

Genetic Factors in Familial Aggregation of Blood Pressure of Portuguese Nuclear Families

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Summary

Background: Despite of the increase in the prevalence of hypertension in Portugal, the importance of genetic factors in blood pressure (BP) has not been studied extensively in our country.

Objectives: To verify the indirect presence of vertical transmission of genetic factors between parents and children in BP values, and to estimate the magnitude of genetic factors contributing for variation in BP values in the population.

Methods: Sample size comprises 367 individuals (164 parents and 203 children) pertaining the 107 nuclear families participating in "Famílias Activas" project, proceeding from different regions of North Portugal. The BP was measured with Omron® model M6 (HEM-7001-E) digital device. SPSS 15.0 was used for data analysis; PEDSTATS was used to verify the structure of each family data. Familial correlations and heritability estimates were computed in FCOR and ASSOC modules of S.A.G.E. version 5.3.

Results: For systolic BP (SBP), correlation values were low to moderate ($0,21 \leq r \leq 0,35$); for diastolic BP (DBP) values were found to be moderate ($0,24 \leq r \leq 0,50$). Genetic factors explain 43 and 49% of the total variation in SBP and DBP, respectively.

Conclusion: A moderate amount of the SBP and the DBP is accounted for by genetic factors. (Arq Bras Cardiol 2009;92(3): 199-204)

Key words: Heredity; genetics; Portugal; quantitative genetics

Introduction

The association between Blood Pressure (BP) levels and the risk of cardiovascular events is continuous and independent from other risk factors¹. The increase in BP represents an important risk factor for the development of cardiovascular diseases, myocardial infarction and coronary artery disease^{1,2}.

Systemic arterial hypertension (SAH) is one of the main Public Health problems in several countries, affects large populations and its prevalence is higher than 20% in the general population³. In the United States, 29% of the adult population is classified as hypertensive⁴. A study carried out in six countries of Europe suggested an even higher prevalence of SAH, i.e., of around 44%⁵. In Portugal, the prevalence of SAH is 42.1%⁶.

Among the determinant causes for the elevation in BP levels, it is known that genetic as well as environmental factors

play an important role⁷. Thus, SAH involves environmental and hereditary⁸ components, being classified as a complex and multifactorial disease, the result of the interaction between these factors⁷.

There is strong evidence, from investigations in Genetic Epidemiology, about the importance of the family history in BP values⁹⁻¹³. This influence is the result of the sharing of genes and a common environment of the members of the same family¹¹. It is estimated that 25¹² to 58%⁹ of the BP variability can be determined genetically. Robinson et al¹⁴ have suggested that the additional effects of the genes can be even higher in SAH (approximately 80%). Fuentes et al² verified that when a parent is hypertensive, the descendant has up to approximately 3.5-fold more chances of developing SAH when compared to a descendant whose parents are normotensive.

Due to the fact of the acknowledged importance of BP control in terms of Public Health, the eventual alteration induced by the salutogenic behavior shared by the family members and the scarcity of information available in the Portuguese language about the aspects of family aggregation in BP values, we established the following objectives for this preliminary investigation:

1) to verify the indirect presence of the vertical transmission of genetic factors between parents and offspring in BP values

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and

2) to estimate the contribution of genetic factors responsible for the variation of BP values in population terms.

Methods

Sample

The “Famílias Activas” (Active Families) project has, initially, the objective of studying and referencing the genetic and environmental aspects in physical activity, physical fitness, metabolic syndrome (MS) components, dietary habits and behavioral risk factors in nuclear families. The second phase will deal with counseling and intervention in families with the purpose of altering risk behaviors and habits. The sampling of this project is divided in different places, based on the volunteer work of children and adolescents that wish to have their families involved in this research, as long as they have at least one brother or sister older than 7 years.

The data used in the present study refer to the pilot study of the first phase of the project. In order to do that we contacted the schools that were more easily accessible in some districts of the North region of the country in order to verify the possible enrollment in the project.

In places with higher accessibility, we sent a written information to each one of the families inviting them to participate in the study. According to the ethical aspects present in the Declaration of Helsinki, the written communication disclosed information about the purpose of the study, as well as the information related to the participation consent. After the informed consent form was duly signed, another communication was sent to the families explaining in details the necessary procedures for data collection, as well as the scheduling of date, time and place.

