Genetics in Autism

DR EBIN ROSHAN PAUL

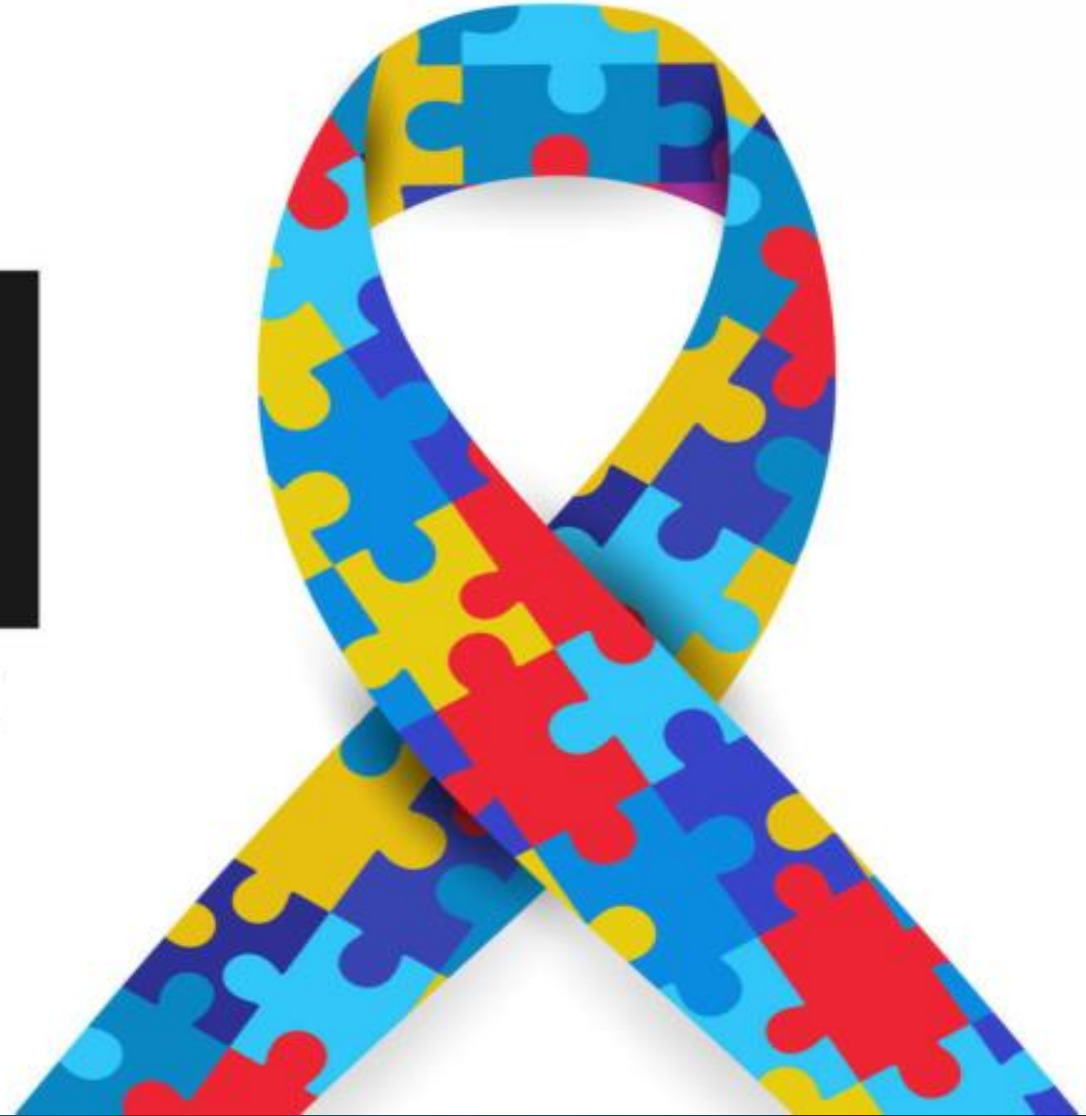
ASSISTANT PROFESSOR & CLINICAL GENETICIST

PKDAS MEDICAL COLLEGE

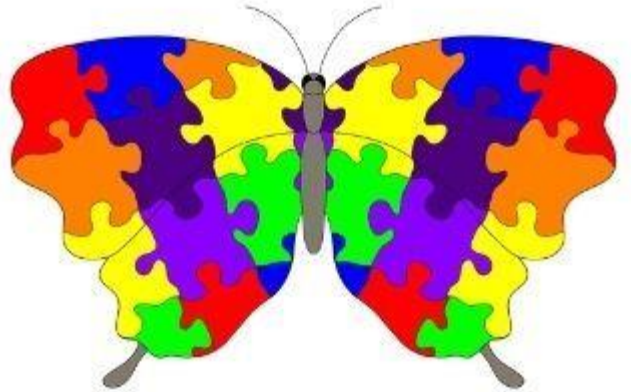
APRIL IS NATIONAL

AUTISM

AWARENESS MONTH

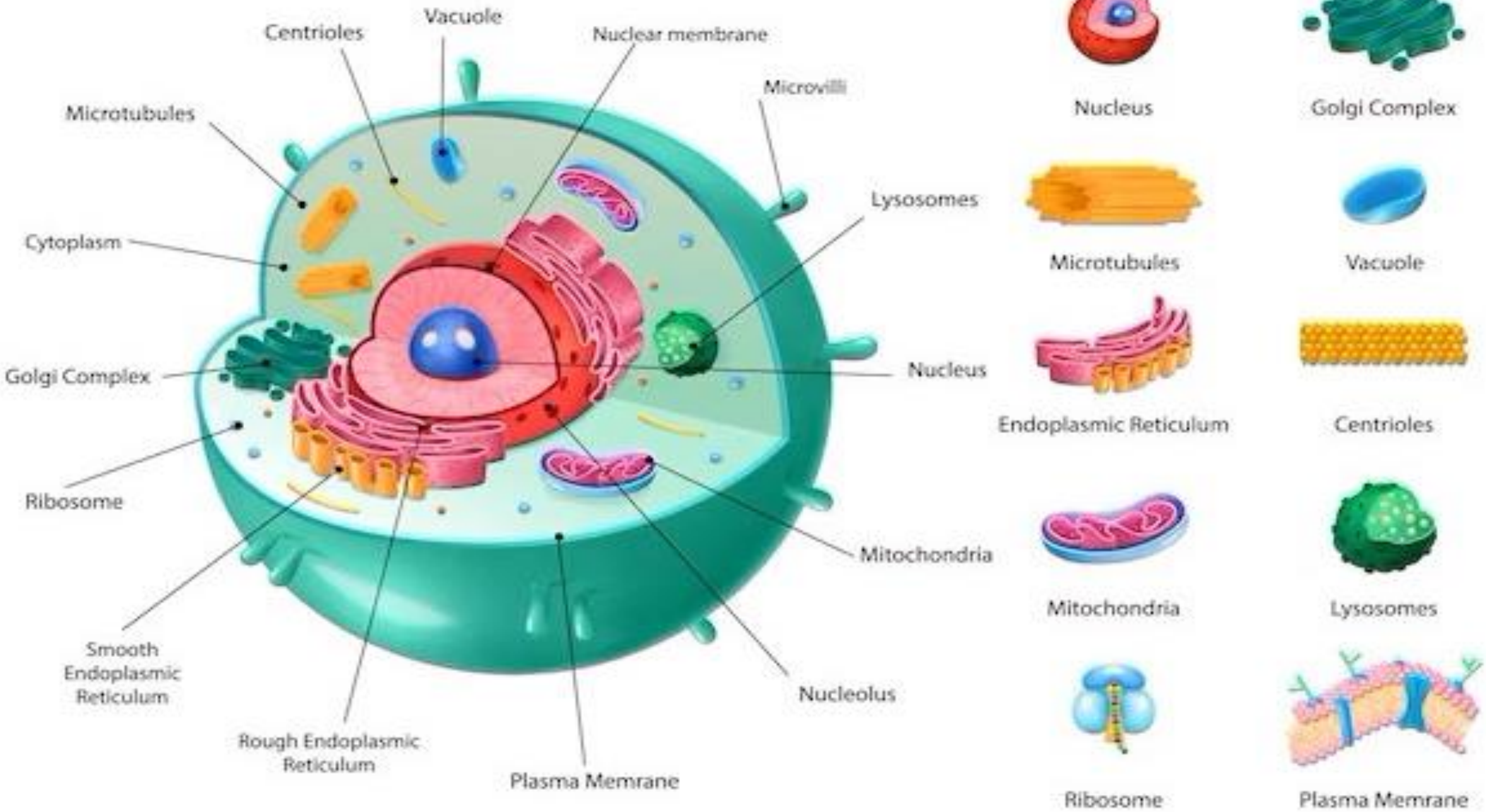


Multi coloured – Diversity & complexity
Puzzle Ribbon– Unknown realms



Topics Today….

- 1. DNA and genes
- 2. Autism genetics – role and issues
- 3. Three: Basic genetic test –Karyo/Array/Sequencing
- 4. Services provided by Genetics in Autism
- 5. Future therapies in Autism (Molecular level)


Centrioles
Vacuole
Nuclear membrane
Microvilli
Microtubules
Lysosomes
Cytoplasm
Golgi Complex
Nucleus
Ribosome
Mitochondria
Smooth Endoplasmic Reticulum
Nucleolus
Rough Endoplasmic Reticulum
Plasma Membrane
Nucleus
Golgi Complex
Microtubules
Vacuole
Endoplasmic Reticulum
Centrioles
Mitochondria
Lysosomes
Ribosome
Plasma Membrane

