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Animals in Human Genetics Research: Models, Applications, and Ethical Considerations

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ABSTRACT

Animal models serve as crucial research tools in human genetics research by combining scientific knowledge from laboratory findings and medicine. Biological study models while also providing the potential to create new treatments. Other species, such as rats, along with zebrafish and non-human primates, offer unique advantages when used in combination with mice in genetic studies, despite mice have been the conventional leaders due to their small size and ease of genetic modification. Rats offer better abilities in scientific studies due to their larger body size, which facilitates extensive experimental tests. These tests enable investigations of complex diseases, such as neurodegenerative disorders, cardiovascular diseases, and metabolic disorders. CRISPR-Cas9 gene editing tools have expanded the diversity of rat models, enhancing their value as more accurate disease research models. Using animals in human genetic research poses several challenges to be addressed. The three primary issues that the debate on the use of animals in scientific research is based on include the differences in biology with the various species and the ethical issues, and the expenditure of keeping the animals as models of research. The ethical factors applied in all the animal studies presented in this review have followed the established ethical principles, such as the 3Rs (Replacement, Reduction, and Refinement), to ensure humane treatment and scientific responsibility. The use of animal models, especially rats, remains significant in a holistic study on human genetic disorders and the advancement of innovative treatment procedures. The particular aim of this review is to offer a comprehensive description of the nature, merits, and demerits of the regularly used animal models in human genetic studies to help researchers in choosing the best models to use in their studies.

Keywords: *CRISPR-Cas9, Animals, Rat model, Ethical, Zebra fish*

1. Introduction

The development of human genetics over the past several decades has occurred at a rapid pace, driven by CRISPR-Cas9 gene editing technology and advancements in next-generation sequencing and bioinformatics tools. Advances in technology have allowed scientists to decode genetic sequences from the human genome and identify the causes of certain diseases, which, in turn, have resulted in the development of specific medical therapies. Scientists have made significant progress in their study, but different essential questions about gene function and heredity, significant improvement in their research, but essential questions about gene function, hereditary patterns, and disease processes still await resolution [1]. Human subject testing in direct experiments is generally always unviable both ethically and practically, thus necessitating alternative models of research [2]. Biomedical science has relied significantly on animals as research surrogates for centuries, and their role in genetic studies has grown exponentially over modern history. Experiments on animal models, such as those conducted by Gregor Mendel using peas, and current applications of transgenic mice have provided vital information regarding genetic principles that operate across species, including humans [3-5]. Mice work perfectly well for studying intricate genetic diseases since they share 99% genetic homology with human protein sequences. Genetic studies on zebrafish and fruit flies are greatly advantaged by their rapid production cycles and transparent embryonic exposure, as well as their well-mapped genomes, which facilitate large-scale genetic testing operations [6-9]. Translational medicine heavily relies on animal models, as they offer invaluable support in the creation of medical applications. The process of scientific approval requires gene therapies and genetic medications to go through testing in animals as an initial step towards determining their safety record and efficacy before conducting human trials [10-16]. Experimental treatments for Duchenne muscular dystrophy in canine and cystic fibrosis in pigs have yielded results that progress toward clinical trials for evaluation. Medical advancements are largely reliant on these animal experiments, as their absence would cause significant complications for patients seeking treatment alternatives [17].

Genetic experimentation with animals generates conflicting debates between researchers and scientists [14], [18-20]. Experiments on animals have sparked constant debates regarding their ethical impact on animal suffering, alongside the moral value of animal species, and the threats of unforeseen outcomes due to genetic alterations [19-27]. The "3Rs" regulatory framework, founded on Replacement and Reduction, and Refinement, endeavors to minimize the use of animals, but animals continue to encounter constant ethical challenges. New advances in technology that incorporate organoids, along with AI simulations and in vitro techniques, raise questions about the role of animals in genetic research [3]. The review discusses how animal models are critical to human genetics research, particularly in clinical and biotechnological applications, while evaluating their ethical implications [28, 29].

Both scientific benefits and ethical considerations enable us to make more informed choices regarding the connection between animal research and human genetic advancement.

