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Drosophila melanogaster as a Model Organism to Facilitate Rare Disease Diagnosis and Therapeutic Research

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Cancer is one of the leading causes of death worldwide accounting for around 10 million deaths in 2020. Cancer is caused by abnormal growth of cells in any part of the body. Genetic causes of cancer can be due to mutations in the genes. Rare mutations in genes show rare types of tumors like Neurofibromatosis and Tuberous sclerosis. The study of model organisms has been pivotal in understanding the causes of various diseases. The studies involve a variety of different methods and out of them the WES (Whole Exome Sequencing) model of research is the most common. Herein lies the future of integrating human genomics with studies in model organisms. It is essential to maintain and expand the current *Drosophila melanogaster* databases this houses the genomic, molecular, and cell biological knowledge on the organism. This can be done by collaboration with the NIH. The understanding of the characteristics of cancer cells plays an important role in terms of

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how to go about with research tumor and normal host cell motility plays a multifaceted role in the metastasis of cancer by allowing the tumor to spread to distant organs, migrate to blood and lymphatic arteries, breach the basement membrane, and escape from the original tumor. The ability to migrate towards favourable environments is a fundamental and evolutionarily conserved cellular behaviour from unicellular organisms to humans. Both normal and cancer cells migrate using diverse modes including amoeboid, mesenchymal, epithelial, collective and individual. Simple model organisms also exhibit these diverse modes of motility and offer experimental advantages such as low cost, amenability to large-scale genetic and pharmacological screening and live imaging of cells interacting within their native environments. This article goes into detail about how drosophila can be used as a model organism to study various diseases such as Duchenne Muscular Dystrophy, Parkinsons disease, Prions diseases, Polyglutamine disorders, Huntington's disease, Machado-Josephs disease, Kennedy disease, Amyotrophic lateral sclerosis, Leigh Disease, Nieman-Pick Disease and a few rare tumours

Keywords: Drosophila melanogaster; Duchenne Muscular Dystrophy; Parkinson's disease; prion diseases; polyglutamine disorders; Huntington's disease.

1. INTRODUCTION

Cancer is one of the leading causes of death worldwide accounting for around 10 million deaths in 2020. Cancer drug trials have been found to have the lowest success rates among all similar diseases despite the extensive studies done on the same. Cancer is caused by abnormal growth of cells in any part of the body [1]. These cells form tumours and can invade other tissues. The most common type of cancer found in humans is breast cancer. Understanding the genetics of cancer can be complicated. The genetic changes that contribute to cancer tend to affect three main types of genes—proto-oncogenes, tumour suppressor genes, and DNA repair genes. The proto-on genes and the tumour suppressor genes are responsible for normal growth and division. DNA repair genes are involved in fixing DNA if there are any mutations or changes [2,3].

The cancer has the ability to spread is known as metastatic cancer. There are various forms of cancer like carcinomas, sarcomas, Leukemia, Lymphoma, melanoma etc. These are differentiated based on the type of cells from which they originate [3]. *Drosophila melanogaster* can be used as an effective model organism. We can study the genes in *Drosophila* and make comparisons with human genes. *Drosophila melanogaster is* commonly known as fruit fly, vinegar fly or pomace fly; it belongs to the family Diptera and is found in most regions of the world [4]

Dipterans form one of the largest insect orders in the world and include many familiar insects such as mosquitoes, midges, sand flies, house flies and blowflies. They have a set of wings and one set of halters [5]. Halters are small modified wings which are used for balance [6]. *Drosophila* consume liquids only through sucking mouthparts. *Drosophila melanogaster* larvae are classified as herbivores and are known to feed on non-carnivorous diet but when nutritionally challenged they exhibit cannibalistic feeding habits. The carnivorous diet is derived from carcasses of organisms belonging to diverse taxonomic groups, including *Musca domestica*, *Apis mellifera* and *Lycosidae sp* [5]. They show Complete metamorphosis and they have large compound eyes.

Some of the reasons why *Drosophila is* commonly used in research is because of its short life span, the presence of only 4 pairs of chromosomes, the fact that it produces a large number of offspring in a short amount of time the fact that a minimal amount of culturing medium is required and they are sexually dimorphic [6].

There are around 205 inbred genes from a single wild population of *Drosophila* [7].

Drosophila melanogaster is considered a wild type of fly; it has black and yellow stripes across its abdomen. Its eyes are red due to the presence of the pigment xanthematin. The life cycle of *Drosophila* is based on temperature for a temperature of around 22 degrees Celsius the life cycle is as follows:(refer to fig.1)

Day 0: The female lays eggs
Day 1: Eggs hatch and release larvae [8]
Day 7: Larvae begin the roaming stage and the pupae are formed.
Day 11-12 adults emerge from pupa (After 8-10 hours the female attains sexual maturity) [9].

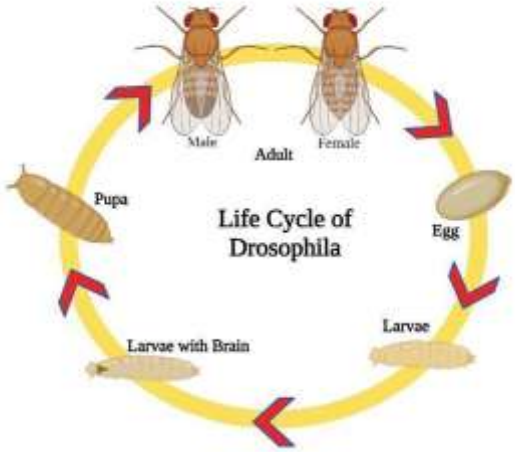

Fig. 1. Life Cycle of Drosophila

The undiagnosed disease program network aims to find diagnostic answers to diseases that have genetic causes but of which we do not know the cause yet. We go into detail about what the undiagnosed disease program is, how it functions currently and what it could be in the future with the advancement of technology [10]

2. INFLUENTIAL FACTORS IN HUMAN CARCINOGENS

Some of the influential factors in human carcinogens include: Environment, Reproductive life, Diet and exercise, Alcohol, and Smoking [11].

2.1 Disease Diagnosis

One of the primary goals of medicine is disease diagnosis. Without knowing the root cause of the problem, it is difficult to accurately treat it. Many patients who are found with rare diseases often undergo a long and frustrating journey to obtain an accurate diagnosis and every so often do not find it. It is estimated that around 80 per cent of genetic diseases go undiagnosed and the patients undergo both physical and psychological stresses. Advanced technology has proved to be transformative for those suffering from Mendelian disorders (Diseases caused due to mutations in the genes) [12]. The WES (Whole Exome Sequencing) method has proved to be very effective as a diagnostic tool for those patients who do not have chromosomal abnormalities [13].(refer to Fig.2 depicting WES procedure)

2.2 Model Organisms

The study of model organisms has been pivotal in giving us insight into the cause of a particular disease at the genetic level; it also helps us understand the pathogenic process of these diseases.

