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RARB DYSTONIA: DIAGNOSIS AND TREATMENT

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Disclosures

- I have no conflict of interest to disclose

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RARB related disease

- MCOPS12
  - Microphthalmia
  - Global developmental delay
  - Hypertonia
  - Chiari type 1
  - Diaphragmatic hernia
  - CHD

- Dystonia without abnormal ocular development
  - (p.Asp281Val; p.Leu285Arg; p.Leu402Serfs*10)

Caron V et al, Genetics in Medicine, 2023; Klein C et al Mvt Disorders 2026

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RARB and motor development

- Variable motor development
- Unable to sit unassisted to no gross motor delay
- Progressive motor impairment

- Abnormal tone:
- Hypotonia (30/38, 79%) >
- Spasticity (25/37, 68%)
- Dystonia (15/34, 44%)

Caron V et al, Genetics in Medicine, 2023, Srour M et al 2016

Movement disorders and RARB

Table 1
Overview of *RARB* variants and associated phenotypes reported in the literature, select database entries, and the present study.

RARB variant(s) (NM_000965.5)	Zygosity	Variant type(s)	Number of individuals identified with the variant (s)	Main associated clinical features
c.355C > T (p.Arg119*); c.1201_1202insCT (p.Ile403Serfs*15)	compound heterozygous	loss-of-function (nonsense); loss-of-function (frameshift)	2 affected siblings (compound heterozygous carriers) and 2 unaffected parents (each a heterozygous carrier) from 1 family (Srour et al., 2013) (Srour et al., 2013)	microphthalmia, diaphragmatic hernia, pulmonary hypoplasia, cardiac defects
c.638 T > C (p.Leu213Pro)	heterozygous[a]	missense	1 patient (Srour et al., 2016) (Srour et al., 2016)	microphthalmia, cardiac defect, developmental delay, movement disorder (dystonia, chorea)
c.887G > C (p.Gly296Ala)	heterozygous[a]	missense	1 patient (Srour et al., 2016) (Srour et al., 2016)	microphthalmia, developmental delay, spasticity, movement disorder (dystonia, chorea)
c.1159C > A (p.Arg387Ser)	heterozygous[a]	missense	1 patient (Srour et al., 2013) (Srour et al., 2013)	microphthalmia, diaphragmatic hernia, developmental delay, spasticity
c.1159C > T (p.Arg387Cys)	heterozygous[a]	missense	10 unrelated patients (Srour et al., 2013 and 2016) (Srour et al., 2013, 2016)	microphthalmia, diaphragmatic hernia, cardiac defects, developmental delay, spasticity, rarely movement disorder (dystonia, chorea)
c.1193C > G (p.Ser398*)	heterozygous[b]	loss-of-function (nonsense)	2 unrelated patients (ClinVar, accession: VCV000988355)	no data available[d]
c.1210C > T (p.Gln404*)	heterozygous[c]	loss-of-function (nonsense)	3 unrelated patients (present study N = 1; ClinVar N = 2, accession: VCV000809439)	microphthalmia, developmental delay, movement disorder (dystonia-predominant) (present patient, no data available for 2 ClinVar-reported individuals)

Dystonia and chorea

Trieschmann G et al Eur J Med Gen 2023

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Dystonia

- **Dystonia** is characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.

- Dystonic movements are typically patterned, twisting, and may be tremulous.

- Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.

Albanese A et al, Movement Disorders, Vol. 28, No. 7, 2013

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Approach to dystonia

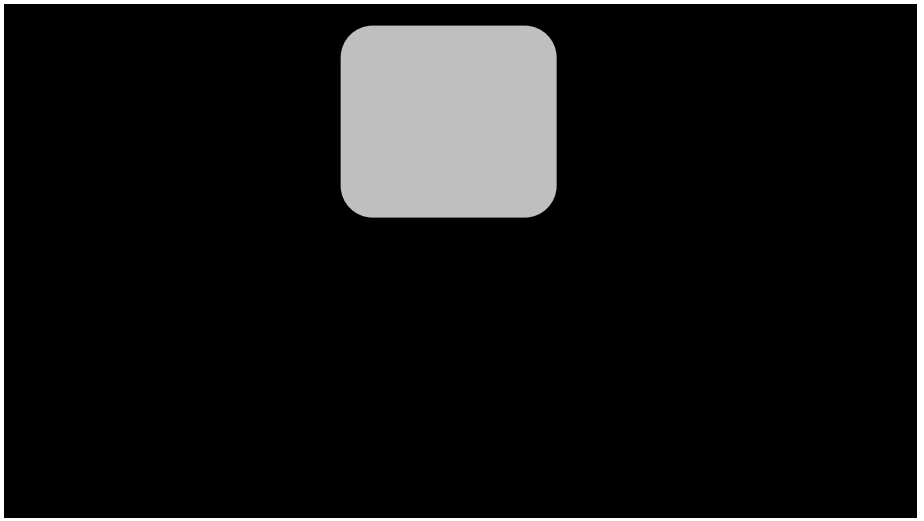
- Phenomenology
  - Tonic vs mobile dystonia
  - Focal vs generalized
  - Isolated vs combined
- Identify treatable conditions
- Treat underlying cause
  - Stop offending agent (neuroleptics)
  - Treat infection (VZV, HSV)
  - Treat autoimmune process (anti-NMDA encephalitis)
  - Gene specific treatment (Wilson's disease)
- Treat dystonia symptomatically
- Treat associated non motor symptoms

HA Jinnah, Neurol Clin 33 (2015) 77–100

Dystonia

- Focal
- Generalized





Klein C et al Mov Disorders 2026

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Spasticity vs dystonia

HYPERTONIA ASSESSMENT TOOL (HAT)

