How genes affect our speech

Heather Workman, MS, CGC
Genetic Counselor
Ohio Region II Genetics Center
Children's Medical Center
Dayton, Ohio

Objectives

- What is a genetic counselor
- Review of problems that can lead to speech issues
- Common genetic syndromes seen by a SLP
- Psychosocial barriers to care

What is a genetic counselor?

- Master's degree prepared health professional with skills in Medical Genetics and Counseling
  - backgrounds in biology, genetics, nursing, psychology, public health, social work

- Genetic counselors work as members of a health care team

Genetic Counselors...

- ***Identify*** families at risk
- ***Investigate*** the problem present in the family
- ***Interpret*** information about the disorder
- ***Analyze*** inheritance patterns and risks of recurrence
- ***Review*** available options with the family.

Genetic Counseling is Non-Directive

to respect Patient Autonomy

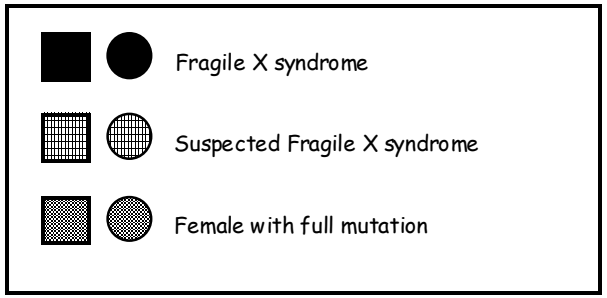
Genetic Counselors Serve...

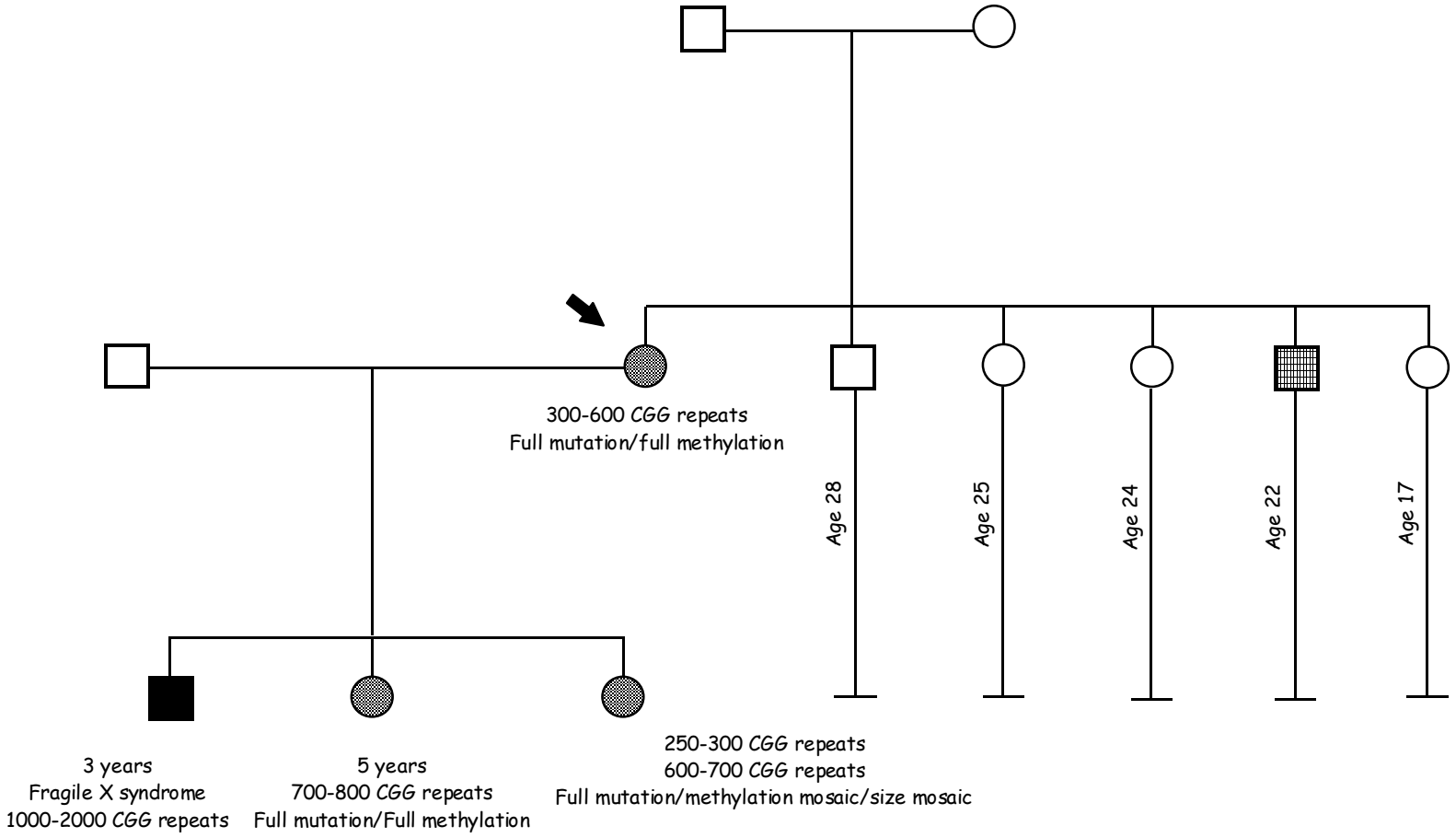
- Families of newborns with congenital anomalies
- Newborns with abnormal newborn screening tests
- Children with developmental delays
- Adolescents with atypical pubertal development
- Adults with infertility / multiple miscarriages
- Families with cancers
- Families with adult onset disorders

A Genetic Counseling Visit

- Introduction
- Contracting
- Medical History
- Family History
- Diagnosis/Differential
- Natural History
- Management
- Inheritance/Implications for Family members
- Testing strategies
- Insurance issues
- Resources/psychosocial implications
- Follow up/Letter

