Tandem Repeats: genotypes, phenotypes and therapies Name,

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Clinical Neurological Society of America

January 17-20, 2026
JUPITER, FLORIDA

Disclosures

Research support

- Avidity, Fulcrum, Reata, Biogen, Sanofi, Biohaven, PTC, Reneo, Vertex, Arthex, Larimar

Ad board

- Avidity, Fulcrum, Reata, PTC, Larimar. Amicus, Solid biosciences

Non-commercial

- Friedreich ataxia research alliance, National Ataxia Foundation, MDA, FDA

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Objectives

Introduce the concept of repetitive DNA elements in the genome

Describe the clinical implications of diseases related to repetitive DNA elements

Illustrate the potential for novel therapies in the field

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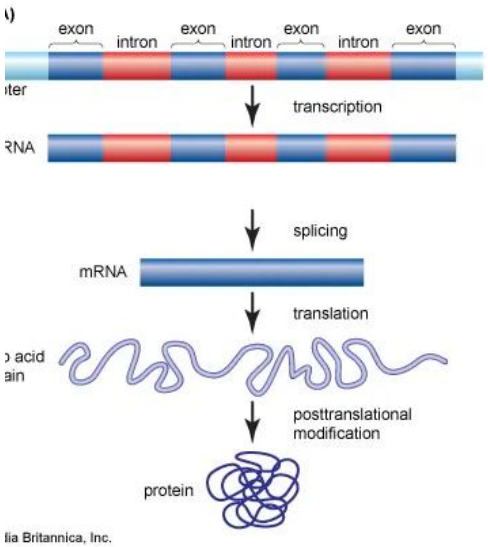
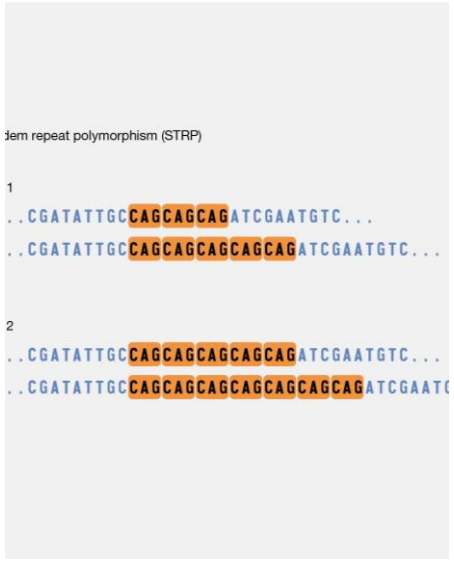
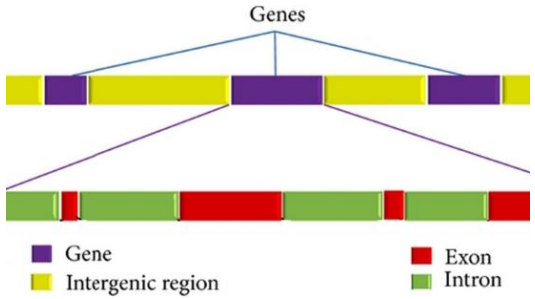




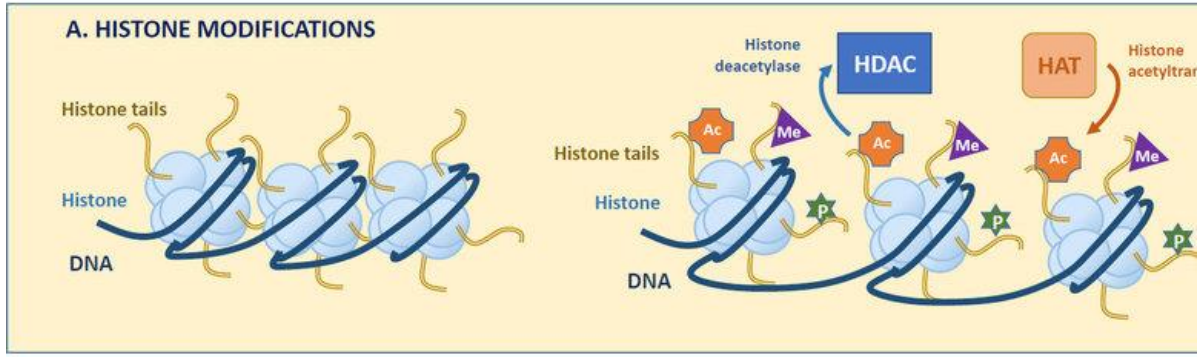


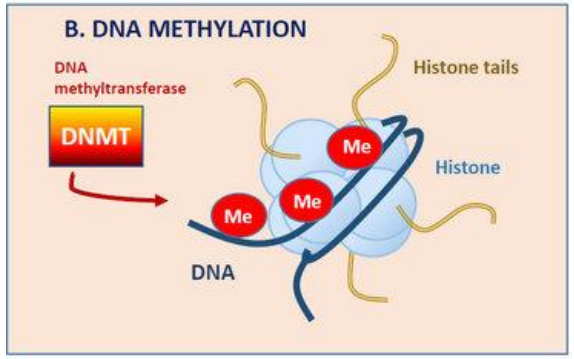
Tandem repeats

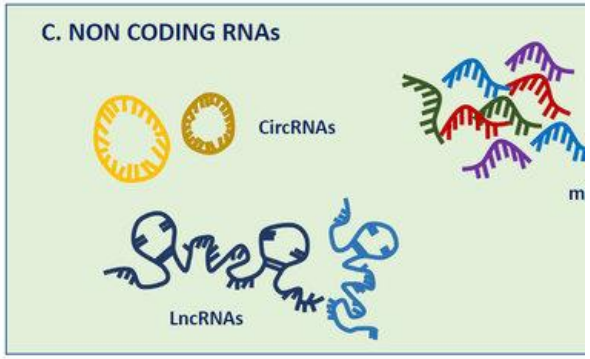
- Human genome has coding and non-coding DNA sequences composed of Adenine, Guanine, Cytosine and Thymine (AGCT)
- Individual genes occupy 1.5% of the genome and have coding and non-coding regions (exons and introns)
- Much of the genome is non-coding regions
- Short tandem repeats (STR)
  - Repetitive DNA sequences up to 6 base pairs in tandem: e.g trinucleotide or pentanucleotide
- One third of the genome has repetitive DNA; STRs occupy 3-5% of human genome
- About 1 million STRs

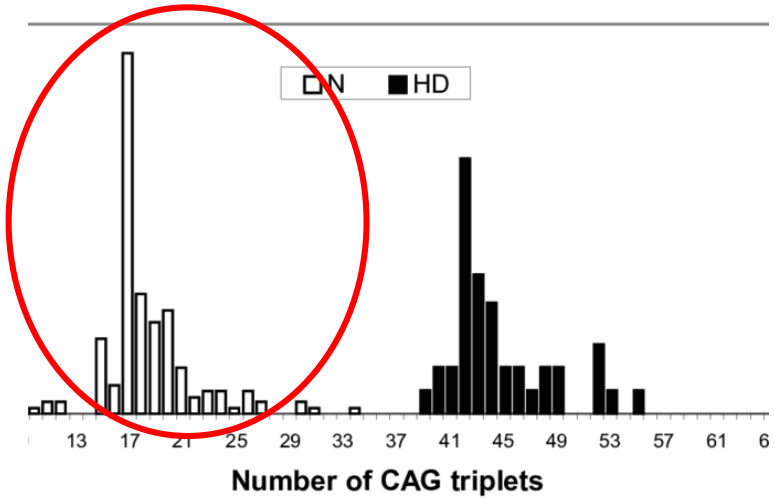
Why have tandem repeats?