DNA

→ 2 meter length

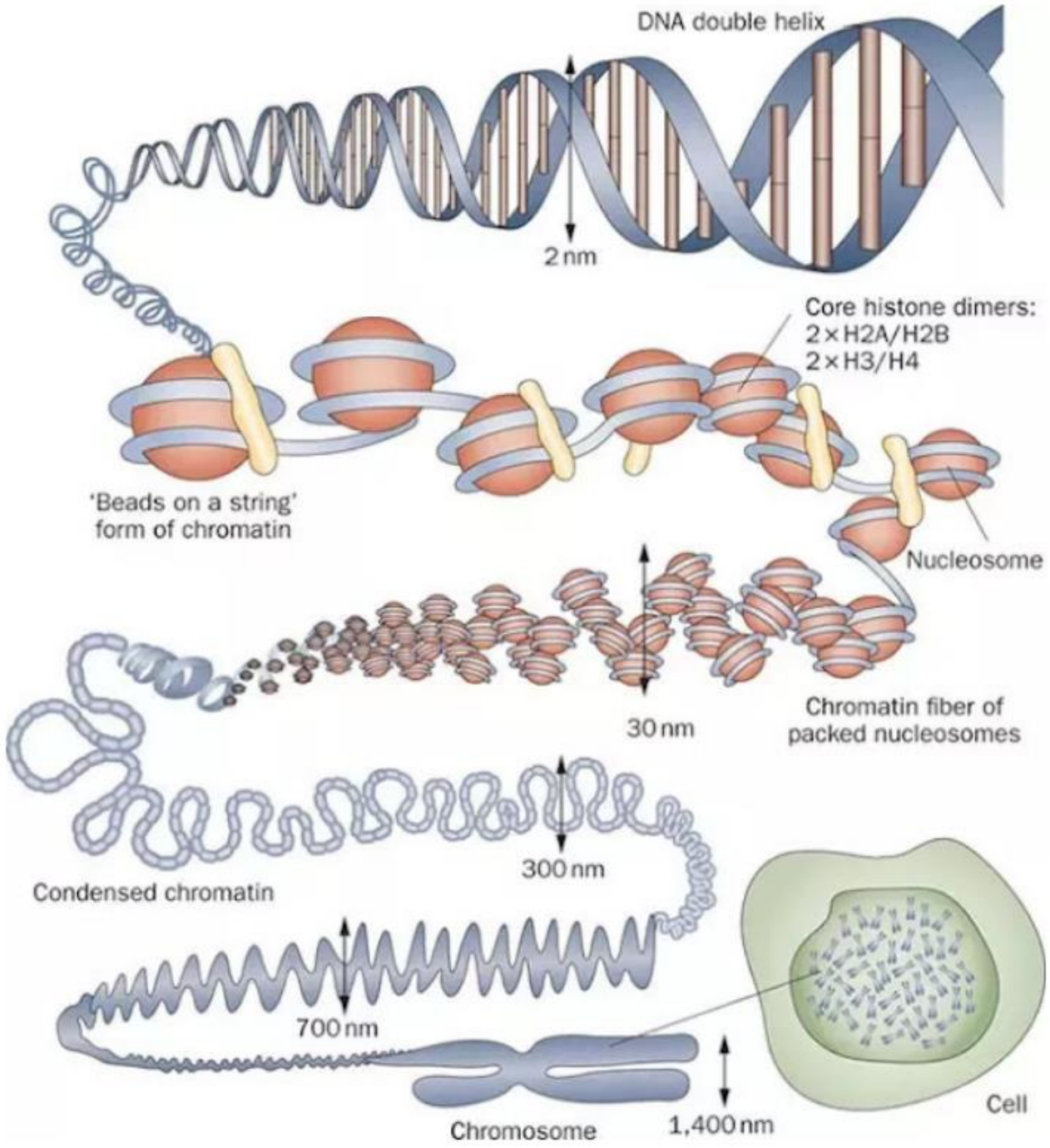
→ 2 % coding→ produce *protein*

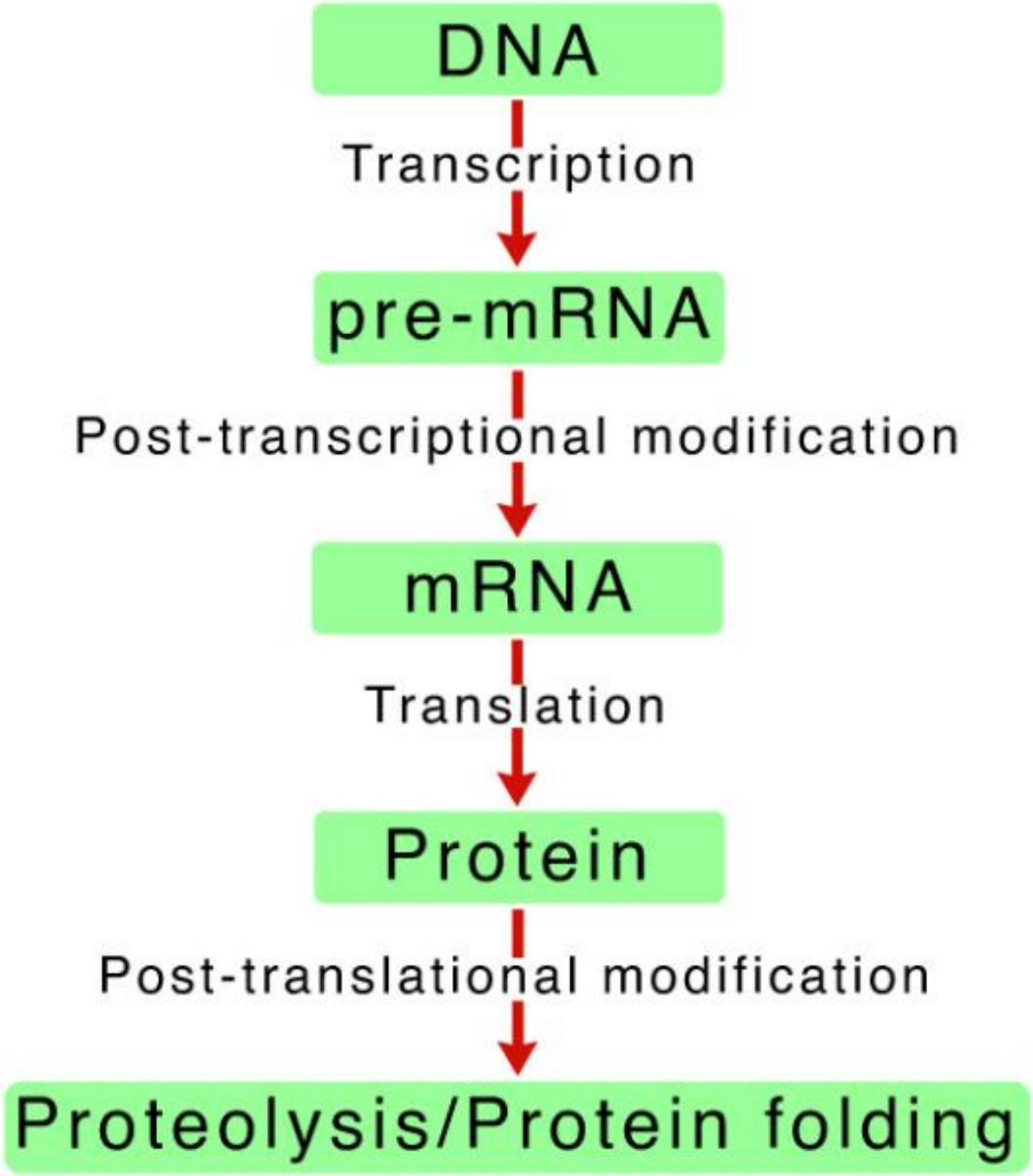
→ 98% junk DNA

→25000 genes present

→ 7000 genes important

→ mutation in gene




DNA
Transcription
pre-mRNA
Post-transcriptional modification
mRNA
Translation
Protein
Post-translational modification
Proteolysis/Protein folding

Flowchart in Autism diagnosis

- Detect some issues – parents/caretaker/teachers/relatives/doctor

- Consult a HCP (Paediatrician/Medical officer/Trained nurse)

