Dominance of Functional Androgen Receptor Allele with Longer CAG Repeat in Hepatitis B Virus-related Female Hepatocarcinogenesis¹

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ABSTRACT

The CAG polymorphism in exon 1 of the androgen receptor (AR) gene has been shown associated with the development of human male hepatocellular carcinoma (HCC) with the shorter AR alleles conferring a higher risk. However, the significance of AR-CAG repeats in female hepatocarcinogenesis remains to be addressed. In this study, seventy-six pairs of female HCCs and corresponding nontumorous tissues were collected, and 180 cirrhotic nodules were microdissected from 7 cirrhotic livers. The clonality status, functional AR alleles, and CAG repeat number of each sample were determined by AR methylation analysis. In a total of 44 monoclonal HCCs, the mean of CAG repeats in the active alleles was significantly longer than that in the inactive alleles (22.0 ± 2.8 versus 20.7 ± 3.6; P = 0.047). When we divided HCCs into hepatitis B virus-positive [HBV(+)] and HBV(−) subgroups, the long AR allele dominance was found only in HBV(+) ones (P = 0.006 versus P = 0.923). Notably, the preference of long CAG repeat has also been found in the 100 monoclonal nodules (P = 0.013). For comparison of monoclonal nodules obtained from the same individual, a dominant long AR allele was found in 6 patients. The proportion of monoclonal cirrhotic nodules and HCCs expressing longer AR allele, 69 and 68%, are both significantly higher than 50%, the assumed value in normal liver (P < 0.001 for cirrhotic livers and P = 0.005 for HCC). The dominance is again only prominent in HBV-infected HCCs [85% for HBV(+) HCC; P < 0.001 but 54% for HBV(−) HCC; P = 0.27]. The results indicated that in female hepatocarcinogenesis, hepatocytes expressing the longer AR allele seem to be favorably selected for autonomous growth and transformation, especially in synergy with HBV infection.

INTRODUCTION

The AR⁳ gene is the essential molecule in relaying the functions of sex hormones, especially in maintaining the renewal and growth of sex organs (1, 2). In addition, it also plays critical roles in carcinogenesis of these organs, best illustrated in the prostate cancers (3, 4). Recently, interest revolving about the carcinogenic effect of the AR gene has been extended to female cancers. This is probably because certain female sex organs, such as the breast and ovary, also express AR, and some female hormones, such as 17β-estradiol, are able to bind to AR and function through specific AR coactivator(s) (5).

The AR gene includes a polymorphic CAG repeat in the first exon. Because this repeat encodes a tract of polyglutamine, its variation will affect the glutamine residues in the encoded protein and influence its biological potency in mediating the activity of androgen. For example, an increase of the repeat number will result in the decrease of its trans-activation activity (6–8). This AR polymorphism was shown associated with the predisposition of prostate cancer. Males carrying fewer repeats have an increased risk (odds ratio, 1.2–2.5) for prostate cancer development (9, 10). However, in breast cancers, the shorter CAG repeats seem to play the protective role against tumor formation, and the longer alleles appear more frequently in breast cancers by case control studies (11–13). Consistently, the expansion of CAG repeats in AR was reported to be associated with higher risk of uterine endometrial carcinoma (14). These observations implicated that the androgen signaling pathway may affect the risk of cancers in females, too. However, the association about the repeat length and the carcinogenic risk seems to be varied between male- and female-specific cancers.

Therefore, we tried to investigate the possible gender difference of the AR CAG repeat in carcinogenesis in the same type of cancer that occurs both in male and female patients. For the following reasons, HCC is a good candidate tumor for such purpose: (a) several clinical observations indicated that the HCC incidence is affected by sex hormones (15); (b) AR expression is found to be elevated in human HCCs and even in cirrhotic livers during the carcinogenic process (16, 17); (c) the significance of sex hormones and AR expression in hepatocarcinogenesis has been clearly demonstrated by evidence from the mouse or rat hepatocarcinogenic model (18, 19). Recently, the AR CAG repeats in male HCCs have been investigated. Similar to prostate cancer, an inverse relationship between the CAG length and carcinogenic risk has been shown in male HCCs (odds ratio, 2.6; Ref. 20). It is thus worthwhile to investigate the effect of AR-CAG repeats in female HCC.

