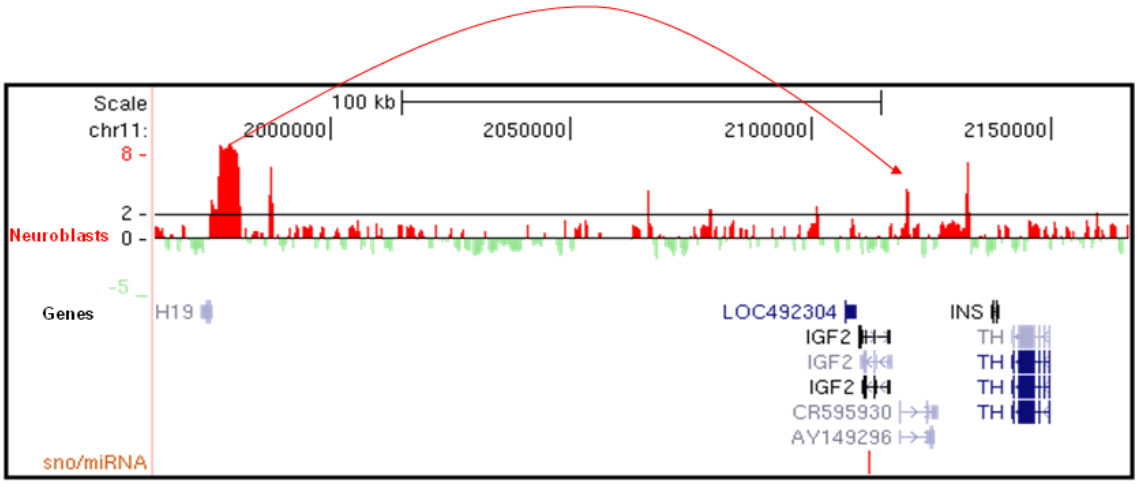
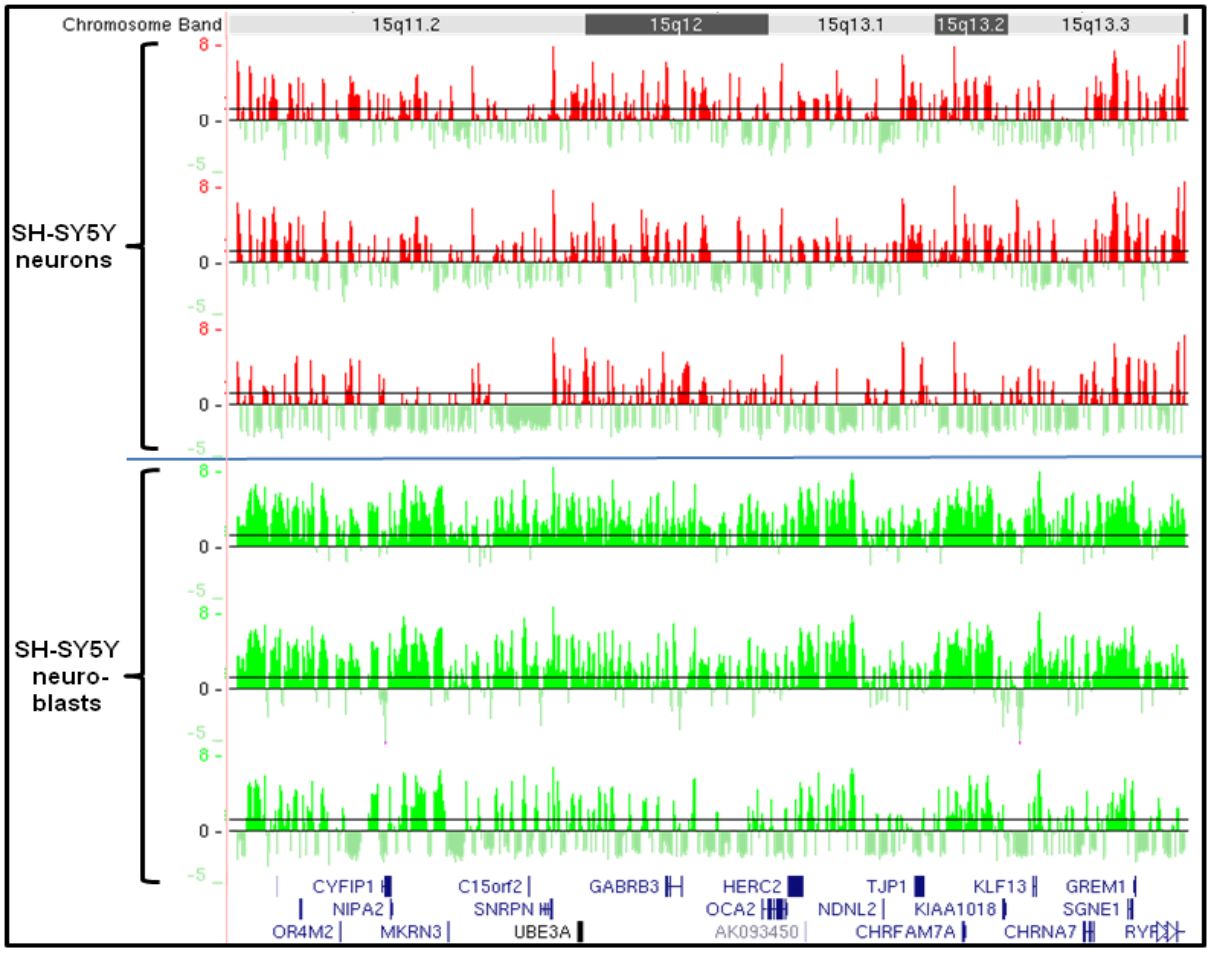


