Differences in Health Status Affect Susceptibility and Mapping of Genetic Loci for Atherosclerosis (Fatty Streak) in Inbred Mice

Ujala Srivastava, Beverly J. Paigen, Ron Korstanje

Objective—We observed differences in atherosclerosis susceptibility in mouse inbred strains over the years as the health status of our animal rooms increased. Therefore, we investigated the effect of animal room health status on atherosclerosis susceptibility in different strains. As these data can also be used for genome-wide association mapping, we performed a mapping study and compared our results with previously found quantitative trait loci for atherosclerosis in mouse and humans.

Methods and Results—Males and females from 48 inbred strains were housed in 2 animal rooms with different health status and given an atherogenic diet. We compared atherosclerosis susceptibility between animal rooms and between sexes and found that susceptibility is dependent on both health status and sex. Subsequently, the data were used for associations with loci on the mouse genome using 63,222 single nucleotide polymorphism. Three loci in males and 4 loci in females were identified using the data from the low-health status room. No significant associations were identified using the data from the high-health status room.

Conclusion—Health status influences susceptibility to atherosclerosis and suggests that microbiological pressure plays an important role in the development of atherosclerosis in many strains. As we were only able to map susceptibility loci using the data from the lower health status room, we argue that susceptibility under these conditions is determined by a few key loci, whereas in the higher health status room different mechanisms might play a role in the differences in atherosclerosis susceptibility between strains and we did not have enough power to map the loci that are involved. (Arterioscler Thromb Vasc Biol. 2012;32:2380–2386.)

Key Words: atherosclerosis ■ inbred strains ■ quantitative trait loci

Cardiovascular disease (CVD) is the leading cause of death in the United States, and more than 81 million Americans experience some form of CVD. The pathological basis of CVD is atherosclerosis, a disease of the arterial blood vessels in which the walls of the blood vessels become thickened by the deposition of plaques composed of cholesterol, other lipids, inflammatory cells, and calcium deposits. Atherosclerosis susceptibility is complex and dependent on multiple environmental and genetic factors, and a number of genes have been identified and studied using both genotype- and phenotype-driven approaches. In a genotype-driven approach the function of a gene suspected to be involved in atherosclerosis is tested with a transgenic or knockout animal model, whereas in a phenotype-driven approach the atherosclerotic phenotype is linked to the chromosome locations or quantitative trait loci (QTL) in a genome-wide scan.

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QTL for atherosclerosis in mice have been found in various studies using mice that have either been induced with atherosclerosis with an atherogenic diet or in mice that are susceptible to atherosclerosis because of the lack of apolipoprotein E or low-density lipoprotein receptor (LDLR). The apolipoprotein E–deficient mouse develops atherosclerotic lesions even on a standard chow diet. The LDLR-deficient mouse has elevated levels of LDL but no or very small lesions on the chow diet. However, when these mice are on a Western-type diet (containing 21% fat and 0.15% cholesterol), atherosclerotic lesions are detectable. Among the 43 QTL for atherosclerosis that have been identified to date, 12 were found in atherogenic diet models and 31 were found in mice deficient for apolipoprotein E or LDLR.

Our lab has studied the genetics of atherosclerosis for many years using the differences in susceptibility between inbred strains. Over the years, our mouse facilities have become cleaner with respect to the microorganisms that are found in the mice. This resulted in a loss of the atherosclerosis phenotype using our standard protocol, which was an 8-week atherogenic diet starting at 8 weeks of age. Increased risk of atherosclerosis has been linked to a wide variety of infectious agents, including Chlamydia pneumoniae, Porphyromonas gingivalis, Helicobacter pylori, influenza A virus, hepatitis C virus, cytomegalovirus, and human immunodeficiency virus. Reports of risk, however, are mixed depending on the pathogen. For example, in the case of H. pylori, 1 study reported that C57BL/6J (B6) female mice on a high-fat diet and infected
with the bacteria had an equal prevalence of atherosclerosis but more foam cells in the plaques, whereas another study reported that both male B6 and male LDLR-deficient mice on a high-fat diet did not show any effect. Overall, it has been observed that C. pneumoniae and some of the periodontal organisms such as P. gingivalis contribute to the risk of atherosclerosis, but for all the other infectious agents reports are conflicting.

To test atherosclerotic lesion development in mice kept in animal rooms of different health statuses, we conducted a study in both males and females in 48 inbred strains. These results were then used for genome-wide association mapping to identify the loci that cause differences in atherosclerosis susceptibility. Identification of new genes involved in the development of atherosclerosis in mice is a potentially powerful approach because these results can be used to find genes related to atherosclerosis in humans. Human orthologs of these novel genes can then be studied for variation and tested for correlation with atherosclerosis. This could be a significant step in the understanding of CVD and for the innovation of new therapies, but it will be imperative to put this in the context of such environmental factors as microbiological status in humans.

