2018 DYRK1A Meetup - Charlotte, North Carolina

DYRK1A Today

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Lecture Topics

- What is the DYRK1A gene and what does the Dyrk1a protein do?
- What are pathological mutations and where are they in the DYRK1A gene?
- What are the main clinical features of a DYRK1A mutations in children?
- What causes movement disorders in a child with a DYRK1A mutation and can this be treated?
- What are other treatments for a child with a DYRK1A mutation?
- What other diseases involve abnormal Dyrk1a dysfunction?

DYRK1A Function

- Dual-specificity tyrosine phosphorylation regulated kinase 1A (DYRK1A) (MIM 600855) is a protein kinase located in the Down syndrome critical region (DSCR) of chromosome 21 (21q22.13)
- DYRK1A is essential for neurogenesis, neuronal differentiation and proliferation, cell cycle and synaptic plasticity.

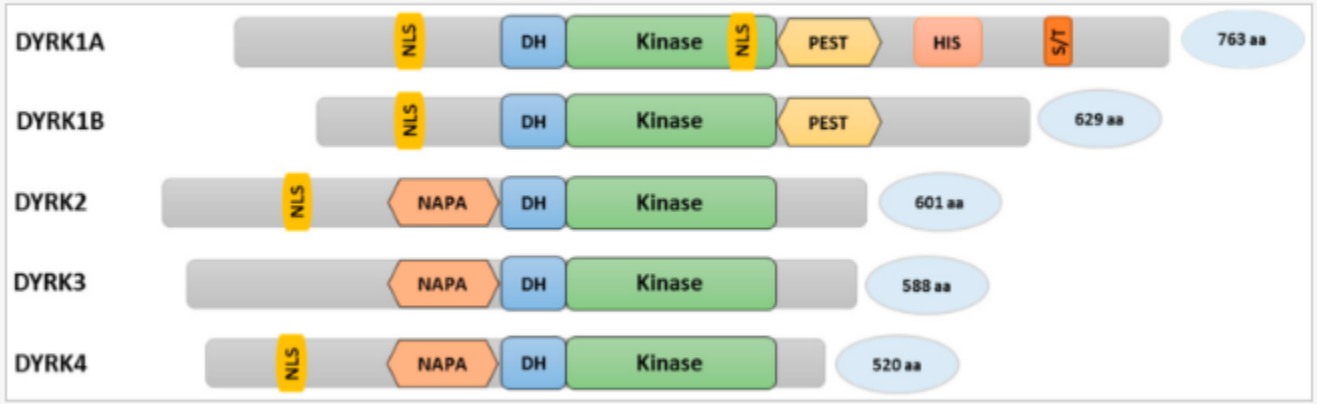
DYRK1A Gene

- DYRK1A GENE
  - Large gene-13 exons and spans ~147.8Kb
  - Codes a 763 amino acid nuclear protein

- Member of the DYRK family of genes

DYRK FAMILY

Figure 1. Schematic representation of the DYRK family of proteins: Distinct sequence motifs such as the nuclear localization signal (NLS); DYRK-homology box (DH); a motif rich in proline, glutamic acid, serine, and threonine residues (PEST); a poly-histidine stretch (HIS); a serine/threonine rich region (S/T); a N-terminal auto-phosphorylation accessory region (NAPA); and a conserved kinase domain comprising the structural and functional features of DYRKs.

