Microarray technology for the timely diagnosis of chromosome disorders in children

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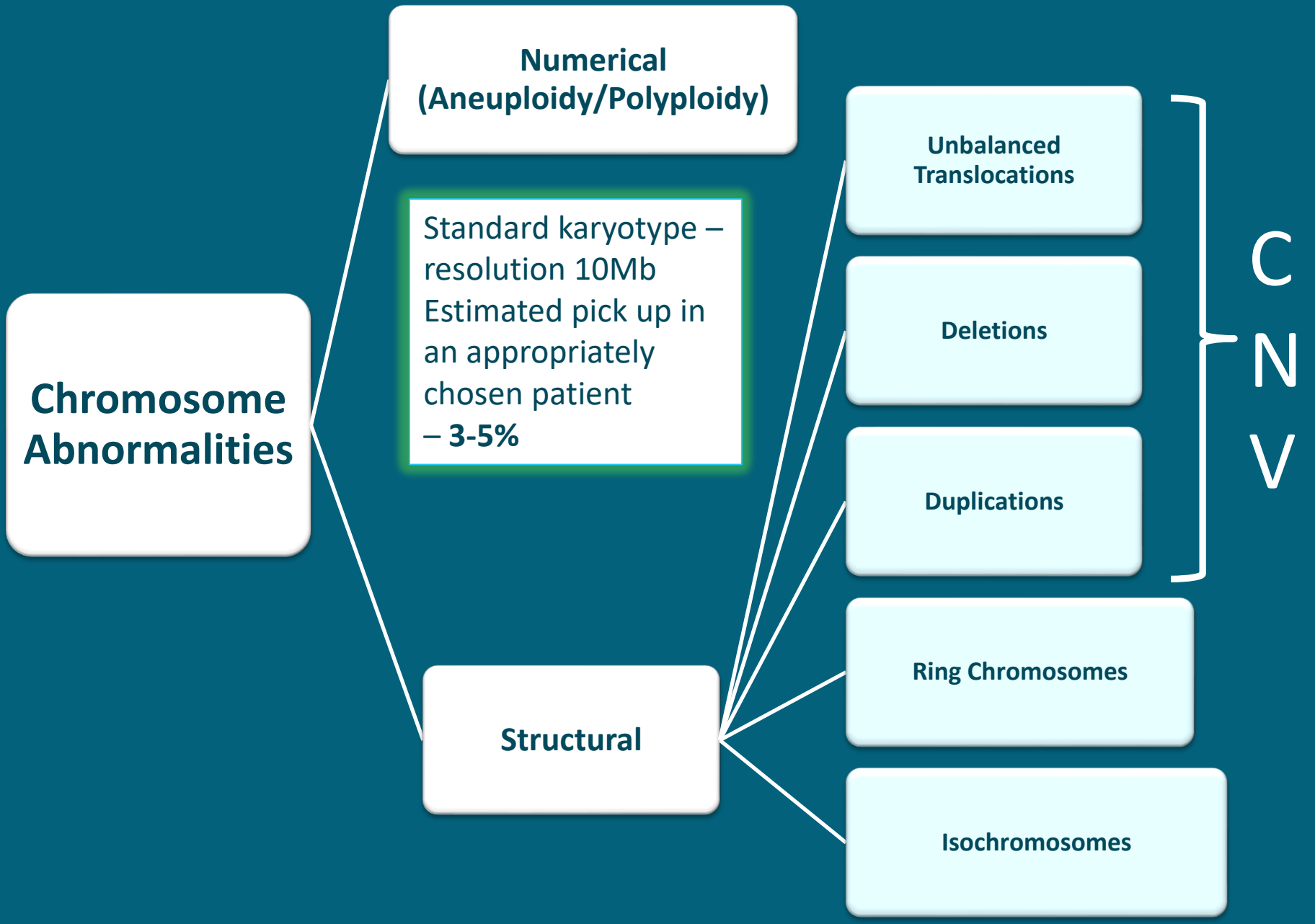
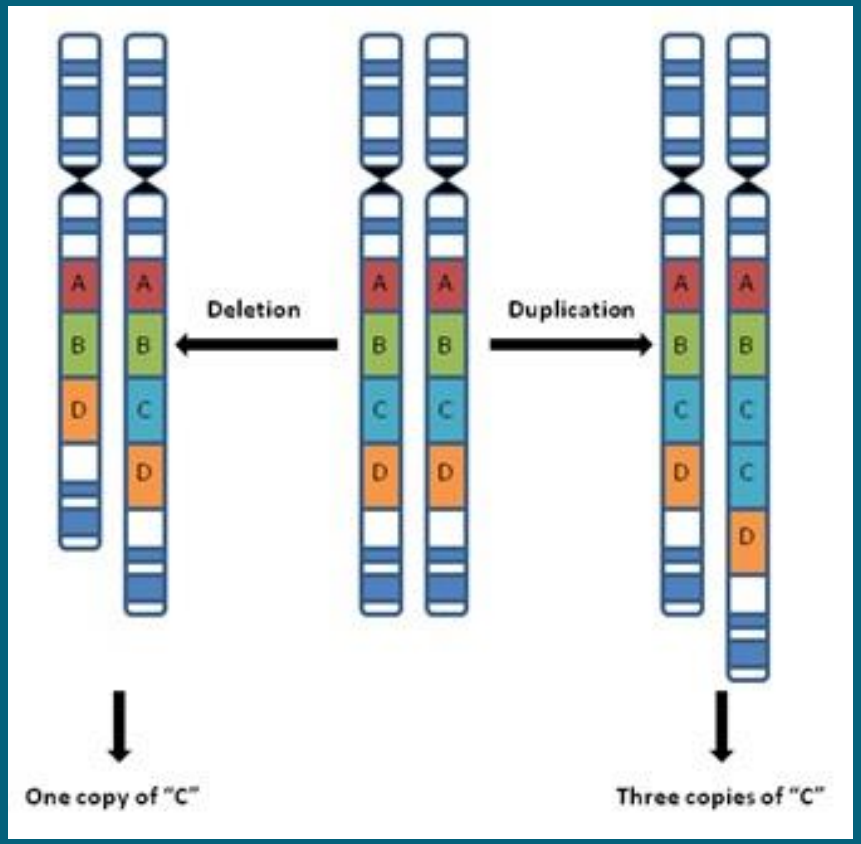
Chromosome disorders in children