Supplementary Figure 1 *H19-IGF2* interaction serves as a 4C positive control

4C analysis was performed to assay a known interaction of *H19* with *Igf2* (66). 4C libraries were prepared from SH-SY5Y cells to capture *cis* interactions of *H19* with other 11p15.5 loci and hybridized to a custom tiling microarray. The specific interaction of a region upstream of *H19* with sites downstream of *IGF2* represented as red peaks in the histogram uploaded to the UCSC genome browser was detected in neuroblasts (red arrow).



Supplementary Figure 2 4C analysis results are consistent in three replicates

4C analyses produced consistent results in three replicate experiments. 4C libraries were prepared from three separate biologic replicates of SH-SY5Y cells treated with PMA (SH-SY5Y neurons) and three untreated replicates (SH-SY5Y neuroblasts). 4C libraries were co-hybridized with differentially labeled input genomic DNA and hybridized to microarrays bearing 15q11.2-13.3 complimentary tiled oligo-nucleotides. Log 2 signal ratios for six separate microarrays, three corresponding to neurons shown in red in the top panel and three corresponding to undifferentiated neuroblasts shown in green in the bottom panel are displayed for all 13 MB of the 15q11.2-13.3 locus. All

experiments are represented as custom tracks in the UCSC genome browser with known genes shown below the histograms in blue font or gray font.