HAT ITEM	SCORING GUIDELINES (0=negative or 1=positive)	SCORE 0=negative 1=positive *(circle score)*	TYPE OF HYPERTONIA
1. Increased involuntary movements/postures of the designated limb with tactile stimulus of another body part	0= No involuntary movements or postures observed	0	DYSTONIA
	1= Involuntary movements or postures observed	1	
2. Increased involuntary movements/postures with purposeful movements of another body part	0= No involuntary movements or postures observed	0	DYSTONIA
	1= Involuntary movements or postures observed	1	
3. Velocity dependent resistance to stretch	0= No increased resistance noticed during fast stretch compared to slow stretch	0	SPASTICITY
	1= Increased resistance noticed during fast stretch compared to slow stretch	1	
4. Presence of a spastic catch	0= No spastic catch noted	0	SPASTICITY
	1= Spastic catch noted	1	
5. Equal resistance to passive stretch during bi-directional movement of a joint	0= Equal resistance not noted with bi-directional movement	0	RIGIDITY
	1= Equal resistance noted with bi-directional movement	1	
6. Increased tone with movement of another body part	0= No increased tone noted with purposeful movement	0	DYSTONIA
	1= Greater tone noted with purposeful movement	1	

Jethwa A et al 2010 Dev Med Child Neurol

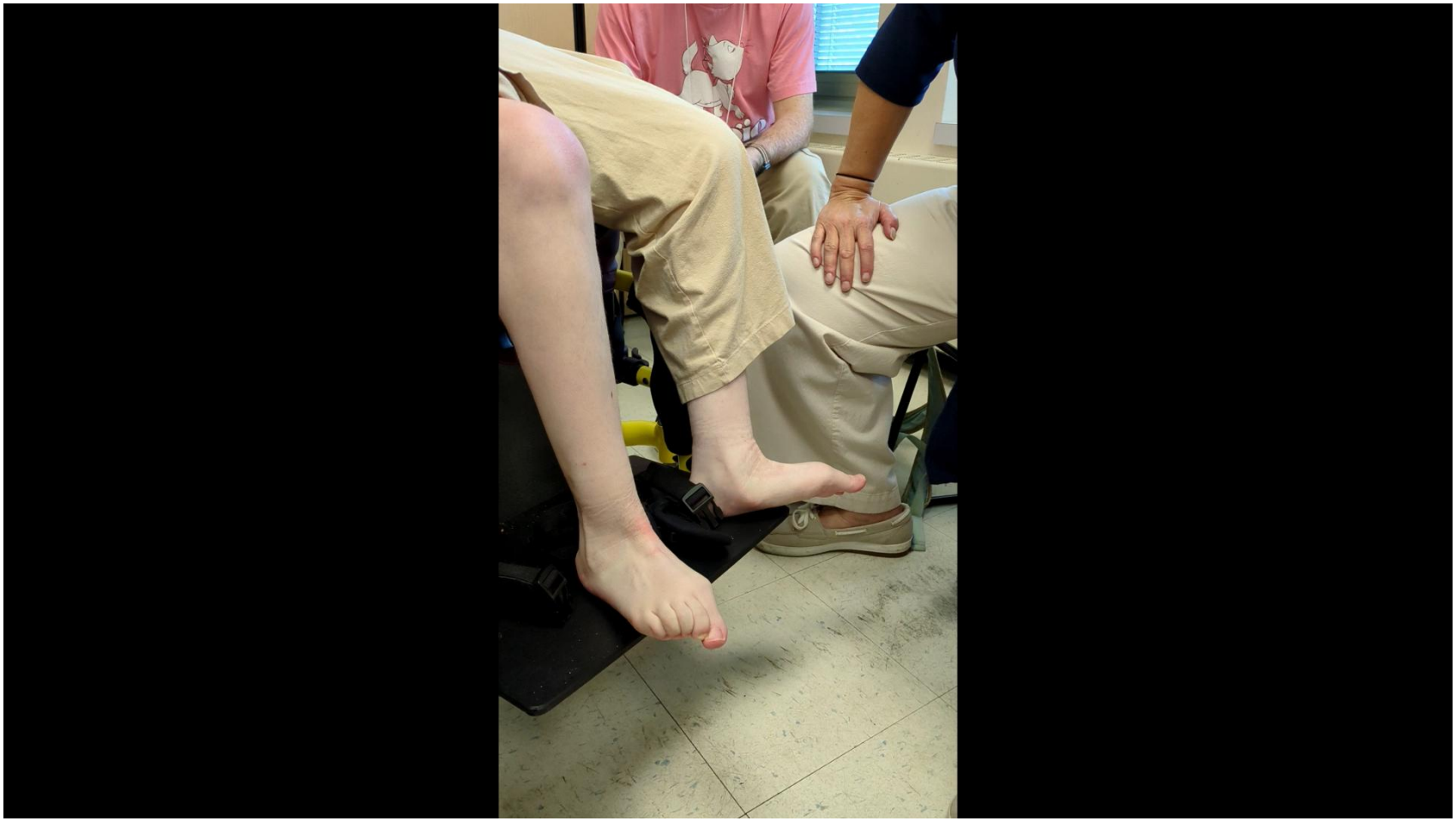
RARB cohort assessment

- Developmental evaluation
- Neurological exam
- Video analysis
- Scales:
  - Gross Motor Function Classification System (GMFCS)
  - Global Dystonia Severity Scale (GDS)
  - The Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) - video
- Brain MRI

