Introduction

Most human hereditable traits share characteristics that can be attributed to genes. The investigation of inheritance as it appears in people is called human genetics. Human genetics research can provide insights into human nature, aid in comprehending diseases, creating efficient treatments, and support in apprehending the genetics of human existence [1].

It is vital to comprehend the fundamental laws of inheritance when it comes to appreciating how conditions are passed on in a family from generation to generation [2]. A comprehensive family medical history can be valuable in demonstrating how diseases are handed down through the generations [3]. Nearly every gene possesses two copies; one comes from the mother, and the other is inherited from the father. Scientists have researched human genes to understand how they function regularly and how gene mutations can alter behavioral patterns or traits [4], [5].

Some modifications are tiny and do not impact the functions of a gene. Single nucleotide polymorphisms (SNPs) or gene variations are commonly used to identify these modifications [6]. Some alterations, known as mutations, impact a gene's functionality and can cause disease [7]. In case-control studies, genetic association with specific traits can be established, and genetic heterogeneity can be measured with the help of genetic markers (SNP, RFLP, RAPD, etc.) [8]. Depending on the location of the gene, and whether one or two regular copies of the gene are present, diseases brought on by mutations in a single gene are typically inherited straightforwardly.

Since Gregor Mendel initially detected similar patterns in garden pea plants, this phenomenon is frequently referred to as Mendelian inheritance [9]. The majority of single-gene illnesses are distinctive, but they collectively affect millions of people [10], [11]. For single-gene illnesses, there are several elemental patterns of inheritance, including...
autosomal dominant, autosomal recessive, X-linked dominant, and X-linked recessive. These patterns do not apply to all genetic disorders, and there are other uncommon types of inheritance, like mitochondrial inheritance [9].

Genetic disorders connected to mutations in genes on the X chromosome are referred to as having an X-linked dominant inheritance [12]. Both males and females can develop the condition with just one copy of the mutation. Males with certain diseases pass away because they lack a functional gene. Males and females are not necessarily more affected by X-linked dominant features (unlike X-linked recessive traits). Some X-linked dominant conditions affect females exclusively because they are embryonic lethal in males [13]. Rett syndrome, X-linked lissencephaly, double-cortex syndrome, and incontinentia pigmenti type 1, marked by skin anomalies, eyes, teeth, and nervous system, are examples of X-linked dominant diseases [14].

Pedigree analysis is a worthwhile method for researching how diseases are passed down in humans. Pedigree charts make it more uncomplicated to visualize the ties between families, especially vast extended groups [15]. Genetic disease inheritance patterns (dominant, recessive, etc.) are frequently specified using this method. The risk assessment technique satisfies the comprehension of inheritance patterns. If there is a familial tendency for common chronic diseases like heart disease, obesity, or diabetes, or if the family history is suggestive of a single-gene problem, it aids doctors in making these determinations [16].

Additionally, the risk calculation based on the individual genotype with the application of the conventional probabilistic approach, and also using the Bayesian technique would be another comprehensive support for this methods of prevention and cure for a particular disease. Here, the Bayes theorem will be applied to calculate genotypic probability. Then, this genotypic probability will be updated based on the prior knowledge for any particular genotype of an individual [17]. This paper demonstrates the individual disease risk calculation process by the aforesaid two ways using the information of a pedigree file for a given family.

2. Materials and Methods

2.1. Pedigree Analysis

A basic genetic approach called pedigree analysis reveals how characteristics or illnesses are passed down across the generations within families [18]. It makes use of graphic family trees with male squares, female circles, and connecting lines, as well as pedigree charts. Specific traits or conditions are revealed via distinct symbols or shading. This is a useful tool for researchers to understand inheritance patterns, determine if a trait is dominant or recessive, and calculate the likelihood of a characteristic being passed down to future generations [19]. Pedigree analysis is crucial for guiding choices to attain desired features in animal and plant breeding programs as well as in human genetics for genetic problem evaluation [20]. This is the key to solving the complex puzzle of heredity.

