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Cytogenetic Analysis of Children With Developmental Delay Referred to a Genetic Clinic

Lorenzo Santangelo¹●, Margaux Fauvel²●, Rui Teixeira³●

¹Associate Professor, Department of Genetics, Monti Lepini Institute of Life Sciences, Frosinone, Italy.

²Scientist, Department of Human Genetics, Vosges Institute of Applied Microbiology, Epinal, France.

³Senior Research Fellow, Department of Human Genetics, Minho Valley Institute of Health Research, Viana do Castelo, Portugal.

Email: ¹l.santangelo@mlils.it, ²m.fauvel@viam-e.fr, ³r.teixeira@mvhr.pt

ORCID: ¹0000-0001-3049-3609, ²0000-0001-3506-7318, ³0000-0001-3303-7465

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ABSTRACT

Children who are late to sit, walk, speak or learn are often referred to a genetics clinic, and one of the first questions asked is whether a chromosome change lies behind the delay. Cytogenetic testing has changed a great deal over the last few decades, from banded karyotypes through fluorescence in situ hybridisation to chromosomal microarray, and the meaning of a normal or abnormal result has changed with it. This narrative review describes what each cytogenetic method can and cannot detect, how findings are interpreted, and why reports of diagnostic yield from different clinics are hard to compare. It draws on published guidelines and primary studies and reports no new data and no patient series. Karyotyping remains the right tool for some questions, notably balanced rearrangements and suspected aneuploidy syndromes, whereas microarray detects small gains and losses that a karyotype cannot see and is widely recommended as a first-tier test. Neither method finds single-gene variants, repeat expansions or most epigenetic changes, so a negative cytogenetic result narrows the search without ending it. Variants of uncertain significance, referral criteria and the order of testing all influence reported yield. The review ends with a short list of what a reader should look for before trusting a stated figure.

Keywords: Developmental delay; Cytogenetics; Karyotype; Chromosomal microarray; Copy number variants; Diagnostic yield; Narrative review

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Article Class: Narrative Review

1. Introduction

Parents usually notice first. A child is slow to sit, slow to walk, or has few words when other children of the same age have many, and a paediatrician agrees that something is amiss. Global developmental delay is the

label commonly given when more than one area of development is affected in a young child, and intellectual disability is the term used once the child is old enough for the pattern to be confirmed (1, 2). Taken together these conditions are common, and



population studies show that intellectual disability is far from rare (3).

The causes are many. Some children have a recognisable syndrome, some have a brain injury before or soon after birth, and some have an inherited metabolic or single-gene disorder. A large share have no cause found at the first visit (4, 5). Changes in the number or structure of chromosomes are one of the oldest explained causes and still one of the most frequent, which is why a genetics clinic will often begin with a chromosome study (5, 6). What that study consists of has changed a good deal, and a reader of an older clinic report may be looking at a very different test from the one a family receives today.

This article reviews the cytogenetic evaluation of children with developmental delay who are referred to a genetic clinic. Its title reads like a local audit, but it is not one. No clinic, district or patient series is described here, and no figures from any particular centre are reported. Instead, the review asks what each cytogenetic method can see, how its findings are interpreted, and how much weight stated rates of abnormal results can carry when they come from clinics that tested different children in different ways. Where a point rests on judgement rather than on data, the text says so.

2. Literature Review

2.1 Developmental Delay and Its Causes

Practice parameters from the early 2000s set out a staged approach to the child with global developmental delay: history, examination, then targeted investigations chosen by what the clinical picture suggests, with chromosome analysis and fragile X testing among the first genetic tests (1). A later clinical report placed chromosomal microarray ahead of the karyotype for most children and added

sequencing-based tests as they became available (2).

Exome sequencing in large cohorts of affected children and their parents showed that new variants arising in the child account for a substantial part of severe disease (7, 8), though chromosomal imbalance remains an important category (9, 10).

2.2 Conventional Karyotyping

Human cytogenetics began in earnest when the correct chromosome number was established in the 1950s (11). Banding methods later let laboratories tell individual chromosomes apart (12), so the G-banded karyotype can show an extra or missing chromosome, large deletions and duplications, and rearrangements in which material has moved without being lost or gained.

Aneuploidy, an extra or missing chromosome, arises mostly from errors in meiosis (13). Down syndrome is the best-known example, and a karyotype remains appropriate there because it shows whether the extra chromosome is free or attached to another, which matters for recurrence counselling (14).

