How to Prepare for the Precision Medicine Era

- A GENOMIC PERSPECTIVE ON HEALTH AND DISEASE

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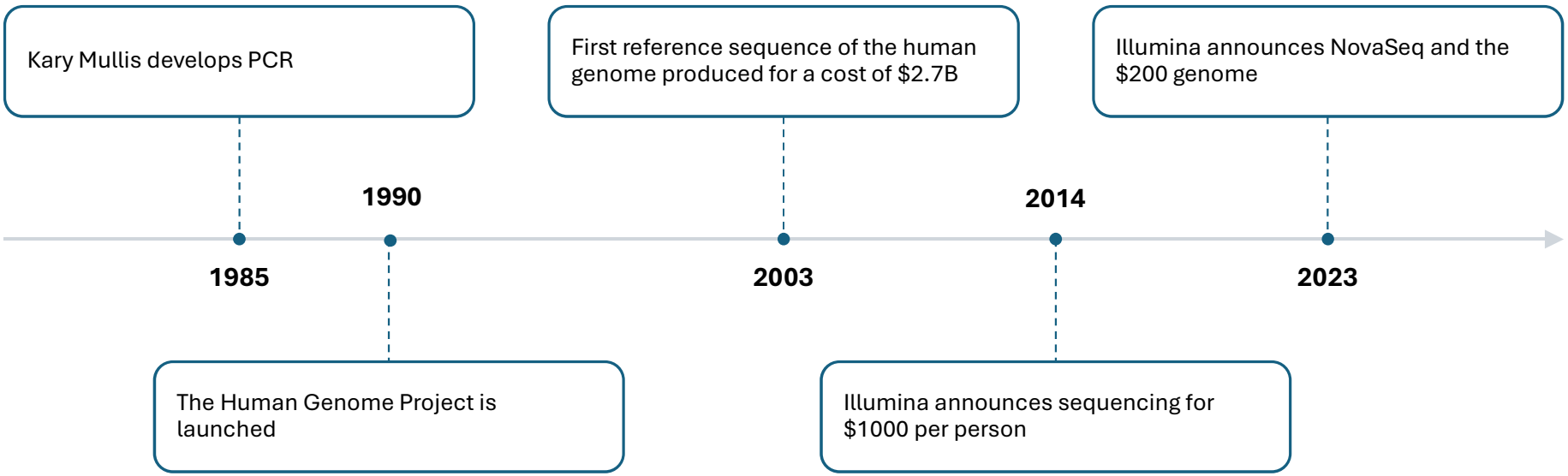
- For: Parker University
- NeuroCon, Dallas, Texas
- July 27, 2024

"In each of us is written the story of our species." –Jacques Monod

- Our DNA is composed of millions of base pairs that code for everything that makes us who we are
- Within DNA are "genes", the units of heredity
- There are differences in the DNA sequences among individuals, called "genetic variants"
- These variants contribute to the uniqueness of each individual

The development of genome sequencing



Genetic variants influence:

- Physical Traits
- Behaviours
- Disease Susceptibility

Variants shape the way we interact with our physical environment, and the way our environment interacts with us

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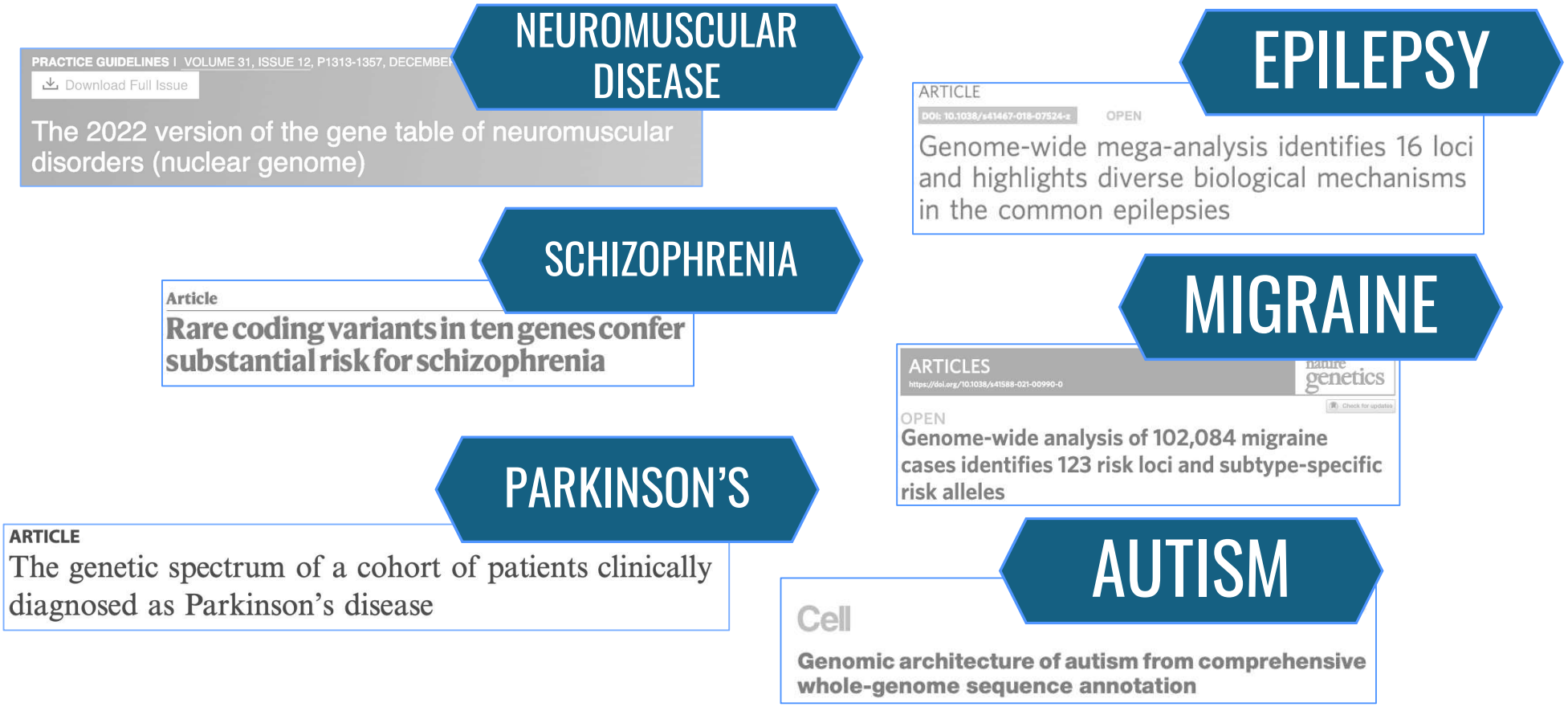
- White coat in *Panthera leo* is caused by a mutation to the Tyrosinase (TYR) gene
- Non-tawny lions camouflage poorly
  - Poorer hunters
  - Vulnerable to human hunting

Variants shape our personality and life

- **Dopamine Receptor D4 and Novelty-Seeking (*DRD4-7R*)**
  - Greater propensity for risk-taking, novelty-seeking, sensitivity to the environment, ADHD, addiction
- **Monoamine Oxidase A and Aggression (*MAOA-3L* and *MAOA-4R*)**
  - Higher levels of aggression and impulsivity; increased risk of antisocial behaviour if exposed to child abuse
- **Cathechol-O-Methyltransferase and Stress Resilience (*COMT* Val158Met)**
  - Greater stress resilience following exposure to trauma, but at the cost of poorer learning + memory
- **Fat Mass & Obesity-Associated Protein and Energy Balance (*FTO* variants)**
  - Increased risk of obesity

It’s becoming clear that common diseases are often constellations of rare single-gene variants



Talk Outline

- How genetic variants are **linked** to disease
- How genetic diseases can be **treated** with precision and personalized medicine
- **Examples** of precision medicines
- How medicine is **changing**
- What **you** should be prepared for in your **practice**

The end of congenital disability?

- 6,800,000 Americans live with congenital disabilities
- Can be diagnosed prenatally, at birth, or in childhood
- 80% are due to genetic variants (mutations)

The end of neurodegeneration?