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2. Major Animal Models in Human Genetics

2.1. Mouse (Mus musculus)

The genetic similarity between mice and humans, at approximately 85%, combined with the availability of highly effective genetic tools such as transgenic and knockout technologies, as well as CRISPR-Cas9, makes them the primary mammalian model for research [30]. Numerous studies for cancer and neurodegenerative diseases, as well as cardiovascular disease and immune system studies, have relied extensively on their utility [31]. Mouse embryonic stem cells allow scientists to perform sophisticated genetic procedures by coupling conditional knockouts with humanized disease models to study rare diseases. The little rodent family Mus musculus plays a critical role in human genetics research by allowing scientists to expand their understanding of genetic function, as well as disease representation and therapeutic progress [32-35]. Mice are an important model organism for biomedical research primarily due to their resemblance to human DNA and their short reproductive cycle and well-defined genomic sequence. Mice play critical research roles in genetic studies due to their capacity to facilitate gene function analysis. The integration of transgenic techniques and gene knockout technologies allows researchers to study how various genes influence normal and disease-related physiological processes [36].

The CRISPR-Cas9 gene editing tool, designed for controlled genome manipulation, provides researchers with improved tools to investigate disease-associated genetic mutations in mice. Mice research has played a crucial role in the investigation of genetic characteristics responsible for causing cancer, diabetes, neurodegenerative, and cardiovascular diseases [37]. Researchers develop mouse models that mimic human genetic diseases to investigate disease progression and evaluate therapeutic possibilities in the laboratory. Alzheimer's disease research using mouse models has yielded critical insight into amyloid plaque development and tau protein activities, thereby contributing to drug discovery [31, 36, 38].

Epigenetics, as well as gene-environment interaction research, is supported by research that has been done using mice [39]. Research using mice has demonstrated that environmental exposures, such as diet, in addition to mental stresses and toxins, alter genetic expression patterns that lead to many complicated health issues. Research findings have direct implications for individual patient care practices, as well as population health intervention strategies [38].

2.1.1. Advantages of Using Mice in Genetics Research

Experiments using mice as model organisms possess a number of beneficial traits because these animals have almost 85% gene similarity with human beings. Studies on genetic inheritance become more effective due to the mice reproduction rate in addition to their short lifespan. Scientists gain the advantage of a completed mouse genome because it facilitates both comparisons with other genomes as well as precise functional analysis [40, 41]. Scientists can carry out targeted studies of gene function through their access to various genetic research models, including knockout, knock-in, and conditional gene expression models [31]. The cost and maintenance aspects involved in mouse research make them better than large mammalian models, thereby allowing extensive genetic study programs. The mouse model remains crucial for augmenting human genetics research, as it generates a wealth of information regarding gene functions, disease processes, and insights into treatment discovery. The significant contributions of mice outweigh their limitations since their research advances humanity despite differences between human and mouse physiological and immunological reactions [42, 43]. The advancement of genetic engineering technologies and computational modelling systems enhances the use of mouse models in biomedical research. Researchers leverage the benefits of mouse models to transfer genetic information from the laboratory to clinical applications, resulting in improved human health outcomes [44, 45]. A rundown of Mus musculus (Mouse) characteristics for human genetics research appears in Table 1. Basics of human genetics utilize Mus musculus to improve many study fields, as indicated in the ensuing table.

Table 1. Summarizing key aspects of Mus musculus (Mouse) in human genetics research.

Aspect	Mouse (Mus musculus)
Genetic Similarity to Humans	~85% of the mouse genome is similar to the human genome
Role in Neurological Research	Models for neurodegenerative diseases (e.g., Alzheimer's, Parkinson's), neurological disorders (e.g., autism, schizophrenia), and brain development
Reproductive Research	Used in studies on fertility, pregnancy, embryonic development, and stem cell research
Infectious Disease Research	Models for a variety of diseases (e.g., influenza, tuberculosis, HIV/AIDS) and immune responses
Metabolic and Cardiovascular Research	Used to model obesity, diabetes, heart disease, and atherosclerosis
Genetic Manipulation	Well-established genetic tools (e.g., knock-out, knock-in, CRISPR-Cas9) for creating specific gene mutations
Developmental Biology	Studies on early development, organogenesis, and genetic pathways governing development
Cost and Complexity	Relatively inexpensive, short lifespan (2-3 years), and well-established protocols for research
Ethical Concerns	Ethical considerations are present but less intense than for primates due to smaller cognitive capacity
Behavioral Studies	Used for studies of anxiety, social behavior, memory, and cognition

2.2. Rat (Rattus norvegicus)

Rats are a typical model for various scientific studies on cardiovascular health and brain activity, along with behavioral tests. Science at an increased complexity is achieved through rats' larger size compared to mice. Genetic manipulation of rats advances through recent improvements in genome editing technology [46]. The coupling of cognitive capacities and socially engaged behaviors in rats

renders them desirable research subjects for addiction and metabolic disease and neurophysiology research because these behaviors closely mimic human behavioral patterns. Since the advent of biological and genetic research, Rats (Rattus norvegicus) have demonstrated their worth as potent model organisms [47].