Karyotyping has real strengths. It looks at the whole genome at once, it sees balanced rearrangements that leave no gain or loss for other methods to find, and it can show mosaicism if enough cells are examined (14, 15). Its weaknesses are as well known. The resolution is limited to changes of several megabases, the method depends on dividing cells and on the skill of the analyst, and the result is slow to produce. A normal karyotype therefore excludes large imbalances and little else. Absence of a finding on one test is not absence of a cause.

Table 1 sets the main methods side by side. The comparison is qualitative on purpose, because resolution varies with the



laboratory and the platform.

Table 1. What common cytogenetic methods can and cannot detect in a child with developmental delay.

Method	Sees well	Misses
G-banded karyotype	Aneuploidy, large gains and losses, balanced rearrangements (11, 12, 14)	Small imbalances; low-level mosaicism in few cells (15)
FISH	Targeted microdeletions and rearrangements (16, 17)	Anything the probe was not chosen to find
Chromosomal microarray	Small gains and losses across the genome (18, 19)	Balanced rearrangements; most single-gene variants (20)
Repeat-expansion testing	Fragile X expansion (21)	Everything outside that locus
Methylation testing	Imprinting disorders at 15q11-q13 (22)	Changes elsewhere in the genome

Note: Qualitative summary; resolution depends on the laboratory and platform.

2.3 Fluorescence In Situ Hybridisation

Fluorescence in situ hybridisation, or FISH, uses labelled DNA probes that attach to a chosen region of a chromosome and glow under the microscope. The method made it possible to test a specific region in a child whose features pointed to a particular microdeletion syndrome, and multicolour versions allowed every chromosome to be painted in a different colour (17). FISH was the workhorse for recognised microdeletion and microduplication syndromes for many years (16).

The method finds only what the probe was designed to find, so a normal result says nothing about other possibilities. Imprinting disorders such as Prader-Willi

and Angelman syndromes are a related case, in which the chromosome region may look normal on a karyotype or even on a probe while a methylation test reveals the problem (22).

2.4 Chromosomal Microarray and Copy Number Variants

Microarray testing compares the child's DNA with a reference at many thousands of points across the genome and reports regions that are present in too few or too many copies. Early clinical arrays targeted known disease regions and soon proved their value in children with normal karyotypes (19, 23). Large series from the late 2000s found that arrays identified more clinically relevant imbalances than karyotyping in children with unexplained delay (24, 25), and a consensus statement recommended microarray as a first-tier test for developmental disabilities and congenital anomalies (18, 26). Later work confirmed the recommendation in children with delay, autism and dysmorphic features (27).

The gain in sensitivity brought a gain in difficulty. Studies of healthy people showed that copy number variation is widespread in the normal human genome, and that many gains and losses, some of them large, are carried by people with no clinical problem (28, 29). An array therefore returns a mixture of findings: clear pathogenic imbalances, clear benign ones, and a middle group in which no one can say (30, 31). Resolving that middle group became a central task of clinical cytogenetics. A result labelled uncertain is still a result, and families deserve to be told what that means.

Recurrent imbalances provided much of the early understanding. Many arise because repeated sequences in the genome mispair during meiosis, so that the same segment is deleted or duplicated in unrelated people (32, 33). Studies of



children with delay produced maps of such regions (9, 34). Some, such as 16p11.2, are linked with autism and delay, though not every carrier is affected to the same degree (35), and others act as one hit among several (36).

Arrays do not see everything. They do not detect balanced rearrangements, and they cannot easily detect low-level mosaicism or distinguish a duplicated segment sitting in tandem from one inserted elsewhere (15, 20). Laboratories are therefore expected to state clearly what their array can and cannot report (20, 26). The same pattern of added findings and added uncertainty was seen when arrays were applied prenatally (37).

2.5 Sequencing and Where Cytogenetics Now Sits

Exome and genome sequencing have added a further layer. Prospective studies of children with suspected genetic disorders showed that sequencing could reach a diagnosis in a worthwhile share of children, including some who had already had array testing (38, 39). Reviews describe sequencing as increasingly used early, sometimes ahead of array, depending on local resources (10, 40).

Cytogenetic methods have not disappeared. They remain the practical way to detect balanced rearrangements and some repeat-rich or structurally complex changes, and the standards for interpreting copy number variants are still maintained alongside those for sequence variants (41, 42). The fragile X expansion, found in the gene characterised in 1991, needs its own targeted test because neither a standard karyotype nor an ordinary array will find it (21). Methylation testing plays a comparable role for imprinting disorders, where the chromosomes may look entirely normal (22).

