Published in final edited form as:

J Pediatr. 2009 January ; 154(1): 143–146. doi:10.1016/j.jpeds.2008.07.045.

Clinical Utility of Array Comparative Genomic Hybridization: Uncovering Tumor Susceptibility in Individuals with Developmental Delay

Margaret P. Adam, M.D.¹, April N. Justice, M.S.¹, Susan Schelley, M.P.H.², Andrea Kwan, M.S.², Louanne Hudgins, M.D.², and Christa L. Martin, Ph.D.¹

¹Department of Human Genetics, Emory University School of Medicine, Atlanta, GA

²Department of Pediatrics, Division of Medical Genetics, Stanford University School of Medicine, Stanford, CA

Abstract

Microarray-based comparative genomic hybridization (aCGH) can determine genome-wide copy number alterations at the kilobase (kb) level. We highlight the clinical utility of aCGH in determining tumor susceptibility in 3 patients with dysmorphic features and developmental delay, likely decreasing both morbidity and mortality in these patients.

Keywords

array comparative genomic hybridization; tumor susceptibility; Li-Fraumeni; Peutz-Jeghers

INTRODUCTION

Cytogenetic imbalances are the most common known cause of mental retardation, but conventional cytogenetic techniques can only detect deletions larger than 5–10 megabases (Mb)(1). With the advent of microarray-based comparative genomic hybridization (aCGH), however, genome-wide high-resolution copy number alterations can be detected at the kilobase (kb) level and smaller. Whereas the primary focus of most articles is on the strengths of aCGH in the diagnosis of individuals with mental retardation and/or congenital anomalies and in the search for disease-causing genes(2), here we highlight a new clinical use for aCGH that has direct bearing on the management of patients with developmental delays and/or dysmorphic features: determination of tumor susceptibility.

METHODS

Each patient was referred for a genetics evaluation to an academic medical center because of developmental delay, dysmorphic features, and/or congenital anomalies. A clinically available 44,000 probe oligonucleotide array (EmArray Cyto6000, Emory University, Atlanta, GA or GenomeDx, GeneDx, Gaithersburg, MD) was used. This array has a ~500 kb

(kilobase) backbone with targeted coverage of telomeric, centromeric, and gene-rich regions at a resolution of ~50 kb. Once an abnormality was found, the gene content of the deleted region was assessed using the UCSC Genome Browser (<http://genome.ucsc.edu>).

ILLUSTRATIVE CASES

All patients had normal growth parameters and noncontributory family histories.

Patient 1 was evaluated at 8 years of age and found to have moderate mental retardation, autistic-like behaviors, and dysmorphic features (Table I, Figure 1). He had no mucocutaneous hyperpigmentation. Routine cytogenetic and metabolic testing was unrevealing. However, oligonucleotide aCGH demonstrated a *de novo* 1.1-Mb deletion of 19p13.3 including *STK11*, which is associated with autosomal dominant Peutz-Jeghers syndrome (PJS)(3).

Patient 2 was evaluated at 11 months of age and found to have dysmorphic features (Table I) and moderate developmental delay. An initial chromosome analysis was normal. Subsequent aCGH (Figure 1) demonstrated a *de novo* deletion of chromosome 17p encompassing the *TP53* tumor suppressor gene responsible for Li-Fraumeni syndrome (LFS)(4) (Figure 1).

Patient 3 was evaluated at 3 years and found to have dysmorphic features (Table I, Figure 1) and mild developmental delay. An initial chromosome analysis was normal, but aCGH demonstrated a *de novo* deletion of chromosome 17p13 encompassing the *TP53* tumor suppressor gene.

DISCUSSION

Traditional techniques for detecting genomic copy number variations have been limited either to abnormalities that can be visualized under the microscope or to smaller deletions or duplications that could be detected by targeted fluorescence *in situ* hybridization (FISH) analysis. The drawback of FISH analysis is the requirement that the clinician already know which area of the genome to target. In our cases the deletion was not cytogenetically visible and could only have been detected by aCGH. While aCGH is unable to detect balanced chromosomal rearrangements, such as translocations or inversions, the majority of individuals with mental retardation have chromosomal imbalances (5). The turn around time and cost of aCGH compared with G-banded chromosome analysis followed by single FISH analysis are comparable, meaning that there is no compelling financial motive to pursue the lower-yield testing first (6). Therefore, it may be more cost-effective to use aCGH as a first line test in individuals with developmental issues.

For most individuals with very rare or unique chromosome conditions, treatment is aimed at addressing pre-existing congenital anomalies and providing therapies to improve developmental outcome. Anticipatory guidance in these cases relies on finding individuals in the literature with similar chromosome anomalies to ascertain their medical histories. Significant limitations of this method are that many affected individuals are never reported in the literature and that most are very young at the time of the report. aCGH allows clinicians to accurately size the imbalance and assess gene content, leading to improved

ability to anticipate future medical issues. While a number of single gene disorders and gross chromosome abnormalities have been associated with tumor predisposition (<http://www.ncbi.nlm.nih.gov/omim>), our cases represent individuals without a clinically recognizable cancer predisposition syndrome.

In case 1, the patient was found to have a deletion involving *STK11* associated with PJS. Genomic deletions of *STK11* account for many cases of classic PJS (7). PJS is characterized by gastrointestinal hamartomatous polyps, mucocutaneous pigmentation, and an increased risk of malignancy. A variety of tumors have been described in PJS, including colorectal, small bowel, stomach, breast, ovarian, uterine, cervical, testicular, and pancreatic cancers (8). Tumor screening protocols for males with PJS generally include the following: upper and lower endoscopy with small-bowel follow-through radiographs beginning at age 8 years and performed every 2 years thereafter; annual testicular evaluations, including testicular ultrasound starting at age 10 years; colonoscopy beginning at age 25 years and performed every 2 years thereafter; and endoscopic or abdominal ultrasound every 1 to 2 years from age 30 to evaluate for pancreatic malignancy. Patient 1 will start with endoscopy now.