The development of female HCC provides an excellent opportunity to examine the effect of AR CAG repeat not only in cancer but also in the precancerous stage if the proper tissue samples are collected and analyzed. Normally, the hepatocytes in the liver of any female individual will express either the longer or shorter AR allele in equal proportion (50% versus 50%). After hepatitis virus infection, either type B or C, the two groups of hepatocytes can be infected equivalently. After recurrent bouts of chronic hepatitis, the infected hepatocytes evolve into liver cirrhosis characterized by inflammation, fibrosis, and most importantly the regeneration into nodules (21). Some of the regeneration nodules are monoclonal in nature and finally transformed into frank liver cancer (22, 23). Because cirrhotic nodules sampled from the same individual are exposed to exactly the same background environments, the comparison of AR CAG repeats in these monoclonal nodules will provide excellent controls to compare the risk attributed by either longer or shorter alleles in tumorigenesis.

Therefore, in this study, we collected cirrhotic nodules and HCC tissues from female patients to follow the proportion of polymorphic AR during evolution from liver cirrhosis into HCCs. The clonality status of each sample was examined, and the functional AR allele of each monoclonal sample was determined. By comparing the number of CAG repeats in these samples, we found a dominance of functional AR alleles with longer CAG repeats in female HCC formation, especially those related to HBV infection.
MATERIALS AND METHODS

Patient Recruitment, Tissue Collection, and DNA Extraction. Seventy-six female patients with HCC were recruited for this study. The primary HCCs and their corresponding nontumor tissues were collected from resected surgical specimens and quick frozen in liquid nitrogen until DNA extraction. The DNA was extracted from the frozen tissues by following the protocols described previously (24). The Institutional Review Board of National Taiwan University Hospital approved the use of these archived tissues. HBV or HCV infection was confirmed by seropositive for hepatitis B surface antigen or anti-HCV (Austria II; Abbott Laboratories, North Chicago, IL). For the patients positive for both HBV and HCV markers, we confirmed the infection of HBV by detection of HBV DNA in tissues by PCR with primers from HBV X and S genes (25).

To collect the tissue from individual cirrhotic nodules, seven patients (patient nos. 12, 13, 26, 27, 49, 50) with severe liver cirrhosis showing distinctively fibrotic cirrhotic nodules were chosen and then processed for microdissection and DNA extraction as described previously (23).

Determination of AR-CAG Repeat Number, Monoclonality, and Functional AR Allele and monoclonality of tissue are set that when the allele ratio not only can determine the clonality of the cells, but it can also point out which the undigested control DNA. Therefore, the methylation inactivation analysis HpaII-digested DNA will be counted as the active allele when compared with HpaII monoclonal cell population. Whereas HpaII will only digest the unmethylation allele (active allele), the allele diminished in the PCR product amplified from HpaII-digested DNA will be counted as the active allele when compared with the undigested control DNA. Therefore, the methylation inactivation analysis not only can determine the clonality of the cells, but it can also point out which allele is the active one in monoclonal cells (27). The criteria for assessment of functional allele and monoclonality of tissue are set that when the allele ratio in HpaII digested DNA relative to that in DNA without HpaII, digestion (control) was <0.5 or >2.0.

Allelic Loss at the AR Locus in Cirrhotic Nodules and HCCs. Because we also have collected the paired nontumor tissues for all HCC patients in this study, the allelic loss can be analyzed by comparing the allelic pattern at the AR locus. Following the protocol (described previously) used in detecting allelic loss, the allelic loss can be determined in the collected DNA samples (24).

