Congenic Rats Reveal Three Independent Copenhagen Alleles within the Mcs1 Quantitative Trait Locus That Confer Resistance to Mammary Cancer

Jill D. Haag, Laurie A. Shepel, Bradley D. Kolman, Dinelli M. Monson, Margaret E. Benton, Kevin T. Watts, Jordy L. Waller, Christine C. Lopez-Guajardo, David J. Samuelson, and Michael N. Gould

McArthur Laboratory for Cancer Research, University of Wisconsin, Madison, Wisconsin 53706

ABSTRACT

It has previously been shown that the Copenhagen (COP) rat contains several genetic loci that contribute to its mammary tumor-resistant phenotype after 7,12-dimethylbenz(a)anthracene (DMBA) administration. One of these loci, mammary carcinoma susceptibility 1 (Mcs1), is located on the centromeric end of chromosome 2 and appears to act in a semidominant fashion. To confirm the existence and independent action of this locus and also aid in the identification of the physical location of the Mcs1 gene, congenic lines were generated by transferring the Mcs1 COP allele onto a Wistar Furth (WF) genetic background. Male carriers were genotyped using microsatellite markers spanning 20–30 cm of the Mcs1 locus. One of the congenic lines minimally retained the COP allele at D2Mit29 on the centromeric end of chromosome 2 and extended distally to D2Rat201. Heterozygous Mcs1 carrier rats were interbred, and the female offspring were treated with DMBA. The female rats from the Mcs1 congenic line that carried one or two COP alleles of the Mcs1 region showed a significantly reduced (65 and 85%, respectively) tumor development (P < 0.001) compared with rats carrying zero COP alleles at this locus. A WF.COP-D2Mit29/D2Rat201 homozygous congenic strain derived at the N10 generation was treated with DMBA, and the COP homozygous rats developed 1.5 ± 0.3 carcinomas/rat versus 6.3 ± 0.5 in WF control rats (P < 0.0001). Fine mapping of this congenic interval using several recombinant lines identified three genetic loci within the Mcs1 congenic region that independently supported a tumor resistance phenotype. These genetic loci have been termed Mcs1a, Mcs1b, and Mcs1c. In rats for which each locus was homozygous for the COP allele, tumor development was reduced by ∼60% compared with littermate controls. The identification of these independent loci within the Mcs1 COP allele provide a model of the genetic complexity of cancer.

INTRODUCTION

The etiology of breast cancer is driven by multiple components that include environmental factors, physiological host factors, and an inherited genetic component. Although it remains difficult to quantify the magnitude of the effect of each of these components on breast cancer etiology, progress is being made to begin to estimate the contribution of the inherited genetic component in breast cancer etiology. These estimates currently rely on twin studies. For example, Lichtenstein et al. (1) estimated that the inherited genetic component in the etiology of breast cancer is ∼30%. Peto, however, points out that 30% is most likely an underestimate and defines the minimal percentage of the contribution of hereditary factors to the etiology of breast cancer (2). The inherited genetic component of breast cancer in a population consists of both highly penetrant genes at a low frequency in the population (e.g., BRCA1, BRCA2) and those that occur at a high frequency but have a low penetrance. The highly penetrant genes BRCA1 and BRCA2 account at most for 25% of the heritable genetic component of breast cancer, with the remainder likely attributable to the additive, dominant, and epistatic effects of low-penetrance genes. Breast cancer is thus a polygenic disease. Current risk models that include family history are limited in their predictive power. In a recent article, Pharoah et al. (3) showed that in current predictive models, only 62% of cases could be predicted to occur in 50% of the population at highest risk, whereas 15% of breast cancer cases can be assigned to 10% of the population at highest risk. In contrast, it has been calculated that if we know half or all of the low-penetration genes that control risk, we will be able to assign, respectively, 80 or 88% of all breast cancer cases to 50% of the population. Also, it is calculated if we have knowledge of only 50% of these genes, then we can assign 32% of cases to 10% of the women at highest risk. With knowledge of all low-penetrance genes, this estimate increases so that we could assign almost half of all cases to 10% of women at high risk (3). Thus, knowledge of such genes would vastly improve our ability to detect and prevent breast cancer.

Finding 50% of such low-penetrance genes using only existing means, which focus on human population studies using the approach of human genetic epidemiology, will be difficult. These methods generally focus on and test known genes that are involved in processes that might lead to breast cancer such as xenobiotic metabolizing enzymes (4) and genes in DNA repair pathways (5). It would be difficult to directly identify unknown or unsuspected genes that lead to an altered level of susceptibility. This is especially true for genes that lead to breast cancer resistance. This is in part because of the fact that identifying a population as resistant to breast cancer cannot be readily accomplished for a disease such as breast cancer that occurs in ∼10% of a population. It is hard to distinguish between individuals with resistant genetics from those with good fortune.

