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Original Article

Genealogy of patients with congenital heart disease in isolated populations

Efrén Martínez-Quintana[1,2], Michelle María Sánchez-Matos[2], Fayna Rodríguez-González[3], Antonio Tugores[4]

[1]Cardiology Service, Complejo Hospitalario Universitario Insular-Materno Infantil, Las Palmas de Gran Canaria, Spain; [2]Medical and Surgical Sciences Department, Faculty of Health Sciences, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain; [3]Ophthalmology Service, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain; [4]Research Unit, Complejo Hospitalario Universitario Insular-Materno Infantil, Las Palmas de Gran Canaria, Spain

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Abstract: In isolated populations rare genetic diseases are important and relatively frequent. The objective of this study is to determine the geographical aggregates of maternal and paternal ancestors of patients with congenital heart disease (CHD) to determine whether there is an association between the different areas and types of cardiac defects. Descriptive, observational, and cross-sectional study of patients with CHD obtained consecutively in a single adult CHD unit between January 2018 and December 2019 in Gran Canaria (Canary Islands, Spain). To be included in the study, at least one of the grandparents (maternal or paternal) should be born in Gran Canaria. 258 out of 353 CHD patients met the inclusion criteria. 58% of CHD patients were male and the median age was of 28 (21-40) years old. The most frequent types of CHD were cardiac septal defects (76 patients), right side cardiac outflow tract anomalies (74 patients) and left side cardiac outflow tract anomalies (58 patients). 13% of the patients had a family history of CHD, 11% showed consanguinity and 7% had an associated polymalformative syndrome. 20% of the four ancestors were born in the same municipality and a significant association was seen between two areas of Gran Canaria, orographically related, and right-side cardiac outflow tract anomalies (P<0.001). In conclusion in patients with tetralogy of Fallot and/or pulmonary valve stenosis/atresia an ancestry's geographic aggregation was seen.

Keywords: Congenital heart disease, ancestors, isolate, tetralogy of Fallot, pulmonary atresia

Introduction

Genetic epidemiology is the study of how genetic factors contribute to health and disease in families and populations, and how genes interplay with environmental factors and genealogy is the study of family origins and history. As genetic changes associated with CHD [1] may be inherited within a family following Mendel's laws of heredity tracing the ancestry and building a family tree may be of great help in population isolates. In this context, a previous study analyzed several genealogical and genetic features related with CHD, revealing the presence of parental consanguinity and extensive familial aggregation in the CHD patients from São Miguel Island in Azores (Portugal) [2]. Similarly, Shieh et al. [3] supported the view that consanguinity increases the prevalence of CHD.

In Gran Canaria, the second most populous island of the Canary Islands an archipelago off the Atlantic coast of Northwest Africa, which is part of Spain, rare genetic diseases are important and relatively frequent [4-6]. This was largely because these islands, especially the inland areas, were separated from their surrounding populations until the beginning of the 20th century reveling previous studies a high consanguinity.

The objective of this study is to determine the place of birth of maternal and paternal ancestors of patients with CHD and whether there is an association between heart defects and the areas of Gran Canaria where their grandparents were born as an initial step to a subsequent genetic study of patients with CHD.

Methods

Subjects

Descriptive, observational, and cross-sectional study of patients with CHD was obtained consecutively in our adolescent and adult CHD unit

