KIF1A Family Meeting

Friday, April 14th, 2017
Agenda

11:00pm  Welcome, Genetics 101  Wendy Chung

11:10pm  Review of KIF1A family responses  Lia Boyle

11:40pm  Answering questions about eye issues with KIF1A  Steven Brooks

12:00pm  Answering questions about neurological issues with KIF1A  Jennifer Bain

12:30pm  What does KIF1A do?  Richard Vallee

1:00pm  Open discussion about future research directions and priorities
Our Genome

1 Genome in a human

46 Chromosomes in a Genome

20,000 Genes in your chromosomes

23 from Mom

23 from Dad
Not all Genetic Conditions Run in Families

*De novo* mutations are common in children with neurodevelopmental problems
When do de novo mutations occur?

• In the egg
• In the sperm
• At or shortly after conception
• No way to know
• Recurrence risk of 1% in future pregnancies
Recessive condition: 25% recurrence for parents
A Clinical Picture of Individuals with *KIF1A* Variants

Lia Boyle
Published Studies

• The first individual with a known KIF1A variant was identified in 2011

• Since then, 16 papers have been published describing a total of 84 individuals from 49 families throughout the world

• 30 different genetic variants identified

• Specific clinical findings are available for 66 individuals
Understanding the layout of the gene

Motor domain (1-361)
NC: Neck coil (365-397)
CC1: Coiled coil 1 (429-462)
FHA: FHA domain (516-572)
CC2: Coiled coil 1 (622-681)
CC3: Coiled coil 1 (801-822)
PH: PH domain (1676-1774)
Variants Identified in Published Studies

NC: Neck coil
CC: Coiled coil
FHA: FHA domain
PH: PH domain

Green: Recessive
White: Dominant, de novo
Yellow: Dominant, familial
## Clinical Information from Published Studies

<table>
<thead>
<tr>
<th></th>
<th>Dominant, Sporadic N=31</th>
<th>Dominant, Familial N=10</th>
<th>Recessive, N=25</th>
<th>Total N=66</th>
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<tbody>
<tr>
<td>Unique variants</td>
<td>19</td>
<td>5</td>
<td>7</td>
<td>31</td>
</tr>
<tr>
<td>Mean age years (SD)</td>
<td>11(8.5)</td>
<td>40 (22.3)</td>
<td>27(16.1)</td>
<td></td>
</tr>
<tr>
<td>Developmental delay</td>
<td>100% (31/31)</td>
<td>0% (0/10)</td>
<td>16% (4/25)</td>
<td>53% (35/66)</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>39% (12/31)</td>
<td>0% (0/10)</td>
<td>16% (4/25)</td>
<td>30% (20/66)</td>
</tr>
<tr>
<td>Spasticity</td>
<td>77% (24/31)</td>
<td>100% (10/10)</td>
<td>100% (25/25)</td>
<td>89% (59/66)</td>
</tr>
<tr>
<td>Seizures</td>
<td>29% (9/31)</td>
<td>0% (0/10)</td>
<td>0% (0/25)</td>
<td>14% (9/66)</td>
</tr>
<tr>
<td>Any optic findings</td>
<td>74% (23/31)</td>
<td>10% (1/10)</td>
<td>12% (3/25)</td>
<td>41% (27/66)</td>
</tr>
<tr>
<td>Optic nerve change</td>
<td>58% (18/31)</td>
<td>0% (0/10)</td>
<td>0% (0/25)</td>
<td>27% (18/66)</td>
</tr>
<tr>
<td>Abnormal MRI</td>
<td>86% (25/29)</td>
<td>25% (1/4)</td>
<td>36% (4/11)</td>
<td>68% (30/44)</td>
</tr>
<tr>
<td>Cerebellar atrophy</td>
<td>75% (22/29)</td>
<td>0% (0/4)</td>
<td>18% (2/11)</td>
<td>55% (24/44)</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>48% (15/31)</td>
<td>0% (0/10)</td>
<td>36% (9/25)</td>
<td>55% (24/66)</td>
</tr>
</tbody>
</table>
Some Examples of Imaging Findings

Patient 1

11 months

3.6 years

12.5 years

Patient 2

6 months

6 years

Study Design

• Individuals with previously identified *KIF1A* mutations through clinical testing

• Recruitment largely through an existing family support group
  – A recruitment letter was shared on a private Facebook group

• Participating families took part in a two hour phone interview involving a detailed medical history as well as a structured developmental interview
Who is included?