Statistical Analysis. The difference of CAG repeat numbers between active and inactive alleles was compared in monoclonal tissue samples and statistically tested by paired t test. The probability of the longer allele being actively expressed in precancerous or cancerous tissues was estimated. To see whether the longer allele has a greater chance to be activated in these tissues, the result was further statistically tested for its deviation from 0.5 (the assumed random activation probability of either allele) according to the binomial distribution. To evaluate the association of the effect of CAG repeats on hepatocarcinogenesis with HBV infection status, data were further separated according to patients’ HBV infection status. The means of difference of CAG repeats number between active and inactive alleles for both of HBV(+) and HBV(−) patients were further compared and statistically tested using two-sample t test. Because various numbers of multiple nodules were taken from one patient, to account for the correlated nature of the observed data, we used the generalized estimating equation to do the analysis for correct statistical testing (28). Statistical package SAS 6.14 for Windows was used for the computation. Two-sided P < 0.05 was considered to be statistically significant.

RESULTS

Identification of Cirrhotic Nodules and HCC Samples Consisted of Cells with Monoclonality. Age and the HBV/HCV status of all patients were summarized in Table 1. In total, 76 HCC and 180...
Cirrhotic nodules that were microdissected from 7 HCC patients have been collected. At first, we tried to determine the heterozygosity of the AR gene and the clonality status of each sample. By PCR amplification with a specific primer set flanking the AR-CAG repeat, the heterozygosity status of the AR alleles in each sample was determined. 15.8% (12 of 76) of HCCs showed homozygous (nonpolymorphic) pattern, making them useless for further clonality analysis. The remaining cases (84.2%; 64 of 76) showed heterozygous pattern at the AR locus with two distinguished alleles (Table 1).

For the samples with heterozygous AR alleles, their clonality was further determined by X chromosome inactivation assay. After digesting with a methylation-sensitive restriction enzyme, HpaII, the representative results showing polyclonality or monoclonality in two HCCs were illustrated in Fig. 1. The results showed 68.8% of HCCs (44 of 64) and 55.6% of cirrhotic nodules (100 of 180) are monoclonal.

The CAG repeats of active AR alleles were significantly longer than those of the inactive alleles in monoclonal HCCs and cirrhotic nodules. The clonality determination by methylation inactivation analysis can also help to calculate the CAG repeat number in each sample and to determine the functional allele in monoclonal samples.

Accordingly, the repeat numbers of AR alleles in each sample were summarized in Table 1. To point out the active allele in each monoclonal cell population, the peak corresponding to the active allele will be diminished after HpaII digestion because it can only digest the active (unmethylated) allele (Fig. 1 B). In Table 1, we also indicated the active allele in each monoclonal HCC. The mean and SD of CAG repeat number of HCCs, classified by their clonality, were shown in Table 2. In the 44 monoclonal HCCs, the mean repeat number of CAG triplet for active alleles was significantly longer than that of the inactive alleles by showing the difference of the repeat number to be

Table 2: Difference of CAG repeat number of active and inactive AR alleles in HCC

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>HBV(+)</th>
<th>HBV(−)</th>
<th>Difference of HBV(+) and HBV(−)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal</td>
<td>44</td>
<td>20</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>22.0</td>
<td>23.25</td>
<td>21.04</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>2.8</td>
<td>1.65</td>
<td>3.13</td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td>20.7</td>
<td>20.45</td>
<td>20.96</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>3.6</td>
<td>3.65</td>
<td>3.61</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>1.3</td>
<td>2.80</td>
<td>0.08</td>
<td>2.72</td>
</tr>
<tr>
<td>P value</td>
<td>0.047</td>
<td>0.006</td>
<td>0.923</td>
<td>0.034</td>
</tr>
<tr>
<td>Homozygous</td>
<td>12</td>
<td>4</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>21.4</td>
<td>22.8</td>
<td>20.8</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>1.9</td>
<td>0.5</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Polyclonal</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>23.2</td>
<td>23.7</td>
<td>22.8</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>2.4</td>
<td>2.2</td>
<td>2.6</td>
<td></td>
</tr>
</tbody>
</table>