- 7,000,000 Americans live with neurodegenerative disease (Alzhiemer's, Parkinson's, ALS)
- Can be early-onset, but usually diagnosed after age 65
- At least 5%, but likely more, are due to monogenetic (single-gene) variants

Emerging therapeutic modalities offer hope for reversal of genetic disease

- Enzyme Repacement Therapies
- Antisense Oligonucleotides
- Gene therapy
- Gene editing

A TALE OF MICE AND MEN:

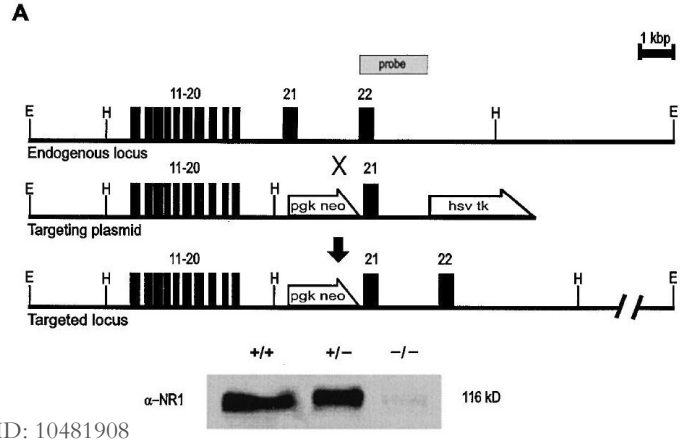
The discovery of GRI Disorder

A non-syndromic epileptic encephalopathy with gene therapy in-development

Bryson MacArthur, first annual GRICon, 2018

An introduction to *Grin1*^{KD} mice

- Insertion of neomycin resistance gene into intron 20 of *Grin1* gene
- *Grin1*^{KD} mice have 7.3% Grin1 protein levels of WT mice; *neo* mutation produces hypomorphic allele
- *Grin1*^{KD} mice have altered motor, stereotypic, social, vocal, and sexual behaviours



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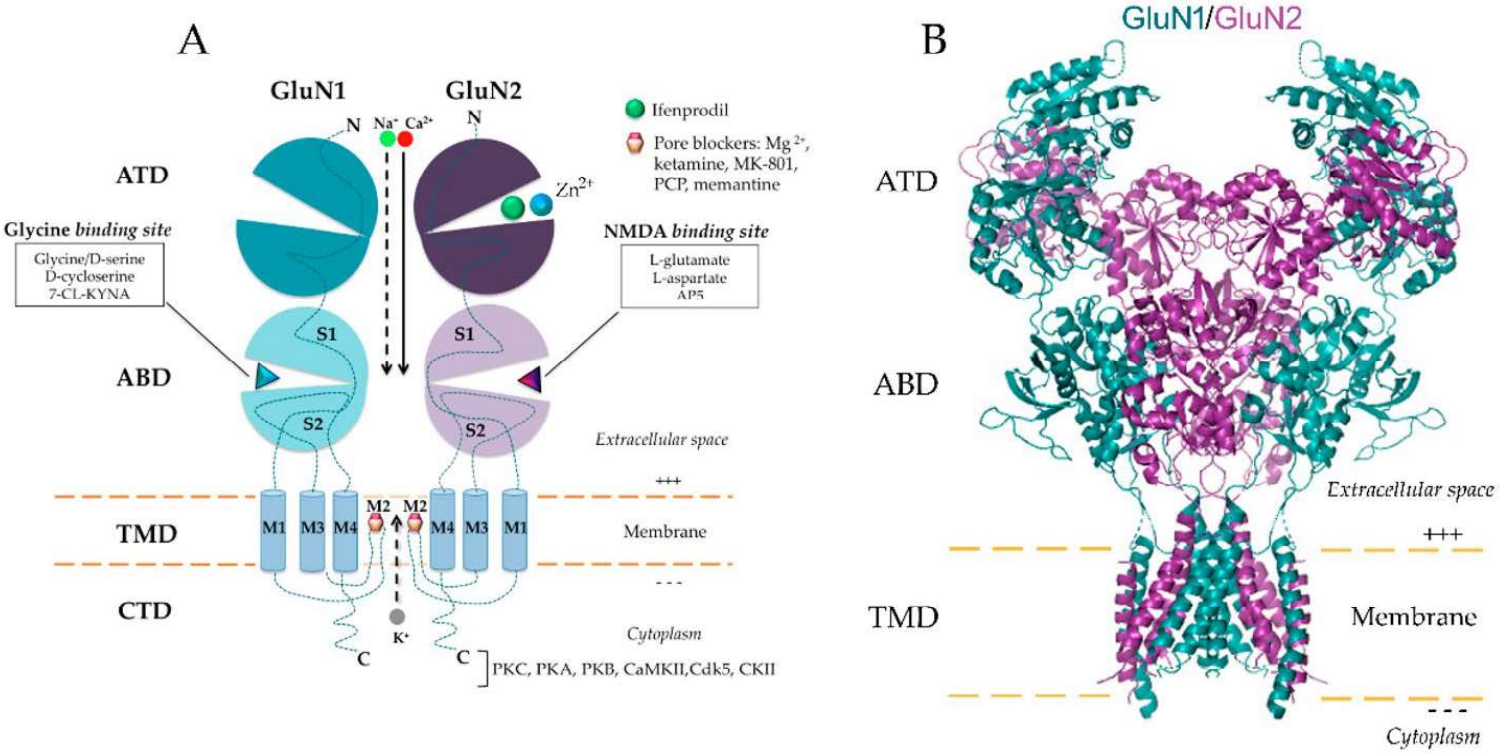
Wild-type (typical) mouse

Grin1^{KD} mouse

Grin1 encodes the must-have subunit of the N-Methyl-D-Aspartate (NMDA) Receptor



It was all for the love of science until the GRIN1 families found us...

These children had been diagnosed with rare or unique variants to the *GRIN1* gene through genome sequencing

