LEIDS UNIVERSITAIR MEDISCH CENTRUM

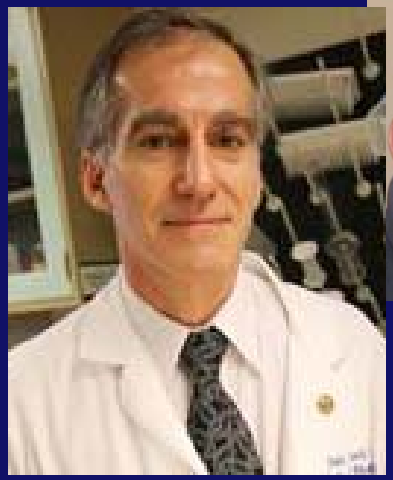
THANK YOU!

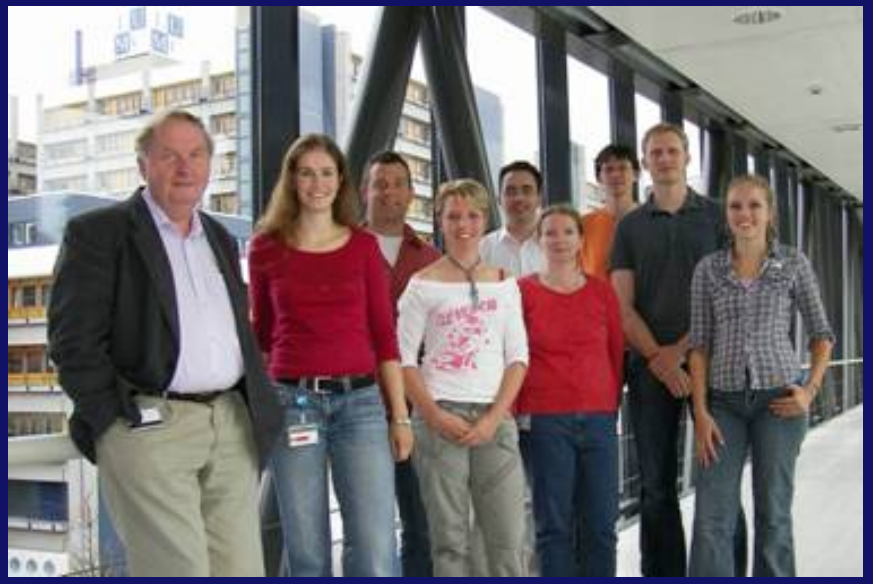
FIELDS
FSHD & Neuromuscular Research
CENTER

Acknowledgements

STICHTING FSHD
HUMERAL MUSCULAR FACIO-SCAPULO DYSTROPHY SOCIETY fsh
NATIONAL INSTITUTES OF HEALTH
NWO
MDA

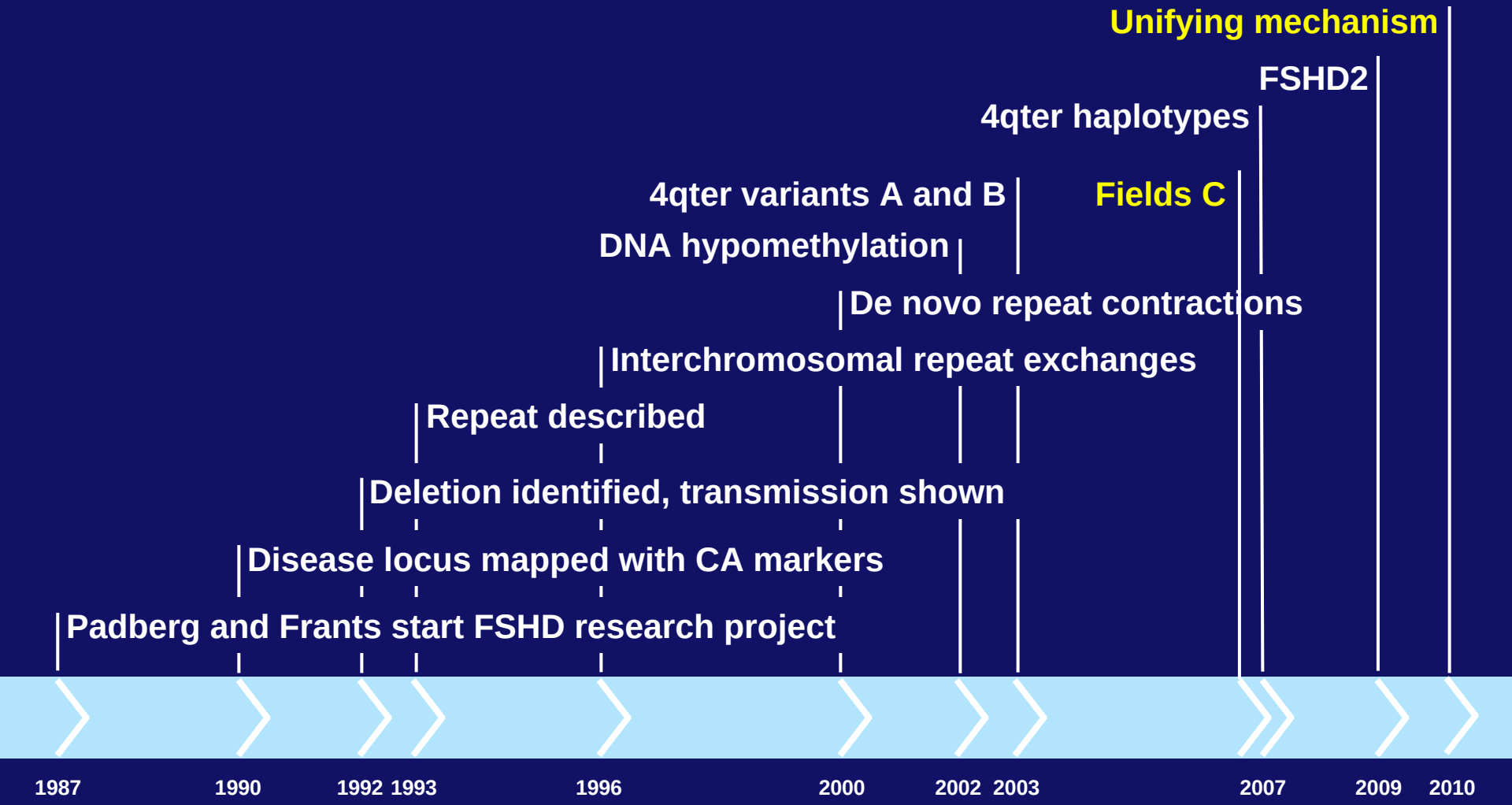
The Rochester-Leiden-Seattle connection



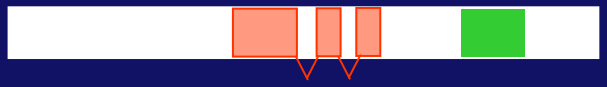


A Unifying Disease Mechanism for FSHD

FSHD genetics in time



Key in biology



DNA contains the information (genes)

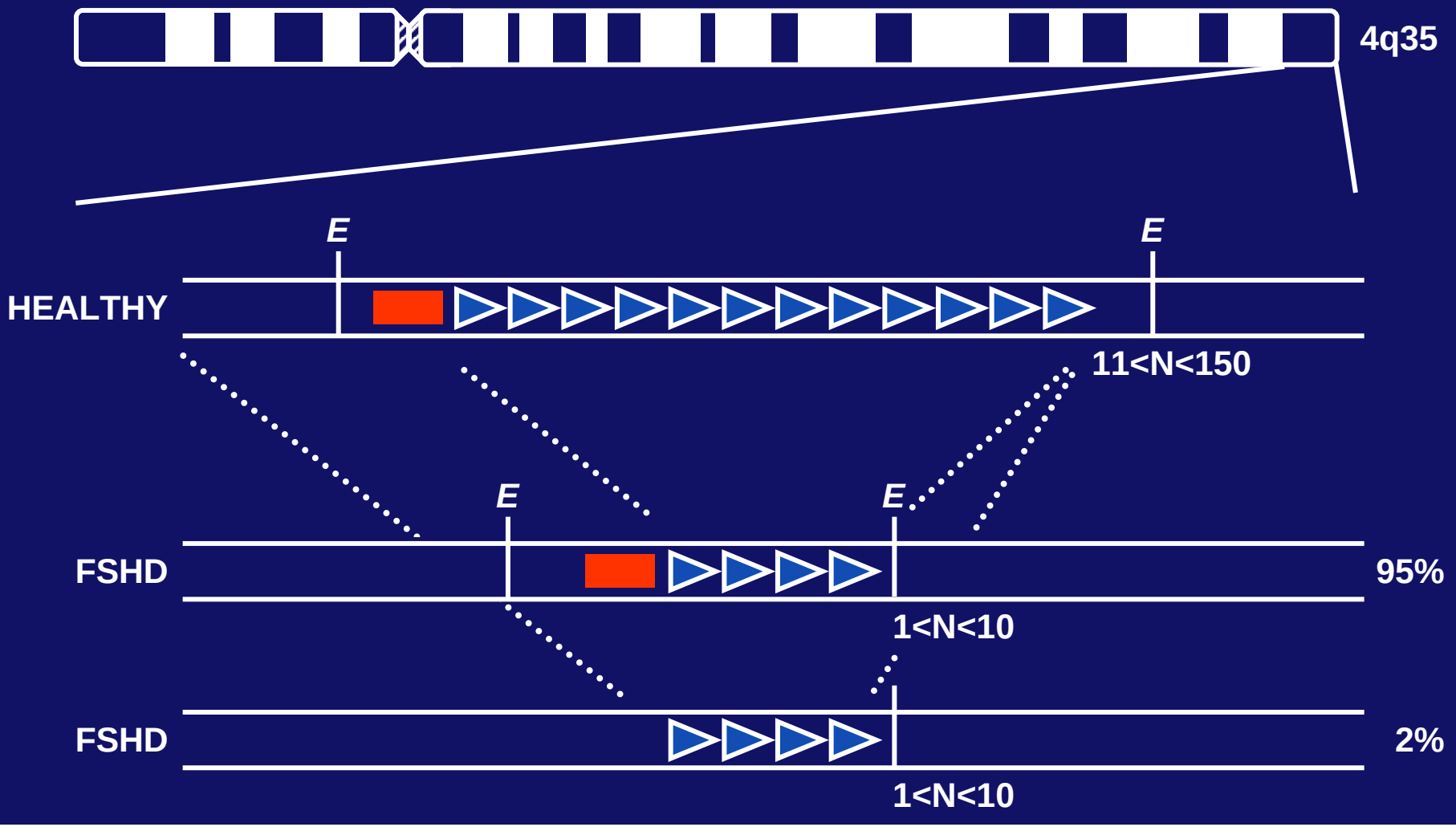
transcription

RNA is the messenger of the information

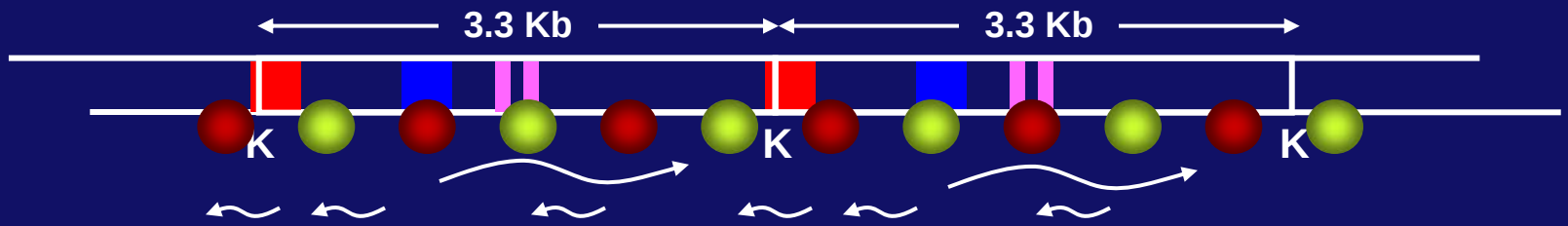
translation

Proteins are generated from the information

Genetic defect



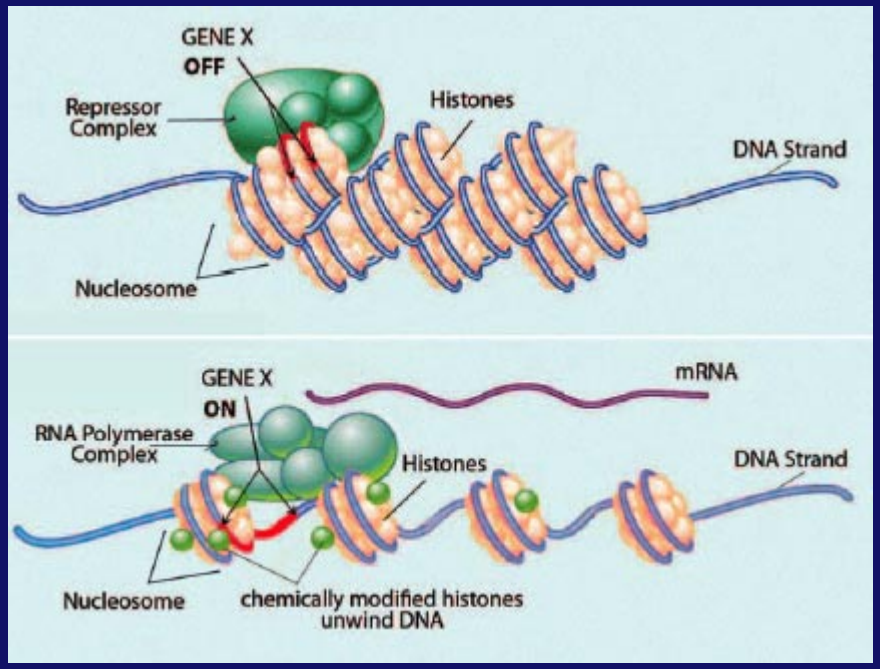
What is D4Z4?



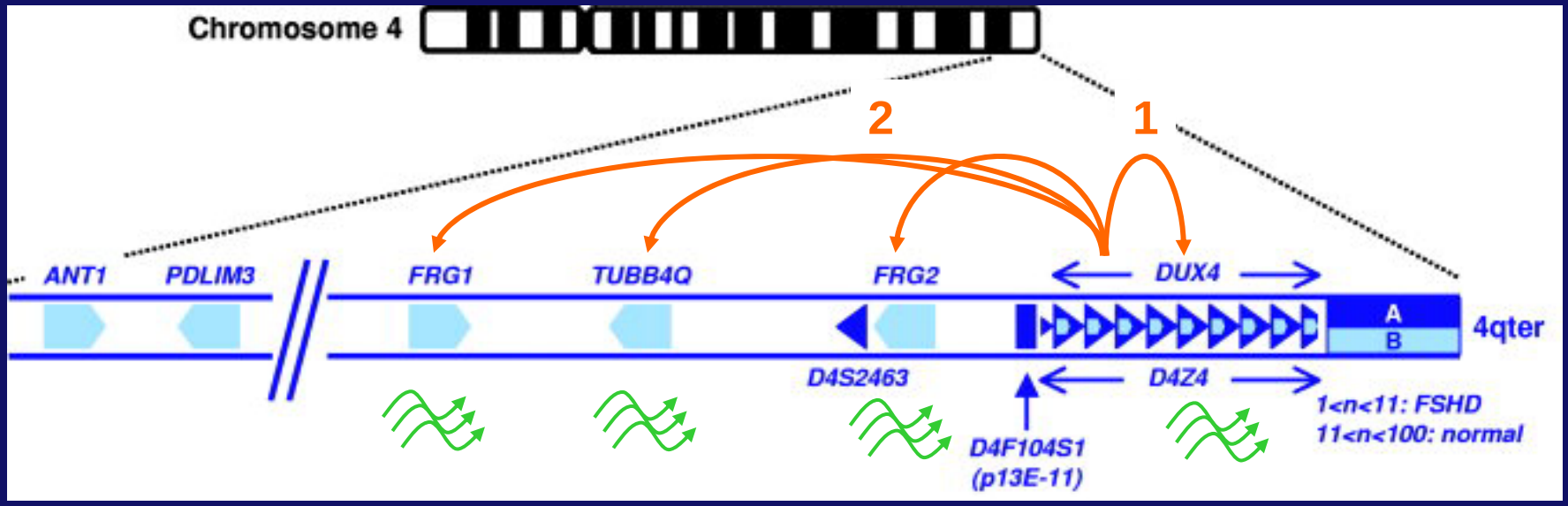
repetitive sequence

Normally closed structure, in FSHD open structure

Allows for production of RNA



Disease mechanisms



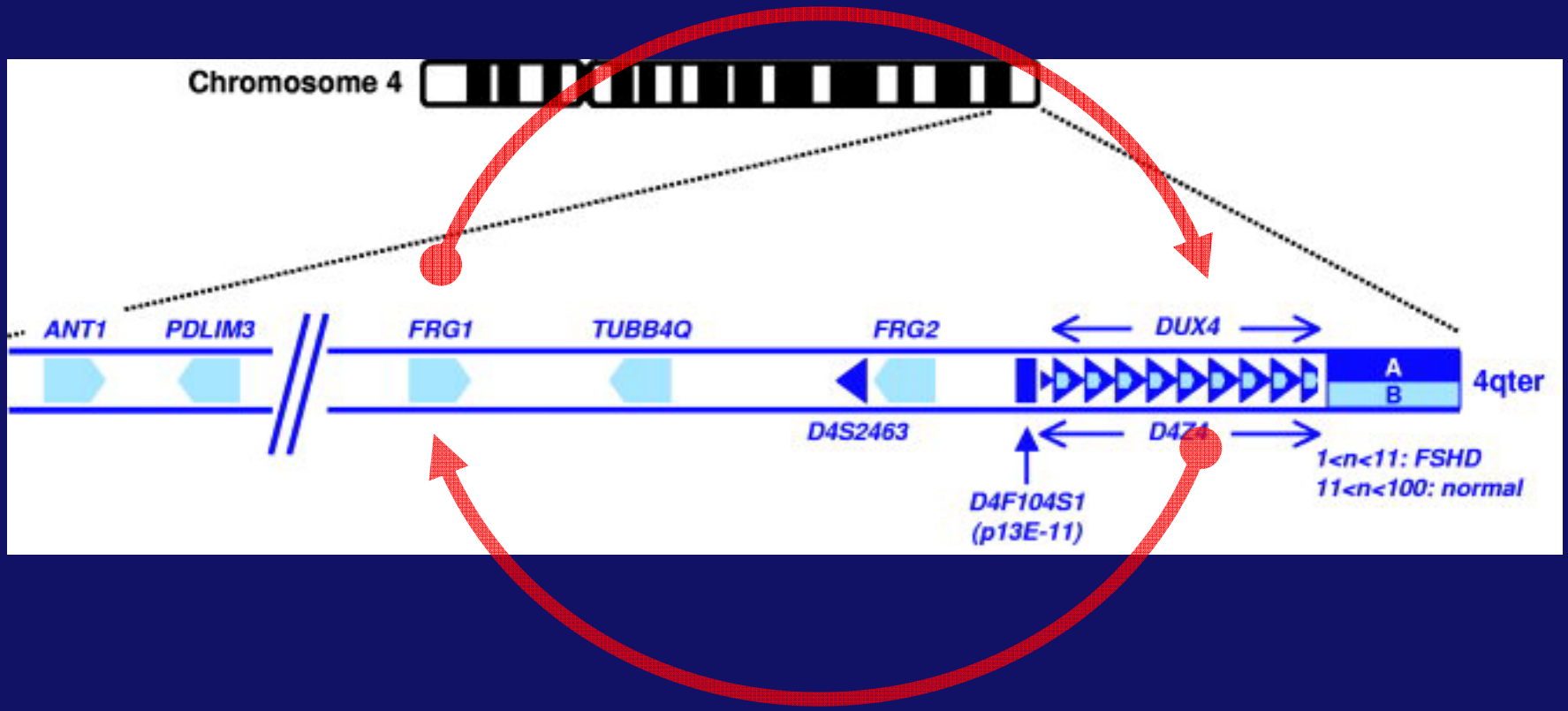
Mechanism 1: direct role for D4Z4

Transcripts emanating from D4Z4 are transcriptionally deregulated

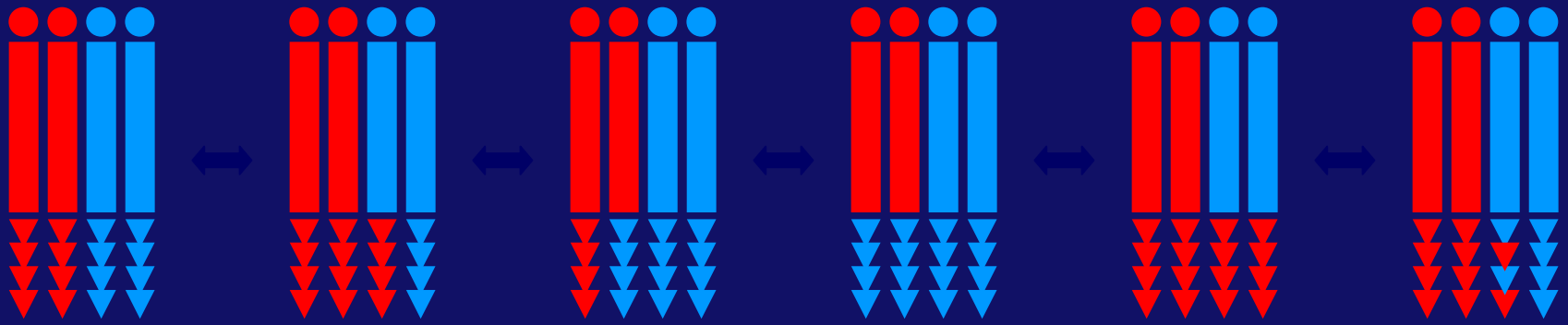
Mechanism 2: indirect role for D4Z4

D4Z4 contraction causes a change in chromatin structure that causes expression changes at distance of D4Z4

