KIF1A-Associated Neurological Disorders: Hunting for a “blockbuster drug”

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**KIF1A-Associated Neurological Disorders (KAND)**

- Brain
- Eyes
- Muscles
- Bones
- Stomach
- Urinary

**Development delay/ ID**
- Optic nerve atrophy
- Abnormal muscle tone
- Epileptic seizures
- Cerebral atrophy
- Spasticity
- Genitourinary malformations

**Constipation**
- Difficulty swallowing
- GERD
- Strabismus
- Diarrhea
- Frequent fevers
- Short stature
- Microcephaly
- Thin/ absent corpus callosum
- Cortical visual impairment

**Rett syndrome**

**PEHO**

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2. Boyle, L et al., HGG Advances, 2021

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Kinesin family member 1A (KIF1A)
Kinesin family member 1A (KIF1A)
KIF1A – Structure and Function
KIF1A – Step by Step walking animation

Efficient KIF1A movement = Healthy synapse function = Proper brain function
KIF1A – Normal versus Variant

Healthy Individual

Normal KIF1A protein

Normal KIF1A gene

Normal movement
KIF1A – Normal versus Variant

Healthy Individual

Normal
KIF1A protein

Normal
KIF1A gene

Normal movement

KAND Individual

Variant
KIF1A gene

Variant
KIF1A protein

Abnormal movement

Boyle, L et al., HGG Advances, 2021
KIF1A – Normal versus Variant

- **Normal movement**
  - Synaptic cargo on a microtubule
  - Normal movement

- **Slow movement**
  - Synaptic cargo on a microtubule
  - Slow movement

- **KIF1A Falling off from microtubule**
  - Synaptic cargo on a microtubule
  - KIF1A falling off

- **No movement**
  - Synaptic cargo on a microtubule
  - No movement
KIF1A – Normal versus Variant

Healthy Individual

KAND Individual

Normal KIF1A protein

Normal KIF1A gene

Variant KIF1A gene

Variant KIF1A protein

Normal movement

Abnormal movement

Drugs or Small molecules

Gene based therapy
KIF1A – Small molecule based therapeutic strategy

**De novo drug synthesis**

- Expensive (~1b USD)
- Time consuming (~15 years)
- Low FDA success rate (0.01%)
KIF1A – Small molecule based therapeutic strategy

**De novo drug synthesis**

- New drug discovery

**Drug re-purposing**

- FDA approved drugs

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

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

KIF1A – Low Throughput versus High Throughput screening

Drug re-purposing

FDA approved drugs

Low Throughput Screening (LTS)

High Throughput Screening (HTS)
HTS - Methodology

COS-7 cells
(Monkey kidney cells)

Normal KIF1A

Variant KIF1A

HTS compatible assay
HTS - Methodology

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
- 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

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)
What about the existing kinesin modulators?

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

- Ap4A
- Diamide
- Kinesore
- Ebselen
- Monastrol
Small molecules in KAND individual’s neuronal cells

- Differentiation of patient derived iPSC into relevant neuronal cell type
Small molecules in KAND individual’s neuronal cells

- Differentiation of patient derived iPSC into relevant neuronal cell type
Small molecules in KAND individual’s neuronal cells

- Introducing fluorescent KIF1A-specific cargo
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 Mendelome

Version 0.5598

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

Raising interest in community – Media etc

FACTS ABOUT HEALTH CONDITIONS CAUSED BY CHANGES IN THE KIF1A GENE

This fact sheet contains information about the possible impact of a change (mutation) in the KIF1A gene on your child and family. You can talk about the information in this fact sheet with your paediatrician or GP./chlamydia doctors.

The links in the fact sheet may help you move forward with family life beyond receiving this rare diagnosis.

Key points
- KIF1A needs for license family member(s).
- Children with a KIF1A-related condition often have developmental delays, intellectual disability, stiffness in their legs, abnormal muscle tone and joint problems.
- Changes in variants in the KIF1A gene that cause health problems may be inherited from a parent or may be a new (de novo) change in adulthood.
- People who carry a KIF1A variant may have this variant. Genetic counseling before or before pregnancy is recommended.
- Symptom treatment is available.
- You and your family are not alone in adapting to the life with this diagnosis of a change in the KIF1A gene. Support is available from a number of different organizations and services.

Other names this condition may be referred to as:
- KIF1A syndrome
- KAND (KIF1A-Associated Neurological Disorder)
- KIF1A-familial mental retardation syndrome
- Hereditary Sensory Neuropathy type 4c
- Hereditary sensory motor neuropathy type 3
- Hereditary sensory neuropathy type 2 (KIF1A)

When a rare condition has been diagnosed

For some children, 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.

Write experiences may be shared, individuals and families are advised to find different forms of support and meet their child's needs 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.
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
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Thank you!

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