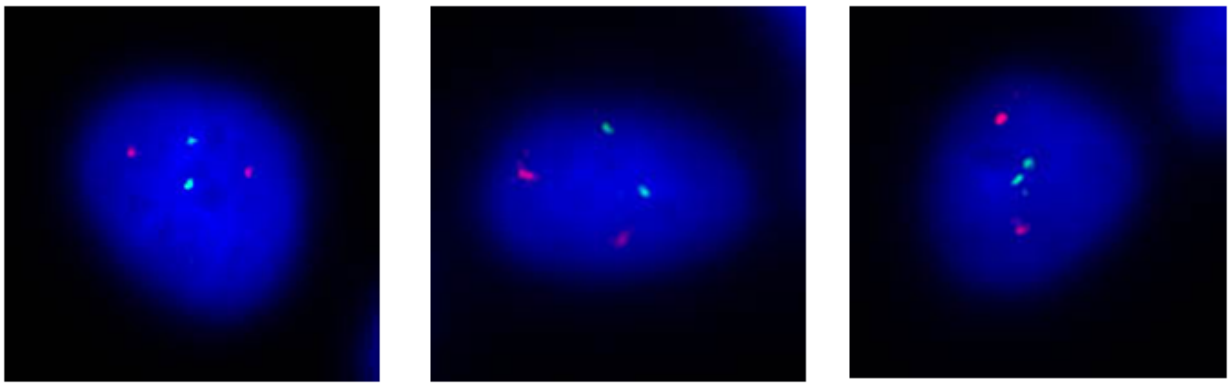
Max distance between peaks	Data	Number close	Number far	proportion	Fisher's Exact test P Value
0 BP	Actual	5	63	0.079	$5.897X10^{5}$
	Random	38	6762	0.0056	
500 BP	Actual	5	63	0.079	$9.901X10^{4}$
	Random	73	6727	0.011	
2000 BP	Actual	5	63	0.079	0.0217
	Random	157	6643	0.0236	

Supplementary Table 1 the number of loci bound by both MeCP2 and the PWS-IC is non-random

Fisher's exact test demonstrates that the overlap of MeCP2 sites with 4C sites in developing neurons is non-random. Actual and randomly generated data (column 2) is compared for overlap at a series of distances (0, 500 and 2000 BP between MeCP2 sites and a 4C peaks (column 1). Sites within this distance are recorded as "number close" and those outside are noted as "number far" with the proportion of the number close to the total shown in column 5. Finally the difference between the actual and random data sets is calculated as a p-value using Fisher's exact test (red) where all values were found to be significant.

PWS-IC: RP11-125E1
PML(15q24.1): RP11-1026C23

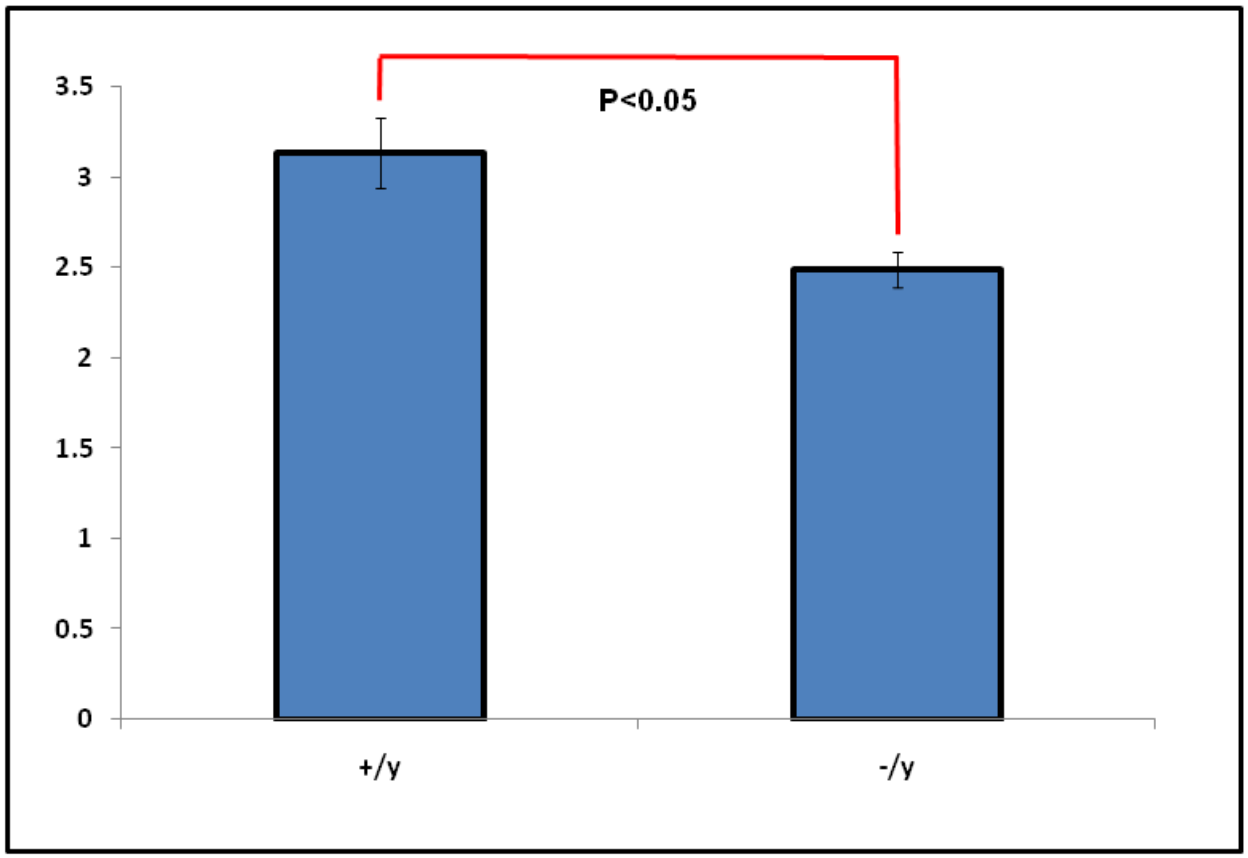
		SH-SY5Y		SH-SY5Y+PMA
Both unpaired	0	81.2%	0	73.5%
One paired	1	18.8%	1	23.5%
Both paired	2	0%	2	3.0%