3. Materials and Methods

3.1 Scope and Question

The review asks a single question in three parts. What can each cytogenetic method detect in a child with unexplained developmental delay? How are the findings classified and communicated? And what should a reader check before relying on a stated rate of abnormal results? The scope is postnatal testing of children, and the review does not cover prenatal diagnosis except where it clarifies a comparison of methods. Each part follows the practical steps a clinic goes through: choosing a test, running it, interpreting the result and counselling the family. None of these steps is difficult, but each is easy to skip in a busy clinic.

3.2 Literature Assembly

The review draws on peer-reviewed guidelines, consensus statements, reviews and primary studies published up to and including 2020, covering the history of chromosome analysis, microarray and copy number interpretation, the genetics of developmental disorders and the reporting of diagnostic yield. Sources were chosen for relevance, influence and clarity of method.

We did not run a formal systematic search and we do not claim one. This is a narrative synthesis, and the selection reflects the authors' judgement.

3.3 Appraisal Framework

To judge how far a stated yield can be trusted, we asked four questions of each source. Who was tested, and by what referral criteria (1, 25)? Which platform was used and at what resolution (24, 27)? How were variants of uncertain significance counted (31, 41)? And were parents tested, so that inheritance could inform classification (30)? Table 2 shows the classification scheme referred to in the third question, and Table 3 lists the sources



of difference that follow from these four questions.

Table 2. Categories used when a copy number variant is reported, and what each means for the family.

Category	Meaning	Typical handling
Pathogenic	Established link to a clinical disorder (30, 41)	Report; counsel; offer parental testing
Likely pathogenic	Strong but incomplete support (41)	Report with stated confidence
Uncertain significance	Evidence insufficient either way (31)	Report cautiously; revisit later
Likely benign	Common in unaffected people (28, 29)	Usually not acted on
Benign	Recognised normal variation (29)	Not reported or noted only

Note: Categories follow the joint ACMG/ClinGen scheme; thresholds for assigning them are given in the cited standard.

4. Results

4.1 What Each Method Sees

Methods differ in scale of change before they differ in anything else. A karyotype sees large structures, an array sees smaller gains and losses, and sequencing sees changes within single genes (Figure 1). That ordering, though simplified, explains most of the history of the field: each new technology resolved a layer that the previous one could not, and each found a new group of children with an explanation (15, 33).

Resolution is only part of the story. A method also differs in what kind of change it is able to see at all. A balanced rearrangement has no gain or loss, so an array reads straight past it; a single-letter variant is invisible to both karyotype and array; a repeat expansion needs a targeted test (20, 21). Table 1 and Figure 3 make

this point from two directions. Such differences look technical, yet they decide whether a finding is reported at all.

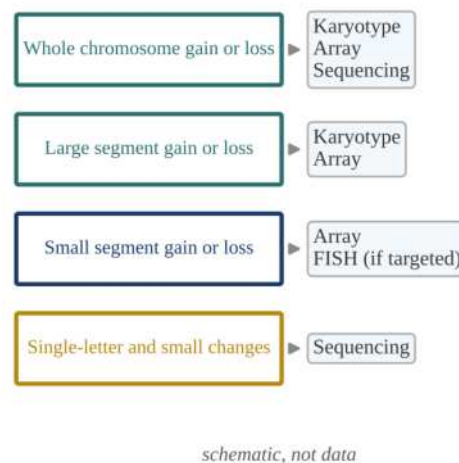


Figure 1. Layered view of what each cytogenetic method sees (schematic, not data).

4.2 Matching the Test to the Question

Guidelines favour microarray as the first cytogenetic test for most children with unexplained delay, and the karyotype for specific situations (2, 18). Those situations include a picture strongly suggesting an aneuploidy syndrome, a family history that points to a balanced rearrangement in a parent, and an array result whose physical arrangement needs explaining (13, 14). For features of a specific microdeletion syndrome, targeted FISH may answer fastest (16).

Fragile X testing deserves a separate mention because it is often requested alongside chromosome studies in boys and girls with delay of unknown cause, and because a normal array or karyotype does not address it (1, 21). A well-ordered clinic treats cytogenetic and molecular tests as a set, chosen to cover different kinds of cause. The order in which tests are done shapes the whole diagnostic journey.

