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Risk Assessment of X-Chromosomal Recessive Inheritance using Bayesian Approach: A Simulation Study

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ABSTRACT

The main objectives of this study were to extract characteristics and to examine the transmission of a trait (disease) through X-linked recessive inheritance patterns in families. The assessment of the risk of inheriting a specific genotype, based on frequentist and Bayesian techniques as well as a comparison between the two approaches, which was the additional objective. To fulfil the objectives, data were simulated for six families, which were then subdivided into three cases. Pedigree analyses were done for the three cases with genotypes and genotypic probability, which was based on the frequentist approach. The genotypic probability for a particular individual remained consistent regardless of family size for a certain set of parents. In the case which was consisted of two families with 28 individuals over six generations, the Bayesian approach was also applied to assess the probability of affected status for a particular individual where the individual had 5% lower probability of being affected male, unaffected male, or carrier female using the Bayesian approach than the frequentist (genotypic) approach, whereas 15% higher probability was found by using the Bayesian approach than the frequentist approach of being unaffected female.

1. INTRODUCTION

Isn't it mystical that sometimes we possess the generational disorder of our grandfathers or ancestors despite having one or two generation gaps? Furthermore, there isn't a question that can arise as to why a disease is transmitted to only male offspring when their mother is affected or carries the disease, whereas their father is solely unaffected. A disease from generation to generation is not something that transmits without any scientific backbone or logical reasoning. The mechanism of trait inheritance, including the phenomenon of skipping generations, was first elucidated by Gregor Mendel [1].

Considering the commencement from the foundational aspects, life starts from the smallest microscopic cell, where the nucleus is considered as the fundamental unit of a cell. A nucleus is an organelle that is surrounded by a membrane and contains the cell's chromosomes. A single nucleus consists of 23 pairs of chromosomes, of which 22 pairs are termed as autosomes, and one pair is a sex chromosome, which is responsible for determining gender. Each chromosome in a pair comes from each of the parents. Therefore, half of the chromosomes are inherited from the mother and the other half from the father. Chromosomes are structured, resembling threads that are composed of protein and a single DNA molecule. They serve the purpose of carrying genetic information from one generation to another generation. A specific segment of DNA is named as gene, which is operated as the repository of genomic information that determines the physical and biological traits or diseases of an offspring from the parents [2]. An allele, a gene variant, is accountable for shaping genotypic outcomes and regulating specific diseases or phenotypes. Following some ancestry patterns, these traits or diseases are dispatched from ancestors to the offspring. Some disorders like Myotonia Congenital [3], Emery-Dreifuss syndrome [4], and Triphalangeal thumb [5] come under relevant examples. The classification of ancestry patterns are Autosomal Dominant, Autosomal Recessive, X-linked

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Dominant, X-linked Recessive, and Y-linked Dominant. Morgan established the "rules" for X-linked dominant and recessive inheritance more than 80 years ago [6]. In a distinct sex chromosome, females have two X chromosomes (XX), while males have one X and one Y chromosome (XY) where Autosomal dominant traits exhibit dominance over recessive traits, resulting in the expression of phenotypes based on the dominant allele [7]. As a consequence, the demonstrated traits are found in every generation of the family, containing identical frequency to both males and females [8]. On the contrary, in autosomal recessive inheritance, the attributes or traits are not identified in every generation of the family. If a person is affected, both parents are at least heterozygous for the disease-causing gene. This study focuses on ancestry patterns related to X-linked inheritance, distinguishing between X-linked dominant and X-linked recessive inheritance. In X-linked dominant inheritance, the disease manifests in every generation. If a male is affected, all of his daughters but none of his sons are affected. If a female is affected, approximately half of their children are also affected, regardless of their gender, for example, Ehlers-Danlos syndrome [9]. In contrast, X-linked recessive inheritance primarily affects males, making it the central focus of this topic. Focusing on the X-linked recessive inheritance patterns distinctly, almost only males are affected, and that is the main concern of this topic. For example, Familial exudative vitreoretinopathy [10], bulbospinal neuronopathy [11] and color blindness [12].

