The Genetics and Pathophysiology of Single Gene Disorders in Human

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Abstract

Single-gene disorders (SGD's), also known as monogenic diseases or monogenetic disorders or unifactorial disorders, are caused by mutations in specific genes and have Mendelian inheritance patterns. These diseases alter molecular and cellular processes, resulting in a variety of clinical symptoms and sometimes abnormalities. The common single gene disorders include cystic fibrosis (CF), sickle cell disease (SCD), Huntington's disease (HD), and Marfan syndrome (MFS). CF is caused by mutations in the CFTR gene, which disrupt chloride ion transport and cause thickened mucus secretions, resulting in respiratory and digestive difficulties. SCD is distinguished by a mutation in the HBB gene, which causes aberrant haemoglobin (Hgb S), red blood cell deformation, and vaso-occlusive crisis. The production of toxic huntingtin protein damage neuronal function and progressively exacerbates motor, cognitive, and mental health issues. This happens due to increase CAG repeats in the HTT gene. The mutation in FBN1 is linked with MFS, which affects the integrity of connective tissue and results in heart issues, bones and eyes diseases. The clinical manifestations of these diseases vary widely. Therefore, understanding the genetic basis is necessary for accurate diagnosis and therapeutic strategies. Advancement in gene therapy and molecular medicines are best options for treating SGD's.

Keywords: Genetics, Pathophysiology, Single Gene Disorders, Mutations

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Introduction

The study of genetic diseases has a long history, including key achievements that have improved our knowledge of human heredity and disease. Gregor Mendel's pioneering work on pea plants in the nineteenth century established the laws of heredity and gave rise to the notion of Mendelian genetics (Furney et al., 2006). By the early twentieth century, researchers realized that same concepts applied to human features and diseases, resulting in the discovery of monogenic disorders caused by mutations in a single gene (Stranneheim & Wedell, 2016).

The severe and sometimes early-onset of monogenic diseases symptoms are extremely important in the area of human health. Diseases like Huntington's disease, sickle cell anemia, and cystic fibrosis (CF) are examples of these illnesses, which have surprisingly straightforward Mendelian inheritance patterns (Raza et al., 2023). However, in single-gene illnesses, the correlation between genotype and phenotype is not always clear. According to Scriver and Dipple, mutations in the genomes of afflicted people may not necessarily correspond reliably with clinical symptoms, as shown in metabolic illnesses such as Gaucher disease, phenylketonuria, and glycerol kinase deficiency (GKD) (Scriver and Waters, 1999). Clinical geneticists find this intricacy difficult to handle, as it challenges the conventional belief that a genotype should predict a phenotype (López-Bigas & Ouzounis, 2004).

Our knowledge of single-gene diseases has been significantly enhanced by the Human Genome Project and further developments in next-generation sequencing (National Human Genome Research Institute). The "common disease-common variant" theory was the focus on early genome research efforts on complex illnesses, but subsequent paradigm shifts have brought Mendelian diseases back into the spotlight. Similarly, the Online Mendelian Inheritance in Man (OMIM) database now has about 2,500 human genes associated with Mendelian illnesses, and many more have not yet been found. The significance of genetic research in comprehending ailment processes and creating novel therapeutics is highlighted by these disorders. Determining the molecular mechanisms of these conditions prove to be the opening of the doors for novel therapeutic and targeted medications (Crabtree, 2019).

The modes of inheritance play a crucial role in single gene disorders with manifestation of abnormalities. The four-inheritance pattern include; autosomal dominant, autosomal recessive, X-linked, and Y-linked inheritance (Oliver et al., 2021). Examples of autosomal dominant diseases are Huntington's disease and Marfan syndrome, probability of 50% transferring to offsprings (Judge and Dietz, 2005). The rate of transmission varies with high rate of abnormalities in consanguinity due to appearance of recessive traits (Lewis & Simpson, 2020). Due to

their X chromosome linked inheritance pattern men are more likely to be afflicted as compared to females. The examples include haemophilia and Duchenne muscular dystrophy (Bushby et al., 2010). The Y chromosome controls male sex traits and reproductive function cause Y-linked disease such azoospermia and Swyer syndrome in men (Singore et al., 2020). Understanding the SGD's pattern of transmission and manifestation is necessary for control and management.

