Basic Genetics for Ophthalmologists (Part 1 of 2)

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Question 1

Which of the following is a disease causing mutation?

1. **Nonsense**
2. **Missense**
3. **Frameshift**
4. **I don’t know**

Question 2

A polymorphism

1. **Causes disease**
2. **Is a normal variant**
3. **Occurs only in affected family members**
4. **Always involves one codon**

Question 3

If the patients has more than one organ system involved…

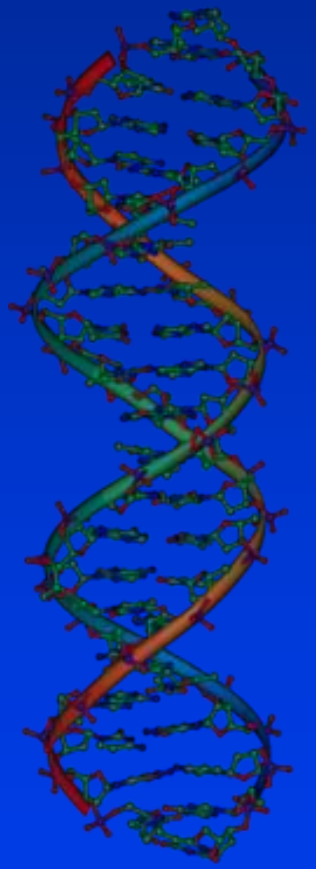
1. **More than one gene must be involved**
2. **miRNA is the cause**
3. **It could be due to a single gene**
4. **Order whole exome sequencing**

Question 4

A “negative” genetic test means

1. Wrong gene tested
2. Wrong disease suspected
3. Wrong test selected
4. Any of the above

Why know this?



What is a gene?

The basic ingredients

A = adenine

G = guanine

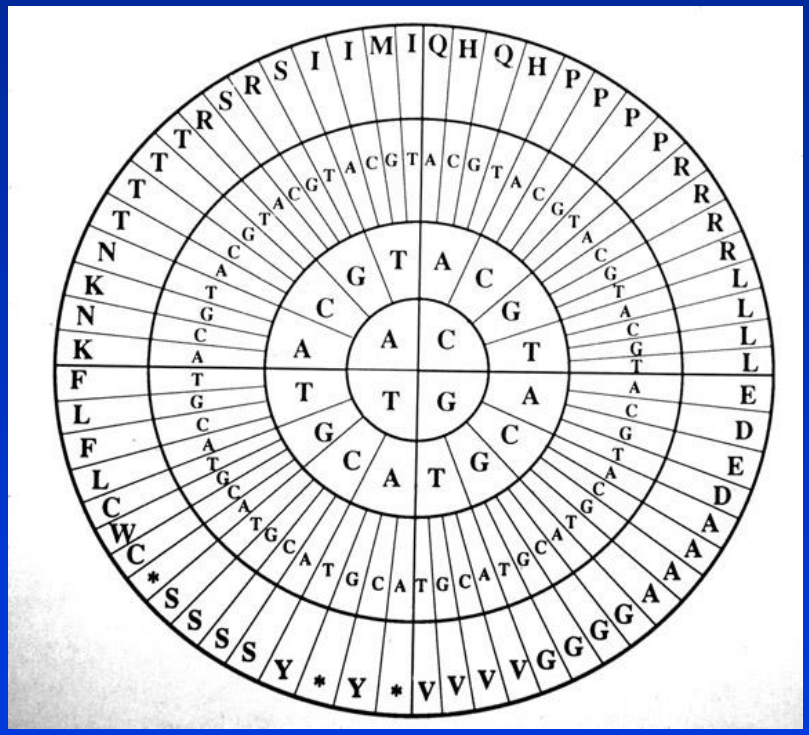
T= thymidine

C = cytosine

(U = uracil)

AGTGGCTACGAATGCAGT

Nucleotide triplets = codons



Symbols for amino acids

Amino acid	Three-letter symbol	One-letter symbol
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Asn and/or Asp	Asx	B
Cysteine	Cys	C
Glutamine	Gln	Q
Glutamic acid	Glu	E
Gln and/or Glu	Glx	Z
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V