- WHO estimates that the birth prevalence of chromosome disorders in Africa is **4/1000** live births
- Change in the chromosome number or chromosome structure
- Wide ranging phenotypic effects
  - Global developmental delay
  - Structural congenital abnormalities
  - Growth disturbances
  - Behavioural abnormalities – ASD, ADHD
  - Functional deficits – hearing/visual impairments
- Changes in genetic testing modalities are advancing our understanding of these conditions and allowing for much higher diagnostic rates


Chromosome Abnormalities
Numerical (Aneuploidy/Polyploidy)
Standard karyotype – resolution 10Mb
Estimated pick up in an appropriately chosen patient – 3-5%
Structural
Unbalanced Translocations
Deletions
Duplications
CNV
Ring Chromosomes
Isochromosomes

What is a chromosome copy number variant?



CLINICALLY RELEVANT CNV'S

Benign CNV – Detectable change in the copy number of a segment of chromosome – previously described in healthy individuals who do not have an known "abnormal" phenotype – contributes to human diversity

CNV of uncertain significance – occurs in apparently normal individuals but also seen in individuals with a clinical phenotype – may represent a susceptibility locus

Pathogenic CNV – Detectable change in the copy number of a segment of chromosome – previously described or can be shown to be causal of the clinical phenotype in the patient

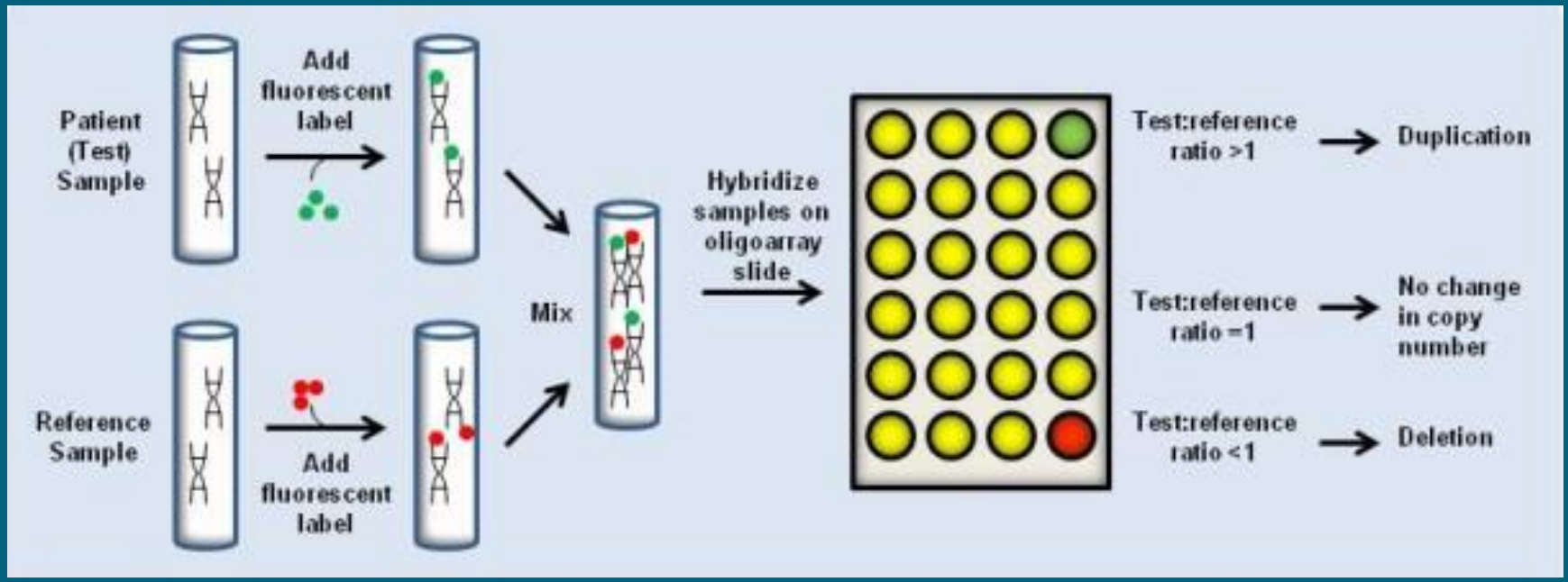
Miller et al. 2010. **Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies.** AJMG. 14(86)5

"Available evidence strongly supports the use of CMA in place of G-banded karyotyping as the first-tier test for patients with developmental delay/intellectual disability, autism spectrum disorders or multiple congenital anomalies"

Coulter et al. 2011. **Chromosomal microarray influences medical management.** Genetics in Medicine 13(9)

"For all test indications, CMA influenced medical management in patients with abnormal variants…"