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RARB related dystonia



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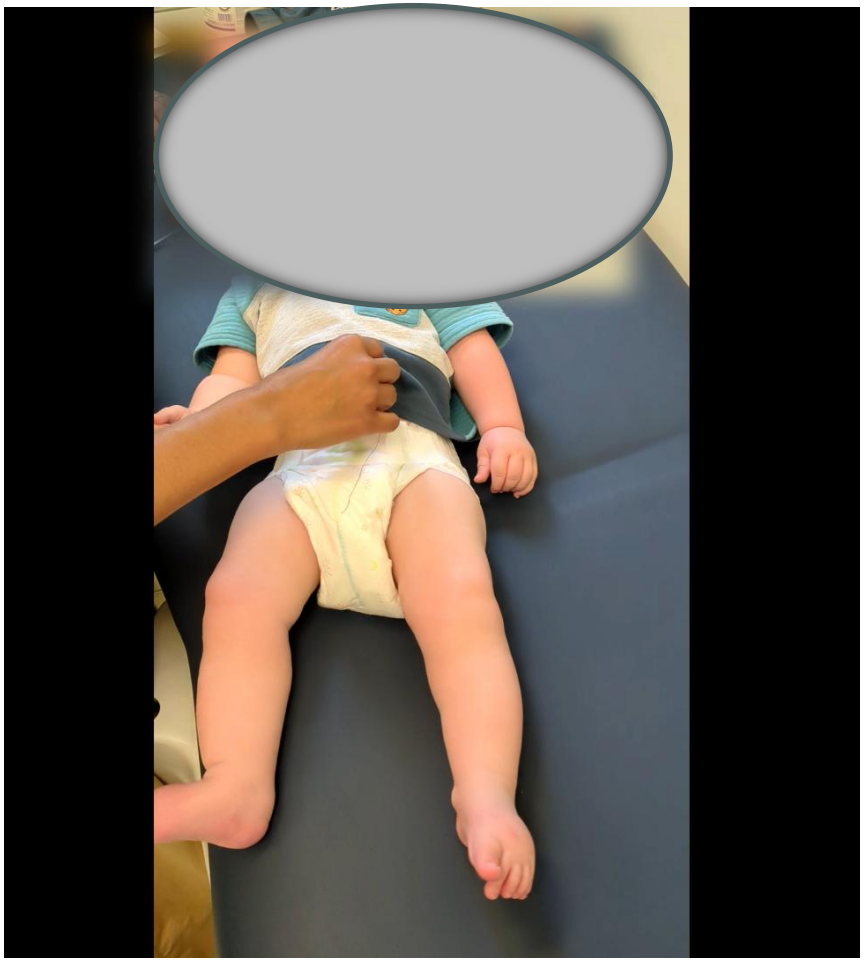
RARB related dystonia



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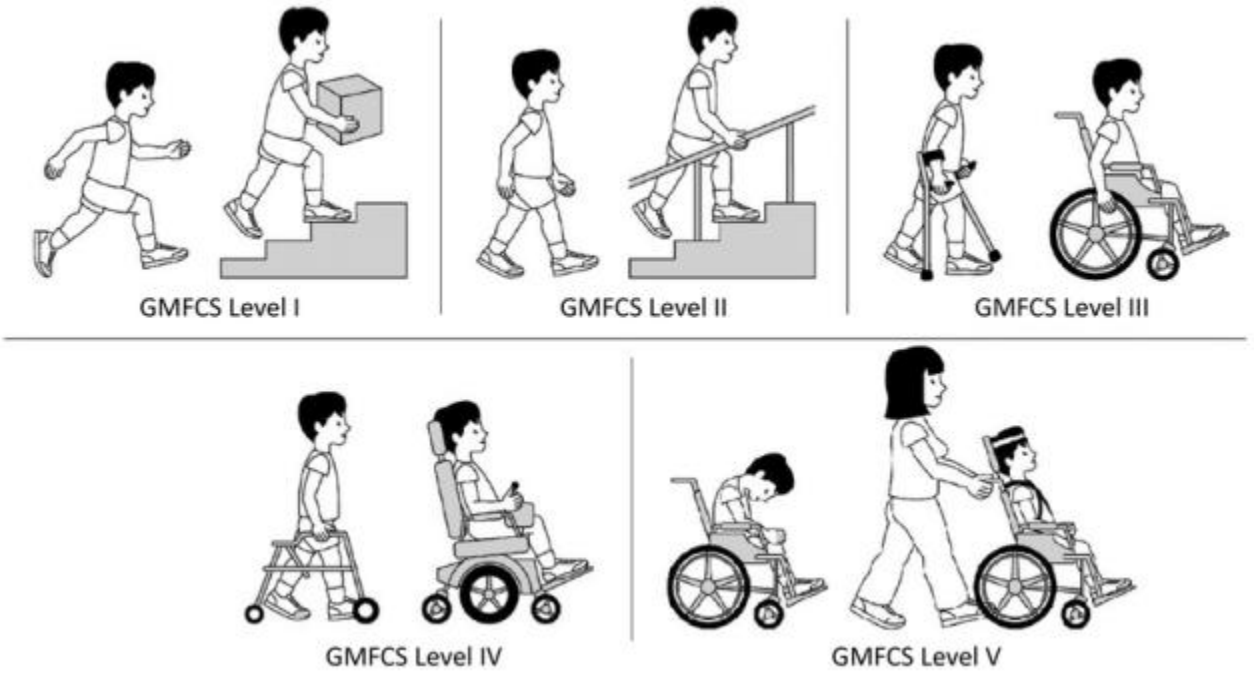
RARB related dystonia

