RANDALL CHILDREN'S HOSPITAL

LEGACY EMANUEL

The Genetics of 5p- and How Genetics Doctors Can Help

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Required Slide
Objectives and Disclosures

Objectives:

- **To review the background of 5p- syndrome**
- **To discuss the role of the genetics clinic and how we can help**

Disclosure of relevant financial relationships in the past 12 months:

I Dr. Petersen have nothing to disclose

What's a geneticist??
How do you become one?

- A geneticist is a doctor who specializes in rare conditions
- 4 years of college
- 4 years of medical school
- 3+ years of primary residency
  - Pediatrics
  - Internal medicine (adult)
  - Family medicine
  - Ob/Gyn → maternal fetal medicine
- 2-4 years of dedicated genetics residency

Why is your field called “genetics”?

- Genes = instructions for how our bodies are made/maintained
- Almost every cell in our bodies contains a complete or near complete set of these instructions
- Missing, extra or misspelled instructions can cause changes
- Genetics: The study of these changes and the patterns that they cause

Who do you care for?

- Patients with rare or unusual features
- Patients with common issues that have rare causes
- Family members with a risk for a genetic condition that runs in their family
- Patients with an already diagnosed genetic condition
- 5p- potentially fits into all of the above!

How do you help your patients and their families?

- Diagnosis
- Counseling
- Management
- Treatment

So why are you here today?

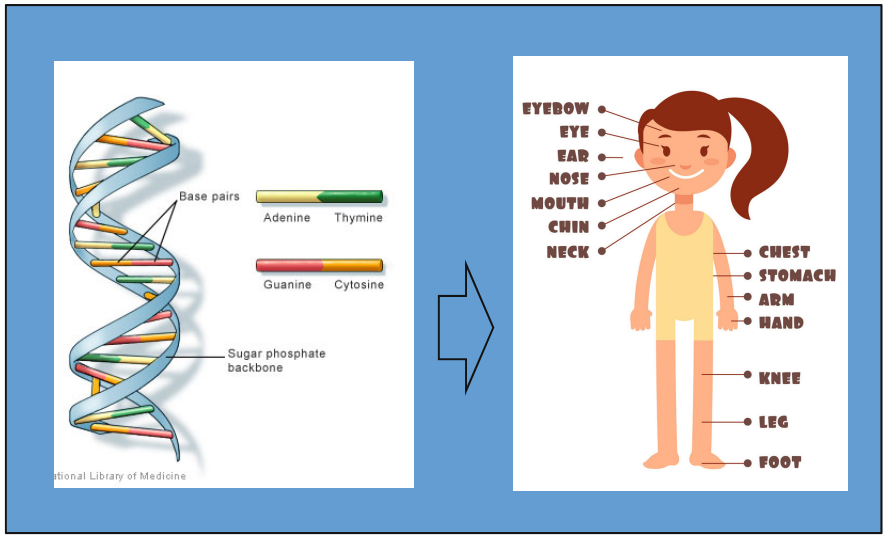
I am deeply committed to helping individuals and families affected by 5p- live the best lives possible!

Background on 5p- syndrome

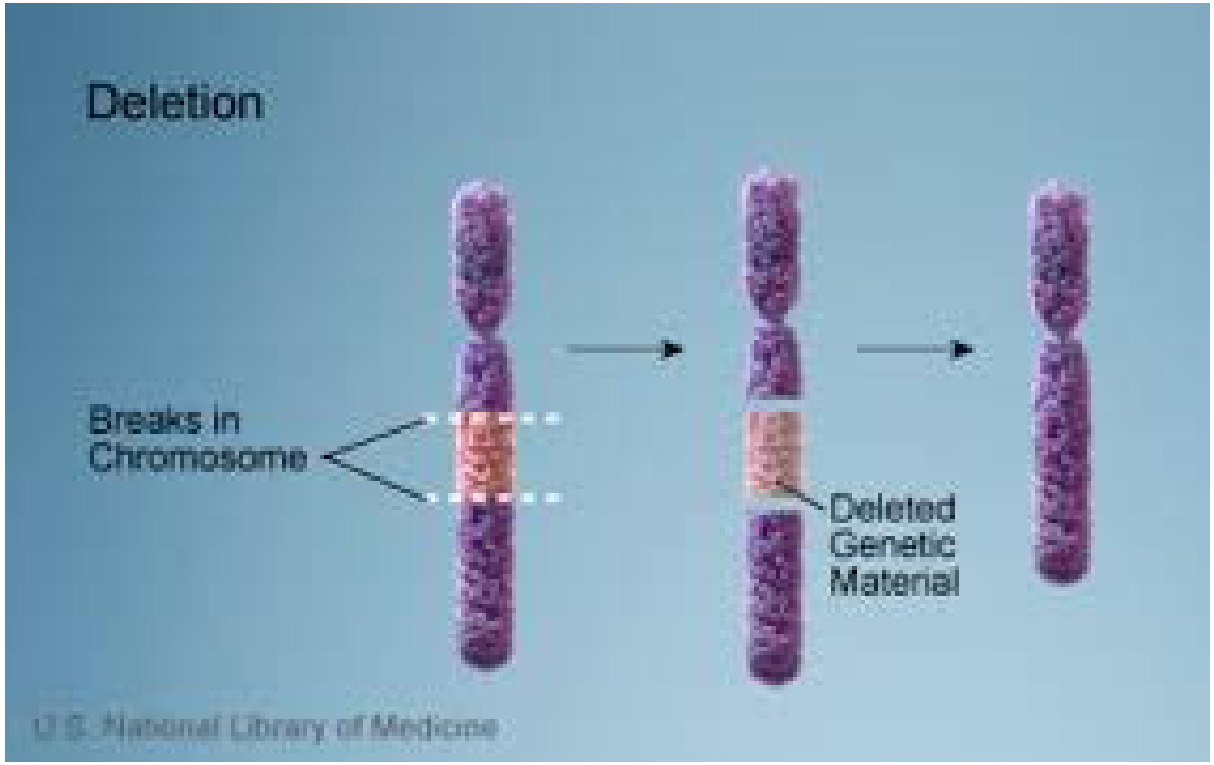
- First described by Dr. Jerome Lejeuene in 1963
- Epidemiology
  - 1 in 15,000 to 1 in 50,000 live births
  - One of the most common genetic deletions