Pedigree analysis is one of the preliminary methods for analyzing such inheritance patterns for investigating the different scenarios (Full penetrance, reduced penetrance, twins) [13]. The data collected from genome sequencing is employed in pedigree analysis to form a visualization depicting how a distinct unit of characteristic, like disease, passes to the offspring from the past generation. Additionally, information gathered from genome sequencing enhances the molecular diagnostic compared to the concurrent diagnostic method. However, it requires a high volume of data, which is very costly. Hence, it is radically difficult to conduct this study using real-life DNA sequencing data as we had no financial and technological support.

This type of bottleneck discourages new researchers from contributing to this field. To mitigate this issue, we generated simulated data to perform initial steps of genetic inheritance based upon X-linked recessive mode, which were resolved by implementing a pedigree chart, which eventually permitted us to inquire about the multiple situations alongside conducting information retrieval from the pedigree chart.

2. MATERIALS AND METHODS

2.1 Pedigree Analysis

In genetic research, pedigree analysis is the initial and most fundamental stage in determining how a trait is inherited from one generation to the next [13]. Usually, A pedigree chart or an ancestry chart consists of some basic shapes including square boxes, circles, and triangles. These shapes are used to indicate different genetic conditions including male, female, affected, unaffected, deceased, twins, adopted, and miscarriage (Figure 1). Additionally, a pedigree chart also helps to understand the relationship between two individuals indicating the marriage line, and sibling line.

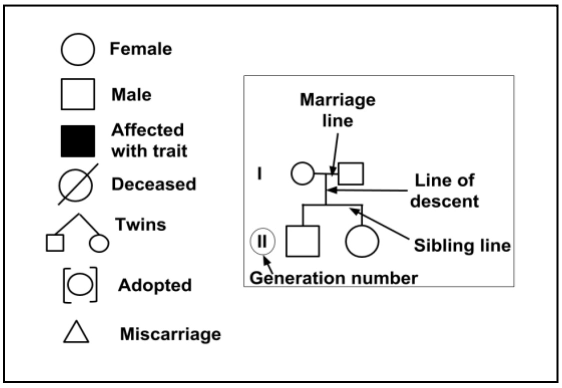


Fig. 1. An cestry Chart with several indicators based on circle, square, and triangle shapes

2.2 X linked recessive inheritance pattern

Considering X-linked recessive inheritance, the gene which is liable for the disease is positioned on the X chromosome. Hence, it is directed to males with one and only X chromosomes being more susceptible to the disorder [14]. Contrariwise, females may function as carriers when they inherit a single affected X chromosome; still, they typically exhibit no symptoms because of the balancing effect of their supplementary X chromosome [15]. Eventually, females get affected when they possess two disease alleles (XX) [16]. Figure 2 illustrates the basic characteristics of X-lined recessive inheritance patterns including males are almost

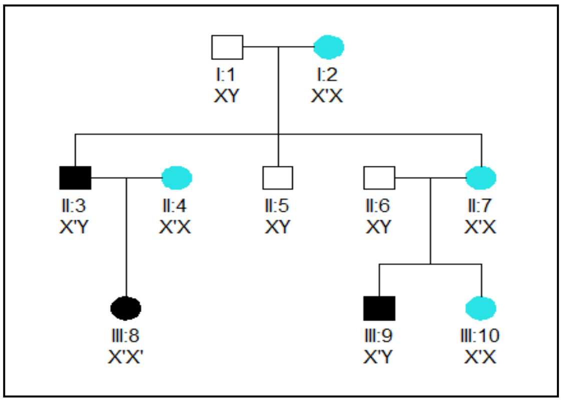


Fig. 2. Ancestry Chart for X-linked Recessive inheritance pattern for 10 individuals where squares indicate male and circles indicate female; Black indicates the affected condition; White indicates unaffected condition, and Blue indicates the carrier

exclusively impacted; Not all generations of the family are afflicted with the disease; In the case of a male being affected, his mother becomes a carrier. Conversely, approximately half of her sons and half of her daughters will exhibit the trait and serve as a carrier; If a female is affected, it indicates that her father is also affected, in addition to her being a carrier. Conversely, the allele is not passed down to any of his sons but rather to all of his daughters[17].

The notion of a "generation gap" is recognized explicitly in X-linked recessive inheritance [18]. Diseases bounce generations, commonly reappearing amidst males. For instance, female carriers might not demonstrate symptoms but can convey the gene to their male children, assembling a fallacy that the disorder overlooked a generation.