The union of thoroughly documented behavioral traits with in-depth physiological data and their augmented sizes compared to mice makes rats ideal subjects for sophisticated medical disease analyses. New CRISPR-Cas9 genome editing tools have boosted the status of rats as experimental animals for neurobiological research and studies of cardiovascular disease and metabolic disorders, and patterns of drug responses. The use of rats in human genetics studies comes under scrutiny regarding their advantages and limitations, and potential advancements within this discipline in this review [48]. Studies of human genetics, in large part, rely on animal models for investigating genetic mechanisms and developing therapeutic options, as well as research into disease mechanisms. Rats are better than mice as a mammalian model for certain research purposes due to their superior performance characteristics. The use of rats enhances translational application-based research because they have a physiological relationship with humans that primarily influences cardiovascular and neurological functions [49]. The assessment centers on rat participation in human genetics and their utilitarian applications, along with the challenges that researchers encounter when using these subjects.

2.2.1. Genetic and Physiological Advantages of Rats

Disease modeling research is aided by rat subjects since their cardiovascular system exhibits close similarities to human physiology, while their renal system and metabolic processes also show similarities with human biology. Rats, due to their large body size, enable precise surgical treatments and pharmaceutical applications, making them ideal for complex neuroscience and cardiovascular clinical studies [47-49]. Rats have sophisticated social behavioral patterns and cognitive functions, which make them the best model of research for schizophrenia and depression studies when examining addiction [50-52]. Genetic tools in the past worked better in mice, but with modern genome-editing techniques, gene modification was possible in rats, which made them increasingly popular.

2.2.2. Applications of Rats in Human Genetics Research

Scientists widely employ rats as biological models to study human psychiatric diseases in combination with neurodegenerative disorders. Investigation of genetically modified rats has provided critical data on the mechanisms by which genetics influence cognitive capacities, social behavior, and memory. Scientists apply rat models for studying both amyloid-beta accumulations and loss of dopaminergic neurons as the major characteristics of these degenerative brain conditions [43, 53, 54]. Thus, rats are used as research models to examine how neurobiology and genetics collectively generate substance abuse disorders. Suggested studies using rats as essential models for examining conditions such as hypertension, along with diabetes and obesity, are based on the fact that these conditions have significant genetic influences. Their greater vasculature and metabolism enable i.e. Hypertension Research: Spontaneously hypertensive rat (SHR) models assist scientists in understanding the genetics of blood pressure control, Diabetes and Insulin Resistance: Genetic rat models like the Zucker diabetic rat are instrumental in learning about Type 2 diabetes and metabolic syndrome and Atherosclerosis and Heart Disease: Rats are used as models to study lipid metabolism and genetic susceptibility to cardiovascular disease. Rats serve significantly in pharmacogenetics and toxicology studies since they possess similar drug metabolic processes as humans, thereby prompting scientists to identify genetic variations in drug response that aid in the formulation of personalized treatment measures [55, 56]. Scientists utilize rats to comprehend hereditary drug reaction susceptibility, hence creating drug use guidelines for human populations. Even though there are rat cancer models, they still provide researchers with vital information regarding how genetic factors, as well as epigenetic factors, influence tumor development. Studies conducted using rats investigate breast cancer susceptibility and determine the impact of hormones on tumor growth. Test subjects of genetically altered rats give researchers vital information regarding genetic changes that lead to gastrointestinal cancers.

2.2.3. Limitations and Challenges of Using Rats in Genetics Research

The advent of CRISPR-based genome editing tools has introduced a vast improvement in genetically available tools for rats, significantly expanding their previously limited supplies. Longer gestation periods and higher resource requirements in rats translate to increased costs for large-scale genetic examinations. While numerous inbred stocks have been established for mice, genetically altered rats are still expanding their available models. The biological similarity of humans and rats does not always ensure that findings from research will translate directly into human health conditions [43, 54]. CRISPR gene editing technology, along with other innovations, will increase the application of rats to human genetic research. Researchers struggle to employ some promising disease-modelling approaches, such as creating rats with humanized genes and immune systems. The integration of genomic techniques along with transcriptomic techniques, along with epigenomic techniques allows investigators to investigate intricate traits and disorders in rat subjects. Sophisticated behavioral test techniques combined with artificial intelligence-based testing offer an avenue to ascertain the genetic origins of neuropsychiatric illnesses [43]. Stem cell therapy and organ regeneration investigation occur through genetic modification research conducted on rats. Rats continue to be a valuable research model because they enable scientists to acquire information regarding neurogenetics as well as cardiovascular diseases and metabolism, and

pharmacogenetics. Biomedical research will benefit from improved outcomes through advances in gene-editing technology and multi-omics system solutions, which will enhance research potential [46, 48]. Rats will continue to play their vital role in the transfer of genetic findings to clinical application through technical and ethical advancement. The table below outlines Rattus norvegicus (Rat) behavior in human genetics research (see Table 2).