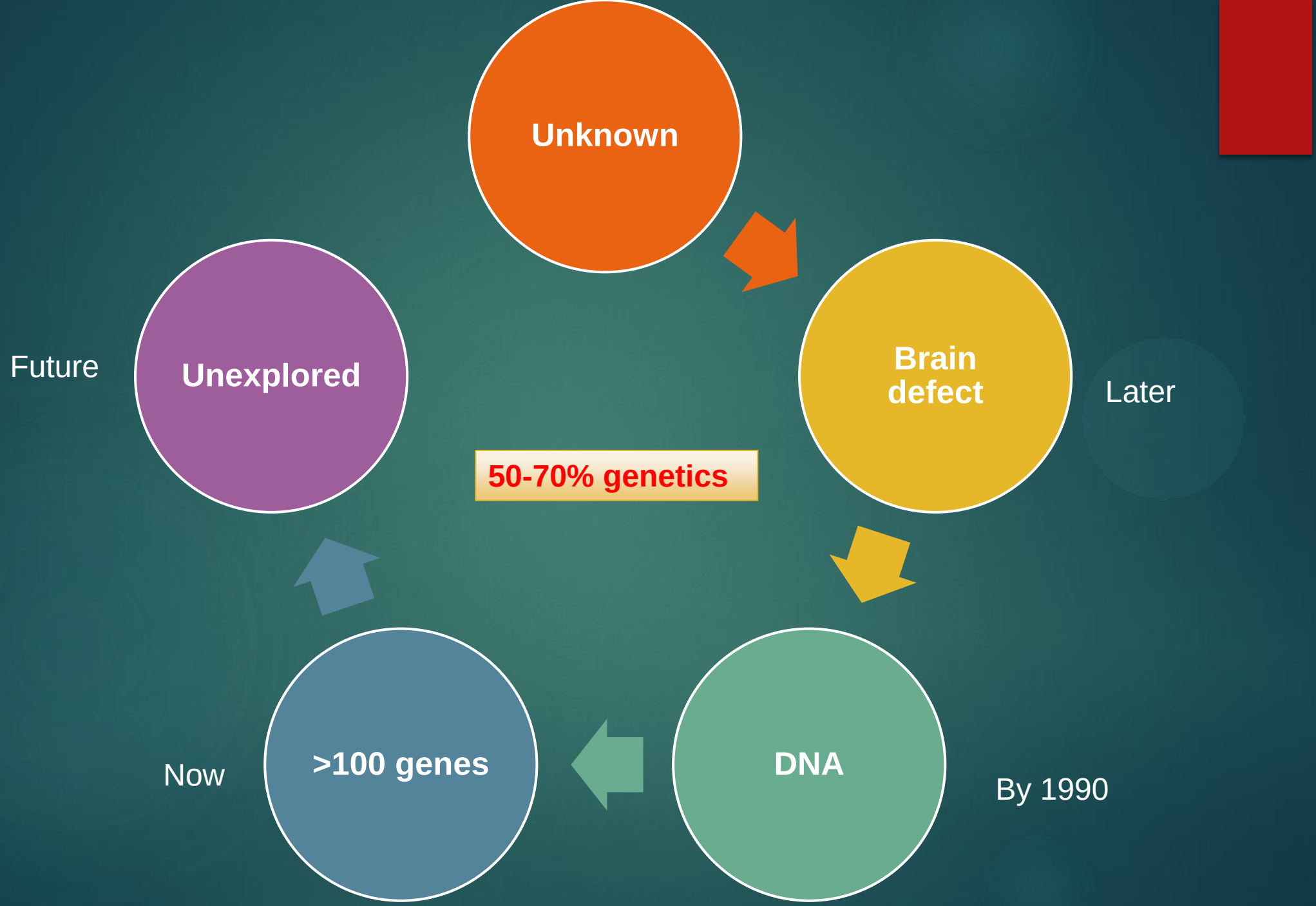
- Refer to a Specialist for diagnosis

- Early Intervention services (EIS) and Follow up

Who will diagnose Autism ?

- Developmental Paediatrician / Trained therapist
- Paediatric Neurologist
- Psychiatrist
- Special Educator/Qualified persons

Genetics in Autism ?


Unknown
Brain defect
Later
DNA
By 1990
>100 genes
Now
Unexplored
Future
50-70% genetics

How mutation causes Autism ?

Or can be associated with other genetic conditions

Autism association in other genetic disorders

- Down syndrome
- About 5000 genetic disorders
- Autism/ADHD/behavioural issues/LD can co exist with these genetic disorders or high risk in developing

Examples of Genetic condition with Autism

- Trisomy’s
- XYY
- XXY
- Turner syndrome
- Down syndrome
- Fragile X syndrome
- Rett syndrome
- Tuberous Sclerosis (TS)
- Smith Magnesis syndrome (SMS)
- Angelman / Prader Willi
- DiGeorge (22q11.2)

3 Basic Genetic Test We do….

- 1) Karyotype
- 2) Microarray (recommended)
- 3) Gene sequencing

1. Karyotype

- Cell culture → Chromosomes arrested in metaphase of cell division.

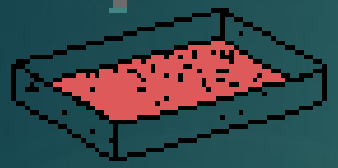
- Chromosomes are photographed, paired and ordered in decreasing length

- Issues like – aneuploidy, large deletion/duplication noted.

"Basic genetic testing offered by most geneticists"

add tissue sample

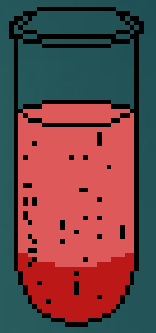
add chemical to stimulate mitosis



Culture in a growth medium

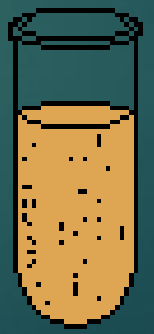
incubate for 2-3 days

add chemical to stop mitosis in metaphase



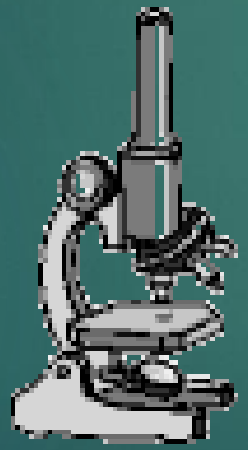
transfer cells to tube and centrifuge to concentrate in layers

