Yield of comparative genomic hybridization microarray in pediatric neurology practice

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Abstract

Objective
The present study investigated the diagnostic yield of array comparative genomic hybridization (aCGH) in a large cohort of children with diverse neurologic disorders as seen in child neurology practice to test whether pathogenic copy number variants (CNVs) were more likely to be detected in specific neurologic phenotypes.

Methods
A retrospective cross-sectional analysis was performed on 555 children in whom a genetic etiology was suspected and who underwent whole-genome aCGH testing between 2006 and 2012. Neurologic phenotyping was performed using hospital medical records. An assessment of pathogenicity was made for each CNV, based on recent developments in the literature.

Results
Forty-seven patients were found to carry a pathogenic CNV, giving an overall diagnostic yield of 8.59%. Certain phenotypes predicted for the presence of a pathogenic CNV, including developmental delay (odds ratio [OR] 3.69 [1.30–10.51]), cortical visual impairment (OR 2.73 [1.18–6.28]), dysmorphism (OR 2.75 [1.38–5.50]), and microcephaly (OR 2.16 [1.01–4.61]). The combination of developmental delay/intellectual disability with dysmorphism and abnormal head circumference was also predictive for a pathogenic CNV (OR 2.86 [1.02–8.00]). For every additional clinical feature, there was an increased likelihood of detecting a pathogenic CNV (OR 1.18 [1.01–1.38]).

Conclusions
The use of aCGH led to a pathogenic finding in 8.59% of patients. The results support the use of aCGH as a first tier investigation in children with diverse neurologic disorders, although whole-genome sequencing may replace aCGH as the detection method in the future. In particular, the yield was increased in children with developmental delay, dysmorphism, cortical visual impairment, and microcephaly.

Glossary

aCGH = array comparative genomic hybridization; **ASD** = autism spectrum disorder; **CGH** = comparative genomic hybridization; **CHW** = Children's Hospital at Westmead; **CI** = confidence interval; **CNV** = copy number variant; **OR** = odds ratio.

Array comparative genomic hybridization (aCGH) is a genetic technology used to identify copy number variants (CNVs). A CNV is a duplicated or deleted segment of DNA, greater than 1 kb in size, which is observed to vary in the comparison of 2 or more genomes.[1] Early studies demonstrated that CNVs provided an important contribution to genetic diversity among healthy individuals.[2,3] However, microdeletions and microduplications also have the potential to cause neurologic disorders by altering gene expression.

A genetic etiology is often suspected in children who present with undiagnosed neurologic disorders. In a proportion of children, the underlying cause is a pathogenic microdeletion or microduplication. The utility of aCGH has been extensively studied in children with developmental delay, intellectual disability, and autism, where a diagnostic yield between 7.8% and 18.6% has been reported.[4–23] Additional studies have focused on children with epilepsy, showing a diagnostic yield between 4.1% and 10.9%.[24–28] However, the diagnostic yield in children presenting to pediatric neurology departments with a broader set of phenotypes remains to be established. Therefore, we examined the diagnostic yield of aCGH in a referred pediatric neurology cohort. In particular, we aimed to identify whether specific neurologic phenotypes, either in isolation or combination, increased the odds ratio (OR) of finding a pathogenic CNV with aCGH technology.

Methods

Patient selection

This study was performed at the T.Y. Nelson Department of Neurology and Neurosurgery at the Children's Hospital at Westmead (CHW) in Sydney, Australia. This is the major referral facility for children with neurologic disorders in the Western Sydney region. A retrospective cross-sectional analysis was conducted on 555 sequential children who had been investigated with aCGH under the care of 11 consultant neurologists (R.D., S.A.H., C.T., S.G., M.M., R.W., P.P., R.O., S.M., D.G., and J.A.) in the department between January 2006 and December 2012. The referral for aCGH testing in each case had been prompted by the presentation of a child with a neurologic disorder of unknown etiology but suspected to be of genetic origin. The list of patients who had been investigated with aCGH was obtained from the clinical genetics department of the hospital. Patients were excluded from the study if there was no available hard copy or electronic medical record outlining their clinical phenotype or if the hard copy notes had been stored in an off-site location and could not

be retrieved. The study included children who had been investigated during inpatient admissions and children seen as outpatients.

