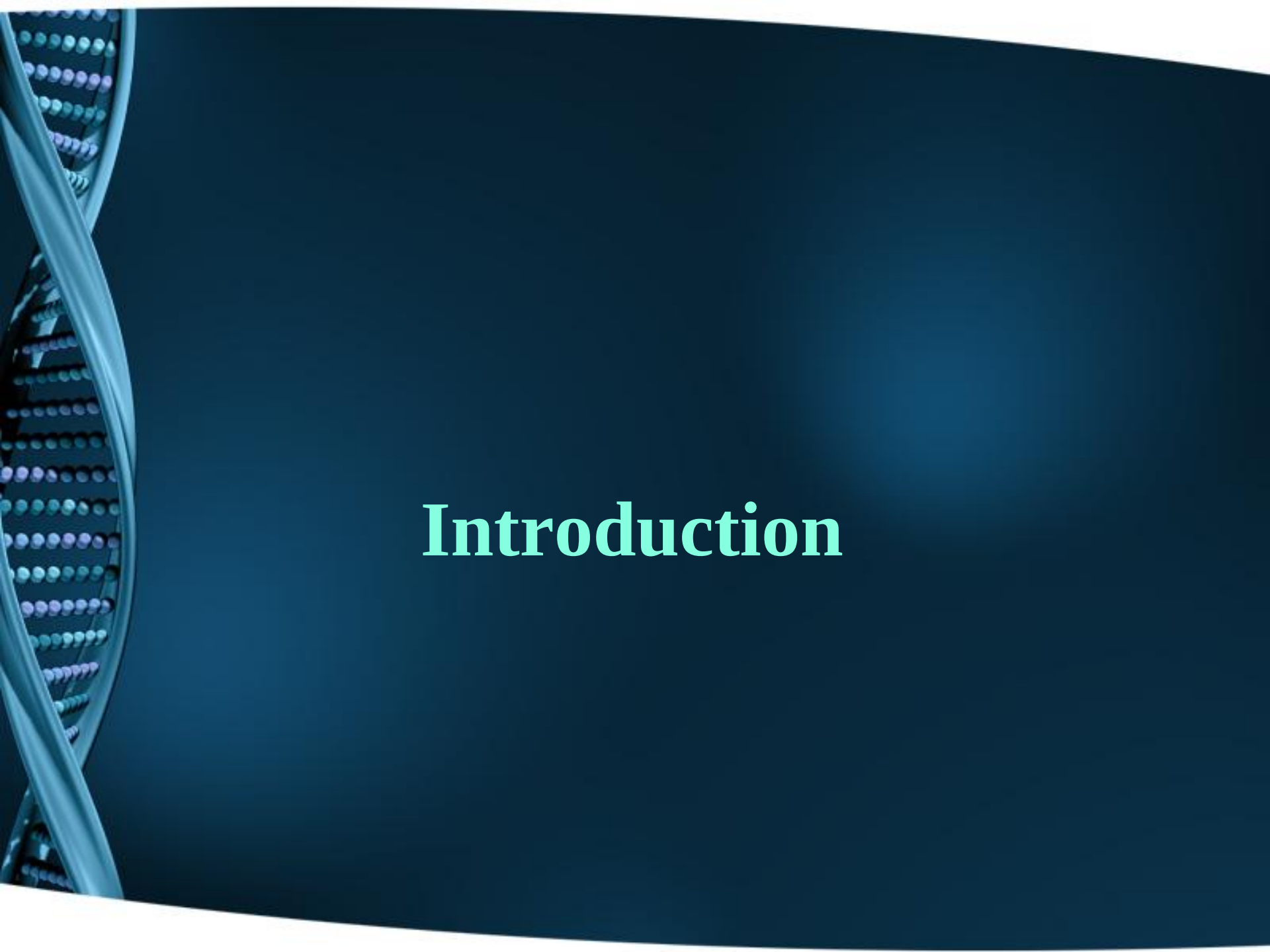
Approach to Mental Retardation and Developmental Delay

SR Ghaffari MSc MD PhD


Introduction

Objectives

- Definition of MR and DD
- Classification
- Epidemiology (prevalence, recurrence risk, …)
- Etiology
- Importance of diagnosis

Higher Cerebral Development Dysfunction

- **Mental retardation**

- Cerebral palsy
  - Abnormal motor actions and postural mechanisms
  - Non-progressive abnormalities of the developing brain
  - limited, stereotypic, and uncoordinated voluntary movements

- Autism
  - A behaviorally defined syndrome characterized by
    - Atypical social interaction
    - Disordered verbal and nonverbal communication
    - Restricted areas of interest
    - Limited imaginative play
    - A need for sameness

Mental retardation

- Mental retardation is a serious and lifelong disability that places heavy demands on society and the health system

American Association on Mental Retardation, 1992

*" mental retardation is not something you have, like blue eyes or a bad heart, nor is it something you are, like short or thin. It is not a medical disorder or a mental disorder… mental retardation reflects the " **fit** " between the capabilities of individuals and the structure and expectations of their environment. "*

Definition

MR is accepted as having three components:

1) Significantly abnormal intellectual performance, generally determined by a test of intelligence

2) Onset during development before the age of 18

3) Impairment of the ability to adapt to the environment

Global developmental delay

- Reserved for children five years of age or younger

Global developmental delay

- Global developmental delay (DD) describes significant delay in two or more of the following areas:
- Cognition
- Speech/language
- Gross/fine motor skills
- Social/personal skills
- Daily living

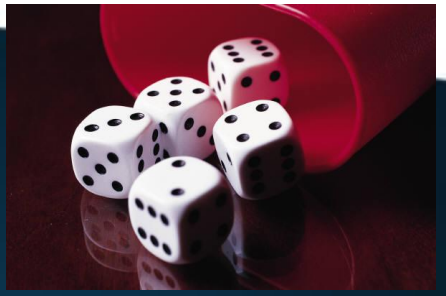
Prevalence

- Prevalence: 1% - 3%
- Mild MR occurring 7-10 times more frequently than moderate or severe MR.
  - Mild MR: 29.8/1000
  - Mod-severe MR: 3.8/1000
- In Iranian population: 1.8 – 2.7%

Why diagnosis?