Materials and Methods

Animals and Housing

Ten males and 10 females of 48 mouse inbred strains (Table 1) were purchased from The Jackson Laboratory (Bar Harbor, ME). At the age of 6 weeks, animals were transferred from the breeding rooms to 1 of the 2 animal rooms designated as having either a low-health status (low status) or a high-health status (high status). Colonies were regularly monitored for viruses, bacterial species, ectoparasites, and endoparasites (see Table 2 for a complete list). The only differences between the rooms were the detection of Pneumocystis carinii, Pasturella pneumotropica, and H spp. in the low-status room, which were not detected in the high-status room. All mouse rooms at The Jackson Laboratory are monitored in the same way by the Lab Animal Health Service using standard methods. All details of the JAX monitoring program are publically available at jaxmice.org/genetichealth/index.html. Same-sex mice were housed 4 per pen in duplex polycarbonate cages equipped with pressurized individually ventilated mouse racks (Thoren Caging Systems Inc) with high-efficiency particulate air–filtered air supply and exhaust. Water and food pellets containing 6% fat (Lab diet 5K52, PMI Nutritional International, Brentwood, MO) were provided ad libitum. Mouse rooms were maintained at an ambient temperature of 21°C to 23°C and a 12:12-hour light:dark cycle. All animals were started on an atherogenic diet (18.5% dietary fat, 1.9% corn oil, 50% sucrose, 4.1% cellulose, 20% casein, 1% cholesterol, 0.5% cholic acid, 5% mineral mix, 1% vitamin mix, 0.3% DL-methionine, 0.13% α-tocopherol, and 1% choline chloride) at 9 weeks of age, as previously described. Animals in the low-status room were kept on this diet for 8 weeks and then euthanized, whereas the animals in the high-status room were kept on the diet for 17 weeks and then euthanized. All animal protocols were approved by The Jackson Laboratory Animal Care and Use Committee. Mouse handling and care complied with the Public Health Service animal welfare policy.

Table 1. List of Inbred Strains Used in This Study

<table>
<thead>
<tr>
<th>Strains</th>
<th>129S1/SvlMj</th>
<th>C57BL/6J</th>
<th>C57BLKS/J</th>
<th>C3H/HeJ</th>
<th>CAST/EJ</th>
<th>DBA/2J</th>
<th>DBA/2J</th>
<th>DBA/2J</th>
<th>DBA/2J</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C57BR/cByJ</td>
<td>C57L/J</td>
<td>C57L/J</td>
<td>C57L/J</td>
<td>C57L/J</td>
<td>C57L/J</td>
<td>C57L/J</td>
<td>C57L/J</td>
<td>C57L/J</td>
</tr>
<tr>
<td></td>
<td>C57BL/10J</td>
<td>C57BL/10J</td>
<td>C57BL/10J</td>
<td>C57BL/10J</td>
<td>C57BL/10J</td>
<td>C57BL/10J</td>
<td>C57BL/10J</td>
<td>C57BL/10J</td>
<td>C57BL/10J</td>
</tr>
</tbody>
</table>

Measurement of HDL Cholesterol Levels and Atherosclerotic Lesions

Blood was collected via retro-orbital sinus from animals that were food deprived for 4 hours in the morning. Serum high-density lipoprotein (HDL) cholesterol was analyzed on a Beckman Coulter Synchro CX5 Delta autoanalyzer (Beckman Coulter, Inc, Brea, CA). The heart and aorta were washed in saline, immersed in a 4% formalin solution overnight, and transferred to a 10% formalin solution. Tissues were then processed as previously described. In brief, hearts were embedded in 25% gelatin and sectioned in a cryostat at −25°C. Fatty streak aortic lesion size was averaged from 5 aortic sections of 10 µm cut at 80-µm intervals. Staining was performed with Oil Red O (neutral lipids) and hematoxylin and counterstained with light green. All results are expressed as log(lesion size +1). Atherosclerosis and HDL data sets are deposited in the Mouse Phenome Database (phenome.jax.org) as Paigen1 and Paigen2.
Statistics
Statistical analyses were performed using JMP7 (SAS Institute). Strain data are presented as the mean±SD. For the genome-wide association mapping, single nucleotide polymorphisms (SNPs) were selected from the following sources: JAX, Oxford, Merck, GNF, and Perlegen (see www.jax.org/phenome for detailed information on the sources). The mouse genome was divided into nonoverlapping 40-kb intervals. For each interval, 1 SNP that best met the following criteria was selected: highly polymorphic among 25 widely used classical laboratory strains, missing in a low number of genotypes, and evenly distributed across the genome. A total of 65,222 SNPs were selected. A hidden Markov model was applied, fitting 5 states at each SNP, for the primary purpose of missing genotype imputation and for the secondary purpose of haplotype identification. A total of 580,781 missing genotypes (28.70%) were imputed for this particular data set. All SNPs with imputed genotypes had a confidence score >0.6, and the average filling accuracy of the imputed genotypes across the whole genome was 89.9%. At each SNP, a strain distribution pattern was determined using the hidden Markov model smoothed haplotype states (HMMpath). We computed F-test statistics to measure the strength of association between the genotype and the phenotype. Its significance was estimated to detect haplotype groups with different mean phenotypes. The segregation of strains into haplotype groups varied widely over haplotype blocks; therefore, P values of the F-test statistic were compared between haplotype blocks. Type I error rates for multiple testing resulting from genome-wide searching were controlled for using family-wise error rate control. The strain label in the phenotype data were shuffled to keep the genotype data intact. The minimum P value was recorded on each permutation, and percentiles of their distribution were used to provide approximate multiple test-adjusted thresholds. The genome-wide type I error thresholds were estimated based on 1,000 permutation tests. Peaks corresponding to P value thresholds adjusted for global significance were defined as significant at α<0.05 level. Because of the genetic relatedness between genomes of inbred strains, genome-wide association mapping analysis has limited power to detect small genetic effects. Furthermore, family-wise error rate control methods generally yield conservative results. To detect peaks with small genetic effects that were biologically relevant, the protection against type I error was relaxed, and genome-wide association mapping peaks that exceed an α=0.20 were considered suggestive evidence of true genetic association. All analysis was done in the MATLAB computing environment (The Mathworks, http://www.mathworks.com), except the imputation of missing genotypes.