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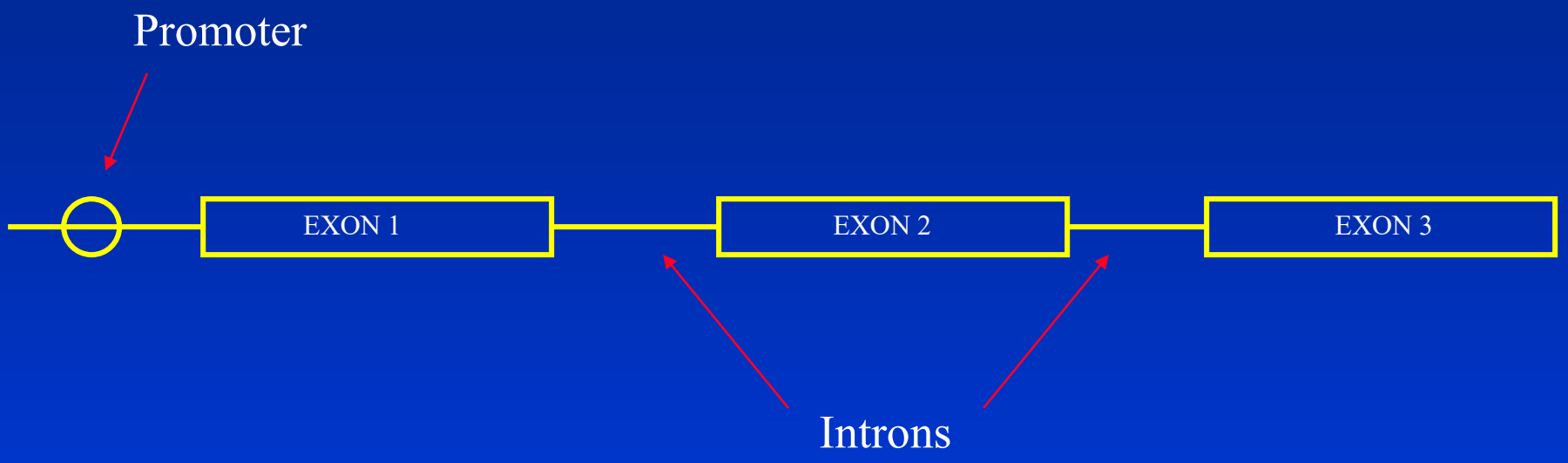

Promoter
EXON 1
EXON 2
EXON 3
Introns

What do genes do?

- Make proteins
  - building blocks
  - enzymes
  - regulators (transcription factors)

DNA

transcription

mRNA

translation

Protein

One gene can make many different proteins

+ posttranslational protein modification

Role of RNA

miRNA = microRNA

noncoding, usually 22nucleotides, inhibit target RNA translation

siRNA = short interfering RNA

binds and repressed mRNA

The Human Genome

3,164,700,000 nucleotides

20,000 genes

function unknown for most genes

< 2% of genome actually codes for proteins

99.92% sequence identical in all people

The Human Genome

90% in common with mice

divergence 50 million years ago

75% genes in common with fly!

Polymorphisms

vs

mutations

Polymorphisms

SNP's > 10 million nucleotides

= 0.3% of genome

submicroscopic copy number variation

del, dup, inversions…

affect up to 500,000 nucleotides

can affect up to 20 genes

we are only 99.8% the same!

Mutations

predict biologic error

not present in ethnic controls

segregates with disease

evolutionary conservation

demonstrated in models

- lab
- animal

Mutation vs Polymorphism

literature/databases

previously reported?

similar variations?

Don’t order a test…

…unless you know what to do with the result!