Supplementary Figure 3 Control FISH analysis of PWS-IC interaction with *PML*

FISH analysis shows low levels of PWS-IC interaction with a control *PML* locus. Genomic BAC clones complementary to the PWS-IC (RP11-125E1) and *PML* loci (RP11-1026C23) were differentially detected as green and red fluorescent signals respectively. PWS-IC and *PML* signals were considered associated if there was any contact between or spatial overlap of the signals. 100 nuclei from undifferentiated neuroblasts (SH-SY5Y) and maturing (SH-SY5Y+PMA) neurons were scored for signal overlap in each allele and the possible combinations were graphed as a percentage of total nuclei. Representative images of unpaired PWS-IC/*PML* signals are shown in the

lower panel.



Supplementary Figure 4 *Chrna7* transcripts are decreased in *MeCP2* null brain

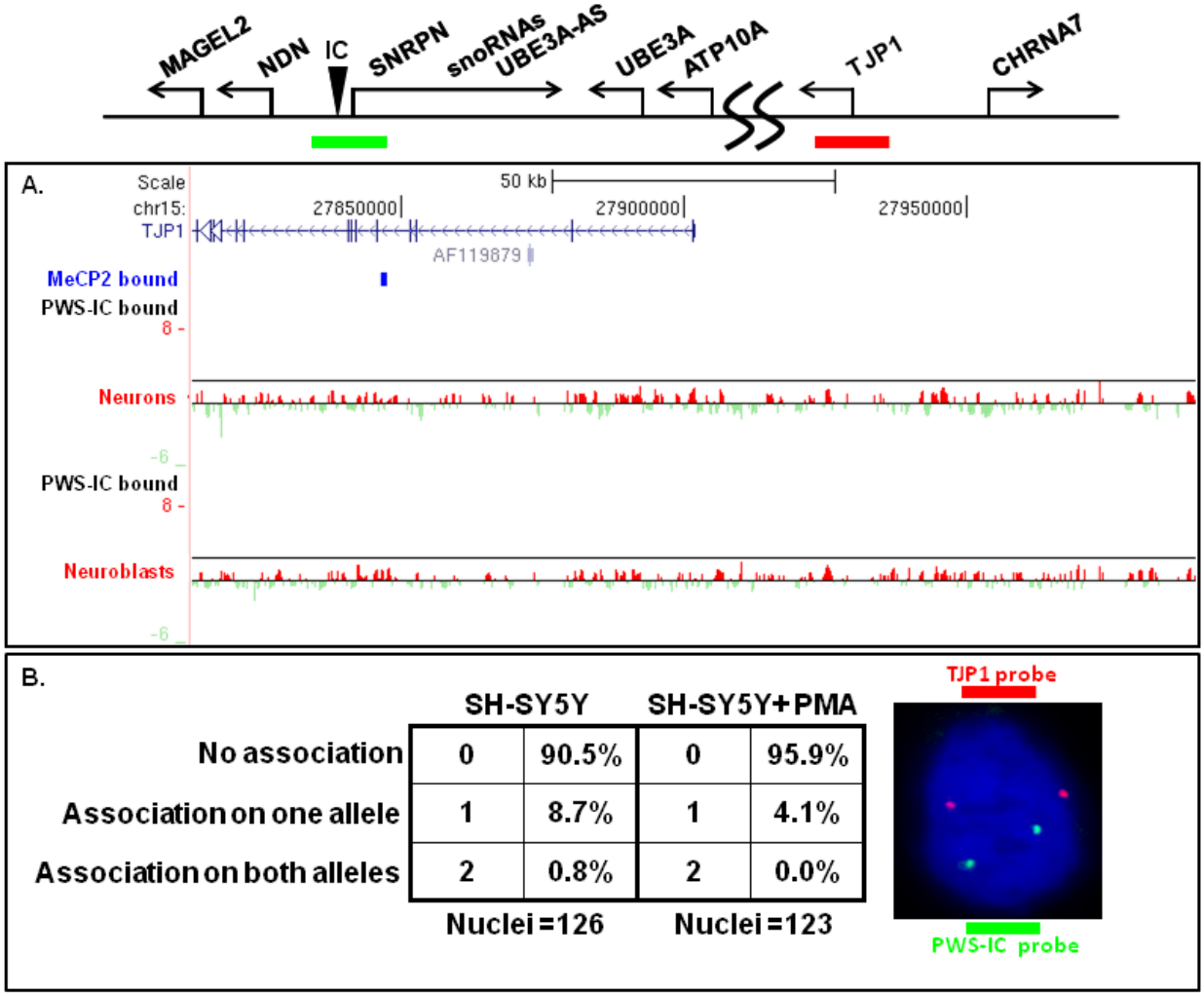