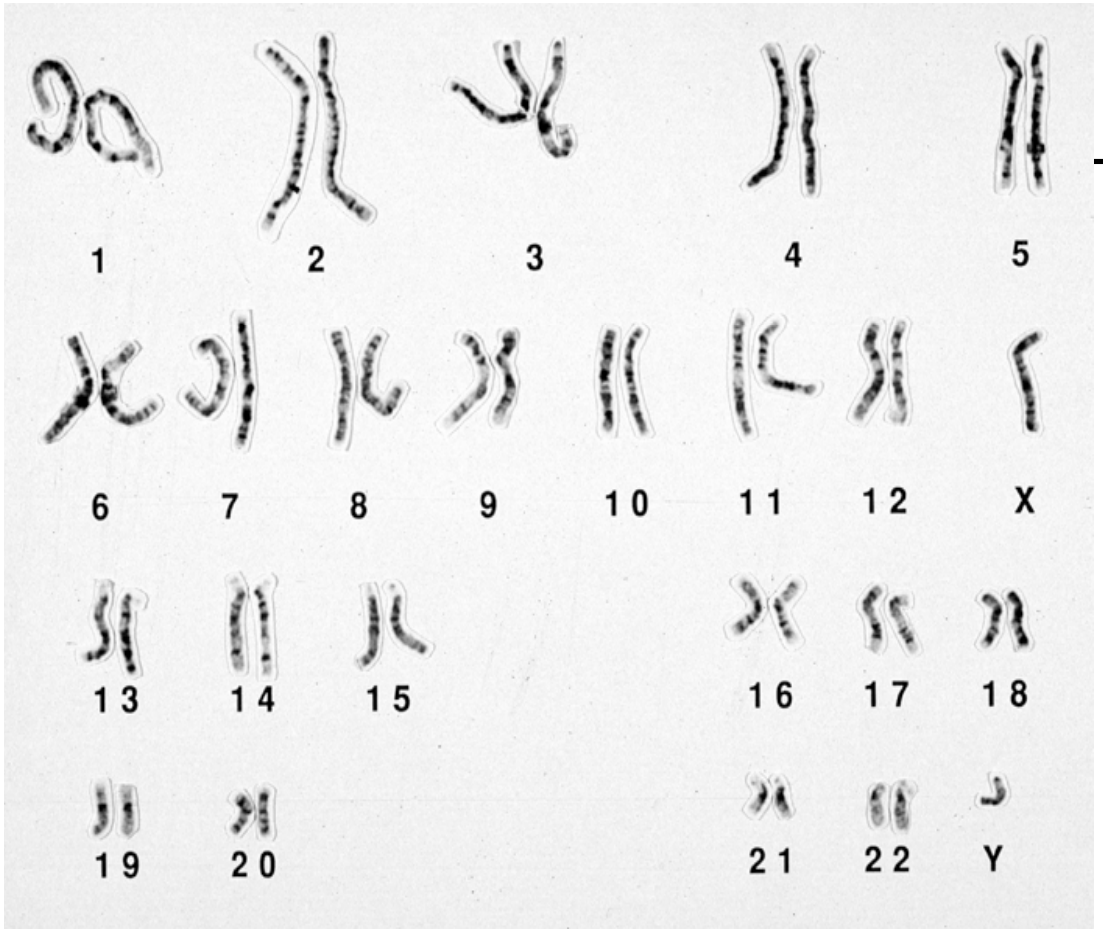
DAYTON CHILDREN'S
The Children's Medical Center of Dayton