Due to the fact that other MS data were collected (glycemia, triglycerides and cholesterol), the individuals were evaluated in the morning and in fasting condition. The following cases were excluded: 1) non-biological father and/or mother (one father) and 2) individuals undergoing treatment with antihypertensive drugs (two cases).

The sample contained 367 individuals (164 parents - 41 ± 4.6 years and 203 descendants - 13.2 ± 3 years) belonging to 107 nuclear families from different regions of Northern Portugal.

Measurement of blood pressure

To evaluate BP, an automatic digital *Omron*® equipment model M6 (*HEM-7001-E*) was used, validated according to The International Protocol of the European Society of Hypertension¹⁵.

The measurement protocol followed the recommendations suggested in the literature^{16,17} and in the beginning, all procedures were explained to the individuals.

- **Individuals:** the assessed individuals remained sitting with the legs uncrossed, feet flat on the floor, the back against the chair and relaxed. The right upper limb was positioned with support at the heart level, with palm turned upwards and the elbow slightly flexed.

- **Measurements:** three measurements were carried out. The first after five minutes of rest and the others after an interval of approximately 3 minutes between them, in order to allow the stabilization of the blood flow. During the intervals, all possible care was taken to minimize anxiety. Individuals were also requested to remain silent during the measurement.

- **Blood pressure cuff size:** we chose a simplified and practical criterion for the cuff selection, for children and adolescents as well as for the adults, that would better attend to the main requirements:

- 1) to use the cuff that was large enough to cover 40% of the arm circumference midpoint between the acromion and the olecranon and

- 2) its length should cover 80 to 100% of the arm circumference, with minimal overlap. The cuff was adjusted firmly around 2 to 3 cm above the antecubital fossa, so it would be centralized over the brachial artery, with perfect contact with the skin; however, it should allow the introduction, without difficulty, of the forefinger between the cuff and the skin.

The BP value considered was the mean obtained from the three measurements. The individuals were classified as normotensive, pre-hypertensive or hypertensive, according to the classifications suggested by the Joint National Committee on Prevention, and Treatment of High Blood Pressure¹ and the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents¹⁷, for adults and children and adolescents, respectively.

Anthropometric measurements

Height was measured with a portable *Siber Hegner*® anthropometer with a precision of 0.1 cm. The equipment was fixed to a wooden base manufactured for this purpose. The barefoot individuals stood, with the heels lying flat on the aforementioned base, with gluteus and back against the anthropometer and the head positioned in the Frankfurt plane. Height was measured between the vertex and the reference plane of the wooden base¹⁸. Body mass was measured in a *Tanita*® scale model *BC-418MA* (*Tanita Corp., Tokyo, Japan*) with a precision of 0.1 kg. The individuals were in the anthropometric position of reference¹⁸, barefoot and wearing light clothes.

Body mass index (BMI) was calculated by dividing the body mass (kg) by the square height (m), obtaining a final value expressed in kg/m². Based on the BMI value, individuals were classified as normal weight, overweight or obese. For the adults, we used the classification suggested by the World Health Organization¹⁹ and for children and adolescents, the cutoffs proposed by Cole et al²⁰.

Statistical analysis

The software SPSS 15.0 was used in the exploratory analysis of data to verify possible data entry errors, the presence of outliers and the normality of the distributions, as well as to calculate the means, standard deviations (SD) and the range of the observations. An independent t-test was applied to verify possible differences in the means of the variables among the

groups. To calculate the confidence intervals of the prevalence among the groups, according to the classification of BP and BMI, the PEPI software was used. The PEDSTATS software was used to verify the structure of each family and to analyze the generic behavior of the variables among the different members of the family. The calculations of the correlations among family members and the heritability (h^2) estimates were carried out with modules FCOR and ASSOC of the S.A.G.E. 5 Genetic Epidemiology software. The Systolic Blood Pressure (SBP) was adjusted to such covariates as age, sex, age², age x sex, age² x sex, BMI and diastolic blood pressure (DBP) was adjusted to age², age x sex, age² x sex and BMI. The level of significance was set at 0.05.

Results

Table 1 shows the main descriptive aspects of the elements of the sample. Parents presented similar BMI values, as they demonstrated overweight levels (≥ 25 kg/m²). The parents presented higher mean BP levels, with the highest difference in SBP, however, not statistically significant. Among the offspring, with the exception of SBP, the girls presented higher BMI and DBP values when compared to boys. However, these results were not significant.

