KIF1A-Associated Neurological Disorders: Hunting for a "blockbuster drug"

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KIF1A-Associated Neurological Disorders (KAND)

Brain

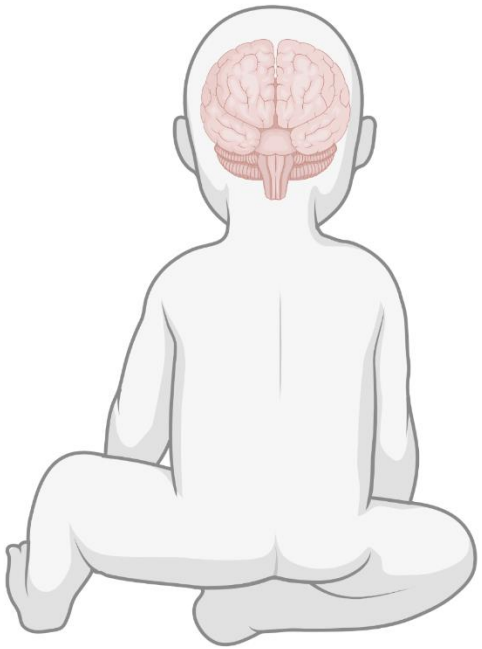
Eyes

Muscles

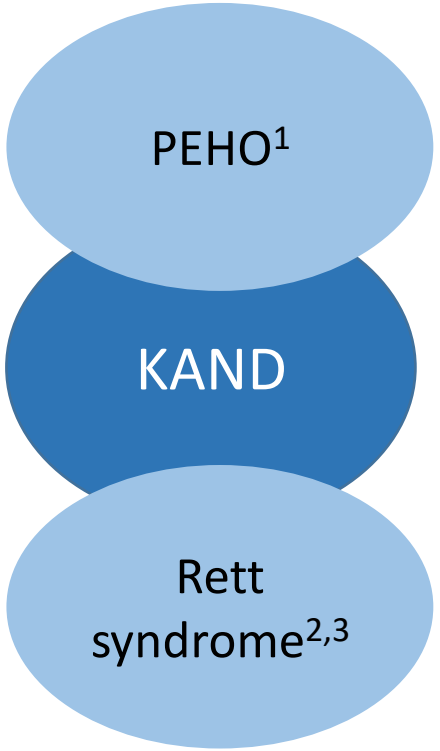
Bones

Stomach

Urinary



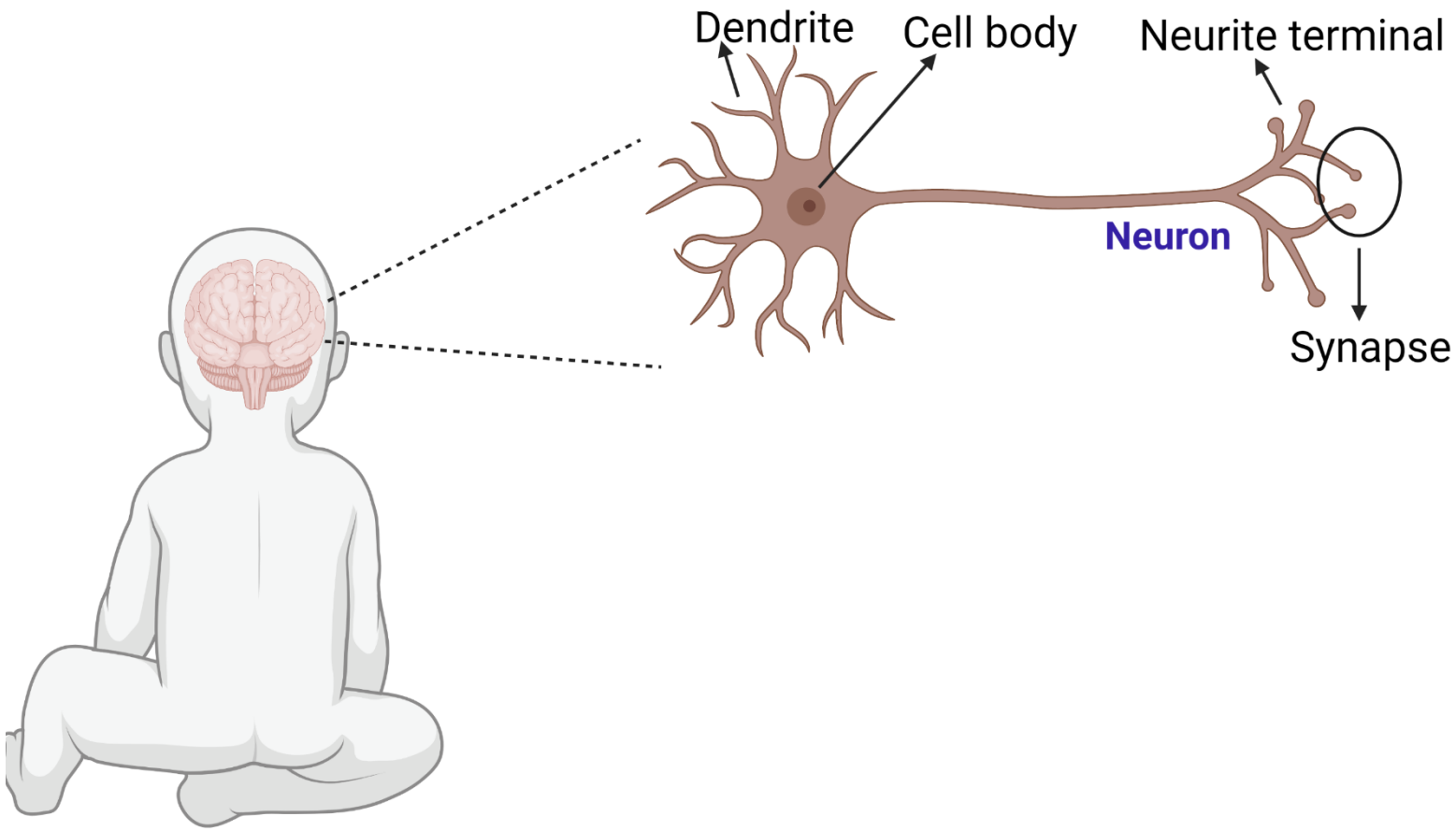
Constipation
Difficulty swallowing
GERD
Strabismus
Diarrhea
Frequent fevers
Short stature
Microcephaly
Thin/ absent corpus callosum
Cortical visual impairment
Development delay/ ID
Optic nerve atrophy
Abnormal muscle tone
Epileptic seizures
Cerebral atrophy
Spasticity
Genitourinary malformations



[2]Research Simplified Article available at: *https://www.kif1a.org/blog/research-simplified-with-dr-simranpreet-kaur-and-prof-john-christodoulou/*

1. Salpietro, V. et al. Brain. 2017
2. Boyle, L et al., HGG Advances, 2021
3. Kaur, S. et al. Human Mutation. 2020

Kinesin family member 1A (KIF1A)