Table 2. Summarizing the key aspects of Rattus norvegicus (Rat) in human genetics research.

Aspect	Rat (*Rattus norvegicus*)
Genetic Similarity to Humans	~90% of the rat genome is similar to the human genome
Role in Neurological Research	Models for neurodegenerative diseases (e.g., Parkinson's, Alzheimer's), brain injury, and psychiatric disorders (e.g., anxiety, depression)
Reproductive Research	Studies on reproductive health, gestation, embryonic development, and stem cell research
Infectious Disease Research	Models for diseases such as HIV, tuberculosis, and respiratory infections, and immune response studies
Metabolic and Cardiovascular Research	Used to study metabolic diseases (e.g., diabetes, obesity), heart disease, hypertension, and stroke
Genetic Manipulation	Advanced genetic tools for creating transgenic models (e.g., knock-out, knock-in)
Developmental Biology	Important in studying organ development, cellular differentiation, and genetic regulation of development
Cost and Complexity	Relatively inexpensive, medium lifespan (2-3 years), and widely used in research due to well-established protocols
Ethical Concerns	Ethical considerations exist but are generally less controversial than for primates, with acceptable standards in place for humane treatment
Behavioral Studies	Used for studying learning, memory, cognition, addiction, and social behavior

2.3. Zebrafish (Danio rerio)

Zebrafish have become crucial organisms for studying developmental genetics, as well as organogenesis and genetic diseases. Since their embryos are transparent and development is rapid, scientists find these organisms convenient to study gene expression as well as mutagenesis studies [57]. The drug screening process conducted using zebrafish models is especially advantageous for cardiovascular diseases and neurodegenerative disorders since these organisms breed in large numbers while producing genetically modified lines rapidly. Human genetics research is increasingly employing the zebrafish (Danio rerio) organism due to its numerous genes shared with humans, which develop rapidly and have clear, transparent embryos [58]. The combination of these unique qualities makes zebrafish a handy resource for studying gene functions while also allowing for abilities in studying diseases in a human-like fashion, along with testing potential therapeutic agents. Zebrafish act as critical organisms that will enable scientists to investigate the behavior of genes along with disease mechanisms. Genetic comparison identifies human zebrafish orthology, which occupies approximately 70% of genes, allowing researchers to study conserved genetic pathways that govern development and disease formation. High-throughput genetic screening within zebrafish labs will enable scientists to identify genes associated with cardiovascular diseases and neurodevelopmental disorders, and cancer conditions [57-59]. Developmental biology is one of the significant scientific advantages of employing zebrafish as a model organism. The study of organogenesis and the impact of genetic mutations on embryonic development becomes easy because zebrafish embryos are transparent throughout external development [60]. The findings of these experimental studies made scientists realize the nature of congenital disorders along birth defects more clearly. Zebrafish research yields valuable information regarding nervous system genetic disorders. The modeling of Parkinson's disease, Alzheimer's disease, and epilepsy in zebrafish allowed scientists to identify novel genetic factors along with possible drug targets. Studies on blood diseases get major impetus by employing zebrafish models that investigate leukemia and anemia. New drug discovery profits a lot from experimenting on zebrafish as model organisms. Zebrafish-based chemical screening helps scientists to screen thousands of compounds for therapeutic uses in a single experiment [61]. This has proven especially useful in identifying drugs for uncommon genetic disorders.