A higher prevalence of SAH was observed among the parents ($\approx 1/3$ vs. $1/5$). Regarding BMI, the highest prevalence of obesity was observed in mothers (23 vs. 15.6%). It is important to emphasize the high prevalence of overweight/

obesity in both sexes (♂ : 78.1% and ♀ : 75%). Among the offspring, for SAH as well as for obesity, we observed a higher prevalence in boys. However, this difference was statistically significant only for obesity. If we add overweight and obesity, the highest prevalence is presented in girls (32% vs. 27.2%) (Table 2).

Correlation coefficient (r) values among family members and the estimates of h^2 (\pm standard error) for SBP and DBP are shown in Table 3. For SBP, the r values among the degrees of family relationship in the nuclear family are low to moderate ($0.21 \leq r \leq 0.35$), except in the mother-son relationship ($r=0.01$). For DBP, the observed values were moderate ($0.24 \leq r \leq 0.50$). The h^2 estimates were moderate and statistically significant ($p < 0.001$). The genetic factors explained around 43% and 49% of the total variation of SBP and DBP, respectively.

Discussion

In general, data of an important and recent epidemiological study carried out by Macedo et al⁶ showed around 42% of SAH in the adult Portuguese population. In the present study, the prevalence among the adults was 26%, with men presenting a 7.5% more elevated prevalence. In the aforementioned study, this difference was even higher (10.6%) and also, when compared to the results obtained, the prevalence was more elevated in both sexes (♂ : 49.5% and ♀ : 38.9% vs. ♂ : 29.7% and ♀ : 22.2%). For the offspring, the prevalence among boys

Table 1 – Descriptive measurements of the sample variables

Variables	Parents						
	Fathers			Mothers			p
	n	m±sd	range	n	m±sd	range	
Age (years)	64	42.5±4.3	33 - 56	100	39.9±4.4	30 - 53	<0.001
Body mass (kg)	64	77.1±11.4	52.8 - 119.2	100	68.5±11.7	47.2 - 103.0	<0.001
Height (cm)	64	168.2±5.6	155.6 - 185.5	100	156.9±5.2	144.2 - 171.6	<0.001
BMI (kg/m ²)	64	27.2±3.7	18.7-42.6	100	27.9±4.9	20 - 43.4	0.379
SBP (mmHg)	64	129.8±14.3	106 - 172	99	126±14.7	97 - 168	0.104
DBP (mmHg)	64	79.1±8.6	62 - 102	99	78.4±10.1	59 - 102	0.604
Variables	Descendants						
	Sons			Daughters			p
	n	m±sd	range	n	m±sd	range	
Age (years)	81	12.8±2.7	7 - 19	122	13.5±3.2	7 - 25	0.112
Body mass (kg)	81	50.7±18.2	20.3 - 114.7	122	50.4±12.3	22.9 - 92	0.908
Height (cm)	81	155.3±15.7	104.4 - 181.0	122	154.1±9.6	119 - 169.5	0.477
BMI (kg/m ²)	81	20.4±4.4	12.6 - 38.5	122	21.1±3.7	14.4 - 35.8	0.294
SBP (mmHg)	80	116.8±14.5	84 - 151	120	113.5±9.8	89 - 144	0.056
DBP (mmHg)	80	63.9±9.8	43 - 92	120	66.6±8.1	43 - 83	0.053

BMI - body mass index, SBP - systolic blood pressure, DBP - diastolic blood pressure, m - mean, sd - standard deviation, p - statistical significance value.