Data collection

The medical records were reviewed to gather information on clinical phenotype, findings on MRI, results of ancillary testing such as EEG/nerve conduction study/muscle biopsy, and specialist consultations. This information was captured in 94 clinical data points (see supplementary text, links.lww.com/NXG/A188). In particular, the outcome of comparative genomic hybridization (CGH) microarray testing was noted, including parental and sibling results wherever available, to determine inheritance. Medical records were in the form of hard copy files or online documentation in the institutional electronic medical record system known as PowerChart. The accuracy of the data was corroborated through intensive review by the treating consultant neurologist in conjunction with the data collector (S.M.), with any discrepancies allayed through discussion and further perusal of notes where appropriate. The purpose of this was to cross-check for accuracy of phenotyping. For further information on the clinical phenotyping, and definitions used to consider a clinical feature as being present, please refer to the supplementary text.

Platforms used for aCGH testing

The aCGH platforms used included SurePrint G3 Custom CGH Microarray 4 × 180K, ISCA 8 × 60K design, and bacterial artificial chromosome Array 4K, as per the manufacturer's instructions. Data analysis was undertaken using Agilent Technologies software, with routine settings as follows: aberration algorithm: ADM-2; threshold 6.7; neutralization: ON; bin size: 10; centralization threshold 6.0; fuzzy zero: ON; combine replicates (intra-array): ON; genome hg18; aberration filters: minProbes = 5 AND minAvgAbsLogRatio = 0.25 AND maxAberrations = 30 AND percentPenetrance = 0; expand non unique probes: OFF.

Interpretation of CNV pathogenicity

As mentioned previously, healthy individuals are known to carry polymorphic CNVs that are effectively benign, which need to be segregated from truly pathogenic CNVs. The CGH microarray results were first distinguished according to whether they included a reportable CNV of potential clinical significance. For those patients with a CNV of potential clinical significance, the report stated the size of the CNV, its location in the genome, whether there were any OMIM genes deleted, and a preliminary conclusion was offered regarding the degree of pathogenicity, in the view of the supervising scientist. The CNV was provisionally described as either

"benign," "likely benign," "a variant of uncertain significance," or "pathogenic". Further reassessment of CNV pathogenicity was performed in 2017–2018 based on the most comprehensive algorithm for CNV interpretation to date, published by Beaudet et al.[29] in *Nature Genetics*. In brief, CNVs were graded into 5 categories of pathogenicity:

- Category 1: severe disability, very high or complete penetrance, de novo inheritance, and nil reproduction
- Category 2: intermediate severity of disability, 50%–90% penetrance, either de novo or inherited genetic defect, and reduced reproduction
- Category 3: mild or absent disability, 5%–100% penetrance, largely inherited transmission of genetic defect, and essentially normal reproduction
- Category 4: Mild or absent disability, 5%–50% penetrance, inherited transmission of genetic defect in virtually all cases, and essentially normal reproduction
- Category 5: nil disability, either de novo or inherited genetic defect, and normal reproduction

The University of California, Santa Cruz genome browser was used to facilitate grading.[30] The browser allowed for comparison with CNVs reported in other genomic databases (Database of Genomic Variants, ExAC, ClinGen, and DECIPHER, UK) and included data on polymorphic CNVs, map locations, OMIM gene content, phenotypic associations, severity of disease, penetrance, and information on established microdeletion and microduplication syndromes. In this study, all genome map references were based on the February 2009 genome assembly (build GRCh37/hg19).

