Genetic Counseling & Testing for FSHD

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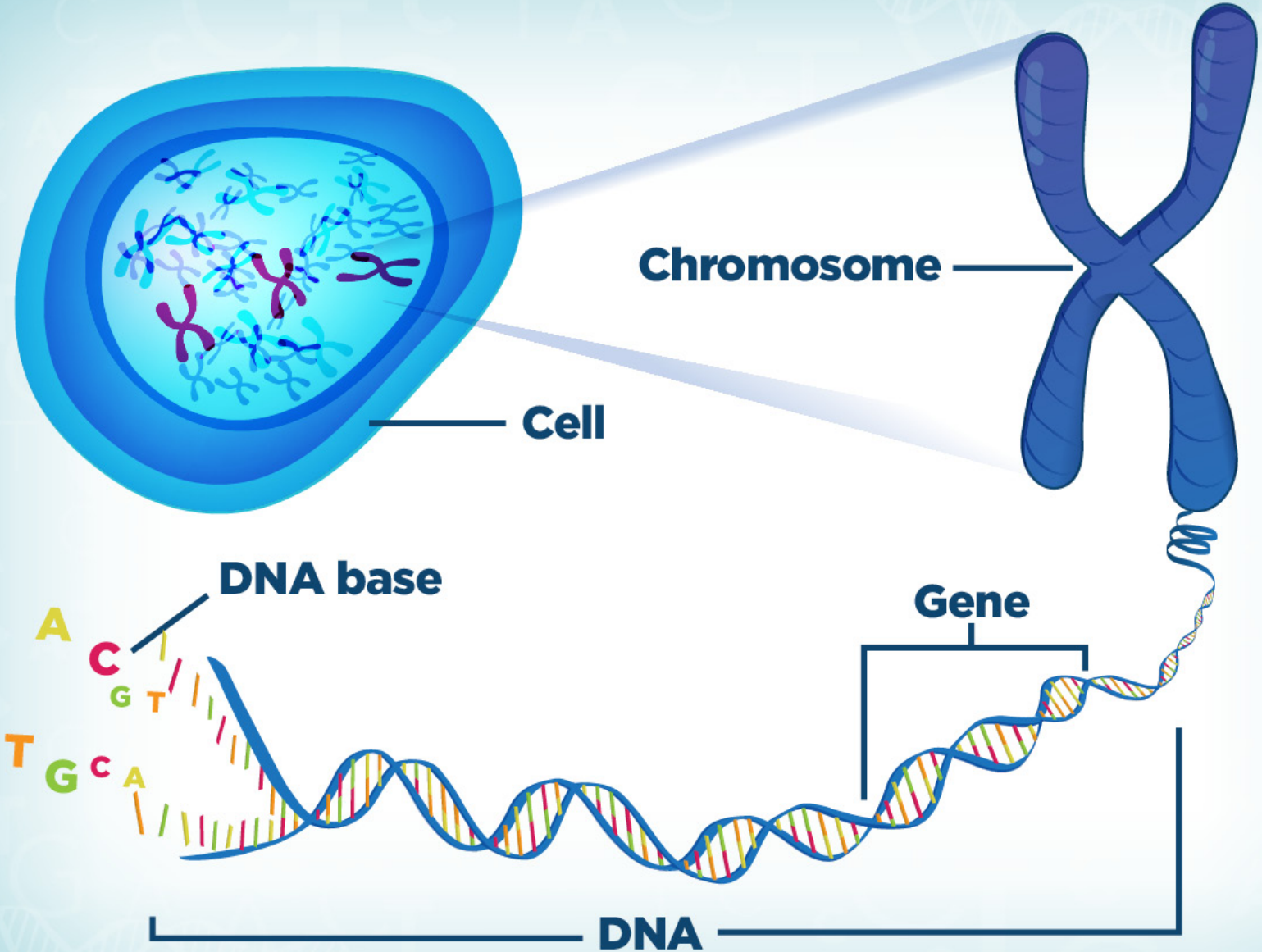
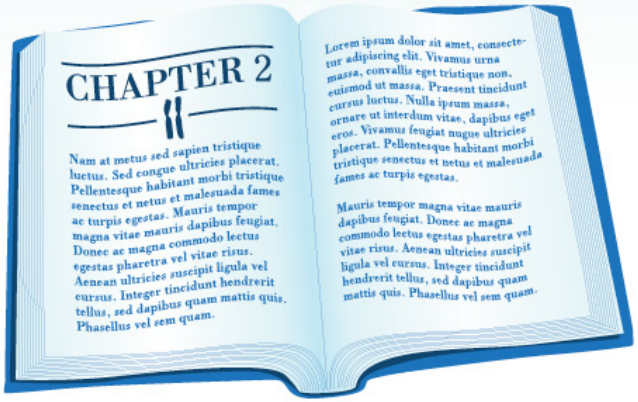
Outline

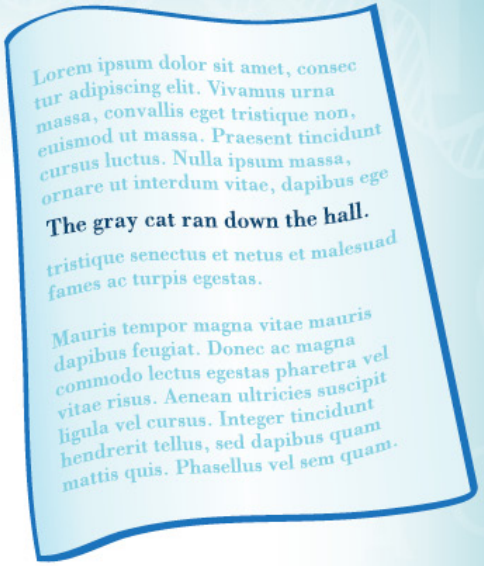
- Genetics of FSHD
- Inheritance of FSHD
- Reproductive and Family-Building Options

What causes FSHD?