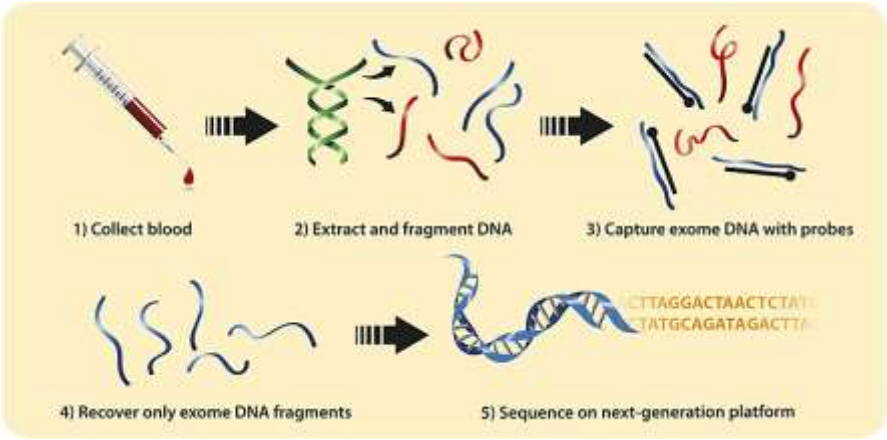

Fig. 2. WES procedure [11]

The study of model organisms is done in collaboration with clinics and researchers examples of a few model organisms are Phi X147(a virus) *Escheria coli,* and *C elegans.* Out of all the model organisms *Drosophila melanogaster* is the most common According to the NIH, 13 model organisms are extensively used in scientific research but recently there are more new model organisms being used like the wallaby. Studying model organisms may be informative, but care must be taken when generalizing from one organism to another [14]. The total number of organisms that are suited for research purposes are hundreds, they are used in a wide range of applications like neurobiology, oncology, physiology etc. It is essential to look into the life history traits of an organism. Life-history traits represent so-called quantitative traits, *i.e.*, characters such as body height in humans for which variation is not discrete but continuous. The main causes for changes in the life history traits include: The effects of many loci and the environmental effects that influence the trait [15].

2.3 List of Common Model Organisms

Escherichia coli, a prokaryote bacterium, is often used to clone DNA sequences from other model organism species [16]. *Caenorhabditis elegans,* a roundworm is a useful model for the development of multicellular organisms, as it is transparent throughout its life cycle, its cells undergo a well-characterized series of divisions to produce an adult body. *Mus musculus, the* mouse is the model organism most closely related to humans. *Danio rerio* the zebrafish has more recently been developed by researchers as a genetic model for most vertebrates. *Arabidopsis thaliana*, a small weed, is the most widely studied plant genetic model organism [17]

3. REQUIREMENTS FOR THE PLAUSIBILITY OF USING A MODEL ORGANISM

Care should be taken so that the organism chosen is feasible and can be taken seriously by the scientific research committee; They should be organisms that have some relation genetically to humans; They should be organisms which we can study using the tools that have already been developed or which we have background knowledge, questions, concepts, technologies, methods, data, and/or materials that researchers are already investigating or using in their work [18].

4. BENEFITS OF MODEL ORGANISMS

Model organisms are widely used in research to study biological processes and understand human disease when human experimentation would be unfeasible or unethical. They are usually organisms that are easy to maintain and breed in a laboratory setting and usually, these organisms have a short life span Some benefits of using model organisms include: They allow researchers to study biological processes in a controlled environment; They are beneficial when the usage of humans for experimentation would be unfeasible or unethical; They can be used to map the genes and create highly detailed genetic maps; They are usually organisms, where one can follow several generations at a time this is done by selecting organisms which have short life, spans and breed in large numbers; Mutants observed in these organisms allow scientists to study certain characteristics or diseases [19].

5. DUCHENNE MUSCULAR DYSTROPHY

One of the most severe types of hereditary muscular dystrophies is Duchenne muscular dystrophy (DMD). Initially, this weakness may cause difficulties walking, but it gradually worsens to the point where affected individuals use wheelchairs in order to do daily activities. Cardiac and orthopedic problems are frequent, and respiratory muscle weakening or cardiomyopathy typically results in death in the twenties. Owing to a mutation in the dystrophin gene, which is found on chromosome Xp21, DMD is a hereditary disorder [20]. Although it is inherited as an X-linked recessive condition, new mutations account for around 30% of cases. It is possible to mimic the dystrophin gene that generates these mutations in drosophila, which results in a wing's posterior cross vein malfunction. We take into consideration changes in wing shape since it is simpler to screen for phenotypic characteristics that are observable. Elevating sphingosine 1-phosphate (S1P) helps prevent dystrophic muscle degeneration, which is the reason why a powerful wing exhibits loss of function. By utilizing easily accessible activity monitors for insect movement and developing a sensitive myofibril integrity assay, employing immuno-histochemical analysis, we were able to quickly evaluate potential genetic and pharmacological possibilities for suppressing muscle atrophy [21].

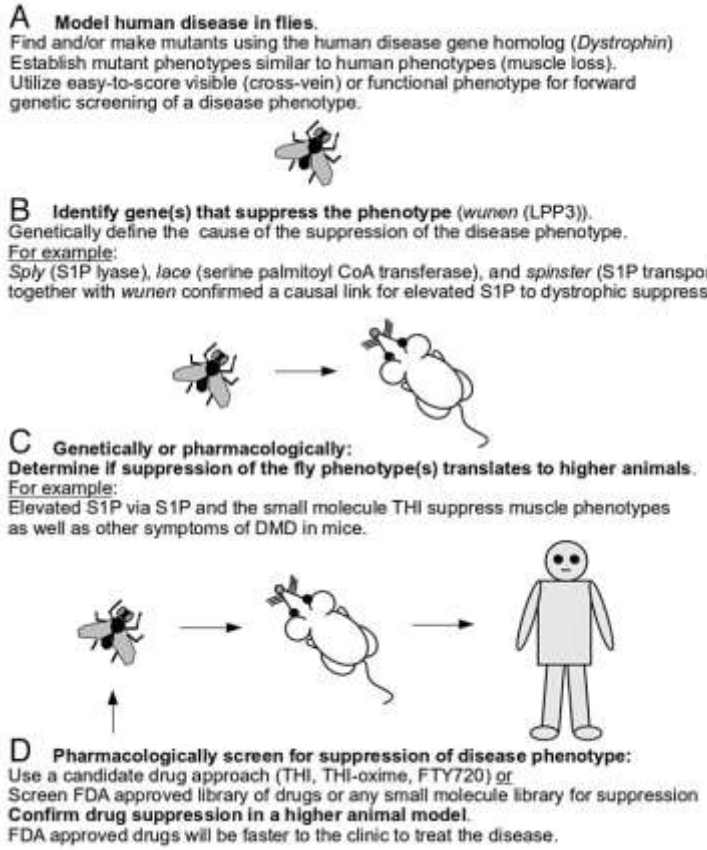

Fig. 3. Method for studying uncommon diseases using model organisms. As well as (B) Create phenotypes and look for modifier candidates of the illness process in easy-to-score phenotypes. Examine recognized routes. Drosophila is a good model organism for DMD, which is characterized by the loss of dystrophin protein. The fly wing's posterior cross-vein may be used to visually evaluate the lack of dystrophin, making modifier screening simple. Muscle wasting was genetically verified to be alleviated by enhanced S1P activity using muscle morphological and functional characteristics. By using pharmacological and/or genetic analysis, expand research to higher animals. We discovered that S1P and the S1P lyase inhibitor, together with THI, partly improved the pathophysiology of DMD in mdx mice. (D)Drugs may be screened using Drosophila. Complete libraries of medications authorized by the FDA may be tested in flies with the aim of repurposing them, which would speed up the process. When a drug's effectiveness is confirmed in mice, it may lead to the identification of potential candidates for clinical trials. Furthermore, any small chemical library may be checked for inhibition of muscle atrophy in flies [17]