One approach to identify low-penetrance genes that modulate breast cancer risk, especially those associated with resistance, is to initially use animal models to identify potential loci and genes and then translate this animal data to populations of women for comparative evaluation. In addition, the full characterization of animal models for breast cancer susceptibility will provide us with a better understanding of the degree of complexity of the polygenic etiology of breast cancer. We have begun the genetic dissection of the inheritable susceptibility to breast cancer with two rat models that use the COP3 rat (6, 7) and the Wistar-Kyoto rat (8) strains. Both rats are resistant to the induction of breast cancer. Using linkage-based mapping studies against a susceptible WF strain, we genetically identified four QTLs in each resistant rat strain and termed them Mcs1–8. Each strain has three QTLs that contribute to resistance and one that increases sensitivity to mammary cancer. Interestingly, only one QTL in each strain overlaps a QTL at the same chromosomal location in the other strain, i.e., only two total QTLs in common (COP Mcs2 and WKy Mcs6). Thus there appear to be many independent rat QTLs that contribute to the sensitivity to mammary cancer. Here, we extend these studies by first physically confirming the prediction of a mammary cancer resistance QTL, Mcs1, in the COP rat by producing and characterizing congenic rats containing the Mcs1 COP allele. In

Received 4/28/03; revised 6/20/03; accepted 6/30/03.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

1 Supported by the NIH Grant CA28954.

2 To whom requests for reprints should be addressed, at McArdle Laboratory for Cancer Research, University of Wisconsin, 1400 University Avenue, Madison, WI 53706.

The abbreviations used are: COP, Copenhagen; WF, Wistar Furth; QTL, quantitative trait locus; DMBA, 7,12-dimethylbenz(a)anthracene; LOD, logarithm of odds ratio; SNP, single nucleotide polymorphism.
QTL 1-LOD interval is also shown between right of the figure with genetic distances in cM to the gous male and female congenic three lines at various backcross generations. For phenotype analysis, heterozygous congenic rats. These genomic regions are shown as /H18554$. The chromosome markers used to identify the congenic rats are listed to the left of the marker names. The $Mcs1$ QTL 1-LOD interval is also shown between $D2Mit29$ and $D2Uwm13$.

In addition, we extend our study of the complexity of the polygenic component of breast cancer by fine-mapping $Mcs1$ to determine that this locus contains more than one gene that contributes to mammary cancer susceptibility.

MATERIALS AND METHODS

Congenic Strain Breeding. Inbred COP and WF male and female rats were obtained from Harlan Sprague Dawley, Inc. (Indianapolis, IN). All rats were provided Teklad lab chow (Harlan, Madison, WI) and acidified water ad libitum. All breeding and experiments were performed at our animal facility under protocols approved by the University of Wisconsin Medical School Animal Care Committee. Male COP rats were bred to WF female rats to produce (WF×COP) F1 rats; F1 rats were backcrossed to WF rats to produce the N2 generation. Heterozygous carriers of $Mcs1$ were continuously bred to determine that this locus contains more than one gene that contributes to mammary cancer susceptibility.

RESULTS

$Mcs1$ Congenic Rats/Strain. We produced a congenic rat line, WF.COP-D2Mit29/D2Rat201, that covered an extended region, including and surrounding the $Mcs1$ 1-LOD interval, termed line B (Fig. 1). Congenic line B was shown to lack all other known COP mammary carcinoma susceptibility loci ($Mcs2$–4) by microsatellite marker genotyping within these loci (Table 1). This line was phenotyped for DMBA-induced mammary cancer induction at the N6 and N9 generations; at each generation, three genotypes at each locus were tested: COP homozygous; WF/COP heterozygous; and WF homozygous. In addition, the parental WF and COP strains were also phenotyped. COP control rats ($n = 16$) developed an average of 0.25 ± 0.1 carcinomas/rat, whereas the WF control rats ($n = 30$) had 8.1 ± 0.7 carcinomas/rat.