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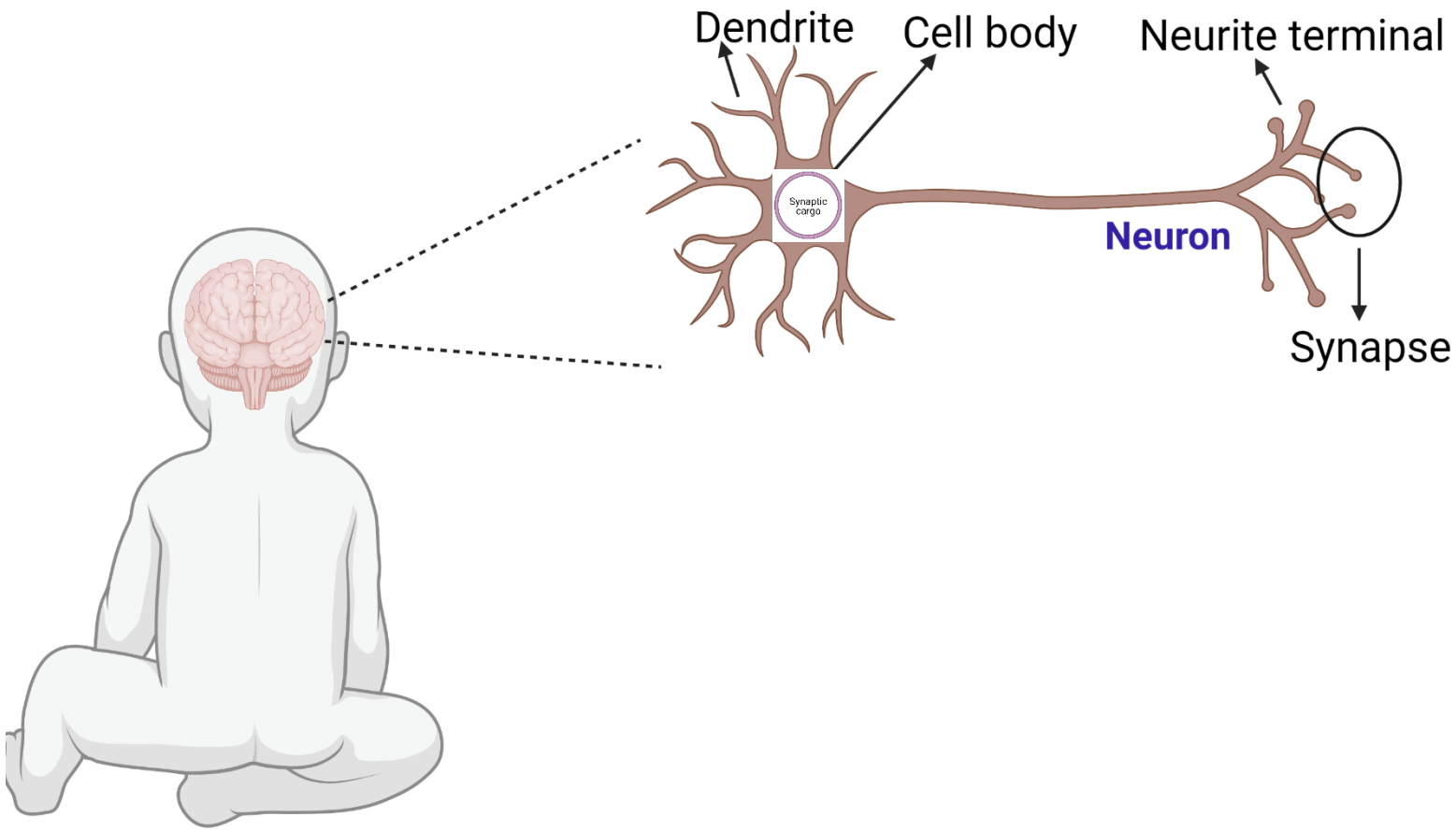
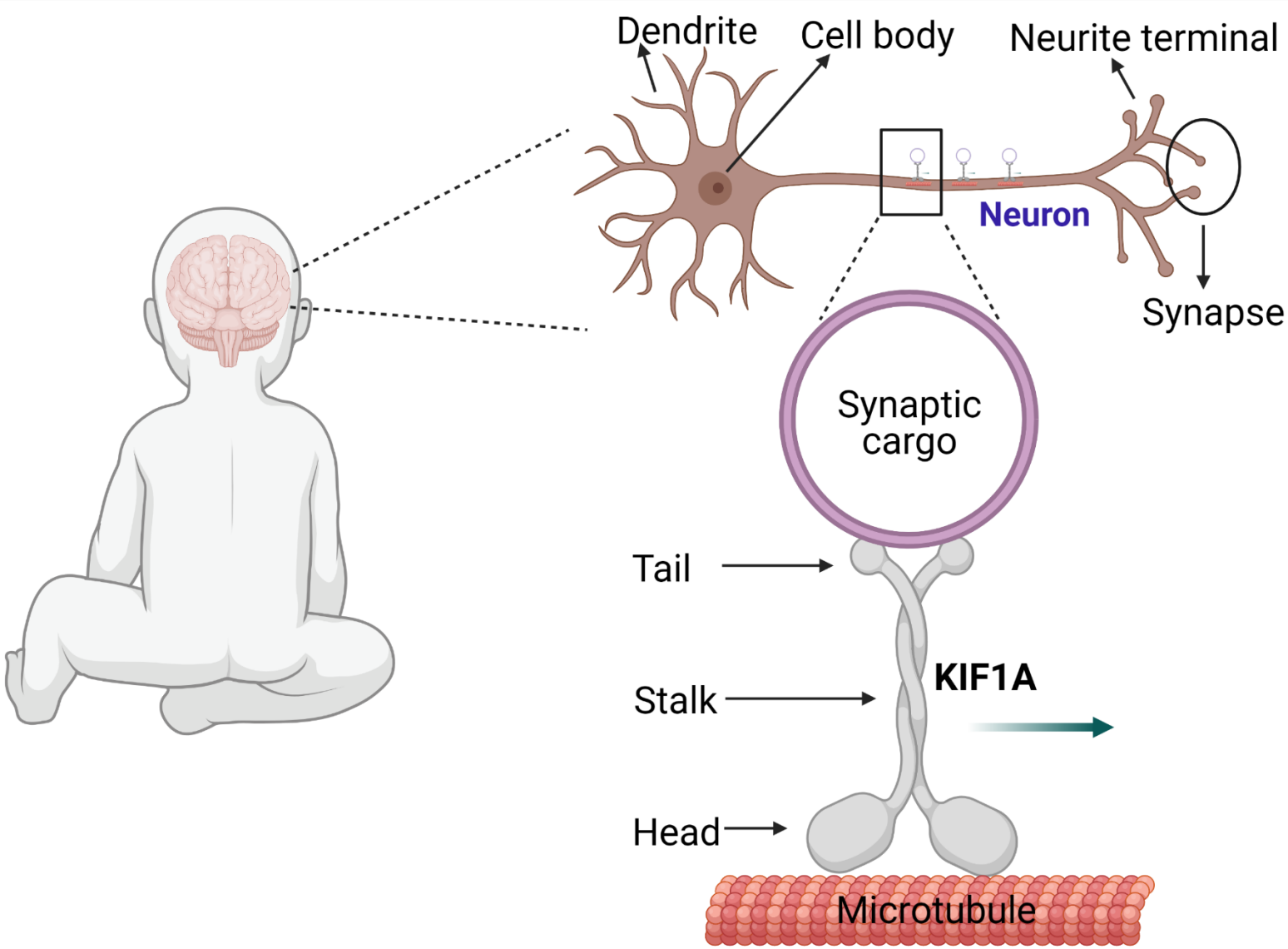
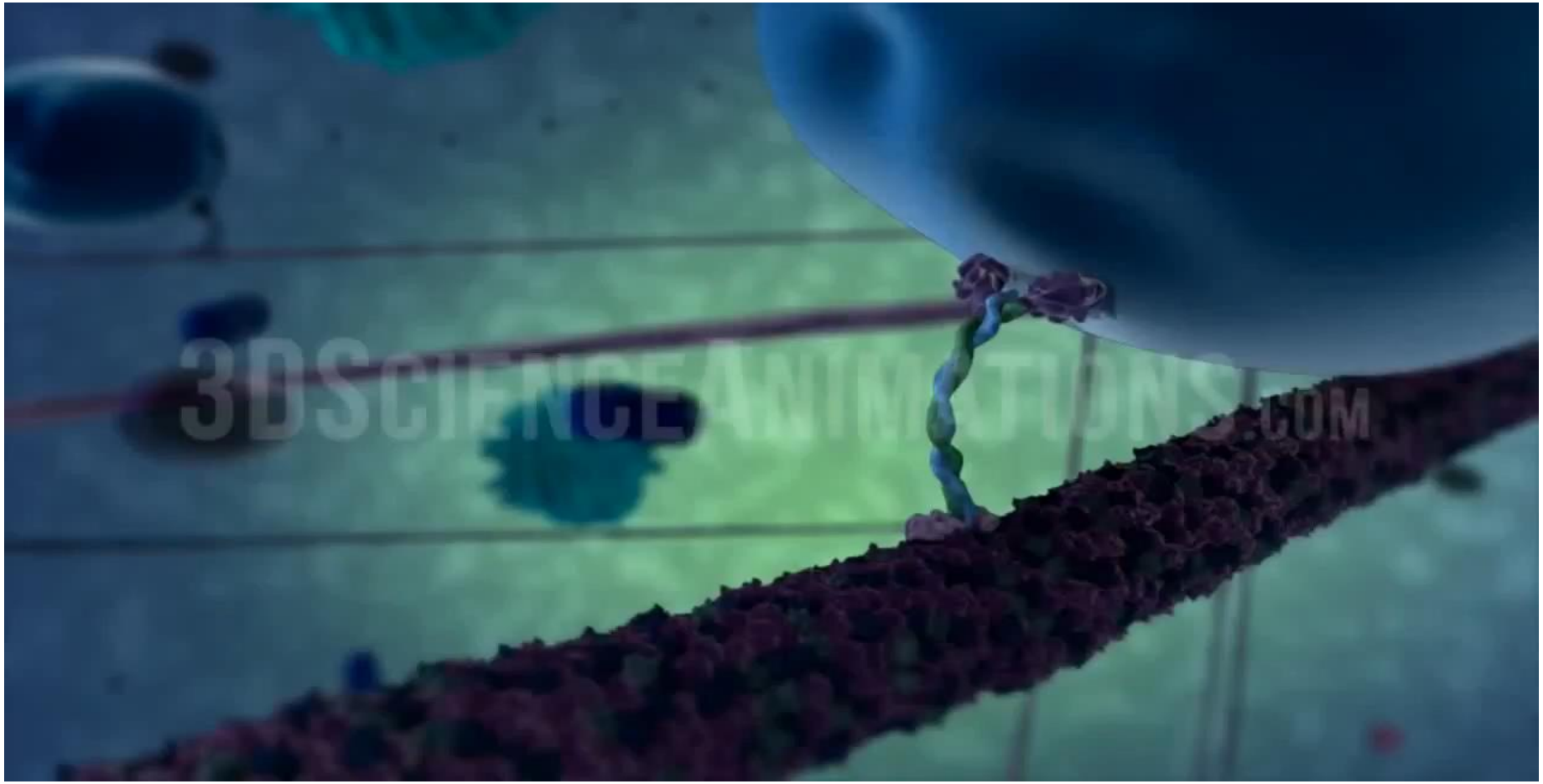


