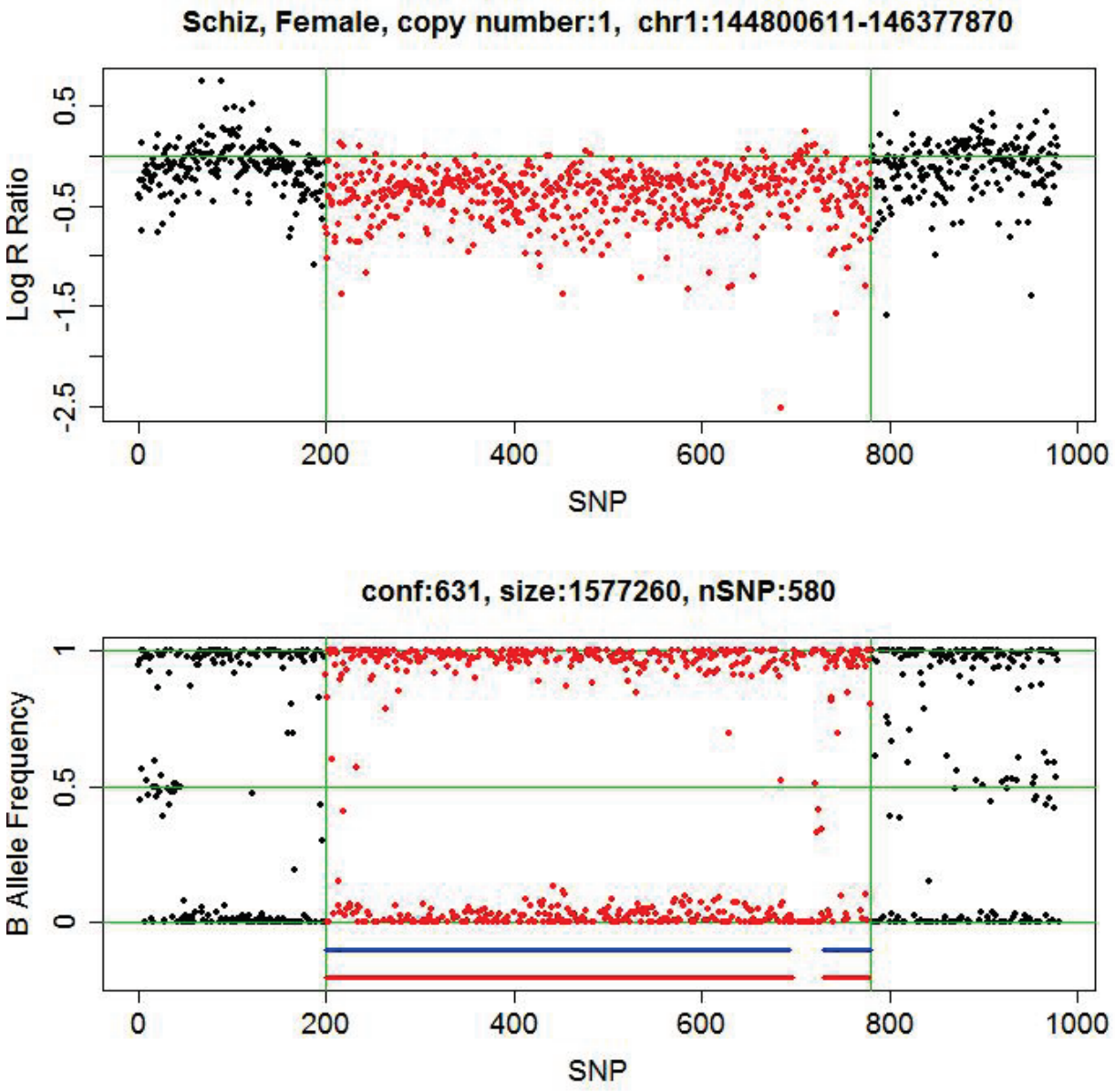

Figure S2. A 1.6 Mb deletion in 1q.21.1 in a female patient with schizophrenia (Sample 2).

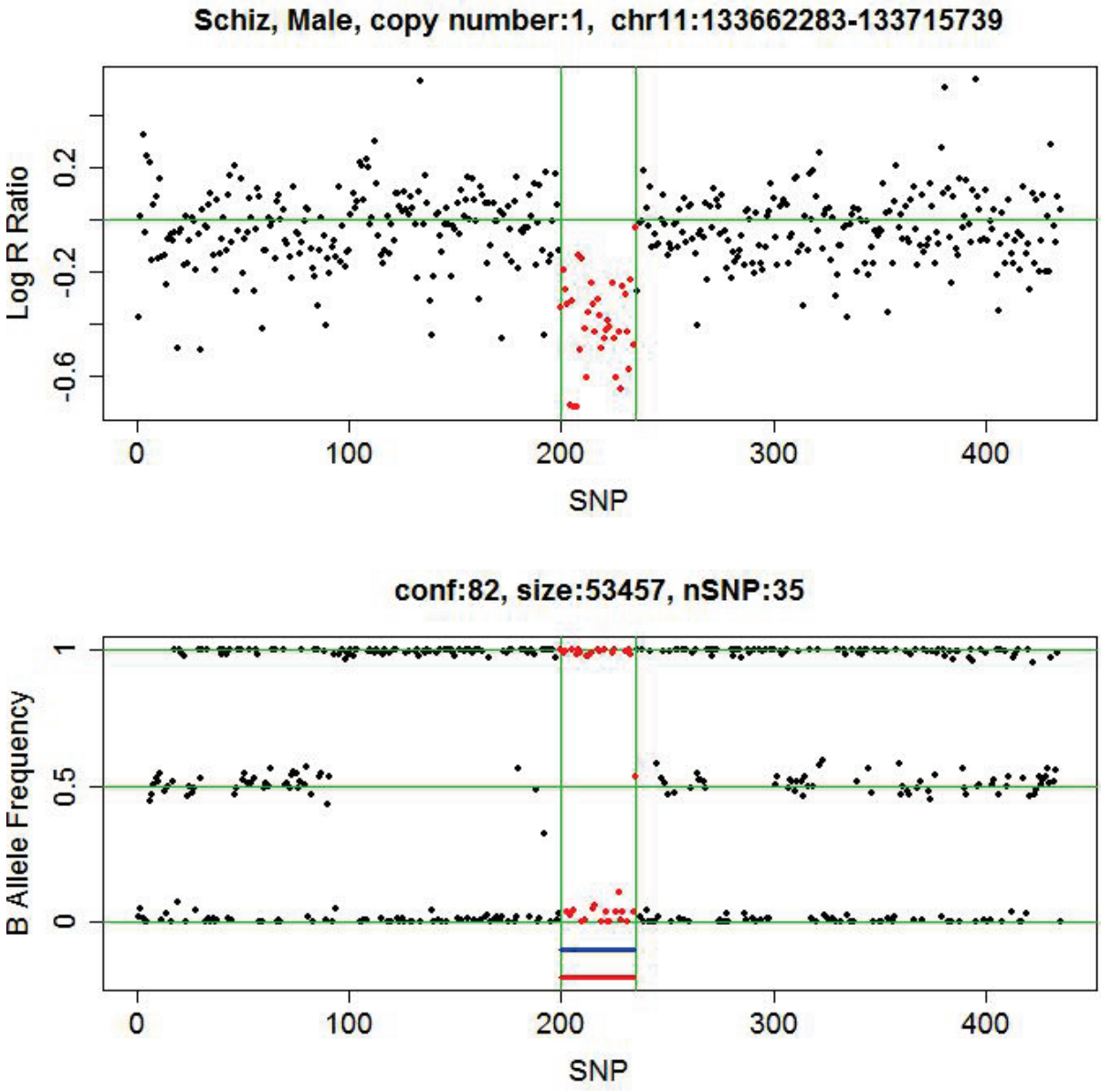

Figure S3. A 53 kb deletion in 11q25 in a male patient with schizophrenia (Sample 3).

