Understanding Human Genetic Diseases through Potential Animal Models and its Therapeutic Perspectives

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Abstract

Animal models are essential for elucidating the genetic and molecular mechanisms underlying human genetic diseases, providing critical insights into disease progression and therapeutic development. Rodents, particularly genetically engineered mouse models such as knockout and transgenic mice, are extensively utilized to investigate genetic disorders, including cystic fibrosis (CFTR mutations), Duchenne muscular dystrophy (DMD mutations), and Huntington's disease (HTT mutations). Zebrafish (Danio rerio), with its transparent embryos and approximately 70% genetic similarity to humans, have proven to be pivotal in modeling cardiovascular and neurodegenerative diseases. Non-human primates offer a distinct advantage for exploring complex conditions such as Alzheimer's disease, which is associated with APOE and PSEN1 gene mutations. There are many major pathways, such as Wnt/β-catenin, PI3K/AKT, and MAPK. These pathways are studied in different models to elucidate their roles in different diseases such as cancer, metabolic disorders, and neurodevelopmental diseases, etc. Additionally, some other models (CRISPR-edited) are being employed to create precise working of them through CRISPR-Cas-9 technology for study of human disorders such as cystic fibrosis. Moreover, some animal models have been created to study conserved pathways in cancer. Furthermore, zebrafish and mice models are being used to study preclinical drug testing to assess the efficacy and safety of novel therapeutics. It is concluded that this chapter has a diverse collection of animal models to be employed in human genetic research in advancing the field of precision medicine.

Keywords: Animal Models, Human Genetic Diseases, Therapeutics, Precision Medicine

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Introduction

Genetic diseases have a significant burden on global health that have genetic disorders such as cystic fibrosis and sickle cell anemia, cancer, diabetes, and many other diseases (Umair, 2024). These are complex diseases and it is very difficult to understand their disease mechanisms without animal model studies because of ethical issues (Bredenoord et al., 2017). Therefore, animal models are very crucial to study disease pathogenesis, genetic variations, and therapeutic plans with and without model organism (Kanakarajan et al., 2024).

In addition to animal models, researchers can repeat their experiments to study different aspects of genetic diseases before the application in human beings. Genetically engineered mice are widely used to study genetic similarity to humans, their reproductive cycles, and some other manipulation (Crispo et al., 2024). Some scientists are working on CFTR mice models to study mutations in cystic fibrosis (Sankar et al., 2024).

Another model is Zebrafish to study genetic diseases at embryos level that have a rapid development system and similar genetic with human genome (Gautam et al., 2024). These are being employed to study cardiovascular diseases and neurodevelopmental disorders. Additionally, primates have 90% genetic similarity with humans to study Alzheimer's disease and AIDS etc. Other models are mimics to study in laboratory for pulmonary and gastrointestinal disorders (Bhardwaj & Nain, 2021).

Some major pathways (PI3K/AKT and MAPK) are very important to study in different genetic disorders such as cardiovascular diseases, diabetes, AIDS etc., (Bryan et al., 2009). Animal models have been developed to study MCEP2 mutations in Rett syndrome while TP53 mutations in different cancers.

Animal models have been created to study comparative genomic analyses for different diseases that have conserved pathways and explored already in genetic disorders. It's very easy to compare evolutionary differences and similarities to design specific drugs for particular targets. Moreover, these days scientists use animal models (Zebrafish and mice) to study preclinical drug development, its efficacy, toxicity, and pharmacodynamics (Kanakarajan et al., 2024).

It is important to remember that variations in genetic models and their physiology and disease symptoms are challenges in the real world. However, advancements in genome editing, bioinformatics, and systems biology may improve these models to be reliable for future research. Therefore, this chapter explores the diverse range of animal models employed in human genetic research and their advancements to study the genetic and molecular basis of human disorders and their drugs.

1. Human Genetic Disorders/Diseases

There is a broad range of human genetic diseases that arise from alterations in the genetic codes such as sickle cell anemia and many others. These diseases are big threats for the world. Therefore, we must work on these to discover their molecular mechanisms and pathways and then finally to identify drug targets and preventive plans (Bredenoord et al., 2017; Kanakarajan et al., 2024; Umair, 2024).

