Original Article

Lack of Association between Y Chromosome Alu Insertion Polymorphism and Hypertension

Masaru SHOJI, Shoji TSUTAYA*, Jun SHIMADA, Keiya KOJIMA*, Takeshi KASAI*, and Minoru YASUJIMA

There is an inherited paternal predisposition to hypertension. Y chromosome alphoid satellite variation was recently reported to be linked to diastolic blood pressure. To determine whether there is also a Y chromosome marker linked to hypertension, we investigated the prevalence of the Y chromosome Alu insertion polymorphism (YAP) at DYS287 and its association with hypertension in the Aomori population in the northern area of Honshu Island, Japan. YAP was present in 98 of 285 male residents and absent in the rest. The YAP prevalence in the present study would appear to suggest that the present study population represents the general male population in central Japan. Within the study population, there were 110 hypertensive subjects and 104 normotensive subjects. YAP frequency in the hypertensive subjects was not different from that in the normotensive subjects. These results suggest that the YAP is not likely to be a genetic-susceptibility factor for hypertension in the Aomori population. (Hypertens Res 2002; 25: 1–3)

Key Words: Y chromosome, Alu insertion, gene polymorphism, hypertension, HDL cholesterol

Introduction

Multiple genes and environmental factors appear to determine the level of one’s blood pressure (1–6). It has been reported that the Y chromosome from spontaneously hypertensive rats has a locus that raises blood pressure (7–10). In humans, genetic loading of a hypertensive father is known to play a critical role in the determination of blood pressure through body mass index (11). Also, it has been reported that borderline hypertensive fathers have children with increased blood pressure reactivity (12). Y chromosome alphoid satellite polymorphism was recently reported to be linked to diastolic blood pressure in the Australian population (13). These results indicate that there is a link between Y chromosome and hypertension in animals and humans.

The Y chromosome Alu insertion polymorphism (YAP) at DYS287 has been reported to be a paternal marker for two major lineages of modern Japanese, Jomon and Yayoi (14). The YAP has been carried by the Jomon people for more than 10,000 years, whereas a large infusion of YAP negative chromosomes entered Japan with the Yayoi migration in 300 B.C. However, the significance of YAP in health and disease has been uncertain. The mortality and morbidity of hypertension and hypertensive cardiovascular diseases are high in the Aomori population in the northern area of the Honshu Island of Japan (15). We therefore identified the prevalence of YAP and its association with hypertension in the Aomori population.
Table 1. Characteristics of the YAP Positive Subjects and Negative Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>YAP (+)</th>
<th>YAP (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>98</td>
<td>187</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56.2 (16.3)</td>
<td>55.0 (16.0)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>143.8 (23.9)</td>
<td>141.6 (20.8)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>84.2 (12.6)</td>
<td>84.4 (12.6)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.9 (3.0)</td>
<td>23.9 (3.1)</td>
</tr>
<tr>
<td>T-Cho (mg/dl)</td>
<td>194.6 (36.1)</td>
<td>194.3 (34.9)</td>
</tr>
<tr>
<td>HDL-Cho (mg/dl)</td>
<td>61.8 (17.1)</td>
<td>57.4 (16.4)*</td>
</tr>
</tbody>
</table>

YAP, Y chromosome Alu insertion polymorphism; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; T-Cho, serum total cholesterol; HDL-Cho, serum HDL cholesterol. Data are expressed by means ± SD. *p < 0.05 vs. YAP (+).

Subjects and Methods

A total of 285 male residents were enrolled in the present study. Subjects consisted of participants in regional medical examinations in 5 cities, 7 towns, and 4 villages in Aomori pref. Informed consent was obtained from each subject at the time of recruitment. The present study was approved by the ethical committee of the School of Medicine, Hirosaki University. Patients who met one or more of the following criteria were considered hypertensive: 1) development of hypertension earlier than age 60; 2) current receipt of medical treatment for hypertension; and 3) systolic blood pressure of 160 mmHg or higher, diastolic blood pressure of 95 mmHg or higher, or both. Normal control subjects were not receiving antihypertensive treatment, and their systolic and diastolic blood pressures were less than 140 and 90 mmHg, respectively.

DNA was extracted from peripheral blood of each subject as previously reported (16). The YAP genotype was determined with electrophoretic patterns of the amplified products. The primers used against YAP were 5'-aggggaagataaa gaata-3' and 5'-actgctaaaaggggatggat-3' (14). The differences in clinical parameters between groups were determined by the unpaired Student’s t-test. The relationship between the gene polymorphism and hypertension was evaluated using the chi-square test. Values of p less than 0.05 were considered to indicate statistical significance.

