

GENETIC PROFILE AND DEMOGRAPHIC DISTRIBUTION OF HEMOPHILIA (A) AND (B) IN THE REPUBLIC OF KOSOVA

Sheval F. MEMISHI*, Altea HABIBAJ

Department of Biology, Faculty of Natural Sciences and Mathematics, University of Tetova, RNM

Corresponding author: sheval.memishi@unite.edu.mk

Abstract

Haemophilia type A type and B are rare congenital recessive X-linked disorders caused by lack or deficiency of clotting factor VIII (F8) or IX (F9), respectively. The severity of the disease depends on the reduction of levels of F8 or F9, which are determined by the type of the causative mutation in the genes encoding these factors, respectively.

The hallmark clinical characteristic, especially in untreated severe forms, is bleeding (spontaneous or after trauma) into major joints such as ankles, knees and elbows, which can result in the development of arthropathy. Intracranial bleeds and bleeds into internal organs may be life-threatening.

The purpose of this study is to identify cases of Hemophilia A and B, its clinical overview by age groups at the level of the Republic of Kosova until 2024, as well as the distribution according to the hemophilia card, as a scientific source of reflection of this genetic disorder.

Statistical data on the disease of Hemophilia A and B, provided by the University Clinical Center of Kosova, Department of Hematology, for the last 15 years (2009-2024) were used as material.

The results show that the municipalities where the most cases of both types of hemophilia have been identified are: Prizren-16, Gjakova-13, Dragash and Suhareka-10, Obiliq and Vushtrri-7, followed by Gjilan- 6, Peja and Ferizaj-5, Drenas, Prishtina, Vitia-4 cases, Malisheva, Fushe Kosova, Mitrovica-3, Kaçanik, Klina, Kamenica-2, Lipjan and Hani i Elezit-1 case respectively.

The hemophilia map of the Republic of Kosovo shows in: Gjakova, Peja, Klina, Istog, Malisheva, Skenderaj, Gllogoc, Fushë Kosovë, Obiliq, Vushtrri Mitrovica, Lipjan and Prishtina (North-West Region) the identification of significantly more cases of Hemophilia A (54), compared to Hemophilia B (4)., while in the municipalities of: Dragash, Prizren, Suhareka, Ferizaj, Viti, Gjilan and Kamenicë (Southern Region), the identification of significantly more cases of Hemophilia B (47), compared to Hemophilia A (7).

Prizren, Gjakova, Suhareka and Dragash represent the red zones in terms of the spread of hemophilia in the Republic of Kosova, because in these municipalities a significant number of cases are observed.

Keywords: Hemophilia A, Hemophilia B, genetic disorder, factor VIII or IX, Republic of Kosova.

1. Introduction

Life depends on the ability of cells to store, reproduce, and translate the genetic instructions necessary to create and maintain a living organism. This inherited information is passed from parent cells to daughter cells by cell division, and from generation to generation in multicellular organisms by reproductive cells, egg cells, and sperm (Alberts B. et al., 2002). This information is stored in every living cell in whose genes the genetic information contains elements that determine the characteristics of a species as a whole.

Heredity is therefore the process of transmission or the ability of organisms to transmit similar characteristics in subsequent generations, or genetic information, in individual development from parents to offspring, respectively from one generation to another subsequent generation (Bentrop E. et al., 2021).

Before understanding the structure of DNA, biologists knew that inherited traits and the genes that determine them were associated with chromosomes. Chromosomes (from the Greek chroma "color", due to their colored properties) were discovered in the 19th century as threadlike structures in the nucleus of eukaryotic cells that began to appear at the beginning of cell division. After cells were discovered, biochemical analyses taught us that chromosomes contain DNA and proteins. But which of these components encodes the genetic information of the organism was not clear. In eukaryotic cells, very long molecules of double-stranded DNA are packaged into structures called chromosomes. These DNA molecules not only fill the space of the nucleus but they can easily be divided between two daughter cells during cell division. The most important function of chromosomes is to carry genes as the functional units of inheritance (Alberts P. Et al., 2002; Pezeshkpoor B et al., 2022). A gene is often defined as a segment of DNA that contains the instructions for making a protein or an RNA molecule. Most RNA molecules encoded by genes are used to synthesize proteins.