What does a “negative” test mean?

right disease, wrong (unknown) gene

wrong disease

not complete analysis

promoter

non paternity etc

error

AGTGGCTACGAATGC

AGTGGCTACGAATGC

AGTGGCTCCGAATGC

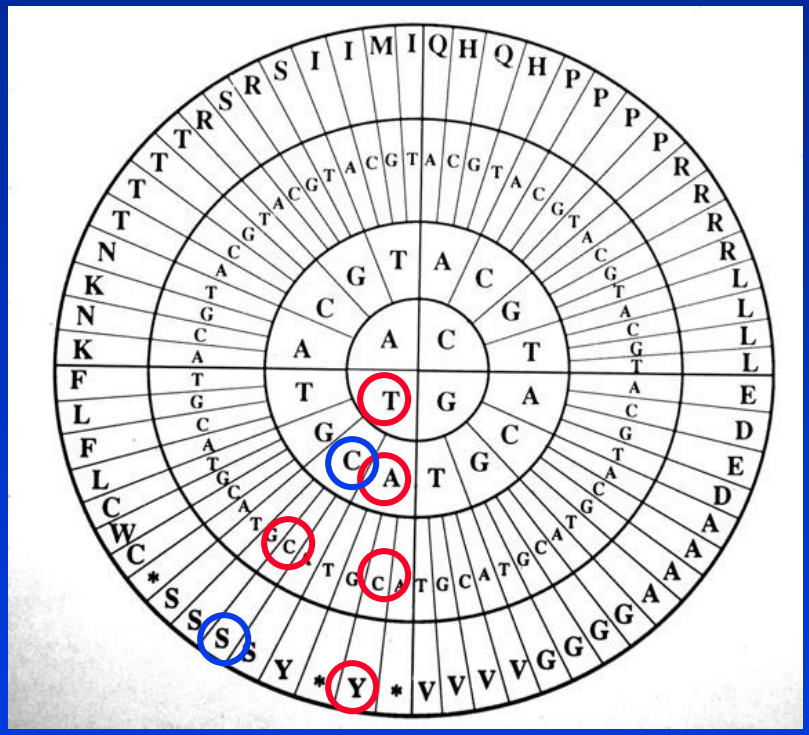
AGTGGCTACGAATGC

AGTGGCTACGAATGC

AGTGGCTCCGAATGC

Mis-sense change

Nucleotide triplets = codons



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Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V

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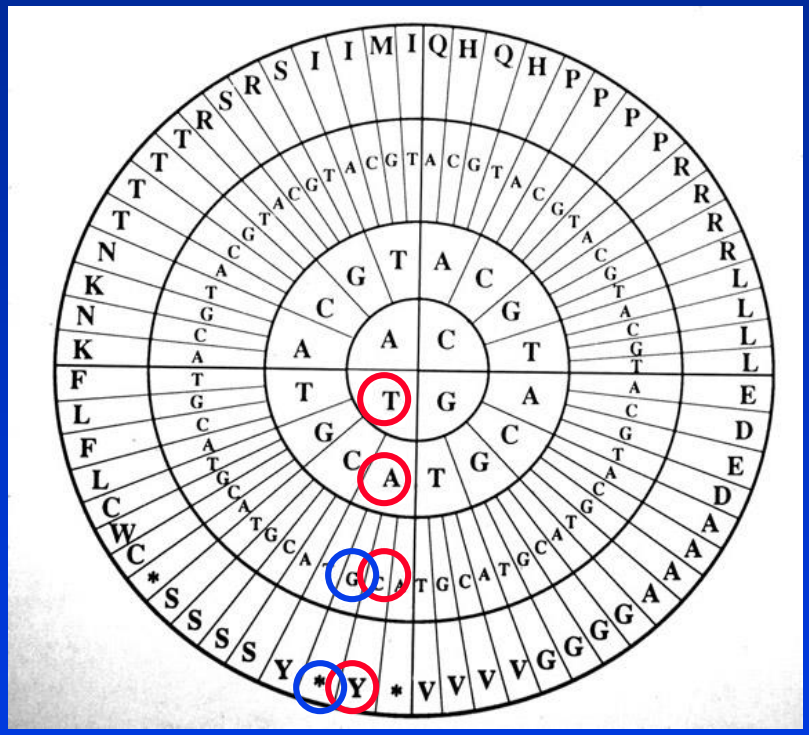
AGTGGCTACGAATGC

