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The Role and Prospects of the *Drosophila* Model System in Human Rare Disease Research

Sung Dae Kim[1,2], Andrew Kim[1,2], Sarita Palacio[1,2], Hyung-Lok Chung[1,2*]

[1]Department of Neurology, Houston Methodist Research Institute, Houston, TX, USA
[2]Department of Neurology, Weill Cornell Medicine, New York, NY, USA

Drosophila melanogaster has served as one of the most powerful and versatile model organisms in biomedical research for over a century. Its high degree of genetic conservation with humans, with approximately 75% of human disease-associated genes having functional orthologs in the fly, combined with sophisticated genetic tools and a short generation time, makes it uniquely suited for investigating the mechanisms underlying human diseases. This review provides a comprehensive overview of the utility of *Drosophila* in rare disease research, highlighting its contributions across multiple disease categories, including neurological and neurodevelopmental disorders, metabolic and mitochondrial diseases, lysosomal storage disorders, sensory disorders, immunological conditions, and cancer. We discuss the technical advantages that make the fruit fly an ideal first-line model for functional genomics, including the GAL4/UAS system, CRISPR/Cas9 gene editing, and humanization strategies. Furthermore, we examine the inherent limitations of the fly model and the innovative approaches developed to overcome them, such as the integration of complementary model systems and the expression of human disease genes in flies. As rare diseases continue to pose significant diagnostic and therapeutic challenges, *Drosophila* remains an indispensable platform for elucidating disease mechanisms, validating patient-derived genetic variants, and identifying potential therapeutic targets.

Key words: *Drosophila melanogaster*, Rare diseases, Disease models (Animal), Genetic research, Neurodegenerative diseases, Lysosomal storage diseases, Neoplasms, Drug discovery, Functional genomics

REVIEW ARTICLE

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Correspondence to: Hyung-Lok Chung, PhD
Department of Neurology, Houston Methodist Research Institute, 6670 Bertner Ave, Houston, TX 77030, USA
E-mail: hchung2@houstonmethodist.org

ORCID
https://orcid.org/0000-0002-6848-0595

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INTRODUCTION

Rare diseases are generally defined as those with a low prevalence in the population, although the specific criteria vary across countries and organizations [1]. For instance, the criteria include a prevalence of 1 or fewer per 1,000 people according to the World Health Organization, affecting fewer than 200,000 people in the United States, fewer than 1 in 2,000 in the European Union, fewer than 50,000 or 1 in 2,500 in Japan, and fewer than 20,000 or being difficult to diagnose in South Korea [1,2]. Rare diseases can be classified based on various factors, such as genetic origin, age of onset, affected organ systems, and prevalence. Many of these conditions have a genetic basis and are characterized by patient-specific mutations [2]. Understanding their classification is crucial for accurate diagnosis, guiding research efforts, and developing targeted therapies. Although individually rare, these diseases collectively represent a significant public health challenge, affecting a substantial portion of the global population (estimated at 3.5%-5.9%, or 263-446 million people) [2]. The estimated number of known rare diseases ranges from 5,000 to over 8,000 [3], and these diseases exhibit highly diverse characteristics. As a result, patients, families, and healthcare systems face significant challenges, including diagnostic delays, a lack of treatments, high medical costs, and psychosocial impacts [2].

Advances in science and technology, particularly genomics, have brought a sig-

nificant turning point to rare disease research. However, effective treatments remain unavailable for most of these conditions, leaving substantial unmet medical needs. While attention has been focused on developing orphan drugs, these efforts only cover a limited number of rare diseases [1]. Furthermore, the small quantity of patients presenting with these diseases gives rise to logistical issues for researchers, like limited funding and insufficient patient cohorts. Restricted resources to fund standard clinical trials lead to a limited understanding of disease progression, which slows the development of adequate treatments and tests. Multifaceted solutions are needed to increase the scope of rare disease research, as well as the resources available to researchers. Using model systems, designing better clinical trials, sharing data between researchers, and having helpful policies in place could provide further advancements in rare disease research [4]. Because human patient data is limited in rare disease research, the use of model organisms to elucidate disease mechanisms and to test therapies is indispensable [5]. Researchers can analyze complex, evolutionary conserved biological processes in simpler systems like nematodes, zebrafish, mice, and fruit flies. Model organisms have emerged as valuable tools for rare disease research, and each one offers distinct advantages that facilitate the investigation of the root causes of diseases, underlying mechanisms and potential therapeutic approaches [6].

Among these systems, *Drosophila melanogaster* has been widely used in genetic research. This species has played a pivotal role in genetics for over a century, beginning with Thomas Hunt Morgan's groundbreaking work linking genes to chromosomes [7]. Subsequent key discoveries include gene mapping by Sturtevant; radiation-induced mutagenesis by H. J. Muller; the genetic control of development by Christiane Nusslein-Volhard, Eric Wieschaus, and Edward B. Lewis; behavioral genetics research by Seymour Benzer; the molecular mechanisms of circadian rhythm regulation by Jeffrey C. Hall, Michael Rosbash and Michael W. Young; and the discovery of conserved pathways of innate immune activation through Jules A. Hoffmann's research on the Toll receptor [7-10]. Many of these studies received Nobel Prizes, highlighting the profound and enduring scientific contributions made through this model organism. *Drosophila*'s utility stems from its short generation time, low maintenance costs, and robust genetic tools [5,6].

The fruit fly exhibits significant genetic similarities with humans; about 75% of human disease-related genes have homologs in *Drosophila*. It also possesses major conserved cellular pathways, such as Notch, Wnt, and JAK/STAT. This strong genetic conservation, paired with low gene redundancy, allows for accurate functional studies and disease modeling. The fly's fully sequenced genome and reduced complexity also make it ideal to investigate biological mechanisms relevant to human health. Consequently, *Drosophila* remains a crucial model for studying genetic diseases, development, immunity, and behavior, providing insights directly translatable to understanding human biology and pathology [5,6,9,11].

In this review, we provide a comprehensive overview of the technical advantages of the fruit fly model and recent utilization trends in rare disease research. We discuss the genetic mechanisms underlying these diseases, explore how *Drosophila* studies have advanced our understanding of disease pathogenesis, and examine the translational potential of these findings for therapy, as well as the limitations and strategies to address them.

TECHNICAL ADVANTAGES OF *DROSOPHILA* FOR MODELING RARE DISEASE

The value of the fruit fly as a model organism lies not only in its individual advantages, but also the powerful synergy between its high genetic conservation with humans, advanced genetic tools, and experimental practicality. For instance, its genetic similarity to humans ensures biological relevance, while its well-developed tools allow precise gene manipulation. Additionally, features like its short generation time and low cost facilitate large-scale experiments. This integration is advantageous for rare disease research, where resources are limited, and candidate variants are few. The convergence of these attributes enables effective translation of human genomic findings, especially single-gene mutations common in rare diseases, into a meaningful understanding of biological function and therapeutic evaluation. This synergistic interplay of its attributes gives the fruit fly a distinct advantage over many other model systems [5,12].