National Society of Genetic Counselors

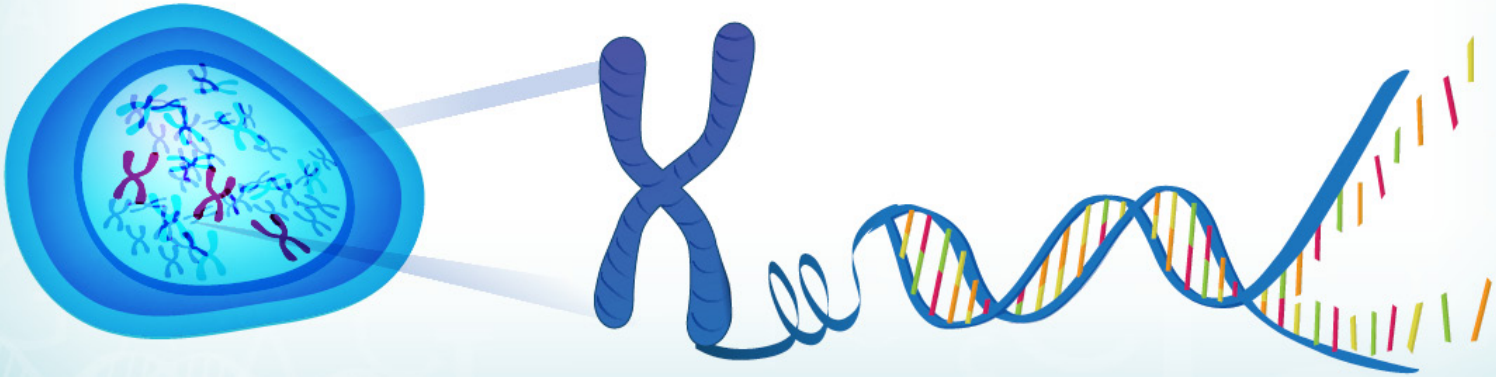




BOOK – GENOME

CHAPTERS – CHROMOSOMES

SENTENCE – GENE



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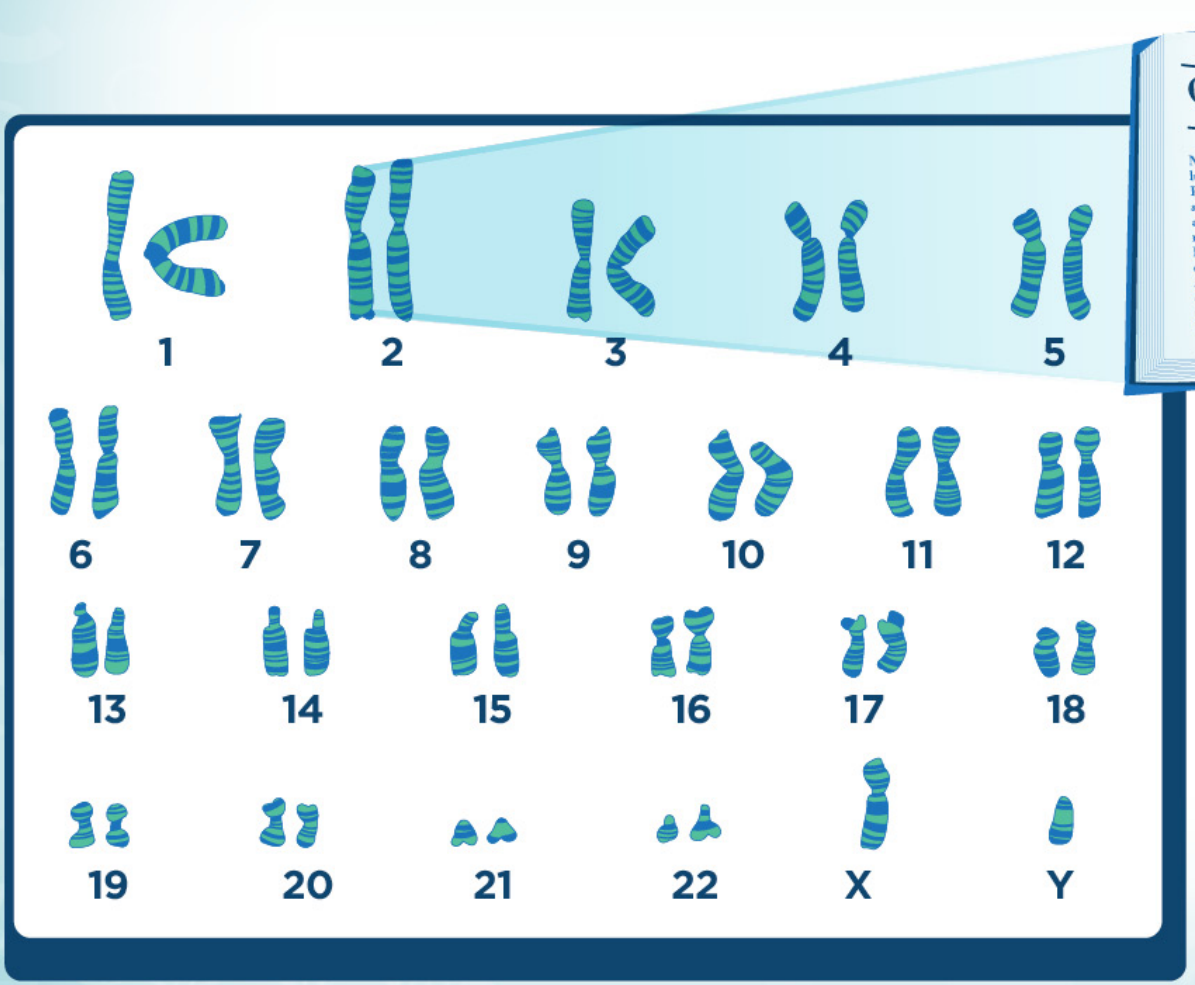
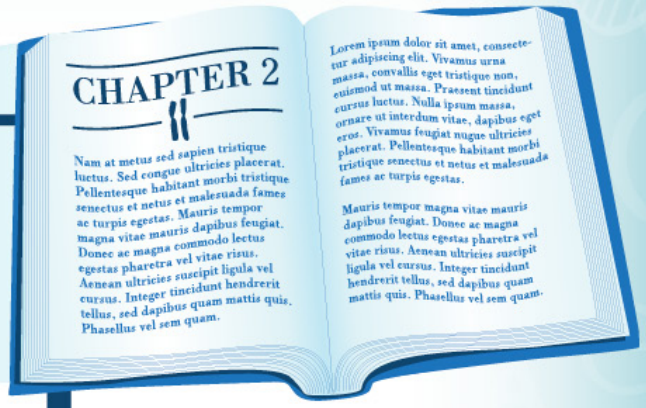
Genome: 46 chromosomes…20,000 genes …3 billion DNA letters!





Females
46,XX

Males
46,XY

National Society of Genetic Counselors

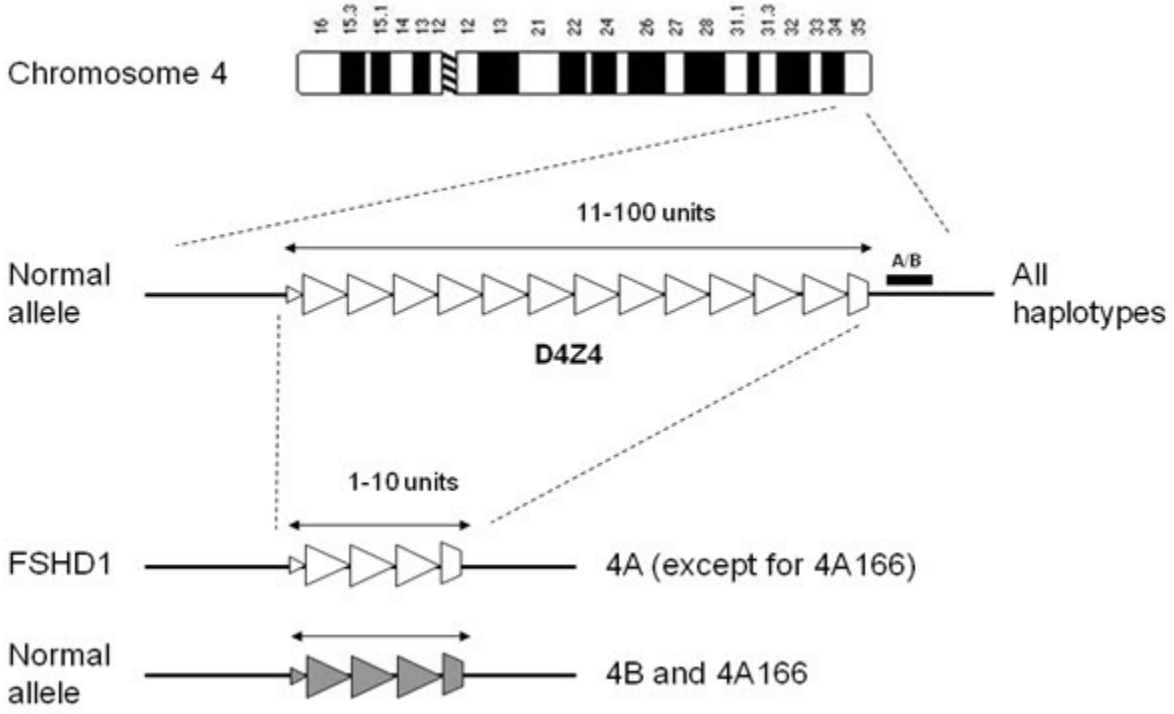
Two Types of FSHD

- **FSHD Type 1**
  - Most common type (~95%)
  - Caused by chromosome 4 deletion + 4qA haplotype