There are many diseases that are associated with single gene mutations such as cystic fibrosis. It is caused by mutations in the CFTR gene that is a deletion at a particular position, therefore it is very easy to design target drugs for them, but their mechanisms and pathways identification is compulsory, and it needs a mice model. Another example is a sickle cell anemia that has a change in HBB gene that causes problems in red blood cells to deform into a sickle shape and impair oxygen transport. Thirdly, Huntington's disease is another crucial neurodegenerative disorder that is caused by a change in CAG repeats in the HTT gene that produces a toxic protein in the brain. These developments need particular animal models to study them, instead of in human beings directly because of ethical issues (Bredenoord et al., 2017; Hocking et al., 2021; Kanakarajan et al., 2024).

Firstly, polygenic and multifactorial disorders are very complex and have multiple gene interactions to study these diseases/disorders (Schork, 1997; Visscher et al., 2021). Type 2 diabetes is involved in many critical mutations such as TCF7L2, PPARG and SLC30A8 etc. to disrupt their normal functions. Secondly, cardiovascular diseases such as atherosclerosis are influenced by genetic variations such as APOE, LDLR, and PCSK9 etc. to disturb the normal functions. Thirdly, cancer is a multifactorial disease with a lot of mutations such as TP53 and BRCA1/2 to develop tumorigenesis. These mutations are being produced by many causative factors such as x-rays, gamma rays and ultrasonic rays (Schork, 1997; Visscher et al., 2021). However, advancements in genome-wide association studies are helping to explore the molecular mechanisms.

There are two types of human chromosomal disorders such as structural or numerical changes such as Down syndrome. It is called trisomy 21, in which an extra copy of chromosome at 21 positions led to intellectual disabilities and increases the risk of many other disorders such as heart defects. Second one is turner syndrome in which an X chromosome in females is lost. There are many symptoms such as short stature, infertility, and cardiovascular diseases (Cohen, 1975). It is due to errors in meiosis or mitosis during cell division.

In addition to epigenetic disorders, which are associated with alterations in gene expression regulation rather than changes in the DNA sequence such as Rett syndrome, is linked to mutations in the MECP2 gene to disrupt the normal regulation of chromatin and gene expression. In another disease, Prader-Willi and Angelman syndromes, there is a loss or dysfunction of genes on chromosome 15 (Van Vliet et al., 2007; Boissonnas et al., 2013; Visscher et al., 2021).

Therefore, advances in sequence technologies such as GWAS and RNA sequence technologies have opened new doors for the treatment of genetic disorders. Many diseases/disorders will be resolved in near future with the help of these technologies as well as animal models. Many other technologies such as gene therapy approaches such as the delivery of drugs on the target of functional mutations via viral vectors are being investigated for treating these disorders such as cystic fibrosis and huntington disease, etc.

2. Genetic Mechanisms of Genetic Disorders

Genetic mechanisms and pathways are always essential to study genetic disorders. These disorders have several molecular processes that lead to dysfunction at the cellular and organismal levels. All these levels have many variations that need to be identified to better understand their genetic mechanisms as well as signaling pathways. These pathways regulate cell growth, survival, and differentiation during the development of such disorders to develop therapeutic strategies (Van Vliet et al., 2007; Boissonnas et al., 2013).

First of all, Wnt/β-catenin signaling pathway that is crucial to regulate cell proliferation, differentiation, and tissue homeostasis etc. While dysregulation of this pathway leads to colorectal cancer. This cancer is associated with many mutations such as APC, AXIN1, and CTNNB1 etc. that initiate Wnt signaling pathway to develop tumorigenesis. Many other disorders follow this pathway to develop different neuro-disorders (Bryan et al., 2009; Bhardwaj & Nain, 2021; Ahmad et al., 2024).

The PI3K/AKT/mTOR pathway regulates cell survival, metabolism, and growth in different tumors and cancers (Cohen, 1975; Bryan et al., 2009; Ahmad et al., 2024). The dysregulation of this pathway is associated with mutations in the critical drivers' proteins, such as PI3K that lead to uncontrolled cell growth. Similarly, alterations in this pathway can play a role in type 2 diabetes. Additionally, this pathway is also associated with Alzheimer's disease that contributes to dysfunction and neuronal degeneration in the latter stages.

Another important pathway is MAPK signaling pathway regulates cell division, differentiation, and response to extracellular signals in different genetic disorders (Schork, 1997; Bryan et al., 2009; Boissonnas et al., 2013; Ahmad et al., 2024). This pathway is dysfunction by the mutations in their drivers to lead various cancers such as lung cancer, etc. Additionally, this pathway is associated with noonan syndrome and costello syndrome.