transfer to tube containing fixative

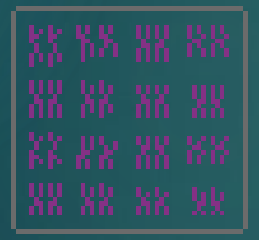


put cells onto microscope slide

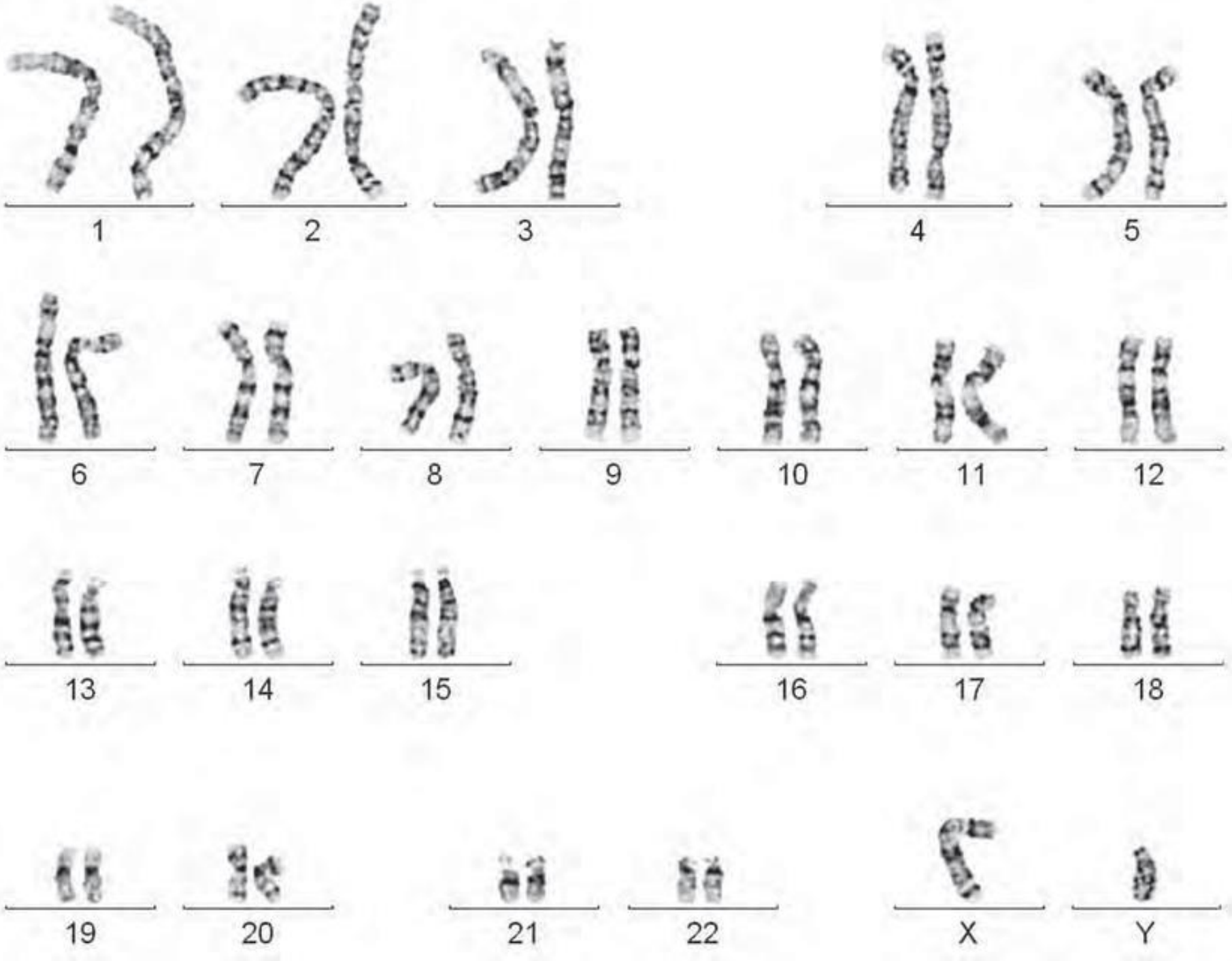
add stain to enhance chromosomes



identify and photograph chromosomes



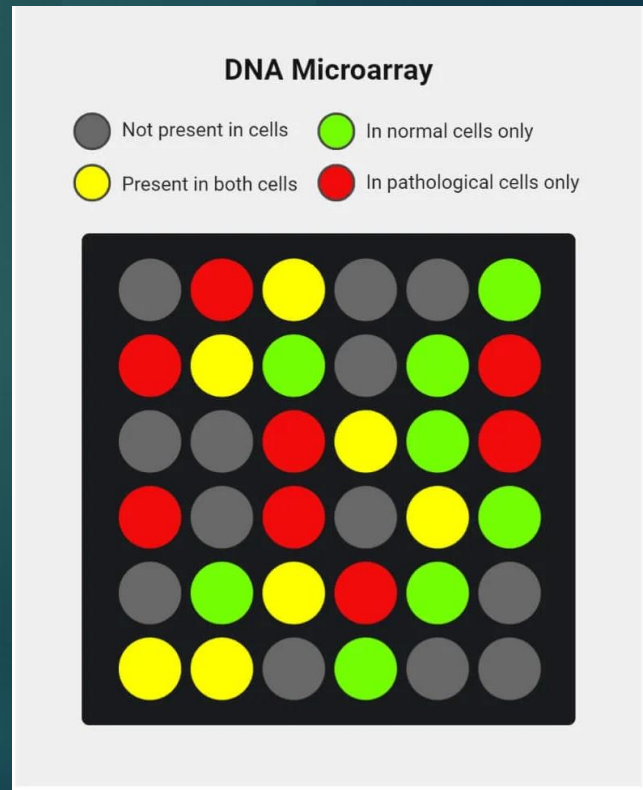
cut out chromosome pictures and arrange into karyotype



46,XY Male

2. Microarray / Array CGH

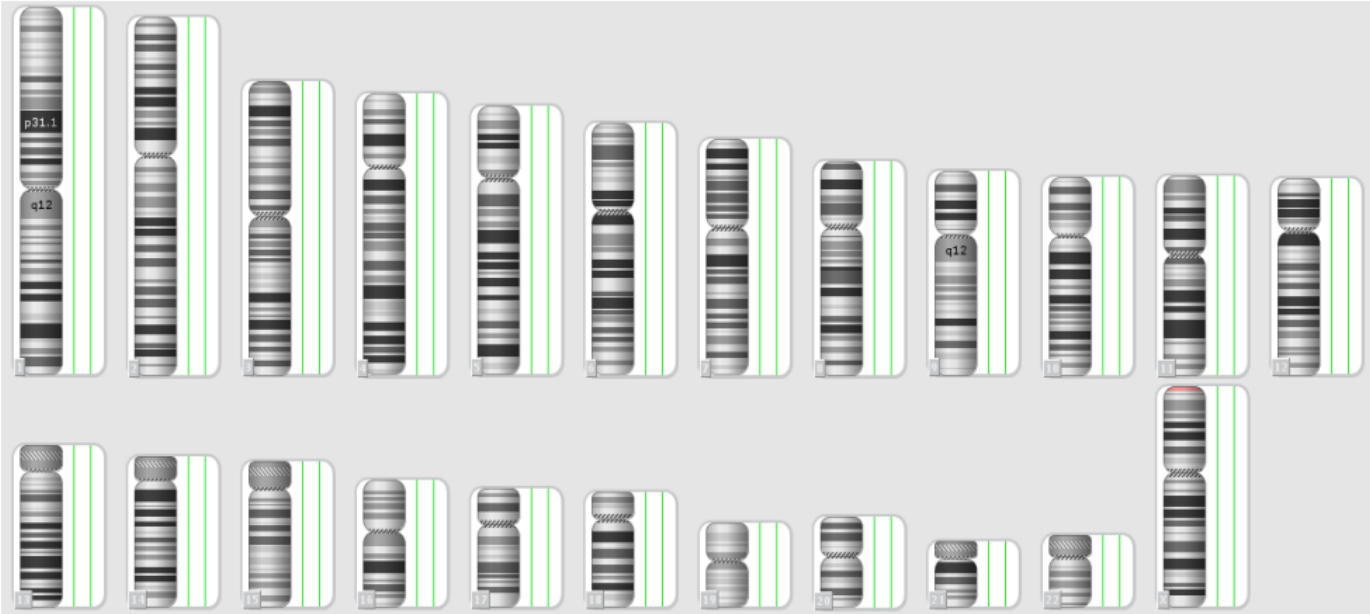
- More precise than karyotype in detect CNV (del/dup) **<10 kb** size.
- To detect small changes **“not seen”** by karyotype
- Recommended in **Autism cases**