Table 2 – Relative frequency of individuals (and respective 95% confidence intervals) according to the blood pressure classifications and body mass index

Relative frequency	Parents		Descendants	
	Fathers	Mothers	Sons	Daughters
Normotensive	29.7% (0.19 – 0.42)	35.4% (0.26 – 0.46)	53.8% (0.42 – 0.65)	67.5% (0.58 – 0.76)
Pre-hypertensive	40.6% (0.29 – 0.54)	42.4% (0.33 – 0.53)	23.7% (0.15 – 0.35)	21.7% (0.15 – 0.30)
Hypertensive	29.7% (0.19 – 0.42)	22.2% (0.15 – 0.32)	22.5% (0.14 – 0.33)	10.8% (0.06 – 0.18)
Normal weight	21.9% (0.13 – 0.34)	25% (0.17 – 0.35)	72.8% (0.62 – 0.82)	68% (0.59 – 0.76)
Overweight	62.5% (0.50 – 0.74)	52% (0.42 – 0.62)	19.8% (0.12 – 0.30)	27.1% (0.19 – 0.36)
Obese	15.6% (0.08 – 0.27)	23% (0.15 – 0.33)	7.4% (0.03 – 0.15)	* 4.9% (0.02 – 0.10)

* - statistically significant difference among descendants.

Table 3 – Correlation coefficients ($r \pm$ standard error) between family members and h^2 estimates for systolic and diastolic arterial pressure

Degree of family relationship	N of de pairs	SBP*	DBP†
		$r \pm se$	$r \pm se$
Spouses	58	0.24±0.13	0.25±0.13
Father – son	53	0.26±0.14	0.26±0.14
Father – daughter	75	0.32±0.11	0.24±0.12
Mother – son	75	0.01±0.12	0.29±0.11
Mother – daughter	117	0.24±0.09	0.29±0.09
Brother – brother	11	0.35±0.28	0.50±0.24
Sister – sister	33	0.21±0.17	0.40±0.15
Brother – sister	57	0.29±0.13	0.29±0.13
h^2		0.43±0.10 (p<0.001)	0.49±0.10 (p<0.001)

SBP - systolic blood pressure, DBP - diastolic blood pressure ; * - adjusted to the covariables: age, sex, age², age x sex, age² x sex and BMI; † - adjusted to the covariables age², age x sex, age² x sex and BMI.

was higher than among the girls (22.5% vs. 10.8%). Sorof et al²¹ found similar results in boys and higher values in girls (♂: 23% and ♀: 16%).

Familial aggregation designs aim at quantifying the contribution of genetic factors that are responsible for the variation of the BP values within the family. One way to interpret this contribution across families at the population level results in the calculations of the h^2 estimates. The values obtained in the present study showed that the genetic factors significantly explained 43 and 49% of the SBP and DBP values, respectively. These results indicate that a significant part of both BP components have a strong genetic component.

A set of factors have been identified in the Portuguese population⁶, which can condition the BP values in population

terms. Among them, we emphasize the most relevant information for our research:

- 1) BP increases with age;
- 2) there is a difference in the mean BP values between the sexes, with men presenting more elevated SBP and DBP; and
- 3) the BMI was significantly higher in individuals with elevated BP.

For children and adolescents, this behavior tends to be similar, as the BP classification for this population is carried out according to age, sex and the height percentile for age¹⁷. These data reinforce and justify the fact that the covariates (and some interactions) showed their significant impact in our results.

Despite the importance of the BP in epidemiological terms, the family aggregation aspects seem to be scarcely studied in Portugal. The only study we had access to was the one carried out by Campos et al¹¹, in which lower h^2 estimates, of 34% and 17% for SBP and DBP, respectively, were found. When compared to the present sample, the sample from the Azores consisted of only 66 nuclear families and almost exclusively by three-member families (father, mother and son or daughter). It is important to emphasize that, in the present study, approximately 87% of the families had four or five members (3.94 ± 0.45). The Azores Islands have an environmental aspect that is distinct from the mainland. It can be inferred that, due to the fact that the Islands consist basically of mountainous landscape, it is possible that the inhabitants present a higher level of physical activity when compared to the mainland dwellers.

Although the authors referred that approximately 60% of the individuals are insufficiently active ($< 10,000$ steps/day), the BP means are lower when compared to the individuals in the present sample. Considering that the h^2 represents a population estimate of the magnitude of the genetic factors' effect, one must be careful when directly comparing it with other studies, especially if the latter presents different characteristics regarding: sample size, family composition, age, socioeconomic level and ethnic and cultural aspects.

It is likely that the environmental differences, inherent to both cases, might have been responsible for the differences found in the h^2 estimates.

