LIFE SCIENCE REVIEW

Review Article

Journal homepage: https://lsr.crcjournals.org/

p-ISSN 3117-3535
e-ISSN 3117-3543

Check for updates

Down Syndrome and Other Common Chromosomal Abnormalities in Humans with Recent Advances in Cytogenetic Diagnosis

Sanjeet Kaur

Department of Zoology GCW, Gandhi Nagar, Jammu and Kashmir 180004, India

Received 04 July 2020 | Revised 05 August 2020 | Accepted 06 September 2020 | Available Online 07 October 2020

*Corresponding Author: **Sanjeet Kaur** | Email Address: **sanjeetsskaur@gmail.com**

Citation: Sanjeet Kaur (2020). Down Syndrome and Other Common Chromosomal Abnormalities in Humans with Recent Advances in Cytogenetic Diagnosis. ***Life Science Review***. **DOI: https://doi.org/10.51470/LSR.2020.04.02.01**

Abstract

Chromosomal abnormalities constitute a major cause of congenital anomalies, intellectual disability, infertility, recurrent pregnancy loss, developmental delay, and various genetic syndromes in humans. These abnormalities may involve numerical changes, such as aneuploidy, or structural alterations including deletions, duplications, translocations, inversions, and ring chromosomes. Among them, Down syndrome remains the most prevalent autosomal chromosomal disorder worldwide, resulting from the presence of an additional copy of chromosome 21. Significant advances in cytogenetic and molecular cytogenetic technologies over recent decades have transformed the diagnosis, characterization, and clinical management of chromosomal disorders. Conventional karyotyping continues to serve as the standard method for detecting large chromosomal abnormalities, while fluorescence in situ hybridization (FISH), chromosomal microarray analysis (CMA), quantitative fluorescence polymerase chain reaction (QF-PCR), multiplex ligation-dependent probe amplification (MLPA), and next-generation sequencing (NGS)-based techniques have substantially improved diagnostic accuracy and resolution. Early prenatal diagnosis, genetic counseling, and personalized clinical management have enhanced healthcare outcomes for affected individuals and their families. This review summarizes the epidemiology, genetic basis, clinical manifestations, classification, and diagnosis of Down syndrome and other common chromosomal abnormalities, with particular emphasis on recent advances in cytogenetic diagnostic technologies and future prospects for precision genomic medicine.

Keywords: *Down syndrome, Chromosomal abnormalities, Cytogenetics, Karyotyping, Fluorescence in situ hybridization, Chromosomal microarray analysis.*

1. Introduction

Human genetic disorders caused by chromosomal abnormalities remain an important global public health concern because of their substantial contribution to congenital malformations, developmental disabilities, infertility, pregnancy loss, and hereditary diseases. Chromosomes are highly organized DNA-protein structures that carry genetic information essential for normal growth, development, and cellular function. Any alteration in chromosome number or structure may disrupt gene dosage or gene expression, leading to a wide spectrum of clinical disorders with varying degrees of severity.

Chromosomal abnormalities are broadly classified into numerical abnormalities and structural abnormalities. Numerical abnormalities arise from errors during meiotic or mitotic chromosome segregation, resulting in gain or loss of entire chromosomes. Common examples include trisomies, monosomies, and polyploidies. Structural abnormalities occur when chromosome segments undergo deletion, duplication, inversion, translocation, insertion, or ring formation due to chromosome breakage and abnormal repair mechanisms. These structural changes may alter gene function, disrupt regulatory sequences, or generate fusion genes responsible for various inherited and acquired disorders [1]. Among all chromosomal disorders, Down syndrome represents the most frequently diagnosed autosomal trisomy compatible with postnatal survival. First described by John Langdon Down in 1866 and later identified cytogenetically as trisomy 21, Down syndrome affects approximately one in every 700 live births worldwide. Individuals with Down syndrome typically exhibit characteristic facial features, intellectual disability, congenital heart defects, immune dysfunction, endocrine disorders, and increased susceptibility to certain hematological malignancies. Maternal age remains one of the most significant risk factors for trisomy 21 because advancing maternal age increases the likelihood of meiotic nondisjunction during oogenesis [2].