Figure 3 gives a qualitative map of which method sees which class of change. Lightly shaded cells mark detection that is



possible only in some circumstances, for example when a probe was chosen in advance (10, 40).

	Karyo	FISH	Array	Seq
Aneuploidy	usually seen	sometimes	usually seen	sometimes
Large deletion	usually seen	sometimes	usually seen	sometimes
Microdeletion	not seen	usually seen	usually seen	sometimes
Balanced rearr.	usually seen	sometimes	not seen	not seen
Single gene	not seen	not seen	not seen	usually seen
Repeat expansion	not seen	not seen	not seen	sometimes

■ usually seen ■ sometimes □ not seen
schematic, not data

Figure 3. Qualitative matrix of variant classes against methods (schematic, not data).

4.3 Interpreting Copy Number Variants

Once an array reports a gain or loss, the laboratory has to decide what it means. The joint ACMG and ClinGen standard sets out a structured approach that considers the content of the region, its overlap with established syndromes, the evidence from the literature and databases, and, where possible, inheritance (31, 41). Public resources that pool cases and phenotypes made such comparisons possible (30, 43). The categories that result, from pathogenic to benign, are listed in Table 2.

Figure 2 shows a simplified path for an abnormal array result. If the region is known and recurrent, or rich in genes whose loss is understood, a causal reading is reasonable. If it is common among healthy people, the finding is probably incidental (28, 29). Between those lie many uncertain findings, and testing the parents often helps, because a variant inherited from a healthy parent is less likely to be the explanation, though reduced penetrance means it cannot be ruled out (30, 36).

Interpretation is not static. A variant labelled uncertain today may be reclassified as more cases are reported, and the converse can also happen (34, 41). A good report states the category, the evidence behind it and the plan for revisiting it. When a pathogenic imbalance arises as a new event in the child the risk to future children is usually low, whereas a parent carrying a balanced rearrangement can raise it substantially. A family hearing a result wants to know what it means for the next child as well as for this one, and the two answers are not always the same.

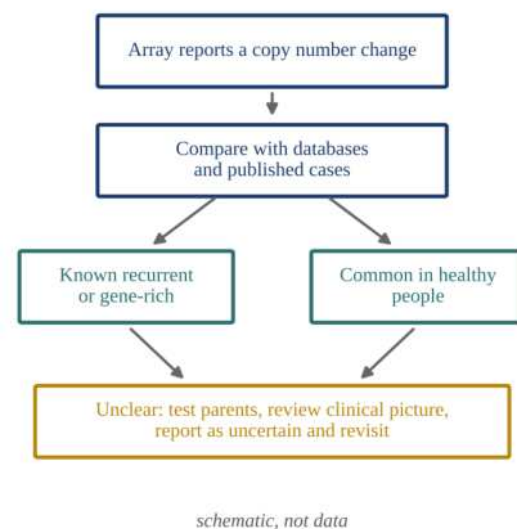


Figure 2. Decision path for an abnormal array result (schematic, not data).

4.4 Reading a Stated Diagnostic Yield

Clinic reports often state the proportion of children with an abnormal result. These proportions vary widely in the literature, and much of the variation reflects differences in who was tested and how, not differences in biology (24, 25). Table 3 lists the main reasons. A clinic that tests only children with several malformations will find more than one that tests every child with mild speech delay (4).

The definition of abnormal also matters. Some reports count only clearly pathogenic findings, whereas others add



likely pathogenic ones or even variants of uncertain significance, and the sum rises with each addition (31, 41). A figure that counts uncertain variants as diagnoses overstates the number of children who received an answer, and a figure that excludes them understates the number who received a finding of some kind. This is why two clinics can use the word abnormal and mean different things.

Table 3. Why reported diagnostic yields from different clinics are hard to compare.

Source of difference	Effect on yield	What to ask
Referral criteria	Narrow criteria raise yield (1, 25)	Who was tested and why?
Test generation	Newer platforms find more (24, 27)	Which platform and resolution?
Handling of uncertain variants	Counting them inflates yield (31, 41)	Were they counted as diagnoses?
Prior testing	Earlier tests remove easy cases (4)	What had already been done?
Parental studies	Inheritance changes classification (30)	Were parents tested?

Note: Issues are those raised in the cited literature and are not attributed to any single study.

In short, the literature gives a clear ordering of methods by sensitivity to small gains and losses, a clear case for microarray as the first cytogenetic test in most children with unexplained delay, and no single figure for how many children will receive a diagnosis. The last depends on who is tested and on what is counted. That is a modest conclusion, but it is the one the literature will bear.