KIF1A – Structure and Function

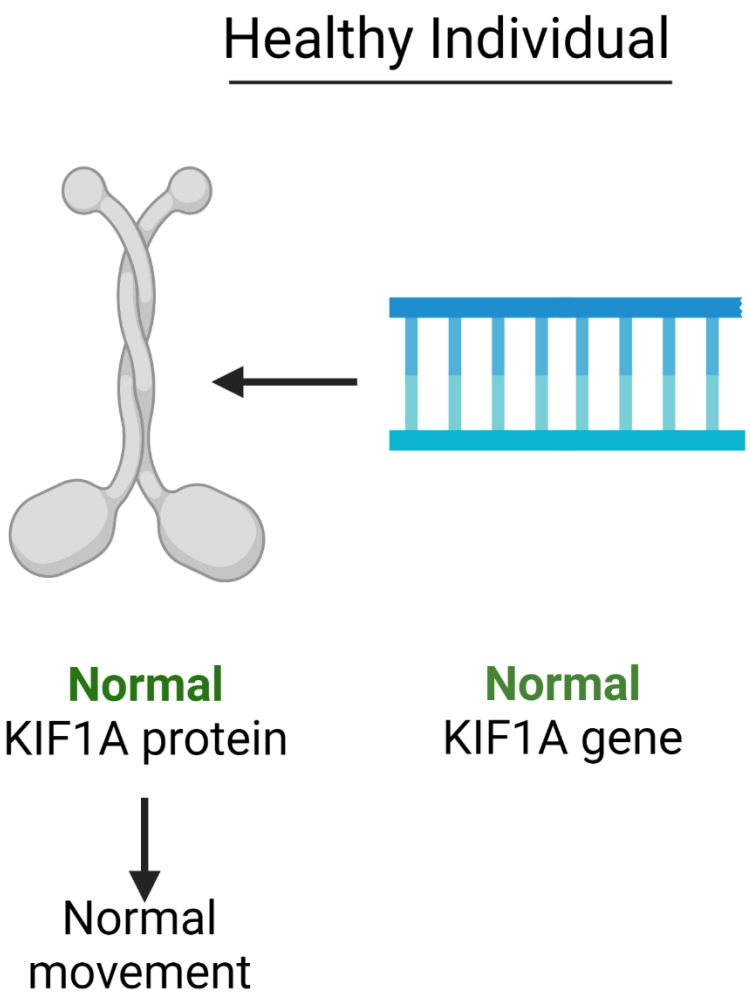


KIF1A – Step by Step walking animation

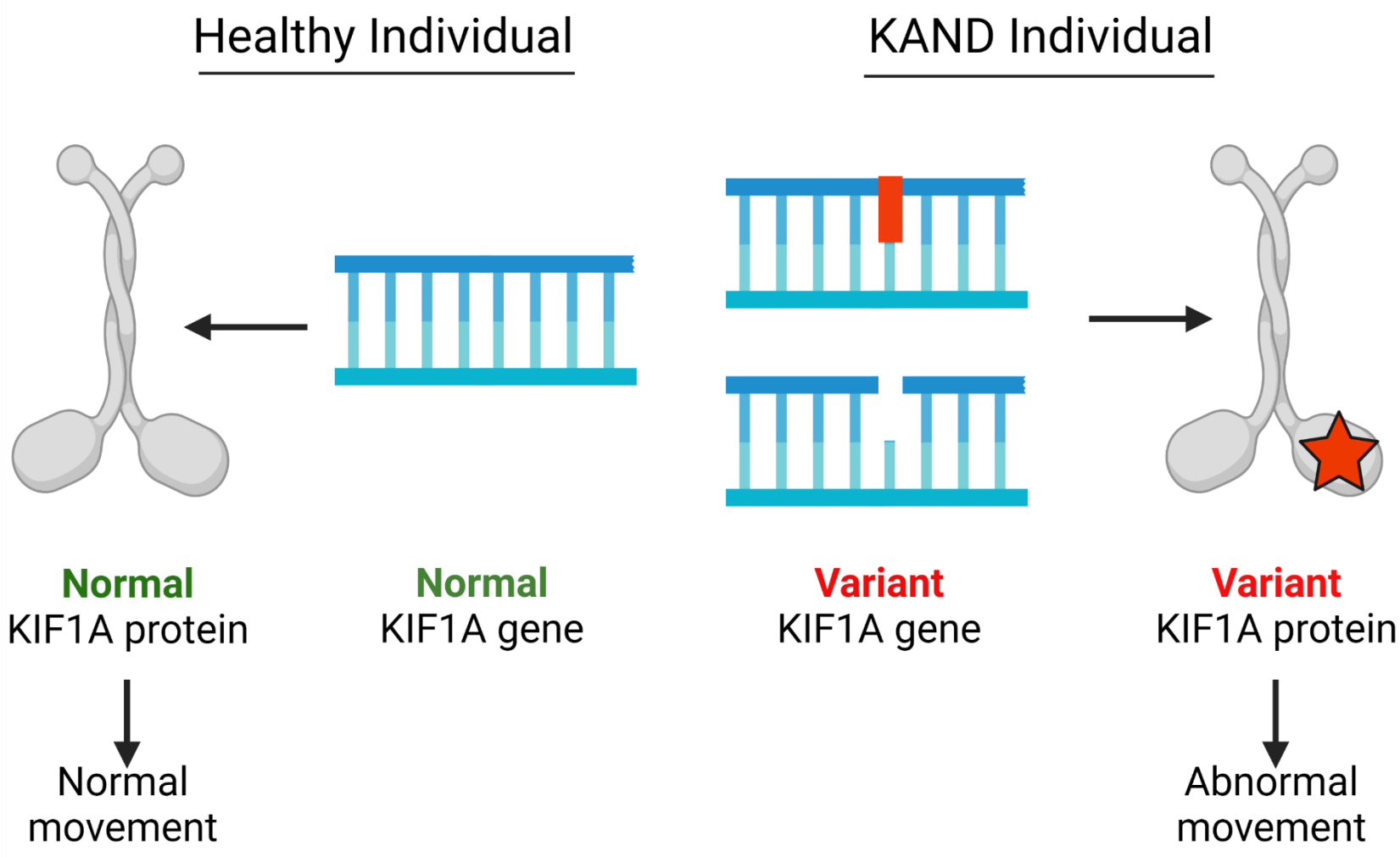


Efficient KIF1A movement = Healthy synapse function = Proper brain function

KIF1A – Normal versus Variant

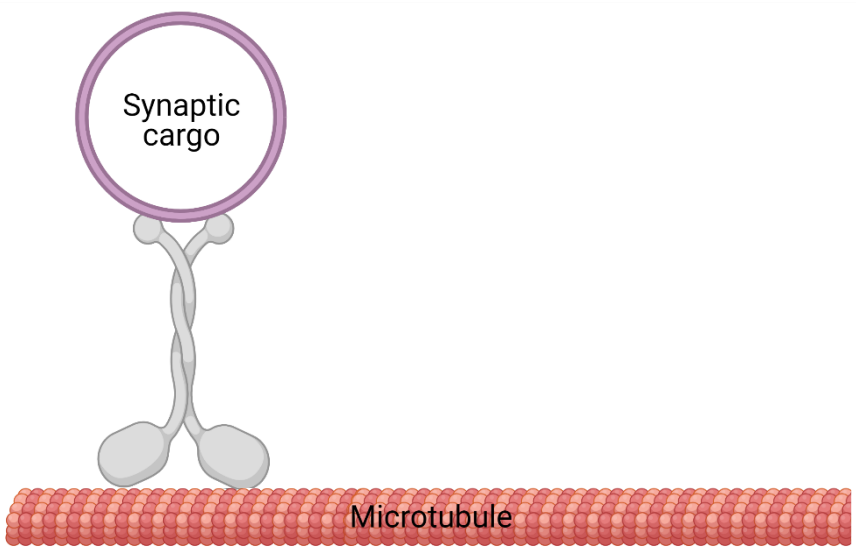


KIF1A – Normal versus Variant

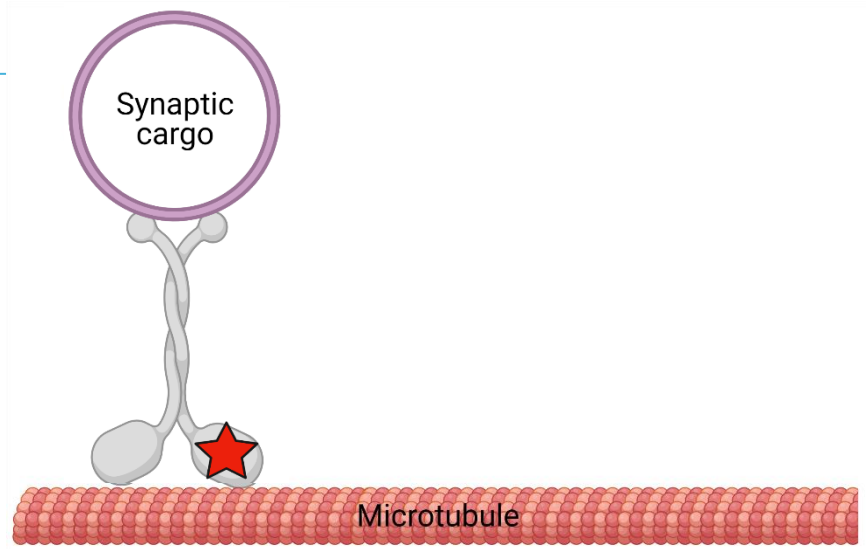


Boyle, L et al., HGG Advances, 2021

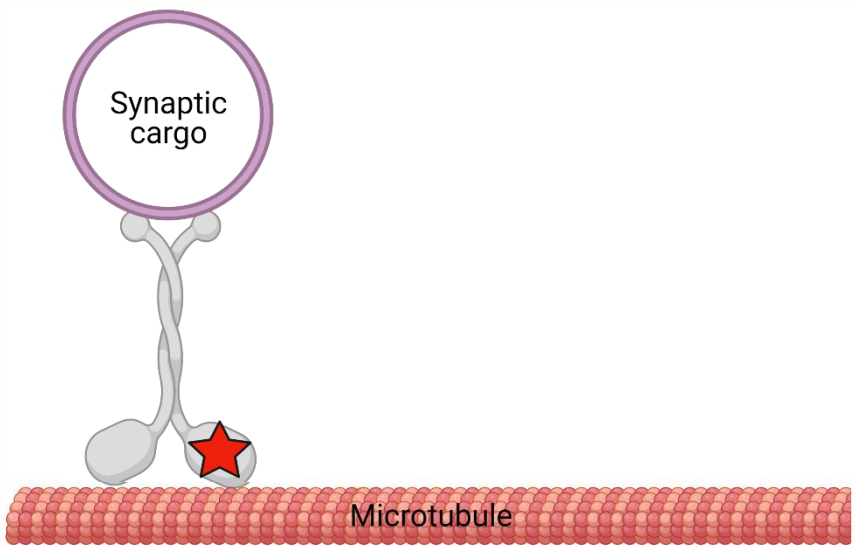
KIF1A – Normal versus Variant



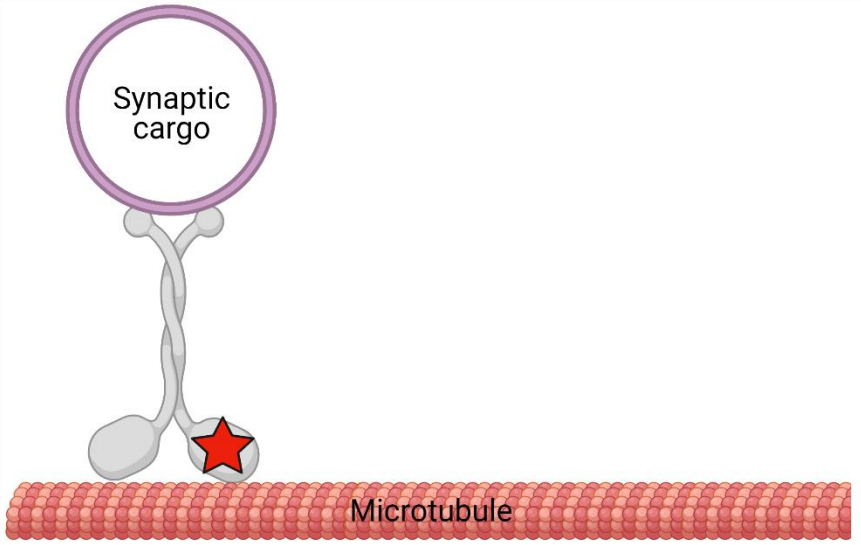
Normal movement



KIF1A Falling off from microtubule

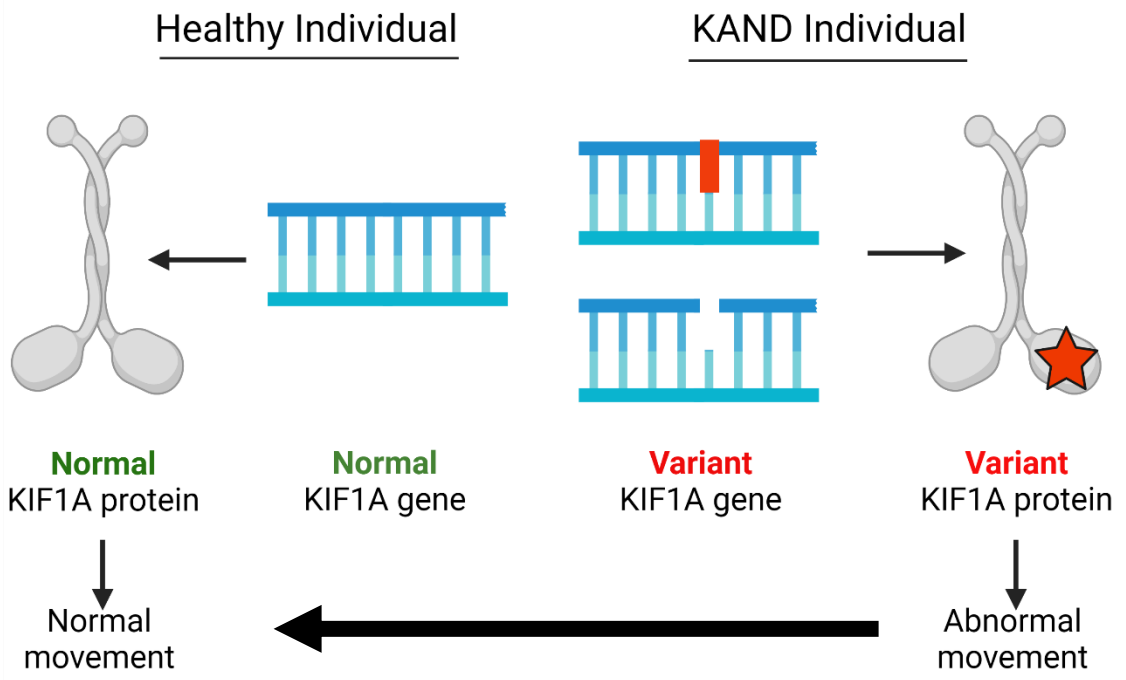


Slow movement



No movement

KIF1A – Normal versus Variant



Drugs or Small molecules

Gene based therapy

KIF1A – Small molecule based therapeutic strategy