2.3.1. Advantages of Using Zebrafish in Genetics Research

The features that make zebrafish suitable for human genetics studies are that they have approximately 70% genetic similarity with humans, including genes associated with human diseases. Due to their transparent nature, zebrafish embryos allow scientists to view developmental dynamics as well as cell motions in real time [62]. Zebrafish embryos accelerate their development process such that major organs are formed within the first 24-48 hours, which facilitates faster genetic studies. The reproductive capacity of a single pair of zebrafish remains at high levels every week since they produce numerous embryos. The research tools that include CRISPR-Cas9 morpholino knockdown and transgenic methods provide accurate genetic modification techniques in zebrafish research [63, 64]. The expenses needed to maintain Zebrafish laboratory populations are less than what is required for mammalian models so researchers can carry out extensive research. Zebrafish are essential model animals for studying human genetics, with distinct advantages that enhance the utility of conventional mammalian models, such as mice. Progress in genetic research relies on studies using zebrafish, which facilitate better advances in developmental biology and disease modeling, and drug discovery. Zebrafish will play an even more prominent role in the study of human genetics and therapeutic discovery due to ongoing advances in genetic engineering technology [65].

Here's a table 3 summarizing the key aspects of *Danio rerio* (Zebrafish) in human genetics research.

This table outlines the key uses and characteristics of zebrafish in human genetics research.

Table 3. Summarizing the key aspects of *Danio rerio* (Zebrafish) in human genetics research.

Aspect	Zebrafish (*Danio rerio*)
Genetic Similarity to Humans	~70% of human genes have a counterpart in zebrafish; many conserved pathways
Role in Neurological Research	Used to study neurodevelopment, neurodegenerative diseases (e.g., Alzheimer's, Parkinson's), and brain function
Reproductive Research	Zebrafish are used in studies on early development, gene expression during development, and reproductive biology
Infectious Disease Research	Models for bacterial and viral infections, including tuberculosis, malaria, and Zika virus
Metabolic and Cardiovascular Research	Zebrafish models are used to study heart development, cardiovascular diseases, and metabolic disorders like diabetes and obesity
Genetic Manipulation	High efficiency in genetic manipulation using CRISPR/Cas9, transgenics, and gene knockdown techniques
Developmental Biology	Zebrafish embryos are transparent, making them ideal for live imaging studies of early development and organogenesis
Cost and Complexity	Inexpensive, short lifespan (3-4 months), and high reproductive output, making them ideal for large-scale genetic screens
Ethical Concerns	Ethical concerns are relatively low due to the small size and developmental similarities to humans, though guidelines still apply
Behavioral Studies	Used to study behavior, sensory processing, and learning, especially in relation to vision, movement, and social behavior

2.4. Fruit Fly (Drosophila melanogaster)

Fruit flies illustrate considerable importance in promoting our understanding of heredity processes alongside developmental processes and nervous system diseases, despite being far from human evolution [66, 67]. Fruit flies have short lives, but have clearly defined genomic information that allows researchers to utilize them economically for massive genetic studies. Research done on Drosophila acts as the epicenter for the identification of Parkinson's and Alzheimer's disease pathways, along with enlightening scientists regarding crucial epigenetic and chromatin transformation mechanisms [67, 68]. The genetics field of research depends on the workhorse organism of Drosophila melanogaster as an anchor organism throughout the past 100 years. In the early 20th century, Drosophila came into view in the work of Thomas Hunt Morgan, which later provided enormous amounts of knowledge related to the formation of genetic inheritance and disease simulation. Its fundamental body organization allows Drosophila to act as a perfect research model for human genetics research due to evolutionary genetic affinities towards human populations [68, 69].

2.4.1. Genetic Advantages of Drosophila melanogaster

Drosophila takes ten to twelve days to complete its life cycle, thereby facilitating rapid genetic studies between consecutive generations of offspring. One female Drosophila lays hundreds of eggs, which are sufficient for statistical data for research. The genetic study and mutation research is easier with Drosophila as it has only four pairs of chromosomes [70, 71]. The full sequence and thorough scientific analysis of the Drosophila genome facilitate the analysis of gene function. Transgenic, RNA interference (RNAi), and CRISPR-Cas9 genome editing are three gene modification methods available to scientists that enable them to make efficient methods of producing gene modifications. In his work on genetics in Drosophila, Morgan discovered sex inheritance functions that led to the development of the chromosome theory of inheritance [72, 73]. Scientists laid down connected genes and genetic recombination in their early experiments using Drosophila. Scientists using Drosophila discovered the Hox gene cluster, which delineated pivotal developmental pattern mechanisms later found to be present all over vertebrate bodies. Biologists' study of segmentation genes in Drosophila produced valuable information on human embryonic development [74, 75]. Over 75% of human disease-causing genes can be traced to similar counterparts in Drosophila. Drosophila serves as a model system for research in three prominent neurodegenerative disorders, like Alzheimer's and Parkinson's, and Huntington's diseases. Oncogenes and tumor suppressor genes, along with cell signaling pathways, have all benefited from Drosophila cancer clinical studies [76-78]. Drosophila circadian rhythm studies revealed genetic elements responsible for timing patterns that researchers later used to develop therapies for sleep disorders in humans. Research on Drosophila synaptic function and neurodegeneration trends has led to greater insight into mental illness and brain disease.