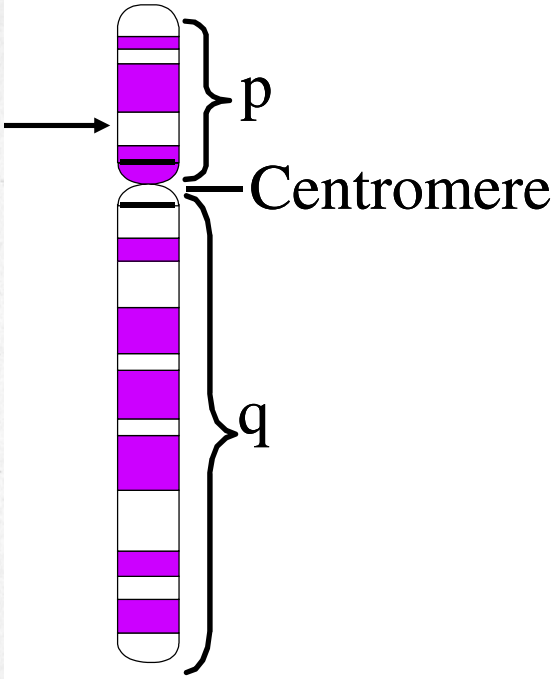




A brief overview…

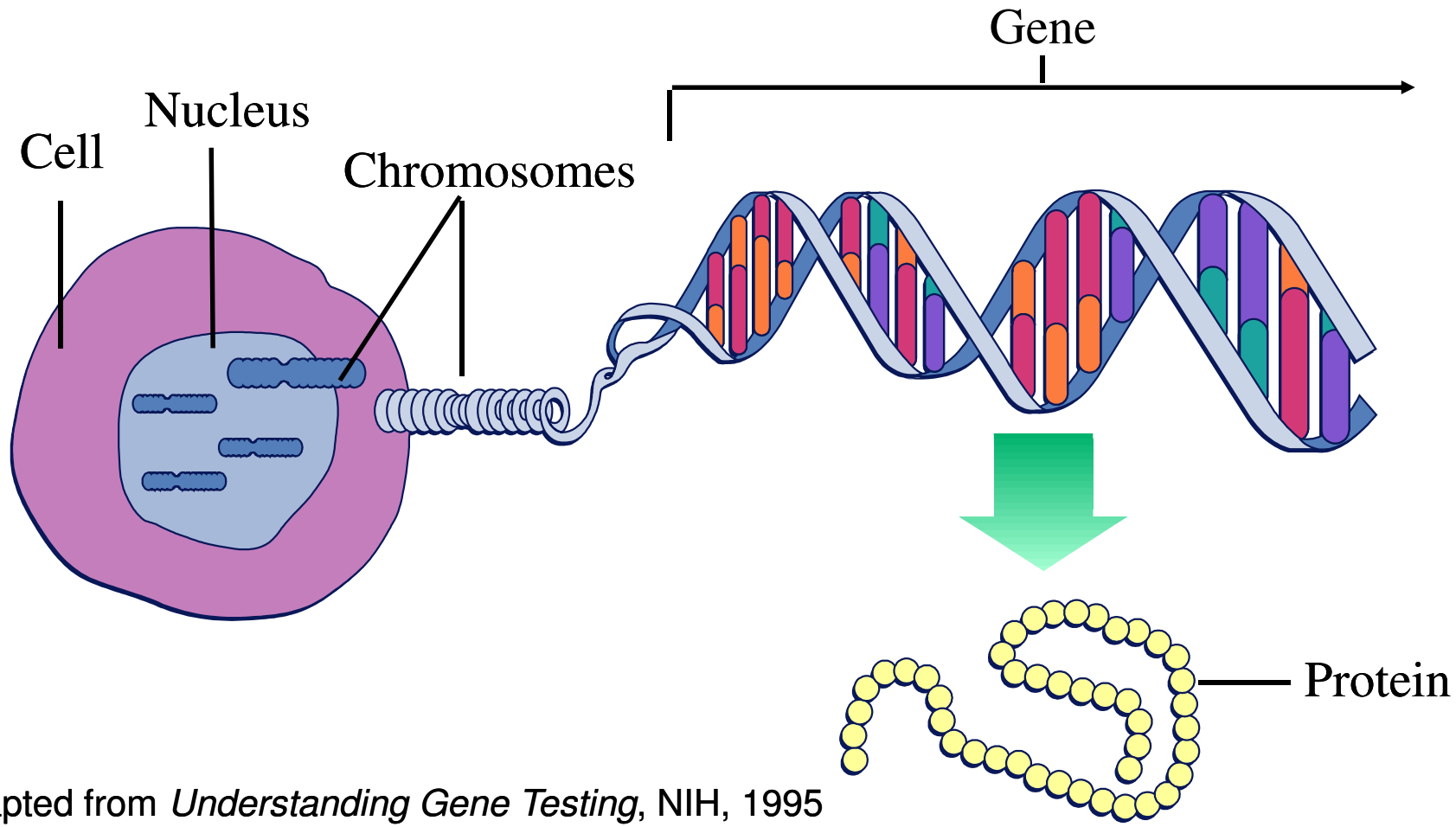
Normal Male Karyotype





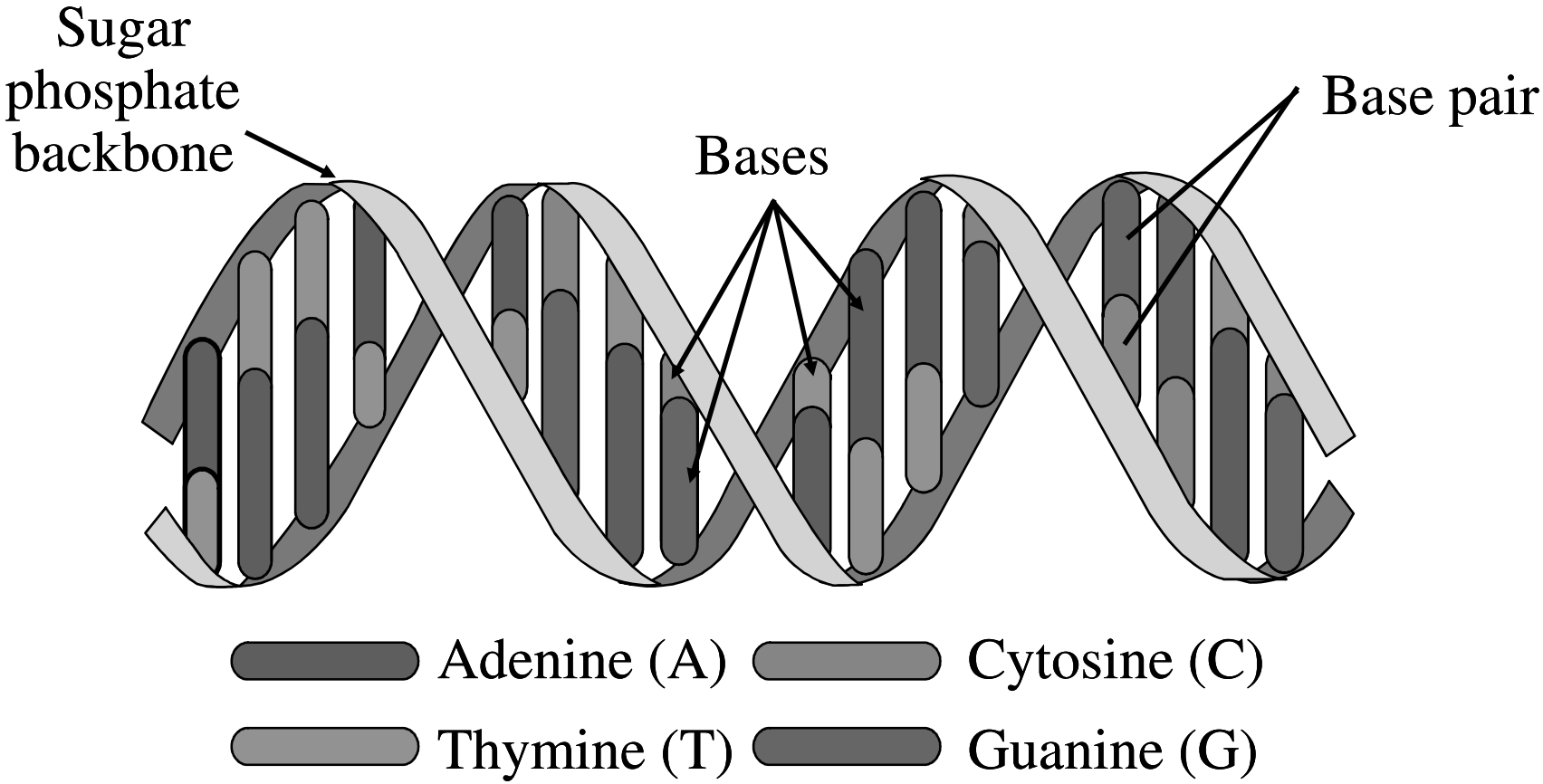
Chromosome 5

Chromosomes, DNA, and Genes



Adapted from *Understanding Gene Testing*, NIH, 1995

The DNA Double Helix



Genome

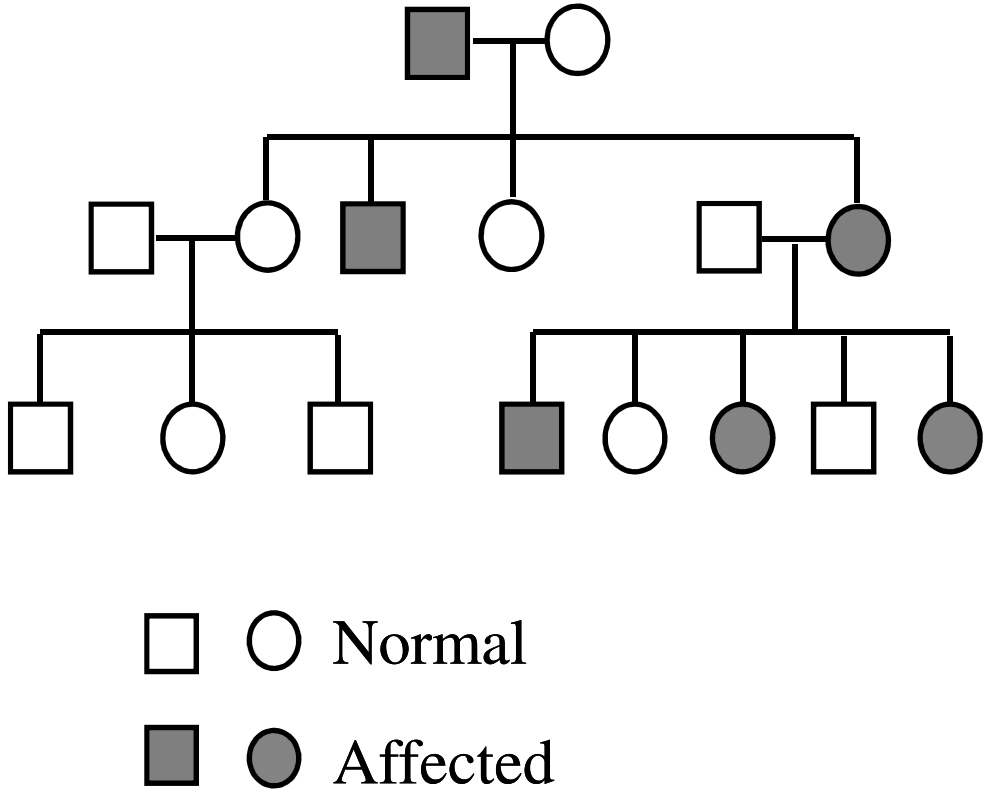
- Complete DNA sequence of an organism
- Estimated 3 billion base pairs DNA in humans, coding for approx. 30,000 genes