Genetic “cause” of 5p-

- Missing genetic material
  - > Genes are the instructions for how our bodies are made
  - > We can have extra or missing instructions
  - > Missing or extra instructions can cause changes in our development

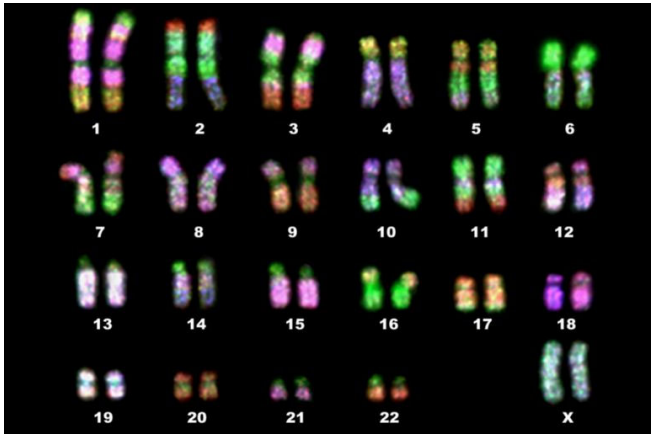


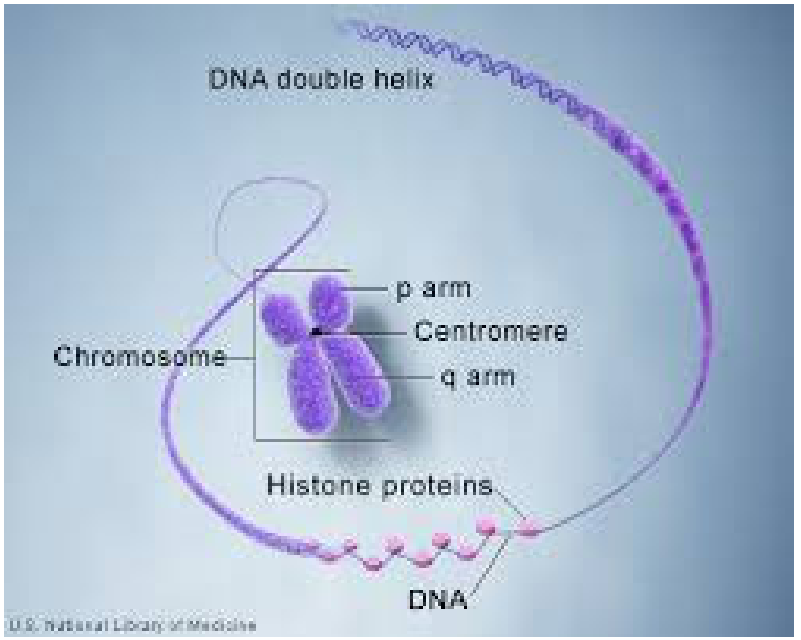
Genetic “cause” of 5p-



What does 5p- mean?

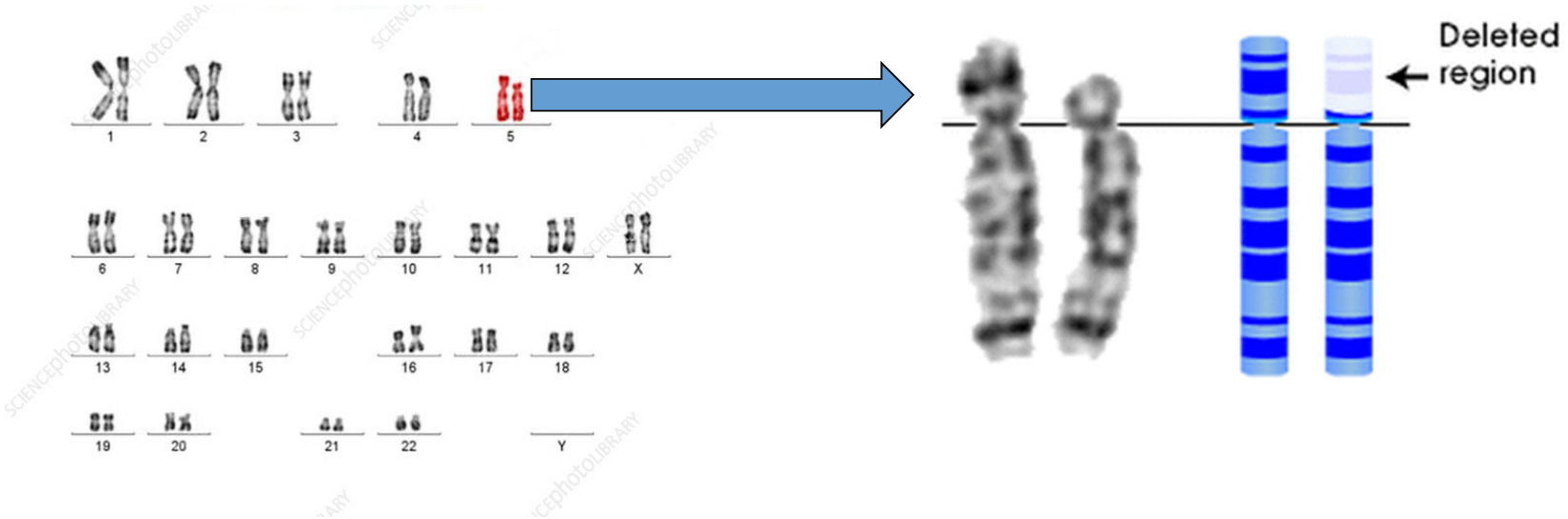
- Chromosomes are packages of genetic material
  - > Most of us have 46 pairs including one pair of “sex chromosomes”
  - > Chromosomes can be seen under the microscope
    - They are numbered according to size
    - Each chromosome has two arms
      - – P = small (“petite” = small in French)
      - – Q = large (looks different than a p!)