A report that cannot answer the four appraisal questions should be read as a description of one clinic on one day, not as an estimate of what another clinic will find (4, 25). The point is not that any one report is poor, only that its headline travels

further than its methods allow.

5. Discussion

5.1 Interpretation and Practical Reading

The central message is conditional. Cytogenetic testing helps most when it is chosen for the question being asked, interpreted against the whole clinical picture, and reported with a statement of what it excluded. A karyotype is not obsolete, an array is not infallible, and neither replaces sequencing for the many causes that lie below their resolution (2, 10).

5.2 Limitations

This is a narrative review and shares the limitations of that form. The selection of sources reflects judgement, no formal search or quality scoring was done, and no yield from an individual series is quoted, because such figures could not be checked against the primary reports for this article. A reader who needs a number should consult the original studies and apply the four appraisal questions, or wait for a formal systematic review. The review also stops at 2020 and does not follow later work on long-read or routine genome sequencing in children. Reviews are more useful when they mark where the evidence stops than when they smooth it over.

5.3 Future Work

Three needs stand out. First, studies that report yield by clearly defined referral group and by clearly defined result category, so that figures from different clinics can be set side by side. Second, prospective follow-up of children with uncertain findings, to show how often and how quickly they are reclassified (34, 43). Third, evaluations of testing pathways that count what families actually receive, not only the proportion with a finding (2, 10).



A practical step is for clinics to publish their testing policy alongside their results: referral criteria, platform and resolution, reporting threshold, classification scheme and policy on parental testing. These are cheap to state and turn a bare percentage into something another clinic can use. Reanalysing older negative results at intervals, where resources allow, would add to the diagnostic return for little extra cost, and it is a habit worth keeping even when the answer is expected. It is a habit worth keeping even when the answer is expected.

6. Conclusion

Cytogenetic analysis remains a core part of the evaluation of a child with developmental delay, though its form has changed. The karyotype sees large structures and balanced rearrangements, FISH answers targeted questions, and microarray detects small gains and losses across the genome and is widely recommended as the first cytogenetic test. None of them finds single-gene variants or repeat expansions, so a normal result narrows the search without ending it. The same caution applies to any new genomic test, not only to arrays.

For the clinician, the message is practical: choose the test for the question, state what a normal result does and does not exclude, and explain uncertain findings plainly. For the researcher, the opportunity is better reporting, with yields tied to who was tested, how, and what was counted.

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9. Conflict of Interest

The authors declare no conflict of interest.

10. Author Contributions

L.S. conceived the review and wrote the sections on conventional cytogenetics and interpretation. M.F. wrote the sections on microarray and molecular methods. R.T. wrote the sections on clinical evaluation and reporting of yield. All authors revised the manuscript and approved the final version.

11. Ethics Statement

This is a review of published literature. No patients or patient data were involved and no ethical approval was required.

12. Data Availability

No new data were generated. All sources are cited in the reference list.

13. References

1. Shevell, M., Ashwal, S., Donley, D., Flint, J., Gingold, M., Hirtz, D., ... Sheth, R. D. (2003). Practice parameter: Evaluation of the child with global developmental delay. *Neurology*, 60(3), 367–380. DOI: [10.1212/01.WNL.0000031431.81555.16](https://doi.org/10.1212/01.WNL.0000031431.81555.16)
2. Moeschler, J. B., & Shevell, M. (2014). Comprehensive evaluation of the child with intellectual disability or global developmental delays. *Pediatrics*, 134(3), e903–e918. DOI: [10.1542/peds.2014-1839](https://doi.org/10.1542/peds.2014-1839)
3. Maulik, P. K., Mascarenhas, M. N., Mathers, C. D., Dua, T., & Saxena, S. (2011). Prevalence of intellectual disability: A meta-analysis of population-based studies. *Research in Developmental Disabilities*, 32(2), 419–436. DOI: [10.1016/j.ridd.2010.12.018](https://doi.org/10.1016/j.ridd.2010.12.018)
4. Srour, M., & Shevell, M. (2014). Genetics and the investigation of developmental delay/intellectual disability. *Archives of Disease in Childhood*, 99(4), 386–389. DOI: [10.1136/archdischild-2013-304063](https://doi.org/10.1136/archdischild-2013-304063)
5. Mefford, H. C., Batshaw, M. L., & Hoffman, E. P. (2012). Genomics, intellectual disability, and autism. *New England Journal of Medicine*, 366(8), 733–743. DOI: [10.1056/NEJMr1114194](https://doi.org/10.1056/NEJMr1114194)
6. Ropers, H. H. (2010). Genetics of early onset cognitive impairment. *Annual Review of Genomics and Human Genetics*, 11, 161–187. DOI: [10.1146/annurev-genom-082509-141640](https://doi.org/10.1146/annurev-genom-082509-141640)



