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Developing breeding strategies for rodent models as per the different patterns of lethal gene inheritance

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Abstract
Understanding the similarities between human and rodent genes with genetic defects and inherited patterns is important in the field of drug discovery and development. Till date, there are more than 1500 human gene with disease or lethal condition and each condition has distinct inheritance pattern and show differences in the expressivity. Several studies revealed that sequence conservation at the nucleotide level between humans and rodents found only a small difference (Lopez -Bigas *et al*., 2004). These studies mostly revealed the genetic basis of diseases and related mutational changes at nucleotide level which are not sufficient to u se in drug discovery and treatment of the genetic basis of diseases. There will be a lot of attention required to understanding of the unique segregation and inheritance pattern of gene sets of a particular disease. These inheritance pattern s are thoroughly examined and detailed discussion about breeding program s with appropriate pedigree charts will be the main aim of this article.

Keywords: Rodent models, patterns, lethal gene inheritance

Introduction
Background
The first person who described the phenomenon of dominance and recessitivity in diploid organisms was Gregor Mendel in 1866. Since then, geneticists have disagreed on how dominance evolved. The peculiar patterns of inheritance of a coat colour gene in mice was first noticed by Lucien Cuenot in 1905. He noticed that the offspring never exhibited a typical 3:1 phenotypic ratio after mating two yellow mice. Instead, there were always two yellow mice for every non-yellow mouse with a 2:1 Ratio. Cuenot came to the conclusion that yellow coat colour was the dominant phenotype, and he demonstrated that all of his yellow mice were heterozygote by performing test crosses and he never got a single homozygous yellow mouse from his numerous crosses. The reason is that the homozygous dominant condition is lethal, which results in the death of mice. This Cuenot's unique segregation ratios were validated in 1910 by W. E. Castle and C. C. Little (Falconer, 1952) [1]. In 1928, R. A. Fisher described the harmony between repeated mutations and natural selection's ability to eliminate them. Sewall Wright (1929) [9] said that the evolution of dominance in this way required unreasonably high levels of selection pressure. It clears how selective breeding is playing major role in the development of unique rodent model and also important in the mimic of similar clinical lesions of human disease condition in that rodent model.

Causes of differences in lethal gene inheritance pattern
There is a difference in lethal gene inheritance pattern due to a single mutated gene or both homozygous mutated gene pair combinations in the locus. There is also a difference in the lethal effect not always immediate during embryo development, which may take a year of post-embryonic life of a rodent. In a rodent's lifetime at any stage, a mutation causes mortality. This suggests that the afflicted gene performs a critical role in the development, growth, and survival of an organism. Therefore, depending on the single mutated gene or both mutant genes at a locus result in death being named as dominant, recessive conditional and semi-lethal, etc. If a gene mutation is said to be dominantly acting, only one mutant gene sufficient to cause the disease state is called haplosufficiecy genes (heterozygote condition with one mutant gene. The protein's function may be lost as a result of the mutation due to dominantly negative consequences, or it may work less effectively. For recessive mutation, both genes must be mutated to cause a disease. Many characteristics of mutation in the genes of autosomal or sex chromosomes diseases were explained with either dominant or recessive condition alone not the others.

When come to the breeding, rodent model with a disease will be explained with all the dominant, heterozygote and recessive conditions together.

Current research and review on lethal mutant inheritance

All the earlier studies have analysed human disease genes and the nature of the mutation underlying the disease phenotype. However, none the research explains the differences between disease genes based on the route or pattern s of inheritance. Smith and Eyre-Walker analyse mutational evolution in the Jimenez-Sanchez *et al*., (2001) [4] dataset and report higher conservation in dominant disease genes compared to recessive disease genes (Huang *et al*., 2004) [3]. However, this study observes less selective constraints on lethal or diseased genes compared to non-lethal/disease genes (Smith and Eyre - Walker, 2003) [5]. A study reveals the molecular evolution of the autosomal hu man disease genes depending on their mode of inheritance; namely genes affected by dominant mutations and by recessive mutations (Furney *et al*., 2006) [7]. The comparison of the evolutionary patterns of dominant and recessive disease genes reveals important differences between these two sets of genes that can be understood in terms of their different hereditary nature, giving further insights into the understanding of hereditary human diseases (Kondrashov *et al*., 2004) [6]. Various breeding methods and techniques are explained by Satheesh *et al*. (2021) [8]. Further, in this review enlighten various lethal inheritance pattern and appropriate breeding program for rodent model.