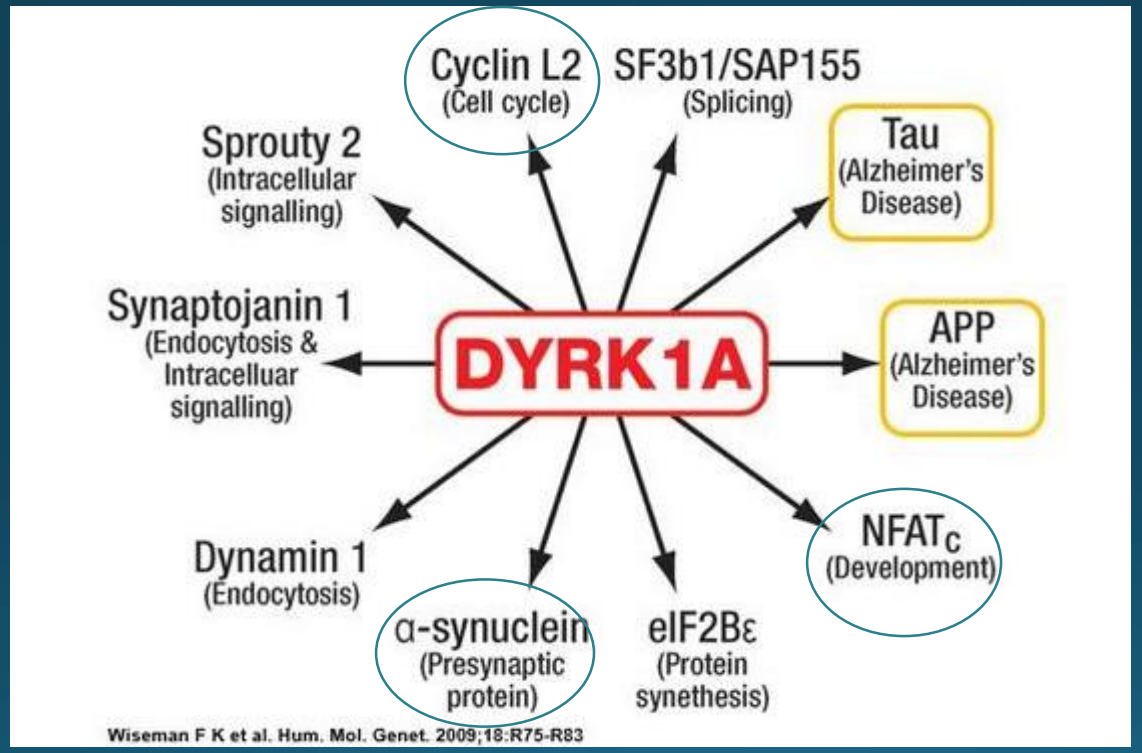


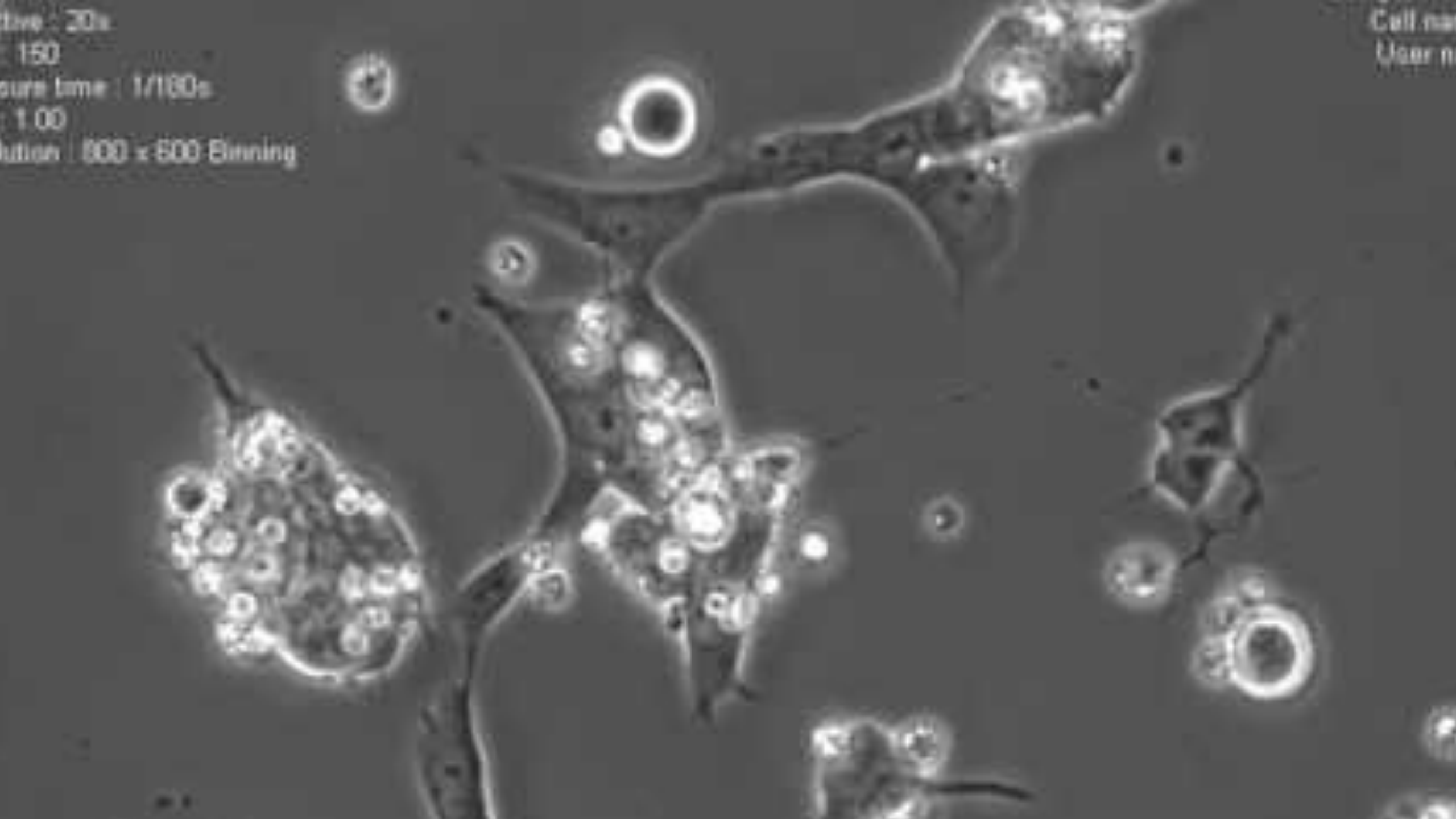
Rajeev Singh and Matthias Lauth,2017

DYRK1A Protein

- DYRK1A PROTEIN
  - The DYRK1A enzyme is a kinase- attaches oxygen and phosphorus atoms to other proteins (called phosphorylation) to regulate the activity of the protein
  - DYRK1A has many critical roles in critical signaling pathways of cell proliferation that in turn are related to neuron differentiation and development and skeletal homeostasis and development.
  - Activation of full kinase activity requires autophosphorylation of a tyrosine in the protein immediately after translation

Phosphorylation Targets of DYRK1A

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Pathologic DYRK1A Mutations in Humans

Genetic Terms
Types of Genetic Variants

- **Benign variant** (Synonym: polymorphism)
  - An alteration in DNA (distinct from the reference sequence) that is not associated with an abnormal phenotype or increased disease risk. (makes a functional protein)
- **Pathogenic Variant**
  - An alteration in a gene (distinct from the reference sequence) that is associated with an abnormal phenotype or increased disease risk. (makes a nonfunctional protein)
- **Likely pathogenic or likely benign variant**
  - Pathogenic- An alteration in a gene (distinct from the reference sequence) that is likely to be associated with an abnormal phenotype or increased disease risk.
  - Benign- An alteration in a gene (distinct from the reference sequence) that is very unlikely to be associated with an abnormal phenotype or increased disease risk.
- **Variant of Unknown significance**

DYRK1A-Related Intellectual Disability Syndrome (Autosomal Dominant MR)

- *DYRK1A*-related intellectual disability syndrome is inherited in an autosomal dominant manner.
  - Only 1 of the 2 DYRK1A genes is mutated
- All of the cases have been de novo (new) mutations