7. Deciphering Developmental Disorders Study. (2015). Large-scale discovery of novel genetic causes of developmental disorders. *Nature*, 519(7542), 223–228. DOI: [10.1038/nature14135](https://doi.org/10.1038/nature14135)
8. Deciphering Developmental Disorders Study. (2017). Prevalence and architecture of de novo mutations in developmental disorders. *Nature*, 542(7642), 433–438. DOI: [10.1038/nature21062](https://doi.org/10.1038/nature21062)
9. Cooper, G. M., Coe, B. P., Girirajan, S., Rosenfeld, J. A., Vu, T. H., Baker, C., ... Eichler, E. E. (2011). A copy number variation morbidity map of developmental delay. *Nature Genetics*, 43(9), 838–846. DOI: [10.1038/ng.909](https://doi.org/10.1038/ng.909)
10. Wright, C. F., FitzPatrick, D. R., & Firth, H. V. (2018). Paediatric genomics: Diagnosing rare disease in children. *Nature Reviews Genetics*, 19(5), 253–268. DOI: [10.1038/nrg.2017.116](https://doi.org/10.1038/nrg.2017.116)
11. Tjio, J. H., & Levan, A. (1956). The chromosome number of man. *Hereditas*, 42(1–2), 1–6. DOI: [10.1111/j.1601-5223.1956.tb03010.x](https://doi.org/10.1111/j.1601-5223.1956.tb03010.x)
12. Seabright, M. (1971). A rapid banding technique for human chromosomes. *The Lancet*, 298(7731), 971–972. DOI: [10.1016/S0140-6736\(71\)90287-X](https://doi.org/10.1016/S0140-6736(71)90287-X)
13. Hassold, T., & Hunt, P. (2001). To err (meiotically) is human: The genesis of human aneuploidy. *Nature Reviews Genetics*, 2(4), 280–291. DOI: [10.1038/35066065](https://doi.org/10.1038/35066065)
14. Shaffer, L. G., & Lupski, J. R. (2000). Molecular mechanisms for constitutional chromosomal rearrangements in humans. *Annual Review of Genetics*, 34, 297–329. DOI: [10.1146/annurev.genet.34.1.297](https://doi.org/10.1146/annurev.genet.34.1.297)
15. Ledbetter, D. H. (2008). Cytogenetic technology — genotype and phenotype. *New England Journal of Medicine*, 359(16), 1728–1730. DOI: [10.1056/NEJMe0806376](https://doi.org/10.1056/NEJMe0806376)
16. Weise, A., Mrasek, K., Klein, E., Mulatinho, M., Llerena, J. C., Hardekopf, D., ... Liehr, T. (2012). Microdeletion and microduplication syndromes. *Journal of Histochemistry & Cytochemistry*, 60(5), 346–358. DOI: [10.1369/0022155412440001](https://doi.org/10.1369/0022155412440001)
17. Speicher, M. R., Ballard, S. G., & Ward, D. C. (1996). Karyotyping human chromosomes by combinatorial multi-fluor FISH. *Nature Genetics*, 12(4), 368–375. DOI: [10.1038/ng0496-368](https://doi.org/10.1038/ng0496-368)
18. Miller, D. T., Adam, M. P., Aradhya, S., Biesecker, L. G., Brothman, A. R., Carter, N. P., ... Ledbetter, D. H. (2010). Consensus statement: Chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *American Journal of Human Genetics*, 86(5), 749–764. DOI: [10.1016/j.ajhg.2010.04.006](https://doi.org/10.1016/j.ajhg.2010.04.006)