The Notch signaling pathway regulates cell fate decisions that are associated with different cancers, such as leukemia (Blank et al., 2008; Perdigoto & Bardin, 2013). Some important proteins, i.e, NOTCH1 contain mutations that lead to heart diseases and cancers. This pathway is also associated with neurodevelopmental disorders such as Alagille syndrome, cardiac diseases, hepatic issues, and skeletal muscle problems. Similarly, the DDR pathway is involved in genomic instability that is associated with variations in BRCA1, BRCA2, ATM and CHEK2 genes to double-strand breaks and single-strand lesions leads to breast and ovarian cancers (Groelly et al., 2023).

The NF-κB signaling pathway regulates immune responses, inflammation, and cell survival. This pathway is associated with autoimmune and inflammatory disorders, such as rheumatoid arthritis and Crohn's disease. Therefore, activation of NF-κB is associated with these conditions. The creation of new animal models will highlight the mechanisms of these conditions as well as identification of targets for therapeutic strategies (Oeckinghaus et al., 2011).

TGF-β signaling pathway is well known to regulate cell growth, differentiation, and immune responses as NF-κB signaling pathway has done. Therefore, the mutations in TGF-β signaling are associated with different cancers, cystic fibrosis, and inherited diseases, i.e. Marfan syndrome and Loeys-Dietz syndrome. It is concluded that TGF-β dysfunction will increase fibrosis, abnormal vascular development, and developmental of cancers as well as degenerative diseases in human beings (Wells, 2000).

3. Innovative Applications of Animal Models in Genetic Studies

The animal models are generally based on selection and experimentation on animals having physiological, anatomical, functional and genetic similarities. Also, the conditions are ensured to be under complete control to record the single variable of interest while keeping all others as constant as possible. The animals used in these studies or experimentation, although have similarities yet, do not have the same genetic disorders as in humans. For this purpose, different techniques are employed to induce such genetic changes in the animals to obtain similar results and approach for therapeutic purposes or for general examinations to record the possible effects of mutations.

The animals have long been used in scientific research with different objective including but not limited to medicine and biological research (Barré-Sinoussi & Montagutelli, 2015). The animal models serve as basic tools for understanding or studying the basics of biological process also including therapeutic, toxicological and pathogenesis studies (Brayton et al., 2018; Wagar et al., 2018; Meyerholz et al., 2020) and translational studies (Beck & Meyerholz, 2020). The animal models helped to clarify the key processes and underlying disease mechanisms (Zeiss et al., 2017; Dawson et al., 2018; Beck & Meyerholz, 2020). The type of animal models that have been opted over time possess huge variations ranging from laboratory animals to large animals. Each of which has its own advantages and limitations (Beck & Meyerholz, 2020) in studying various variables under observation. Over time, scope, application and types of animal models have been refined, and new approaches have been introduced.

Animals in general yet mammals in particular have been part of scientific research and animal models to understand the key mechanism of physiological processes and related functions. In the twentieth century, rodents, particularly rats and mice, have been used as animal models. Later, through application of biotechnology, new animals were introduced for example Dolly the sheep was developed using single cell nuclear transfer techniques and presented the opportunity to develop transgenic large animal models (Tan et al., 2016; Meyerholz et al., 2020). Moreover, recently genome editing technique has created ease in developing large animal models and introducing new variations (Kalds et al., 2019; Krishnamurthy et al., 2019; Moon et al., 2019). Although transgenic rats were developed in 2009, yet, the efforts were employed to develop transgenic animals including chicken, cats, rats, rabbits, dogs, pigs, goats, sheep, cattle, zebrafish and non-human primates (Ericsson et al., 2013).

The mouse models have been used in identifying and studying the basics of many human diseases, including cancers, neurodegenerative disorders, diabetes, metabolic and hormonal disorders (Rosenthal & Brown, 2007; Simmons, 2008; Beck & Meyerholz, 2020). The mouse has a high gene homology with human (Barré-Sinoussi & Montagutelli, 2015).

However, other animals and insects have also been used in these studies, whichever presents the closest similarities to humans. The nine-banded armadillo has been used as a spontaneous animal model in studying leprosy (Ericsson et al., 2013). The horses have been used as large animal model to understand the spontaneous occurrence and lungs remodeling the asthma in humans (Bullone & Lavoie, 2020). The RSV infection in infants was explored through the animal model using newborn lambs (Sitthicharoenchai et al., 2020). Validation of non-invasive ultrasound for pulmonary edema was performed through animal modeling (Grune et al., 2020). The animals were developed and refined for the natural model to present similar susceptibility to a disease (McGill et al., 2019). For studying social bond's neurobiology, as a natural model monogamous prairie has been used. (Bales, 2011; Ericsson et al., 2013). Cell cultures or organoids were used as in vitro models which are used for cellular studies to understand basic mechanism and for preliminary studies as these require small sample size yet the genetic and environmental complexities (Chandra et al., 2019) may render hindrance in complete understanding of the mechanism as the internal environment and life span exposures acts differently when compared to in vitro studies which only yields preliminary or basic mechanism.