Mutations

The permanent irreversible alterations in the sequence of DNA that effects the synthesis of proteins. These alterations are broadly classified into two categories, occur either in gene or whole chromosome. Mutation plays a critical role in genetic diversity and evolution but can also results genetic abnormalities. Mutation can be classified into gene mutation or chromosomes mutation.

Types of Mutations

1) Gene/Point mutation: Any alteration in the gene's nucleotide sequence is referred to as a gene mutation. Depending on the kind of genetic material alteration, these mutations can result various abnormalities. This is further categorized into various types.

i) Insertion mutation: One or more nucleotides are added to the DNA sequence during insertions. If the inserted nucleotides do not occur in multiples of three, these mutations may cause frameshift mutations. The introducing additional sequences may alter protein structure or regulatory elements, large insertions have the potential to completely alter gene function (Lumen, 2020).

ii) Deletion mutation: One or more nucleotides are deleted from the DNA sequence. Frameshift mutations, which can produce non-functional proteins, are caused by deletions that are not multiples of three, just like insertions. Gene function may be completely lost as a result of large deletions that eliminate crucial functional regions of a protein (Berdan et al., 2021).

iii) Duplication: Mutations caused by duplication of DNA fragment in which it is reinserted into the genome, is known as duplication. Depending on the location and amount of the duplication, this may result in the overexpression of certain genes or the synthesis of abnormal proteins. Gain-of-function effects can occasionally be caused by duplication (Berdan et al., 2021).

iv) Expansion mutation: Mutations in an unnatural rise in the quantity of repeating DNA sequences within a gene is known as an expansion mutation. Trinucleotide sequences for CAG are frequently used in these repetitions, which grow over typical threshold and impair gene activity. The CAG repeats occur in the HIT gene result causes Huntington's disease (Strauss, 2016).

v) Silent Mutation: A silent mutation changes a nucleotide without altering the amino acid it encodes due to the redundancy of the genetic code and do not affect protein composition, but influence processes like mRNA stability or the efficiency of translation, potentially affecting gene expression (Lumen, 2020).

vi) Missense Mutation: A single nucleotide changes results in the substitution of one amino acid for another in a protein sequence. This type of mutations alters the protein's structure and function depending upon the properties of the substituted amino acid. For instance, replacing a hydrophobic amino acid with a hydrophilic one could drastically change the protein's folding and functionality (Berdan et al., 2021).

vii) Nonsense Mutation: A single nucleotide change converts a codon encoding an amino acid into a stop codon that leads to premature termination of protein synthesis to truncated or nonfunctional proteins. Duchenne muscular dystrophy is an example of this type (Lumen, 2020).

vii) Frameshift Mutation: This results from the insertion or deletion of nucleotides that are not in multiples of three. This disrupts the reading frame of the genetic code, causing all downstream amino acids to be incorrectly translated. Frameshift mutations often produce nonfunctional proteins, as the sequence after the mutation becomes meaningless (Lumen, 2020).