2.2. X-linked dominant inheritance pattern

The X-chromosome comprises of 867 known genes, the majority of which are involved in the development of tissues such as bone, neural, blood, hepatic, renal, retina, ears, ear, cardiac, skin, and teeth. There are at least 533 diseases caused by X-chromosomal gene involvement [21]. A 'trait' or 'disease' caused by an X-chromosome gene reveals X-linked inheritance. In the broader perspective, diseases or traits related to the X-chromosome are passed down from generation to generation in two subtypes, which are X-linked dominant and X-linked recessive.
Among the two categories, in the X-linked dominant pattern, when both father and mother are unaffected, all the children, whether male or female, will remain unaffected. On the contrary, when the father is affected, all of his daughters will get affected because all of their daughters will receive a copy of their father's affected allele [22]. In this distinct inheritance pattern, in every case, the father-to-daughter disease or trait transmission is witnessed, whereas there will be no father-to-son transmission. Additionally, when the mother is affected, and the father is unaffected, both half of the sons and half of the daughters will be affected even though the other half will remain healthy. Sons can only possess the trait if their mother also contains it [23]. Eventually, when both father and mother are affected, all the daughters will be affected, whereas half of the sons will be affected. Here is some disease for reasons of X-linked dominant like, intellectual disability, neurobehavioral abnormalities [24], Incontinentia pigmenti (Bloch-Sulzberger syndrome) [25], and intellectual disability (ID) [26] etc.

The underlying notion of an X-linked dominant inheritance pattern can be articulated for genotype counts of Single Nucleotide Polymorphisms (SNP). For instance, the genotype counts for a SNP with disease allele \{X'\} and normal allele \{X\} are homozygous \{X'X'\}, heterozygous \{X'X\}, and opposite homozygous \{XX\}. The dominant model (for the \(X'\) allele) assumes that having one or more copies of the \{X'\} allele increases risk compared to the \{X\} allele. As a consequence, genotypes \{X'X'\} or \{XX\} have a higher risk.

### 2.3. Genotypic Probability

Assuming some of the cases of X-linked dominant inheritance patterns to cultivate the descriptive structure of X-linked dominant inheritance pattern. It is apprehended that each female carries XX chromosomes [27], and each male carries XY chromosomes [28]. The possible parental genotypes for X-linked dominant inheritance pattern are affected mother \{X'X\} or \{X'X'\}, affected father \{X'Y\}, unaffected father \{XY\}, and unaffected mother \{XX\}. Some examples of X-linked dominant inheritance patterns where the parental genotypic combinations alongside their offspring’s genotypic probability generalization are demonstrated below:

**Possible cases**

**Case-1: Affected mother \{X'X\} and unaffected father \{XY\}**

When the mother is affected with genotype \{X'X\}, and the father is unaffected with genotype \{XY\}, then 50% of the male and female offspring will be affected possessing a genotype of \{X'X\}, and \{X'Y\}, whereas 50% of the male \{XY\} and female \{XX\} offspring will be thoroughly unaffected.

**Case-2: Affected mother \{X'X'\} and unaffected father \{XY\}**

When the mother is affected having genotype \{X'X'\}, and the father is unaffected with genotype \{XY\}, then 100% of the offspring will be affected, where female offspring will have genotype \{X'X\}, and male offspring will have genotype \{X'Y\}.

**Case-3: Affected mother \{X'X'\} and affected father \{X'Y\}**

If mother and father both are affected having genotypes \{X'X'\} and \{X'Y\}, respectively, then 100% of the offspring will be affected. Female offspring will have genotype \{X'X'\}, and male offspring will have genotype \{X'Y\}.
Case-4: Affected mother {X’X} and affected father {X’Y}

When mother and father both are affected with genotypes {X’X} and {X’Y} respectively, then 100% female offspring will be affected, and 50% male offspring will be affected. Half of the female offspring will have genotype {X’X’}, and another half will have genotype {X’X}. Also, half of the male offspring will have genotype {X’Y}, and another half will have genotype {XY}.

Case-5: Unaffected mother {XX} and affected father {X’Y}

When the father is affected with genotype {X’Y}, and the mother is unaffected having genotype {XX}, then 100% of the female offspring, and no male offspring will be affected. Female offspring will have genotype {X’X} and male offspring will have genotype {XY}.