Other common chromosomal disorders include Edwards syndrome (trisomy 18), Patau syndrome (trisomy 13), Turner syndrome (45,X), Klinefelter syndrome (47,XXY), Triple X syndrome (47,XXX), and XYY syndrome (47,XYY). These conditions display diverse clinical manifestations affecting growth, reproductive development, cognitive function, and multiple organ systems. Early diagnosis facilitates appropriate medical management, rehabilitation, educational support, and genetic counseling for affected families. The field of cytogenetics has undergone remarkable technological advancements over the past five decades. Conventional G-banded karyotyping remains an essential diagnostic tool for identifying numerical abnormalities and large structural rearrangements. However, molecular cytogenetic techniques such as fluorescence in situ hybridization (FISH), spectral karyotyping (SKY), comparative genomic hybridization (CGH), chromosomal microarray analysis (CMA), quantitative fluorescence polymerase chain reaction (QF-PCR), multiplex ligation-dependent probe amplification (MLPA), and next-generation sequencing (NGS) have significantly enhanced the detection of submicroscopic chromosomal abnormalities. These technologies have improved diagnostic precision, enabled earlier prenatal diagnosis, and contributed to personalized genomic medicine.

2. Human Chromosomal Organization and Classification of Chromosomal Abnormalities

Human somatic cells normally contain 46 chromosomes arranged into 23 homologous pairs, including 22 pairs of autosomes and one pair of sex chromosomes. Females possess two X chromosomes (46,XX), whereas males possess one X chromosome and one Y chromosome (46,XY). Chromosomes consist of highly condensed chromatin composed of DNA, histone proteins, and non-histone proteins that regulate gene expression and genome stability. During cell division, chromosomes undergo condensation, enabling accurate segregation of genetic material into daughter cells.

Chromosomal abnormalities originate primarily through errors during meiosis or mitosis. Meiotic nondisjunction occurs when homologous chromosomes or sister chromatids fail to separate properly during gamete formation, producing gametes with abnormal chromosome numbers. Fertilization involving these abnormal gametes results in aneuploid offspring possessing either extra or missing chromosomes. Structural abnormalities generally arise from chromosome breakage followed by abnormal repair or unequal recombination during meiosis [3]. Numerical chromosomal abnormalities include trisomy, monosomy, tetrasomy, and polyploidy. Trisomy results from the presence of an additional chromosome, whereas monosomy involves the absence of one chromosome from a homologous pair. Polyploidy involves complete duplication of the entire chromosome set but is generally incompatible with human survival.

Structural abnormalities encompass deletions, duplications, inversions, reciprocal translocations, Robertsonian translocations, ring chromosomes, and isochromosomes. Balanced structural rearrangements often produce no clinical symptoms in carriers but may increase reproductive risks, recurrent miscarriages, or offspring with unbalanced chromosomal complements. Unbalanced rearrangements alter gene dosage and frequently produce congenital anomalies and developmental disorders [4]. Recent molecular cytogenetic technologies have substantially improved the identification of both visible and cryptic chromosomal abnormalities, enabling clinicians to detect submicroscopic deletions and duplications previously undetectable using conventional microscopy.

