

ORIGINAL ARTICLE

The possible role of chromosome X variability in hypertensive familiarity

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Familiarity participates in the pathogenesis of hypertension, although only recently, whole genome studies have proposed regions of the human genome possibly involved in the transmission of the hypertensive phenotype. Although studies have mainly focused on autosome, hitherto the influence of sex on familial transmission of hypertension has not been considered. We analysed the database of the Campania Salute Network of Hypertension center of the Federico II University Hospital of Naples (Italy), using dichotomous variables for paternal and maternal familiarity and gender (male and female) of 12 504 hypertensive patients (6868 males and 5636 females) and 6352 controls (3484 males and 2868 females), totaling 18 856 subjects. In the hypertensive group, familiarity was present in 75% of cases with odds of 3.77 and in only 26% of the normotensives with odds of 0.94. The odds ratio (OR) indicated that familiarity increases the risk of developing hypertension by 2.91 (95% confidence interval (CI) = 2.67–3.17, $P < 0.001$) times. Additionally, maternal familiarity was 37% (OR = 3.01, 95% CI = 2.66–3.41, $P < 0.001$), paternal familiarity was 21% (OR = 2.31, 95% CI = 2.01–2.68, $P < 0.001$) and the double familiarity was 17% (OR = 3.45, 95% CI = 2.87–4.01, $P < 0.001$), thus suggesting a plausible association between maternal familiarity and development of hypertension; this finding was observed both in male and in female patients, although the phenomenon was larger in males. Given the dominance of maternal transmission in males, by genome-wide analysis of the X chromosome, we found two regions that were differently distributed in male hypertensives with maternal hypertension. Our data highlight the importance of genetic variants in the X chromosome to the maternal transmission of the hypertensive phenotype.

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INTRODUCTION

Blood pressure, like height and weight, is a continuous biological variable. The relationship between the level of blood pressure and cardiovascular risk has led to a definition of hypertension for those of arterial blood pressure associated with doubling of long-term cardiovascular risk.¹

About one-fourth of the world's population (70 million in the United States and 1 billion worldwide) is affected by arterial hypertension, which is the main cardiovascular risk factor and the leading cause for an outpatient visit to physician.²

Currently, about 54% of strokes and 47% of ischaemic heart disease worldwide are attributable to high blood pressure. In addition, because of increasing rates in obesity and aging, hypertension is projected to affect 1.5 billion people, that is, about one-third of the world population, by the year 2025.²

Essential hypertension is a disease with a significant phenotypic heterogeneity and among hypertensives several differences can be considered. Indeed, hypertension phenotypes can involve different mechanisms, such as the increase in aortic stiffness, the presence of metabolic syndrome and endothelial dysfunction, which influence can greatly differ within populations.³ For example, aortic stiffness accounts for mostly of the isolated systolic hypertension observed in elderly patients.^{4,5} On the contrary in young adult, hypertension is often associated with metabolic abnormalities or metabolic syndrome that includes

different clinical conditions such as the association of visceral obesity and metabolic disorders.⁶ Nonetheless, clinical manifestations of hypertension can be determined by the variability of genetic variants along with epigenetic components in the human genome.

In essential hypertension, familiarity is present in 90% of cases, but a Mendelian transmission of hypertension is rarely observed. For complex and polygenic diseases such as hypertension, two main strategies are available to map and identify the genes involved: (1) Linkage studies (Genome Wide Linkage), which are based on a known genetic model or when the model is unknown, studying pairs of affected relatives; and (2) Association studies (Genome Wide Association), where disease genes can be mapped using allelic association studies under a hypothesis-free approach.⁷ The influence of specific genes on blood pressure level has been demonstrated by family studies, showing increased prevalence among siblings and between parents and children. Moreover, blood pressure level can be accounted for by genetic factors, spanning from 25% in pedigree studies to 65% in twin studies.^{8,9}