Grin1^{KD} mice as a model of human *GRIN1* variants

MICE

Seizures

Progressive volume reductions in some brain structures + white matter

Impaired learning + executive function in tasks

Altered social communication measured via USV

Hyperlocomotion in OFT

Possible cortical blindness

PATIENTS

Epilepsy

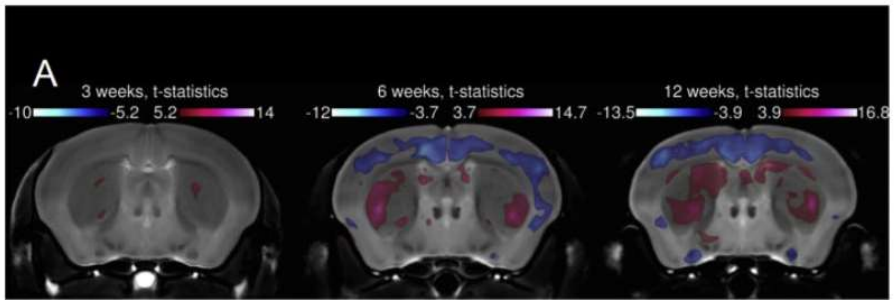
Generalized cerebral atrophy

Intellectual disability PMID: 27164704

Non-syndromic or severe speech delay

Hyperkinetic movement disorders

Cortical blindness



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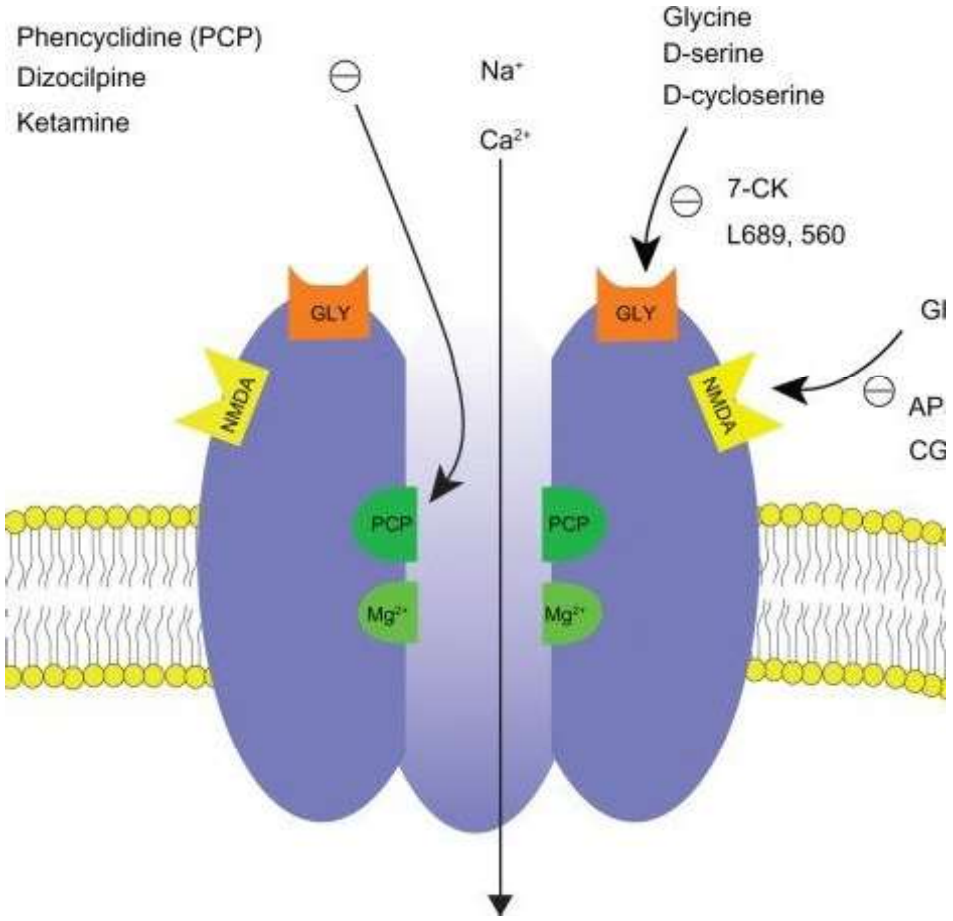
What changes occur to the kids' NMDA receptors as a result of variants to the *GRIN1* gene?

- Total protein expression level
- Protein folding, degradation
- Subunit interaction and assembly
- Receptor trafficking
- Sensitivity to ligands
- Channel open time/probability, channel conductance, Mg++ stickiness, leakiness
- Receptor desensitization or deactivation
- Binding of exogenous modulators
- Impaired excitation/inhibition balance
- Impaired synaptic plasticity