Together, the complete genetic information carried by all the chromosomes found in a cell or organism constitutes its genome. Complete genome sequences have been determined for thousands of organisms from *E. coli* to humans (Sopi R. et al., 2024).

In humans, each cell normally contains 23 pairs of chromosomes, for a total of 46 chromosomes. Twenty-two of these pairs, called autosomes, look the same in both males and females. The 23rd pair, the sex chromosomes, differ between males and females. Females have two copies of the X chromosome, while males have one X and one Y chromosome. Of these, 22 autosomes are numbered by size. This view of human chromosomes lined up in pairs is called a karyotype (US National Library of Medicine, 2020).

There are many types of chromosomal abnormalities, but they can be categorized as numerical or structural.

Most X-linked disorders are recessive and are transmitted from heterozygous female carriers only to male offspring, who are of course hemizygous for the X chromosome.

X-linked recessive disorders are: Color blindness, Hemophilia A, Hemophilia B, Duchenne muscular dystrophy, Becker's muscular dystrophy, X-linked ichthyosis (Kumar, V. et al., 2007; Shoukat H.M et al. 2020).

Hemophilia is an inherited disorder that prevents the blood from clotting properly. It is caused by a lack or decreased concentration of one of the blood clotting factors, which are proteins needed to form a blood clot after an injury or trauma.

Hemophilia is usually classified into two main types: Hemophilia A: Caused by a lack of factor VIII (8), and is the most common form, and Hemophilia B: Caused by a lack of factor IX (9).

Hemophilia A is the most common inherited disease associated with serious bleeding (Konkle B.A. et al., 2023). It is an X-linked recessive disorder caused by decreased factor VIII activity. It affects mainly males, but excessive bleeding occurs much less frequently in heterozygous females, apparently as a result of extremely unfavorable lyonization (inactivation of the normal X chromosome in most cells). About 30% of cases are caused by de novo mutations; in the remainder there is a positive family history.

Severe factor IX deficiency is an X-linked disorder that is clinically indistinguishable from hemophilia A, but is rarer. Hemophilia B or Christmas disease (named after the first patient with the disease) is diagnosed by specific factor IX assays (Stonebraker, J. S. et al., 2012).

The Molecular Basis of Hemophilia A and Hemophilia B corresponds to the F8 or F9 gene located on Xq28 and Xq27 of the X chromosome, respectively (Pezeshkpoor B et al., 2022).

The F8 gene is extremely large (~ 180 kb) and structurally complex (26 exons), while the F9 gene is significantly smaller (~ 34 kb) and structurally simpler, containing only eight exons (Castman G. et al., 2019).

