Association between family history and essential hypertension in Han population in Shanghai China

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Abstract

Backgrounds Genetic factor is one of important influencing factors of essential hypertension, and family history (FH) is an important marker of genetic factors. Objective To explore the association between family history and essential hypertension in Han population in Shanghai China. Methods The method of case-control study was used 342 cases of hypertension and 342 controls were selected and investigate their nuclear family members in the both study groups. The diagnostic information of hypertension in all relatives of these two groups was investigated. The method of genetic epidemiology research was used to explore the effect of family history. Results The average prevalence of hypertension was 23.32%. The prevalence of hypertension of first-degree relatives was 33.99%; the prevalence of second- degree relatives was 17.60%; the prevalence of third-degree relatives was 13.51%. All prevalence of hypertension of case group relatives was significantly higher than that of control group relatives. The average onset age in population with positive FH was 48.74±11.16 years old, and the average onset age in population with negative FH was 54.38±9.87 years old. The difference about two FH groups showed statistically significant (t=4.589, P<0.001). The average onset age of offspring with father, mother, grandpa, grandma, maternal grandpa or maternal grandma positive was respectively 48.42, 49.16, 39.55, 39.88, 43.67 or 43.64 years old; and the average onset age of children with father, mother, grandpa, grandma, maternal grandpa or maternal grandma negative was respectively 51.90, 51.17, 51.07, 51.08, 50.50 or 50.57 years old. The difference about two groups showed statistically significant. Conclusion Family history had a positive effect on the occurrence of hypertension, and led to earlier age of onset of offspring. The effects were different among parent and grandparent in Han in Shanghai China.

Introduction

According to the research report of Nature Genetics, scientists at Lancaster University have identified 535 new genes related to hypertension through genetic analysis of the largest population (more than 1 million people) so far. The results of this study told people that hypertension was related to heredity, but there were many genes that affect hypertension [1-3]. Genome-Wide Association Study (GWAS), There were tens of thousands of samples in European and American population, more than 10 gene loci related to blood pressure have been reported, but the effect on blood pressure level of the population was extremely weak, and more gene variation need to be found [4-8]. At present, there was no established method model for hypertension genetic research. We could have a general understanding of the disease only by comprehensively analyzed different phenotypes of different populations. There was no doubt that hypertension was a complex disease with genetic and environmental factors and their interaction. Its pathogenesis, treatment and target organ damage were all affected by genetic, environmental and their interaction. Therefore, it has become a major medical research topic to carry out more adequate etiology research, find more effective treatment methods, and control and reduce the occurrence of hypertension.

Essential hypertension was heterogenous and delayed externality. The related genes of essential hypertension were a group, which played different roles in different stages of the formation and development of hypertension and interact with each other. It was generally believed that the mode of

action of micro effect genes played a major role in the genetic mechanism of essential hypertension, most risk alleles from multiple loci had a very low frequency in the group, and there were the interaction, through the dose-response relationship of quantitative characters, reaches the critical threshold of disease occurrence, and jointly determines the genetic susceptibility of essential hypertension.

Family history was an important sign of genetic factors. Most of hypertension patients had family history, and the blood pressure level of their directly-related members of one's family was higher than that of their collateral relatives [9-13]. At present, although there were many studies on the influencing factors of hypertension, there were few reports on the interaction between the risk factors of hypertension.

This study used methods of genetic epidemiology study, based on the investigation of the essential hypertension cases family and the control family, to explore the association between family history and the onset age of essential hypertension in Han in Shanghai China.

Methods

Source of cases and controls

All cases were randomly selected from hypertension registry and follow-up management system in Jiading district in Shanghai, and all controls were randomly selected from the community population. According to l:l matched pairs design, all controls had no hypertension, and controls were required the same sex, same race, living in the same community as cases, and the difference of age was not more than 5 years old and at the same age group. Every case or control gave informed consent to participate in the study which was approved by the local ethics committee (JD-2016-KY-18). They were able to correctly respond to the investigators for the health information of themselves and their nuclear family members.

Investigation method and content

Investigation was conducted by trained public health investigators, using a unified questionnaire. Using direct survey method, the contents of the questionnaire mainly include: age, sex, age of onset, diagnosis time, hospital name, family members and so on. The family members mainly included: spouses, parents, siblings, children, uncle, aunt and cousin. The criteria for judging whether all the respondents had essential hypertension (all relatives of cases and controls): whether they had been diagnosed with essential hypertension in the hospital before this investigation. If they had been diagnosed with essential hypertension in the hospital, it is “Yes”; if they had not been diagnosed, it is “No”.

Statistical analysis method

Statistical analyses were performed using the statistical software package (IBM SPSS statistics version 21). Case-control study and genetic epidemiological data analysis were used to analyze the differences between the two groups and the variations among different family histories. The comparison of counting data was examined by Chi-square test, and the comparison of measurement data was examined by t test. When P values <0.05, the difference is considered statistically significant.

