Prevalence and geographic distribution of haemophilia in Costa Rica

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Summary
Haemophilia is the most frequent hereditary haemorrhagic illness and it is due to the deficiency of coagulation factors VIII (haemophilia A, HA) or IX (haemophilia B, HB). The prevalence of this disease varies according to the country, those having better survival rates having also higher prevalences. Specifically in Costa Rica, there are around 130 HA and 30 HB families. This study reports the prevalence and a spatial distribution analysis of both types of the disease in this country. The prevalence of haemophilia in this country is 7 cases per 100 000 men, for HA it is 6 cases per 100 000 and for HB it is 1 case per 100 000 male inhabitants. The prevalence of this disease is low when compared with other populations. This low prevalence could be due to the many patients that have died because of infection with human immunodeficiency virus during the 1980s. The prevalence of haemophilia in Costa Rica is almost one half of that present in developed countries. Nevertheless, the ratio between HA and HB follows world tendency: 5 : 1. In this study, nationwide geographical distribution maps were drawn in order to visualize the origin of severe cases and how this influences the pattern of distribution for both types of haemophilia.

In developed countries the prevalence of haemophilia ranges between 13 and 18 cases per 100 000 males. The ratio is 5–6 : 1 for haemophilia A and B (4–6).

The genes responsible for haemophilia are located on chromosome X, thus being an X-linked disease. There is a 50% chance that a mother with a mutated gene inherits it to her child (1, 2). HA and HB are clinically indistinguishable. Both diseases present with bleeding into joints and muscles.

The diagnosis of haemophilia is based on clinical symptoms and the concentration of coagulation factors (2, 7, 8). The bleeding disorder is classified (2) as
- mild (5–40% of normal),
- moderate (1–5% of normal) or
- severe (<1% of normal) cases.

Molecular genetic diagnosis elucidates the mutations associated. These mutations can stop or disturb the synthesis of the encoded protein in severe cases, while point mutations located in non-coding regions can result in silent, mild or moderate haemophilia (2, 8).

The Costa Rican haemophilia population are 130 HA and 30 HB well-characterized families. This country has few studies about geographical distributions of genetic diseases including sex-linked haemophilia (9). This report studies the prevalence and spatial distributions of the HA and HB genes in this population.

Patients, material, methods

Spatial analysis

The area inhabited by a population is where the genetic factors interact with lifestyle and environmental factors in order to model the course of multifactorial diseases (10, 11). The factors interacting can be as-
associated to higher susceptibility in the development of a special disease.

The geographic distribution analysis can be a tool, because it informs and helps to visualize the distribution of risk factors involved. They can be of physical, environmental, social, economical, cultural and/or genetic origin (10, 12).

Some diseases are strongly associated with environmental factors or with genetic predisposition. Age, sex, or socioeconomic factors can vary from one geographic area to the other, and they have an influence in the risk of development of that disease in a certain geographic area (12).

So-called disease maps are a graphic representation of the spatial distribution of cases. They allow the geographical determination of the rate of incidence or mortality and can help to establish hypotheses related to the etiology of the disease. These graphic representations allow having better visualization of the geographic information than normal graphs or tables (13, 14). These maps can identify changes in the characteristics of the disease and distribution with time (14). Such information is useful for national health authorities, e.g. for the distribution of resources for the prevention and treatment of the disease, with the goal to diminish the cases or give better quality of life for patients (14, 15).

 Patients, methods

In order to determine the prevalence of haemophilia in Costa Rica we used data from the haemophilia patients of the Haematology Department of Mexico Hospital and from the Costa Rican National Hae-mophilia Patient Association. To determine the number of Costa Rican men at the time of the study, we used the demographic projections data at the electronic sites of The National Institute of Statistics of Costa Rica (INEC, www.inec.go.cr) and the Centre for Research on the Central American Population of the University of Costa Rica (CCP, http://ccp.ucr.ac.cr). The Geographic Information System (GSI) uses information technology that allows to capture, store and analyze spatial information related to health through maps (12). The geographical information is referred to the respective position of cases on the maps. The punctual data are the location of the homestead of the case with respect to geographic coordinates and a specific region, district, or province within the territory (14, 15).

The prevalences of total haemophilia, HA and HB, were calculated with respect to the Costa Rican 2007 male population (cases per 100 000 men). A ratio of HA and HB prevalences and the mean age of patients were also calculated as usual.