Microarray test for CNV

CNVs: NO SIGNIFICANT COPY NUMBER VARIATION DETECTED
ROHs : LONG CONTIGUOUS STRETCH OF HOMOZYGOSITY ON CHROMOSOME 15 - CLINICAL SIGNIFICANCE UNKNOWN

KARYOVIEW_CNVs



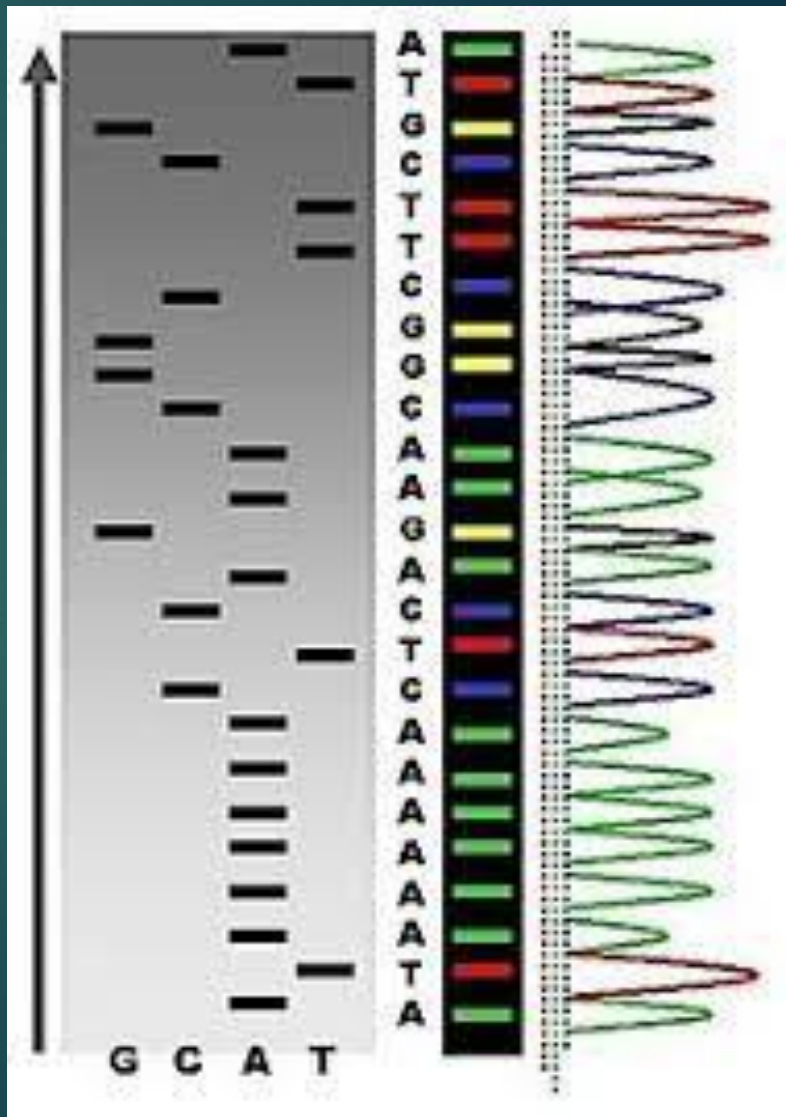
Name: RUDRA S
Order ID/Sample ID: 527084/7739945
Page **1** of **4**

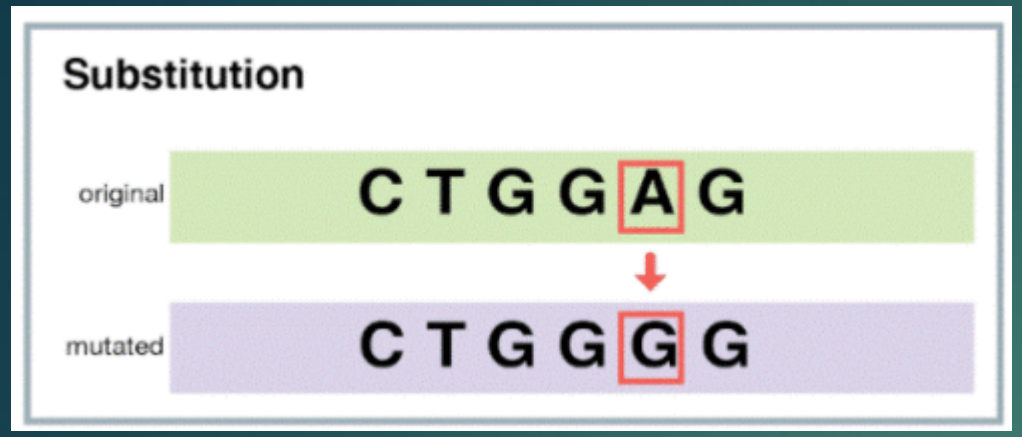
CAP ACCREDITED
COLLEGE of AMERICAN PATHOLOGISTS