Distinct models employed in genetic research for apprehending X-linked recessive patterns are equivalent to those for autosomal recessive inheritance. However, this approach accounts for both male and female inheritance technicality and the possibility of bypassing generations. Operated models like these also assess the penetrance of the gene and statistical correlations between the gene's existence and disease embodiment.

2.3 Genotypic Probability

Assuming some of the cases of X-linked recessive inheritance patterns to cultivate the descriptive structure of X-linked recessive inheritance pattern. It is comprehended that each female carries XX chromosomes (18), and each male carries XY chromosomes (19), where X'X' genotypic formation of two disease alleles is the reason behind females getting affected (20). On the other side, X'Y is eligible enough to affect a male with a disease, and it happens because of the fact that X' is the only disease-causing allele in a male body (21). Based on these criteria, let us consider some cases of X-linked recessive inheritance patterns.

- When a father (X'Y) is affected, and a mother is unaffected, then 100% of the female offspring will be carrier possessing a genotype of X'X, whereas 100% of the male (XY) offspring will be thoroughly unaffected [23]. Based on case-1, hypothetically, other cases of X-linked recessive inheritance patterns can be formulated.
- When a father is affected (X'Y), and a mother (X'X) is considered as the carrier, 25% of the male offspring is unaffected (XY), and 25% of the female offspring is affected (X'X'). Similarly, 25% of the male offspring is affected, and the remaining 25%, female offsprings, are considered carriers [17].
- If the mother is affected, and the father is unaffected, then 100% of the male offspring will be affected, and 100% of the female offspring will be the carriers[17] .
- When the father is absolutely unaffected, and the mother is a carrier, then affected and unaffected male offspring will be 25% and 25%, respectively. Similarly, as in the cases stated above, the probability of unaffected female offspring is 25%, and carrier female offspring is 25% [17].
- When both father and mother are affected with disease, then 100% of the male and female offspring will be affected [17].

2.4 Bayesian Technique

The Bayesian technique is another method, used for updating the probability of occurring any particular event based on prior knowledge and newly updated evidence. In genetics, this method is usually used to assess the risk of being diseased due to related genotypes [19], estimate the allele frequency, estimate missing value of genotype data, etc. The following mathematical expression of the Bayesian technique was used to estimate the probability of risk of having different genetic conditions.

$$P(H_{0i}|O) = \frac{P(H_{0i})\,P(O|H_{0i})}{\sum_{i=1}^{n} P(H_{0i})\,P(O|H_{0i})} \quad (1)$$

Where, $P(H_{0i})$ is the prior probability of ith hypothesis; $P(O|H_{0i})$ is the conditional probability of occurring an event O given that H_{0i} is true, and $P(H_{0i}|O)$ is the posterior probability that H_{0i}will occur given that event *O* is true.

2.5 Data Generation

Data were simulated for six families using statistical software "R". The simulated data consisted of several variables including Family ID, Individual ID, Paternal ID, Maternal ID, Sex, Phenotype, Carrier, Genotype, and Probability. Family ID represented the identity of six families whereas Individual ID was the indicator of personal identification under each family. Paternal and maternal ID were the identifying of individual's fathers and mothers. Sex denoted the gender (male or female) of an individual, whereas Phenotype indicated whether or not the individual was affected (affected or unaffected). Carrier denoted the carrier status (carrier or unaffected) of an individual. The variables Genotype and Probability indicated the genotype of an individual and the genotypic probability (frequentist approach) of having the particular genotype respectively.

3. RESULTS

The data generated for six families were subdivided into three cases where case 1 included the first two families (Family ID: 1 and 2); case 2 included the second two families (Family ID: 2 and 3); case 3 included the last two families (Family ID: 5 and 6).