Pathological DYRK1A Mutations

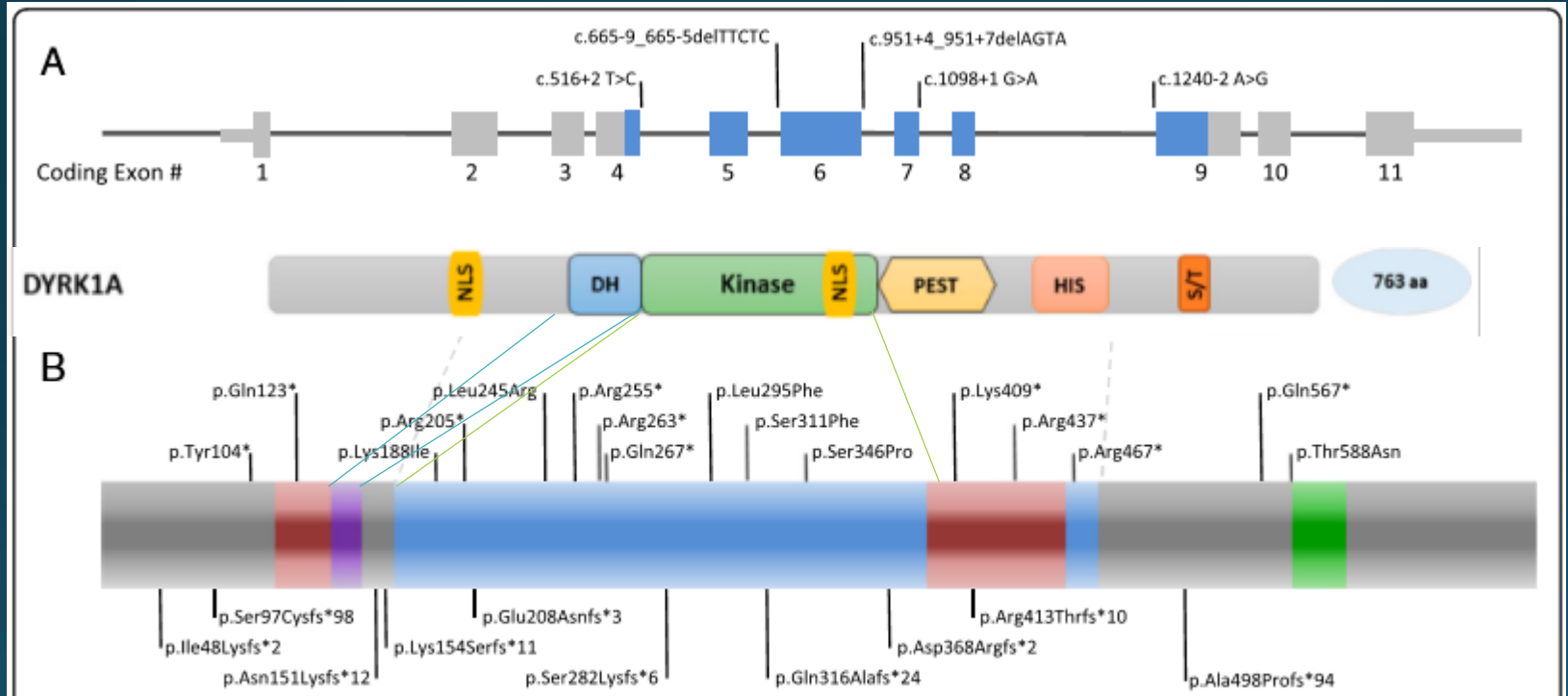


Fig. 3 a The *DYRK1A* coding sequence with the 5 reported splice site mutations. **b** The DYRK1A protein with the missense and nonsense mutations shown above, and the frameshift variants indicated below. The nuclear localization signal shown in red, the DYRK homology (DH) box shown in purple, the kinase domain shown in blue, and the speckle-targeting signal shown in green. Two mutations were identified in multiple individuals: p.Arg205* in 4 individuals and p.Glu208Asnfs*3 in 2 individuals

Prominent Features of DYRK1A Mutations in Humans

- IUGR, postnatal growth retardation, microcephaly, seizures, severe speech delay (speech apraxia), behavior abnormalities, ataxia, eye defects, brain findings (gliosis, cortex atrophy, and white matter hypomyelination), minor skeletal anomalies, feeding, and GI issues