Well-Established genetic tools and resources

Drosophila has an extensive set of genetic tools, developed and refined over decades, which are very useful for complex studies of gene function and for modeling human diseases. Foundational to this are potent binary expression approaches, such as the GAL4/UAS method (Fig. 1) [13]. These systems offer precise spatiotemporal control over when and where genes are active. These instruments allow investigators to activate

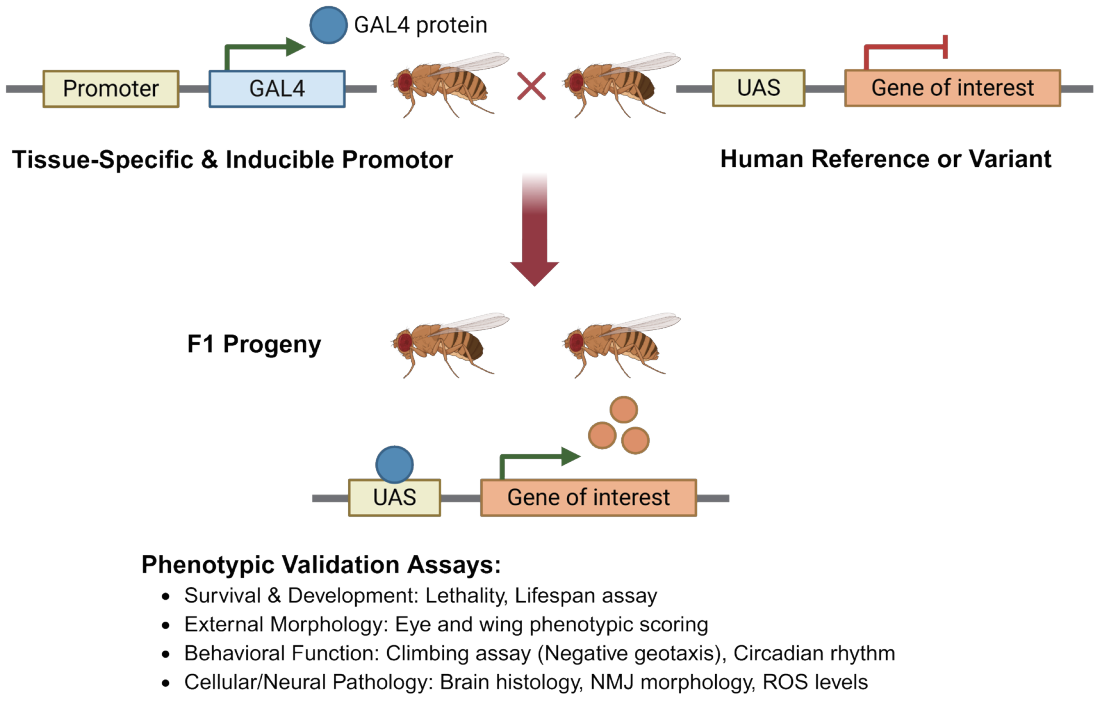


Fig. 1. Schematic of the GAL4/UAS system for enabling tissue-specific and inducible (temporal) gene expression in *Drosophila*.

transgenes (e.g., human cDNAs relevant to diseases) or RNA interference constructs for the silencing of targeted genes, within distinct cells or tissues and at defined developmental times, supported by extensive collections of driver lines [14]. Established transgenesis protocols further enhance functional genomics. These protocols permit the reliable introduction and expression of foreign DNA, including human gene orthologs, often by utilizing site-specific integration strategies, such as Minos-mediated integration cassettes (MiMIC) and the PhiC31 integrase system [15]. To investigate cell-autonomous gene functions, mosaic analysis methodologies, including FLP/FRT or mosaic analysis with a repressible cell marker (MARCM), are employed to generate and study mutant cell clones within an otherwise wild-type tissue background. Additionally, inducible systems, namely drug-activated GeneSwitch or temporal and regional gene expression targeting (TARGET), provide control over gene activity based on time and are activated by external signals, like drug exposure or temperature changes [13].

The advent of CRISPR/Cas9 technology has greatly improved our ability to accurately edit genomes [16]. This versatile tool enables scientists to introduce a variety of targeted genomic modifications, including precise insertions, deletions, and point mutations. Gene modifications are especially important for creating models of human genetic diseases, as they allow for the creation of fruit fly models genetically matched to patients. By introducing patient-specific mutations into corresponding *Drosophila* genes, researchers can test whether these gene modifications can cause disease. These tests are indispensable when the effects of these gene variants are unknown, as is often the case with rare diseases. These specially designed fly models also contribute to a better understanding of disease mechanisms.

Conservation of genetic pathways in *Drosophila melanogaster* and *Homo sapiens*

Comparative genomic analyses reveal that 60-85% of human genes have identifiable homologs in the *Drosophila* genome, with the proportion rising to approximately 75%-85% for disease-associated genes, demonstrating the fly's relevance as a model for human biology [17,18]. This conservation extends beyond individual genes, encompassing core biological pathways crucial for development and cellular function. Major signaling pathways (e.g., Wnt, Notch, Hippo, JAK/STAT, and RAS) and fundamental processes (e.g., apoptosis, the cell cycle, metabolism, neurogenesis, and innate immunity) are highly conserved between flies and humans [19]. This extensive conservation of genes, pathways, and cell functions provides a biological rationale for using fruit fly models to investigate the mechanisms of human health and disease.

Table 1. Summary of *Drosophila* models for human rare disease pathogenesis and therapeutic discovery

