GENES FROM THE PHEWAS STUDIES WITH POTENTIAL ASSOCIATION (DIRECT/INDIRECT) TO RLS IN MICE

{Phewas1 and 2 groups}

1. Map2k5

- **What It Is and Does in Mice:** *Map2k5* encodes a kinase that activates ERK5 in the MAPK/ERK5 pathway. In mice, it's essential for embryonic cardiovascular development (knockouts die at E10.5 due to heart defects), neuroprotection (e.g., in cortex, hippocampus), and stress responses, with high expression in brain, heart, and skeletal muscle.
- **Relation to RLS in Mice:** No direct mouse studies link *Map2k5* to RLS. However, its human GWAS association with RLS (e.g., Yang et al., 2011) and its role in neuronal survival and motor control suggest a potential indirect link. Conditional brain knockouts show motor changes (e.g., anxiety-like behavior), which could resemble RLS-like restlessness if tested in sleep/movement assays.
- **Pharmacological/Brain Imaging Links in Mice:**
    - **Dopaminergic:** ERK5 signaling might influence dopamine neurons (e.g., substantia nigra), but no mouse studies confirm this for RLS**.**
    - **Opiate:** No opiate pathway evidence in mice.
    - **Iron:** No iron-related data in mice.
    - **Studies:** Limited mouse-specific imaging/pharmacology; brain expression supports hypothetical dopaminergic/stress roles.

2. Ptprd

- **What It Is and Does in Mice:** *Ptprd* encodes a receptor tyrosine phosphatase regulating synaptic organization and neuronal development, expressed in mouse brain (e.g., cortex, hippocampus, striatum). Knockouts show impaired learning and motor coordination.

- **Relation to RLS in Mice:** No direct RLS models exist, but *Ptprd* is a strong human RLS candidate (Schormair et al., 2008). In mice, knockouts exhibit motor deficits, suggesting a possible RLS-like phenotype if studied in sleep or locomotor contexts**.**
- **Pharmacological/Brain Imaging Links in Mice:**
    - **Dopaminergic:** Expressed in striatum; knockouts alter synaptic plasticity, potentially affecting dopamine signaling relevant to RLS.
    - **Opiate:** No opiate link.
    - **Iron:** No iron evidence.
    - **Studies:** No RLS-specific mouse imaging/pharmacology, but synaptic roles hint at striatal involvement.

3. Ccdc148

- **What It Is and Does in Mice:** *Ccdc148* encodes a coiled-coil protein with unclear function, minimally studied in mice. Expression is low and nonspecific (e.g., testis, per MGI).
- **Relation to RLS in Mice:** No evidence ties *Ccdc148* to RLS in mice or humans.
- **Pharmacological/Brain Imaging Links in Mice:**
    - **Dopaminergic/Opiate/Iron:** No known roles.
    - **Studies:** No mouse data for RLS or pathways.

4. Crbn

- **What It Is and Does in Mice**: *Crbn* encodes a ubiquitin ligase component, expressed in the mouse brain (e.g., cerebellum). Knockouts show learning deficits and are models for thalidomide effects.
- **Relation to RLS in Mice**: No RLS association in mice.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic**: Possible indirect effect on dopamine neurons via protein regulation, untested.
    - **Opiate/Iron**: No links.
    - **Studies**: No RLS-specific mouse studies

5. Sumf1

- **What It Is and Does in Mice**: *Sumf1* encodes an enzyme activating sulfatases, vital for lysosomal function. Knockouts in mice cause multiple sulfatase deficiency, with brain and skeletal defects.
- **Relation to RLS in Mice**: No RLS link in mice.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No direct roles.
    - **Studies**: No RLS-related mouse data.

6. Lrrn1

- **What It Is and Does in Mice**: *Lrrn1* encodes a neuronal adhesion protein involved in synapse formation, expressed in mouse brain (e.g., cortex, hippocampus). Knockouts affect neural connectivity.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic**: Possible striatal role, untested for RLS.
    - **Opiate/Iron**: No evidence.
    - **Studies**: No RLS mouse studies.

7. Dach1

- **What It Is and Does in Mice**: *Dach1* encodes a transcription factor regulating eye, limb, and brain development, expressed in mouse retina and neural tissues. Knockouts show developmental defects.
- **Relation to RLS in Mice**: No RLS link.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No roles.
    - **Studies**: No RLS data.