6. PARKINSONS DISEASE

Parkinson's disease (PD) is a movement disorder marked by akinesia, stiffness, postural instability, and resting tremor. Less than 10% of PD patients have hereditary cases, with the majority of cases developing randomly.Familial cases of Parkinson disease have been associated with genetic variations in SNCA (α-synuclein)/PARK1, parkin/PARK2, UCHL-1 (ubiquitin carboxy-terminal hydrolase L1)/PARK5, DJ-1/PARK7, PINK-1 (PTEN-induced putative kinase)/PARK6, LRRK2/PARK8, ATP13A2 (p-type ATPase)/PARK9, and HTRA2 (HtrA serine peptidase 2)/PARK13. Despite the discovery of more PARK loci, the changed gene is yet unknown. Neuropathology is characterized by the loss of dopaminergic nigrostriatal neurons and the typical aggregation of α-synuclein in cytoplasmic inclusions called Lewy bodies (LB) and Lewy neurites.A fly model of Parkinson's disease was created by expressing wildtype human α-synuclein in dopaminergic neurons together with two familial mutant variants (A30P and A53T). α-synuclein expression led to age-

related loss of dopaminergic neurons, LB-like accumulations, and behavioral abnormalities. In flies expressing mutant α-synuclein in a pan-neuronal pattern, α-synuclein inclusions were also seen in non-dopaminergic neuronal cell bodies, akin to those in human Parkinson disease (PD) brains. Neuropathology is characterized by the loss of dopaminergic nigrostriatal neurons and the typical aggregation of α-synuclein in cytoplasmic inclusions called Lewy bodies (LB) and Lewy neurites. A fly model of Parkinson's disease was created by expressing wildtype human α-synuclein in dopaminergic neurons together with two familial mutant variants (A30P and A53T). α-synuclein expression led to age-related loss of dopaminergic neurons, LB-like accumulations, and behavioral abnormalities. In flies expressing mutant α-synuclein in a pan-neuronal pattern, α-synuclein inclusions were also seen in non-dopaminergic neuronal cell bodies, akin to those in human Parkinson disease (PD) brains [22]. The ultrastructurally composed of filaments with granular material similar to human Lewy bodies, the fly's LB-like structures were positive for α-synuclein. l-DOPA, a medication used to treat Parkinson's disease (PD), may lessen aberrant behavior.Alzheimer's disease (PD) with an early onset is caused by mutations in the human PINK-1 gene. Degeneration of dopaminergic neurons, degeneration of the flying muscles, anomalies in locomotion, and deficits in the mitochondria are the consequences of mutations leading to loss of function in the Drosophila PINK1 homolog. Interestingly, expression of parkin may enhance PINK1 phenotypes.DJ-1 mutations result in an early-onset autosomal recessive variant of PD. The loss of Drosophila DJ-1α and DJ-1β, the two DJ-1 homologs, was investigated. It was demonstrated that DJ-1β and DJ-1β-deficient flies were alive, fertile, and had a typical life span. It's interesting to note that these flies were specifically harmed by rotenone and paraquat, which have been linked to sporadic Parkinson's disease in humans.The reduction of DJ-1β function led to locomotor deficits even in the absence of dopaminergic neurons.When LRRK2 mutations happen, PD presents as a late onset autosomal-dominant form. Defects were not seen in flies expressing wildtype fly LRRK and the Arg1069Cys mutation, which corresponds to the pathogenic Arg1441Cys mutation in LRRK2 linked with Parkinson's disease (PD), when several GAL4 driver lines were used to induce expression specific to the total body, muscle, eye, and dopaminergic neurons. On the other hand, dopaminergic neurons and locomotor activity were both reduced in LRRK loss-of-function mutants. A second gain-of-function LRRK2-PD model was constructed using human LRRK2, LRRK2-G2019S, and another PD-related mutation. Human LRRK2 expression, both wildtype and mutant, resulted in neuronal degeneration in photoreceptor cells via gmr-GAL4, but expression in dopaminergic neurons led those neurons to be destroyed preferentially, impairing movement and shortening life span [23,24].

7. PRION DISEASES

Most prions illnesses are rare, fatal neurological conditions that are either infectious or inherited in origin. Humans can contract variant (vCJD) Creutzfeldt-Jakob disease, kuru, Gerstmann-Sträussler-Scheinker disease (GSS), familial (fCJD), sporadic (sCJD), and fatal familial insomnia (FFI). Prions diseases are caused by the misfolding of the prion protein PrPC into one of many toxic isoforms.

A single mutation in the prion protein gene at codon 102 and methionine at position 129 mostly causes GSS illness, one of the hereditary prion syndromes. Large, widespread, multicentric amyloid plaques with satellite globules encircling them and a thick center are the histological hallmarks of GSS. The cerebral cortex and cerebellum are the main locations of these plaques, which are favorably stained by PrP antibodies. There include gliosis, NFTs, spongiform alterations, and white matter degeneration next to these plaques. Amyloid plaques with a particular ultrastructure consist of radiating bundles of bent filaments that are not clearly periodic [25].

8. POLYGLUTAMINE DISORDERS

PolyQ diseases are a group of hereditary neurodegenerative illnesses caused by an excess in CAG repeats within the relevant disease genes. These include Huntington disease, X-linked spinobulbar muscular atrophy (SBMA, Kennedy disease), SCA6, SCA7, SCA17, and spinocerebellar ataxias SCA1, SCA2, SCA3 (also termed Machado-Joseph disease), SCA6, SCA7, and dentatorubral pallidoluysian atrophy (DRPLA).