- Estimating the recurrence risk in future pregnancies
- Prenatal diagnosis
- Minimizing the number of diagnostic procedures
- Short-term and long-term prognosis
- Treatment options

Recurrence risk



- Variable depending on the etiology
- From very low (the same as normal population) to 50% and even in rare situations to 75 -100%
- Irrespective of etiology, empiric risk: 8.4%

Recurrence Risks for Severe MR

Study	Brothers	Sisters	All Sibs
Male index case			
Herbst and Baird (1982)	***1 in 12***	***1 in 33***	***1 in 18***
Bundey et al. (1985)	***1 in 10***	***1 in 20***	***1 in 13***
Female index case			
Herbst and Baird (1982)	***1 in 22***	***1 in 17***	***1 in 19***

Classification

- **Severity:**

Mild
(IQ : 50-70)

Moderate
(IQ : 35-50)

Severe
(IQ : 20-35)

Profound
(IQ < 20)

Classification

⑩ **Pedigree analysis:**

Sporadic

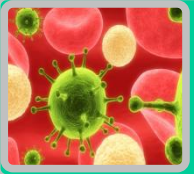
Familial

Etiology

Genetic

Non-genetic

Prenatal and perinatal events



Infections

Environmental factors

Genetic causes

- Cytogenetically visible abnormalities
- Fragile-X syndrome
- Submicroscopic chromosomal abnormalities
- Single gene disorders

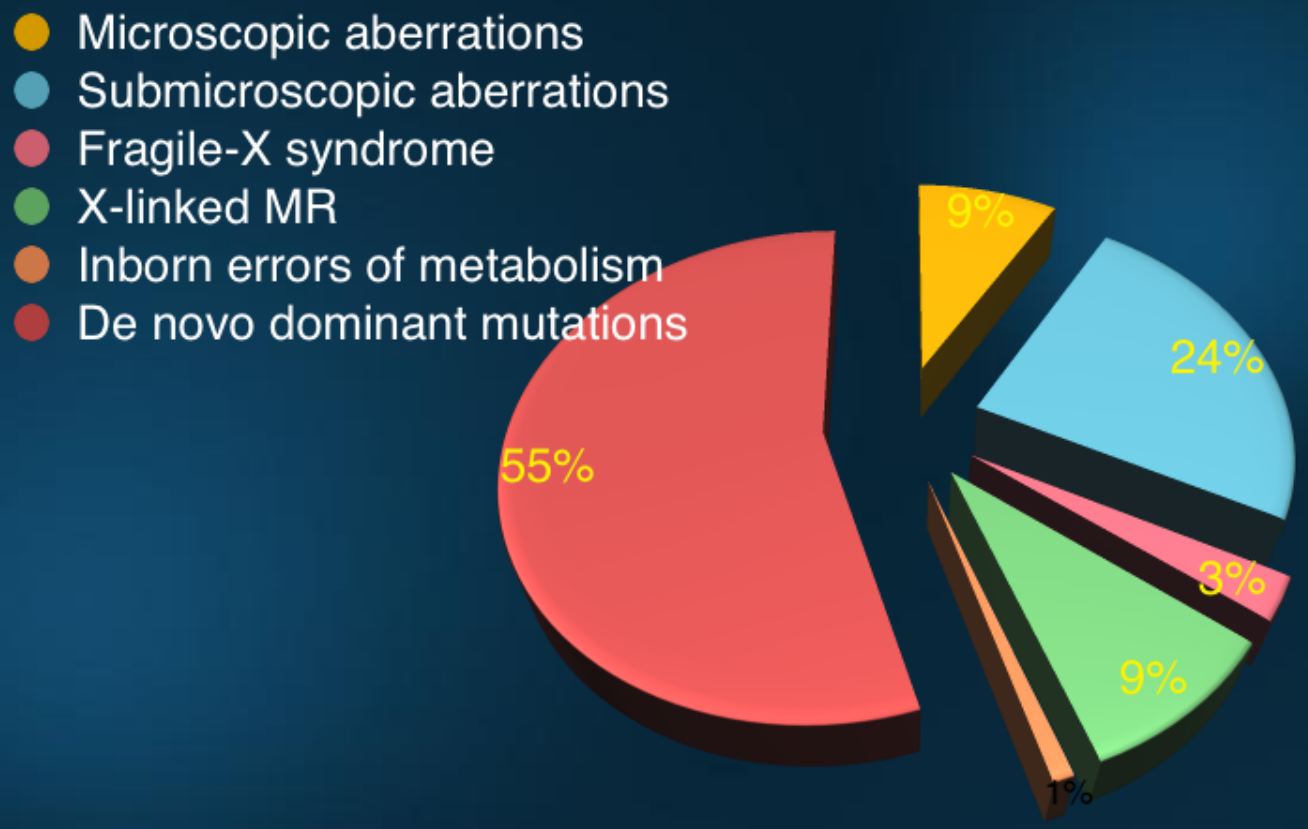
Second Session

Genetic Causes of Mental Retardation

Objectives

- Contribution of different genetic disorders to MR/DD
- Cytogenetically visible abnormalities
- Fragile-X syndrome
- X-liked MR/DD
- Subtelomeric rearrangements
- Common microdeletion/duplication syndromes
- Copy number variation of other genomic regions
- Inborn errors of metabolism: 1% of MR/DD patients
- De novo dominant mutations
- Autosomal recessive MR/DD

Genetic causes of sporadic MR



Cytogenetically visible abnormalities

- Prevalence among MR/DD patients: 9%
- Aneuploidies
  - Trisomy (Down syndrome)
  - Monosomy
- Structural abnormalities
  - Deletions
  - Duplications

Cytogenetically visible abnormalities

- Often associated with
  - Dysmorphism
  - Multiple congenital anomalies
  - Prenatal onset
    - IUGR
    - Abnormal ultrasound findings