- 14 individuals from 4 countries & 10 states
- 11 months to 20 years old
- Average age 8 years old
All Identified Variants

NC: Neck coil  
CC: Coiled coil  
FHA: FHA domain  
PH: PH domain

Top: our cohort  
Bottom: previous publications

Green: Recessive  
White: Dominant, de novo  
Yellow: Dominant, familial  
Orange: Parental status unknown

Columbia University Medical Center
Groupings for Analysis

• Participants were grouped according to genetic status
• Group 1: Individuals with single, dominant mutations in motor domain
• Group 2: Individuals who have two mutations, one from each parent
• Group 3: Individuals of unknown genetic status

<table>
<thead>
<tr>
<th></th>
<th>Dominant N=10</th>
<th>Recessive N=2</th>
<th>Unknown N=2</th>
<th>Total N=14</th>
</tr>
</thead>
</table>

## Groupings for Analysis: Dominant

<table>
<thead>
<tr>
<th>Variant</th>
<th>Inheritance</th>
<th>Seen before?</th>
</tr>
</thead>
<tbody>
<tr>
<td>p.Y89D</td>
<td>De novo</td>
<td>Novel</td>
</tr>
<tr>
<td>p.T99M</td>
<td>Parental testing unavailable</td>
<td>Seen de novo in 7 individuals</td>
</tr>
<tr>
<td>p.S217T</td>
<td>De novo</td>
<td>Novel</td>
</tr>
<tr>
<td>p.G251R</td>
<td>De novo</td>
<td>Novel</td>
</tr>
<tr>
<td>p.E253K</td>
<td>De novo</td>
<td>Seen de novo in 3 individuals</td>
</tr>
<tr>
<td>p.L278P</td>
<td>De novo</td>
<td>Novel</td>
</tr>
<tr>
<td>p.P305L</td>
<td>De novo</td>
<td>Novel</td>
</tr>
<tr>
<td>p.R307Q</td>
<td>De novo</td>
<td>Seen de novo in 2 individuals</td>
</tr>
<tr>
<td>p.R316W</td>
<td>De novo</td>
<td>Seen de novo in 1 individual</td>
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## Groupings for Analysis: Recessive

<table>
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<tr>
<th>Variant</th>
<th>Inheritance</th>
<th>Seen before?</th>
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<tbody>
<tr>
<td>p.E179G; p.D479V</td>
<td>Maternal; Paternal</td>
<td>Both novel</td>
</tr>
<tr>
<td>p.R229C; p.R1490W</td>
<td>Maternal; Paternal</td>
<td>Both novel</td>
</tr>
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## Neurological Features

<table>
<thead>
<tr>
<th></th>
<th>Dominant N=10</th>
<th>Recessive N=2</th>
<th>Unknown N=2</th>
<th>Total N=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotonia</td>
<td>90% (9/10)</td>
<td>100% (2/2)</td>
<td>50% (1/2)</td>
<td>86% (12/14)</td>
</tr>
<tr>
<td>Hypertonia</td>
<td>60% (6/10)</td>
<td>50% (1/2)</td>
<td>100% (2/2)</td>
<td>64% (9/14)</td>
</tr>
<tr>
<td>Seizures</td>
<td>60% (6/10)</td>
<td>100% (2/2)</td>
<td>100% (2/2)</td>
<td>71% (10/14)</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>100% (10/10)</td>
<td>100% (2/2)</td>
<td>100% (2/2)</td>
<td>100% (14/14)</td>
</tr>
<tr>
<td>Abnormal MRI</td>
<td>40% (4/10)</td>
<td>50% (1/2)</td>
<td>100% (2/2)</td>
<td>50% (7/14)</td>
</tr>
</tbody>
</table>
### Additional Seizure Findings

