Supplementary Table S3. Pathophysiological mechanism, clinical phenotypes, and therapeutic targets in different neurons with *MECP2* deletions

Neuron types	Pathophysiological mechanism	Clinical phenotypes	Therapeutic targets
Dopaminergic neurons	Affect dopaminergic nervous system	Motor disorder: stereotyped hand-wringing, progressive rigidity, dyskinesia, and dystonia	Dopaminergic agents: levodopa and benserazide
Cholinergic neurons The basal forebrain-hippocampus The striatum	Affect cholinergic neural circuit Up-regulation of α2-GABA receptor	Anxiety/depression-related behavioral changes, abnormal social skills, susceptibility to epilepsy, and loss of fear memory	Cholinergic Drugs: Choline
GABAergic neurons Brain stem / basal forebrain The hippocampus	GABAergic signaling dysfunction	Repetitive behaviors, impaired motor coordination, increased social interest, and altered sensorimotor gating and arousal	GABAergic modulators: $GABA_A$ antagonist GABA reuptake inhibitors
Forebrain excitatory neurons	Down-regulation GABA receptor	Motor disorder, increased anxiety-like behaviors and impaired fear conditioning and social behavior	GABAergic modulators
Glutamatergic neurons The frontal cortices The hippocampus	Glutamatergic signaling dysfunction leads to repetitive glutamate transients	The motor performance, clasping behavior and fear-conditioning defects, sleep dysfunction, susceptibility to epilepsy	Glutamatergic modulators: NMDA receptor antagonist mGlu5 modulator
BDNF expression neurons The cerebral cortex, hippocampus and cerebellum	BDNF-TrkB signaling dysfunction: Decrease in BDNF and TrkB receptor protein levels	Motor deficits, breathing dysfunction, heart rate disorder, neural morphology abnormality, life span influence	Growth factor therapy BDNF mimetics or boosters
HDAC expression neurons	HDAC overexpression and decrease in acetylated tubulin levels Affect BDNF signaling	Motor deficits, breathing dysfunction, heart rate disorder, neural morphology abnormality, life span influence	HDAC inhibitors
Serotoninergic neurons	Down-regulation serotonin receptor	Increased aggression, irregular breathing and apnoea	Serotonin receptor agonist Dopamine D_2 partial agonist
Catecholaminergic neurons Neurons in the locus coeruleus	Norepinephrine system dysfunction	Impairment of cognitive and attention, anxiety, psychosis, motor disorder, breathing	Adrenergic receptor agonist

The brain stem		dysfunction, and social abnormalities	
***Sim1*-expressing neurons in the hypothalamus**	Disruptes MC4R signaling pathway Decreased expression of *Crh* and BDNF in PVN	Alterations in feeding behavior, aggression and stress response	Adrenergic drugs BDNF mimetics or boosters
Somatosensory neurons in the barrel cortex	Impaired E/I balance	Leads to anxiety, social interaction abnormalities, and tactile sensory and motor problems	Antidepressants

BDNF, brain-derived neurotrophic factor; *Crh*, Corticotropin-Releasing Hormone; E/I, excitation/inhibition; GABA, γ-aminobutyric acid; HDAC, histone deacetylase; *MECP2*, methyl-CpG binding protein gene 2; mGlu5, metabotropic glutamate 5 receptor; NMDA, *N*-methyl-D-aspartate; PVN, paraventricular nucleus; TrkB, tyrosine receptor kinase B.