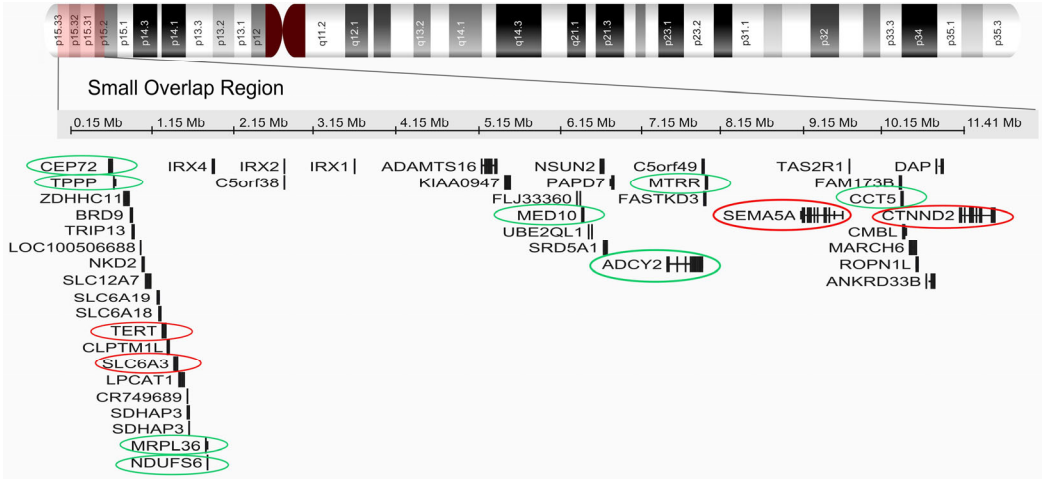
What does 5p- mean?

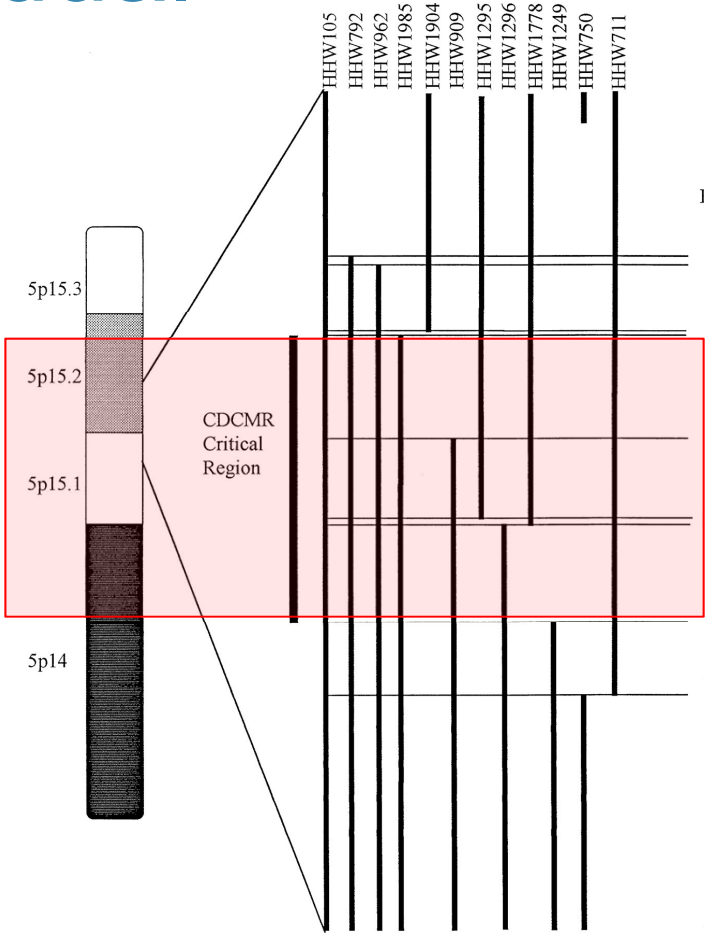
- 5p-
  - > 5 = chromosome number 5/5th largest of the chromosomes
  - > P = the shorter arm
  - > "-" = material is missing



Missing material is not the same in every individual

- 560kb-40Mb in size
- Different breakpoints
- “Critical region” 5p15.2-15.3



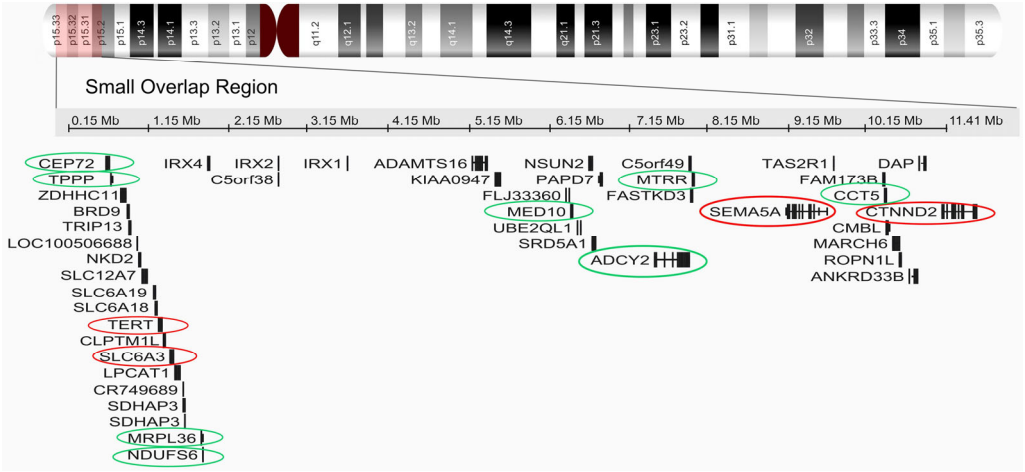


How does missing material cause problems in 5p-?

