PREVENTION OF CONGENITAL DISORDERS [CDs]: IN CLINICAL PRACTICE

DR N MABASO
Medical Geneticist
[t] 011 489 9223 [e] njabulo.mabaso@nhls.ac.za
Clinical Section, Division of Human Genetics, School of Pathology
The University of the Witwatersrand and the National Health Laboratory Service (NHLS)
Chairman: Medical Geneticists Group (MGG) of the SASHG

NATIONAL HEALTH LABORATORY SERVICE

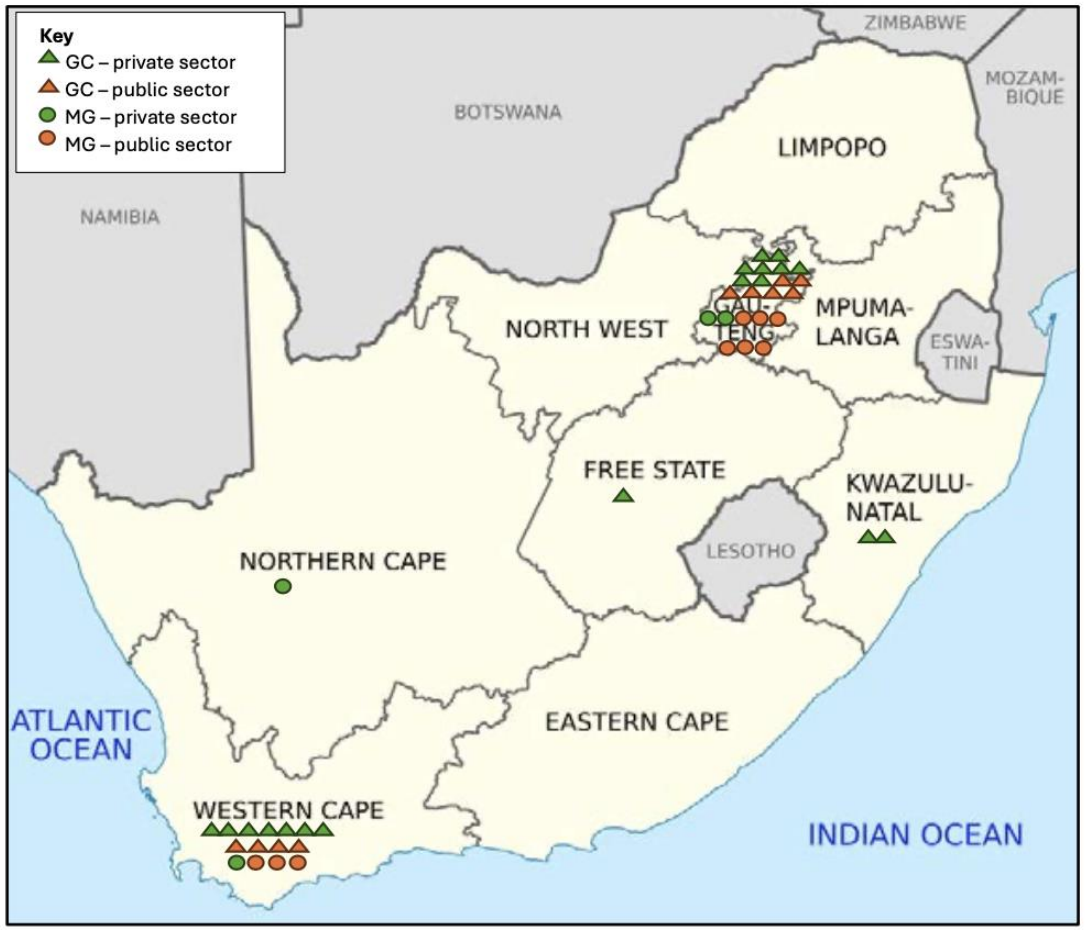
SASHG
SOUTHERN AFRICAN SOCIETY FOR HUMAN GENETICS

WITS UNIVERSITY

Presentation outline

1. Who attends the Genetics Clinic ? & receives Laboratory Genetics Services?
2. Why is Genetics training relevant to clinical practice?
3. Causes of birth defect(s) & prevention of congenital disorders
4. Common Congenital Disorders in SA & a Clinical Approach to prevention in a child with a birth defect(s)
5. How to refer a patient to Clinical Genetics?

Who attends the genetic clinic?