Two measures are typically used to evaluate the genetic component of a phenotype: (1) heritability (h^2), measuring susceptibility to develop the disease due to genetic factors and (2) sibling recurrent risk (λ_s), which is the degree of risk of illness for a sibling of an affected individual compared with the general

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population. However, both heritability and sibling recurrent risk have shown a high variability on the related impact of the genetic trait to the observed phenotype. In hypertension, heritability changes from 15 to 40% and 15 to 30% for systolic and diastolic blood pressure, respectively, while the sibling recurrent risk ranges from 1.2 to 1.5, indicating a phenotype with a modest genetic effect.^{10,11}

Therefore, the overall search for genetic determinants of hypertension has incurred in several difficulties mainly related to the extreme variability of hypertensive phenotypes.^{10,11}

A different approach may involve evaluation of intermediate phenotypes of hypertension by using techniques of genetic association. Specifically, patients clustering could be helpful in reducing the interference produced by the background and leading to a more homogeneous sample.

In the present study, we aimed to a selected population from the 'Campania Salute Network—CSN' database following a clustering approach taking into account phenotype, gender and familiarity, and found that prevalence of maternal transmission is a strong contributor for development of hypertension in the male population.

MATERIALS AND METHODS

Population sample-CSN database

For this study, we selected a total of 18 856 subjects consisting of 12 520 hypertensive patients (6868 males and 5636 females) and 6352 patients (3484 males and 2868 females) with cardiovascular disease excluding hypertension, which were used as controls. All parameters, including anamnesis, physical examination, blood and urinary biochemistry, EKG, cardiac and vascular ultrasound and ambulatory blood pressure monitoring were collected during ambulatory visits and stored in the server of the CSN outpatient clinic, an open registry collecting information from general practitioners and community hospitals in Campania Region, Italy. The Federico II University Institutional Ethic Committee approved both the database and the informed consent form of CSN. Detailed characteristics of CSN population have been previously reported.^{12–14}

DNA extraction

Genomic DNA was extracted from whole blood sample of 1200 patients using a commercially available extraction kit (QuiagenMidi, Chicago, IL, USA).¹⁵

Informed consensus to the study was obtained from patients, which was previously approved by the Institutional Ethics Committee. The study was conducted according to the ethical principles that have their origins in the Declaration of Helsinki.

Genotyping

Genotyping was performed with 320 K Infinium II Assay-HumanHap 317 K duo BeadChip system SNP-array, according to the manufacturer's protocol (Illumina, San Diego, CA, USA). Quality of genotypes was evaluated by the GenCall score, which reflects the proximity within a cluster plot of the intensities of that genotype to the centroid of the nearest cluster. The score ranges from 0 to 1.

Quality control

Single-nucleotide polymorphisms (SNPs) with call rate < 95%, minor allele frequency < 5% and Hardy-Weinberg Equilibrium $P < 1 \times 10^{-3}$ were

excluded from the analysis. Quality control filters output 218 000 SNPs from the 317 K array. Samples that had call rate < 95% were also excluded. Moreover, exclusion of samples due to population stratification was performed using principal component analysis, which was conducted on a reduced set of autosomal markers showing $r^2 < 0.2$ and using the default outliers removal threshold ($\sigma = 6$) as implemented in Eigenstrat software.¹⁶

Imputation

Quality-controlled data set was imputed using build 36, release 22 HapMap CEU populations as the reference. Approximately 2.5 million SNPs were imputed using maximum likelihood method implemented in the MACH 1.0 software.^{17,18}

Linkage disequilibrium analysis

Haploview v4.2 software was used for linkage disequilibrium analysis.¹⁹ We estimated Haplotype blocks using the confidence intervals rule while Haplotype phases were inferred using the default expectation maximization algorithm.