We considered categories 1, 2, and 3 to be "pathogenic" and categories 4 and 5 to be "benign." We took Beaudet category 3 as the lower limit of "pathogenic" because this category contained CNVs that have traditionally been considered pathogenic, whereas there were no such CNVs in category 4. The archetypal example of a category 3 CNV is the microduplication at locus 17p12, containing the gene *PMP22*, causing Charcot-Marie-Tooth 1A neuropathy. This microduplication, known to be causative of the phenotype, is Beaudet category 3 because there is mild or absent disability, 5%–100% penetrance, established inheritance of genetic defect, and essentially normal reproduction.

Patients who manifested whole chromosomal aneuploidies such as trisomy 21, Klinefelter syndrome 47XXY, and Turner syndrome 45X deviated from the outcome of interest (namely chromosomal microdeletions or microduplications), and they were therefore excluded from analysis.

Statistical analysis

The SAS 9.4 software was used to analyze the data. Associations between clinical phenotypes and pathogenic CNVs on aCGH testing were established using χ^2 tests and logistical regression. Results were described using ORs and 95% confidence intervals (CIs). ORs for predicting a pathogenic CNV were obtained for clinical features in isolation and in combination. The latter combinations were chosen before statistical analysis, and these combinations of clinical features were deemed to reflect common combinations of neurologic disorders in the pediatric cohort.

Standard protocol approvals, registrations, and patient consents

The ethics committee at the CHW, Sydney, granted approval for this study (Ethics Number—LNR/14/SCHN/112). The study did not require individual patient registration or consent, and data were collected in a deidentified manner.

Data availability

Anonymized data not published in the content of this article will be shared upon request from any qualified investigator.

Results

The cohort comprised 555 children with neurologic disorders, of which 316 were boys and 239 were girls. The mean age at the time of data collection was 10.01 years (age range 0.25–23 years at data collection). The frequency of neurologic phenotypes in our cohort is shown in table 1.

There was a notably high prevalence of global developmental delay (n = 359), intellectual disability (n = 277), epilepsy (n = 272), autism spectrum disorder (ASD) (n = 92), movement disorders (n = 94), and psychiatric comorbidity (n = 121). There was an approximately even distribution of developmental delay into mild (n = 157), moderate (n = 135), and severe (n = 129) phenotypes. A relatively even spread was also seen for mild (n = 76), moderate (n = 100), and severe (n = 101) intellectual disability. Approximately 30% of the cohort had an abnormal brain MRI, with white matter abnormalities (n = 108) and cerebellar pathologies (n = 55) being the most common findings.

Diagnostic yield

As shown in table 2, there were 132 patients reported as carrying a CNV in the form of a microdeletion, microduplication, or another complex combination of the two. Where available, parental testing was reviewed to clarify whether the CNV occurred de novo. Forty-seven of 132 patients were considered to have a pathogenic CNV (category 1 to 3 CNVs). In contrast, there were 79 patients for whom the CNV detected was considered benign and therefore noncontributory to the patient phenotype (category 4 and 5 CNVs).

By taking the 47 patients with pathogenic CNVs from 547 patients with available data (8 with omitted data), the overall absolute diagnostic yield was 8.59%. For a full list of the 47 patients with pathogenic CNVs, please refer to table e-1, table e-2, and table e-3 in supplementary text 1 (links.lww.com/NXG/A188). A description of CNV location and clinical phenotype is provided.

