article

How physicians use array comparative genomic hybridization results to guide patient management in children with developmental delay

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Purpose: Array comparative genomic hybridization is an emerging test used clinically to identify the etiology of children with developmental delay, yet little data are available regarding how physicians use these results. This pilot study evaluated how positive test results were used to influence patient management. **Methods:** We surveyed 14 physicians of 48 patients who had copy number changes detected by microarray technology. **Results:** Of 48 patients, 34 (70.8%) had 65 management changes after receiving the test result (with individual patients having 1–3 changes). Most commonly, physicians provided patients' families with a recurrence risk for affected subsequent pregnancies (35% of patients). Patients avoided other forms of testing (35%) and had improved access to services (25%). In 27% of patients, physicians altered medical management by referring patients to a specialist or recommending medical screening. Patients with known syndromes had multiple changes, but patients with novel copy number changes also had recommendations made based on the array result. **Conclusions:** Overall, physicians reported making changes in management among most patients with positive test results, in ways similar to abnormalities detected by conventional cytogenetics. Our study demonstrates that this testing, in our clinical setting, is affecting management of children with developmental delay. ***Genet Med* 2008:10(3):181–186.**

Key Words: *CGH microarray, medical management, developmental delay*

Developmental delay and mental retardation (DD/MR) are common conditions affecting 1–3% of the population.[1,2] Understanding the underlying etiology of DD/MR can provide families and physicians with beneficial information such as recurrence risk and guidelines for medical management.[3] The underlying etiology is known for only 40–60% of cases of DD/MR,[4] but new technologies offer the potential to identify the etiology in more patients.

Deletions or duplications of specific regions of the genome are known to be associated with syndromes that cause DD/MR along with other medical problems. However, standard karyotyping is limited to detection of alterations that are at least 3–5 Mb or larger. Microarray comparative genomic hybridization (aCGH) can identify substantially smaller changes in copy number size and target-specific DNA regions of interest. Thus, aCGH can screen for both novel causes of DD/MR and for known syndromes.

Several recent studies using a variety of aCGH platforms have found that this testing identifies deletions or duplications likely to be causative in 8–17% of patients.[5–9] These studies were performed on a research basis, yet aCGH technology is rapidly emerging as a "routine" clinical test in the United States for the evaluation of patients with DD/MR of unknown etiology. One study reported the use of a targeted aCGH platform in 1500 clinical cases of which 5.6% were shown to have a clinically significant copy number change.[10] No studies to date have documented how aCGH results are affecting patient management. We interviewed the physicians of 48 patients with normal karyotypes and who received a positive aCGH result to determine how this test altered the management of these patients.

METHODS

Array CGH was performed in the University of Utah CGH Microarray Laboratory on two types of bacterial artificial chromosome (BAC) array chips from Spectral Genomics Inc./Perkin Elmer (Houston, TX). Both the Constitutional Chip ™ and the SpectralChip 2600 ™ were used, depending on physician preference. The Constitutional Chip is targeted, that is, it is focused on known syndromes and subtelomere regions without extensive coverage elsewhere in the genome. The SpectralChip 2600 has 2621 clones spaced approximately every

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1 Mb. Results from aCGH testing were analyzed for detection of abnormal results. Positive results were those that showed genomic copy number alterations believed (or suspected) to be of clinical significance. Only clinically abnormal patients who were previously determined to have normal karyotypes were included in this study. All positive results were confirmed by fluorescence in situ hybridization (FISH) with a BAC clone or commercial probe within the abnormal chromosomal region. Alterations previously identified as copy number variants in the Database of Genomic Variants (http://projects.tcag.ca/variation/?source=hg18) or an internal University of Utah database were not counted as positive results. Results were analyzed on consecutive samples from January 2005 to March 2007.

Survey

Twenty-two physicians (with 70 patients) with positive aCGH results from the University of Utah Cytogenetics Laboratory were contacted and asked to participate in the study. Upon their consent to enroll they were interviewed in person or over the telephone. Physicians were asked about each patient separately. This study was approved by the Institutional Review Board of the University of Utah School of Medicine.

The interview consisted of three questions. The first was, "Has this child been diagnosed with developmental delay or mental retardation?" Interviews in which the answer to this question was "no" were excluded from the study. Two children were excluded based on this question, as they were too young to be accurately assessed. One of these children died in the neonatal period due to congenital anomalies. For the second question, the physician was asked what criteria were part of the decision to order aCGH testing. This question was asked as an open-ended question and served to gain clinical information about the patients receiving a positive result and also prompted the physician about the specific patient to improve recall for the third question. The physician was then specifically asked if there was a family history of DD/MR, growth problems, dysmorphic facial features, or congenital anomalies. This list of anomalies is based on the de Vries score.[11] The de Vries score was developed in a comparison of patients diagnosed with DD/MR who had subtelomeric gain or loss versus those with no subtelomere abnormalities.