Power calculation

QUANTO software was performed to evaluate Power Calculation. Specifically, we used the following settings: allele frequency ranging from 0.05 to 0.95, and significance threshold (P) for the screening analysis set to $P < 1 \times 10^{-4}$ evaluating allelic, dominant and recessive genetic models.²⁰

This last was identified by estimating the false-positive fraction on simulated data sets. Data simulation was carried out by generating 100 independent data sets composed by 317 K SNPs, with minor allele frequency distribution ranging from 5 to 50%, and 963 controls of which 410 were labelled as 'case' and 553 as 'control' in a random manner. We tested for association between each marker and case/control status assuming allelic, dominant and recessive genetic models and then selected the most significant model as the most informative for the SNP of interest.

For each significant threshold (ranging $0.05 < P < 1 \times 10^{-7}$), the mean fraction of false-positive associations (a false-positive association was defined as an SNP with P lower than the selected significance threshold, P) was estimated over 100 simulated data sets for each P .

Statistical analysis for association

Distribution analysis was performed using the chi-squared test. When comparing family history of hypertension frequencies, those observed in male hypertensive patients were referred to those observed in female hypertensives.

Association between the set of SNPs passing the quality control criteria and the phenotype selected was tested by Pearson chi-squared allelic association test with one degree of freedom (df) (a (minor allele) vs A (major allele), assuming a dominant (aa/aA vs AA, 1 df) and a recessive (aa vs aA/AA, 1 df) genetic effect. Logistic regression under additive, dominant and recessive genetic models was applied to estimate the odd ratio (OR) and 95% confidence interval (CI) for each of the different genetic models to ascertain potentially confounding gender-specific effects. Adjustment for potential confounding effects was considered by genomic control approach.²¹ PLINK²² was used for all statistical procedures, except when specified.

RESULTS

Population

Our study was carried out in a total of 18 856 subjects, that is, 12 504 patients with clinical history of hypertension (6868 males and 5636 females), and 6352 cardiovascular patients without

Table 1. Anthropometric data of 12 504 patients with clinical history of hypertension (6868 male and 5636 female) compared with the data of 6352 patients without diagnosis of hypertension (designated as controls)

	Age (years)	Gender F/M(%)	Weight (kg)	Height (cm)	BMI (kg m ⁻²)	SBP (mm Hg)	DBP (mm Hg)
Hypertensive	52.44 ± 0.1	44%/56%	78.2 ± 0.2	167.41 ± 0.1	27.85 ± 0.05	142.25 ± 0.2	88.44 ± 0.1
No hypertensive	45 ± 0.54	48%/52%	74.91 ± 0.7	169.18 ± 0.5	26.3 ± 0.6	128.44 ± 2.1	81.06 ± 1.8

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

diagnosis of hypertension (3484 males and 2868 females) that are enrolled in the database, and that had access to the outpatient clinic for possible diagnosis hypertension that was eventually excluded, or for ischaemic, cardiac valve or arrhythmic disease that was not associated with hypertensive status. Population was homogenous for prevalence of cardiovascular disease (coronary artery disease, heart failure and implantation of electrical stimulation devices) (Table 1).

Phenotype and familiarity

Familiarity was present in 75% of the hypertension cases and only in 26% of the normotensives (Figure 1). The likelihood (defined by the odds) of familiarity was significantly higher in the hypertensive group with respect to the normotensive patients (3.77 vs 0.94). Likewise, the relative risk expressed as OR was 2.91 (95% CI= 2.66–3.17, $P < 0.001$) times more frequent in the hypertensive patients than in normotensives (Figure 2). These results suggest that offspring of parents with hypertension have three times higher risk to develop hypertension in adult life than children of normotensive parents.

Familiarity and gender in the hypertensive group

We divided hypertensive patients with family history of hypertension into subcategories according to the presence of maternal, paternal or double familiarity. We found that almost 50% of hypertensive patients had maternal familiarity, and this number increased to almost 75% when considering those hypertensives with double familiarity, as illustrated in Figure 3. Analysis of familiarity in relation to gender revealed that in the female hypertensive group, 69% had maternal familiarity, alone or in double familiarity (Figure 3), whereas in the male hypertensive group this percentage raised to 76%, as 51% had maternal familiarity and 25% had double familiarity (Figure 3). The difference in the observed cases of maternal hypertension observed in hypertensive males compared with those observed in hypertensive females was very statistically significant, when compared by the chi-square test ($P < 0.0001$). Therefore, the maternal transmission of hypertension is more often observed in male than in female hypertensives in our population.