- **FSHD Type 2**
  - Rarer type (~5%)
  - Caused by SMCHD1 gene change + 4qA haplotype

- Same symptoms, different inheritance pattern
- Only one type per family
- Genetic testing needed to distinguish type 1 from type 2

FSHD1: Chromosome 4q35 deletion



Allele sizes:

- Normal = >42kb
- Borderline = 38-41kb
- Abnormal (FSHD-associated) = <38kb

Haplotype:

- Permissive = 4qA
- Non-permissive = 4qB

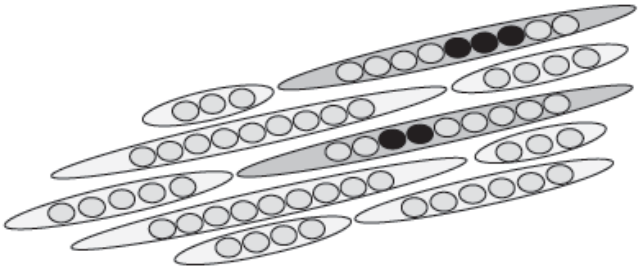
[GeneReviews]

FSHD: Expression of DUX4 gene

- **DUX4:** Double Homeobox 4
  - Transcription factor – controls expression of other genes

- DUX4 is normally expressed only in germline (e.g. sperm/eggs cells), it is repressed ("turned off") in all other cells and tissues
  - Exact function in germline in unknown

- FSHD muscle cells show DUX4 expression
  - When mis-expressed in muscle cells, DUX4 activates many genes that are normally expressed only in the germline

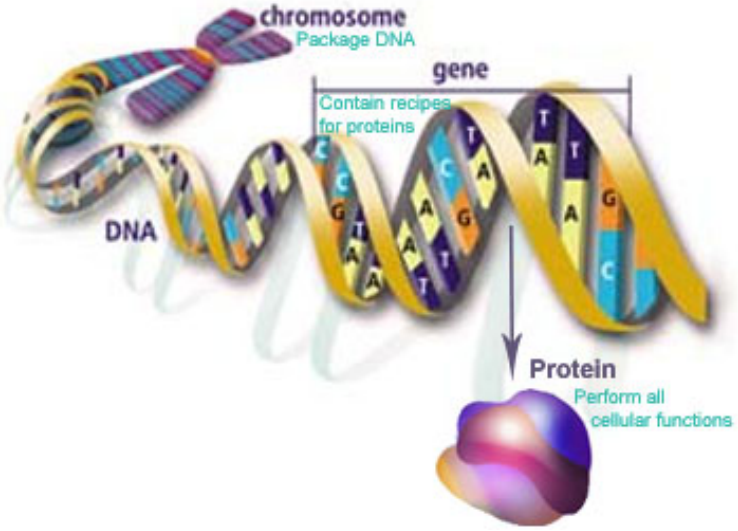


How do genes get expressed?

DNA —Transcription→ **RNA** —Translation→ **Protein**

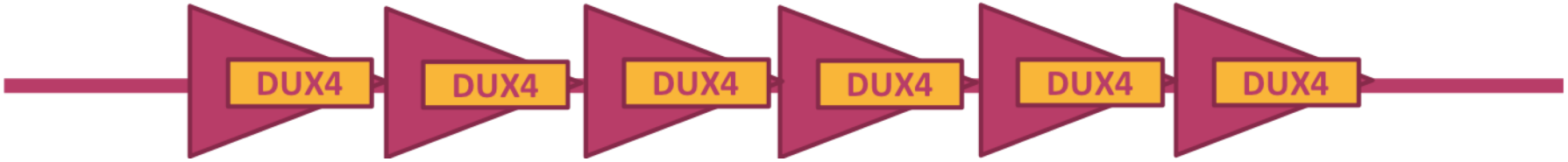
- Genes may be active only in certain cells/tissues or at certain times during development and throughout lifetime

- **Methylation** is one mechanism that controls gene expression



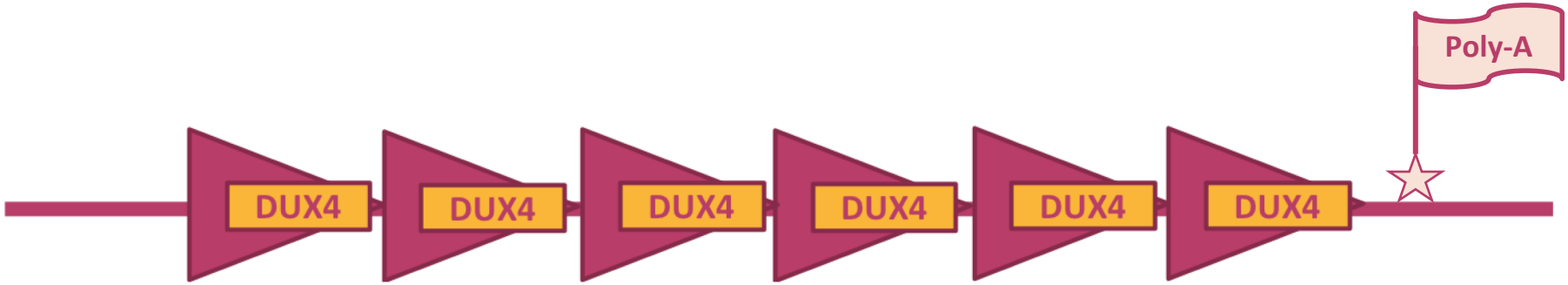
FSHD: Expression of DUX4 gene

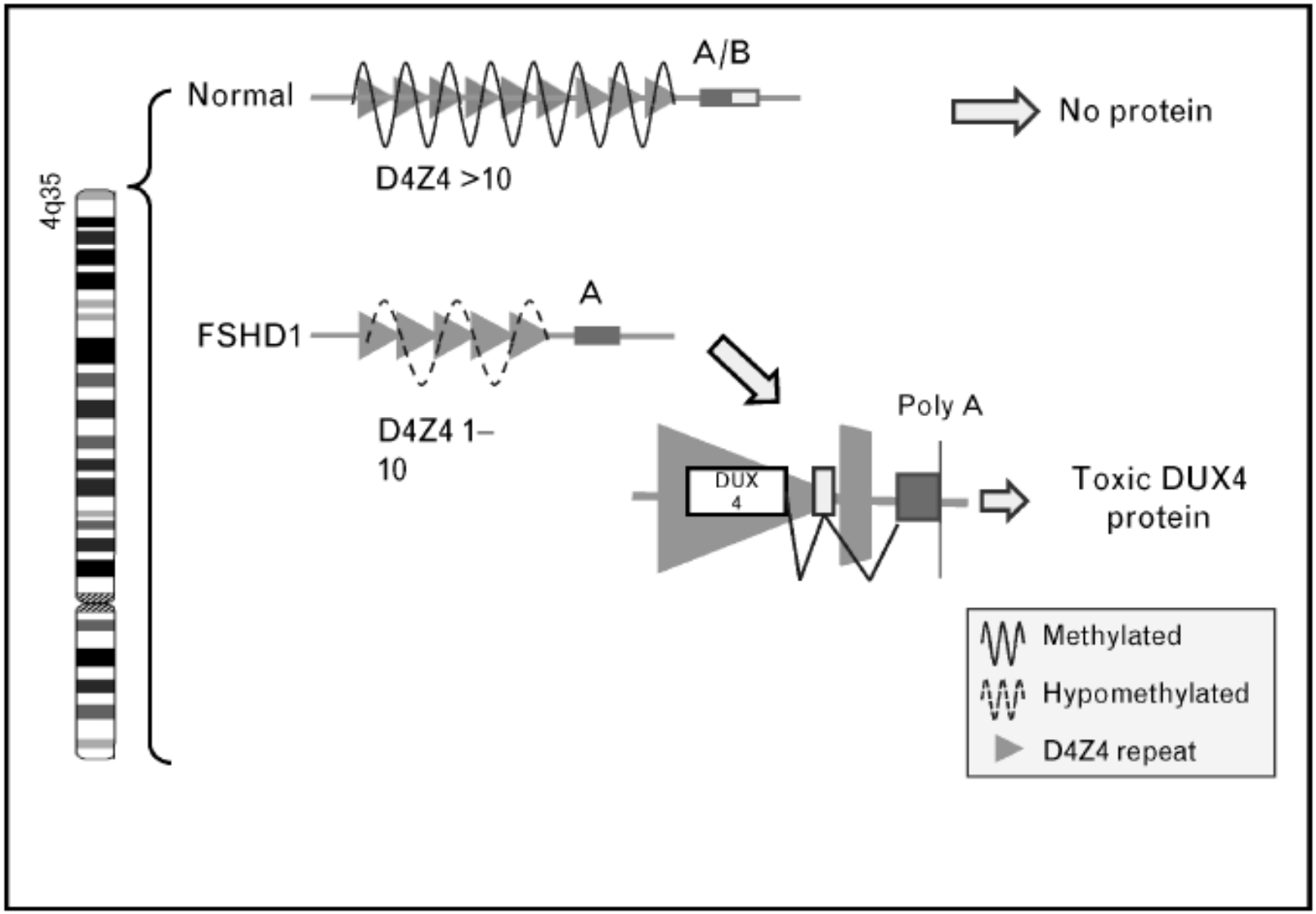
- Each D4Z4 unit contains copy of DUX4 gene
- However, DUX4 is not expressed because:
  - D4Z4 array is methylated and chromatin is condensed
  - DUX4 does not have a polyadenylation (PolyA) signal, so the RNA transcript is unstable and gets degraded