2.4. Bayesian Technique

In this study, the Bayesian technique was used to estimate the risk of being an affected offspring in an X-linked dominant inheritance pattern for different parental genotypic combinations. The mathematical expression of the Bayesian technique is given below,

\[
P(H_0|O) = \frac{P(H_0) \cdot P(O|H_0)}{\sum_{i=1}^{n} P(H_0) \cdot P(O|H_0)}
\]

where, \( P(H_0) \) is the prior probability of the \( i^{th} \) event; \( P(O|H_0) \) is the conditional probability of occurring event \( O \) when \( P(H_0) \) is true, and \( P(H_0|O) \) is the posterior probability that \( H_0 \) will occur given that event \( O \) is true.

2.5. Data Generation

Simulated data were generated for four families and 45 individuals through the computer simulation using Statistical software “R”. Table 1 presents the simulated data set used in this study. Here, the incorporated variables were Family ID, Individual ID, Paternal ID, Maternal ID, Sex, Phenotype, Carrier and Genotype. The personal identification factor is labeled by the 'Individual ID' under each family. The 'Paternal ID' and 'Maternal ID' are the identification of individual's fathers and mothers. Gradually, the 'Sex' column is considered for the gender (1 = male, 2 = female) of a distinct individual. The 'Phenotype' column indicated whether an individual is affected or not (1 = affected, 0 = unaffected), and likewise, the 'Carrier' column is applied for mentioning the carrier status (1=carrier, 0= unaffected). The genotype of an individual is denoted through the 'Genotype' column.

Table 1. The simulated pedigree information of four families and 45 individuals.

<table>
<thead>
<tr>
<th>Family ID</th>
<th>Individual ID</th>
<th>Paternal ID</th>
<th>Maternal ID</th>
<th>Sex</th>
<th>Phenotype</th>
<th>Carrier</th>
<th>Genotype</th>
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<tbody>
<tr>
<td>1</td>
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<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<tr>
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<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>X’X</td>
</tr>
<tr>
<td>2</td>
<td>201</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<td>0</td>
<td>X’X</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>103</td>
<td>104</td>
<td>101</td>
<td>102</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
3. Results

3.1. Frequentist genotypic probability and pedigree analysis

This analysis started with the pedigree analysis of the X-linked dominant inheritance pattern based on the frequentist genotypic probability of 45 individuals from 4 families. Families were denoted by “Family ID: 1”, “Family ID: 2”, “Family ID: 3”, and “Family ID: 4”. Individuals had unique IDs, in which the first digit of the individual ID corresponded to the family ID number. For different parental genotypic combinations, the 5 possible cases were found in X-linked dominant inheritance. Two pedigree charts (Figure 1(a) and Figure 1(b)) were constructed on the genetic heritage simulated data of 45 individuals of 4 families to analyze these possible cases. Here, the Figure 1(a) considers the family information of family 1 and 2, whereas, the family information from family 3 and 4 were considered in the pedigree of Figure 1(b). For an individual genotype, the risk was calculated using the conventional probabilistic approach by considering all possible combinations of the parents.

Case 1: Affected mother {X'X} and unaffected father {XY}

In Figure 1(a), the “ID 209” individual was an affected mother having one disease allele with genotype {X'X}, and the IV:210 individual was an unaffected father with genotype {XY}. They had four offspring with Individual IDs V:212, V:213, V:214, V:215 having different genotypes, {X'X}, {X'Y}, {XX}, and {XY}, of which 2 offspring were female (V:212, V:214) and 2 offspring were male (V:213, V:215). Each of the offspring had the same genotypic probability of \( \frac{1}{4} \) of being affected. From the pedigree chart it was observed that 50% of the offspring were affected, and 50% of the offspring were unaffected. Among the affected offspring, 50% were male, and another 50% were female (Figure 1(a)).

Case 2: Affected mother {X'X'} and unaffected father {XY}

This case were observed in the generation IV, whereas it was started in the generation III from mating an affected mother (III:108) having genotype {X'X'} with an unaffected father (III:205) with genotype {XY} (Figure 1(a)).
This couple had 2 offspring (IV:208, IV:209), and both of them were affected. Of these 2 offspring, one was female (IV:209), and another was male (IV:208) with the genotypes \{X'X\} and \{X'Y\}, respectively. The genotypic probability of developing disease was $\frac{1}{2}$ for both.