2) Chromosomal Mutation: Chromosomal mutation alters the structure or number of chromosomes. These mutations can have a greater impact on an organism than gene or point mutations because it affects many genes at a time. Chromosomal mutations can be classified into two main types:

a) Change in Chromosome Numbers

Errors during cell division (meiosis or mitosis) can cause changes in chromosomal number (Potapova & Gorbsky, 2017), which can lead to either:

i) Aneuploidy: The abnormal number of chromosomes (Selmecki et al., 2010). Examples include:

a) Monosomy (2n-1): The absence of one of a pair of chromosomes.

b) Trisomy (2n+1): The presence of an additional pair.

ii) One or more than one additional sets of chromosomes that can be found prominently in plants but also detectable in animals as well are called Polyploidy.

b) Change in Chromosome Structure

Changes in chromosomal structures due to breakage, sometime rearrangement or fusion of chromosome have a profound impact on genetic and cellular functions (Burssed et al., 2022). Some of these changes are listed below.

i) **Deletion**: Deletion of a genes or chromosomes cause the elimination of information present in genetic material which resultantly impair the function of genes or suppression of particular phenotypic (Salem, 2016).

ii) Duplications: In duplication, segment of a chromosome makes its extra copy of certain genes which depends upon the location and size. This may cause overexpression of genes, problems in developmental phenomenon and sometime leads to serious diseased conditions (Jackson et al., 2018).

iii) Inversions: Failure or breakage of chromosomal fragments cause reorientation in either way. Interestingly, it leads to either loss or gain of genetic information which may cause disruption in gene control (Hardy et al., 2010). This happens especially during meiosis to cause

infertility and genetic abnormalities.

iv) Translocations: When a segment or gene translocate from one chromosome to another in a reciprocal or non-reciprocal term, this is known as translocation phenomenon (Javadekar & Raghavan, 2015).

a) Reciprocal: In this segments exchange occurs between two non-homologous chromosomes that might impair the function or regulatory mechanisms of components.

b) Non-reciprocal: A reciprocal exchange of chromosomal segment that result in gene dysregulation is called non-reciprocal translocation (Burssed et al., 2022).

v) Insertions: Insertion of chromosomal fragment from one to another chromosome that led to alteration in normal gene sequencing and function. These changes put a significant impact on genes and may cause cancer progression, serious disorders, and boost evolutionary mechanisms (Potapova & Gorbsky, 2017; Salem, 2016).

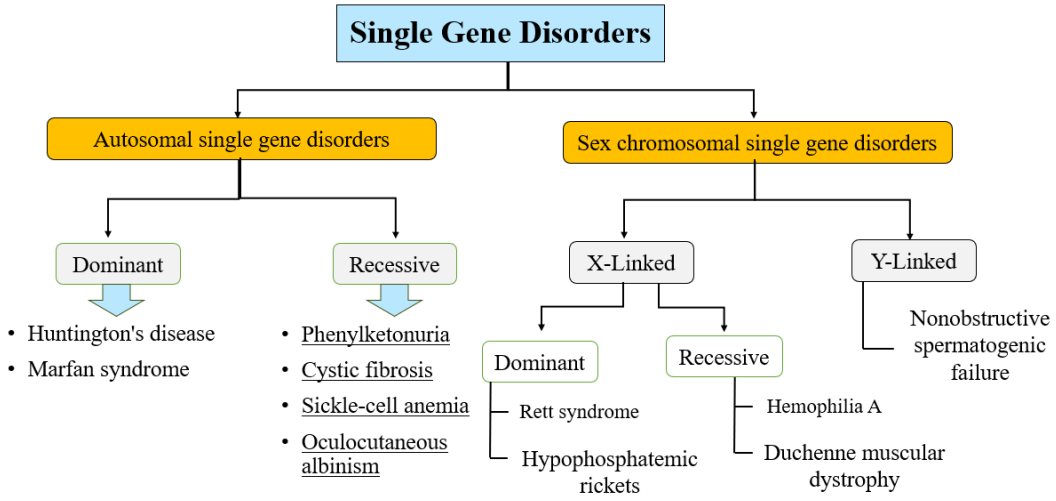

Fig. 1: Types and examples of single gene disorders.

Similarly, single gene disorder may be either X linked or Y linked which exhibits various mode of inheritance as autosomal dominant or recessive and sex chromosomal dominant or recessive. Figure 1 shows the types and few examples of single gene disorders.