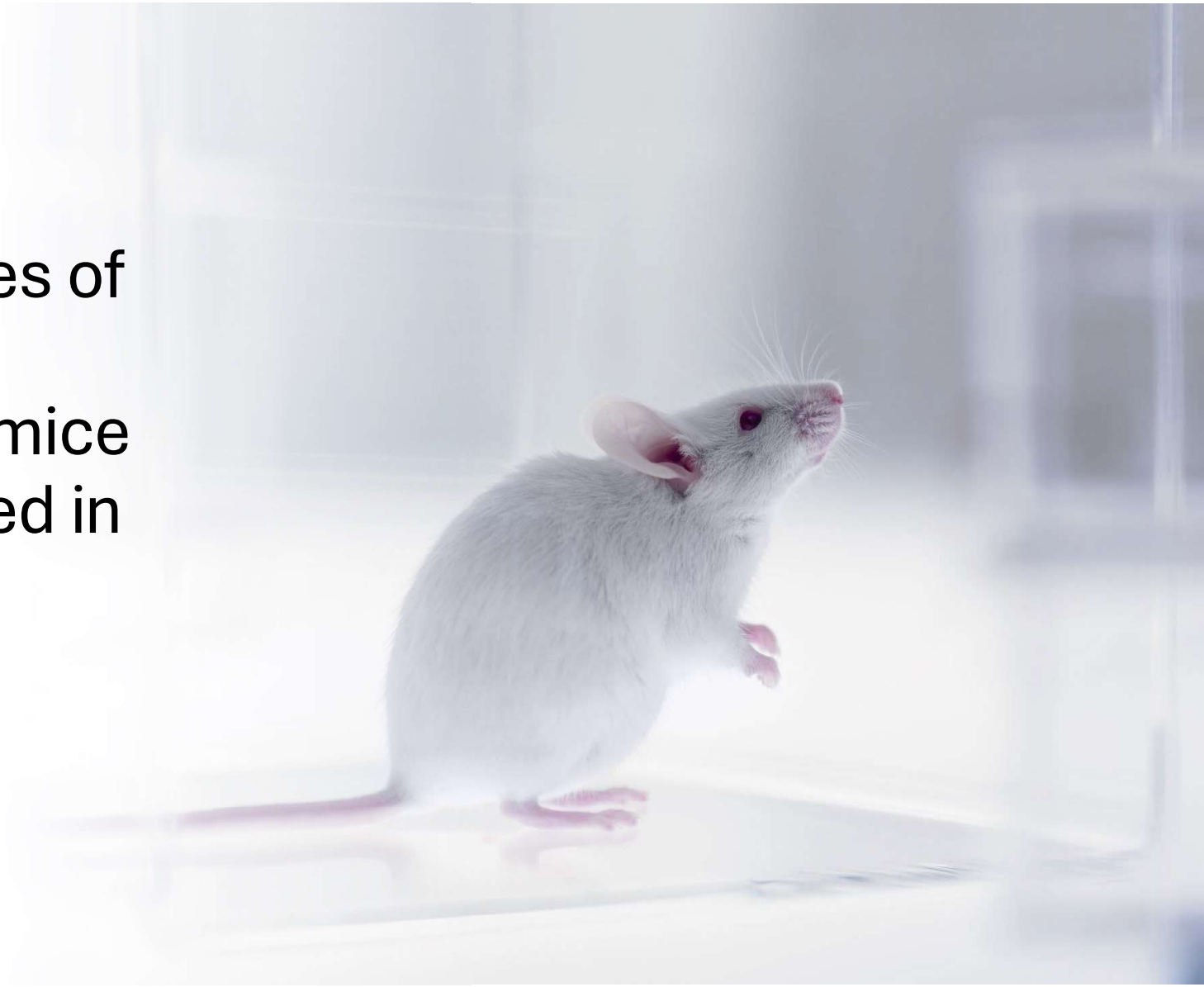
Small Molecule Drugs

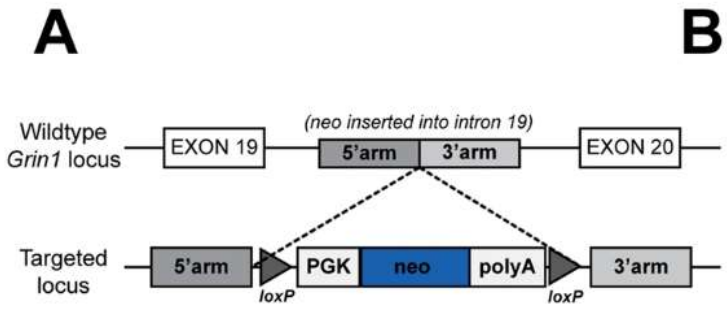
Enzyme Repacement Therapies

Antisense Oligonucleotides

Gene therapy

Consequences of lifelong Grin1 mutations in mice can be rescued in adulthood





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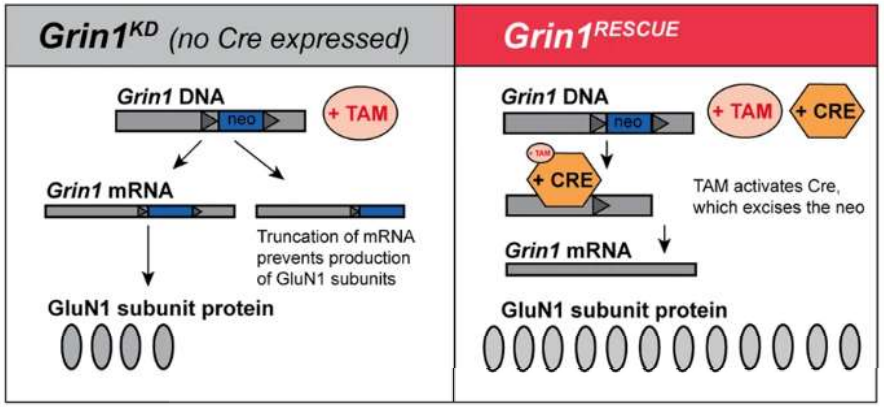
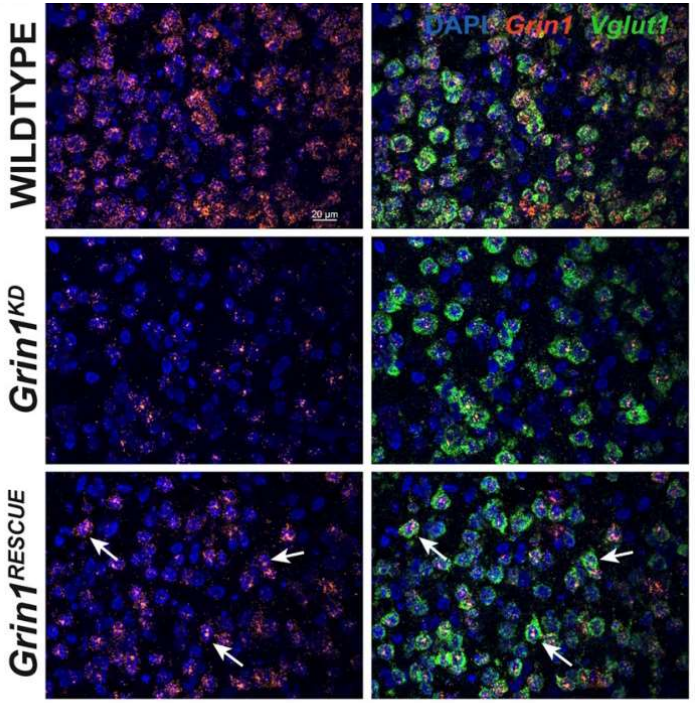
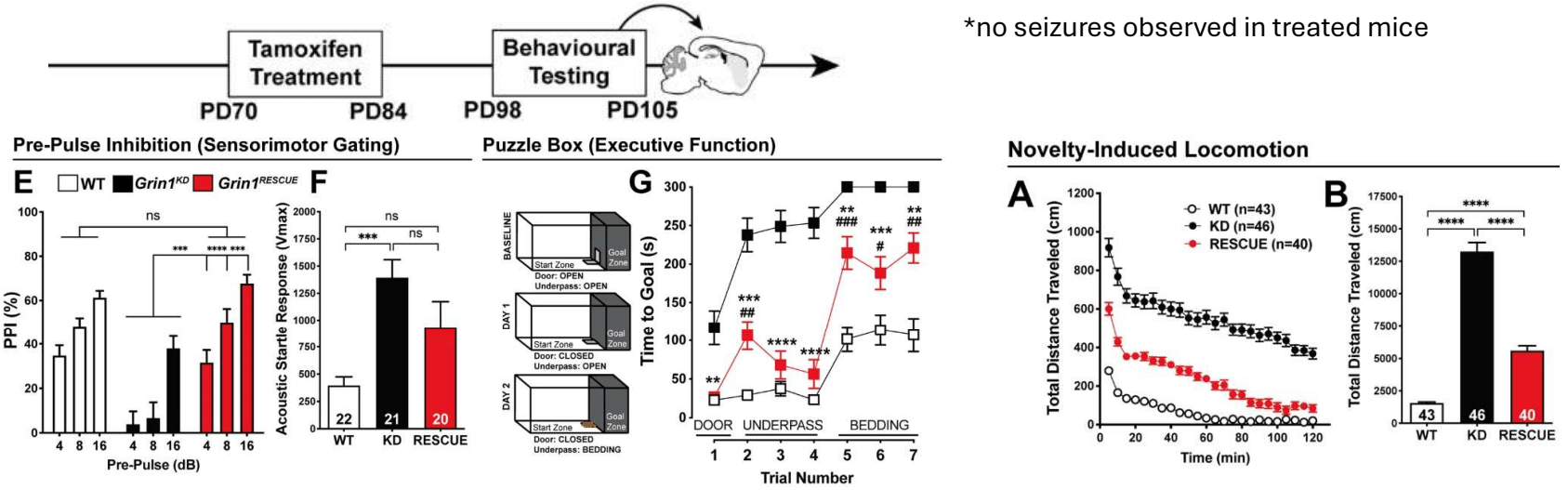


Generation of *Grin1*^{RESCUE} mice



Cognitive impairments and seizures are improved by intervention in adult mice



*no seizures observed in treated mice

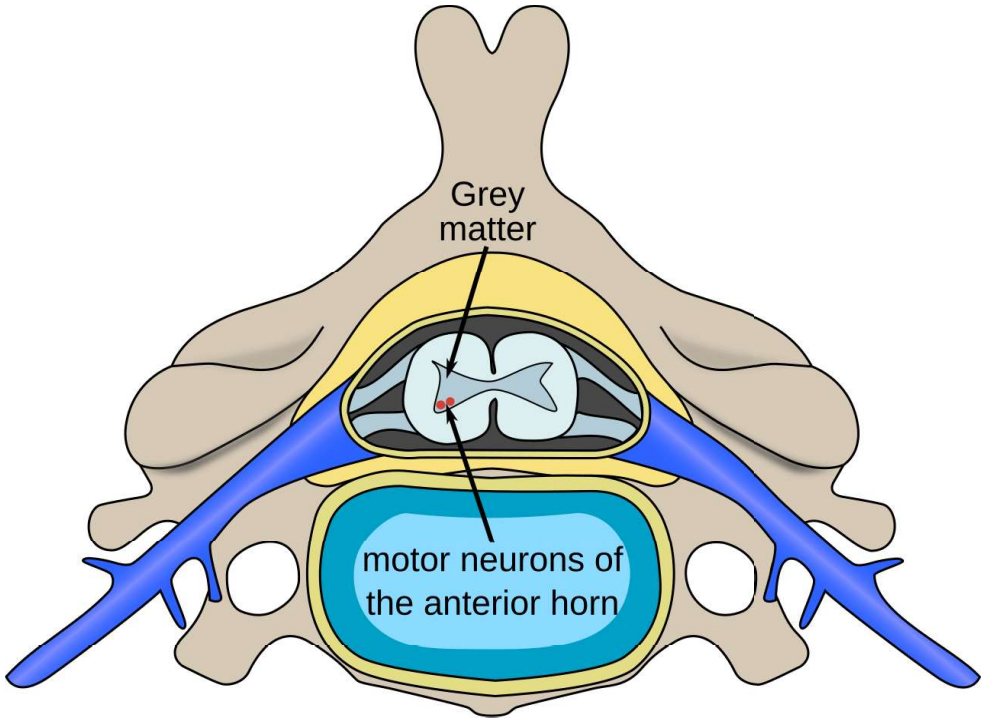
Takeaways

- Remarkable recovery from lifelong deficiencies in Grin1/NMDARs is possible in adult animals
- Gene therapy likely holds promise for children with Grin1 variants
- Gene therapy development now in-progress, preliminary results showing reversal of phenotype
- If you are diagnosed with a genetic variant, try to get a sense of the gene's function in your body

Gene therapy already in the clinic

Example: Spinal Muscular Atrophy

- Progressive degeneration of motor neurons in the spinal cord beginning at age 6 months
- Usually autosomal recessive, caused by variants to Survival Motor Neuron 1 (SMN1) gene
- SMA Type 1, SMA Type 2, SMA Type 3, SMA Type 4 diagnoses based on onset/severity of symptoms



Historically, SMA Type 1 was a death sentence for children

Stage 1 (Birth to 6 months)

- Hypotonia, difficulty moving, difficulty feeding, shallow breathing

Stage 2 (6 months to 1 year)