Closing the circle

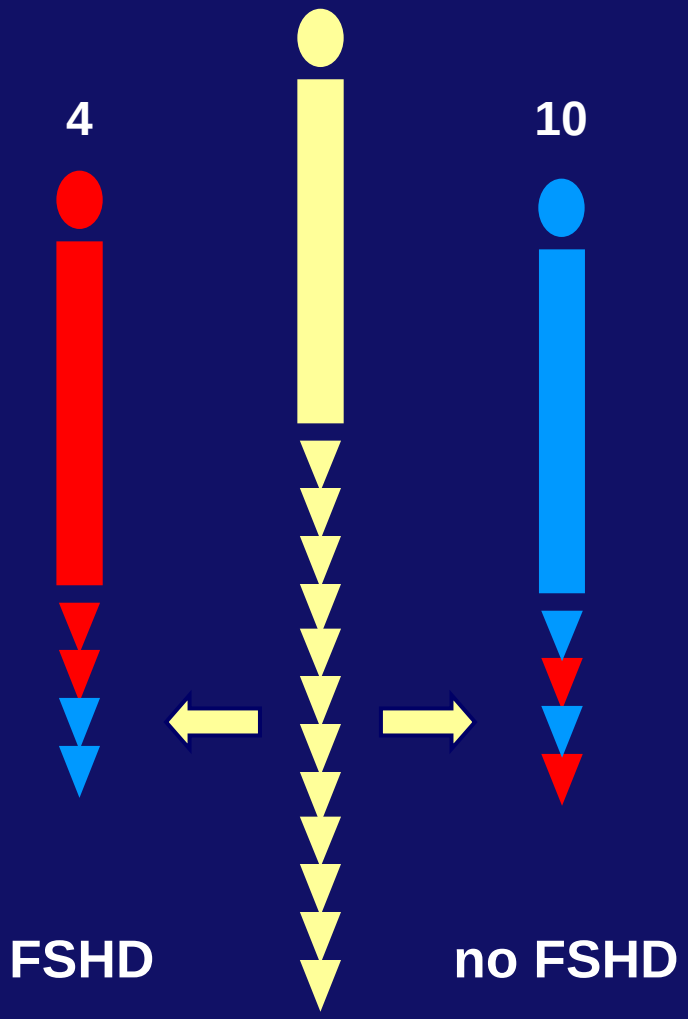


Plasticity between 4qter and 10qter



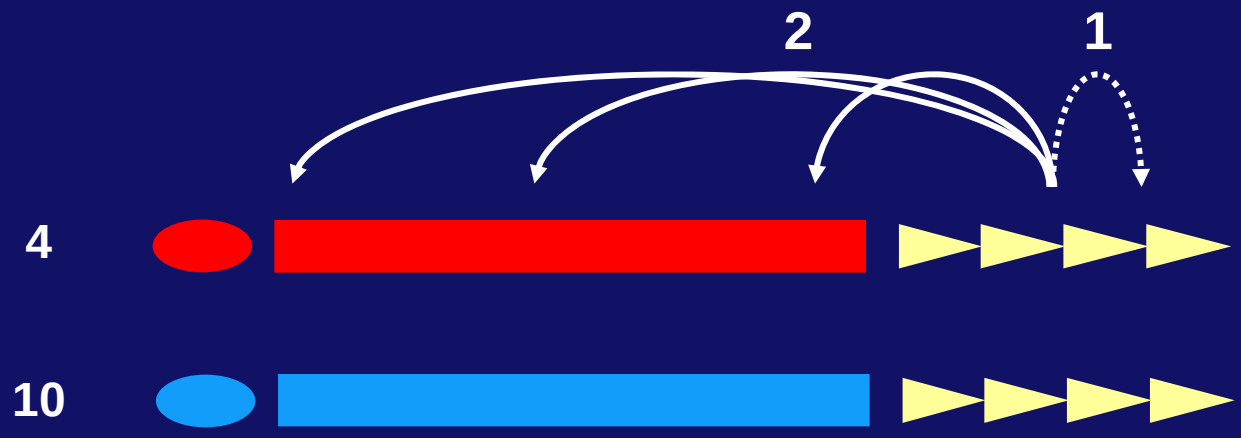
Repeat array exchanges in the population

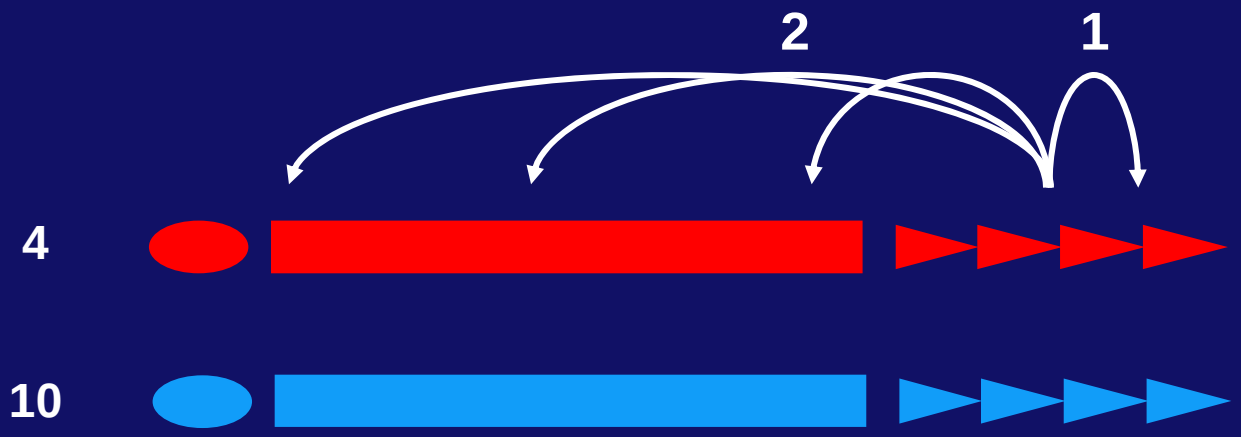
FSHD is linked to chromosome 4



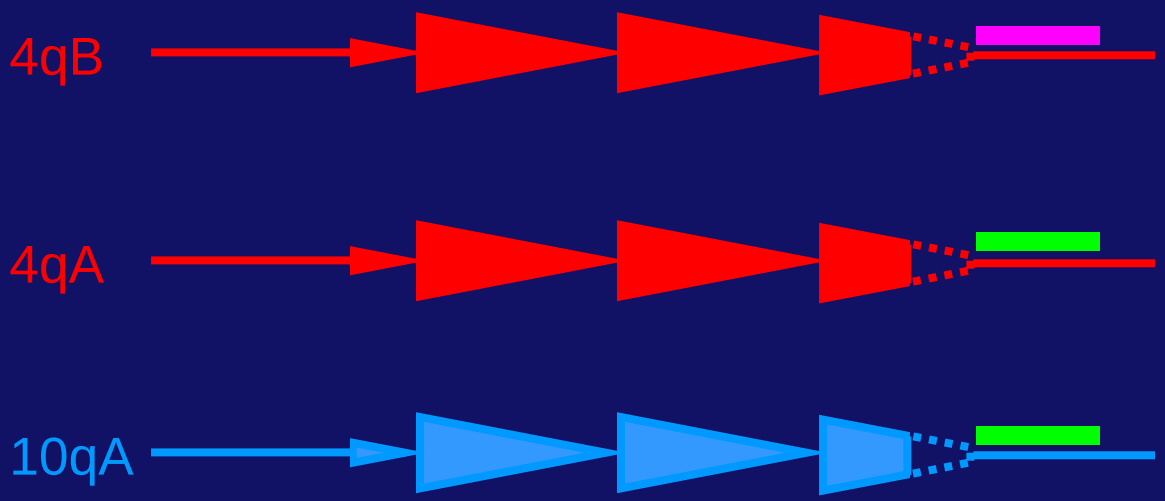
- Small hybrid repeat arrays on chromosome 4 cause FSHD
- Small repeat arrays on chromosome 10 are non-pathogenic
- Translocated or hybrid alleles: rare or recurrent?

Identical or distinct?





Association of FSHD with 4qA

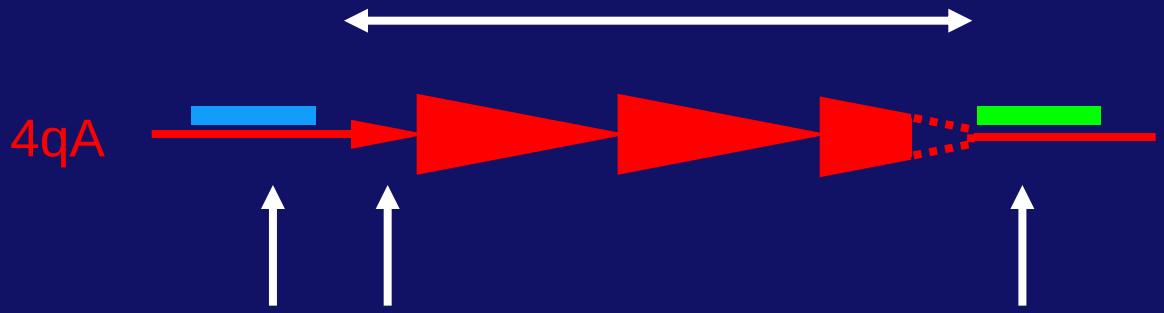


	Control chrom.	FSHD chrom.
4qB	55%	0%
4qA	45%	100%
10qA	100%	0%

$P<10^{-17}$

FSHD is exclusively associated with partial D4Z4 repeat array deletions on 4qA alleles

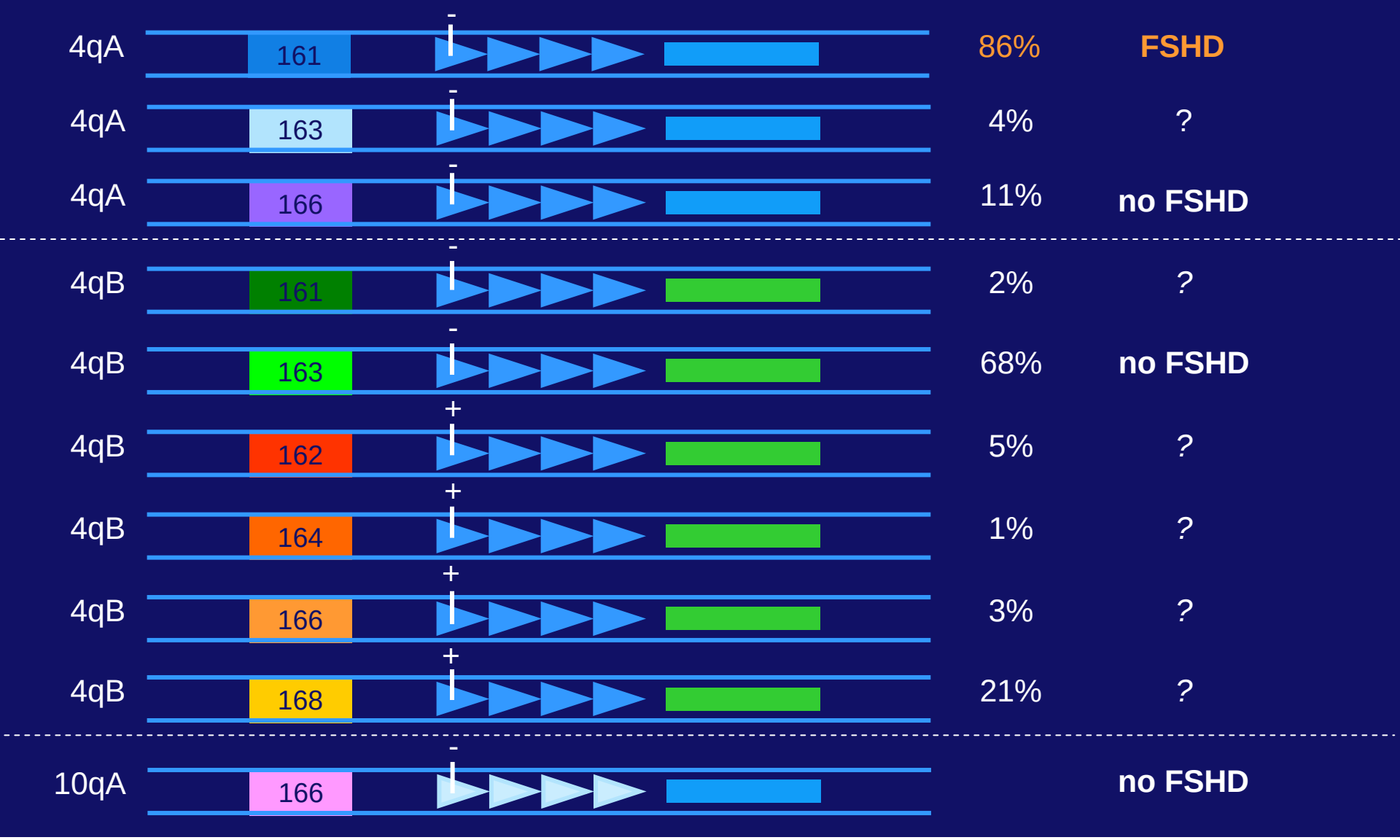
Genotyping D4Z4 alleles (4qA - 4qB)



Genetic analysis of small sequence variations at 4 different postions in the FSHD locus

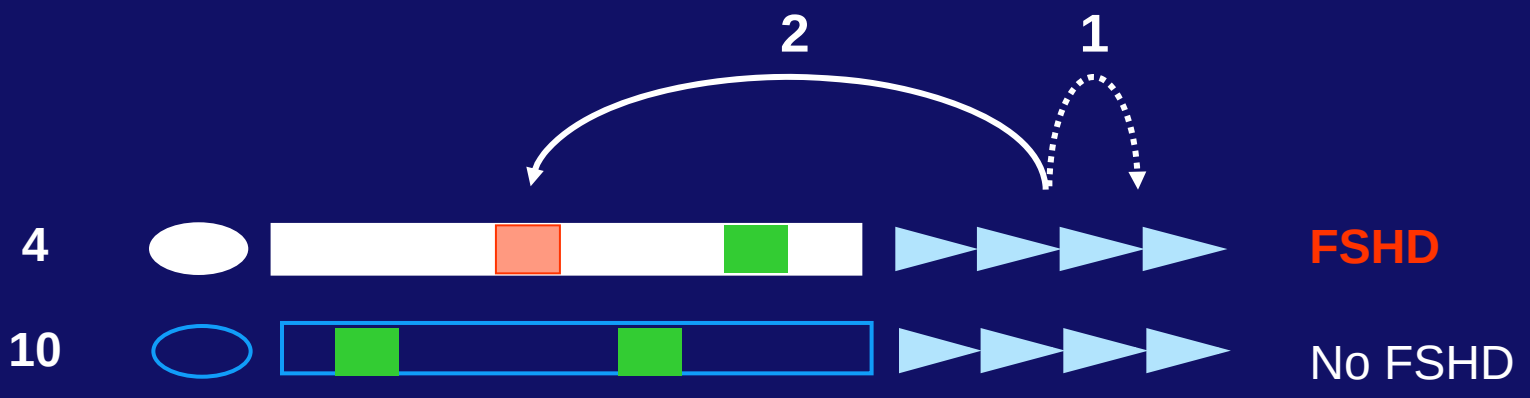
Analysis 450 unrelated control individuals

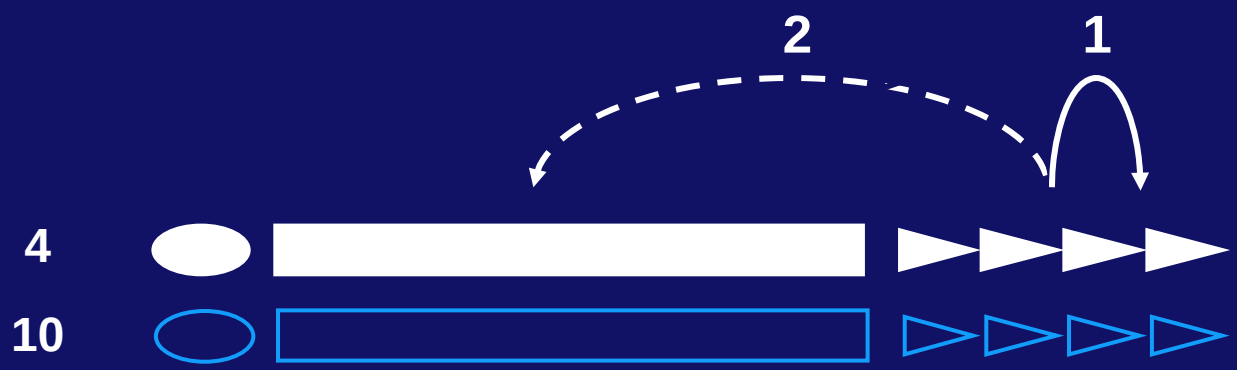
4q chromosomes



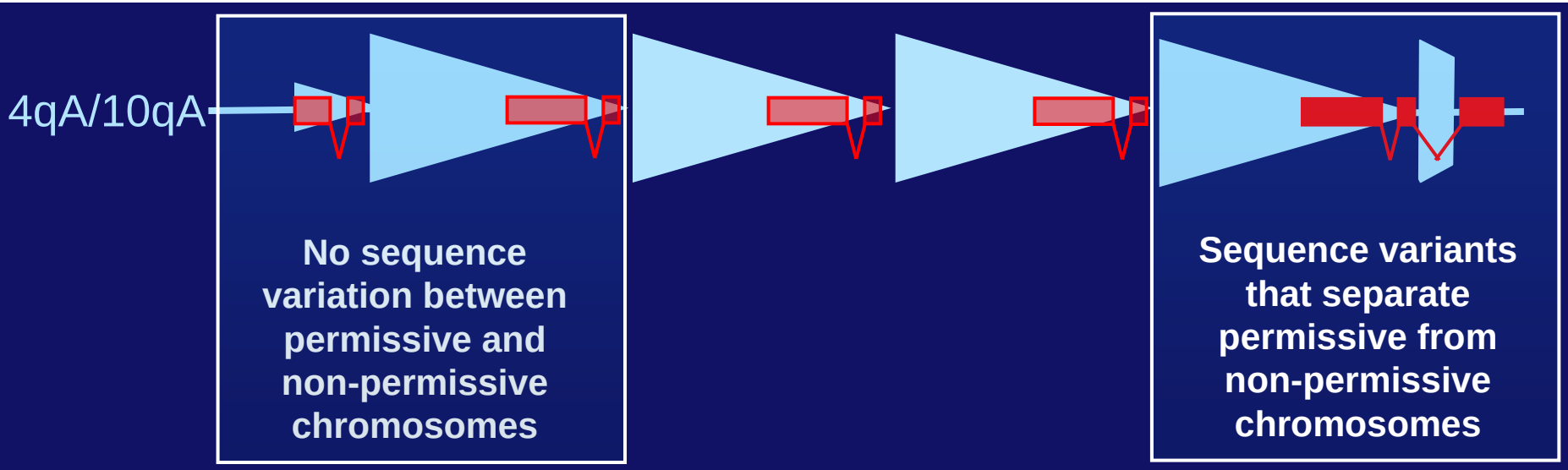
Paradigm shift

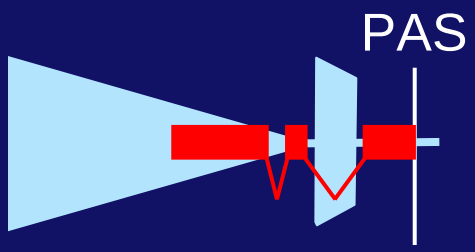
Sequence transfers between chromosomes 4 and 10: rare or recurrent?