<table>
<thead>
<tr>
<th>Chromosome markers used to make congenic rats/strains</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chromosome 1</strong></td>
</tr>
<tr>
<td>D1Mit59, D1Mit11, D1Uwm2, D1Wos5, D1Mit13, D1Uwm9</td>
</tr>
<tr>
<td><strong>Chromosome 2</strong></td>
</tr>
<tr>
<td>D2Mit29, D2Rat305, D2Uwm14, D2Uwm13, D2Wos2,</td>
</tr>
<tr>
<td>D2Uia5, D2Rat2, D2Mit326, D2Rat309, D2Rat203,</td>
</tr>
<tr>
<td>D2Rat194, D2Uwm17, D2Uib4, D2Rat9, D2Rat16,</td>
</tr>
<tr>
<td>D2Rat200, D2Rat201, D2Rat202</td>
</tr>
<tr>
<td><strong>Chromosome 7</strong></td>
</tr>
<tr>
<td>D7Mgh11, D7Mgh9, D7Mgh15, D7Uwm7, D7M28,</td>
</tr>
<tr>
<td>D7Uwm10</td>
</tr>
<tr>
<td><strong>Chromosome 8</strong></td>
</tr>
<tr>
<td>D8Mgh4, D8Rat23, D8Rat35, D8Mit16, D8Rat44</td>
</tr>
</tbody>
</table>

Table 1 Chromosome markers used to make congenic rats/strains

5809
rat at week 15 after DMBA treatment. The results of phenotyping are shown in Table 2. For congenic line B, statistical analysis using ANOVA showed no significant difference between the N6F1 and N9F1 generations (P = 0.91), allowing us to pool these data for analysis. It can be seen that after averaging over both generations there was an effect of genotype (P < 0.0001). COP-homozygous Mcs1-congenic rats developed the least number of carcinomas, averaging 1.2 ± 0.6 carcinomas/rat (n = 5, P < 0.001), whereas WF/COP-heterozygous rats had an average of 3.0 ± 0.4 carcinomas/rat (n = 29, P < 0.0001). The WF-homozygous rats developed an average of 8.5 ± 1.1 carcinomas/rat (n = 8) that was not different from WF control rats. A congenic strain of line B, WF.COP-CONGENIC line Q, was produced from N10 carriers that had a COP-homozygous genotype at the marker D2Uwm14/H11006 and distally defined by congenic line QQ. The region of Mcs1a-congenic strain re-Mcs1b was mapped from the distal marker D2Uwm14 to D2Mit29, which was significantly less than WF-homozygous littermate females (7.6 ± 0.7, n = 20). This genomic region of Mcs1a was additionally reduced to the distal marker D2Uwm14 after phenotyping congenic line W. Congenic line W did not confer a resistance phenotype with these COP-homozygous and WF/COP-heterozygous rats developing an average of 7.2 ± 1.0 and 6.8 ± 0.8 carcinomas/rat, respectively. The production of a congenic strain for line Q, WF.COP-D2Mit29/D2Uwm13 at the N12 generation verified the Mcs1a resistance phenotype with these COP-homozygous rats developing 3.6 ± 0.4 carcinomas/rat (n = 37, P < 0.0001) compared with WF controls with 6.3 ± 0.5 (n = 29; Table 3).

The region of Mcs1c (~6 cm) was defined by congenic line QQ with the proximal marker D2Rat2 and distal marker D2M13Mit286. Rats produced from the N10 carriers that had a COP-homozygous genotype at Mcs1c developed 3.0 ± 0.6 carcinomas/rat (n = 11), which was significantly less than WF-homozygous littermate females (7.1 ± 0.7, n = 19, P = 0.0003). The WF/COP-heterozygous females yielded an average carcinoma/rat of 5.6 ± 1.0 (n = 17) that, although intermediate between the COP- and WF-homozygous littersmates, was not significantly different from either of these groups.

Mcs1b was defined proximally by marker D2Uwm17 and distally by D2Rat16, a region of ~13 cm. Line K, which overlaps line T minimally at the genetic marker D2Uwm17, did not show a resistance phenotype because COP-homozygous rats developed 8.8 ± 1.3 carcinomas/rat (n = 8). In contrast, COP-homozygous rats of the N9 and N10 generations for line T developed 3.5 ± 0.5 carcinomas/rat (n = 21, P < 0.0001). The heterozygous females in this region averaged 7.6 ± 0.8 mammary carcinomas/rat (n = 18), which was not statistically different from the WF-homozygous littermate data (8.3 ± 0.8, n = 18) but was significantly different (P < 0.0001) from the line T COP-homozygous rats.