QRT-PCR analysis of RNA from mouse brain reveals a significant decrease in *Chrna7* expression. Total RNA was isolated from 1 week old brain of male hemizygous (**-/y**) and wild-type control male littermates (**+/y**) and amplified with *Chrna7* and *Gapdh* specific primers. Fold change was calculated using the comparative Ct method with error bars corresponding to the standard error of the mean. P-value was derived using the Mann-Whitney non-parametric t-test.

Sample	Case #	Age	Ethnicity	Gender	PMI (hr)	MeCP2 mutation
CTRL	390	00y125d	CA	F	18	-
CTRL	510	02y171d	CA	F	20	-
CTRL	21	04y232d	CA	M	18	-
CTRL	629	07y306d	AA	M	18	-
CTRL	738	08y336d	CA	F	12	-
CTRL	M3835M	09y000d	AA	F	8	-
CTRL	662	12y353d	CA	F	18	-
CTRL	1297	15y081d	AA	M	16	-
CTRL	1322	16y000d	CA	M	25	-
CTRL	1080	16y000d	AA	M	21	-
CTRL	812	18y130d	AA	F	16	-
CTRL	1027	22y163d	CA	M	9	-
CTRL	602	27y042d	CA	M	15	-
CTRL	1029	29y300d	HP	M	12	-
CTRL	285	30y188d	AA	M	20	-
CTRL	1136	33y362d	CA	F	22	-
CTRL	1406	38y364d	CA	F	22	-
CTRL	B4192	46y000d	CA	M	26	-
CTRL	B4503	56y000d	CA	M	24	-
CTRL	1206	57y119d	CA	M	16	-
AUT	M3871M	05y211d	HP/CA	M	14	-