X-chromosome SNPs and hypertensive familiarity

Prevalence of maternal familiarity of hypertension suggests that the X chromosome is involved in determining the hypertensive phenotype. To explore this hypothesis, we used genome-wide genotype data of 615 hypertensive patients currently available in our database. Our analysis identified two genetic regions in the X

chromosome that were significantly associated with the familiarity phenotype (Figure 4). The polymorphisms included in these regions, with levels of association by a P -value of $< 10^{-3}$, are illustrated in Tables 2 and 3.

Weight of X-chromosome SNPs in clustered hypertensive patients

The specific weight of the X chromosome in the transmission of the hypertensive phenotype was evaluated by dividing the hypertensive population by gender and maternal familiarity (Table 4). This table shows all SNPs located in the X chromosome with $P < 0.001$. We observed a difference in allele frequency distribution of SNPs in male patients compared with female patients. Moreover, within male group, a comparison of SNPs allele frequency between 'hypertensive mother male' and 'not hypertensive mother male' showed opposite findings. For example, the frequency of allele B in the first group was higher than the one detected in all hypertensive patients and lower in the second group, or vice versa. However, these observations were not found in the female group (Table 4). Therefore, these data show that in males, a maternal family history of hypertension is associated with a higher SNPs variability on the X chromosome with respect to either female group or the general hypertensive population.

DISCUSSION

This work can be summarized in three key points: (1) the prevalence of maternal familiarity in the hypertensive population,

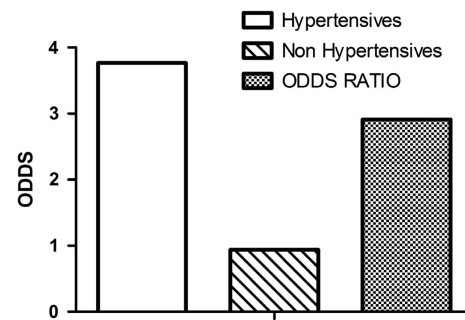


Figure 2. Likelihood of a family history of hypertension expressed as odds is different between hypertensive patients (in green) and non-hypertensive patients used as controls (in red). The relative risk expressed as the OR indicates that familiarity increases the risk of developing hypertension by 2.91 (95% CI=2.67–3.17, $P < 0.001$) times.

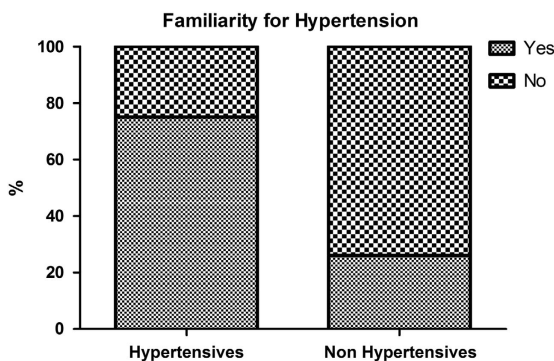


Figure 1. Higher frequency of family history of hypertension among hypertensive patients. Patients with hypertension presented more often family history of hypertension (left column) than non-hypertensive patients used as a control (right column). Statistic significance was assessed by chi-square test, $P < 0.001$.