**Case 3: Affected mother \{X'X'\} and affected father \{X'Y\}**

In the third case, the mother (II:403) had genotype \{X'X'\}, and the father (II:304) had genotype \{X'Y\}. They had 2 offspring (III:308, III:309). One of the 2 offspring was affected male (III:308), and one was affected female (III:309) with individual genotypes \{X'Y\} and \{X'X'\}, respectively. In this case, 100% of male and female offspring were affected and they had the same genotypic probability of $\frac{1}{2}$ (Figure 1(b)).

**Case 4: Affected mother \{X'X\} and affected father \{X'Y\}**

The mother (IV:312) and the father (IV:313) had the genotypes \{X'X\}, \{X'Y\}, respectively (Figure 2(b)). This couple had four offspring, of which three were affected (V:314, V:316, V:317; genotypes: \{X'Y\}, \{X'X'\}, \{X'X\}), and one was unaffected (V:315, genotype: \{XY\}). All had the same genotypic probability of $\frac{1}{4}$. In this case, two female offspring, or 100% female offspring were affected (V:316, V:317), and one of two male offspring, or 50% male offspring was affected (V:314) (Figure 1(b)).

![Ancestry charts for X-linked dominant inheritance patterns](image)

**Figure 1.** Ancestry charts for X-linked dominant inheritance patterns, where squares indicate male and circles indicate female; deep black indicates the affected condition and white indicates the unaffected condition. The generations in each chart is denoted by the roman letters. The individual genotype is presented by the combination of two uppercase letters (X or Y), the risk obtained from the conventional probabilistic approach is shown by the fraction number. (a) For 23 individuals of family 1 and family 2, (b) For 22 individuals of family 3 and family 4.
Case 5: Unaffected mother \{XX\} and affected father \{X'Y\}

There were two offspring (IV:311, IV:312), where one was an affected female (IV:312), and one was an unaffected male (IV:311). The combinations of their parental genotypes were \{XX\} (III:307) and \{X'Y\} (III:308), respectively. Offspring genotypes were \{XY\} and \{X'X\} with the same genotypic probability of developing a particular disease that is 1/2. In this case, 100% of female offspring were affected and the male offspring were unaffected (Figure 1(b)).

3.2. Genotypic probability based on the Bayesian approach

The Bayesian technique was used to calculate the genotypic probability for each of the observed five possible cases (Case 1 to Case 5) for different parental genotype combinations using equation (1). In each case, the parent has a specific genotype combination can have several offspring with different genotypes. For each type of offspring genotype, a specific genotypic probability (risk) was calculated using conventional probabilistic approach (Figure 1(a) and Figure 1(b)), which will be further used as the prior information of the Bayesian approach. Since, the individual offspring genotype can be inherited from different parental genotype combinations, hence, this genotype based probabilistic information will be used to update our prior genotypic probability, and got a posterior genotypic probability (Table 2).

<table>
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<tbody>
<tr>
<td>Case 1:</td>
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<td></td>
</tr>
<tr>
<td>{X'X}, {XY}</td>
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</tr>
<tr>
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<tr>
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<td>{X'Y}</td>
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<td>0.25</td>
<td>0.0625</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>{XY}</td>
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<td>0.25</td>
<td>0.0625</td>
<td>0.20</td>
</tr>
<tr>
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<td>0.125</td>
<td>0.50</td>
</tr>
<tr>
<td>{X'Y}, {XY}</td>
<td>{X'Y}</td>
<td>0.50</td>
<td>0.25</td>
<td>0.125</td>
<td>0.50</td>
</tr>
<tr>
<td>Case 3:</td>
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<tr>
<td>{X'Y}, {XY}</td>
<td>{X'Y}</td>
<td>0.50</td>
<td>0.25</td>
<td>0.125</td>
<td>0.33</td>
</tr>
<tr>
<td>Case 4:</td>
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<td>0.125</td>
<td>0.40</td>
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<td>{X'Y}, {XY}</td>
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<td>0.0625</td>
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</tr>
<tr>
<td></td>
<td>{X'Y}</td>
<td>0.25</td>
<td>0.25</td>
<td>0.0625</td>
<td>0.20</td>
</tr>
<tr>
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<td>{XY}</td>
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<td>0.25</td>
<td>0.0625</td>
<td>0.20</td>
</tr>
<tr>
<td>Case 5:</td>
<td>{XX}, {X'Y}</td>
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<tr>
<td></td>
<td></td>
<td>{XY}</td>
<td>0.50</td>
<td>0.25</td>
<td>0.125</td>
</tr>
</tbody>
</table>
Case 1: Affected mother \{X'X\} and unaffected father \{XY\}