Fragile-X syndrome

- The most common cause of inherited MR/DD
- Prevalence: 1/4000 (males)
- Prevalence among MR/DD patients: 3-5%
- Both males and females are affected

Fragile-X syndrome

- Major clinical features
  - Speech delay
  - Dysmorphic features
    - Long face
    - Large ears
    - Macrocephaly
  - Psychologic disorders
    - Autism
    - Behavioral disorders
  - Macro-orchidism

Submicroscopic chromosomal abnormalities

- Subtelomeric rearrangements
- Common microdeletion/duplication syndromes
- Copy number variation of other genomic regions

Submicroscopic Cromosomal Abnormalities

Subtelomeric Rearrangements

0.5-15% •

Unselected patients: 5% •

Common Microdeletion and Microduplication (CMMSs) Syndromes

5.8-9.5% •

Genomic Copy Number Variations (CNVs)

10-17% •

Subtelomeric rearrangements

- Prevalence among MR/DD patients:
  - 0.5-15%
  - Unselected patients: 5%
- Major clinical features
  - Prenatal onset growth retardation
  - Multiple congenital anomalies
  - Dysmorphism
  - Moderate to severe MR

Common microdeletion/duplication syndromes (CMMSs)

- Prevalence among MR/DD patients: 5.8-9.5%
- CMMSs: 50% of total interstitial Microdeletion and Microduplication syndromes
- **Overlapping clinical features**

Microdeletion syndromes

Microdeletion Syndromes

- DiGeorge syndrome
- Williams-Beuren syndrome
- Prader-Willi syndrome
- Angelman syndrome
- Miller-Dieker syndrome
- Smith-Magenis syndrome
- Wolf-Hirschhorn syndrome
- Cri du Chat syndrome
- Langer-Giedion syndrome
- DiGeorge Syndrome 2

OVERALL – occurs 1/1600 deliveries

Genomic copy number variations

- Prevalence among MR/DD patients: 10-17%

Single gene disorders

- Inborn errors of metabolism: 1% of MR/DD patients
- X-liked MR/DD: 9-10%
- De novo dominant mutations
  - Recently proposed
  - Estimated prevalence: 50-60%
- Autosomal recessive MR/DD
  - Mostly in familial MR/DD

Autosomal dominant single gene disorders

- 2009-2011, Hamdan et al.
  - Investigation of 197 synaptic genes (glutamate receptor, …) in 95 patients: 11 new mutations found
- 2011, *Nature*, Vissere et al.
  - Exome sequencing of 10 patients with sporadic MR: 6 pathogenic mutations found (60%)
  - More than all of the previous investigations

New paradigm of de novo dominant mutations in MR

Familial MR/DD

Genetic causes of familial MR/DD

- Low contribution of chromosomal abnormalities
- Single gene disorders:
  - Fragile X syndrome
  - Other X-linked disorders
  - Autosomal recessive MR/DD
  - Autosomal dominant MR/DD

Diagnostic Methods

- Karyotype
- Assessment of fragile-X syndrome
- FISH
- MLPA
- Array-based techniques
  - Array-CGH
  - SNP Array
- Exome sequencing
- Next-generation sequencing

Third Session

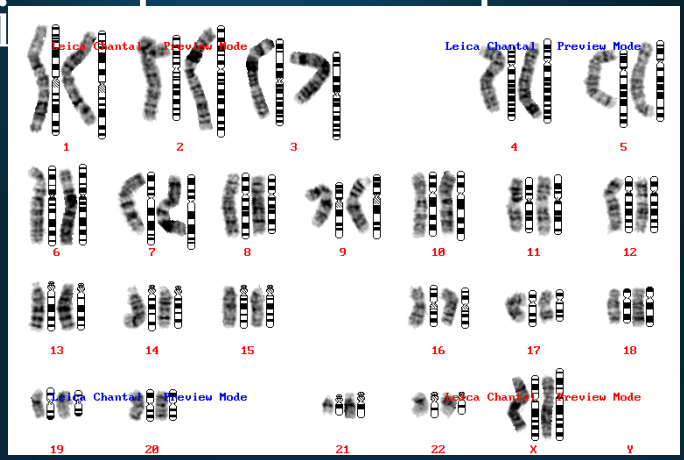
Diagnostic Techniques

Objectives

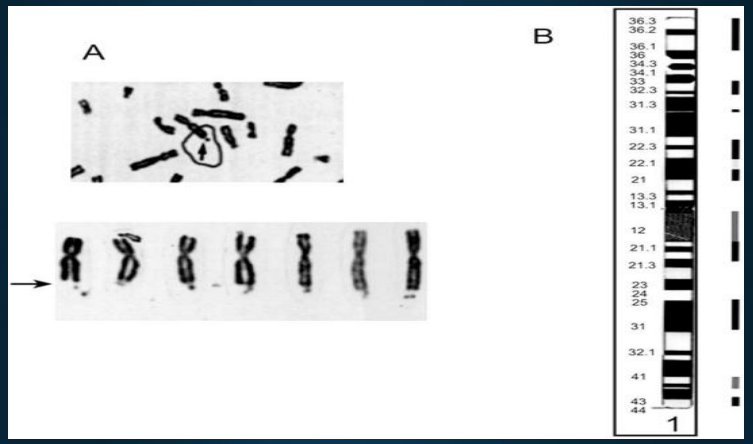
- Advantages and disadvantages of different diagnostic techniques
  - Karyotype
  - PCR screening of Fragile-X syndrome
  - FISH
  - MLPA
  - Array based techniques
  - Next generation sequencing
  - Exome sequencing

Karyotype

- The first technique for studyi abnormalities
- Diagnostic yield: 9%
- Advantages:
  - Genomic
  - Detection of balanced abnormalities
- Disadvantages:
  - Low resolution (3-5 Mb)
  - Labor intensive



Fragile-X syndrome



- Cytogenetic studies:
  - Replaced by molecular studies
- PCR screening:
  - Determining CGG repeat expansion of FMR1 gene
- Triplet-primed PCR:
  - Determining pre-mutations and full mutations
- Diagnostic yield: 3-5%