In cases 2 and 3, the patients were found to have different sized deletions involving the *TP53* tumor suppressor gene, which leads to LFS. This condition is characterized by a variety of tumors, including osteosarcomas, soft-tissue sarcomas, premenopausal breast cancer, brain tumors, adrenal cortical tumors, and acute leukemias. While most families with LFS have mutations detectable by sequence analysis, there is at least one report of a family with classic LFS who had a whole *TP53* gene deletion (9). Tumor screening protocols for this condition are controversial but generally include the following on an annual basis in childhood: complete physical examination, urinalysis, complete blood count, and abdominal ultrasound. Women with LFS should start breast cancer screening between 20–25 years of age with annual breast MRI with or without mammography.

We have illustrated that aCGH can have a significant impact on patient management and should be viewed as a clinically useful test that can help guide patient management in developmentally delayed individuals. Since aCGH can accurately determine the size and gene content of genomic imbalances, aCGH should also be considered in individuals with cytogenetically visible abnormalities, where knowledge of which genes are impacted by the imbalance may help clinicians anticipate future medical issues.

References

1. Menten B, Maas N, Thienpont B, Buysse K, Vandesompele J, Melotte C, et al. Emerging patterns of cryptic chromosomal imbalance in patients with idiopathic mental retardation and multiple congenital anomalies: a new series of 140 patients and review of published reports. *J Med Genet.* 2006; 43(8):625–33. [PubMed: 16490798]
2. Aradhya S, Manning MA, Splendore A, Cherry AM. Whole-genome array-CGH identifies novel contiguous gene deletions and duplications associated with developmental delay, mental retardation, and dysmorphic features. *Am J Med Genet A.* 2007; 143(13):1431–41. [PubMed: 17568414]
3. Hemminki A, Markie D, Tomlinson I, Avizienyte E, Roth S, Loukola A, et al. A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. *Nature.* 1998; 391(6663):184–7. [PubMed: 9428765]

4. Olivier M, Goldgar DE, Sodha N, Ohgaki H, Kleihues P, Hainaut P, et al. Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype. *Cancer Res.* 2003; 63(20):6643–50. [PubMed: 14583457]
5. de Vries BB, Pfundt R, Leisink M, Koolen DA, Vissers LE, Janssen IM, et al. Diagnostic genome profiling in mental retardation. *Am J Hum Genet.* 2005; 77(4):606–16. [PubMed: 16175506]
6. Wordsworth S, Buchanan J, Regan R, Davidson V, Smith K, Dyer S, et al. Diagnosing idiopathic learning disability: a cost-effectiveness analysis of microarray technology in the National Health Service of the United Kingdom. *Genom Med.* 2007; 1:35–45.
7. Aretz S, Stienen D, Uhlhaas S, Loff S, Back W, Pagenstecher C, et al. High proportion of large genomic STK11 deletions in Peutz-Jeghers syndrome. *Hum Mutat.* 2005; 26(6):513–9. [PubMed: 16287113]
8. Wirtzfeld DA, Petrelli NJ, Rodriguez-Bigas MA. Hamartomatous polyposis syndromes: molecular genetics, neoplastic risk, and surveillance recommendations. *Ann Surg Oncol.* 2001; 8(4):319–27. [PubMed: 11352305]
9. Bougeard G, Brugieres L, Chompret A, Gesta P, Charbonnier F, Valent A, et al. Screening for TP53 rearrangements in families with the Li-Fraumeni syndrome reveals a complete deletion of the TP53 gene. *Oncogene.* 2003; 22(6):840–6. [PubMed: 12584563]

Figure 1.

A and B, Chromosome ideogram and gene content for patient 1 (A) and patient 2 (B). The upper portion highlights the deletion on the chromosome ideogram (red box) and the lower portion lists all known genes in the deleted area. The cancer susceptibility gene is indicated by a red box. **C,** Chromosome 17 ideogram (left) with aCGH (right) for patient 2. Each array dot represents the log₂ ratio for a single oligonucleotide probe. The black dots are oligonucleotides with normal values, while the green dots indicate a loss of genetic material (blue bar). **D,** Patient 1. Note the dysmorphic features. **E and F,** Patient 3 in infancy and later childhood, respectively. Note the dysmorphic features.

Table 1

Summary of patient data.

Case	Dysmorphic features	Routine cytogenetics	Array results	Estimated No. of genes deleted	Cancer predisposition gene	Cancer syndrome
1	Long palpebral fissures, mild eversion of the lower lids, right eye ptosis, high-arched palate, low-set and posteriorly rotated ears, bilateral single transverse palmar creases, fifth finger clinodactyly, persistent fetal finger pads, short fifth toes, and an increased gap between the first and second toes	Normal 46,XY at 550 bands	De novo 1.1 Mb deletion of 19p13.3	30	<i>STK11</i>	Peutz-Jeghers
2	Upslanting palpebral fissures, short columella, upswept ear lobules, down-turned corners of the mouth, shawl scrotum	Normal 46,XY at 550 bands	De novo 2.3 Mb deletion of 17p13.1	50	<i>TP53</i>	Li-Fraumeni
3	Prominent forehead, broad and flat nasal bridge, epicanthal folds, lateral buildup to the nose, depressed nasal tip, and bifid uvula	Normal 46,XX at 650 bands	De novo 499 kb deletion of 17p13.1	12	<i>TP53</i>	Li-Fraumeni