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G. 知的所有権の取得状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

II. 研究成果の刊行に関する一覧表

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III. 研究成果の刊行物・別刷

Geriatrics and Gerontology International 2003; **3:** *150–153*

ORIGINAL ARTICLE

Genetic risk factors for cerebral infarction using data from a large-scale genetic epidemiological study: the Ohasama Study

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Background: With the imminent advent of an extremely aged society, there will be an increasing requirement for the prediction, early detection and treatment of cerebral infarction. Involved in the etiological mechanisms of cerebral infarction are a number of complex genetic and environmental factors related to the onset and progression of hypertension and arteriosclerosis. Elucidation of the significance of the various risk factors will require definite identification of phenotypes using large numbers of subjects.

Methods: The present study was conducted as part of a cohort study with subjects from the general population of a rural community (the Ohasama Study). Blood pressure (BP) patterns were assessed through random home-based and clinical measurements, as well as 24 h ambulatory BP monitoring. Magnetic resonance imaging of the brain was carried out in some subjects in order to detect asymptomatic cerebral infarcts, the maximum intima–media thickness was determined by carotid high-resolution ultrasonography, and cognitive function was assessed using the mini mental state examination. Correlation analysis of these parameters and the candidate hypertensive genotypes was then performed.

Results: Significant associations were seen between (i) gene polymorphisms in the renin–angiotensin system and asymptomatic cerebral infarction and the non-dipper pattern of circadian blood pressure variation; and (ii) endothelial nitric oxide synthase (eNOS) gene polymorphism and arterial pressure, lacunar score and cognitive function. An association was seen between the endothelin-1 polymorphism and hypertension, but only in obese subjects.

Conclusion: There are interactions between genes and the environment in the etiology of cerebral infarction.

Keywords: essential hypertension, genetics, genetic susceptibility, renin–angiotensin system, single nucleotide polymorphisms.

This article is a winner of the Novartis Prize of the Japan Geriatric Society

Introduction

One of the greatest problems faced by Japan, where the aging of society is proceeding even more rapidly than in Western countries, is the increasing economic, as well as medical and welfare, cost to society of cardiovascular disease. Hypertension is a well-known risk factor for

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cardiovascular disease, and through the introduction of effective antihypertensive medications and lifestyle interventions such as a reduction in salt intake, there has been a definite reduction in the incidence of cerebral hemorrhage and infarction. However, despite the widespread adoption of these measures, the mortality from cardiovascular diseases in the present rapidly aging society has again begun to increase, and further elucidation of the causes, as well as new approaches to prevention and treatment, of cerebral infarction will be required.

In order to elucidate the causes of essential hypertension, which accounts for more than 90% of all cases of hypertension, and the risk factors for progression to end-organ disease, we have previously performed genome screening on spontaneously hypertensive rats and also conducted analyses of genetic susceptibility to hypertension in human populations. These efforts failed to isolate what could be called a definite 'hypertensive' gene. The aims of the present study, part of the Ohasama Study, a large-scale cohort study using the general population of a rural community, are to examine the significance of both genetic factors and the traditional environmental risk factors, and also to examine the interaction between environmental and genetic factors in cardiovascular disease.

Rationale for examination of genetic susceptibility for hypertension

If we plot the frequency of blood pressure (BP) values, it will resemble the normal distribution, indicating that BP has a quantitative character and is derived from a number of different factors. The onset of hypertension is therefore not related to an abnormality of a single gene, but rather it is reasonable to assume that hypertensive patients possess several genes that tend to raise BP (i.e. hypertension susceptibility genes). The number of such genes can be extrapolated from the BP histogram of the general population, and statistical analysis suggests the existence of no less than 10 separate genes. A gene that exerts a particularly great effect on the phenotype (BP) is called a main effective gene, but there have to date been no reports of any single gene increasing BP by 10 mmHg or more. Unlike the situation in which a single mutation in one gene determines the pathology in its entirety, the role of genes in a multifactorial condition can be understood only through the interaction of a number of genetic and environmental factors. Base pair (bp) substitutions are known as gene polymorphism, a typical form being the single nucleotide polymorphisms (SNP), and are seen at a certain level in the general population in a state of equilibrium. This means that they do not confer any extreme survival disadvantage in the absence of any major environmental change, and that the influence they have on the phenotype in question is small; indeed, they may have a beneficial effect on a different phenotype. Carriers of the homozygous deletion polymorphism (*DD*) in the angiotensin-converting enzyme gene (*ACE*), for example, with a homozygous 287 bp deletion at intron 16, are known to have a high susceptibility to ischemic heart disease,[1] but at the same time many are long-lived, with a low incidence of Alzheimer's disease. We must therefore recognize that the significance of gene polymorphism can change with time (i.e. age and the passage of time) and situation (i.e. environment).

