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Cinderella of genetics (*Drosophila melanogaster*): Population genetics to genomics

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Abstract
Drosophila melanogaster is a well-studied and extremely efficacious genetic model organism in order to analyse several genetic processes common to higher organisms including humans. Little more than a few years back, *Drosophila* emerges as a prototype for the study of genomics and became the third eukaryote to be fully sequenced and used for the application of complete genome sequencing by whole-genome shotgun in eukaryotic genomes. Almost all of coding portion of the Drosophila genome (approximately 120-megabase) has been determined. Fifty years ago, molecular population genetics originated with the first allozyme loci estimation, progressed with the era of nucleotide sequencing, and are now in the age of population genomics. Many regulatory pathways are maintained in *Drosophila* compared to humans, making it a strong model for the study of epigenetic mechanisms. Many signalling pathways are conserved between humans and fly that's why various studies have been successfully conducted in *D. melanogaster* such as comparative genomics, disease mechanism, toxicogenomic studies, Immunogenetics studies. Here, we offer a brief description of the genetic history of *Drosophila*. We hope that an acknowledgement of how we got where we are today and an overview of past studies will help to position the current curiosity about molecular population genetics and genomics.

Keywords: *Drosophila melanogaster*, Allozyme, DPGP, DGRP, nucleotide sequencing, FlyBase

Introduction
Drosophila melanogaster (also called vinegar fly or fruit fly), belongs to the order Diptera and family Drosophilidae; has been exploited for many years as a model species for different aspects of genetics. It is an ideal species for different studies such as neurobiology, development science, behavioural science, etc. *Drosophila* arose as a model species because of its ease of handling, small size, easy feeding habit, high fecundity (100 eggs/day), and short period of generation (12 days for the egg, larva, pupa, and adult succession) [1]. *Drosophila* can be grown in media containing corn, sugar, yeast extract, and dextrose [2]. It carries four pairs of chromosomes and 139.5 million base pairs which are fully sequenced [3]. It contains around 17,000 genes in which almost 2/3rd is euchromatin and the presence of polytene chromosomes which show high levels of gene expression [3]. Morphologically male is slightly smaller than female and possess distinct black patches on the abdomen, forked bristles, sex comb, and claspers. *D. melanogaster* follow a complete metamorphosis so it is a holo-metabolous organism. The life cycle is divided into different four stages that start from the embryo followed by the larva, pupa, and adult.

When we compare it with the human genome, *Drosophila* has many similar features and pathways. About 75% of disease-linked genes in humans show homology with *Drosophila*. In terms of base pairs, the fly genome is only around 5% of the size of the human genome that is the fly comprises 132 million bps compared with 3.2 billion base pairs for humans [4]. The fly contains approximately 15,500 genes and human have about 22000 genes thus the density of genes per chromosome in *Drosophila* is higher than the human genome. It is used as a model for neurodegenerative diseases such as Parkinson's, Huntington's, and Alzheimer's disease [5]. There are more than 2000 described species of *Drosophila* and nearly more than 1800 labs related to different species of *Drosophila* [6].

Little more than 100 years have passed since T. H. Morgan and his colleagues redefined essential *Drosophila* principles at Columbia University's famed "fly-room". He explained Mendel's previously defined inheritance principle, and he got the Nobel Prize for Physiology and Medicine for the role of chromosomes in heredity in 1993.

Since then, research using fruit flies has led to various findings that prompted the recognition of components of fundamental genetics. First used as a research tool by Morgan and Muller, *Drosophila* had played a crucial role in all the fields of genetic analysis and population genetics. *Drosophila* is the third eukaryote to be fully sequenced and used for the application of complete genome sequencing by whole-genome shotgun in eukaryotic genomes [7]. The advancement of high throughput sequencing technology allowed the sequencing of more than 200 complete sequences of the genome of *D. melanogaster* in DPGP (Drosophila population genomics project) [8]. Big data collections of complete genome sequences of several species have transformed population genetic conclusions into population genomics: genome-wide pattern analysis of DNA variation within and between organisms. Catalogues with almost all polymorphic forms for *Drosophila melanogaster* are currently available [9, 10]. In *D. melanogaster*, more than 6,000,000 natural variants have been found to date. This review presents the findings and works carried out in *Drosophila* genetics since the 1920s, which extends from population studies to present-day advanced genomics and its prospects.

