VOLUME - 15, ISSUE - 07, JULY - 2026 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Microbiology

GENETIC DISORDERS --DEFECTS IN THE DNA MACHINERY AND REPLICATION

Dr. Raghavendra Rao M V*	Professor of Microbiology, Chairman of the National Council of India, and Senior Executive Vice President, World Academy of Medical Sciences, Netherlands (Europe).*Corresponding Author
Dr. Chinna Babu Sunkavalli	Clinical Director & Consultant Surgical Oncologist, Hiteck City Yashoda Hospital, Hyderabad, India
Dr. Daniel Finney Sankuru	Senior resident, Department of Community Medicine, Government Medical College and Hospital, Eluru, AP, India
Dr. Vijay Raj Bollapalli	Department of Special Education, Rehabilitation & Empowerment of Persons with Disabilities (CRC) Davangere ,Karnataka,India

ABSTRACT Genetic disorders are health problems that result from an abnormality in a person's genetic material. There are several types of genetic disorders. Some disorders are caused by a genetic change (mutation) in a single gene; some are caused by an abnormality in one of the chromosomes; and some are complex, involving numerous genes and influences from environmental factors. Gene editing offers hope to patients with inherited disorders. Stem cell therapy can treat genetic diseases. Genetic diseases are caused by changes or "errors" in DNA sequences. These mutations can range from tiny spelling mistakes in a single gene (like in Sickle Cell Anemia) to missing or duplicated entire chromosomes (like in Down Syndrome

KEYWORDS : Cystic fibrosis, Deafness that's present at birth (congenital), Duchenne muscular dystrophy, Hemochromatosis, Sickle cell disease.Down syndrome, Fragile X syndrome, Klinefelter syndrome, Turner syndrome.

INTRODUCTION

Long-term issues include difficulty breathing and coughing up mucus due to frequent lung infections. Other signs and symptoms may include sinus infections, poor growth, fatty stool, clubbing of the fingers and toes, and infertility in most males (1)

In epithelial cells, CFTR, an ABC protein, exhibits the properties of a chloride and anionic channel involved in a variety of physiological processes. (2)

In lower and upper airways, the intestine, pancreatic, and liver ducts, lack of functional CFTR is the major factor in determining the degree of disease expression and eventually mortality. (3)

Although cystic fibrosis is a monogenic disease, its phenotypic variability is substantial — as shown by the broad range of disease severity observed in patients with the same genotype(4)

CFTR mutations have also been described in patients with cystic fibrosis-like organ manifestations including pancreatitis, sinusitis or 'idiopathic' bronchiectasis . (5)

The introduction of prenatal genetic screening in Western countries seems to correlate with decreasing incidence in some countries. Although the incidence is decreasing, data from registries suggest that the prevalence is increasing because of improvements in survival (6)

Sickle cell disease is common in African Americans, affecting approximately 1 of 375 persons of African ancestry. Sickle cell disease is a group of inherited red blood cell disorders. People who have sickle cell disease have an abnormal protein in their red blood cells. (7)

In sickle cell anemia, the red blood cells become rigid and sticky and are shaped like sickles or crescent moons. These irregularly shaped cells can get stuck in small blood vessels, which can slow or block blood flow and oxygen to parts of the body (8)

.In the United States, most of the people with SCD are African American. About 1 in 13 African American babies is born with the sickle cell trait. About 1 in every 365 black children is born with sickle cell disease.SCD also affects some people who come from Hispanic, southern European, Middle Eastern, or Asian Indian backgrounds.(9)

The most frequent complications requiring hospital admissions for patients with sickle cell disease are painful vaso-occlusive crises and osteomyelitis. Other acute bony problems that have been described in sickle cell disease are stress fractures. (10)

Hereditary hemochromatosis is an autosomal recessive disorder with estimated prevalence in the population of 1 in 200 among patients with European ancestry, with lower incidence in other ethnic groups (11)

The gene responsible for hereditary hemochromatosis (known as the HFE gene) is located on chromosome 6 (12)

Iron overload indicates increased total accumulation of iron in the body from any cause and resulting organ damage (13)

Duchenne muscular dystrophy (DMD) is a genetic disease due to the mutation of the dystrophin gene located on chromosome Xp21. It is inherited as an X- X-linked recessive trait; however, approximately 30% of cases are due to new mutations (14)

