GRI neurodevelopmental disorders ICD-10-CM Codes Request

ICD-10 Coordination and Maintenance Committee

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Disclosures: Tim Benke

Rett Clinic at Children's Hospital Colorado

Rocky Mountain Rett Association

Role: PI/Medical Director

CDKL5 Center of Excellence

International Foundation for CDKL5 Research

Role: PI

Simons/GRIN2B/CURE (Traynelis).

Functional and clinical evaluations of glutamate receptor mutations in epileptic encephalopathies.

Role: site PI

Clinical Trials:

Present: Acadia (Phase 3, Trofinetide, Rett Syndrome)

Past: RSRT, Marinus, Ovid/Takeda, GW

Role: site PI

Scientific Advisory (past/present):

Alcyone, Avexis, CureGri, GW, GRIN2B Foundation, GrinTX, IFCR, IRSF, LGS, LouLou, Neuren/Acadia, Marinus, Ovid/Takeda, Taysha, Ultragenyx, Zogenix

(all remuneration to my department)

U01NS114312 (Benke)

NIH/NINDS

Multi-site validation of biomarkers and core clinical outcome measures for clinical trials readiness in CDKL5 Deficiency Disorder

Role: PI/PD.

R01DC018786-01A1 (Rennie)

NIH/NIDCD

Ion Channels and Excitability in the Peripheral Vestibular System

Role: CoI

R01 AG073997 (Rennie)

NIH/NIDCD

Aging and dysfunction in the peripheral vestibular system

Role: CoI

The diagnostic experience of male Rett Syndrome

IRSF

Role: PI

Ponzio Family Chair in Neurology Research

Children's Hospital Colorado Foundation

GRI neurodevelopmental disorders are unique, well-defined syndromes (1)

- GRI = Glutamate receptor, ion channel
- Responsible for ***almost all excitatory neurotransmission in the CNS***
- 3 “types”: GRIN, GRIA, GRIK
- Each type contains 4 subunits (5 for GRIK)
- Each subunit is a different gene on a different chromosome
- Genetic alteration of any gene causes ***a different*** neurodevelopmental syndrome
- There are specific therapies for each syndrome

➢ Nine (9) different syndromes = GRIN1, GRIN2A, GRIN2B, GRIN2D, GRIA1, GRIA2, GRIA3, GRIA4, GRIK2

GRI disorders are unique, well-defined syndromes (2)

- GRI disorders are common neurodevelopmental disorders:
  - Birth incidence (Lemke, 2020)
    - GRIN1 5:100,000
    - GRIN2A 3:100,000
    - GRIN2B 6:100,000
    - GRIN2D 5:100,000
    - GRIA1 3:100,000
    - GRIA2 3:100,000
    - GRIA3 3:100,000
    - GRIA4 2:100,000
    - GRIK2 2:100,000
    - Compare to Rett Syndrome (10:100,000) (F84.2) or Dravet (4:100,000) (G40.834)
- Many medical practitioners will see GRI disorders
  - Symptoms cross specialties
  - Currently coded for symptoms instead of diagnosis
- Clinical trials are underway
  - Urgent need to identify GRI cases as new treatments are approved
    - Ongoing clinical trials: L-serine (GRIN2A, GRIN2B), Radiprodil (GRIN2B)
    - Preclinical studies: GRIN1 and GRIN2B AAV gene therapy, GRIN2A RNAi therapy

All GRI patients share core symptoms: **genotype** indicates unique syndromic features

- **GRIN DISORDERS**
  - **VARIES BY SYNDROME:** developmental delay, intellectual disability, autism, speech deficiency, inability to walk, low muscle tone, gastrointestinal issues, feeding difficulties, cortical visual impairments, dystonia, seizures, and paroxysmal sympathetic hyperactivity (PSH)
  - **SPECIFIC TO EACH SYNDROME**
    - GRIN1 present in infancy (< 2yo) with severe developmental delays and epilepsy
    - GRIN2B present in infancy with variable, less severe developmental delays, less frequent epilepsy; brain malformations
    - GRIN2A present with distinct forms of epilepsy and language disorders in childhood
    - GRIN2D present with medically refractory epilepsy in the newborn period (< 1mo).