Drosophila in preliminary population genetics

At the beginning of 1900, T.H. Morgan began to breed fruit fly in his laboratory. After mating millions of *Drosophila* in his laboratory, in 1910, He observed one fruit fly with a distinct feature: white eyes instead of red. Morgan demonstrated that this distinct eye colour transmission is associated with X chromosome inheritance and eye colour and gender are linked traits [11, 12]. In an article entitled "Sex Limited Inheritance in *Drosophila*" Morgan published descriptions of his work. He earned the Nobel Prize in Medicine (1933).

While working on the chromosomal theory of heredity, Morgan suggested that the farther apart two genes on the chromosome, the more likely they would be to exhibit crossing-over [13]. In 1913, Sturtevant used crossing-over data to construct the first genetic map. He realized that the amount of the frequency of cross-overs (COs) can give an estimation of the gap between genes on the chromosomes. To prove his theory, he considered six traits in *Drosophila* arranged along a linear chromosome which are yellow body, white eyes, vermilion eyes, miniature wings, and rudimentary wings. He determined the likelihood of recombination between each of those factor pairs by dividing the corresponding number of recombinant offspring by the total number of offspring (Table 1.)

Table 1: A summary chart showing the different ratio of X and A controlling sex in *Drosophila*

Sl. No.	Number of X chromosomes	Number of sets of autosomes	X/A ratio	Sex of the individuals
1	3	2	1.50	Metafemale
2	4	3	1.33	Metafemale
3	4	4	1.00	Normal female
4	3	3	1.00	Normal female
5	2	2	1.00	Normal female
6	2	3	0.66	Intersex
7	1	2	0.50	Normal male
8	1	3	0.33	Metamale

Along with Sturtevant and Morgan, C.B. Bridge was part of the famous "Fly-Room". In 1926, the theory of genic balance given by Calvin Bridge states that in *Drosophila* sex determination is achieved by a balance between female factors on the X chromosome (X) and male factors on the autosomes (A).

While working in Morgan's fly lab, in 1927, H. Muller used the fruit fly to classify and physically map chromosomal aberrations and even more importantly to decode the chemical nature of the mutation. Muller was also a Nobel Prize laureate (1946) - "for the discovery of mutation production by X-irradiation".

Population genetics in last 50 years

Until 1966, population genetics had developed a wide and sophisticated theoretical base. However, due to the technological inability to evaluate genetic variability, this exhaustive systematic analysis occurred in a virtual empirical vacuum. After decades of immense efforts, an extensive range of research on electrophoretic variation has finally opened the requisite dialogue between data and theory. Since then, these dialogues have continued to catalyze key innovations in the field of genetics and the molecular age of population genetics starts with the study of electrophoretically detectable variation i.e. Allozyme.

Measurement of genetic variation in *Drosophila* (Allozyme Era)

Allozyme is a protein that varies in electrophoretic mobility due to allelic differences in protein sequence, which eventually result from the variations in the related DNA sequence [14]. Every strategy which is required for allozyme polymorphism study necessitated the following criteria: Phenotypic variations caused by single-loci allelic substitution must be observable among the individuals; allelic substitutions at one locus must be distinguishable from substitutes at another locus; a significant portion (ideally all) of allelic substitutions shall be distinguishable from each other; and the loci analyzed shall be an unbiased genome selection concerning the physiological effects and degree of variations. The analysis of the electrophoretic mobility of enzymes and proteins satisfies the above-mentioned criteria almost completely and shows phenotypic differences in a single individual. Genetic polymorphism is expressed at any point in the populations and *Drosophila* proved to be a great model organism for conducting studies of polymorphism [15] because between the different species of *Drosophila*, there is a wide variation in allozyme polymorphism and heterozygosity rates. With the help of an allozyme study, Genetic diversity is measured in two ways: the mean proportion of heterozygous loci (H) in individuals and the

proportion of polymorphic loci (P) in the population. In *Drosophila,* 12% of loci were heterozygous and 43% were polymorphic [16]. In 1966, Lewontin and Hubby were the first to demonstrate allozyme loci by gel electrophoresis in *D. psuedoobscura* [17].