- Repeat length is polymorphic: different lengths in different persons
- Likely has a role in normal phenotypic variation; unlike SNPs which are yes/no, repeats can function in shades of grey
- Humans have more widespread expansions, have longer STRs
- Repetitive DNA from non-coding regions regulate gene expression
- Expansion across vertebrates suggests evolutionary advantage and many of them affect genes with neuronal function, leading to better neuronal capability









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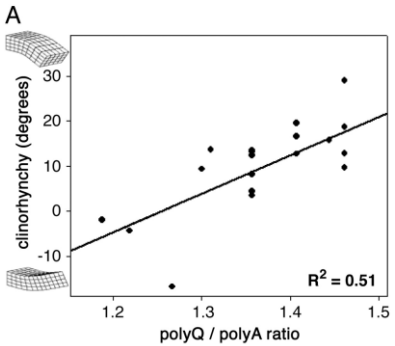

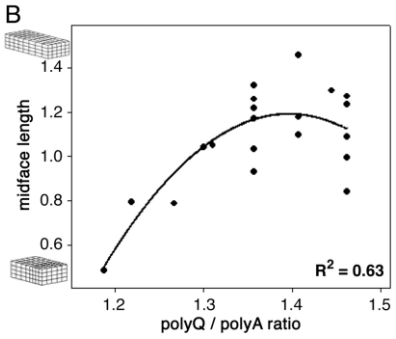

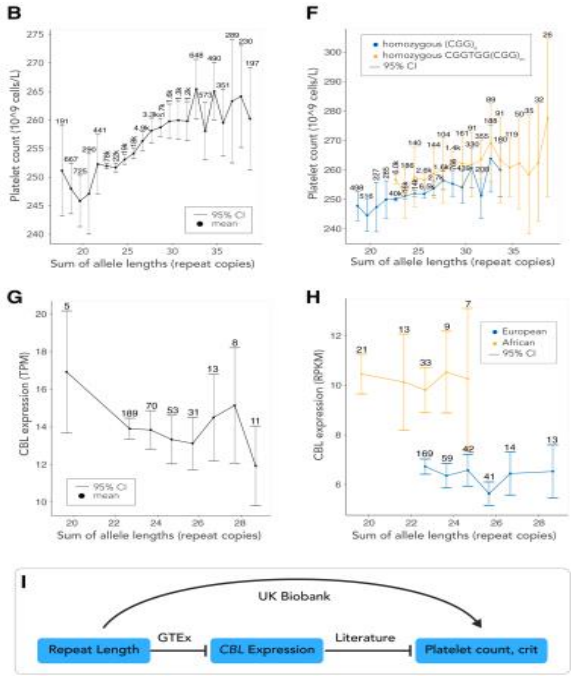

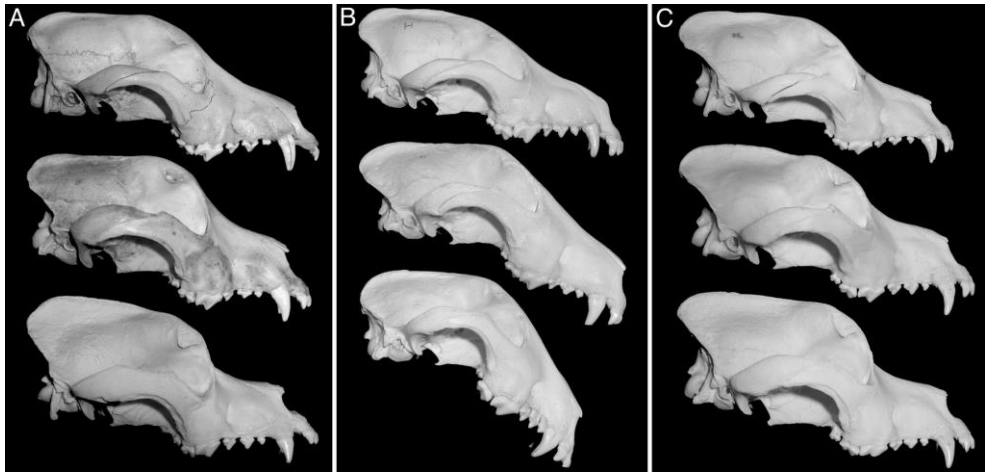

Phenotypic variation related to STRs

Alterations in the lengths of repetitive DNA over evolutionary time scales create diversity in the species

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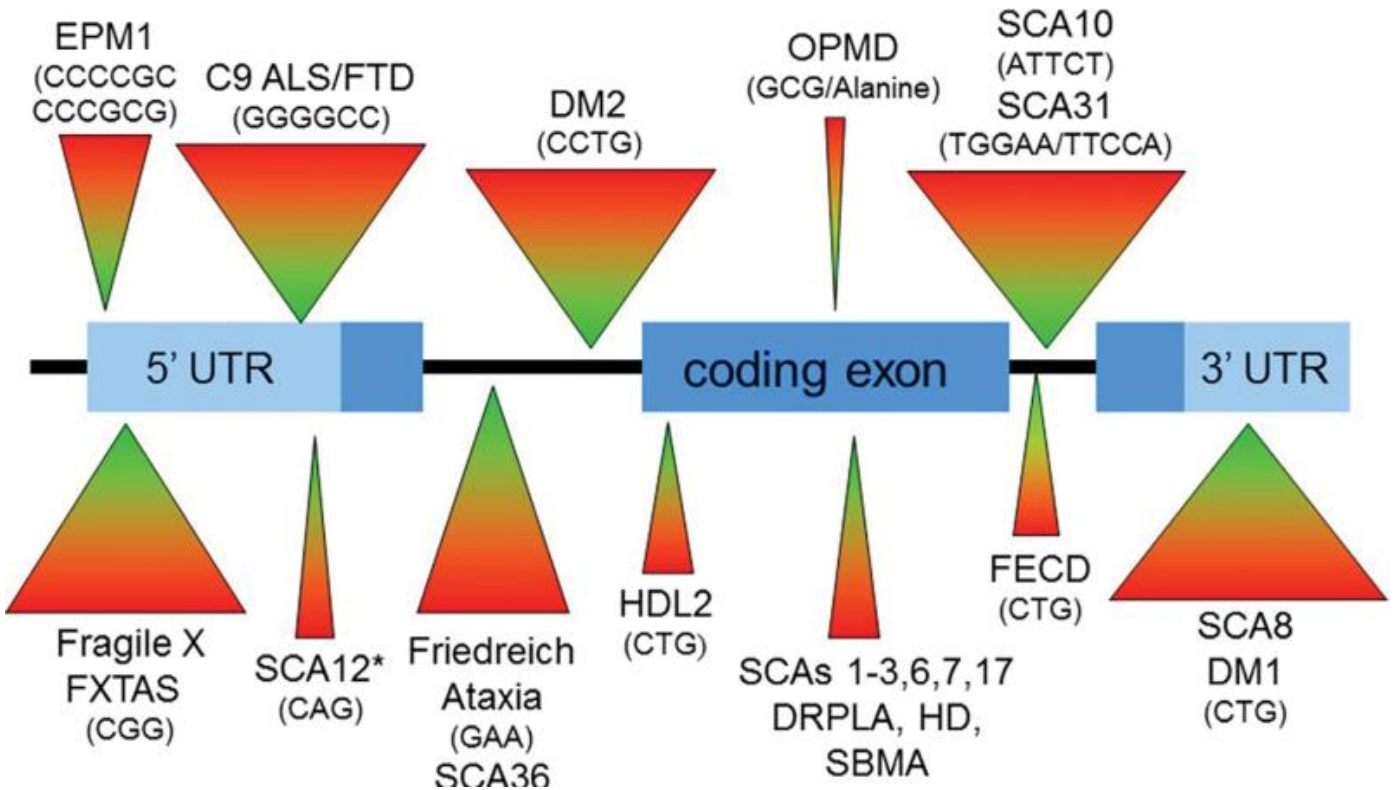