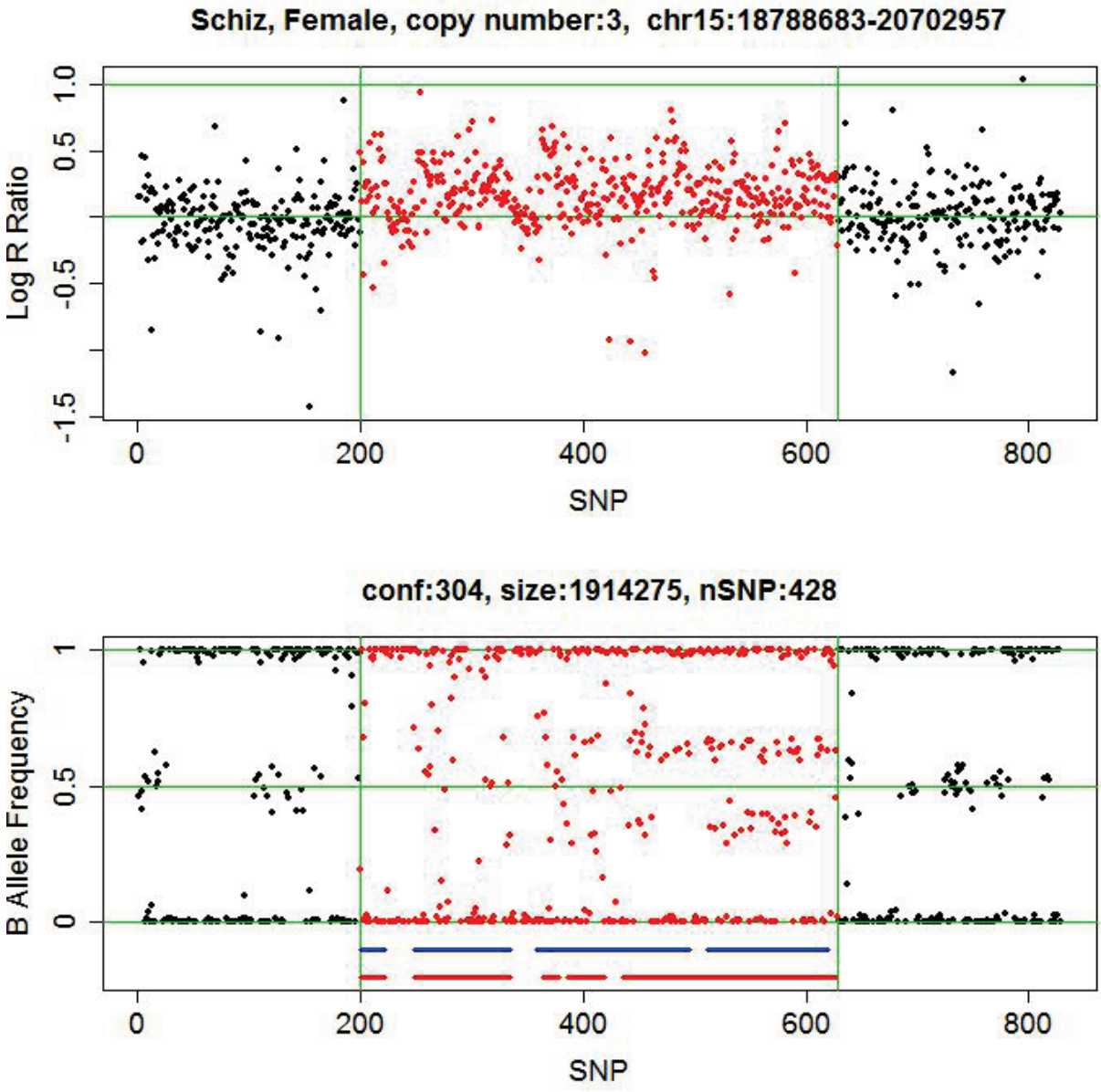

Figure S4. A 1.9 Mb duplication in 15q11.2 in a female patient with schizophrenia (Sample 4).

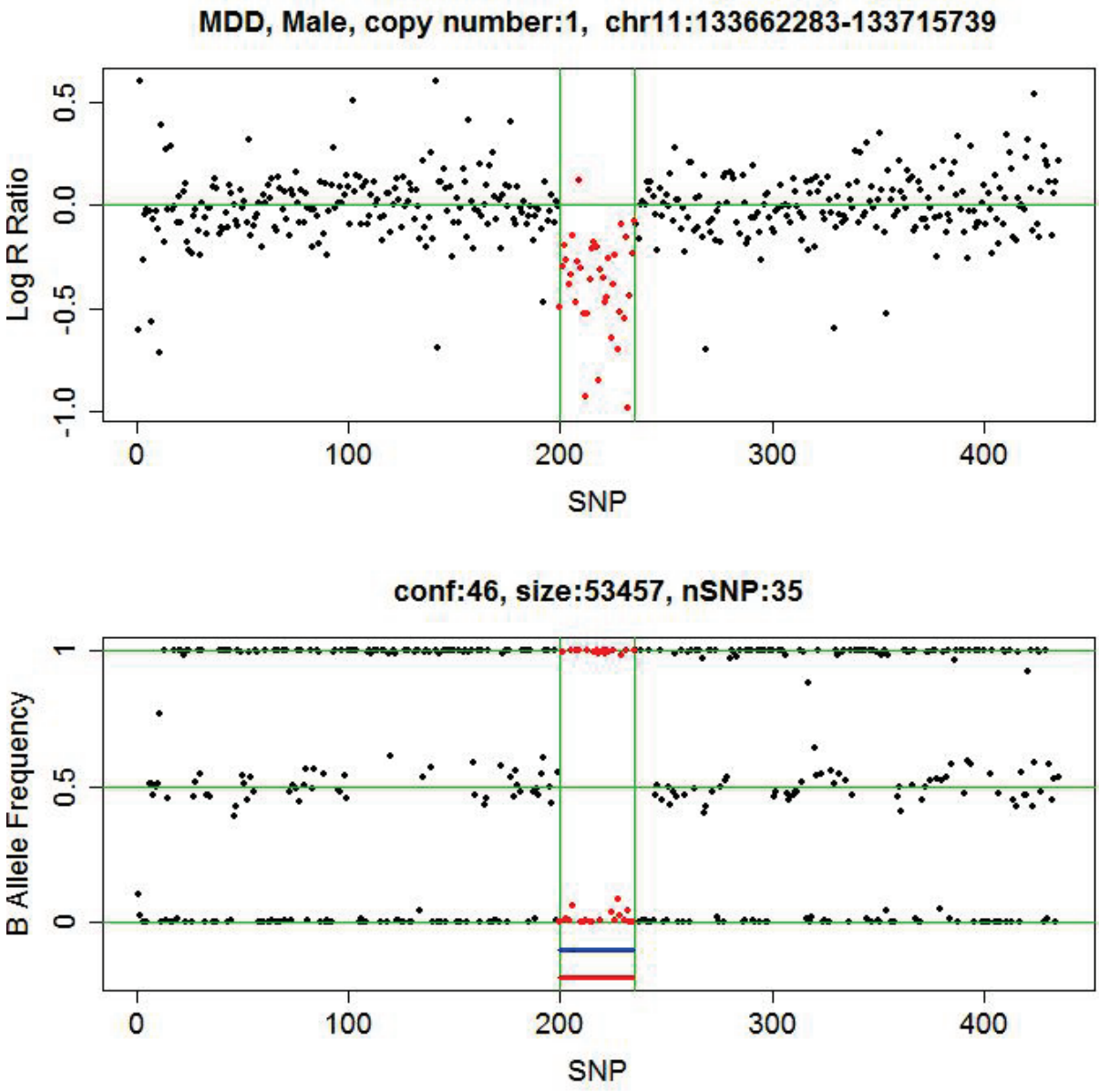

Figure S5. A 53 kb deletion in 11q25 in a male patient with major depression (Sample 5).

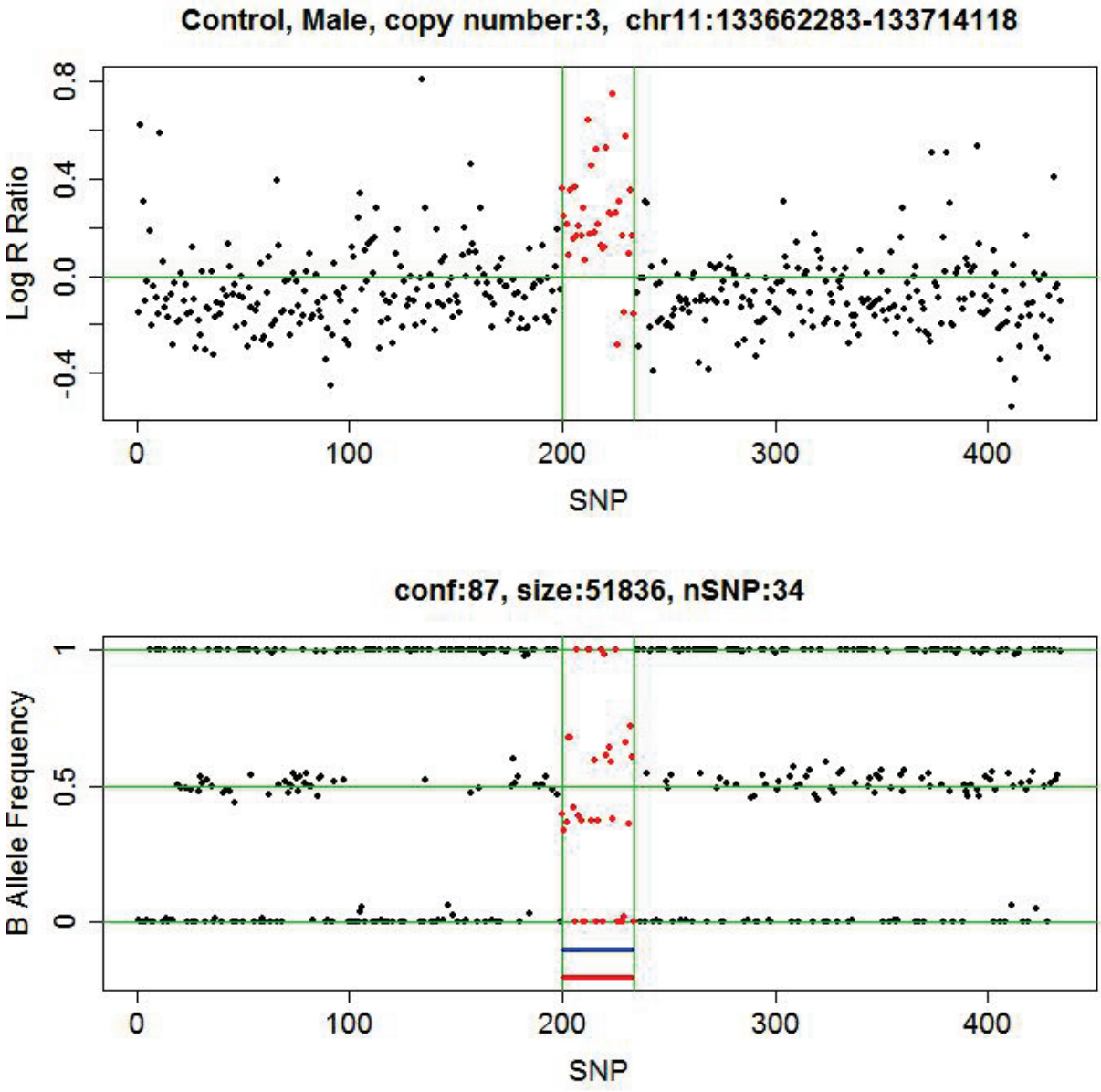

Figure S6. A 52 kb duplication in 11q25 in a male control subject (Sample 6).