By this allozyme study, the neutral theory was derived to account for the molecular evolution, Motoo Kimura proposed a theory and in this theory, he states that at the molecular level, major evolutionary substitutions and species variations occur due to genetic drift of selectively neutral (nonselective) mutant alleles. He termed this theory as "neutral theory of molecular evolution". This theory permits the probability that most of the mutations are detrimental and they do not make any notable contribution to differences between and within species and vanished by natural selection from the population [18]. Evidence supporting neutral theory is as follows; when a single copy of a gene exists in a species, it usually plays a functional role similar to that of the homologous gene in another species (hox gene in *Drosophila*). The hox cluster is great evidence of how developmental genes can be preserved through evolution [19]. Another evidence is that the amount of genetic variation between the amino acid coding sequence of human alpha-globin and beta-globin genes is approximately the same as the difference between globin gene in the horse., When comparing the nucleotide within homologous genes of modern species nucleotide sequences are more likely to occur in wobble bases as a mutation in these bases is silent., introns sequences evolve more rapidly than the exon sequences.

Some limitations about protein electrophoresis are; Allozyme polymorphism occurs only when DNA variation alters the amino acid sequences. Only those amino acids can be detected by electrophoresis which affects the mobility of protein in the gel (*i.e*. charged amino acids) and the number of charged amino acids are only one-fourth of all the possible mutational changes [20].

The era of nucleotide sequencing

Along with being a landmark, the study of allozyme polymorphism also has some limitations in the investigation of genetic variation, so it was an insufficient milestone in the study of population genetics. To conquer these shortcomings, it was apparent that the direct study of DNA variation would be necessary, and thus, nucleotide sequencing came into existence. It is the process of analysing the exact order of nucleotide in a DNA molecule. In the 1980s, DNA technology allowed population geneticists to analyze genetic diversity in populations in new ways, either by sequencing [21] or by restrictive mapping techniques [22]. The initial attempts were mainly to achieve a provisional approximation of the DNA polymorphism in *D. melanogaster*. In the 1980s, using a restriction enzyme, the first DNA sequence variation study was performed to identify variations at restriction sites; this approach was extensively used in *Drosophila*.

The pioneering study of the sequencing of nucleotide variation was performed by Kreitman in 1983, by the sequencing of various copies of a whole region of the genome [alcohol dehydrogenase gene (*Adh)*] of *Drosophila*. Kreitman used the Maxam-Gilbert sequencing method and he uncovered 43 SNPs in that only one was responsible for the two allozyme variants that were fast (*Adh –f)* and slow (*Adh-s)* alcohol dehydrogenase, other 42 were silent polymorphisms in coding and non-coding regions which had been invisible to protein electrophoresis. After some years of Kreitman's study, the discovery of automated sequencing of Sanger carried new variations data of dozen genes in many organisms including fruit fly [23]. Kreitman chose *Drosophila* amongst all the species for sequencing study, because in *Drosophila*, haplotypes can be obtained directly by the extraction of a single chromosome using balancers. The availability of such haplotype sequences has allowed the design of more efficient statistical metrics to evaluate variability than the preceding era of allozymes. Sequencing research results are similar in structure (homologous) and separate sequences tested in the zone of interest of DNA. With the help of these haplotype sequences, nucleotide diversity can be measured, this estimation can be done in the area by supposing each nucleotide site as a single unit (c/a as one-dimensional measure of variation) or as a dependent or clustered unit (c/a as multi-dimensional measure of variation) since in *Drosophila* genome alleles are clumped in complexes from 100-150 bp to 2 kb. Such multi-dimensional diversity measurements include important information of chronology and evolution of DNA, including the effective integration rate i.e. $\rho = 4Ner$. Where ρ is the recombination rates in the population, Ne is the effective population size and r is the recombination rate [24].