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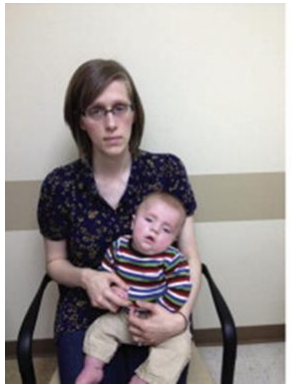
Disorders related to repeat expansions

FXS

Neurodevelopmental syndrome

FXTAS

Neurodegenerative syndrome



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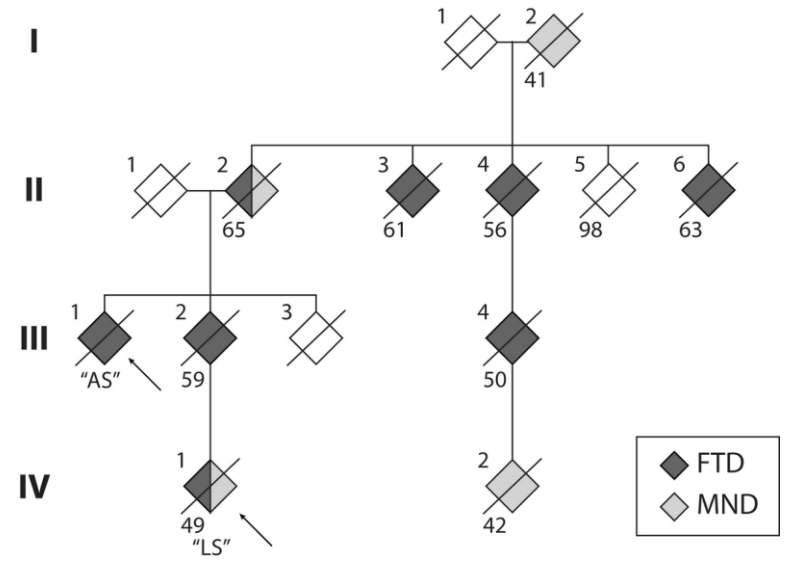
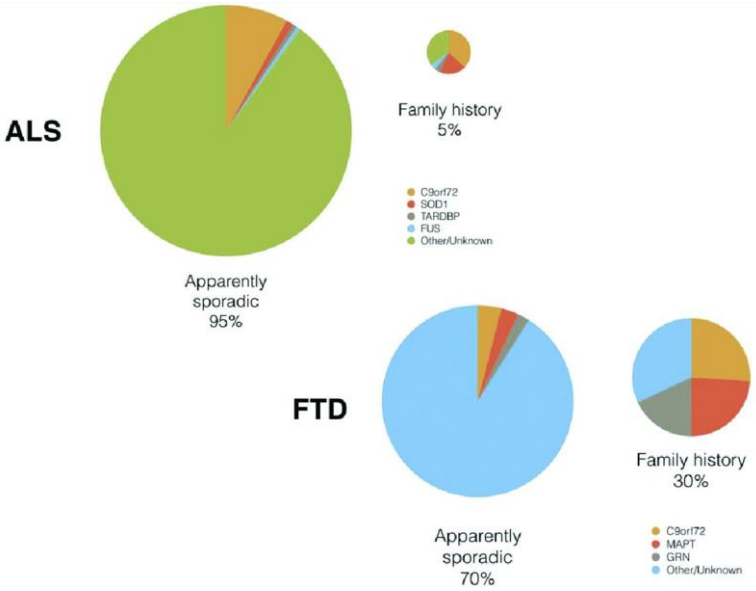
REDs are characterized by extreme clinical variability (variable expressivity)

- Myotonic dystrophy: from floppy babies to ADHD to muscular dystrophy to cataracts only
- Fragile X syndrome and FXTAS: early onset developmental deficits to late onset tremor-ataxia
- Huntington disease: adult-onset dementia, chorea to juvenile onset rigid syndromes
- SCAs: Ataxia, EP signs, UMN signs, LMN signs, cognitive decline, epilepsy, retinal pathology
- C9Orf 72: ALS, FTD

Diagnostic delays





REDs are characterized by extreme phenotypic variability

Profile of Families With Parkinsonism-Predominant Spinocerebellar Ataxia Type 2 (SCA2). Furtado et al 2004

- Taken together, these observations would suggest a prevalence of SCA2 among cases of familial parkinsonism ranging between 1.5 and 8%.

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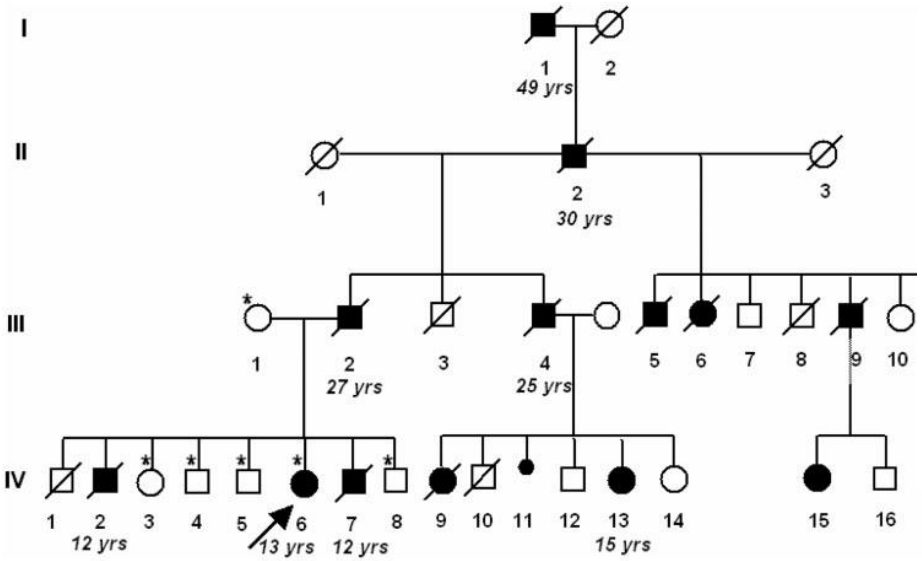
REDs often show extreme anticipation

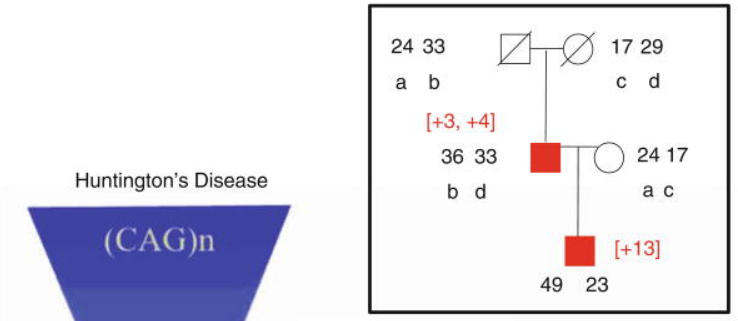
Massive SCA7 expansion detected in a 7-month-old male with hypotonia, cardiomegaly, and renal compromise. Dev Med Child Neurol, 49 (2007), pp. 140-143