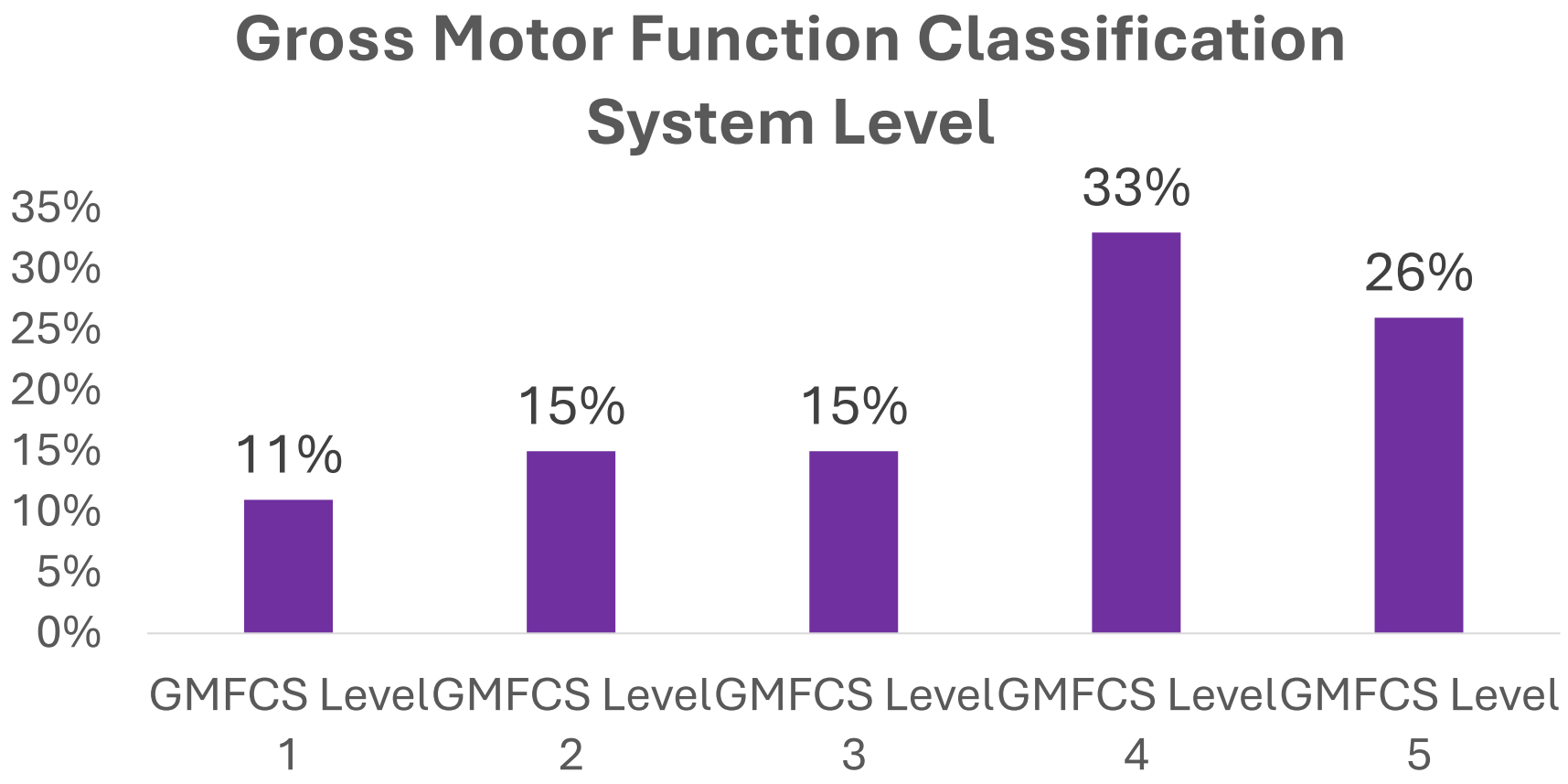


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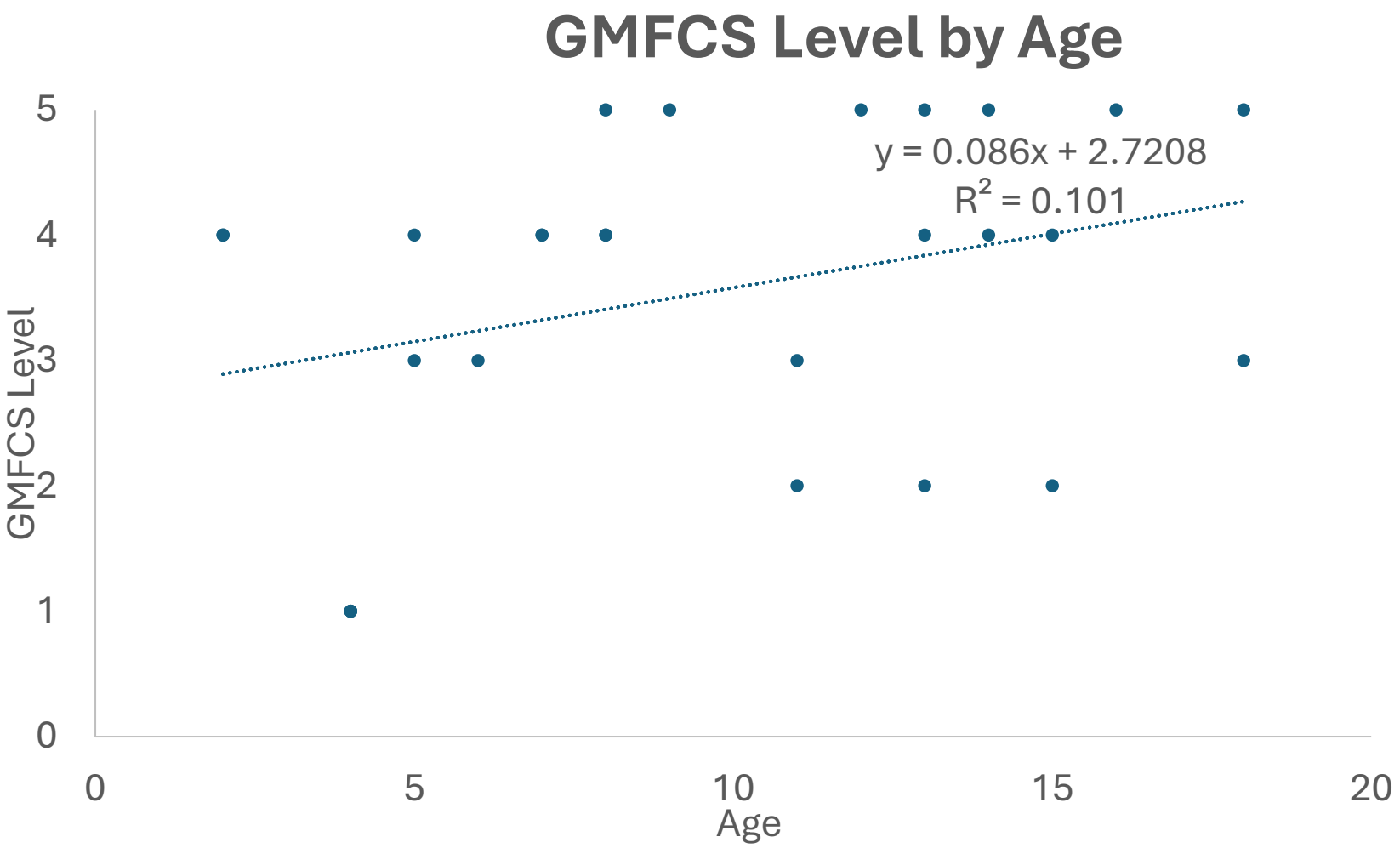
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Gross Motor Function Classification System (GMFCS)