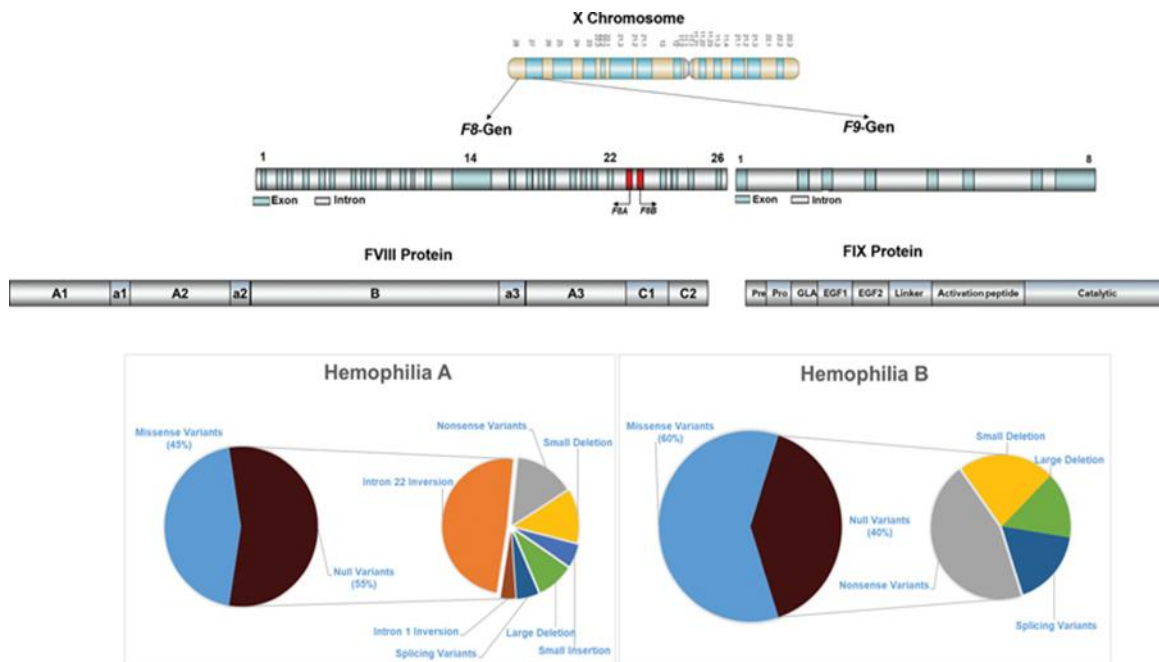


Figure 1. Profile of genetic variants in hemophilia A and hemophilia B
<https://pmc.ncbi.nlm.nih.gov/articles/PMC9779947/>

2. Materials and Methods

For the realization of this study, statistical data on Hemophilia type A and Hemophilia type B, provided by the University Clinical Center of Kosovo (UCCCK), Department of Hematology, for the last 15 years (2009-2024), were used as material.

To inspect the regional demographic distribution of hemophilia A and hemophilia B in the Republic of Kosovo, cartographic and ethnographic materials corresponding to family traditions, regional, tribal traditions and especially the geographical position of specific regions have been used. All these factors have been considered as elements that have contributed to the limited spread of these two X-linked genetic disorders, which are an important reflection of their spread in regions, isolated areas, or municipalities with certain traditional specificities.



Figure 2. Ethnographic regions of the Republic of Kosovo

3. Results and Discussion

In this study, Hemophilia A and hemophilia B, which are caused as a blood clotting disorder, which results from defects in the respective genes F8 and F9 on the X chromosome, which is directly related to sex determination, respectively inheritance from parents to children, results in the fact that it mostly affects the male sex, precisely because in their chromosome set, in the 23rd chromosome pair they are missing one X chromosome, so they have XY.

Based on the molecular genetic aspects and especially the demographic distribution in the human population in the Republic of Kosovo, the results of research, are presented in tabular and graphical form as follows:

Table No. 1. Individuals affected by hemophilia type A and hemophilia type B during the time period 2009-2024.

Age Group	0-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	Total
Hemophili a A	0	16	12	13	9	7	3	0	60
Hemophili a B	2	7	16	9	9	4	3	1	51
Total	2	23	28	22	18	11	6	1	111