Microarray testing – array-CGH

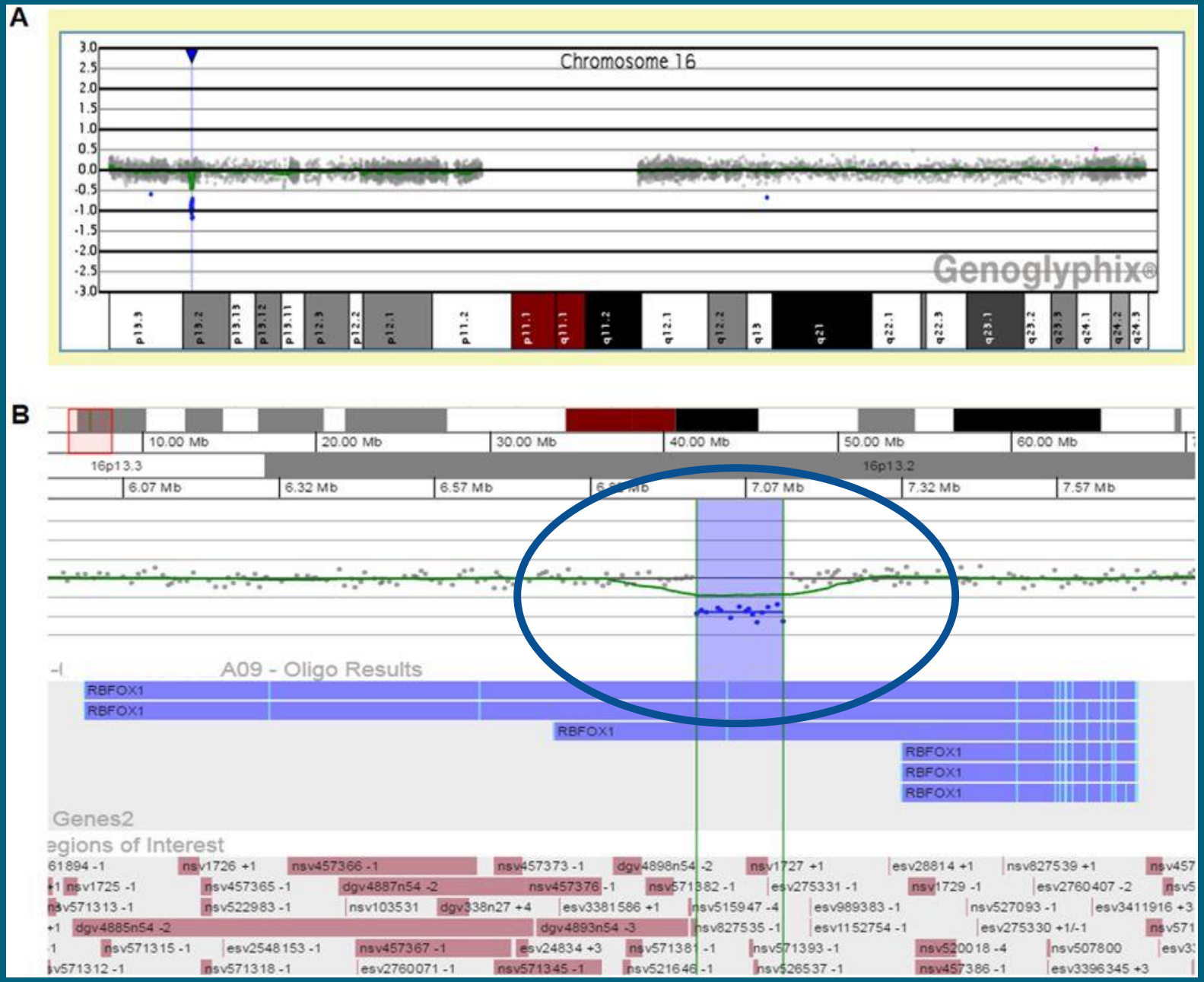


Reference sample: Pooled DNA samples of apparently healthy individuals from different populations

Oligonucleotide probes: Short DNA sequences which are complementary to the reference sequence

Density of the probes determines the resolution of the test – number of probes, spread of probes across certain areas of the chromosomes, average distance between probes

Standard array-CGH density : 60000 probes (60K)