8. Cd1 (Cd1d1 in Mice)

- **What It Is and Does in Mice**: *Cd1d1* encodes an MHC-like protein presenting lipid antigens to NKT cells, expressed in immune cells, not neurons.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No neural roles.
    - **Studies**: No RLS relevance.

9. Mir196a-1

- **What It Is and Does in Mice**: *Mir196a-1* is a microRNA regulating Hox genes, involved in limb and neural patterning. Knockouts alter development.
- **Relation to RLS in Mice**: No RLS link.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: No RLS mouse data.

10. Myt1

- **What It Is and Does in Mice**: *Myt1* encodes a transcription factor promoting neuronal differentiation and myelination, expressed in mouse brain (e.g., oligodendrocytes). Knockouts impair myelination.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No roles.
    - **Studies**: No RLS data.

11. Pik3r4

- **What It Is and Does in Mice**: *Pik3r4* encodes a PI3K regulatory subunit involved in autophagy, expressed in mouse brain and other tissues. Knockouts affect cellular homeostasis.
- **Relation to RLS in Mice**: No RLS link.
- **Pharmacological/Brain Imaging Links in Mice**:

    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: No RLS mouse studies.

12. Atp2c1

- **What It Is and Does in Mice**: *Atp2c1* encodes a calcium pump maintaining cellular calcium levels, expressed in mouse brain and muscle. Knockouts cause skin and neural defects.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No ties.
    - **Studies**: No RLS data.

13. Igf1

- **What It Is and Does in Mice**: *Igf1* encodes a growth factor promoting neurogenesis and muscle growth, expressed in the mouse brain (e.g., hippocampus). Knockouts show growth retardation.
- **Relation to RLS in Mice**: No direct RLS link, but neural repair roles are speculative.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic**: Supports dopamine neuron survival indirectly, untested for RLS.
    - **Opiate/Iron**: No links.
    - **Studies**: No RLS-specific mouse data.

14. Kif5a

- **What It Is and Does in Mice**: *Kif5a* (kinesin family) encodes a motor protein for axonal transport, expressed in mouse neurons. Knockouts cause neurodegeneration.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:

    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: No RLS mouse data.

15. Pmch

- **What It Is and Does in Mice**: *Pmch* encodes a neuropeptide regulating appetite and sleep, expressed in mouse hypothalamus. Knockouts alter sleep and feeding.
- **Relation to RLS in Mice**: No direct RLS link, but sleep disruption could overlap with RLS symptoms (hypothetical).
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate**: Hypothalamic influence possible, untested.
    - **Iron**: No link.
    - **Studies**: No RLS mouse studies.

16. Ranbp17

- **What It Is and Does in Mice**: *Ranbp17* encodes a nuclear transport protein, expressed in the mouse brain. Function is poorly defined; knockouts are unstudied.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: No RLS data.

17. Slc40a1

- **What It Is and Does in Mice**: *Slc40a1* (Ferroportin) encodes an iron exporter, critical for brain and systemic iron homeostasis, expressed in mouse brain (e.g., neurons, glia). Knockouts cause iron overload or deficiency depending on context.

- **Relation to RLS in Mice**: Yes, indirectly. Iron deficiency in the brain is a hallmark of RLS; *Slc40a1* dysregulation in mice mimics this, though not directly tested in RLS models.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Iron**: Key role in brain iron export; knockouts show iron deficits in neurons (e.g., Connor et al., 2011).
    - **Dopaminergic**: Iron-dopamine interplay suggested, but unproven in mice for RLS.
    - **Opiate**: No link.
    - **Studies**: Mouse iron imaging (e.g., MRI) exists, but not RLS-specific.

18. Syt4

- **What It Is and Does in Mice**: *Syt4* encodes a synaptotagmin protein regulating neurotransmitter release, expressed in mouse brain (e.g., hippocampus). Knockouts impair synaptic function.
- **Relation to RLS in Mice**: No RLS link.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic**: Possible dopamine release role, untested for RLS.
    - **Opiate/Iron**: No evidence.
    - **Studies**: No RLS mouse data.