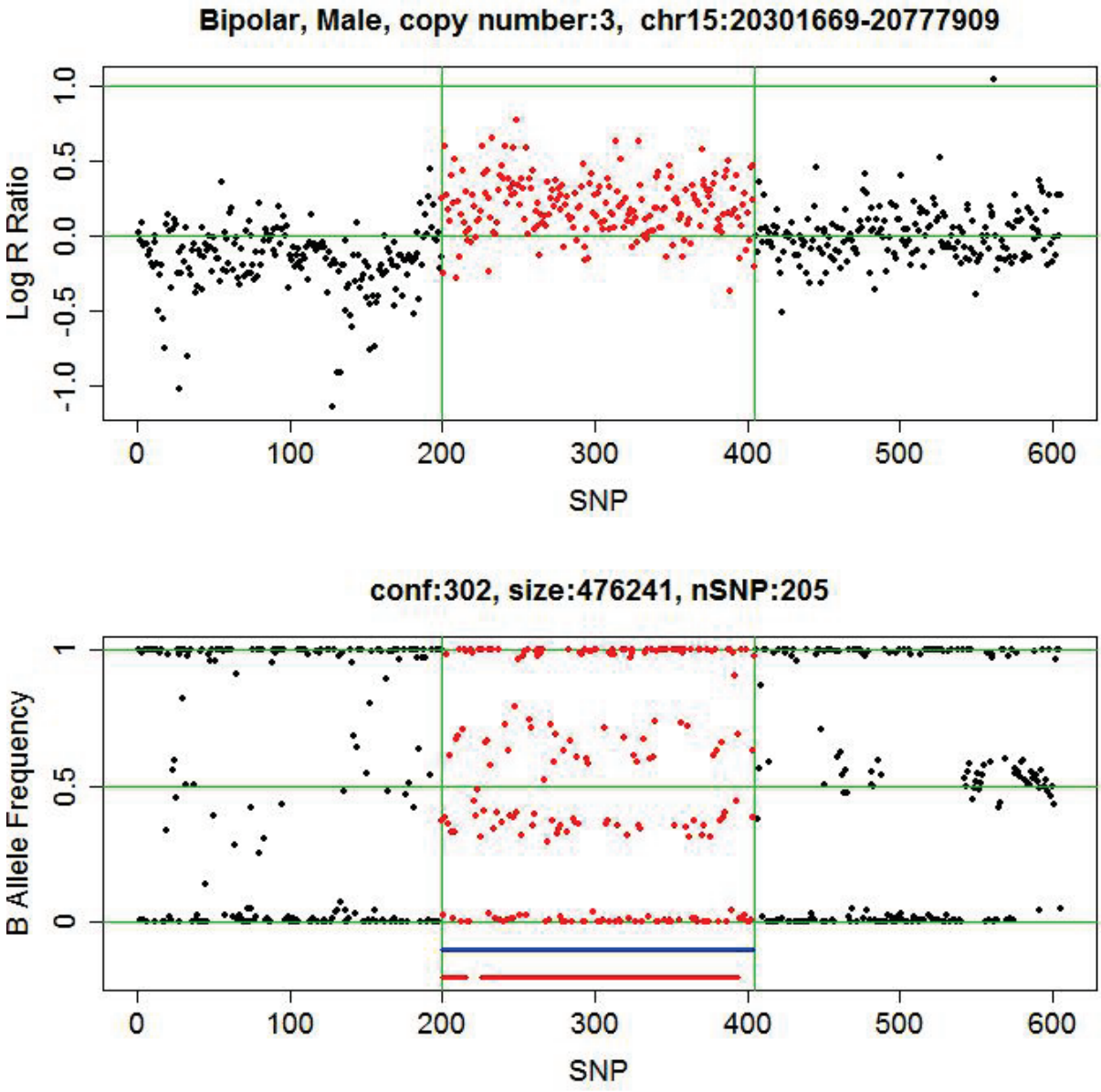

Figure S7. A 476 kb duplication in 15q11.2 region in a male patient with bipolar disorder (Sample 7).

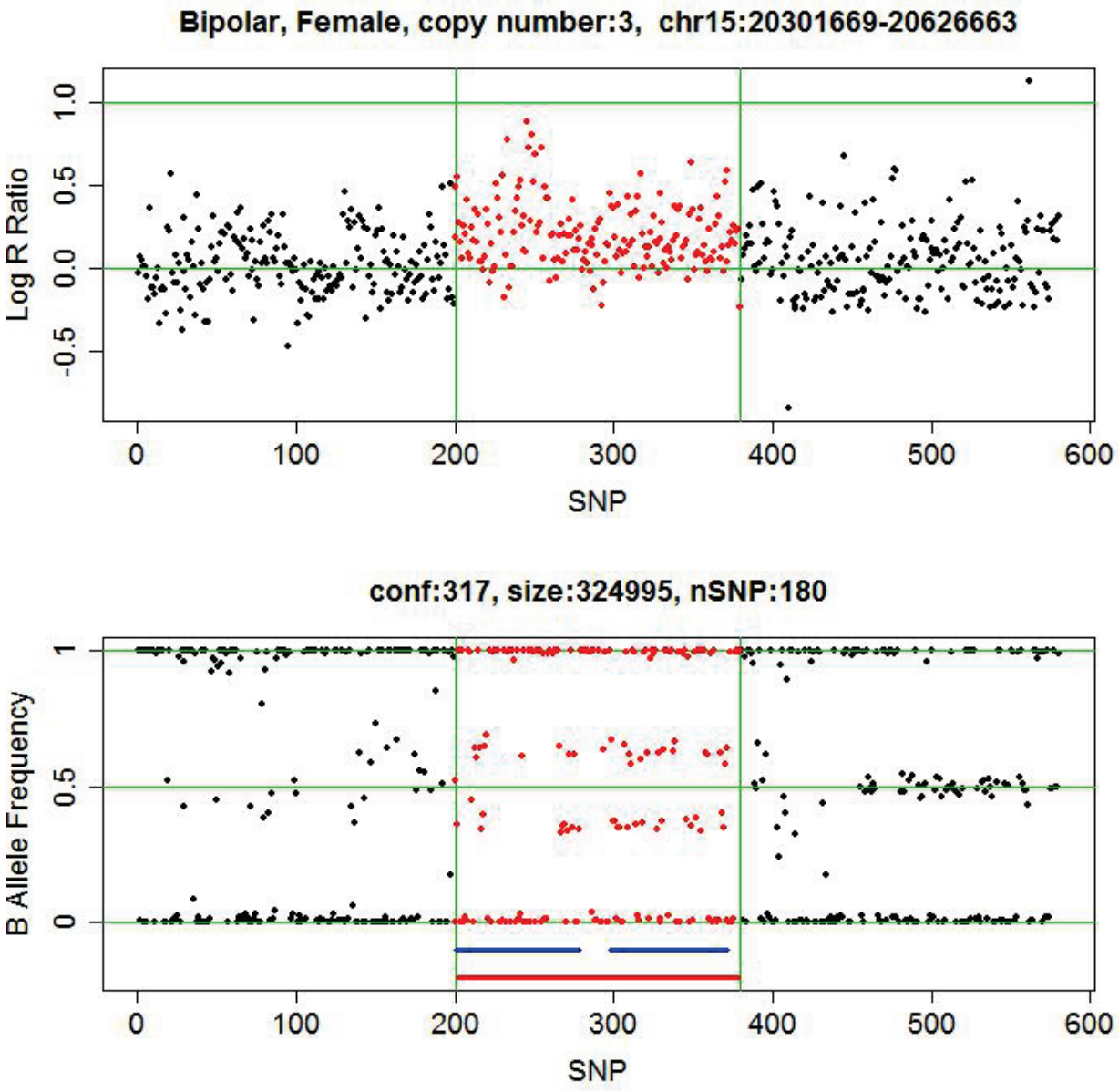

Figure S8. A 325 kb duplication in 15q11.2 in a female patient with bipolar disorder (Sample 8).

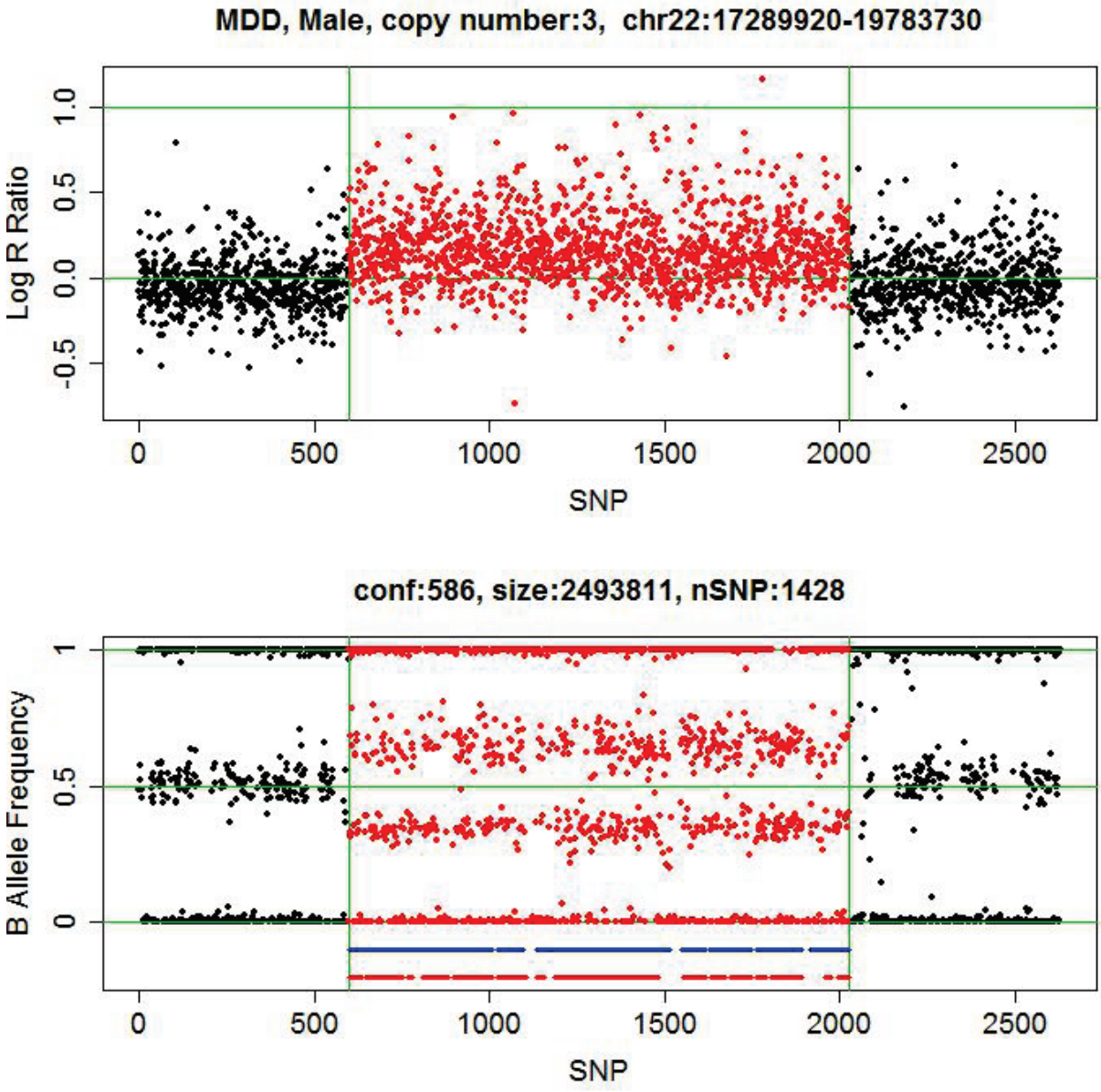

Figure S9. A 2.5 Mb duplication in 22q11 in a male patient with major depression (Sample 9).