Duchenne muscular dystrophy (DMD) is one of the most severe forms of inherited muscular dystrophies. It is the most common hereditary neuromuscular disease and does not exhibit a predilection for any race or ethnic group. Mutations in the dystrophin gene lead to progressive muscle fiber degeneration and weakness.(15)

Down syndrome (DS) is the most common genomic disorder of intellectual disability and is caused by trisomy of *Homo sapiens* chromosome 21 (HSA21). The eponym of the syndrome is from Down, who described the clinical aspects of the syndrome in 1866 (16)

Klinefelter syndrome is a genetic condition that affects males and is characterized by the presence of 2 or more X chromosomes. The clinical phenotype was first described in 1942 by American physician Dr. Harry Klinefelter (17)

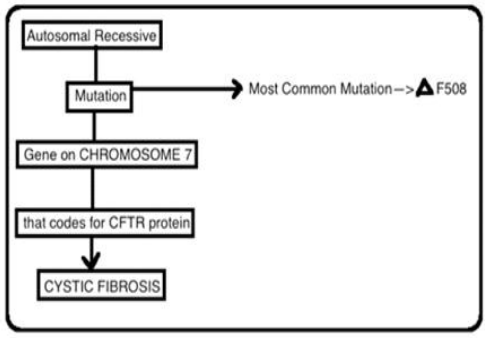
Affected individuals often present with tall stature, small testes, gynecomastia, and azoospermia. The genetic etiology—supernumerary X chromosomes, typically 47, XXY—was identified in 1959.(18)

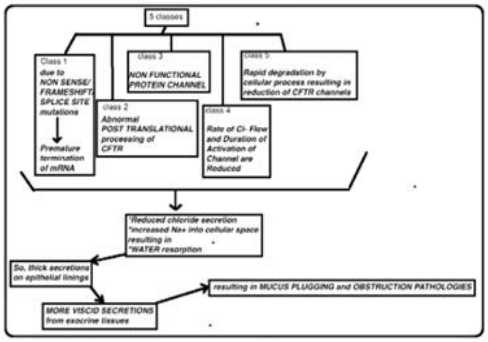
Turner syndrome (TS) occurs when the X chromosome is completely or partially missing in females. This is the only monosomy syndrome that humans can survive. TS is a relatively common type of human chromosomal aberration that occurs in 1:2,500 female live births.(19)

The features of TS were first described by Turner in 1938, pathogenicity X chromosome monosomy was identified in 1959 (20)

Monogenic disorders

- **Cystic fibrosis.**
- Cystic fibrosis affects the cells that produce mucus, sweat, and digestive juices. The thick, sticky mucus plugs up tubes, ducts, and passageways. Symptoms vary and can include cough, repeated lung infections, inability to gain weight and fatty stools. Cystic Fibrosis (CF), a genetic, life-limiting disease of Caucasians and Indians. The discovery of the Cystic fibrosis (CF) gene has paved the way for incredible progress in treating the disease. Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that encodes a cAMP-regulated anion channel. Although CF is a multi-organ system disease, most people with CF die of progressive lung disease that begins early in childhood and is characterized by chronic bacterial infection and inflammation. Cystic fibrosis (CF), a monogenic disease caused by mutations in the CFTR gene on chromosome 7, is complex and greatly variable in clinical expression. Airways, pancreas, male genital system, intestine, liver, bone, and kidney are involved. The lack of CFTR or its impaired function causes fat malabsorption and chronic pulmonary infections leading to bronchiectasis and progressive lung damage.





Pathophysiology underlying CF lung disease

Following the defective CFTR protein in the airway epithelium, chloride secretion and epithelial sodium channel regulation are damaged.

As a result, a reduction in anion secretion combined with increased sodium and water reabsorption from the ASL through the apical cellular membrane occurs. (21)

The first line of defense in the respiratory system against pathogens is blocked because of the severe reduction of mucociliary clearance.