2.4.2. Limitations of Drosophila in Human Genetics

The lack of circulatory system activities, combined with adaptive immunity and multicellular organization, such as lungs and kidneys, hinders Drosophila from reproducing all human physiological activities [79, 80]. There are differences between flies and human beings regarding both control components and epigenetic control, even in cases of genomic conservation. Genetic findings in Drosophila need mammalian experiments for medical applications in human beings. Drosophila melanogaster remains one of the most important model organisms for human genetic research, despite certain limitations [81-83]. The union of rapid reproduction time and effective genetic design capacity, combined with intact biological pathway function, renders Drosophila melanogaster the ideal organism for fundamental genetic studies and research on human diseases. The ongoing advancement in DNA manipulation technology continues to expand the research potential of Drosophila, enabling it to maintain its crucial role in future biomedical research [84, 85]. The following table 4 gives an overview of

key elements involved in Drosophila melanogaster (Fruit Fly) research for human genetics purposes. A comprehensive overview of the human genetics research role of Drosophila melanogaster is found within this table.

Table 4. Summarizing the key aspects of *Drosophila melanogaster* (Fruit Fly) in human genetics research.

Aspect	Fruit Fly (Drosophila melanogaster)
Genetic Similarity to Humans	~60% of human genes are conserved in fruit flies; many basic genetic pathways are shared
Role in Neurological Research	Used to study neurodegenerative diseases (e.g., Alzheimer's, Parkinson's), circadian rhythms, and synaptic function
Reproductive Research	Studies on sex determination, fertility, and genetic inheritance
Infectious Disease Research	Models for viral infections, such as dengue and Zika virus, and bacterial pathogenesis
Metabolic and Cardiovascular Research	Fruit flies are used to study metabolic pathways, obesity, and aging, as well as genes involved in cardiovascular diseases
Genetic Manipulation	High ease of genetic manipulation using RNAi, CRISPR-Cas9, and transgenic techniques for gene function studies
Developmental Biology	Key model for studying embryogenesis, gene regulation during development, and organogenesis
Cost and Complexity	Inexpensive, short lifespan (10-12 days), and large numbers of offspring, making them ideal for genetic screens and high-throughput studies
Ethical Concerns	Ethical concerns are minimal due to the simple anatomy and short life cycle of fruit flies
Behavioral Studies	Used to study learning, memory, sensory processing, and behavior in relation to genetics and neurobiology

2.5. Non-Human Primates (e.g., Macaques, Marmosets)

The shared basic link between non-human primates and humans in terms of physiology and genetics makes them tremendously valuable for research on complex brain functions and neurological disorders, and genomic intervention strategies. Due to ethical issues as well as costly maintenance, their use continues to remain strictly regulated [86]. Such modeling techniques drive medical research, particularly in infectious disease research to aid AIDS and the new coronavirus vaccine, autism spectrum studies, and organ transplantation research. Macaques, as well as marmosets, are also essential primates in the clinical research of human genetics. The evolution between the two primates is human like and therefore these primates are very useful in enabling scientists to study genetic disease, as well as the neurobiological functions and complex traits. The extension of human genetic correspondences in NHPs makes them important for translating laboratory knowledge into human therapy, compared to other model species [87].

2.5.1. Genetic Advantages of Non-Human Primates

The genetic composition of NHPs intersects with human DNA at the 93 to 98 percent level which results in more effective disease modeling outcomes [88]. Their brain structure along with their immune mechanisms and metabolic pattern closely resemble human neuroanatomy. The high-level learning capabilities along with social behavior and intellectual capability of NHPs, make them ideal subjects to study neurological as well as psychiatric disorders. Genome-editing technology CRISPR-Cas9 offers researchers the capability of creating genetically engineered primate disease models for human medicine studies. NHPs' developmental time frame parallels human development, which allows researchers to examine genetic disorders that emerge with age [89, 90].