4. Animal Models for Human Genetic Disorders

In humans, nearly 7000 rare genetic diseases have been reported (Pinnapureddy et al., 2015) which presents several challenges in studying these diseases. In such cases, animal models become more important to understand the mechanism of these diseases.

The histocompatibility complex locus HLA-B27 in humans increases susceptibility to autoimmune conditions. The transgenic rats with HLA-B27 gene insertion (Taugor et al., 1999) have been known to immunocompromised and hence were used as animal models for studying the MHC related disorders.

The animal models for adult-onset neurodegenerative diseases have been used for understanding molecular pathogenesis of frontotemporal dementia, Parkinson's disease, amyotrophic lateral sclerosis and Alzheimer's disease (Dawson et al., 2018). Although the polygenicity and lack of causal alleles were considered as barriers in understanding basic mechanism of Alzheimer's disease risk yet single nucleotide polymorphisms were located in open chromatin of immune cells particularly in monocytes and the macroglia and macrophages also presented similar enrichments (Tansey et al., 2018).

Sheep model have been implemented to study the disorders such as hemophilia (Porada et al., 2010; Porada et al., 2011), inherited cataracts (Morton et al., 2013), achromatopsia (Banin et al., 2015), and many others (Pinnapureddy et al., 2015). The sheep models have been used for studying juvenile neuronal ceroid lipofuscinoses disorders of humans as the mutations in 13 CLN genes have been reported as causing similar mutations in sheep model and other animals have been observed (Pinnapureddy et al., 2015). Also the Meckel syndrome, a rare, lethal, genetic disorder, Tay-Sachs disease or GM2 gangliosidosis variant B, and Gaucher disease, a lysosomal storage disorder, have been studied through sheep model (Pinnapureddy et al., 2015).

5. Therapeutic Perspectives

The implications of animal models in all fields of medicine and biomedical research are the key indicators of the use of animal models from a therapeutic perspective. The concept of comparative medicine is based on the idea that numerous animal species have similarities with humans in physiology, behavioral and functional characteristics (Ericsson et al., 2013). This leads to the use of animal models in studying infectious diseases, genetic disorders, behaviors, immunological studies and even ecology.

The mice were used in the efforts of humanization of animal's models. In this case the mice were developed with an entire human immune system by implanting mice with peripheral blood leukocytes or fetal lymphoid tissue having spontaneous severe combined immunodeficiency. These mice, after refining, were used in studying hematopoiesis, infectious disease, basic immunology and autoimmunity (Shultz et al., 2012; Ericsson et al., 2013). Likewise humanized mice for human organs, such as liver, were used in studying viral hepatitis and drug metabolism using mice model (Yoshizato et al., 2012). Genetically engineered mice have been used in drug development (Webster et al., 2020).

Cancer cell lines have been used as in vitro animal models in biomedical research. Likewise, xenograft cancer model, using any of the techniques, either ectopic or orthotopic in immunocompromised rodents, has been extensively used in cancer studies. This also provides opportunities for in-vivo trials. Moreover, chemically induced cancer in rodents has been used for preparation of animal models. While genetically modified rodents for cancer have also been used as animal models (Bibby, 2004; Cekanova & Rathore, 2014; Ruggeri et al., 2014). Animal models have a tremendous role in drug development (Mukherjee et al., 2022) along with the roles in understanding the basic mechanisms of the diseases and disorders. The choice of animal models is of prime importance in these studies.

Conclusion

The monogenic and polygenic diseases or syndromes in human populations have been identified and reported for a considerable time. Monogenic inheritance is usually easy to understand as these follow simple Mendelian inheritance patterns. Yet, polygenic and mutational changes causing several disorders need more attention to understand the root cause of the disease. For rare genetic disorders, particularly, it becomes important to have animal models for understanding the basics of the diseases and identify the therapy well before its reappearance in the human population. The animal models, in all terms spontaneous, natural or in vitro cell culture, serve the purpose, and each has its own advantages and limitations. It reveals the fact that animal's models, including small and large animals, have been extensively used in understanding the basic mechanism and remain helpful in identifying therapeutic perspectives, including drug development.

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