Concomitantly, insufficient HCO3 -secretion lowers ASL pH. Acidic conditions have been shown to alter bacterial killing by reducing the activity of ASL antimicrobial peptides and ciliary movement frequency while activating deleterious proteases (22)

Overall, impaired lung innate immunity predisposes to pathogen colonization, which subsequently triggers neutrophil recruitment and proinflammatory cytokine secretion. (23)

This attempt by the immune system is in most cases unsuccessful and leads to a deleterious cycle of persistent infection combined with deregulated inflammation. Tissue destruction ensues and results clinically in chronic respiratory infection, lung function decline, and ultimately, respiratory failure. (24)

Pathogenesis of cystic fibrosis lung disease

This life-threatening genetic disorder causes a buildup of thick, viscous mucus secretions in various organ systems, most commonly the gastrointestinal, pulmonary, and genitourinary systems. (25)

A major emphasis is placed on the active transport systems that regulate the airway surface liquid (ASL) volume and, particularly, regulate the volume of the periciliary liquid (PCL) layer. A sequence is developed for CF whereby there is a depletion of the PCL that reflects the combined dysfunctions of accelerated Na(+)-dependent volume absorption and failure to secrete Cl(-). Both dysfunctions are a direct consequence of missing cystic fibrosis transmembrane conductance regulator (CFTR) at the apical membrane of airway epithelial cells. PCL depletion leads to failure of mucus transport, which is associated with persistent mucin secretion and formation of adherent mucus plaques and plugs.(26)

The Role of Cftr in Pancreatic Disease Pathogenesis

Cystic fibrosis is the most common autosomal recessive genetic disease characterized by multiorgan pathology and significantly decreased life expectancy caused by the impaired function or expression of CFTR. Due to recent therapeutic developments, the life expectancy of patients with CF has increased significantly in the past decades; however, the average age of death (usually caused by respiratory failure) is still 31.4 years (27)

A combination of decreased mucociliary clearance and an altered ion transport allows for bacterial colonization of the respiratory tract, most commonly *Pseudomonas*, *Haemophilus influenzae*, and *Staphylococcus aureus*. These pathogens cause an overwhelming inflammatory response. (28)

- Hemochromatosis
- Iron poisoning is one of the most common toxic ingestions and one of the most deadly among children. "Excess of iron is harmful to the body as it may lead to deposition of iron in organs and cause organ failure. Hemochromatosis is an iron-overload disease in which iron is directly

deposited in the tissues (Liver, spleen, heart, pancreas, and skin). An abnormal gene on chromosome 6 is linked with hemochromatosis. The amino acid tyrosine in the normal protein encoded by this gene is replaced by cysteine. This abnormal protein is responsible for excessive iron absorption from the intestine, which accumulates in various tissues, leading to their damage and malnutrition. A gene called HFE is most often the cause of hereditary hemochromatosis. Primary hemochromatosis is unusual in India.

SICKLE CELL DISEASE

The sickle mutation results in replacement of valine with glutamic acid in the 6 th position of the beta chain. The deformed RBCs obstruct small vessels, and they are prone to destruction. The life span of an RBC is 120 days, but the sickle cell lives for only 10 to 20 days. The sickle cell adheres to the walls and interferes with the flow of blood. As a result, oxygen supply to the cells is obstructed. This results in pain crises. The pain crises attacks will come without any warning signals. The blockage of capillaries of lung produce cough, chest pain, breathing problems, fever, and severe anemia. It produces a fast heartbeat. People with sickle cell disease will easily get bacterial diseases. Signs can include headache, seizure, weakness, difficulty in talking, and loss of consciousness. Because of a shorter life span and rapid RBC destruction, the patient gets jaundice.

Duchenne muscular dystrophy (DMD)

It is not only one of the most severe forms of inherited muscular dystrophies but also the most common hereditary neuromuscular disease. Sadly, no known treatment modality halts the progression of the disease; available treatment options are palliative. Affected patients usually die in their twenties due to respiratory muscle weakness or cardiomyopathy. Current therapy is centered on treatment with glucocorticoids and physiotherapy to prevent orthopedic complications. This activity illustrates the pathophysiology and current management options for DMD and highlights the role of the interprofessional team in caring for affected patients and families (29)

Multifactorial disorders

- Alzheimer's disease.Autism spectrum disorder, Cancer, Coronary artery disease, Diabetes, Migraine headaches, Spina bifida.