Results

Characteristics of population

In this study, 342 cases (male 171, female 171) and 342 controls (male 169, female 173) were investigated, male was 50.73%; female was 49.27%. Their age from 28 to 87, the average age was 62.4±10.7 years old, and the average age in the case group was 62.4±10.7 years old, the average age in the control group was 61.7±10.7 years old. The total number of family members investigated was 8599 (4353 in case group and 4246 in control group). The average number of family members in each family was 12.57 (12.73 in case group and 12.42 in control group). Their races were Han. The difference of age and sex between case group and control group were not significant (t_{age}=0.894, p_{age}=0.372; x^2_{sex}=0.119, p_{sex}=0.730).

Total number of nuclear family members investigated was 8814 (4454 in case group, 4360 in control group), and the average nuclear family member was 12.88 (case group is 13.02; control group is 12.74). Among 4104 investigated population in the elder member of a family (include father, mother, grandpa, grandma, maternal grandpa and maternal grandma), there were 839 relatives were definitely diagnosed with hypertension. The prevalence of hypertension was 20.44% in the elder relatives of this investigation. Among 3265 non-hypertensive relatives, there may also be some patients with potential or recessive hypertension who have not been clearly diagnosed. There is no reverse effect on the results of this study, so no further discussion will be conducted.

Family history

If one or more relatives of the first-degree relatives (include father, mother, grandpa, grandma, maternal grandpa and maternal grandma) have been definitely diagnosed with hypertension, family history (FH) was called positive, otherwise was called negative.

Among 4104 investigated population in the elder member of 684 families (include father, mother, grandpa, grandma, maternal grandpa and maternal grandma), there were 575 hypertension cases in parent population (include father and mother), the prevalence rate of parent was 42.03%; and 89 hypertension cases in grandparent population (include grandpa and grandma), the prevalence of grandparent was 6.51%; and 69 hypertension cases in maternal grandparent population (include maternal grandpa and maternal grandma), the prevalence of maternal grandparent was 5.04%. Because most of the grandparents and maternal grandparents have been died before this investigation, a part of hypertension cases may be omitted because of unknown or not diagnosed in the retrospective investigation, resulting in the low prevalence of these two groups of elder relatives. See table 1.

Table 1: The hypertension prevalence rate (%) of elder member in case and control group

	Control group			Case group			x^2	p
	No	Yes	%	No	Yes	%		
father	222	120	35.08	170	172	50.32	16.158	<0.001
mother	234	108	31.48	167	175	51.29	27.057	<0.001
grandpa	323	19	5.57	311	31	9.03	3.107	0.078
grandma	323	19	5.57	322	20	5.81	0.027	0.869
maternal grandpa	331	11	3.28	324	18	5.16	1.764	0.184
maternal grandma	324	18	5.25	320	22	6.45	0.426	0.514

Note: “No” was number of non-hypertension, “Yes” was number of hypertension, x^2 and p value were calculated by x^2 test.

FH affects onset age of hypertension

Among 342 cases in the case group, the total number of family members investigated was 2052. There were 499 have been definitely diagnosed with hypertension; the positive rate of family history was20.42%. The result in Table 2 showed that the average onset age in population with positive family history was 48.74±11.16 years old, and the average onset age in population with negative FH was 54.38±9.87 years old. The difference about two FH groups showed statistically significant (t=4.589, P<0.001). Family history had a positive effect on the occurrence of hypertension, and lead to earlier age of onset of offspring. Among the first-degree relatives, the efficacy on the age of onset of hypertension in offspring was different for different relatives.

Table 2 showed that either parents or grandparents or maternal grandparents in the first-degree relatives could affect the onset age of hypertension of children, it's just that the level of effect was different. Grandpa and grandma are particularly influential among the first-degree relatives. The average onset age of children with grandpa or grandma positive was respectively 39.55 (39.55±11.95) or 39.88 (39.88±11.90) years old; and the average onset age of children with grandpa or grandma negative was respectively 51.07 (51.07±10.59) or 51.08 (51.08±10.60) years old. The difference about two groups showed statistically significant (see table3). The results suggest that the onset age of hypertension of children with grandpa or grandma positive was about 11 years earlier likely than that of children grandpa or grandma negative.