Breeding of rodent model with lethal gene

The breeding goal is understanding the different mutations and inheritance patterns as per selecting the animal for breeding and creating a pedigree chart that displays a specific trait or disorder inherited from parent generation to subsequent generation. Pedigrees are important in rodent breeding which are helps for breeder in selecting rodents with specific diseased trait in parental generation and brings the selected trait in the offspring through selective mating. Pedigree charts are visual representations of family tree and frequently used to investigate the transmission of genetic traits and diseases. It refers to the genetic representation that depicts the biological relationship between individuals and their ancestors and descendants and shows the phenotypes and/or genotypes of each individual of a pedigree. So, it gives better understanding of different patterns of inheritance and entails information about genetic disorders in family history.

Symbols Used in Constructing a Pedigree Chart

Geneticists using the following standardized set of symbols to represent an individual 's sex, family relationships, and phenotype. For indicating male and female in the pedigree tree square and circle were used respectively. In a particular generation multiple individuals were indicated by numbers denoted within the symbols of square and/or circle. An affected or disorder in individual of pedigree indicated by a symbol with colours and those affected individual called *proband individual*. Similarly, a central dot within a symbol represents a *carrier* individual. In pedigree tree *slashes* were connecting the symbol the parent to descendant of all the individuals. If one or two arrows merging on the top of two symbols determine monozygotic twin (identical twin) or fraternal twin (non-identical twin) respectively. These symbols were introduced because all the symbols given in the diagram are very easy to memorize and help breeders for heredity analyse of traits and/or disorders followed by developing suitable breeding strategies.

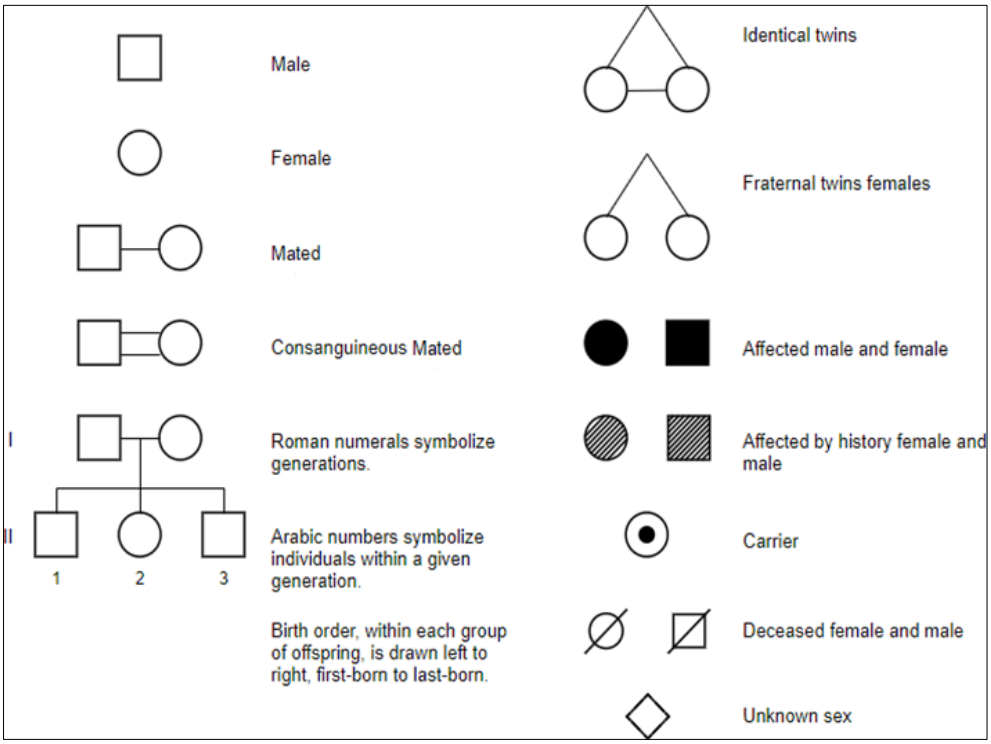
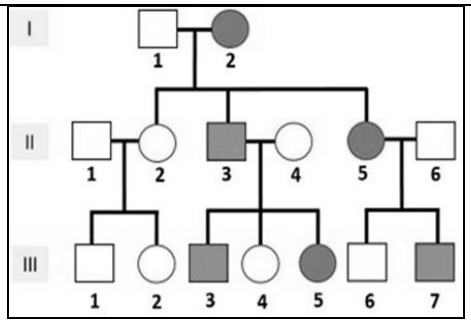
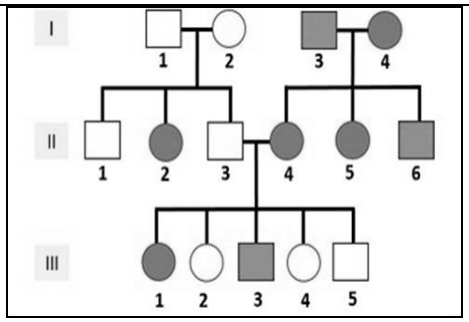
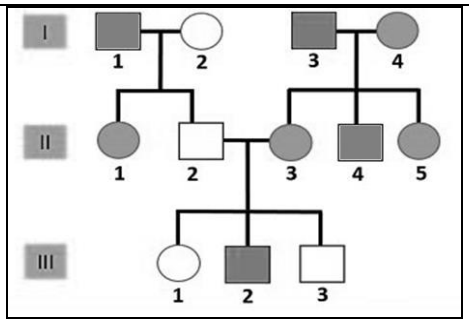
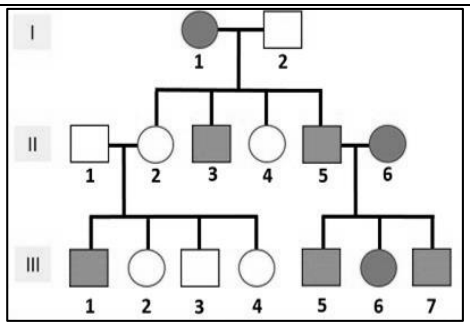
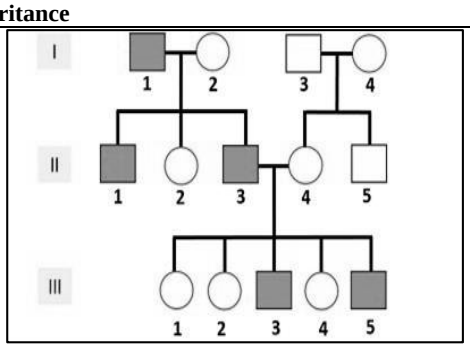