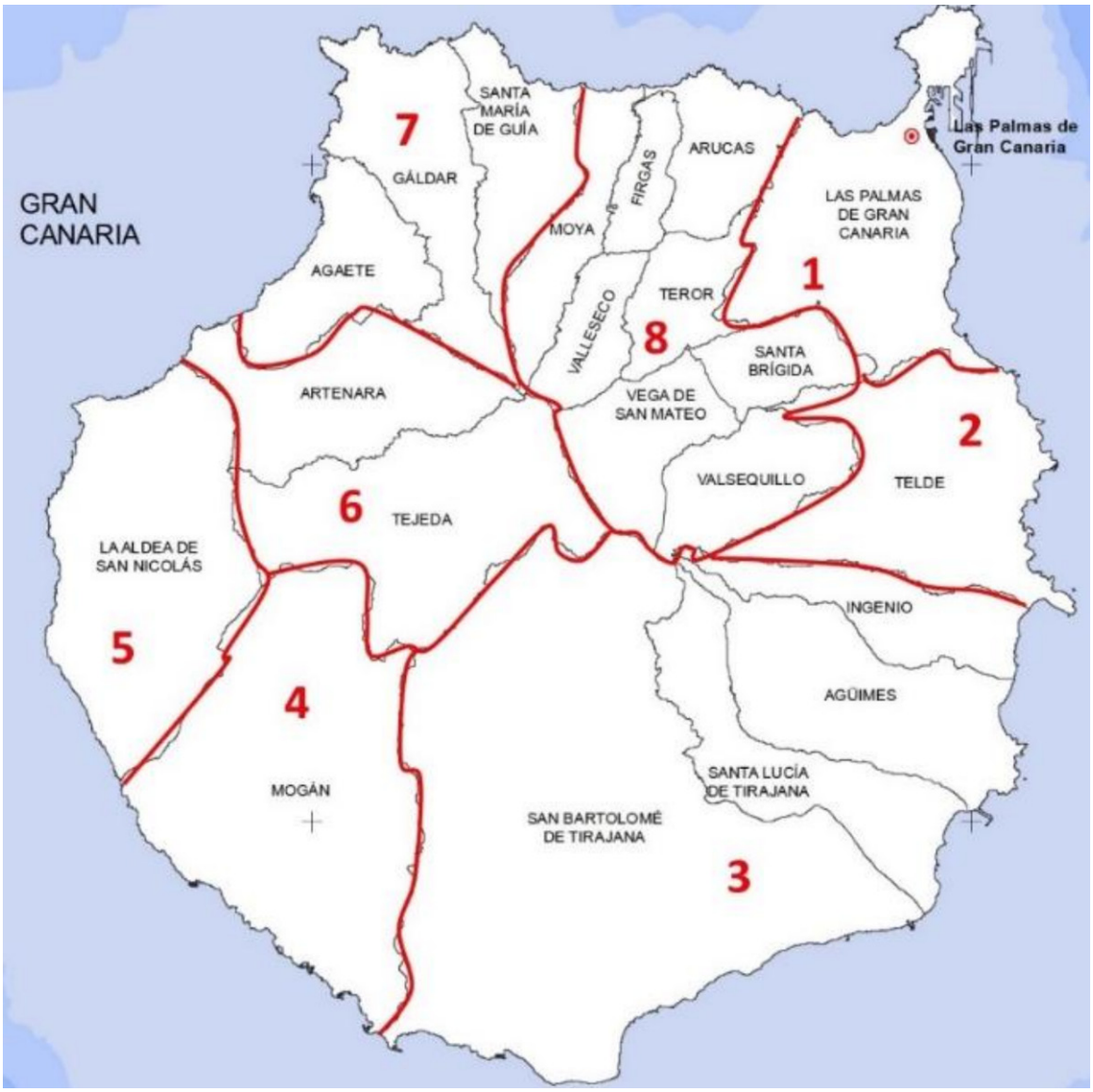

Figure 1. Municipalities distributed by areas on the island of Gran Canaria. The population of the island of Gran Canaria in 1930 (date on which most of the second-generation ancestors of congenital patients were born) was: area 1 (78.264 inhabitants); area 2 (16.457 inhabitants); area 3 (19.596 inhabitants); area 4 (1.600 inhabitants); area 5 (3.351 inhabitants); area 6 (4.251 inhabitants); area 7 (22,608 inhabitants) and area 8 (56.808 inhabitants) [6]. In total, 202.935 people lived on the island of Gran Canaria in 1930, as opposed to the 855.521 who live today.

between January 2018 and December 2019. Inclusion criteria were (a) being older than 14 years old and having a CHD confirmed with imaging techniques, (b) being at least one of their maternal or paternal grandparents born in Gran Canaria and (c) signing a written informed consent to participate in the study. On the other hand, CHD were excluded if it was impossible to determine the birthplace of the ancestors or the patient did not sign the informed consent for the study.

