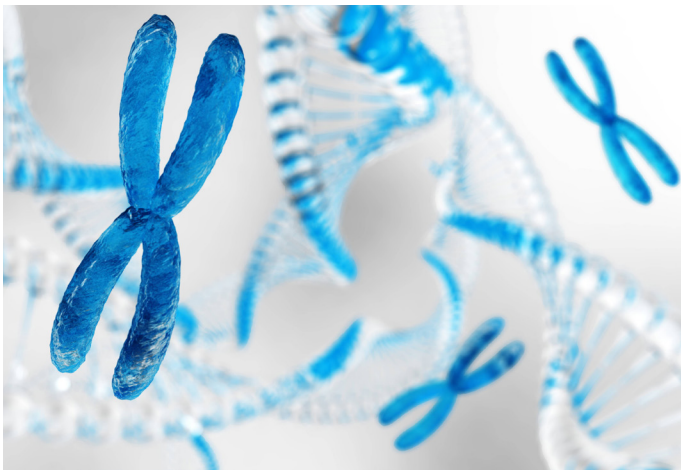
ARRAY COMPARATIVE GENOME HYBRIDISATION (ARRAY CGH)

AMPATH LABORATORIES

Array Comparative Genome Hybridisation (Array CGH) for detection of constitutional submicroscopic chromosomal imbalances.



Chromosomal abnormalities are a major cause of human malformation and intellectual disability. The incidence of major congenital anomalies is approximately 2–3%, and most studies report a prevalence of 1–2.5% for intellectual disability (IQ<70). More than 50% of first trimester miscarriages are due to chromosomal abnormalities and in 0.5–1% of live births, a recognisable chromosome abnormality is present.

The human chromosome number of 46 was discovered as recently as 1956, and in 1959, Lejeune reported trisomy 21 to be the common underlying cause in individuals with Down syndrome. The development of better cell-culturing techniques and slide preparations, and the introduction of banding techniques in the 1970s, facilitated the identification of each individual chromosome, and soon, chromosome aberrations were reported in a number of patients with syndromes, as well as in miscarriages and stillborn foetuses. The occurrence of non- pathogenic chromosome variations was also observed.

Standard karyotyping (which requires cell culture), detects numerical and structural chromosome abnormalities (including deletions, duplications, inversions and translocations) with a maximum resolution of 5–10Mb of DNA. In the 1980s, fluorescence in situ hybridisation (FISH) was developed as a "molecular cytogenetic test". Labelled DNA probes, designed to bind to a specific known DNA sequence of a chromosome, are visualised under a fluorescent microscope, to confirm suspicion of known microdeletion syndromes, subtelomeric deletions, or determine the number of chromosome copies present. However, the ability of FISH to detect chromosomal imbalances is limited by its targeted nature. Array CGH offers an advanced approach to screen the genome for chromosomal copy number variants.

CHROMOSOMAL MICROARRAY

Chromosomal microarray (CMA) is a molecular cytogenetic test used to detect copy number variants (CNVs) (deletions and duplications of chromosome material), ranging in size from a few kilobases to many megabases across the genome. These CNVs may be benign (normal variants), pathogenic, or of uncertain clinical significance.

The most common types of CMA are oligonucleotide array comparative genomic hybridisation (array CGH), single nucleotide polymorphism genotyping array (SNP array) and a combination of both. CMA can have numerous designs (identifying CNVs across the genome, or only in specific regions) and applications: tumour genetics, gene expression studies and of course, constitutional genetics.

USE OF CMA IN CONSTITUTIONAL DEVELOPMENTAL DISORDERS

CMA has been used as a clinical diagnostic test since about 2004, and in 2011, CMA was recommended as a first-tier test for individuals with unexplained developmental delay/intellectual disability (DD/ID), autism spectrum disorders (ASD) or multiple congenital abnormalities (MCA). It is significantly more sensitive at detecting CNVs than standard karyotype analysis. Excluding Down syndrome and other recognisable chromosomal syndromes, the diagnostic yield of conventional karyotyping is approximately 3%. CMA increases the diagnostic yield to 15%–20%, when testing individuals with unexplained DD/ID, ASD or MCA.