3.1 Case 1: Two families with 14 individuals over four generations

In Figure 3(a), The first family(left) started with two individuals with IDs 1 (affected male) and 2 (unaffected female) in the first generation. The genotype of the first individual was X'Y whereas the genotype for the second individual was XX. As one disease-causing allele was located on one of the sex chromosomes, the individual with ID 1 was impacted according to its hemizygous status. On the other hand, due to two normal alleles located on two sex chromosomes, the second individual was unaffected. They met and had two children with the IDs 5 (carrier female) and 6 (unaffected male) in the second generation where the 5th individual possessed one disease-causing allele on one of her X chromosomes, making her a carrier according to recessive inheritance pattern. Based on the genotypes of the parents, the genotypic probability for a carrier female (II:5) and an unaffected male (II:6) was 1/2. A carrier female (X'Y) with ID 7 mat with a male (II:6) in the second generation of the first family and gave birth to two male offsrings, one of whom was affected (III:11) and one of whom was unaffected (III:12). The genotype of the affected male was X'Y with a genotypic probability of 1/4, whereas the genotype of the unaffected male was XY with the same genotypic probability in the third generation. The second family(right) began with two individuals with IDs 3 (male) and 4 (female) and genotypes XY and X'X respectively in the first generation, where female (I:4) was a carrier due to one disease-causing allele located on one of the sex chromosomes denoted by X' and male(I:3) was unaffected due to having two normal alleles on two sex chromosomes. They met and had two children with the IDs 9 (unaffected female) and 10 (affected male) with genotypes XX and X'Y. The genotypic probability of this affected male (II:10) and unaffected female (II:9) were the same 1/4 in these second generation. The unaffected female (II:9) with genotype X'Y met with an affected male (II:8) and gave birth to one daughter (III:13) who was a carrier with genotype X'Y with the genotypic probability 1/2. In the third generation, the unaffected male (III:12) of the first family and the carrier female (III:13) of the second family met and gave birth to a male child who belonged to the fourth generation. X'Y was the genotype with genotype probability 1/4 of the 14th and last individual of the family.

3.2 Case 2: Two families with 16 individuals over four generations

In Figure 3(b), a pedigree chart was generated for the third (left) and fourth (right) families. The third family started with two individuals with IDs 1 (male) and 2 (female) in the first generation. The genotype of the first individual was X'Y whereas the genotype for the second individual was X'Y. They met and had three children with IDs 5 (affected female), 6 (affected male) and 7 (carrier female) in the second generation. The genotypes of the 5th, 6th, and 7th individuals, with equal genotypic probability, were X'X, X'Y, and X'X, respectively. Among the three siblings, the female with ID 7 met with the 8th affected male with genotype X'Y and gave birth to one affected male with genotype XY and genotypic probability 1/4 and one carrier female with genotype X'Y and genotypic probability 1/4 in the third generation. The fourth family began with two individuals with IDs 3 (unaffected male) and 4 (affected female) with genotypes XY and X' X' respectively in the first generation. They met and had two children with the IDs 9 (affected male) and 11 (affected male) with genotypes X'Y and X'Y. The genotypic probabilities of these affected males (II:9, II:11) were the same 1/2 in the second generation. The affected male (II:9) with genotype X'Y met with a carrier female (II:10) and gave birth to one daughter (III:15) who was affected whose genotype was X' X' with the genotypic probability 1/4 and one affected son (III:14) whose genotype was X'Y with genotypic probability 1/4. In the third generation, the affected male (III:14) of the fourth family and the carrier female (III:13) of the third family met and gave birth to a female child who belonged to the fourth generation. X'Y was the genotype with genotype probability 1/4 of the 16th and last individual of the family.