In the third question, the physician was asked if the aCGH result had changed patient management and if so, how. Again, this question was first asked as an open-ended question, but the interviewer then reviewed a checklist to determine if specific management changes had been made. This list included referral to a specialist, recommendation for medical screening, discontinuation of previously recommended screening, recommendation for family testing for reproductive reasons, provision of recurrence risk for family, and improved access to services for family. A management change was defined only if the physician specified that the change was made because of the aCGH result.

Fourteen physicians were interviewed representing 49 patients. One patient interview was excluded as the aCGH test was erroneously ordered before learning that a gene-specific FISH test was positive. Results were reported on the remaining 48 patients. Of the 14 physicians, 2 were neurologists and 12 were medical geneticists.

RESULTS

Detection rate

Of the 490 aCGH tests performed on patients with normal karyotypes from January 1, 2005 to March 8, 2007, 87 had gains or losses of at least one clone that were confirmed by FISH. A summary of specific abnormalities seen in the patients represented in this survey and the corresponding management issues are listed in Table 1. The overall abnormality detection rate was 17.6%. We contacted the ordering physicians of 70 of these patients, and surveys were ultimately analyzed on 48 patients. Of these 48 patients, four had known syndromes: Sotos syndrome, Duchenne muscular dystrophy, deletion 1p36, and Prader–Willi syndrome. None of these known syndromes had been clinically diagnosed before aCGH testing. The patient with Sotos syndrome had overgrowth features of mental retardation that were much more severe than is usual with Sotos syndrome. The discovery of a large deletion in the Sotos syndrome region explains this discrepancy. The patient with Prader–Willi and deletion 1p36 had an unusual presentation of these syndromes. The patient with Duchenne muscular dystrophy was brought to the attention of geneticists based on feeding problems and microcephaly. The child was tested below 1 year of age, before the muscular symptoms were apparent.

Survey results

Clinicians who participated in the study had between 1 and 12 patients. Of the 48 patients in this study, 14 (29.2%) had no changes in management based on the aCGH result. The 34 remaining patients had a total of 65 changes (Table 1). The most common "change in management" was that the physician was able to provide the family with a recurrence risk for affected subsequent pregnancies (17 patients).

Medical management

We established 3 categories of changes in medical management. These categories were (1) referral to a specialist, (2) recommendation of medical screening, and (3) stopping previously recommended screening. Thirteen of 48 patients had at least one of these changes in their care based on the aCGH result (Table 2). Seven patients were referred to at least one specialist: three to cardiology, one to endocrinology, and one to ophthalmology. The three patients seen by neurologists were referred to a medical geneticist. Eight patients had medical screening recommended, as noted in Table 1 five of these included kidney ultrasound, four included echocardiogram, and one was referred for thyroid screening. One patient diagnosed with Sotos syndrome was able to stop previously recommended screening for cancer.

Table 1
Medical management decisions affected by aCGH result

Patient	Specialist referral	Medical screening	Recurrence risk	Access to services	Avoid diagnostic Testing	Avoid genetic testing	Total changes
Del 1p36	Ophthalmology, cardiology	Thyroid testing		Speech, occupational therapy			3
PWS	Endocrinology		Yes	Educational			3
Sotos syndrome[a]			Yes	Educational			3
Del Xp21 DMD			Yes		Yes	Yes	3
Dup11q25		Kidney Ultrasound (US)		Insurance	Muscle biopsy		3
Del 10q11			Yes		MRI	FGFR2 testing	3
Dup 22q12			Yes	Educational	MRI		3
Dup 1p33				Insurance	Muscle biopsy	CFC testing	3
Del 10q26	Cardiology		Yes				2
Dup 3q26		Echocardiogram		Educational			2
Del 12p13/Dup 20qter			Yes			Yes	2
Dup 4p16/Del 18p11			Yes		MRI		2
Dup 18q22		Kidney US	Yes				2
Del 6q21	Cardiology					Sotos syndrome	2
Del 17q23			Yes			Yes	2
Del 1p31			Yes			Yes	2
Dup 11q25	Genetics	Kidney US Echocardiogram					2
Del 15q24			Yes	Support groups			2
Dup 2q24.3			Yes	Educational			2
Dup 17p11			Yes	Educational			2
Dup 2q12				Educational insurance	Muscle biopsy		2
Del 15q11	Genetics	Kidney US Echocardiogram					2
Dup 11q1				Insurance	TORCH		2
Del 14q21						Rett syndrome	1
Dup 5p13						CHARGE syndrome	1
Dup 4q35						Yes	1
Del 3p12			Yes				1
Dup 11q25			Yes				1
Dup 18p11		Kidney US					1
Del 14q22		Echocardiogram					1
Del 2q21						Waardenburg syndrome	1
Del 22q13	Genetics						1
Dup 17q24						Yes	1
Dup 8q12.1/Del 16p12			Yes				1