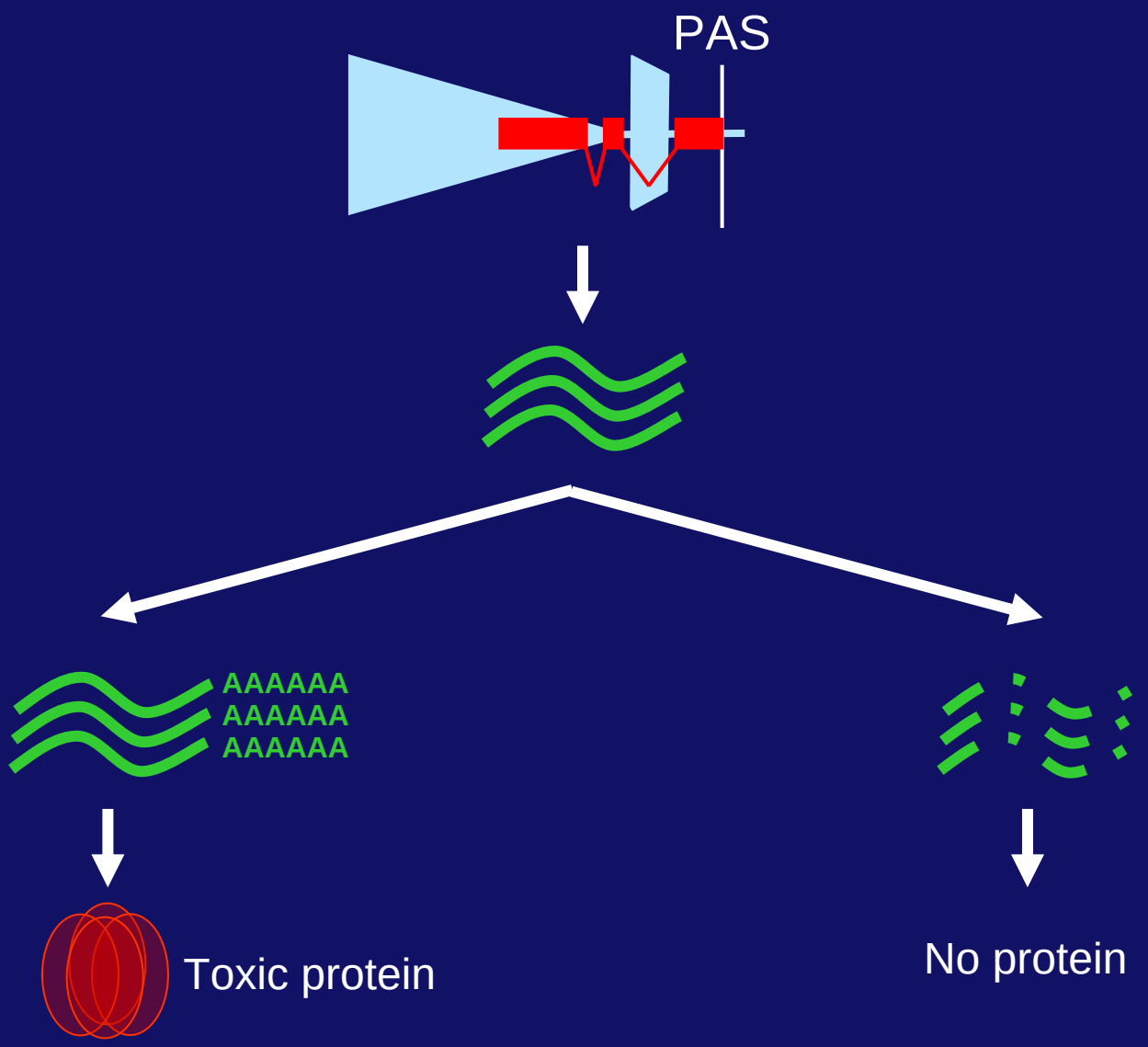
Consistent sequence variations





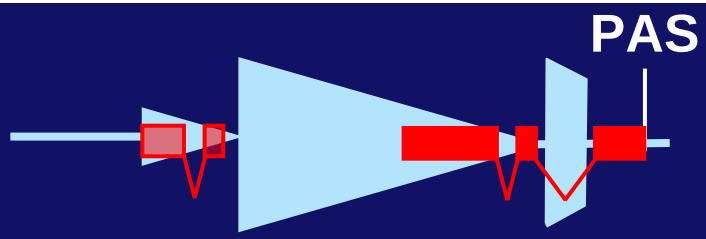
Permissive chromosomes:	ATTAAA	16%
Non-permissive chromosomes:	ATCAAA	0%
	ATTTAA	0%

A polyadenylation signal stabilizes

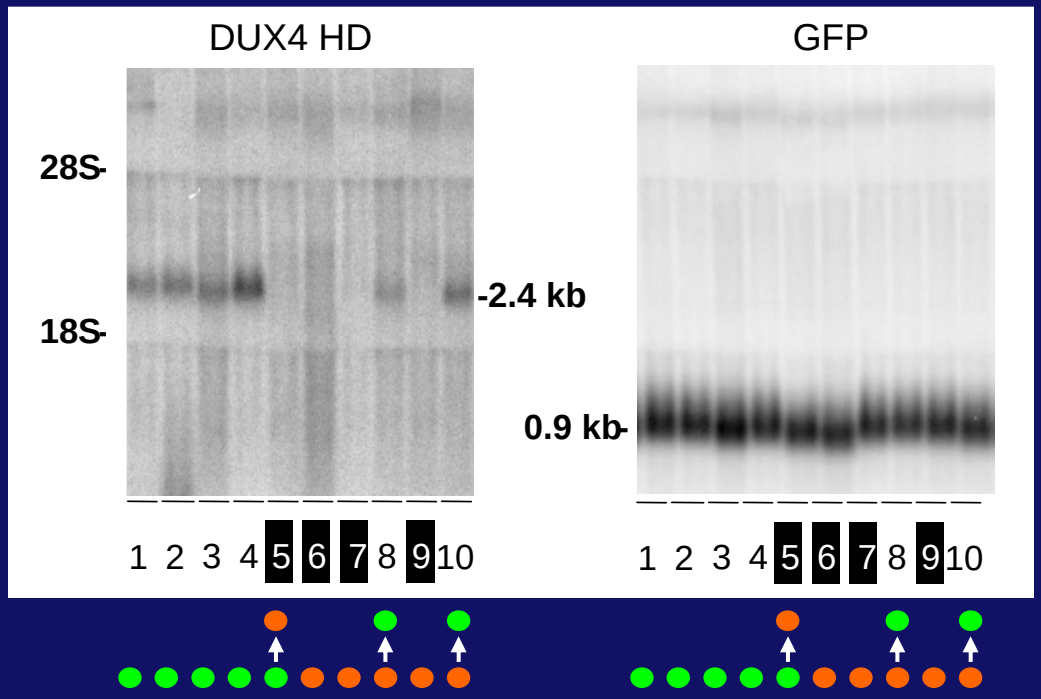


Importance of PAS

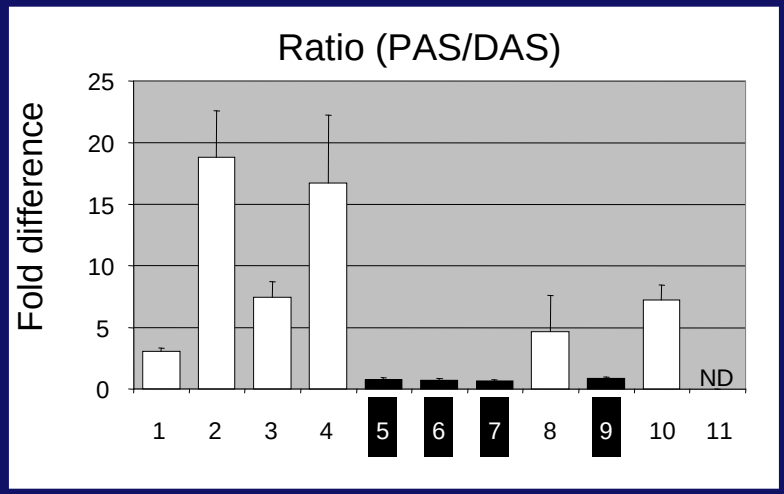
Transfection of distal repeat unit and flanking sequence from permissive and non-permissive chromosomes in C2C12

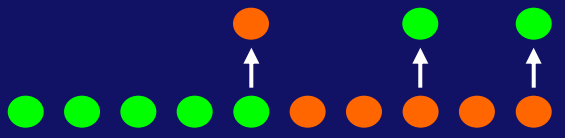


Northern blot



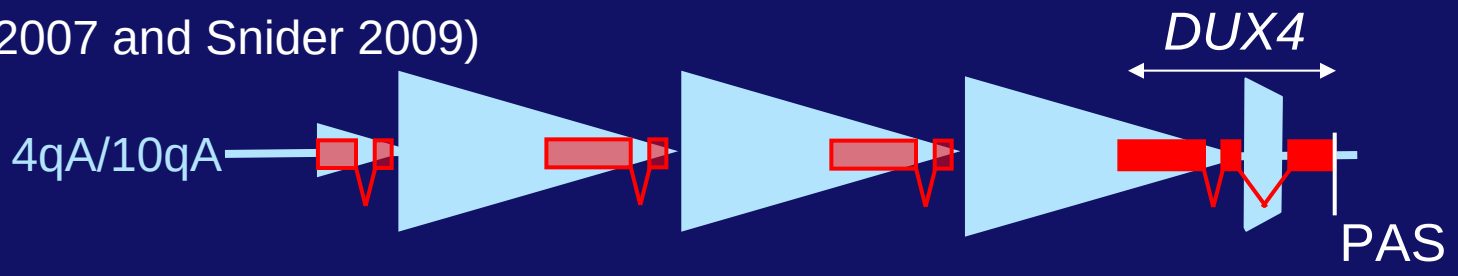
PAS usage

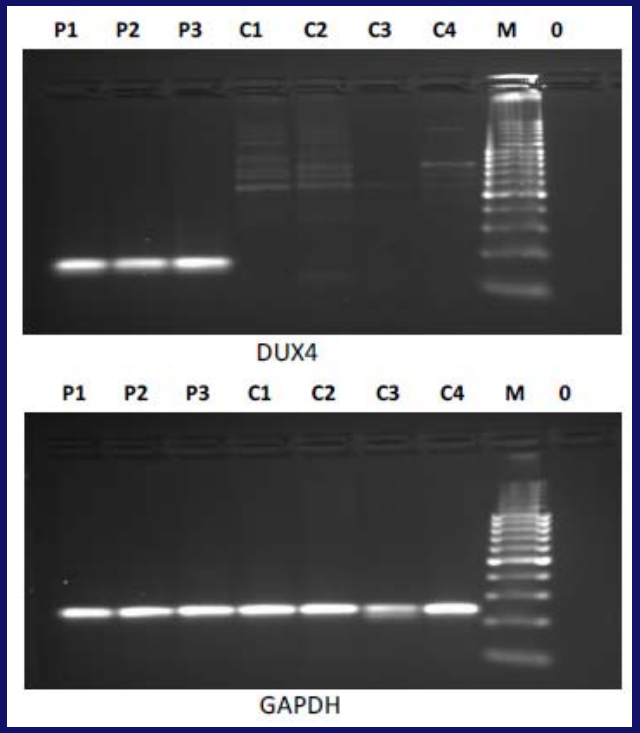




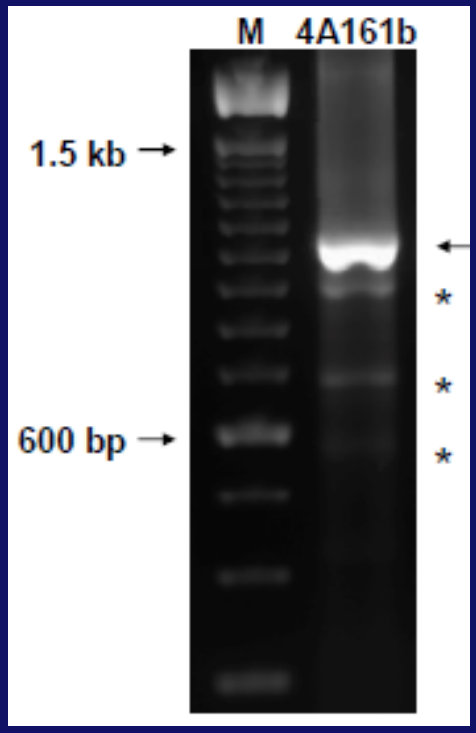
Toxic *DUX4* in D4Z4 is expressed in FSHD

(Dixit *et al.* 2007 and Snider 2009)



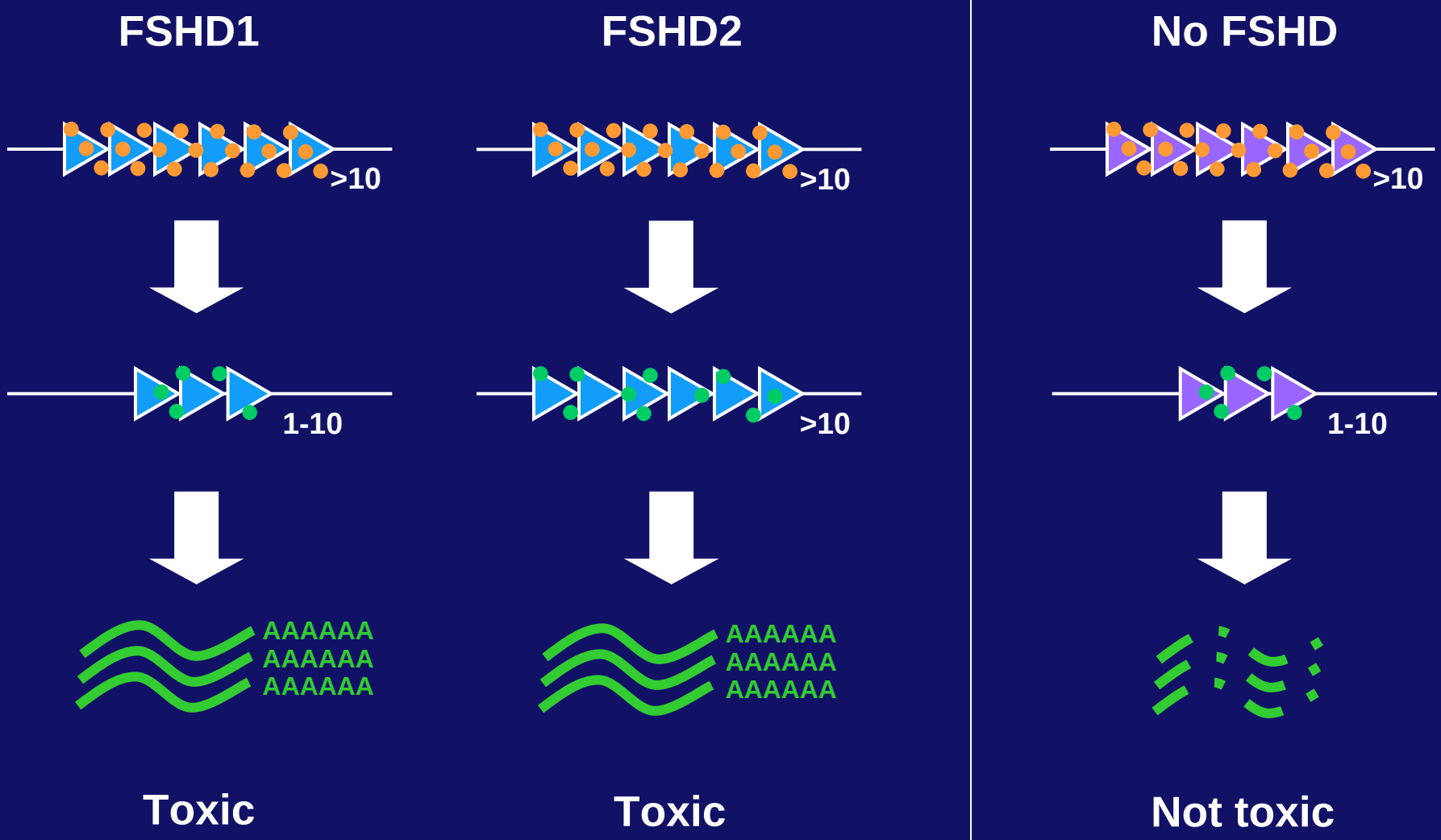


Toxic *DUX4* is expressed in FSHD muscle cells



usage of predicted PAS

The disease mechanism in FSHD



Importance

We have identified the target!

2008

2010

The New York Times

Science

WORLD | U.S. | N.Y. / REGION | BUSINESS | TECHNOLOGY | SCIENCE | HEALTH | SPORTS | OPINION

ENVIRONMENT | SPACE & COSMOS

Reanimated 'Junk' DNA Is Found to Cause Disease

By GINA KOLATA
Published: August 19, 2010

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The human genome is riddled with dead genes, fossils of a sort, dating back hundreds of thousands of years — the genome's equivalent of an attic full of broken and useless junk.

Science AAAS

Some of those genes, surprised geneticists reported Thursday, can rise from the dead like zombies, waking up to cause one of the most common forms of muscular dystrophy. This is the first time, geneticists say, that they have seen a dead gene come back to life and cause a disease.

"If we were thinking of a collection of the genome's greatest hits, this would go on the list," said Dr. Francis Collins, a human geneticist and director of the National Institutes of Health

BIOONNEWS

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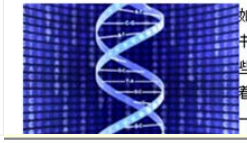
来源 新华网

2010-8-23 9:06:31

Science：一死亡基因的表达导致FSHD疾病发作

生物谷 加入收藏 【大 中 小】



如果将人类的基因组比喻成一本书，那么这本书的编排并非如有些人想象的那样精良，而是充斥着不少错漏，因为基因组中存在一些垃圾信息——人类长期演化

热点推荐

aerzteblatt.de

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Freitag, 20. August 2010

FSHD: Entfesseltes Gen löst Muskelschwäche aus

Leiden – Ein Forscherteam aus den Niederlanden und den USA hat die Pathogen fazioskapulohumeralen Muskeldystrophie (FSHD) weiter entschlüsselt. Ursache der Publikation in Science (2010; doi: 10.1126/science.1189044) die Reaktivier eines archaischen Gens.

