Supplementary Table S1. Imaging studies of patients in Rett syndrome with *MECP2* mutation

Imaging modality	Imaging phenotype	Samples size (mean age in years)	Primary results	Reference
MRI	Dimensions of cerebral, cerebellum, and brainstem structures	13 RTT (12.0); 10 HC (15.4)	↓ Global hypoplasia of brain (cerebral, cerebellum, corpus callosum and brainstem) ↓ Progressive cerebellar atrophy increasing with age	Murakami et al. 1992 (52)
	TBV, cortical GM and WM Subcortical gray nuclei CSF volumes	11 RTT (10.1); 15 HC (11.2)	↓ Volumes in cerebrum, basal ganglia, and brainstem ↓ Loss of GM in comparison to WM, with largest decrease in frontal regions and CN and midbrain volume	Reiss et al. 1993 (43)
	TBV, cortical GM and WM, Subcortical GM, CSF and posterior fossa volumes	20 RTT (9.8); 20 HC (9.0)	↓ GM volume most pronounced in prefrontal, posterior-frontal, and anterior-temporal regions ↓ WM volume uniformly throughout brain ↓ CN volume No differences in midbrain volumes	Subramaniam et al. 1997 (44)
	Quantitative shape analysis	8 RTT (5.3); 10 HC (7.0)	↓ Whole brain hemisphere ↓ Both right and left caudate	Manuel et al. 1991 (51)
	Absolute and relative changes in GM and WM volumes	22 RTT (8.6) ((12 more severe (8.8); 10 less severe (8.3)); 25 HC (8.9)	↓ TBV ↓ Relative parietal lobe GM volume, particularly dorsal ↓ Cortical WM volume ↓ Anterior frontal lobe volumes in more	Carter et al. 2008 (50)

			severely affected subjects	
	Surface- and voxel-based brain morphological measurements including cortical thickness and cortical gyrification, global/regional GM and WM volumes	7 RTT (5.2); 16 HC (gender- and age-matched)	↓ Decreased total volumes of the cerebellum. No differences in global cerebral cortical surface areas, global/regional cortical thicknesses, the degree of global gyrification, and global/regional gray and white matter volumes	Shiohama et al. 2019 (54)
	Volumetric measurements of basal ganglia	9 RTT (18.4); 9 HC (20-29 years)	↓ Significant reduction in the size of the caudate heads and thalami	Dunn et al. 2002 (53)
DTI	FA	32 RTT (5.5); 37 HC (6.1)	↓ FA in genu and splenium of CC and external capsule, and regions of cingulate, internal capsule, posterior thalamic radiation, and frontal WM. No differences in visual pathways ↓ FA in superior longitudinal fasciculus in patients who were nonverbal or speaking only single words	Mahmood et al. 2010 (68)
	FA	9 RTT; 13 HC (gender- and age-matched)	↓ FA in the left peripheral white matter areas (the middle temporal, middle occipital, pre-cuneus, and the post-central white matter) ↓ FA in left major white matter tracts (the superior longitudinal fasciculus, sagittal stratum, corpus callosum)	Oishi et al. 2013 (48)

			↓ FA in the bilateral cingulum	
MRS	NAA, Glu/Gln, Cho, Cre, and GABA	9 RTT (9.9)	↓ NAA decreased with increasing age ↓ Glu/Gln decreased ↓ Cho, Cre slightly decreased ↑ GABA increased	Hanefeld et al. 1995 (94)
	Glu, Cr, and NAA	6 RTT (4.5-6 years); 4 HC (5.5-13 years)	↓ NAA level reduced ↑ Cr/NAA ratio was elevated in WM, and normal in GM ↑ Glu/NAA ratio was elevated in GM, and normal in WM	Pan et al. 1999 (93)
	NAA, Cr, Cho, and mI peaks were quantitatively evaluated NAA/Cr, NAA/Cho, and Cho/Cr, mI/Cr ratios were calculated	7 RTT (7.7); 5 HC (6.4)	↓ NAA level reduced ↓ Decreases in NAA/Cr, and NAA/Cho radios. No differences in Cho/CR ratios and mI/Cr ratios.	Gokcay et al. 2002 (92)
SPECT	Brain blood flow detected with ^{133}Xe SPECT	7 RTT (10.1); 9 HC (13.6)	↓ Global CBF Hypoperfusion foci were located mainly in the prefrontal and temporoparietal areas	Nielsen et al. 1990 (72)
	Brain blood flow detected with ^{99m}Tc-ECD SPECT	12 RTT (11.4); 9 HC (7.3)	↓ Global reduction in cerebral perfusion, especially in the frontal and fronto-parietal regions bilaterally ↓ Brain perfusion abnormalities were more often in stage IV than the stage III No significant right-to-left asymmetry was found in any ROIs of the cortex	Burroni et al. 1997 (74)