19. Tox3

- **What It Is and Does in Mice**: *Tox3* encodes a transcription factor involved in neuronal development, expressed in the mouse brain (e.g., cortex). Knockouts affect neural differentiation.
- **Relation to RLS in Mice**: No direct mouse RLS studies, but human GWAS links *TOX3* to RLS (Moore et al., 2014). Mouse motor phenotypes are untested but plausible.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic**: Possible striatal role, unproven.
    - **Opiate/Iron**: No links.

    - **Studies**: No RLS-specific mouse data.

20. Micall2

- **What It Is and Does in Mice**: *Micall2* encodes a cytoskeletal protein, expressed in mouse brain and muscle. Function is unclear; knockouts are unstudied.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: No RLS data.

21. Uncx

- **What It Is and Does in Mice**: *Uncx* encodes a transcription factor regulating spinal cord and cerebellar development, expressed in mouse neural tissues. Knockouts impair motor neuron development.
- **Relation to RLS in Mice**: No RLS link, but spinal role is intriguing.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No ties.
    - **Studies**: No RLS mouse data.

22. Utrn

- **What It Is and Does in Mice**: *Utrn* encodes utrophin, a cytoskeletal protein supporting neuromuscular junctions, expressed in mouse muscle and brain. Knockouts enhance muscular dystrophy phenotypes.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: No RLS data.

Key Insights (Mouse-Specific)

- **RLS-Linked Genes in Mice**:
    - *Slc40a1*: Strongest candidate due to its iron export role; knockouts mimic brain iron deficiency, a known RLS feature in mice (e.g., *Btbd9* models).
    - *Map2k5*, *Ptprd*, *Tox3*: Indirect links via human GWAS and mouse neuronal/motor roles, but no direct RLS models. Knockout phenotypes (e.g., motor changes) suggest potential if tested.
    - *Pmch*: Hypothetical link via sleep regulation, untested.
- **Dopaminergic Pathways**: *Ptprd*, *Map2k5*, *Tox3*, *Syt4*, *Igf1*, *Pmch* have plausible but unconfirmed roles in dopamine-related regions (e.g., striatum, substantia nigra) in mice.
- **Iron Pathways**: *Slc40a1* is the only gene with a clear iron role in mice, supported by knockout studies showing brain iron deficits.
- **Mouse Studies**: Sparse RLS-specific pharmacological or imaging data in mice for these genes. *Slc40a1* has some iron-related imaging (e.g., MRI in iron deficiency models), but others rely on human RLS associations or general mouse knockout phenotypes.

{Phewas1 and 2 groups}

1. Gria1

- **What It Is and Does in Mice**: *Gria1* encodes a subunit of AMPA-type glutamate receptors (GluA1), critical for synaptic transmission and plasticity, highly expressed in mouse brain (e.g., hippocampus, cortex).
- **Relation to RLS in Mice**: No direct RLS link in mice or humans. Its role in excitatory signaling could theoretically affect motor control, but no evidence exists.
- **Pharmacological/Brain Imaging Links in Mice**:

    - **Dopaminergic**: Indirectly influences dopamine-glutamate interactions in striatum; no RLS-specific data.
    - **Opiate/Iron**: No links.
    - **Studies**: Mouse imaging (e.g., fMRI) shows *Gria1* in synaptic activity, but not RLS-related.

2. Lingo2

- **What It Is and Does in Mice**: *Lingo2* encodes a leucine-rich repeat protein involved in neuronal development, expressed in mouse brain (e.g., cortex). Function is poorly defined.
- **Relation to RLS in Mice**: No RLS association in mice or humans.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: No RLS mouse data.

3. Loc101927870 (Human SLC26A5-AS1; Mouse Reln)

- **What It Is and Does in Mice**: *Reln* encodes reelin, an extracellular matrix protein guiding neuronal migration and synaptic plasticity, expressed in mouse brain (e.g., cortex, cerebellum). Knockouts cause ataxia (reeler phenotype).
- **Relation to RLS in Mice**: No direct RLS link. Motor deficits in knockouts suggest a speculative connection, untested.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic**: Possible striatal role, but no RLS evidence.
    - **Opiate/Iron**: No links.
    - **Studies**: Mouse imaging shows cerebellar defects, not RLS-specific.

