Review

UHN Microarray Centre

Finding *de novo* copy number variants using aCGH

Review of: Toruner GA, Streck DL, Schwalb MN, and Dermondy JJ. An Oligonucleotide Based Array-CGH System for Detection of Genome Wide Copy Number Changes Including Subtelomeric Regions for Genetic Evaluation of Mental Retardation. Am J Med Genet Part A, 2007, 143A:824-829

Array Comparative Genomics Hybridisation (aCGH) is a technique widely used to identify deletions or duplications in very small segments of chromosomes genome-wide. aCGH has been successfully used to characterise various carcinomas and to identify and map disease genes involved with complex multigenic disorders such as mental retardation (MR) and developmental delay (DD)[1-3]. The advantage of aCGH over other techniques is that it allows rapid genome-wide detection of smaller genomic aberrations that are not detectable by conventional methods. Also, the information provided by aCGH experiments can be directly linked to physical and genetic maps of the human genome.

Detectable chromosomal abnormalities are the most recognised cause of MR, but gain or loss of chromosomal segments that are too small to be detected by conventional cytogenetic analysis is another important cause[2]. One of the main challenges in genetic testing for MR is to find a method that can provide a complete analysis of quantitative genomic-associated changes. Currently, several tests including conventional cytogenetic testing (karyotyping), fluorescent in situ hybridisation (FISH) and BAC-clone aCGH are used, and often all three are performed for a complete analysis[1]. Karyotyping is used to identify large chromosomal duplications and deletions and FISH analysis is often performed when a patient's phenotype suggests a specific syndrome (for example, 22q deletion syndrome and Williams syndrome (deletion of chromosome 7q11.2)). For patients with a normal karyotype and a phenotype that is not characteristic of a particular syndrome, aCGH can be performed in an attempt to increase the resolution of the assay. Until recently, arrays spotted with bacterial artificial chromosome (BAC) were used for aCGH, however, a major limitation of BAC-based CGH arrays is their low resolution (approximately 1Mb) and the suboptimal coverage particularly in the subtelomeric regions[1].

Currently, there are several commercially available high-density oligonucleotide aCGH platforms including Agilent. For the genetic analysis of MR, CGH arrays should detect all known genetic aberrations and provide sufficient probe density (resolution) for the discovery of novel aberrations. In addition, probes representing the subtelomeric regions should be included; as studies have found that genetic aberrations in the subtelomeric regions are common in MR[3].

In the study published by Toruner *et al.*, a novel aCGH chip was designed to provide high-density representation of the subtelomeric regions in addition to sufficient density throughout the genome to provide comprehensive coverage for MR/DD. The custom CGH array was based on Agilent's Human CGH 44K array. Using eArray 4.0 (Agilent), a web-based microarray design tool that allows for custom array design, users can choose from a database of over 8 million aCGH probes that span exonic, intronic, intergenic and subtelomeric DNA regions. In this study, every third probe sequence of the CGH 44K array was removed and replaced with a probe representing a subtelomere region (from within 1Mb of the telomere for 41 telomeric regions). This custom CGH array, with enriched subtelomere representation, covered the entire genome with an average resolution of 5kb in subtelomere regions and 125kb in the remaining genome.

In this study, the custom CGH array was used for the genetic evaluation of 15 patients with known chromosomal abnormalities. Concordance of the aCGH data and prior karyotyping/FISH results were 100%. In addition, two novel aberrations were found using the CGH array, a 3.5Mb deletion in 14q11 and a 3Mb deletion in 17q24.3-17q25.1. Despite the small sample size of this study, another study has found that aCGH is a useful technique for discovering copy number variants in patients with idiopathic MR[2].

The results from this study demonstrate that custom designed array CGH platform can detect chromosomal aberrations including deletions, duplications, trisomies and unbalanced translocations (throughout the genome including subtelomeric regions) associated with MR/DD[1].

References

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