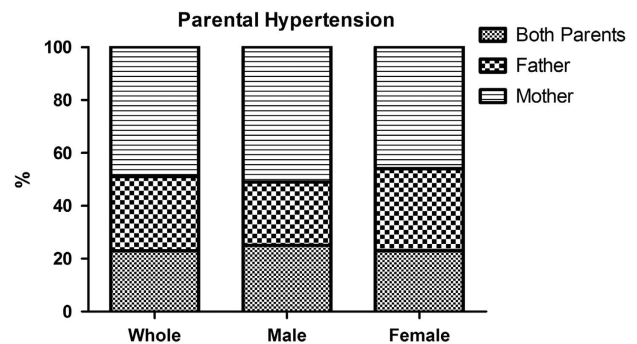


Figure 3. Presence of maternal, paternal or double familiarity of hypertension among the hypertensive patients with family history of hypertension, as whole or divided by gender. The number of observed cases of maternal hypertension history among hypertensive males was much larger than that expected using hypertensive female as a reference (5220 vs 4769, $P < 0.0001$, chi-square test).

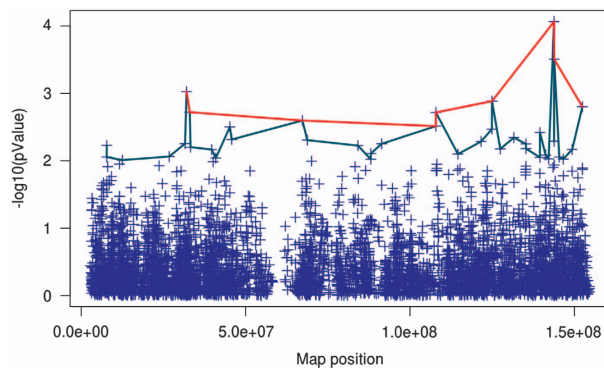


Figure 4. Summary of the levels of significance for all SNPs on the X chromosome as two peaks are observed. The green line links SNPs that have $-\log_{10}(P\text{-value}) > 2.5$ (i.e., $P < 0.001$), while the red line links SNPs with $-\log_{10}(P\text{-value}) > 2$ (i.e., $P < 3.1 \times 10^{-3}$). Two regions of chromosome X associate with a higher level of significance to maternal history of hypertension: one is comprised between 10000000 and 52058362 bp; the other one ranges from 123825787 to 168825787 bp.

Table 2. Summary of SNPs that are located in the region of the X chromosome that extends up to the position 52058362

SNPs	Position	$-\log_{10}(P\text{-value})$	P-value	Gene
rs3915296	7788738	2.22879	0.005905	No
rs845122	7790764	2.055776	0.008795	No
rs2304605	12537957	2.011001	0.00975	FRMPD4
rs5986678	26751837	2.063741	0.00864	No
rs10521976	31606813	2.255675	0.00555	DMD
rs1317098	32058362	3.027029	0.00094	DMD
rs2182289	33035448	2.722287	0.0019	DMD
rs4366220	33277344	2.203242	0.00626	No
rs5917336	39704495	2.167296	0.0068	No
rs2284116	40936724	2.039422	0.00913	USP9X
rs5952767	45222263	2.504622	0.00313	No
rs2148106	45783625	2.470942	0.00338	No

Abbreviations: DMD, Duchenne Muscular Dystrophy; SNP, single-nucleotide polymorphism.

(2) the association between familiarity and maternal X chromosome and (3) the observation that maternal familiarity has a greater weight in hypertensive men.

The link between familiarity and hypertension is well demonstrated in the literature.^{8,9} Moreover, in selected populations the role of genetic factors appears to be likely predominant with respect to the environment.^{23,24} However, the specific weight of familiarity is still underestimated for confounding factors in the general population. Our data support the hypothesis that the role of genetic trait on hypertension phenotypes can be unveiled by filtering and clustering a selected population, and allows to identify specific genetic factors for hypertension.

Our study takes place by the observed lack of data on maternal familiarity, probably due also to the low diffusion of detailed database. We overcame this limitation by using a digital medical record, started in 1997 with a high level of Information Communication Technology. This technology has allowed an easy clustering of patients present in the database into subcategories.