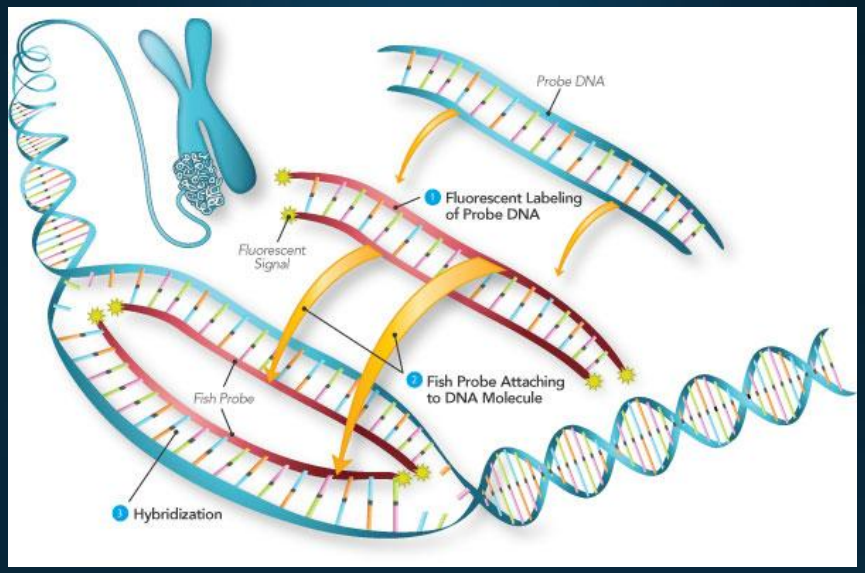
Diagnostic techniques of subtelomeric aberrations

- FISH
  - Costly
  - Labor intensive
- MLPA
- Array-CGH
  - costly

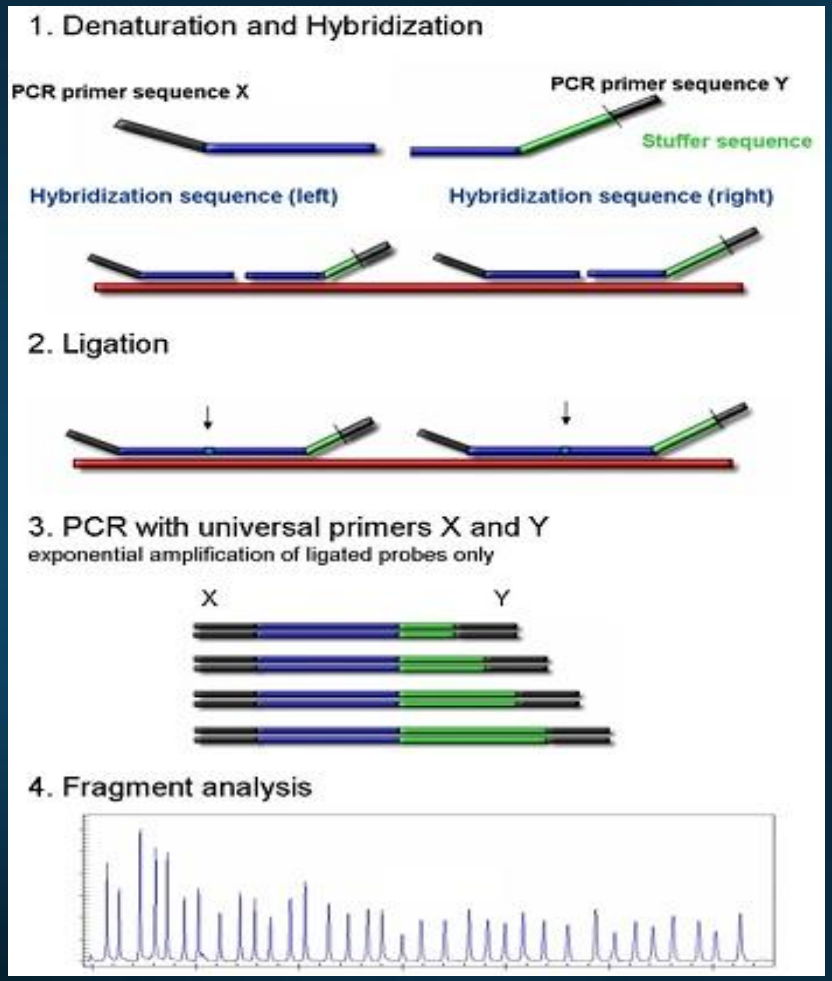
FISH

- The first molecular cytogenetic technique
- Advantages:
  - Higher resolution
- Disadvantages:
  - Limited tergets

☹ You must know what you are looking for



MLPA


1. Denaturation and Hybridization
PCR primer sequence X
PCR primer sequence Y
Stuffer sequence
Hybridization sequence (left)
Hybridization sequence (right)
2. Ligation
3. PCR with universal primers X and Y
exponential amplification of ligated probes only
X
Y
4. Fragment analysis

Diagnostic techniques of CMMSs

- In the past:
  - "Phenotype -first approach"
  - One genetic test (FISH) for one syndrome
  - Screening was not feasible
- At present:
  - "Genotype -first approach"
  - One genetic test for all of the known and even unknown syndromes
    - MLPA
    - Array-based techniques
  - Screening rather than targeted diagnosis