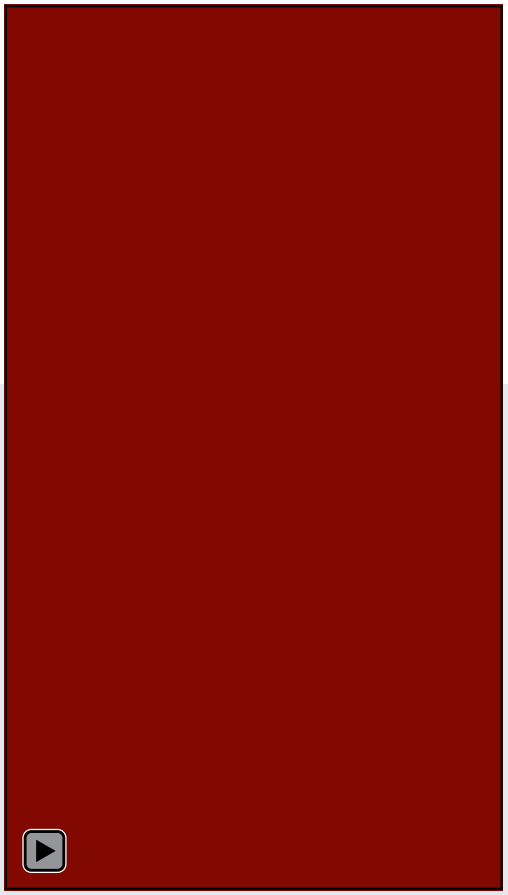
- Regression of motor skills, loss of reflexes, respiratory issues, swallowing challenges

Stage 3 (1 year onward)

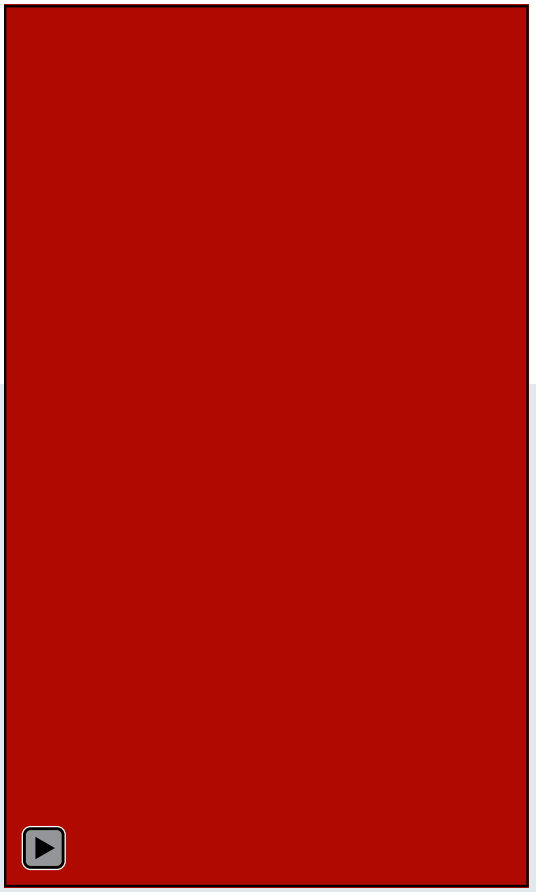
- Severe motor impairment, skeletal deformities, ventilation, food aspiration, infection