Geographical Distribution of currently practicing Medical Geneticists & Genetic Counsellors in RSA

- Gomes, et al (2024)

- Indications for referral, various genetic clinics, range of patients, cross disciplines
- Genetic counsellors and Clinicians (Medical Geneticists)
- Role of Medical Geneticists: diagnosis, management and counselling

Clinical disciplines that would often refer to Medical Genetics

Prenatal & Childhood

- Obstetrics & Gynaecology (and Fetal Medicine)
- Pediatrics
  - Neonatal
  - Neurology & Neurodevelopment
  - Cardiology
  - Metabolic / Bone Metabolic
  - Rheumatology
  - Oncology
  - Surgery
  - ENT
  - Dermatology
  - Ophthalmology

Adolescent & Adulthood

- Oncology (adult onset familial cancer syndromes)
- Internal / General Medicine
  - Neurology
  - Cardiology
  - Others

Referral to Genetics

Common reasons for referring patients to the Genetic Clinic:

Newborn to Childhood

Serious **birth defect**(s) / Congenital anomaly

Severe **developmental delay** / Neurobehavioural problems

Dysmorphic features

Growth related problems: failure to thrive / short stature/ tall stature

Inherited **metabolic** disorders

Disorders of **sexual differentiation (DSDs)**

Adults

Prenatal diagnosis: fetal anomalies, carrier testing, positive family history of a genetic disorder

Adult-onset inherited conditions: Familial cancer, Huntington disease, Neuromuscular disorders etc

Why is Genetics training relevant to clinical practice?

- Birth defects (BD) definition and prevalence; Brief epidemiology information, BDs
- Role /expectations of primary care doctors / nurses

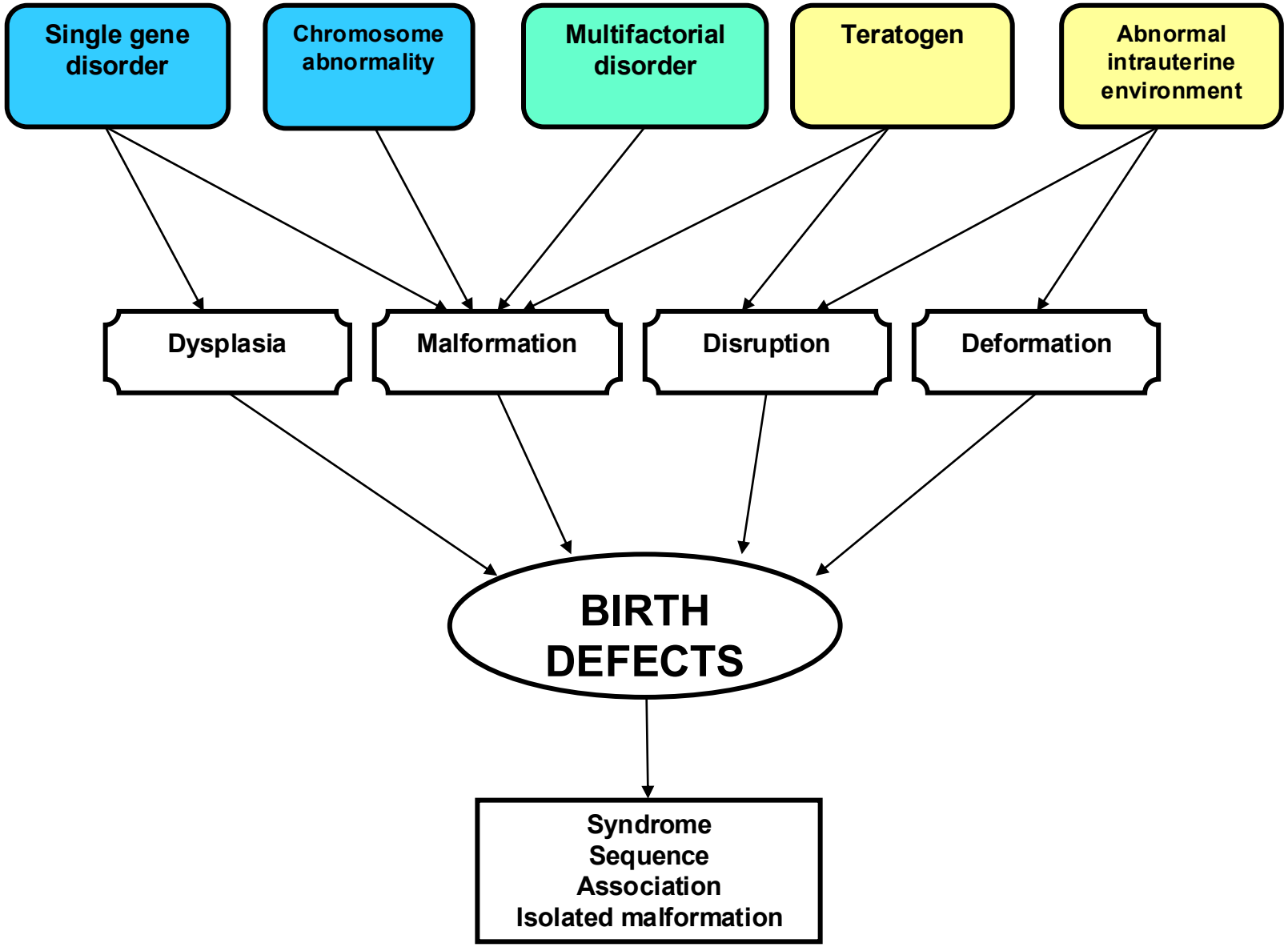
Birth defects *(a.k.a congenital disorders) are structural or functional abnormalities, present at birth.*