Disorder	Human Gene/ Protein Affected	Drosophila Model	Contribution to Pathogenesis	Therapeutic Insight
Rett Syndrome	*MECP2*	Overexpression of human *MECP2* and RTT patient-derived mutant alleles	Loss of *Sin3A* function exacerbated phenotypes, while loss of *Smr* and *crol* suppressed them	*MECP2*-interacting factors identified as potential therapeutic targets
MECP2 Duplication Syndrome	*MECP2* Duplication (Xq28)	Overexpression of human *MECP2*	Discovered pathways disrupted by *MECP2* duplication via genetic screens	Genetic screening elucidated candidate therapeutic targets
Fragile X Syndrome	*FMR1*	Knockout of fly homolog (*dfmr1*)	Synaptic dysfunction and dysregulated protein translation identified	Minocycline treatment restored synaptic structure, leading to subsequent clinical trials
Mitchell Syndrome	*ACOX1* (p.N237S)	*acox1* (p.N250S) mutant model	fly model with dACOX1 N250S mutation demonstrated neurodegenerative phenoypes, decreased axon number, and elevated ROS levels	Antioxidant treatment suppressed neurodegenerative phenotypes in fly models
Huntington's Disease	*HTT* protein	Mutant flies expressing human *HTT* in cardiomyocytes	Replicated neural pathology and clinical cardiac phenotypes (cardiac amyloidosis)	Combined rapamycin+lithium therapy provided enhanced neuroprotection
Spinal Muscular Atrophy	*SMN1*	Transgenic flies expressing patient-derived *SMN* missense mutations	Successfully replicated motor dysfunction observed in human patients	Provides a framework for disease modeling and therapeutic focus
Duchenne Muscular Dystrophy	*DMD* (*Dys*)	Ortholog mutant (*dys*) reproducing defective Dg-Dys complex	Demonstrated that DMD involves significant neurologic abnormalities	The multifactorial nature of DMD increases options for therapeutic targets
Myotonic Dystrophy	*CNBP*	Selective silencing of *cnbp* gene	Allowed for the study of dual mechanisms in MD pathogenesis	Future screening of therapeutic agents can be conducted using patient-specific models
Barth Syndrome	*TAFAZZIN*	*Tafazzin* (ortholog) mutant model	Allowed for the study of cardiolipin remodeling and mitochondrial dysfunction	Potential therapeutic avenues targeting mitochondrial membrane composition
Leigh Syndrome	*SURF1*	Post-transcriptional silencing of *surf1* ortholog	Replicated decreased COX activity and mitochondrial DNA haplotype-driven severity	Variable expressivity allows for patient-specific therapeutic studies
Niemann-Pick Disease type C	*NPC1/NPC2*	Null mutants of *npc1a* (ortholog)	Linked lipid dysregulation to altered neurotransmission and neurodegeneration	Findings led to clinical trials studying cyclodextrin for cholestoral homeostasis
Mucopolysaccharidosis	*HGSNAT/NAGLU*	Drosophila knockdown mutants	Replicated neurological defects, sleep disturbances, and clinical pathologies	Knockdown models help elucidate cellular pathways involved in MPS
Fabry Disease	*GLA* (alpha-Gal A)	Transgenic fly model expressing human *GLA* variants	Premature cell death in dopaminergic cells due to misfolded alpha-Gal A	Migalastat (chaperone) relieved ER stress response in certain fly mutants
Gaucher Disease	*GBA1* (Gcase)	Mutated *gba1a* and *gba1b* (orthologs)	Homozygous mutants replicated symptoms of neuronopathic GD	Rescued with Ambroxol, establishing GD mutants as a robust drug-screening models
Usher Syndrome	USH gene family (e.g., *USH1, USH2*)	Orthologs Usher network (e.g.,*sano*)	Useful in explaining why patients experience hearing and vision loss	Genetic interaction screens identified modifiers of Usher-associated degeneration
Retinitis Pigmentosa	*PRPF8*	Ortholog *prp8* mutant model	Enabled tracking of the clinical severity of patient-specific mutations	Better understanding of mutations helps understand the disease process
Charcot-Marie-Tooth	*ARS* family, *MFN2, SORD*	Flies expressing *YARS/TyrRS* or *SORD* deficiency	TyRS nuclear localization disrupts transcription; *SORD* deficiency identified polyol pathway	Highlighted axonal maintenance; i dentified polyol pathway as a target for intervention
Chronic Granulomatous Disease	NADPH Oxidase	Drosophila *dDuox* model	Important for studying conserved ROS-dependent antimicrobial mechanisms	Provide a foundation to study potential therapeutic targets for CGD
MyD88 & IRAK4 Deficiency	*MyD88* & *IRAK4*	dmyd88 (ortholog) and *tube* mutants	Increased susceptibility to fungal and gram-positive bacterial infections	Pinpointed protein functions and subsequent pathogen susceptibility
Crohn's Disease	*NOD2*, *JAK/STAT*	Conserved *JAK/STAT, MAPK*, and *Wnt* pathways	Studied effects of chronic intestinal inflammation on gut homeostasis	Studies on novel mechanisms in gut homeostasis provide future interventions
Gliomas	*EGFR*, *PI3K*	Co-activation of *EGFR* and *PI3K* in glial cells	Replicated high-grade gliomas characteristics; identified *cic* as a MAPK effector	Identified Artemisinin as a selective apoptosis inducer in tumor cells
Colorectal Cancer	*APC* (Loss of function)	*apc* knockout and multigenic *CRC* variants	Wnt/beta-catenin pathway dysregulation; enabled HTS for drug discovery	Led to the identification of combination therapies (e.g., trametinib and panitumumab)
Medullary Thyroid Carcinoma	*RET* proto-oncogene	Models expressing human *RET*	Allowed for rapid screening of potential anti-cancer compounds	Fly-based screens helped identify Vandetanib as a therapeutic target for MTC
Cancer Cachexia	*Upd3, ImpL2* (IL-6)	Tumor-bearing Drosophila models	Identify *ImpL2* as a protein driving tissue wasting and cachexia	Understanding the pathogenesis allows for refined candidate targets

Efficiency, scalability, and cost-effectiveness of *Drosophila* in research

A further significant advantage of the fruit fly is its rapid life cycle of approximately 10-14 days and high reproductive capacity, allowing for rapid generation of large experimental populations, multigenerational studies, and statistically robust analyses. Compared to vertebrate models, maintaining these insects in the laboratory is simpler and far more cost-effective, requiring only basic food and minimal space. These features, along with their small size and ease of handling, make this model organism an ideal platform for high-throughput screening (HTS). This enables large-scale genetic and pharmacological screens of compound libraries, facilitating the early assessment of bioavailability and potential toxicity [20,21].

APPLICATION OF *DROSOPHILA* MELANOGASTER IN RARE DISEASE MODELING

As a key model organism in biomedical research, *Drosophila* provides valuable insight into the mechanisms underlying a broad range of human diseases. Due to the fruit fly's evolutionarily conserved major signaling pathways, simplified biology, and genetic tractability, it serves as an ideal platform for studying human diseases. Through this model, researchers have identified disease-associated genes, uncovered pathogenic mechanisms, and investigated potential therapeutic strategies. Consequently, the fruit fly remains central to advancing our understanding of complex diseases. This section reviews the utilization of *Drosophila* in rare disease research, with a focus on neuronal diseases, muscular disorders, metabolic diseases, sensory disorders, immunological disorders, and rare cancers (Table 1). In addition, this section examines the experimental strategies utilized to dissect the genetic, molecular, and cellular mechanisms underlying these processes.