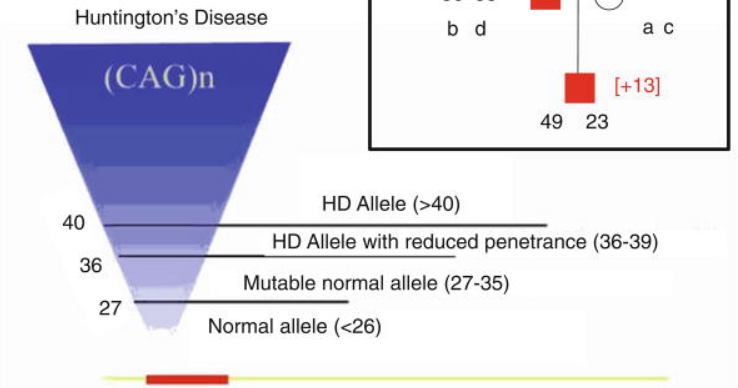
4 month old boy with poor feeding, hypotonia, absent DTR, respiratory failure

Infantile childhood onset of spinocerebellar ataxia type 2. Cerebellum. 2012 Jun;11(2):526-30

1 year old girl with facial dysmorphism, dystonia, developmental delay and retinitis pigemntosa







"Sporadic" appearance of the disease in a child when affected parent has not developed symptoms. Problems with detecting large expansions

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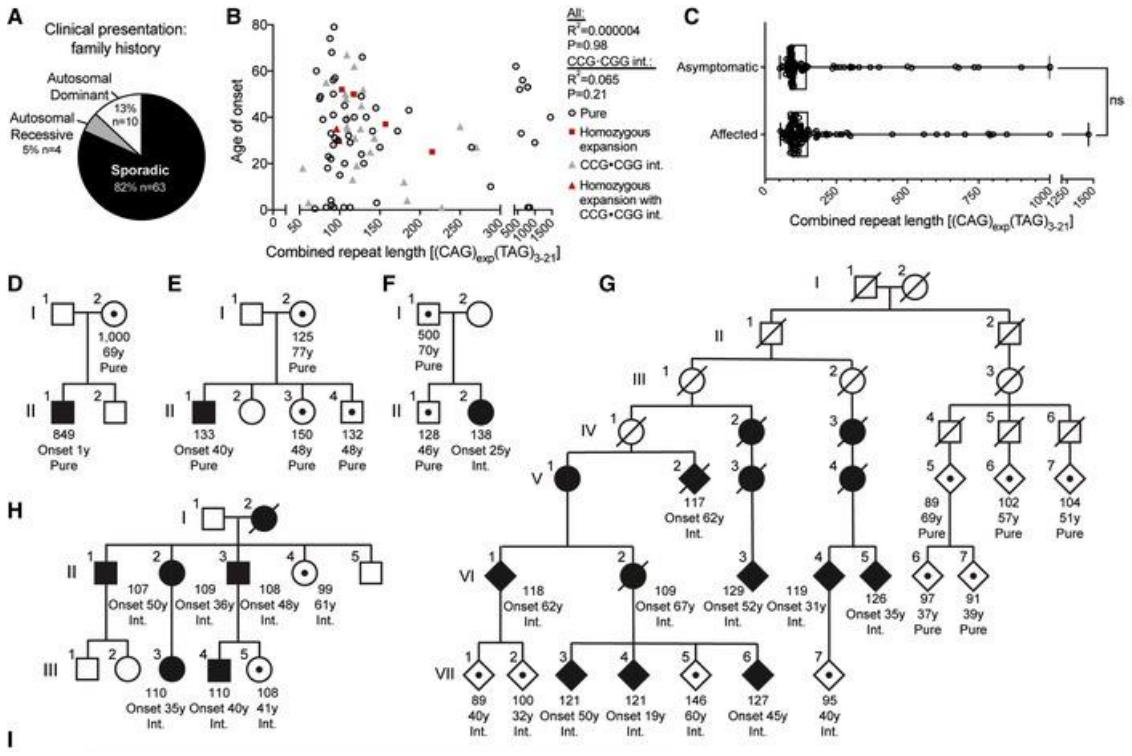
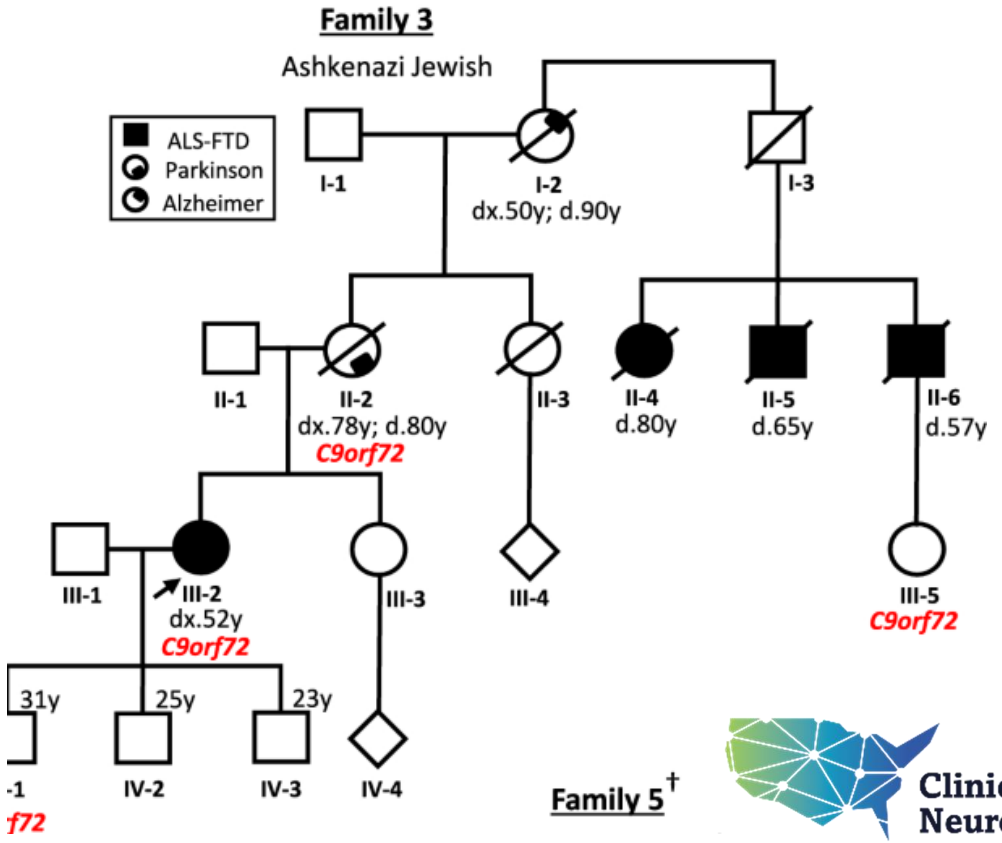
REDs often have variable penetrance



RED related diseases may present as sporadic cases



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REDs may present as late onset neurodegeneration with no family history

- SCA 27b: Heterozygous intronic GAA.TTC STR expansion in the FGF 14
  - 15 to 50% sporadic ataxia patients
  - 5 to 28% of previously undiagnosed ataxias
  - Median AO 60 years

- CANVAS syndrome: biallelic intronic AAGGG STR expansion in RFC 1 gene
  - 20% cases of late onset ataxias
  - AR inheritance