9. HUNTINGTON DISEASE

The coding region of the gene IT15 on 4p16.3 is home to the unstable proliferation of CAG

repeats, which is the hallmark of Huntington's disease (HD), an autosomal dominant illness. Mental, cognitive, and motor symptoms, such as chorea, are characteristics of HD. The sickness appears when the number of polyQ repetitions exceeds 37. In most cases, bilateral striatal atrophy and frontal lobe atrophy are seen. In the caudate nucleus, reactive astrocytosis and neuronal loss are seen. Widespread nuclear inclusions in neurons

Exon 1 of the human IT15 gene, which has 2, 75, or 120 polyglutamine repeats, is directedly expressed in Drosophila, and the outcome is a late-onset progressive neurodegeneration that depends on the number of the repeats, much like in human HD. Rather than forming HD-specific inclusions, the protein huntingtin accumulates in the nucleus and may be detected by anti-huntingtin antibodies. Transposable elements found in some fly strains were found to produce spherical particles inside nuclei that were indistinguishable from particles that looked like viruses.Knocking down huntingtin (htt), the Drosophila homolog of the IT15 gene, causes defects in axonal transport that phenomenologically mirror overexpression of the human HD gene. This implies that proper axonal transport depends on Drosophila htt.

A study found that a key characteristic of polyQ diseases is recurrent instability of an HD Httexon1Q93 transgene. Several genes linked to both illnesses were found by a comparison of modifier screens between SCA1 and a Drosophila Huntington model; nevertheless, several genes even showed contradicting effects in the different disease models. The subject of how polyglutamine expansion promotes toxicity was explored using different human ATXN1 constructs with varied phosphorylation status at serine 776 (S776) and wildtype (30 Q) or expanded (82 Q) polyglutamine tracts, utilizing a yeast two-hybrid screen in a Drosophila SCA1 model.The screen showed that polyQ expansion increases the development of a protein complex comprising RBM17 (RNA-binding motif protein 17) and attenuates the formation and function of a protein complex containing the HMG-box protein capicua (CIC).The molecular pathophysiology of SCA is clarified by this research, and it is probably indicative of other polyglutamine illnesses as well.

10. MACHADO-JOSEPHS

Patients with Machado-Josephs disease, sometimes referred to as Spinocerebellar ataxia type 3, exhibit eyelid retraction, facial fasciculation, peripheral neuropathy, pyramidal indications, extrapyramidal symptoms, and cerebellar ataxia. Ataxin-3, a gene on chromosome 14q32.1 containing an unstable CAG repeat, is associated to this dominantly inherited illness. Among the symptoms that people experience include nystagmus, peripheral neuropathy, cerebellar ataxia, pyramidal signs, extrapyramidal symptoms, eyelid retraction, and facial fasciculation. The unstable CAG repeat-containing gene Ataxin-3, located on chromosome 14q32.1, is linked to this dominantly inherited disease.

The first model of a polyQ disease in Drosophila was established by producing the C-terminally truncated domains of the pathogenic human protein (SCA3tr-Q78) and the control protein (SCA3tr-Q27). Phenotypes were only observed in fly strains harboring the bigger polyglutamine repeat. When SCA3tr-Q78 was expressed in the eye using gmr-GAL4, pigment loss, retinal degeneration, and nuclear inclusions were the outcomes. The fly SCA3 model is intriguing because it exhibits several key features of human illness, such as trinucleotide repeat instability, nuclear inclusions, and neuronal degeneration.Coexpression of the pathogenetic human Atx3 UAS-SCA3trQ78 with the Drosophila homolog of ATAXN2 utilizing a UAS-Atx2 construct under gmr-GAL4 control greatly accelerated inclusion development and eye degeneration. Future treatment developments may depend heavily on our ability to comprehend the interplay of many SCA-related genes and RNA-based trinucleotide repeat expansion disorders.

11. KENNEDY DISEASE

Kennedy disease, also known as X-linked spinobulbar muscular atrophy, is an uncommon X-linked progressive motor neuronopathy brought on by an amplification of the CAG repeat in the androgen receptor (AR) gene's first exon on Xq13–21. Muscle cramps, proximal muscle weakness, atrophy, and fasciculations are among its characteristics, along with endocrine abnormalities such gynecomastia and testicular shrinkage. Pathologically, the facial, hypoglossal, and spinal anterior horns have reduced motor neurones. There are granular dense clumps of AR-positive materials called intranuclear inclusions in the epidermis, testis, and surviving motor neurons, among other organs.An SBMA fly model expressing mutant hAR (polyQ 52), a

pathogenic variant of the androgen receptor gene controlled by gmr-GAL4, showed ligand-dependentneurodegeneration, characterized by a major disturbance of the eye, a reduction in the number of ommatidia, and a loss of pigmentation due to retinal thinning. This model shows loss of neurons, but it is devoid of other features of the real illness, such inclusions and involvement of other organs like the testis and skin. One need for toxicity was the nuclear localization of the mutant protein. The hoi-polloi (hoip) gene has been identified as a modulator screen enhancer of neurodegeneration, linking dysregulation of translational activity to polyQ toxicity. The hoip gene is involved in small nucleolar RNA-protein (snoRNP) complexes that are important in ribosomal RNA processing.

12. AMYOTROPHIC LATERAL SCLERO-SIS

ALS is characterized by anomalies of the upper and lower motor neurons, including spasticity, rapid reflexes, pathological reflexes, fasciculations, and weakness. Though the disease can also be inherited as an X-linked or autosomal family problem, over 90% of ALS cases are unintentional. Fifteen percent of familial instances are caused by gene mutations encoding the enzyme superoxide dismutase-1 (SOD1). Histologically, ALS is characterized by motor neuron loss in the brain and spinal cord. The characteristic features of ALS include hyaline inclusions, TDP-43 positive filamentous inclusions, ubiquitin-positive inclusions (sometimes called "skein-like," "Lewy body-like," or a mix of the two), microscopic eosinophilic inclusions in "Bunina bodies," or spinal motor neurons, and microscopic eosinophilic inclusions.

The expression of hSOD1 (WT and A4V and G85R mutants) in motor neurons using the D42 motor neuron driver led to an increase in motor impairment, but the expression of Drosophila Superoxide dismutase (Sod) using the same driver line had no impact. Loss of climbing ability was not exclusive to hSOD1 mutants; wildtype hSOD1 exhibited this characteristic as well. Given that hSOD1 was discovered to be a dangerous mutant form of SOD1 in Drosophila, it seems plausible that hSOD1 had this effect. Notably missing were retinal degeneration and loss of motor neurons.HSOD1 produces intracellular inclusions but does not alter in solubility.The mutant protein clumps, is ubiquitinated, and draws wild type protein into aggregates, as shown by a recent publication of a Drosophila model of ALS8. The equivalent Drosophila mutation (dVAP33A) of the dominant mutation of VABP (vesicle-associated membrane protein (VAMP)-associated membrane protein B) that causes the human illness was used to develop the model. Furthermore, it's possible to identify a unique mechanism involving BMP signaling pathways that drives the neuromuscular junction development of ALS. Drosophila's glutamatergic neuromuscular junction synapses resemble the spinal cord synapse that is crucially implicated in ALS in humans.

13. LEIGH DISEASE

Leigh sickness is a progressive mitochondrial encephalopathy that manifests as psychomotor delay in the first few months of infancy. It should take one to four years. Additionally, optic atrophy is frequently observed. The illness is brought on by genetic abnormalities in genes linked to nuclear and mitochondrial energy metabolism, including those encoding the respiratory chain complexes I, II, III, IV, and V of the mitochondria, which are crucial for electron transport.