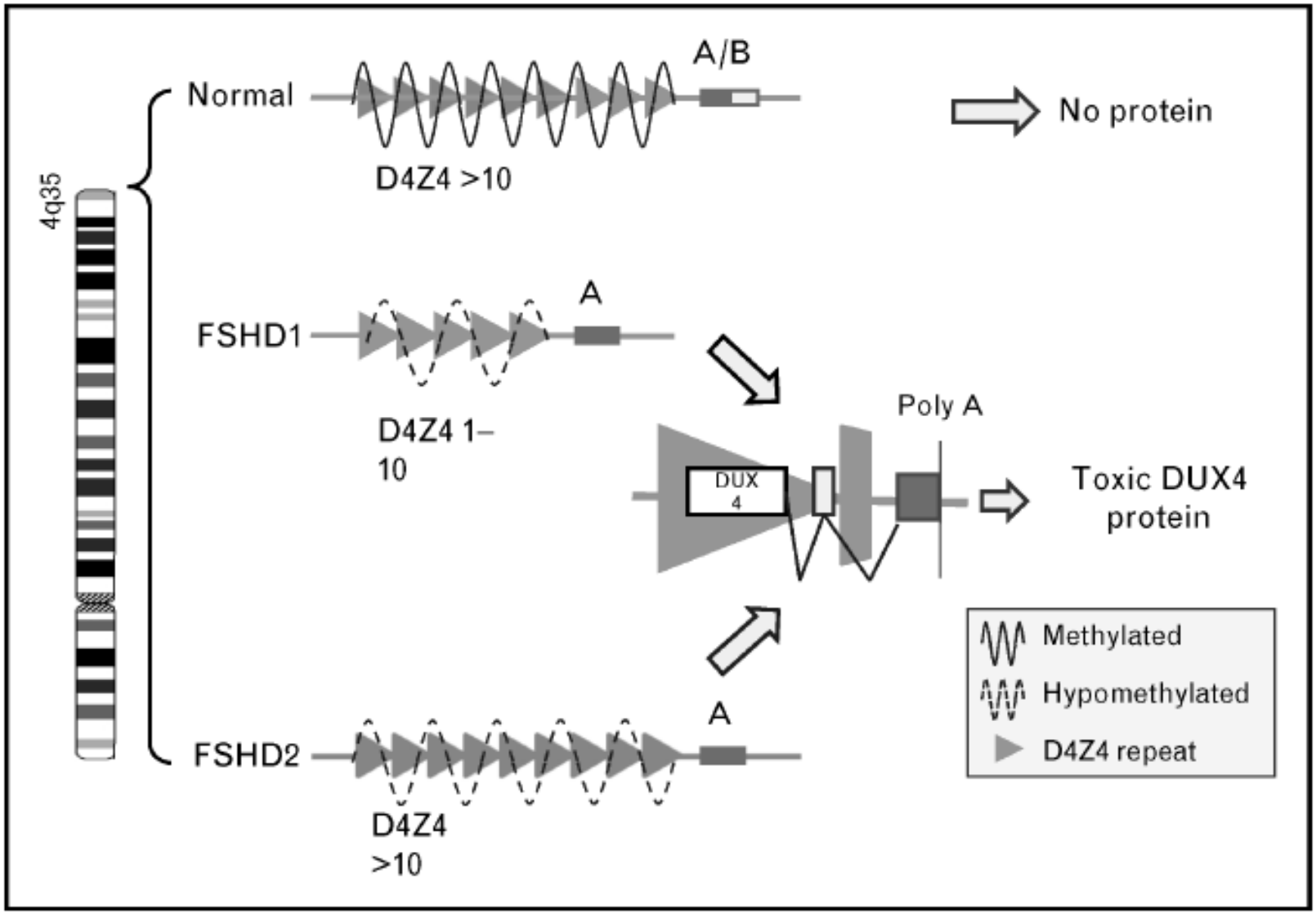
FSHD: Expression of DUX4 gene

- Contraction/deletion of D4Z4 array to 10 units or less causes chromatin to relax and region to become hypomethylated
- Permissive alleles (4qA haplotype) have poly-A signal
- **Contraction + 4qA haplotype = DUX4 expression (FSHD1)**





[Statland & Tawil 2011]