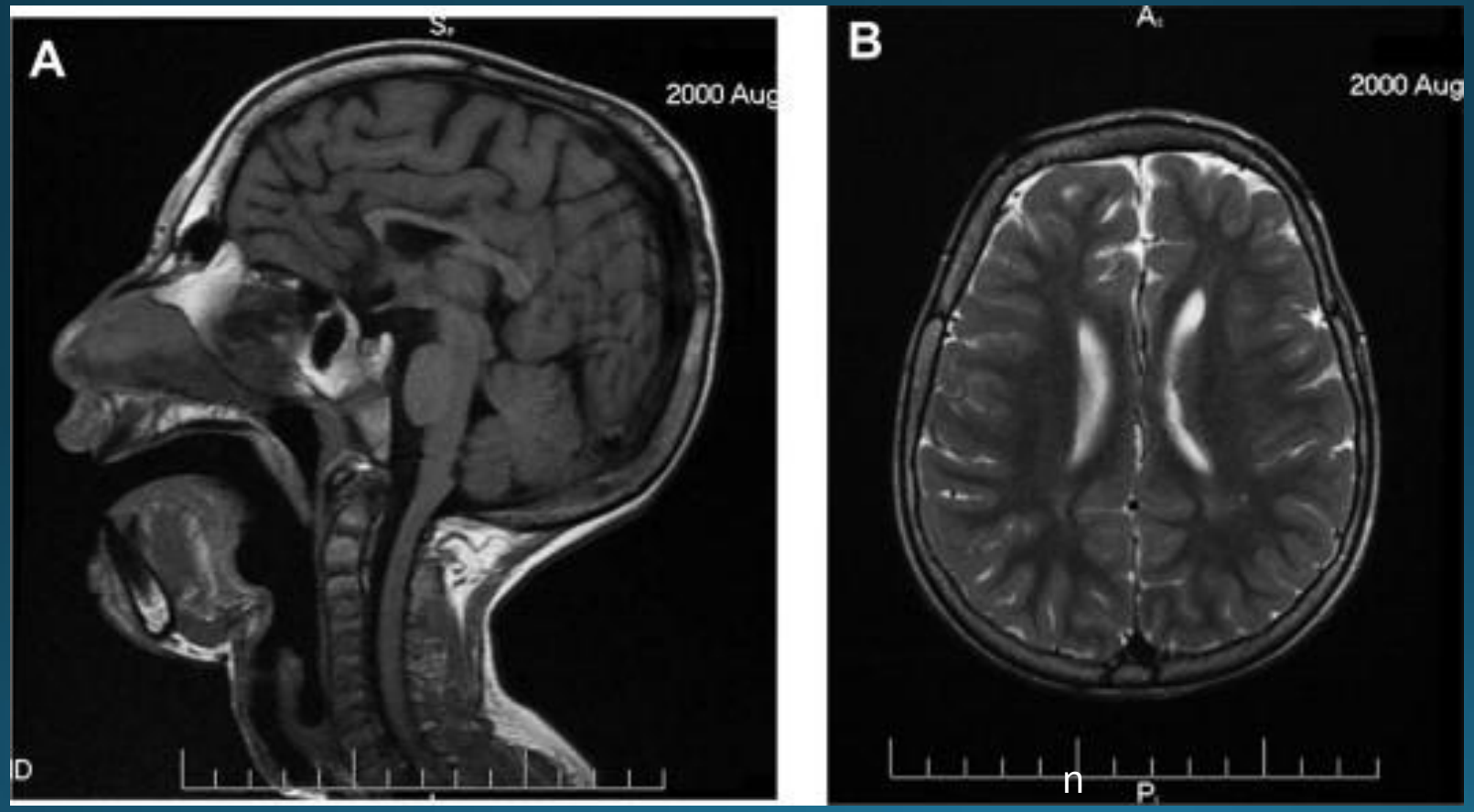
DYRK1A Clinical Features

Common Features (Luco, Pohl et al. 2016)	Number	Percentage
Intrauterine Growth Retardation	33/43	77%
Global Developmental Delay	53/53	100%
Speech Delay	51/51	100%
Motor Delay/Delayed Walking	35/36	97%
Autism Spectrum Disorder	16/35	46%
Febrile Seizures	31/46	67%
Epilepsy	28/47	60%
Visual Impairment	25/32	78%
Dysmorphic Face	53/54	98%

DYRK1A Clinical Features

- Other Features-(Luco, Pohl et al. 2016)
  - Optic Disc Abnormality
  - Hypoplastic Corpus Callosum
  - Thin Brainstem
  - Enlarged Ventricles
  - Increased CSF Space