Macroscopic findings show symmetric necrotizing lesions associated with astrocytosis, demyelination, and spongiosis in subcortical parts of the central nervous system (brain stem, cerebellum, diencephalon, and corpus striatum). Ultrastructural mitochondrial inclusions are seen in the neurons of the brain, and the plexus, arteries, astrocytes, and neurons all exhibit higher levels of mitochondrial antigens.Fly photoreceptor cells with succinate dehydrogenase (Sdh) mutants grow normally and innervate the appropriate synaptic partners. Receptor cells eventually experience profound structural changes and progressively cease to exhibit synaptic markers. As a consequence, this model could be able to represent certain features of human sickness.

A different Leigh disease model was developed by downregulating Surfeit1 (Surf1), which resulted in a variety of behavioral and electrophysiological abnormalities, including impaired optomotor response, decreased locomotor speed, decreased photoresponsiveness, and aberrant electroretinograms with distinct driver lines. While Surf1 downregulation caused by an actin-GAL4 line indicated an underdeveloped CNS, CNS wide silencing of Surf1 driven by elav-GAL4 led to a longer lifespan, normal CNS

development, slight impairment of locomotor activity and photobehavior, and a reduced histochemical reaction to COX in the optic lobes. Ultrastructural study revealed that the body wall muscle fibers of actin-GAL4 driven flies had larger mitochondria, a different distribution, and morphological alterations, but no other significant features of human brain disease were seen.

14. NIEMAN-PICK-DISEASE

The Niemann-Pick disease is one of the disorders associated with lysosomal lipid storage. Niemann-Pick type C (NPC) is an autosomal-recessive disease with a wide variety of features that change from the prenatal to adult stages. The primary neurological symptoms are progressive dementia, seizures, dysphagia, dysarthria, and cerebellar ataxia. Features of NPC include glycospingolipids, other lipid accumulation, and chlorophyll.

Mutations in NPC1 or NPC2 result in a failure in lipid homeostasis and a significant deficit in organelle trafficking. Lipid storage, the development of meganeurites and ectopic dendrites, a progressive loss of neurons, particularly Purkinje cells in the cerebellum, and the emergence of neurofibrillary tangles are the histological characteristics of non-proliferative cerebellar disease (NPC).NPC1a null alleles in Drosophila cause the larvae to die early. Nevertheless, NPC1a deletion results in decreased ecdysone synthesis since NPC1a mutants live longer when given the steroid hormone 20-hydroxyecdysone (20E). Eating too many meals high in cholesterol extends life till maturity. Drosophila dnpc1a fly models showed sterol accumulation akin to human disease. By giving dnpc1a mutants 7-dehydrocholesterol, their life expectancy might be extended to maturity. The brain's morphology was normal and did not exhibit any signs of neurodegeneration.

In a second research, a more comprehensive analysis of the brain using the same dnpc1a mutants showed the accumulation of multilamellar structures, age-dependent vacuolization, and cholesterol deposits in neurons. Age-dependent neurodegeneration, anomalies in mobility, and early mortality may all be partially or completely reversed in glia by expressing the wild-type dNPC1a transgene. Mutants deficient in PC2a had shorter lifespans but no evidence of brain vacuolization. Apoptotic neurons are identified by TUNEL staining. The neurodegenerative and cholesterol-storing parts of NPC can be precisely simulated in Drosophila when combined. However, there are two potential issues with the invertebrate model that need to be taken into account while analyzing the data. First off, Drosophila and other insects have redundant NPC1 and NPC2 genes (npc1a, npc2a), but mammals, including humans, only have one NPC1 and one NPC2 gene.The roles of the extra npc genes are yet unclear. Second, the steroid activities of flies are quite different from those of humans because they are unable to manufacture steroids, namely the hormone 20E, which is involved in molting.

15. CEROID LIPOFUSCINOSES

Ceroid lipofuscinoses cause a variety of symptoms, most commonly affecting children, such as vision loss, motor dysfunction, seizures, and a decrease in intellectual capacity. It was discovered that several genes, including PPT1, MFSD8, CLN2-3, 5–8, and 10, were implicated. Infantile neuronal ceroid lipofuscinosis (INCL), caused by loss of palmitoyl-protein thioesterase 1 (PPT1) on 1p32, is characterized by brain atrophy, neuronal swelling, sudanophilic alterations, granular osmiophilic deposits, lysosomal accumulation positive for acidic phophatase in neuronal and astrocytic cells, rarefaction, and shrinkage of corticabasal and bulbar neurons. Shorter lifespans and CNS-specific accumulations of autofluorescent storage material are seen in mutants of palmitoyl-protein thioesterase 1 (Ppt1).These autofluorescent deposits have a uniform structure and are composed of concentric layers of material, unlike human granular osmiophilic deposits. Given that lipophilic stains were unable to show up on the deposits, biochemical differences may exist.Targeted overexpression of Ppt1 induces apoptotic neuronal cell death in the Drosophila visual system, leading to disordered ommatidia. A gain-of-function modifier screen might be performed using encoder-promoter lines, connecting Ppt1 function to synaptic vesicle cycling, endolysosomal trafficking, and synaptic plasticity. Since downregulation of Ppt1 results in an accumulation of storage material, which is distinct from human GRODs without neurodegeneration, Ppt1 in Drosophila may have a different role than PPT1 in humans. As a result, observations made of Drosophila require careful consideration. Although PPT1 misregulation may lead to neuronal death, evidence from Drosophila studies imply that PPT1 overexpression is not the cause of human illness. This suggests that

precise calibration of enzyme activity may be important. On the other hand, modifier screens could emphasize Ppt1's physiological role in Drosophila, which could improve our understanding of human disease [26].

16. NEUROFIBROMATOSIS 1

Neurofibromatosis type 1 (NF1) is an autosomal dominantly inherited neurocutaneous disorder caused by mutations in NF1 on 17q11.Two NF1 is a common disease that mainly affects the skin and the nervous systems (astrocytomas, neurofibromas, optic gliomas, and malignant peripheral nerve sheath tumors). It can also cause osseous lesions, iris hamartomas, cerebral handicap, hematopoietic tumors, and neuroendocrine/neuroectodermal tumors.According to histology, plexiform neurofibromas, which result in a widespread expansion of nerve trunks, and dermal neurofibromas, which are benign tumors composed of Schwann cells that are well-circumscribed, are the most prevalent forms of neurofibromas [27].

Extremely aggressive cancers called malignant peripheral nerve sheath tumors originate in nerve fascicles and spread to neighboring soft tissues [28]. Their cell growth follows a herringbone pattern, which sets them apart. Gliomas in the optic nerve are often pilocytic astrocytomas, and NF1 persons commonly develop bilaterally. The neurofibromin gene is involved in learning, tissue growth in all developmental stages, lifespan determination, interactions between Ras and cAMP, and stress tolerance, according to studies on NF1 gene modification in Drosophila conducted over the past 10 years [29]. Whether these findings will have practical ramifications—For example, whether to utilize antioxidant medications—is up for debate. Simulating neurofibromatosis in Drosophila is still problematic since not all studies have included the crucial discovery that the illness is characterized by the formation of many tumors in humans [30].