19. Cheung, S. W., Shaw, C. A., Yu, W., Li, J., Ou, Z., Patel, A., ... Beaudet, A. L. (2005). Development and validation of a CGH microarray for clinical cytogenetic diagnosis. *Genetics in Medicine*, 7(6), 422–432. DOI: [10.1097/01.GIM.0000170992.63691.32](https://doi.org/10.1097/01.GIM.0000170992.63691.32)
20. Vermeesch, J. R., Fiegler, H., de Leeuw, N., Szuhai, K., Schoumans, J., Ciccone, R., ... Carter, N. P. (2007). Guidelines for molecular karyotyping in constitutional genetic diagnosis. *European Journal of Human Genetics*, 15(11), 1105–1114. DOI: [10.1038/sj.ejhg.5201896](https://doi.org/10.1038/sj.ejhg.5201896)
21. Verkerk, A. J. M. H., Pieretti, M., Sutcliffe, J. S., Fu, Y.-H., Kuhl, D. P. A., Pizzuti, A., ... Warren, S. T. (1991). Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. *Cell*, 65(5), 905–914. DOI: [10.1016/0092-8674\(91\)90397-H](https://doi.org/10.1016/0092-8674(91)90397-H)
22. Nicholls, R. D., & Knepper, J. L. (2001). Genome organization, function, and imprinting in Prader-Willi and Angelman syndromes. *Annual Review of Genomics and Human Genetics*, 2, 153–175. DOI: [10.1146/annurev.genom.2.1.153](https://doi.org/10.1146/annurev.genom.2.1.153)
23. Stankiewicz, P., & Beaudet, A. L. (2007). Use of array CGH in the evaluation of dysmorphism, malformations, developmental delay, and idiopathic mental retardation. *Current Opinion in Genetics & Development*, 17(3), 182–192. DOI: [10.1016/j.gde.2007.04.009](https://doi.org/10.1016/j.gde.2007.04.009)
24. Hochstenbach, R., van Binsbergen, E., Engelen, J., Nieuwint, A., Polstra, A., Poddighe, P., ... Hamers, G. (2009). Array analysis and karyotyping: Workflow consequences based on a retrospective study of 36,325 patients with idiopathic developmental delay in the Netherlands. *European Journal of Medical Genetics*, 52(4), 161–169. DOI: [10.1016/j.ejmg.2009.03.015](https://doi.org/10.1016/j.ejmg.2009.03.015)
25. Rauch, A., Hoyer, J., Guth, S., Zweier, C., Kraus, C., Becker, C., ... Trautmann, U. (2006). Diagnostic yield of various genetic approaches in patients with unexplained developmental delay or mental retardation. *American Journal of Medical Genetics Part A*, 140(19), 2063–2074. DOI: [10.1002/ajmg.a.31416](https://doi.org/10.1002/ajmg.a.31416)
26. Manning, M., & Hudgins, L. (2010). Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. *Genetics in Medicine*, 12(11), 742–745. DOI: [10.1097/GIM.0b013e3181f8baad](https://doi.org/10.1097/GIM.0b013e3181f8baad)
27. Battaglia, A., Doccini, V., Bernardini, L., Novelli, A., Loddo, S., Capalbo, A., ... Carey, J. C. (2013). Confirmation of chromosomal microarray as a first-tier clinical diagnostic test for individuals with developmental delay, intellectual disability, autism spectrum disorders and dysmorphic features. *European Journal of Paediatric Neurology*, 17(6), 589–599. DOI: [10.1016/j.ejpn.2013.04.010](https://doi.org/10.1016/j.ejpn.2013.04.010)