PWS, Prader Willi syndrome; DMD, Duchenne muscular dystrophy; MRI, magnetic resonance imaging; FGFR2, fibroblast growth factor receptor 2; CFC, cardio facial cutaneous syndrome; TORCH, Toxoplasmosis, Rubella, Cytomegalovirus and Herpes simplex virus.
[a]The patient with Sotos syndrome stopped medical screening after diagnosis.

Table 2
Management changes

Management change	No. patients (48)	Percent
Specialist referral	7	14.6
Medical screening	8	16.7
Stop medical screening	1	2.1
Avoid genetic testing	12	25.0
Avoid diagnostic testing	8	16.7
Recurrence risk	17	35.4
Improved access to services	12	25
No changes	14	29.2

Reproductive risk

The families of 17 patients were given a recurrence risk. Two patients had known syndromes (i.e., Sotos syndrome and Prader–Willi syndrome) with well-established recurrence risks. Deletion 1p36 also has a well-established recurrence risk, but this family was not interested in recurrence risk so this was not counted as a management change for that patient.

Four families were tested for conditions that could affect other family members. This group included three patients with duplications and deletions consistent with an unbalanced translocation. Parents of these children were tested to see if they carried the balanced form of the translocation. Of the three sets of parents, one parent was found to carry a balanced translocation. The mother of a child with Duchenne muscular dystrophy was tested for carrier status.

The other 11 patients had deletions or duplications that remained uncharacterized. We recommend that parents be tested to determine if these copy number alterations are de novo in the patient. Nine of the 11 families underwent further testing to clarify their risk. For one family, one parent was shown to have the same deletion as the patient. As this parent had symptoms similar to the child (developmental delay and dysmorphic features), the family was given a recurrence risk of 50%. In eight other families, the deletion or duplication was found to be de novo in the patient. These families were given a recurrence risk of $<1\%$. The remaining two families are currently being tested with the aim of clarifying recurrence risk.

Avoiding other testing

Physicians reported that 17 patients (35.4%) avoided other testing based on their positive aCGH result (Table 2). Twelve of the patients were being considered for other genetic testing for conditions such as CHARGE (*C*oloboma of the eye, *H*eart defects, *A*tresia of the choanae, *R*etardation of growth and/or development, *G*enital and/or urinary abnormalities, and *E*ar abnormalities and deafness) syndrome, Sotos syndrome, Rett syndrome, and fibroblast growth factor receptor 2 (FGFR2) mutations. Eight patients were scheduled for other diagnostic tests including muscle biopsy, brain magnetic resonance imaging, and TORCH testing (*To*xoplasmosis, *R*ubella, *C*ytomegalovirus, and *H*erpes simplex virus). Physicians reported that they did not follow-up on this testing after receiving the aCGH results.

Access to services

Physicians reported that 12 of 48 patients (25%) had improved access to services, especially insurance and educational services (Table 2). For example, one patient was going to be dropped from the Children's Health Insurance Program based on parental income but because of her genetic diagnosis, she qualified for a Medicaid program in her state.

Other

Two other changes were identified during the study process but were not counted as management changes. Four patients will participate in clinical research studies based on the aCGH result. We did not define this as a management change as it is not clear that research will affect the child's care. For 13 patients, the physician noted that the family "felt better" having a diagnosis; we did not count this subjective assessment as a management change. Physicians did, however, perceive that many families appreciated having a test result even if that test result was unlikely to change the management of the child. This is also consistent with a large study recently conducted in the United Kingdom on the value of diagnosis in patients with DD/MR.[12]

DISCUSSION

The Committee on Genetics of the American Academy of Pediatrics has stated that "There is no systematic study of the benefits (or harms) of a comprehensive evaluation of the child with DD/MR."[13] Still, many families and physicians have a strong desire to identify an etiology of a child with developmental delay. Our study shows that diagnosis by aCGH is particularly important in four key areas: clarifying the recurrence risk, providing better access to services, avoiding other testing, and guiding medical referrals.