In order to exemplify how the abovementioned factors can influence the h^2 estimates, we mention the study by Gu et al¹³. The purpose of their study was to verify family aggregation in the BP of sedentary nuclear families of different ethnicities. A total of 434 individuals from 86 families of Caucasian origin (85 fathers, 85 mothers, 127 sons and 137 daughters) and 193 individuals from 74 families of Black origin (22 fathers, 37 mothers, 50 sons and 84 daughters) participated in *The HERITAGE Family Study*. Regardless of gender and the condition of being a parent or a descendant, the Black individuals presented higher mean SBP and DBP values when compared to Caucasian individuals. It was observed that the genetic factors had a higher contribution in BP among Black individuals than among those of Caucasian origin (SBP: 68% vs 43% and DBP: 56% vs 24%).

Recent evidence provided by studies in Genetic Epidemiology carried out in populations from several countries supports the assertion that the genetic factors have an important influence on BP values^{8,10,13,22-25}. Some studies analyzed nuclear families^{13,22,25}, whereas others assessed extensive pedigrees^{8,10,23,24}. The results found showed values between 16²⁴-68%¹³ and 6²²-62%¹⁰ of the accountability of the SBP and DBP values, respectively, which can be attributed to genetic factors.

Rice et al²⁶ carried out a study that shows the importance of aerobic exercise in the estimates of h^2 for BP. Using a sample of 529 sedentary individuals belonging to 99

nuclear families from *The HERITAGE Family Study*, the authors calculated h^2 for SBP and DBP, before and after an intervention program of 20 weeks of aerobic training. The results demonstrated that, at the start of the study, the h^2 estimates were moderate (SBP $h^2=0.51$ and DBP $h^2=0.42$)²⁵. However, after the exercise-induced effect, the values decreased, especially for SBP (SBP $h^2=0.18$ and DBP $h^2=0.14$)²⁶. These results are interesting, as they demonstrate that both BP components are strongly influenced by the aerobic exercise.

A complementary form to interpret the h^2 estimates is the verification of family aggregation based on r values. The results found in the present study were low to moderate (0.21 – 0.50), in the 8 correlations calculated between the degrees of family relationship in both BP components. Although a distinct pattern of similarity between the pairs of related individuals (parents-descendants: $0.24 \leq r \leq 0.32$ and siblings: $0.21 \leq r \leq 0.50$) was verified when compared to unrelated individuals (spouses: $r \approx 0.25$), these values suggest the presence of family aggregation in BP values. Among related individuals, this similarity can be attributed to genetic factors. However, the similarity found between spouses expresses an important influence of the common environment. The only discordant correlation was observed in the mother-son association for SBP. This fact suggests that, only for this component, the male descendants are not like their mothers.

Similar results were found in the study by Campos et al¹¹. The authors found r values between -0.08 and 0.38, for DBP (father-son) and SBP (mother-daughter), respectively.

In the parent-offspring association, the values were $-0.05 \leq r \leq 0.38$ and $-0.08 \leq r \leq 0.27$ for SBP and DBP, respectively. Between spouses, the similarity was 0.34 for SBP and 0.14 for DBP. As in the results of the present study, the similarity between mother and son in SBP was low ($r=0.09$). In a general context, although the correlations were similar to those of the present study ($0.27 \leq r \leq 0.38$), the results showed negative values.

Other studies with nuclear families^{2,22,27} and in extensive pedigrees²³ showed a similar pattern of family aggregation in BP among family members. The values obtained varied from 0.03²³ to 0.51²² and 0.06^{2,22} to 0.33²² for SBP and DBP, respectively.

The results of the family aggregation clearly show the magnitude of the influence of genetic factors on BP levels. These results are of utmost importance to carry out further studies in the area of molecular genetics, based on the genome wide scans, in order to identify possible chromosomal regions that may harbor genes whose mutations maybe responsible for the variability in BP values. Some studies have shown significant linkages, only for SBP, in chromosomes 2 (D2S1788/2p22.1-2p21), 5 (D5S1471/5q33.3-5q34), 6 (D6S1009-D6S1003/6q23.1-6q24.1), 15 (D15S652/15q25.1-15q26.1)²⁸ and 17 (D17S1299 and ATC6A06)⁸, where the genes responsible for the control of this BP component are probably located. A recently published study²⁹ demonstrated some SNPs in the vicinity of the genes, of which mutations can influence BP values.

Conclusions

The results showed a strong family aggregation in both BP components, with a moderate degree of variation of this complex phenotype being attributed to genetic factors.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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