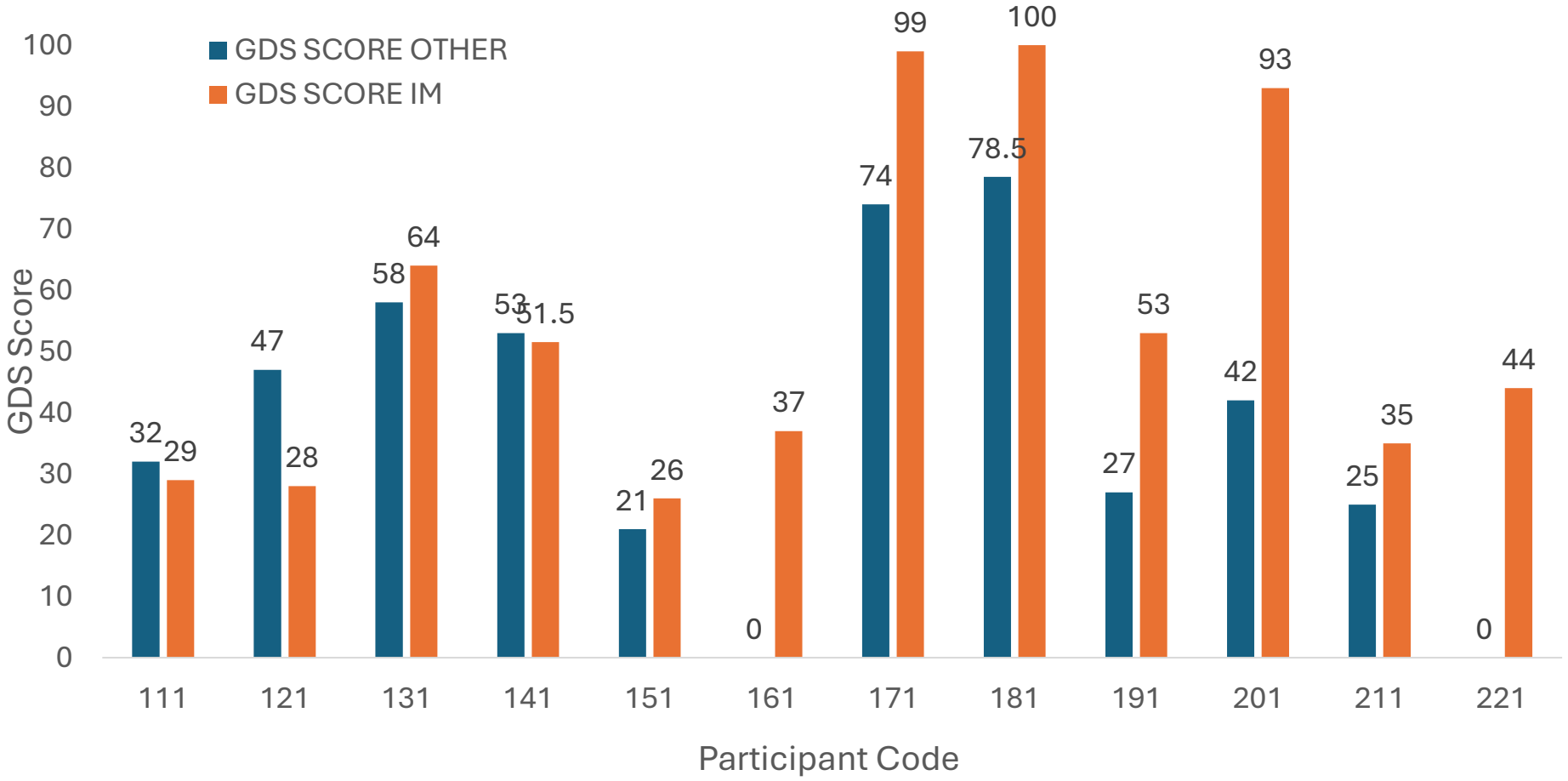


Courtesy of V. Chu



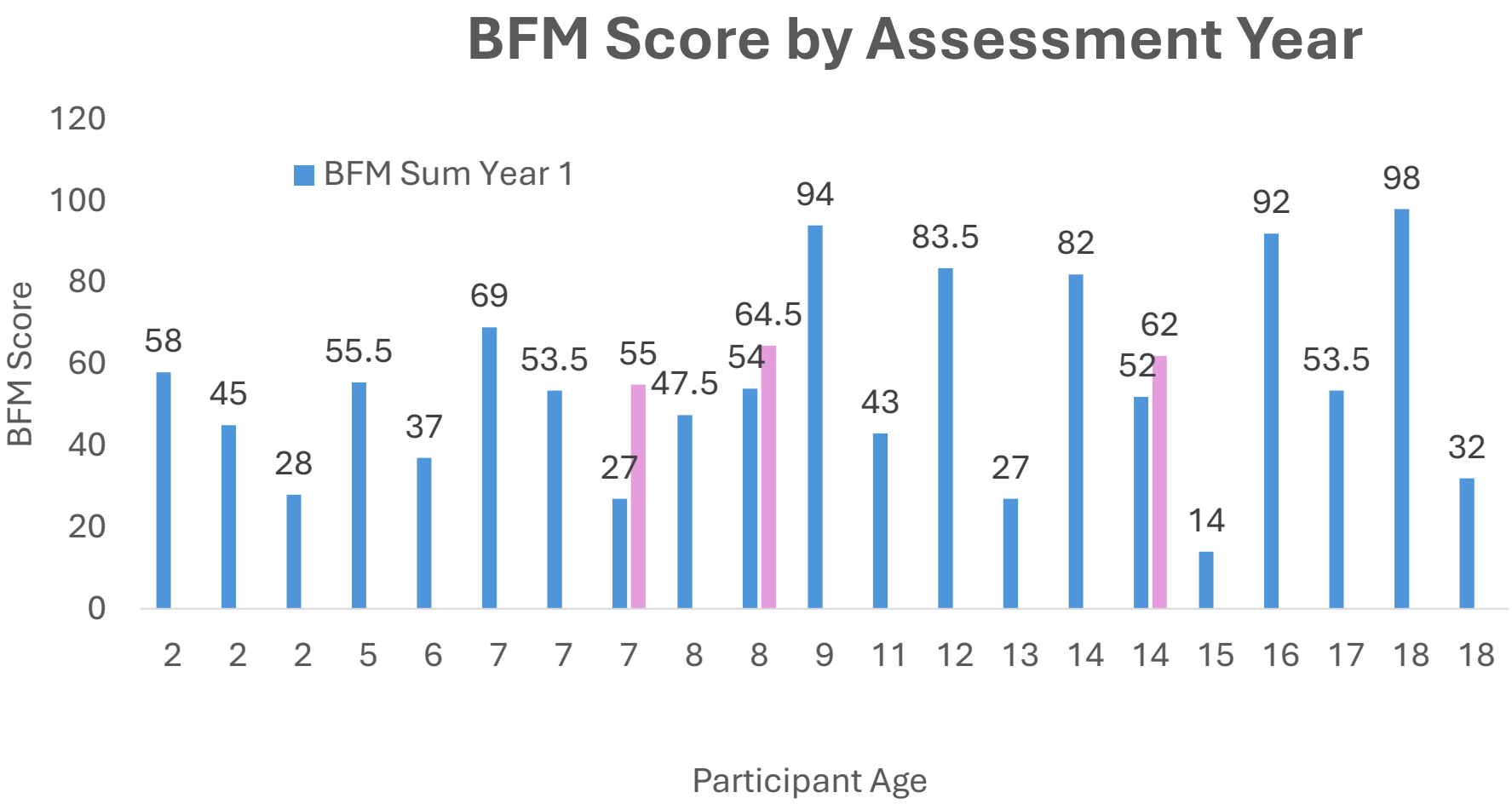
Courtesy of V. Chu

GDS Score Comparison

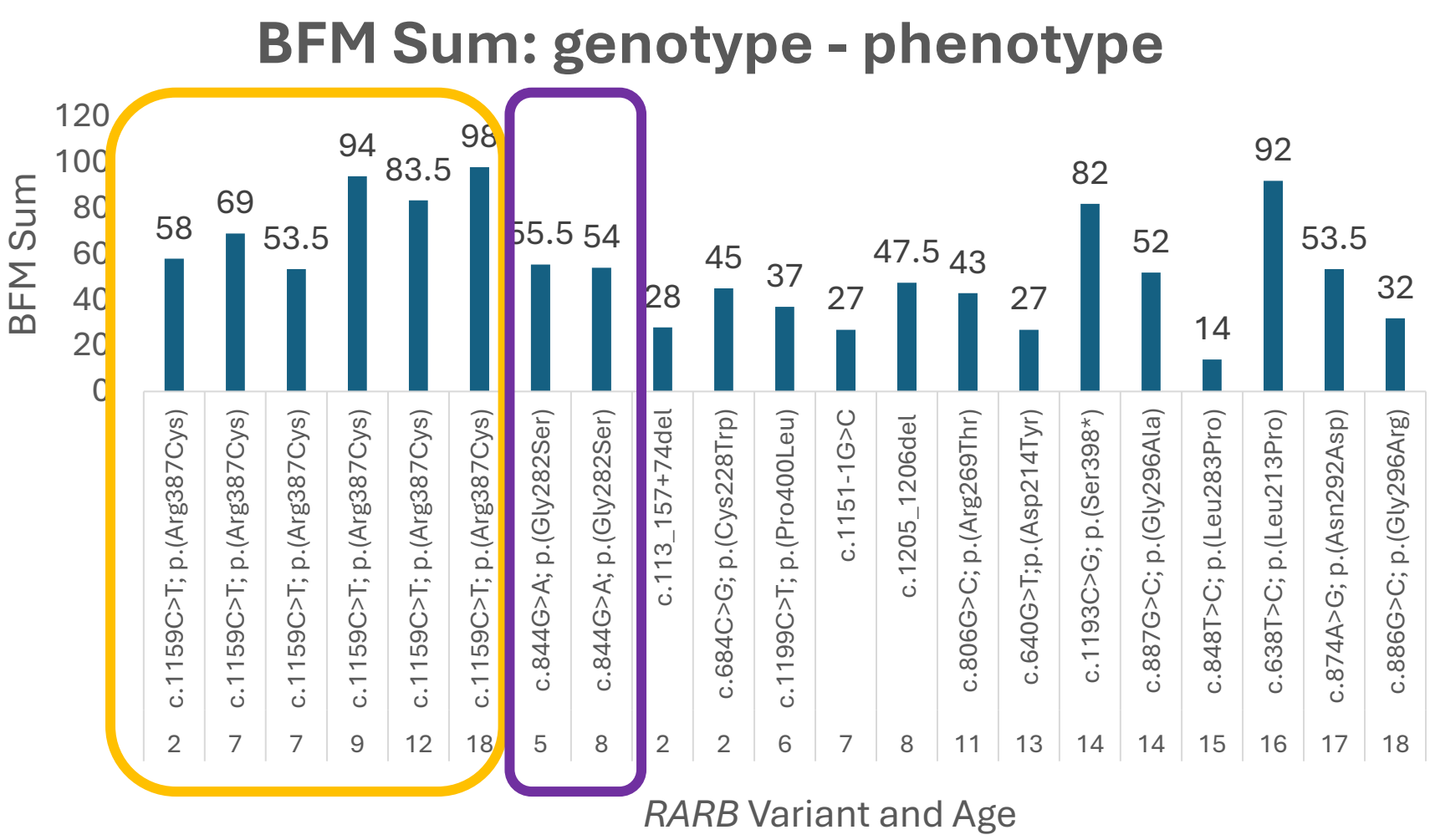


Paired t-test:
P < 0.05 (0.0176)
IM tended to assign higher scores than MDs

Courtesy of V. Chu

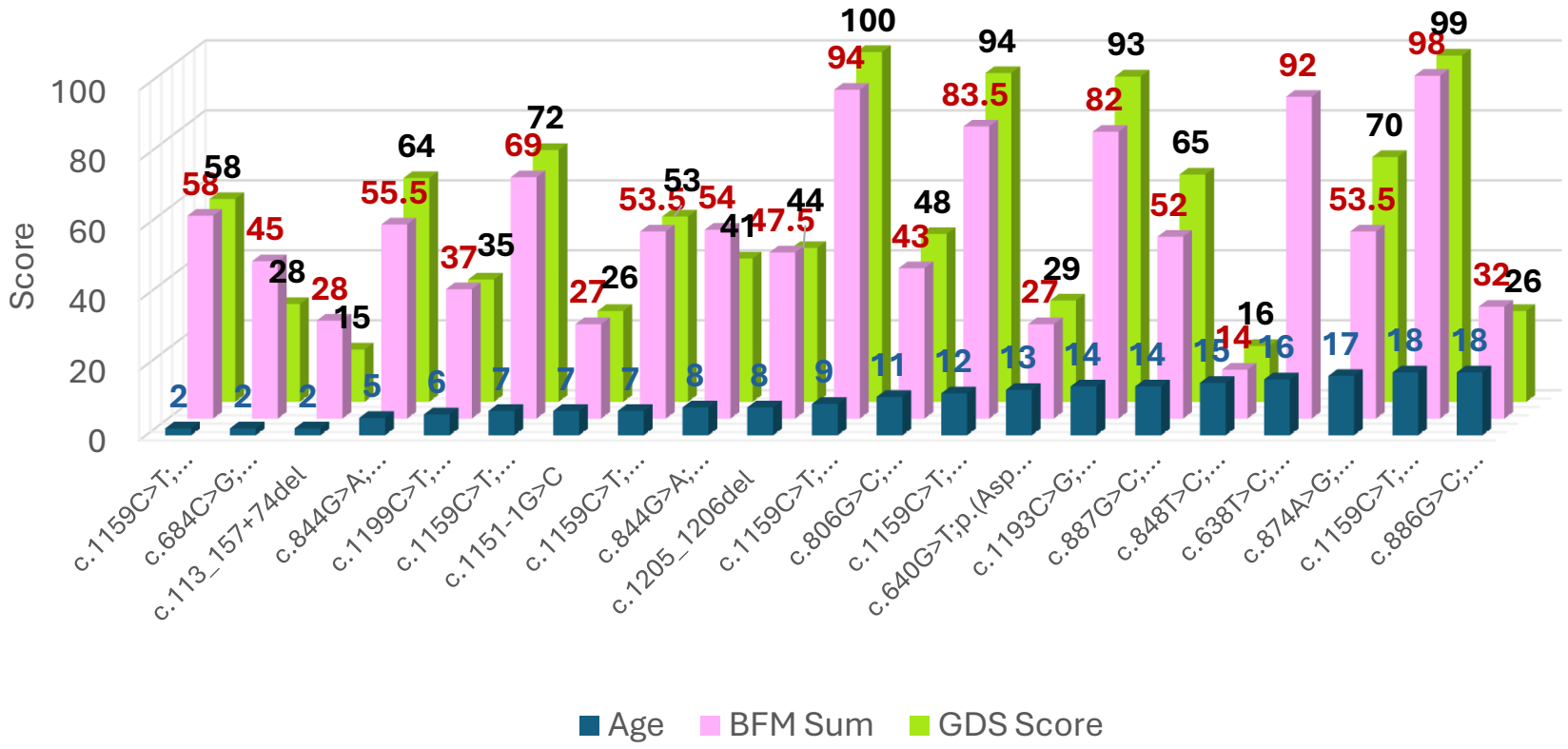


Courtesy of V. Chu



Courtesy of V. Chu

BFM + GDS Scores with RARB variant



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Approach to dystonia

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  - Gene specific treatment (RARB disease)
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HA Jinnah, Neurol Clin 33 (2015) 77–100

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Dystonia and rehabilitation

- Establish specific goals
- Positioning
- Equipment:
  - braces, Wheelchair
  - communication tablet
- Dysphagia
- Speech therapy
- Behavioral therapy

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Dystonia and rehabilitation

- Improve abnormal postures
- Prevent contractures
- Activate anti dystonia muscles
- Avoid training dystonic muscles
- Sensory training

Movement Disorders rehabilitation 2017, Prudente C 2018, Bleton JP 2009

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When to treat

- Injuries (e.g. pressure wounds in hands)
- Pain related to posturing
- Facilitate diaper changes
- Improve fine motor skills
- Prevent status dystonicus?
- Prevent contractures

VL Shanker, Continuum 2016;22(4):1227–1245

Symptomatic treatment in dystonia

Medications

- Trihexyphenidyl (A)
- Benzodiazepines (B)
- Baclofen (B)
- Clonidine (C)
- Levodopa (D)
- Tetrabenazine (D)
- Gabapentin

Other considerations

- Botulinum toxin
- Deep Brain Stimulation
- Intrathecal baclofen
- PT
- OT
- Psychology
- Hygiene