The geographic distribution of the haemophilia genes was done with a retrospective study using the databases mentioned. The province, canton and district of residence of each patient, as stated by the CCP (http://ccp.ucr.ac.cr), were included in the analysis. PC surfer software (Golden Software, version 4.15, Golden, Colorado) was used to build the map of Costa Rica with the interpolation of the HA and HB gene coefficient ($\alpha$). The face is interloped with a rectangle spherical limited by the parallels 8°N and 11°5' north and with meridians 82° y 86° west (15). The areas of light and heavy colour represent low and high genetic frequency, respectively.

 **Results**

<table>
<thead>
<tr>
<th>country</th>
<th>prevalence*</th>
<th>A/B</th>
<th>reference</th>
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</tr>
<tr>
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<td>1</td>
</tr>
<tr>
<td>Chile</td>
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<td>8:1</td>
<td>1</td>
</tr>
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<td>7</td>
<td>5:1</td>
<td>this report 2008</td>
</tr>
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<td>NR</td>
<td>7</td>
</tr>
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<td>14</td>
<td>6.6:1</td>
<td>1</td>
</tr>
<tr>
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<td>2.2</td>
<td>4:2:1</td>
<td>1</td>
</tr>
<tr>
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<td>6.2:1</td>
<td>1</td>
</tr>
<tr>
<td>Sweden</td>
<td>6.8</td>
<td>4:1</td>
<td>1</td>
</tr>
<tr>
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<tr>
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<td>3.6:1</td>
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<td>11.0</td>
<td>NR</td>
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</tr>
<tr>
<td>Hispanics</td>
<td>11.5</td>
<td>NR</td>
<td>18</td>
</tr>
</tbody>
</table>

*per 100 000 male births; NR: no report

For haemophilia A it is 6 cases, for haemophilia B 4 cases per 100 000 men. The ratio of HA and HB in this country is 5:1. The mean age of the haemophilic population is 23.7 years (Tab. 1).

**Haemophilia A in Costa Rica**

The Costa Rican Central Valley is the region with the highest prevalence of cases of haemophilia A (Fig. 1a). The highest frequency of the mutated gene is located in the cantons of Desamparados, Goicoechea and Santa Ana, all belonging to the province of San José, and in the central cantons of the provinces of Alajuela and Heredia. The rest of the country presents an important number of HA-associated mutations in the canton of Pococi (Limón province), the central canton of Puntarenas and the canton of Santa Cruz in the northwestern province of Guanacaste. The cantons having the least frequency of hemophilia cases are Montes de Oca, Vázquez de Coronado, León Cortés, Grecia, Sarapiquí, Liberia and Parrita.

Severe HA is most frequent in the province of Heredia, followed by San José and Alajuela (Fig. 1b). Moderate cases are more frequently found in the central canton of Alajuela and the canton of Desamparados in San José (Fig. 1c). Finally, the mild haemophilia cases are mainly distributed around the Central Valley cantons of Escalú.
and Santa Ana (San José), Alajuela and, to a lesser extent, in Nicoya (Guanacaste), Desamparados and Curridabat (San José) and in the province of Heredia, (Fig. 1d).

**Haemophilia B in Costa Rica**

HB-associated mutations are almost restricted to the Central Valley, mainly in the cantons of Vázquez de Coronado, Tibás, Goicoechea, Tres Ríos, Barva and Santo Domingo (Fig. 1e). Outside the Central Valley, Pococi is the canton that presents more cases of HB. The provinces of Alajuela and Puntarenas do not present cases of HB.

Severe HB cases are present in the cantons of La Unión (province of Cartago), Barva and Santo Domingo (Heredia) and Tibás (San José) (Fig. 1f). Moderate HB is prevalent in the canton of Vásquez de Coronado (San José), whereas mild HB cases are distributed throughout Escazú, Goicoechea and Moravia around the capital city of San José (Fig. 1g, Fig. 1h).

**Discussion, conclusions**

The total prevalence of haemophilia in Costa Rica is 7 cases per 100,000 men (6 HA, 1 HB). This prevalence is lower than reported for the general world population where HA is estimated to be around 1 case per 5000 or 10,000 (10 : 100,000) male newborns and HB 1 case per 30,000 to 50,000 men (3 to 5 : 100,000) (6, 16, 17). Nevertheless, the ratio between both haemophilia types follows world tendency: 5 : 1 (2, 6, 17). The Costa Rican ratio is similar to those found in populations in Sweden, India, although it is small in comparison with some Latin American populations as those of Chile and Brazil (Tab. 1).