AGTGGCTAGGAATGC

Nucleotide triplets = codons



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Valine	Val	V

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AGTGGCTACGAATGC

AGTGGCTCCGAATGC

Nonsense change

AGTGGCTACGAATGC

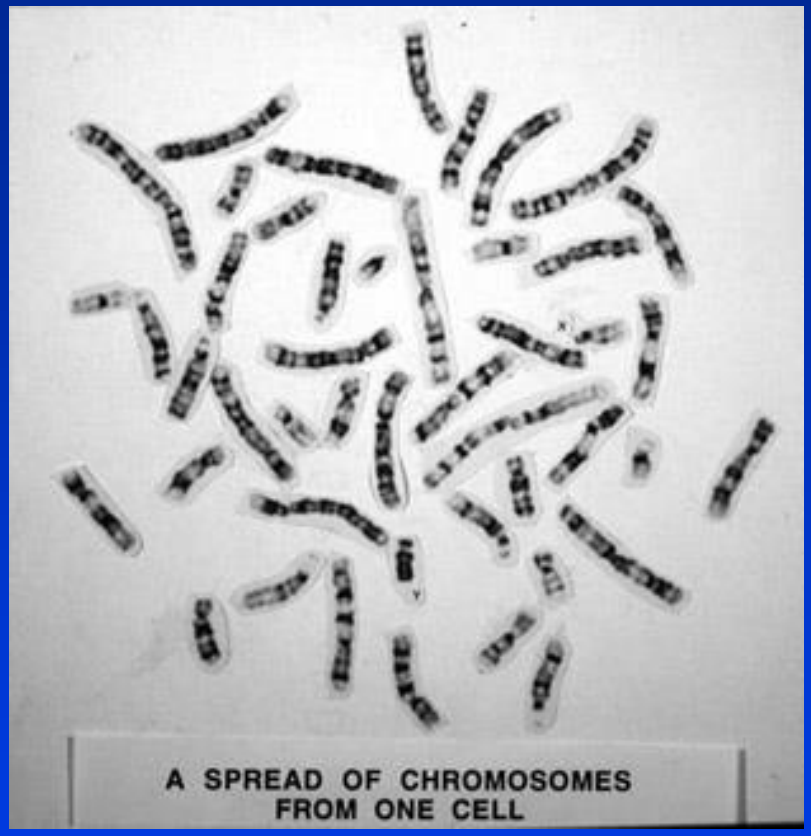
AGTGGCTCCGAATGC

AGTGCTCCGAATGC…

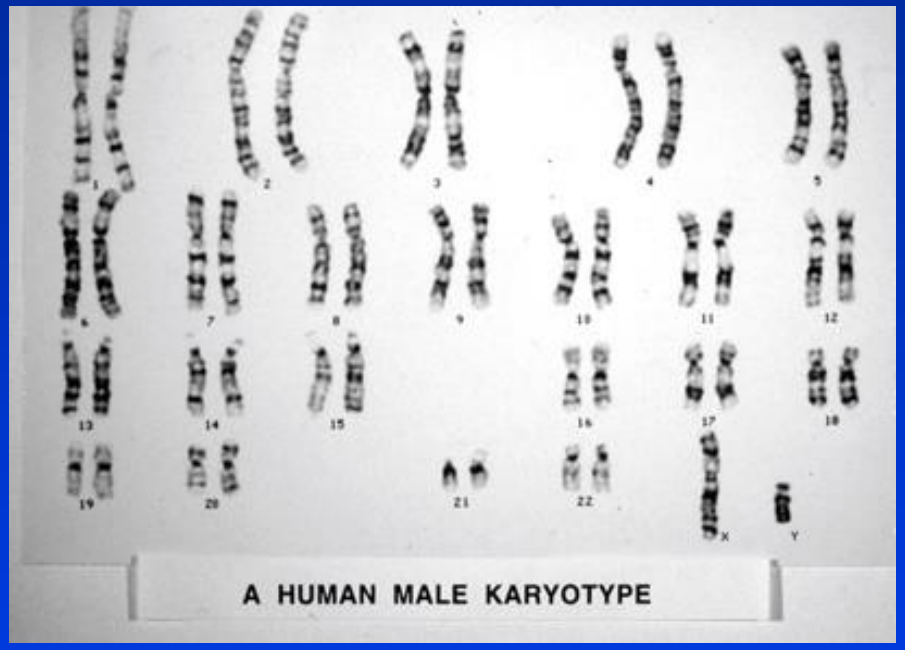
Frameshift

Where do genes live?