A
Chromosome 16
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
Genoglyphix®
p13.3
p13.2
p13.13
p13.12
p13.11
p12.3
p12.2
p12.1
p11.2
p11.1
q11.1
q11.2
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q22.1
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RBFOX1
RBFOX1
RBFOX1
RBFOX1
RBFOX1
Genes2
egions of Interest
61894 -1
nsv1726 +1
nsv457366 -1
nsv457373 -1
dgv4898n54 -2
nsv1727 +1
esv28814 +1
nsv827539 +1
nsv1725 -1
nsv457365 -1
dgv4887n54 -2
nsv457376 -1
nsv571382 -1
esv275331 -1
nsv1729 -1
esv2760407 -2
nsv571313 -1
nsv522983 -1
nsv103531
dgv338n27 +4
esv3381586 +1
nsv515947 -4
esv989383 -1
nsv527093 -1
esv3411916 +3
dgv4885n54 -2
dgv4893n54 -3
nsv827535 -1
esv1152754 -1
esv275330 +1/-1
nsv571315 -1
esv2548153 -1
nsv457367 -1
esv24834 +3
nsv571381 -1
nsv571393 -1
nsv520018 -4
nsv507800
nsv571312 -1
nsv571318 -1
esv2760071 -1
nsv571345 -1
nsv521646 -1
nsv526537 -1
nsv457386 -1
esv3396345 +3

Interpretation of the CNV

Detailed clinical phenotyping is key

Segregation analysis may be important

Databases:

1. Databases linking clinical phenotype with CNV

2. Databases of CNV's in healthy people

Benign or Pathogenic?

Size of the CNV

Deletion vs duplication

Genomic content :

1. Gene rich region / dosage sensitivity

2. Single gene model

3. Contiguous gene model

4. Genetic modifiers

Value-add ?

- Pick up rate of array-CGH in an appropriately chosen patient – **15-20% -** at least 4x diagnostic yield of karyotype
- Diagnosis translates to:
  - **Implications of the CNV on the patient**
    - Screening / surveillance / prognosis
  - **Risk of recurrence in the family**
    - Prenatal testing / PGD
  - **Genetic Counselling**
    - Support services / Access to social grants

The case of Baby K

- Pregnancy complicated by polyhydramnios; ultrasound evaluation showed bilateral club feet, an absent stomach bubble and short long bones – NIPT was negative for aneuploidy.
- No significant family history.
- Examination of baby revealed prenatal onset short stature, a number of unusual features and a large PDA (on echo)
- Array-CGH – 10.7Mb deletion on chromosome 1q23

Clinical Implications

- Increased incidence of cardiac and renal malformations
- Significant pre and postnatal growth restriction; occasionally associated with GH deficiency
- Cleft palate in 35% of cases; often feeding difficulties
- Significant developmental delay

Familial Implications

- Most likely de novo event in the affected child; risk for another affected child is low; familial testing can be offered

Psychosocial Implications

- Address issues of guilt and blame
- Access appropriate support – rare chromosome abnormality family support groups
- Manage expectations, address issues of loss/grief

When is array-CGH testing indicated?

- Multiple congenital malformations
- Single congenital malformation with a number of dysmorphic features
- Intellectual disability / developmental delay of unexplained aetiology or in association with a congenital anomaly / dysmorphic features
- Significant growth disturbances
- Certain isolated congenital malformations
  - Cardiac malformation (especially cono-truncal) – 10% P/U
  - Holoprosencephaly
  - Congenital diaphragmatic hernia

Some indication that earlier testing (i.e in the neonatal period) is beneficial in terms of limiting additional and unnecessary testing and streamlining care

Take home messages

- Array-CGH testing allows for at least 4X better pick up rate of chromosome abnormalities than standard karyotype analysis
- Array-CGH should be considered a baseline/ first-tier investigation in patients with congenital anomalies, developmental delay, dysmorphic features, growth abnormalities or behavioural deficits
- Correct interpretation of test results is crucial to allow for accurate and tailored genetic counselling – pre- and post test counselling is recommended
- If you are unsure if an array-CGH is indicated, you can discuss your patient with a genetic professional who can guide you

ANY QUESTIONS?