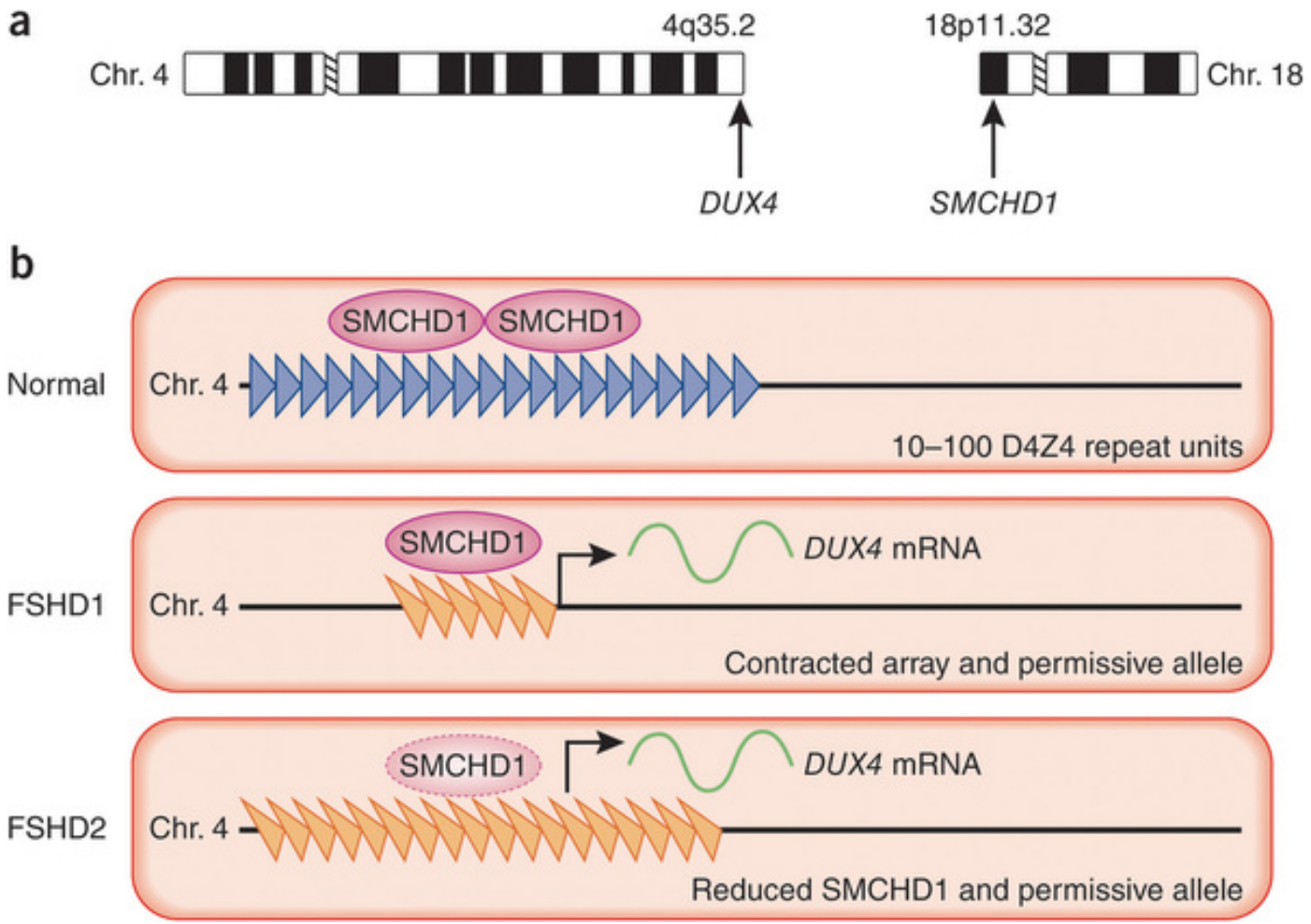
What about FSHD2 (no contraction/deletion) ?

SMCHD1 gene

- ***SMCHD1****: structural maintenance of chromosomes flexible hinge domain containing protein 1*
  - Located on chromosome 18

- SMCHD1 functions to keep D4Z4 array methylated (silenced)

- SMCHD1 mutation results in D4Z4 hypomethylation; if person also has permissive 4qA haplotype, DUX4 will be expressed



(**a**) Digenic inheritance of variants at *DUX4* on chromosome 4 and *SMCHD1* on chromosome 18 causes FSHD2. (**b**) Schematic of the FSHD-related locus on chromosome 4. Blue triangles represent D4Z4 repeats. Orange triangles represent D4Z4 repeats with relaxed chromatin and a polyadenylation signal that is permissive for *DUX4* expression. FSHD1 is associated with a contracted D4Z4 array, relaxed chromatin and *DUX4* expression. FSHD2 is associated with a normal-size D4Z4 array, relaxed chromatin, reduced SMCHD1 protein levels due to genetic variants in *SMCHD1* on chromosome 18 and *DUX4* expression.

[Lupski 2012]

HOW IS FSHD INHERITED?

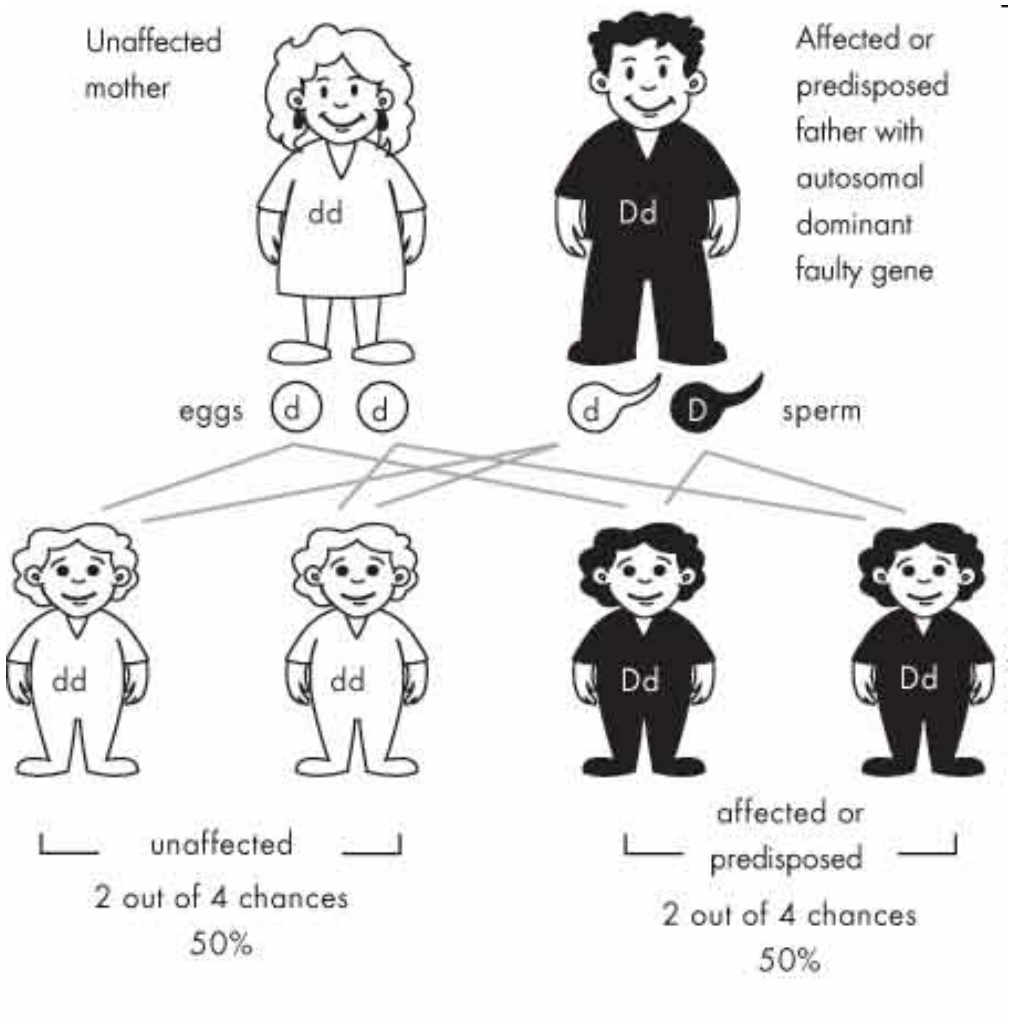
Inheritance Patterns

- We inherit one copy of each chromosome (and therefore one copy of each gene) from each of our parents

- Patterns of inheritance:
  - Autosomal Dominant
  - Autosomal Recessive
  - X-linked

- Genetic disorders are not always inherited
  - Sporadic or “de novo”

FSHD1: Autosomal Dominant



- **50%** chance in each pregnancy to have affected child
- Same for males and females
- Some people w/ deletion may not show symptoms, or milder

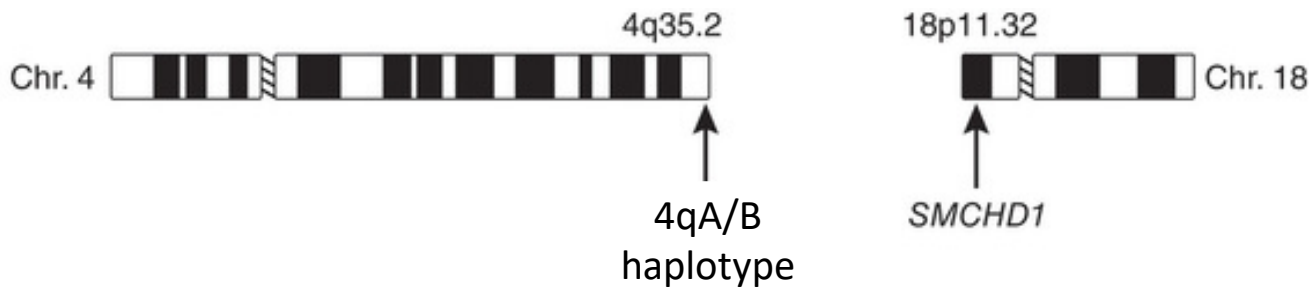
FSHD1: Tricky Issues

- Some individuals (~30%) have ***de novo*** deletions:
  - Deletion happened new in their conception, not inherited from parent
  - Genetic testing in parents' blood is normal/negative