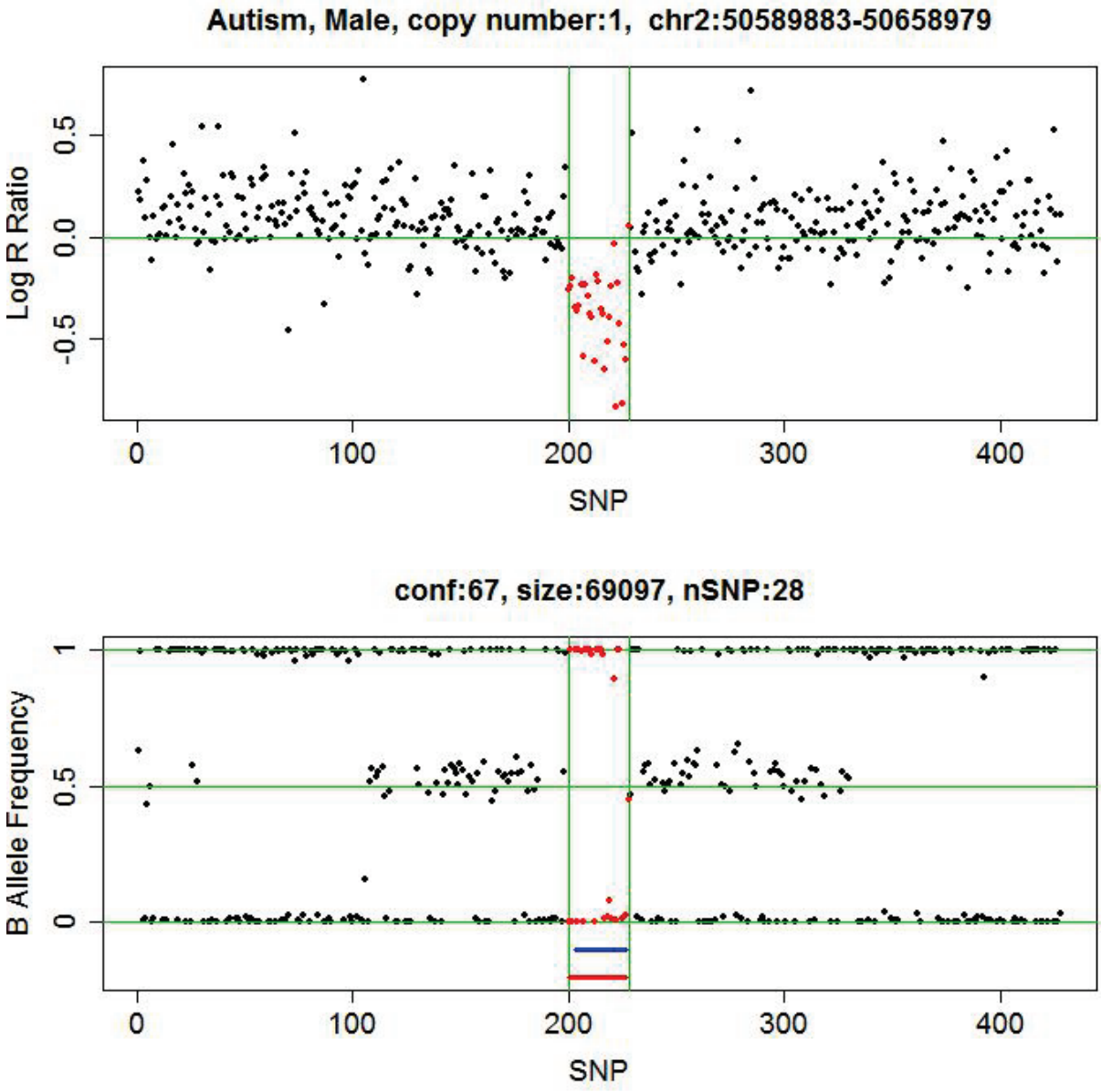

Figure S10. A 69 kb deletion in 2p16.3 in a male patient with autism (Sample 10).

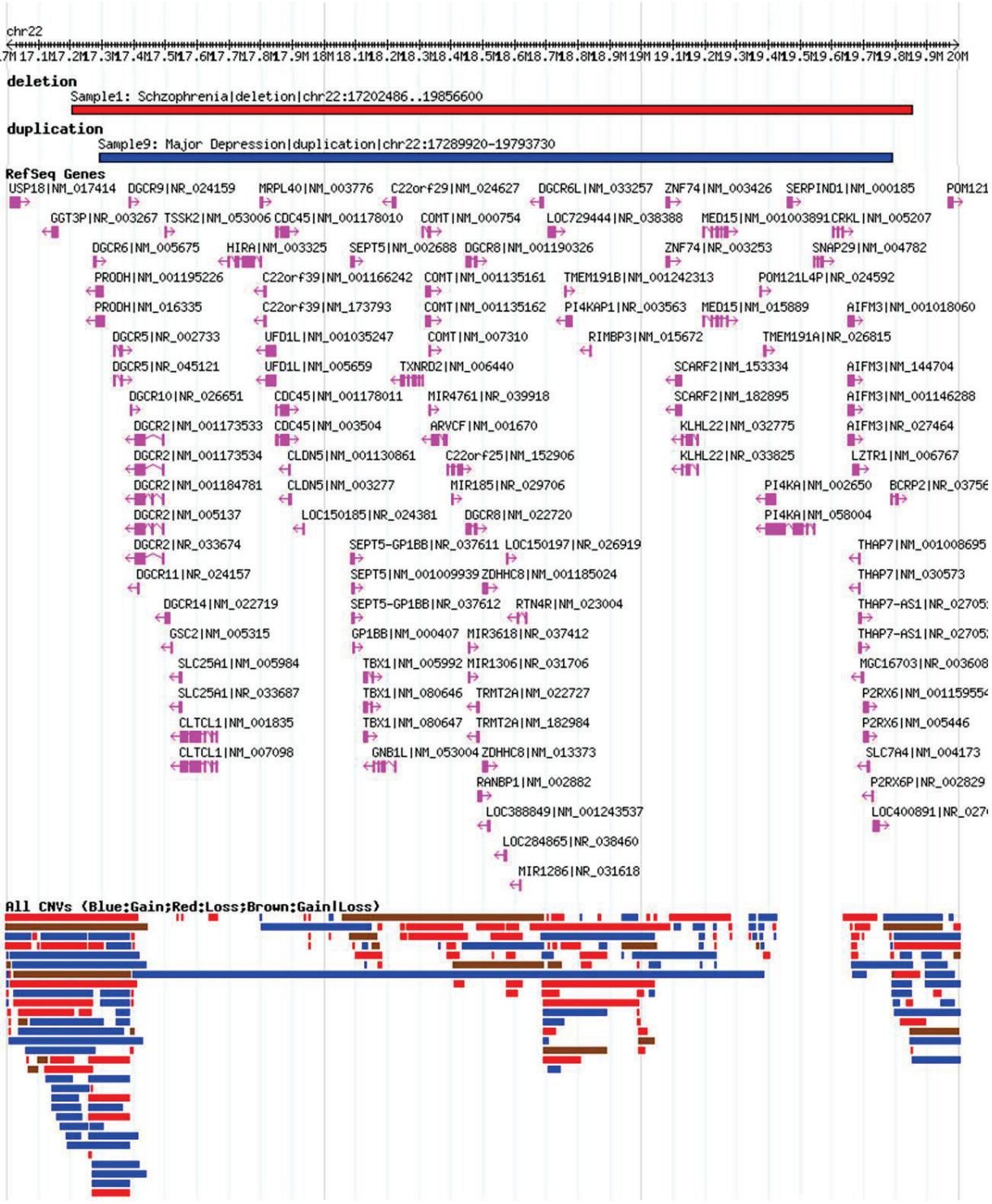

Figure S11. Depiction of CNVs in 22q11 in samples 1 (deletion) and 9 (duplication). The maps were created using the Database of Genomic Variants http://projects.tcag.ca/cgi-bin/variation/gbrowse/hg18/ , build 36, hg18 with selected tracks: Refseq Genes, All CNVs and

a custom CNV track indicating the location of the CNVs found in our cases. CNVs in our Samples 1 and 9 are shown at the top (red and blue bars, respectively). Below RefSeq genes, the location of all CNVs >1kb reported in peer reviewed research studies in healthy controls are depicted. Blue bars indicate gains, red bars: loss, brown bars: gains/loss.