Other genomic CNVs

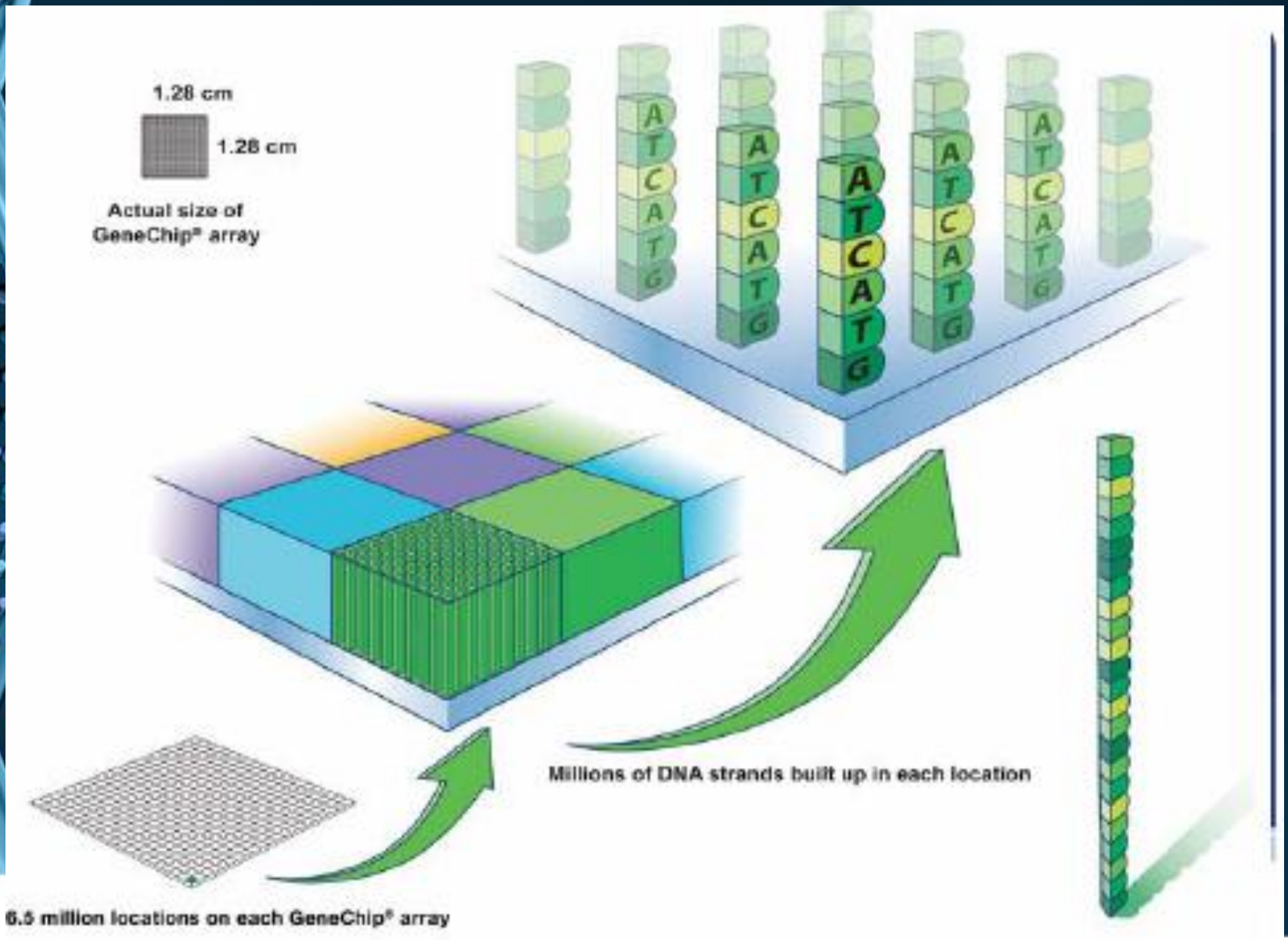
- Prevalence: 10-17%
- Diagnosis: array-based techniques

- **First tier test for:**
  - **Developmental delay/intellectual disability (DD/ID)**
  - **Multiple congenital anomalies (MCA)**
  - **Autistic spectrum disorder (ASD)**

Platforms

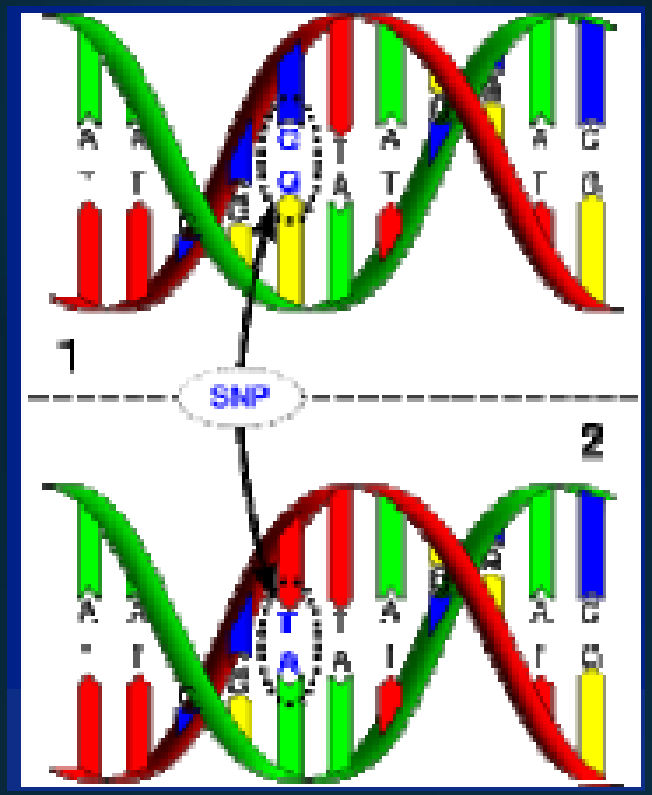
- Selected probes:
  - Targeted CMA
  - Whole genome CMA
- Resolution:
  - BAC array (probe size: **75-150 Kb)**
  - Oligonucleotide array: **(50-60 bp)**
    - SNP array
    - Non-SNP array