The low prevalence in this country could be partly explained because of the large amount of patients who died as consequence of human immunodeficiency virus (HIV) infections, in the 1980s. As with other countries, HIV-contaminated plasma derivatives caused a widespread infection within the haemophilic population. This situation clearly increased the death rate of this population in the world (5, 16, 17). Also, this factor has reduced the affected adults as reflected in the median age of this population:

- Only 7 Costa Rican patients are older than 50 years of age (4.2%).

The patients of 30–49 years account for 20%. The majority is within the range of 10–29 years (54%). The other 22% are 0–9 years old. Infections and complications increase the rate of death, and, according to the World Federation of Haemophilia

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**Fig. 1** Geographic distribution of haemophilia A (a–d) and B (e–h) in Costa Rica

(a) HA; (b) severe HA; (c) moderate HA; (d) mild HA

(e) HB; (f) severe HB; (g) moderate HB; (h) mild HB

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(WFH), about one half of the haemophilic population is infected with hepatitis C virus and 10% is infected with HIV (3, 7).

When the prevalence of haemophilia in the male Costa Rican population was compared with other populations (►Tab. 1), it turned out to be similar to those reported for Chile, Brazil and Sweden and differed with respect to Greece, India and Georgia. India reports a higher prevalence, with 13.4 cases per 100,000 men (10.5 for HA and 2.9 for HB) (7). In the population of Hispanic men in the United States, the prevalence is also higher than between Costa Ricans: 11.5 cases per 100,000 men (18). The median age of the haemophilic population in Costa Rica (23.7 years of age) is similar to that of US-American (25 years) (18) and Georgian patients (25 years) (7, 19).

Other factors known to influence the prevalence of haemophilia are socioeconomic levels, as low prevalences are found in poor countries which have a more premature death and shorter life expectancies. Thus, very few of haemophilia patients reach an old age (3, 7, 8, 16). The WFH informs that countries with low gross national product (GNP) in general have little organization regarding care (3, 6). Countries with low GNP like the Philippines, Venezuela, Vietnam and Costa Rica as well, may have health programs that are comparable to developed countries (7, 20).

This factor could help to improve the capacity that these countries have to diagnose, give a special treatment (concentrated coagulation factor) and clinical care (treatment for inhibitors and prophylaxis), grant physical therapy (improve articulation state) and psychosocial assistance. Developing an integral treatment for HA and HB patients will increase their life expectancy and quality of life (7).

The results of the spatial analysis suggest that the distribution of haemophilic patients depends on the migratory processes within the country. The highest frequencies of cases are concentrated within the region of the Central Valley of Costa Rica, because this area represents more opportunities for employment, education and healthcare. Also, some national reports state a high endogamy in some populations of the Central Valley, a factor that could be important with respect to our results (9, 21). Some cantons of this area may have more cases of HA related to familial aggregation in comparison with cases reported in the cantons of Alajuela, Santa Ana, Pococi and Desamparados.

HB cases are even more concentrated in the Central Valley. The reported families are specifically localized in the cantons of Vásquez de Coronado, Tres Ríos, Santo Domingo and Barva and there is just a small amount of cases outside this region, on the Atlantic canton of Pococi. Even though haemophilia cases had a particular spatial distribution within this country, there was no association between the maximum intensity of the mutation prevalence and ethnicity (9, 21).

Finally, we present the utility of disease maps individualized by the specific types of haemophilia. These resources can help us visualize in which cantons are the cases with severe, moderate and mild haemophilia. The information in these maps will be important to detect the areas where more patients will need specialized personnel to treat complications and to give a quick answer in the event of an emergency. Depending on the amount and the different categories of patients of a specific region, it could be decided where to construct specific facilities which would offer laboratory and clinical service to this population. Also, the development of educational programs for the most affected areas in order to support the families of patients would be desirable. The geographic distribution of mutations associated with haemophilia is also important so that health authorities of every country are able to develop a genetic counseling policy towards these populations and prevent new cases. Such a program can improve the assistance given to the haemophilic population. It can supply an integral net to successfully treat the patients in the high prevalence areas.

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Conflict of interest
All authors declare that there is no conflict of interest.

References

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