Table 1 Frequency of neurologic phenotypes for the 555 patients

Phenotype	Frequency (% of cohort)
Parental consanguinity	30 (5.41)
Positive first-degree family history	151 (27.21)
Developmental delay	421 (75.86)
Global	359 (64.68)
Significant language delay	211 (38.02)
Motor delay in isolation	22 (3.96)
Language delay in isolation	37 (6.67)
Severity of developmental delay	
Mild	157 (28.29)
Moderate	135 (24.32)
Severe	129 (23.24)
Autistic spectrum disorder	92 (16.58)
Intellectual disability	277 (49.91)
Mild	76 (13.69)
Moderate	100 (18.02)
Severe/profound	101 (18.20)
Cortical visual impairment	43 (7.75)
Sensorineural hearing impairment	30 (5.41)
Dysmorphism	75 (13.51)
Neurocutaneous syndrome	11 (1.98)
Abnormal head circumference	95 (17.12)
Microcephaly	67 (12.07)
Macrocephaly	28 (5.05)
Epilepsy	272 (49.01)
Focal	133 (23.96)
Generalized	192 (34.59)
Myoclonic	39 (7.03)
Tonic	57 (10.27)
Status epilepticus	57 (10.27)
Epileptic encephalopathy	65 (11.71)
Medically refractory seizures	75 (13.51)
Ataxia or cerebellar syndrome	46 (8.29)
Movement disorder	94 (16.94)
Tourette syndrome	6 (1.08)
Other tic disorder	3 (0.54)
Chorea	23 (4.14)
Dystonia	60 (10.81)
Myoclonus	9 (1.62)

Table 1 Frequency of neurologic phenotypes for the 555 patients *(continued)*

Phenotype	Frequency (% of cohort)
Tremor	24 (4.32)
Psychiatric comorbidity	121 (21.80)
Attention-deficit hyperactivity disorder	85 (15.32)
Depression	11 (1.98)
Anxiety	34 (6.13)
Obsessive compulsive disorder	5 (0.90)
Psychosis	2 (0.36)
Oppositional defiant disorder	19 (3.42)
Abnormality of tone	292 (52.61)
Hypotonia	142 (25.59)
Hypertonia	84 (15.14)
Spasticity	66 (11.89)
Cerebral palsy	73 (13.15)
Hemiplegic	2 (0.36)
Diplegic	13 (2.34)
Quadriplegic	14 (2.52)
Dyskinetic (dystonic/choreoathetoid)	16 (2.88)
Ataxic	7 (1.26)
Hypotonic	8 (1.44)
Quadriplegic and dyskinetic	6 (1.08)
Diplegic and ataxic	1 (0.18)
Worster-Drought phenotype	1 (0.18)
Unclear/unclassified	5 (0.90)
Weakness not otherwise specified	42 (7.57)
Myopathy	14 (2.52)
Neuropathy	17 (3.06)
Spastic hereditary paraplegia	7 (1.26)
Abnormal brain MRI	167 (30.09)
Malformation	29 (5.23)
Dysplasia	36 (6.49)
Ventricular pathology	28 (5.05)
Cerebellar pathology	55 (9.91)
White matter abnormality	108 (19.46)
Abnormal spine MRI	15 (2.70)
Abnormal EEG	238 (42.88)
Seen by a geneticist	219 (39.46)

The number and percentage of each feature is presented.

Table 2 Diagnostic yield of aCGH testing

aCGH testing	Result
Number of patients studied	555
No reported CNV	421
Reported CNV	132
Pathogenic aCGH result	47
Beaudet category 1	8
Beaudet category 2	27
Beaudet category 3	12
Benign aCGH result	79
Beaudet category 4	55
Beaudet category 5	24
Data omitted from analysis	8
Excluded (whole chromosomal aneuploidies)	6
Insufficient DNA	1
Test canceled	1

Abbreviations: aCGH = array comparative genomic hybridization; CNV = copy number variant.

OR for predicting a pathogenic CNV

Given that the diagnostic yield of aCGH was 8.59%, we next determined the clinical features that were predictive of a pathogenic CNV using univariate analysis and ORs. ORs could not be calculated when no pathogenic CNV was detected in association with the phenotype in question, as was seen for parental consanguinity, depression, myopathy, and spastic hereditary paraplegia.

As shown in table 3, a number of neurologic phenotypes were associated with pathogenic CNVs on aCGH testing. Developmental delay showed OR 3.69 (1.30–10.51), cortical visual impairment OR 2.73 (1.18–6.28), dysmorphism OR 2.75 (1.38–5.50), and microcephaly OR 2.16 (1.01–4.61).