Study variables

The variables analyzed were full name of patients with CHD, their date of birth, gender, type of CHD, family history of CHD, consanguinity, associated polymalformative syndromes and the place of birth (municipality, island, and country) of parents and grandparents of patients with CHD. The different municipalities of the island were grouped into 8 geographical areas according to their economic and social interrelationship at the beginning of the 20th century (**Figure 1**). Patients born outside the

Table 1. Types of congenital heart disease grouped according to geographical area of the ancestors

	RVOTO	LVOTO	AVSD	TGA	UV	Others	
No GC	2	2	2	1	0	0	7
A_1	30	28	21	13	4	5	99
A_2	13	9	16	1	0	1	40
A_3	18	14	18	4	0	8	59
A_4	1	1	1	0	0	0	3
A_5	2	0	1	0	0	2	4
A_6	0	0	0	0	0	0	0
A_7	1	2	5	2	1	2	13
A_8	7	2	12	2	1	4	25
Total	74 (30)	58 (23)	76 (30)	23 (9)	6 (2)	21 (8)	258

Data are presented in number and percentages in brackets; P=0.438. A_1: Las Palmas de Gran Canaria; A_2: Telde; A_3: Ingenio, Agüimes, Santa Lucía and San Bartolomé; A_4: Mogán; A_5: La Aldea; A_6: Artenara and Tejeda; A_7: Agaete, Gáldar and Guía; A_8: Moya, Valleseco, Firgas, Arucas, Teror, San Mateo, Santa Brígida and Valsequillo; No GC: other Canary Islands, rest of Spain or abroad. RVOTO: right ventricular outflow tract obstruction, LVOTO: left ventricular outflow tract obstruction, AVSD: auricular and ventricular septal defects, TGA: Transposition of the great arteries, UV: Univentricular defects; others: other types of congenital heart disease not included in the other subgroups (8 patients presented a combination of several congenital heart diseases).

island of Gran Canaria (GC), regardless of the location, were classified as "No GC".

Cardiovascular imaging established the diagnosis of the CHD and patients were classified into six groups according to the anatomical findings: cardiac septal defects (atrial septal defect, ventricular septal defect and atrioventricular septal defects); right side cardiac outflow tract anomalies (pulmonary valve stenosis, pulmonary atresia and tetralogy of Fallot); left side cardiac outflow tract anomalies (valve and sub/supra valvular aortic stenosis and coarctation of the aorta); transposition of the great arteries (dextro and levo transpositions), univentricular physiology and other types of CHD. The study was approved by the Hospital's Ethics Committee and the approval number of the manuscript was CEIm-CHUIMI-2016/890.

Statistical analysis

Quantitative variables were expressed as mean and standard deviation or median and quartiles depending on the normality of the distribution using the Kolmogorov-Sirmov test. Possible associations between categorical variables were evaluated using the Chi-Square test. *P* values less than 0.05 were considered statistically significant. Data analysis was performed with the statistical software package SPSS v.24 (IBM Corporation, Armonk, NY).

Results

Subjects

258 (73%) out of 353 CHD patients met the inclusion criteria. 95 patients were excluded due to the following causes: 66 patients because none of their second-generation ancestors were born in the island of Gran Canaria, 6 patients because they did not give their consent to participate in the study and 23 patients due to an incomplete data collection. 58% of patients with CHD were male and the median age was of 28 (21-40) years old.