<table>
<thead>
<tr>
<th></th>
<th>Dominant N=10</th>
<th>Recessive N=2</th>
<th>Unknown N=2</th>
<th>Total N=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any seizures</td>
<td>50% (5/10)</td>
<td>100% (2/2)</td>
<td>100% (2/2)</td>
<td>64% (9/14)</td>
</tr>
<tr>
<td>Generalized Tonic Clonic</td>
<td>60% (3/5)</td>
<td>0% (0/2)</td>
<td>100% (2/2)</td>
<td>56% (5/9)</td>
</tr>
<tr>
<td>Absence</td>
<td>100% (5/5)</td>
<td>50% (1/2)</td>
<td>50% (1/2)</td>
<td>78% (7/9)</td>
</tr>
</tbody>
</table>
# Eye Findings

<table>
<thead>
<tr>
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<th>Dominant N=10</th>
<th>Recessive N=2</th>
<th>Unknown N=3</th>
<th>Total N=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any eye findings</td>
<td>90% (9/10)</td>
<td>100% (2/2)</td>
<td>100% (2/2)</td>
<td>93% (13/14)</td>
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<tr>
<td>Optic nerve change</td>
<td>70% (7/10)</td>
<td>0% (0/2)</td>
<td>100% (2/2)</td>
<td>64% (9/14)</td>
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<tr>
<td>Strabismus</td>
<td>10% (1/10)</td>
<td>100% (2/2)</td>
<td>0% (0/2)</td>
<td>21% (3/14)</td>
</tr>
<tr>
<td>Cataracts</td>
<td>10% (1/10)</td>
<td>50% (1/2)</td>
<td>0% (0/2)</td>
<td>14% (2/14)</td>
</tr>
</tbody>
</table>
## Additional Findings

<table>
<thead>
<tr>
<th></th>
<th>Dominant N=10</th>
<th>Recessive N=2</th>
<th>Unknown N=2</th>
<th>Total N=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric reflux</td>
<td>50% (5/10)</td>
<td>100% (2/2)</td>
<td>100% (2/2)</td>
<td>64% (9/14)</td>
</tr>
<tr>
<td>Severe ear infections</td>
<td>20% (2/10)</td>
<td>50% (1/2)</td>
<td>0% (0/2)</td>
<td>21% (3/14)</td>
</tr>
<tr>
<td>Eczema</td>
<td>40% (4/10)</td>
<td>100% (2/2)</td>
<td>50% (1/2)</td>
<td>50% (7/14)</td>
</tr>
<tr>
<td>Genital abnormalities*</td>
<td>30% (3/10)</td>
<td>0% (0/2)</td>
<td>0% (0/2)</td>
<td>21% (3/14)</td>
</tr>
<tr>
<td></td>
<td>M: 43% (3/7)</td>
<td>M: 0% (0/2)</td>
<td>M: 0% (0/0)</td>
<td>M: 33% (3/9)</td>
</tr>
<tr>
<td></td>
<td>F: 0% (0/3)</td>
<td>F: 0% (0/0)</td>
<td>F: 0% (0/2)</td>
<td>F: 0% (0/5)</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>10% (1/10)</td>
<td>0% (0/2)</td>
<td>100% (2/2)</td>
<td>21% (3/14)</td>
</tr>
<tr>
<td></td>
<td>M: 0% (0/7)</td>
<td>M: 0% (0/2)</td>
<td>M: 0% (0/0)</td>
<td>M: 0% (0/9)</td>
</tr>
<tr>
<td></td>
<td>F: 33% (1/3)</td>
<td>F: 0% (0/0)</td>
<td>F: 100% (2/2)</td>
<td>F: 60% (3/5)</td>
</tr>
</tbody>
</table>