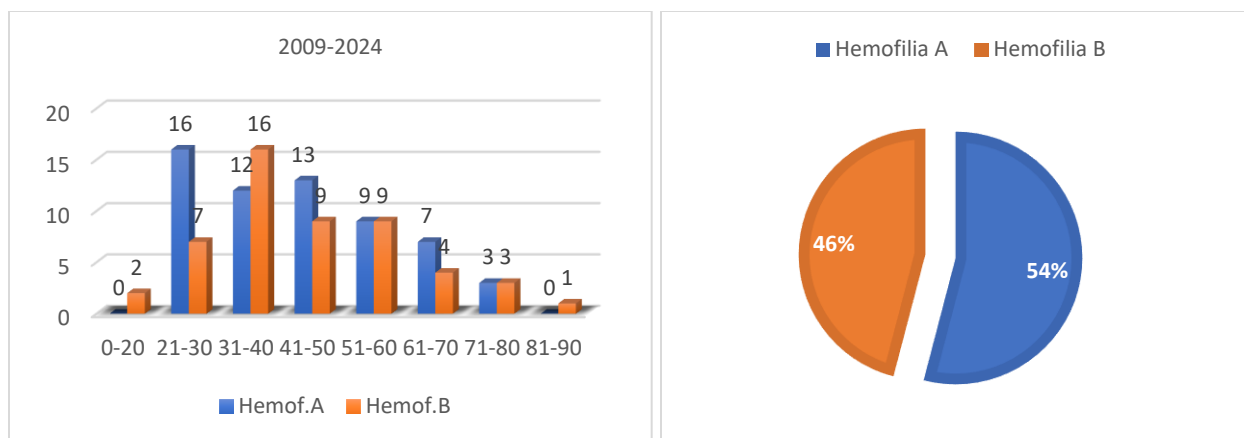


Figure 3. Cases of hemophilia type A and hemophilia type B by age group and their percentage

For a two-year period from 2022 when statistical data was obtained until 2024 with the latest data from the Hematology Department at UCK, it can be concluded that there is a doubling of the number of people affected by hemophilia, if during the period 2009-2022 there were 50 cases of hemophilia reported (22 cases of hemophilia A and 28 cases of hemophilia B), now with the latest data until 2024, 111 cases of hemophilia have been reported (60 cases of hemophilia A and 51 cases of hemophilia B).

Table no 2. Hemophilia type A and Hemophilia type B in individuals of the human population in different municipalities in the Republic of Kosovo.

Municipality	Hemophilia A	Hemophilia B
Dragash	2	8
Drenas	4	0
Ferizaj	1	4
FushëKosovë	3	0
Gjakovë	11	2
Gjilan	2	4
Istog	2	1
Kamenicë	0	2
Klinë	2	0
Hani i Elezit	1	0
Kaçanik	2	0
Lipjan	1	0
Mitrovicë	3	0
Obiliq	7	0
Pejë	5	0
Malishevë	3	0
Prishtinë	3	1
Prizren	0	16
Suharekë	1	9
Viti	0	4

Vushtri	7	0
Republika of Kosova	60	51

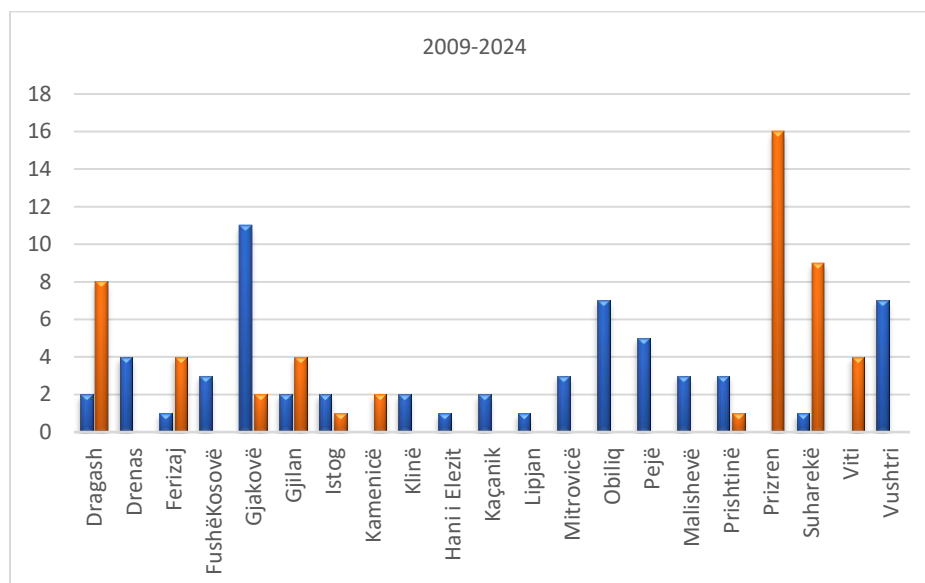


Figure 4. Cases of hemophilia type A and hemophilia type B by cities in the Republic of Kosovo.