Die Chromosomen sind nicht nur der Sitz des menschlichen Genoms. Sie sind a eine Müllgrube der Evolution, angefüllt mit Genen, die durch Mutationen ihre Fu eingebüßt haben oder einfach nicht mehr benötigt werden. Darunter sind auch die – wenn sie zum Leben erweckt würden – der Gesundheit schaden. Genau di scheint bei Menschen mit FSHD zu passieren.

QUEST
MDA'S Research & Health Magazine

MDA

Current Issue
July - Sept 2010
Table of Contents
Thursday August 19, 2010

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il POST

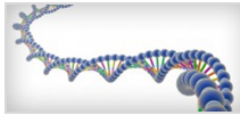
Lunedì 23 agosto 2010

ITALIA | MONDO | POLITICA | TECNOLOGIA | INTERNET | SCIENZA | CULTURA | ECON

A volte il DNA morto si rianima e combina guai

- Alcuni genetisti hanno scoperto un gene "zombie" che potrebbe essere la causa di una grave forma d distrofia
- Il gene si trova in un'area del DNA che si pensava non contenesse informazioni importanti

20 AGOSTO 2010 | SCIENZA



lavoro di ricerca potrebbero ora accele muscolare.

The Seattle Times | Health

Winner of a 2010 Pulitzer Prize

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Originally published Thursday, August 19, 2010 at 9:43 PM

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Revived gene linked to muscular dystroph

Identifying a new disease mechanism, geneticists have found that the reawakening of a ger or junk, DNA causes a common form of muscular dystrophy.

By GINA KOLATA
The New York Times

Identifying a new disease mechanism have found that the reawakening of a of seemingly useless, or junk, DNA c form of muscular dystrophy.

It is almost certain, experts say, that o will be found to have similar causes. also points the way, they say, toward treatment of this disease.

The human genome is riddled with s genes that have not been active for ag amount of the genome that has no kn this is the first time, geneticists say, that they have seen a dead gene come back to life and cause a disease.

"If we were thinking of a collection of the genome's greatest hits, this would go on the list," said Dr. Francis Collins, a geneticist and director of the National Institutes of Health (NIH).

2010-08-23 01:09:29

海外発表、オランダLeiden Universityら、筋ジストロフィーズムを解明、RNAが毒に

DNA DNA

米国立神経疾患脳卒中研究所(NINDS)は2010年8月 Leiden Universityらの研究チームが顔面肩甲上腕型筋 (FSHD)の筋損傷を引き起こすメカニズムについて論文 た。同研究は米国立衛生研究所(NIH)の助成を受けて 論文はScience誌上で発表された。

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続きを読む

U.S. Department of Health and Human Services

NIH News

National Institutes of Health

Embargoed for Release
Thursday, August 19, 2010
2 p.m. EDT

Not One But Two DNA Changes Are Needed to Cause FSHD

Two DNA changes on chromosome 4 — a contracted DNA segment and a "permissive" DNA signal — are needed to cause FSHD

Discovery opens door to therapeutic development for FSH muscular dystrophy

Scientists are closer to understanding what triggers muscle damage in one of the most common forms of muscular dystrophy, called facioscapulohumeral muscular dystrophy (FSHD).

FSHD affects about 1 in 20,000 people, and is named for progressive weakness and wasting of muscles in the face, shoulders and upper arms. Although not life-threatening, the disease is disabling. The facial weakness in FSHD, for example, often leads to problems with chewing and speaking.

The new research was funded in part by the National Institutes of Health and appears in the journal Science. Until now, there were few clues to the mechanism of FSHD and essentially no leads for potential therapies, beyond symptomatic treatments, said John Porter, Ph.D., a program director at NIH's National Institute of Neurological Disorders and Stroke (NINDS).

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Benefit Representatives of America Inc.

- David Penrose
- Peter Siracuse

Both of us previously worked for the Social Security Administration for a combined 25+ years of direct insider experience.

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SSA Benefits

- Retirement
- Disability
- Survivor(s)
- Medicare
- Supplemental Security Income-SSI

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Social Security Disability Benefits

- There are 2 separate programs that Social Security administers.
- Supplemental Security Income also know as **SSI**.
- Social Security Disability also known as **SSD**.

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How much work does a person need to qualify?

- Retirees must have 40 quarters of coverage (also referred to as points or credits).
- Disabled people must have 20 quarters of coverage within the last 40 quarters before becoming disabled. (5 years of steady work within the last 10 years)
- Survivor benefits- The number of credits needed varies with a persons age at the time of their death.

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Why is it so difficult to get approved for Social Security disability benefits?

Answer: It's due to the complexity and subjective nature of the program and the laws that govern it.

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Almost everyone is denied Social Security disability benefits when they first apply.

"From 1999-2008 the percentage of disability applicants awarded benefits at the initial level has averaged 28%. The final award rate after the appeals process averaged 45%.

Source: Chart 11 Annual Statistical Report on SSA Disability program

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To Qualify for SSD or SSI disability benefits you must meet Social Securities definition of disability.

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SSA'S Definition of Disability:

"For all individuals applying for disability benefits under Title II, and for adults applying under Title XVI, the definition of disability is the same. The law defines disability as the inability to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment(s) which can be expected to cause death or which has lasted or can be expected to last for a continuous period of not less than 12 months. "

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The disability application process and what is really involved.

-Initial Application (70% Denial Rate)
-Reconsideration
-Hearing by Administrative Law Judge
-Appeals Council Review
-Federal District Court

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5 Step Sequential Evaluation Process

Step 1) Is the individual currently engaging in SGA?

Step 2) Does the individual have any severe impairment(s)?

Step 3) Does the individual have any impairment(s) which meets or equals the listing?

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Step 4) Does the individual have any impairment(s) which prevents past relevant work?

Step 5) Does the individual's impairment(s) prevent other work? This last step considers your age, education, and work experience.

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The Appeals Process

-Hearing with Administrative Law Judge

-Appeals Council Review

-Federal District Court

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The Hearing

The average waiting time to get to a hearing in Upstate NY is 18 months.

What's involved at the hearing?

The claimant, the judge, v.e.'s, m.e.'s witnesses, representative, sworn testimony, medical records, briefs, exhibits, claim file, etc.

What should be done to prepare before the hearing?

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You have a right to representation!

Why should you have a representative?

-Greatly increases your chance of approval.

What will my representative do?

-Complete all paperwork for you.

-Help obtain medical records/documents.

-Prepare written hearing brief for the judge.

-Attend hearing with you and represent you in front of the administrative law judge.

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When do my SSD benefits begin?

-Must serve a 5 month waiting period.

-If approved you may be paid retroactively back to the date of your application or up to 1 year before that.

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Medicare Health Insurance

Who is eligible for Medicare?

* 65 or older or
* Receiving Social Security Disability benefits for 2 full years or
* Permanent kidney failure (ESRD) or
* Lou Gehrig's Disease (ALS)

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3 Parts to Medicare

- **Part A**- Hospitalization Coverage
  - Usually no charge

Part B- Supplementary Medical Ins.
- $93.50 monthly premium for 2007

Part D- Prescription Drug Plan
- Cost varies with each provider

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How do I apply for benefits?

- Go into the local SSA office and make an appointment or
- Apply online at SSA.GOV or
- Call SSA at 1-800-772-1213 or
- Call us at 585-663-8071

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Developing a Treatment for FSHD: Understanding the Process

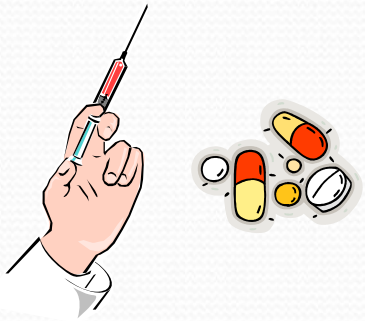
Rabi Tawil, MD

3rd Fields Center Patient Day

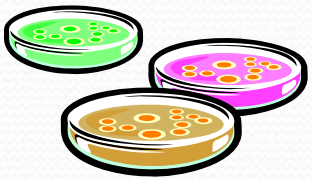
September 18, 2010

Find Gene

Find out what it Does



Screen Drugs/Treatment



CLINICAL TRIALS

Stages of Clinical Trials in Humans

- Phase I: First stage of testing new drug/treatment in humans; healthy human volunteers
  - Determine that the drug is safe
  - Determine the maximum tolerable dose
  - This phase can be skipped if the drug is FDA (Food and Drug Administration) is already approved

Stages of Clinical Trials in Humans

- Phase II: Determine that the drug is safe and tolerable in patients with the disease under study
  - Typically a short trial with small numbers of study subjects needed
  - The investigators hope to see some signs that the drug is effective

Example of a Phase II Study : MYO-029

- Recruited about 40 patients with FSHD:
  - 10 received placebo
  - 30 divided into groups of 10, each received a different dose of MYO-029
- Even though the drug proved to be safe, Wyeth chose not to go to a phase III study because there were no signs of benefit from the drug.

Stages of Clinical Trials in Humans

- Phase III: Study to determine if the drug is effective
  - Double blind and placebo controlled:
    - A fraction of the study subjects take placebo
    - Neither the study subjects nor investigators know who is taking active drug or placebo

Getting a Treatment Approved

- Need FDA approval to get drug on the market
- FDA approval requires:
  - Two positive phase III trials
  - For rare diseases (like FSHD), FDA may accept a single convincing positive phase III trial

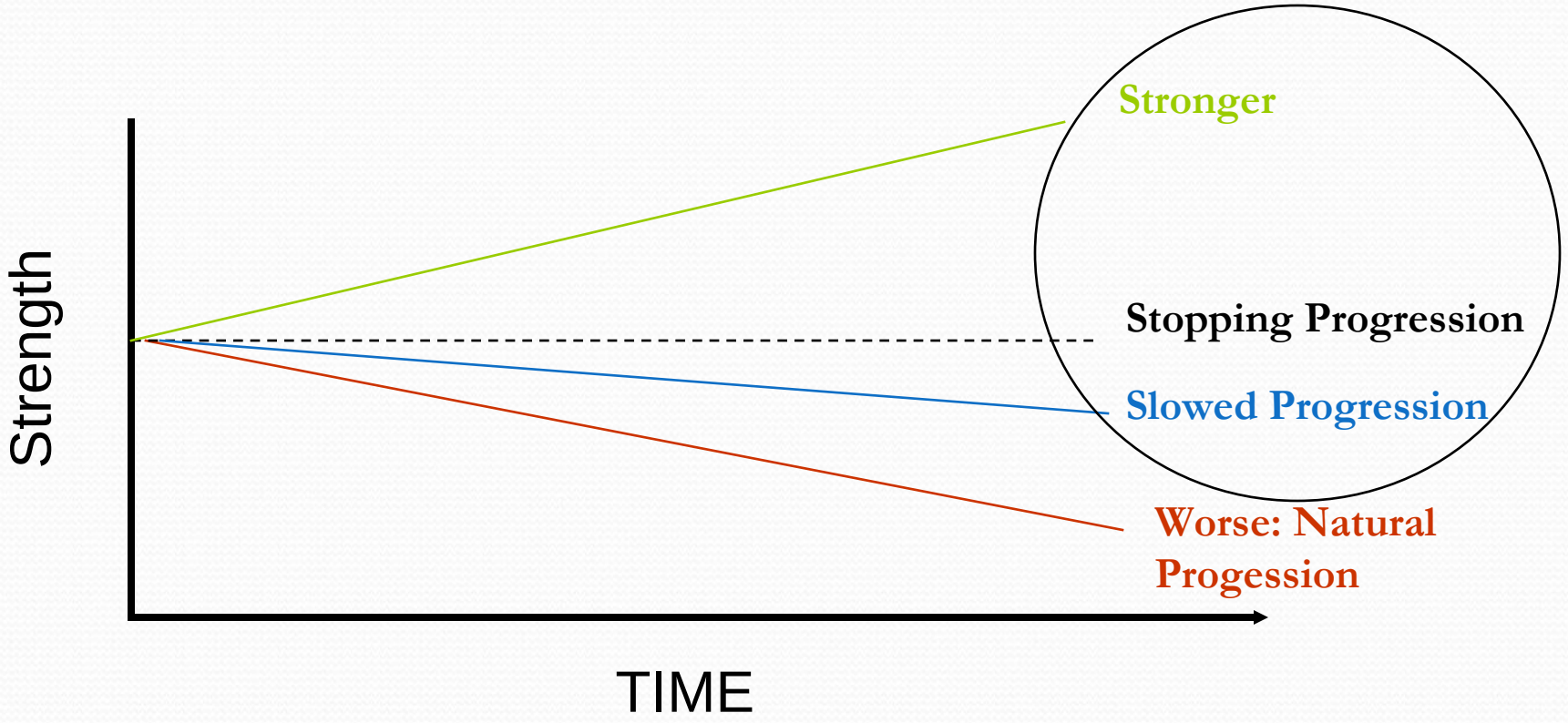
How do you show that a drug works?

- Need to show directly or indirectly that muscle function improves with treatment
- Outcome measures:
  - Direct measure of muscle strength
  - Functional measures: how fast you can run 30 feet, climb stairs, etc.
  - Indirect measures: increased muscle mass, improved muscle appearance under the microscope

How do you show that a drug works?

- Outcome measures:
  - FDA requires that the outcome measures be "clinically relevant":
    - Showing that strength measurements went up by 10% is not necessarily clinically relevant
    - Showing that a treatment made someone able to get up from a chair without using their arms when they couldn't before treatment is a clinically relevant outcome measure

What is a positive outcome?



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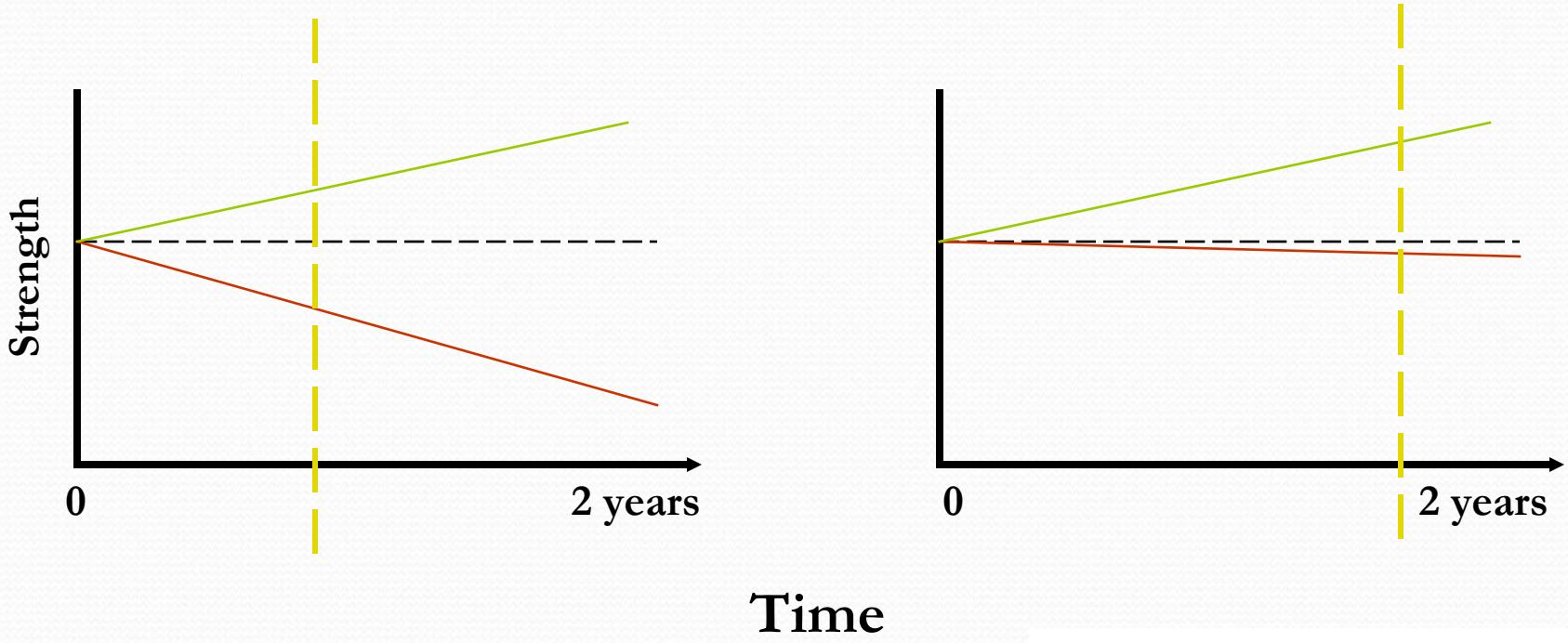
Challenges in FSHD Trials



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Components of a Successful Trial

- You need to know how fast the disease progresses:
  - Determines how long a study should be
  - Determines how many patients are needed
- You need appropriate outcome measures **In Progress**
  - Sensitive and clinically relevant measures
- Need access to patients

AND

- You need a drug that works **In Progress**

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University of Rochester Medical Center

LUMC Leiden University Medical Center

Home Care versus Care in the Community

Debra Guntrum MS, FNP

Nurse Practitioner

Neuromuscular Disease Center

University of Rochester

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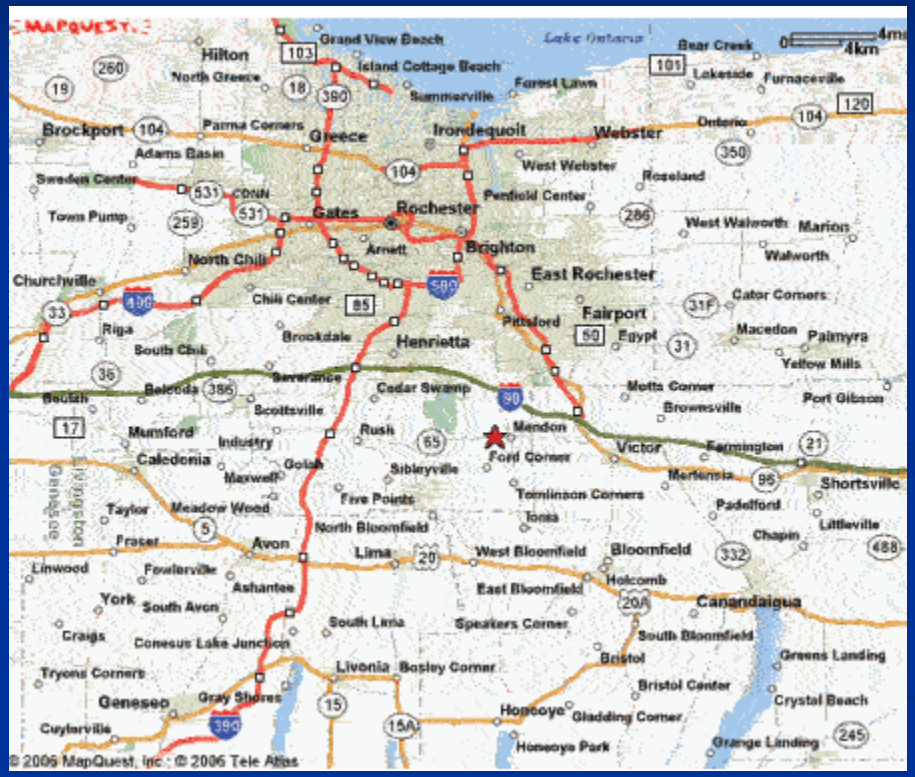

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What is Community Care?

- Medical care in the community that the patient transports him or herself to.
- Physical therapy
- Occupational therapy
- Speech therapy
- Orthotics
- Medical appointments

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What is Home Care?