Autism spectrum disorder

- Autism spectrum disorders (ASD) are a heterogeneous group of neurodevelopmental disorders with social communication, social interaction, or restricted behaviors.

ASD is comorbid with other disorders including epilepsy, Rett syndrome, and Fragile X syndrome. The degree of variation in ASD phenotype caused by genetic variation has been estimated at between 40 and 90%. Specific genetic variations in ASD have been studied by measuring single nucleotide variants (SNVs), copy number variants (CNVs), and cytogenetic abnormalities (30)

How do epimutations contribute to the molecular pathogenesis of autism spectrum disorder?

The prevalence of autism has increased rapidly. Many monogenetic mutations and single nucleotide polymorphisms have been associated with autism spectrum disorders (ASD). Genetic alterations do not explain the etiology of an elevated number of ASD cases. Recent research is now focusing on the role of environmental/epigenetic factors, which by themselves and/or in combination with classical genetic factors, may be the root cause of a large number of ASDs.

Diabetes

- Diabetes is not caused by a single gene but by a complex combination of genetic and environmental factors.

It is one of the world's fastest-growing diseases, and patients suffer from cerebrovascular disease, cardiovascular disease, and peripheral vascular disease, and complications like retinopathy, nephropathy, and neuropathy. Increase mortality, blindness, kidney failure, and overall quality of life in individuals with diabetes. Clinical risk factors and glycemic management alone cannot predict the development of vascular problems; multiple genetic investigations have revealed a clear hereditary component to both diabetes and its related complications. In the twenty-first century, technological advancements (genome-wide association studies, next-generation sequencing, and exome-sequencing) have led to the identification of genetic variants associated with diabetes; however, these variants can only explain a small proportion of the total heritability of the condition.

Family and twin studies have reported 20%-80% of heritability in diabetes. First-degree relatives of people with T2DM are three times more likely to get the disease than people without a positive family history (31)

Even though diabetes from both the maternal and paternal side increases the risk of acquiring diabetes, the Framingham Offspring research reported that offspring with maternal diabetes had a slightly higher risk of impaired glucose tolerance than those with paternal diabetes (32)

Multiple twin concordance studies in T2DM found that monozygotic twins had a greater concordance rate than dizygotic twins, indicating that the condition has a significant genetic component. (33)

Genetic linkage studies

Linkage analysis is based on the principle that genetic sequences located on the same chromosome tend to be inherited together and are not separated during meiotic homologous recombination. (34)

It is typically used in family studies to determine the position of an associated variant(s) (35)

Linkage studies have successfully uncovered genetic variations that cause monogenic diseases such as MODY (36)

In 1996, using linkage analysis, major histocompatibility complex (HLA) loci on chromosome 6 were identified as genetic susceptibility loci for T1DM (37).

In 2004, the calpain-10 gene (*CAPN10*) on chromosome 2 was identified as the cause of T2DM using genome-wide screening and positional cloning (38)

TCF7L2, the now well-known T2DM gene, was mapped to chromosome 10 in a Mexican-American group in the year 1999 and has been replicated several times in T2DM genome-wide association studies (GWAS) (39)

TCF7L2 plays an important role in the Wnt/ -catenin signaling pathway and helps in regulating the expression of genes in lipid metabolism in adipocytes and glucose-induced insulin exocytosis.(40)

Chromosomal disorder

FRAGILE X SYNDROME:

Fragile X syndrome (FXS) is the most common known cause of inherited intellectual disability. It is a genetic condition that causes a range of developmental problems, including learning disabilities and cognitive impairment. Incidence:1 in 3600 to 4000 males; 1 in 4000 to 6000 females. Inheritance: It is an X-linked dominant disorder. Usually, males are more severely affected by this disorder than females. When the

mother is a carrier of the fragile X chromosome, each child has a 50% chance of inheriting it. Since females have two X chromosomes, they are less severely affected.It is a genetic disorder in which the development of individuals is affected mainly by behavior and learning abilities. It can also affect an individual's communication skills, physical appearance, sensitivity to light, noise, and other sensory information. It is the most common cause of inherited intellectual and developmental disability. People with Fragile X syndrome sometimes do not have many noticeable symptoms sometimes, and sometimes can have serious symptoms which might range from simple learning difficulties to cognitive and behavioral problems also. Fragile X syndrome can be caused by a mutation in the gene FMR1, which is found on the X chromosome. This mutation affects the individual's body in how it makes Fragile X Mental retardation protein (FMRP). Individuals with Fragile X can have intellectual problems and functioning that might affect an individual's ability to think, reason, and learn. Physical signs such as narrow face, large ears and head, reduced joint flexibility, flat feet, and forehead prominence. Behavioral, social, and emotional problems can be present along with speech and language impairment.