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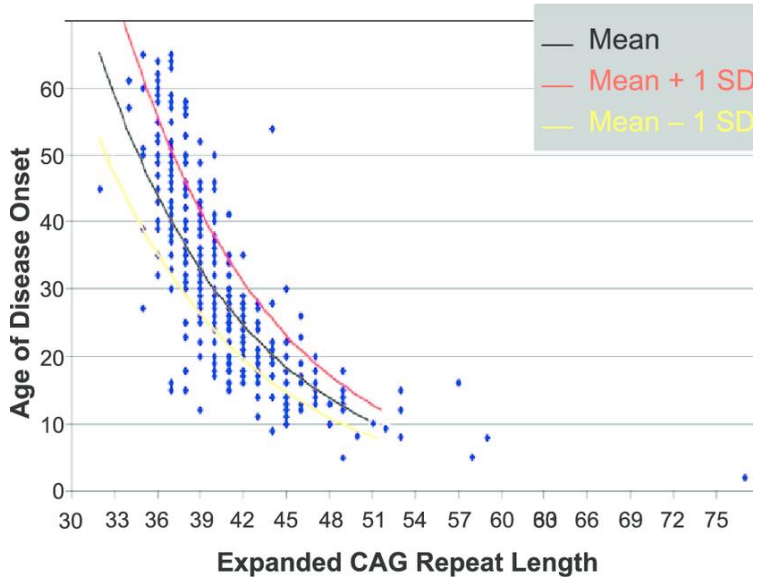
Pathobiology of phenotypes



- Size of the repeat
- Instability of the repeat during meiosis
  - Maternal vs paternal factors
- Somatic instability leading to widely different repeat sizes in different tissues
  - Post-mitotic cells
  - Tissue susceptibility
  - Threshold values for disease progression
- Interruptions of the sequence
  - Pure vs interrupted

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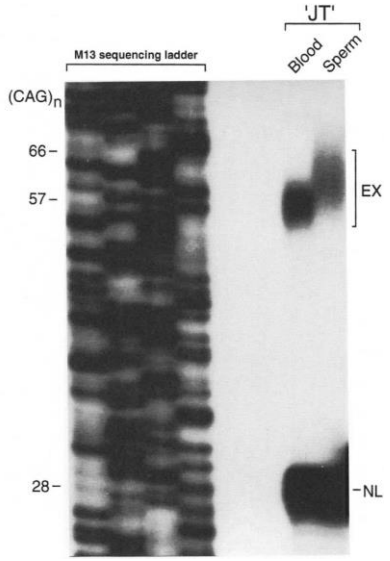

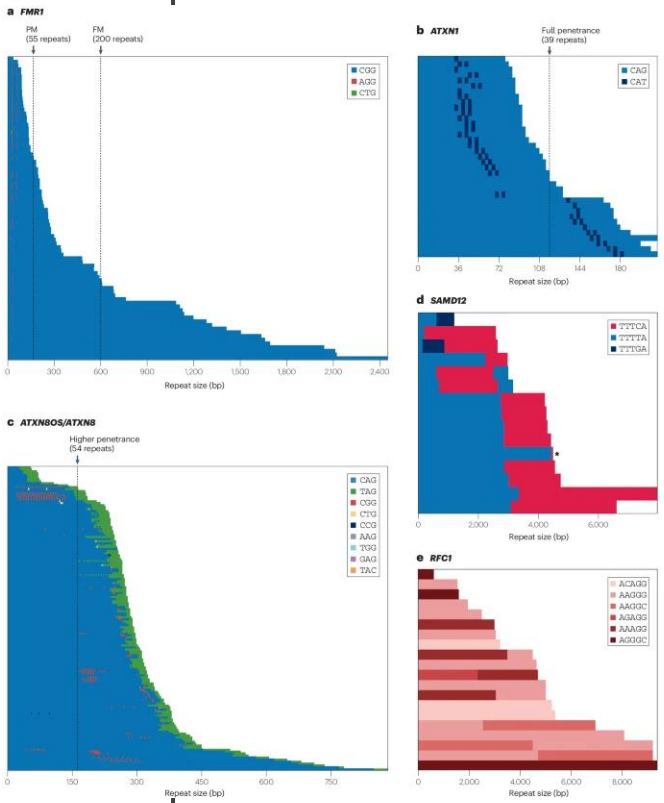

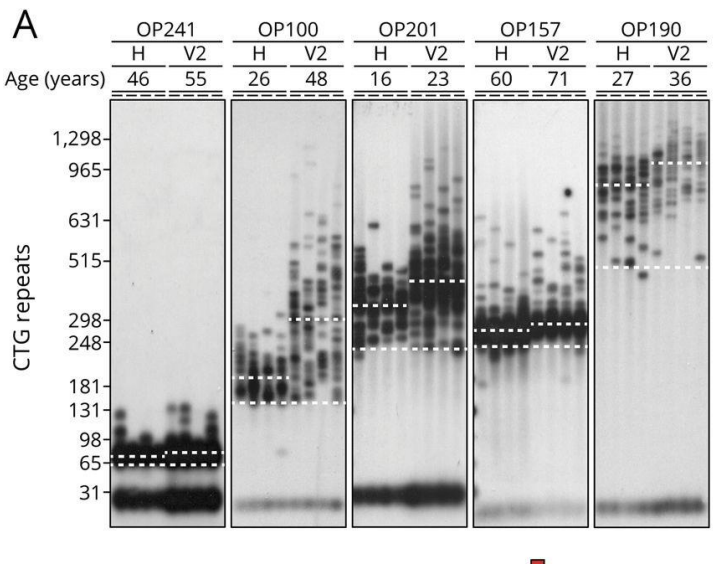

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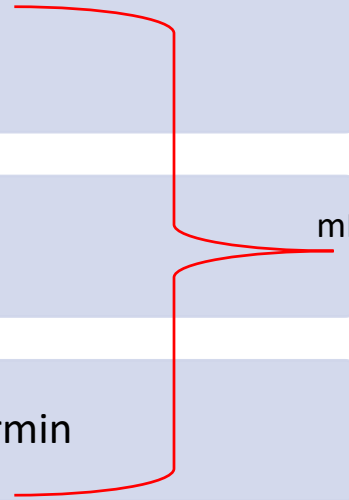
Pathobiology of cellular degeneration

Loss of gene function. Reduced transcription and reduced protein: e.g. Friedreich ataxia, Fragile X syndrome	• Replace gene or stimulate gene expression • Replace protein
Enhanced gene function. E.g. SCA 12, CAG expansion in promoter sequence may increase its activity. E.g. FSHD: D4Z4 repeat contraction causes aberrant expression of DUX 4 which is deleterious	
Toxicity of mRNA. E.g. myotonic dystrophy, FXTAS	• Gene knockdown by reducing mRNA (ASO, shRNA)
Toxicity of protein E.g. CAG repeat expansion diseases (Huntington, SCA 1,2,3,6,7)	• Gene knockdown by reducing mRNA (ASO, shRNA)
Aberrant protein production. RAN proteins. E.g many polyglutamine diseases, FXTAS, myotonic dystrophy	• Manipulate translation of aberrant protein e.g. Metformin



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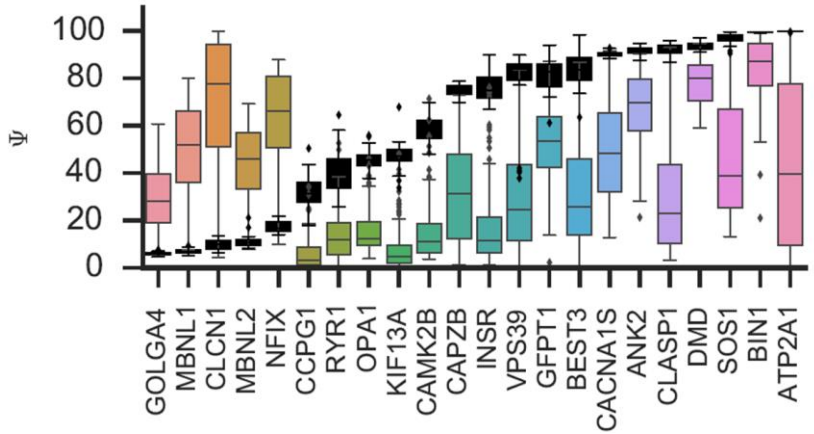