Prevalence of birth defects: 6% of total births worldwide (estimated 7.9 million children/year).

(**mostly genetic**)

Need to train Medical graduates, doctors, allied health professionals, nurses, community workers for effective care and prevention.

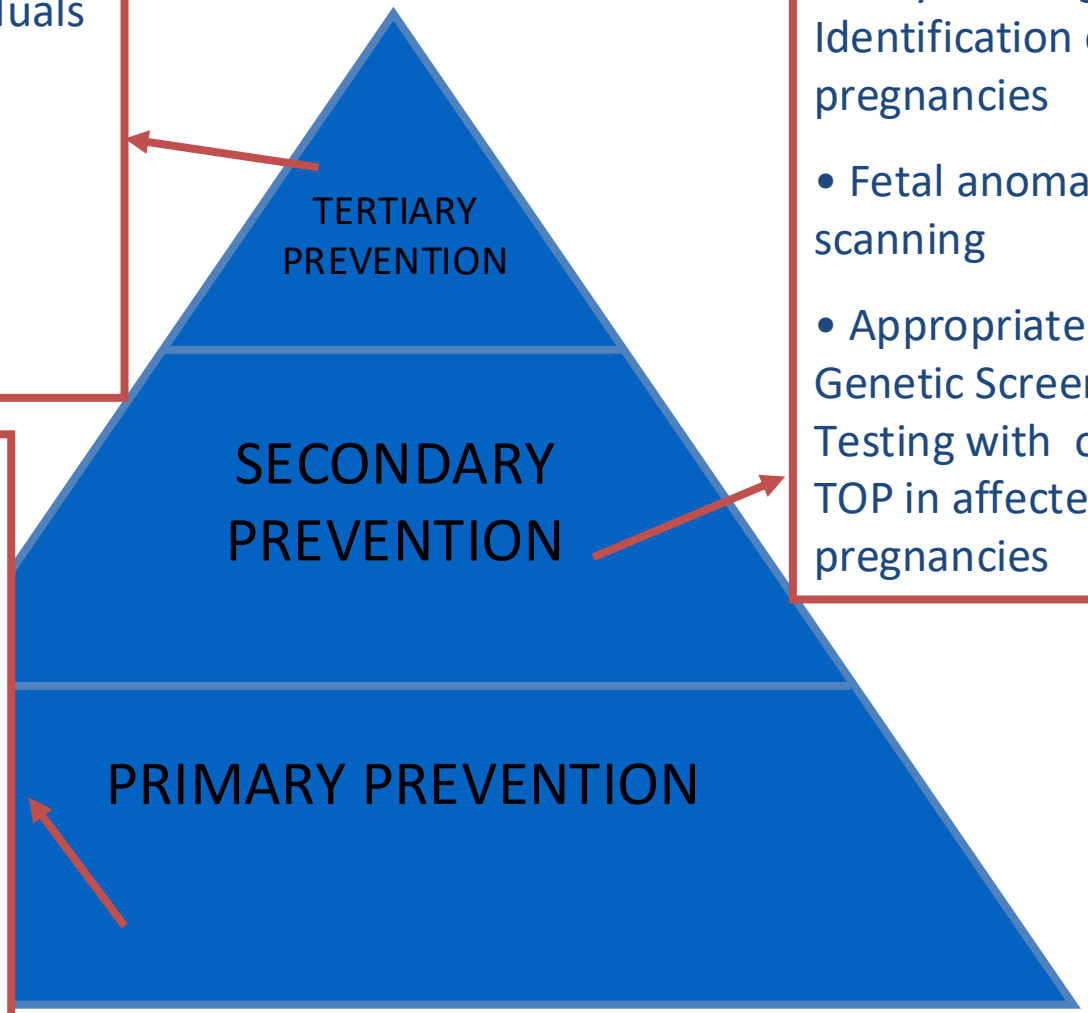
Causes of Birth Defects



Principles of Prevention

- Appropriate care for affected individuals
- NBS & Early Genetic Testing
- surgical intervention
- remedial intervention
- palliative care

- Early booking & Identification of at risk pregnancies
- Fetal anomaly scanning
- Appropriate Prenatal Genetic Screening / Testing with options of TOP in affected pregnancies



- Maternal education & counselling
- Focus on maternal health –treatment & prevention of illness
- Folic acid fortification of staple foods / Vaccinations & other supplements
- Family planning / contraception (including genetic carrier screening) & spacing
- Identification & treatment of maternal

Approach to a patient with a birth defect (s)

History

Presenting problems, **family** (drawing 3-generation family pedigree), **prenatal**, **birth**, **medical, surgical** and **developmental** history

Examination

Systematic examination (from head to toe)

Investigations

Non-genetic: X-rays, echocardiogram, Abdominal-renal U/S, metabolic screen, enzyme testing, baseline blood tests (e.g. FBC, TSH etc)

Genetic testing: FISH, chromosome analysis, MLPA/Array CGH, Next generation sequencing (NGS)/single gene/multigene panels, whole exome sequencing (WES), whole genome sequencing (WGS)

Genetic counselling

Process of helping families understand and adapt to a diagnosis

Help to understand the inheritance pattern, medical, psychosocial, family, financial implications

Discuss options of prenatal and postnatal and adult testing and management options

Assist with informed decision making

"Prevention" of birth defect (s)

Primary, Secondary, Tertiary

Practical Approach

A clinician faced with an affected individual (birth defect/complex disorder etc) needs to answer five questions:

1) What is it? – type of **birth defect**
2) What caused it? – **genetic/multifactorial** (environment & genetic)/**non-genetic** (environmental)
3) What does it mean? – **prognosis/management/treatment**
4) Will it happen again? – **recurrence** risks
5) Can it be **prevented**? – primary/secondary/tertiary

(Un)Common Birth Defects

- Rare Genetic conditions, collectively make up a large proportion of Congenital Disorders
- More genomic testing approaches are becoming available
- Environmental causes of Congenital Disorders requires to be more alert in primary care, for effective Primary Prevention
- Prevention: Available; Acceptable; Affordable; Accessible