Chromosomal Disorders and the Genetic Basis of Down Syndrome

Chromosomal disorders are genetic conditions resulting from abnormalities in the number or structure of whole chromosomes rather than mutations in individual genes. Because chromosomes contain thousands of genes that regulate growth, development, and cellular homeostasis, alterations in chromosome number produce widespread disturbances in gene dosage and cellular function. Consequently, chromosomal abnormalities are among the leading causes of congenital anomalies, intellectual disability, infertility, and spontaneous pregnancy loss (41)

Among chromosomal disorders, **Down syndrome (DS)** is the most common viable autosomal aneuploidy and represents the best-characterized example of a numerical chromosomal abnormality. Down syndrome is primarily caused by the presence of an additional copy of chromosome 21 (**Trisomy 21**), resulting in the expression of three copies of chromosome 21 genes instead of the normal two. This increased gene dosage disrupts numerous developmental pathways and produces the characteristic clinical phenotype, including craniofacial dysmorphism, hypotonia, congenital heart disease, delayed physical growth, cognitive impairment, immune dysfunction, and an increased susceptibility to leukemia and early-onset Alzheimer's disease (42)

Aneuploidy: The Underlying Genetic Mechanism

The underlying genetic defect in Down syndrome belongs to a broader category known as **aneuploidy**, a condition in which cells contain an abnormal number of chromosomes rather than the normal human complement of **46 chromosomes arranged in 23 pairs**. Aneuploidy arises when chromosomes fail to segregate accurately during cell division, producing gametes or daughter cells with either extra or missing chromosomes. It is estimated to occur in approximately **5–10% of all human conceptions**, making it one of the leading genetic causes of spontaneous miscarriage and congenital abnormalities (42)

Forms of Aneuploidy

Aneuploidy is broadly classified according to whether chromosomes are gained or lost.

Trisomy (2n + 1) involves the presence of an additional chromosome, resulting in three copies instead of the normal pair. Clinically important viable autosomal trisomies include:

- **Trisomy 21 (Down syndrome)**
- **Trisomy 18 (Edwards syndrome)**
- **Trisomy 13 (Patau syndrome)**

Among these, **Trisomy 21** is the most frequent and compatible with long-term survival.

Monosomy (2n – 1) refers to the absence of one chromosome from a homologous pair. The only viable complete monosomy in humans is **Turner syndrome (45, X)**, in which affected females possess only one X chromosome (6-8).

Nondisjunction: The Molecular Origin of Trisomy 21

Approximately **95% of Down syndrome cases** result from **meiotic nondisjunction**, a chromosome segregation error that occurs during gametogenesis. Normally, homologous chromosomes separate during meiosis I and sister chromatids separate during meiosis II, ensuring that each gamete receives one copy of every chromosome. However, when chromosome 21 fails to segregate correctly, one gamete receives **two copies of chromosome 21**, whereas another receives none.

Genetic Mechanism Underlying Down Syndrome

Approximately **95% of Down syndrome cases** result from **meiotic nondisjunction**, a random error during gamete formation in which homologous chromosomes or sister chromatids fail to separate properly. As a result, one gamete receives **two copies of chromosome 21**, while another receives none. Fertilization of the abnormal gamete by a normal gamete produces a zygote containing **47 chromosomes**, including **three copies of chromosome 21 (47,+21)**. Because this error occurs before fertilization, every cell derived from the zygote generally carries the additional chromosome, producing **complete Trisomy 21**. The remaining cases arise from **Robertsonian translocation** or **mosaicism**, but nondisjunction remains the predominant genetic mechanism responsible for Down syndrome.