Types of CHD

The most frequent CHD were cardiac septal defects (76 patients), followed by right side cardiac outflow tract anomalies (74 patients) and left side cardiac outflow tract anomalies (58 patients) (**Table 1**). On the other hand, 13% of patients had a family history of CHD, 11% of patients reported having consanguinity between their ancestors and 7% of patients with CHD had associated polymalformative syndromes. No significant differences were seen between the different CHD types and having a family history of CHD or a polymalformative syndrome. Similarly, no significant association was seen between the surnames of our CHD patients and the different types of CHD.

Ancestors' geographic distribution

Table 2 shows the distribution of patients with CHD and their maternal and paternal grandparents according to their birthplace while **Table 3** shows paternal and maternal grandparents born in the same geographical area. As can be seen from the table, 92 (36%) of the ancestors were born in the same area (P=0.036).

In relation to the CHD anatomical classification, we found no significant differences between the type of CHD and the grandparent's birthplace except for patients with right side cardiac

Table 2. Geographic distribution of patients with CHD and their maternal and paternal grandparents

	Patients	Maternal grandparents	Maternal grandmohers	Paternal grandparents	Paternal grandmothers
A_1	102 (39)	67 (26)	73 (28)	63 (24)	61 (24)
A_2	42 (16)	27 (11)	23 (9)	27 (11)	32 (12)
A_3	59 (23)	23 (9)	30 (12)	37 (14)	35 (14)
A_4	3 (1)	3 (1)	2 (1)	1 (0)	1 (0)
A_5	4 (2)	3 (1)	2 (1)	8 (3)	4 (2)
A_6	0 (0)	5 (2)	6 (2)	6 (2)	5 (2)
A_7	13 (5)	21 (8)	25 (10)	19 (7)	20 (8)
A_8	28 (11)	67 (26)	70 (27)	44 (17)	55 (21)
No GC	7 (3)	40 (15)	25 (10)	41 (16)	29 (11)
Unknown*	0 (0)	2 (1)	2 (1)	12 (5)	16 (6)
Total	258	258	258	258	258

The data are presented in number and percentages in brackets. CHD: congenital heart disease. A_1: Las Palmas de Gran Canaria; A_2: Telde; A_3: Ingenio, Agüimes, Santa Lucía and San Bartolomé; A_4: Mogán; A_5: La Aldea; A_6: Artenara and Tejeda; A_7: Agaete, Gáldar and Guía; A_8: Moya, Valleseco, Firgas, Arucas, Teror, San Mateo, Santa Brígida and Valsequillo; No GC: other Canary Islands, rest of Spain or abroad. *, Patients who the birthplace of one of their grandparents was unknown.

Table 3. Areas of birth of maternal and paternal grandparents of patients with CHD

		Areas of birth of paternal grandparents		Total
		Different areas	Same areas	
Areas of birth of paternal grandparents	Different areas	56 (51)	55 (37)	111 (43)
	Same areas	55 (49)	92 (63)	147 (57)
Total		111	147	258

CHD: congenital heart disease. Data are presented in number and in percentages in brackets; P=0.036.

Table 4. Geographical areas of the maternal grandparents and grandmothers of patients with Tetralogy of Fallot and pulmonary valvular disease

		Maternal grandmothers									
		No GC	A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8	Total
Maternal grandfathers	No GC	5	3	0	2	1	0	0	0	1	12
	A_1	2	14	1	0	0	0	0	0	3	19
	A_2	1	0	8	0	0	0	0	0	0	9
	A_3	0	2	1	5	0	0	0	0	0	8
	A_4	0	0	0	0	0	0	0	0	0	0
	A_5	0	0	0	0	0	1	0	0	0	1
	A_6	0	0	0	0	0	0	4	0	0	1
	A_7	0	0	0	0	0	0	0	2	0	2
	A_8	0	0	0	1	0	0	0	1	16	18
Total		8	19	10	8	1	1	4	3	20	74

