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GENETIC TESTING IN CLINICAL PRACTICE - DIAGNOSTIC STEWARDSHIP

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Abstract: *Advances in the field of molecular medicine and genetic engineering have found applications in clinical practice in the form of diagnosis, treatment and prevention of genetic disorders. Cytogenetics refers to the description of chromosome structure and the identification of genomic aberrations that cause diseases. 'Fluorescence in situ hybridization' is a process whereby chromosomes or portions of chromosomes are vividly painted with fluorescent molecules that anneal to specific regions. Detecting the changes in DNA (mutation) responsible for the genetic disease is the diagnostic test for single gene disorders. 'Chromosomal microarray' is a high resolution, whole-genome screening technique that can identify most of the chromosomal imbalances detected by conventional cytogenetic analysis, as well as smaller sub-microscopic deletions and duplications that are referred to as copy-number variants that may be missed in the conventional karyotyping. 'Next generation sequencing' is a powerful platform that has enabled the sequencing of thousands to millions of DNA molecules simultaneously. This article review the rational use of various investigations used for the diagnosis of genetic disorders in clinical practice.*

Keywords: *Cytogenetics, Chromosomal microarray analysis, Next generation sequencing.*

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Points to Remember

- ***The indications of genetic testing include diagnosis of genetic disorders, prenatal diagnosis, carrier testing and pre symptomatic diagnosis.***
- ***Genetic testing in clinical situation should be accompanied by pre-test and post-test genetic counselling.***
- ***Cytogenetic methods include conventional cytogenetics, FISH and microarray which can detect chromosomal aberrations and copy number variants.***
- ***Rational selection of molecular methods depends on the type of mutation to be tested in the specific genetic disorder.***
- ***Always consider the three principles – analytical validity, clinical validity and clinical utility when considering a specific genetic test in a given clinical scenario.***

References

1. Gersen, Steven L, Keagle, Martha B. (Eds.) The Principles of clinical cytogenetics published by Springer, New York, 3rd Edn; 2013; 23-65.
2. Berisha SZ, Shetty S, Prior TW, Mitchell AL. Cytogenetic and molecular diagnostic testing associated with prenatal and postnatal birth defects. Birth Defects Res 2020; 112(4):293-306.
3. Test and Technology Transfer Committee, American College of Medical Genetics, 9650 Rockville Pike, Bethesda, MD 20814-3998, United States. Technical and clinical assessment of fluorescence in situ hybridization: an ACMG/ASHG position statement. I. Technical considerations. Test and Technology Transfer Committee. Genet Med 2000; 2(6):356-361.
4. Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet 2010; 86(5): 749-674.
5. Dugoff L, Norton ME, Kuller JA. Society for Maternal-Fetal Medicine (SMFM). The use of chromosomal microarray for prenatal diagnosis. Am J Obstet Gynecol 2016; 215(4):B2-9. doi: 10.1016/j.ajog.2016.07.016.

Epub 2016 Jul 15. Erratum in: Am J Obstet Gynecol 2017; 216(2):180.

6. Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, Korbel JO, Marchini JL, McCarthy S, McVean GA, Abecasis GR .1000 Genomes Project Consortium. A global reference for human genetic variation. Nature 2015; 526(7571):68-74.
7. Waseem AS, Singh V, Makker GC, Trivedi S, Mishra G, Singh K, et al. AZF deletions in Indian populations: original study and meta-analyses. J Assist Reprod Genet 2020; 37(2):459-469.
8. Patil SJ, Banerjee M, Phadke SR, Mittal B. Mutation analysis in Indian children with achondroplasia - utility of molecular diagnosis. Indian J Pediatr 2009; 76(2):147-149.
9. Stuppia L, Antonucci I, Palka G, Gatta V. Use of the MLPA assay in the molecular diagnosis of gene copy number alterations in human genetic diseases. Int J Mol Sci 2012; 13(3):3245-3276.
10. Gitman MR, Shaban MV, Paniz-Mondolfi AE, Sordillo EM. Laboratory Diagnosis of SARS-CoV-2 Pneumonia. Diagnostics (Basel) 2021; 11(7):1270.
11. Smith A, Hung D. The dilemma of diagnostic testing for Prader-Willi syndrome. TranslPediatr 2017; 6(1):46-56.
12. Tassone F. Advanced technologies for the molecular diagnosis of fragile X syndrome. Expert Rev MolDiagn 2015; 15(11):1465-1473.
13. Yohe S, Thyagarajan B. Review of Clinical Next-Generation Sequencing. Arch Pathol Lab Med 2017; 141(11):1544-1557.
14. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. ACMG Laboratory Quality Assurance Committee. 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. Genet Med 2015; 17(5):405-424.
15. Richardson A, Ormond KE. Ethical considerations in prenatal testing: Genomic testing and medical uncertainty. Semin Fetal Neonatal Med 2018; 23(1):1-6.