Integrated Molecular Pathway of Down Syndrome

The pathogenic sequence can be summarized as follows:

Chromosomal disorder
↓
Aneuploidy (Trisomy 21)
↓
Meiotic nondisjunction
↓
Gene dosage imbalance (≈1.5-fold increase in chromosome 21 gene expression)
↓
Overexpression of DYRK1A, APP, RCAN1, SOD1, RUNX1, ETS2, IFNARs, CBS, and miRNAs
↓
Cell-cycle dysregulation, oxidative stress, mitochondrial dysfunction, impaired neurogenesis, altered immune signaling, and apoptosis
↓
Neurodevelopmental abnormalities, congenital malformations, intellectual disability, Alzheimer's disease, immune dysfunction, and leukemia
↓
Clinical phenotype of Down syndrome

Klinefelter syndrome

It is a genetic condition characterized by the presence of 2 or more X chromosomes in a phenotypic male. The clinical features were first described in males with tall stature, small testes, gynecomastia, and azoospermia. The underlying genetic etiology—supernumerary X chromosomes—was identified in 1959. Additional X chromosomes contribute to testicular hyalinization, fibrosis, and hypofunction, often leading to hypogonadism, genital abnormalities, and infertility. Neurocognitive differences associated with Klinefelter syndrome were increasingly recognized during the

mid-to-late 20th century. Androgen replacement, along with neuropsychological and adaptive therapies, frequently supports effective medical management. In addition to infertility, individuals with Klinefelter syndrome are at increased risk for complications such as osteoporosis, metabolic syndrome, breast cancer, and autoimmune disorders. However, early diagnosis and comprehensive care, including hormonal, psychological, and educational support, can help many individuals achieve good long-term outcomes.(43)

Turner syndrome (TS)

It is also known as Congenital ovarian hypoplasia syndrome and occurs when the X chromosome is partially or completely missing in females. Its main clinical manifestations include growth disorders, reproductive system abnormalities, cardiovascular abnormalities, and autoimmune diseases. TS is highly prevalent in China. Timely diagnosis is crucial, and non-invasive prenatal DNA testing can identify TS and other diseases. Treatment of TS mainly involves administration of growth hormone combined with very low doses of estrogen to increase the patient's height
(44)

CONCLUSION

India faces a high burden of rare genetic disorders. Genetic disorders often stem from small errors in the DNA sequence with major consequences. Many diseases like cystic fibrosis and Batten disease can be traced to changes disrupting the cell's ability to build a complete, functional protein. One particularly common culprit is the nonsense mutation, where a single incorrect DNA letter inserts a premature stop signal. When the cell encounters it, protein production ends too early, leaving the body without important enzymes, transporters, or structural components. Genetic disorders originating from defects in **DNA machinery and replication** occur when cells fail to accurately copy their genome or repair damage during division.