- Care provided in the home by health care professionals
- Physical therapy
- Occupational therapy
- Speech therapy
- Nursing care

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Definitions

- Activities of Daily Living (ADLs): Bathing, dressing, using the toilet, eating, walking (ability for self care).
- Instrumental Activities of Daily Living (IADLs): Light housework, meal preparation, taking medication, shopping for food or clothes, using the phone, managing money (ability to live independently in the community.

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Resources

- www.medicare.gov
- www.medicare.org
- www.nahc.org (National organization for Home Care and Hospice)
- www.cdc.gov
- www.cms.gov (Centers for Medicare and Medicaid Service)

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How does your care provider decide between home care and community care?

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Community Care

- You are able to get to and from appointments easily.
- You require use of the specialized equipment that an outpatient physical or occupational therapy office has.
- There is a specific problem or goal to the therapy (gait training, strengthening, bracing, pain management)

- Community care is time limited.
- Insurance policies often cap the number of visits allowed.
- There is usually a copay involved.

Home Care

- According to Medicare guidelines (most insurances follow these guidelines), your must be homebound to receive care in the home.

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Definition of Homebound

- Leaving the home is a major undertaking and person is unable to leave the home unassisted.
- Person leaves their home only for medical appointments or for short, infrequent non-medical reasons.
- Person is in need of skilled nursing or rehab staff to manage, observe, and evaluate your care.

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Examples

- We often refer physical therapy to the home to evaluate for safety and equipment needs in the home. Physical therapy can also work on and teach transfers in the home. They can review home exercises and range of motion exercises.
- We would refer nursing to monitor wounds, for medication or disease teaching, to care for IV lines or feeding tubes.

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- Occupational therapy can assist with activities of daily living in the home.
- A home care case has to be opened and managed by either a nurse or a physical therapist.
- Once a nurse or physical therapist is not longer needed in the home, the case is closed.

- Insurance will not pay for on going personal care or custodial care (nonskilled personal care).
- Insurance will not cover 24 hour care in the home. Coverage allowances vary by insurance policies and what is determined as needed by the home nurse or home physical therapist.
- There is often a copay involved.
- There is often a cap on the number of visits allowed.

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Options to Supplement Home Care

- Family or friends
- Private pay for additional help
- Consider moving to a higher level of care

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Cost of Home Care

- Average cost for home care in the U.S. for 2009
- $198 per day in a semi private nursing home room
- $219 per day in a private room in a nursing home
- $3,131 per month in an assisted living facility
- $21 per hour for a certified home health aide
- $19 per hour for homemaker services
- $30-55 per hour for a registered nurse

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References

- www.medicare.gov
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- www.nahc.org (National organization for Home Care and Hospice)
- www.cdc.gov
- www.cms.gov (Centers for Medicare and Medicaid Services)
- www.longtermcare.gov

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<u>Kees van der Graaf</u>
Founder FSHD Foundation (1997)
Co-founder FSHD Europe Foundation (2009)

September, 2010

First, the good news: a scientific breakthrough!

FIELDS Canadian Mathematical Research CENTER

Sciencexpress Report

A Unifying Genetic Model for Facioscapulohumeral Muscular Dystrophy

Richard J. L. F. Lemmers,[1] Patrick J. van der Vliet,[1] Rinse Klooster,[1] Sabrina Sacconi,[2] Pilar Camaño,[3,4] Johannes G. Dauwerse,[1] Lauren Snider,[5] Kirsten R. Straasheijm,[1] Gert Jan van Ommen,[1] George W. Padberg,[6] Daniel G. Miller,[7] Stephen J. Tapscott,[5] Rabi Tawil,[8] Rune R. Frants,[1] Silvère M. van der Maarel[1]*

U.S. Department of Health and Human Services
NIH News
National Institutes of Health

National Institute of Neurological Disorders and Stroke (NINDS)

Embargoed for Release
Thursday, August 19, 2010
2 p.m. EDT

Contact:
Daniel Stimson, NINDS
301-496-5751

Discovery opens door to therapeutic development for FSH muscular dystrophy

Scientists are closer to understanding what triggers muscle damage in one of the most common forms of muscular dystrophy, called facioscapulohumeral muscular dystrophy (FSHD).

FSHD affects about 1 in 20,000 people, and is named for progressive weakness and wasting of muscles in the face, shoulders and upper arms. The facial weakness in FSHD often leads to problems with chewing and speaking. Most people with FSHD have a normal life span, but in some cases, weakness spreads to the diaphragm and causes respiratory problems.

Wassenaarder Van der Graaf: 'Nu doorpakken!'

Succes in strijd tegen spierziekte FSHD

door Sonja van Gerven

Patiënten met de erfelijke spierziekte FSHD hebben een stukje van chromosoom 4. Dit was al langer bekend, maar de vraag was hoe dit tot verlies van spierweefsel leidt. Onderzoekers van het Leids Universitair Medisch Centrum (LUMC) hebben samen met collega's van het Fields Center (Rochester-Leiden-Seattle) en UMC St. Radboud Nijmegen de oorzaak gevonden; een enorme doorbraak in de strijd tegen FSHD. Hun bevindingen staan in het toonaangevende, wetenschappelijke tijdschrift 'Science' van 19 augustus. De publicatie heeft internationaal zeer veel lovende reacties gekregen.

De FSHD stichting uit Wassenaar heeft het onderzoek mede mogelijk gemaakt. Voorzitter Kees van der Graaf: "Wij feliciteren het Leids Universitair Medisch Centrum met

De stichting werft fondsen voor het stimuleren, faciliteren en financieren van het wetenschappelijk onderzoek naar de oorzaken en achtergronden van FSHD, om zo genezingswijzen te ontdekken die de kwaliteit van leven van FSHD-patiënten kunnen verbeteren. FSHD (facio scapulo humerale spierdystrofie) is een van de meest voorkomende, erfelijke spierziekten ter wereld: 1 op de 20.000 mensen lijden aan deze ziekte. De ziekte komt wereldwijd bij ongeveer 300.000 mensen voor. Vaak treden de eerste symptomen rond het 20e levensjaar op, maar ook kinderen kunnen het krijgen. De ziekte uit zich in een progressief verlies van spierkracht in vooral het gezicht, de bovenarmen en bovenbenen. Erg aangedane patiënten kunnen volledig rolstoelafhankelijk worden.

Veel steun nodig

Kees van der Graaf: "De FSHD stichting heeft met haar 'roadmap

hebben hierbij veel steun nodig". De FSHD stichting heeft LUMC afgelopen jaren ondersteund met AIO- en postdoc financiering, de organisatie van seminars, (mede) financiering van onderzoeksprojecten alsook door het verstrekken van garantiesubsidies.

Onderzoeksleider prof. dr. Silvère van der Maarel van de LUMC-afdeling Humane Genetica: "Deze doorbraak is mede te danken aan de steun die de FSHD stichting heeft gegeven. De stichting is altijd bereid in te springen, zelfs bij te bieden en pilotstudies te financieren, waardoor ons team kan doorgaan. Nu weten we de oorzaak en kunnen we proberen om de ziekte te behandelen door het specifieke gen uit te schakelen. Dit gaat zeker niet van vandaag op morgen. Er is nog veel geld en tijd voor onderzoek nodig, voordat we de patiënten een therapie kunnen aanbieden". Meer info. op www.fshd.nl.

FSH Society Applauds Study Pinpointing Genetic Causes of FSHD, Most Common Muscular Dystrophy

FSHD Foundation

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- **Founded in 1997 by Kees and Renée van der Graaf, parents of a son that suffers from FSHD**

- **Our goal is to stimulate, facilitate and financially support solid scientific research into the causes of FSHD, in order to find treatments and develop solutions that help improve patients' quality of life**

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FSHD Foundation

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- Our Executive committee consists of a small group of highly motivated volunteers that in their daily lives are engaged in business or science

- The committee is assisted by members of the FSHD patients' association, medical and biochemical specialists and experienced directors and managers

- The FSHD foundation closely cooperates with the VSN (patients' organisation), the Princess Beatrix Fund, and the American FSH Society

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FSHD Foundation - Fundraising

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- **Our added value lies in the fact that we can financially support small (pilot) projects seen as important for our overall strategy, and that are not easily funded through other sources**

- **To do this, we generate around €200.000 per annum through our own fundraising activities. In addition, we continue to do our best to find sponsors for the bigger and more comprehensive projects**

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Co-founding FSHD Europe

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Last year, the FSHD Foundation joined forces with 3 other local FSH organisations to set up FSHD Europe, to better represent the needs of people with FSHD.

Our goals:

- **Raise awareness and understanding of FSHD at European level (EU Advisory Committee for rare diseases)**
- **Stimulate more FSHD funding & research, concentrated on finding a cure, and setting up appropriate care and support programmes**
- **Promote the creation of a European patient registry**
- **Work with local governments & dystrophy organizations**
- **Share best practise in care, welfare, support and diagnostics for people with FSHD and their families**

FSHD Foundation – our vision and strategy

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- **Given the complexity of FSHD, we believe that a multidisciplinary and integrated approach, whereby each research project is part of a bigger plan, will multiply the chances of success**

- **Together with leading scientists in FSHD, we have formulated a comprehensive research strategy that looks at key research areas that are seen to be crucial in FSHD Research.**
  We call this strategy our Roadmap to Solutions

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FSHD Foundation – Roadmap to Solutions

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- **Our first Roadmap (2003-2007) focused on 7 important projects:**

- Fatigue (calcium regulation and mitochondria)
- Oxygen damage
- Epigenetics
- System Biology
- Database systems
- Non-invasive techniques
- FRG1 and expression in FSHD patients

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FSHD Foundation – Roadmap to Solutions

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- These projects led to the following achievements:
  - a large project on mitochondria was funded by the Dutch Ministry of Economic Affairs
  - the University of Montpellier (France) was able to find indications of oxygen damage in muscle tissue and blood components in FSHD patients
  - we got a better understanding of the mechanisms of epigenetics, specifically the role of methylation on gene expression, chromatin and myoblasts
  - the update and completion of the Nijmegen (Holland) databank of FSHD patients

FSHD Foundation – Roadmap to Solutions

FIELDS FSHD & Neuromuscular Research CENTER

- These projects led to the following achievements (2):
  - considerable progress and ongoing studies in the area of non-invasive techniques
  - Evidence that FRG1 (protein) plays an important role in the development of FSHD

- In the period 2003-2007 the FSHD Foundation donated nearly €1 mln to Roadmap projects. Also, significant funds from governmental organisations were channelled towards FSHD Research through our intervention

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FSHD Foundation – Roadmap 2007-2011

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- **In November 2007 the FSHD Foundation organized a second scientific symposium to discuss the most recent scientific developments, and develop its research strategy (roadmap) for the next 5 years**

- **It was decided that next to continuous support of research that will increase our understanding of the causes of FSHD, our Roadmap should also focus on studies that can improve the day to day quality of life of FSHD patients**

FSHD Foundation – Roadmap 2007-2011

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Our 2007-2011 Roadmap focuses on 6 projects:

1. **follow-up studies on aerobic training and fatigue**
2. **new comprehensive bioinformatics analysis**
3. **continued studies on the effects of oxygen damage and inflammation in FSHD**
4. **studies on the changes in the chromatin structure which may lead to therapeutic solutions for patients**
5. **bringing together European stakeholders to discuss international standards for clinical and molecular diagnosis and procedures for treatment and care**

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FSHD Foundation – Roadmap 2007-2011

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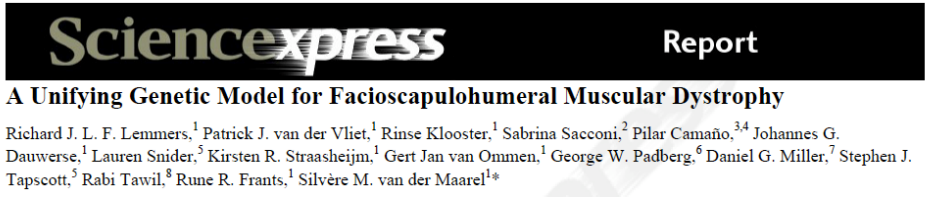
Our 2007-2011 Roadmap focuses on 6 projects:

6. **Studies on FRG1 and DUX4 (the 2 most promising 'candidate genes' in the cause and expression of FSHD). The recent scientific breakthrough/publication in Science was a direct result of ongoing support and funding of pilot studies by the FSHD Foundation**



Sciencexpress Report

A Unifying Genetic Model for Facioscapulohumeral Muscular Dystrophy

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In addition, a project on angio-mesoblasts was added to our Roadmap

FSHD Foundation – looking at the future

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- **Need to refocus research from understanding the genetic mechanism to developing a cure and treatment for patients**

- **Trial readiness: need to develop a good international patient registry as soon as possible**

- **Funding, funding, funding!**

- **A stronger voice from the people with FSHD**

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European Voice of People With FSHD

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www.fshd.nl

www.fshd-europe.org

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MDA®

Muscular Dystrophy Association

Services for the Individual, Family & Community

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MDA®

MDA is a voluntary health agency - a dedicated partnership between scientists and concerned citizens aimed at conquering neuromuscular diseases that affect more than a million Americans.

MDA covers over 40 neuromuscular diseases whose conditions vary in age of onset, rate of progression and the muscle groups affected.

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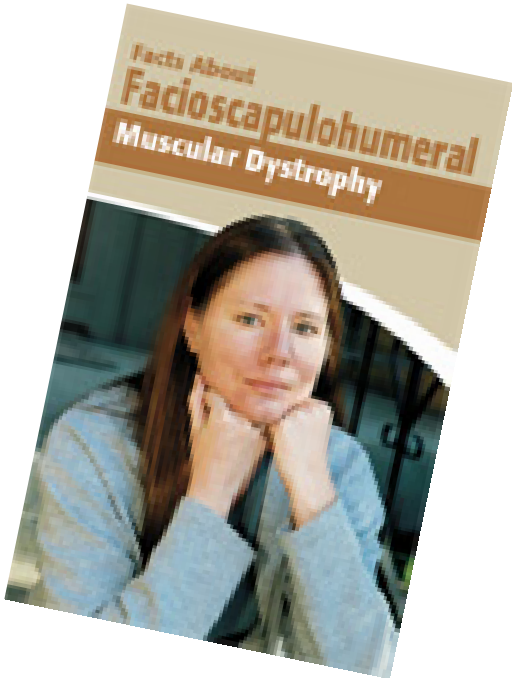
MDA®

MDA works in the community to combat neuromuscular disease by (1) supporting basic and clinical scientific research, (2) offering a comprehensive program of clinical care and support services to individuals and their families, and (3) providing widespread professional and public health education.

MDA is the largest non-governmental supporter of muscle research in the world.

Programs available through local MDA offices are funded entirely by individuals and private contributors. The Association receives no government grants.



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Providing hope for the future through
Worldwide Research

and help for today through
Essential Services . . .

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Hope through Worldwide Research

MDA directs over $34 million toward research, more than any other private-sector organization in the world, seeking causes of, and cures and treatments for, neuromuscular diseases.

Through MDA, some 350 research projects are funded annually.

MDA-funded scientists are in the forefront of gene therapy research and are testing potential treatments for several neuromuscular disorders.

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Help through Assistance

Nationwide Clinic Network

Support- Equipment

Support- Emotional

Community Connections

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MDA's Nationwide Clinic Network

MDA supports some 235 hospital-affiliated clinics through a block-grant funding arrangement.

MDA provides block grants to institutions to provide selected medical services that may otherwise be cost prohibitive for families served by MDA.

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MDA's Nationwide Clinic Network

MDA clinics are staffed by teams of top health professionals skilled in the diagnosis and medical management of neuromuscular diseases.

Such management ranges from measures for controlling symptoms to medical intervention designed to assist individuals in maintaining the highest possible quality of life.

Annual flu shots, and consultations such as physical, occupational, respiratory and speech therapy may also be provided.

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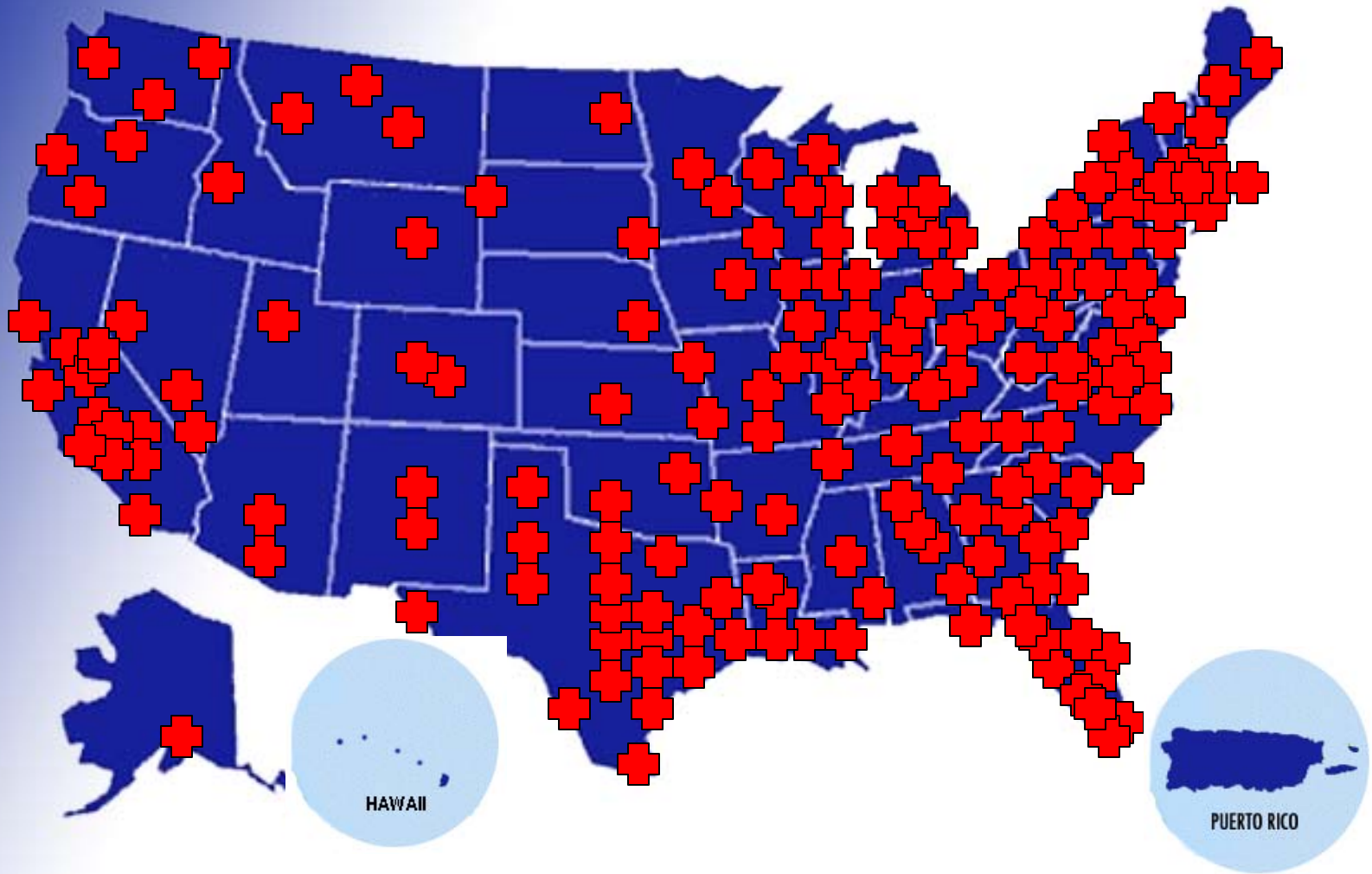
MDA's Nationwide Clinic Network



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Equipment Loan and Repairs

Medical equipment loan closets are available through local MDA offices and are a vital part of MDA's program for individuals with neuromuscular disease who have no alternative resources for such equipment.

