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PEDIATRIC HYPERTENSION:

GENETICS OF HYPERTENSION • CURRENT STATUS

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Abstract

Genetics of hypertension is complex with no known single gene playing a major role, but rather many genes each with mild effects reacting to different environmental stimuli contribute to blood pressure. The heritable component of blood pressure has been documented in familial and twin studies suggesting that 30%–50% of the variance of blood pressure readings are attributable to genetic heritability and about 50% to environmental factors. Early studies in hypertension identified specific enzymes, channels and receptors implicating sodium handling in the regulation of blood pressure including genes involved with the renin-angiotensin-aldosterone system controlling blood pressure and salt-water homeostasis, proteins in hormonal regulation of blood pressure (enzymes and receptors of the mineralo- and gluco-corticoid pathways) and proteins coded by genes involved in the structure and/or regulation of vascular tone (endothelins and their receptors).

The field of molecular genetics has revolutionized the study of hypertension by identifying single gene syndromes or Mendelian forms and several candidate genes for blood pressure variance. Genes have been localized to at least 20 chromosome regions. For example, recent genome-wide association studies (GWAS) of common genetic variants found 13 single nucleotide polymorphisms (SNPs) or variants in systolic and 20 for diastolic blood pressure readings representing different genes and genetic heterogeneity. Further understanding of the genetics of hypertension will require the use of advances in bioinformatics tools and genetic technology [e.g., SNP, exon and non-coding (micro) RNA arrays]. New approaches will allow for identification of not only single genes, but other interacting genes contributing to hypertension by merging multiple genetic data sets (structural and functional) from individuals with hypertension and development of new molecular targets for study and treatment.

RÉSUMÉ

La génétique de l’hypertension est complexe, sans gène particulier connu pour jouer un rôle majeur mais plutôt de nombreux gènes, chacun ayant un effet léger, réagissant à différents stimuli environnementaux et contribuant à l’hypertension. La composante génétique de la pression artérielle a été documentée lors de plusieurs études au niveau de familles et de jumeaux hypertendus, suggérant que 30 à 50% de la variance au niveau des lectures de la pression artérielle sont attribués à des facteurs héréditaires, et à peu près 50% à des facteurs environnementaux. Les

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premières études en matière d'hypertension ont identifié des enzymes spécifiques, des canaux et des récepteurs impliquant le sodium dans la régulation de la pression artérielle comprenant des gènes impliqués dans le système rénine-angiotensine-aldostérone, lui-même responsable du contrôle de la pression artérielle et de l'équilibre hydrosodé, des protéines dans la régulation hormonale de la pression artérielle (enzymes et récepteurs des voies minéralo- et gluco-corticoïdes) et des protéines codées par des gènes impliqués dans la structure et/ou la régulation du tonus vasculaire (les endothélines et leurs récepteurs).

Le domaine de la génétique moléculaire a révolutionné l'étude de l'hypertension en identifiant des syndromes à gène unique ou formes mendéliennes, et plusieurs gènes possibles pour la variance de la pression artérielle. Des gènes ont été localisés dans au moins vingt régions chromosomiques. Par exemple, les récentes études GWAS (*Genome-wide association studies*) de variantes génétiques communes ont trouvé treize SNPs (*Single nucleotide polymorphisms*) ou variantes dans l'hypertension systolique, et vingt pour l'hypertension diastolique, représentant différents gènes et hétérogénéités génétiques. Ultérieurement, la compréhension de la génétique de l'hypertension fera appel aux progrès en bioinformatique et en technologie génétique [ex. SNP, tableaux d'exons et de (micro) ARN non-codants]. Ces nouvelles approches permettront non seulement l'identification de gènes particuliers, mais aussi d'autres gènes en interaction contribuant à l'hypertension, en fusionnant plusieurs bases de données génétiques (structurelles et fonctionnelles) provenant d'individus hypertendus, et en développant de nouvelles cibles moléculaires pour l'étude et le traitement.