VL Shanker, Continuum 2016;22(4):1227–1245, Fehlings D 2018

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Dystonia medications

Medication	Starting dose mg/day	Dose range mg/day	Comments
Trihexyphenidyl	0.095 mg/kg/day; 1 mg BID *	15 - 40	Constipation, thick saliva
Clonazepam	0.25 - 0.5 HS	1 - 4 mg/day	Sedation, hypersalivation
Diazepam	0.12 - 0.8 mg/kg/day	10 - 40	
Carbidopa/levodopa	0.1 - 1 mg/kg/day	5 - 10 mg/kg/day	Nausea, somnolence
Tetrabenazine	6.5 - 12.5 mg *	50 - 150	Suicidality
Baclofen	0.3 mg/kg/day; 2.5 mg/day	100	Hypotonia
Clonidine	0.002 mg/kg (max 0.1)	0.012 mg/kg/dose	Bradycardia
Gabapentin	5 mg/kg/day	35 - 50 mg/kg/day	

VL Shanker, Continuum 2016;22(4):1227–1245, L A Rasmussen Pead Child Health 2015

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Medical cannabis

- Health Canada report
  - Inhaled cannabis and oral CBD improved dystonia in small limited studies
  - Synthetics showed no benefit

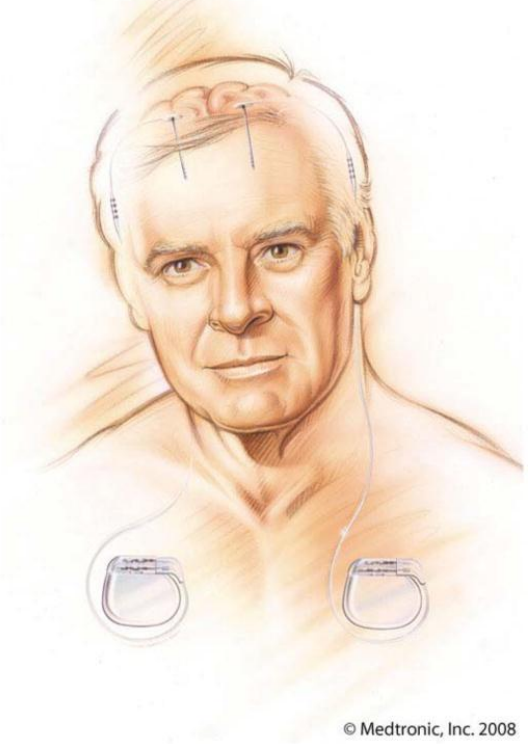
- Small pediatric observational study
  - 25 patients with various movement disorders
  - Δ9 -THC and CBD
  - Not recommended in CP guidelines

- PKAN: subjective benefits

Wilson J 2020, Libzon S 2018, Bohn E et al 2021

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DBS therapy



- Risks:
  - 10% infection rate
  - 0.8 - 3% bleeding risk
- Unclear mechanism of action
- No reported DBS implantation for RARB
- Review of 321 dystonic children
  - 277 (86.3%) improvement in dystonia

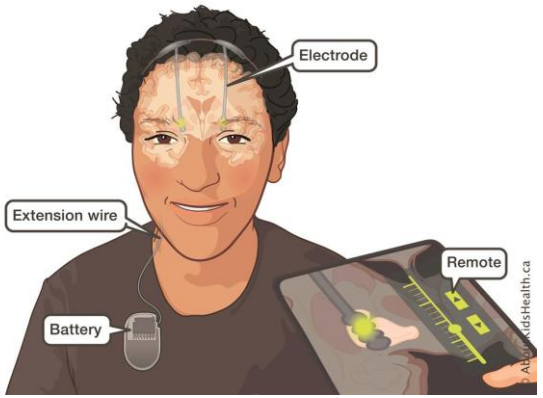
Elkaim LM 2018, Jinnah HA et al J Neural Transm (2017) 124:417–430, Kaminska M 2017, Kyle K 2021

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Factors predicting good DBS outcome in children

Short duration of life with dystonia
Monogenic dystonia > neurodegenerative dystonia > acquired dystonia
Mobile dystonia
Dystonia affecting mainly the neck, trunk, upper and lower extremities (lack of bulbar involvement)
Absence of fixed skeletal deformities
Absence of significant neurological comorbidities (ataxia, spasticity, weakness, etc)



Gorodetsky & Fasano 2022, Courtesy of C. Gorodetsky

DBS in dystonia

Pre-surgery

Post surgery

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Status dystonicus

- Emergency characterized by severe episodes of generalized or focal hyperkinetic movements that have necessitated urgent hospital admission because of the direct life-threatening complications
- Most common trigger infection or medication change
- DxD: SE, NMS, Serotonin syndrome, Malignant hyperthermia, acute dystonic reaction

Termsarasab Journal of Clinical Movement Disorders (2017), Meijer IA Mvt disorder emergencies 2021

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SD prevention

- Regular clinical visits
- Prompt management of potential triggers
- Early introduction of treatments for dystonia
- Home dystonia action plan
- Prompt DBS referral

Termsarasab Journal of Clinical Movement Disorders (2017), Meijer IA Mvt disorder emergencies 2021

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Non motor symptoms in dystonia

- Mood disorders
- Pain
- Cognitive difficulties
- Sleep disturbance
- Fatigue
- Dysautonomia (sweating, increased heart rate)

Klingerhoeven L et al . 2019 Sep 27;6(10):2054–2065

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Chorea

- Involuntary dance like movements that rapidly change from region to region in an irregular, flowing, nonstereotyped pattern

Harting I 2020; Herman A 2015

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Chorea treatment

- Only treat if interference

- Tetrabenazine
- Antipsychotic drugs olanzapine and quetiapine
- Watch for worsening Parkinsonism
- Anti-seizure medication

Herman A 2015

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Conclusion

- This presentation highlighted the clinical spectrum of movement disorders associated with RARB
- Overview of symptomatic treatments
- Current natural history study will improve our understanding of the range of movement disorders and aid in developing new therapies.