Research on neuronal disorders using *Drosophila* models

Rett syndrome

Rett Syndrome (RTT) is a severe neurodevelopmental disorder predominantly affecting females, primarily caused by mutations in the methyl-CpG binding protein 2 (MECP2) gene [22]. As the fruit fly lacks a direct homolog of MECP2, disease models were created by overexpressing the human MECP2 gene and RTT patient-derived mutant alleles (R106W, R294X, and D166) in the fly. This model displayed abnormal phenotypes in the eye, wing veins, and motor function [23]. A genetic screen using this overexpression model revealed that a loss of function in Sin homolog A (Sin3A), a component of the histone deacetylase complex, amplified the phenotypes, while a loss of function in the co-repressors Smr and the transcription factor crooked legs (crol) suppressed them. This finding suggests that potential RTT treatment strategies could target MeCP2-interacting factors [23].

Drosophila models of Rett syndrome have further demonstrated that MeCP2 dysfunction leads to alterations in synaptic plasticity and dendritic morphology, phenotypes that are amenable to genetic suppressor screening. These studies have identified chromatin-remodeling factors and signaling molecules that partially rescue MeCP2-associated neuronal defects, providing candidate targets for therapeutic development.

MECP2 duplication syndrome

MECP2 duplication syndrome is a rare X-linked genomic disorder caused by duplications encompassing the MECP2 gene at Xq28, primarily affecting males. Clinical features include severe intellectual disability, infantile hypotonia, progressive spasticity, recurrent respiratory infections, and epilepsy [22]. While Rett syndrome results from loss-of-function mutations in MECP2, duplication syndrome represents the reciprocal gain-of-function condition, underscoring the critical importance of MECP2 dosage balance for normal neurological development. In *Drosophila*, overexpression of human MeCP2 in neurons has been shown to cause locomotor dysfunction, neurodegeneration, and alterations in dendritic morphology, recapitulating key aspects of the human disease [23]. These fly models have been instrumental in dissecting the molecular pathways disrupted by MeCP2 overexpression, including alterations in chromatin remodeling and transcriptional regulation. Furthermore, *Drosophila*-based genetic screens have identified modifiers of MeCP2-induced toxicity, providing candidate therapeutic targets that warrant further investigation in mammalian systems [23].

Fragile X Syndrome

Fragile X Syndrome (FXS) is the most common heritable cause of intellectual disability, resulting from the loss of function of the FMR1 gene. Studies using the *Drosophila* model with a knockout of the FMR1 homolog (*dfmr1*) have provided a multifaceted understanding of pathogenic mechanisms [24]. In this model, GABAergic circuit dysfunction was observed in the mushroom body, the learning and memory center of the fly brain, accompanied by downregulation of the GABA syn-

thesis enzyme glutamic acid decarboxylase and reduced GABA receptor protein levels [23]. Beyond neuronal defects, *dfmr1* mutant flies exhibited impaired phagocytic activity by both innate immune cells and glial cells, resulting in delayed neuronal clearance following injury and postponed mushroom body development [25]. This dual phenotype highlights that FXS pathology is not confined to neuronal dysfunction but also involves complex interactions with brain immune responses. The fly model thus enables the dissection of these multi-systemic effects, offering valuable insight for identifying novel therapeutic targets, including strategies for immune modulation [25].

Mitchell Syndrome

Mitchell Syndrome, which results from *de novo* gain-of-function mutations in the Acyl-CoA oxidase 1 (ACOX1, human p.N237S; *Drosophila* p.N250S), has been modeled using the fruit fly [21,26]. Unlike ACOX1 loss-of-function mutations, this variant leads to elevated ACOX1 protein levels and enzymatic activity, resulting in excessive production of reactive oxygen species (ROS) in glial cells rather than accumulation of very long-chain fatty acids (VLCFAs). Flies expressing the equivalent dACOX1^{N250S} mutation exhibit severe neurodegenerative phenotypes, including marked lethality within two days, impaired locomotion, and extensive glial and axonal degeneration [26]. Transmission electron microscopy revealed a drastic reduction in axon number, along with abnormal multilamellar bodies and disrupted membrane structures. Notably, wrapping glia were vulnerable to elevated ROS levels induced by dACOX1^{N250S} expression [26]. These gain-of-function phenotypes driven by ROS were potently suppressed by antioxidant treatment, including N-acetyl cysteine amide (NACA) administration and catalase overexpression. Importantly, NACA treatment restored viability, locomotor activity, as well as mating and reproductive capacity [26].

Huntington's disease

Huntington's disease (HD) is a fatal neurodegenerative disorder caused by an abnormal polyglutamine (polyQ) repeat expansion in the Huntingtin (HTT) protein [27]. Although HD primarily affects the nervous system, more than 30% of patients die from heart failure, suggesting a strong association between neurodegeneration and cardiac dysfunction. The fly model has been instrumental in elucidating not only neural pathology but also cardiac amyloidosis associated with HD [27]. Flies expressing mutant HTT in cardiomyocytes recapitulate key clinical cardiac phenotypes, including severe cardiac dilation, contractile impairment, and arrhythmias, closely resembling those observed in patients. These abnormalities are linked to oxidative stress induced by amyloid aggregates, disorganization of myofibrils, and loss of actin-myosin-containing fibers. Notably, cardiac-specific expression of toxic polyQ alone was sufficient to induce both functional and structural cardiac defects [27].

Spinal Muscular Atrophy

Spinal Muscular Atrophy (SMA) is a neurodegenerative disorder caused by mutations in the SMN1 gene and is characterized by progressive muscle weakness and paralysis [28]. A loss-of-function *Drosophila* model for the Smn gene has been established, and notably, 14 transgenic fly lines expressing patient-derived *SMN* missense mutations have been generated [29]. These models faithfully recapitulate the progressive motor dysfunction observed in human patients. Consistent with the human condition, adult flies exhibited a progressive loss of motor function that initially manifested in the posterior limbs. The severity and onset of phenotypes varied depending on the specific mutation, and importantly, even late-onset SMA, which has been challenging to model in other animal systems, was effectively reproduced in *Drosophila* [28,29].

Research on muscular disorders using *Drosophila* models

Duchenne Muscular Dystrophy

Duchenne Muscular Dystrophy (DMD) is a progressive muscle-weakening disorder caused by mutations in the Dystrophin (Dys) gene [30]. A *Drosophila* model that reproduces defects in the Dystroglycan-Dystrophin (Dg-Dys) complex successfully mimics the muscle degeneration phenotypes observed in human patients. Mutant flies exhibit age-dependent muscle degeneration and locomotor impairment. Additionally, this model demonstrated that the Dg-Dys complex is essential for proper axon pathfinding in muscle cells, glial cells, and neurons. These findings indicate that DMD is not solely a myopathy but also involves neurological abnormalities, underscoring the utility of the fly model in dissecting the multi-systemic pathology of the disease [30].