Table 1: Classification of Human Chromosomal Abnormalities

Category	Type	Examples	Clinical Significance
Numerical	Trisomy	Down syndrome (Trisomy 21), Edwards syndrome, Patau syndrome	Developmental disorders
Numerical	Monosomy	Turner syndrome (45,X)	Gonadal dysgenesis, infertility
Structural	Deletion	Cri-du-chat syndrome	Developmental delay
Structural	Duplication	Partial trisomy syndromes	Variable congenital anomalies
Structural	Translocation	Robertsonian translocation	Reproductive disorders
Structural	Inversion	Pericentric inversion	Usually asymptomatic carriers
Structural	Ring chromosome	Ring chromosome syndromes	Growth and developmental abnormalities

3. Down Syndrome and Other Common Chromosomal Disorders

Down syndrome is the most common viable autosomal trisomy and accounts for approximately 95% of cases due to complete trisomy 21 caused by meiotic nondisjunction. Around 3–4% result from Robertsonian translocations involving chromosome 21, while approximately 1–2% arise from mosaic trisomy 21 [5]. The clinical phenotype includes hypotonia, characteristic craniofacial appearance, intellectual disability, congenital heart defects, gastrointestinal abnormalities, thyroid dysfunction, hearing impairment, visual disorders, immune dysregulation, and increased susceptibility to acute leukemia and early-onset Alzheimer's disease. Advances in multidisciplinary medical care have substantially improved life expectancy and quality of life among affected individuals.

Edwards syndrome (Trisomy 18) represents the second most common autosomal trisomy among live births. Affected individuals commonly exhibit severe growth restriction, clenched fists, rocker-bottom feet, congenital heart defects, renal anomalies, and profound developmental delay.

Most affected infants experience high mortality during the first year of life [6]. Patau syndrome (Trisomy 13) is characterized by severe congenital malformations including holoprosencephaly, cleft lip and palate, microphthalmia, polydactyly, congenital heart defects, and central nervous system abnormalities. Like Edwards syndrome, survival beyond infancy is uncommon.

Sex chromosome abnormalities generally produce milder phenotypes than autosomal aneuploidies because of X chromosome inactivation and relatively fewer genes located on the Y chromosome. Turner syndrome results from complete or partial monosomy of the X chromosome and is characterized by short stature, primary amenorrhea, infertility, cardiovascular abnormalities, and ovarian insufficiency. Klinefelter syndrome (47,XXY) affects males and presents with hypogonadism, infertility, tall stature, gynecomastia, and varying degrees of learning difficulties. Triple X syndrome and XYY syndrome usually produce relatively mild clinical manifestations, although developmental and behavioral variations may occur [7]. The introduction of molecular cytogenetic diagnostic techniques has greatly improved the identification of these disorders, facilitating early clinical intervention, genetic counseling, and reproductive planning.

4. Recent Advances in Cytogenetic Diagnosis

The field of cytogenetics has undergone remarkable transformation with the introduction of molecular and genomic technologies that complement conventional chromosome analysis. While G-banded karyotyping remains the gold standard for detecting large numerical and structural chromosomal abnormalities, its resolution is limited to alterations larger than approximately 5–10 Mb. The integration of molecular cytogenetic techniques has significantly improved diagnostic sensitivity, enabling the identification of submicroscopic chromosomal rearrangements, copy number variations (CNVs), and complex genomic abnormalities associated with congenital disorders and developmental disabilities [8]. Conventional karyotyping continues to play a central role in the diagnosis of Down syndrome, Turner syndrome, Klinefelter syndrome, balanced translocations, inversions, and other chromosomal abnormalities. Chromosome preparations obtained from peripheral blood lymphocytes, bone marrow, amniotic fluid, chorionic villus samples, or fetal tissues are stained using Giemsa staining to produce characteristic banding patterns that facilitate chromosome identification. Although highly reliable for detecting large abnormalities, conventional cytogenetics cannot identify cryptic microdeletions or microduplications.

Fluorescence in situ hybridization (FISH) has substantially enhanced cytogenetic diagnosis by using fluorescently labeled DNA probes that hybridize to specific chromosomal regions. FISH allows rapid detection of aneuploidies involving chromosomes 13, 18, 21, X, and Y, making it particularly useful for prenatal diagnosis and neonatal confirmation of chromosomal disorders. It also enables the identification of microdeletion syndromes, gene rearrangements, marker chromosomes, and chromosomal translocations associated with hematological malignancies [9]. Chromosomal microarray analysis (CMA), including array comparative genomic hybridization (aCGH) and single nucleotide polymorphism (SNP) arrays, has become the first-line diagnostic test for individuals presenting with unexplained developmental delay, intellectual disability, autism spectrum disorders, and multiple congenital anomalies. CMA detects submicroscopic deletions and duplications across the entire genome with much higher resolution than conventional karyotyping. However, balanced chromosomal rearrangements and low-level mosaicism remain difficult to detect using microarray technologies.