Drugs or Small molecules

***De novo* drug synthesis**

New drug discovery

- Expensive (~1b USD)
- Time consuming (~15 years)
- Low FDA success rate (0.01%)

KIF1A – Small molecule based therapeutic strategy

Drugs or Small molecules

De novo drug synthesis

New drug discovery

- Expensive (~1b USD)
- Time consuming (~15 years)
- Low FDA success rate (0.01%)

Drug re-purposing

FDA approved drugs

- Cost effective (250k USD)
- Time friendly (3-12 years)
- High FDA success rate (30%)

https://www.koreabiomed.com/news/articleView.html?idxno=9911

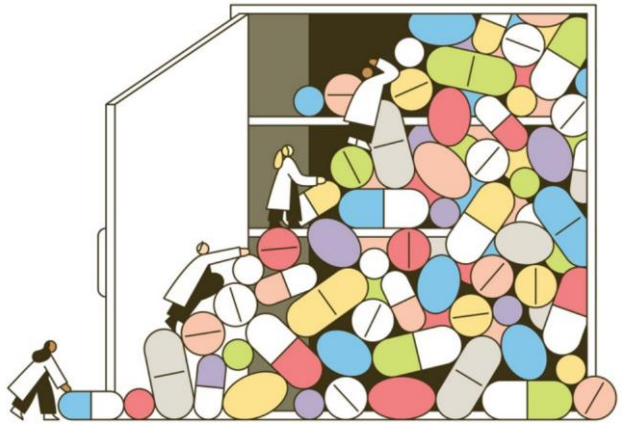
KIF1A – Low Throughput versus High Throughput screening

Drugs or Small molecules

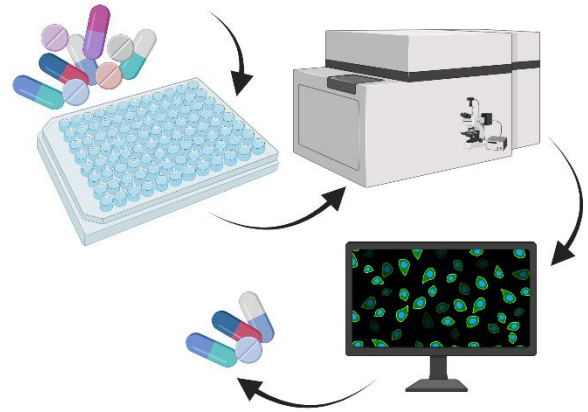
Drug re-purposing

FDA approved drugs

Low Throughput Screening (LTS)