Myotonic Dystrophy

Myotonic Dystrophy (DM) is a multisystem disorder caused by the expansion of CTG or CCTG repeats. Specifically, Myotonic Dystrophy type 2 (DM2) results from a CCTG repeat ex-

pansion in the CNBP gene and involves two main pathogenic mechanisms: loss of gene function and toxic RNA gain of function. The *Drosophila* model has been instrumental in investigating these two mechanisms independently [30]. Selective silencing of the CNBP gene in fruit flies leads to severe locomotor defects, which are attributed to the loss of CNBP-mediated regulation of polyamine metabolism. In contrast, the expression of the toxic CCTG repeat sequence alone reproduces key molecular phenotypes, such as the formation of ribonuclear foci, sequestration of the Muscleblind-like (MBNL) protein, and resulting defects in alternative splicing. Significantly, drug screening using this model has identified several candidate compounds that improve locomotor dysfunction [30].

Research on metabolic disorders using *Drosophila* models

Barth syndrome

Barth syndrome (BTHS) is an X-linked multi-systemic disorder caused by a mutation in the TAFAZZIN gene and characterized by dilated cardiomyopathy, skeletal muscle weakness, and abnormal metabolism of the mitochondrial phospholipid cardiolipin [31]. The *Drosophila* Tafazzin mutant model recapitulates the key pathological features of the disease, including an approximately 80% reduction in cardiolipin levels, abnormalities of mitochondrial morphology such as defects in the cristae membrane, and motor weakness as measured by flight and climbing assays [31].Importantly, the *Drosophila* Tafazzin model has facilitated the investigation of cardiolipin remodeling pathways and their relationship to mitochondrial dysfunction. Genetic interaction studies have identified suppressors of tafazzin-associated phenotypes, suggesting potential therapeutic avenues targeting mitochondrial membrane composition [31]. These findings complement mammalian studies and underscore the utility of the fly model for dissecting the metabolic and bioenergetic defects underlying Barth syndrome.

Leigh syndrome

Leigh syndrome is a mitochondrial disease caused by loss-of-function mutations in mitochondrial proteins involved in the mitochondrial respiratory chain, particularly the Surfeit locus protein 1 (SURF1) protein, which is required for the proper assembly of cytochrome c oxidase (COX). It is phenotypically varied but is generally characterized by early-onset neurological decline, altered energy metabolism, intellectual and motor impairment, and early death [32]. *Drosophila* models of Leigh syndrome, generated through post-transcriptional silencing of the Surf1 ortholog, accurately recapitulate the clinical hallmark of decreased COX activity *in vivo*. These flies exhibit reduced lifespan, locomotor impairment, and mitochondrial morphological abnormalities, including disorganized cristae. Additionally, mito-nuclear interaction studies in the fly have revealed that the severity of Leigh syndrome phenotypes is modulated by mitochondrial DNA haplotype, providing insight into the variable expressivity observed in patients [32].

Lysosomal Storage Disorders

Lysosomal Storage Disorders (LSDs) are a heterogeneous group of rare inherited metabolic diseases caused by mutations in genes encoding lysosomal acid hydrolases, membrane proteins, or transporters, leading to the accumulation of undegraded substrates within the endolysosomal system [33]. This impaired degradative capacity disrupts key cellular processes, including endolysosomal trafficking and autophagy, and results in a wide spectrum of clinical manifestations, frequently involving the central nervous system as well as multiple peripheral organs [33]. Although significant progress has been made in understanding LSD pathogenesis, effective therapies remain limited, particularly for neurological symptoms. In this context, the fruit fly has emerged as a useful *in vivo* model for studying lysosomal function and related cellular pathways. Among the various LSDs, several representative disorders have been extensively modeled in *Drosophila*, including Niemann-Pick Disease (NPD), Mucopolysaccharidoses (MPS), Fabry Disease, and Gaucher Disease (GD). NPD is a rare lysosomal storage disorder caused by mutations that result in loss of function in the Sphingomyelin Phosphodiesterase 1 (SMPD1) gene (type A and B) or the Niemann-Pick type C1 (NPC1)/NPC2 genes (type C). These mutations impair intracellular lipid trafficking, leading to the accumulation of cholesterol, glycosphingolipids, and other lipid species within late endosomes and lysosomes. This accumulation disrupts cellular lipid homeostasis, contributing to progressive neurodegeneration and systemic complications. [34]. In *Drosophila*, null mutants of the NPC1 homolog Npc1a, which is ubiquitously expressed, show cholesterol accumulation and disrupted lipid trafficking, recapitulating key features of NPD [35]. These mutant flies exhibit increased glutamatergic neurotransmission, a trait also found in flies with mutations in the brainiac gene, which inhibits glycosphingolipid synthesis. This suggests a connection between lipid dysregulation, altered neurotransmission, and neurodegeneration [35]. In parallel, flies lacking the acid sphin-

gomyelinase orthologue dASM, which corresponds to the human SMPD1 gene, display developmental and respiratory defects associated with sphingolipid storage dysfunction, and their phenotypes can be partially rescued by genetic or pharmacological interventions [34]. These findings in the *Drosophila* NPD have provided a framework for understanding the neurodegenerative cascade triggered by lipid accumulation, and have facilitated the testing of pharmacological agents, including cyclodextrin derivatives, aimed at restoring cholesterol homeostasis. MPS are LSDs that result from an inability to properly break down cellular glycosaminoglycans (GAGs) and their subsequent accumulation in lysosomes. Enzymes responsible for GAG breakdown include heparan-α-glucosaminide N-acetyltransferase and alpha-*N*-acetylglucosaminidase. These are implicated in MPS types IIIC and IIIB, respectively [36,37]. To simulate enzymatic dysfunction, researchers have used *Drosophila* knockdown mutants and have observed neurological defects, sleep and activity disturbances, and clinically equivalent disease pathologies [36,37]. Further use of *Drosophila* as an MPS model may provide further insight into the cellular pathways involved in MPS-mediated neurodegeneration and a platform to develop therapeutics targeting implicated genes.