- We each have two copies of chromosome 5
- No copies of chromosome 5 = incompatible with life
  - > = too many missing instructions or “genes”
  - > There are at least 37 genes on 5p
- In 5p-
  - > One chromosome copy with missing genes
  - > The other copy has all genes present
  - > From some genes, no copies are “essential” → no issues with deletion
  - > For some genes, one copy is all you need → no issues with deletion
  - > For some genes, you need two copies → changes with deletion

How does missing material cause problems in 5p-?

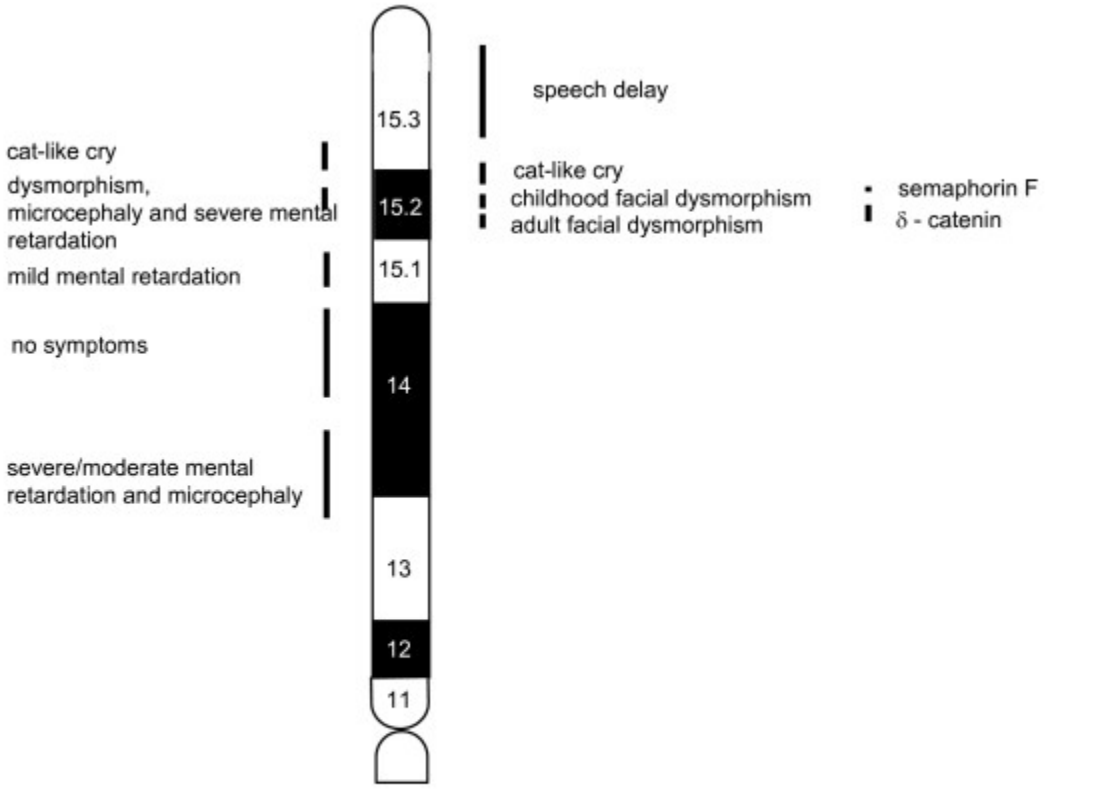
- For at least 5 genes on 5p, you need two copies
  - > =haploinsufficiency
  - > *TERT* (onset of hair greying/aging?)
  - > *SEMA5A* and *CTNND2* (brain development)
  - > *MARCH6/TEB4* and *FLJ25076* (cry pitch?)



What about genes and environment?

- For some genes, environment plays a role too
  - > = conditional haploinsufficiency
  - > At least 6 genes on 5p
    - *SLC6A3*
    - *CDH18*
    - *CDH12*
    - *CDH10*
    - *CDH9*
    - *CDH6*

Genetic “cause” of 5p-?



Overhauser *et al*., 1994 [2]
Gersh *et al*., 1995 [53]
Cerruti Mainardi et *al*., 2001 [56]

Church *et al*., 1995 [54],1997 [55]

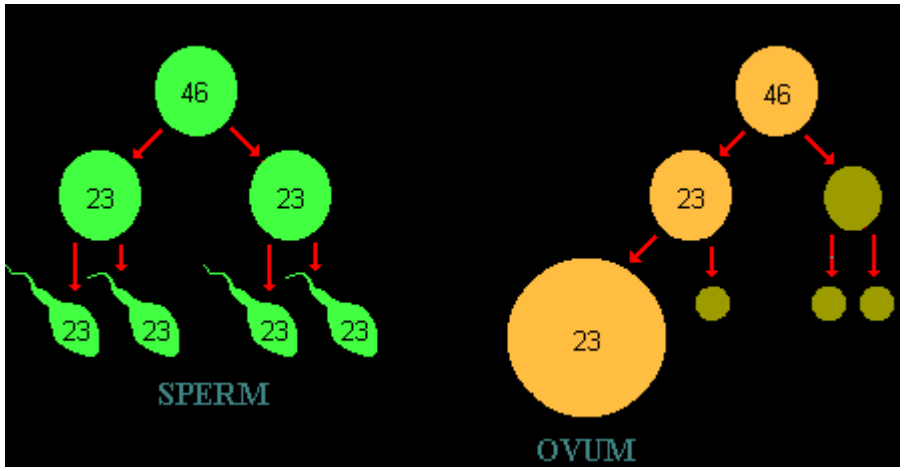
Simmons *et al*.,1998 [63]
Medina *et al*., 2000 [59]

Genetic does not always mean inherited!