17. NEUROFIBROMATOSIS 2

Bilateral vestibular schwannomas are a primary sign of neurofibromatosis type 2 (NF2), a neurological impairment. In addition, schwannomas of different cranial nerves, meningiomas, glial hamartomas, and ocular abnormalities may be present. NF2, an autosomal dominantly inherited neurocutaneous disorder, is caused by mutations in NF2 on 22q12.2. [31]. It has been shown that Merlin mutations regulate the cell cycle and proliferation of Drosophila. It might be shown that Merlin belongs to the hippos route. Drosophila tumor growth was not established by Merlin mutations. It's unclear how these results would influence NF2 patients' possible course of treatment [32].

18. TUBEROUS SCLEROSIS

The heterozygous mutations that result in tuberculosis (TSC), an autosomal dominant illness, are located on chromosomes 9q34 (TSC1) or 16p13 (TSC2). TSC is a neurocutaneous disorder characterized by anomalies in the brain (cortical tubers, subependymal giant cell astrocytomas (SEGAs), subependymal glial nodules, seizures, mental retardation, autism, and attention deficit-hyperactive disorders), the heart, and the kidneys (angiomyolipomas, cysts, and renal tumors) [33]. Cortical tubers are strongly associated with the development of epilepsy, especially infantile spasms. Among their components are giant cells, dysmorphic neurons, calcifications, gliosis, and disrupted cortical lamination. SEGAs are well-circumscribed, mixed glioneuronal tumors that often exhibit calcification.It was shown that the homolog of TSC2, gigas (gig) in Drosophila, causes abnormal cell cycle progression, cell expansion, and imaginal discs. Although hypertrophy changes are seen in the same Drosophila tissues of gigas-mutant flies, no discernible brain tumors are seen, despite the presence of enormous cells in human SEGAs [34].

19. THERAPEUTIC RESEARCH

The goal of therapeutic research in medicine is to provide novel medications or other forms of therapy for illnesses. It generally entails testing novel medicines on humans and animals in a laboratory environment. The discovery of novel therapies for illnesses or ailments is the aim of therapeutic research [35] Due to its shared molecular subgroups, mouse model data appears to represent the future of treating small cell cancer NK The innate immune system's cytotoxic lymphocytes, known as natural killer (NK) cells, have the power to eliminate malignant or virally-infected cells. They have become products as an adjunctive means of treating cancer [24]. Therapeutic research has several advantages, such as the potential to discover novel therapies for illnesses or ailments, enhance the lives of those who suffer from long-

term problems, and lower healthcare costs via the creation of more efficient medical interventions [36].

20. DROSOPHILA AS A TOOL FOR PERSONALIZED MEDICINE

Treating each patient with the best medication that offers the most therapeutic advantages and the fewest adverse effects is the primary objective of customized medicine.A more thorough knowledge of the role of genetics in human disorders has been made possible by recent developments in the fields of genomic sciences, medical genetics, and human genetics. The identification of the reference sequence for the human genome, the creation of multisite partnerships that enable the pooling of thousands of human subjects for association research, and the advancement of systemic whole-genome analysis via array utilization are some of the advancements.As seen by the 1000 Genomes Project, The Cancer Genome Atlas, and exomic sequencing of uncommon Mendelian disorders, we can now more precisely characterize the degree of variation among individuals and connect it to the sick state thanks to next-generation sequencing technology.Since practically every gene in drosophila may be altered in almost every type of cell and at any stage of development, it is a good model for this [37]. Relevant techniques include the use of inverted repeats to produce RNAi-mediated gene knockdown, the GAL4/upstream activation sequence (UAS) system for mis-expression studies, and the FRT/FLP recombination approach to create discrete patches of mutant tissue in a wild-type background.The genetic modifier screen is the most crucial instrument for using Drosophila as a model organism for customized therapy. Functionally linked loci will exhibit a dominant genetic interaction, which is the foundation of the genetic modifier screen.After removing genes from their loci, phenotypic effects are examined, and pathways are identified. For precision work, techniques like knockdown and targeted expression are helpful.targeted expression of transgenes [38]. The production of isoforms of certain proteins that are particular to a disease causes many illnesses. For instance, the oncogenic Ras isoform is expressed in many solid tumors, which activates the Ras signal transduction system and causes carcinogenesis. Fly expression of one or more disease genes may be easily achieved by researchers using the GAL4/UAS mis-expression system or direct fusing of a helpful promoter to the gene of interest.(refer to Fig.4)

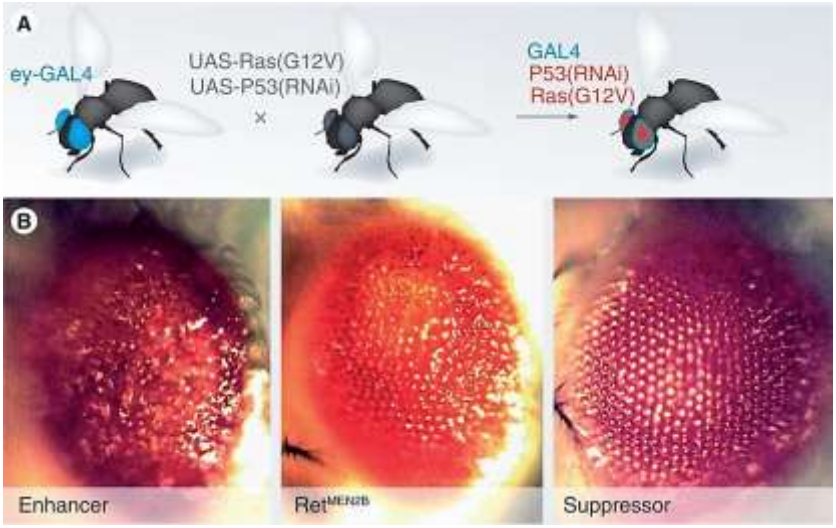

Fig. 4. Tools used to generate disease models
(A) Crossing a fly line containing eye-targeted GAL4 to a fly line with one or more transgenes results in progeny that express the transgenes in the tissue of interest (e.g., the eye). (B) Targeting expression of the oncogenic isoform Ret^{MEN2B} to the eye results in a 'rough eye' phenotype, best observed with misplaced outer lenses. Genetic enhancers (left panel) lead to a more extreme phenotype including outgrowths, while genetic suppressors (right panel) bring the eye closer to its normally smooth lens array. Data taken from [Read R, Cagan R, Unpublished Data]

One use of targeted knockdown is the capacity to eliminate genes in certain tissues. A more popular strategy for illness models has been targeted silencing of a gene via RNA interference (RNAi); this strategy lowers gene activity by destabilizing the transcript. When inverted repeat-containing dsRNA is expressed, homologous regions are targeted for degradation by a complex mediated by a diger.One piece of the RNA interference (RNAi) machinery is the dicer, which breaks down certain double-stranded RNAs into the smaller RNAs involved in the several RNAi pathways that impact gene expression. In-situ research can also be conducted using Drosophila. For illness research, the whole-animal method is also very helpful. Many of the challenges faced by translational researchers might be attributed to conceptual differences, variations between sick tissue within an animal, or variances across cell culture models [39].