Fabry disease is an X-linked recessive LSD caused by mutations in the galactosidase alpha (GLA) gene, which encodes lysosomal α-galactosidase A (α-Gal A). Mutant α-Gal A is retained in the endoplasmic reticulum (ER), leading to organelle stress, ER-associated degradation (ERAD), and unfolded protein response (UPR), which were tracked by Braunstein et al. *in vivo* with transgenic *Drosophila* expressing α-Gal A variants [38]. In dopaminergic cells, misfolded α-Gal A was shown to have led to premature cell death due to the associated consequences of ER retention, but an α-Gal A chaperone, migalastat, was shown to relieve the ER stress response with certain α-Gal A mutants [38]. GD is an LSD caused by mutations in the GBA1 gene, which codes for acid-β-glucocerebrosidase (GCase). Similarly to Fabry disease, mutant GCase is retained in the ER, leading to ERAD and UPR [38]. Cabasso et al. mutated GBA1 orthologs in *Drosophila*, GBA1a and GBA1b and examined the effects of sequence truncations. The GBA1b homozygous mutant exhibited ERAD, UPR activation, reduced GCase activity, inflammation, and neuroinflammation that is seen in neuronopathic GD [39]. This mutant was partially rescued with Ambroxol, relieving all inflammatory effects and UPR, but did not increase GCase activity. Altogether, researchers have concluded that GBA1b homozygous mutant flies can serve as a robust model for neuronopathic GD and can be used to test therapies and for further study of disease mechanisms [39]. Overall, *Drosophila* models of LSD effectively replicate the common pathogenic cascade of protein misfolding, ER stress, and subsequent cellular dysfunction. This provides a robust *in vivo* platform for validating pharmacological chaperones as a universal therapeutic strategy.

Research on sensory disorders using *Drosophila* models

Usher Syndrome

Usher Syndrome (USH) is a genetic disorder that leads to both hearing and vision loss, and is characterized by defects in proteins involved in sensory cell function. Several USH-associated proteins have conserved functional counterparts in flies, enabling genetic analysis of sensory protein networks *in vivo* [40], For example, components of the Usher protein network, including scaffold proteins such as harmonin (USH1C) and SANS (USH1G), have conserved functional roles in sensory systems, and *Drosophila* orthologs or functional homologs of these proteins are used to study their roles in cellular organization and trafficking in sensory cells [40]. Additionally, fruit fly sensory organs such as Johnston's organ are used to study mechanosensory transduction mechanisms that are evolutionarily conserved and relevant to understanding hereditary hearing loss [40].

The *Drosophila* Usher syndrome model has been valuable for understanding the mechanistic basis of sensory cell degeneration. Studies have shown that disruption of the Usher protein complex leads to defects in mechanotransduction and photoreceptor maintenance, providing insight into why patients experience both hearing and vision loss. Furthermore, genetic interaction screens in the fly have identified modifiers of Usher-associated photoreceptor degeneration, offering candidate targets for therapeutic intervention aimed at slowing retinal deterioration.

Retinitis pigmentosa

Retinitis pigmentosa (RP) is a group of hereditary retinal disorders characterized by the progressive degeneration of retinal photoreceptor cells [41]. RP type 13 is linked to pre-mRNA processing factor 8 (PRPF8), an important spliceosome component. Over 20 different mutations of PRPF8 have been clinically identified, and Stanković et al. have used the *Drosophila* model to elucidate the mechanisms of its expression *in vivo* using prp8, a fly ortholog. They used the GAL4/UAS system to induce tissue-specific expression of mutant prp8 transgenes and tracked the development of prothoracic gland cells and

eye/antennal imaginal discs. The two most pathogenic prp8 mutants contributed to adult eye defects, suggesting induction of cell death, and the clinical severity of each respective mutation matched the pathogenicity of the same mutants overexpressed in *Drosophila* [41].

Charcot-Marie-Tooth disease

Charcot-Marie-Tooth disease (CMT) is a group of inherited motor and sensory neuropathies characterized by progressive distal muscle weakness and sensory loss. More than 100 genes containing disease-causing mutations have been identified to date, reflecting the high genetic heterogeneity of the condition [42]. One of the most common implicated groups of genes is the aminoacyl-tRNA synthetase (ARS) family, which is the largest class of proteins associated with axonal CMT and is crucial for protein translation and neuronal maintenance [43].

In *Drosophila* models, several CMT-associated ARS genes have been functionally analyzed. For instance, expressing mutant tyrosyl-tRNA synthetase (YARS/TyrRS) in flies leads to progressive motor dysfunction and neurodegeneration, reproducing key features of human CMT [44]. These models demonstrate that CMT-linked ARS mutations act mainly through toxic gain-of-function mechanisms rather than a simple loss of enzymatic activity [44]. Notably, the nuclear localization of mutant TyrRS has been shown to contribute to the disease by disrupting transcriptional regulation in neuronal tissues. Preventing the entry of mutant TyrRS into the nucleus in *Drosophila* can significantly rescue neurodegenerative symptoms, emphasizing nuclear dysfunction as a potential therapeutic target [44].

Beyond ARS genes, fly models have also provided crucial insights into mitochondrial dynamics, particularly regarding mutations in Mitofusin 2 (MFN2), which is the most common cause of CMT2A. The *Drosophila* ortholog Mitochondrial assembly regulatory factor (Marf) is essential for mitochondrial fusion and axonal transport. Research using Marf-deficient models has shown that mitochondrial depletion in distal axons is accompanied by increased endoplasmic reticulum stress, evidenced by the upregulation of markers such as Xbp1 and Bip [42]. Furthermore, these models suggest that neuronal survival is more dependent on the mitochondrial capacity for ATP production than on their specific physical distribution, providing a deeper understanding of axonal maintenance [42]. Recent studies in flies have also expanded the focus to metabolic and membrane trafficking pathways. The loss of sorbitol dehydrogenase (SORD) was recently identified as a common cause of recessive CMT2. *Drosophila* models lacking SORD show elevated intracellular sorbitol levels and progressive motor impairment, identifying the polyol pathway as a novel target for intervention [42]. Similarly, models of FIG4 (associated with CMT4J) have revealed that defects in phosphoinositide metabolism led to enlarged endolysosomal vesicles and impaired membrane trafficking [42]. Collectively, these fly models have provided vital insights into conserved disease mechanisms, including axonal degeneration, transcriptional dysregulation, and metabolic imbalances, serving as powerful platforms for evaluating new therapeutic strategies.

Research on immunological disorders using *Drosophila* models

Although *Drosophila melanogaster* lacks an adaptive immune system, it has emerged as a pivotal model for studying innate immunity due to its evolutionary conservation of key signaling pathways with humans [45]. The immune response in flies can be divided into two main systems, humoral and cellular. The humoral response involves the production of antimicrobial peptides (AMPs) through the Toll and signaling network. In contrast, the cellular response is mediated by specialized cells called hemocytes, including Plasmatocytes and lamellocytes, which function similarly to human macrophages [45]. Interestingly, the discovery of mammalian Toll-like receptors (TLRs) originated from research on the *Drosophila* Toll pathway. This highlights how studying this simplified model can provide valuable insight into the complex cell-signaling mechanisms that are involved in human immunological disorders [45].