In terms of inheritance, which means genetic inheritance, in some population groups, especially those with a long history of marriages within the tribe or isolated groups, there may be a higher distribution that makes them more prone to having more cases of hemophilia. Genetic isolation in some regions or populations has proven that there has been a greater chance that a certain gene, such as the one that causes hemophilia, has spread within a certain group. This isolation has occurred for geographical, cultural, or even social reasons, but has also manifested itself at the level of different regions in the Republic of Kosovo.

Also, the spread, centuries-old continuity and the transmission of local traditions and culture, proves that in some regions, there may be a tendency for marriages within certain groups, increasing the possibility that hemophilia genes are passed on to different generations and appear more frequently.

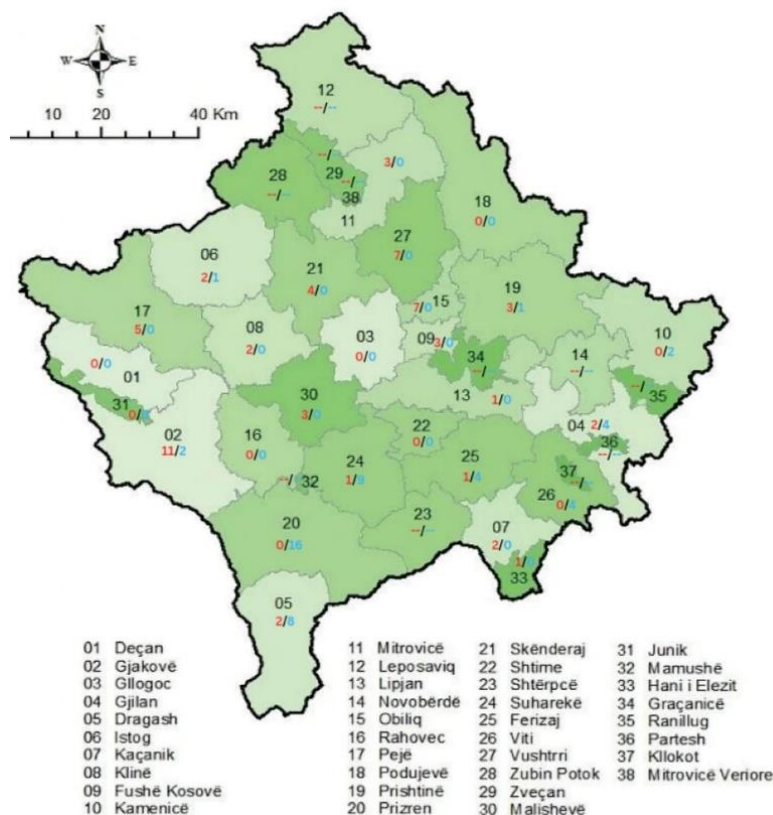


Figure 5. Hemophilia map of the Republic of Kosovo

Precisely, when a reflection of the hemophilia map of the Republic of Kosovo is made, it is found that for example in: Gjakova, Peja, Klina, Istog, Malisheva, Skenderaj, Glllogoc, Fushë Kosovë, Obiliq, Vushtrri Mitrovica, Lipjan and Prishtina (North-West Region) significantly more cases of Hemophilia type A (54), compared to Hemophilia type B (4).

On the other hand, in the municipalities of: Dragash, Prizren, Suhareka, Ferizaj, Viti, Gjiilan and Kamenicë (Southern Region), more cases of Hemophilia type B (47) are identified, compared to Hemophilia type A (7) cases.

The hemophilia map of the Republic of Kosovo highlights that type A hemophilia is inherited more in the North-West region, while type B, in the South-East region, as a scientific source of reflection of this genetic disorder, with the different specificities that the human population possesses in the Republic of Kosovo, where several influential factors can be listed such as: geographical position, proximity between settlements, friendly ties, tribal traditions, regional and provincial traditions and marriages, pronounced localisms, etc.