Types of equipment available for loan often include hospital beds, lift chairs, walkers, respiratory equipment and much more.

Each MDA registrant receives a $500 annual equipment repair budget.

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Support and Education

Support Groups & Seminars

MDA offers some 290 support groups nationwide to assist individuals and their families in coping with neuromuscular diseases.

Support groups provide valuable emotional support and practical help. It's MDA's goal to ensure this service is available to as many people as possible.

In addition, MDA chapters nationwide coordinate educational seminars for health professionals and those served by the Association.

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Virtual Support

myMDA

MDA's website features scheduled "chat rooms" on a number of topics ranging from living with ALS to chats for kids and young adults. These online forums are an excellent way for people to communicate to others affected by similar neuromuscular diseases or to obtain valuable information about MDA's services and research developments.

Chats are a particularly valuable resource to those who cannot or are reluctant to attend physical gatherings.

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Websites

www.mda.org ◆ www.als-mda.org

MDA's award-winning website is packed with over 12,000 pages of information about neuromuscular disease, research, MDA's services, locating a local MDA office or clinic, publications, and much more.

MDA's website is also available in Spanish at www.mdaenespanol.org.

MDA®

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Publications

- MDA Services
- Recent Research Developments
- Quest Magazine
- MDA/ALS Newsmagazine
- MDA Fact Sheet
- “Facts About” disease booklets
- A Parent’s Guide
- MDA Summer Camp

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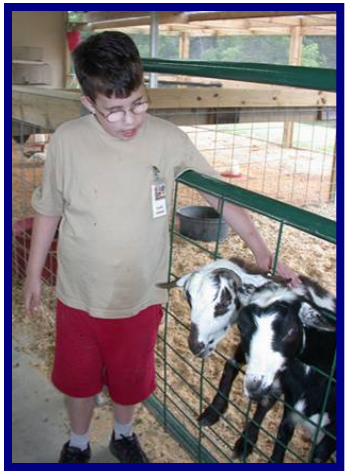
MDA's Nationwide Summer Camp Program

Each year MDA sponsors nearly 90 summer camps offering a wide range of activities to some 4,200 youngsters affected by neuromuscular disorders.

Activities are geared to the abilities and needs of MDA campers and may include adapted outdoor sports such as fishing, swimming, horseback riding, and boating.



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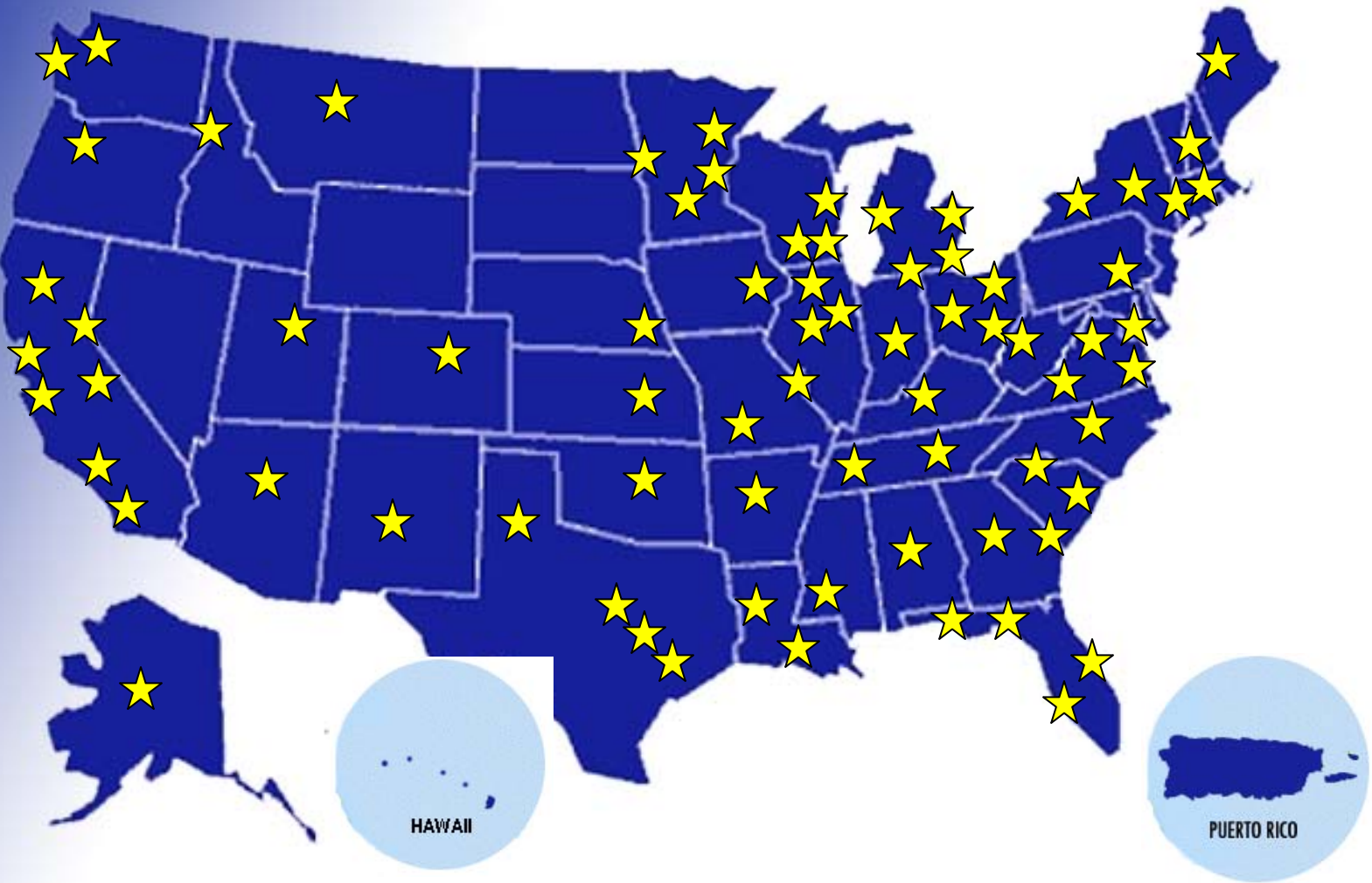
MDA’s Nationwide Summer Camp Program



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Help through Advocacy

In any moment of decision,
the best thing you can do is the right thing.
The worst thing you can do is nothing.

~Theodore Roosevelt

Muscular Dystrophy Association

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MDA®

Advocacy Made Easy…

Websites simplify the issues

Reach decision makers at the click of a button

Schedule the time to stay informed!

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Current Advocacy Issues

On MDA's Advocacy Radar:

-ABLE Act of 2009

-Competitive Bidding Repeal Act

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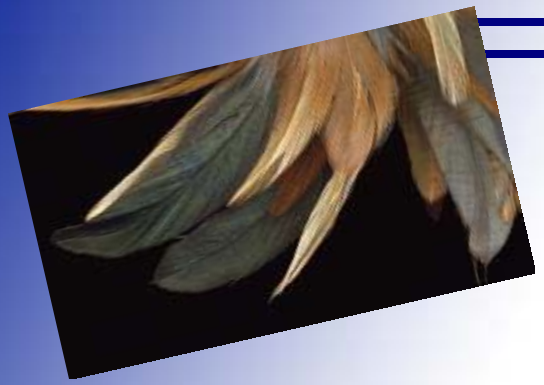
Help through Attitude



The meaning of things lies not in the things themselves, but in our attitude towards them.

-Antoine de Saint-Exupery

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Thank you *to the*

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and guests for the opportunity
to share this day with you.

-Susan Staples

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Taking Care of Yourself A Physical Therapists Perspective

Katy Eichinger, PT, DPT, NCS
Department of Neurology
University of Rochester Medical Center

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Health and Wellness

Health is a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity. ~World Health Organization, 1948

Wellness is an active process through which people become aware of and make choices toward a more successful existence. ~ National Wellness Institute

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General Recommendations

- Regular check-ups
- Medications
- Nutrition
- Exercise
- Rest

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Health and Wellness Concerns with FSHD

- Pain
- Fatigue
- Exercise

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Pain

- Several studies in which >50 percent of patients report pain
- Low back and legs
- Multiple causes of pain

Pain Management

- Maintain a log
- Medications
- ROM/Exercise
- Modalities
- Bracing

Fatigue

- "Overwhelming sense of tiredness, lack of energy and feeling of exhaustions…" (Krupp 2003)
- 139 patients surveyed: 61% report severe fatigue (Kalkman 2005)
- Causes/mechanisms not well understood
- Exercise (aerobic training) and energy conservation may be beneficial

Energy Conservation

- Daily routine
- Use of assistive devices and powered mobility

Exercise

- Limited literature
- Moderate intensity strength training and aerobic training safe
- Exercise programs need to be individualized

Exercise Recommendations

- Based on consensus
  - Active lifestyle
  - ROM
  - Moderate intensity strength training
  - Moderate intensity aerobic training

The "Four S Approach" to Managing FSHD

John T. Kissel, MD
The Ohio State University

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3rd Annual Fields
Center Patient Day
September 18, 2010

Disclosures

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- Receive grant support from Alexion for a clinical trial in myasthenia gravis
- Consulted for Genzyme, Alexion, and Acceleron
- Receive medication from Abbot Labs for clinical trial of VPA in SMA
- Will mention off label use of drugs

Therapy of FSHD
Objectives

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- Present framework for approaching FSHD therapy & management – "Four S's"
  - Doctor to patient…and patient to doctor!
- Present selected topics in treating important aspects of FSHD
- Outline general thoughts on providing therapy and support for patients
  - Counseling patients and families

Treating the "Untreatable"

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"I treat all of my patients. Some of them I have nothing to offer, but I **treat** them all."

Nicholas Vick, MD

August,1976

Therapy in FSHD

Case Presentation

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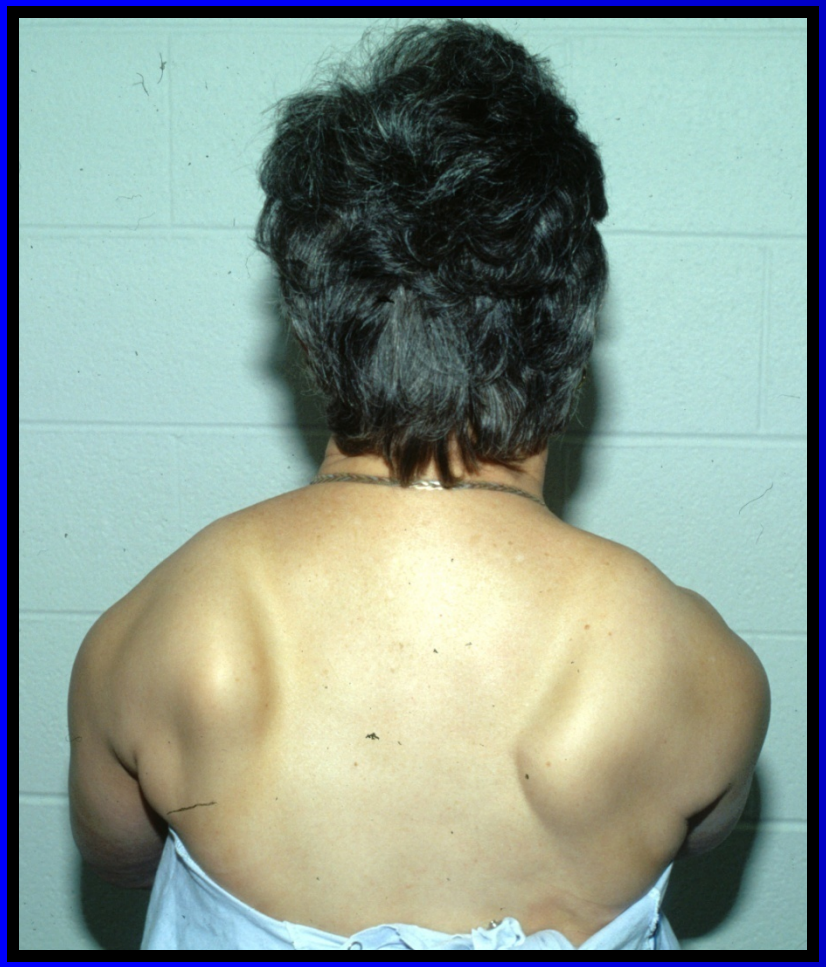

43 yo WF – fell at work

- Progressive scapular winging; can't lift arm to mouth; functional decline
- DNA + for FSHD
- She wants help!!
- What do we do?

Therapy of FSHD

The Four S's

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1. **Strength** Therapy
(eg. Prednisone in DMD)

4. **Solid Information**
(eg. counseling & genetic info)

2. **Symptomatic** Therapy
(eg. vision, hearing)

3. **Supportive** Therapy
(eg. bracing, surgery)

FSH Dystrophy

Overview

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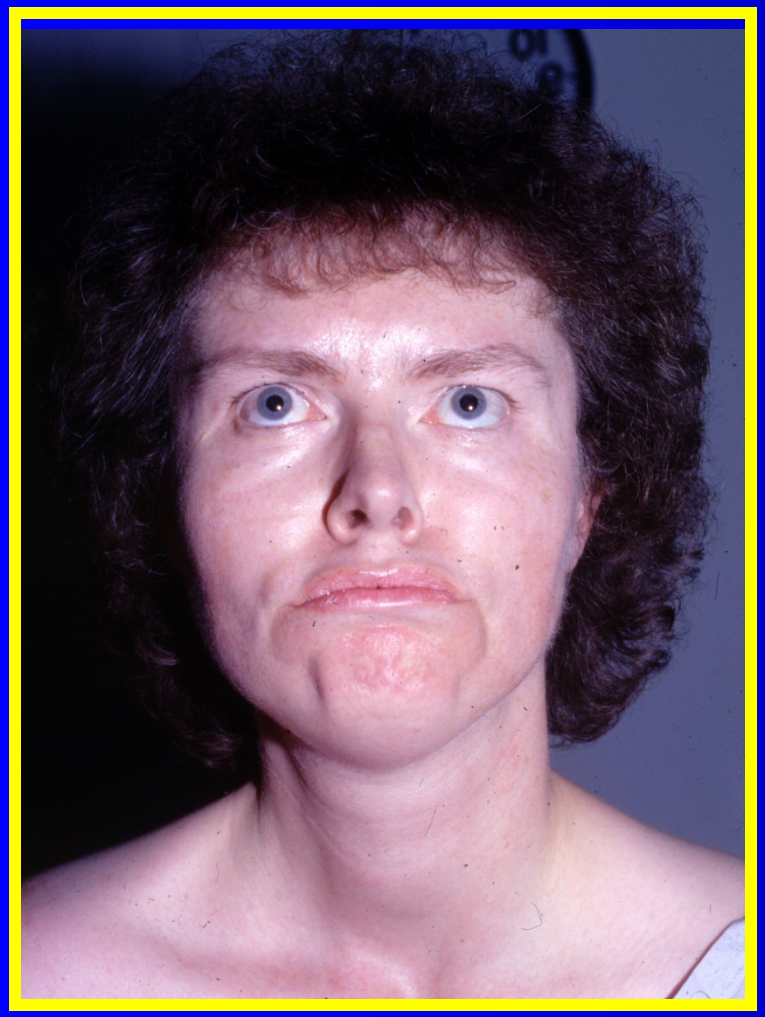

- AD; prevalence 1:20,000
- Sx. begin < age 20
  - 20% need WC
- Variable deletion in 3.3 kb repeat sequence at 4q35
  - Short fragment in 95%
  - Inv. corr. with severity
- Gene and pathogenesis still ? (inc. DUX4 gene)
- No strength therapy yet; neg Myo29 study major disappointment!

Sciencexpress Report

A Unifying Genetic Model for Facioscapulohumeral Muscular Dystrophy

Richard J. L. F. Lemmers,[1] Patrick J. van der Vliet,[1] Rinse Klooster,[1] Sabrina Sacconi,[2] Pilar Camaño,[3,4] Johannes G. Dauwerse,[1] Lauren Snider,[5] Kirsten R. Straasheijm,[1] Gert Jan van Ommen,[1] George W. Padberg,[6] Daniel G. Miller,[7] Stephen J. Tapscott,[5] Rabi Tawil,[8] Rune R. Frants,[1] Silvère M. van der Maarel[1]*

- **Paper published 8/19/10** in *Science*:
- In addition to DNA deletion in D4Z4 region, a DNA variant containing a polyadenylation signal is required for FSHD symptoms
- This fragment (also on chromosome 4) stabilizes otherwise fragile RNA transcripts
- Signal makes it possible for 1 or more toxic proteins to be produced

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Strength Therapy in FSHD

Clinical Drug Trials

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Author	Year	Agent	N	Weeks	EFFECT
Tawil	1997	Prednisone	8	12	NS
Walter	2000	Creatine	12	8	NS
FSH-DY	2001	Albuterol	90	52	NS
Van der Kooi	2004	Albuterol Exercise	65	26	NS
Elsheikh	2005	Diltiazem	20	24	NS
Payan	2009	Salbutamol	112	24	NS

Strength Therapy – Exercise ?

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- Does exercise training (strength or aerobic)
- Improve muscle strength, and/or
- Benefit cardiorespiratory function, and/or
- Prevent disuse atrophy, and/or
- Improve overall well-being (QOL)

OR

- ***Accelerate*** muscle breakdown, disease progression and weakness?
  - ? Overuse syndrome

Strength Training
van der Kooi et al, 2004

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Strength training and albuterol in facioscapulohumeral muscular dystrophy

E.L. van der Kooi, MD; O.J.M. Vogels, MD, PhD; R.J.G.P. van Asseldonk; E. Lindeman, MD, PhD; J.C.M. Hendriks, PhD; M. Wohlgemuth, MD; S.M. van der Maarel, PhD; and G.W. Padberg, MD, PhD

- RCT of 65 patients randomized to train (EF, ADF) for one year; albuterol added after 26 wks.
- 1º outcome change in MVIC at 52 weeks
- No effect of training on EF isometric strength (MVICT)
  - + effect on EF dynamic strength
- Slight albuterol effect in 11/12 untrained muscles

Aerobic Training
Olsen et al, 2005

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Aerobic training improves exercise performance in facioscapulohumeral muscular dystrophy

Abstract—Exercise programs have been shown to increase strength and endurance in patients with myopathic disorders. The authors investigated the effect of aerobic training in patients with facioscapulohumeral dystrophy (FSHD). Twelve weeks of low-intense aerobic exercise improved maximal oxygen uptake and workload with no signs of muscle damage. The authors conclude that aerobic training is a safe method to increase exercise performance in patients with FSHD.