Death

Motor Milestones: 10.5 Months

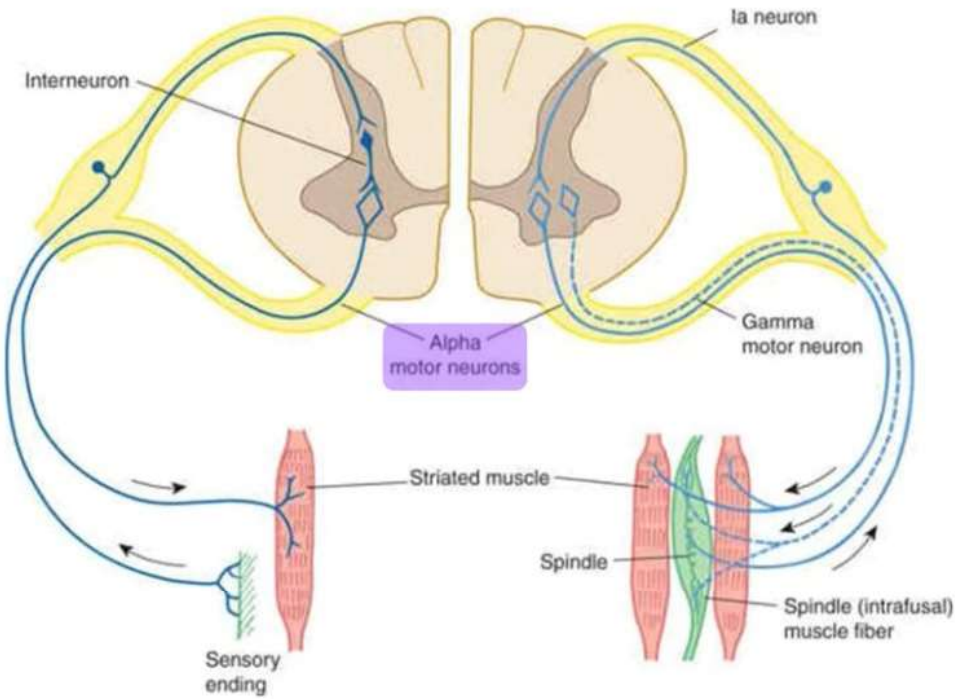


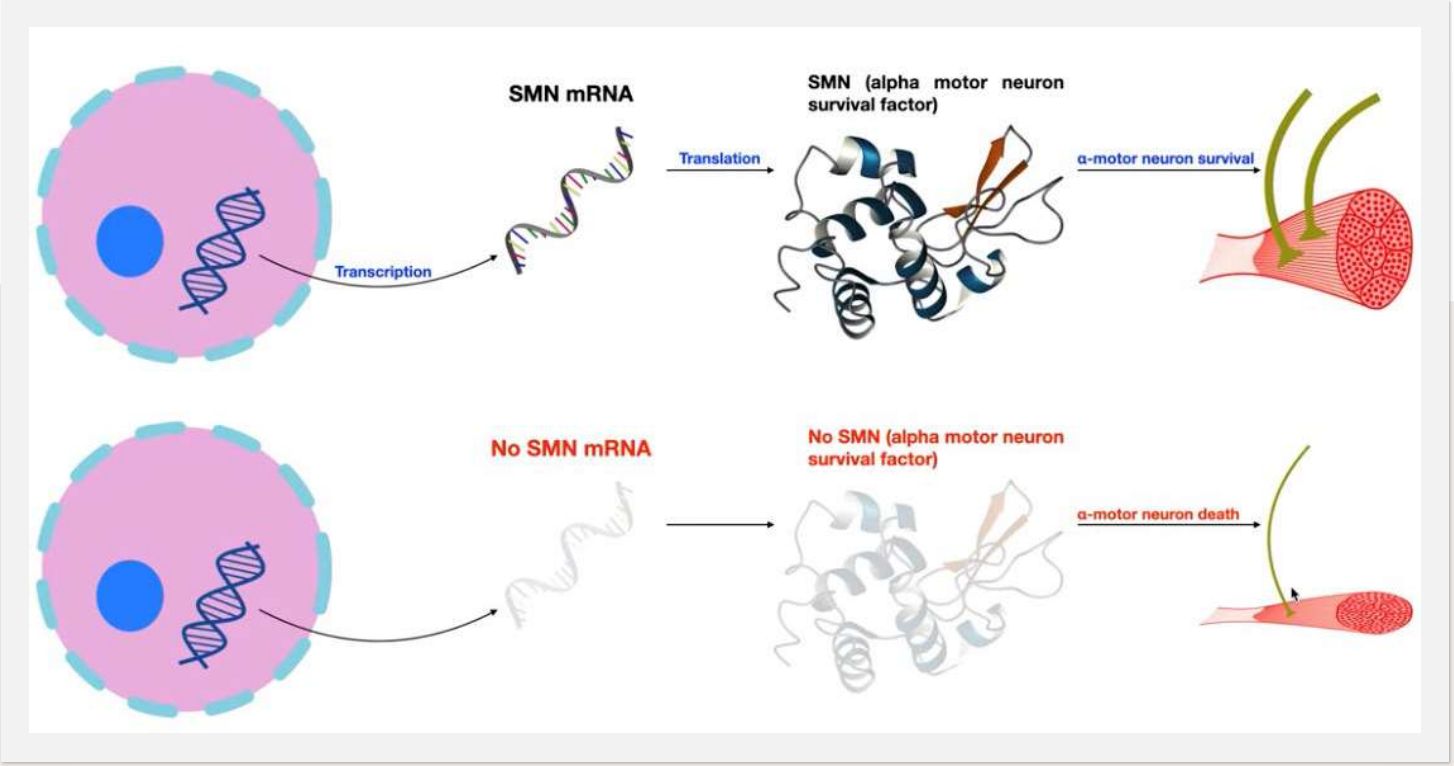
Typical Development



SMA Type 1/SMA+ Zolgensma

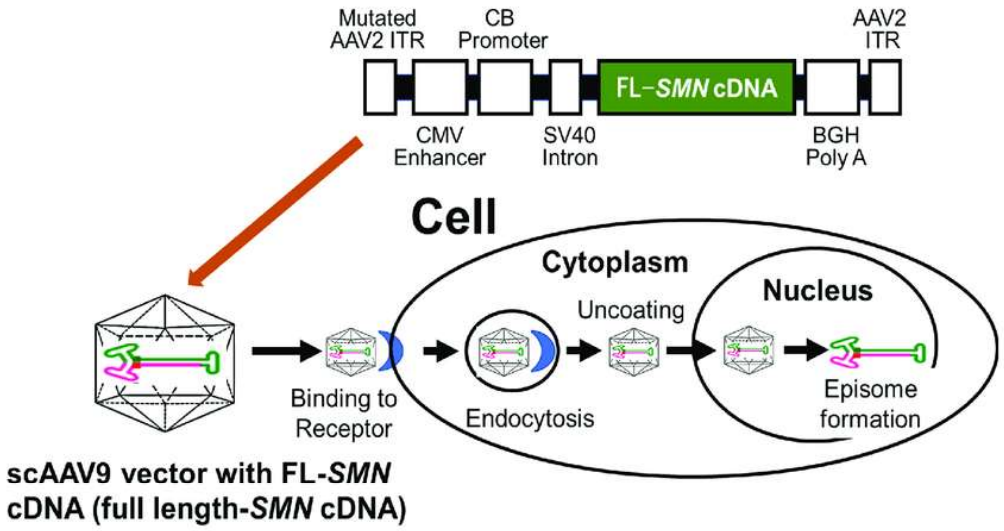
α-Motor Neurons

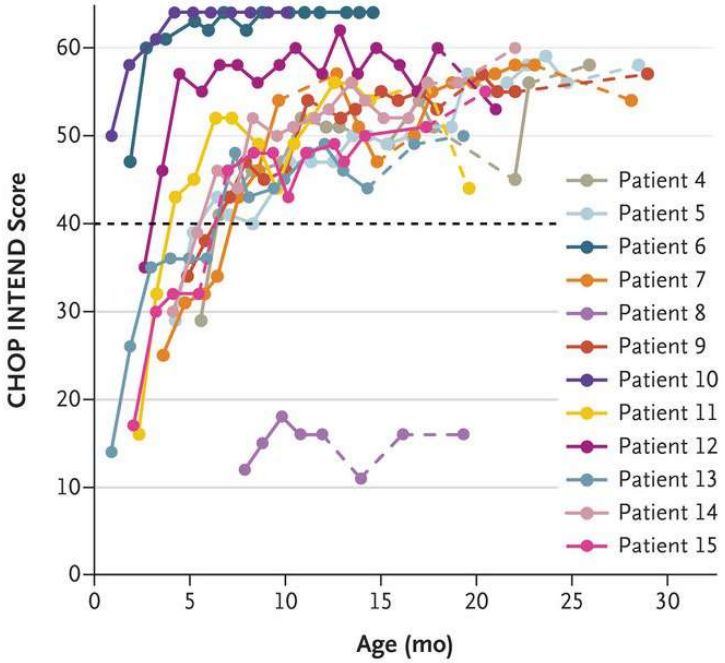




SMN1 protein promotes survival of α motor neurons

Gene therapy is capable of halting and reversing disability in SMA





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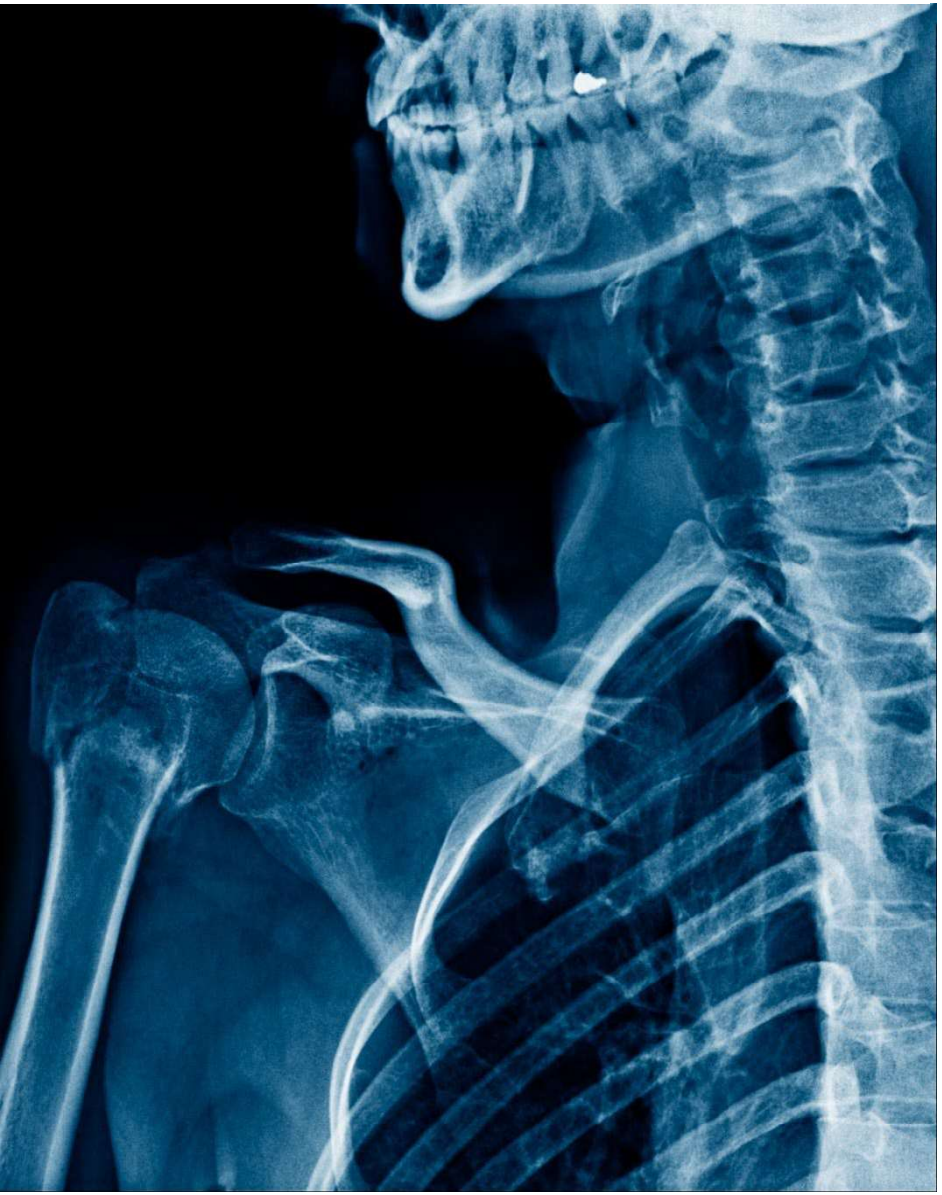

Children with neuromuscular disorders who receive gene therapy may still struggle with:

- Scoliosis
  - Atypical curvature leading to discomfort/pain
- Joint contractures
  - Stiffness and reduced range of motion
- Hip dysplasia
  - Misalignment or instability of the hip joint
- Muscle weakness
- Fractures
  - Osteopenia, osteoporosis increasing risk of fractures