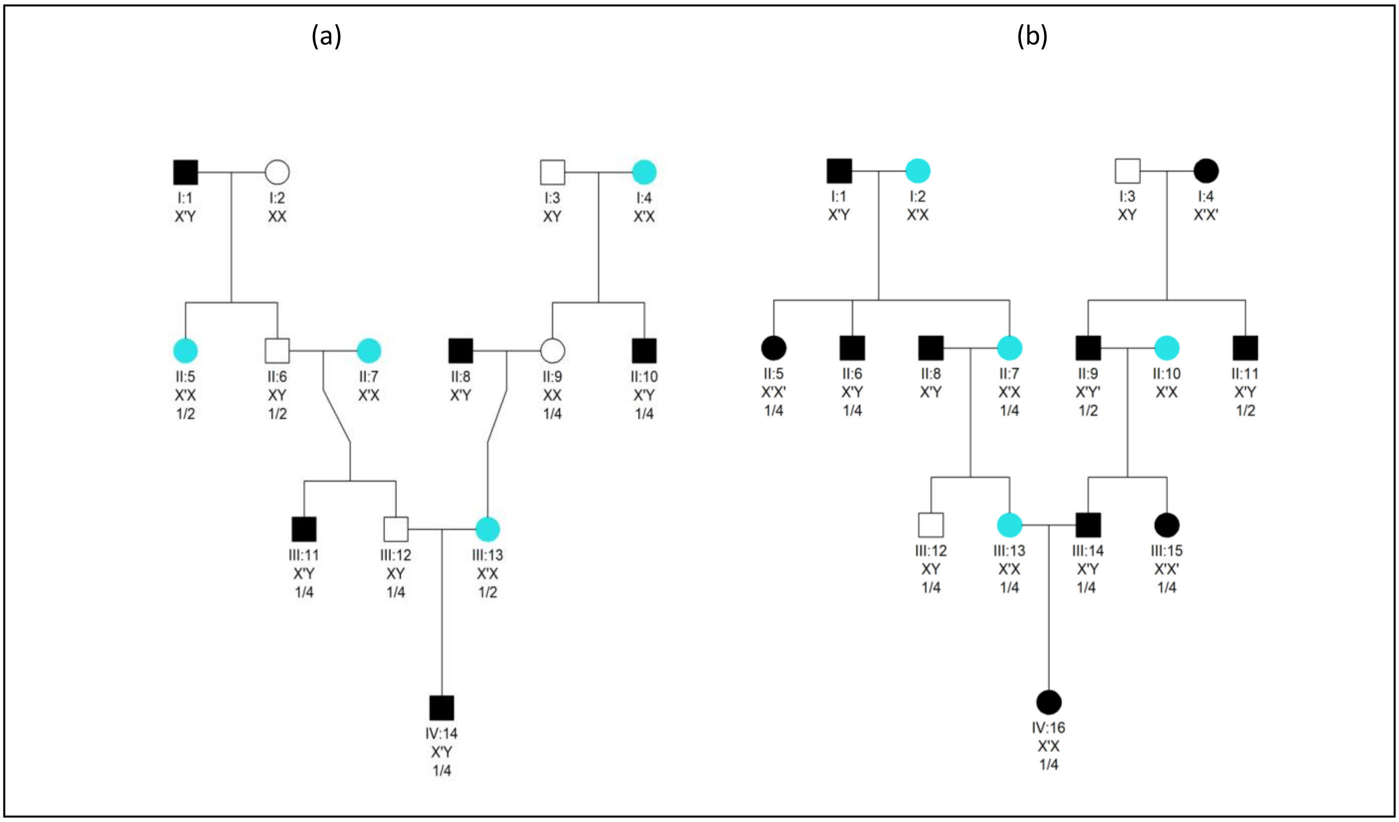


Fig. 3(a). Ancestry Chart for X-linked Recessive inheritance pattern for 14 individuals where squares indicate male and circles indicate female; Black indicates the affected condition; White indicates unaffected condition, and Blue indicates the carrier

Fig. 3(b). Ancestry Chart for X-linked Recessive inheritance pattern for 16 individuals where squares indicate male and circles indicate female; Black indicates the affected condition; White indicates unaffected condition, and Blue indicates the carrier

3.3 Case 3: Two families with 28 individuals over six generations

Two families of 28 individuals are illustrated in Figure 4. The fifth family(left) began with one affected male (I:1) and one unaffected female (I:2) with genotypes X'Y and XX respectively. They mat and had three offspring: two unaffected males (II:5 & II:7) with the genotype XY and one carrier female (II:6) with the genotype X'X. The genotypic probability of three progeny was half. One of the two unaffected males met with an affected female (II:8) with genotype X'X' in the second generation and gave birth to one affected male child (III:13) with genotype X'Y and one carrier female child (III:14) with genotype X'X where their genotypic probability was same 1/2. In the third generation, the affected male individual (III:13) of the fifth family met with an unaffected female (XX) and they had one unaffected male child (IV:18) with genotype XY and one carrier female child (IV:19) with equal genotypic probability (1/2) in the fourth generation. The 20th individual who is male and unaffected with genotype XY met with the carrier female (IV:19) and gave birth to one affected male child (V:24) with genotype X'Y and one female child (V:25) with genotype X'X where their genotypic probability was same 1/4. On the other hand, the sixth family(right) began with one unaffected male (I:3) and one carrier female (I:2) with genotypes XY and X'X respectively. The rest of the members of the sixth family can be described in a similar manner. Finally, in the fifth generation, the carrier female (V:25) of the fifth family with an unaffected male (V:26) of the sixth family with genotype XY whose genotype was 1/4. They gave birth to one child (VI:28) whose gender was unknown. The possible genotypes with corresponding genotypic probability and the probability using the Bayesian technique are described in the next section.