4. Mllt10

- **What It Is and Does in Mice**: *Mllt10* encodes a transcriptional regulator involved in hematopoiesis and chromatin remodeling, expressed in mouse brain and blood cells.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: No RLS mouse data.

5. Camk2g

- **What It Is and Does in Mice**: *Camk2g* encodes a calcium/calmodulin-dependent kinase (CaMKIIγ) involved in synaptic plasticity and memory, expressed in mouse brain (e.g., hippocampus).
- **Relation to RLS in Mice**: No RLS link.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic**: Possible dopamine modulation in striatum, untested for RLS.
    - **Opiate/Iron**: No links.
    - **Studies**: Mouse imaging (e.g., calcium imaging) exists, not RLS-related.

6. Negr1

- **What It Is and Does in Mice**: *Negr1* encodes a neuronal growth regulator involved in synapse formation, expressed in mouse brain (e.g., hippocampus). Knockouts show social behavior changes.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence.

    - **Studies**: No RLS mouse data.

7. Sgcz

- **What It Is and Does in Mice**: *Sgcz* encodes zeta-sarcoglycan, a dystrophin-associated protein in muscle and brain, maintaining membrane stability. Knockouts affect muscle function.
- **Relation to RLS in Mice**: No RLS link.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No roles.
    - **Studies**: No RLS mouse data.

8. Sema6d

- **What It Is and Does in Mice**: *Sema6d* encodes a semaphorin protein guiding axon growth, expressed in mouse brain (e.g., cortex, spinal cord). Knockouts impair neural wiring.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence; spinal role is intriguing but untested.
    - **Studies**: No RLS mouse data.

9. Ca10; Linc01982 (Mouse Car10)

- **What It Is and Does in Mice**: *Car10* encodes carbonic anhydrase X, a neuronal enzyme regulating pH, expressed in mouse brain (e.g., cerebellum). Function is unclear.

- **Relation to RLS in Mice**: No RLS link.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No roles.
    - **Studies**: No RLS mouse data.

10. Pou6f2

- **What It Is and Does in Mice**: *Pou6f2* encodes a transcription factor regulating retinal and brain development, expressed in mouse retina and cortex.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: No RLS mouse data.

11. Nfe2l1

- **What It Is and Does in Mice**: *Nfe2l1* (Nrf1) encodes a transcription factor regulating antioxidant responses and proteostasis, expressed in mouse brain and other tissues.
- **Relation to RLS in Mice**: No RLS link.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No direct roles; oxidative stress could overlap with RLS, untested.
    - **Studies**: No RLS mouse data.

12. Linc01568; Loc101928035 (Mouse Zfhx3)

- **What It Is and Does in Mice**: *Zfhx3* encodes a zinc finger transcription factor regulating circadian rhythms and neural development, expressed in mouse brain (e.g., hypothalamus).
- **Relation to RLS in Mice**: No direct RLS link, but circadian role might overlap with RLS sleep disruption (speculative).
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: Mouse circadian imaging exists, not RLS-specific.

13. Kcnk13

- **What It Is and Does in Mice**: *Kcnk13* encodes a potassium channel (TASK-3) regulating neuronal excitability, expressed in mouse brain (e.g., cerebellum).
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No roles.
    - **Studies**: No RLS mouse data.

14. Trim35

- **What It Is and Does in Mice**: *Trim35* encodes a TRIM family ubiquitin ligase, possibly involved in immune responses, with low brain expression in mice.
- **Relation to RLS in Mice**: No RLS link.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: No RLS mouse data.

15. Linc01812; C1d

- **What It Is and Does in Mice**: *C1d* encodes a nuclear protein involved in DNA repair, expressed ubiquitously in mice, including brain.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No roles.
    - **Studies**: No RLS mouse data.

16. Lig3

- **What It Is and Does in Mice**: *Lig3* encodes DNA ligase III, essential for DNA repair, expressed in mouse brain and other tissues. Knockouts are lethal.
- **Relation to RLS in Mice**: No RLS link.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: No RLS mouse data.

17. Nrip1

- **What It Is and Does in Mice**: *Nrip1* encodes a nuclear receptor co-repressor (RIP140) regulating metabolism and reproduction, expressed in mouse brain (e.g., hypothalamus).
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No roles.
    - **Studies**: No RLS mouse data.