Methods

Investigation of genetic factors in the Ohasama Study

The subjects consisted of 1490 residents of Ohasama City in Iwate Prefecture, aged 40 years and over, who consented to participate in the study and undergo genetic analysis. Blood was taken from subjects, and after separation of the white cells, DNA was extracted using the QIAamp DNA Blood Kit (Qiagen, Valencia, CA, USA). As well as BP measurements at the time of medical consultations (casual BP (CBP)), subjects underwent 24 h ambulatory BP monitoring (ABPM), with measurements taken every 30 min using the ABPM-630 (Colin Corporation, Japan). The mean daytime and night-time BP were then calculated. Subjects were also asked to measure their BP at home (HBP), using the HEM-401C (Omron Life Science, Kyoto, Japan), for 4 weeks within 1 h of both waking and retiring, and the mean BP for that 4 week period was calculated from these measurements. Some of the subjects underwent magnetic resonance imaging of the brain and the following indices of asymptomatic cerebral infarction were calculated: lacuna score, a count of areas 3–10 mm in diameter with low intensity on T_1-weighted images and high intensity on T_2-weighted images; and periventricular hyperintensity (PVH) grade, scoring the periventricular areas of low intensity. A selected group of subjects also underwent carotid Doppler imaging to measure the maximum intima–media thickness (max IMT), and assessment of cognitive function using the mini mental state examination (MMSE).

The TaqMan polymerase chain reaction (PCR) and PCR-restriction fragment length polymorphism (RFLP) methods were used to determine the *M235T* polymorphism of the angiotensinogen gene (*AGT*), the insertion/deletion (*I/D*) polymorphism of *ACE*, the *A1166C* polymorphism of the angiotensin II type 1 receptor gene (*AT1*), the *C3123A* genotype of the angiotensin II type 2 receptor gene (*AT2*), the *Gly460Trp* (*G/T*) polymorphism of the α-adducin gene (*ADD1*), the *Lys198Asn* (*G/T*) genotype of the endothelin 1 gene (*ET1*), the *Glu298Asp* polymorphism of the endothelial nitrous oxide gene (*eNOS*), and the UCSNP-*43G/A* polymorphism of the

Table 1 Association between α-adducin Gly460Trp polymorphism and hypertension in younger subjects with low renin activity (< 1.0 ng/mL per h)

ADD1 genotype	*GG* (mean ± SEM)	*GG* + *TT* (mean ± SEM)	*P*
24 h ABPM (n = 90)			
n	46	144	
Daytime BP			
Systolic BP (mmHg)	127.8 ± 2.0	131.8 ± 1.5	< 0.04
Diastolic BP (mmHg)	77.7 ± 1.3	79.7 ± 0.9	0.09
Night-time BP			
Systolic BP (mmHg)	110.5 ± 1.9	114.0 ± 1.3	< 0.05
Diastolic BP (mmHg)	65.6 ± 1.1	67.0 ± 0.8	0.17
Home BP (n = 235)			
n	55	180	
Systolic BP (mmHg)	121.5 ± 1.7	124.7 ± 1.2	< 0.05
Diastolic BP (mmHg)	77.0 ± 1.3	78.2 ± 0.9	0.37

ADD1, α-adducin gene; BP, blood pressure; ABPM, ambulatory BP monitoring.

calpain-10 gene (*CAPN10*). Associations between blood pressure readings and genotype were examined using ANOVA, and those between these data and genotype with the χ^2 test using contingency table analysis.

Results

The *AGT/M235T* polymorphism was significantly associated ($P < 0.05$) with the scores for the brainstem, basal ganglia and cerebral lacuna. The *AT1/A1166C* polymorphism was also associated in younger subjects with the basal ganglia and cerebral lacuna scores, and with the PVH grade. Multivariate analysis confirmed the significance of these associations, suggesting that these genotypes are independent risk factors for asymptomatic cerebral infarction.[2] Examination of the relationship between diurnal variation in BP on ABPM, and the *AGT/T* + *31C*, which is in the highest linkage dysequilibrium with *M235T* polymorphism, revealed a significant tendency to a higher incidence of the non-dipper pattern, with a reduced nocturnal drop in BP, in response to an increase in the number of *C* + *31* alleles (= *T235* allele).

