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Article

Genetic Characteristics of the Patients with Young-onset Hypertension

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Abstract: Hypertension with an onset at younger age is so-called young-onset hypertension (YOH). The relative risk for YOH in subjects with positive family history was much higher than subjects aged between 50 and 69 years, which suggested a greater proportion of the BP variation may be explained by genetic factors in YOH. On the other hand, the earlier onset and longer duration of hypertension will result in greater risks of future cardiovascular events. To prevent future cardiovascular events, it is important to identify YOH early in life. Therefore, we aimed to review the literatures about genetic characteristics of YOH comprehensively.

Keywords: gene, hypertension, young-onset hypertension

1. Introduction

Hypertension is one of the most important risk factors for cardiovascular diseases. The relation between blood pressure (BP) and the risk of cardiovascular disease is direct and continuous over a wide range, apparently beginning at 115 mmHg systolic and 75 mmHg diastolic [1]. While the incidence of essential hypertension continues to increase, it remains inadequately treated in the majority of patients [2,3]. These findings suggest that more detail understanding of the etiologies of hypertension and more efficient antihypertensive strategies should be applied.

Hypertension with an onset at younger age, so-called young-onset hypertension (YOH), is different from that developed in older age [4–6]. The relative risk for YOH in subjects with positive family history was much higher than subjects aged between 50 and 69 years [4], which suggested a greater proportion of the BP variation may be explained by genetic factor in YOH. On the other hand, the earlier onset and longer duration of hypertension will result in greater risk of future cardiovascular events [5]. To prevent future cardiovascular events, it is important to identify YOH early in life.

2. The prevalence of young-onset hypertension

The prevalence of hypertension in young population differs due to different inclusion criteria for the age, different definitions for BP or hypertension, different ethnicity background of the population, different study year, and so on.

In a cross-sectional study in 5,131 Northern Italian children (age 5-11 years), the prevalence of hypertension was 3.4% according to the definitions of the systolic BP and/or diastolic BP at first

screening $\geq$ 90th percentile and the mean of three subsequent measures $\geq$ 95th percentile [7]. A screening campaign during the World Hypertension Day showed that high BP values (BP $\geq$ 140/90 mmHg) were found in 11 % young Italian adults (aged 18-35 years) in 2014 [8].

In a cross-sectional assessment of BP in 6,790 adolescents (age 11-17 years) in Houston schools in USA from 2003 to 2005 [9], the prevalence of hypertension was 3.2% according to 3 screenings. It has reached 19 % in USA in 2008 in the 24–32 age group, according to the National Longitudinal Study of Adolescent Health (Add Health) study [10]. The prevalence of hypertension continues to rise, especially in young adults [11].

In Japan, however, hypertension was noted in only 0.1% of the participants in a university health check-up at the Tohoku University Health Center over 2 years (n= 33,496, age mostly 18-24 years) [12].

3. Clinical characteristics of young-onset hypertension patients

Some studies have found out some clinical characteristics associated with BP in patients with YOH.

In the cross-sectional study in Northern Italian children, weight class and waist circumference were associated with BP [7].

A screening campaign during the World Hypertension Day in 2014 [8] showed that male sex, adiposity and alimentary habits were the main determinants of high BP values in Italians. In a cross sectional survey of 2,334 high school people in Italy (age 18-21 years), a significant correlation exists between BP and fat free mass; uric acid has proven to be the most important systolic BP determinant [13].

In the cross-sectional assessment of BP in Houston schools in USA, overweight was noted to be associated with hypertension [9]. In cross-sectional analyses of Coronary Artery Risk Development in Young Adults Study (CARDIA) data for 5,031 US adults age 18-30 years, mean systolic BP was directly associated with daily alcohol intake in white and black males and in white females [14]. In the National Longitudinal Study of Adolescent Health, a US longitudinal study of >15 000 young adults (median age 29 years), higher household income and being married were independently associated with lower systolic BP; higher body mass index, greater waist circumference, smoking, and higher alcohol intake were each independently associated with higher systolic BP [15].

In a university health check-up at the Tohoku University Health Center (age mostly 18-24 years) [12], the clinical parameters indicated that male gender, genetic background, and excessive weight were risk factors for YOH [12]. Excess plasma renin activity was one of additional characteristics of YOH to male gender, genetic background, and increased body mass after continuing the screening for seven consecutive years [16].

In a case-control study in Taiwan [6], YOH patients (age of onset of hypertension under 40 years) had increased serum triglyceride levels when comparing to the control. Serum triglyceride level was significantly correlated to body mass index, serum cholesterol and glucose level in male patients but only to serum uric acid level in female ones. The findings suggested the gender-specific presence of metabolic syndrome in YOH.

4. Genetic characteristics of young-onset hypertension patients

Numerous genes had been identified to be associated with BP or hypertension by Genome-wide association studies (GWASs) in Caucasian populations [17–23], African Americans [24], and Chinese populations [25]. More than 25 rare mutations and 53 single-nucleotide polymorphisms (SNPs) had been reported to contribute to the genetic architecture of BP and hypertension [26]. However, the results were different among different populations and ethnicities. Furthermore, few studies focus on the population of YOH patients, which may be genetically disposed for hypertension.