	rCBF detected with ^{99m}Tc-HMPAO SPECT	13 RTT (8.4); 9 HC (-)	↓ Frontal hypoperfusion was the most frequent abnormality ↓ Parietal and temporal hypoperfusion was detected in some patients No hypoperfusion in occipital lobes	Lappalainen et al. 1997 (73)
	rCBF detected with ^{133}Xe SPECT	11 RTT (7.9); 8 HC (8.1)	No significantly difference in young RTT patients	Chiron et al. 1993(75)
	^{123}I-Iodolisuride detected striatal D_2 receptors	11 RTT (7.9); 8 HC (8.1)	↑ Increased ^{123}I-Iodolisuride uptake in the striatum	Chiron et al. 1993(75)
	Evaluate BZD receptor binding in adult females with stage IV RTT by using ^{123}I- iomazenil	3 RTT (34.3); 5 HC (24-61 years)	↓ A decreased in BZD receptor binding in the cortex of adult patients with RTT ↓ The BP for the BZD receptor was significantly decreased in the fronto-temporal cortex of the RTT patients	Yamashita et al. 1998 (87)
PET	CBF, $CMRO_2$	6 RTT (8.7); 3 HC (6.3)	↓ CBF reduced in the frontal cortex and the temporal cortex ↓ $CMRO_2$ reduced in the frontal cortex and the temporal cortex	Yoshikawa et al. 1991 (76)
	CBF, $CMRO_2$ by using ^{15}O labeled water	4 adult RTT; age-matched HC	↓ CBF in the frontal regions	Naidu et al. 2001 (6)
	Uptake of ^{18}F-FDG	6 RTT (9); 18 HC (age-matched)	↑ Significant increase in relative glucose utilization was observed in the frontal areas in the younger group ↑ Increase in cerebellar glucose metabolism in both age group ↓ The lower relative glucose metabolism	Villemagne et al. 2002 (78)

			detected in the occipital visual association areas in both age group	
	Uptake of ^{18}F-FDG	RTT compared with HC	↓ Decrease in visual association areas of the occipital lobe ↑ Raised in the cerebellum	Naidu et al. 1992 (81)
	Uptake of ^{18}F-6-fluorodopa and ^{11}C-raclopride	9 RTT (18.4); 9 HC (20-29 years)	↓ Fluorodopa was reduced in caudate and putamen ↑ Dopamine D_2 receptor binding was increased in caudate and putamen	Dunn et al. 2002 (53)
	Uptake of ^{11}C-N-methyl-spiperone	12 RTT (15-39); HC (age-matched)	Low normal levels of post-synaptic D_2Rs in caudate	Naidu et al. 2001 (6)
	3-N-^{11}C-methylspiperone uptake detect D_2R	10 RTT (20.7); 16 HC (age-matched)	↓ D_2R was significantly lower in women with RTT with no significant age-related changes	Wong et al. 2018 (82)
	^{11}C-WIN35,428 uptake detect DAT	9 RTT (20.8); 8 HC (age-matched)	↓ DAT density was lower in the caudate in women with RTT	Wong et al. 2018 (82)

^{18}F-FDG, fluorine 18-fluorodeoxyglucose; PET, positron emission tomography; BZD, benzodiazepine; CBF, cerebral blood flow; CC, corpus callosum; Cho, choline; CMRO, cerebral metabolic rate of oxygen; CN, caudate nudeus; Cr, creatine; CSF, cerebrospinal fluid; D_2R, D_2 dopamine receptor; DAT, dopamine transporter; DTI, diffusion tensor imaging; FA, fractional anisotropy; GM, gray matter; HC, health control; *MECP2*, methyl-CpG binding protein gene 2; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, N-acetyl aspartate; ROI, regions of interest; RTT, Rett syndrome; SPECT, single positron emission computed tomography; TBV, total brain value; WM, white matter.