### Table 2. Mean number of carcinomas developing/rat (±SE) after DMBA administration in Mcs1-congenic rats

<table>
<thead>
<tr>
<th>Genotype</th>
<th>N6F1</th>
<th>N9F1</th>
<th>Combined</th>
<th>Parental lines</th>
</tr>
</thead>
<tbody>
<tr>
<td>COP/COP</td>
<td>0.5 ± 0.5 (n = 2)</td>
<td>1.7 ± 0.9 (n = 3)</td>
<td>1.2 ± 0.6 (n = 5)</td>
<td>COP control 0.25 ± 0.1 (n = 16)</td>
</tr>
<tr>
<td>WF/COP</td>
<td>2.7 ± 0.6 (n = 15)</td>
<td>3.2 ± 0.5 (n = 14)</td>
<td>3.0 ± 0.4 (n = 29)</td>
<td>COP/COP 1.5 ± 0.3 (n = 19)</td>
</tr>
<tr>
<td>WF/WF</td>
<td>8.8 ± 1.1 (n = 6)</td>
<td>7.5 ± 3.5 (n = 2)</td>
<td>8.5 ± 1.1 (n = 8)</td>
<td>WF control 8.1 ± 0.7 (n = 30)</td>
</tr>
</tbody>
</table>

*Statistically different from WF/WF littermate controls, P < 0.001.

### Table 3. Mean number of carcinomas developing/rat (±SE) after DMBA administration in Mcs1-recombinant congenic rats

<table>
<thead>
<tr>
<th>Genotype</th>
<th>N10F1</th>
<th>N10F1</th>
</tr>
</thead>
<tbody>
<tr>
<td>COP/COP</td>
<td>3.3 ± 0.4 (n = 38)</td>
<td>7.2 ± 1.0 (n = 16)</td>
</tr>
<tr>
<td>WF/COP</td>
<td>5.0 ± 0.4 (n = 33)</td>
<td>6.8 ± 0.8 (n = 27)</td>
</tr>
<tr>
<td>WF/WF</td>
<td>7.6 ± 0.7 (n = 20)</td>
<td>5.7 ± 0.8 (n = 14)</td>
</tr>
</tbody>
</table>

*Statistically different from WF/WF littermate controls, P < 0.01.

*Statistically different from COP and WF controls, P < 0.001.

When the Mcs1a-congenic line Q, spanning genetic markers D2Mit29 to D2Uwm13 (~2 cm), was phenotyped in the N10 generation, COP-homozygous rats developed an average of 3.3 ± 0.4 carcinomas/rat (n = 38, P < 0.0001), whereas WF/COP heterozygous rats had an average of 5.0 ± 0.4 carcinomas (n = 33, P = 0.0018), both statistically significant from WF-homozygous littermate rats (7.6 ± 0.7, n = 20). This genomic region of Mcs1a was additionally reduced to the distal marker D2Uwm14 after phenotyping congenic line W. Congenic line W did not confer a resistance phenotype with these COP-homozygous and WF/COP-heterozygous rats developing an average of 7.2 ± 1.0 and 6.8 ± 0.8 carcinomas/rat, respectively. The production of a congenic strain for line Q, WF.COP-D2Mit29/D2Uwm13 at the N12 generation verified the Mcs1a resistance phenotype with these COP-homozygous rats developing 3.6 ± 0.4 carcinomas/rat (n = 37, P < 0.0001) compared with WF controls with 6.3 ± 0.5 (n = 29; Table 3).

The region of Mcs1c (~6 cm) was defined by congenic line QQ with the proximal marker D2Rat2 and distal marker D2M13Mit286. Rats produced from the N10 carriers that had a COP-homozygous genotype at Mcs1c developed 3.0 ± 0.6 carcinomas/rat (n = 11), which was significantly less than WF-homozygous littermate females (7.1 ± 0.7, n = 19, P = 0.0003). The WF/COP-heterozygous females yielded an average carcinoma/rat of 5.6 ± 1.0 (n = 17) that, although intermediate between the COP- and WF-homozygous littersmates, was not significantly different from either of these groups.