28. Iafrate, A. J., Feuk, L., Rivera, M. N., Listewnik, M. L., Donahoe, P. K., Qi, Y., ... Lee, C. (2004). Detection of large-scale variation in the human genome. *Nature Genetics*, 36(9), 949–951. DOI: [10.1038/ng1416](https://doi.org/10.1038/ng1416)
29. Redon, R., Ishikawa, S., Fitch, K. R., Feuk, L., Perry, G. H., Andrews, T. D., ... Hurles, M. E. (2006). Global variation in copy number in the human genome. *Nature*, 444(7118), 444–454. DOI: [10.1038/nature05329](https://doi.org/10.1038/nature05329)
30. Kaminsky, E. B., Kaul, V., Paschall, J., Church, D. M., Bunke, B., Kunig, D., ... Martin, C. L. (2011). An evidence-based approach to establish the functional and clinical significance of copy number variants in intellectual and developmental disabilities. *Genetics in Medicine*, 13(9), 777–784. DOI: [10.1097/GIM.0b013e31822c79f9](https://doi.org/10.1097/GIM.0b013e31822c79f9)
31. Kearney, H. M., Thorland, E. C., Brown, K. K., Quintero-Rivera, F., & South, S. T. (2011). American College of Medical Genetics standards and guidelines for interpretation and reporting of postnatal constitutional copy number variants. *Genetics in Medicine*, 13(7), 680–685. DOI: [10.1097/GIM.0b013e3182217a3a](https://doi.org/10.1097/GIM.0b013e3182217a3a)
32. Lupski, J. R. (1998). Genomic disorders: Structural features of the genome can lead to DNA rearrangements and human disease traits. *Trends in Genetics*, 14(10), 417–422. DOI: [10.1016/S0168-9525\(98\)01555-8](https://doi.org/10.1016/S0168-9525(98)01555-8)
33. Stankiewicz, P., & Lupski, J. R. (2010). Structural variation in the human genome and its role in disease. *Annual Review of Medicine*, 61, 437–455. DOI: [10.1146/annurev.med.100708.204719](https://doi.org/10.1146/annurev.med.100708.204719)
34. Coe, B. P., Witherspoon, K., Rosenfeld, J. A., van Bon, B. W. M., Vulto-van Silfhout, A. T., Bosco, P., ... Eichler, E. E. (2014). Refining analyses of copy number variation identifies specific genes associated with developmental delay. *Nature Genetics*, 46(10), 1063–1071. DOI: [10.1038/ng.3092](https://doi.org/10.1038/ng.3092)
35. Weiss, L. A., Shen, Y., Korn, J. M., Arking, D. E., Miller, D. T., Fossdal, R., ... Gusella, J. F. (2008). Association between microdeletion and microduplication at 16p11.2 and autism. *New England Journal of Medicine*, 358(7), 667–675. DOI: [10.1056/NEJMoa075974](https://doi.org/10.1056/NEJMoa075974)
36. Girirajan, S., Rosenfeld, J. A., Cooper, G. M., Antonacci, F., Siswara, P., Itsara, A., ... Eichler, E. E. (2010). A recurrent 16p12.1 microdeletion supports a two-hit model for severe developmental delay. *Nature Genetics*, 42(3), 203–209. DOI: [10.1038/ng.534](https://doi.org/10.1038/ng.534)
37. Wapner, R. J., Martin, C. L., Levy, B., Ballif, B. C., Eng, C. M., Zachary, J. M., ... Jackson, L. (2012). Chromosomal microarray versus karyotyping for prenatal diagnosis. *New England Journal of Medicine*, 367(23), 2175–2184. DOI: [10.1056/NEJMoa1203822](https://doi.org/10.1056/NEJMoa1203822)
38. Stark, Z., Tan, T. Y., Chong, B., Brett, G. R., Yap, P., Walsh, M., ... White, S. M. (2016). A prospective evaluation of whole-exome sequencing as a first-tier molecular test in infants with suspected monogenic disorders. *Genetics in Medicine*, 18(11), 1090–1096. DOI: [10.1038/gim.2016.1](https://doi.org/10.1038/gim.2016.1)
39. Srivastava, S., Cohen, J. S., Vernon, H., Barañano, K., McClellan, R., Jamal, L., ... Fatemi, A. (2014). Clinical whole exome sequencing in child neurology practice. *Annals of Neurology*, 76(4), 473–483. DOI: [10.1002/ana.24251](https://doi.org/10.1002/ana.24251)
40. Vissers, L. E. L. M., Gilissen, C., & Veltman, J. A. (2016). Genetic studies in intellectual disability and related disorders. *Nature Reviews Genetics*, 17(1), 9–18. DOI: [10.1038/nrg3999](https://doi.org/10.1038/nrg3999)
41. Riggs, E. R., Andersen, E. F., Cherry, A. M., Kantarci, S., Kearney, H., Patel, A., ... Martin, C. L. (2020). Technical standards for the interpretation and reporting of constitutional copy-number variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen). *Genetics in Medicine*, 22(2), 245–257. DOI: [10.1038/s41436-019-0686-8](https://doi.org/10.1038/s41436-019-0686-8)
42. Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., ... Rehm, H. L. (2015). Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in Medicine*, 17(5), 405–424. DOI: [10.1038/gim.2015.30](https://doi.org/10.1038/gim.2015.30)
43. Firth, H. V., Richards, S. M., Bevan, A. P., Clayton, S., Corpas, M., Rajan, D., ... Carter, N. P. (2009). DECIPHER: Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources. *American Journal of Human Genetics*, 84(4), 524–533. DOI: [10.1016/j.ajhg.2009.03.010](https://doi.org/10.1016/j.ajhg.2009.03.010)