2.5.2. Contributions to Human Genetics

The Neurological and Psychiatric Disorders (NHPs) have proven indispensable in studies of Alzheimer's, Parkinson's, and Huntington's diseases, as they possess a mature brain anatomy. Using the NHP models of autism spectrum disorders and schizophrenia, research helps to discover the core genetic factors behind the disorders [91, 92]. HIV/AIDS and tuberculosis, and malaria combined have received key insights from NHPs' studies. Through research on how primates cope with genetic predispositions in conjunction with their immune system reactions, scientists become better equipped to understand human disease resistance. Atherosclerosis research, as well as obesity and diabetes in primates, has revealed genetic elements at play in these diseases [89, 90]. Scientists utilize NHPs for medical research to examine how lipids function within the body as well as to research insulin resistance. The progress in research on infertility and in vitro fertilization, as well as fetal development, depends on NHP models. The investigation of primate embryonic stem cells yields crucial information for the development of novel medical treatment techniques.

2.5.3. Limitations of Non-Human Primates in Human Genetics

NHP-based research raises ethical issues related to animal well-being that need intense regulatory control. This type of research involves harvesting NHPs at a far greater expense and requires significantly extended experimental periods compared to both mouse and fruit fly models. The genetic and environmental features of Earth primates are very different from those in inbred rodent models so experimental outcomes have more variability. Scientists continue to advance genome editing methods in NHPs despite the techniques being challenging to employ and less efficient compared to rodent models [90]. Non-human primates are better than humans in human genetics studies due to their identical genetic backgrounds with human beings and complementary physiological functions. Researchers still find NHPs useful due to their extensive applications in the research of neurological diseases, as well as infectious and metabolic diseases in biomedical research. Genetic engineering advancements result in increased non-human primate applications in genetic studies, which guarantee their relevance to future medical findings despite some existing ethical and logistical challenges [89].

Table 5 highlights the differences and similarities between macaques and marmosets in the context of their use in human genetics research. The comparative role of animal models in human genetic research is illustrated in Figure 1.

Table 5. Summarizing the key aspects of non-human primates (e.g., Macaques, Marmosets) in human genetics research.

Aspect	Macaques	Marmosets
Genetic Similarity to Humans	~98% of genome shared with humans	~93% of genome shared with humans
Role in Neurological Research	Used extensively to model neurodegenerative diseases (Alzheimer's, Parkinson's, Huntington's)	Studied for cognitive and psychiatric disorders, including autism and schizophrenia
Reproductive Research	Models of infertility, IVF, and developmental genetics	Used for studies on reproductive health and stem cell research
Infectious Disease Research	HIV/AIDS, tuberculosis, and malaria modeling	Malaria, Zika virus, and immunology studies
Metabolic and Cardiovascular Research	Models for atherosclerosis, obesity, diabetes	Used to study insulin resistance, lipid metabolism
Ethical Concerns	High ethical scrutiny due to intelligence and social behaviors	Ethical concerns similar to macaques, but smaller size may reduce some concerns
Cost and Complexity	Expensive, long lifespan, and complex models	Smaller, shorter lifespan, more cost-effective for certain studies
Genetic Manipulation	Advanced genetic tools available (e.g., CRISPR)	Genetic modifications possible but less efficient than macaques
Behavioral Studies	Used for studies of cognition, social behaviors, and learning	Significant focus on social behavior and communication abilities

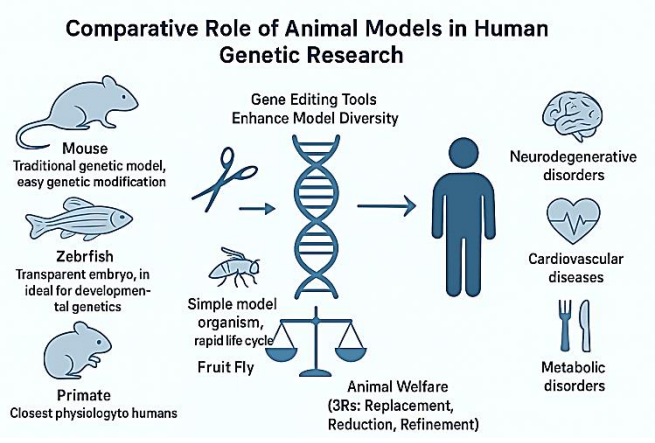

Fig. 1: Comparative role of animal models in human genetic research.