- **Mosaicism:** deletion is present in a subset of cells/tissues
  - Germline mosaicism = only in egg/sperm cells
  - Somatic mosaicism = present in cells throughout body (+/- germline)
  - If present in germline, can be transmitted to children

FSHD2: Digenic Inheritance

- Two genetic changes (4qA/B haplotype and SMCHD1 gene) are located on two different chromosomes and inherited independently from one another
- Child must inherit both 4qA haplotype and SMCHD1 gene change to have FSHD
- Recurrence risk depends on genotype of partner too



Genetic Testing & Counseling

Why is genetic testing important for FSHD?

- Determine whether FSHD type 1 or type 2
- Reproductive options and testing
- Eligibility for research and clinical trial participation
- For relatives without symptoms, to know for sure that they are not at risk

Genetic Testing

- Understand benefits, limitations, and risks
- Genetic test results often have implications for family members
- Not “just” a blood test
- Importance of counseling before and after testing

The Decision to be Tested

- When you learn you are at risk there is no “correct” way to feel
- Individuals will respond very differently; some will avoid testing and others will be very anxious and will want testing right away
- Remember that testing is intended to **HELP** you
  - Seek treatment as early as possible if necessary
  - Prepare/plan for the future
  - Seek reproductive counseling, information about family planning options
  - For those who test negative, testing can provide reassurance and freedom from worry!

Genetic Testing in Children

- We typically do not perform predictive or carrier testing in asymptomatic children unless there is something we would do to help them in childhood (if they tested positive)

- People absorb and respond to genetic information better when it is their *own* decision to be tested

- Childhood isn't the best time to discuss reproductive implications of test results

- **There are always exceptions**

Genetic Counseling

Genetic Counseling

"The process of helping people **understand** and **adapt** to the medical, psychological and familial implications of genetic contributions to disease. This process integrates:

- ***Interpretation*** of family and medical histories to assess the chance of disease occurrence or recurrence;
- ***Education*** about inheritance, testing, management, prevention, resources, and research;
- ***Counseling*** to promote informed choices and adaptation to the risk or condition."

National Society of Genetic Counselors

Genetic Counseling

- Genetic counselors (GCs) are Master's level health professionals with advanced training in medical genetics *and* counseling
- While GCs are not medical doctors, we are part of your healthcare team, and work with you and your doctor to help you understand:
  - Your genetic risks based on your family history
  - Whether genetic testing might be right for you
  - What the results of genetic tests may mean for you and your family
- With expertise in counseling, GCs can also provide emotional support as you make decisions

www.findageneticcounselor.com

Reproductive & Family-building Options

Family-Building Options

Preimplantation Genetic Diagnosis

Prenatal Diagnosis

Donor Eggs/Sperm

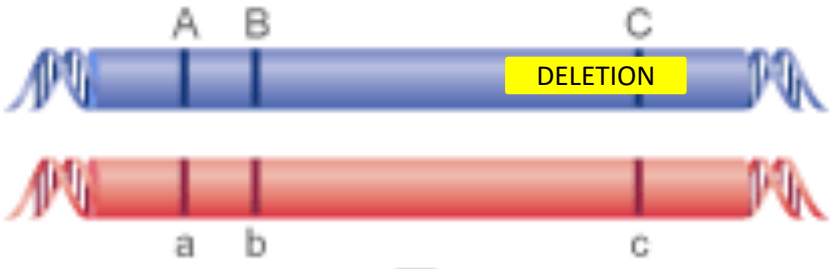
Adoption

Preimplantation Genetic Diagnosis (PGD)

- Genetic analysis of one or two cells from the early embryo conceived through *in vitro* fertilization (IVF)
- Allows only unaffected embryos to be transferred into the uterus to start the pregnancy
- Highly accurate (~98%) though prenatal testing still recommended for confirmation
- **PGD is only an option for FSHD1 if there is a family member with FSHD – not an option for de novo deletions**
- Sometimes may require DNA samples from more than one affected family member ("linkage analysis")

PGD for FSHD1

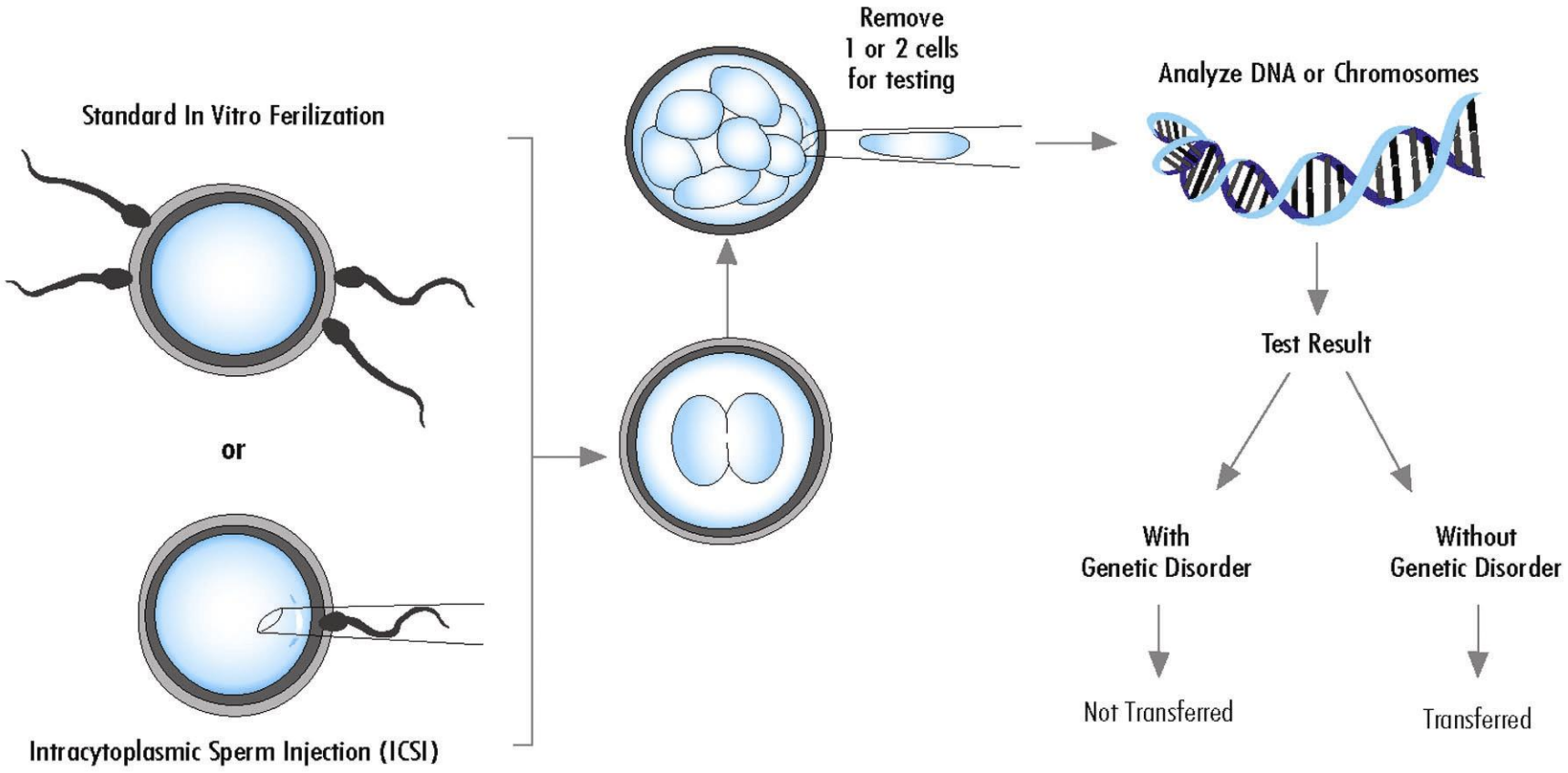
- Performed using **linkage** rather than direct testing for the deletion
  - Tests for “markers” located nearby deletion region
  - Need multiple affected family members to determine the markers that track with the deletion
  - Therefore, PGD can only be done for patients with a family history of FSHD (e.g. affected parent), not in *de novo* cases