In the context of what is observed from the Hemophilia Map, it can be seen that settlements that are known for a more pronounced proximity between their populations with centuries-old local traditions, such as the cities of Prizren, Gjakova, Suhareka and Vushtrri, have a higher number of cases of hemophilia: Prizren 16 cases of Hemophilia B, Suhareka with 9 cases of Hemophilia B, Dragash with 8 cases of Hemophilia B, while Gjakova with 11 cases of Hemophilia type A and Vushtrri with 7 cases of Hemophilia type A. When it comes to the spread of these two diseases at the municipal level, the hemophilia map of the Republic of Kosovo highlights the municipalities

with cases of hemophilia type A in order: Gjakova -11, Vushtrri and Obiliq -7, Peja -5, Skenderaj -4, Malisheva, Fushë Kosova, Prishtina and Mitrovica -3, Istog, Klina, Dragash, Kaçanik and Gjilan-2, while Suhareka, Ferizaj and Hani i Elezit only with 1 case each.

The municipalities with cases of hemophilia type B in order are: Prizren-16, Suhareka-9, Dragash-8, Ferizaj, Vitia and Gjilan-4, Gjakova and Kamenica-2, while Prishtina and Istog with 1 case each. This map also highlights the absence of one or the other type of hemophilia in some of the municipalities, i.e. with zero cases. In this regard, the municipalities of Deçan, Rahovec, Shtime, Glllogovc and Podujeva stand out.

4. Conclusions

From the analysis, comparison, and discussion of the data we can come to the following conclusion:

For 15 calendar years, a total of 111 cases of hemophilia type A and hemophilia type B have been identified.

Hemophilia type A is more present compared to hemophilia type B in a ratio of 60/51 cases.

The age groups most affected by both types of hemophilia A and B are those from 21-50 years with a total of 73 cases.

Hemophilia type A shows a linear line of cases in the age groups 21-30 years (16 cases), 31-40 years (12 cases), 41-50 years (13 cases), while the age group 0-20 has no cases, with a linearity of numbers in the age groups 51-60 years (9 cases) and 61-70 years (7 cases), as well as a decrease in the number in the age group 71-80 years (3 cases).

Hemophilia type B shows a variable number of cases for the respective age groups, from 2 cases of those affected in the age group 0-20 years, to 7 cases of those affected in the age group 21-30 years, while the age groups 41-50 and 51-60 years, are evidenced with 9 cases each, as well as (1 case) 81-90 years.

The hemophilia map of the Republic of Kosovo shows in: Gjakova, Peja, Klina, Istog, Malisheva, Skenderaj, Glllogoc, Fushë Kosovë, Obiliq, Vushtrri Mitrovica, Lipjan and Prishtina (North-West Region) the identification of significantly more cases of Hemophilia type A (54), compared to Hemophilia type B (4).

In the municipalities of: Dragash, Prizren, Suhareka, Ferizaj, Viti, Gjilan and Kamenicë (Southern Region), more cases of Hemophilia type B (47) are identified, compared to Hemophilia type A (7) cases.

The municipalities with the most cases of hemophilia type A, in order, are: Gjakova-11, Vushtrri and Obiliq-7, Peja-5, Skenderaj-4, Malisheva, Fushë Kosova, Prishtina and Mitrovica-3, Istog, Klina, Dragash, Kaçanik and Gjilan-2, while Suhareka, Ferizaj and Hani i Elezit only have 1 case each.

The municipalities with the most cases of hemophilia type B, in order, are: Prizren-16, Suhareka-9, Dragash-8, Ferizaj, Vitia and Gjilan-4, Gjakova and Kamenica-2, while Prishtina and Istog have 1 case each.

The municipalities where the most cases of hemophilia of both types have been identified are Prizren (16), Gjakova (13), Dragash and Suhareka (10), Obiliq and Vushtrri (7), followed by Gjilan with 6 cases each, Peja and Ferizaj with 5 cases each, Drenas, Prishtina, Vitia with 4 cases each, Malisheva, Fushe Kosova, Mitrovica with 3 cases each, Kaqanik, Klina, Kamenica with 2 cases each, and Lipjan and Hani i Elezit with 1 case each.

In the municipalities: Deçan, Rahovec, Shtimje, Glllogoc and Podujeva, no cases have been identified.

Prizren, Gjakova, Suhareka and Dragash represent the red zones in terms of the spread of hemophilia in the Republic of Kosovo, because in these municipalities a significant number of cases are observed.

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