Nucleotide sequencing has some limitations that can lead to problems with results. Nucleotide sequencing showed genetic diversity in specific sampled genome areas, rather than offering accurate genome-wide measurements (300 to 1000 base pairs) and sequence quality degrades after 700 to 900 bases. It was clear that the next logical step in the analysis of genetic variation would be the sequencing of entire genomes.

The Genomics Era (Genomics in Drosophila)

A genome is defined as the complete set of DNA of each cell in an individual. In 1920, the term was given by Winkler. In 1990, Drosophila was selected as one of the prototype species to be researched under the HGP (Human Genome Project). *Drosophila melanogaster* was the first metazoan in which genomic sequencing was performed [25] and published on March 24, 2000 issue in Science. The project can be followed by *fruitfly.org*. The *Drosophila* genome (180mb) is divided into two large metacentric autosomes, sex chromosomes, and a smaller heterochromatic autosome. Each chromosome (except the Y chromosome) has a DNA molecule of as much as 5 cm but must be compressed into a nucleus with a diameter of as little as 5 μm [26]. Therefore, in linear form, chromosomes must be compressed many times to fit into the nucleus. Importantly, the compaction of chromatin must be accomplished in a way that enables access to machines conducting all DNA-dependent processes, such as replication, transcription, and recombination. It is done by the folding of chromatin into some structures, called nucleosome [27].

The techniques based on the sequencing of the whole-genome shotgun, robust clone-based sequencing, and physical map bacterial artificial chromosome were utilized to determine the base sequence of almost all the *Drosophila's* euchromatic portion genome (120-megabase). Continuous efforts are going on to fill the remaining loops; however, the sequence is of adequate precision and contiguity to be significantly considered complete and to enable the initial study of the genome structure and preliminary annotation and description of genes. The genome encodes the DNA of 13,600 genes. WGS is to shear DNA into segments of a few thousand bps and cloned it into a plasmid vector favourable for DNA sequencing. After sequencing fragments are arranged in overlapping segments to reconstruct a complete genome

sequence. WGS1 (first assembly) employed only paired-end sequences of plasmid and BAC. The second added both draft and finished sequences based on BAC and P1. GenBank issued the Joint Assembly as Release [28]. This series included lots of gaps and a low-quality sequence. Release 2 (second version), rectified some errors in the arrangement and organization of small scaffolds found in Release 1 and filled them out with comparatively high precisions. Third version Release 3 closed all gaps, improved low-sequence regions, extended the sequence at the ends of each chromosome, and verified the entire genome assembly. Release 3 offered a euchromatic sequence that is completely free of gaps and high accuracy [29]. The euchromatic genome sequence of Release 3 has been re-annotated and submitted in GenBank (Table 2).

Table 2: Some important databases and stock collections of *Drosophila*

Databases	Released date	Developed by
FlyBase	1992	Michael Ashburner
Exelixis	1994	Harvard Medical School Boston, MA, USA
Kyoto Stock Center	1999	Kyoto Institute of Technology Kyoto, Japan
NIG-FLY	2002	National Institute of Genetics Mishima, Japan
FlyMine	2007	Gos Micklem
DroID	2008	Russell L. Finley
THFC	2011	Tsinghua University Beijing, China
FlyFactorSurvey	2011	Michael H. Brodsky
OnTheFly	2013	Barry Honig
BDSC	-	Indiana University Bloomington, IN, USA
FlyORF	-	University of Zurich Zurich, Switzerland