Fig 1: Symbols Used in Constructing a Pedigree

Types of lethal genes inheritance explained by Pedigree Analysis

Breeding of rodent diseased model with lethal genes may affected by dominant or recessive or codominant and/or sex-linked mutations. A breeder can use the following analytical method for understanding of unique pattern of inheritance by displaying data on the heredity of traits and/or disorders by using specific symbols with colours in the pedigree chart.

Table 1: Types of lethal genes inheritance explained by Pedigree Analysis

1. Autosomal dominant lethal gene inheritance	
In autosomal dominant lethal inheritance both the males and females get affected in the same ratio. The lethal trait was expressed themselves in each generation. If both parents have homozygous dominant lethal, then they produce all affected offspring. If both parents have heterozygote dominant lethal then they may produce at least one unaffected offspring. Individuals with heterozygotes lethal condition are affected. Unaffected parents produce unaffected offspring.	 Autosomal dominant lethal gene inheritance on pedigree chart
2. Autosomal recessive lethal gene inheritance	
In autosomal recessive lethal inheritance both males and females are affected in the same ratio. The lethal trait may not be expressed in each generation. Two parents with recessive lethal will only produce affected offspring. Unaffected parents may produce affected offspring since they are carriers or heterozygotes. Individual with carriers/heterozygotes have a normal phenotype.	 Autosomal recessive lethal gene inheritance on pedigree chart
3. X-linked dominant lethal gene inheritance	
In X-linked dominant lethal gene inheritance both males and females are likely to be affected. The lethal trait may express themselves in each generation. The affected male parent can transfer the disease to all female offspring not to male offspring. The affected female parent can transfer the disease to all male offspring not to female offspring.	 X-linked dominant lethal gene inheritance on pedigree chart
4. X-linked recessive lethal gene inheritance	
In X-linked recessive lethal gene inheritance males are relatively more affected than females. The lethal trait may not be expressed in each generation. The affected female parent can transfer the disease to the male offspring. The unaffected carrier female parent can also transfer the lethal gene to the 50% of male offspring. The affected male parent cannot transfer the lethal gene to the male offspring.	 X-linked recessive lethal gene inheritance on pedigree chart
5. Y-linked lethal gene inheritance	
In Y-linked lethal gene inheritance only males. Y-chromosome carries the lethal gene or diseased trait. Disease transmission occurs only from a male parent to all male offsprings. The affected male parent never transfers the lethal gene to the female offspring.	 Y-linked recessive lethal gene inheritance on pedigree chart

Conclusion

When lethal genes are categorized according to their method of inheritance, we find considerable disparities in terms of phenotypes as well as DNA sequence conservation. According to several findings, dominant lethal genes are more conserved than recessive disease genes. Recessive mutations are masked in heterozygote conditions that act as carriers during selection, allowing recessive disease genes to accumulate a greater number in heterozygote conditions in the population. At any condition, genotyping of lethal genes by using suitable markers and identifying the genotypes of all individuals in the pedigree will be highly helpful for accurate selective breeding of rodent models. Several genotyping studies have attempted to computationally identify disease genes. Disease genes were viewed as a homogeneous dataset in this research. We propose that future lethal gene prediction studies should consider the distinctions among homozygous dominant and recessive and heterozygous genotype conditions with respect to their related phenotypic characteristics.

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