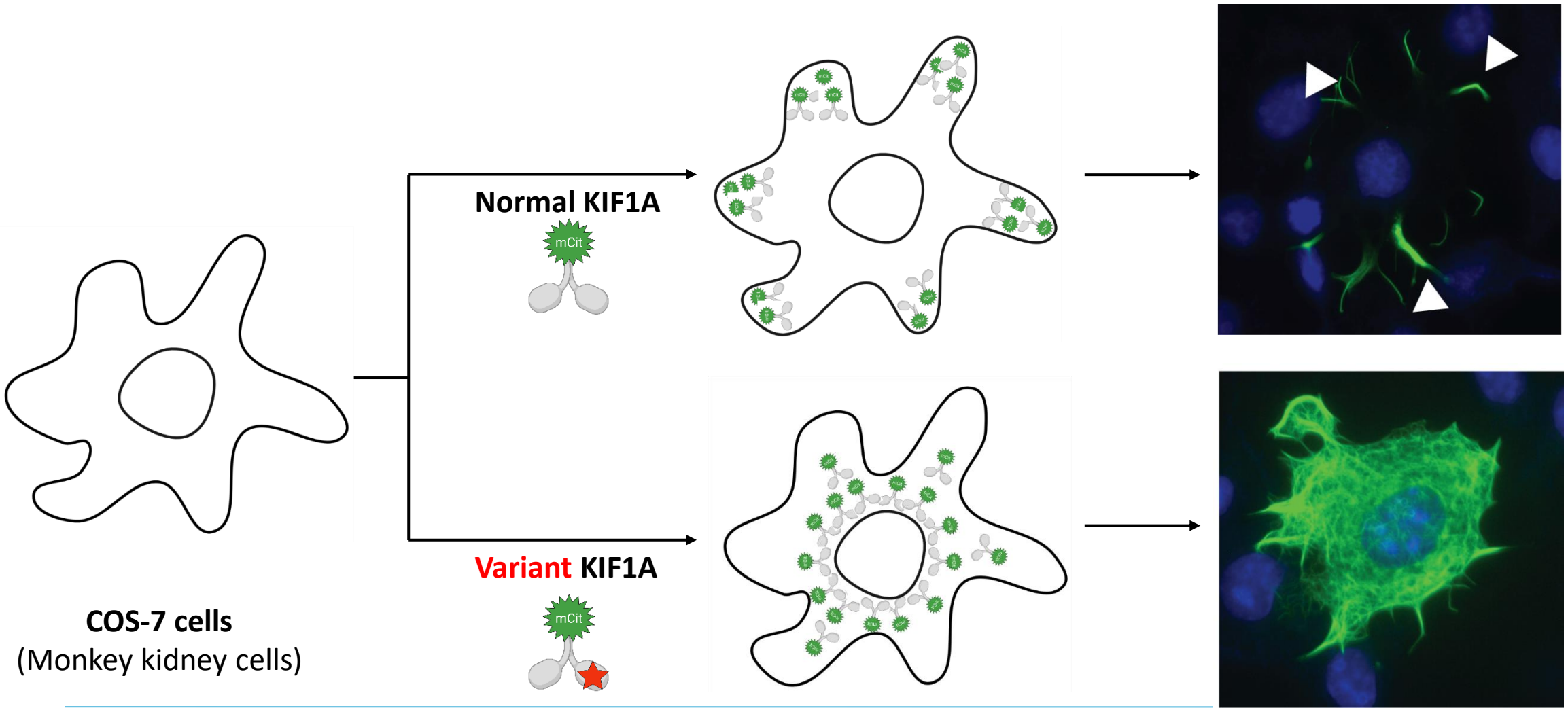


High Throughput Screening (HTS)



HTS - Methodology

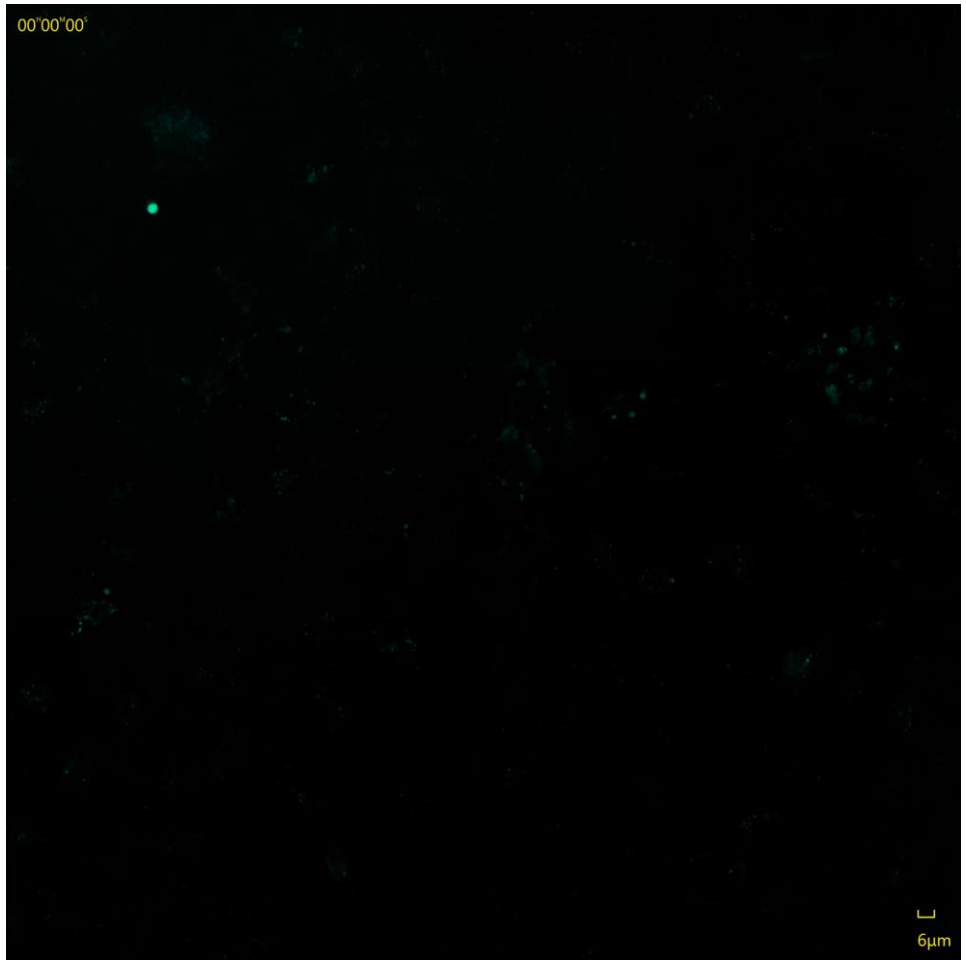
HTS compatible assay



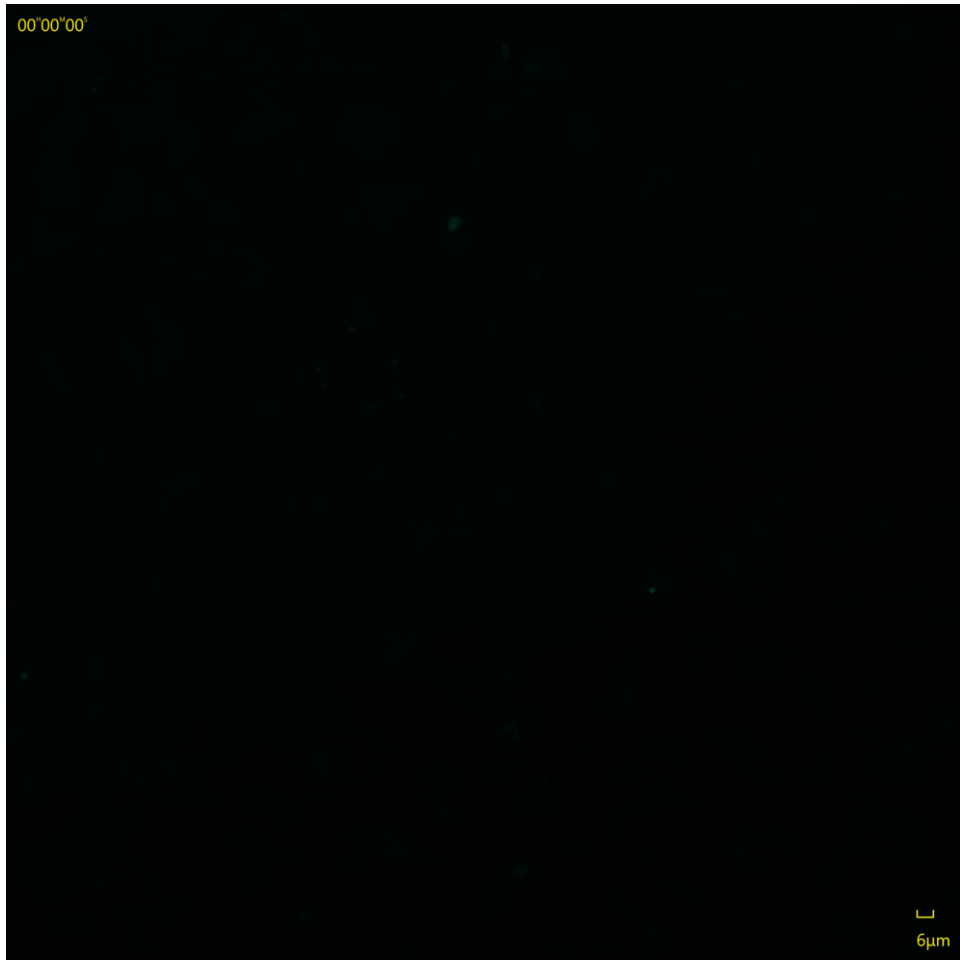
HTS - Methodology

HTS compatible assay

Normal KIF1A



Variant KIF1A



Dr. Alejandro Hidalgo-Gonzalez

Dr. Holly Voges

HTS - Methodology

Assay development/ optimisation

- HTS adaptable assay

Assay validation

- Selecting suitable controls'
- Low variability and good reproducibility

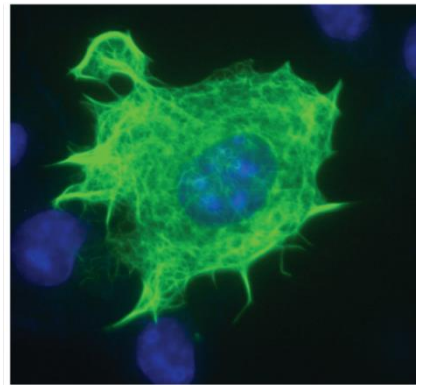
Primary Screen (Hits)