INTRODUCTION AND BACKGROUND

Blood pressure (BP) is a major risk factor for cardiovascular disease. Hypertension (HT) affects about one-third of adults and contributes to 13.5 million deaths world-wide each year [1]. About one-half of individuals with stroke and ischemic heart disease can be attributed to the effects of HT. In addition, up to 50% of individuals with high BP have genetic factors that contribute to their HT [2], while families with genetic syndromes in which high or low BP readings are features have been found with mutations with either gain or loss of function in about a dozen renal sodium regulatory genes [3]. These genes often affect the renin-angiotensin-aldosterone system controlling BP and salt-water homeostasis [3]. Common variants in two renal sodium regulatory genes are associated with BP regulation in the general population; however, only a few variants were associated with inter-individual BP variation indicating genetic heterogeneity [4]. Using various genetic techniques, over 20 chromosomal regions have been identified whereby genes are located contributing to essential or non-syndromal HT (OMIM #145500 – www.ncbi.nlm.nih.gov/OMIM) although syndromic forms of hypo- and HT do exist. A recent online computer search (June 11, 2009) using key words "genes and hypertension" found 5491 published references in the medical literature. Therefore, no single gene plays a major role, but many genes with mild effects reacting to environmental stimuli contribute to HT.

Only recently have new bioinformatics tools and advanced genetic technology using SNP (single nucleotide polymorphism), gene, exon or non-coding RNA arrays and genome-wide association studies (GWAS) been proposed or employed to investigate the role of genetics in HT (both syndromic or essential forms). For example, a recent GWAS analysis of BP

readings in 10 families (440 individuals) showed a heritability of 0.21 and suggested regions on chromosomes 7,8,18 and 21 as playing a role [5]. In addition, using creatinine clearance measurements in a large bi-racial sample of hypertensive siblings, De Wan et al [6] showed that a locus on chromosome arm 3q contributes to the degradation of renal function affecting BP measurements. Furthermore, Lifton et al. [3] found at least 10 genes that alter BP readings with most genes containing rare mutations imparting quantitative effects that either raise or lower BP through a common pathway by changing salt and water reabsorption in the kidney. Hypertensive disorders that fall into this category include glucocorticoid remediable aldosteronism, the syndrome of apparent mineralocorticoid excess and Liddle syndrome. Liddle syndrome, an autosomal dominant disorder, is caused by a mutation in either the beta or gamma subunit of the renal epithelial sodium channel gene. Conversely, hypotensive disorders such as pseudohypoaldosteronism type 1, an autosomal recessive disorder, can be produced by a mutation in either the alpha or beta subunit gene of the same renal epithelial sodium channel involved in Liddle syndrome while Gitelman syndrome is caused by mutations in the thiazide-sensitive Na-Cl cotransporter gene. Furthermore, Hasstedt et al. [7] measured red cell sodium in a large study of normotensive members ascertained through hypertensive or normotensive probands, sibs with early stroke death, or brothers with early coronary disease and found that red blood cell sodium levels were determined by four recessive alleles at a single gene locus. The gene locus was thought to explain 29% of the variance in red blood cell sodium levels which could impact on the onset of HT while polygenic inheritance explained another 55%. Impairment of the baro-reflex-system and its control of BP may also be influenced by genetic factors.

Blood pressure has a continuous distribution and multiple genes and environmental factors are involved that determine the level of one’s blood BP similar to the inheritance of stature and intelligence which are multi-factorial. For example, low birth weight is associated with the subsequent development of HT in adult life while maternal malnutrition and fetal exposure to maternal glucocorticoids could impact on the hypertensive state in an individual.

GENE MAPPING

Essential HT is therefore the upper end of the distribution of BP readings in humans and not due to a recognized syndrome. The person with essential HT is one who inherits an aggregate of genes determining HT and is exposed to environmental factors that favor HT. Examination of the biochemistry and processes that affects BP homeostasis should elucidate interactive physiologic regulators that malfunction in persons with elevated pressure. Therefore, identification of single genes with large effects on the biochemical processes would be of importance in understanding HT. The following is an abbreviated description of chromosome locations or gene mapping sites thought to be involved with essential HT arranged by chromosome number (see www.ncbl/nlm.nih.gov/OMIM for review).