Although table 3 demonstrated analysis on clinical features in isolation, we acknowledged that this was the exception in clinical practice. It was more common for patients to express multiple clinical features simultaneously. Therefore, we determined the OR of predicting a pathogenic CNV for the more common combinations of neurologic phenotypes.

As illustrated in table 4, the combination of developmental delay or intellectual disability with dysmorphism predicted for a pathogenic CNV on aCGH testing, with OR 2.86 (1.43–5.72). A similar combination of developmental delay or intellectual disability with dysmorphism and abnormal head circumference also predicted for a pathogenic CNV on aCGH testing, with OR 2.86 (1.02–8.00).

We had hypothesized that an increasing number of clinical features in an individual patient would increase the likelihood of detecting a pathogenic CNV on aCGH testing. The 17 broad clinical data points considered in our study, comprising the most common features on presentation, were positive family history, developmental delay, intellectual disability, ASD, cortical visual impairment, sensorineural hearing loss, dysmorphism, neuro-cutaneous lesions, abnormal head circumference, epilepsy, ataxia or cerebellar syndrome, movement disorder, psychiatric comorbidity, cerebral palsy, myopathy, neuropathy, and abnormal karyotype or MRI. There were 18 patients with none of these clinical features, 63 with 1 clinical feature, 86 with 2 clinical features, 98 with 3 clinical features, 107 with 4 clinical features, 77 with 5 clinical features, 61 with 6 clinical features, 25 with 7 clinical features, 6 with 8 clinical features, 2 with 9 clinical features, 2 with 10 clinical features, and 1 patient with 11 clinical features in combination (maximum). Logistic regression analysis showed that for every additional clinical feature in an individual patient, there was an OR 1.18 (1.01–1.38, $p = 0.03$) for detecting a pathogenic CNV on aCGH testing.

Discussion

Our experience with whole-genome aCGH returned a diagnostic yield of 8.59%, falling on the lower end of the range reported in the literature. However, this study analyzed CNVs using a graded level of pathogenicity. It is now well established that microdeletions and microduplications cannot be adjudicated to a dichotomous outcome of "normal" and "abnormal." The classification system adopted here, first presented by Beaudet,[29] was the most comprehensive algorithm for interpretation at the time of this study. Based on our didactic experience with the Beaudet algorithm, we strongly advocate for its use as a standardized approach in future studies. Indeed, table 2 exhibits that only 47 of the 132 CNVs detected by our genetics laboratory were ultimately considered "pathogenic." As mentioned previously, these were the variants that fell into Beaudet categories 1–3. The objectivity of the Beaudet interpretation protocol is reflected by the fact that almost two-thirds of our laboratory-reported CNVs were classified as benign.

Our study cohort comprised patients with varying combinations of neurologic features, each of which could increase or decrease the diagnostic yield of aCGH testing if examined in isolation. One group of investigators reported compelling evidence that ASD was associated with a reduction in diagnostic yield on aCGH testing. For patients with ASD alone, their diagnostic yield for a pathogenic CNV was 4.4%. In their entire cohort, the diagnostic yield was 8.6%, which increased to 12.5% when ASD was removed as an indication for testing.[20] Our results for ASD demonstrated an OR 0.32 (95% CI 0.10–1.05) in predicting for a pathogenic CNV. Although this did not provide statistical evidence, the trend was similarly toward a reduction in diagnostic yield. In addition, our cohort had 73 patients with cerebral palsy (13.15% of cohort). The etiology of cerebral palsy can be a perinatal hypoxic insult or

Table 3 OR of predicting a pathogenic result on array comparative genomic hybridization for neurologic phenotypes in isolation