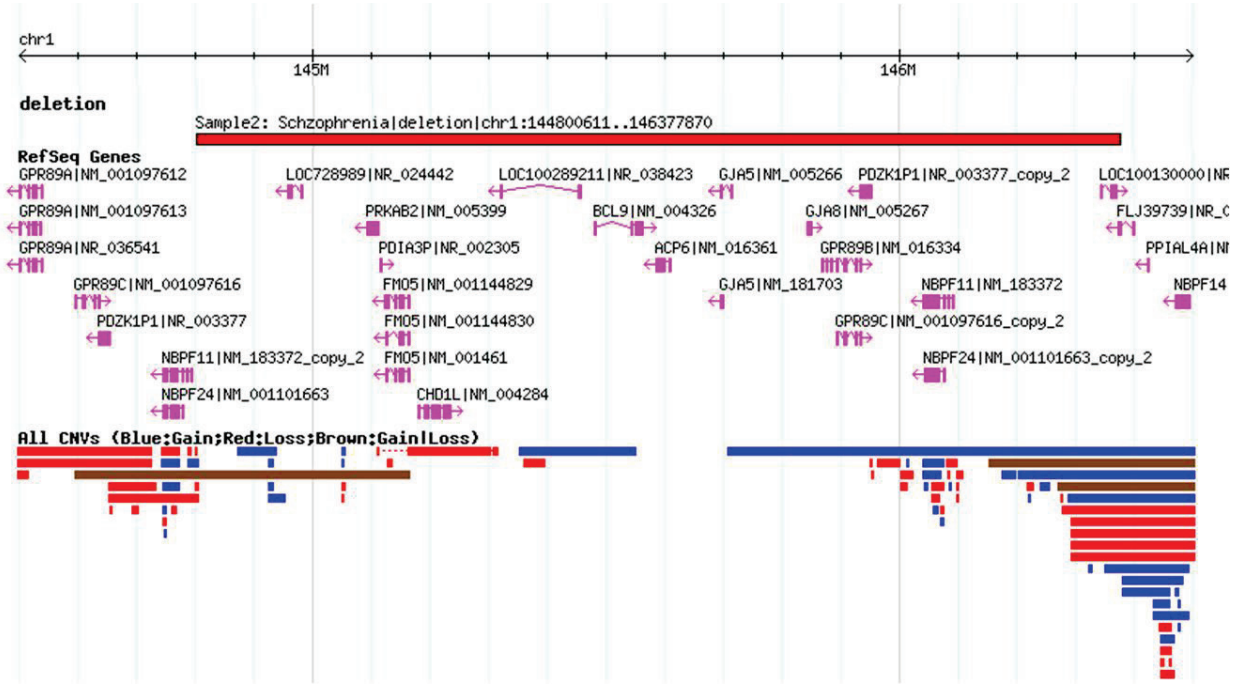

Figure S12. Depiction of the CNV in Sample 2 (1q21.1 deletion).

Figure S13. Depiction of CNVs in 11q25 of samples 6 (duplication), 5 and 3 (deletions).

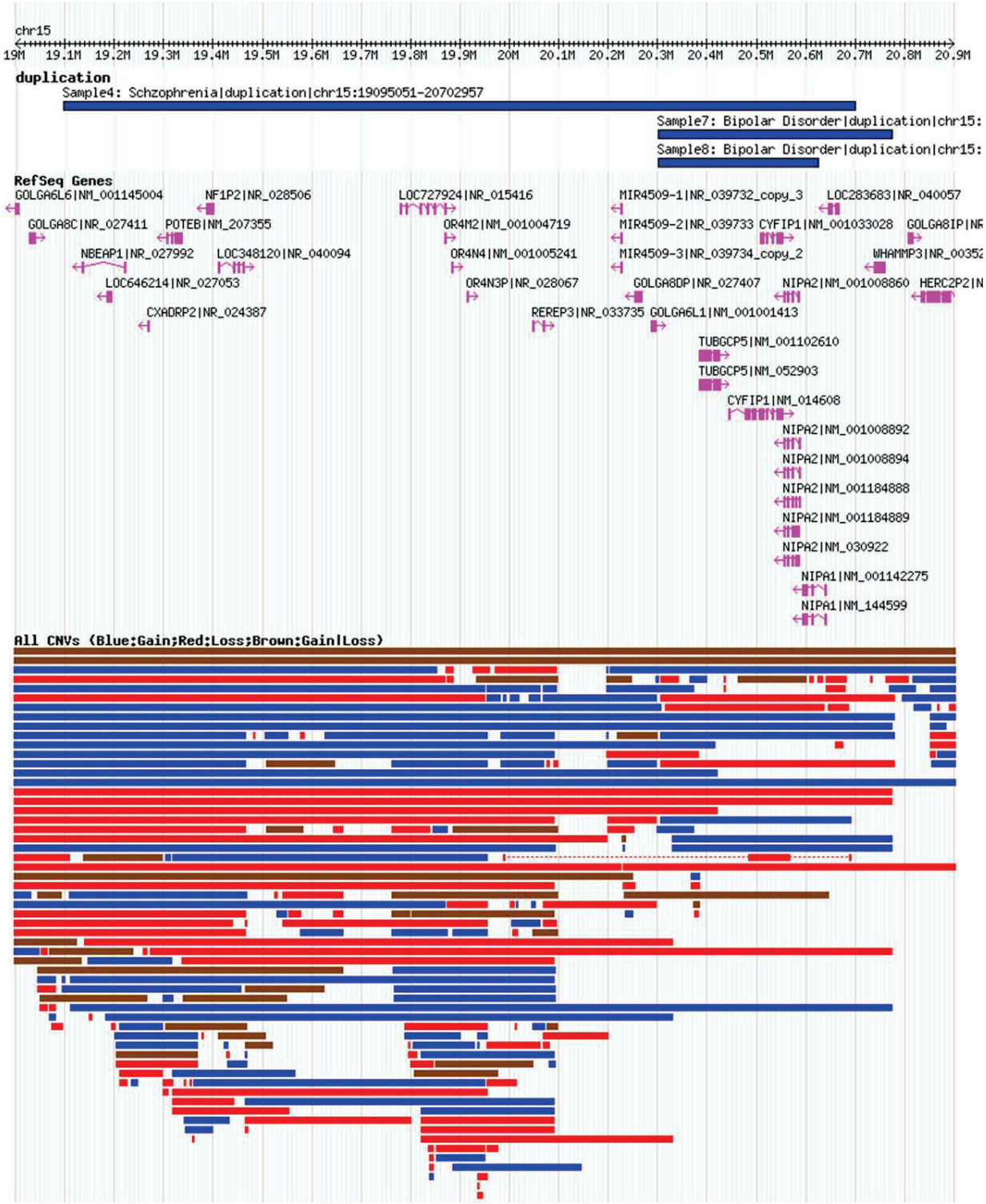

Figure S14. Depiction of CNVs in 15q11.2 of samples 4, 7 and 8 (all duplications).

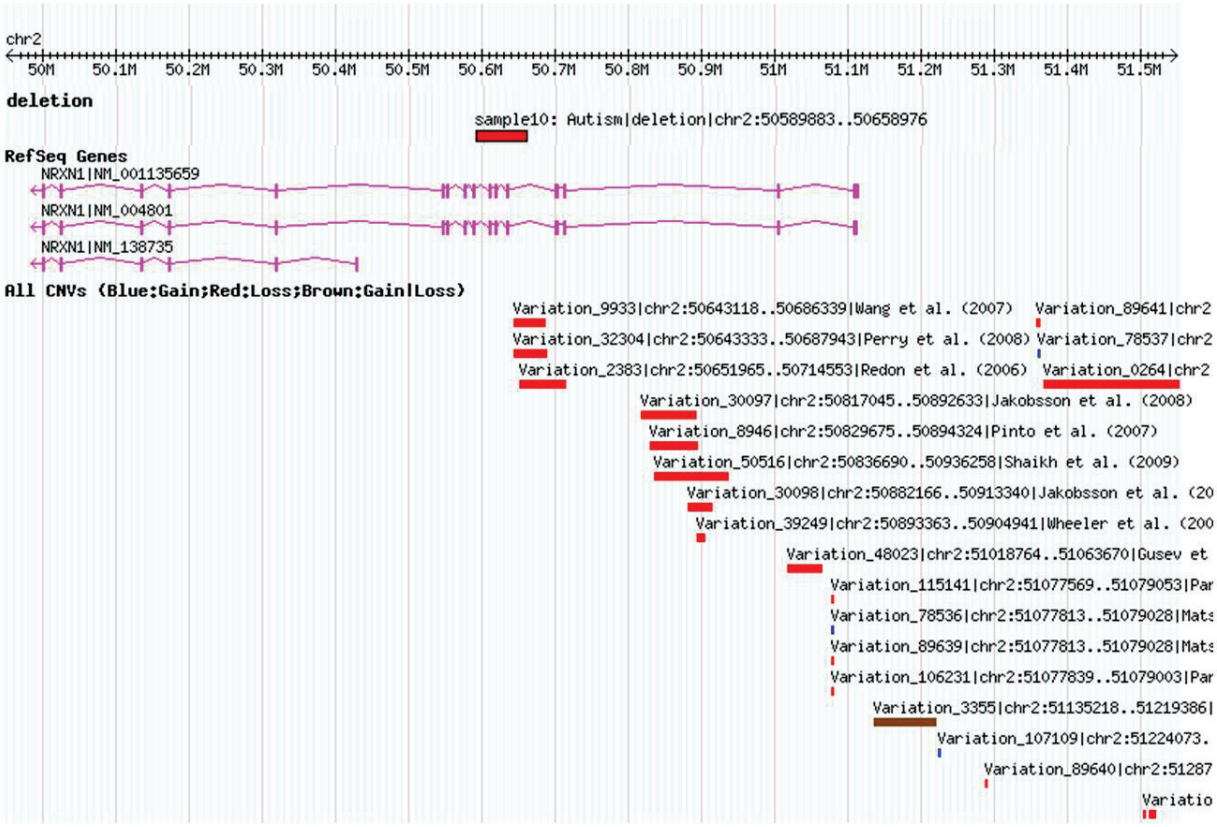

Figure S15. Depiction of the CNV in 2p16.3 of sample 10 (deletion).