The interviewer, J.S., asked physicians if the aCGH results specifically changed the management of the patient. We used a broad definition of management to include giving the family a recurrence risk, the avoidance of other genetic and diagnostic testing, and increasing patient access to medical and educational services. Of the 48 patients, 34 (70.8%) had some management change. Of the original population referred for testing, 34 of 490 (6.9%) had a management change that was attributed to the positive aCGH test result (although we only interviewed physicians of 48 of the 87 patients with an aCGH result and had no information about the patients with a negative aCGH test result). The physicians directed the medical care of these patients in ways similar to those of the patients with de novo cytogenetic abnormalities.

Thirteen patients (27%) had medical management changes (referred to a specialist, referred for medical screening, or had medical screening stopped) based on the array result itself and not on other symptoms. This result shows that physicians in

this setting are using the array results to identify a patient population that they believe are at a higher risk for other medical problems. In our study, four patients (8.3%) had well-characterized syndromes with established medical management guidelines (Sotos syndrome, Duchenne muscular dystrophy, deletion 1p36, and Prader–Willi syndrome). However, most alterations identified were novel and no guidelines for their follow-up have been established. Regardless, the physicians used the aCGH test result in guiding some aspect of medical care of these patients.

The recurrence risk for developmental disabilities with unknown etiology has been estimated to be 3–7%.[14] In our study, 17 families (35%) were given a recurrence risk based on the aCGH result. Two of these had known conditions with a known recurrence risk. Thirteen of the other 15 families had further testing performed to clarify the risk. A very high percentage of parents in our survey who were concerned about recurrence risk were tested to see if the alteration was de novo, suggesting that recurrence risk is a strong motivating factor in parents getting tested after a positive aCGH result.

Many doctors noted that the parents of their patients felt better receiving a diagnosis even if there were no other management changes. Of the 14 patients who did not have management changes, the physicians specifically mentioned that eight of the families were relieved to finally have an explanation for the developmental delay. It has been reported that mothers of children with disabilities of unknown etiology suffer from more distress than mothers of children with Down syndrome, suggesting that the lack of a diagnosis negatively impacts families.[15] Rosenthal et al.[16] studied the issues associated with a parent's desire for a diagnosis for a child with developmental delay. They found that parents were most interested in many of the issues identified in our study such as medical prognosis, recurrence risk, and educational services. In our study, one physician spoke of a mother who had been told that her child's problems were caused by her ibuprofen used during her pregnancy. She was greatly relieved to discover that her child's condition was due to a chromosomal abnormality.

In our study, physicians had two general categories of patients. One set of patients had been on a long diagnostic journey having new genetic tests as they became available. Fewer of these patients had management changes based on the test because many had already had medical referrals based on their symptoms; families had often already dealt with reproductive concerns, and they had already had the full gamut of genetic and diagnostic testing. The other category represented patients at an earlier phase of their medical testing. These patients were often younger, and recurrence risk was a higher concern for their families. These patients were also less likely to have had diagnostic screening before having aCGH testing.

One limitation of this study is that it is exclusively from the physician perspective, which defined the outcomes of interest, i.e., changes in patient management. Had we examined outcomes from the patient/family perspective, we would have likely chosen and evaluated a completely different set of parameters. This study also depended on physician recall. We also cannot be sure that every copy number change identified is causative of the phenotype. Benign copy number variants are common in the normal population, and we determine that a particular change observed by aCGH testing is benign based on the presence of this change in both public and internal databases.[17] While we assume that abnormalities noted in this study represent clinically relevant copy number alterations, the goal of this study was to understand how physicians are using the results from aCGH testing at this time. Interestingly, a study in Great Britain by the Public Health Genetics Unit found that 80% of families with a child with a chromosomal disorder felt that a genetic diagnosis did not "make a substantial difference" for the patient in terms of medical and education management.[12] Parents may not be aware of the way physicians use a genetic diagnosis to guide future management. Our study would suggest that there is, in fact, a difference in genetic diagnosis, at least when assessed by the physician provider.

Array CGH is becoming a routine diagnostic test for the child with developmental delay or mental retardation. We surveyed physicians regarding 48 patients with a positive aCGH result and found that 70% of the time there was a direct impact on the family by offering a recurrence risk, improving access to services, guiding medical management, and/or preventing other testing. The primary goal of genetic testing is to improve the quality of life of patients and their families. As new technologies become available, it is important to monitor the impact of that testing on medical management.

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