CASE APPLICATIONS

1. Teratogen Embryopathy

2. Aneuploidy / Chromosome abnormality

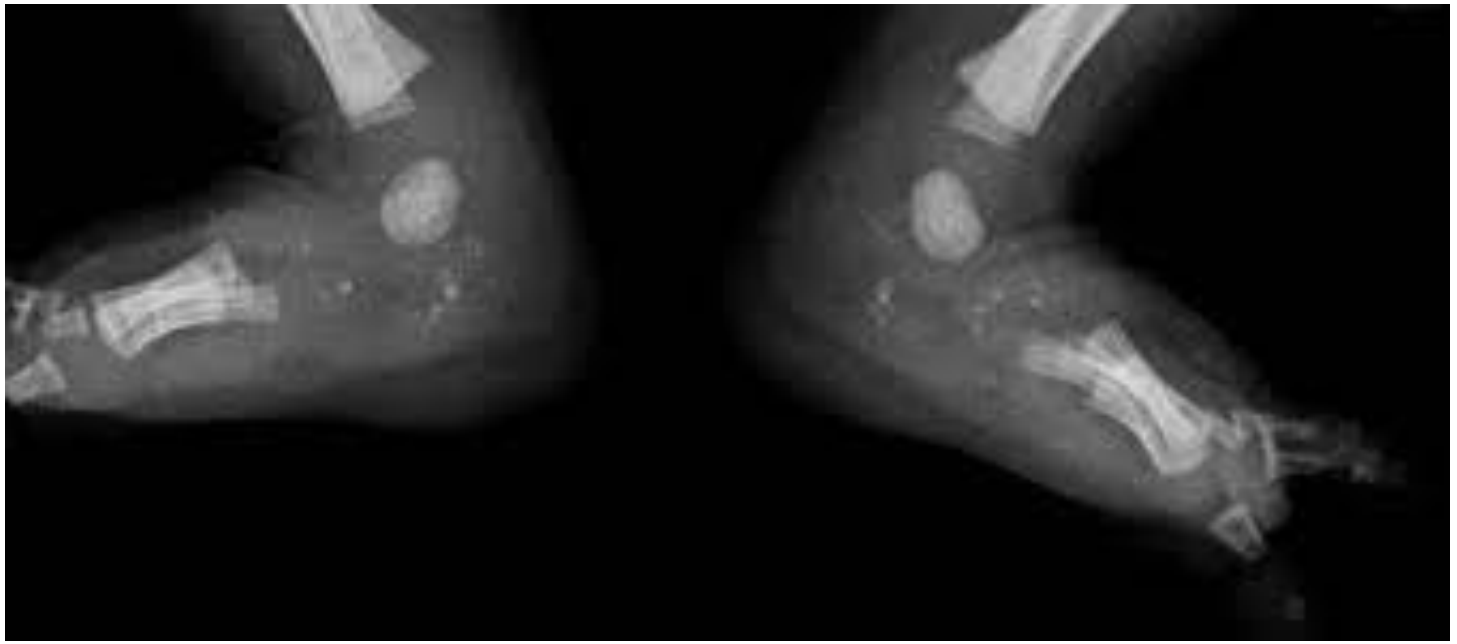
3. Single gene disorder / inborn error of metabolism

Case 1: Primary Prevention

- A newborn baby born with severe upper airway obstruction. Mother is a known cardiac patient on drugs.

1. What is it?

- Baby born with severe nasal hypoplasia
- Midfacial hypoplasia
- Stippling of epiphyses



2. What caused it?

- Teratogen –first trimester Warfarin

Leading to Warfarin embryopathy

3. What does it mean?

Complications: Warfarin embryopathy

- Severe nasal obstruction –choanal atresia requiring emergency surgery for nasal stents

- Calcium deposition during bones formation (embryogenesis)
- Bleeding in the fetus

4. Will it happen again?

- Teratogen
- Yes If mother is on Warfarin in the next pregnancy
- No if she is not

5: Can it be prevented?

- Yes
- Avoid Warfarin in early pregnancy
- Mother not to take Warfarin 6-12 weeks of gestation-Obstetrician to change to heparin
- Early fetal sonar

Case 2: Secondary Prevention

A 3 year old girl is referred for assessment of dysmorphic features and developmental delay. Mother was 41 years old at conception and is concerned about the future of her daughter.