The data are presented in number and percentages in brackets; P<0.001 A_1: Las Palmas de Gran Canaria; A_2: Telde; A_3: Ingenio, Agüimes, Santa Lucía and San Bartolomé; A_4: Mogán; A_5: La Aldea; A_6: Artenara and Tejeda; A_7: Agaete, Gáldar and Guía; A_8: Moya, Valleseco, Firgas, Arucas, Teror, San Mateo, Santa Brígida and Valsequillo; No GC: other Canary Islands, rest of Spain or abroad.

outflow tract anomalies (P<0.001) [**Table 4** shows maternal grandparents and **Table 5** outlines paternal grandparents in patients with tetralogy of Fallot and pulmonary valve disease]. Meanwhile, **Table 6** shows the geographical distribution of maternal and paternal grandparents, of patients with right cardiac outflow tract anomalies, who were all born in the same areas. 14 (19%) out of 74 patients with right side cardiac outflow tract defects had all their ancestry born in the same place drawing particular attention that 6 (43%) of them had all their ancestors born in the geographical areas 3 and 8 of Gran Canaria despite these areas were sparsely populated at the beginning of the 20th century compared to area 1 (the capital of the island that had the largest number of inhabitants in 1930 as may be seen in the legend of **Figure 1** [7]).

Discussion

Genetic isolates are subpopulations derived from a small number of founders that have

Table 5. Geographical areas of the paternal grandparents and grandmothers of patients with Tetralogy of Fallot and pulmonary valvular disease

		Paternal grandmothers									
		No GC	A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8	TOTAL
Paternal grandfathers	No GC	6	3	1	0	0	0	1	0	3	14
	A_1	1	16	0	0	0	0	0	0	3	16
	A_2	0	0	11	0	0	0	0	0	0	10
	A_3	0	0	1	9	0	0	0	0	2	12
	A_4	0	0	0	0	0	0	0	0	0	0
	A_5	0	0	0	0	0	2	0	1	0	3
	A_6	0	0	0	0	0	0	1	0	0	1
	A_7	0	1	0	0	0	0	0	0	0	1
	A_8	0	3	1	1	0	0	0	1	6	12
Total		7	23	14	10	0	2	2	2	14	74

The data are presented in number and percentages in brackets; P<0.001 A_1: Las Palmas de Gran Canaria; A_2: Telde; A_3: Ingenio, Agüimes, Santa Lucía and San Bartolomé; A_4: Mogán; A_5: La Aldea; A_6: Artenara and Tejeda; A_7: Agaete, Gáldar and Guía; A_8: Moya, Valleseco, Firgas, Arucas, Teror, San Mateo, Santa Brígida and Valsequillo; No GC: other Canary Islands, rest of Spain or abroad.

Table 6. Geographic distribution of maternal and paternal grandparents with a same municipality of birth in patients with tetralogy of Fallot and/or pulmonary stenosis

	Maternal and Paternal Grandparents
A_1	3 (21)
A_2	4 (29)
A_{3+8}	6 (43)
A_{4+5+6}	1 (7)
A_7	0 (0)
Total	14 (100)

The data are presented in number and percentages in brackets; P<0.001 A_1: Las Palmas de Gran Canaria; A_2: Telde; A_3: Ingenio, Agüimes, Santa Lucía and San Bartolomé; A_4: Mogán; A_5: La Aldea; A_6: Artenara and Tejeda; A_7: Agaete, Gáldar and Guía; A_8: Moya, Valleseco, Firgas, Arucas, Teror, San Mateo, Santa Brígida and Valsequillo.

been isolated for many generations due to geographical and/or cultural barriers. Isolated populations, such as Finnish, Old Order Amish or Jewish have proved to be invaluable resources for mapping genes involved in rare diseases that show a Mendelian recessive mode of inheritance due to very restricted genetic exchange with other subpopulations. Therefore, understanding of the genetic structure of such populations may be extremely useful for mapping and identification of genes providing a useful resource to understand the biology underlying them [8].