- 80-90%: material lost during formation of sperm > eggs
- 10-15%: a parent carries a “balanced translocation”
- Other genetic variations are also possible

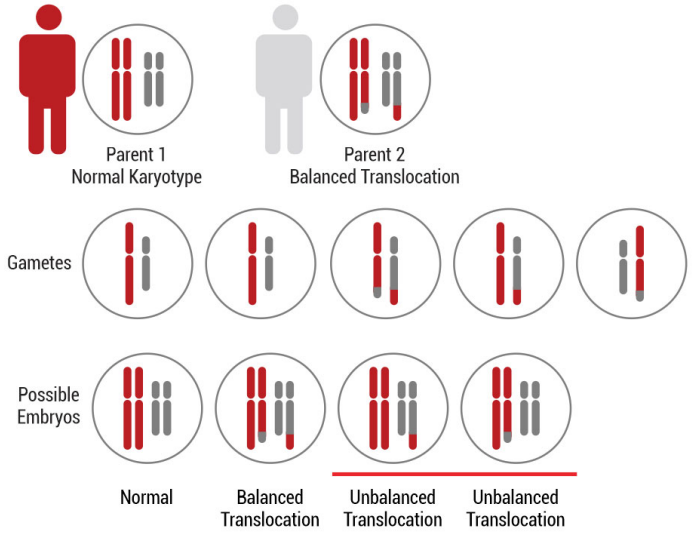
Genetic does not always mean inherited!

- 80-90%: material lost during formation of sperm > eggs
  - > Random occurrence
  - > Not because of any factor under our control
  - > Very low recurrence risk



Genetic does not always mean inherited!

- 10-15% of cases, a parent carries an “unbalanced translocation”
  - > Parent has a full set of genetic instructions in a different location
  - > Recurrence is subsequent pregnancies is possible

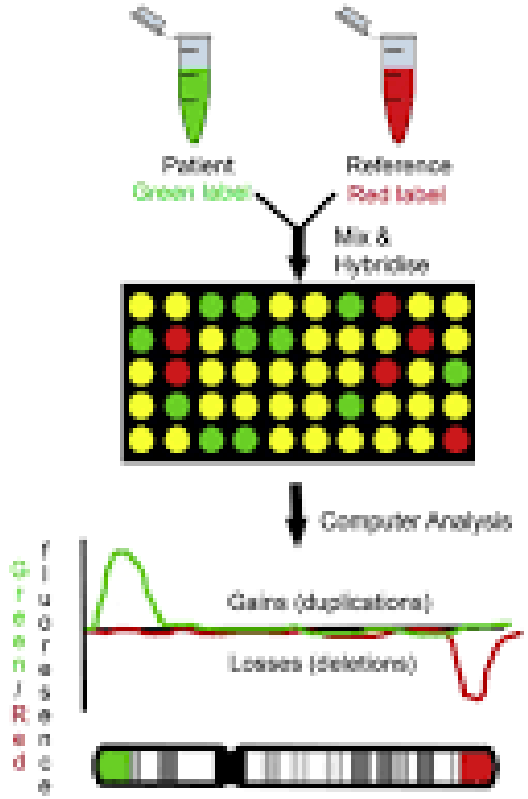


How is 5p- diagnosed

- Chromosome microarray
- FISH
- Karyotype
- Prenatal studies
  - NIPT?
  - CVS
  - Amniocentesis