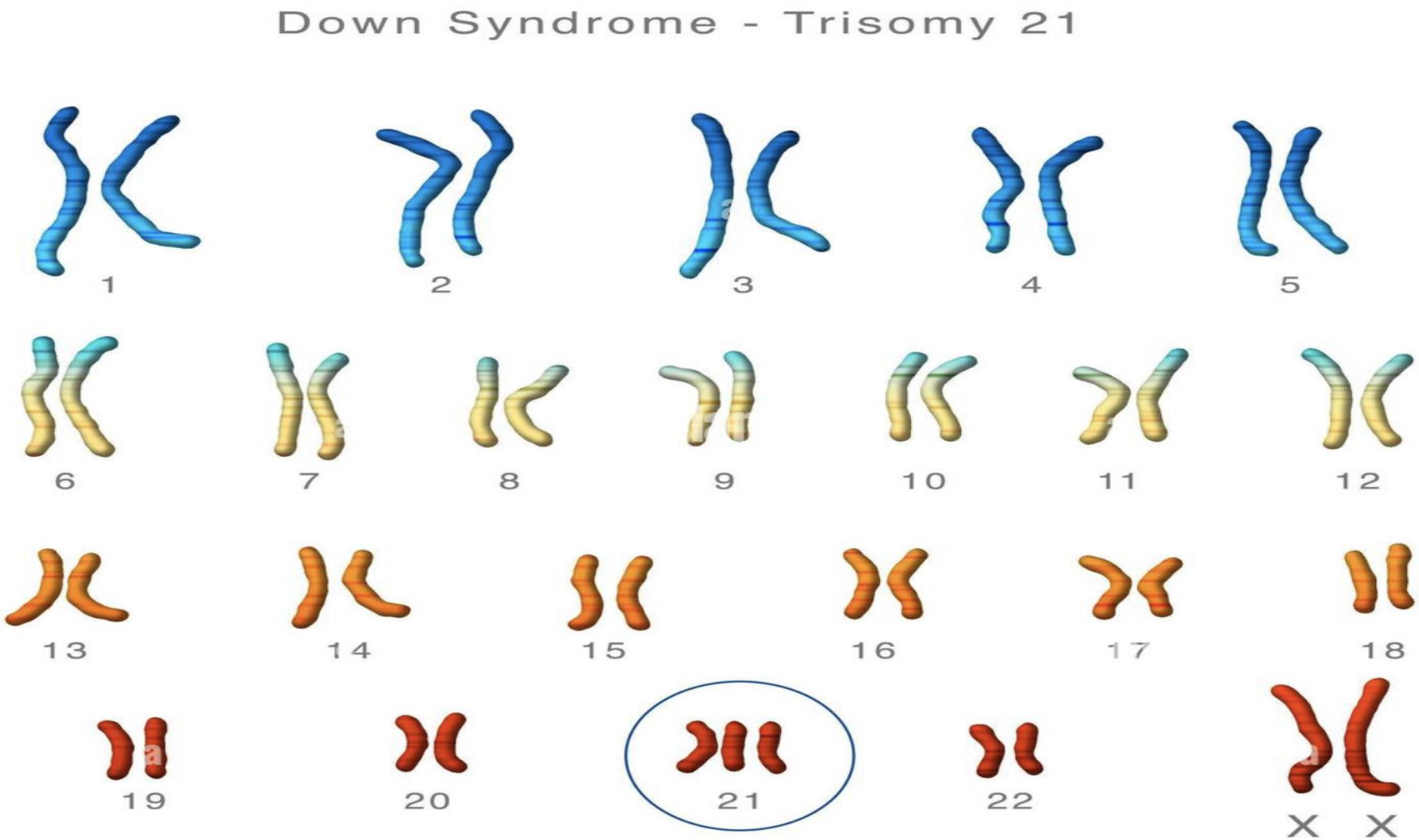
1. What is it?

Dysmorphic features in keeping with Down syndrome

What are the typical clinical features of DS ?

- Epicanthal fold (fold of skin covering inner corner of eye)
- Flat facial profile
- Abnormal ears
- Transpalmar crease (a single crease across the palm of the hand)

2. What caused it? - Do karyotype vs QF-PCR



Answer:

- Karyotype: 47,XX +21
- Non – Disjunction Down syndrome (2 other types)
- What caused it?

3. What does this mean?

Discuss with parents the implications (prognosis and long-term treatment)

Problems found in older children are:

- Increased risk of heart disease, leukemia, gastrointestinal problems (duodenal atresia, gastro-oesophageal reflux
- Global developmental/ Intellectual delay (mild to moderate)
- Visual problems and hearing loss
- Hypothyroidism

Management: First send bloods –FBC, TFTs. Refer:

- Cardiologist for heart echo to exclude congenital heart disease early
- Neuro-development Clinic, Eye Clinic for visual assessment (cataracts/strabismus),
- Audiology for Hearing tests or for Treatment of ear infection
- Physio-OT and Speech therapy for stimulation therapy
- DS Support group

