



## **An Introduction to Comparative Genomic Hybridization**

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Conventional cytogenetics with karyotyping is useful in the diagnosis of chromosomal abnormalities related to developmental delay, mental retardation, and dysmorphic features. However, these studies are limited by their inability to detect chromosomal anomalies less than 2–3 megabases in size. A relatively new molecular cytogenetic test, comparative genomic hybridization (CGH), is now being used to detect smaller chromosomal abnormalities. CGH is useful for detecting small genetic imbalances (gains or losses of chromosomal material), also known as genomic copy number changes, which may not be detectable by routine cytogenetics. In microarray CGH, short DNA sequences corresponding to known chromosomal loci spanning the genome are fixed to a solid surface. The composition of these sequences affects the size of the smallest detectable chromosomal anomaly. The typical array will include loci of common microdeletion/duplication syndromes, as well as numerous subtelomeric and pericentromeric regions. Subtelomeric locations are sites known to be commonly involved by DNA copy number alteration.

To conduct the test, fluorescently labeled DNA from both the patient and a control is hybridized to the array. Different fluorescent probes are used for the patient and control. After hybridization, the signals are detected and software-assisted interpretation of the generated data is performed to determine any copy number change between control and patient DNA. Testing is performed on whole blood samples and usual turnaround time can vary from one to three weeks depending upon the lab and any confirmation studies needed.

Common indications for CGH testing include developmental delay, failure to thrive, dysmorphic features, multiple congenital abnormalities, short stature, seizure disorder, and autism spectrum disorder. CGH can also be useful in characterizing the specific genes involved and in sizing/characterizing a chromosomal abnormality detected by conventional cytogenetics. Current practice guidelines recommend CGH to supplement conventional karyotype analysis in patients with developmental delay or congenital anomalies.<sup>1</sup> However, CGH is not currently recommended for prenatal diagnosis.<sup>1</sup> Good practice involves confirmation of any copy number change by FISH analysis or some other proven technology, and detection of a genomic imbalance frequently requires follow-up testing of a parental sample.

The limitations of CGH include false-negatives if the patient has a copy number change not covered by the specific array used in the laboratory. Balanced chromosomal translocations cannot be detected. Point mutations and duplications/deletions less than those which can be resolved by the particular array (typically 50–100 Kb) cannot be detected.

Detected abnormality rates range from between 8% to 20%.<sup>1</sup> However, not all copy number changes are clinically significant, and, when detected, need to be classified as benign, pathogenic, or of unknown significance.<sup>2</sup> A large study by Shaffer et al showed that CGH detected a clinically significant (pathogenic) copy number change in 5.6% of cases without a previously detected cytogenetic abnormality.<sup>3</sup> A majority of their patients were referred for developmental delay.<sup>3</sup> Aston et al report an abnormal rate of 10.8% in 669 patients with normal karyotypes.<sup>4</sup> Furthermore, they found that greater than 70% of such cases experienced at least one change in medical management.<sup>4</sup> From early reports, it is clear that CGH testing is a useful supplement to traditional cytogenetic analysis. As the use of CGH testing increases, more data will become available and new clinically significant chromosomal loci involved in genomic disorders will be identified.

#### References:

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