- > 20% of genes in each individual differs from population “norm”
- Mutation = alteration in DNA sequence
- Polymorphism = benign genetic variation
- When mutation changes normal function of protein, result may be genetic disease

Mendelian Inheritance

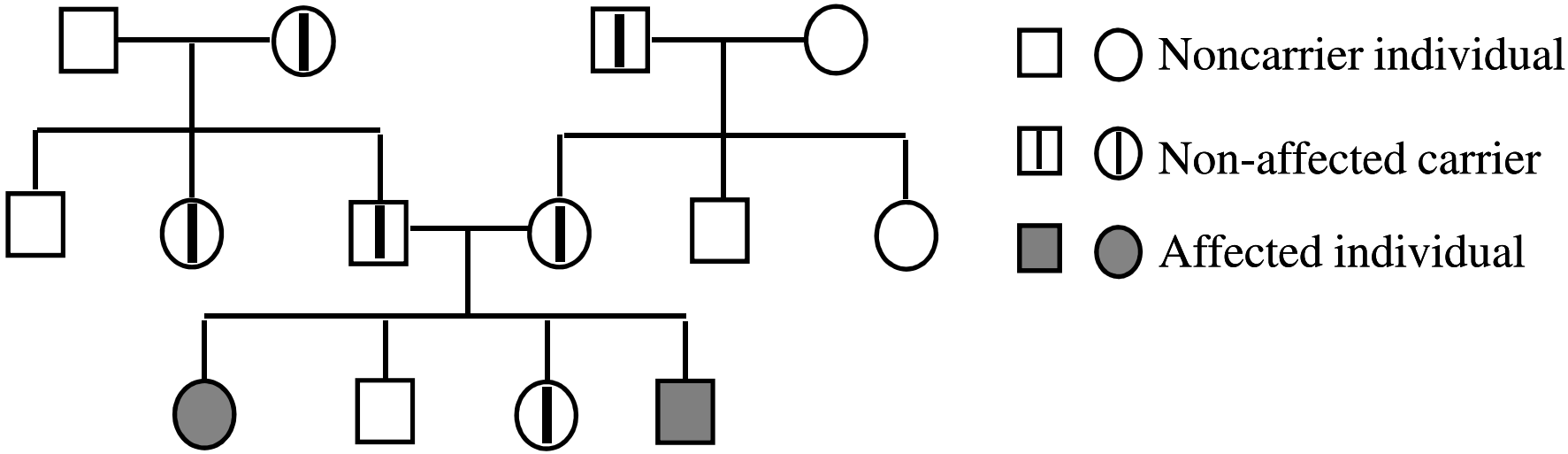
- Dominant
- Recessive
- X-linked
- Other
  - New mutations
  - Imprinting
  - TrinAutosomal Dominant Inheritance
  - Triucleotide repeats