ARRAY CGH

Array CGH compares a characterised 'control' genome to a patient genome using multiple targets (probes) on a slide. These targets are oligonucleotides (short DNA sequences).

Control and patient DNA are labelled and mixed, then applied to a slide (Figure 1a). At targets where patient DNA is deleted, the control DNA colour will predominate, and at targets where patient DNA is duplicated, the patient DNA colour will predominate (Figure 1b). The slide is read in a scanner and the software converts the information into a karyogram for further interpretation (Figure 1c).

PATHOLOGY IS IN OUR DNA

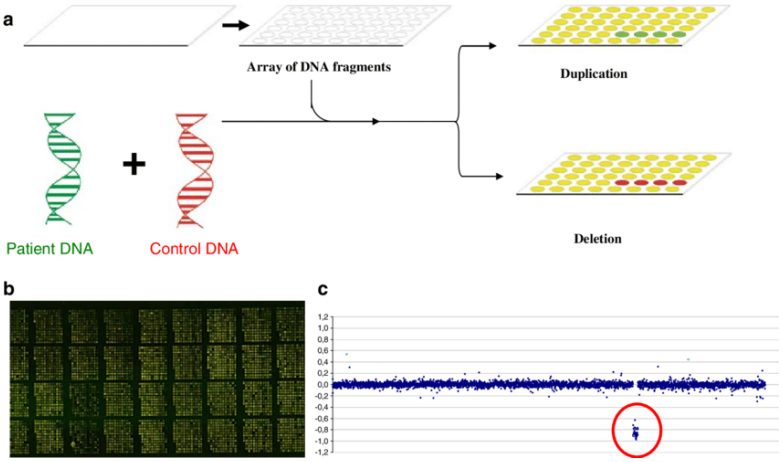


Figure 1 (image derived from De Ravel, Devriendt, Fryns, and Vermeesch, 2007)

Interpretation and reporting is performed by medical scientists and clinical geneticists at Ampath Genetics, and the interpretation of results is linked to the clinical phenotype provided by the referring clinician.

CMA is unable to detect balanced structural chromosome rearrangements (where there is no net gain or loss of genetic material), small CNVs below the level of resolution of the platform, or low level mosaicism. Follow up parental studies (which may include CMA, standard karyotype and/or FISH studies) are at times required to elucidate the inheritance or underlying mechanism of imbalances detected in a patient. Only SNP arrays are able to detect loss of heterozygosity due to consanguinity or uniparental disomy.

Standard karyotyping retains a place in the investigation of the common autosomal trisomies, suspected sex chromosome aneuploidies and disorders of sexual differentiation, some cases of recurrent miscarriages as well as in elucidating the mechanism/microscopic structure of CMA findings.

ARRAY CGH AT AMPATH GENETICS

Since 2016, Ampath Genetics has been offering array CGH testing using the Signature Genomics' CGX Oligo Arrays printed by Agilent. With 60 000 oligonucleotide probes, the resolution of this array is about 200kb across the backbone of the genome and about 30kb in specific targeted regions. The targeted regions include over 200 recognised syndromes and many other functionally significant gene regions. Subtelomeric and pericentromeric probes are included in this array. Array CGH is offered for constitutional chromosome imbalances in the postnatal setting.

For more information, please contact Ampath Genetics on 012 678 1350. Enquiries regarding genetic counselling can be made on 012 678 0645 or via email at geneticsclinic@ampath.co.za.

Fast Facts

SPECIMEN REQUIREMENTS
3–5 ml EDTA blood, sent at room temperature

MNEMONIC
ACGHGENO

TURNAROUND TIME
4 weeks from receipt of specimen