Functional Impacts on Protein Synthesis and Cellular Processes

Various mutations at different loci, multiple types and extent phenomenon puts various types of effect from minimal or no effect to highly significant disruption of protein synthesis and cellular functions (Goldenzweig & Fleishman, 2018).

1. Effects on Protein Synthesis

Alterations in genetic instructions due to mutations changes the patterns of translation, production of faulty or non-functional proteins. It is because of disruption of active site of an enzyme or breakage in binding domain or a receptor due to mutational changes, render the protein functions potentially. For example, cystic fibrosis (CF) is a notable case occurs due to mutations in CFTR gene. In this case, chloride ion transporters get badly affected (Saint-Criq & Gray, 2017). Whereas, on the other hand, mutations lead the proteins to overexpression or novel functions for detrimental effects. For instance, mutation acquired by oncogenes lead to uncontrolled cellular proliferation or additionally, interference with normal functions to exacerbate the mutational impact (Zhang et al., 2024).

2. Effects on Cellular Processes

Disruptions in cellular mechanisms, pathways and processes, lead to impaired cell cycle regulation, metabolic activities, and cellular communication due to mutation in signaling molecules. For example, EGFR gene mutation is associated with alteration of cell signaling pathways lead to cancer development, TP53 gene mutation leads to cell division and tumor development and in context of metabolism, PAH gene cause phenylketonuria (Restrepo et al., 2023).

Impact on Genetic Stability

Mutations that destabilize and lead to acquire additional mutations such as mutations in DNA mismatch repair system cause microsatellite instability and cancerous Lynch syndrome (Tamura et al., 2019).

Conclusively, mutations have a crucial impact in genetics and are known as double-edged sword in the realm of genetics. Because they had been proved not only to be the drivers of evolution and genetic versatility but also had a great role in disease management and cellular processes.

Molecular Mechanisms

Exceptionally varied molecular or Mendelian mechanism explains fundamental and clinical importance of dominant and recessive traits. Dominant trait is defined as the development in offspring of certain characters of one parent while contrasting characters of the other parent remain unexpressed (Magrinelli et al., 2021). Both dominant and recessive pose a significant impact on each other; for example, a mutation is

enough to cause diseased state with insight of either negative or positive. Haploinsufficiency (deficiency of the mutant protein) cause dominance of another trait to make dominant negative that interferes with normal protein and lead to toxic gain of function. In contrast to dominant, most of the time, naturally recessive are loss of functions either completely or partially. Likewise, in haploinsufficiency, any of the dominant of recessive trait, if they express, they may exert a very different phenotypic impression to an organism for physical or physiological role. If they are not haploinsufficient, dominant and recessive alleles would be quite distinct to each other Dominant genes often suppress the expression of recessive alleles.

Pathophysiology of Common Single Gene Disorders

Single-gene disorders (SGOs) result from genetic mutations and following Mendelian inheritance patterns. These mutations impair normal molecular and cellular processes, resulting in unique clinical presentations. Examples include cystic fibrosis (CF), sickle cell disease (SCD), Huntington's disease (HD), and Marfan syndrome (MFS). CF is caused by mutations in the CFTR gene, which encodes a chloride channel required for ion balance in epithelial cells (Spitalieri et al., 2016). CFTR dysfunction affects a variety of organs, most notably the lungs and digestive tract, with pulmonary impairment the leading cause of mortality. CFTR's widespread influence on ion channels and metabolic pathways highlights its significance in systemic problems (Fernandez Fernandez et al., 2018). Sickle cell disease (SCD) is a disease of hemoglobin that occurs due to mutation in α or β chain. Annually 300,000 newborn cases of SCD have been reported. In SCD the life span of red blood cell reduces, oxidative damage and poor erythropoiesis occur. In HbE β Thalassemia the amount of oxygen supply especially in babies depleted. Beta thalassemia intermedia, characterized by high level of hemoglobin. All these monogenic disorders have huge impact on human health (Kato et al., 2018; Sahu et al., 2023).