Autosomal Dominant Inheritance

- Each child has 50% chance of inheriting the mutation
- No “skipped generations”
- Equally transmitted by men and women

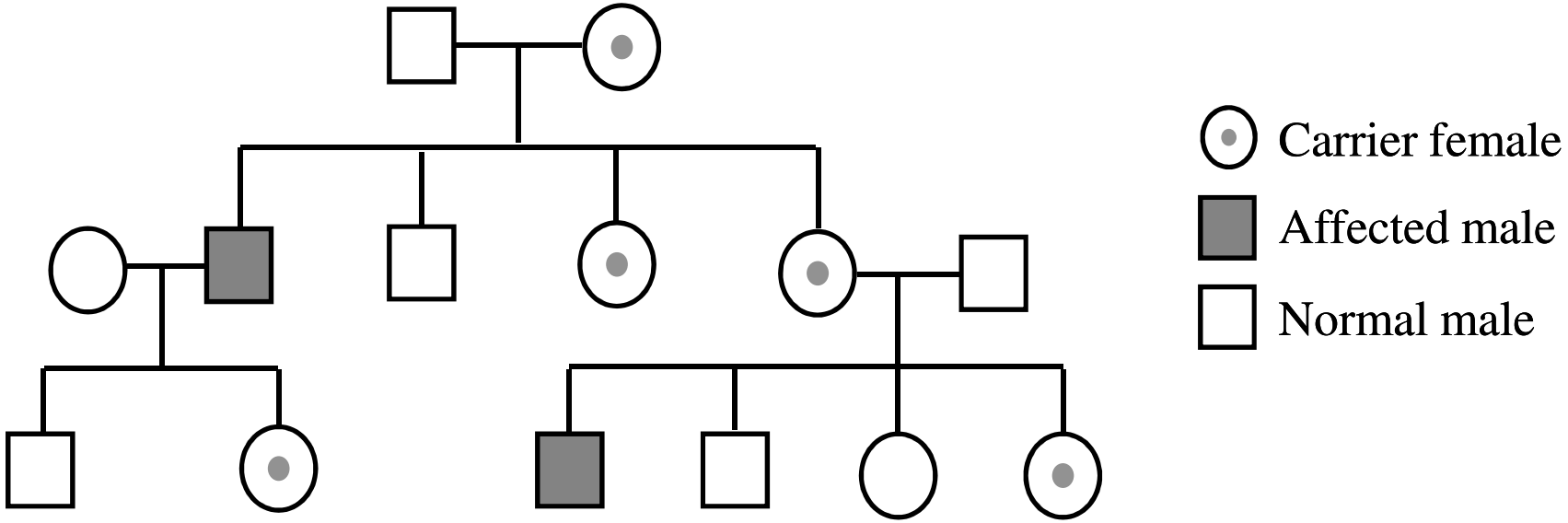


Autosomal Recessive Inheritance



- Two germline mutations (one from each parent) to develop disease
- Equally transmitted by men and women

X-Linked Recessive Inheritance



- Mutant genes are on the X (sex) chromosome
- Women must inherit 2 mutated copies to be affected
- All men who inherit the mutation are affected (only one X chromosome)

Etiology

- Environmental factors
- Genetic syndrome/birth defect
- Prenatal perinatal factors
- Traumatic brain injury
- Hearing disorders
- Anatomic problems
- Family history
- Processing defect

Genetic Factors

- The family history
  - 39% will have a positive family history of language problems (range: 24-77%)
- Twin studies
  - 72-90% for monozygotic twins
  - 49-62% for dizygotic twins

Candidate Genes

- Identified using linkage studies
  - Identify genetic loci shared between affected individuals in a family
- No one candidate gene has been associated
- May be a combination of multiple genes
- May be distinct to a single family

Genetic syndrome/Birth defect

- Cleft lip and/or palate
- Non-syndromic mental retardation
- Williams syndrome
- Fragile X syndrome
- Down syndrome
- 22q deletion syndrome (VCF)
- Chromosomal anomaly