* The difference of the mean CAG repeat number of active alleles and inactive alleles in the HBV(+) and HBV(−) subgroups of HCC.
1.3 (P = 0.047; Table 2). Intriguingly, when we divided the HCCs into HBV and non-HBV subgroups, the difference was more apparent in HBV-related HCCs by showing the difference of 2.8 (P = 0.006). In contrast, such a significant difference is not shown in HBV(−) HCCs (the number difference is 0.08 and P = 0.923). Actually, the size of the number difference, 2.72, is itself significantly different between the two subgroups (P = 0.034).

The mean repeat number of active and inactive alleles for nodules from the seven cirrhotic livers processed for microdissection have been summarized individually in Table 3. Comparing the all monoclinal cirrhotic nodules together, the difference of the mean value of CAG repeat number for active versus inactive alleles, 0.83, also showed a significantly longer allele dominance (P = 0.013; Table 3). Although the longer alleles were more dominant to be the active ones, there is not much of a difference between the HBV and non-HBV nodules.

### Significant Proportion of Cirrhotic Nodules and HCCs Showed a Dominant Preference for the Functional Longer Active AR Allele

Presumably, equal proportions of either the longer or the shorter alleles will be active in normal cell populations (50% versus 25%). However, in precancerous lesions and HCCs, hepatocytes expressing longer AR alleles may be selected toward dominance of longer AR alleles, with the percentage of longer allele ranging from 61 to 89% (Table 4). Moreover, when we count their deviation from 50% individually, cases 27 and 50 showed significant longer allele preference with 61% and 89%, respectively.

In addition to the nodules with allelic loss, the nodules from the same individual originally grew from hepatocytes that were genetically identical except for the expression of functional long allele. Therefore, nodules sampled from the same individual can serve as perfectly matched controls for comparing the significance of longer allele dominance during hepatocarcinogenesis. In the normal liver, 50% of hepatocytes will express longer AR allele, and the other 50% express shorter AR allele. However, after chronic hepatitis, some hepatocytes will obtain a growth advantage to become the monoclonal cirrhotic nodules. At this stage, we noted that in the 7 female patients, cirrhotic nodules from 6 patients (except patient 12) showed a clear dominance of longer AR alleles, with the percentage of longer allele ranging from 61 to 89% (Table 4). Moreover, when we count their deviation from 50% individually, cases 27 and 50 showed significant longer allele preference with Ps of 0.04 and 0.001 (Table 4).

### The longer AR Alleles in DNA Samples Showing Allelic Imbalance at AR Were Preferentially Retained in HCCs

In addition to analyzing the clonality of precancerous lesions and HCCs as described, we also included nontumorous tissue from the corresponding individuals for detecting the pattern of allelic loss at the AR locus. Only DNA samples showing monoclinal and heterozygous pattern at the AR locus were selected for such LOH analysis. In 44 monoclinal HCC samples, 14 samples showed allelic loss (32.0%; a representative result is shown in Fig. 1C); in 100 monoclonal cirrhotic nodules, 47 samples showed allelic loss (47%). Interestingly, for HCCs showing allelic loss at the AR locus, the long alleles were retained in 9 of the 14 HCCs (64.3%), and all are actively expressed. In the 14 samples with allelic loss, 7 cases were HBV(+) and 7 cases were HBV(−).