Mcs1b was defined proximally by marker D2Uwm17 and distally by D2Rat16, a region of ~13 cm. Line K, which overlaps line T minimally at the genetic marker D2Uwm17, did not show a resistance phenotype because COP-homozygous rats developed 8.8 ± 1.3 carcinomas/rat (n = 8). In contrast, COP-homozygous rats of the N9 and N10 generations for line T developed 3.5 ± 0.5 carcinomas/rat (n = 21, P < 0.0001). The heterozygous females in this region averaged 7.6 ± 0.8 mammary carcinomas/rat (n = 18), which was not statistically different from the WF-homozygous littermate data (8.3 ± 0.8, n = 18) but was significantly different (P < 0.0001) from the line T COP-homozygous rats.
DISCUSSION

The congenic phenotyping data presented here show that the predicted Mcs1 QTL (7) was independently capable of reducing the risk for developing DMBA-induced mammary cancer. This resistance phenotype was shown in a Mcs1-congenic rat strain, suggesting that the Mcs1 gene(s) lie within the COP genomic region located on the centromeric portion of rat chromosome 2. The predictions of the Poisson regression model previously presented for Mcs1 suggested that it was a semidominant locus showing the effect of gene dosage (7). This model predicted that having one COP allele at Mcs1 would result in a ~47% reduction in the number of DMBA-induced mammary carcinomas developing while having two COP alleles at Mcs1 would result in a 74% reduction in the absence of the Mcs2, Mcs3, Mcs4 QTLs (7). If the congenic results presented in Table 2 are used to provide an estimate of the effects of the Mcs1 COP allele in its heterozygous and homozygous forms versus littermate WF-homozygous rats, one observes 1.2, 3.0, and 8.5 carcinomas/rat for rats, which carry two, one, and zero copies of the COP allele at Mcs1, respectively. Thus, rats with two copies show a statistically significant reduction of ~85% compared with rats with zero copies while having one copy also produces a significant reduction of ~65% compared with having no copies. The actual reductions because of having one or two copies of a COP allele at the Mcs1 QTL approximates the predicted degree of resistance from the Poisson regression model (7). The congenic strain for line B data showed a 76% reduction compared with WF control rats, additionally confirming the predicted value of 74% tumor reduction in rats with two copies of the Mcs1 COP allele.

A statistically significant difference also exists between the average number of carcinomas developing in the Mcs1 COP-homozygous and the WF/COP-heterozygous rats. This observation supports the hypothesis of the presence of a semidominant Mcs1 gene that yields a phenotype of mammary cancer resistance. Alternatively, the Mcs1 locus, which covers ~30 cM, might contain multiple genes that together produce a high degree of resistance to breast cancer. We addressed this alternative hypothesis by collecting recombinant lines within the Mcs1 interval. These recombinant rats served as founders of new congenic lines. Rats in these lines were phenotyped for their sensitivity to DMBA-induced mammary cancer. Interestingly, we found several subloci, each defined by nonoverlapping genetic markers that acted independently to confer resistance to DMBA-induced mammary carcinogenesis. These subloci were termed Mcs1a, Mcs1b, and Mcs1c.

Mcs1a was defined by congenic lines Q and W. COP-homozygous rats at the Mcs1a locus (line Q) had a ~57% reduction in the development of mammary carcinomas/rat as littermates that were homozygous for the WF allele. An intermediate number of carcinomas were found in the heterozygotes, which was significantly different from rats homozygous for the COP allele at this Mcs1a locus, making Mcs1a a semidominant locus with respect to the resistance phenotype and additive with respect to tumor multiplicity.

Mcs1c defined by congenic line QQ had a ~58% reduction in the development of carcinomas/rat in rats homozygous for the COP allele compared with those littermates homozygous for the WF allele. There was no significant difference in carcinoma development between Mcs1c COP-homozygous and -heterozygous rats, nor was the heterozygous group different from the WF-homozygous littermates. Although it is not possible to make a definitive conclusion regarding the heterozygous female phenotype in this Mcs1c region, this is most likely because of insufficient power. It should be noted that a strong trend (P = 0.059) suggests the possibility that the Mcs1c COP allele acts in a semidominant manner with respect to the resistance phenotype.

Mcs1b defined by line T had a ~58% reduction in carcinomas/rat in rats homozygous for the COP allele at this sublocus compared with littermates that were homozygous for the WF allele and ~54% reduction compared with females that were heterozygous. Thus, one copy of the COP allele has no effect on tumor development, suggesting that the Mcs1b is a recessive locus or the WF allele is completely dominant to the COP allele at this locus.

These data suggest that genetically identified QTLs can be complex, harboring multiple genes. It is likely that these genes act in the same direction to confer resistance and not an increase in sensitivity. If they did not act in the same direction, their combined effects and close proximity would likely have prevented the Mcs1 locus from being identified initially by linkage analysis. As it is, all of the Mcs1 subloci/gene contribute to mammary cancer resistance. One can speculate that it is likely that many of the QTLs identified as components in multigenic disease may contain several genes acting in the same quantitative direction. A corollary to this speculation is that it would be difficult to identify QTLs in regions of the genome in which two or more genes are present that contribute similarly to the genetic etiology of a disease but act in opposing directions. The closer these genes are linked, the more difficult is their identification using genetic linkage analysis. The genetic identification of such individual genes in such a complex genetic environment may require moving from a linkage/microsatellite approach to an association/SNP3 methodology.

