Summary of CK2a K198R/+ mouse model

Cruz-Gamero JM, Ballardin D, Lecis B, Zhang CL, Cobret L, Gast A, Morisset-Lopez S, Piskorowski R, Langui D, Jose J, Chevreux G, Rebholz H. **Missense mutation in the activation segment of the kinase CK2 models Okur-Chung neurodevelopmental disorder and alters the hippocampal glutamatergic synapse.** *Mol Psychiatry*. 2025 Apr;30(4):1497-1509. doi: 10.1038/s41380-024-02762-8. Epub 2024 Oct 4. PMID: 39367055.

📌 1. Molecular & Biochemical Assays

Assay	Purpose	Findings (compared to WT)	Figure Reference
Western blot (striatal lysates)	- Quantify CK2 subunits (α, α', β) - Quantify substrate phosphorylation	- No change in α, α', β protein levels - K198R/+ showed ↓ pS97 DARPP-32 ; ↑ pS240/244 S6 ribosomal protein; no difference in pS129 AKT; trend toward increased phosphorylation of Ser473 AKT	Fig. 2A-D, G-K
qPCR	CK2α mRNA expression	No difference between genotypes	Fig. 2E
Capillary electrophoresis-based CK2 activity assay	Measure net CK2 kinase activity in brain extracts	~25 % reduction in CK2 activity in K198R/+ mice	Fig. 2F
Immunohistochemistry (coronal brain slices)	CK2α subcellular localization	Predominantly nuclear and excluded from nucleoli, but also present in dendrites or axons; no change between WT and K198R/+	Fig. S2A, B
Mass spectrometry (phosphoproteomics)	Identify altered phosphorylation sites and pathways	13,017 phosphopeptides detected; 394 changed ≥ 1.5-fold (231 enriched in K198R/+ mice; synaptic proteins most affected; glutamatergic synapse as the primary affected pathway	Fig. 3A-E
Bioinformatic sequence logos (weblogos)	Assess CK2 substrate consensus changes	Showed altered acidic residue preferences in mutant CK2 substrates	Fig. 3F, G

🧠 2. Morphological and Structural Measures

Assay	Readout	Finding (compared to WT)	Figure Reference
Embryonic viability and gross morphology (E10.5–E15.5)	Heart and neural tube defects	At E11.5, homozygotes non-viable; 50 % of K198R/+ mutants were viable and resembled WT, others exhibited heart defects, developmental delays and resembled homozygotes at E10.5 Hets born at a lower-than-expected mendelian ratio	Fig. 1A-C
Body weight curve and femur length	Growth assessment	K198R/+ mice show ↓ Body weight; ↓ femur length	Fig. 1E, F
Survival	Survival	K198R/+ mice have ↑ mortality rates during adulthood	Fig. 1D
Brain morphometry	Brain dimensions and ventricular volume	K198R/+ show normal brain length, width, and height; ↑ lateral ventricle area; ↓ corpus callosum height/thickness	Fig. 1G-M
Electron microscopy (hippocampus)	Synapse ultrastructure	K198R/+ mice show no difference in presynaptic vesicles per synapse or post synaptic density thickness; ↑ postsynaptic density disc diameter and ↑ synapse density	Fig. 4A-F
Primary neuron culture + Sholl analysis	Dendritic branching	No difference between WT and K198R/+	Fig. 4G
Immunostaining (VGLUT1 + PSD-95)	Synapse formation quantification	K198R/+ mice show ↓ colocalized puncta → reduced synapse formation	Fig. 4H, I

⚡ 3. Electrophysiological Assay

Assay	Region	Finding (compared to WT)	Figure Reference
Field extracellular recordings (LTP)	Hippocampus CA3→CA1 pathway	Theta-burst stimulation revealed attenuated long-term potentiation in K198R/+ mice (↓ early and late phases)	Fig. 5A-E

🧩 4. Behavioral Assays

Domain	Assay	Readout	Outcome (compared to WT)	Figure Reference
Working memory	Y-maze spontaneous alternation	% of alternations	K198R/+ mice show ↓ alternation performance	Fig. 6A
Reference memory	Y-maze recognition	Novel vs familiar arm entries	No difference	Fig. S6A
Spatial learning & flexibility	Barnes maze	Escape latency & probe time	Normal learning/reversal; no deficit in spatial learning or cognitive flexibility in K198R/+ mice	Fig. 6B, C
Fear memory	Contextual & cued conditioning	% freezing	K198R/+ mice show ↓ contextual and cue recall	Fig. 6D, E
Sensorimotor gating	Prepulse inhibition (PPI)	Startle amplitude & % PPI	K198R/+ mice show ↓ amplitude and PPI	Fig. 6F, G
Repetitive behavior	Home-cage rearings	Count of rearings (3–4 a.m.)	K198R/+ mice show ↑ rearings per hour	Fig. 6H
Cognitive self-care	Nesting test	Scored nest quality	K198R/+ mice show ↓ nesting score	Fig. 6I
Perseveration / anxiety	Marble burying test	# buried marbles	K198R/+ mice show ↓ # of marbles buried	Fig. 6J
Activity	Open field test	Distance traveled	K198R/+ mice show slight hypoactivity in first 20 min	Fig. 6K
Social interaction	Three-chamber assay	Time with stranger mouse	K198R/+ mice show normal sociability	Fig. S7B-D
Motor coordination	Rotarod	Latency to fall	K198R/+ mice show normal performance	Fig S7E
Grip strength	Two-paw / inverted screen	Force and duration	K198R/+ mice show normal grip strength	Fig S7F, G
Seizure susceptibility	Picrotoxin challenge	Latency to immobilization/seizure	K198R/+ mice show earlier seizure and immobilization onset in K198R/+ mice	Fig. 6L, M
Anxiety / mood	Light-dark box, novelty suppressed feeding	Time in light box / latency to feed	K198R/+ mice show ↓ anxiety	Fig. S8A, B

Domain	Assay	Readout	Outcome (compared to WT)	Figure Reference
Stress metrics	Elevated plus maze, tail suspension, forced swim	Exploration & immobility	No difference	Fig. S8C-E

✅ **Summary of Major Phenotypes Validated in CK2a K198R/+ Mice**

- Embryonic lethality (homozygotes), reduced viability in hets
- Reduced growth and femur length
- Larger ventricles + thinner corpus callosum
- Reduced CK2 activity and DARPP-32 phosphorylation
- Synaptic plasticity deficit
- Cognitive impairments
- Increased repetitive behaviors, poorer nesting, altered seizure threshold