- Drug repurposing
- FDA approved
- Small molecule library

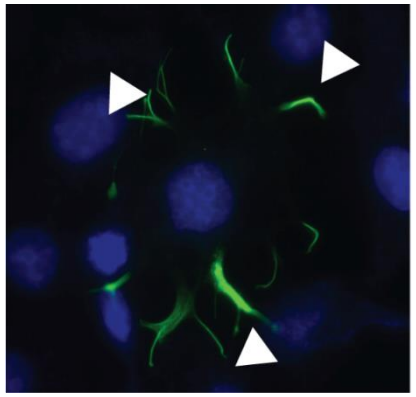
- N=3000
- Low cost
- Academic and not-for-profit researchers
- Small molecules: Neuroscience, cell signalling etc

HTS - Methodology

Assay development/ optimisation	Assay validation	Primary Screen (Hits)
• HTS adaptable assay	• Selecting suitable controls' • Low variability and good reproducibility	• Drug repurposing • FDA approved • Small molecule library • MFI analysis



Small molecule



HTS - Methodology

Assay development/ optimisation

- HTS adaptable assay

Assay validation

- Selecting suitable controls'
- Low variability and good reproducibility

Primary Screen (Hits)

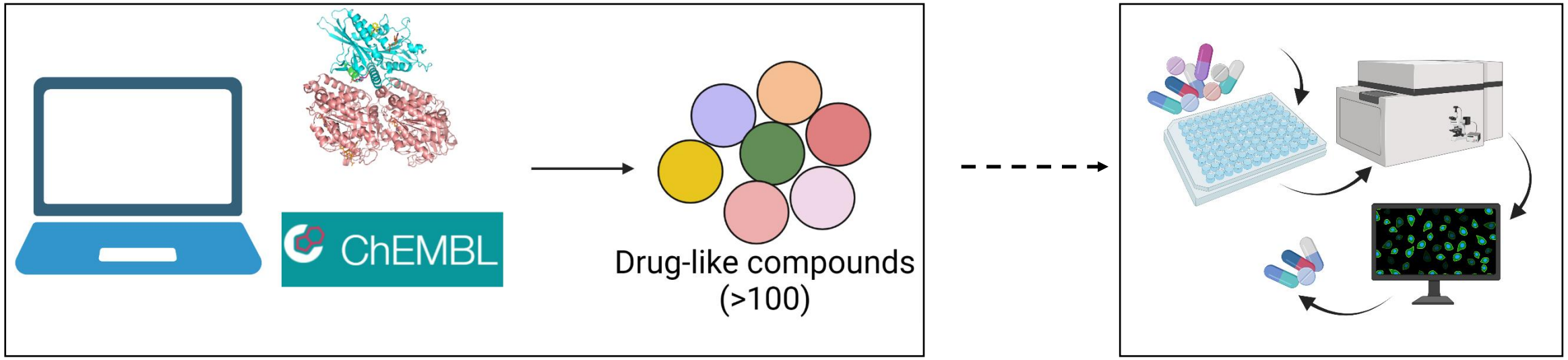
- Drug repurposing
- FDA approved
- Small molecule library
- MFI analysis

Unbiased hit selection

Hit validation

In-silico drug-like compound screening

- Computer Aided Drug Discovery (AMRI - Dr. Douglas B. Kitchen and Dr. Kathleen Bove)

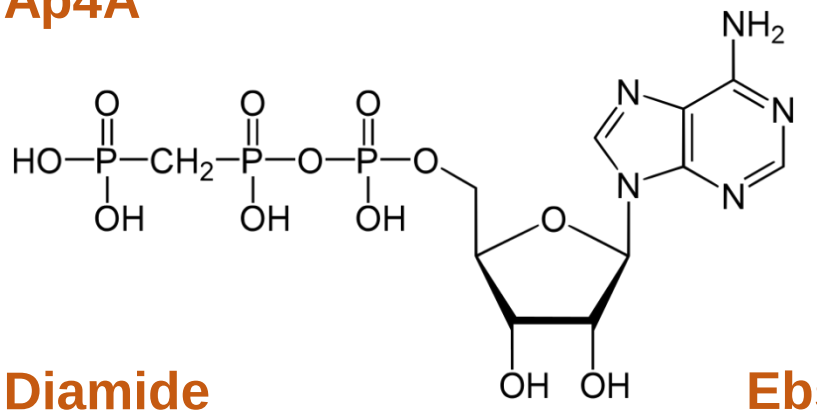


Complex Science. Expert Solutions.

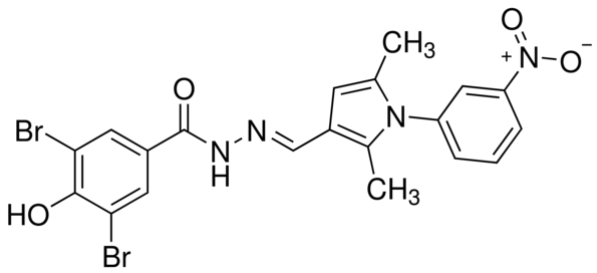
What about the existing kinesin modulators?

- Existing compounds reported in literature (KIF5 and other motor proteins)