Oligonucleotide array



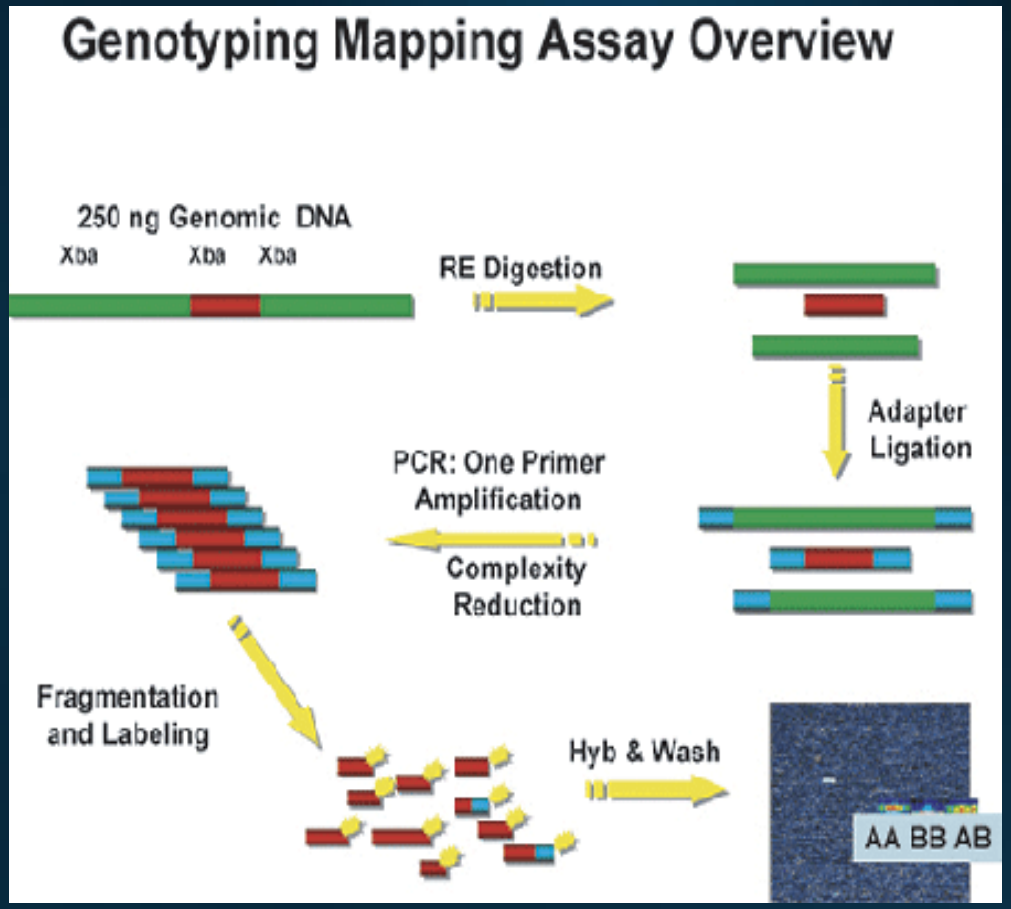
SNP array

- SNP ARRAYS
- A **Single nucleotide polymorphism is a DNA sequence variation occurring when a single nucleotide in the genome differs between members of a species (or between paired chromosomes in an individual).**



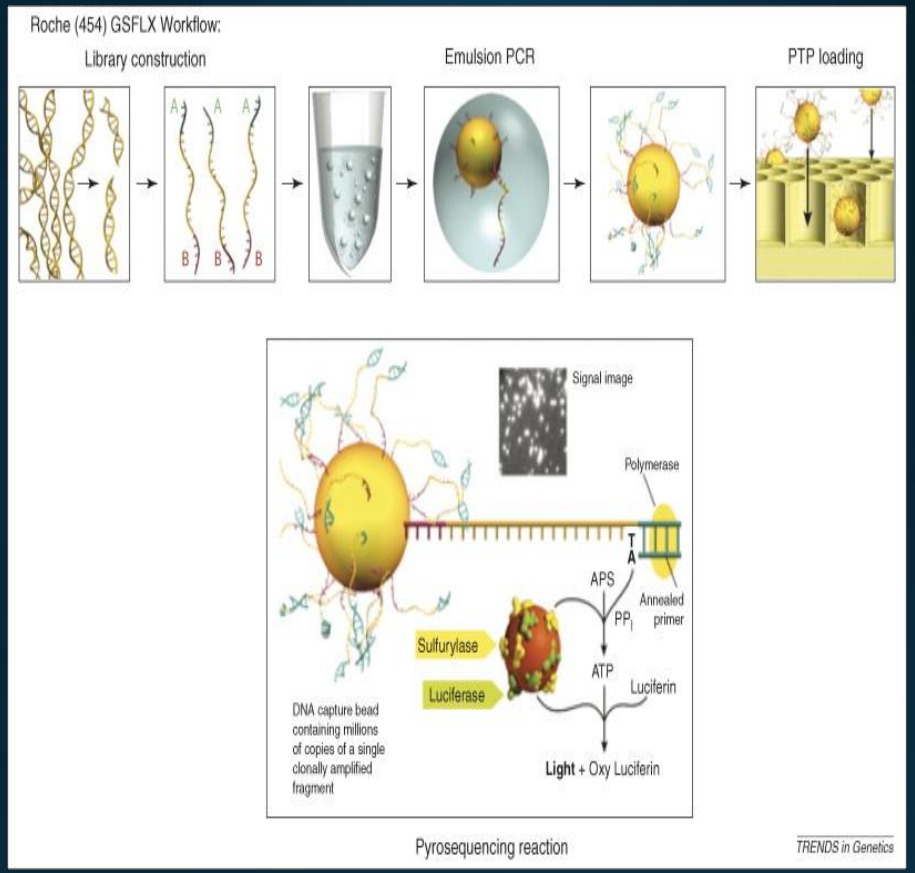
SNP array

- Advantages:
  - Very high resolution (>1000000 probes)
  - Detection of LOH



Next-generation sequencing
Exome sequencing

- Promising technique in detecting novel genetic changes (CNVs, single gene disorders)
- Technique of choice in near future



Forth Session

Diagnostic Approach to MR/DD

Objectives

- Different steps of any proposed diagnostic approach
- Limitations of each diagnostic approach
- How to select an appropriate diagnostic approach