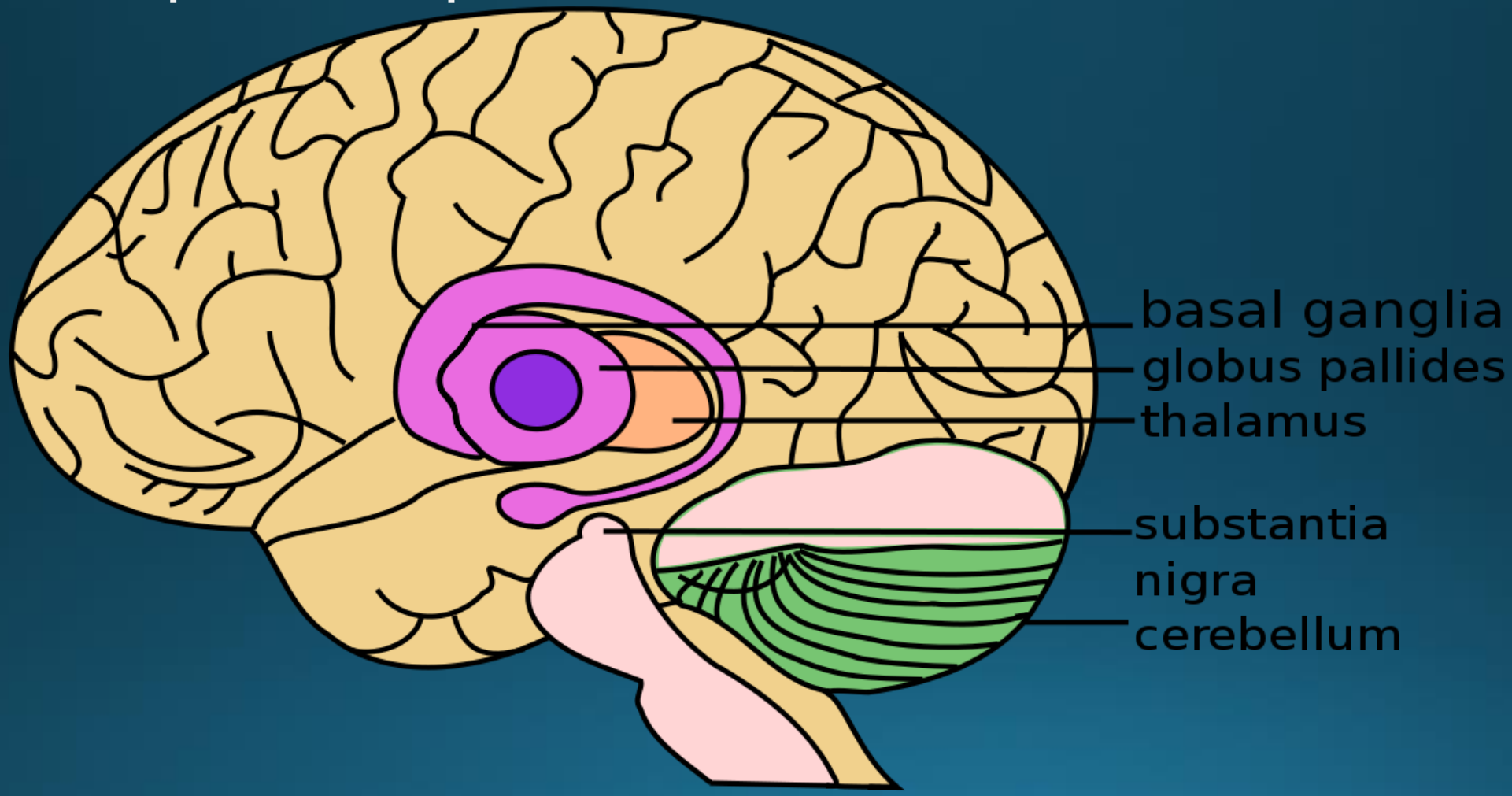
DYRK1A Brain MRI



How Does DYRK1A Affect Movement?

Basal Ganglia of the Brain

An important part of the brain for movement



Parkinson's Disease as a Model for Basal Ganglia Dysfunction

- **Pathophysiology**
  - Brain histology shows loss of dopaminergic cells in the substantia nigra and Lewy bodies in nerve cells before they die.
  - Aggregated synuclein is present in the Lewy bodies.

Parkinson's Disease

An example of basal ganglia disease causing extrapyramidal symptoms

- Parkinson's disease is a degenerative disease affecting approximately 1% of the population over 65.
- Clinical Features:
  - A "pill-rolling" tremor
  - Abnormal posturing
  - Shuffling gait
  - Slow movement
  - Muscle rigidity
- Carbadopa/levodopa greatly improves Parkinsonian symptoms

Parkinson's Disease Video

https://www.youtube.com/watch?v=D7ngF1DFgBs

How the Basal Ganglia and Movement are Affected in DYRK1A Mice

- Mice with one functional copy of Dyrk1A (Dyrk1A(+/-)) display a marked hypoactivity and altered gait dynamics (extrapyramidal signs).
- The basal ganglia of the brain control movement and dopamine(DA) is one of the critical neurotransmitters in the basal ganglia
  - DYRK1A mice have abnormal DA neurotransmission.
    - Decreased striatal DA levels
    - Reduced number of DA neurons in the substantia nigra pars compacta
    - Reduced striatal DA release
    - PET scans show forebrain activation when challenged with amphetamine