*Genital abnormalities include micropenis, small scrotum, and undescended testicles*
Vineland Adaptive Behavior Scales

- Adaptive behavior: the performance of daily activities required for personal & social sufficiency
  - Age related
  - Evaluated in a social context
  - Modifiable
  - Defined by typical performance, not ability

- The Vineland Adaptive Behavior Scale (Vineland) is a structured phone interview

- Parents are asked about areas of functioning and whether a child does something never, sometimes, or usually

- Limitations: verbal ability, vision
## Communication Domain

**Response Options:** 2 = Usually, 1 = Sometimes or Partially, 0 = Never, DK = Don't Know

- **Understanding**
- **Listening and Attending**
- **Following Instructions**

<table>
<thead>
<tr>
<th>Score</th>
<th>Task</th>
<th>Score</th>
<th>Score</th>
<th>Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>- Turns eyes and head toward sound.</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>DK</td>
</tr>
<tr>
<td></td>
<td>- Looks toward parent or caregiver when hearing parent's or caregiver's voice.</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>DK</td>
</tr>
<tr>
<td></td>
<td>- Responds to his or her name spoken (for example, turns toward speaker, smiles, etc.).</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>DK</td>
</tr>
<tr>
<td>1</td>
<td>- Demonstrates understanding of the meaning of no, or word or gesture with the same meaning (for example, stops current activity briefly).</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>DK</td>
</tr>
<tr>
<td></td>
<td>- Demonstrates understanding of the meaning of yes, or word or gesture with the same meaning (for example, continues activity, smiles, etc.).</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>DK</td>
</tr>
<tr>
<td></td>
<td>- Listens to story for at least 5 minutes (that is, remains relatively still and directs attention to the storyteller or reader).</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>DK</td>
</tr>
<tr>
<td>2</td>
<td>- Points to at least three major body parts when asked (for example, nose, mouth, hands, feet, etc.).</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>DK</td>
</tr>
<tr>
<td></td>
<td>- Points to common objects in a book or magazine as they are named (for example, dog, car, cup, key, etc.).</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>DK</td>
</tr>
<tr>
<td></td>
<td>- Listens to instructions.</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>DK</td>
</tr>
<tr>
<td></td>
<td>- Follows instructions with one action and one object (for example, “Bring me the book”; “Close the door”; etc.).</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>DK</td>
</tr>
<tr>
<td>3</td>
<td>- Points to at least five minor body parts when asked (for example, fingers, elbows, teeth, toes, etc.).</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>DK</td>
</tr>
</tbody>
</table>

**Scoring based on 4 consecutive ‘2’s and 4 consecutive ‘0’s**
Vineland Adaptive Behavior Scales: Scoring

Score Profile

90 % Confidence Level

Domain Score Profile

<table>
<thead>
<tr>
<th>Domain</th>
<th>Std. Score</th>
<th>Conf. Int.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adaptive Behavior Composite</td>
<td>74</td>
<td>70-78</td>
</tr>
<tr>
<td>Communication</td>
<td>89</td>
<td>83-95</td>
</tr>
<tr>
<td>Daily Living Skills</td>
<td>75</td>
<td>68-82</td>
</tr>
<tr>
<td>Socialization</td>
<td>86</td>
<td>80-92</td>
</tr>
<tr>
<td>Motor Skills</td>
<td>62</td>
<td>55-69</td>
</tr>
</tbody>
</table>
Vineland Domains

![Box plot of Vineland Domains, N=14]

- **Domain**
  - Communication
  - Daily Living Skills
  - Social
  - Motor

- **Standard Score**

- **Vineland Domains, N=14**
Vineland Subdomains

**Vineland Communication**

- VSS
- Receptive
- Expressive
- Written

Communication Subdomains, N=14

**Vineland Daily Living Skills**

- VSS
- Personal
- Domestic
- Community

Daily Living Skills Subdomains, N=14

**Vineland Socialization**

- VSS
- Interpersonal Relationships
- Play
- Coping Skills

Socialization Subdomains, N=14

**Vineland Motor Skills**

- VSS
- Gross Motor
- Fine Motor

Motor Subdomains, N=14
Next Steps

• Confirm genetic testing results

• Continue recruitment (multiple additional families interested in participating)