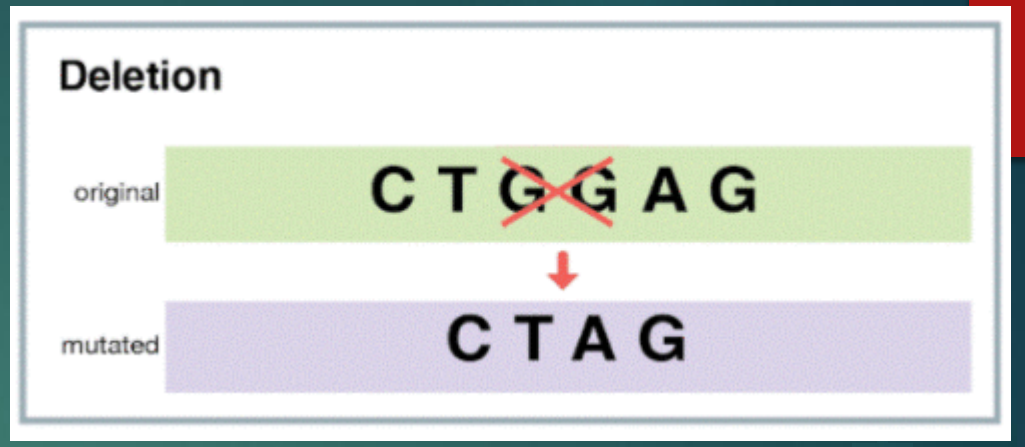
3) Gene sequencing

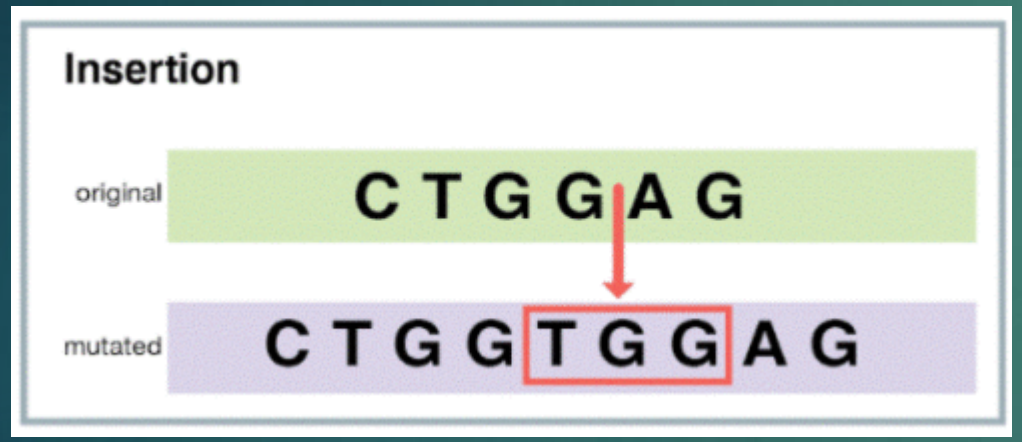
- Checking the sequence of **A T C G** in DNA strand

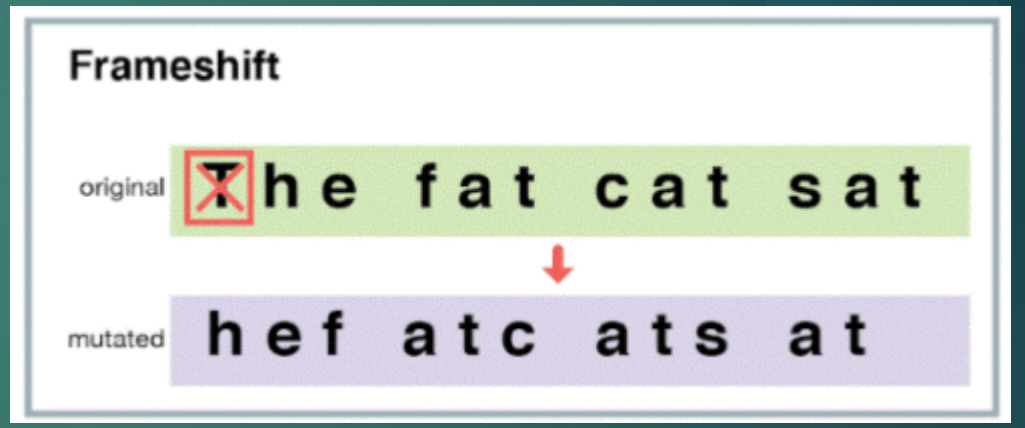
- a) substitution
- b) insertion
- c)deletion
- d) frame shift




Substitution
original
C T G G A G
mutated
C T G G G G


Deletion
original
C T G G A G
mutated
C T A G


Insertion
original
C T G G A G
mutated
C T G G T G G A G


Frameshift
original
T h e f a t c a t s a t
mutated
h e f a t c a t s a t

Why Gene testing ?

- 1. **Getting Diagnosis / Etiology**
- 2. **Removing “Guilt”**
- 3. **counselling → Prognosis and Preparedness**