REFERENCES

1. O'Sullivan BP, Freedman SD (May 2009). "Cystic fibrosis". *Lancet*. **373** (9678): 1891–904. doi:10.1016/s0140-6736(09)60327-5.
2. Keiser NW, Engelhardt JF (2011) New animal models of cystic fibrosis: what are they teaching us? Curr Opin Pulm Med 17:478–483
3. Ciro D, Padoan R, Blau H, Marostica A, Fuoti M, Volpi S, Pilotta A, Meyerovitch J, Sher D, Assael BM (2013) Growth retardation and reduced growth hormone secretion in cystic fibrosis. Clinical observations from three CF centers. J Cyst Fibros 12:165–169
4. Weiler, C. A. & Drumm, M. L. Genetic influences on cystic fibrosis lung disease severity. Front. Pharmacol. 4, 40 (2013)
5. Gonska, T. et al. Role of cystic fibrosis transmembrane conductance regulator in patients with chronic sinopulmonary disease. Chest 142, 996–1004 (2012).
6. Leer en español, Sickle cell in focus conference, October 10 - 11, **2019** Jamaica, West Indies
7. Mayo Foundation for Medical Education and Research (MFMER) ,**2018-2019.**
8. U.S. National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894 U.S. Department of Health and Human Services, National Institutes of Health,**2019**
9. Bahebeck, J., Ngowe, N.M., Monny, L.M., Sosso, M. & Hoffmeyer, P. **2002,** Stress fracture of the femur: a rare complication of sickle cell disease. *Revue de Chirurgie Orthopedique et Reparatrice de l'Appareil Moteur*, **88**, 816–818
10. Frenette, P.S. **(2004)** Sickle cell vas occlusion: heterotypic, multicellular aggregations driven by leukocyte adhesion. *Microcirculation*, **11**, 167–177.
11. "Hemochromatosis". Archived from the original on 2007-03-18. Retrieved 2012-10-05
12 Hsu CC, Senussi NH, Fertrin KY, Kowdley KV (June 2022). "Iron overload disorders". *Hepatol Commun*. doi:10.1002/hep4.2012. PMID 35699322.
13. Hsu CC, Senussi NH, Fertrin KY, Kowdley KV (June 2022). "Iron overload disorders". *Hepatol Commun*. doi:10.1002/hep4.2012. PMID 35699322
14. Paquin RS, Fischer R, Mansfield C, Mange B, Beaverson K, Ganot A, Martin AS, Morris C, Rensch C, Ricotti V, Russo LJ, Sadosky A, Smith EC, Peay HL. Priorities when deciding on participation in early-phase gene therapy trials for Duchenne muscular dystrophy: a best-worst scaling experiment in caregivers and adult patients. Orphanet J Rare Dis. 2019 May 09;14(1):102
15. Cai A, Kong X. Development of CRISPR-Mediated Systems in the Study of Duchenne Muscular Dystrophy. Hum Gene Ther Methods. 2019 Jun;30(3):71-80.
16. Down JLH Observations on an ethnic classification of idiots. Lond. Hosp. Rep 3, 259–262 (1866).
17. Bonomi M, Rochira V, Pasquali D, Balercia G, Jannini EA, Ferlin A., Klinefelter ItaliaN Group (KING). Klinefelter syndrome (KS): genetics, clinical phenotype and hypogonadism. J Endocrinol Invest. 2017 Feb;40(2):123-134. [PMC free article]
18. JACOBS PA, STRONG JA. A case of human intersexuality having a possible XXY sex-determining mechanism. Nature. 1959 Jan 31;183(4657):302-3
19. Boucher RC. Cystic fibrosis: a disease of vulnerability to airway surface dehydration. Trends Mol Med. 2007;13(6):231–240.
20. Pezzulo AA, Tang XX, Hoegger MJ, et al. Reduced airway surface pH impairs bacterial killing in the porcine cystic fibrosis lung. Nature. 2012;487(7405):109–113
21. Johansson J, Gudmundsson GH, Rottenberg ME, Berndt KD, Agerberth B. Conformation-dependent antibacterial activity of the naturally occurring human peptide LL-37. J Biol Chem. 1998;273(6): 3718–3724.
22. Clary-Meinesz C, Mouroux J, Cosson J, Huitorel P, Blaive B. Influence of external pH on ciliary beat frequency in human bronchi and bronchioles. Eur Respir J. 1998;11(2):330–333
23. Goldani AA, Downs SR, Widjaja F, Lawton B, Hendren RL. Biomarkers in autism. *Front Psychiatry* (2014) **5**:100. Boucher,An overview of the pathogenesis of cystic fibrosis lung disease, Adv Drug Deliv Red, 2002 Dec 5;54(11):1359-71. *JAAPA* 30(5):p 23-27, May 2017. | *DOI:* 10.1097/01.JAA.0000515540.36581.92
24. Yuk Jing Loke1, Anthony John Hannan2, and Jeffrey Mark Craig1,The role of epigenetic change in autism spectrum disorders, Front. Neurol., 26 May 2015