• Obtain medical records to get additional details
Questions?
Answering questions about eye issues with KIF1A

Steven Brooks, MD
Pediatric Ophthalmologist
Healthy Optic Nerve

Optic Nerve Atrophy
Answering questions about neurological issues with *KIF1A*

Jennifer Bain, MD PhD

Pediatric Neurologist
Neurological Assessment in Children with KIF1A

Jennifer Bain, MD, PhD
Assistant Professor
Department of Neurology
Division of Child Neurology
Outline

Who is a pediatric neurologist?

What are the neurological problems associated with KIF1A?
Who is a pediatric neurologist?

Who? *What training do they have?*
- Four years of medical school
- At least 1 to 2 years of pediatric residency
- Three or more years of residency training in adult and child neurology

What? *What diseases do they care for or study?*
- Diagnose and treat disorders of the nervous system
  - Inclusive of brain, spinal cord, muscles, nerves
  - Both acute and chronic care problems
What types of concerns do they evaluate?

Developmental concerns:
  – Delays, regression, attention deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), autism spectrum disorders (ASD), intellectual disabilities

Head problems
  – Big heads (macrocephaly) or little heads (microcephaly)

Weird episodes
  – Concern for seizures or movement disorders

Febrile seizures or epilepsy

Head complaints
  – Concussion, headaches, migraines, brain tumors

Sleep problems

Genetic disorders with known neurological problems
Where? *Where do they practice?*
- Children’s hospitals
- University-based medical centers
- Community-based outpatient practices
- Private offices

When? *What ages do they treat?*
- Prenatally, birth and beyond

Why?
- Special understanding of medical disorders in childhood
- Special needs of the child and his or her family and environment
A typical neurological consultation:

History (interview and perhaps review of medical records)

Physical examination

Neurological examination
Neurological Exam

Mental status
- Developmental assessment: Speech & language, gross & fine motor, personal & social skills

Cranial nerves = basic functions of the head & neck

Motor skills

Sensory exam

Reflexes

Coordination

Gait = walking
Neurological Exam

Mental status
- “Who are you?”
- Developmental assessment: Speech & language, gross & fine motor, personal & social skills

Cranial nerves = basic functions of the head & neck

Motor skills

Sensory exam

Reflexes

Coordination

Gait = walking
Functional Organization of the Cerebrum

Primary motor cortex (voluntary movement)

Premotor cortex (coordinates voluntary movements)

Central sulcus

Primary somatosensory cortex (somesthetic sensations and proprioception)

Sensory association areas (integration of sensory information)

Visual association areas (higher vision processing)

Primary visual cortex (vision)

Wernicke’s area (language comprehension)

Prefrontal association areas (idea and plan for voluntary movement, thoughts, personality)

Broca’s area (speech formation)

Olfactory cortex (smell)

Limbic association cortex (emotions, learning, and memory)

Primary auditory cortex (hearing)

Auditory association areas
Developmental Delays $\rightarrow$ Intellectual Disability

Developmental delays:
- Speech & language
- Gross & fine motor
- Personal & social skills
- Global developmental delay (GDD)

After age 5, the term intellectual disability is used

**Three** criteria must be met:
- A. Deficits in intellectual functions
- B. Deficits in adaptive functioning
- C. Onset of intellectual/adaptive deficits during developmental period (<18 yo)
Motor exam

Bulk (how much is there?):
• Too much = Hypertrophy
• Too little? Atrophy

Tone: The resting state of muscle
• Too much = Hypertonia
• Too little = hypotonia

Strength: The active state of muscle (how strong are you?)

Weakness, asymmetry when using hands, early hand preference (cerebral palsy)
What mediates tone?