How is 5p- diagnosed

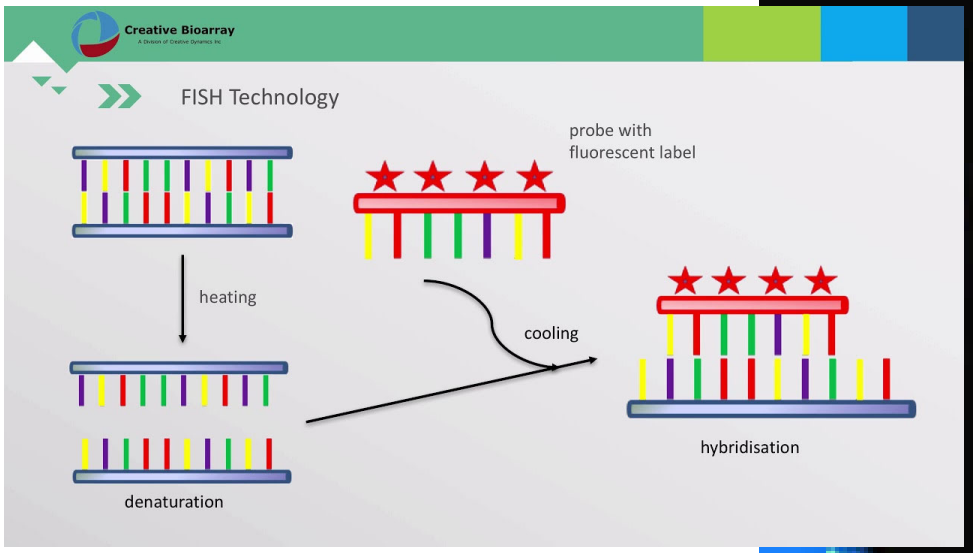
- Chromosome microarray

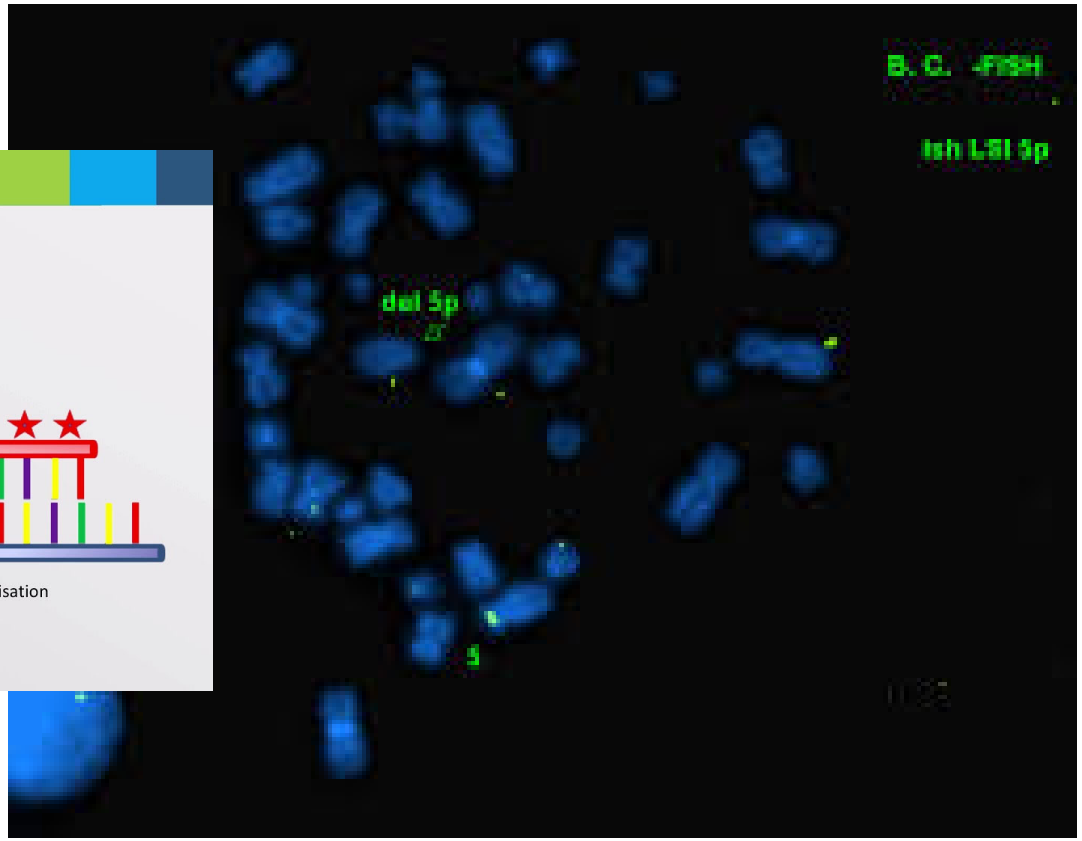


Spot	Patient	Control	Green : Red
	2 copies	2 copies	1.0 : 1.0
	3 copies	2 copies	1.5 : 1.0
	1 copy	2 copies	0.5 : 1.0