If we limited our analyses to the elderly group, aged 65 or over, of the Ohasama subject population, we found a relative weakening of the effect of genetic factors in comparison to the younger group. No influence on BP was seen for *ADD1* polymorphism in the entire population or the elderly group but when we examined its influence in younger subjects with low renin activity, known to be closely related to salt sensitivity, we found that, as in Caucasian subjects, BP was significantly elevated in subjects with the *Trp640* allele (Table 1).[3]

We examined the relationships between the lacuna score, PVH grade and max IMT, as the risk factors for

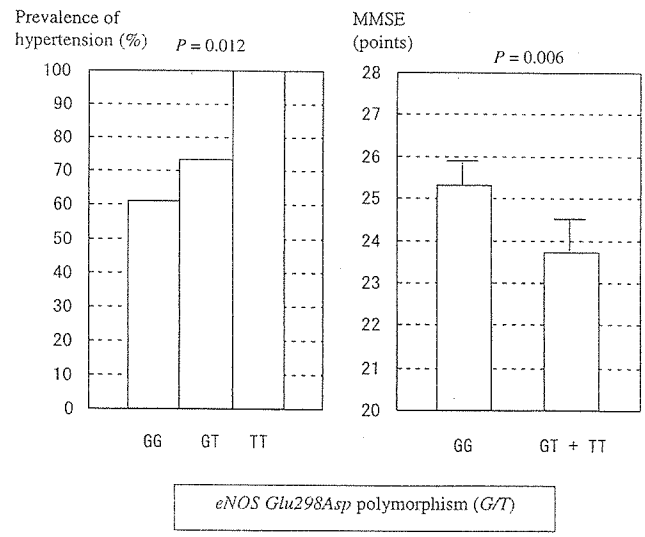

Figure 1 Association between endothelial nitric oxide synthase gene (*eNOS*) polymorphism and hypertension and cognitive function in the elderly.

asymptomatic cerebral infarction, and each genotype. No significant associations were found, apart from the basal ganglia lacunae and border regions in the *ACE/DD* and *AT1/C1166* allele carriers. The prevalence of hypertension was associated significantly ($P < 0.015$) with the *AT1/C1166* allele but with no others, and no associations were seen between the HBP or mean BP measurements during 24 h ABPM and any polymorphisms. Because the G allele carriers of *eNOS* polymorphism increased the prevalence of hypertension, BP tended to rise, and the MMSE score decreased significantly (Fig. 1; $P < 0.006$). The effect of this polymorphism on cognitive function in the elderly is particularly of note

with the increasing emphasis on the consequences of increased BP.

Discussion

Interactions between genes and the environment, and the advent of 'tailor-made' therapies

The 'thrifty gene', thought to aid survival in times of famine, is known to cause lifestyle illnesses such as hypertension in times of abundance. Possession of the *AGT/T235* allele, useful for retaining water and salt in the body, held a survival advantage for peoples living in the African savanna or making long ocean voyages, but for those living in cold European climates with a comfortable lifestyle, this genotype is transformed into a risk factor for cardiovascular disease.[4] It has been known for some time that the non-dipper pattern, with high nocturnal BP, is common in salt-sensitive hypertensives, and the high incidence of the non-dipper pattern in carriers with the *AGT/T235* allele has interesting implications for the production of 'tailor-made' therapies. In a large-scale cohort study conducted in the USA into the effects of 3 years of weight loss and salt restriction in normotensive subjects, the risk of developing hypertension was definitely higher in carriers with the *AGT/T235* allele, but the interventions were also more effective.[5] This indicates that the risk of developing hypertension can be effectively reduced in carriers with the *AGT/T235* allele through intensive lifestyle modification.

The results of the present study also demonstrated that, solely in overweight subjects with a body mass index (BMI) = 25 kg/m^2, the *Lys198Asn* (*G/T*) polymorphism of the *ET1* significantly increased susceptibility to hypertension,[6] which agrees with results obtained from Caucasian subjects, indicating that *ET1* polymorphism carries a risk of hypertension only in the pathological state of obesity. In other Japanese study populations, different β2 adrenergic receptor genotypes have also affected the raised BP associated with obesity and it can therefore be expected that intensive dietary advice and exercise regimens will be effective in such patients.

A person's genotype is unchanged throughout life, and if it becomes clear that certain genotypes modify the influence of environmental exposure, then it may become possible to reduce the likelihood of developing some diseases through stringent control of the relevant environment factors. These tailor-made therapies will therefore consist not only of choosing the appropriate medication for the individual patient's constitution, but will also include ancillary therapies based on the results of genetic analysis. In fact, the nationwide Millenium Project in Japan is now in progress, and the stated final aims of the Council on High Blood Pressure are (i) the discovery of at least 30 genes associated with diseases and drug responsiveness; (ii) improved therapeutic results through the selection of the most appropriate medication for the individual patient (i.e. tailor-made therapy); and (iii) development of landmark new drugs, with the aim of reducing estimated admissions for cardiovascular diseases by 20% and the requirement for treatment of stroke by 20%.