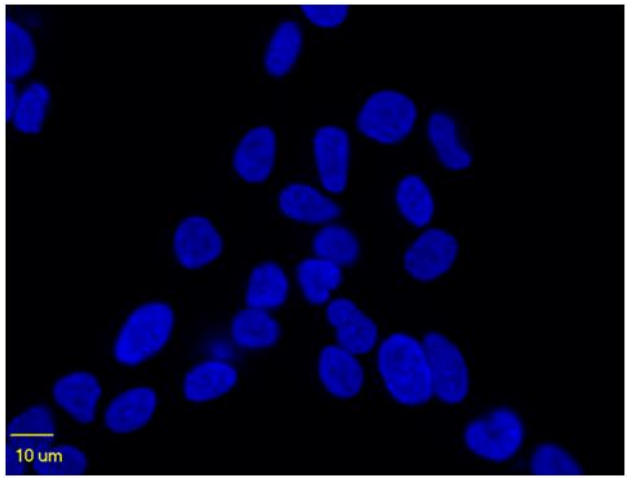

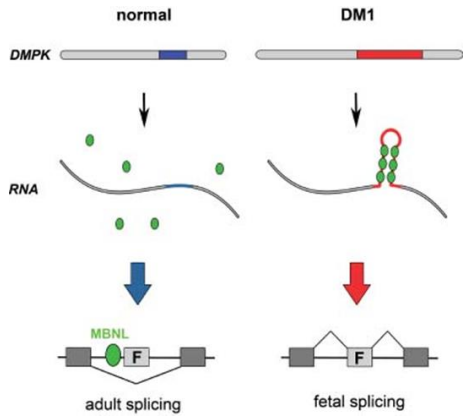

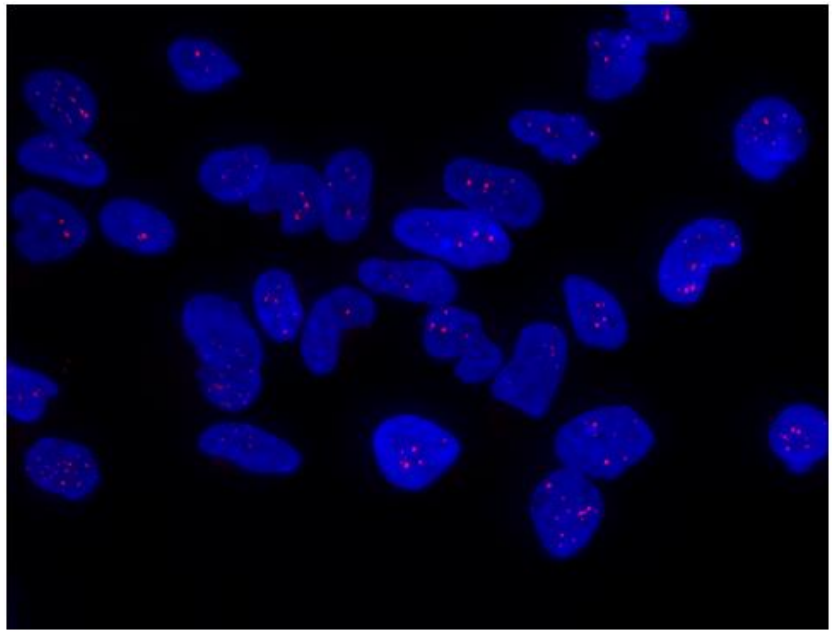

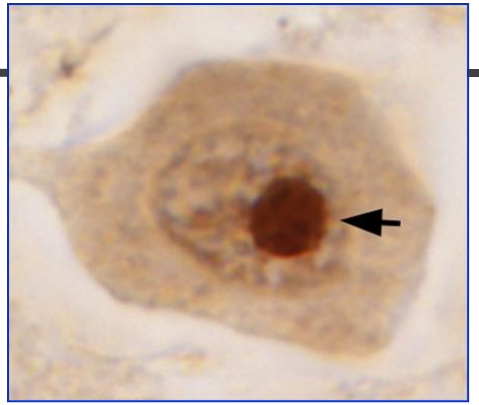

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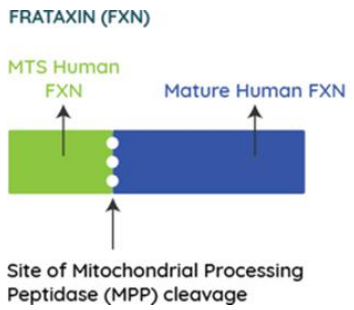
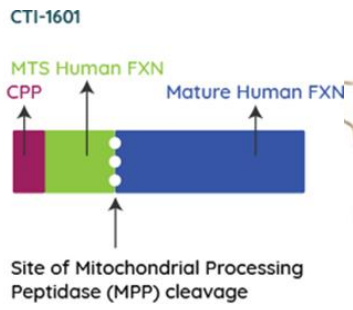
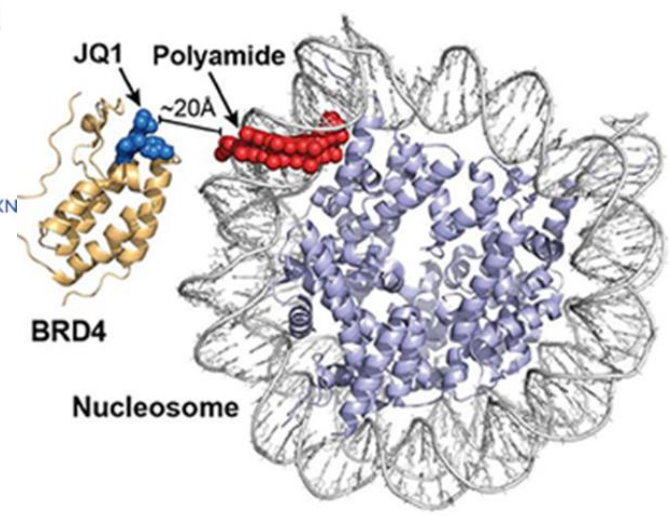
Increases in skin FXN levels with short- and long-term daily nomlabofusp; 10/10 participants with data at 6 months achieved skin FXN levels over 50% of median levels in healthy volunteers

Anaphylaxis has been reported in 7 participants in the OL study, with most events occurring on the initial day of administration and all occurring within the first 6 weeks of dosing; excluding these events, long term dosing of nomlabofusp was generally well tolerated

Larimar Press release Sep 2025







Gene based approaches to loss of function: Friedreich ataxia

DT-216 (Design therapeutics) increases FXN mRNA ten-fold in PBMC and improves mitochondrial function

In Phase 1 trial: 100, 200 and 300 mg cohort, 3 IV doses in a week. No major safety issues except phlebitis. FXN mRNA in muscle up by 30% after dose 3

No SAEs. Injection related thrombophlebitis

DT-216P2: improved version for both IV and subQ administration in trial (RESTORE-FA)

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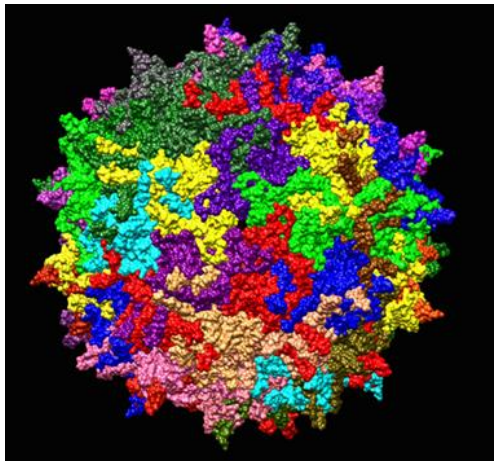