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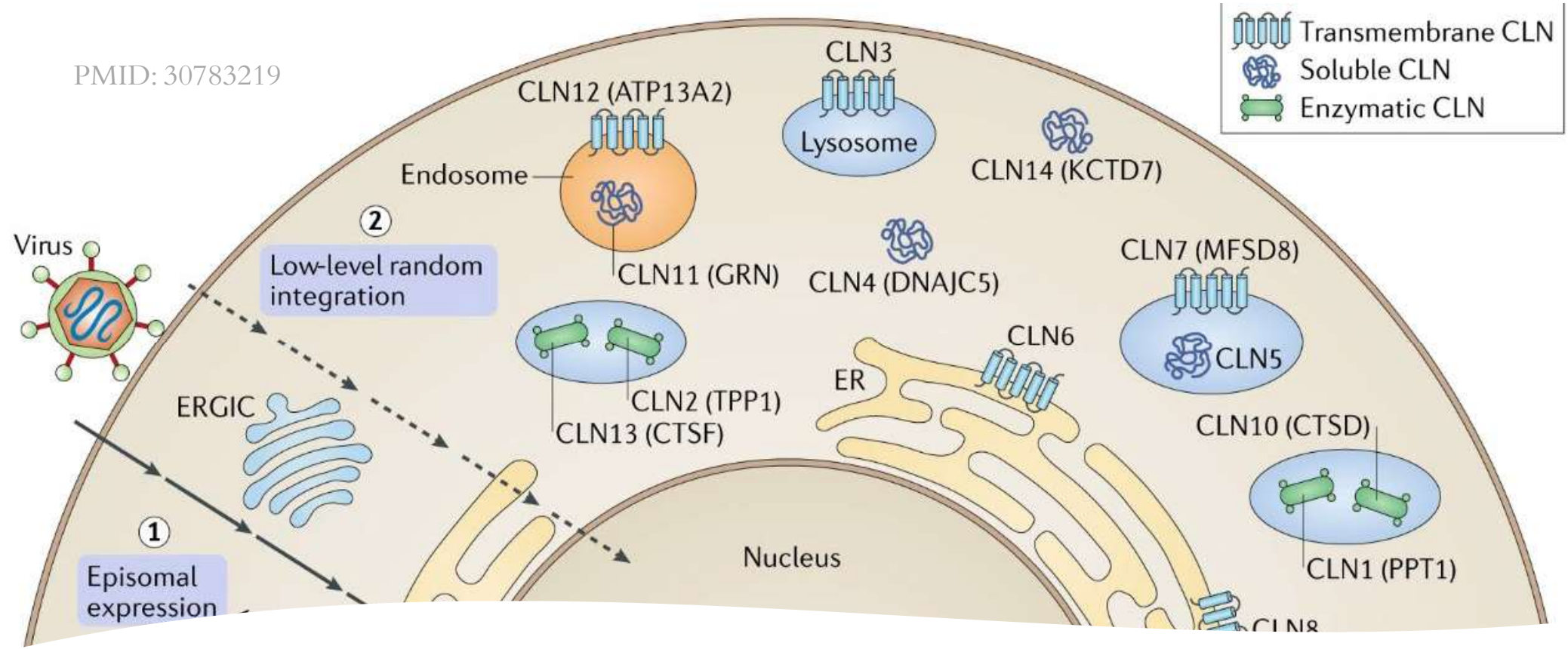


Example: Batten's Disease

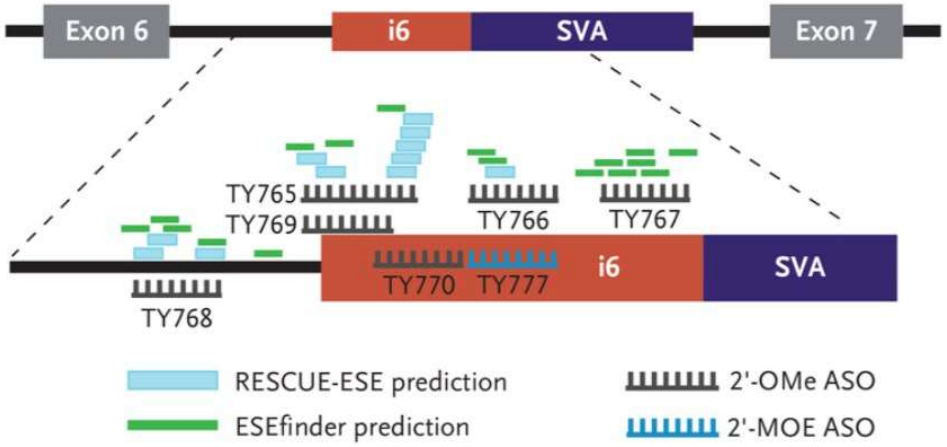
- Progressive accumulation of lipofuscins due to poor lysosomal clearance from neurons and other tissue
- Usually autosomal-recessive, caused by mutations to genes that encode proteins essential for lysosomal function (*PPT1, TPP1, CLN3, CLN5, CLN6, CLN7, CLN8*)

Personalized medicine from bench to bedside

Mila, 2019

“N of 1” therapy in Batten’s Disease

- **Age 3**: Typical development
- **Age 4**: Vision difficulty
- **Age 5**: Language and social regression, clumsiness, stumbling
- **Age 6**: Rapid vision loss, falls, difficulty swallowing, motor speech disorder, epileptiform brain activity
- Discovery of loss-of-function *CLN7* variants



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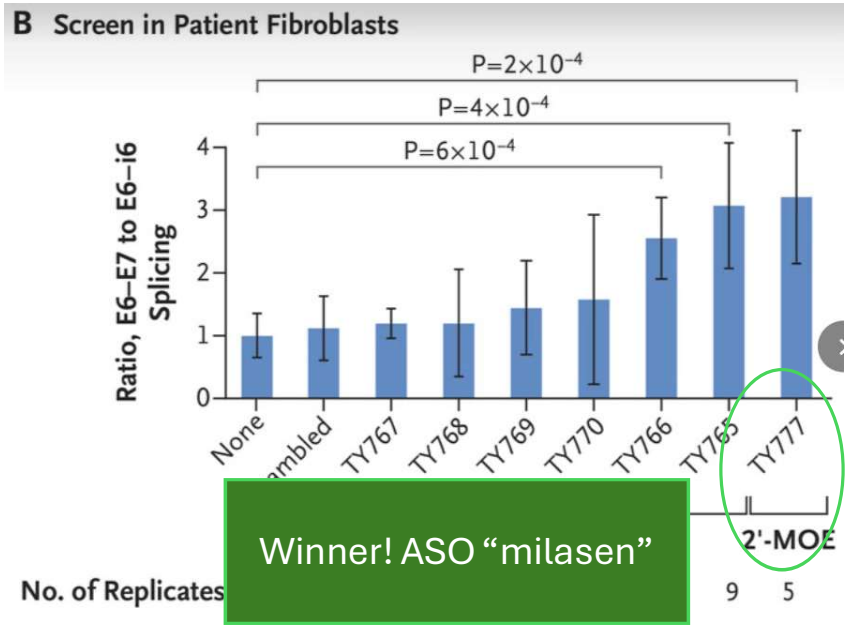
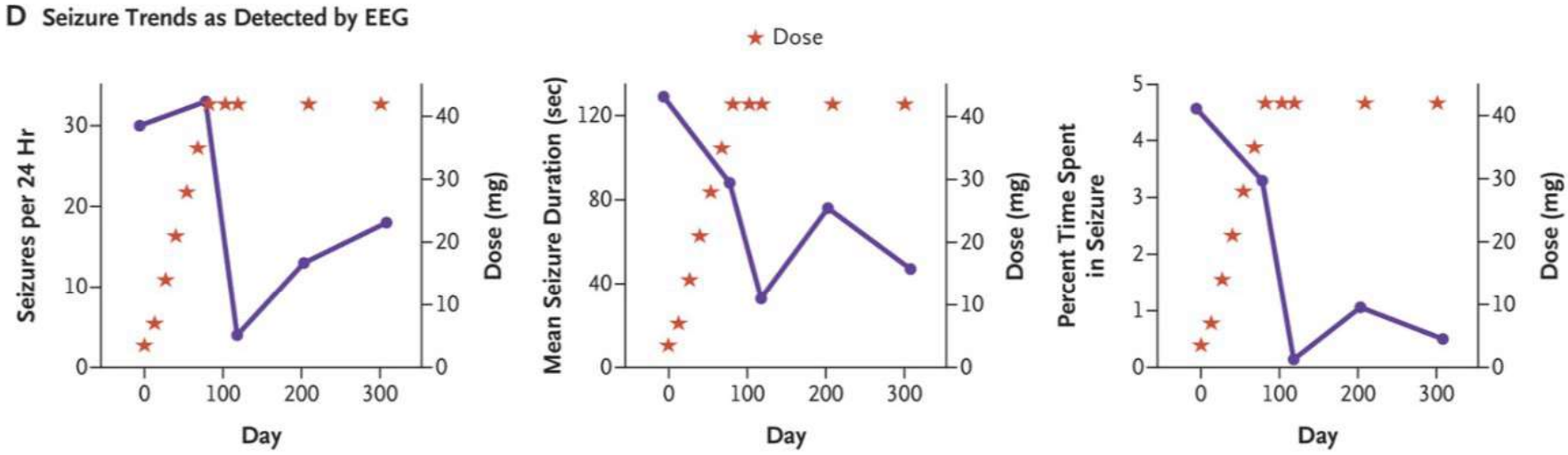