Quantitative fluorescence polymerase chain reaction (QF-PCR) provides rapid prenatal diagnosis of common chromosomal aneuploidies within 24–48 hours. Similarly, multiplex ligation-dependent probe amplification (MLPA) enables the identification of specific chromosomal deletions and duplications with high sensitivity and relatively low cost. More recently, next-generation sequencing (NGS)-based technologies, including whole-genome sequencing (WGS), whole-exome sequencing (WES), and low-pass genome sequencing, have expanded the ability to detect complex structural variants, copy number changes, and mosaic chromosomal abnormalities [10]. Non-invasive prenatal testing (NIPT), based on analysis of cell-free fetal DNA circulating in maternal plasma, represents one of the most significant advances in prenatal cytogenetics. NIPT demonstrates excellent sensitivity and specificity for detecting trisomy 21, trisomy 18, trisomy 13, and selected sex chromosome abnormalities without the miscarriage risks associated with invasive procedures such as amniocentesis and chorionic villus sampling. Although positive NIPT results require confirmation through diagnostic testing, this technology has substantially improved prenatal screening worldwide. The combination of classical cytogenetics with molecular genomic technologies has revolutionized clinical genetics by improving diagnostic accuracy, reducing turnaround time, enabling earlier intervention, and supporting personalized patient management.

Table 2: Major Cytogenetic Diagnostic Techniques

Technique	Resolution	Major Applications	Advantages
G-Banded Karyotyping	5–10 Mb	Numerical and structural abnormalities	Whole chromosome analysis
FISH	100 kb–1 Mb	Aneuploidy, translocations, microdeletions	Rapid and targeted diagnosis
Chromosomal Microarray Analysis	25–100 kb	Copy number variations	High-resolution genome-wide detection
QF-PCR	Gene-specific	Prenatal aneuploidy screening	Rapid results
MLPA	Gene-specific	Microdeletion and duplication syndromes	Cost-effective targeted testing
Next-Generation Sequencing	Base-pair resolution	Structural variants and genomic analysis	Comprehensive genomic profiling
Non-Invasive Prenatal Testing	Cell-free fetal DNA	Prenatal screening	Non-invasive and highly sensitive

5. Clinical Applications and Genetic Counseling

Accurate diagnosis of chromosomal abnormalities is essential for clinical management, prognosis, reproductive counseling, and long-term healthcare planning. Cytogenetic investigations are routinely performed in newborns with congenital anomalies, children presenting with developmental delay or intellectual disability, individuals with infertility or recurrent pregnancy loss, patients with hematological malignancies, and pregnancies identified as high risk through prenatal screening [11]. Prenatal diagnosis has become one of the most important applications of modern cytogenetics. Pregnant women with advanced maternal age, abnormal ultrasound findings, positive biochemical screening results, family history of chromosomal disorders, or previous affected pregnancies are frequently offered prenatal genetic testing. Chorionic villus sampling performed during the first trimester and amniocentesis during the second trimester provide fetal cells suitable for chromosomal analysis using karyotyping, FISH, CMA, or molecular testing. Early diagnosis allows informed reproductive decision-making and facilitates preparation for specialized neonatal care.

