KIF1A-Associated Neurological Disorders
Advancing therapeutic pipeline

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

Our vision is to develop a therapeutic pipeline that is meaningful for the KAND families.

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

**Symptoms:**
- 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

Boyle, L. et al, HGG Advances 2021
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Seizures 42%
Normal 58%

Boyle, L. et al., HGG Advances 2021
KAND and Epilepsy

Diagram showing a neuron with labeled parts: dendrite, cell body, neurite terminal, synapse, synaptic cargo, KIF1A, tail, stalk, head, and microtubule.
Accelerating treatment for epilepsy in children with KAND

Hypothesis: Characterising the cellular and seizure phenotype of KIF1A-mutant patient neurons and brain organoids and identifying small molecules that ameliorate the seizure phenotype will accelerate novel therapeutic options for KIF1A-related epilepsies.
KAND and Epilepsy

Dendrite → Cell body → Neurite terminal → Neuron 1 → Neuron 2

Normal brain

Electroencephalogram (EEG)

Normal electrical activity

Epileptic brain

Abnormal electrical activity
KAND and Epilepsy – Seizure Prediction Model
KAND and Epilepsy – Seizure Prediction Model

Kelley Gao
KAND and Epilepsy – Seizure Prediction Model

Diagram showing the process:
- KIF1A individual's somatic cells
- NGN2 differentiation method
- CRISPR/Cas9
- Mutation-carrying neurons
- Corrected neurons (isogenic control)
- Neuronal phenotype characterisation

- KIF1A individual-derived iPSC
- Genetically-corrected iPSC

- Synaptic characterisation
- Organoid phenotype characterisation
- Mutation-carrying brain organoid
- Corrected brain organoid

- Multi-Electrode Array (MEA)
- EEG reports
- KIF1A variants

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KAND and Epilepsy – Seizure Prediction Model

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KAND and Epilepsy – Drug Discovery

High throughput screening of small molecules using custom made cell models

KIF1A variants EEG reports

Multi-Electrode Array (MEA)
KAND and Epilepsy – Validation in Disease Models

Phenotypic characterisation

Validation of top 5 hits in iPSC derived neurons

High throughput screening of small molecules using custom made cell models

Mutation-carrying neurons

KIF1A variants  EEG reports

Multi-Electrode Array (MEA)
KAND and Epilepsy – Validation in Disease Models

Phenotypic characterisation
- Neuronal phenotype
- KIF1A-cargo trafficking

Functional characterisation
- Gene expression analysis (RNA-Seq)
- Protein expression analysis (Proteomics)
- Pathway analysis

Validation of top 5 hits in iPSC derived neurons

High throughput screening of small molecules using custom made cell models

Mutation-carrying neurons

KIF1A variants
- p(Pro305Leu)
- p(Arg318Tyr)
- p(Glu224Lys)
- p(Asp248Glu)
- p(Arg203Ser)
- p(Cys151Thr)

EEG reports

Multi-Electrode Array (MEA)
KAND and Epilepsy – Validation in Disease Models

Assessment of top 3 small molecules in iPSC derived organoids

Mutation-carrying brain organoid

Phenotypic characterisation

Neuronal phenotype  KIF1A-cargo trafficking

Functional characterisation

Gene expression analysis (RNA-Seq)  Protein expression analysis (Proteomics)  Pathway analysis

Validation of top 5 hits in iPSC derived neurons

High throughput screening of small molecules using custom made cell models

UoM ECR Grant Prof Kristen Verhey
Significance and outcomes

Outcomes:

- Develop a seizure phenotype prediction model.
- Create a cost- and time-efficient way of identifying targeted treatments for KAND individuals with refractory seizures.

Significance:

- 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

Our Purpose