NEUROLOGY 2005;64:1064–1066

David B. Olsen, MD; Mette Cathrine Ørngreen, BS; and John Vissing, MD, PhD

- 8 FSHD patients age 18-55; 7 normal controls
- 12 weeks of 65% VO2 max aerobic exercise on bicycle ergometer; 35 min sessions 5x per week
  - HR monitor & patient diaries
- Muscle biopsies done pre/post-exercise in 6
- CK, QOL, monitored

Aerobic Training
Olsen et al, 2005

- VO2 max up by 16%
  - 13% in normals
- Max work up by 17%
- QOL “generally improved”
- No change in HR, CK, histology, capillary density; no signs of overuse!
- Adherence to regimen 95%
- No information on patient follow up with exercise

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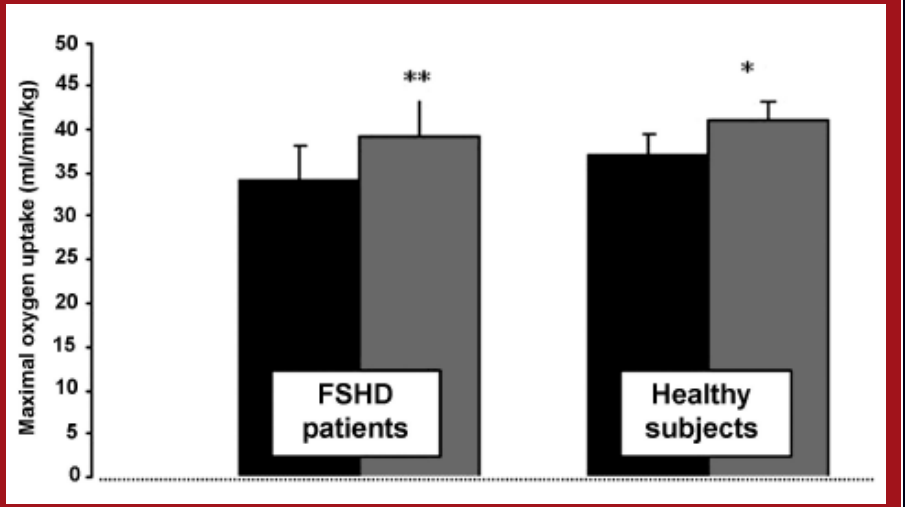
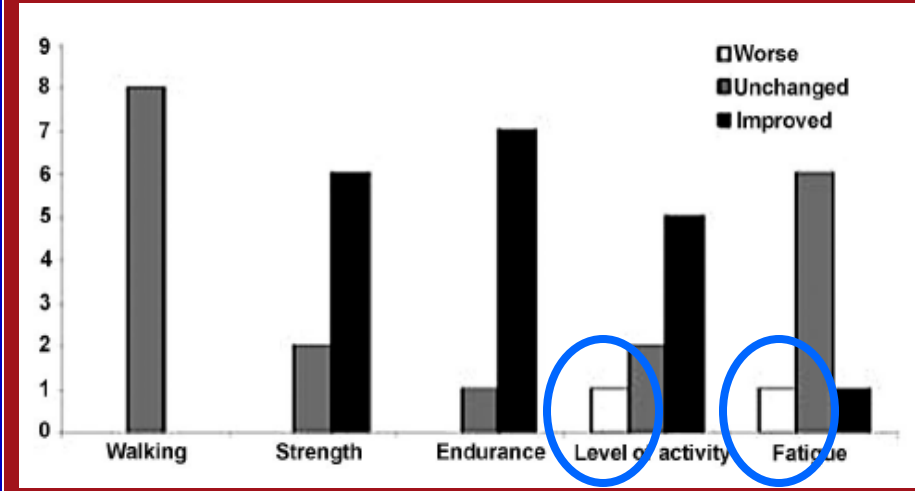
Change in VO2 max



Subjective QOL



Exercise in FSHD

Tentative Conclusions

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- "We recommend that patients with FSHD perform regular aerobic exercise to maintain CV fitness."
- No evidence of overuse weakness;

BUT

- No obvious strength improvement
- No effects (+ or -) on pain, fatigue, functional status, psychological distress

Cochrane Review
van der Kooi et al; 2010

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- "…patients with these specific disorders can be advised that "normal" participation in sports and work appears not to harm their muscles, but there is still insufficient evidence that it offers benefit".
- "There is insufficient evidence for general prescription of strength and aerobic exercise programs in myotonic dystrophy and FSHD…. Unfortunately, no clearly defined exercise protocols can be drawn from current research."

Therapy of FSHD

The Four S's

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1. Strength Therapy
   (eg. none currently)

2. Symptomatic Therapy
   (eg. vision, hearing)

Symptomatic Therapy
Retinal Disease

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- Retinal vascular problems: Rare - can cause retinal hemorrhage & detachment.
  - Occurs in early onset, severe FSHD.
- Preventable with early diagnosis
- Ophthalmologic examination
  - Fluorescine angiogram if abnormal
  - No need for repeated exams if initial exam is normal

Symptomatic Therapy
Hearing Loss

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- Can be detected with accurate testing in ~60% of FSHD patients
  - Usually mild and sub-clinical
  - Routine testing not needed
- More severe in early infantile FSHD
  - Routine hearing tests indicated in young FSHD patients.

Symptomatic Therapy
Other Concerns

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- Rhythm & subtle contractile abnormalities in ~ 5%; almost always insignificant
  - Hard to tell from “regular” cardiac disease
  - Routine EKGs as for all adults
- Respiratory involvement in minority of patients
  - 1% ventilator assist in Dutch study
- Pregnancy: outcome usually good
  - 25% report persistent worsening function (Ciafaloni et al, 2006)

Therapy of FSHD

The Four S's

FIELDS FSHD & Neuromuscular Research CENTER

1. **Strength** Therapy
   (eg. none currently)

2. **Symptomatic** Therapy
   (eg. vision, hearing)

3. **Supportive** Therapy
   (eg. bracing, surgery)

Supportive Therapy
Pain

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- Survey of 270 FSHD patients in France, only 5% reported no pain, 32% reported daily pain
- Dutch survey of 109 patients, 58% reported pain > 4 days/week, 32% pain reported daily pain
- Survey of 127 FSHD patients in USA, 82% reported pain, 23% severe (Jensen et al, 2008)

- Areas most often affected:
  - Low back, shoulders, hips

Pain in FSHD
USA Survey

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- Ibuprofen or aspirin is most common tx, followed by heat
- Greatest pain relief from severe pain:
  - Marijuana
  - Opioids
  - Massage
  - Chiropractic manipulation

Supportive Therapy
Pain & Fatigue

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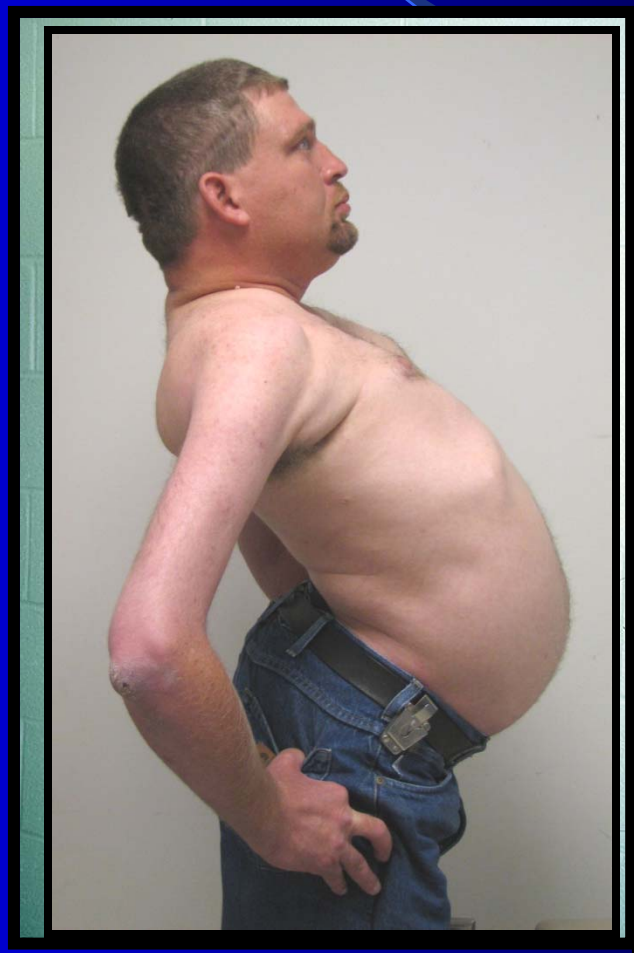
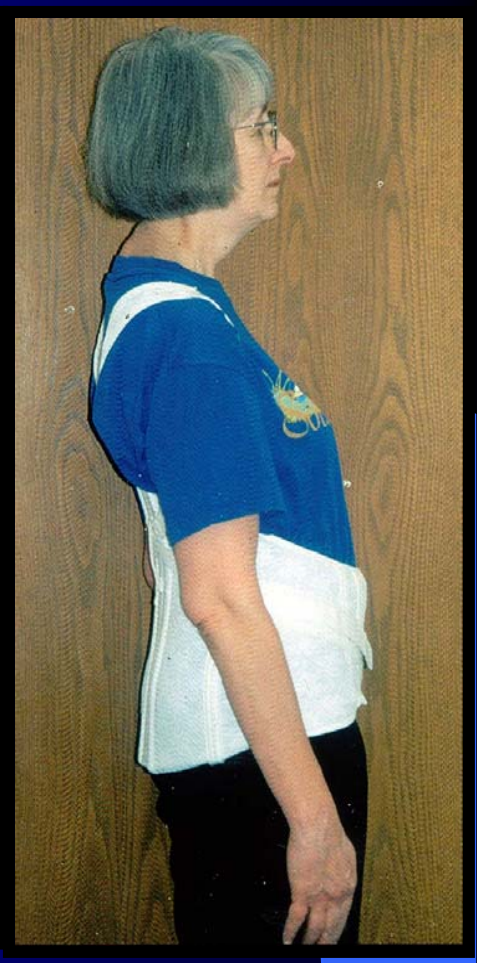
- Shoulder, back pain
  - NSAIDs, muscle relaxants
  - Physical therapy
- Abdominal pain
  - LS corset/binder
- Fatigue in 60%
  - ? medications





Supportive Therapy

Bracing

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- Custom-molded AFOs for foot drop
- "Stance control" KAFOs for more proximal & quad weakness
  - Provides automatic release at knee during push-off phase
  - Lock during stance

Stance-Control KAFO

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Supportive Therapy
Scapular Stabilization

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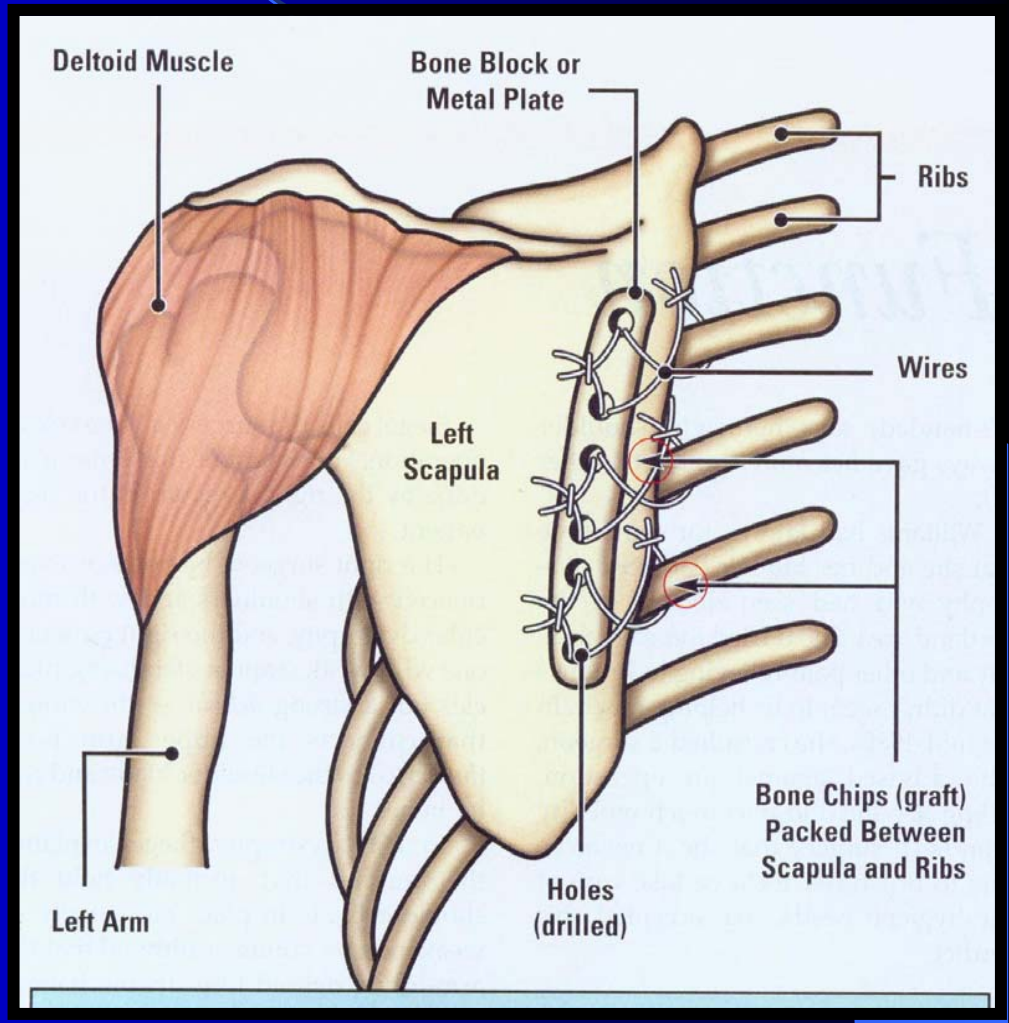
- For *some* with good deltoid, bicep function
- Increases leverage arm but decreases ROM
- Complications- rib fx. hemo-pneumothorax, pleurisy, bleeding, failure, brachial plex.
- 10-12 weeks immobility
- Experienced surgeon!
  - Motivated patient!!



Scapular Stabilization

Dr. Anthony Romeo

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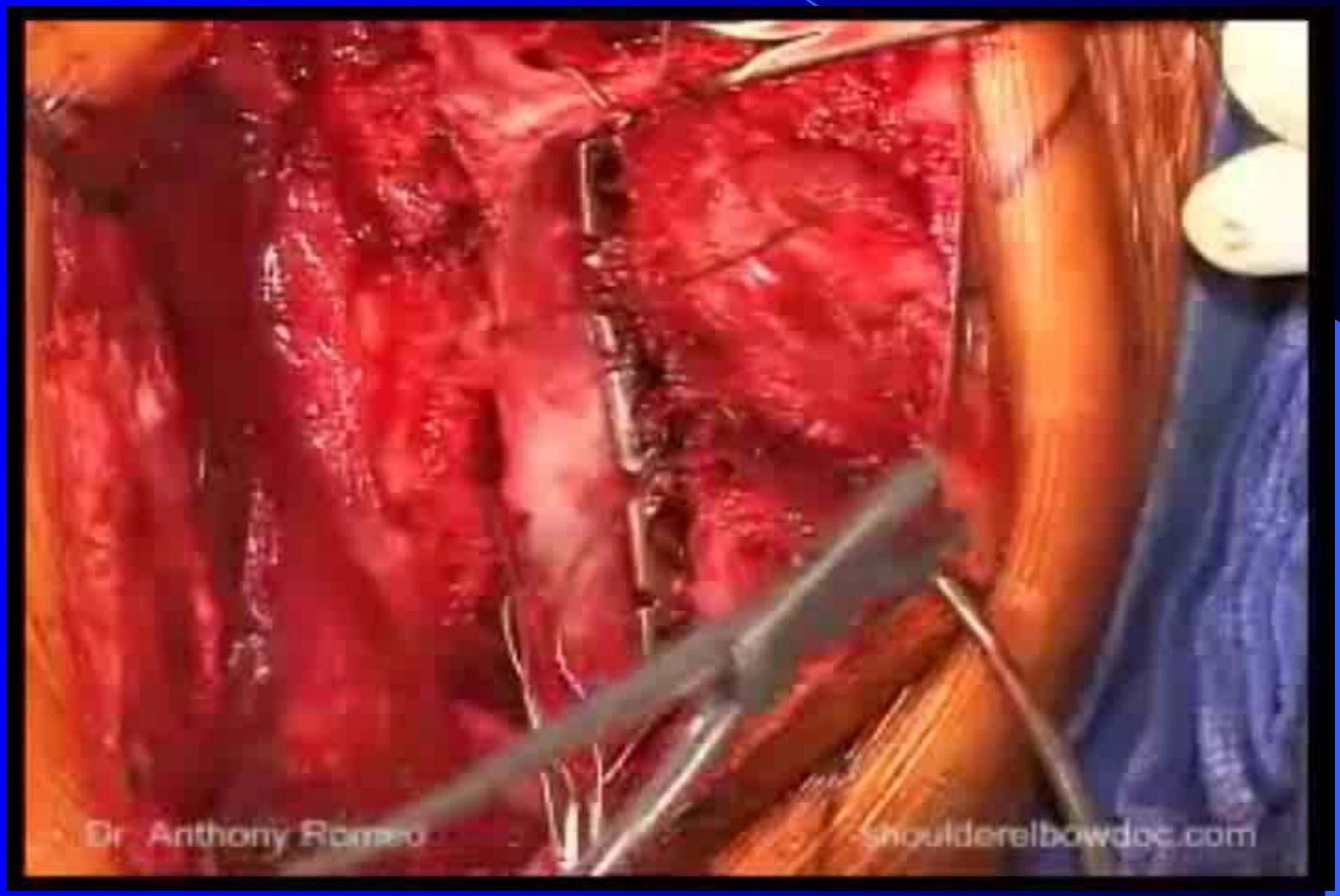
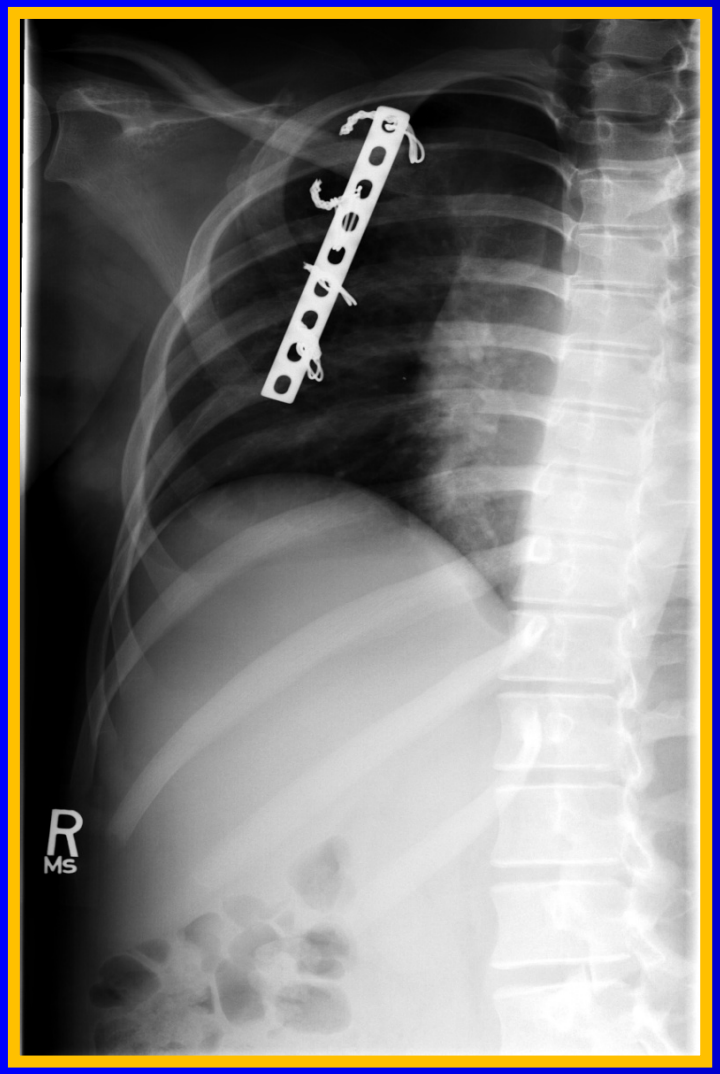
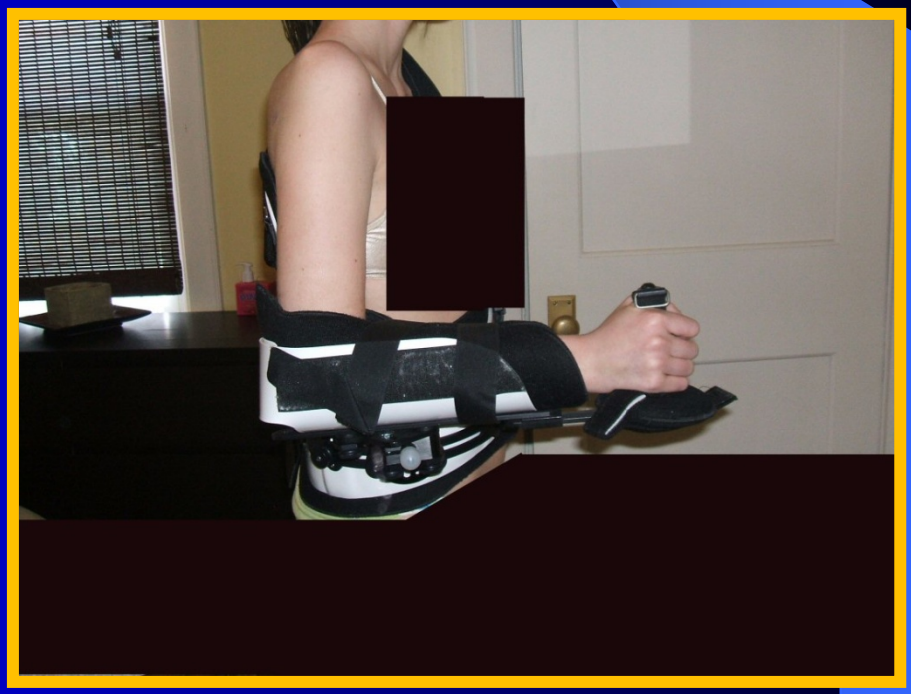
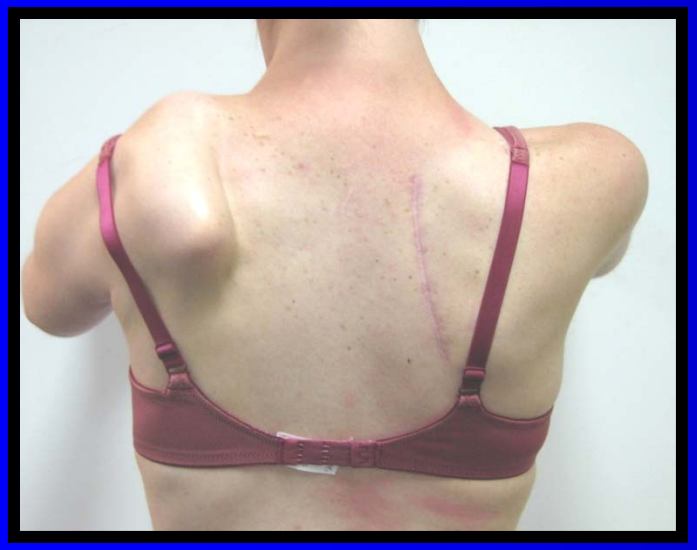