Other population genetics related studies in *Drosophila*

Clone-based physical map across the genome

A clone-based physical map consists of a series of organized, overlapping inserts of cloned genomic DNA. Such a map offers an informative source to study the structure and function of the genome. Clone-based physical maps have been compiled for a variety of species chosen as model organisms in the HGP [30]. The physical maps were assembled for various organisms selected as the model in the HGP, *Drosophila* is distinctive among all the breeds because in *Drosophila* polytene chromosomes are found in the salivary glands of the larva [31]. The first physical map of the *Drosophila* genome was described using yeast artificial chromosomes (YACs) ordered by in situ hybridization by Ajioka *et al*. in 1991 [32]. The YAC clones have molecular access to a big segment of the fly genome, but the vector has a small copy number and it is difficult to distinguish large amounts of YAC from contaminating yeast [33].

A second-level structure map based on clones with P1 bacteriophage has been constructed. The map is relied on more number of clones with insert sizes of 80kb by in-situ hybridization. The P1 map comprises an estimated 85 percent of the Euchromatic Genome [34].

Description of the patterns of polymorphism and divergence in *Drosophila*

In *D. Melanogaster*, a preliminary analysis has been undertaken by Sackton *et al*. (2009). He investigated natural variability in 9 strains from African (n=3) and North American (n=6) populations sequencing strains. Later, two pioneer population genomics projects in one species were provided for two separate population genomics studies. The DGRP, a group tool for evaluating population genomics and quantitative characteristics, has entirely sequenced 158 inbred lines, later expanded to a total of 205 lines, originating from a human population in North America (RAL). An integrated genotyping technique has been used to recognize variants in which 4,853,802 SNPs and 1,296,080 non-SNPs. Variation patterns were measured throughout the chromosome arms by following measures – utilizing various non-overlapping window-sized units and through various functional DNA regions [synonymous and nonsynonymous], 5′ and 3′ UTR, intron, and intergenic. In *Drosophila*, mainly three types of variation occur-

Nucleotide variation: The polymorphism pattern and differentiation by site functional class are consistent among chromosomes and within a chromosome (πnonsynonymous< πUTR< πintergenic< πintron< πSynonymous). Autosomal nucleotide diversity is diminished in centromeric regions on average by two to four times compared to non-centromeric segments, as well as in telomeres; while it is fairly stable along the X chromosome. X chromosome possesses average polymorphism is reduced compared to the autosome [35].

Indel variation (*π* Indel): All chromosome arms have a strong positive association that occurs between nucleotide diversity and indel variation [36]. The deletion: insertion Ratio in *D. melanogaster* is 2.2:1. This result is relevant with preceding studies indicating a tendency towards higher deletion rates than the insertion rates [37, 38]. On average there are 60 percent deletions and 74 percent insertions on the X, which is associated with stronger selection on the X chromosome against indels.

TE variation: Rubin and Spradling first introduced the utilization of P-elements for transgenesis, who restored wild-type activity to rosy mutant flies by injecting a P-element containing a functional rosy gene into *Drosophila* embryos and restoring saved flies among the progeny of the injected individuals**.** TEs account for ~20% of the genomic sequence. Population dynamics experiments in *Drosophila melanogaster* of TEs (transposable elements) suggest that consistent factors influence TEs freely of their manners of and regulation [39]. Most TEs are present at the frequency with a low population, especially those located in high recombination genome regions [40], and primarily reside outside exons or untranslated regions.

Pattern of variation determinants

Recombination and linked selection

Recombination itself tends to be the principal process that decides the distribution of nucleotides along the genome. Evolutionary models of repeated related selection, such as genetic draft (hitchhiking), for all variants, predict a beneficial correlation between recombination and polymorphism [41]

that's why the recombination rate through recurrent linked selection is the possible explanation for the observed variant clustering. The positive association between polymorphism and recombination reflects the footmark of natural selection in the genome. Nonetheless, the most striking example of the genetic draft is *Drosophila*. Genetic hitchhiking, also referred to as genetic draft, occurs when a variant allele converts its frequency because it is nearer (linked) to another gene that undergoes selective sweep and is on the nearby location of the same DNA chain. Using genomic data of *D. melanogaster*, it was found that diverseness in polymorphism across dissimilar classes of coding fixations is noticeable even within 25 base pairs of point substitutions, which was interpreted as a consequence of small-scale draft or hitchhiking effects [42].