4.1. Lipoprotein lipase gene and hypertension

Lipoprotein lipase (LPL) is a key enzyme in lipid metabolism and is associated with obesity, dyslipidemias, hypertension, and type 2 diabetes mellitus. Association of the LPL gene S447X variant with hypertension has been investigated extensively. A meta-analysis with a total of five studies (960 cases and 1145 controls) for hypertension and four studies (n=2777) for BP demonstrated that LPL gene S447X variant was significantly associated with hypertension [27]. One study conducting in ninety members of 30 Mexican families showed that the HindIII and S447X LPL gene polymorphisms can confer susceptibility for the development of hypertension and also type 2 diabetes mellitus [28]. Data from YOH had confirmed the association between LPL and hypertension [29–31]. An genetic linkage study of YOH performing on 59 nucleus families of Han Chinese residing in Taiwan showed positive signs of linkage for markers of LPL, atrial natriuretic peptide gene (NPPA), angiotensinogen gene (AGT), and angiotensin converting enzyme gene (DCP1) [29]. Data from 213 individuals in 59 nuclear families of YOH showed that LPL variants may play a causal role in the development of hypertension in Taiwan Han Chinese [30]. Data from a family-based haplotype association study further showed that two LPL intronic variants may be associated with development of the hypertension endophenotype with elevated plasma triglyceride [31].

4.2. Angiotensin converting enzyme gene and hypertension

Angiotensin converting enzyme (ACE) plays major roles in the pathogenesis of cardiovascular diseases (CVD). Serum ACE activity was a heritable endophenotype of CVD.

By carrying out a genome-wide scan for ACE activity in 1,271 individuals from 373 YOH pedigrees, a previously unknown quantitative trait loci (QTL) on chromosomes 9 at 149.4 cM was identified affecting ACE activity in addition to a strong linkage peak near the ACE structural locus on chromosome 17 at 89.6 cM [32]. From a 2-stage GWAS (400 YOH subjects in the first stage and an additional 623 YOH subjects in the second stage), three SNPs were significantly associated with ACE activity, including rs4343 in ACE gene, rs495828 and rs8176746 in ABO gene) [33]. Replication study in an independent YOH family study (428 hypertension pedigrees) showed the association between ABO genotype/blood types and ACE activity, and a potential differential BP response to ACEI in subjects with varied numbers of ACE-activity-raising alleles [33]. Further study discovered a moderate effect variant upstream of ACE promoter for YOH and two QTLs of ACE activity, one from exon 13 to intron 18 and the other from intron 20 to 3′ UTR [34].

4.3. Other loci associated with hypertension

There were still some other loci found to be associated with YOH. By a two-stage association study, a SNP quartet 219 kb and 495 kb downstream of LOC344371 (a hypothetical gene) and RASGRP3 on chromosome 2p22.3 were identified as YOH susceptibility genes [35]. By analyzing GWAS and gene expression data, seventeen of the 100 genes exhibited differential allelic and expression distributions between patient and control groups. Among the 17 genes, IGF1, SLC4A4, WWOX, and SFMBT1 were also replicated by the Hong Kong Hypertension Study (HKHS). GRB14, TMEM56 and KIAA1797 exhibited highly significant differential allelic and expressed distributions between hypertensive patients and normotensive controls. TMEM56 and KIAA1797 may be specific to Taiwanese populations, because they were not validated by HKHS and the Wellcome Trust Case- Control Consortium Hypertension Study (WTCCCHS) [36].

By performing a two-stage matched case-control study, two SNPs were identified to be strongly associated with hypertension in Han Chinese population with YOH, including rs2301339 located at guanine nucleotide-binding protein 3 subunit (GNB3) and rs17254521 located at insulin receptor (INSR) [37]. By performing a 3-stage study (1st-stage multilocus GWASs, 2nd-stage gene expression analysis, and 3rd-stage multilocus confirmatory study), 4 previously unknown loci were identified in Han Chinese population with YOH, including a locus near intron 1 of the ACTN4 gene and loci

upstream or downstream of GSN and LARS. The ACTN4 locus and LARS locus were associated with the respective BP or hypertension traits by the HKHS or WTCCCHS. However, GSN was not associated with BP or hypertension traits by either the HKHS or the WTCCCHS, which mean that GSN may be specific to Taiwanese individuals [38].

Further study showed that the SNP rs1501299 (G276T) but not rs2241766 (T45G) in adiponectin (ADIPOQ) gene was associated with the presence of hypertension in a total of 962 participants from 302 families from the Taiwan YOH genetic study [39]. No association of ADIPOQ gene with hypertension alone or metabolic syndrome without hypertension was observed. The significant association of the SNP rs1501299 (G276T) with the phenotype of presence of hypertension in metabolic syndrome was confirmed in the replication study of 1448 unrelated participants [39].

4.4. Loci associated with other BP phenotype

There were also some studies reporting the genetic loci associated with other BP phenotype derived from 24-hour ambulatory BP monitoring (ABPM). GWAS data of pulse pressure (PP) from ABPM data showed that rs897876 at 2p14 was highly associated with nighttime PP in YOH patients. Subjects carrying the TT genotype of rs897876 had a higher nighttime PP, suggesting that the T allele of rs897876 was an independent predictor in determining ambulatory nighttime PP and could be a genetic prognostic factor of CVDs [40].

Another association study showed that five tag SNPs were significantly associated with the non-dipper phenotype in YOH patients, including rs3888170 in NPAS2, rs6431590 in PER2, rs1410225 in ROR, rs3816358 in BMAL1, and rs10519096 in ROR. A genetic risk score was independently associated with the presence of non-dippers among subjects with YOH. Genetic variants in circadian genes were associated with the diurnal phenotype of hypertension, suggesting a genetic association with diurnal BP changes in essential hypertension [40].

5. Conclusion

There are still few studies concerning about the YOH patients. Since YOH patients may have greater genetic susceptibility and greater risks of future cardiovascular events, further studies are needed to deepen our understanding of the clinical and genetic characteristics of YOH. The findings may also help us to have more information about the physiology of BP control and the pathophysiology of hypertension.

Conflicts of Interest:
The authors declare no conflict of interest.

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