In “Case 1” the mother had the genotype \{X'X\}, and the father had the genotype \{XY\}. For this parental genotypic combination, there were four different offspring genotypes, \{X'X\}, \{XX\}, \{X'Y\}, and \{XY\}. The offspring genotypes \{X'X\}, \{X'Y\}, and \{XY\} can be inherited from four different parental genotype combinations. And offspring genotype \{XX\} can be inherited from two different parental genotype combinations. Prior information or prior genotypic probability was 0.25 for all the offspring genotypes (\{X'X\}, \{XX\}, \{X'Y\}, and \{XY\}) (Figure 1(a)). Using the information of parental genotypic combinations, the posterior genotypic probabilities were calculated as 0.20, 0.40, 0.20, and 0.20 for the genotypes \{X'X\}, \{XX\}, \{X'Y\}, and \{XY\} (Table 2).

Case 2: Affected mother \{X'X'\} and unaffected father \{XY\}

In the second case, the mother had genotype \{X'X'\}, and the father had genotype \{XY\}. This couple have only two offspring having genotypes \{X'X\}, and \{X'Y\}, respectively. Both offspring genotypes can be inherited from four different parental genotype combinations. Prior information or prior genotypic probability was 0.50 for both offspring genotypes (\{X'X\}, and \{X'Y\}) (Figure 1(a)). The calculated posterior genotypic probability were also 0.50, and 0.50 for offspring genotypes \{X'X\}, and \{X'Y\}, respectively (Table 2).

Case 3: Affected mother \{X'X'\} and affected father \{X'Y\}

Here, the parental genotype combinations are \{X'X'\} and \{X'Y\}, respectively. Their possible offspring genotypes were \{X'X'\}, and \{X'Y\}. The offspring genotype \{X'X\} can be inherited from two different parental genotype combinations, and the offspring genotype \{X'Y\} can be inherited from four different parental genotype combinations. Prior information or prior genotypic probability was 0.50 for both offspring genotypes (\{X'X'\}, and \{X'Y\}) (Figure 1(b)). The calculated posterior genotypic probability was 0.67, and 0.33 for offspring genotypes \{X'X'\}, and \{X'Y\}, respectively (Table 2).

Case 4: Affected mother \{X'X\} and affected father \{X'Y\}

In “Case 4”, the genotypes \{X'X\} and \{X'Y\} belong to the mother and father, respectively. Their possible offspring genotypes were \{X'X\}, \{X'X\}, \{X'Y\}, and \{XY\}. The offspring genotypes \{X'X\}, \{X'Y\}, and \{XY\} can be inherited from four different parental genotype combinations. And offspring genotype \{X'X'\} can be inherited from two different parental genotype combinations. Prior genotypic probability was 0.25 for all the offspring genotypes (\{X'X\}, \{X'X\}, \{X'Y\}, and \{XY\}) (Figure 1(b)). The calculated posterior genotypic probabilities were 0.40, 0.20, 0.20, and 0.20 for the genotypes \{X'X\}, \{X'X\}, \{X'Y\}, and \{XY\} (Table 2).