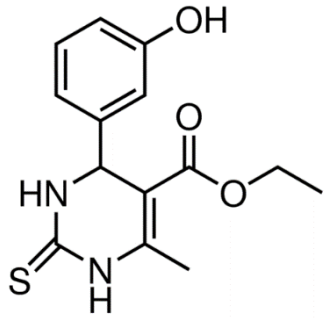
Ap4A



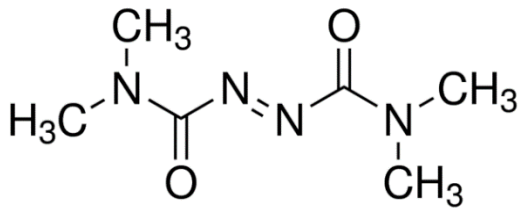
Kinesore



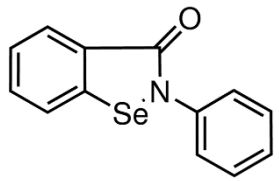
Monastrol



Diamide

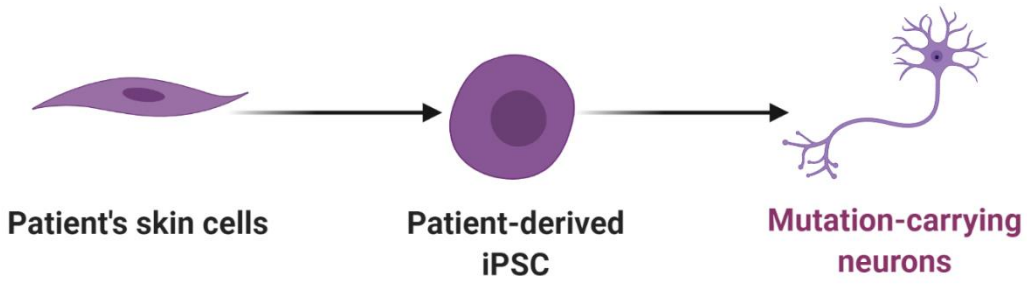


Ebselen



Small molecules in KAND individual's neuronal cells

- Differentiation of patient derived iPSC into relevant neuronal cell type



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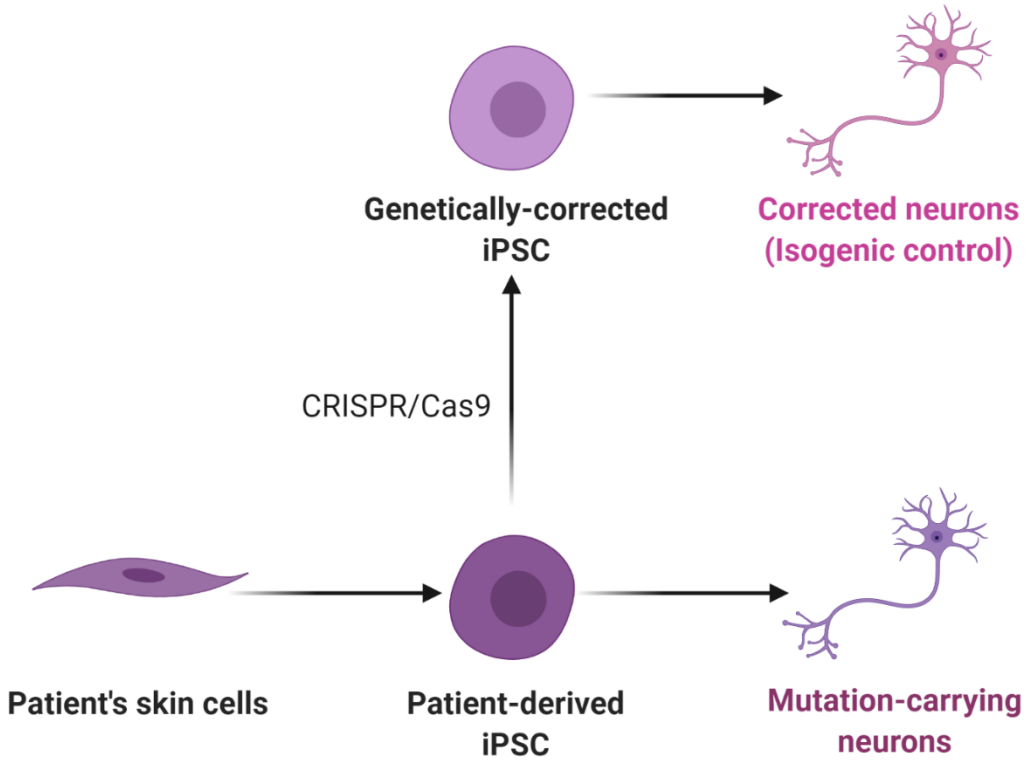
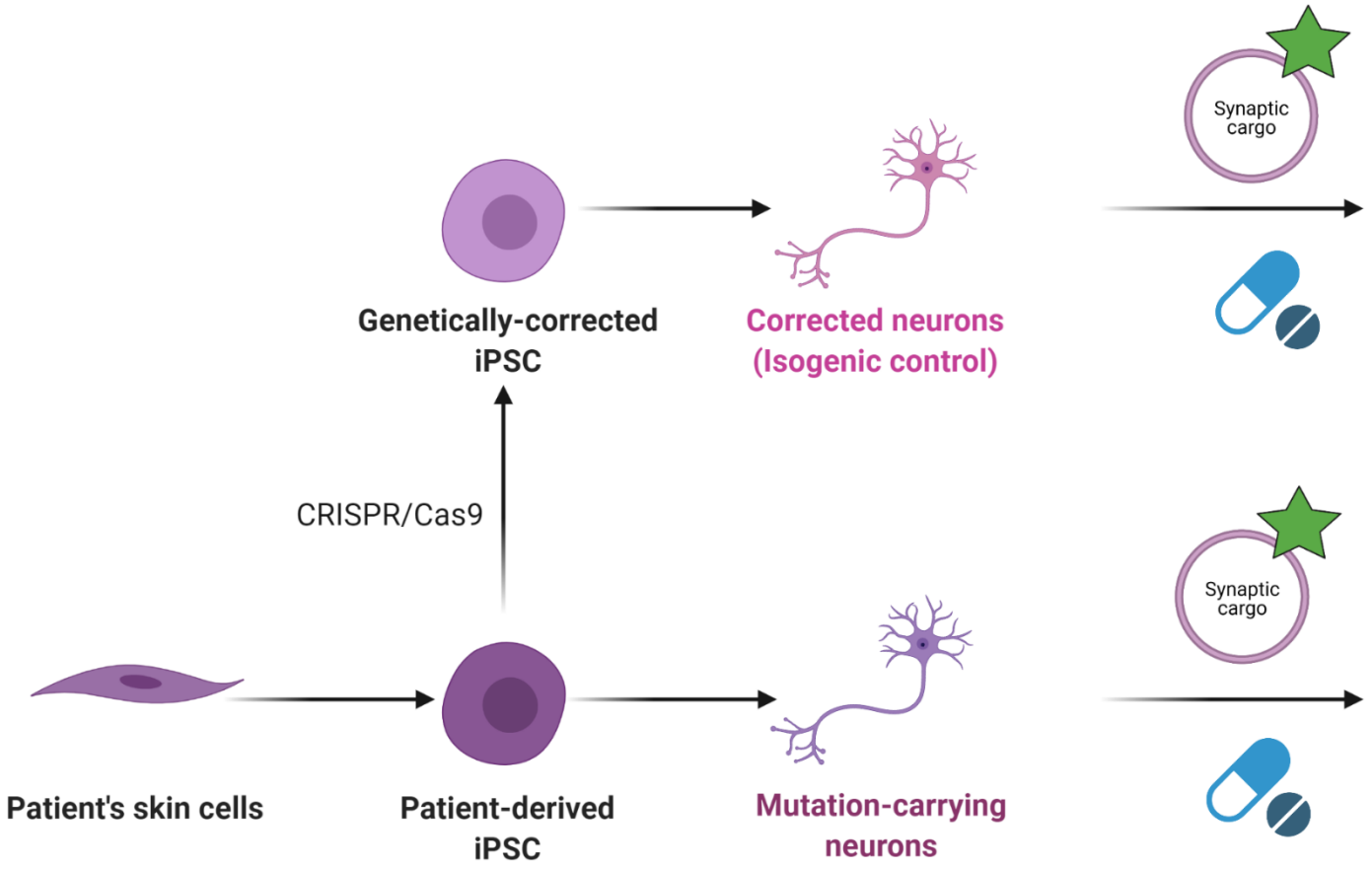


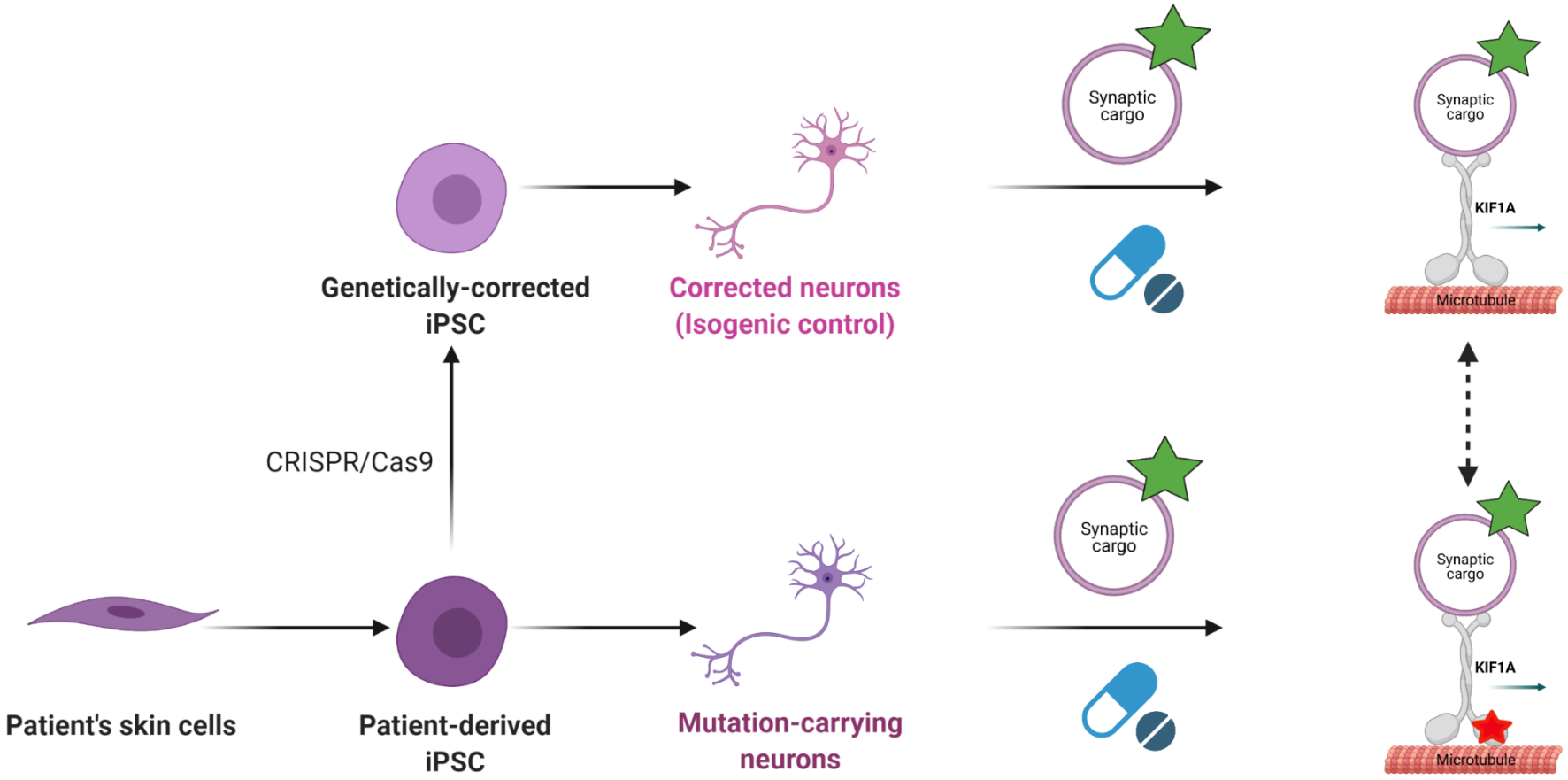
Small molecules in KAND individual's neuronal cells