AUT	**B5144**	**07y000d**	**CA**	**M**	**23.7**	**-**
AUT	**1174**	**07y283d**	**CA**	**F**	**14**	**-**
AUT	**B4925**	**09y000d**	**CA**	**M**	**27**	**-**
AUT	**B5342**	**11y000d**	**CA**	**F**	**12.9**	***MECP2* g.-1398 T>C variant**
AUT (suspected)	**732**	**15y146d**	**CA**	**M**	**28**	**-**
AUT	**1638**	**20y000d**	**CA**	**F**	**50**	***MECP2* c.1035 A>G variant**
AUT	**4999**	**20y000d**	**CA**	**M**	**14**	**-**
AUT	**5176**	**22y199d**	**AA**	**M**	**18**	**-**
AUT	**B5000**	**27y000d**	**CA**	**M**	**8.3**	**-**
AUT	**5027**	**37y353d**	**AA**	**M**	**26**	**-**
RTT	**B4687**	**08y000d**	**CA**	**F**	**2.9**	***MECP2* p.R255X mutation**
RTT	**B5214**	**10y000d**	**ND**	**F**	**24**	***MECP2* p.R270X mutation**
RTT	**1815**	**18y130d**	**CA**	**F**	**5**	***MECP2* c.378-2 A>G mutation**
RTT	**B5075**	**20y000d**	**ND**	**F**	**14.1**	**Mut(-)**
RTT	**1420**	**21y022d**	**CA**	**F**	**18**	**Mut(-)**
RTT	**1748**	**22y017d**	**CA**	**F**	**8**	**Mut(-)**
RTT	**B5020**	**24y000d**	**CA**	**F**	**15.8**	***MECP2* p.R255X mutation**

Supplementary Table 2 Frontal cortices used for RT-PCR analyses.

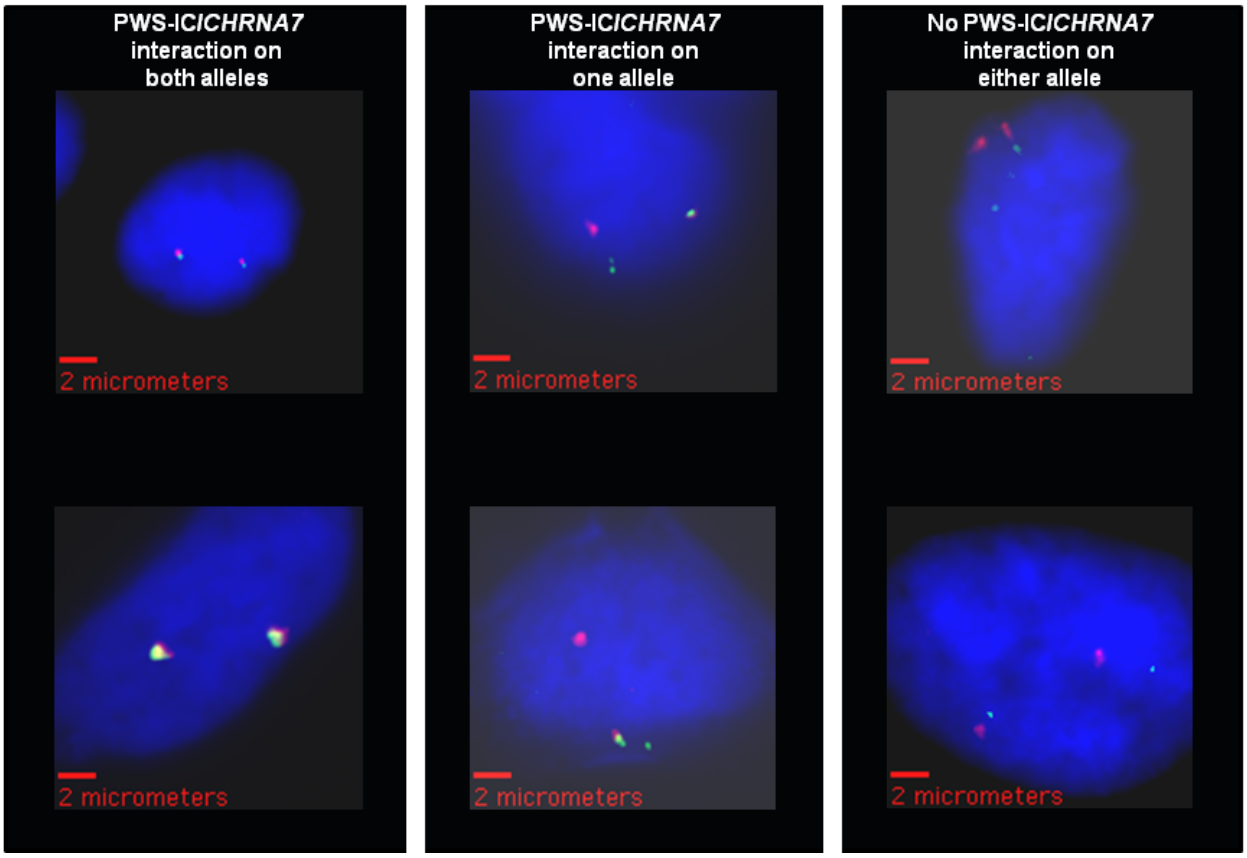
Brodmann area 9 from frozen brain samples were obtained through the Autism Speaks supported Autism Tissue Program (ATP) at the Harvard Brain Tissue Resource Center (HBTRC) and the University of Maryland Brain Tissue Resource Center and from the University of Miami Brain and Tissue Bank for Neurodevelopmental Disorders. ***MECP2*** mutations are listed if known. – means no data was available.