18. Mlf2; Ptms

- **What It Is and Does in Mice**: *Mlf2* encodes a myeloid leukemia factor, expressed in mouse brain; *Ptms* encodes parathymosin, with unclear neural roles. Limited data.
- **Relation to RLS in Mice**: No RLS link.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: No RLS mouse data.

19. Bcl11b; Setd3

- **What It Is and Does in Mice**: *Bcl11b* encodes a transcription factor for neuronal differentiation, expressed in mouse brain (e.g., cortex); *Setd3* encodes a histone methyltransferase. Knockouts affect brain development.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No roles.
    - **Studies**: No RLS mouse data.

20. Fign; Grb14 (Fign; Prps1p1)

- **What It Is and Does in Mice**: *Fign* encodes fidgetin, a microtubule-severing protein, expressed in mouse brain; *Grb14* regulates insulin signaling. Knockouts show motor defects (*Fign*).
- **Relation to RLS in Mice**: No direct RLS link; *Fign* motor phenotypes are speculative.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: No RLS mouse data.

21. Mir8068; Linc01616 (Linc02546; Linc02755)

- **What It Is and Does in Mice**: Non-coding RNAs (e.g., microRNAs, long non-coding RNAs) with unclear functions, possibly regulatory, expressed in mouse brain.
- **Relation to RLS in Mice**: No RLS link.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: No RLS mouse data.

22. Lmx1b; Zbtb43

- **What It Is and Does in Mice**: *Lmx1b* encodes a transcription factor for limb and dopamine neuron development, expressed in mouse midbrain; *Zbtb43* is less studied. Knockouts affect dopamine cells.
- **Relation to RLS in Mice**: No direct RLS link, but *Lmx1b*'s dopamine role is suggestive.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic**: *Lmx1b* regulates TH+ neurons in substantia nigra, relevant to RLS dopamine hypotheses.
    - **Opiate/Iron**: No links.
    - **Studies**: Mouse imaging shows dopamine defects, not RLS-specific.

23. Rflna; Znf664

- **What It Is and Does in Mice**: *Rflna* (likely *Rnf10*) encodes a ring finger protein; *Znf664* encodes a zinc finger protein, both with unclear neural roles in mice.
- **Relation to RLS in Mice**: No RLS association.

- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: No RLS mouse data.

24. Npbwr2; Myt1 (Myt1)

- **What It Is and Does in Mice**: *Npbwr2* encodes a neuropeptide B/W receptor, expressed in mouse brain (e.g., hypothalamus); *Myt1* promotes myelination (see prior list).
- **Relation to RLS in Mice**: No RLS link.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate**: *Npbwr2* might influence hypothalamic circuits, untested.
    - **Iron**: No link.
    - **Studies**: No RLS mouse data.

25. Pcsk2

- **What It Is and Does in Mice**: *Pcsk2* encodes proprotein convertase 2, processing neuropeptides, expressed in mouse brain (e.g., hypothalamus). Knockouts affect peptide signaling.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate**: Possible peptide-dopamine overlap, untested.
    - **Iron**: No link.
    - **Studies**: No RLS mouse data.

26. Linc02339; Linc00358 (Linc02339; Rac1p8)

- **What It Is and Does in Mice**: Non-coding RNAs with regulatory potential, expressed in mouse brain.
- **Relation to RLS in Mice**: No RLS link.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: No RLS mouse data.

27. Tet2-As1 (Tet2, Rn7sl89p)

- **What It Is and Does in Mice**: *Tet2* encodes a DNA demethylase regulating hematopoiesis and neural function, expressed in mouse brain. Knockouts affect memory.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No direct roles.
    - **Studies**: No RLS mouse data.

28. Alkal2

- **What It Is and Does in Mice**: *Alkal2* encodes an ALK and LTK ligand, possibly involved in neural signaling, expressed in mouse brain.
- **Relation to RLS in Mice**: No RLS link.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: No RLS mouse data.

29. Loc101929243; Snrpc (Ilrun-As1; Snrpc)

- **What It Is and Does in Mice**: *Snrpc* encodes a small nuclear ribonucleoprotein, involved in splicing, expressed ubiquitously in mice.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No roles.
    - **Studies**: No RLS mouse data.