Chromosome 1

Funke-Kaiser et al. [8] proposed that the *ECE1* gene on chromosome band 1p36.1 is a candidate for human BP regulation and identified five polymorphisms in this same gene among a cohort of European hypertensive patients. In addition, Caufield et al. [9] presented

evidence of genetic linkage between the angiotensinogen gene (*AGT*) located at chromosome region 1q42-q43 and HT in humans and found significant differences in plasma levels of angiotensinogen among hypertensive subjects with different *AGT* genotypes. Secreted by the liver, angiotensinogen undergoes sequential cleavage by renin and angiotensin I-converting enzyme to produce the active hormone angiotensin II, which promotes the rise in BP.

Chromosome 2

Angius et al. [10] found evidence for linkage of an essential HT susceptibility locus, *HYT3*, to chromosome region 2p25-p24.

Chromosome 3

Bonnardeaux et al. [11] further identified an association between HT and several polymorphisms in the *AGTR1A* gene on chromosome region 3q21-q25. Using meta-analysis method of genome-wide data for blood pressure variation and HT in Caucasians, Koivukoski et al. [12] found strong evidence of linkage to chromosome region 3p14.1-q12.3 (*HYT7*).

Chromosome 4

A polymorphism in the gene encoding adducin-1 (*ADD1*) on chromosome band 4p16.3 has been associated with salt-sensitive essential HT.

Chromosome 5

Wallace et al. [13] found evidence for linkage with HT and high renal function on chromosome 5p (*HYT6*).

Chromosome 7

A polymorphism in the *CYP3A5* gene on chromosome band 7q22.1 has been associated with salt sensitivity in patients with essential HT. A mutation in the nitric oxide synthetase (*NOS3*) gene on chromosome band 7q36 has been associated with resistance to conventional therapy for essential HT and also with pregnancy-induced HT.

Chromosome 11

Rutherford et al. [14] reported a chromosome 11q quantitative trait locus that influences changes in BP measurement over time in Mexican-Americans.

Chromosome 12

Significant linkage to chromosome 12p (*HYT4*) in a genome-wide scan of a large Chinese family with primary HT was reported as well as a novel polymorphism (825C-T) in exon 10 of the gene encoding the beta-3 subunit of heterotrimeric G proteins (*GNB3*) on chromosome band 12pl3 associated with essential HT [15].

Chromosome 15

Xu et al. [16] reported significant linkage of essential HT with the telomeric end of chromosome arm 15q (*HYT2*) in extreme lower diastolic BP readings in affected sib pairs.

Chromosome 17

Rutherford et al. [17] provided evidence for the location of at least one HT susceptibility locus on chromosome 17 (*HYT1*) in analyses of affected sib pairs and concluded that the *NOS2A* gene, which maps to chromosome 17cen-q11 may play a role. A polymorphism within the promoter of the gene showed increased allele sharing among sib pairs and a positive association with the *NOS2A* gene and essential HT. By testing a series of microsatellite markers in the chromosome 17q, the location of a BP genetic trait was confirmed in a collection of both white and black sib pairs in the U.S. The presence of two separate genomic regions were further identified containing loci affecting human BP.

Chromosome 18

Guzman et al. [18] observed significant overrepresentation of two SNPs (rsl941958 and rs1893379) in the *MEX3C* gene located on chromosome band 18q21 (*HYT8*) in hypertensive patients compared with controls while Rutherford et al. [19] reported sib pair data further implicating chromosome 18 in essential HT.

Chromosome 20

Wallace et al. [13] found evidence for linkage with HT and the covariates of lean body mass on chromosome arm 20q (*HYT5*). Nakayama et al. [20] also identified a mutation in the *PTGIS* gene which maps to chromosome band 20q13 in three siblings with essential HT.