5. Could this condition been preventable?

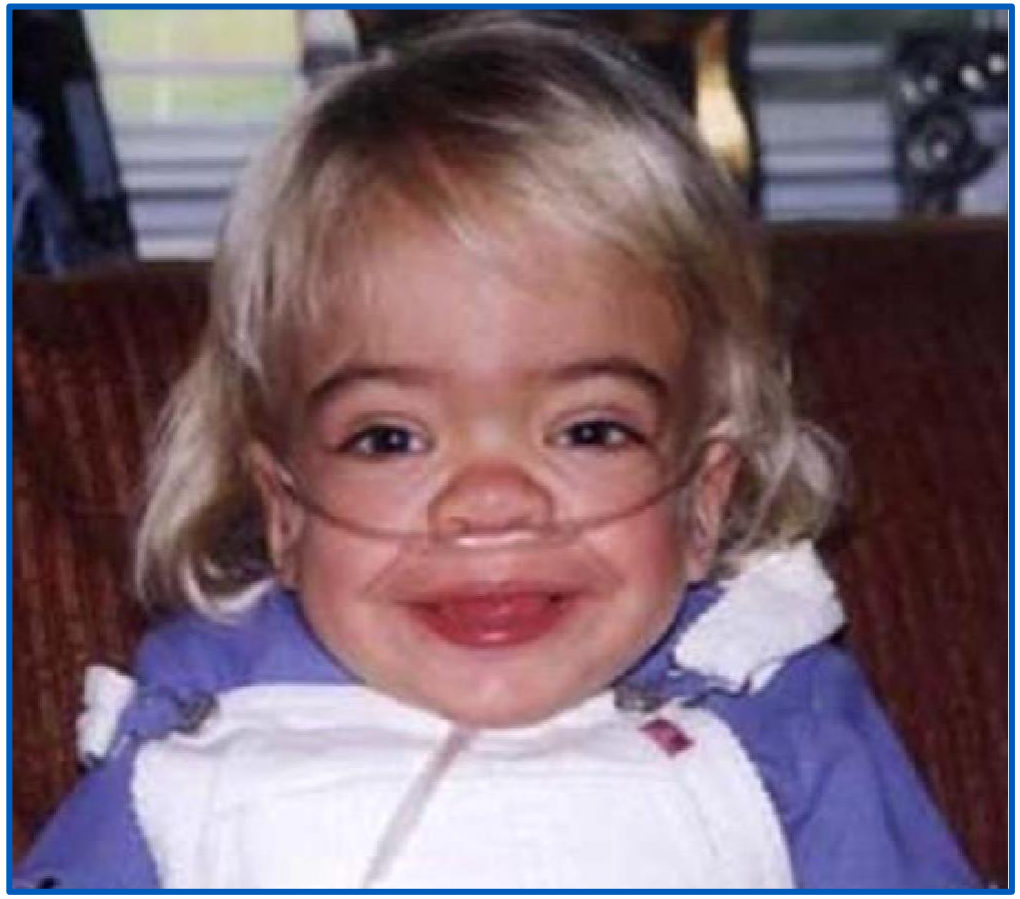
Genetic counselling early in the pregnancy for AMA:

- Prenatal screening: *Early fetal sonar-increased nuchal thickness, flat nasal bone, congenital heart disease & NIPT (not yet widely available)*
- Prenatal diagnosis: *Chorionic villus sampling / amniocentesis – for karyotype / QF-PCR aneuploidy*
- Further discuss options – Including TOP

Case 3: Tertiary Prevention

- A 8 months old baby presented with upper airway obstruction and recurrent otitis media. Seen by ENTs.
- History taking: Normal at birth but progressive facial dysmorphism

1. What is it ?



- Dysmorphic features
  - Macrocephaly
  - Flat nasal bridge –Respiratory distress with UAO
  - Spinal and skeletal deformities
  - Coarse facial features and macroglossia

2. What caused it?

Make Diagnosis-Lysosomal Storage Disorder ? Mucopolysaccharidosis (MPS) I /II

- Urine GAGS –Positive dermatan and keratin sulphate

- Skeletal X-rays –Multiplex Dysostosis

- Enzyme testing - α-L-iduronidase Deficiency

- Confirm diagnosis by DNA mutation analysis-MPS I (Hurler syndrome)

3. What does it mean?

- Shortened lifespan if not treated
- Progressive UAO

- Cardiomyopathy
- Hydrocephalus and intellectual delay

- Progressive skeletal deformities /short stature
- Requires enzyme replacement therapy [Aldurazyme]

4. Will it happen again?

- Metabolic disorder -Autosomal recessive condition
- 25% recurrence risk

5. Can it be prevented ?

- Genetic counselling
- Prenatal diagnosis / Expanded carrier screening panels
- Newborn screening (NBS)
- Early treatment

REFERRAL TO CLINICAL GENETICS

A clinician/doctor should refer if :

- The diagnosis is not clear. MG/GC for downstream co-ordinated management
- The patient needs further genetic work up.
- If the clinician does not have all the necessary information to fully inform the family (e.g. the doctor lacks knowledge of recurrence risks, genetic testing that is required etc.)
- If the clinician does not have time to address the family's questions
- The family has psychosocial issues they need to discuss, related to the patient's abnormalities.

THE END

THANK YOU