30. Astn2

- **What It Is and Does in Mice**: *Astn2* encodes a protein regulating neuronal migration, expressed in mouse brain (_registry cortex). Knockouts affect behavior.
- **Relation to RLS in Mice**: No RLS link.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: No RLS mouse data.

31. Linc02024; Loc105374060 (Linc03051; Igsf11)

- **What It Is and Does in Mice**: *Igsf11* encodes an immunoglobulin superfamily protein, expressed in mouse brain. Function unclear.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No roles.
    - **Studies**: No RLS mouse data.

32. Linc01680; Rgs18

- **What It Is and Does in Mice**: *Rgs18* encodes a regulator of G-protein signaling, expressed in mouse brain and blood cells. Knockouts affect signaling.
- **Relation to RLS in Mice**: No RLS link.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: No RLS mouse data.

33. Lpar5

- **What It Is and Does in Mice**: *Lpar5* encodes a lysophosphatidic acid receptor, expressed in mouse brain and immune cells. Function unclear.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No roles.
    - **Studies**: No RLS mouse data.

34. Xkr6

- **What It Is and Does in Mice**: *Xkr6* encodes an XK-related protein, possibly involved in membrane function, expressed in mouse brain.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No roles.
    - **Studies**: No RLS mouse data.

35. Tfap2d

- **What It Is and Does in Mice**: *Tfap2d* encodes a transcription factor (AP-2 delta) regulating neural crest development, expressed in mouse brain.
- **Relation to RLS in Mice**: No RLS link.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: No RLS mouse data.

36. Aspscr1

- **What It Is and Does in Mice**: *Aspscr1* encodes a tethering protein involved in vesicle trafficking, expressed in mouse brain.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No roles.
    - **Studies**: No RLS mouse data.

37. Diaph3

- **What It Is and Does in Mice**: *Diaph3* encodes a diaphanous-related formin regulating actin dynamics, expressed in mouse brain and muscle.
- **Relation to RLS in Mice**: No RLS link.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No evidence.
    - **Studies**: No RLS mouse data.

38. Frem1

- **What It Is and Does in Mice**: *Frem1* encodes an extracellular matrix protein for tissue development, expressed in mouse brain and skin. Knockouts cause craniofacial defects.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No roles.
    - **Studies**: No RLS mouse data.

39. Mpped2; Dcdc1

- **What It Is and Does in Mice**: *Mpped2* encodes a metallophosphoesterase, expressed in mouse brain; *Dcdc1* regulates microtubules in neurons. Knockouts affect brain development.
- **Relation to RLS in Mice**: No RLS association.
- **Pharmacological/Brain Imaging Links in Mice**:
    - **Dopaminergic/Opiate/Iron**: No roles.
    - **Studies**: No RLS mouse data.

Key Insights (Mouse-Specific with Human Context)

- **RLS-Linked Genes in Mice**:
    - *Lmx1b*: Strongest candidate due to its role in dopamine neuron development in mice (e.g., substantia nigra TH+ cells); knockouts show dopamine deficits, a key RLS feature, though not directly tested for RLS.
    - *Zfhx3*: Indirect link via circadian regulation, potentially overlapping with RLS sleep disruption, untested in mice.

    - Others: No direct RLS evidence in mice; human GWAS candidates (e.g., *LMX1B*) suggest potential if studied in mouse models like *Btbd9* or *Meis1*.
- **Dopaminergic Pathways**:
    - *Lmx1b*: Direct role in dopamine neuron differentiation; mouse studies show TH reduction in knockouts (e.g., Deng et al., 2011).
    - *Gria1*, *Camk2g*, *Syt4*, *Pcsk2*, *Npbwr2*: Plausible but unconfirmed roles in dopamine-related regions (e.g., striatum, hypothalamus).
- **Iron Pathways**: No genes here have a clear iron role in mice, unlike *Slc40a1* from your prior list.
- **Mouse Studies**:
    - Limited RLS-specific pharmacological or imaging data for these genes in mice.
    - *Lmx1b* has dopamine-related imaging (e.g., TH staining); *Gria1*, *Camk2g*, *Reln*, *Zfhx3* have general brain imaging (e.g., fMRI, calcium imaging), not RLS-focused.