Results

The Alu insertion genotype was found in 98 subjects and the deletion genotype in the rest. When clinical parameters were compared between the YAP-positive and the YAP-negative group, there were no differences in ages, body mass indices, total cholesterol, or systolic or diastolic blood pressures (Table 1). There were 51 hypertensive subjects (13 YAP-positive and 38 YAP-negative) receiving antihypertensive medication. After removing these subjects, the systolic and diastolic blood pressures were 143.0 (24.9) and 83.4 (12.7) mmHg in the YAP-positive group, and 137.7 (19.7) and 83.2 (13.0) mmHg in the YAP-negative group, respectively. There was no difference in systolic or diastolic blood pressure between the groups. The YAP-positive subjects had higher HDL cholesterol than the YAP-negative subjects (p < 0.05). For some individuals (2 YAP-positive and 3 YAP-negative), serum lipids were measured under lipid-lowering medication. The significant difference in HDL cholesterol levels remained even after removing hyperlipidemic patients (data not shown).

Within the study population, there were 110 hypertensive subjects and 104 normotensive subjects. In the hypertensive subjects, the genotype frequency in the YAP was 29.8% for Alu insertion and 70.2% for deletion (Table 2). The genotype frequency in the normotensive control group was 35.5% for Alu insertion and 64.5% for deletion. There was no significant difference in genotype between hypertensive patients and normotensive control subjects (p = 0.3788). YAP frequency in the hypertensive subjects was not different from that in the normotensive subjects (Odds ratio, 1.29; 95% confidence interval, 0.73–2.30). The prevalence of the YAP alleles in each of the groups satisfied the Hardy-Weinberg equilibrium law.

Discussion

The Y chromosome is unique because more than 90% of its region is not involved in recombination during meiosis, and most of the Y chromosome is inherited from father to son without variation. Therefore, polymorphisms of the Y chromosome are powerful tools to trace paternal lineages (17). Indeed, YAP is within the nonrecombinant region and has been reported to be a paternal marker for two major human lineages of modern Japanese (14). The aforementioned study posited that YAP-positive individuals were the descendants of prehistoric Jomon foragers, and YAP-negatives were Yayoi rice agriculturalists. In the present study, 34.4% of Aomori residents were YAP-positive. The YAP prevalence in Aomori in the present study is not different from that in Shizuoka in central Japan, as reported by Hammer and Horai (14). Therefore, it is likely that the subjects in the
present study are representative of the general Japanese male population.

The significance of YAP in hypertension has been uncertain. In the present study, we found a lack of association between YAP and hypertension. YAP frequency in the hypertensive subjects was not different from that in the normotensive subjects. The odds ratio for YAP-positive vs. negative individuals distributed over the odds ratio 1.0. These results suggest that there may be no difference in the incidence of hypertension between the two major human lineages of modern Japanese, Jomon and Yayoi. Our findings are consistent with the findings by Vincent et al. (18) that Lyon hypertensive rats have no hypertensive loci on sex chromosomes. On the other hand, our negative finding might contribute to determination of the precise locus of a hypertension-related gene(s) on the Y chromosome. In a similar related study, Ellis et al. (13) found that the alphoid satellite polymorphism had a positive association with diastolic blood pressure. The YAP is about 4 Mbp distant from the centromeric alphoid satellite polymorphism toward the q terminal. Furthermore, Santos et al. (19, 20) showed that YAP was not in linkage disequilibrium with the alphoid satellite polymorphism. The Y chromosome may play an important role in lipid metabolisms. Ken et al. (9) recently found that Y chromosome transfer carried both blood pressure levels and lipid profiles. In the present study, the YAP-positive subjects had higher HDL cholesterol levels than the YAP-negative subjects. YAP might be related to the Jomonese hunting life style. YAP-positive individuals may have an advantage in avoiding atherosclerotic disorders characterized by hypertensive complications because HDL cholesterol is strongly protective against atherosclerosis (21). More comprehensive studies will be required to exclude the possibility of false-positive results and to establish the precise role of YAP on the metabolism of lipids.

In conclusion, it is likely that YAP is not a genetic susceptibility factor for hypertension in the Aomori population.

Acknowledgements

The authors are grateful to Dr. Paul Hollister for his careful reading of the manuscript and to Mrs. Akiko Tamura for her expert secretarial assistance.

References