Chronic Granulomatous Disease

Chronic Granulomatous Disease (CGD) is caused by a defect in Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase, an enzyme used by mammalian phagocytes to eliminate invading pathogens through reactive oxygen species (ROS) [46]. Impaired ROS generation leads to recurrent infections and dysregulated inflammatory responses [46]. In *Drosophila*, the NADPH oxidase homolog dual oxidase (dDuox) plays a central role in mucosal immunity by generating ROS in the gut epithelium, thereby restricting microbial growth [47]. In addition to dDuox, ROS-mediated immune responses are tightly regulated to maintain intestinal homeostasis, preventing excessive damage to host tissues [48]. Moreover, both ROS production and its regulation are essential for sustaining intestinal immune homeostasis in *Drosophila* [48]. Although the fruit fly does not have professional phagocytes equivalent to

those found in mammals, it serves as a valuable model for investigating conserved ROS-dependent antimicrobial mechanisms and their regulation. These features make the fly a useful complementary model for understanding key aspects of CGD-related pathophysiology.

MyD88 and IRAK4 deficiency

MyD88 deficiency is an autosomal recessive mutation in myeloid differentiation primary response 88 (MyD88) adaptor protein that impairs toll-like receptor signaling [49]. When a PAMP binds to a TLR in the innate immune response, MyD88 is recruited and subsequently activates interleukin-1 receptor-associated kinase-4 (IRAK-4) [49]. IRAK-4 later activates NF-κB, which calls for transcription of pro-inflammatory cytokines, such as IL-1, IL-6, and TNF- α. Impaired MyD88 and IRAK4 increase susceptibility to bacterial infections, especially *Streptococcus pneumonia*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* [49]. Additionally, MyD88 deficiency disrupts NF-κB activation, thereby impairing IL-1 receptor and TLR ligand responses [49]. The conservation and homology of the TLR pathway in flies and humans have allowed researchers to study these primary immunodeficiencies [50]. The *Drosophila* protein Tube acts downstream of TLR, like IRAK-4 in mammals, to promote signal transduction [50]. DmMyD88 in *Drosophila* is the homolog of mammalian MyD88, and a deficiency in this protein was shown to increase susceptibility to fungal and gram-positive bacterial infections in flies [51].

Crohn's disease

Drosophila melanogaster has been used to study inflammatory bowel disease, like Crohn's disease, for many years [52]. Crohn's disease is characterized by chronic intestinal inflammation, leading to repeated epithelial injury. The fly models helped elucidate that EGFR/MAPK/Ras activation promotes cell growth and proliferation in order to repair the intestinal epithelium [53]. Additionally, epithelial immune responses in mammals are similar to those seen in *Drosophila*. JAK/STAT, EGFR/MAPK, JNK, and Wnt/β-catenin regulate inflammation and epithelial regeneration in flies and mammals [54]. Through the study of intestinal inflammation using conserved pathways, novel insights into the molecular regulation of gut homeostasis and epithelial repair have been identified [52].

Research on Cancer Using *Drosophila* Models

The fruit fly has emerged as a valuable model for cancer research, offering unique advantages for studying the fundamental mechanisms of tumorigenesis, metastasis, and therapeutic responses. Approximately 70% of known human cancer genes have conserved orthologs in the fly, including key tumor suppressors and oncogenes such as Rb, p53, PTEN, APC, Ras, and Notch [20]. The genetic tractability of *Drosophila* allows researchers to model specific oncogenic mutations and study their effects on cell growth, invasion, and tissue homeostasis *in vivo*.

Glioma and neurological malignancies

Malignant gliomas are characterized by the co-activation of EGFR and PI3K signaling pathways, leading to aggressive brain tumor progression. The co-activation of EGFR and PI3K in *Drosophila* glial cells successfully replicates the characteristics of human high-grade gliomas. Additionally, studies on the capicua (cic) gene in flies have elucidated its role as a MAPK effector and its involvement in oligodendrogliomas [55]. Pharmacological interventions in these models have shown that compounds like artemisinin can selectively induce apoptosis in tumor cells and improve locomotor activity in affected larvae [55].

Colorectal cancer

Colorectal cancer (CRC) is primarily caused by the abnormal activation of the Wnt signaling pathway, with loss-of-function mutations in the Adenomatous Polyposis Coli (APC) gene occurring in approximately 80% of human cases. In *Drosophila* midgut models, the loss of APC induces epithelial hyperplasia, resembling human adenomas. This process has been found to require the activation of the non-receptor tyrosine kinase c-Src [55]. Furthermore, personalized fly models incorporating complex multigenic CRC patients have enabled HTS. This approach has led to the identification of effective combinations such as trametinib and panitumumab that were subsequently validated in clinical settings [20].

Thyroid and lung cancer

Medullary thyroid carcinoma (MTC) frequently arises from oncogenic mutations in the RET proto-oncogene. *Drosophila* models expressing human RET mutants have served as robust platforms for identifying therapeutic inhibitors. Notably, the multi-kinase inhibitor Vandetanib (ZD6474) was identified through fly-based screens and later approved for clinical use in MTC patients [20,55]. Similarly, models of EGFR-mutant lung cancer in flies have been used to evaluate the *in vivo* efficacy of various tyrosine kinase inhibitors against specific oncogenic

variants, enabling rapid screening of potential anti-cancer compounds [20,55].

Cancer cachexia and systemic paraneoplastic syndromes

Advanced cancer often triggers cachexia, a systemic wasting syndrome responsible for up to 30% of cancer-related deaths, characterized by progressive loss of muscle and adipose tissue. Research using tumor-bearing *Drosophila* has identified ImpL2, an insulin-binding protein, as a critical tumor-derived factor that antagonizes systemic insulin signaling to drive wasting [56]. Beyond localized energy loss, these models have revealed that inflammatory mediators like TNF-α (Eiger) and IL-6 (Upd) induce multifactorial pathologies, including renal dysfunction, hepatic gluconeogenesis, and the breakdown of the blood-brain barrier (BBB), highlighting the complexity of tumor-host interactions [56].