How is 5p- diagnosed

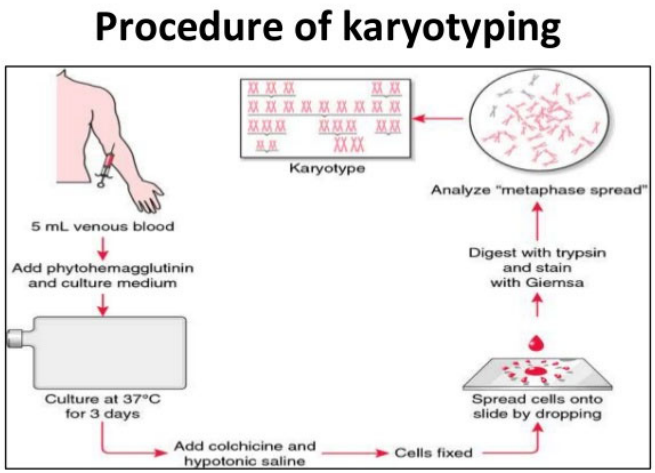
- FISH

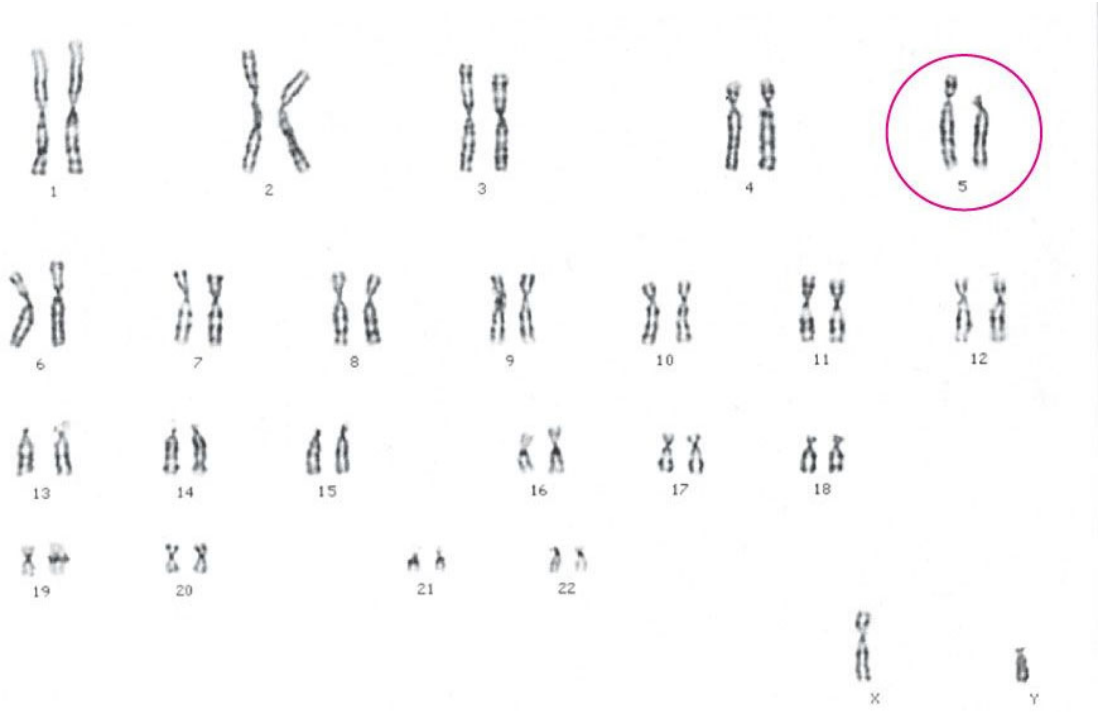




How is 5p- diagnosed

- Karyotype





Features of 5p-

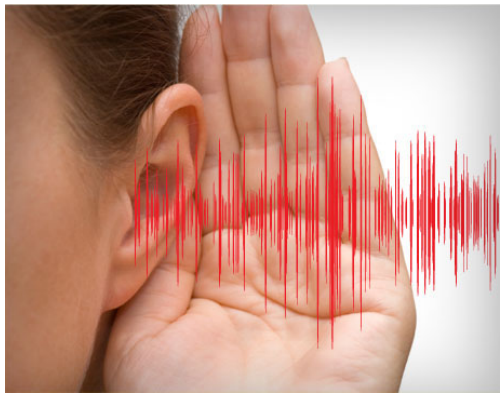
- Differ from individual to individual
- Distinctive cry in infancy
  - > https://www.youtube.com/watch?v=TYQrzFABQHQ

Features of 5p-: Appearance

- Individuals with 5p- look like their family members!
- Some features in common with other individuals with 5p-
  - > Smaller head
  - > Rounder face
  - > Wider spacing of the eyes
  - > Slant to the eye opening
  - > Extra folds at the inner corners of the eye
  - > Smaller jaw with dental crowding

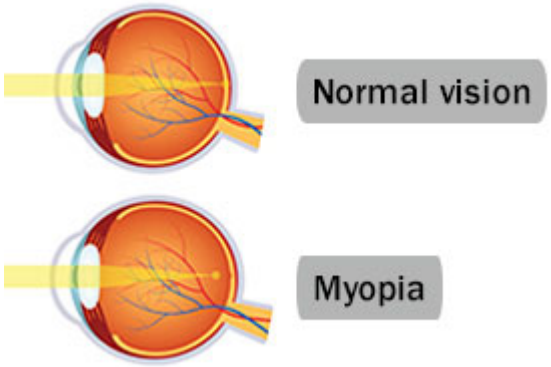
Features of 5p-: Hearing

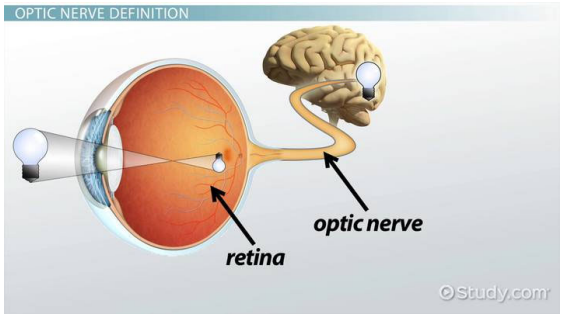
- Conductive loss is relatively common
  - > Recurrence or chronic ear infections
  - > 15% of children need tubes vs 1% of peers
- Sometimes, sensorineural loss occurs
- Up to 80%: extreme sensitivity to sound
  - > "Hyperacusis"
    - Persists into adulthood
    - Progresses over time
  - > →agitation, distress, easy startle



Features of 5p-: Vision

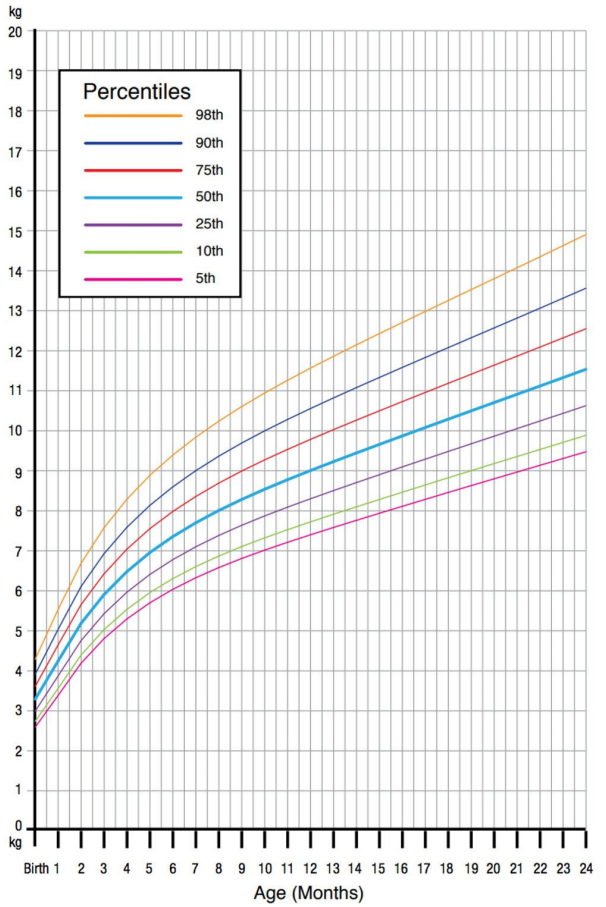
- Up to 50%
  - Nearsightedness (myopia)
  - Eye-crossing/Strabismus
  - Cataracts
  - Optic nerve issues