3.4 Risk assessment for the 28th individual of case 3

The 28th individual was unknown in Figure 4 although Bayesian approach as well as the frequentist approach according to the parent's genotype. The unknown status (genotype, phenotype and gender) of the 28th individual and its parent's genotypes, gender and phenotype that the mother was carrier and father was unaffected were shown in the first column of Table 1 in which the square shape indicates male, the circle indicates female and the diamond shape indicates unknown status. Furthermore, the phenotype was denoted by the colors of the square and circle illustrations: black for affected, blue for carrier, and white for unaffected. According to the parent's genotypes, there were four possible genotypes (X'Y, XY, X'X, XX) that determined the gender and phenotype of the 28th individual. Therefore, four possible hypotheses were assumed based on the possible genotypes shown in the second column of Table 1 where the parent's genotypes were constant. *Hypotheses:* H_{01}:The 28th individual is an affected male (X'Y); H_{02} : The 28th individual is an unaffected male (XY); H_{03}: The 28th individual is a carrier female (X'X); H_{04}: The 28th individual is an unaffected female (XX). The genotype probabilities were calculated using frequentist approach and assumed as the Prior Probabilities shown in the third column. As there were four possible genotypes of the 28th individual, therefore the probability of having a particular genotype among four is 1/4 . *Prior Probabilities:* $P(H_{01}) = P(H_{02}) = P(H_{03}) = P(H_{04}) =$ 1/4. Assuming an event *"O"* where the father (XY) with ID 26 was unaffected and the mother with ID 25 (X'X) was a carrier, the forth column explains conditional probabilities. *Conditional Probabilities:* $P(O|H_{01})$: The probability that the event *"O"* will occur given that H_{01} is true. As there are four possible combinations of parents genotype {(XX, X'Y), (X'X, X'Y), (X'X, XY), (XX, XY)} for which H_{01} is true, the conditional probability that the event *"O"* will occur when

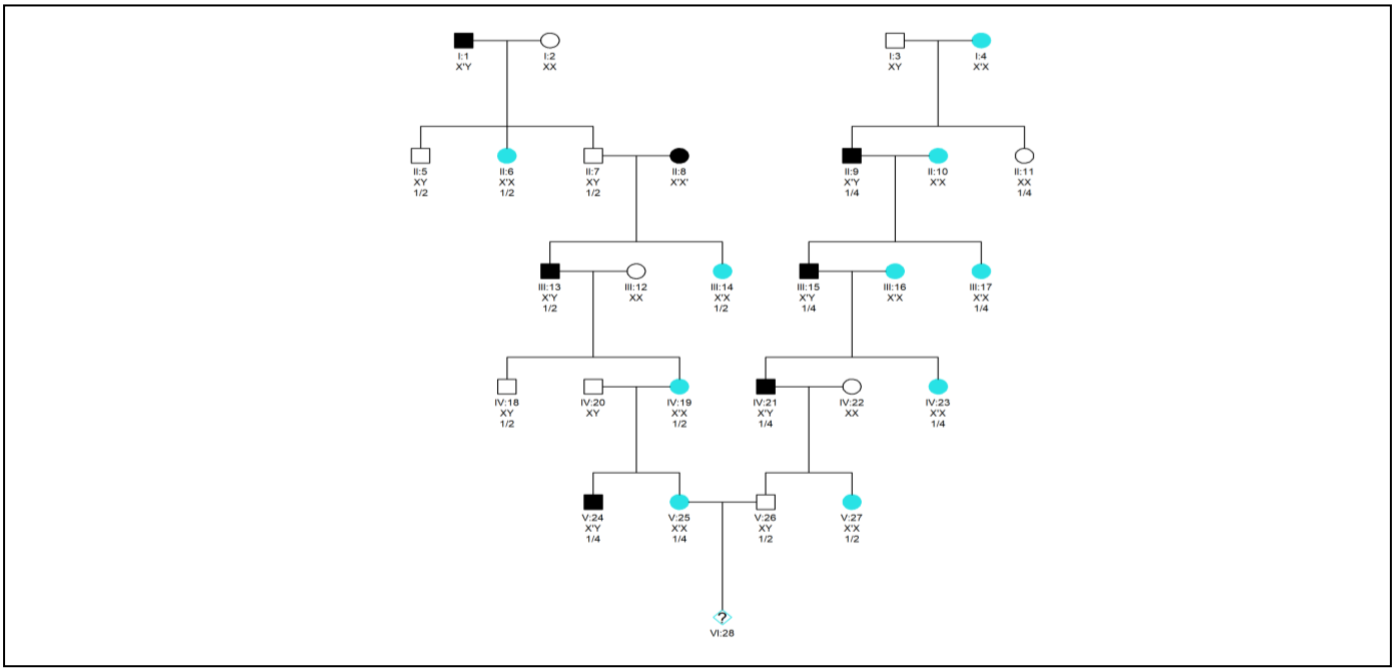
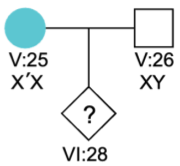
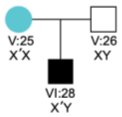
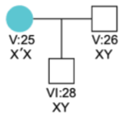
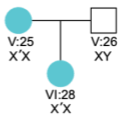
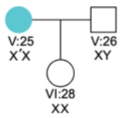