Clinical feature	OR (95% CI)	p Value
Parental consanguinity	—	—
Positive first-degree family history	1.17 (0.61–2.26)	0.64
Developmental delay	3.69 (1.30–10.51)[a]	0.01
Global	1.87 (0.93–3.77)	0.07
Significant language delay	1.12 (0.61–2.05)	0.72
Motor delay in isolation	0.50 (0.07–3.77)	0.49
Language delay in isolation	2.29 (0.90–5.83)	0.07
Autism spectrum disorder	0.32 (0.10–1.05)	0.05
Intellectual disability	1.28 (0.70–2.33)	0.42
Cortical visual impairment	2.73 (1.18–6.28)[a]	0.01
Sensorineural hearing impairment	0.78 (0.18–3.38)	0.74
Dysmorphism	2.75 (1.38–5.50)[a]	0.003
Neurocutaneous syndrome	2.42 (0.51–11.57)	0.25
Abnormal head circumference		
Microcephaly	2.16 (1.01–4.61)[a]	0.05
Macrocephaly	1.54 (0.44–5.38)	0.50
Epilepsy	0.83 (0.45–1.51)	0.54
Focal	0.63 (0.29–1.38)	0.24
Generalized	1.08 (0.58–2.01)	0.81
Status epilepticus	0.80 (0.28–2.32)	0.68
Epileptic encephalopathy	1.12 (0.45–2.74)	0.81
Medically refractory seizures	0.77 (0.30–2.03)	0.60
Ataxia or cerebellar syndrome	1.33 (0.50–3.55)	0.56
Movement disorder	1.19 (0.55–2.55)	0.66
Chorea	2.36 (0.77–7.24)	0.12
Dystonia	2.13 (0.97–4.66)	0.05
Tremor	0.50 (0.07–3.77)	0.49
Psychiatric comorbidity	0.61 (0.27–1.41)	0.24
Attention-deficit hyperactivity disorder	0.64 (0.25–1.68)	0.36
Depression	—	—
Anxiety	1.07 (0.31–3.64)	0.92
Opposition defiant disorder	0.62 (0.08–4.75)	0.64
Abnormality of tone		
Hypotonia	1.10 (0.56–2.15)	0.78
Hypertonia	1.79 (0.87–3.67)	0.11
Spasticity	1.31 (0.56–3.05)	0.53

Table 3 OR of predicting a pathogenic result on array comparative genomic hybridization for neurologic phenotypes in isolation *(continued)*

Clinical feature	OR (95% CI)	p Value
Cerebral palsy	1.37 (0.61–3.07)	0.44
Myopathy	—	—
Neuropathy	2.37 (0.66–8.55)	0.18
Spastic hereditary paraplegia	—	—
Abnormal brain MRI	1.20 (0.64–2.27)	0.56
Abnormal spine MRI	0.75 (0.10–5.87)	0.79
Abnormal EEG	0.89 (0.49–1.64)	0.71

Abbreviations: CI = confidence interval; OR = odds ratio.
[a] Indicates statistical significance.

trauma to the CNS during early development. Such etiologies are not intuitively genetic and thus may also have contributed to a low diagnostic yield for cerebral palsy.

Only one other group based in Melbourne, Australia, have investigated the diagnostic yield of aCGH in a broad cohort of children seen in the pediatric neurology setting, similar to this study.[31] Their sample size of 215 included patients with epilepsy, movement disorders, neuromuscular conditions, microcephaly, and congenital malformations. In accordance with our study, they found pathogenic CNVs in all the above neurologic phenotypes, with a diagnostic yield of at least 9.3%. However, they particularly emphasized the utility of aCGH in patients with severe epilepsy and epileptic encephalopathy, in whom they achieved their highest diagnostic yield of approximately 21%. In contrast, epilepsy did not predict for pathogenic CNVs in our study, returning an OR 0.83 (95% CI 0.45–1.51). Epileptic encephalopathy was also insignificant with OR 1.12 (95% CI 0.45–2.74). Further studies are needed to ascertain the relative contribution of point mutations vs CNVs in genetic epilepsies and epileptic encephalopathies.