The association between maternal familiarity and hypertension has been previously occasionally reported, with opposite outcomes.²⁵ The genetics analysis was previously performed on the variation of the mitochondrial DNA, which is maternally

Table 3. SNPs located within the region of the X chromosome that extends from 123825787 to 168825787 base pairs

SNPs	Position	$-\log_{10}(P\text{-value})$	P-value	Gene
rs582694	125000000	2.471	0.00338	No
rs209637	125000000	2.885	0.00130	No
rs5932441	127000000	2.176	0.00666	No
rs243451	132000000	2.345	0.00452	HS6ST2
rs912002	135000000	2.250	0.00562	GPR112
rs6635268	135000000	2.181	0.006586	GPR112
rs6634180	140000000	2.051	0.00889	No
rs6528726	140000000	2.419	0.00381	No
rs5908269	141000000	2.086	0.00820	No
rs1989382	142000000	2.029	0.00934	No
rs5920360	144000000	4.066	0.00009	No
rs5966378	144000000	2.291	0.00512	No
rs7881233	144000000	3.507	0.00031	No
rs5920193	145000000	2.056	0.00880	No
rs7883888	147000000	2.025	0.00945	No
rs524400	149000000	2.169	0.00678	MAMLD1
rs743642	152000000	2.803	0.00158	BGN

Abbreviation: SNP, single-nucleotide polymorphism.

transmitted.²⁶ Our study identifies for the first time the possible role of the X chromosome in familiar transmission of hypertension. The X chromosome appears to be neglected in genome-wide association studies despite several works in the literature showing the role of sex chromosomes in increased susceptibility to hypertensive mice.^{25,27}

Therefore, using a Genome Wide Analysis method in combination with a clustering approach for investigating the role of the X chromosome, we identified a number of SNPs that are associated with defined trait 'maternal familiarity for hypertension'.

The X-chromosome SNPs observed in our study are also associated with other diseases, such as SNP rs10521976 located in the *DMD* gene, which is responsible for Duchenne Muscular Dystrophy (DMD) and Becker Muscular Dystrophy. DMD is a fatal X-linked recessive disease that affects 1 in 3500 males and at an advanced stage the disease progresses to left ventricular dysfunction and development of pulmonary hypertension.²⁸ This observation supports the role of the X chromosome in the determination of blood pressure and hypertensive phenotype with mechanisms that are yet to be elucidated. The male patients, genetically equipped with only one X chromosome, appear to be a category in which the weight of the X-chromosome variability is stronger.

Some limitations of this study need to be considered: (1) the small number of patients subjected to genetic evaluations for which the values of P-values are not genome-wide significant (defined as $P < 1 \times 10^{-6}$). However, the clustering of data from a well-documented database allowed us to be confident that the results presented herein are plausible; (2) we did not propose a specific pathogenic hypothesis since we have considered only two regions in the X chromosome and the relative SNPs without focusing on specific gene(s). However, this could also be considered as a more realistic approach given the multifactorial nature of hypertension.

In the future, investigation of the role of sex in transmittance of the hypertensive phenotype should take into account the X chromosome and the mitochondrial DNA variability in an integrated manner.

Finally, trying to translate our findings onto the clinical scenario, we found that the presence of maternal familiarity can predict development of hypertension in males.

Table 4. Minor allele frequency distribution of captured SNPs located in the X chromosome *P*-value < 0.001 among various categories