- **GRIA DISORDERS**
  - **VARIES BY SYNDROME:** developmental delay, intellectual disability, autism.
  - **SPECIFIC TO EACH SYNDROME**
    - GRIA1 severe intellectual disability, language disorder, distinct facial features
    - GRIA2 epileptic encephalopathy
    - GRIA3 X-linked intellectual disability, moderate; distinct facial features; sleep disorder; epilepsy; movement disorder
    - GRIA4 +/- epilepsy; gait disturbance; behavioral disturbances

- **GRIK2 DISORDER**
  - Intellectual disability, developmental delay, seizures, and visual or sensory changes

Lack of a unique ICD-10-CM code for GRI Syndromes leads to errors

- Diagnoses under code Q93.5, “Other deletions of part of a chromosome”, have very diverse phenotypes.
- Q93.5 is incorrectly applied to GRI Syndromes
  - Not all are due to chromosomal abnormalities
- Clinicians may code non-deletions under different ICD-10 codes
  - GRI syndromes are therefore not grouped together
- Patients seen by separate medical services may be coded for sub-diagnoses, rather than GRI syndromes
  - Speech therapist may code for communication defect (F80.2 for language disorders)
  - Neurology may code for epilepsy (G40.*), M62.89 for hypotonia, F70-79 for intellectual disabilities, H54.7 for cortical visual impairment, G25.* for movement disorders, and F88 for global developmental delay.
  - Lack of coding specificity may impact patient care

Unique ICD-10-CM codes for each GRI Syndrome will lead to better clinical care

- Access to disability benefits and school services
  - Example: Rett syndrome logically leads to communication interventions
- Epidemiological research and estimates of prevalence
  - Example: Alzheimer's disease in Down syndrome
- Ability to track outcomes of clinical interventions
  - Example: Preventive therapy in Huntington's disease reduces suicide
- Research on genotype-phenotype correlations
  - Example: Identification of symptoms in Fragile X carriers led to treatments
- Development of protocols for standard of care
  - Example: Diagnostic code for cystic fibrosis leads to standard protocols
- Facilitate recruitment to clinical trials

Unique GRI Syndrome specific ICD-10-CM codes could encourage syndrome specific treatment protocols

Specific therapies for specific syndromes related to specific symptoms (for example):

- Anti-seizure medications
  - Rescue meds provided before first seizure
- Physical and Occupational Therapy
  - Early, intensive and consistent for both fine and gross motor skills
- Behavioral Therapy
  - ABA therapy for living skills
- Speech Therapy
  - Assistive communication over pre-verbal training

Unique Specific codes for each GRI Syndrome are important to understand drivers of severity, risk of certain symptoms, and comorbidities

- Autism
  - Risk related to specific GRI syndromes
- Language abilities
  - Risk related to specific GRI syndromes
- Movement disorders
  - Risk related to specific GRI syndromes
- Seizures
  - Higher risk in specific GRI syndromes
  - Higher risk of specific seizure types, age of onset and severity in specific GRI syndromes

Summary

- Rationale for a unique code for each of 9 GRI Syndrome
  - 9 unique chromosome locations
  - 9 unique syndromes
  - Each syndrome is not always caused by chromosomal deletion
  - Prevalence of each syndrome is emerging (challenge in identifying prevalence without ICD codes, especially since diagnosis is based on genetic sequencing, which is still limited).
  - Clinical trials in unique GRI syndromes are underway and a unique ICD code will be required to *identify* the patients who would benefit from these therapies
  - GRI syndromes
    - Genotype/phenotype correlations for each syndrome will inform clinical management and drug discovery
  - Therapies may be more successful in some GRI Syndromes and unsafe and thus contraindicated in others