Table 2: The average onset age of hypertension in case group with different family history

	Hypertension	N	Onset age (y)		t	p
			mean	SD		
father	Yes	167	48.42	11.16	3.194	0.002
	No	175	51.90	10.81		
mother	Yes	166	49.16	11.12	1.832	0.068
	No	176	51.17	11.04		
grandpa	Yes	26	39.55	11.95	5.768	<0.001
	No	316	51.07	10.59		
grandma	Yes	27	39.88	11.90	5.682	<0.001
	No	315	51.08	10.60		
maternal grandpa	Yes	15	43.67	9.77	2.883	0.010
	No	327	50.50	11.09		
maternal grandma	Yes	18	43.64	10.21	3.086	0.005
	No	324	50.57	11.06		

Note: “N” was the number of people, “mean” and “SD” were the mean and standard deviation of onset age, t and p value were calculated by t test.

Discussion

Clinically, hypertension could be divided into two categories: one was essential hypertension, it’s an independent disease with elevated blood pressure as its main clinical manifestation and unclear etiology, accounting for more than 90% of all hypertensive patients; the other is secondary hypertension, also known as symptomatic hypertension, it has a clear etiology, and it mainly caused by renal artery stenosis, pheochromocytoma, hyperaldosteronism and other diseases. This study mainly studied the influence of family history on hypertension, in order to exclude the interference of other factors, it was necessary to exclude secondary hypertension and only study primary hypertension. Therefore, in the case selection of design stage in this study, only primary hypertension was selected.

It’s well known that the genetic factors played an important basic role in the occurrence of hypertension, and family history was a sign reflecting the main role of genetic factors. It’s showed that family history played an important role in the development of hypertension through interaction with acquired risk factors such as body mass index (BMI), and the interaction of family history and BMI is greater than the sum of two independent actions [14-17]. In this study, the genetic epidemiological results showed that the prevalence of hypertension in three degree relatives was different. The prevalence in the first degree relatives (including parents, siblings and offspring) was the highest (33.99%), the prevalence in the second degree relatives (including paternal siblings and maternal siblings) was the next (17.60%), and the prevalence in the third degree relatives (including paternal cousin and maternal cousin) was lowest (13.51%). The difference of hypertension prevalence among three degree relatives in Han in Shanghai China were significantly (P<0.05). All prevalence rates of three degree relatives of case group relatives were significantly higher than that of control group relatives. It was suggested that genetic factors have obvious influence on the occurrence of essential hypertension, and the genetic potency may be decrease with the increase of degree relatives.

Among 684 families, the prevalence of parent population (include father and mother) was high (42.03%), and the prevalence of case group relatives were significantly higher than that of control group relatives. The prevalence of grandparent population (include grandpa and grandma) or maternal grandparent population (include maternal grandpa and maternal grandma) was lower, and the difference of prevalence between case group and control group. Owing to most of the grandparents and maternal grandparents have been died before investigation, a large number of hypertension cases may be omitted because of unknown or not diagnosed in the retrospective investigation, resulting in the low prevalence of these two groups of population. If we update the data collection methods and increase the sample size in future studies, we may be able to find differences between the two groups.

Some studies showed that the heritability of hypertension was 20%~55% [18-20]. It indicated that there were also ethnic differences in hypertension susceptibility genes among different ethnic groups. In order to further quantitatively assess the impact of family history on hypertension, we chose age of onset as an indicator. In this study, the result showed that the average onset age in population with positive FH was 48.74 years old, and the average onset age in population with negative FH was 54.38 years old, the difference about two FH groups showed statistically significant. The average onset age of hypertension in cases with positive family history was likely 5 years earlier than that of cases with negative family history. The efficacy on the age of onset of hypertension in offspring was different for different relatives. The average onset age of children with father or mother positive was respectively 48.42 or 49.16 years old; and the average onset age of children with grandpa or grandma negative was respectively 51.90 or 51.17 years old. The average onset age of hypertension in cases with positive parents was likely 2-3 years earlier than that of cases with negative parents. The average onset age of children with grandpa or grandma positive was respectively 39.55 or 39.88 years old; and the average onset age of children with grandpa or grandma negative was respectively 51.07 or 51.08 years old, the average onset age of hypertension in cases with positive grandparents was likely 11 years earlier than that of cases with negative grandparents. The average onset age of children with maternal grandpa or grandma positive was respectively 43.67 or 43.64 years old; and the average onset age of children with maternal grandpa or grandma negative was respectively 50.50 or 50.57 years old, the average onset age of hypertension in cases with positive maternal grandparents was likely 7 years earlier than that of cases with negative maternal grandparents.

Conclusion

Family history had a positive effect on the occurrence of hypertension, and led to earlier age of onset of offspring. The effects were different among parent and grandparent in Han in Shanghai China.

Declarations

Ethics approval and consent to participate

Ethical approval was granted by Jiading district center for disease control and prevention research ethics committee (JD-2016-KY-18). All subjects gave informed consent to participate in the study, they would like to participate in investigation and answer all the related questions in the questionnaire.

Consent for publication

Not applicable.