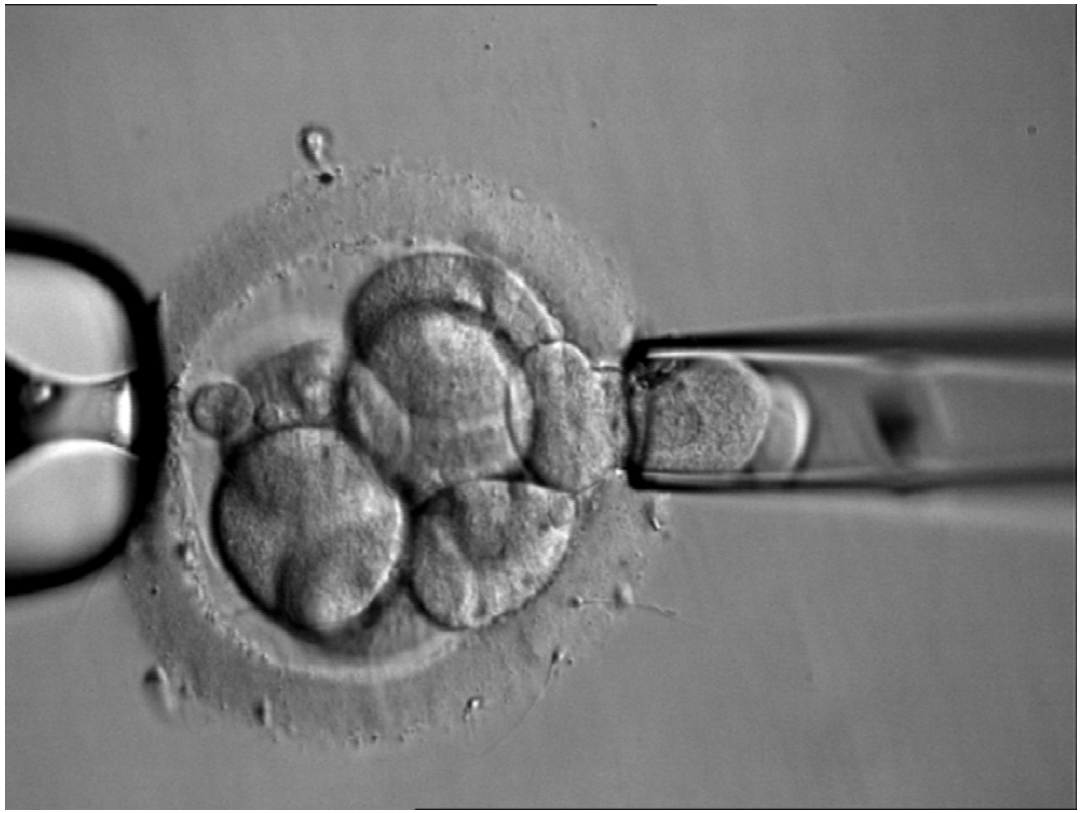
PGD: IVF Procedure

- Female partner receives medications (oral and injections) to regulate cycle and stimulate ovaries to produce multiple eggs, monitored by frequent ultrasounds and blood tests
- Egg retrieval, male partner provides semen sample
- Fertilization by intracytoplasmic sperm injection (ICSI)
- Early embryos grow in culture for several days
- **PGD:** Embryo biopsy 3-6 days after fertilization, perform genetic testing on single cells (results may take several days or longer so often embryos will be frozen and transferred in a subsequent cycle)
- Transfer of one or more embryos to womb

PGD: Embryo Biopsy and Testing



PGD: Embryo Biopsy and Testing



PGD: Pros & Cons

ADVANTAGES

- Increases likelihood of birth of unaffected child without need for termination of an ongoing pregnancy
- Highly accurate

DISADVANTAGES

- IVF not always successful, may need multiple cycles
- Costly, may not be covered by insurance
- Not currently an option for de novo cases

PGD: Financial Considerations

	Approximate Cost
Fresh IVF Cycle	$12,400*
ICSI	~ $1,500
Medications	~ $3,000-5,000
PGD	~ $5,000
TOTAL	~20,000-25,000

- Costs and insurance coverage varies widely
- Don’t assume it’s not covered! Schedule consultation with IVF/PGD clinic to find out actual costs, your specific insurance coverage, and financial options

**U.S. average [source: www.asrm.org]*

PGD: Financial Considerations

- Many resources available:
  - Refund programs through IVF clinics
  - Discounts for military/veterans
  - Financing and loans
  - Grants
  - Crowdfunding

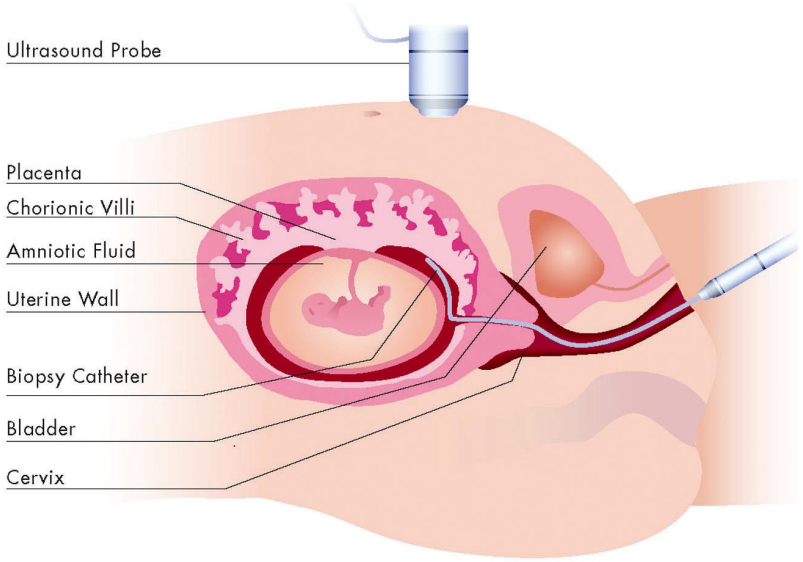
www.resolve.org

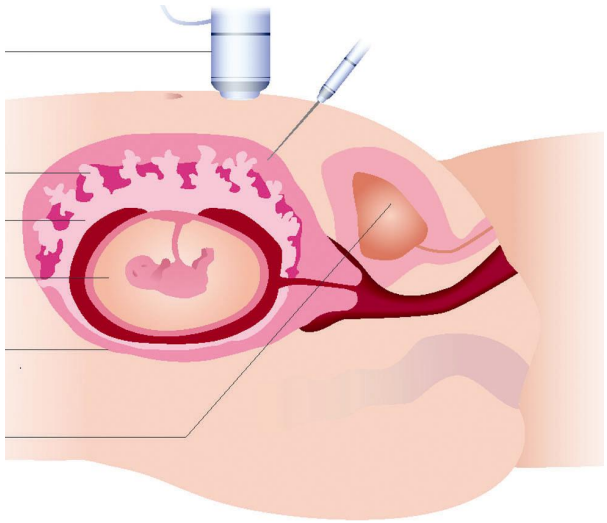
Prenatal Diagnosis

- Conceive pregnancy “naturally” and test fetus during first or second trimester, option to terminate pregnancy if affected
- Two procedures
  - **Chorionic villus sampling (CVS)**: performed 11-13 weeks
  - **Amniocentesis**: performed at 15-20 weeks
- Highly accurate, small risk of miscarriage