Diagnostic approach to sporadic MR

- Guidelines based on the assessment of

1. Chromosomal abnormalities
   - Microscopic
   - Submicroscopic

2. Fragile-X syndrome

Diagnostic approach to sporadic MR

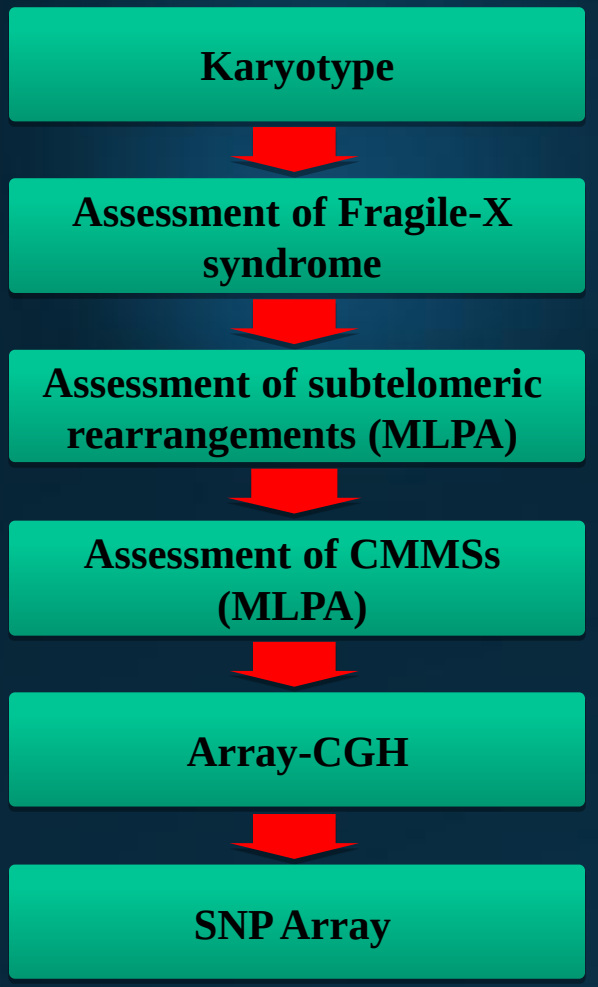
1. Karyotype
2. Assessment of Fragile-X syndrome
3. Assessment of DNA copy number differences (Array-CGH, MLPA, …)

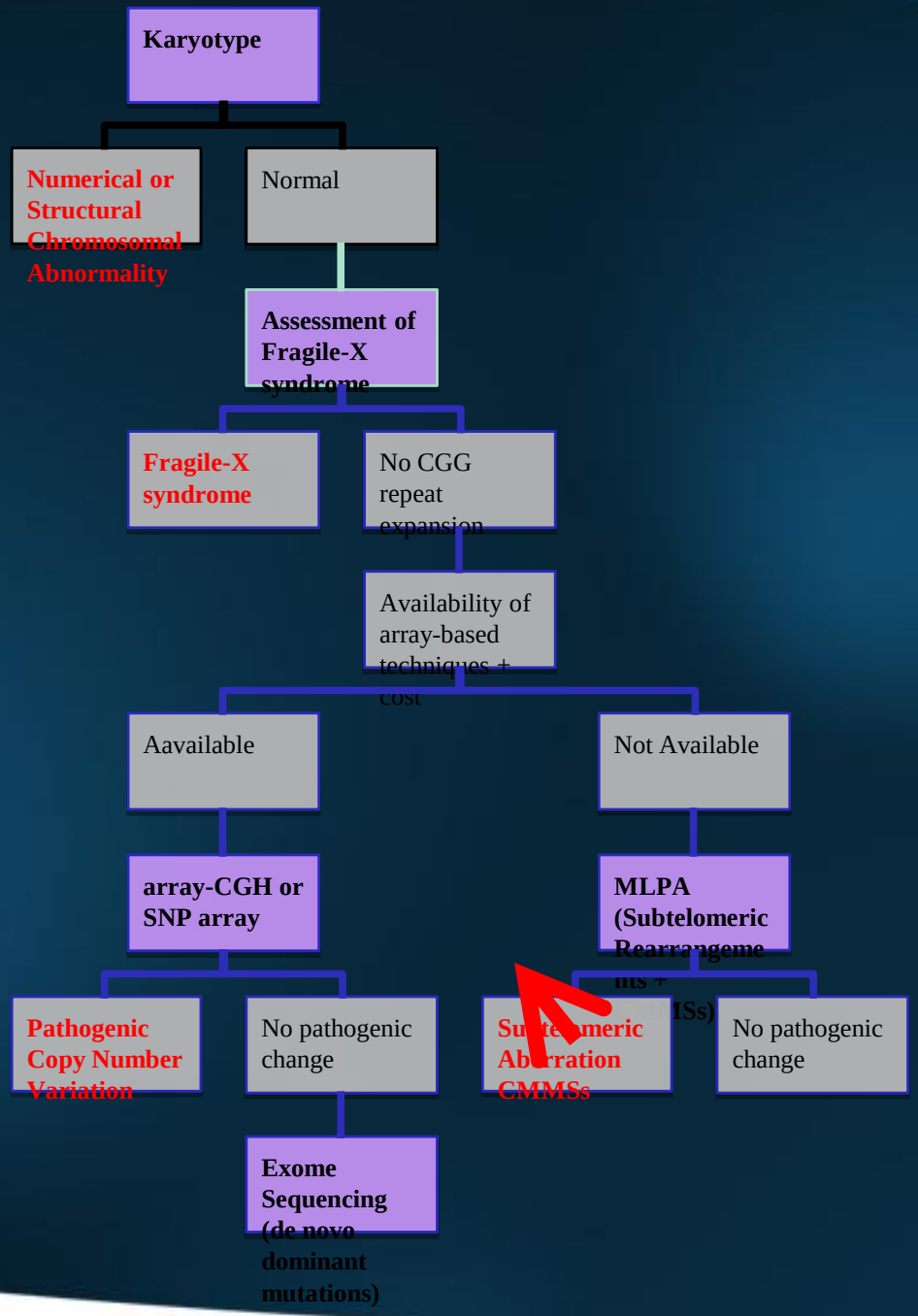
Stepwise approach to sporadic MR

- Guidelines based on the assessment of

1. Chromosomal abnormalities
   - Microscopic
   - Submicroscopic

2. Fragile-X syndrome




Karyotype
Numerical or Structural Chromosomal Abnormality
Normal
Assessment of Fragile-X syndrome
Fragile-X syndrome
No CGG repeat expansion
Availability of array-based techniques + cost
Aavailable
Not Available
array-CGH or SNP array
MLPA (Subtelomeric Rearrangements + ISs)
Pathogenic Copy Number Variation
No pathogenic change
Subtelomeric Aberration CMMSs
No pathogenic change
Exome Sequencing (de novo dominant mutations)