3. Applications of Animal Models in Human Genetics

i. Disease Modeling: Genetic diseases in animals can be used to model human diseases, indicating pathogenesis and treatments [93].

ii. Drug Development: Efficacy and safety testing of new drugs in animals precedes trials in humans [94].

iii. Gene Function Studies: Knockout and transgenic models enable the identification of the function of individual genes in disease and health [95].

iv. Regenerative Medicine: Research in animals gives rise to progress in stem cell therapy and organ transplantation [96].

v. Behavioral Genetics: Rodent models help elucidate genetic contributions to neuropsychiatric illnesses like autism and schizophrenia [97].

vi. Cancer Research: Mouse models of human tumor xenografts (patient-derived xenografts, or PDX) are employed for testing personalized cancer therapy [98].

vii. Cardiovascular and Metabolic Disease Research: Animal models play a key role in understanding diseases like diabetes, obesity, and hypertension, resulting in the creation of targeted interventions [99].

viii. Aging and Longevity Studies: The employment of short-lived organisms like nematodes (Caenorhabditis elegans) and fruit flies in aiding the identification of longevity genes and aging pathways [100].

4. Limitations and Challenges

Genetic Differences: Despite similarities, genetic and physiological differences between animals and humans may limit the direct application of findings.

Ethical Concerns: The application of animals for research purposes has ethical implications involving their welfare and the need for alternative models [101].

Cost and Maintenance: Large animal studies may be costly and resource-intensive. Reproducibility Issues: Lack of consistency in experimental conditions can influence reproducibility and the interpretation of findings [102].

Limited Success in Translating to Humans: Though encouraging results are reported in animal models, numerous drug candidates fail in human clinical trials because of species-specific reactions [103].

Alternative Models and Technologies: Technological breakthroughs in organoids, induced pluripotent stem cells (iPSCs), and computational models are expected to diminish dependency on animals in future research [104].

5. Ethical Considerations

Genetic Differences: Despite the similarities, genetic and physiological differences between animals and humans might limit the direct use of findings.

Ethical Concerns: The use of animals as research models raises ethical issues, including their potential suffering and the need for alternative models.

Cost and Maintenance: The large animal studies can be expensive and resource-consuming. Reproducibility Problems: The lack of consistency in experimental conditions may ruin reproducibility and findings interpretation.

Poor Track Record in Translating to Humans: Despite promising results reported in animal models, many drug candidates have failed in human clinical trials due to species-specific reactions.

Alternative Models and Technologies: Future research is anticipated to reduce the animal use in technological breakthroughs in organoids, induced pluripotent stem cells (iPSCs), and computational models. [88, 91, 105-109].

6. Future Directions

Genetic Engineering Progress: CRISPR-based genome editing in larger mammals could lead to more effective systems for treating complex human diseases. Humanized Animal Models: Animal models can be humanized by gene transfer, tissue transfer, or immune-cell transfer, which opens promising prospects of personalized medicine. Emerging Technologies: Systems of organoid culture technologies, artificial intelligence, and synthetic biology could reduce the use of animal models [110, 111].

7. Conclusion

Human genetics heavily depends on animal models as an essential study because animal models offer important information on the functioning of genes, mechanisms of diseases, and the possible approach to therapy. The future of biomedical research is being informed by advancements in alternative model construction in association with the innovations in genetic technologies, including CRISPR-Cas9 and genome editing. The developments will allow more accurate models that are human-relevant and will enhance the understanding of more complex diseases as well as expedite the translation application. Despite these improvements, there are still gaps in the research. Some of the limitations are that the current models have not fully replicated human disease phenotypes, experimental procedures are variable, and multi-omics data have not been sufficiently integrated in the models. There is a need to fill these gaps to enhance the predictive capabilities and translational relevance of animal models. The ethical consideration is also an important focus as it is necessary to follow some principles, including the principles of replacement, Reduction and Refinement (3Rs) to provide a humane treatment without violating the principles of scientific rigor. Research in the future is expected to combine computational models, organoids, and multi-species solutions and increase reproducibility, decrease the use of conventional animal models, and increase the opportunities to personalized medicine. In general, the further development of animal models alongside the technological progress, interest to gaps in research, and the ethical duty will lead to the considerable advance in the knowledge of human genetics, finding new therapeutic targets, and eventually to the better patient care. Continuous attempts to standardize protocols, integrate ethical models, and formulate alternative or more humanized models will be vital in ensuring the research is as far-reaching as it can be in the coming years.

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Authors' Contribution:

Aiman Saeed Khan, Maria Shafiq, Nazia Farid Burki, Shaista Naz, Afsar Zada, and Hunza Malik did data collection and drafting: Ali Ahmad Khan, Murtajiz Hussain, Suleman Khan, and Sana Fatima did editing and drafting: Muzammil Ahmad Khan did Literature review and English setting, and Muhammad Muzammal did supervision, drafting, and data collection.

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