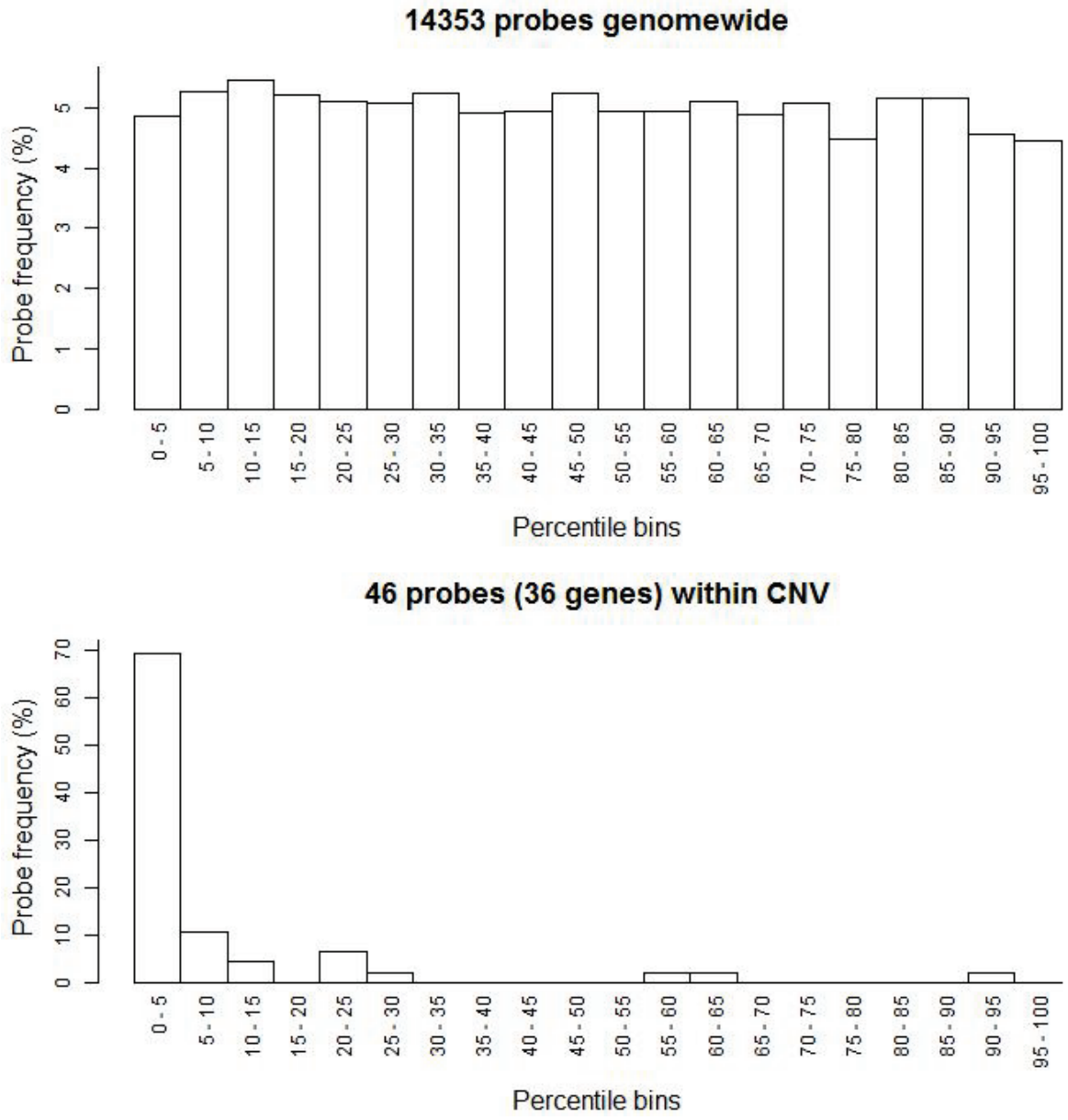

Figure S16. Histograms depicting the distribution of gene expression in the dorsolateral prefrontal cortex of Sample X compared with all other subjects. The expression levels of probes in the sample were rank ordered in comparison to expression of the same probes in all other subjects and the ranks were binned by 5% increments. Thus, each bin represents the ranks of relative gene expression in 5% of the sample, from lowest expression to highest, and the distribution pattern reflects whether Sample X deviates in expression ranks relative to the other subjects. For example, if the subject has a majority of probes that are expressed at low levels compared to other subjects, the histogram pattern of expression will show enrichment in low percentile bins.

The upper plot shows the distribution of the relative expression levels of 42,742 probes across the whole genome in **Sample 1** (deletion in 22q11) compared to the distribution of expression of the same probes in all other subjects and indicates a relatively uniform pattern of how Sample 1 ranks compared to other subjects, as would be expected.

The lower plot shows the distribution of relative expression levels of the 46 probes in 36 genes in the CNV region in **Sample 1** compared with the relative expression of the same probes in all other subjects. Here, this subject ranks primarily within the lowest expression bins for the genes in the CNV region (~70% of probes in this region in Sample 1 fell into the lowest 5% bin as compared to how these genes are expressed in all other subjects). The most dramatically downregulated genes included *DGCR6, PRODH, DGCR2, SLC25A1, MRPL40, UFD1L, CLDN5, TXNRD2, COMT, C22orf25, RANBP1, ZDHHC8,* and *ZNF74*.

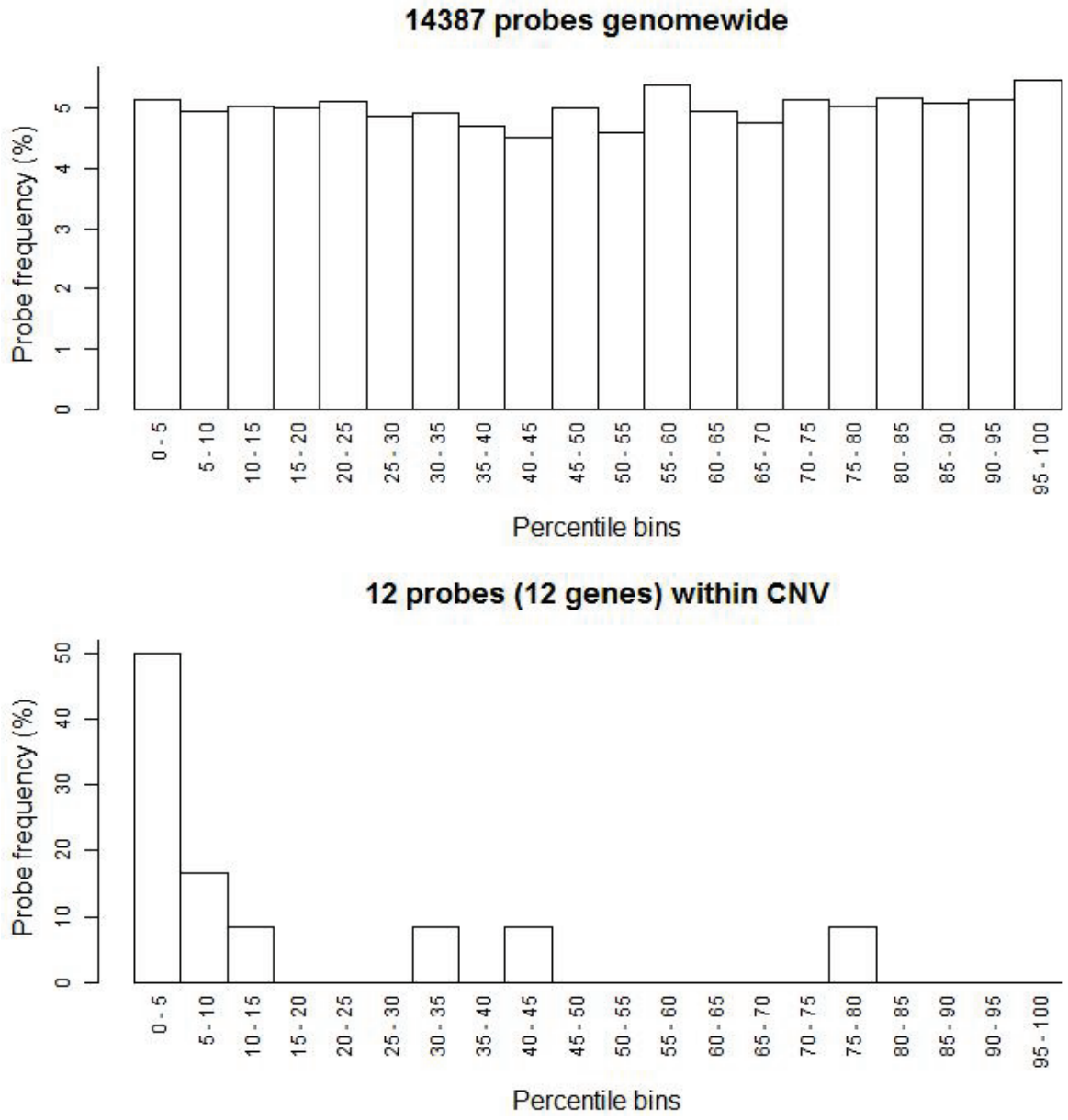

Figure S17. Distribution of the relative expression levels of the genes across the whole genome (upper plot) and genes in the CNV region (lower plot) in the dorsolateral prefrontal cortex of **Sample 2** (deletion in 1q21.1). The lower plot shows enrichment of low expressed genes among 12 genes in the CNV region in this case as compared to all other subjects. There were 2 genes in this region that showed dramatically lower expression in Sample 2 compared to all other 567 subjects on the array (*CHD1L, BCL9*).