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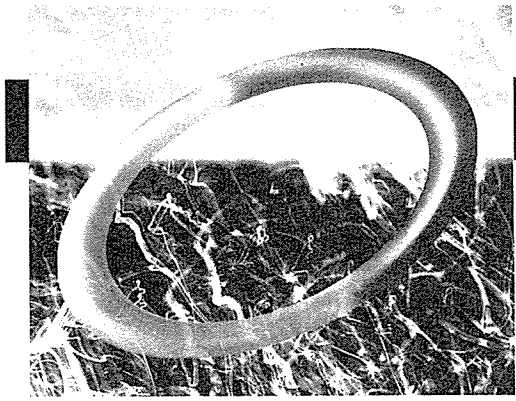

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日本人の高血圧と合併症—特徴と治療 No.6

大迫研究にみる家庭血圧の重要性

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はじめに

従来，血圧は診察室ないし健診などの医療環境下において測定されるものであった．その結果，医療環境下での血圧，いわゆる「随時血圧」の値を基に高血圧の診断・予防・治療が行われてきた．

随時血圧の有用性は，これまでの多くの観察研究や介入試験の成績から明らかである．しかし，非致死性脳血管障害は依然減少せず，相対的にはむしろ増加しつつある現状がある．その原因の一つとして，随時血圧のみに基づく高血圧診療の限界があるのではないか．

随時血圧は医療環境下という特殊な状態における血圧であり，防御反応・警鐘反応に由来すると考えられる白衣効果などのバイアスが加わった血圧である．また，一機会における測定頻度が少なく，ランダムな測定値変動の影響を受けているため，必ずしもその人個人の真の血圧値を表していない場合がある．

一方，家庭における自己測定血圧（家庭血圧）を用いることにより，非医療環境下において多数の血圧測定値が得られる．そのため個体の血圧をよりよく反映し，個々の患者レベルの高血圧診療に威力を発揮する．しかしながら，大迫研究（The Ohasama Study）の登場まで，家庭血圧の分布・基準値や随時血圧との差異の程度など，家庭血圧についての詳細は明らかではなかった．

大迫研究は1986年に開始された，岩手県大迫町の一般住民を対象とした高血圧・循環器疾患に関する長期前向きコホート研究である[1~3]．大迫研究は家庭血圧を用いた世界初の住民ベースの疫学研究という特色を持ち，これまでの平均10年近くにもおよぶ追跡により，「わが国発，世界初」のエビデンスを発信し続けてきた．1997年米国合同委員会報告[4]，1999年WHO/ISH高血圧ガイドライン[5]，2003年ESH/ESC高血圧ガイドライン[6]において家庭血圧，自由行動下血圧の臨床的意義に関する記述の一部が大迫研究の成果を基として提示されたことは，本邦の臨床疫学データが国際的ガイドラインの基盤となったという点で希有なことであった．

本稿では，大迫研究およびその知見を主たる根拠として作成された「日本高血圧学会　家庭血圧測定条件設定の指針」[7]（**表1**）に基づいて，家庭血圧の臨床的意義について述べたい．

1. 家庭血圧測定値の意義

家庭血圧の意義は血圧の「定点観測」である．すなわち，一定の測定時間・測定条件のもとで連日，長期間にわたり血圧を測定することで，血圧値におよぼすと考えられる各種の因子，たとえば日常生活に伴う身体的，精神的変動，血圧のランダムな変動を除外した，その個体のある定点における血圧値の近似値を得るものと考えられる（**表2**）．

そのような「定点観測」を行うために，われわれは患者に対して，朝は起床後1時間以内・服薬前・食事前・排尿後に，また晩は就眠前に，いずれも座位にて2分間の安静後に，朝晩それぞれ少なくとも1回は測定するように指導している（表1，指針4，5）．また，その測定値の評価は，朝の1回目の血圧および晩の1回目の血圧のある期間にわたる平均値を用いて，それぞれ別に評価することを勧めている（表1，指針7）．

家庭血圧は次のような状況で有用である（表2）．家庭血圧には白衣効果がないため，白衣高血圧の診断に有用である．また，長期にわたる測定が可能であることから，特に白衣高血圧患者の長期間