LIMITATIONS AND ADVANCES IN MODELING RARE DISEASE USING *DROSOPHILA*

Despite its widespread use as a genetic model organism, *Drosophila melanogaster* has several intrinsic limitations when applied to human rare disease research. Anatomically, it lacks key organs involved in many human pathologies, including the lungs, kidneys, and components of the adaptive immune system. These structural differences constrain its ability to recapitulate certain tissue-specific conditions [12]. Moreover, while many core signaling pathways are evolutionarily conserved, approximately 25 to 30 percent of human genes lack direct orthologs in the fly genome, posing challenges in modeling gene-specific disorders [57]. To overcome these limitations, researchers have developed innovative strategies that extend the utility of the fly model (Fig. 2). One such approach is the use of "humanized flies", where human disease-causing genes or their variants are expressed in flies to assess function, pathogenicity, and interaction with conserved pathways [12,58]. Moreover, genome editing tools such as CRISPR/Cas9 allow precise substitution of endogenous sequences with human counterparts, facilitating the creation of phenotypes with higher degrees of clinical accuracy [57]. In parallel, behavioral tests such as climbing assays or circadian rhythm measurements are used as functional indicators of disease-related phenotypes, including motor impairment and muscle degeneration [58]. Importantly, insights gained from the fruit fly experiments are often complemented with data from other model systems, including zebrafish, murine models, and patient-derived cells (e.g., human induced pluripotent stem cells). This integrative approach helps validate findings across species and adds translational depth to genetic and molecular discoveries [12,57]. While the fruit fly, as a model organism, cannot fully replicate human complexity, its genetic tractability and efficiency make it an indispensable first-line tool for functional genomics and

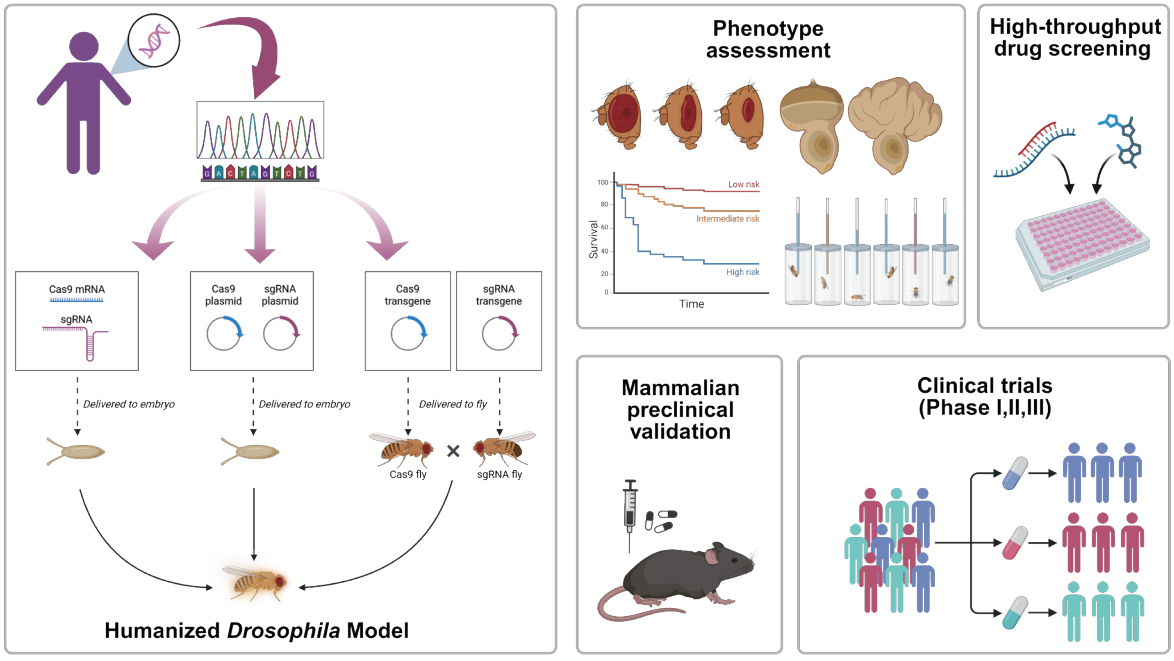


Fig. 2. From Gene to Clinic: A Translational Framework for Human Disease Modeling in *Drosophila*.

rare disease research [58,59]. Notably, collaborative initiatives such as the Undiagnosed Diseases Network (UDN) have demonstrated the power of integrating *Drosophila* functional studies with clinical genomics to resolve undiagnosed cases. In the UDN pipeline, candidate variants of uncertain significance identified through exome or genome sequencing are modeled in *Drosophila* to assess pathogenicity, leveraging the rapid generation of transgenic and knockout flies to provide functional evidence within clinically relevant timescales. Complementary bioinformatic resources, including the Model Organism Aggregated Resources for Rare Variant ExpLoration (MARRVEL) database, facilitate the cross-referencing of human genetic data with model organism phenotypes, streamlining variant interpretation and accelerating diagnosis.

CONCLUSION

The wide variety of animal models available in biomedical research has greatly enhanced our understanding of human physiology and disease. Among these, *Drosophila melanogaster* has played an essential role in scientific advancements for over 120 years, making it an attractive model for studying both established and emerging diseases. Although fly models have inherent limitations, these can be mitigated by focusing on conserved biological pathways, integrating complementary model systems, and employing humanization strategies. Moreover, combining *Drosophila* with other animal models provides a more comprehensive framework for understanding complex disease mechanisms. This approach is particularly valuable in preclinical drug evaluation and translational research.

Rare diseases continue to pose significant medical and social challenges, and research in this area faces numerous obstacles. Over more than a century, research using the fruit fly has generated extensive genetic knowledge and yielded robust experimental tools, establishing it as an indispensable platform for investigating complex biological processes. Its applications span elucidating fundamental biological principles, dissecting mechanisms of human disease, validating patient-derived genetic variants, and identifying novel therapeutic candidates.

Despite evolutionary and physiological differences between fruit flies and humans, these challenges can be mitigated through the study of conserved pathways, the use of complementary models, and humanization approaches. In addition, recent advances in multi-omics approaches, integrating transcriptomics, proteomics, and metabolomics, have enabled a more comprehensive understanding of disease mechanisms at the systems level in *Drosophila*. By combining fly models with patient-derived organoids and induced pluripotent stem cell-based systems, researchers can enhance translational relevance and support precision medicine efforts. Together, these strategies will ensure that *Drosophila* models continue to play an important role in diagnosing and developing therapies for rare diseases.

NOTES

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical statement

This article is a review and does not involve any studies with human participants or animals performed by the authors. No ethical approval was required.

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Author contributions

S.K. drafted the initial and revised manuscript. A.K. contributed to writing the sections on retinitis pigmentosa and Charcot-Marie-Tooth disease, as well as Fig. preparation. S.F. contributed to writing the sections on lysosomal storage disorders and table preparation. H.-L.C. conceived the review, supervised all aspects of the work, and critically revised the manuscript. All authors read and approved the final manuscript.

Use of artificial intelligence

During the preparation of this manuscript, the authors used PubMed, Google Scholar, ChatGPT, and Gemini to assist with literature searches. All references were independently reviewed and verified by the authors before being selected for inclusion. AI tools were also used for English-language editing, including grammar correction and tone refinement. These tools were not used to generate scientific content or figures. The authors carefully reviewed all content, including the references, and assumed full responsibility for the published work.

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