HRi (Hill-Robertson interference) and pervasive selection

The vast number of chosen variants suggested that the genetic variants in linkage disequilibrium are distributed simultaneously in the genome at any time. Such variants interfere, and slow down the process of evolution in small size population and known as the HRi. Two or more distinct adaptive (+) mutations that occur in different low-recombining haplotypes fight for fixation, reducing the average adaptive fixation rate; and deleterious (−) and adaptive variants coexist in a low-recombinant genome block [43]**.** It is expected that HRi will be higher in the segment of low recombination region, a larger number of selected sites, and more severe selection.

Epigenetic studies in *Drosophila*

Epigenetics is the cumulative total of inherited modifications in the phenotype, without any dependency on the genotype [44]. Advanced research of *D. melanogaster* epigenetics aids to explain genomic imprinting, aging, carcinogenesis, neural memory, circadian rhythms. Many regulatory processes are maintained in *D. melanogaster* which is similar in humans, making *Drosophila* a strong and ideal organism for the study of epigenetic mechanisms. There are several epigenetic processes in *Drosophila*, such as methylation of DNA, histone modifications, RNA-associated silencing, dosage compensation, genomic imprinting, and PcG-TrxG-mediated heterochromatin dynamics [45]. Epigenetic regulation in chromosomes has been studied in *Drosophila* and various important elements have been identified in this organism [46, 47]. *Drosophila* has issued precious insights into the role of generating and sustaining different epigenetic patterns in chromatin that regulate processes unique to fly, such as X-linked dosage compensation, and in processes conserved in human, such as epigenetic mechanisms underlying gene regulation, positioning effect variability, developmental programming, epigenetic inheritance, and neuronal plasticity guiding learning and memory [48].

Study of comparative genomics

As we have known that there are more than 2000 described species of *Drosophila*, nearly two dozen species of *Drosophila* have available genome sequences [49]. Together, these species cover huge variability of ecological environments, features of life history, and periods of evolutionary divergence. This traceable complexity makes *Drosophila* a strong model for the study of comparative genomics. After *D. melanogaster, D. pseudoobscura* was the next sequenced genome for *Drosophila*, a transformative genetic group of historical importance [50]. *D. pseudoobscura* is well known for its prevalence of chromosomal inversions [51] and the likelihood of these genomic structures leading to the adaptation and development of new species [52, 53]. One main thrust for sequencing *D. pseudoobscura* was to find cis-regulatory elements; it turned out, notwithstanding, that there is little conservation of these elements between the non-coding zones of *D.melanogaster* and *D. pseudoobscura* [54]. The nearest relative to *D. melanogaster* is *D. simulates* which is a geographically distributed and multicultural population [55]. The most distant relative to *D. melanogaster* is the Hawaiian "picture wing" *D. grimshawi* [56]. Population genomic tools now exist for several intimate species to *D. melanogaster*, including *D. simulans*, *D. mauritiana*, and *D. yakuba* with several additional data sets undergoing. Since the genus *Drosophila* differs widely in several phenotypic dimensions [57], these resources allow researchers to study the function and evolution of species genomes in a comparative framework.

***Drosophila* as *in vivo* model organism**

Since many years ago, *Drosophila* has been utilised as *in vivo* model organism in various studies because of its short life span, persuadable development cycle, and highly resembling probability with humans. Here we have tried to incorporate some studies in brief related to Drosophila as *in vivo* model.