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表1 日本高血圧学会 家庭血圧測定条件設定の指針

指針 1	家庭用血圧計は聴診法で裏付けを得たカフーオシロメトリック法に基づく上腕カフ血圧計を用いる.
指針 2	測定部位：上腕. 家庭用血圧測定装置の腕帯は軟性腕帯を使用するのが望ましい, 標準的体格の対象では硬性腕帯も適用となる. 測定においては座位でカフが右心房の高さにあるよう指導する. また腕は伸ばした状態で上腕の筋肉の緊張をとくため, 前腕を机, テーブルの上に置き, 必要ならば枕などの支持を用いる. 極端に太い腕, 細い腕ではそれぞれ大型カフ, 小型カフの使用が望ましい. 小児においても上腕サイズによっては小型カフの使用が望ましい. 原則的に利き腕の対側を用いるが, 左右差の明らかな場合は常に高く出る側の血圧測定をすすめる.
指針 3	精度確認 ： ある個体と装置の適合性は聴診との較差が5mmHg以内であることを必要とする. 検定には片側交互法あるいは両側同時法を用いることが推奨される. 装置の精度確認は使用開始時とともに使用中も定期的に行われることが推奨される.
指針 4	家庭血圧は以下の条件で測定されることが望ましい. すなわち朝の家庭血圧は起床後1時間以内, 排尿後, 座位1～2分の安静後, 服薬前, 朝食前である. 一方, 晩の家庭血圧は就床前, 座位1～2分の安静後とする.
指針 5	(1)家庭血圧は朝晩それぞれ少なくとも1回は測定する. (2)家庭血圧はできるだけ長時間測定する. (3)観察期(無治療)の場合：外来随時血圧がSBP179mmHg以下かつDBP109mmHg以下(軽中等症)の場合, 7日間に少なくとも5日間の測定を行う. 状況により観察期間は1～2週間とする. 重症高血圧の場合はすみやかに治療に入るか, 医師の判断で, 1～3日間の家庭血圧測定を行う. (4)安定期(良好な血圧コントロール期)：少なくとも1週間に3日間の測定を行う. (5)薬剤変更期：7日間に少なくとも5日間の測定を行う.
指針 6	すべての測定値は, 時刻, 心拍数とともに記録されることが望ましい. 記録に際して対象の選択バイアスが入らないよう指導する. プリンターによる記録の打ち出しあるいは電子メモリーによる血圧値の記録が望ましい.
指針 7	家庭血圧は朝の1回目の血圧, 晩の1回目の血圧のある期間にわたる平均値を用いて, それぞれ別個に評価する. 同時に標準偏差を算出することも必要である. (また記録されたすべての値は評価の対象となることから, 別途すべての値も集計されることが望ましい.)
指針 8	家庭血圧は135/80mmHg以上をもって高血圧と診断し, 135/85mmHg以上ならば確実な高血圧として降圧治療の対象とする. 一方, 125/80mmHg未満を家庭血圧の正常とし, 125/75mmHg未満を確実な正常血圧と判断する.

の追跡に適している. また, 随時血圧には平均収束効果が認められるが, 頻回の測定を行う家庭血圧にはない(表1, 指針5). 高血圧患者, 特に不良な薬剤コンプライアンスに起因する難治性高血圧患者にも有用である. さらに, 家庭血圧を導入することで, 患者に高血圧治療に参加しているという実感を与え, 結果として, 高血圧治療コンプライアンス自体も向上する. 加えて家庭血圧はコストが低く, 費用効果に優れ, 導入により医療費が抑制されたとする報告がある. 降圧薬の効果の評価において家庭血圧は優れており, 降圧薬に対する反応性の再現性は, 随時血圧のみならず自由行動下血圧よりも高かったという(表1, 指針5).

家庭血圧を利用する際に注意すべき点がある. いわゆる「手首」血圧計の中には誤差が大きいものがあり[8], カフーオシロメトリック法に基づく上腕血圧計が最も推奨される(表1, 指針1). また, 定期的な精度確認も重要である(表1, 指針3). しかし, いかに正確な血圧計を利用しても, 患者が正しく血圧値を申告しなければ当然正確な血圧値は把握できない. メモリー機能のある家庭血圧計を用いた研究で, 患者の自己申告した血圧をメモリーに記録された血圧とを比較すると, 約20%の値は本来の血圧と10mmHg以上の差が認められたという報告もあり[9], メモリー機能, 印刷機能を持つ家庭血圧計の使用が望まれる(表1, 指針6).

2. 家庭血圧値と心血管合併症

横断研究において, 家庭血圧は外来随時血圧より心肥大, 眼底, 心電図, 腎機能などの臓器障害と関連が深い. 前向き研究である大迫研究は初め