GENOME-WIDE LINKAGE AND ASSOCIATION STUDIES

To search for chromosomal regions containing genes that regulate BP, Xu et al. [16] scanned the entire auto-somal genome using 367 polymorphic DNA markers selected from more than 200,000 Chinese adults. Their sampling design consisted of sib pairs with and without HT and the availability of genotyped parents. In this study, no regions achieved a 5% genome-wide significance level, but maximum lod scores were greater than 2.0 for regions of chromosomes 3, 11, 15, 16, and 17. Using expanded genome-wide association studies (GWAS) with over 2 million SNPs or DNA variants, Newton-Cheh et al. [21] identified an association between systolic and diastolic BP and common variants in eight regions near the *CYP17A1, CYP1A2, FGF5, SH2B3, MTHFR, C10orfW7, ZNF652* and *PLCD3* genes. These genes become candidates for further investigation in their role in HT.

Because BP is a major cardiovascular disease risk factor, Levy et al. [22] recently reported results from an expanded genome-wide association study of systolic (SBP) and diastolic (DBP) BP readings in a large consortium of Cohorts for Heart and Aging Research in Genome Epidemiology (CHARGE) genetic dataset in a replicated fashion and identified 13 SNPs for SBP and 20 for DBP. Through joint meta-analysis of over 30,000 individuals in this study, four loci (*ATP2B1, CYPJ7A1, PLEKHA7, SH2B3*) attained genome-wide significance for SBP and six for DBP (*ATP2B1, CACNB2, CSK-ULK3, SH2B3, TBX3-TBX5, ULK4*). Prevalence of HT increased in relationship to the number of risk alleles carried for each gene.

The proportion of statistically significant SNPs that were intragenic in their study was 47% for systolic and diastolic BP versus an average of 37% for all SNPs in the meta-analysis of the CHARGE consortium data [22]. For systolic BP (SBP), their meta-analyses identified 13 SNPs with significant values with the strongest signal for SNP rs2681492 in the *ATP2B1* gene located on chromosome region 12q21-q23. A signal was also identified on chromosome band 12q24 for the *SH2B3* gene and for the *ATXN2* gene, which is nearby. The *PLEKHA7* gene, which is located on chromosome band 11p15.1 through these association studies, recorded a significant SNP (rs381815). A locus on chromosome region 2q31-q33 adjacent to *PMS1* and *MSTN* genes also showed evidence for an association. Their study further showed that many of the top systolic BP markers or associated SNPs were associated with other BP phenotypes.

For diastolic BP (DBP), there were 20 SNPs with significant association signals particularly on chromosome band 12q24 that included the *SH2B, TRAFD1* and *ATXN2* genes. In addition, the *ATP2B1* gene (on chromosome band 12q21), *TBX3-TBX5* (on chromosome band 12q24), and *PLEKHA7* (on chromosome band 11p15) also showed an association with DBP. Other suggestive associations were seen for loci in or adjacent to the *ULK4* gene (on chromosome band 3p22.1), *C5K-ULK3* (on chromosome band 15q24) and *CACNB2* (on chromosome band 10p12).

A further analysis on the type of SNP (silent or synonymous; nonsynonymous or when a different polypeptide sequence is produced) was reported by Levy et al. [22] in their BP association research. They found that five SNPs were of the nonsynonymous type implying a potential significant change in protein production including rs3184504 in the *SH2B3* gene, rs267561 in the *ITGA9* gene and three linked nonsynonymous SNPs in the *ULK4* gene (rs2272007, rs3774372 and rs1716975). Expression studies were then reported which showed that some SNPs did alter gene expression and therefore protein production including rs2272007 and rs1716975 in the *ULK4* gene using lymphoblastoid cell lines compared with cell lines not including these SNPs.

SUMMARY

Several genes and SNPs causing alterations in gene function and protein production (regulatory or structural) play a role in regulating BP readings in humans requiring further research. Using advanced genetic methods including SNP, exon and non-coding (micro) RNA arrays and bio-informatics tools in extended and sporadic families with either syndromic or essential HT should further characterize candidate genes, their protein products and determine pathophysiology of HT. Potential new drug targets for pharmaceutical intervention and treatment should be possible. The characterization of biologic and clinical phenotypes and cardiovascular end points should further highlight the contributions of genes that directly or indirectly regulate BP and its complications in humans.

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