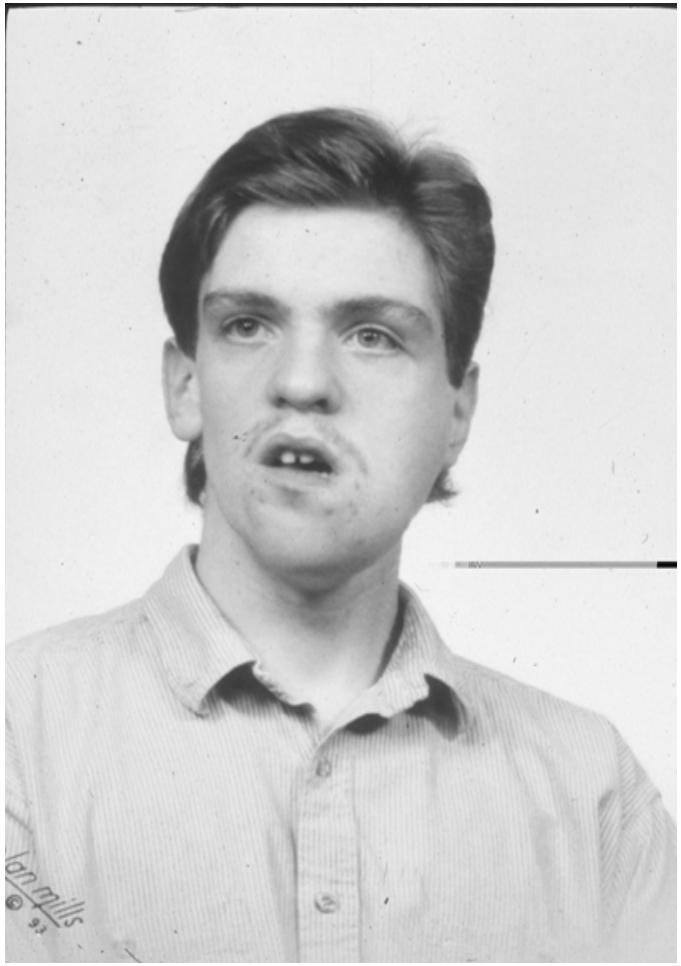
Isolated speech issues/Syndrome

- Other areas of development
- Family history of similar issues (
- Dysmorphic facial features
- Multiple Birth defects/health issues (i.e. heart, kidneys, etc.)
- More than three major anomalies

Fragile X Syndrome

- Defect on X chromosome
- Affects 1 in 2000 males and 1 in 4000 females

Fragile X Syndrome



- Long face/large ears
- Enlarged testes
- Hypotonia/loose joints
- Mental retardation/ learning disabilities
- Behavior problems/ autism
- Hyperactivity/ attention problems
- Speech delay

Fragile X

- CGG repeat on X chromosome
- Normal size between 6-50 repeats
- Premutation between 50 and 200 repeats (variable phenotype; expansion during meiosis in females)
- Full mutation greater than 200 repeats (nearly all males display fragile X phenotype and 2/3 of females have some degree of mental retardation)

Trinucleotide Repeat Disorder

Nucleotide runs of three are excessively repeated in the DNA.

CGGCGGCGGCGGCGGCGGCGGCGG

Features of Trinucleotide expansions

- Dynamic Mutation Triplet repeats become unstable once they reach a certain size and can increase in size over successive generations.
- Anticipation A genetic condition has an earlier age of onset and worsens over successive generations.
- Premutation Trinucleotide repeat of intermediate size between normal (*stable*) length and expanded (*disease-associated*) length.

Features of Trinucleotide Expansions

In general, the greater the expansion, the more significant the condition.

The stability of the trinucleotide is sometimes influenced by the sex of the transmitting parent.

Fragile X

- A male carrying a premutation is known as a "transmitting" male. He has a normal phenotype but will pass the premutation to all of his daughters.

- His daughters will have normal phenotypes, but their repeat size may increase significantly when passed on to their offspring, who will be affected.

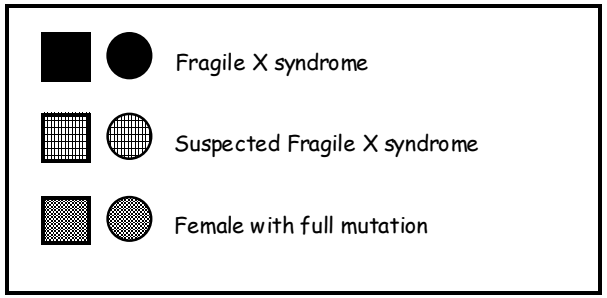
Case example: Sara

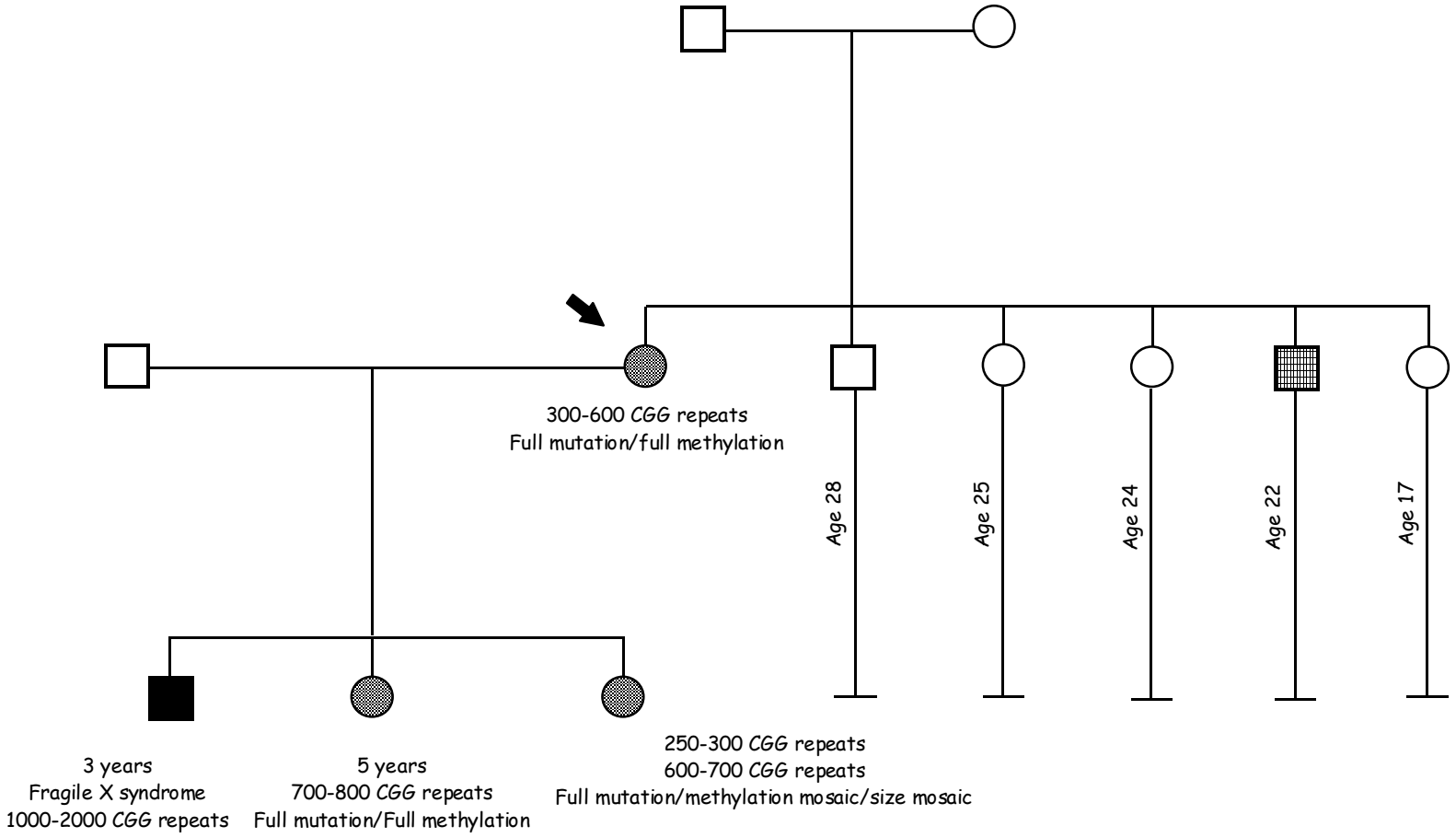
- Sara was referred to Dev Peds to rule out a diagnosis of autism
- Sara's mother reported that she had a brother (Sara's uncle) with MR
- Years later, Sara had a little brother who was eventually diagnosed with gross motor and language delays