Study of Circadian rhythm

The circadian rhythm seeps through all the aspects of behaviour and physiology and has broad consequences for the wellbeing of both humans and animals [58, 59]. The study of the circadian clock on *Drosophila* provides a model system with notable resemblances to mammals. There are numerous explanations why fly clocks would be of interest to geneticists. The earliest and most popular *Drosophila* circadian clock study was performed by Konopka and Benzer, in which chemical mutagenesis of the X chromosome was identified [60]. The Jerk gene was recognized in *Drosophila* and the DNA sequence revealed that it was the mammalian Clk homolog. Since then the fly mutant has been assigned with Clk^{jerk}. There is one particular human syndrome, where circadian clocks have been directly linked that is Familial advanced sleep phase syndrome (FASPS) [61]. This is equivalent to the traditional pers mutant in *Drosophila*, due to which their locomotive activity occurs a few hours earlier than in the wild type fly when they are put in a 12 h light schedule: 12 h dark (LD12:12) [62, 63]. Scientists may also take the benefits of growing mechanistic analysis of other behaviours, *viz* brain growth, mating behaviour, and aggressiveness, to explain how sleep deprivation affects certain activities. Thus, flies remain a precious tool for both the creation of new substances and a good mechanistic interpretation of the biological clock [64].

Study of Development genetics

Drosophila and human development are phenomena that resemble each other. They utilize closely associated genes with highly preserved functional mechanisms. *Drosophila*, unlike humans, faces simple genetic modification. As a result, much of what we learned about animal development has originated from the analysis of model organisms like *Drosophila*. *Drosophila's* development is focused on three scientists; Lewis, Nusslein-Volhard, and Wieschaus isolating and classifying the developmental mutants. Nusslein-Volhard and Wieschaus worked on the process of early embryogenesis

while Lewis performed late embryogenesis research [65]. Nusslein-Volhard and his colleagues worked to recognize genes in the embryo of *Drosophila* needed for initial pattern formation. They examined for recessive mutations lethal for the embryo, and before death categorized them as per their phenotype. Lewis found homeotic mutants. The homeotic genes contain a series of 180 nucleotides, the homeobox, translated into a domain of 60 amino acids, called the homeodomain. Among normal flies, body parts such as legs, wings, and antennae grow on different segments, and this procedure involves the involvement of homeotic genes. Mutant flies, in which characteristic structures of one section of the embryo are located at another place. This research in *Drosophila* set the stage for our modern understanding that HOX genes help to establish segmental variations in a manner that is commonly maintained across widely varying species. Several human developmental disorders emerge from anomalies in all of these genes.

Human Diseases model

Even though human beings and flies vary considerably from one another in terms of their general anatomical and cellular features, several pathophysiology pathways are similar in both. Nearly 65% of genes which cause disease in human are considered to have analogous in *Drosophila* [66, 67]. To analyse diseases utilizing *Drosophila* as a model species, mainly three strategies were taken into account; forward [68, 69], reverse genetics [70], and diagnostic strategy [71, 72]. The different assay was designed for the fly organ system to the study of functionally related genes that cause disorders and affect various systems in humans. Nervous system assay, cardiovascular system assay, Malpighian tubules assay, fat bodies assay [73], tracheal system assay [74], and gut assay [75] are some important examples of them. Based on all these assay, it has been proved that *Drosophila* offers an effective forum to conduct functional annotations on human genes and disease variants. Signalling mechanisms that regulate mammalian cell development and invasion have a retained role in *Drosophila* that mimics tumour biology in the fly [76]. Nearly 90 percent of tumours are of epithelial origin [77]. Loss of cell adhesion and polarity with elevated motility of the cells are primary symptoms of cancer. *Drosophila*'s imaginal discs are monolayer epithelium comparable morphologically and biochemically with human epithelia [78]. Recent surveys utilizing fly's imaginal discs investigated the processes that control epithelial tumour development and its association with local cells [79]. Fly society has been involved in the creation of novel genetic platforms over the previous few years, which will expand further utilization of *Drosophila* in the field of medicine [80].