25. Hallmayer J, Cleveland S, Torres A, Phillips J, Cohen B, Torigoe T, et al. Genetic heritability and shared environmental factors among twin pairs with autism. *Arch Gen Psychiatry* (2011) **68**:1095–102
26. Cohen-Cymberknoh M, Shoseyov D, Kerem E. Managing cystic fibrosis: strategies that increase life expectancy and improve quality of life. *Am J Respir Crit Care Med*. 2011;183(11):1463–1471.
27. Brown, Sheena D. PhD, MSCR; White, Rachel MMSc, PA-C; Tobin, Phil DHSc, PA-C. Keep them breathing, Cystic fibrosis pathophysiology, diagnosis, and treatment,32. Bell SC, De Boeck K, Amaral MD. New pharmacological approaches for cystic fibrosis: Promises, progress, pitfalls. *Pharmacol Ther*. 2015;145:19–34.
28. Bello L, Pegoraro E. The "Usual Suspects": Genes for Inflammation, Fibrosis, Regeneration, and Muscle Strength Modify Duchenne Muscular Dystrophy. J Clin Med. 2019 May 10;8(5)
29. Zhang F, Zhang Z. Advances in the study of the diagnosis and treatment of Turner syndrome. Journal of China-Japan Friendship Hospital. 2015; 29:192-194. [Google Scholar
30. Ford CE, Jones KW, Polani PE, De Almeida JC, Briggs JH. A sex-chromosome anomaly in a case of gonadal dysgenesis (Turner's syndrome). Lancet. 1959; 1:711-713.
31. Ali O. Genetics of type 2 diabetes. World J Diabetes. 2013;4:114–123. doi: 10.4239/wjd.v4.i4.114. [
32. Kyvik KO, Green A, Beck-Nielsen H. Concordance rates of insulin-dependent diabetes mellitus: a population-based study of young Danish twins. BMJ. 1995;311:913–917. doi: 10.1136/bmj.311.7010.913.
33. Ott J, Wang J, Leal SM. Genetic linkage analysis in the age of whole-genome sequencing. Nat Rev Genet. 2015;16:275–284. doi: 10.1038/nrg3908.
34. Hattersley AT, Turner RC, Permutt MA, Patel P, Tanizawa Y, Chiu KC, O'Rahilly S, Watkins PJ, Wainscoat JS. Linkage of type 2 diabetes to the glucokinase gene. Lancet. 1992;339:1307–1310. doi: 10.1016/0140-6736(92)91958-b.
35. Vaxillaire M, Froguel P. Genetic basis of maturity-onset diabetes of the young. Endocrinol Metab Clin North Am. 2006;35:371–384, x. doi: 10.1016/j.ecl.2006.02.009.
36. She JX, Marron MP. Genetic susceptibility factors in type 1 diabetes: linkage, disequilibrium and functional analyses. Curr Opin Immunol. 1998;10:682–689. doi: 10.1016/s0952-7915(98)80089-7.
37. Song Y, Niu T, Manson JE, Kwiatkowski DJ, Liu S. Are variants in the CAPN10 gene related to risk of type 2 diabetes? A quantitative assessment of population and family-based association studies. Am J Hum Genet. 2004;74:208–222. doi: 10.1086/381400.
38. Tripathy D, Eriksson KF, Orho-Melander M, Fredriksson J, Ahlqvist G, Groop L. Parallel manifestation of insulin resistance and beta cell decompensation is compatible with a common defect in Type 2 diabetes. Diabetologia. 2004;47:782–793. doi: 10.1007/s00125-004-1393-8
39. Duggirala R, Blangero J, Almasy L, Dyer TD, Williams KL, Leach RJ, O'Connell P, Stern MP. Linkage of type 2 diabetes mellitus and of age at onset to a genetic location on chromosome 10q in Mexican Americans. Am J Hum Genet. 1999;64:1127–1140. doi: 10.1086/302316.
40. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet. 2006;38:320–323. doi: 10.1038/ng1732
41. Nagaoka, S. I., Hassold, T. J., & Hunt, P. A. (2012). Human aneuploidy: Mechanisms and new insights into an age-old problem. *Nature Reviews Genetics, 13*(7), 493–504.
42. Antonarakis, S. E., Skotko, B. G., Rafii, M. S., Strydom, A., Pape, S. E., Bianchi, D. W., Sherman, S. L., & Reeves, R. H. (2020). Down syndrome. *Nature Reviews Disease Primers, 6*, Article 9. https://doi.org/10.1038/s41572-019-0143-7
43. Sandhya J. Kadam; Stephen W. Leslie; George A. Ford., Klinefelter Syndrome, National Library of Medicine,2025, National Center for Biotechnology
44. Xiaoxiao Cui 1,2, Yazhou Cui 2, Liang Shi 2, Jing Luan 2, Xiaoyan Zhou 2, Jinxiang Han 2,,A basic understanding of Turner syndrome: Incidence, complications, diagnosis, and treatment,Intractable Rare Dis Res. 2018 Nov;7(4):223–228.