(Martinez de Lagran, Bortolozzi et al. 2007)

Evidence for DYRK1A Mutation Affecting Movement

- Mouse with DYRK1A mutation has abnormal movement and reduced dopaminergic neurons and dopaminergic neurotransmission.
- Normal levels of DYRK1A kinase are necessary for the survival of midbrain DA neurons during development and in the adult brain. (M.J. Barallobre,2014)
- α-Synuclein plays an important roles in the development of Parkinson's disease pathologies and DRYK1A abnormalities can increase α-Synuclein in neurons
- Homozygosity for the DYRK1A rs8126696 allele increased the risk of Parkinsonism especially early onset. (Cen, Xiao et al. 2016)

Treatment With Dopamine in Children with DYRK1A Mutations May Improve Movement

A Case

- At age 13 this child was not able to speak clearly, he moved slowly and had poor coordination.
- He was placed on a tapering-up dose of Parcopa (carbidopa/levodopa)
- 1 year later
  - His teachers saw significant improvement and commented to his mother that he was functioning better in school even though they were unaware he was being treated with Parcopa.
  - He was speaking in sentences and was using first person pronouns. He moved much faster (he caught a cell phone thrown to him) and he was eating better.

Treatment of Children with DYRK1A Mutations

- Treatments used for children with developmental delay and autism
  - ABA therapy, Speech therapy, PT, OT and others
- Diet to provide adequate nutrition.
- Drugs used for attention deficit disorders, obscessive-compulsive behavior (stereotypy) and aggressive behaviors.
- Drugs that may benefit cognitive function- amantadine;
- Drugs that improve movement- carbidopa/levodopa
- Drug, vitamins and cofactor treatment for seizures
  - Use drugs for generalized epilepsy- levetiracetam, clobazam and other benzodiazepines, zonisamide, valproic acid, lamotrigine, topiramate, ketogenic diet
  - Folinic acid, pyridoxine, biotin, vitamin D3
  - L-carnitine

DYRK1A in Other Diseases

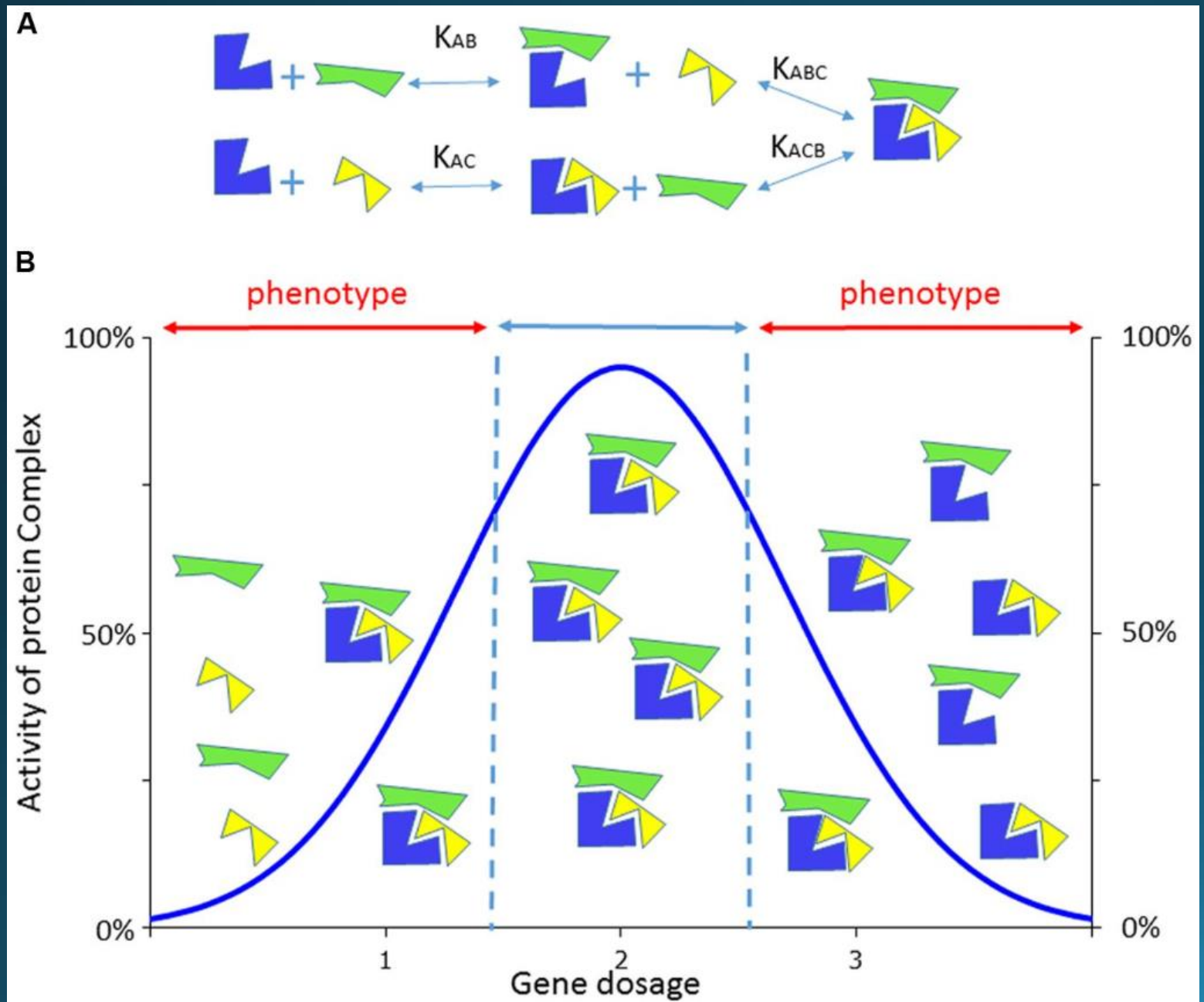
Too Much DYRK1A Activity in Other Diseases