Overview of Molecular and Cellular Basis of Each Disease

Cystic fibrosis (CF): It is an autosomal recessive disease that occurs due to CFTR gene, on chromosome number seven. In this case, the most prevalent changes in gene occurs in ΔF508 which leads to disruption of proteins folding and ion transporters (Farinha & Callebaut, 2022). This cause thick lungs secretions, intestines and pancreas due to airway blockage, respiratory failure and persistent inflammation of tissues. In conditions can cause morbidity and mortality. The symptoms include respiratory infections, cough with mucus, and pancreatic insufficiency, diabetes and infertility in males

Sickle Cell Disease (SCD): SCD is also an autosomal recessive condition due to single mutation in HBB gene present on chromosome 11. In this case, valine substitute the glutamic acid in hemoglobin chain, thus results in hemoglobin S (HbS). This cause hemytic anemia and other circulatory issues (Tebbi, 2022). Vasculopathy also emerges due to reduction in nitric oxide that is caused by the hemolysis. The symptoms are painful vaso-occlusive crises, chronic anemia, splenomegaly, and increased susceptibility to infections. Rarely, organ damage such as kidneys and liver and stroke

Huntington's Disease (HD): An autosomal dominant condition, in which neurodegeneration occurs due to enlarges CAG trinucleotide repeats in HIT gene on chromosome number 4. More precisely, neuronal dysfunction particularly in the striatum and brain due to huntingtin protein aggregation results in motor, cognitive and behavioral disorders. Early signs include mood changes, irritability, and cognitive decline. Progression leads to involuntary movements (chorea), severe motor dysfunction, and dementia (Reetz et al., 2015).

Marfan syndrome (MFS): Another autosomal dominant disease of connective tissues. These conditions appear when mutation occurs in fibrillin-1 gene (FBN1) on chromosome 15 that affects fibrillin-1 protein. This affects actually, weakens the extracellular matrix and puts elasticity in fiber rich tissues of aorta, skin and eyes at risk. However, symptoms vary depending upon hereditary and environmental factors. The symptomology includes, tall stature, long extremities, joint hypermobility, lens dislocation. Rarely, cardiovascular issues such as aortic root dilation and dissection (Du et al., 2021).

Management and Treatment

Gene Therapy and Molecular Medicine Approaches

Gene therapy offers significant potential for treating inherited disorders like cystic fibrosis. Difficulty associated with cystic fibrosis in achieving efficient delivery and adequate expression of therapeutic genes arises from various factors, including the broader defensive mechanisms of the airways and molecular-level obstacles to effective cDNA delivery (Yan et al., 2019).

Gene Therapy in Cystic Fibrosis

Cystic fibrosis (CF) is an excellent candidate for gene therapy because of its single-gene mutation origin, recessive nature, accessible target tissue (lungs), and early treatment window. Restoring 5-10% of normal CFTR activity can repair damaged chloride channels (Farinha & Matos, 2016). Two means of delivery have been investigated: viral vectors, which easily integrate CFTR cDNA into host cells but elicit immunological reactions, and cationic liposomes, which are less immunogenic but struggle with adequate gene expression. An optimal CF gene delivery method must have adequate carrying capacity, avoid immune detection, prevent inflammation, and maintain long-term CFTR expression. The challenges include overcoming thick mucus, addressing inaccessible basolateral receptors on airway cells, and assuring the safety of inflamed lungs. Developing a vector that balances efficiency, low immunogenicity (Gonçalves & Paiva, 2017).