Genetic counseling constitutes an integral component of cytogenetic services. Counselors explain the genetic basis of chromosomal disorders, recurrence risks, inheritance patterns, available diagnostic options, reproductive choices, and long-term management strategies. Families affected by Down syndrome, Turner syndrome, Klinefelter syndrome, balanced translocations, or recurrent miscarriages particularly benefit from comprehensive counseling regarding future reproductive planning [12]. Management of individuals with chromosomal abnormalities requires multidisciplinary care involving pediatricians, clinical geneticists, cardiologists, endocrinologists, neurologists, psychologists, speech therapists, physiotherapists, occupational therapists, and special education professionals. Early intervention programs focusing on developmental support, educational assistance, behavioral therapy, and rehabilitation significantly improve functional outcomes and quality of life.

Chromosomal analysis also plays a major role in oncology. Numerous hematological malignancies are characterized by recurrent chromosomal translocations, deletions, and gene rearrangements that influence diagnosis, prognosis, and therapeutic selection. Cytogenetic findings therefore contribute directly to precision medicine and individualized cancer treatment. Population-based cytogenetic screening and newborn screening programs continue to improve early detection of chromosomal disorders, particularly in regions with limited access to specialized healthcare services. Public awareness programs and expanded genetic services are essential for reducing the burden of inherited disorders and improving reproductive health outcomes.

Table 3: Clinical Applications of Cytogenetic Analysis

Clinical Situation	Recommended Cytogenetic Test	Clinical Purpose
Down syndrome diagnosis	Karyotyping, FISH	Confirmation and subtype identification
Prenatal screening	NIPT, QF-PCR, CMA	Early fetal diagnosis
Developmental delay	Chromosomal microarray	CNV detection
Recurrent miscarriage	Karyotyping	Balanced translocation detection
Infertility	Karyotyping	Sex chromosome abnormalities
Hematological cancers	FISH, Karyotyping, NGS	Prognosis and treatment planning
Congenital anomalies	CMA, NGS	Identification of genomic abnormalities

6. Future Perspectives and Challenges

Although remarkable advances have been achieved in cytogenetic diagnostics, several challenges remain. Conventional cytogenetic techniques require skilled personnel, specialized laboratory infrastructure, and high-quality chromosome preparations. Molecular cytogenetic methods provide greater resolution but often involve higher costs and limited accessibility in low-resource healthcare settings. Standardization of laboratory protocols, quality assurance measures, and interpretation guidelines is essential for ensuring accurate and reproducible diagnostic results. Future developments are expected to focus on integrating cytogenetics with genomic, transcriptomic, epigenomic, and proteomic data to provide comprehensive molecular characterization of genetic disorders. Artificial intelligence and machine learning are increasingly being incorporated into automated chromosome analysis, image interpretation, variant classification, and clinical decision support, improving both diagnostic efficiency and accuracy. Long-read sequencing technologies, optical genome mapping, single-cell genomics, and spatial genomics represent promising innovations capable of identifying

complex chromosomal rearrangements that remain challenging for existing diagnostic approaches. These technologies may ultimately replace several conventional methods by providing comprehensive genome-wide structural analysis with unprecedented resolution. Ethical considerations surrounding prenatal diagnosis, incidental genomic findings, genetic privacy, informed consent, and equitable access to advanced genomic technologies will require continued attention. International collaboration, public education, and expanded genetic counseling services will be essential for maximizing the benefits of precision genomic medicine while addressing associated ethical and social challenges.

7. Conclusion

Chromosomal abnormalities remain among the leading genetic causes of congenital anomalies, developmental disabilities, infertility, pregnancy loss, and inherited diseases worldwide. Down syndrome continues to be the most prevalent autosomal chromosomal disorder, while other conditions such as Edwards syndrome, Patau syndrome, Turner syndrome, and Klinefelter syndrome contribute substantially to the global burden of genetic disease. Early and accurate diagnosis is fundamental for appropriate medical management, genetic counseling, reproductive planning, and long-term patient care. Conventional cytogenetic methods, particularly G-banded karyotyping, continue to provide the foundation for chromosomal analysis. However, the introduction of molecular cytogenetic techniques including FISH, chromosomal microarray analysis, MLPA, QF-PCR, non-invasive prenatal testing, and next-generation sequencing has revolutionized diagnostic capabilities by enabling the detection of increasingly subtle genomic abnormalities. These advances have significantly improved diagnostic accuracy, prenatal screening, clinical prognosis, and personalized medical management. Future progress will likely be driven by the integration of cytogenetics with genomics, artificial intelligence, single-cell technologies, and precision medicine. Continued technological innovation, multidisciplinary collaboration, expanded genetic counseling, and equitable access to advanced diagnostic services will further improve outcomes for individuals and families affected by chromosomal disorders. Consequently, modern cytogenetics will remain a cornerstone of clinical genetics, reproductive medicine, and genomic healthcare.