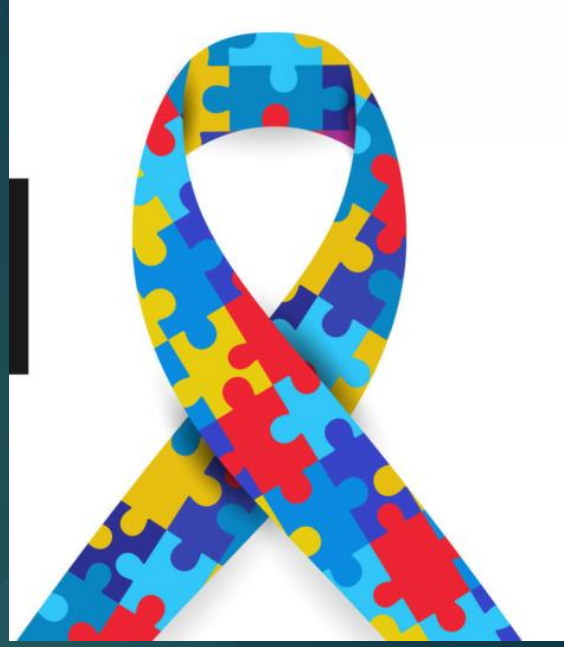
4. Recurrence risk and Prenatal options

Relation	Recurrence Risk
Identical Twin	60%
Next sibling	20%

- 5. Identify other conditions and Treatment

Assure a Healthy baby (~90%) in next pregnancy

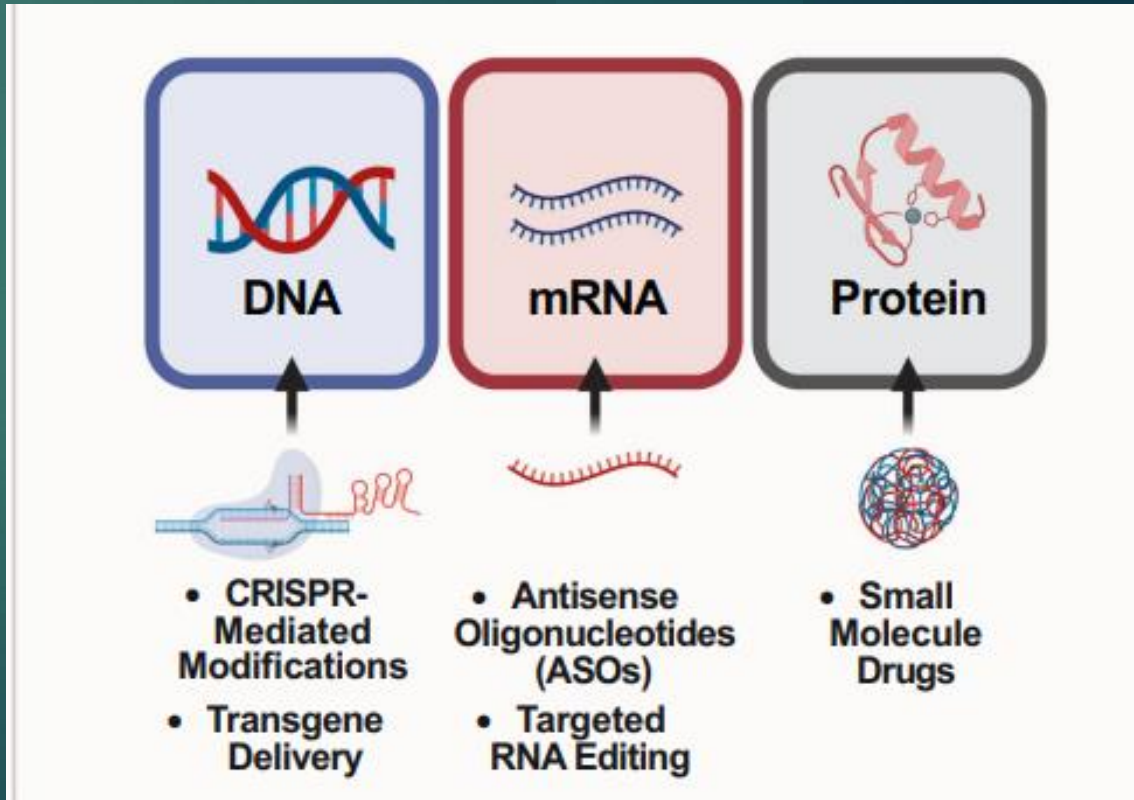
Issues in Genetic Counselling ?



- Each child is Unique because not a single gene disorder
- >100 direct genes and ~800 indirect genes associated
- Still unexplored areas → difficult in counselling
- so each case is different and cannot group together and make a common protocol like in other syndromic cases.

Future promising therapies

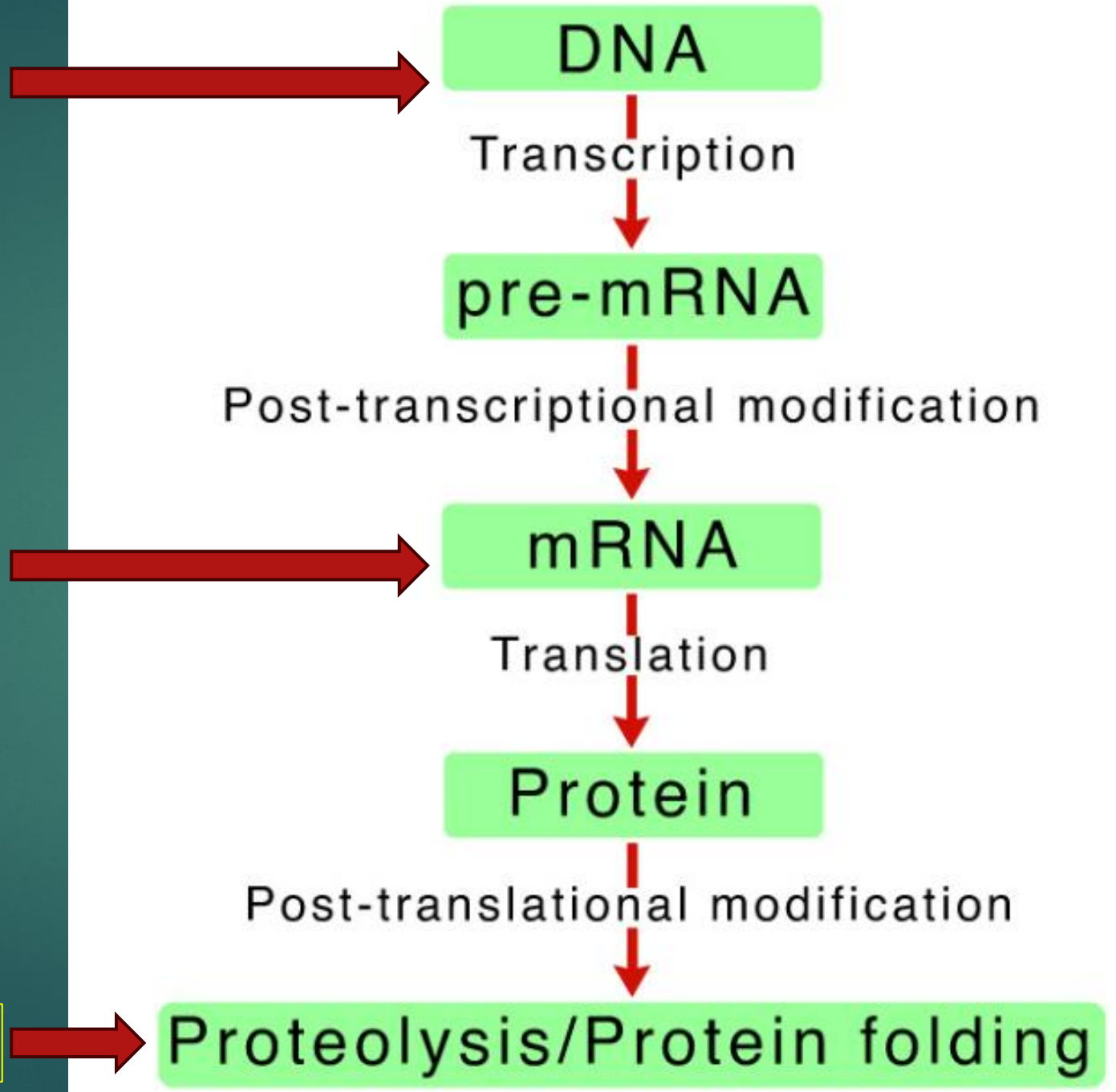
- CRISPR editing and gene replacement
- Antisense Oligonucleotides (ASOs)
- Protein replacement



CRISPR edit and Transgene placement

Antisense Oligonucleotides (ASOs)

Protein replacement therapy



Doubts ???


Thank
you!