In the Canary Islands the incidence and prevalence of genetically determined diseases has been shown to be far greater than expected due to geographic barriers and the homogeneity of the shared environmental factors. In fact, the isolation from neighboring populations and, in many cases, the settlement as small communities in secluded areas makes Gran Canaria a privileged place for the genetic study of CHD. García-Villarreal L et al. [9], for instance, found that mutations in the ATP7B gen, among patients with Wilson disease, was 10 times greater than in the European population. Similarly, Sánchez-Hernández et al. [10], described a specific mutation in the low-density lipoprotein receptor gene, related to familial hypercholesterolemia. In the same line, Wangüemert et al. [6] found a specific mutation in the Ryanodine Receptor 2 gene related to a catecholaminergic ventricular arrhythmia among the island's inhabitants.

As a similar situation may occur in patients with CHD we carried out a genealogical research among patients with CHD who had at least one of their grandparents born in Gran Canaria and to achieve a more complete characterization we divided the population of Gran Canaria into 8 areas according to their relationship from an economic and social point of view. In addition, we studied the surnames of patients with CHD since founder-surnames sampling does not appear to be affected by recent gene flow and is therefore a signature of the ancestral. Although we did not observe an interrelation between the surnames of our CHD patients and the type of CHD, we did see a strong association between the place of birth of the maternal and paternal grandparents in patients with right ventricular outflow tract obstruction.

Advances in our molecular understanding of normal heart development have led to the identification of numerous genes necessary for cardiac morphogenesis leading to the identification of numerous transcriptional regulators, signaling molecules and structural genes that are critical for normal cardiac morphogenesis [11, 12]. Despite of this, the exact cause of most heart defects is not known but it is thought to be due to the additive effect of many genes (polygenic) with an environmental trigger that produces a cardiovascular malformation [13]. Also, few articles provide an overview of

the genes currently implicated in the tetralogy of Fallot or the pulmonary stenosis [14-16]. In this context, findings support the importance of ultra-rare variants disrupting genes involved in the vascular endothelial growth factor (VEGF) and NOTCH signaling in the genetic architecture of tetralogy of Fallot. Similarly, previous results suggested that ultra-rare nonsynonymous variants, which change the protein sequences and are frequently subjected to natural selection, make an important contribution to the genetic etiology of CHD, especially to tetralogy of Fallot [17].

Therefore, carrying out a guided study in populations with common ancestors should be considered essential when conducting a genetic study in non-syndromic patients as the advent of contemporary genomic technologies, including single nucleotide polymorphism arrays, next-generation sequencing, and copy number variant platforms, are accelerating the discovery of genetic causes of CHD.

There are, however, limitations in our study that may impact our findings. Firstly, we have studied adolescent and adult patients with CHD and not pediatric patients or patients who died due to CHD, which may have altered, at least in part, the genealogical analysis. Secondly, we studied CHD patients as anatomical groups that included various CHD and not as individualized CHD. However, we think that this group study is more anatomical from an embryological point of view. Nonetheless, we must bear in mind that patients with CHD represent a very heterogeneous population which may lead to difficulty in data analysis.

In conclusion, although frequently discussed, ancestry itself is rarely defined in patients with CHD [18] despite the number and variety of problems that can be transmitted by Mendelian inheritance, multifactorial influences, or chromosomal abnormalities [19, 20]. Therefore, well characterized human populations provide excellent study samples for many different genetic investigations, ranging from genome-wide association studies to the characterization of interactions between genes and the environment [8]. Genealogy and genetic epidemiology, of affected patients and their relatives, will be crucial in a near future to shed light on important biological mechanisms involved in abnormal embryonic development and define the CHD populations with the highest genetic risk.

Disclosure of conflict of interest

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Address correspondence to: Efrén Martínez-Quintana, Servicio de Cardiología, Complejo Hospitalario Universitario Insular-Materno Infantil, Avenida Marítima del Sur s/n, Las Palmas de Gran Canaria, Spain. Tel: +34-928441360; E-mail: efrencardio@gmail.com

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