Supplementary Figure 5 4C analysis of the *TJP1* locus serves as a negative control for PWS-IC interaction with *CHRNA7*

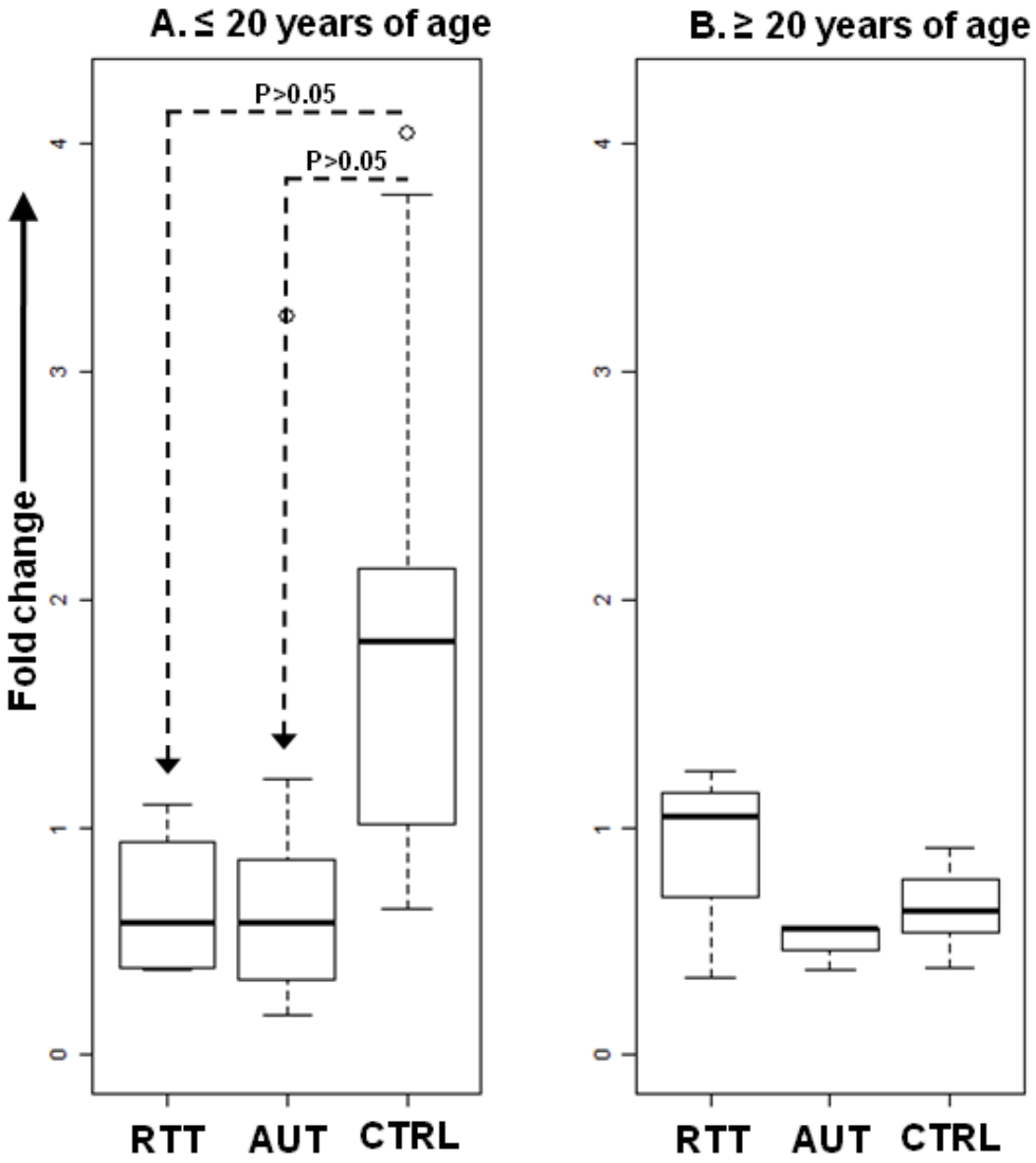
A. 4C analysis does not show PWS-IC interaction with *TJP1*. 4C analysis was performed in SH-SY5Y neurons and neuroblasts where the absence of Log 2 signal peaks (histograms) suggests that the PWS-IC does not contact *TJP1* during neuronal maturation. These results are consistent with FISH results shown in **B**.