CHROMOSOMES



A SPREAD OF CHROMOSOMES
FROM ONE CELL



A HUMAN MALE KARYOTYPE

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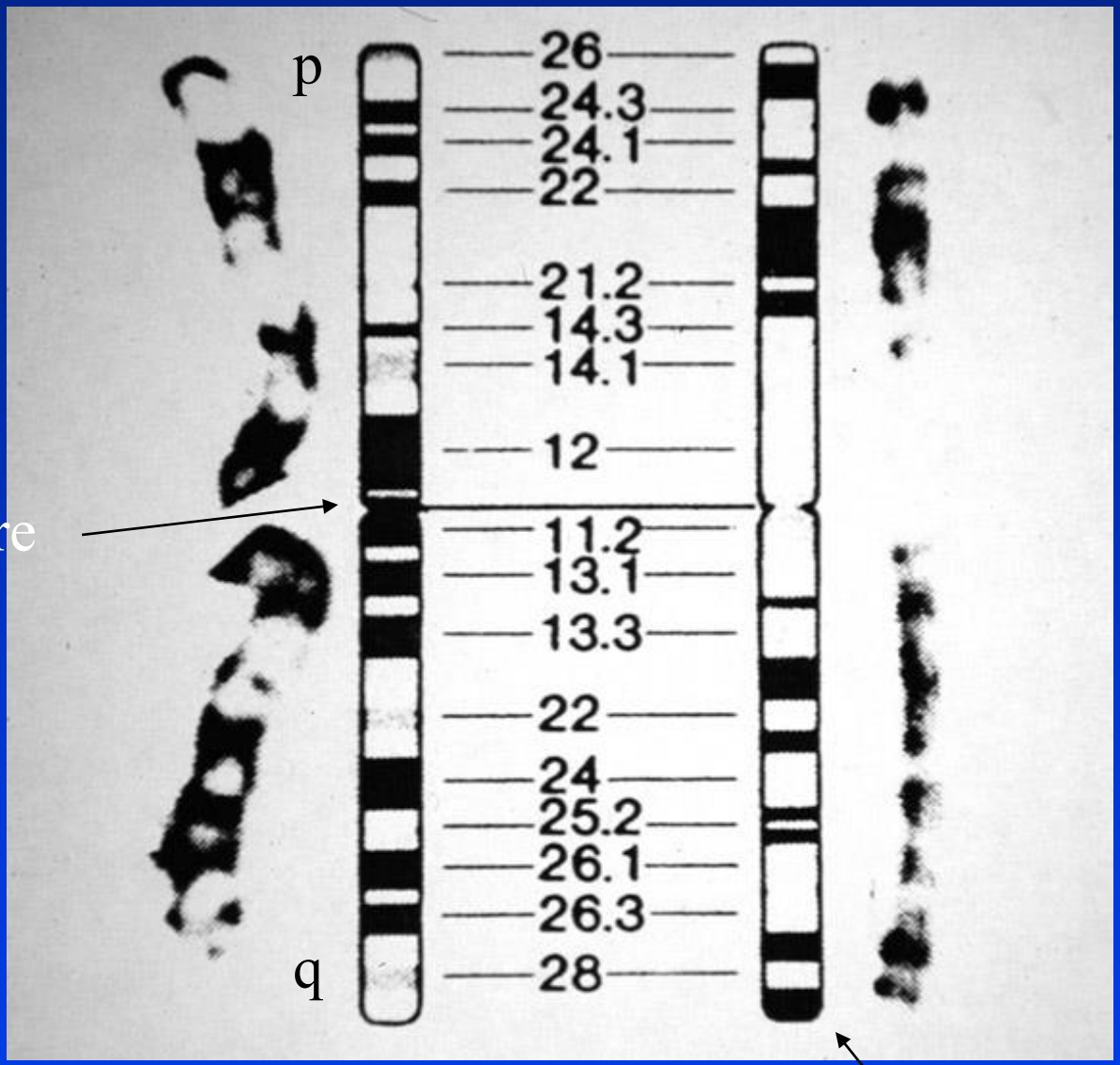
We each have