Fig. 4. Ancestry Chart for X-linked Recessive inheritance pattern for 28 individuals where squares indicate male and circles indicate female; Black indicates the affected condition; White indicates unaffected condition, Blue indicates the carrier, and the question marks indicate unknown gender

H_{01} is true is 1/4. Similarly, the remaining conditional probabilities $P(O|H_{02})$=1/4, $P(O|H_{03})$=1/4, and $P(O|H_{04})$=1/2 was derived. The fifth and sixth column explains joint and posterior probabilities. *Joint Probabilities:* The joint probability for each case was derived by multiplying the prior and conditional probabilities. *Posterior Probabilities:* Using (1) and obtaining prior, conditional and joint probability for each case, the posterior probability was calculated. The last column represents genotypic probabilities for each case which were calculated using the frequentist approach.

Table 1: Risk assessment using the Bayesian approach and genotype-based probability for the 28th individual in Figure 4

Parents Genotype	Hypothesis	Prior Probability	Conditional Probability	Joint Probability	Poserior Probability	Genotypic Probability
	H_{01}: 	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{16}$	$\frac{\frac{1}{16}}{\frac{1}{16}+\frac{1}{16}+\frac{1}{16}+\frac{1}{8}}=0.20$	0.25
	H_{02}: 	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{16}$	$\frac{\frac{1}{16}}{\frac{1}{16}+\frac{1}{16}+\frac{1}{16}+\frac{1}{8}}=0.20$	0.25
	H_{03}: 	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{16}$	$\frac{\frac{1}{16}}{\frac{1}{16}+\frac{1}{16}+\frac{1}{16}+\frac{1}{8}}=0.20$	0.25
	H_{04}: 	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{8}$	$\frac{\frac{1}{8}}{\frac{1}{16}+\frac{1}{16}+\frac{1}{16}+\frac{1}{8}}=0.40$	0.25

Key: Roman numerals (V, VI) indicate the generations; The squares and circles filled with black, blue, and white indicate affected, carrier, and unaffected status respectively.

4. Discussion

The genotypic probabilities remained constant based on their parent's genotypes for different sizes of family (case1, case2, case3) regardless of the generation. In case 3, the Bayesian method was used to quantify the risk for an individual (VI:28), yielding posterior probability for four alternative situations that were distinct from genotypic probabilities (Table 2). For instance, Using the Bayesian method, the probability of being an afflicted man (X'Y), an unaffected male (XY), or a carrier female was 5% lower than the genotypic probability. In contrast, it was 15% higher than the genotypic probability in the case of an unaffected female (XX).

5. Limitations

The original data were not used due to some constraints including lab facilities, and lack of funding. The results of the analyses would be the same if the original data were utilized.

6. Conclusion

Among all other sex-linked disorders, X-linked disorder is most prevalent among male children. For extracting features and assessing the risk of an individual having a disorder through X-linked inheritance pattern, six families of varying sizes were divided into three cases, revealing that the probability of having a particular genotype based on the frequentist method does not change for specific parents regardless of family size. In contrast, the probability of having a particular genotype was different for each genotype using the Bayesian method, which yields more exact risk estimates due to its consideration of maximum information.

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