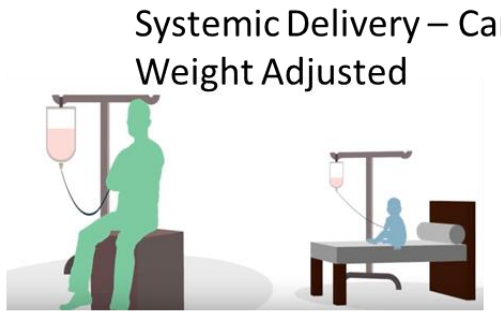

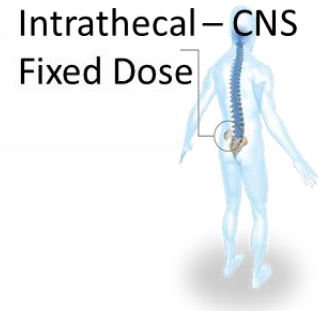

AAV mediated gene transfer

- Issues
  - Optimal vector design
  - Best route of delivery and how to get adequate transduction
  - Specific targets
  - Overexpression
  - Immune response
  - Irreversibility
- Current studies
  - Lexeo cardiac targeted
  - Solid: simultaneous IV and dentate delivery

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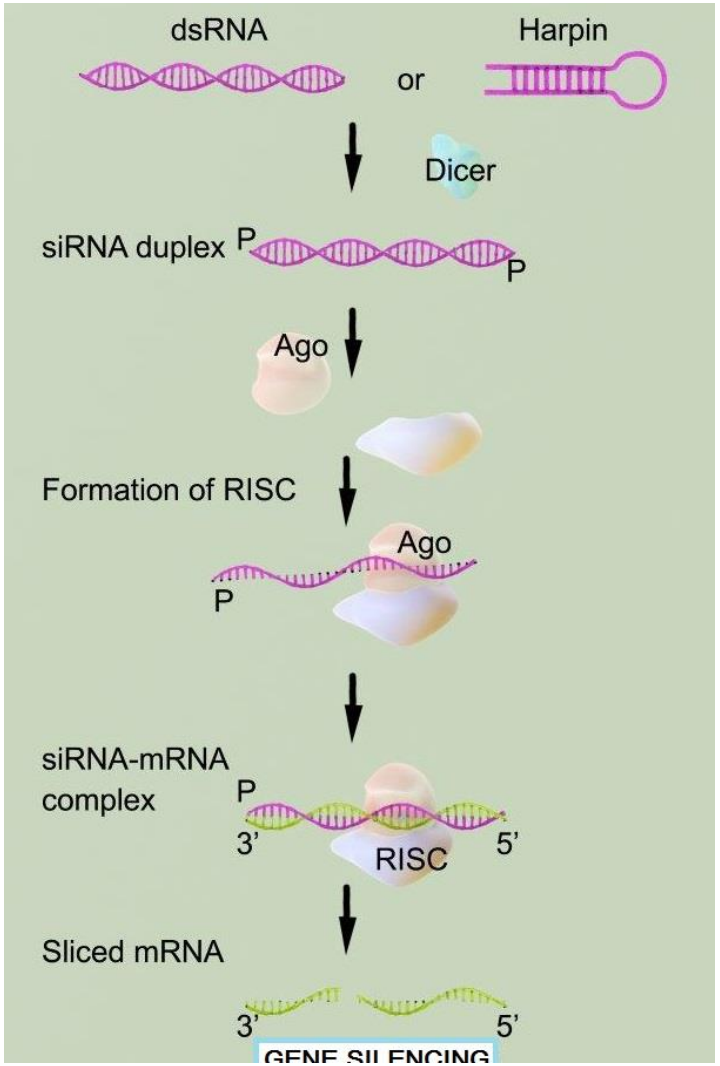
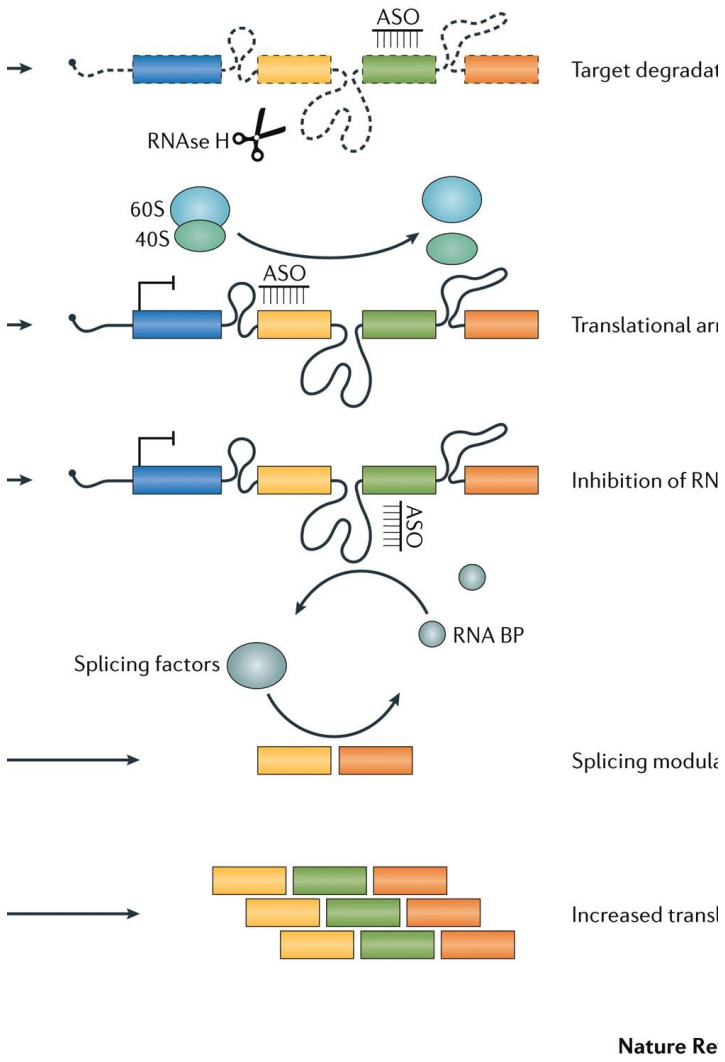
Gene knockdown: ASOs and siRNAs





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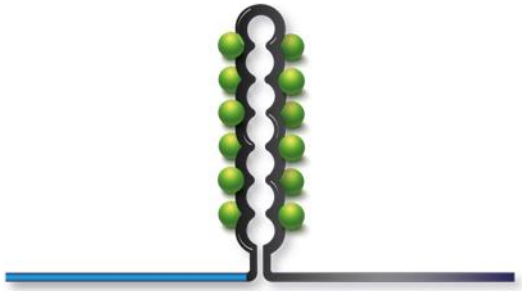
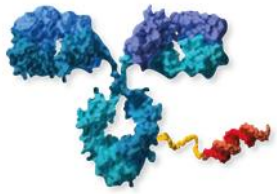
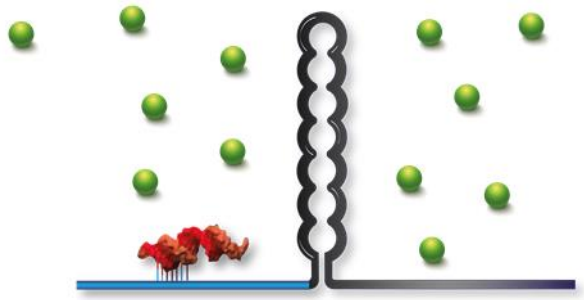
AOC in myotonic dystrophy