Array CGH technology is now used on a routine basis for the investigation of various neurologic disorders. However, it is unclear which patients are likely to benefit most from this technology and how exactly the test should be directed and interpreted. In clinical practice, whole-genome CGH microarray platforms are generally indicated for the investigation of patients with developmental delay, intellectual disability, ASD, or at least 2 congenital abnormalities. We identified pathogenic CNVs in patients of all neurologic phenotypes, not just those with developmental delay, intellectual disability, autism, and congenital malformations. Certain phenotypes were identified that showed an increased correlation with pathogenic CNVs. These were developmental delay (OR 3.69 [95% CI 1.30–10.51]), cortical visual impairment (OR 2.73 [95% CI 1.18–6.28]), dysmorphism (OR 2.75 [95% CI 1.38–5.50]), and microcephaly

Table 4 OR of predicting a pathogenic result on array comparative genomic hybridization for neurologic phenotypes in combination

Combination of phenotypes	OR (95% CI)	*p* Value
Developmental delay/intellectual disability and dysmorphism	2.86 (1.43–5.72)[a]	0.002
Developmental delay/intellectual disability and epilepsy	1.06 (0.58–1.95)	0.85
Developmental delay/intellectual disability and autism spectrum disorder	0.35 (0.11–1.15)	0.07
Developmental delay/intellectual disability I psychiatric comorbidity	0.70 (0.29–1.71)	0.44
Developmental delay/intellectual disability and movement disorder	1.56 (0.72–3.37)	0.26
Developmental delay/intellectual disability and epilepsy and movement disorder	0.67 (0.16–2.90)	0.59
Developmental delay/intellectual disability and cerebral palsy	1.42 (0.64–3.18)	0.39
Developmental delay/intellectual disability and dysmorphism and abnormal head circumference	2.86 (1.02–8.00)[a]	0.04
Developmental delay/global developmental delay and intellectual disability and epilepsy	0.67 (0.33–1.39)	0.28

Abbreviations: CI = confidence interval, OR = odds ratio.
[a] Indicates statistical significance.

(OR 2.16 [95% CI 1.01–4.61]). Furthermore, we have shown that the combination of developmental delay or intellectual disability with dysmorphism and abnormal head circumference also predicted for the presence of a pathogenic CNV (OR 2.86 [95% CI 1.02–8.00]). For every additional clinical feature recorded in our study, there was an OR 1.18 (95% CI 1.01–1.38, *p*-value 0.03) for finding a pathogenic CNV on aCGH testing, suggesting that aCGH should be strongly considered in patients with complex neurologic phenotypes.

Although aCGH will likely be replaced by whole-exome and genome sequencing as a method of detecting microdeletions and duplications in the future, regardless of detection method the associations described in the present study will remain relevant. Furthermore, although we have defined clinical associations of pathogenic CNVs detected with aCGH, our study did not capture how these findings resulted in a change in clinical practice, such as an end to the diagnostic odyssey or avoidance of further expensive or invasive investigations. Further studies are warranted to review how the diagnostic yield of aCGH has changed over time and altered clinical management, particularly in the context of newer sequencing technologies, which are increasingly being used in child neurology.

In our cohort of 555 patients, we have identified pathogenic CNVs in children with a wide spectrum of neurologic disorders. Our results support the more liberal (rather than restricted) use of aCGH technology as a first-tier investigation in patients with diverse neurologic conditions, particularly in those with complex neurologic phenotypes. Restricting the indication for testing to developmental delay or intellectual disability is likely to constrain the potential utility of this technology. In particular, our results indicate that the highest yield may be obtained in patients with a combination of developmental delay, dysmorphism, and microcephaly and those individuals with numerous neurologic comorbidities. Further studies using

a consecutive cases approach and randomized allocation are warranted to substantiate these findings.

Study funding

Disclosure

Disclosures available: Neurology.org/NG.

Publication history

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