Winner! ASO “milasen”

Bespoke antisense oligonucleotide therapy for CLN7 Batten Disease

- The problem: therapeutics for Mila cannot be scaled to treat other CLN7 children due to the uniqueness of her variant



Milasen reduced Mila's seizures over 200 days

- Mila's seizures were reduced from occurring for 5% of her entire day to 0.5%
- Some improvements in adaptive skills, such as communication, socialization, and daily living skills

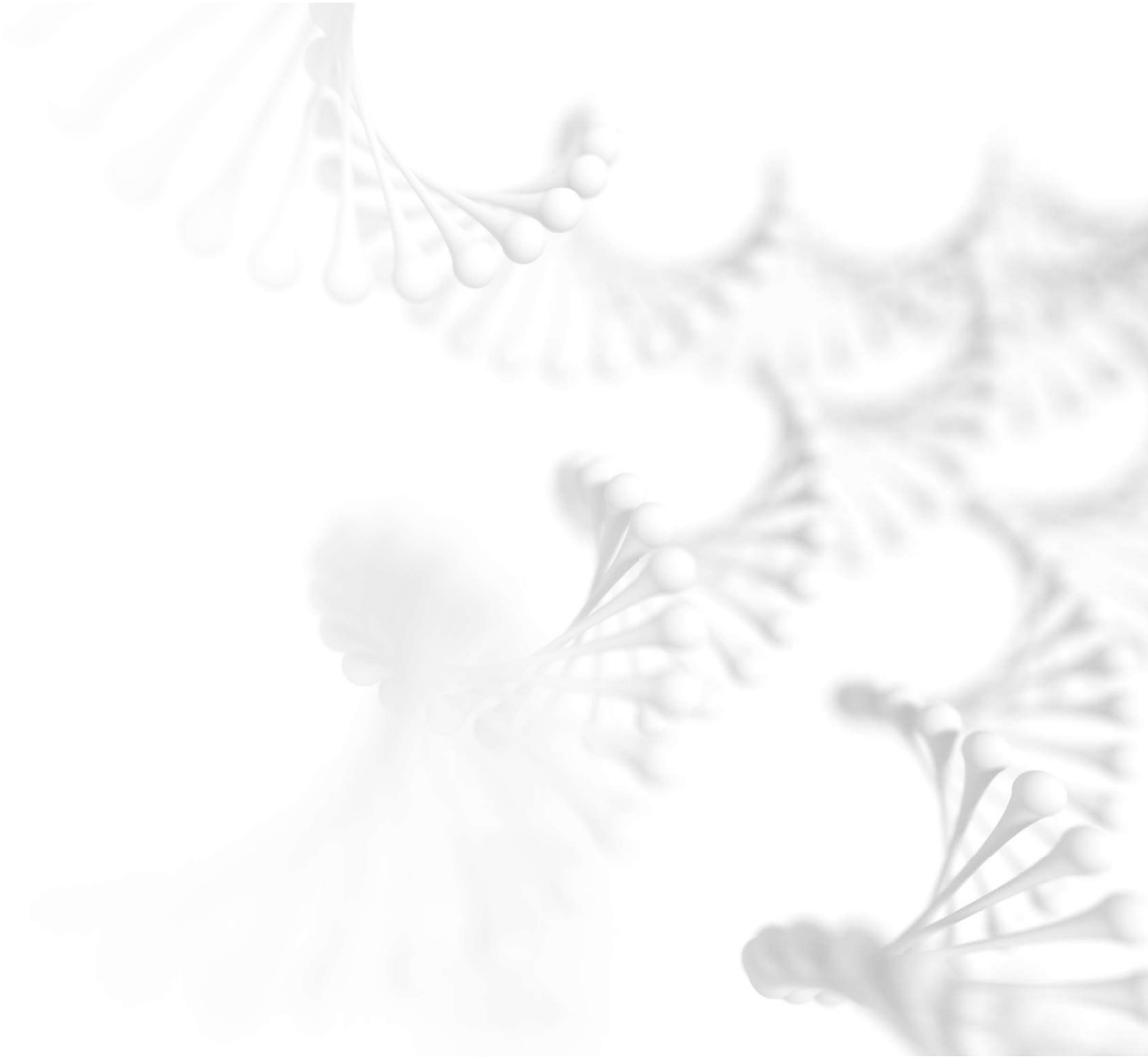
Lessons learned from Mila

- Ultimately, focus on the brain lead to improvement of neurological symptoms, but not others
- Bespoke therapies are feasible, but costly
- … at this present time

What's next? 5-year timeline

- Systematic prioritization of genetic subgroups in diseases of aging
  - E.g., LYS3884961 by Lilly/Prevail for Parkinson's patients with *GBA* variants
- Gene editing in reprogrammed cell populations or localized to specific organs
  - EDIT-101 by Editas Medicine for blindness due to *CEP290* variant IVS26
  - CTX001 by CRISPR Therapeutics for gene-edited hematopoietic stem cell therapy due to *HBB* variants
- Explosion of gene replacement therapeutic development for LoF variants

Gene editing in humans



The curious case of Lulu, Nana, and Amy

- Unpublished, shrouded in mystery
- Parents part of project involving HIV-positive fathers
- Twins conceived via IVF, additional child conceived via IVF
- Underwent CRISPR/Cas9-mediated germline deletion of 32 base pairs of the CCR5 gene
- Goal: confer resistance to HIV acquisition
- Questions regarding informed consent, scientific validity and priority, off-target effects, non-publication of results

Principal Investigator Dr. He Jiankui

The black box has been opened

- We are all living with medically-actionable, rare genetic variants
- Many of us will receive gene therapies within our lifetime
- It remains to be seen whether germline editing (heritable changes) will be ethically permitted

Impact of precision medicine on functional medicine

- Halted disease progression
  - Stability at advanced stages of disease requires ongoing care
- Reversal of disability
  - Greater need for providers trained in rehabilitation
- Expanded scope of practice + increased work in disciplinary teams
- Greater need for geriatric and pediatric providers
  - Treatment of developmental disease and disorders of aging

Areas of expected change in functional medicine within your career

- Musculoskeletal issue focus in obesity recovery (Ozempic, *FTO* gene therapy)
- Pediatric rehabilitation (neuromuscular disorders, neurodevelopmental disorders, epilepsies, cerebral palsy, mitochondrial disorders, lysosomal storage disorders)
- Geriatric rehabilitation (neurodegenerative disorders)
- Pain management demand in above populations
- Fewer arthritis, migraine patients (gene therapies in development)
- Greater development of subspecialties

Thank you!

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