Oligonucleotide binds mutant DMPK mRNA



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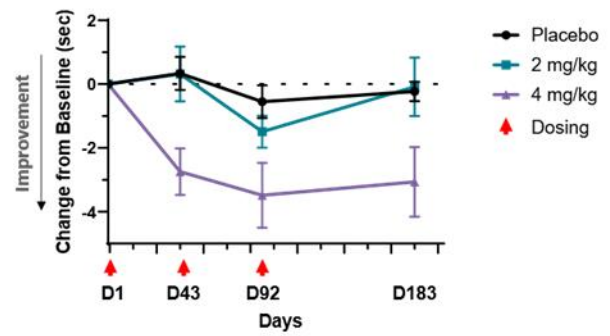
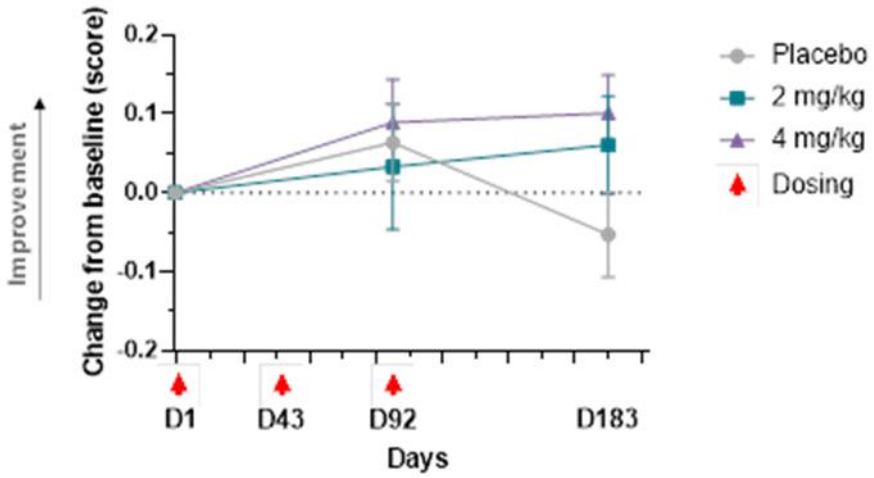
Change from Baseline of the Third Digit vHOT



	D43 Mean CFB (SE)	D43 Mean Difference (95 % CI)	D92 Mean CFB (SE)	D92 Mean Difference (95 % CI)	D183 Mean CFB (SE)	D183 Mean Difference (95 % CI)
Placebo	0.332 (0.520)		-0.551 (0.517)		-0.233 (0.305)	
2 mg/kg	0.315 (0.859)	-0.017 (-2.226,2.193)	-1.489 (0.503)	-0.938 (-2.479,0.603)	-0.087 (0.919)	0.146 (-2.026,2.318)
4 mg/kg	-2.744 (0.732)	-3.076 (-5.171,-0.980)	-3.488 (1.018)	-2.937 (-5.721,-0.153)	-3.069 (1.091)	-2.836 (-5.610,-0.063)

Change From Baseline of MMT Total Muscle Composite Score

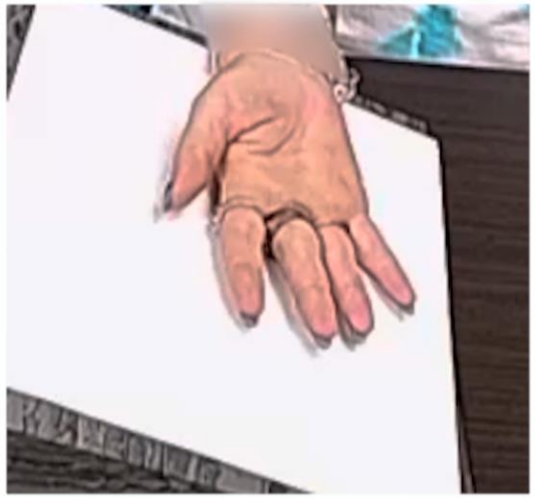


AOC 1001 Demonstrates Myotonia Reduction in Early Responder from 2mg/kg Cohort

Participant from 2mg/kg Multidose

Baseline vHOT

Day 43 vHOT
6 weeks after first dose



Day 92 vHOT
6 weeks after second dose

Day 183 vHOT
12 weeks after third dose

Improvement visible at Day 43 that is sustained for at least 12 weeks following the third dose at 2 mg/kg

vHOT = video hand opening time

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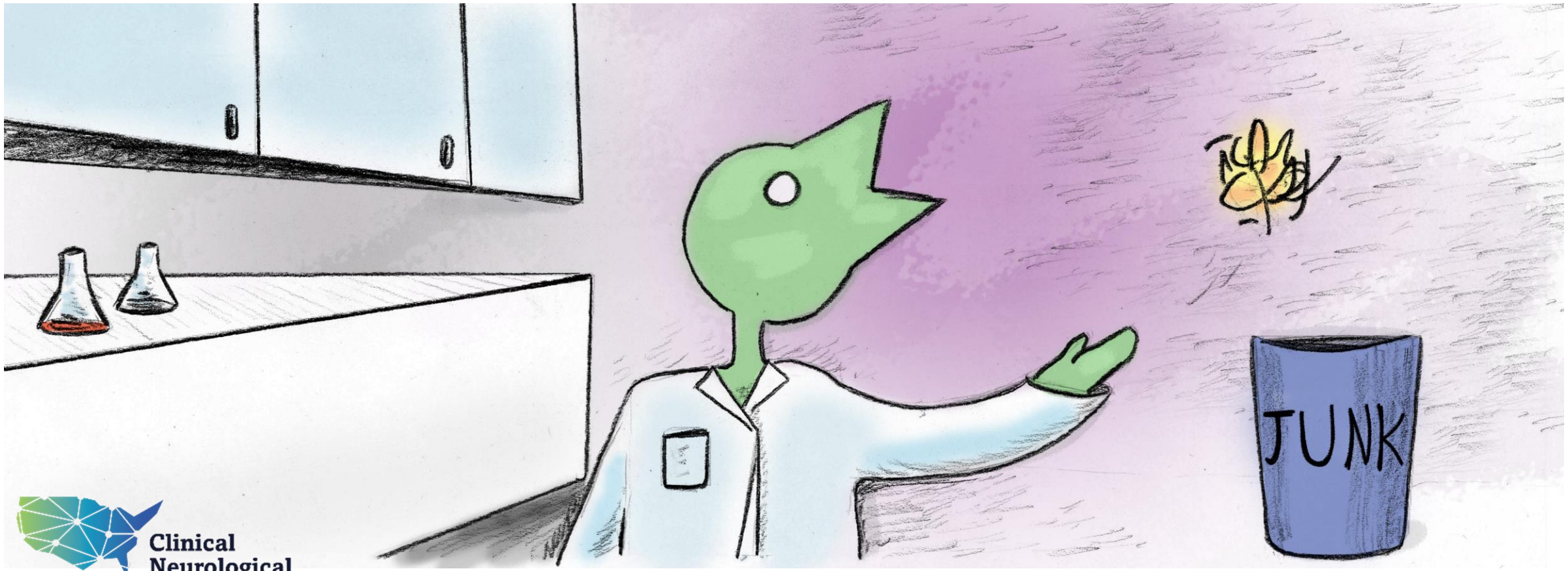
Thank you!



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Questions