22 autosomes (1 thru 22)

2 sex chromosomes

XY = male

XX = female



centromere

telomere

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Chromosomal aberrations

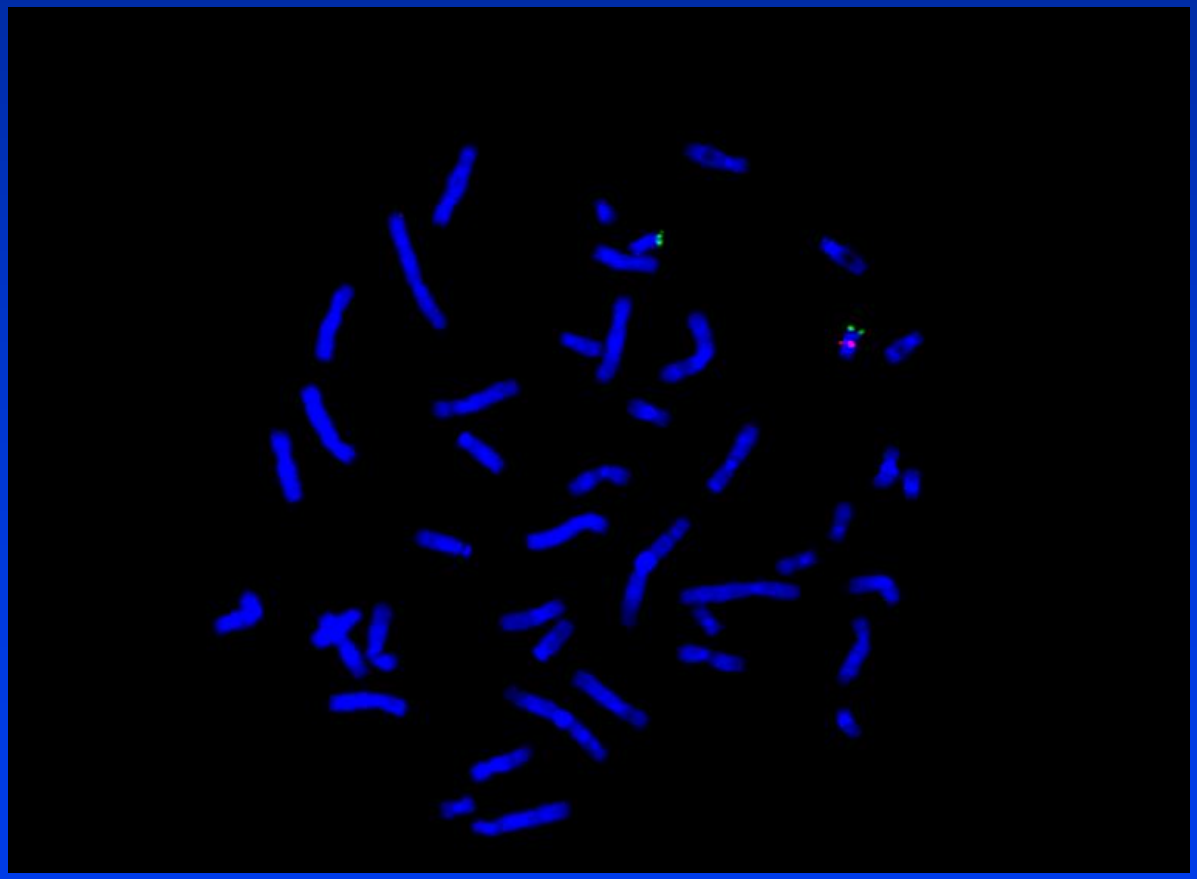
must be > 1 gene involved!

duplication (trisomy)
    e.g. dup5q22
deletion (monosomy)
    e.g. del5q22
translocation
inversions, rings….