2 Genetic Variations

The Human Genome Project (HGP) was completed in 2003, found roughly 20,500 human genes, 99.5% of which are common to all humans. The remaining 0.5% is used to account for individual variables such as physical characteristics, illness susceptibility, and treatment response (Engku Alwi, 2017). Genetic variations, particularly single nucleotide polymorphisms (SNPs) and structural variants (SVs), have an

impact on illness risk, progression, and treatment results. Genes regulating pharmacokinetics (PK) and pharmacodynamics (PD) are important in drug development. The Pharmacokinetics describes a drug's absorption, distribution, metabolism, and excretion (ADME), which determines its availability at target locations. The Pharmacodynamics studies how pharmaceuticals affect the body, particularly their interaction with target cells (Tibbitts et al., 2016). Genetic differences can cause imbalances in Pharmacokinetics and Pharmacodynamics, affecting therapeutic effectiveness as shown in Fig. 2.

Pharmacogenomics (PGx) combines genetic testing with environmental and lifestyle variables to provide personalized therapies. Tailoring drugs to individual genetic profiles can improve treatment outcomes with minimizing side effects (Fig. 3).

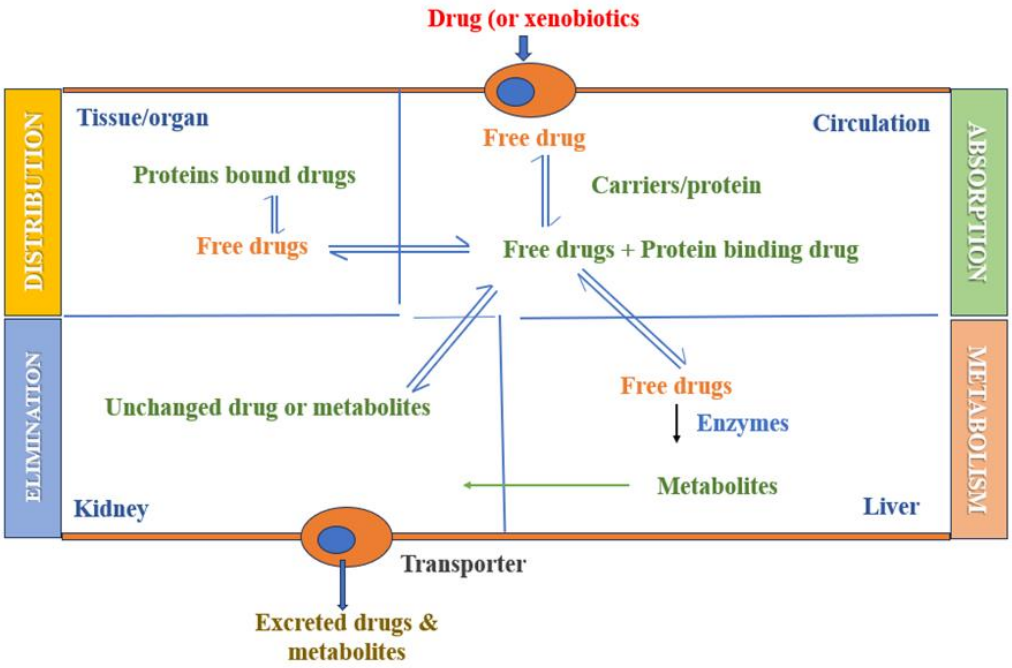

Fig. 2: The pharmacokinetics process

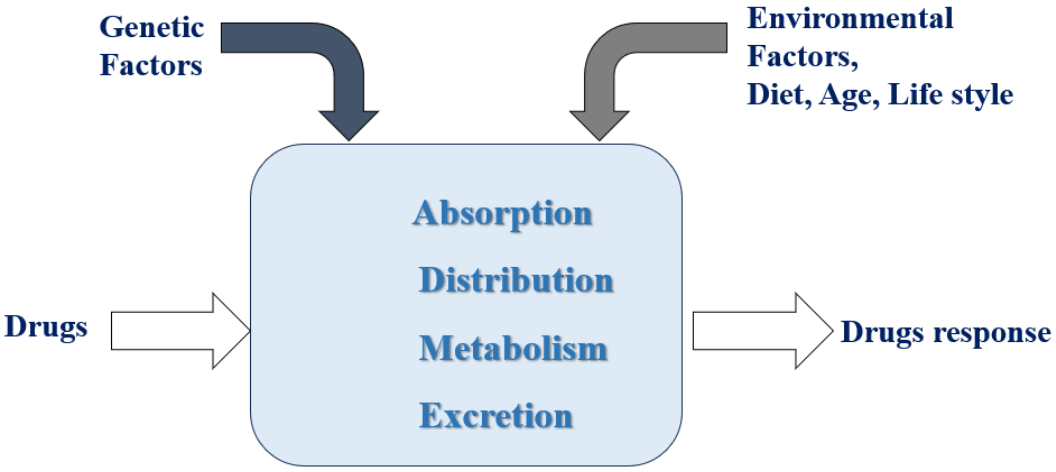

Fig. 3: Factors responsible for variations in drug response.

3. Recent Advances in Research and Therapeutics

3.1 CRISPR and Gene-editing Advancements

Past couple of decades achieved advanced genome editing tools to address human genetic diseases include mega-nucleases, zinc finger nucleases (ZFN), transcription activator-like effector nucleases (TALENs), clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated nuclease system (Cas) (Siva et al., 2021).

CRISPR/Cas system was initially used for prokaryotic then transformed into effective mammalian genome editing tool. Streptococcus pyogenes (SpCas9), a type II CRISPR Cas nuclease in prokaryotes, has been the most extensively researched. This method was later evolved into the first instrument for genome editing in mammalian cells (Javed et al., 2018). Single-guide RNA (sgRNA) assists SpCas9 for target specific recognition via binding to Cas protein and specifies genomic editing site.