Case example: Sara

- Sara's brother was diagnosed with Fragile X syndrome
- A referral was made to genetics at which time Sara, her typical sister and mother also had testing

DAYTON CHILDREN'S
The Children's Medical Center of Dayton





Psychosocial barriers to care

- Multiple children affected with Fragile X syndrome (dev delay, autism, speech and language delay)
- Maternal factors
- Insurance issues
- Resources
- Guilt/anxiety

For more information

National Fragile X Foundation

www.FragileX.org

Contiguous gene syndromes

Microdeletions or microduplications of chromosomal material resulting in disruption of function in several genes located in a row, each independently contributing to the phenotype

Contiguous gene syndromes

- May or may not have a visible cytogenetic abnormality
- Usually occur sporadically but may be familial (dominant)
- Specific features of the syndrome may occur as single mendelian traits
- Ex: 22q11.2 deletion syndrome

22q11.2 deletion syndrome

- Velocardiofacial Syndrome
- Cleft palate/ velopharyngeal insufficiency
- Hypernasal speech
- Congenital heart defects (conotruncal)
- Characteristic facies
- Learning disabilities
- Behavioral problems

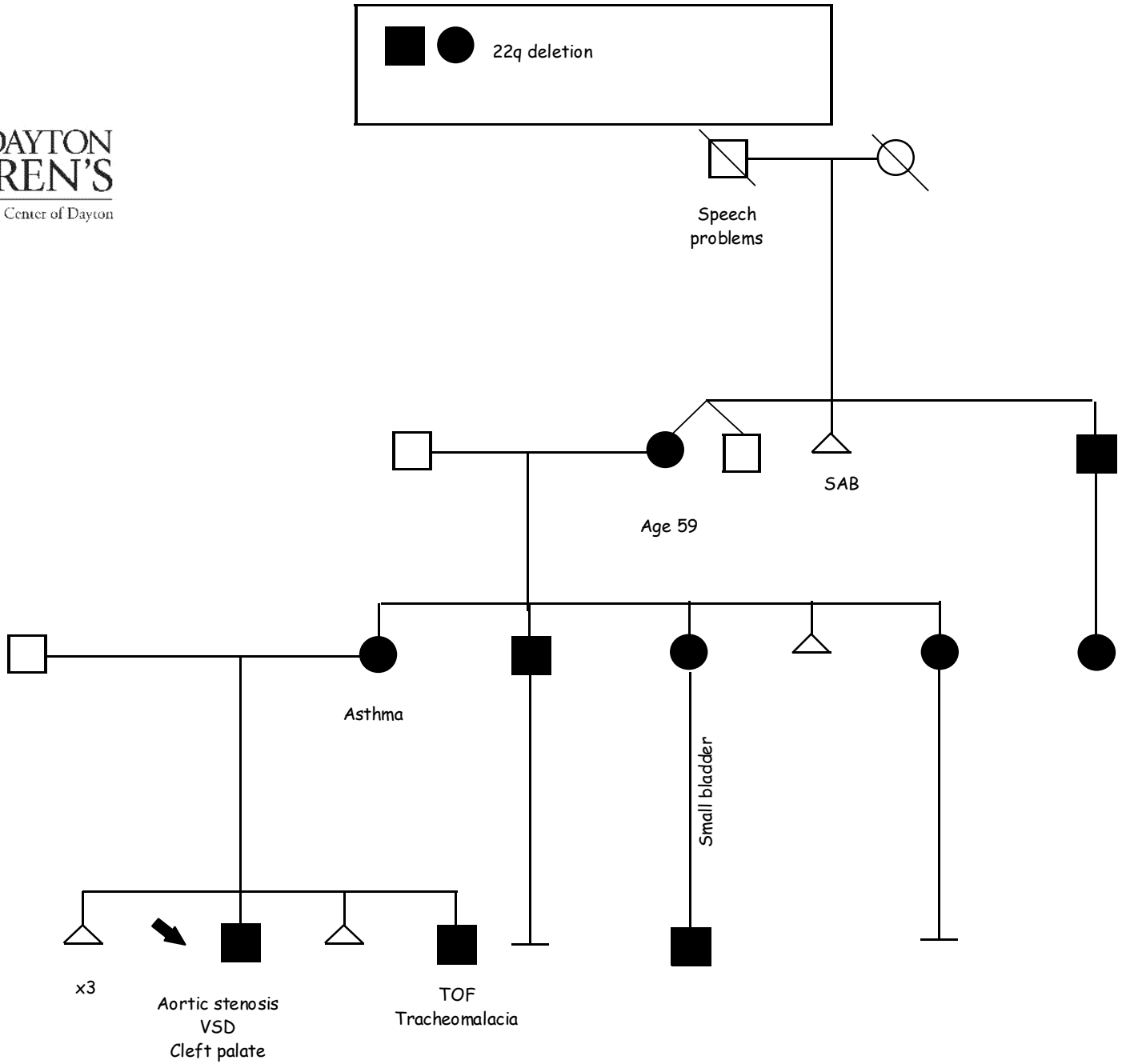
22q11.2 deletion syndrome

- Velocardiofacial Syndrome
- Cleft palate/ velopharyngeal insufficiency
- Hypernasal speech
- Congenital heart defects (conotruncal)
- Characteristic facies
- Learning disabilities
- Behavioral problems

Case example: Ryan

- Ryan was born with a conotruncal heart defect
- Around the time of heart surgery he was diagnosed with 22q11.2 deletion syndrome
- There was no family history of features of 22q to suggest this had been inherited….

DAYTON CHILDREN'S
The Children's Medical Center of Dayton



Barriers to care…

- Childhood
  - Speech, behavior problems, dev delays
- Adolescence
  - Speech, psychiatric disease, socialization problems
- Adulthood