Case 5: Unaffected mother \{XX\} and affected father \{X'Y\}

In the fifth case, the mother had genotype \{XX\} and the father had genotype \{X'Y\}. Their possible offspring genotypes were \{X'X\}, and \{XY\}. Both offspring genotypes can be inherited from four different parental genotype combinations. Prior genotypic probability was 0.50 for both offspring genotypes (\{X'X\}, and \{XY\}) (Figure 1(b)). The calculated posterior genotypic probability was also 0.50, and 0.50 for offspring genotypes \{X'X\}, and \{XY\}, respectively (Table 2).
4. Discussions

From the pedigree charts (Figure 1), there are five possible cases based on parental genotype combinations. In "Case 1" the mother (IV:209) was affected with genotype \{X'X,\} and the father (IV: 210) was unaffected with genotype \{XY\}, and 50% of the offspring was affected of which 25% of the offspring was female and rest of the 25% of the offspring was male. The frequentist genotypic probability (0.50) was the same for all the offspring (Figure 1(a)). But, in the Bayesian approach, it was found that 40% of offspring had the chance of being affected of which 20% would be female and 20% would be male (Table 2). In "Case 2" the mother (III:108) was affected having genotype \{X’X’\}, the father (III:205) was unaffected having genotype \{XY\}, and 100% of the offspring were affected. The Genotypic probability calculated by the frequentist approach was 0.50 for all (Figure 1(a)). The genotypic probability of offspring genotypes calculated in the Bayesian approach was also 0.50 for this parental combinations (Table 2). This means that 50% of female offspring and 50% of male offspring of the “Case 2” parents had the chance of being affected. For "Case 3", mother (II:403) and father (II:304) both were affected and had genotype \{X’X’\} and \{X’Y\}, respectively. In this case, 100% of the offspring were affected, and had the same genotypic probability of 0.50. Among all the affected offspring 50% was female and 50% was male (Figure 1(b)). But, in the Bayesian approach, it was found that 67% of female offspring and 33% of male offspring had the chance of being affected (Table 2). In "Case 4", the mother (IV:312) was affected with genotype \{X’X\} and the father (IV:313) was affected having genotype \{X’Y\}, and 75% of the offspring were affected of which 50% of the offspring was female and 25% of the offspring was male. All offspring genotypes had the same genotypic probability (0.25) (Figure 1(b)). But, in the Bayesian approach, it was observed that 80% of the offspring of the "Case 4" parent had the chance of being affected of which 60% were female and 20% were male (Table 2). For "Case 5", the mother (III:307) was unaffected and the father (III:308) was affected, and had genotypes \{XX\} and \{XY\}, respectively. Their male or female offspring had the same genotypic probability of 0.50 and 50% offspring were affected. All affected offspring were male. The genotypic probability (0.50) calculated in the Bayesian approach was found same as the frequentist approach (Figure 1(b), Table 2).

5. Conclusions

The genotype-based risk analysis was practically demonstrated in this paper for the X-linked dominant inheritance pattern. The two approach were applied for this assessment. One is the conventional probabilistic approach (frequentist) and the other is the Bayesian approach. Based on the simulated pedigree information of 45 individuals from the four distinct families, two pedigree analysis were done at the preliminary stage. Further, five different types of cases were identified from these two pedigree based on different parental genotype combinations. The genotypic probability for every individual was calculated for each of the observed cases using both the frequentist and the Bayesian approach. It was also observed that every identified cases were observed due to the affected status of the mother. Between the two allele, when one disease allele is present in the mother’s genotype, 50% of the offspring from each gender were affected. On the other hand, the two alleles of the mother is disease allele, 100% offspring were affected regardless the gender. For an affected father, all female offspring were affected. The genotypic probability (risk) of the offspring varies depending on the parental genotypic combinations. In most cases, it was observed that the chances of being affected were higher in females than in males. Though the simulated
data was used in this study due to some constraints, the methodological structure and the ways of feature extraction will help the introductory genetic researchers to cope with such type of genetic study of inheritance.

**Limitations**

Due to some limitations such as insufficient lab-server facilities and lack of financial support, the real data can’t be applied for this analysis. However, the methodological process and the features of the results would be similar if the real data set were used.

**Declarations**

**Source of Funding**

This study did not receive any grant from funding agencies in the public or not-for-profit sectors.

**Conflict of Interest**

The authors declare that they have no conflict of interest.

**Consent for Publication**

The authors declare that they consented to the publication of this study.

**References**