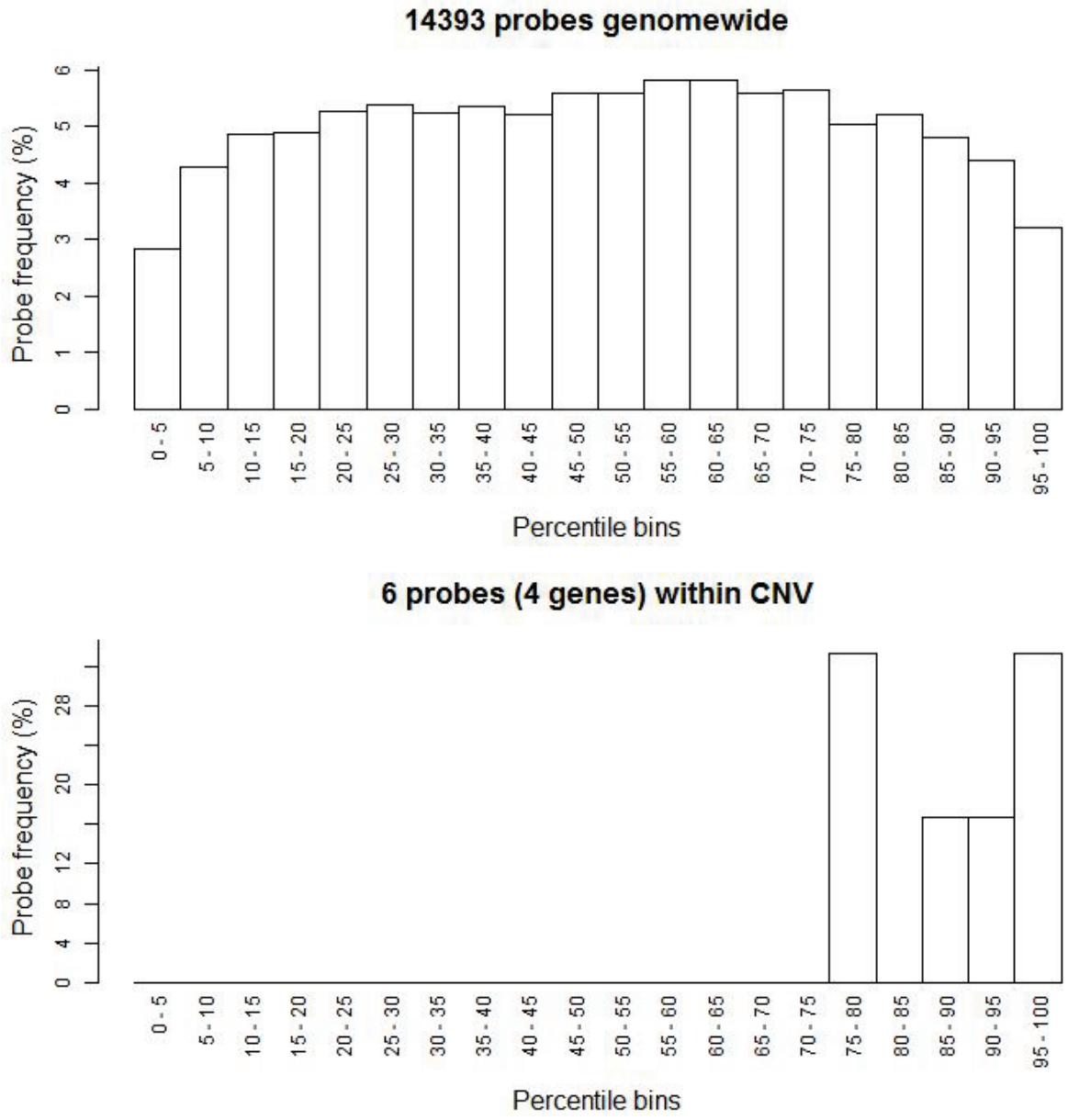

Figure S18. Distribution of the relative expression levels of the genes across the whole genome (upper plot) and the genes in the CNV region (lower plot) in the dorsolateral prefrontal cortex of **Sample 4** (duplication in 15q11.2) obtained from Illumina BeadArrays. The lower plot shows enrichment of highly expressed genes among 4 genes in the CNV region. *NIPA2* showed dramatically higher expression in sample 4 compared to the other 567 subjects on the array.

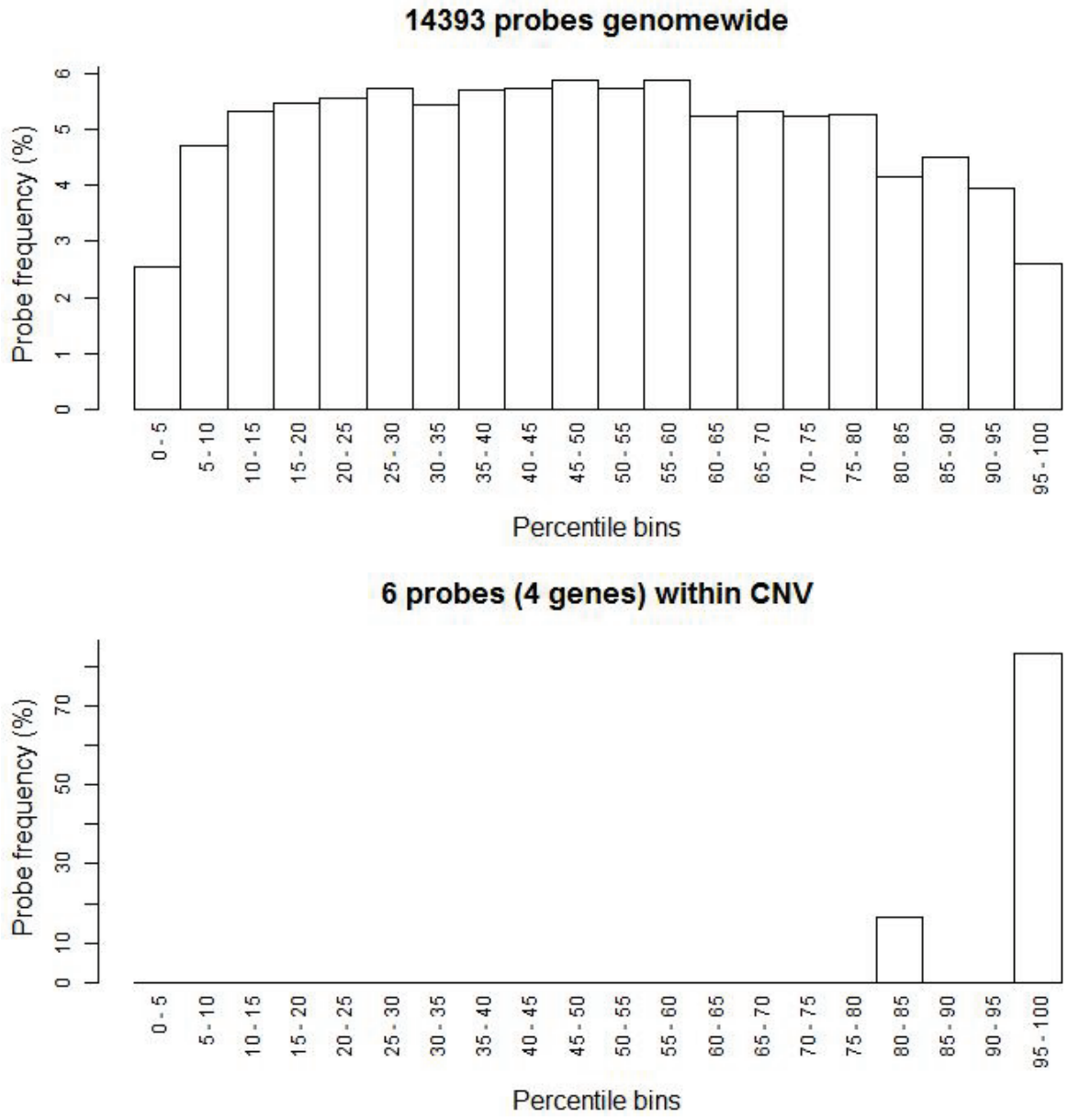

Figure S19. Distribution of the relative expression levels of the genes across the whole genome (upper plot) and the genes in the CNV region (lower plot) in the dorsolateral prefrontal cortex of **Sample 7** (duplication in 15q11.2) obtained from Illumina BeadArrays. The lower plot shows enrichment of highly expressed genes among 4 genes in the CNV region. There were 3 genes showing dramatically higher expression in sample 7 as compared to the other 567 subjects on the array (*NIPA2, NIPA1* and *LOC283683*).