In the study of toxicogenomics

The *Drosophila* has also recently been successfully deployed in toxicology investigations as a research subject [81]. Due to physiological similarities between humans and fly and cost-effective laboratory production, *Drosophila* has been advised as a model of choice for toxicogenomics studies [82]. The new term Drosophotoxicology has been suggested [83]. Municipal solid waste, which is the major problem of urban areas and the major source of pollution in the environment. Transgenic flies (hsp-70) have been utilized to study the effect of solid waste [84-86]. *Drosophila*, as a laboratory organism, fulfilled the requirements of ECVAM (European Centre for the Validation of Alternative Methods): 3Rs (Reduction, Refinement, and Replacement) [87]. *Drosophila* has been deployed to the study of the pathophysiology of free radicles and oxidative stress also the acceptance of *Drosophila* for the study of diseases under toxicants stress has largely been accepted [87-89]. The susceptibility of toxins also depends on various genetic factors. Due to variations in clinical symptoms and unrelated phenotypic effects, studies of these genetic factors are challenging. *D. melanogaster* is a robust model that allowed genome-wide analysis of variations in alleles, responsible for the variable effect of toxins [90]. Although *Drosophila* does not possess lungs still have similarity with airway system of human so it is an excellent model to study of response to inhalant toxins [91]. Inhalant toxicity tests of various chemicals such as formaldehyde and toluene have been conducted on *Drosophila* and analysis is done using computational behaviour and comprehensive [92]. There are enough studies that prove the effectiveness of *Drosophila* as a potential model in toxicity screening.

In the study of immunogenetics

With the discovery of the role of toll receptors in innate immune activation, *Drosophila* has been established as an appreciable model in immunity analysis [93]. In 1996, Jules Hoffman worked on the response of innate immunity in *D. melanogaster*. To fighting against pathogens, *Drosophila* depends on both types of immune responses; cell-mediated and humoral. The fly provides various experimental pros and widely contributed to the study regarding the activation of signals of innate immunity [94]. Many viruses affect humans and have complex replication phenomena which are difficult to understand but by using *Drosophila* as an experimental organism, innate restriction mechanisms related to the virus can be identified [95, 96]. Fruit fly can be utilized for screening of host-pathogen interaction as the fly is economically affordable and have few or no ethical concern. Its simplified structure provides a manner of reaction and expression between microbes and host. In recent studies, it has been proved that *Drosophila* and human have the same microbial population, being tolerated by intestinal epithelium and provide an important function to the host. Since *Drosophila'*s digestive tract is much simpler than humans, it is easy to assess bacterial-host interactions.

Conclusion

In brief, *Drosophila melanogaster* has been thoroughly studied as an organism of choice for genetic research for over a century. It was almost 100 years ago, in 1909, when Morgan selected the fly for an experimental study of evolution. Since Morgan's fortunate choice of *Drosophila* as an experimental organism, Scientists have been eyewitnesses to the enormous power of *Drosophila* genetics. In this review, we have talked about various scientific efforts implemented in *Drosophila* genetics since the 1900s, which expanded from population genetics to present-day modern genomics. We have also reported progressive advancement of population genetics with the first allozyme loci estimation, progressed with the era of nucleotide sequencing, and are now in the age of population genomics. We have also discussed several important studies in which *Drosophila* has been chosen as model species. However, *Drosophila* is not about to retire as a model system for cutting-edge science to resolve the pressing issues of biology. In addition to the features that made *Drosophila* so popular to study in the last century, modern and efficient tools and experimental possibilities make research as exciting and

desirable as ever in the last century for young and well-established scientists. The DGRP (*Drosophila* Genetic Reference Panel) genome sequences, all databases, and stock collections (DroID, FlyBase, FlyFactorSurvey, FlyMine, etc.) created by the fly community will continue to provide useful resources for the challenges that we will face and enjoy in the next century. Besides, given the continued introduction of new technologies, support for *Drosophila* genomics will continue to increase in the future. Last but not the least, due to bearing genetically a strong resemblance with human gene and model of choice right from the beginning of the 20th century till the era of multi-omics, *Drosophila* is honoured as the "Cinderella" of genetics.

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Competing Interests
The authors declare that they have no competing interests.

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