Diagnostic approach to familial MR/DD

Low contribution of chromosomal abnormalities to "Familial" MR

High contribution of single gene disorders

Familial MR/DD

- An extremely heterogenous disorder
  - More than 10000 genes involved
- New genomic approach
  - Exome sequencing

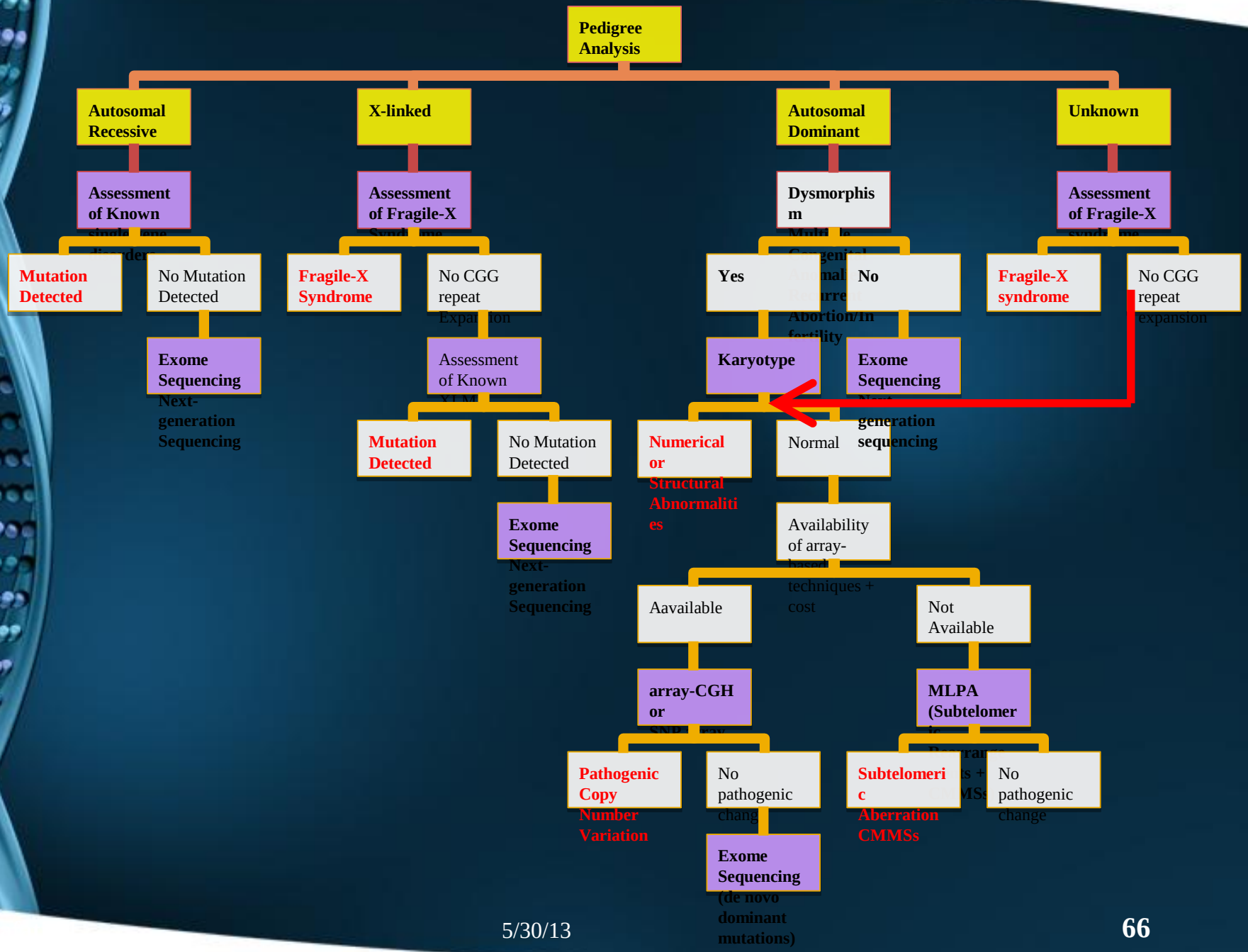
Diagnostic Algorithms

Diagnostic approach

- Pedigree analysis
- The presence of dysmorphism and/or multiple congenital anomalies

Diagnostic approach

- Familial MR/DD with dysmorphism and/or MCA:
  - The same as sporadic MR/DD
- Familial MR/DD without dysmorphism and/or MCA:
  - Focusing on single gene disorders


Pedigree Analysis
Autosomal Recessive
X-linked
Autosomal Dominant
Unknown
Assessment of Known
Assessment of Fragile-X
Dysmorphism
Assessment of Fragile-X
Mutation Detected
No Mutation Detected
Fragile-X Syndrome
No CGG repeat
Yes
No
Fragile-X syndrome
No CGG repeat
Exome Sequencing
Next-generation Sequencing
Assessment of Known
Karyotype
Exome Sequencing
Next-generation sequencing
Mutation Detected
No Mutation Detected
Numerical or Structural Abnormalities
Normal
Exome Sequencing
Next-generation Sequencing
Availability of array-based techniques + cost
Aavailable
Not Available
array-CGH or
MLPA (Subtelomeric
Pathogenic Copy Number Variation
No pathogenic change
Subtelomeric Aberration CMMSs
No pathogenic change
Exome Sequencing (de novo dominant mutations)

Conclusion

Genetic Counseling Issues

با تشکر از توجه شما