B. FISH analysis shows low levels of PWS-IC interaction with the 15q11.2-13-3 control locus *TJP1*. Genomic BAC clones complementary to the PWS-IC and *TJP1* loci were differentially detected as green and red fluorescent signals respectively. PWS-IC and *TJP1* signals were considered associated if the signals were in contact or had any overlap. Nuclei from undifferentiated neuroblasts (SH-SY5Y) and maturing (SH-SY5Y+PMA) neurons were scored for signal overlap in each allele and the possible combinations were graphed as a percentage of total nuclei. Representative images of unassociated PWS-IC and *TJP1* signals are shown in the lower panel at right.



Supplementary Figure 6 Additional images of PWS-IC and CHRNA7 allelic association patterns.

FISH analysis as shown in Figure 3 confirms that the PWS-IC makes specific contact with *CHRNA7* in maturing SH-SY5Y neurons. PWS-IC signals are shown in green and CHRNA7 alleles are shown by red signals. Unprocessed versions of PWS-IC and *CHRNA7* interaction images shown in Figure 3 are shown in the top row while additional examples of PWS-IC and *CHRNA7* interactions patterns are shown below. A scale bar representing 2 micrometers is shown on the original images.



Supplementary Figure 7 ***CHRNA7*** transcripts are significantly reduced in Rett and autism cortices from patients 20 years of age and younger. Box plots were generated using the R software package from *CHRNA7* QRT-PCR data generated from analysis of typically developing (n=20), Rett syndrome (n=7), and autism (n=11) human cortices. (**A**) QRT-PCR results from patients no older than 20 years old reveal that both Rett

syndrome (p=0.04226, n=4) and autism (p=0.01834, n=8) showed a significant (p<0.05) reduction in *CHRNA7* transcripts. (**B**) However, after the age of 20 there is no significant decrease in *CHRNA7* expression for either disease phenotype. Two-tailed p-values were derived from Mann-Whitney U test.

Supplementary Figure 8 MeCP2 protein levels are reduced in SH-SY5Y neurons following treatment with *MECP2* targeted small interfering RNA (siRNA). Protein from specific siRNA treated (MeCP2) versus control siRNA (control) was assayed by western blot analysis using antibodies against MeCP2 (anti-MeCP2) and GAPDH (anti-GAPDH) as a protein loading control.