<table>
<thead>
<tr>
<th>P’t no.</th>
<th>Nodule no.</th>
<th>Active</th>
<th>Inactive</th>
<th>Difference</th>
<th>All</th>
<th>HBV(+)</th>
<th>HBV(−)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>6</td>
<td>23.7</td>
<td>21.0</td>
<td>−1.7</td>
<td>1.67</td>
<td>1.67</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>14</td>
<td>24.9</td>
<td>23.1</td>
<td>1.7</td>
<td>1.71</td>
<td>1.71</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>18</td>
<td>21.6</td>
<td>21.4</td>
<td>0.22</td>
<td>0.22</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>8</td>
<td>25.5</td>
<td>22.5</td>
<td>3.00</td>
<td>3.00</td>
<td>3.00</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>22</td>
<td>23.6</td>
<td>23.4</td>
<td>0.27</td>
<td>0.27</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>14</td>
<td>19.2</td>
<td>17.8</td>
<td>1.43</td>
<td>1.43</td>
<td>1.43</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>18</td>
<td>21.9</td>
<td>21.1</td>
<td>0.78</td>
<td>0.78</td>
<td>0.78</td>
<td></td>
</tr>
</tbody>
</table>

Average of difference: 0.83; 0.91; 0.67; P = 0.013; 0.186; 0.007

a Average and P were calculated by generalized estimating equation analysis to account for multiple observations from one patient.
HBV(−)). Among them, the active longer alleles were remained in 6 of the 7 HBV(+) cases. In the 7 HBV(−) cases, the longer allele was only retained in 3 liver tissues (Table 1). We then calculated their deviation from 50%, the expected percentage of random allelic loss. The HBV(+) subgroup showed significance, \( P = 0.008 \), for the dominance of the longer active allele; the HBV(−) subgroup showed an insignificant value, \( P = 0.5 \), suggesting no significant difference of the loss of either allele (Table 4). However, in cirrhotic nodules with allelic loss, the ratio of longer:shorter retained allele is 24:23, without showing the significant longer active allele preference.

**DISCUSSION**

On the basis of the previous epidemiological studies (the cohort and the case-control studies), a possible opposite role of AR repeat length in carcinogenesis of male- and female-specific tumors was suggested (9, 10, 11–14). However, such results remained highly controversial in different studies, especially in female tumors (29–32).

One reason for the major discrepancy may be attributable to the DNA samples they used for the CAG number determination, mainly from the peripheral blood. By such material, two critical problems cannot be addressed. Peripheral blood DNA cannot reflect which AR allele to be actively expressed in tumorous tissues. Therefore, in most studies, they included both alleles for calculating the average repeat number, which will greatly confound the results and cannot reflect the genuine repeat number correlated with the tumorigenesis process. In our attempt to solve this problem by investigating the DNA from tumorous tissues, we indeed provided strong evidence for the AR alleles with longer CAG repeats to be significantly correlated with the female HCC predisposition. The evidence showed that the mean of the CAG repeat length of the active alleles is significantly longer than the inactive alleles (\( P = 0.047 \)), and that the percentage of longer active alleles is significantly different from 50%, the normal distribution in normal tissues (\( P = 0.005 \)). The second problem concerns about the direct or indirect role of specific allele in tumorigenesis. Two possibilities can be proposed to explain the specific allele in exerting its carcinogenic effect. One is the allele may directly enhance the transformation of target cells per se. The other is an indirect effect that host tissues other than target cells expressing functional AR allele will accelerate the transformation of target cells through endocrine or paracrine pathways. This problem can only be solved in female cancers by studying the status of functional allele in the cancerous or even the precancerous target tissues once they have started autonomous growth. Our results here provide evidence that the longer AR alleles apparently increase the hepatocarcinogenic risk in a direct way instead of in an indirect way.

Another possible explanation for the discrepancy may come from the reason that most cohort or case-control studies are conducted using samples from numerous, different individuals living in different environments. Although analytic procedures can be carefully adapted to minimize these differences, this can still confound the observed risk. In fact, even identical twins are not perfectly suited for such analysis, given their different external and internal environments. However, these concerns can be resolved when we analyze the cells sampled from the same person. In our study, we followed the fate of hepatocytes expressing either longer or shorter AR allele from the same individual in the hepatocarcinogenic process. Both groups of cells are genetically identical except for the difference of their activation of either paternal or maternal X chromosome. They are subjected to exactly the same physiological conditions, including hormones, metabolites, cytokines, and even viruses. Therefore, they provide a perfect matched group of samples for evaluating the carcinogenic association of either AR allele. In our result, cirrhotic nodules in 6 of 7 patients showed longer allele preference, and 2 cases showed significant results (patients 27 and 50). Moreover, functional longer AR alleles were dominantly expressed in the resulting HCCs. Our approach can be applied for studying the relative risk of all other polymorphic genes located on X chromosome. This represents one step further toward examining the conclusion obtained from genetic epidemiological study of cohorts that are conducted in different subjects.