Features of 5p-: Stature and growth

- Most individuals are small-statured
  - Relative to family and peers
  - specific growth charts have been proposed
- Poor feeding (50%)
- Severe constipation (25%)
  - Can continue into adulthood



Features of 5p-: Ageing

- Puberty timing is normal
- Hair greying can occur in adolescence
- Life expectancy
  - > Most vulnerable period: 0-12 mo.
  - > Major mortality contributors
    - Heart conditions
    - Respiratory infections
  - > Can approaches the general population

Features of 5p-: Body systems

- Skeletal system
  - > 45% of individuals have spinal curvature (scoliosis)
- Nervous system
  - > Low tone/extra floppiness is very common
  - > Changes on brain imaging (MRI)
- Heart and Blood Vessels
  - > 30% of individuals are born with structurally different hearts
- Kidney
  - > Structural changes that affect the kidneys/urinary system

Features of 5p-: Immunity

- More frequent infections
  - Ear infections
  - Respiratory infections
- Longer course of infections
- Higher likelihood complications
- But NOT “true” immunodeficiency

Features of 5p-: Development

- Most children will reach developmental milestones later than their peers
  - > Sitting up at 14 months
  - > Walking unassisted at 3-4 years
  - > Dressing at 6-7 years
  - > Potty training at 7-8 years
- Improvement with good support!
  - > Prior to 1960s vs. now
  - > Early intervention results in 2-18 month improvement

Features of 5p-: Development

- Intellectual disability is common
  - > Mild to profound range
  - > Rare cases of no intellectual disability are reported
- Speech delays are common
  - > Children generally can understand a lot more than they can say
  - > Communication devices and/or sign language are helpful for many
- Behavior
  - > Most children are very busy and have challenges focusing
  - > Anxiety, difficulty with routine disruption, and stereotypies are common

Medical Management

- There is currently no “cure” for 5p-
- Management is symptom-driven
  - > Screening for issues known to be associated with 5p-
  - > Treatment of issues identified in screening
  - > Therapy support to promote developmental progress
  - > Behavioral health support
  - > Educational modification
  - > Goals:
    - Maximize quality of life
    - Reach full potential
    - Minimize health problems

How might a geneticist help?

- Making the diagnosis
  - > Based on features of 5p-
  - > Confirmatory testing
- Explaining the diagnosis to loved ones
  - > Genetics and testing results
  - > What to expect
- Health and well-being promotion
  - > 5p- specific “know-how”
  - > Advocacy!

What to expect from your genetics team

- First visit
  - We will spend a long time with you! Visits are typically an hour long
  - Geneticist and genetic counselor
  - Health history, family history, detailed exam
  - Baseline management plan based on 5p- specific considerations
- Follow up
  - At least annually
  - Review interim health and social history
  - Revise management plan
  - We want to work with and compliment your PCP and other docs!

Management: Hearing and Vision

- Ensuring that screenings and follow-up have occurred
  - Vision
  - Hearing
- Reviewing history for “sub-clinical” infections
- Exam for “sub-clinical” features
  - Eye crossing
  - Tracking
  - Fluid in the ears

Management: Hearing and Vision

- Interdisciplinary referral/discussion
  - > ENTs regarding tubes
  - > Audiology regarding hearing loss
    - Follow up on conductive losses, hearing aids, etc.
  - > Audiology regarding hyperacusis
    - Ear-plugs, noise dampening usually NOT ideal long-term solutions
    - Broadband noise therapy
    - Cognitive behavioral therapy
  - > Ophthalmology regarding specific concerns

Management: Stature and growth

- Is growth in all three parameters progressing appropriately?
  - Height, weight, head-circumference
  - We “allow” small stature, but need to see progress!
- Poor feeding
  - General screening questions if growth looks good
  - If growth is poor, further management
    - Dietician?
    - Therapies?
    - Multi-Disciplinary “feeding clinic”?
- Severe constipation
  - Often underrecognized by families and healthcare professionals
  - Questions to frame the scope of the problem
  - Review of treatment options/referral if needed

Management: Body systems

- Heart and Blood Vessels
  - > Exam for murmurs/other features
  - > ECHO
  - > Consider of cardiology referral
- Kidney
  - > Blood pressure check
  - > Exam
  - > Consideration of nephrology or urology referral

Management: Body systems

- Skeletal system
  - > Clinical exam
  - > +/- xrays
  - > +/- referral to orthopedics
- Nervous system
  - > Anticipatory guidance for hypotonia and imaging findings
  - > Assess for progress in tone
  - > Therapy and/or physiatry referral

Management: Immunity

- Anticipatory guidance
- Prevention
  - Immunization review
    - Patient
    - Close contacts
  - Synagis eligible?
  - Good handwashing

Planning for school success

- Consideration of formal neuropsychology assessment
  - Ideal if prior to starting school
  - Often requires insurance appeal for “medical necessity”
- Assist families in choosing a school
  - Where to attend
  - When to start
- Advocate for services in school
  - Point of contact for teachers (if desired)
  - Letters of support
  - Suggestions for modifications

Management: anything else?

- We want to help!
- Often a good go-to when you're not sure where to go!
- Letters for accommodations
  - School
  - Airport security
  - Noisy environments
- Counseling
  - Disclosure of diagnosis
  - Dealing with family/friends
- Support groups/networking

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Questions?

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Thank you!