**Single Nucleotide Polymorphism Microarray testing**

**INTRODUCTION**

For patients with intellectual disability, developmental delay, autism spectrum disorder or multiple congenital anomalies, conventional cytogenetic testing (karyotyping) has previously been the diagnostic investigation of choice for the detection of chromosomal imbalance. However, excluding trisomy 21 (Down syndrome), the detection rate of karyotyping in these patients is only 3–5%.

Studies have shown that genome-wide microarrays detect a clinically significant genomic imbalance in up to 10% of patients with normal karyotype results. In unselected patients with developmental delay, microarrays have a detection rate of 15–20%, more than double the detection rate of conventional karyotyping.

Microarray testing is now recommended internationally as the first-tier test in patients with intellectual disability/developmental delay. This has been recognised in Australia, with the introduction of a Medicare Benefits Schedule item specifically for microarray testing.

Genome-wide Single Nucleotide Polymorphism Microarray (SNP microarray) testing is available through Sonic Genetics, using the Illumina Cyto SNP 850K array platform.

**WHAT IS MICROARRAY TESTING?**

DNA is extracted from a patient’s blood sample, processed, and applied to glass slide that is covered with millions of small beads. Each bead has thousands of ‘oligonucleotide’ probes attached, corresponding to a specific region of each chromosome. Reactions then take place on this slide, involving fluorescently labelled reagents. Regions where the genomic copy number differs between the patient’s DNA and a reference sample set can be detected as a difference in signal intensity.

In this way, deletions and duplications of genetic material can be detected, at a resolution that is an order of magnitude higher than conventional karyotype. Thus, a wide range of such ‘copy number changes’ can be detected by microarray – from whole chromosome aneuploidies such as trisomy 21 to small deletions affecting only a few genes, which could not be detected by karyotype.

Each copy number change is analysed for possible clinical significance in the laboratory, and results are reported to the requesting clinician. In some cases parenteral studies may be required to determine whether a change is familial.

In addition to detecting copy number changes, Single Nucleotide Polymorphism microarrays can also detect large regions of homozygosity in a chromosome, also known as ‘long contiguous stretches of homozygosity’ (LCSH). CGH microarrays cannot detect LCSH.

Presence of LCSH on a single chromosome can be an indicator of Uniparental Disomy (UPD) for that chromosome. UPD is associated with a clinical phenotype for certain chromosomes. In addition, presence of LCSH across multiple chromosomes can indicate inheritance from a common ancestor (‘identity by descent’), which may be associated with an increased risk of a recessive single gene disorder.

**LIMITATIONS OF MICROARRAY TESTING**

Microarray testing cannot detect balanced genomic rearrangements, such as translocations. However, it is estimated that these changes account for < 1% of clinically significant abnormalities in patients with intellectual disability. In addition, low level mosaic copy number changes may not be detected by array technology.

Finally, genetic changes affecting single genes cannot be detected by either microarray or karyotype. These include point mutations and triplet repeat expansions (such as the repeat expansion that causes Fragile X syndrome).

**COMPLEXITIES OF MICROARRAY TESTING**

In some patients, novel copy number changes are detected, where there is insufficient current evidence to classify them as either clinically significant or benign variants. These are known as ‘variants of unknown clinical significance’ (VUCS).

In addition, emerging data suggests that certain recurrent copy number changes, although not having a known direct clinical consequence, might be regarded as ‘susceptibility alleles’ for neurodevelopmental disorders. For these copy number changes, clinical outcome may be determined by a combination of as yet unknown additional genetic and environmental factors.

Finally, ‘incidental findings’ may be detected. These are genomic imbalances which affect genes unrelated to the clinical presentation of the patient, but which may have significant clinical consequences (e.g. deletion of a tumour suppressor gene may indicate that the patient has an increased risk of developing cancer in later life).

In patients with ‘variants of unknown significance’, ‘susceptibility alleles’ or ‘incidental findings’, referral of the patient and their families to clinical genetics services for further assessment and counselling is recommended.
SPECIMEN COLLECTION

How to request microarray testing

Please request ‘Microarray testing’ on the request form, and provide full clinical information. Clinical information is needed for analysis of the microarray results, and to determine whether the patient is eligible for a Medicare Benefits Schedule (MBS) rebate. When testing the parent of a child with an abnormality detected by microarray analysis, please note the child’s name and date of birth for cross-referencing.

Peripheral blood samples (preferably 5 ml in EDTA + 5 ml in lithium heparin; minimum 1 ml in each) should be collected for microarray testing.

COST

An MBS rebate is available for microarray testing (Item 73292). The item descriptor limits microarray testing to patients with intellectual disability, developmental delay, autism spectrum disorder or multiple congenital anomalies. Additional samples from parents and siblings may be required in some cases to clarify preliminary microarray results; an MBS rebate will also apply for these samples.

TURN-AROUND TIMES

Expected turn-around time of this test is 8 weeks.

NOTE

The MBS specifically excludes a rebate for karyotype analysis when performed on the same sample as a microarray test. If both karyotype and microarray are required, please send two separate sets of samples. These will need to be taken on different days, according to Medicare regulations.

References

Kimonis (2014) Clinical utility and dilemmas of SNP microarray testing. Molecular Cytogenetics 7(Suppl 1):84