By showing the longer AR alleles dominantly expressed in HCCs and cirrhotic nodules, our results suggested that the longer AR alleles indeed provide an advantage for carcinogenic proliferation of hepatocytes, and it starts from the early carcinogenic process. In line to support this, in our analysis of the corresponding nontumor tissues adjacent to the 44 monoclonal HCCs, 24 cases (54.5%) already showed a monoclonal pattern in the adjacent flank nontumor tissues (without microdissection), and 15 cases (62.5%) showed longer active alleles. It confirms the associations between AR-CAG length and the risk of benign prostatic hyperplasia in earlier prostate carcinogenesis (33, 34).

The LOH analysis further revealed that AR allelic loss indeed occurs frequently in HCCs and even in precancerous lesions. Nine of the 14 HCCs showed allelic loss, including 6 of 7 HBV(+) HCCs and 3 of 7 HBV(−) HCCs, and have longer alleles retained in the tumors. It again supports the significance of longer AR alleles in carcinogenesis, especially in HBV-related HCC. Compared with the approximate equal proportion of either allele remained in the cirrhotic nodules with allelic loss, seemingly there exists a selection pressure for the retention of the longer allele in the resulting HCC. The results implied that two mechanisms may favor the longer allele to be actively expressed in the carcinogenesis process: one by LOH and the other by methylation. However, LOH seems to occur randomly at the stage of liver cirrhosis.

Notably, our study clearly indicated that the significant longer AR allele expression was more prevalent in HBV-infected HCCs rather than in HBV(−) HCCs (Tables 2 and 4). It is possible that there exists a synergistic effect between HBV and the longer AR allele in the process of carcinogenic transformation. When considering the age of HCC onset (Table 1, receiving the surgical operation), it is obvious that the HCC in HBV(+) patients with longer active alleles generally occurred younger than HBV(−) HCCs (55.1 ± 14.7 versus 64.4 ± 8.7; \( P < 0.005 \) by \( t \) test), supporting the synergistic effect of HBV infection and longer AR-CAG in female hepatocarcinogenesis. It should be noted that the association of AR-CAG repeats with male HCC is also more evident in HBV-infected patients (20). The interaction between HBV genes and AR polymorphism becomes a very interesting model to understand how both viral and host genes contribute to cancer development. Finally, it also points out the possible different carcinogenic pathways attributed by HBV versus non-HBV infection, which has been noted as in the case of \( \beta \)-catenin mutations that are rare in HBV-related HCCs but common in non-HBV HCCs (35).

Because our results evidently support the inverse effect of the AR repeats on hepatocarcinogenesis in different sexes, the possible underlying mechanism will be the following critical question to be addressed. Two levels of regulation may be proposed for the gender difference. One is at the level of extracellular sex hormone ligand context, and the other is at the level of intracellular coregulator context. Both are different in males and females. Recently, more and more AR coregulators have been identified, such as ARA24, ARA160, ARA70, ARA54, ARA55, BRCAl, c-jun, and Rb (36). Some of them may bind to the poly-Q containing NH\(_2\)-terminal domain of AR gene and activate the transcription of target genes in a length-dependent manner (37–39). The complex cross-talk occurs
either among the coregulators or among connections with other signaling pathways, which therefore deserves further analysis. Prospectively, it will clarify the mechanism for this gender distinct carcinogenic effect of AR polymorphism in HCC.

REFERENCES


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