These data together with other published data regarding rat breast cancer susceptibility models help to delineate the complexity of the multigenic model of breast cancer. Using two rat strains resistant to mammary cancer, we have identified six loci that contribute to mammary cancer resistance and two to increased sensitivity (6–8). Using a new statistical approach, we are also beginning to identify loci that, while having no significant main effect on mammary cancer susceptibility (e.g., Mcs1m1), do act to modify the actions of loci with main effects (8). The results presented here, together with our previously published results (8), begin to model the high level of genetic complexity underlying the multigenic disease of breast cancer. The Mcs1 locus was chosen for our first detailed characterization based on its small 1-LOD interval; however, it is interesting to note that only Mcs1a falls within this interval. This observation supports using a wide genetic interval (~20–30 cm) surrounding the 1-LOD interval in producing initial congenic animals for any QTL under study.

The COP rat is resistant to spontaneous (9), hormonally induced (10–12), and directly acting (9, 13) carcinogen-induced cancers of the mammary gland. Our model of chemically induced mammary cancer uses the indirectly acting carcinogen DMBA, a synthetic polycyclic aromatic hydrocarbon. It was selected for both pragmatic and theoretical reasons over other possible mammary carcinogens, including the directly acting carcinogen N-nitroso-N-methylurea, ionizing radiation, as well as hormones such as estrogens or prolactin. Although all of these various carcinogens are indeed important, the main reason we chose DMBA is that it is a very efficient mammary carcinogen that produces ~6–10 carcinomas/susceptible (WF) rat in these studies. In contrast, COP rats developed 0.25 carcinomas/rat. This large ratio of developing carcinomas not only allows us to distinguish between WF and COP rats but also allows us the ability to phenotype many loci and subloci that control susceptibility to mammary cancer in the COP rat. It has been shown that the COP and WF rat strains were equally able to activate DMBA and showed a similar mammary spectrum of DNA adducts (14, 15). The pleiotropic effects of DMBA as a carcinogen make it more likely to identify many susceptibility genes than, for example, mammary cancer induced by the activation of a specific oncogene. In this context, it must be stressed that DMBA is a very poor activator of ras as compared with N-nitroso-N-methylurea (16–
Finally, DMBA-induced rat mammary carcinomas share morphological similarities with most common human breast carcinomas (20), and this model system is widely used for preclinical evaluations.

Comparative analysis of rat, human, and mouse bacterial artificial chromosome sequences has shown that all three genomes are collinear in the Mcs1 region. The region of rat chromosome 2 encompassing Mcs1a, Mcs1c, and Mcs1b is collinear with human chromosome 5q14-q12 (inverted orientation) and mouse chromosome 13C1 (same orientation). The genome sequence of these three species is near completion as the individual genome project groups continue to fill gaps and finalize the assemblies. Although there is no evidence, to date, that the human region homologous to Mcs1 is implicated in breast cancer, this could be attributable to the high complexity of this multigenic disease and the difficulty in identifying low-penetrance genes in the human population. The identification of the Mcs1 loci in the rat is thus likely to lead to the identification of novel and important genes involved in human breast cancer.

In conclusion, we have physically verified the existence and effect of the Mcs1 QTL. The identification of three independent resistance subloci within the Mcs1 allele demonstrates an additional layer of genetic complexity underlying mammary cancer that will likely extrapolate to breast cancer. These data will provide important mapping information that will be critical in positionally cloning multiple Mcs1 cancer susceptibility genes. Delineation of the function of such genes will hopefully translate into prevention and/or treatment targets for human breast cancers.

REFERENCES

Congenic Rats Reveal Three Independent Copenhagen Alleles within the \textit{Mcs1} Quantitative Trait Locus That Confer Resistance to Mammary Cancer

Jill D. Haag, Laurie A. Shepel, Bradley D. Kolman, et al.


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/63/18/5808

Cited articles
This article cites 18 articles, 8 of which you can access for free at:
http://cancerres.aacrjournals.org/content/63/18/5808.full#ref-list-1

Citing articles
This article has been cited by 4 HighWire-hosted articles. Access the articles at:
http://cancerres.aacrjournals.org/content/63/18/5808.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.