Availability of data and material

The questionnaire and database supporting the conclusions of this article are available, through contact with anle_li@aliyun.com.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

The original idea for the project was conceived by An-le LI. Qian Peng（Yue-qin Shao, Yi-ying Zhang, Xiang Fang participated in the collection of early data, quality control, and gave a lot of administrative support. LI An-le conceptualized the paper, analyzed data and wrote a first draft of the manuscript. All authors contributed to subsequent drafts and approved the final manuscript.

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References

1. Warren HR, Evangelou E, Cabrera CP, et al. Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk [J]. Nature Genetics, 2017;49(3):403-415.
2. Evangelou E, Warren HR, Mosen-Ansorena D, et al. Publisher Correction: Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits[J]. Nature Genetics, 2018;50(12):1755.
3. Evangelou E, Warren HR, Mosen-Ansorena D, et al. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits[J]. Nature Genetics, 2018 Oct;50(10):1412-1425.

4. Kim HJ, Seo YS, Sung J, et al. A genome-wide by PM10 interaction study identifies novel loci for lung function near BICD1 and IL1RN-IL1F10 genes in Korean adults [J]. Chemosphere, 2019 Dec 9;245: 125581.
5. Malaria Genomic Epidemiology Network. Insights into malaria susceptibility using genome-wide data on 17000 individuals from Africa, Asia and Oceania [J]. Nat Commun. 2019 Dec 16;10(1):5732.
6. Hill WD, Davies NM, Ritchie SJ, et al. Genome-wide analysis identifies molecular systems and 149 genetic loci associated with income [J]. Nat Commun. 2019 Dec 16;10(1):5741.
7. Kämpe A, Enlund-Cerullo M, Valkama S, et al. Genetic variation in GC and CYP2R1 affects 25-hydroxyvitamin D concentration and skeletal parameters: A genome-wide association study in 24-month-old Finnish children [J]. PLoS Genet. 2019 Dec 16;15(12):e1008530.
8. Feng Y, Zhang Y, Chen Y, et al. The associations between three genome-wide risk variants for serum C-peptide of T1D and autoantibody-positive T1D risk, and clinical characteristics in Chinese population [J]. J Hum Genet. 2019 Dec 12. doi: 10.1038/s10038-019-0705-2.
9. Whelton PK, He J, Appel LJ, et al. Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program[J]□□□□□□2002□288(15)□1882-1888□
10. Lahiri D□Maloney B□Genes are not our destiny□the somaticepi type bridges between the genotype and the phenotype□Nat Rev Neurosci□2006□7(12)□DOI:01038/nrn2022-c1□
11. Uher R□ne implications of gene-environmem interactions in depression□will cause inform cure? MoI Psychiatry□2008□13(12)□1070-1078□
12. Ehrel GB. Genome-Wide Association Studies□Contribution of Genomic to Understanding Blood Pressure and Essential Hypertension [J]. Curr Hypertens Report□2010,12:17-25.
13. An-le Li, Xiang Fang□Yi-ying Zhang, Qian Peng, Xian-hong Yin. Familial aggregation and heritability of hypertension in Han population in Shanghai China: a case-control study[J]. BMC□Clinical hypertension. 2019□25□17□1-7.
14. An-le Li, Qian Peng, Yue-qin Shao, Xiang Fang and Yi-ying Zhang. The effect of body mass index and its interaction with family history on hypertension: a case–control study [J]. BMC: Clinical Hypertension. 2019, 25(6): 1-8.
15. Macumber IR□ Weiss NS□ Halbach SM□ et al□The association of pediatric obesity with nocturnal non-dipping on 24-hour ambulatory blood pressure monitoring [J]□Am J Hypertens□ 2016, 29 (5) : 647 -652□
16. Olack B, Wabwire-Mangen F, Smeeth L, et al□Risk factors of hypertension among adults aged 35-64 years living in an urban slum Nairobi, Kenya[J□□ BMC Public Health, 2015□15(1):1□
17. JOshi MD, Ayah R, Njau EK, et al□Prevalence of hypertension and associated cardiovascular risk factors in an urban slum in Nairobi, Kenya□ A population-based survey[J□□BMC Public Health□2014□14(1)□1□
18. Aune D, Sen A, Norat T, et al. Body Mass Index, Abdominal Fatness, and Heart Failure Incidence and Mortality: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies [J].

Circulation,2016, 133(7): 639-649.

19. Jeanemaitre X，Gimenez-Roqueplo A，Disse-Nicodeme S，et a1．Emery and rimoin’s principles and practice of medical genetics e-dition principles of medic H genetics．5th ed．philadelphia．Churchill lying-ston Elsevier．2007．283-330．
20. Levy D，Ehret GB，Rice K，et a1．Genome-wide association study of blood pressure and hypertension[J]．Nat Genet．2009．41(6)．677—687．