References

1. Asim, A., Kumar, A., Muthuswamy, S., Jain, S., & Agarwal, S. (2015). Down syndrome: an insight of the disease. *Journal of biomedical science*, *22*(1), 41.
2. Wiseman, F. K., Alford, K. A., Tybulewicz, V. L., & Fisher, E. M. (2009). Down syndrome—recent progress and future prospects. *Human molecular genetics*, *18*(R1), R75-R83.
3. Kazemi, M., Salehi, M., & Kheirollahi, M. (2016). Down syndrome: current status, challenges and future perspectives. *International journal of molecular and cellular medicine*, *5*(3), 125.
4. Caine, A., Maltby, A. E., Parkin, C. A., Waters, J. J., & Crolla, J. A. (2005). Prenatal detection of Down's syndrome by rapid aneuploidy testing for chromosomes 13, 18, and 21 by FISH or PCR without a full karyotype: a cytogenetic risk assessment. *The Lancet*, *366*(9480), 123-128.
5. Ogilvie, C. M. (2003). Prenatal diagnosis for chromosome abnormalities: past, present and future. *Pathologie Biologie*, *51*(3), 156-160.
6. Ferguson-Smith, M. A. (2008). Cytogenetics and the evolution of medical genetics. *Genetics in Medicine*, *10*(8), 553-559.
7. Shaffer, L. G., Bejjani, B. A., Torchia, B., Kirkpatrick, S., Coppinger, J., & Ballif, B. C. (2007, November). The identification of microdeletion syndromes and other chromosome abnormalities: cytogenetic methods of the past, new technologies for the future. In *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* (Vol. 145, No. 4, pp. 335-345). Hoboken: Wiley Subscription Services, Inc., A Wiley Company.
8. Shen, J. J., B. J. Williams, A. Zipursky, J. Doyle, S. L. Sherman, P. A. Jacobs, A. L. Shugar, S. W. Soukup, and T. J. Hassold. "Cytogenetic and molecular studies of Down syndrome individuals with leukemia." *American journal of human genetics* 56, no. 4 (1995): 915.
9. Polipalli, S. K., Karra, V. K., Jindal, A., Puppala, M., Singh, P., Rawat, K., & Kapoor, S. (2016). Cytogenetic analysis for suspected chromosomal abnormalities; a five years experience. *Journal of clinical and diagnostic research: JCDR*, *10*(9), GC01.
10. Ogilvie, C. M., Lashwood, A., Chitty, L., Waters, J. J., Scriven, P. N., & Flinter, F. (2005). The future of prenatal diagnosis: rapid testing or full karyotype? An audit of chromosome abnormalities and pregnancy outcomes for women referred for Down's Syndrome testing. *BJOG: An International Journal of Obstetrics & Gynaecology*, *112*(10), 1369-1375.
11. Mutton, D., Alberman, E., & Hook, E. (1996). Cytogenetic and epidemiological findings in Down syndrome, England and Wales 1989 to 1993. National Down Syndrome Cytogenetic Register and the Association of Clinical Cytogeneticists. *Journal of medical genetics*, *33*(5), 387-394.
12. Santesmases, M. J. (2014). The human autonomous karyotype and the origins of prenatal testing: Children, pregnant women and early Down's syndrome cytogenetics, Madrid 1962–1975. *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences*, *47*, 142-153.