Scapular Stabilization Surgery

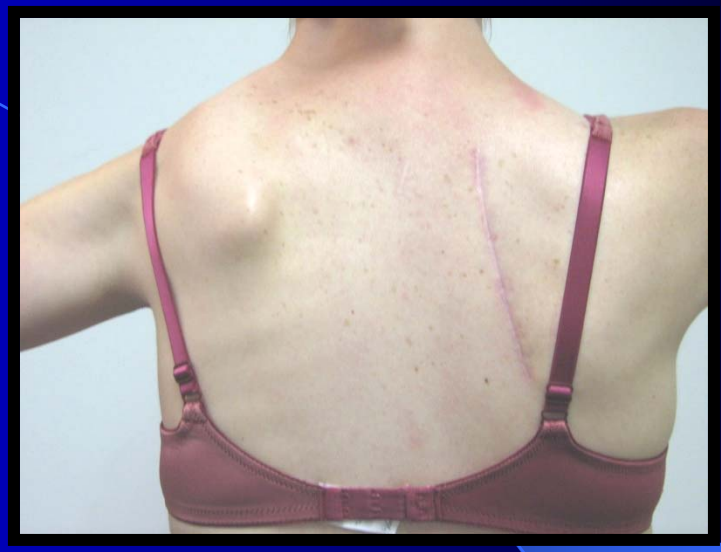


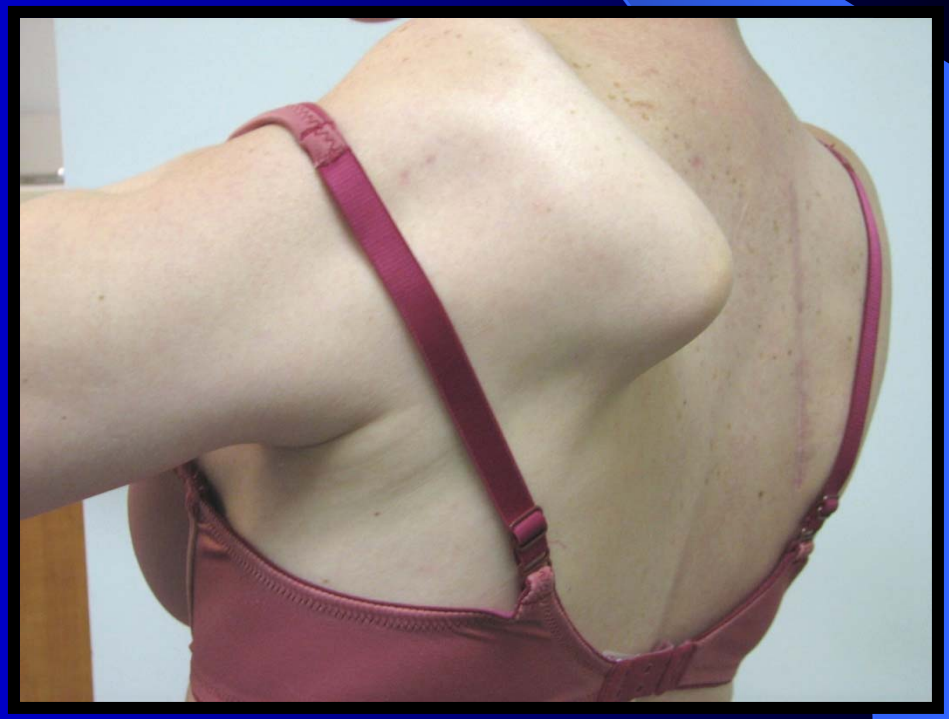


Active shoulder flexion



Active shoulder abduction





Scapulothoracic fusion performed four months earlier

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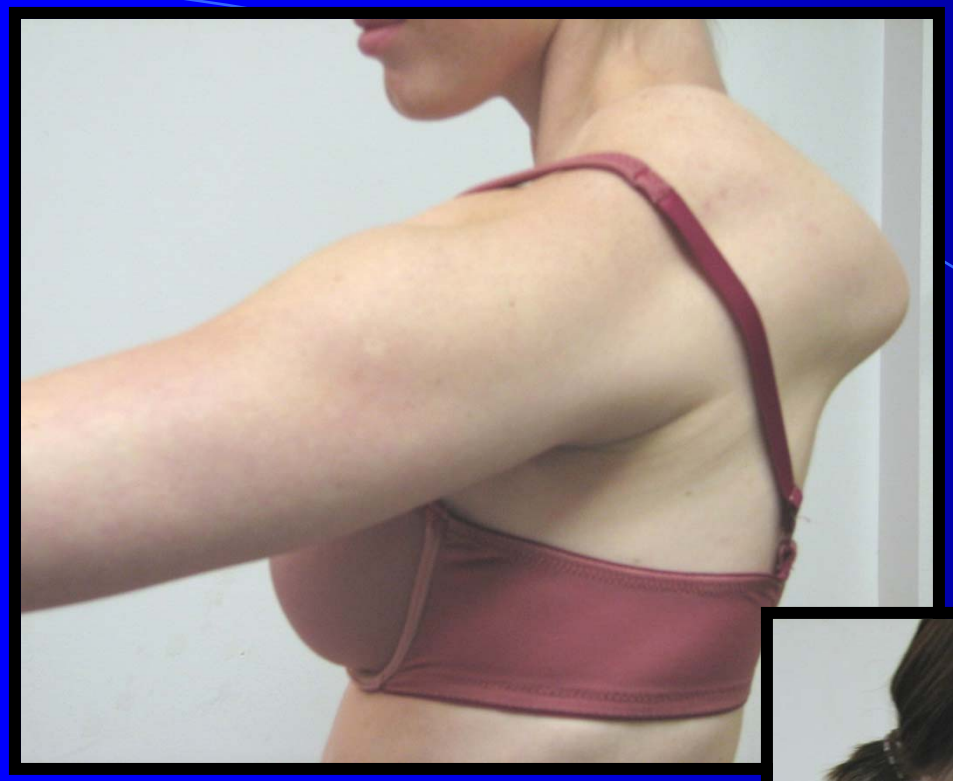
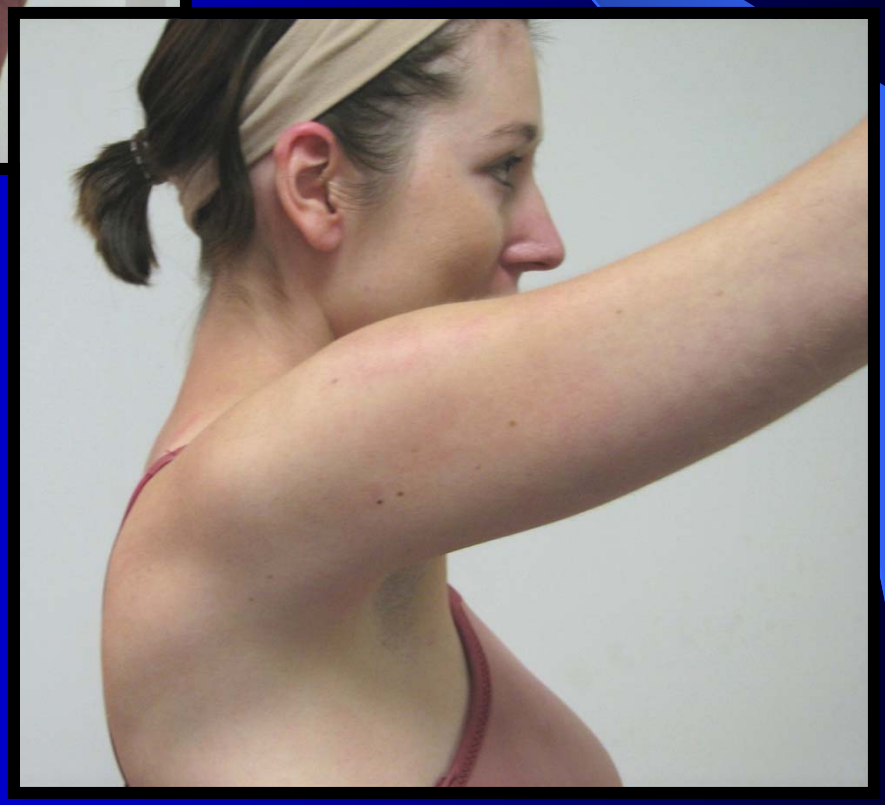


Left:
Surgery
to be scheduled



Right:
4 months post surgery

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Restoration of muscles' "normal" mechanical Advantage

Decreased pain, Increased function

Supportive Care
Occupational Therapy

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Weak shoulder, elbow, wrist, finger muscles

Occupational therapy consults often appropriate

Supportive Care
Occupational Therapy

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- Maintain flexibility, ROM and strength of the UE's/hands; minimize contractures
- Assess functional abilities as related to strength
- Develop compensatory strategies that maximize physical abilities
- Watch for fatigue, overuse, endurance
- Splinting for UE's

Therapy of FSHD

The Four S's

FIELDS FSHD & Neuromuscular Research CENTER

1. **Strength** Therapy
(eg. none currently)

4. **Solid Information**
(eg. counseling & genetic info)

2. **Symptomatic** Therapy
(eg. vision, hearing)

3. **Supportive** Therapy
(eg. bracing, surgery)

pSychologic Support

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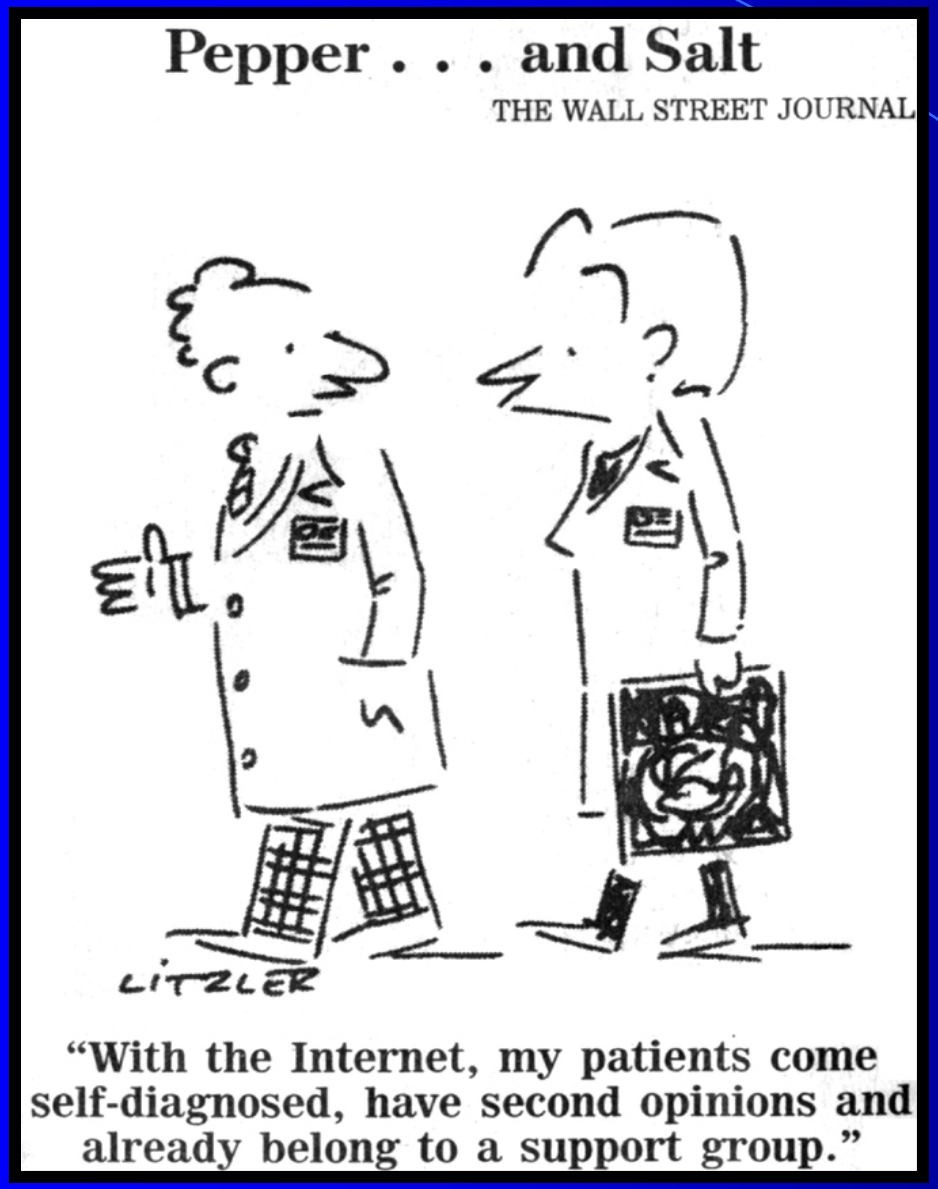

Patients often know more than the doctors!!

Solid Information
Three Major Concerns

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- Patients want to **know** what is going on!
  - Drs *must* understand genetics/pathogenesis
  - Demand from them *specifics* about advances
- "All the work is in DMD"; FSHD patients often feel abandoned
  - DMD, LGMD work will apply to other MDs
- It's not happening fast enough!
  - Highlights importance of other 3 S's!

Treatment of MD
General Principles

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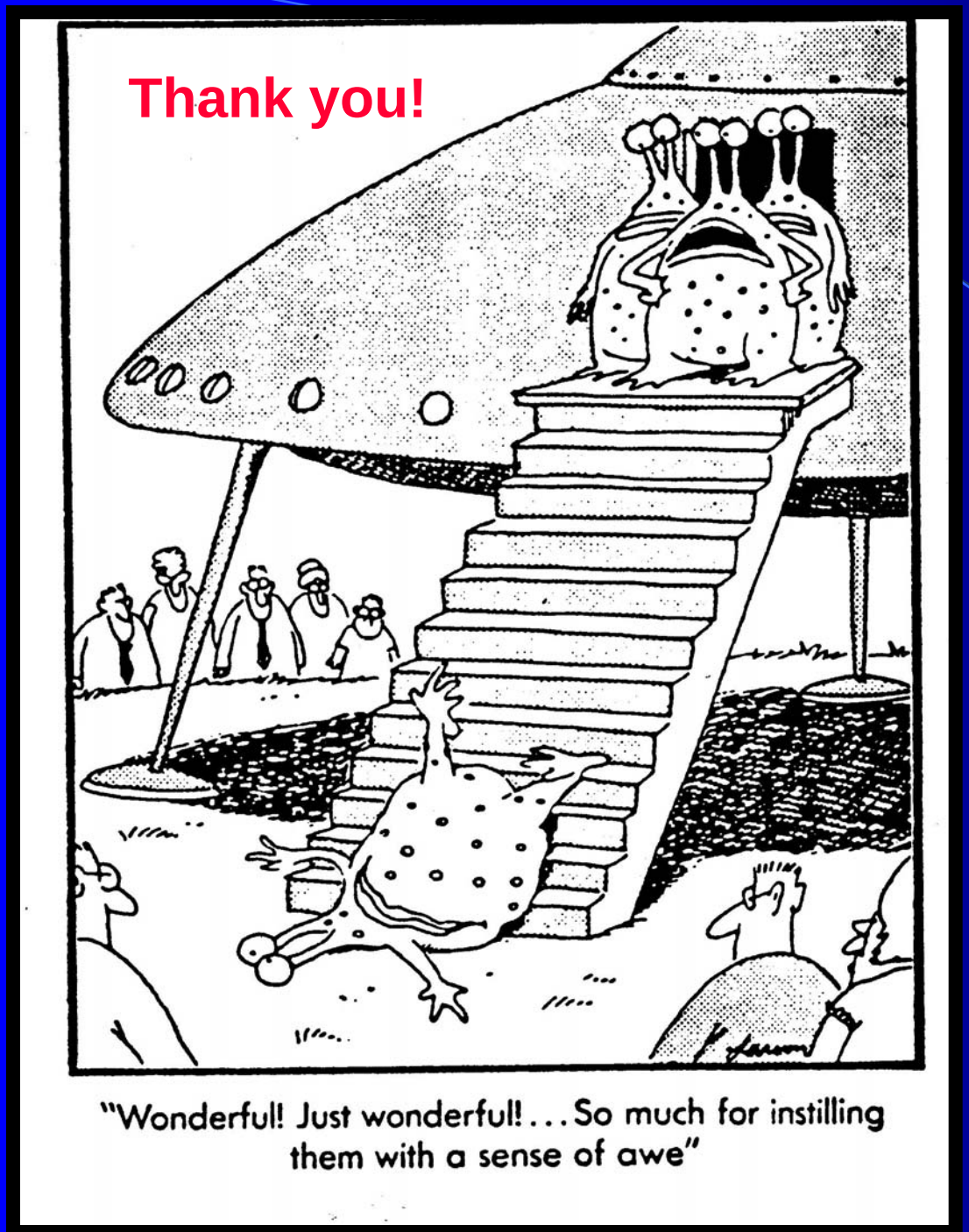
- Leave enough time for counseling
  - Understand genetics/pathogenesis of dx.
  - Give SOLID info on *any* new advances
- Always consider "A-B-Cs"
  - **A**ctivity (i.e. ADL and *QOL* issues)
  - **B**reathing/resp. status & **C**ardiac function
- Rally the alphabet troops - RN, PT, OT, ST, SW, RT, PM&R, orthopedics, cardiology
  - Refer early and often if needed!



Acknowledgement

Wendy King; RT

Rabi Tawil
Silvere van de Maarel

Therapy of FSHD

The Four S's

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(eg. none currently)

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(eg. bracing, surgery)