CRISPR/Cas-based methods have been utilized across a wide range of cell types and organisms. For therapeutic applications targeting monogenic diseases, CRISPR offers the possibility of being implemented either in vivo or in vitro (Javed et al., 2018; Siva et al., 2021).

3.1.1 Recent Advances in CRISPR/Cas Technology

Since the use of SpCas9 for mammalian genome editing, several Cas9 proteins have been produced, including smaller variations such as SaCas9 from Staphylococcus aureus and Nme2Cas9 from Neisseria meningitidis. Smaller proteins, such as SpCas9 (~4.3kb), are more effective and suitable for in vivo delivery (Wu et al., 2020).

Advances in CRISPR/Cas9 technology have broadened its possibilities beyond genome editing. Nuclease-deficient Cas9 proteins, such as dCas9, can attach to particular genomic areas without producing double-strand breaks. CRISPR activators (CRISPRa) and inhibitors (CRISPRi) were developed by combining dCas9 with transcriptional regulatory domains to control gene expression (Javed et al., 2018; Wu et al., 2020). By combining dCas9 with enhanced green fluorescent protein (EGFP), researchers may examine repetitive or non-repetitive DNA sequences. David R. Liu's team's innovations, such as base editing, have enabled accurate nucleotide transitions through the use of cytidine base editors (CBEs) and adenine base editors. Similarly, improvements in the prime editors (PEs), allow for all 12 base-to-base conversions as well as targeted insertions or deletions without the need of DSBs (Dai et al., 2024).

3.1.2 Applications of CRISPR in Genetic Diseases

CRISPR/Cas systems have been employed extensively in research to explore target genes in various contexts, including genome modification, splicing, transcription, and epigenetic regulation. Such tools are crucial in terms of study, diagnostic or addressing the genetic disorders, some infectious diseases and uncontrolled growth phenomenon like cancer and tumor along with some of the immunological conditions (Heidenreich & Zhang, 2016). Such as, CRIPR/Cas9 is strong tool for studying human genome to modify it using genetic engineering skills and refrain from diseased conditions as well as for research purposes. This section highlights recent applications of CRISPR/Cas technology in developing disease models and treating genetic conditions both in vitro and in vivo (Xiong et al., 2016).