- Down Syndrome
  - Since this is caused by trisomy 21, children with Down syndrome have excessive DYRK1A gene activity.
  - They have fewer neurons because their neurons differentiate too early.
  - They have increased risk for Alzheimer neurodegeneration
- Alzheimer neurodegeneration
  - DYRK1A phosphorylates beta amyloid precursor protein forming amyloid plaques, a hallmark of Alzheimer's dementia pathology.

Too Little DYRK1A Activity in Other Diseases

- 1:70 (1.4%) of patients with microcephaly, seizures and absent language have a DYRK1A mutation.

- DYRK1A gene abnormalities in patients with global developmental delay with or without dysmorphic features- 1 in 719 patients tested by microarray and 2 in 170 patients tested by whole exome screening.



Consequence of the dosage effect on the activity of a multiprotein complex.
(A) Example of a dosage sensitive gene whose encoded protein (in blue) is able to form a tripartite complex with two partners (in yellow or green), using different constant of association/dissociation.
(B) The formation of the complex will be altered by the level of expression of the blue protein compared to the yellow or green ones which are not dosage dependent here.

(Veitia et al., 2008).

Proteins that regulate Dyrk1A activity

Symbol	Name	Subcellular location	Biological process	Mouse Protein identification	Interaction	Reference
14-3-3	14-3-3 proteins	Nucleus	Brain development	Q9CQV8, P62259, P61982, P68510, P68254, P63101, O70456	Binding	Kim et al., 2004; Alvarez et al., 2007
Fgfb	Basic fibroblast growth factor	Nucleus	Angiogenesis, Differentiation	P15655	Not described	Yang et al., 2001
E1A	Human adenovirus early region 1A	Nucleus	Oncoprotein		Protein Interaction	Zhang et al., 2001
E2f1	Transcription factor E2F1	Nucleus	Apoptosis, Cell cycle, Transcription	Q61501	Not described	Maenz et al., 2008
Lats2	Large tumor suppressor 2	Cytoplasm, Nucleus	Cell cycle, Cell division, Mitosis	Q7TSJ6	P	Tschop et al., 2011

Duchon A & Herault **Y, 2016**

The Future for Treatment of Genetic Diseases Looks Bright

Treatment has been or is being developed for other genetic diseases that cause developmental delay and seizures. Tuberous sclerosis is the best example

DYRK1A- We know what causes the problem and how it works. Now we have to find a way to increase DYRK1A activity early in life.

Thanks and Questions