The patellar tendon (knee jerk) reflex illustrates a monosynaptic stretch reflex and reciprocal inhibition of the antagonistic muscle.

Stimulus: Tap to tendon stretches muscle.

Receptor: Muscle spindle stretches and fires.

Afferent path: Action potential travels through sensory neuron.

Integrating center: Sensory neuron synapses in spinal cord.

Effectors:
- Effector 1: Quadriceps muscle
- Effector 2: Hamstring muscle

Response:
- Quadriceps contracts, swinging lower leg forward.
- Hamstring stays relaxed, allowing extension of leg (reciprocal inhibition).

Fig. 13-7

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Low tone = Hypotonia
High tone = spasticity or rigidity
Coordination

Finger to nose = grabbing objects

Dysmetria

Truncal instability = wobbly when sitting up
Reflexes

- 0/4 = Absent
- 1/4 - 2/4 = Normal Range
- 3/4 = Pathologically Brisk
- 4/4 = Clonus

If ABSENT, think nerve or muscle!
Gait

Wobbly
Clumsy
Wide-based
Unsteady
Frequent falls
Shuffling

If in doubt, ask parents!
Seizures

Electrical activity is caused by complex chemical changes that occur in nerve cells; brain cells either excite or inhibit (stop) other brain cells from sending messages.

Usually there is a balance of cells that excite and those that can stop these messages.

However, when a seizure occurs, there may be too much or too little activity, causing an imbalance between exciting and stopping activity. The chemical changes can lead to surges of electrical activity that cause seizures.

Seizures are not a disease in themselves. Instead, they are a symptom of many different disorders that can affect the brain. Some seizures can hardly be noticed, while others are totally disabling.
Where do the seizures come from?

Sometimes focal (1 spot)

Sometimes multi focal (more than 2 spot)

Sometimes everything fires off abnormally at that same time (generalized)
How to treat seizures?

Find the underlying cause!
Thank you!

Any questions?

Jennifer Bain jb3634@cumc.columbia.edu
What does *KIF1A* do?

Richard Vallee, PhD

Molecular Geneticist
Open discussion
Gene Therapy & Genome Editing

- Promising individualized medicine

Are we there yet?

- Not quite for most conditions
- Recent developments in research advanced the field
What can families do?

Organize the families: family networking/facebook page

Family meeting

Standardized clinical data collection
  – Genetic test reports
  – Medical history interview
  – Medical record review
  – Vineland
  – Biorepository
Next steps

Increase the number of identified individuals and confirm the correct diagnosis
  – Generalize to other conditions?

Care until the cure
  – Understand the natural history and document it well
  – Learn practical tips from each other

Understand molecular mechanism

Develop reagents to enable researchers and make the reagents widely available
  – Cell lines
  – Mice

Determine if the condition is reversible and if so when

Learn from other diseases
1. Collect human cells
2. Induced pluripotent stem cells
3. Neurons
4. Define aberrant protein phosphorylation
5. Define a cellular phenotype
6. High throughput drug screen
7. Test lead compound in animal models and test for efficacy and toxicity
8. Create mouse models
9. Characterize the brain and behavior and how these develop
10. Define aberrant protein phosphorylation in different brain regions
11. Test for reversibility

Additional steps:
- 3-D protein structure
- Determine the location of the 4 mutations and the change in protein conformation with the mutations
- Map protein-protein interactions
Gene Therapy & Genome Editing

• Getting there will hopefully take less time

  ➢ Cystic fibrosis (CF) gene was discovered in 1989

  ➢ 1\textsuperscript{st} drug approved in 2012 (23 years later!) – targets 4\% of patients with cystic fibrosis

  ➢ 2\textsuperscript{nd} drug approved in 2015 – targets 50\%
Gene Therapy

Technique designed to introduce genetic material into cells to compensate for an abnormal gene or to make a beneficial protein
Gene editing

Edit the genetic code making a new generation of medical treatments possible. Can be done precisely but there are challenges.