3 MALFORMATIONS = KARYOTYPE

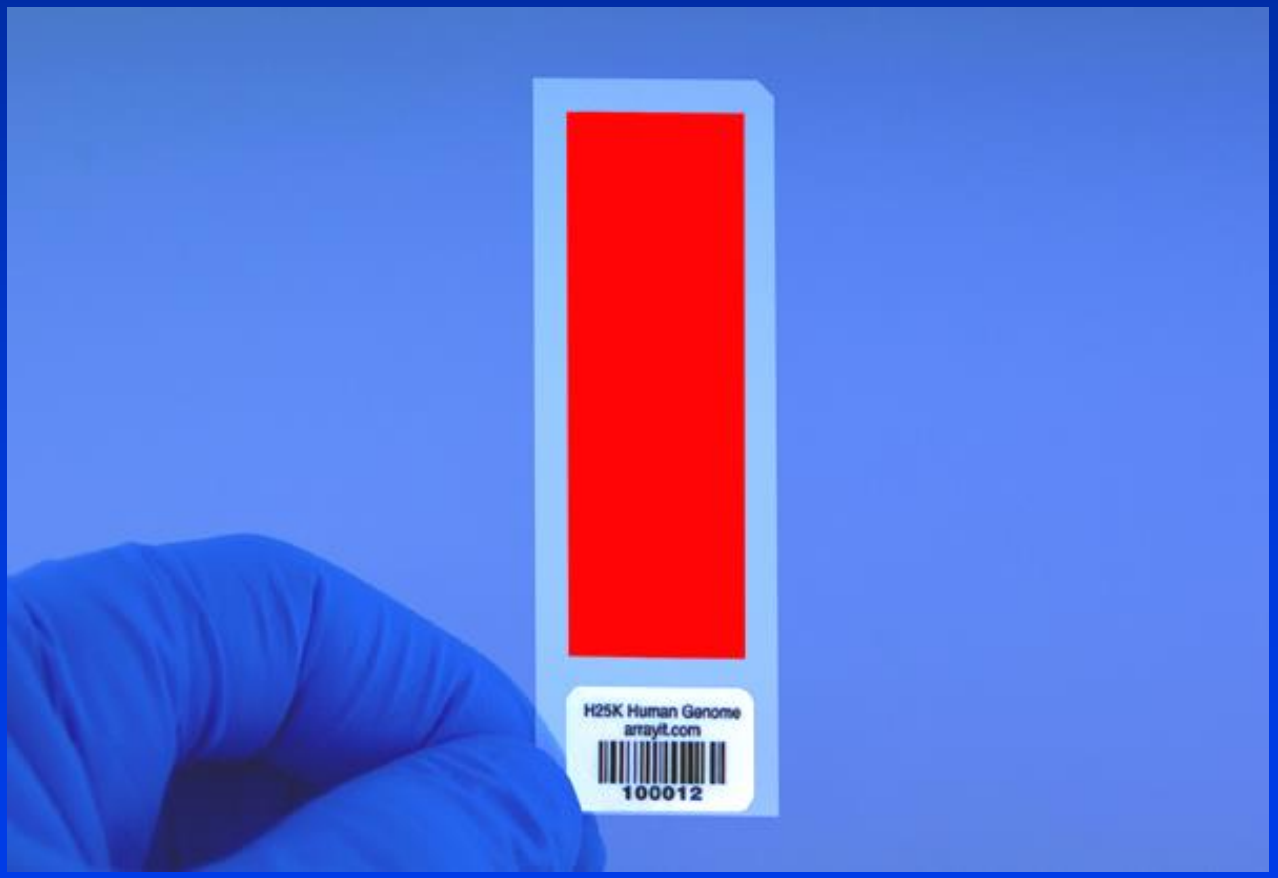
If karyotype normal….

FISH (fluorescent in situ hybridization)



If karyotype normal….

Microarray



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Microarray

1 million mutation screen in hours

<$500

< 10 years ago would have taken months and > $500,000!

Multisystem disease

1 gene causing multiple problems

= gene used in > 1 site

or more than one gene affected

Contiguous Gene Deletion Syndromes

WAGR

Wilms tumour

Aniridia

Genital abnormality

Retardation

Which test do I order?

Single gene sequencing

Panel of genes

Whole exome

Whole genome

Microarray

….. PHENOTYPE!

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Single gene inheritance =

Mendelian inheritance

Remember: we each have 2 copies of every gene

Inheritance patterns and pedigrees

Autosomal dominant

Autosomal recessive

X linked dominant

X linked recessive

Mitochondrial