3.2 Stem Cells and Regenerative Medicine

In regenerative medicine, stem cells provide a unique potential to treat diseases for which there are currently only symptom-managing treatments. Haemoglobin polymerisation and sickle-shaped red blood cells result from a single nucleotide change in the β-globin gene, which substitutes valine for glutamic acid at position 6 and causes sickle cell disease (SCD). Haemolysis, anaemia, and vaso-occlusive problems are brought on by this mutation. Allogeneic haematopoietic stem-cell transplantation (HSCT) is the only curative treatment available. It has a 95% disease-free survival rate in paediatric patients and has demonstrated remarkable success rates. The disease phenotype may be reversed in the majority of patients with donor cell replacement, with some displaying mixed chimerism. Because myeloablative regimens are hazardous, nonmyeloablative conditioning is necessary for adults. However, limited results were observed in early trials. Nonetheless, in preclinical animals, sirolimus and low-dose radiation have demonstrated promise in causing long-term chimerism and reversing the sickle cell phenotype.

3.3 Emerging Therapies and Experimental Treatments

Researchers are looking for new treatments for the uncommon neurodevelopmental condition known as Angelman syndrome (AS). There are many hallmarks of AS such as Developmental delays, intellectual impairment, seizures, ataxia, and motor abnormalities, which affects 1 in 15,000 people. It is caused by the UBE3A gene on maternal chromosome 15 becoming inactive and being silenced in neurones. The paternal allele is rendered inactive by this silencing, which is brought on by a long non-coding RNA (UBE3A-ATS). Interstitial deletions, mutations, uniparental disomy, or imprinting abnormalities are the most common causes of AS. Reactivating the suppressed UBE3A allele may offer a potential therapeutic solution, making AS a promising target for precision medicine. Recent advancements in gene therapy, particularly in the development of effective delivery methods, offer hope for a cure. Despite the lack of a comprehensive disease-modifying therapy, new gene and cellular treatments are being investigated. Although they may mainly relieve symptoms, these methods seek to restore the cellular pathways that UBE3A deficiency has disturbed. They also have a great deal of promise for new therapeutic developments.

Ethical and Social Considerations

In the past decade there are many issues such as ethical, legal, and social issues related to genetic testing and research have emerged regarding about genetic counseling, patient consent, and reproductive options. Rare diseases impact over 300 million individuals globally; 72% of these are hereditary, and many are untreatable. In order to identify the risk of transmission a detail family history is necessary. Large-panel tests and other population-based genetic carrier screening are becoming more common and provide more thorough insights into genetic risks, but they also make counselling even more difficult due to lack of prior experience. The professional organization and expert geneticists now advise providing genetic screening to all women especially in pregnancy conditions. The insufficiency of skilled genetic counsellors raises issues about who should give advice and how to ensure its implementation. Significant ethical questions about data privacy and familial disclosure are also brought up by genetic testing. Particularly when genetic information may influence the medical conditions of others, it is crucial to strike a balance between patient confidentiality and the possible health effects on family members. Although the American Medical Association stresses secrecy, it nevertheless recognises that in some situations, the obligation to notify family members may take precedence over personal privacy. The need for ethical and legal standards in genetic counseling is evident from the differing court rulings on the extent to which doctors are required to disclose genetic information to at-risk relatives.

Conclusion

Single gene disorders (SGDs) are major concern of genetic abnormalities caused due to mutation in a single gene. The genetic disorders are transfer from parents to offspring. The inheritance of transmission may be X linked, Y linked, autosomal. Further, compromise of dominant and recessive disorders. The common genetic disorders are Cystic fibrosis and Huntington's disease are the result of particular genetic defects. Accurate diagnosis and therapeutic strategies are necessary for control and management of genetic abnormalities.

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