21. FUTURE OF DROSOPHILA AS A MODEL ORGANISM

There are four primary topics to investigate about the future use of Drosophila as a model organism.Personalized medicine using genomic data, susceptibility loci, genome-wide association studies, and medication development are only a few of them.

Data on genomes is perhaps the most promising area for future development in the field of Drosophila in terms of personalized medicine over the next years is their ability to give biological meaning to the deluge of genetic data [40]. When conducting a study, why a powerful wing exhibits loss of funtion, evaluating functional relationships and creating new pathways depending on functional requirements [41]. This section includes recent instances where the successful application of flies to solve particular problems that arose from studies on genetic diseases.Even fly researchers underestimate the potential value of using fly genetic methods to uncover susceptibility (modifier) loci. Enhancers found in genetic screens are frequently very good candidates to modify the main genetic insult.The ability to correlate genetic modifiers from Drosophila to SNPs or relevant genome-wide association study mapping in human patients is another overlooked use of Drosophila genetics. These methods frequently find candidate areas but struggle to identify the precise gene within a region that causes the disease or to assess the likelihood that a candidate gene with a small genetic change would be functional [42]. Drosophila has long been regarded as a genetic "powerhouse." In recent times, Drosophila has also aided in the hunt for chemical therapies for a select few other illnesses. With its capacity to be employed in a reasonably high-throughput drug screen and its advanced multigenic models, Drosophila offers considerable promise for drug screening. Using this method might help find substances that are less hazardous to animals overall and have higher overall animal effectiveness. Our understanding of complicated illnesses like diabetes and cancer is still in its infancy. Personalized medicine will benefit from model systems that have demonstrated effectiveness in developmental research, such as Drosophila: Many of the presumptive distinctions will vanish when we transition from studying flies to studying mammals.

22. CONCLUSION

In 2020, cancer will be responsible for around 10 million deaths globally, making it one of the major causes of mortality. Any area of the body's aberrant cell proliferation is what leads to cancer. Depending on the kind of cell they come from, they are distinguished into different types Drosophila *melanogaster* is a useful model organism that may be employed in research. We are able to examine Drosophila genes and draw parallels with human genes. Among the world's largest orders of insects are the dipterans, which contain many well-known insects as house flies, blowflies, midges, sand flies, and mosquitoes.

A few of the factors that make Drosophila a popular study subject are its brief life span, the fact that it has just four pairs of chromosomes, and the fact that it procreates quickly. Because of the pigment xanthematin, its eyes appear red. Temperature is the basis of the Drosophila life cycle, with a temperature of about 22 degrees Celsius.The goal of the undiagnosed disease program network is to discover diagnostic solutions for illnesses with genetic underpinnings but unknown etiology. Diagnosing diseases is one of medicine's main objectives. Understanding the pathogenic process of various diseases and gaining insight into the genetic origin of a certain disease have both been made possible by the study of model organisms. Examining an organism's life history characteristics is crucial. The impacts of several loci and environmental factors that affect the trait are the primary sources of changes in life history

characteristics. Prokaryote bacteria like Escherichia coli are frequently employed to clone DNA sequences from different model organism types.The roundworm Caenorhabditis elegans is a helpful model for studying the formation of multicellular creatures because, during its life cycle, its cells divide into an adult body by a well-defined set of divisions. The model creature closest to humans is the mouse, Mus musculus. These are often creatures with a brief lifespan that are simple to care for and reproduce in a lab environment. Using model organisms has several advantages, such as: They make it possible for scientists to examine biological processes in a lab setting;

They are useful in situations where it would be impractical or immoral to utilize people in experiments; they can be used to map genes and produce incredibly comprehensive genetic maps; These are often creatures that allow for the observation of several generations at once. This is accomplished by choosing species that have short life spans and procreate widely. By observing mutations in these organisms, scientists may investigate certain traits or illnesses. It has been successful, for example, to target mutant p53. One of the most severe types of hereditary muscular dystrophies is Duchenne muscular dystrophy (DMD).Initially, this weakness may cause difficulties walking, but it gradually worsens to the point where affected individuals use wheelchairs in order to do activities of daily life. Method for studying uncommon diseases using model organisms. Despite the discovery of more PARK loci, the changed gene is yet unknown. Neuropathology is characterized by the loss of dopaminergic nigrostriatal neurons and the typical aggregation of α-synuclein in cytoplasmic inclusions called Lewy bodies (LB) and Lewy neurites. A fly model of Parkinson's disease was created by expressing wildtype human α-synuclein in dopaminergic neurons together with two familial mutant variants (A30P and A53T). The ultrastructurally composed of filaments with granular material similar to human Lewy bodies, the fly's LB-like structures were positive for α-synuclein. Degeneration of dopaminergic neurons, degeneration of the flying muscles, anomalies in locomotion, and deficits in the mitochondria are the consequences of mutations leading to loss of function in the Drosophila PINK1 homolog. Most prions illnesses are rare, fatal neurological conditions that are either infectious or inherited in origin. A single mutation in the prion protein gene at codon 102 and methionine at position 129 mostly causes GSS illness, one of the hereditary prion syndromes. PolyQ diseases are a group of hereditary neurodegenerative illnesses caused by an excess in CAG repeats within the relevant disease genes. Mental, cognitive, and motor symptoms, such as chorea, are characteristics of HD. In the caudate nucleus, reactive astrocytosis and neuronal loss are seen. Exon 1 of the human IT15 gene, which has 2, 75, or 120 polyglutamine repeats, is directedly expressed in Drosophila, and the outcome is a late-onset progressive neurodegeneration that depends on the number of the repeats, much like in human HD. Rather than forming HD-specific inclusions, the protein huntingtin accumulates in the nucleus and may be detected by anti-huntingtin antibodies.

Several genes linked to both illnesses were found by a comparison of modifier screens between SCA1 and a Drosophila Huntington model; nevertheless, several genes even showed contradicting effects in the different disease models. The molecular pathophysiology of SCA is clarified by this research, and it is probably indicative of other polyglutamine illnesses as well. Patients with Machado-Josephs disease, sometimes referred to as Spinocerebellar ataxia type 3, exhibit eyelid retraction, facial fasciculation, peripheral neuropathy, pyramidal indications, extrapyramidal symptoms, and cerebellar ataxia. Ataxin-3, a gene on chromosome 14q32.1 containing an unstable CAG repeat, is associated to this dominantly inherited illness. Among the symptoms that people experience include cerebellar ataxia, pyramidal signs, extrapyramidal symptoms, nystagmus, peripheral neuropathy, eyelid retraction, and facial fasciculation.