- Introducing fluorescent KIF1A-specific cargo

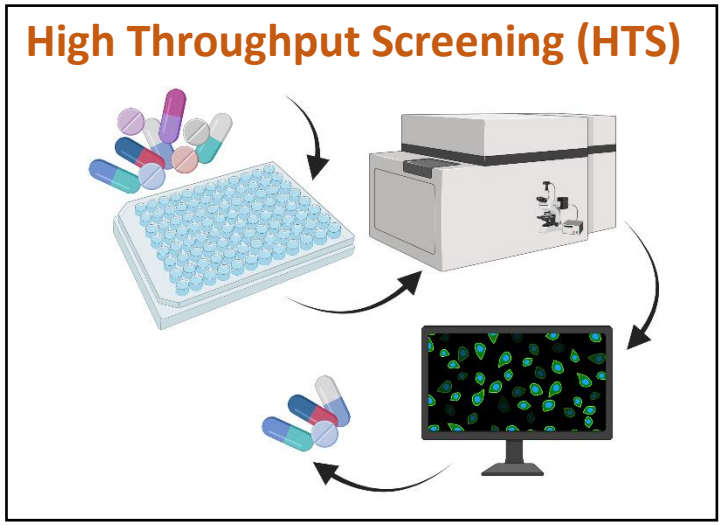


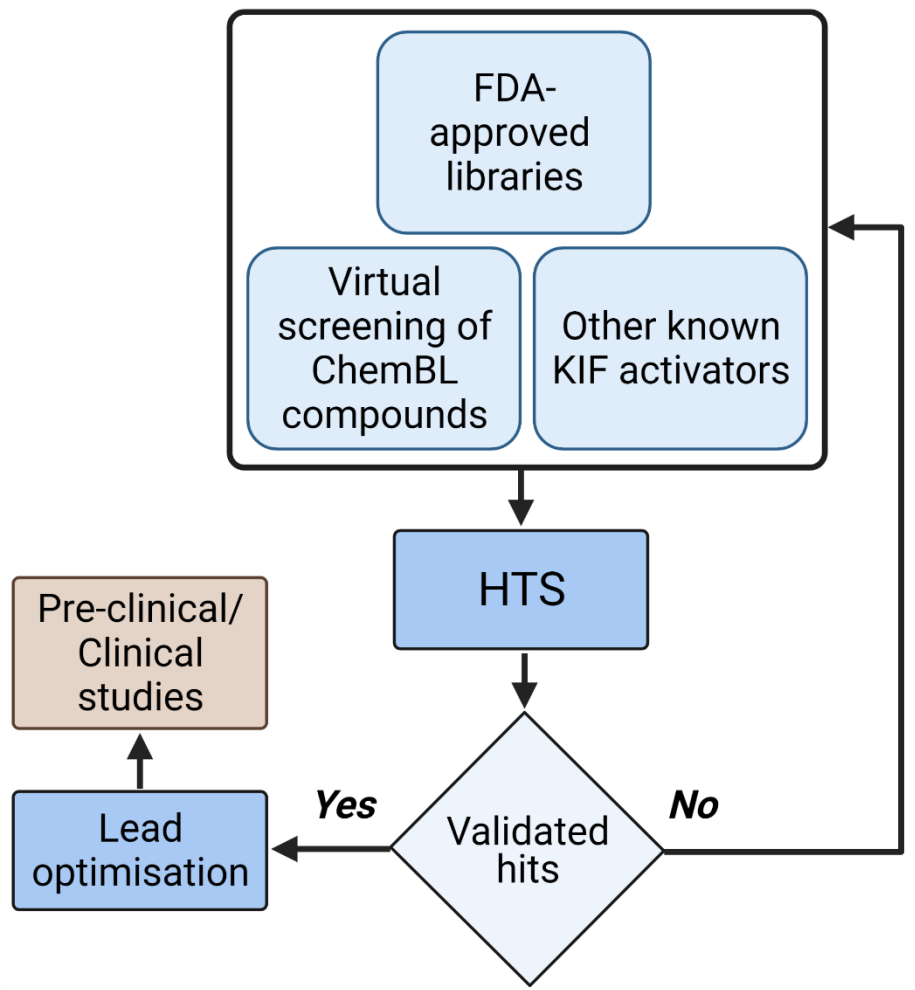
Small molecules in KAND individual's neuronal cells

- Examining the effect of key drugs on the speed of KIF1A movement



KIF1A – HTS Plan of Action





KIF1A – Improving KAND diagnosis and raising awareness

Include KIF1A gene on PanelApp: routinely used genetic testing panels

Green KIF1A in Angelman Rett like syndromes

Level 2: Dysmorphic and congenital abnormality syndromes
Version 0.46

Green KIF1A in Cerebral Palsy

Level 2: Neurology and neurodevelopmental disorders
Version 0.56

Green KIF1A in Mendeliome

Version 0.5590

Green KIF1A in Genetic Epilepsy

Level 2: Neurology and neurodevelopmental disorders
Version 0.952

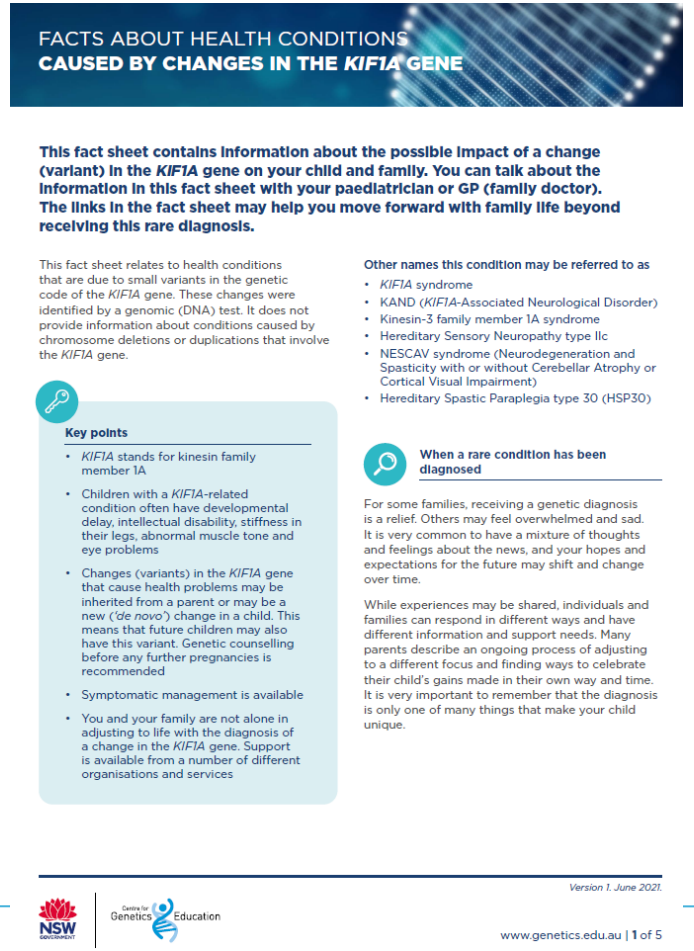
Green KIF1A in Regression

Level 2: Neurology and neurodevelopmental disorders
Version 0.220

Green KIF1A in Intellectual disability syndromic and non-syndromic

Level 2: Neurology and neurodevelopmental disorders

Provide educational resources for the affected families



FACTS ABOUT HEALTH CONDITIONS
CAUSED BY CHANGES IN THE *KIF1A* GENE

This fact sheet contains information about the possible impact of a change (variant) in the *KIF1A* gene on your child and family. You can talk about the information in this fact sheet with your paediatrician or GP (family doctor). The links in the fact sheet may help you move forward with family life beyond receiving this rare diagnosis.

This fact sheet relates to health conditions that are due to small variants in the genetic code of the *KIF1A* gene. These changes were identified by a genomic (DNA) test. It does not provide information about conditions caused by chromosome deletions or duplications that involve the *KIF1A* gene.

Other names this condition may be referred to as

- *KIF1A* syndrome
- KAND (*KIF1A*-Associated Neurological Disorder)
- Kinesin-3 family member 1A syndrome
- Hereditary Sensory Neuropathy type IIc
- NESCAV syndrome (Neurodegeneration and Spasticity with or without Cerebellar Atrophy or Cortical Visual Impairment)
- Hereditary Spastic Paraplegia type 30 (HSP30)

Key points

- *KIF1A* stands for kinesin family member 1A
- Children with a *KIF1A*-related condition often have developmental delay, intellectual disability, stiffness in their legs, abnormal muscle tone and eye problems
- Changes (variants) in the *KIF1A* gene that cause health problems may be inherited from a parent or may be a new ('*de novo*') change in a child. This means that future children may also have this variant. Genetic counselling before any further pregnancies is recommended
- Symptomatic management is available
- You and your family are not alone in adjusting to life with the diagnosis of a change in the *KIF1A* gene. Support is available from a number of different organisations and services

When a rare condition has been diagnosed

For some families, receiving a genetic diagnosis is a relief. Others may feel overwhelmed and sad. It is very common to have a mixture of thoughts and feelings about the news, and your hopes and expectations for the future may shift and change over time.

While experiences may be shared, individuals and families can respond in different ways and have different information and support needs. Many parents describe an ongoing process of adjusting to a different focus and finding ways to celebrate their child's gains made in their own way and time. It is very important to remember that the diagnosis is only one of many things that make your child unique.

Version 1. June 2021.

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www.genetics.edu.au | 1 of 5

Raising interest in community – Media etc

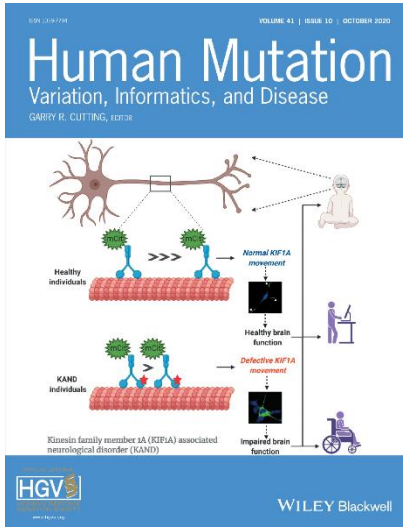
Science News *from research organizations*

Breakthrough discovery in gene causing severe nerve conditions

Date: October 8, 2020

Source: Murdoch Childrens Research Institute

Summary: Researchers have made a breakthrough genetic discovery into the cause of a spectrum of severe neurological conditions.



Significance and outcomes

- Cost- and time-efficient way of identifying targeted treatments for children with abnormalities in KIF1A function
- Critical impact on affected children and their families
- Wide clinically applicability

Acknowledgements

Prof John Christodoulou Dr. Nicole van Bergen Dr. Alejandro Hidalgo-Gonzalez Dr Holly Voges

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Dr. Wendy Chung
Ms. Lia Boyle

Cameron Nowell

Prof Kristen Verhey
Dr. Yang Yue
Ms Breane Budaitis

Research Roundtable network members

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KIF1A.org: Salary support and project grant

Figures created with BioRender.com

A huge thank you to all the lovely super-heroes and their families!

Thank you!

We want all children to have the opportunity to live a healthy and fulfilled life