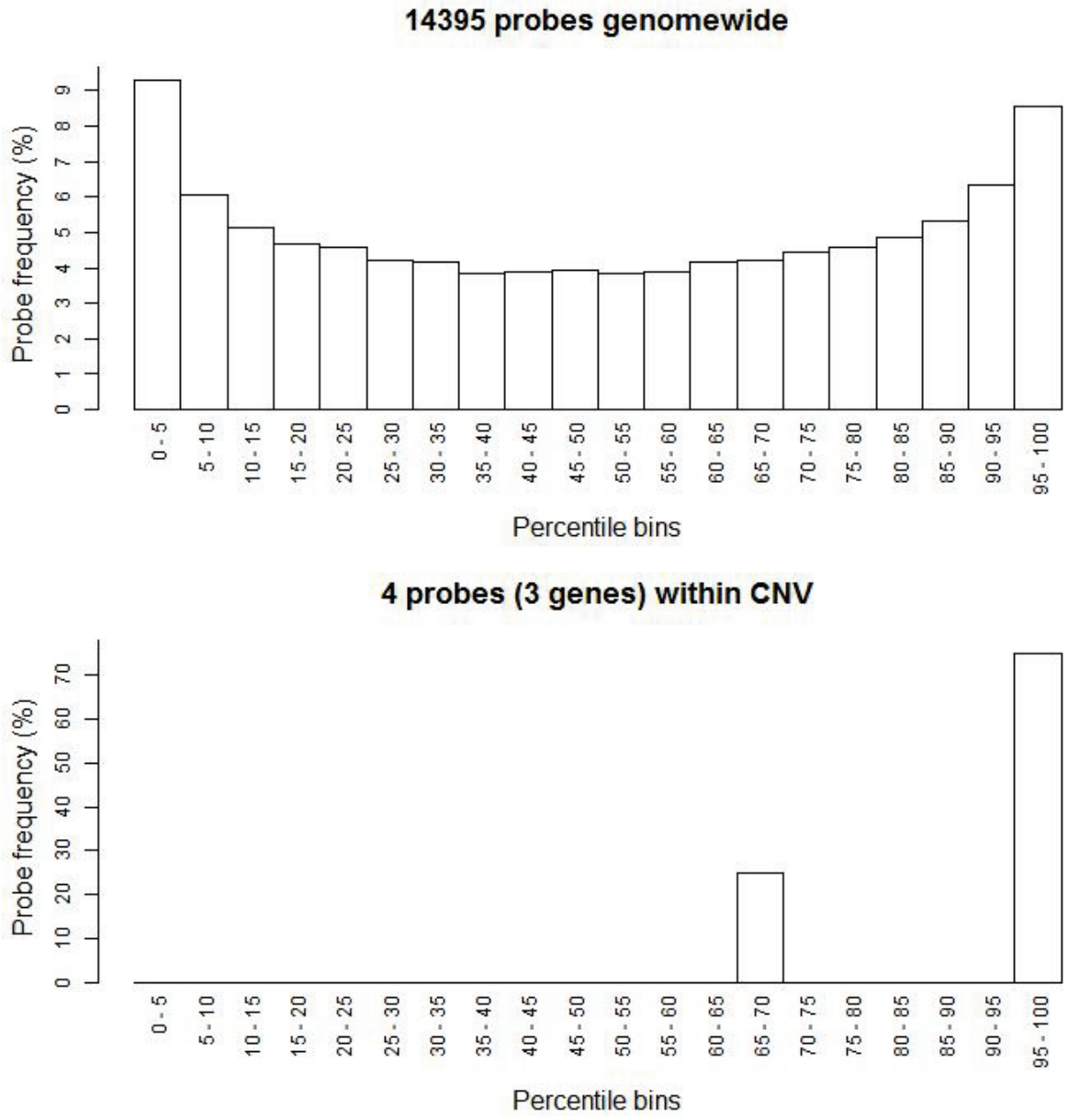

Figure S20. Distribution of the relative expression levels of the genes across the whole genome (upper plot) and the genes in the CNV region (lower plot) in the dorsolateral prefrontal cortex of **Sample 8** (duplication in 15q11.2) obtained from Illumina BeadArrays. The lower plot shows enrichment of highly expressed genes among 3 genes in the CNV region. *NIPA2* showed dramatically higher expression in sample 8 compared to the other 567 subjects on the array.

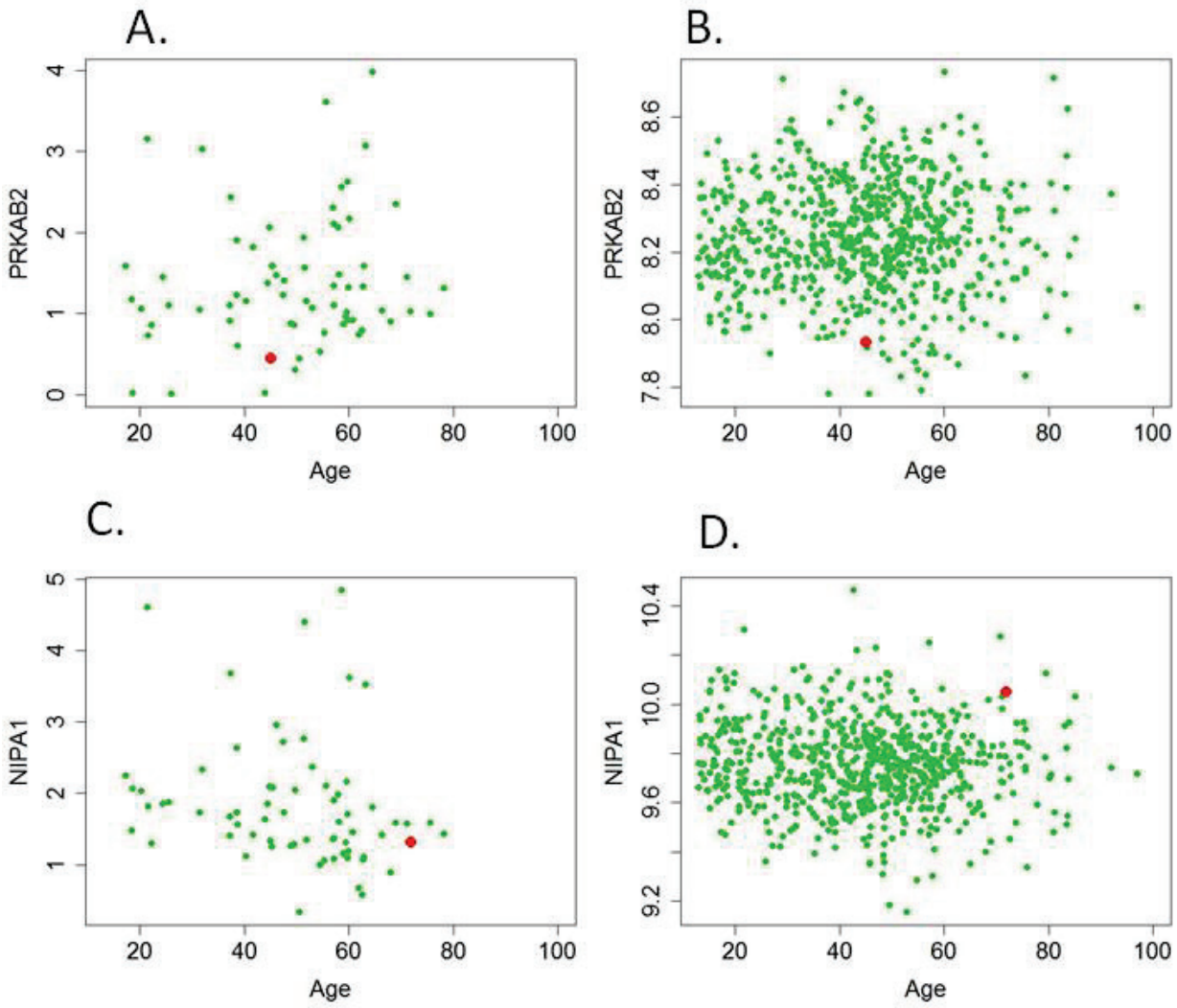

Figure S21. Expression of targeted genes in the CNV regions of two patients (Samples 2 and 4) measured by quantitative polymerase chain reaction (left panels **A,C**) and Illumina BeadArrays (right panels **B,D**) in the postmortem dorsolateral prefrontal cortex. Y axes represent expression of targeted genes normalized as described in the Methods. X axes represent age of subjects at death. Every dot represents a subject. Red dots represent the cases. (**A,B)** Expression levels of *PRKAB2* in **Sample 2** (schizophrenia, deletion in 1q21.1) as compared to all other subjects. (**C,D)** Expression levels of *NIPA1* in **Sample 4** (schizophrenia, duplication in 15q11.2) as compared to all other subjects. It is interesting to note that while deletion cases tend to be at the extreme low extent of expression, duplications less consistently show an increase relative to the distribution of the controls.

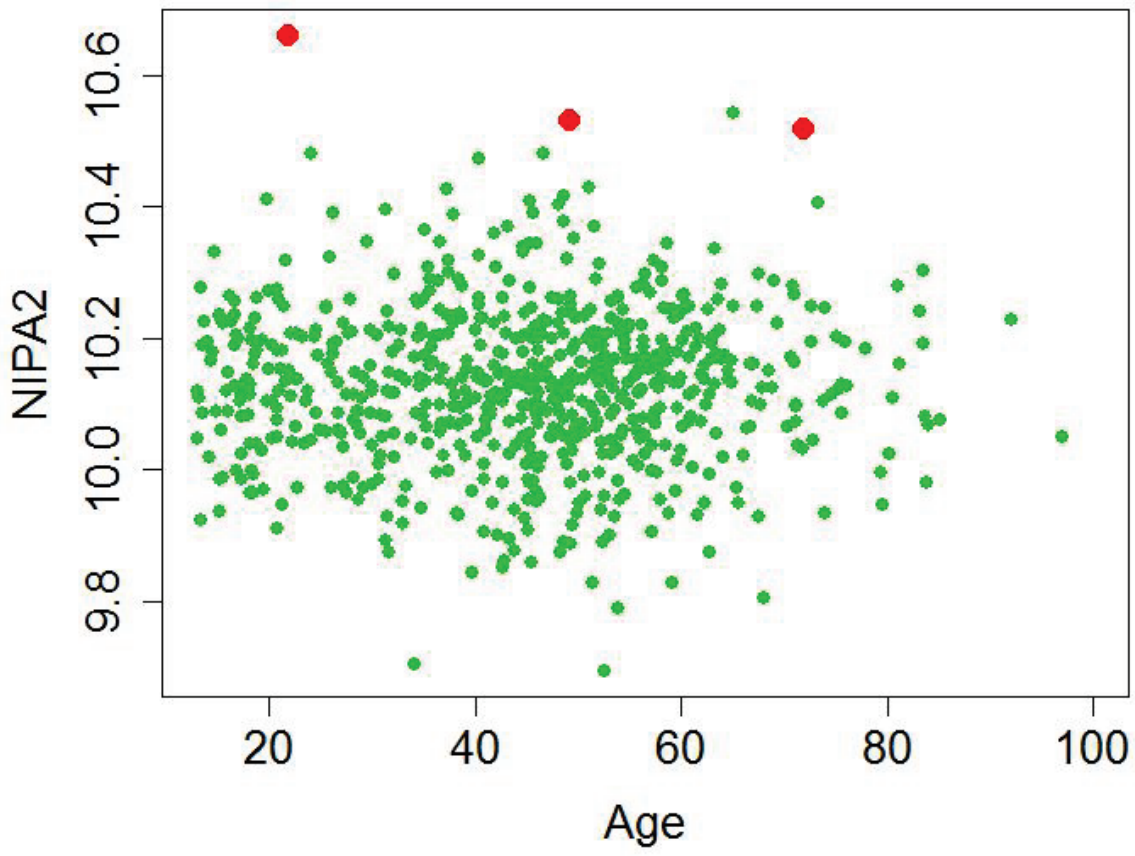

Figure S22. Expression of *NIPA2,* a gene in the region 15q11.2, in the dorsolateral prefrontal cortex of three cases with duplications in this region (red dots) as compared to all other subjects on the Illumina BeadArrays (green dots, total number of subjects 568). Every dot represents a subject. Y axis shows normalized expression of *NIPA2* as described in the Methods. X axis shows the age of subjects at death. Cases with duplications are (from left to right) **Sample 7, Sample 8** and **Sample 4**. All three cases with duplications in 15q11.2 show extremely high expression of *NIPA2* as compared to all other subjects. The fourth subject showing extreme expression of this gene (a green dot between the two red dots) is a male subject with bipolar disorder with no detected CNV on chromosome 15.