Phenotypes were only observed in fly strains harboring the bigger polyglutamine repeat. Future treatment developments may depend heavily on our ability to comprehend the interplay of many SCA-related genes and RNA-based trinucleotide repeat expansion disorders. Kennedy disease, also known as X-linked spinobulbar muscular atrophy, is an uncommon X-linked progressive motor neuronopathy brought on by an amplification of the CAG repeat in the androgen receptor (AR) gene's first exon on Xq13–21. Muscle cramps, proximal muscle weakness, atrophy, and fasciculations are among its characteristics, along with endocrine abnormalities such gynecomastia and testicular shrinkage. There are granular dense clumps of

AR-positive materials called intranuclear inclusions in the epidermis, testis, and surviving motor neurons, among other organs. An SBMA fly model that expressed mutant hAR (polyQ 52), a pathogenic form of the androgen receptor gene regulated by gmr-GAL4, showed signs of ligand-dependent neurodegeneration, including severe eye disruption, a reduction in the number of ommatidia, and pigmentation loss with thinning retinas. ALS is characterized by anomalies of the upper and lower motor neurons, including spasticity, rapid reflexes, pathological reflexes, fasciculations, and weakness. Though the disease can also be inherited as an X-linked or autosomal family problem, over 90% of ALS cases are unintentional. Given that hSOD1 was discovered to be a dangerous mutant form of SOD1 in Drosophila, it seems plausible that hSOD1 had this effect. HSOD1 produces intracellular inclusions but does not alter in solubility. The mutant protein clumps, is ubiquitinated, and draws wild type protein into aggregates, as shown by a recent publication of a Drosophila model of ALS8. Leigh sickness is a progressive mitochondrial encephalopathy that manifests as psychomotor delay in the first few months of infancy. Additionally, optic atrophy is frequently observed. Macroscopic findings show symmetric necrotizing lesions associated with astrocytosis, demyelination, and spongiosis in subcortical parts of the central nervous system (brain stem, cerebellum, diencephalon, and corpus striatum). Therefore, this model could be able to represent certain features of human sickness. A different Leigh disease model was developed by downregulating Surfeit1 (Surf1), which resulted in a variety of behavioral and electrophysiological abnormalities, including impaired optomotor response, decreased locomotor speed, decreased photoresponsiveness, and aberrant electroretinograms with distinct driver lines. The Niemann-Pick disease is one of the disorders associated with lysosomal lipid storage. Mutations in NPC1 or NPC2 result in a failure in lipid homeostasis and a noticeable deficit in organelle trafficking. Lipid storage, the development of meganeurites and ectopic dendrites, a progressive loss of neurons, particularly Purkinje cells in the cerebellum, and the emergence of neurofibrillary tangles are the histological characteristics of non-proliferative cerebellar disease (NPC). Drosophila dnpc1a fly models showed sterol accumulation akin to human disease. By giving dnpc1a mutants 7-dehydrocholesterol, their life expectancy might be extended to maturity. In second research, a more comprehensive analysis of the brain using the same dnpc1a mutants showed the accumulation of multilamellar structures, age-dependent vacuolization, and cholesterol deposits in neurons. Age-dependent neurodegeneration, anomalies in mobility, and early mortality may all be partially or completely reversed in glia by expressing the wild-type dNPC1a transgene. Given that lipophilic stains were unable to show up on the deposits, biochemical differences may exist. Targeted overexpression of Ppt1 induces apoptotic neuronal cell death in the Drosophila visual system, leading to disordered ommatidia. Modifier screens, however, have the potential to emphasize Ppt1's physiological role in Drosophila, which might improve our understanding of human disease.19. Neurofibromatosis type 1 (NF1) is an autosomal dominantly inherited neurocutaneous illness caused by mutations in NF1 on 17q11.Neurofibromas, optic gliomas, astrocytomas, and malignant peripheral nerve sheath tumors are among the common conditions caused by NF1. Other symptoms include hematopoietic tumors, osseous lesions, iris hamartomas, neuroendocrine/ neuroectodermal tumors, and cerebral handicap. According to histology, plexiform neurofibromas—which result in a widespread expansion of nerve trunks—and dermal neurofibromas—which are well-circumscribed benign tumors composed of Schwann cells—are the two most prevalent kinds of neurofibromas. X and Li. Their cell growth follows a herringbone pattern, which sets them apart. Gliomas in the optic nerve are often pilocytic astrocytomas, and NF1 people commonly develop bilaterally.The neurofibromin gene is involved in learning, tissue growth in all developmental stages, lifespan determination, interactions between Ras and cAMP, and stress tolerance, according to studies on NF1 gene modification in Drosophila conducted over the past 10 years. Bilateral vestibular schwannomas are a primary sign of neurofibromatosis type 2 (NF2), a neurological impairment. The heterozygous mutations that result in tuberculosis (TSC), an autosomal dominant illness, are located on chromosomes 9q34 (TSC1) or 16p13 (TSC2). TSC is a neurocutaneous disorder characterized by anomalies in the brain (cortical tubers, subependymal giant cell astrocytomas (SEGAs), subependymal glial nodules, seizures, mental retardation, autism, and attention deficit-hyperactive disorders), the heart, and the kidneys (angiomyolipomas, cysts, and renal

tumors).Cortical tubers are strongly associated with the development of epilepsy, especially infantile spasms. It generally entails testing novel medicines on humans and animals in a laboratory environment. The discovery of novel therapies for illnesses or ailments is the aim of therapeutic research. Because small cell carcinoma shares several genetic subtypes, mouse model data appears to hold the key to its future treatment. The innate immune system's cytotoxic lymphocytes, known as natural killer (NK) cells, have the power to eliminate malignant or virally-infected cells. Treating each patient with the best medication that offers the most therapeutic advantages and the fewest adverse effects is the primary objective of customized medicine. A more thorough knowledge of the role of genetics in human disorders has been made possible by recent developments in the fields of genomic sciences, medical genetics, and human genetics. R. Ankeny and P. Many illnesses are caused by the production of isoforms of certain proteins that are particular to that disease. For instance, the oncogenic Ras isoform is expressed in a large number of solid tumors, which activates the Ras signal transduction pathway and causes carcinogenesis. (B) When the oncogenic isoform RetMEN2B is expressed specifically in the eye, it causes a "rough eye" phenotype, which is most noticeable when the outer lenses are misaligned. One use of targeted knockdown is the capacity to eliminate genes in certain tissues. In situ research can also be conducted using Drosophila. For illness research, the whole-animal method is also very helpful. Translational researchers have faced several challenges, many of which can be attributed to variations in sick tissue within an animal, in cell culture models, or in conceptually related xenograft models. genetic data: In terms of customized medicine, the Drosophila area may have the most room to expand in the next years because to their ability to provide the deluge of genetic data a biological context.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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