Chorionic Villus Sampling (CVS)

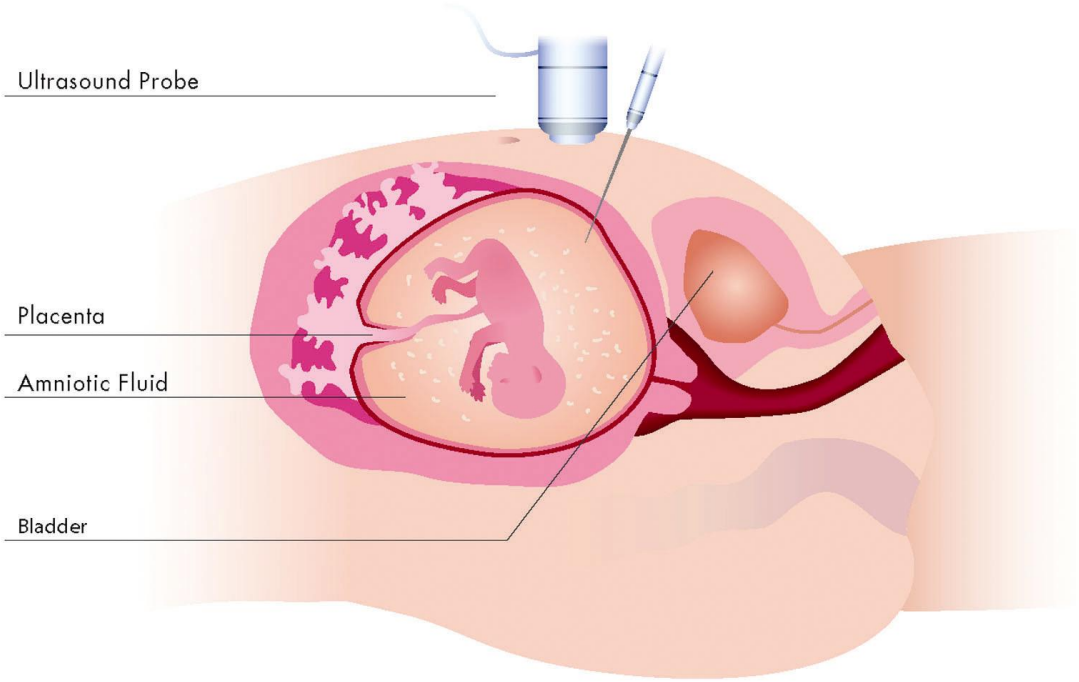
- Cells from chorionic villi (part of placenta) obtained by needle through abdomen or catheter through cervix
- Quick procedure, ultrasound guided, no anesthesia needed
- Performed at 11-13 weeks gestation (after last menstrual period)
- Risk of miscarriage = 1/200 (0.5%)





Amniocentesis (Amnio)

- Amniotic fluid obtained by needle through abdomen
- Quick procedure, ultrasound guided, no anesthesia needed
- Performed at 15-20 weeks gestation (after last menstrual period)
- Risk of miscarriage = 1/300 (0.3%) or less



Prenatal Diagnosis: Pros & Cons

ADVANTAGES

- Highly accurate (>99%)
- Likely covered by insurance

DISADVANTAGES

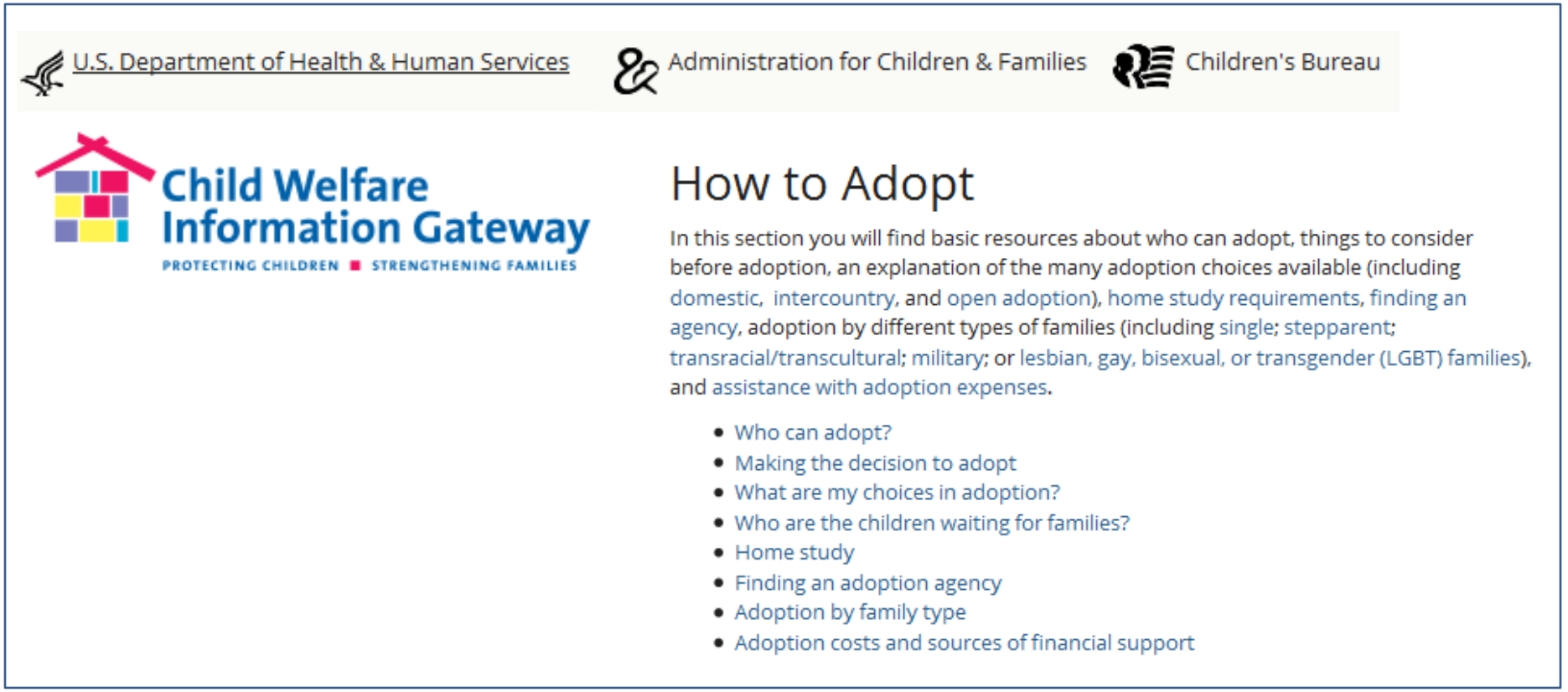
- Cannot fix abnormal gene/chromosome, option is to terminate affected pregnancy
- Earliest time for results would be beginning of second trimester

Donor Eggs or Sperm

- Available from storage banks; frozen and stored
- Donor can be tested for genetic conditions but policies of cryobanks vary, so *ask*
- Donors can be either anonymous or known; selected by prospective recipient or by the sperm bank
- Donor sperm can be inseminated directly into the uterus or used in IVF procedures
- Donor eggs are used in IVF procedures

Adoption

- https://www.childwelfare.gov/topics/adoption/



Questions?

Thank you!

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