  - Psychiatric disease, employment, independence, chronic medical issues

For more information

Velo-Cardio-Facial Syndrome Education Foundation

www.vcfsef.org

The International 22q11.2 Deletion Syndrome Foundation, Inc.

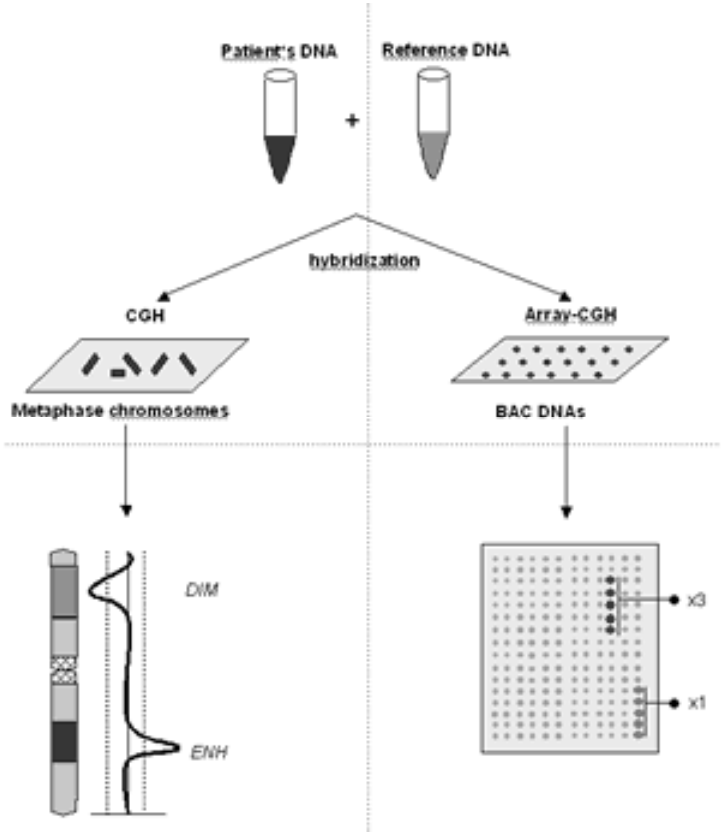
www.22q.org

Case examples from cleft lip and palate clinic

- Case example: Holly
  - cleft palate
  - Significant speech delays
  - Dysmorphic facial features
  - Failure to thrive
  - Mom has a history of receiving speech therapy; normal intelligence
- Case example: Matt
  - Cleft palate
  - Signifigant motor and speech delays
  - Dysmorphic facial features
  - Failure to thrive
  - Mom has a history of receiving speech therapy; learning disabilities

Chromosome Comparative Genomic Hybridization

- Microarray
- Can detect small deletions/duplications within the genome
- Different types/cover different areas of chromosomal material
- Should be done after or with traditional karyotype
- Will not detect balanced rearrangements or small DNA mutations


Patient's DNA
Reference DNA
+
hybridization
CGH
Array-CGH
Metaphase chromosomes
BAC DNAs
DIM
ENH
x3
x1

Case example

- Both Holly and Matt had normal karyotypes
- Both were tested using the chromosome microarray
- Holly reported as a normal female
- Matt was found to have a small deletion on chromosome 9

Case example: Matt

- Parents should be tested
- Matt's mom
  - Dysmorphic facial features
  - Short stature
  - Learning disabilities
- Found to have the same chromosome 9 deletion

What to tell family?

- Most likely related to findings in Mom and Matt
  - Explanation?
  - Information for future generations
- Little information available
  - No natural history
  - Little/no information available on outcomes

Contact Information

Heather Workman, MS, CGC
Certified Genetic Counselor
Department of Medical Genetics
Dayton Children's Medical Center
One Children's Plaza
Dayton, OH 45404
Ph: 937-641-3800
Fax: 937-641-5325
Workmanh@childrensdayton.org