SNP	A1	A2	Frequency of A1 in hypertensive patients (HP)	A1 in HP with maternal familiarity	A1 in HP without maternal familiarity	A1 in male HP with maternal familiarity	A1 in male HP without maternal familiarity	A1 in female HP with maternal familiarity	A1 in female HP without maternal familiarity
rs3915296	A	G	0.367	0.399	0.322097	0.441	0.305	0.325	0.354
rs845122	T	G	0.491	0.459	0.637176	0.429	0.663	0.504	0.489
rs2304605	T	G	0.072	0.096	0.042435	0.093	0.029	0.102	0.068
rs5986678	C	T	0.269	0.237	0.310861	0.192	0.308	0.313	0.316
rs10521976	G	A	0.112	0.093	0.137	0.075	0.166	0.123	0.083
rs1317098	A	G	0.229	0.192	0.273	0.164	0.306	0.24	0.214
rs2182289	T	C	0.31	0.267	0.368	0.221	0.364	0.345	0.374
rs4366220	T	C	0.193	0.156	0.242	0.146	0.257	0.172	0.214
rs5917336	A	G	0.096	0.069	0.13	0.065	0.149	0.075	0.095
rs2284116	A	C	0.08	0.101	0.055	0.114	0.041	0.079	0.08
rs5952767	G	A	0.415	0.372	0.472	0.321	0.468	0.457	0.479
rs2148106	T	C	0.168	0.199	0.131	0.216	0.109	0.169	0.174
rs7050085	G	A	0.122	0.099	0.151	0.066	0.163	0.156	0.13
rs5936709	G	T	0.099	0.073	0.131	0.066	0.155	0.084	0.089
rs675728	C	T	0.306	0.338	0.267	0.35	0.223	0.317	0.347
rs4545257	T	C	0.297	0.264	0.338	0.243	0.364	0.299	0.289
rs663737	T	G	0.291	0.255	0.334	0.238	0.362	0.283	0.282
rs117393	G	A	0.154	0.124	0.19	0.103	0.203	0.16	0.167
rs2346677	G	A	0.144	0.118	0.173	0.09	0.194	0.164	0.135
rs2346678	G	A	0.143	0.116	0.173	0.086	0.194	0.168	0.135
rs6655312	T	C	0.244	0.282	0.198	0.308	0.19	0.238	0.214
rs5909899	G	A	0.241	0.199	0.297	0.202	0.327	0.194	0.242
rs582694	G	A	0.308	0.339	0.268	0.363	0.225	0.298	0.346
rs209637	A	C	0.289	0.324	0.243	0.344	0.197	0.29	0.33
rs5932441	A	G	0.269	0.225	0.327	0.224	0.349	0.226	0.287
rs243451	T	C	0.149	0.125	0.181	0.1	0.202	0.168	0.141
rs912002	C	T	0.485	0.522	0.439	0.564	0.422	0.452	0.469
rs6635268	G	A	0.485	0.521	0.44	0.564	0.424	0.448	0.469
rs6634180	A	G	0.457	0.491	0.417	0.514	0.38	0.452	0.484
rs6528726	G	A	0.245	0.277	0.202	0.294	0.168	0.248	0.266
rs5908269	A	G	0.447	0.4	0.502	0.383	0.517	0.428	0.474
rs1989382	C	T	0.411	0.439	0.375	0.476	0.345	0.375	0.431
rs5920360	A	C	0.121	0.086	0.165	0.056	0.183	0.138	0.132
rs5966378	A	G	0.203	0.176	0.238	0.127	0.236	0.26	0.242
rs7881233	T	C	0.123	0.095	0.159	0.061	0.177	0.154	0.125
rs5920193	C	T	0.071	0.088	0.047	0.105	0.035	0.06	0.068
rs7883888	T	C	0.25	0.21	0.297	0.186	0.299	0.25	0.295
rs524400	C	T	0.454	0.414	0.504	0.388	0.526	0.46	0.464
rs743642	G	T	0.069	0.048	0.095	0.023	0.098	0.091	0.089

Abbreviation: SNP, single-nucleotide polymorphism. In the red cells are marked the higher values than those detected in all patients, while in blue cells are show the lower ones.

What is known about this topic?

- Familiarity has a big role in the setup of hypertension and hypertension-related complications.
- Contradictive data are available for the prevalence of maternal transmission of hypertension.
- Some mechanistic data suggest that mitochondrial DNA variability might participate to maternal transmission of hypertension to offspring.

What this study adds?

- Confirms and quantifies the impact of maternal transmission of hypertension.
- Identifies in males a population more prone to maternal transmission of hypertension.
- Proposes that X-chromosome variability participates in maternal transmission of hypertension to male offspring.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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