Discussion
In this study, we extensively surveyed the formation of atherosclerotic lesions present in both female and male mice. The differences between females and males in the low-status and high-status rooms are shown in Figure 1C and 1D. In the low-status room, we see that C57L females develop atherosclerotic lesions, whereas C57L males do not. In the high-status room, we see more strains with differences between males and females: SM, BTBR, SEA, C57BR, and SWR females show lesions but males do not; RIII, NZB, and A males show lesions but females do not. It is believed that elevated levels of plasma HDL cholesterol protects against CVD in humans. We, therefore, measured HDL in all animals and looked for a correlation between HDL levels and atherosclerosis both at the individual level (Figure II in the online-only Data Supplement) as at the strain level (data not shown). We did not observe any correlation in either males or females, in either room. This suggests that HDL cholesterol levels are not a major determining factor for the development of atherosclerosis in our inbred strains.

Genome-Wide Association Analysis Reveals Differences in Genetic Loci
The data sets that we assembled for the above comparisons are suitable for genome-wide association mapping. We used the logarithm of the lesion size in males and females in both rooms. We did not observe any significant associations in either males or females in the high-status room, but we did observe significant loci in both males and females in the low-status room (Figure 2 shows the scan for females). We found 3 loci in males with a P value <10^{-8} and 4 loci in females with a P value <10^{-6} (Table 3). Interestingly, 5 of the 7 loci are within the confidence intervals of previously mapped QTL for atherosclerosis (Table 4).

Results
Differences in Atherosclerosis Susceptibility Between Health Statuses
As previously shown, there is variation in atherosclerosis susceptibility among mouse inbred strains (Figure I in the online-only Data Supplement). The differences between the low-status and high-status rooms were the detection of additional pathogens P carinii, P pneumotropica, and H spp as determined by sentinel screening in the low-status room. Strain distributions in the low-status versus the high-status rooms are plotted in Figure 1A and 1B. Although some strains seem to have similar susceptibility in both rooms (eg, C57BR and BTBR females), many strains developed lesions only in the low-status room (males—SM, SJL, SEA, C3H, BTBR, NOD, SWR, C57BR, and B10; females—B6, C57L, SJL, D2, and C3H) but not in the high-status room even after longer exposure to the atherogenic diet.

Differences in Atherosclerosis Susceptibility Between Males and Females
In humans, few studies have been conducted on differences in the pathogenesis and progression of CVD between males and females. The general perception is that CVD is predominantly a male disease, primarily because women develop CVD almost 10 years later. However, the reason for cardioprotection in females is still unclear and remains under investigation. In this study, we extensively surveyed the formation of atherosclerotic lesions present in both female and male mice. The differences between females and males in the low-status and high-status rooms are shown in Figure 1C and 1D. In the low-status room, we see that C57L females develop atherosclerotic lesions, whereas C57L males do not. In the high-status room, we see more strains with differences between males and females: SM, BTBR, SEA, C57BR, and SWR females show lesions but males do not; RIII, NZB, and A males show lesions but females do not. It is believed that elevated levels of plasma HDL cholesterol protects against CVD in humans. We, therefore, measured HDL in all animals and looked for a correlation between HDL levels and atherosclerosis both at the individual level (Figure II in the online-only Data Supplement) as at the strain level (data not shown). We did not observe any correlation in either males or females, in either room. This suggests that HDL cholesterol levels are not a major determining factor for the development of atherosclerosis in our inbred strains.

Discussion
In this study, we completed a strain survey for atherosclerotic lesions in inbred mice that were on an atherogenic diet in animal facilities with different health statuses. We showed that (1) difference in health status alters the atherosclerosis susceptibility of different inbred strains, with some strains more susceptible in the low-status room and others more susceptible in the high-status room; and (2) susceptibility differs between males and females, with males more susceptible than females in some strains and females more susceptible in others.

Because the duration of the atherogenic diet was different between the low-status and high-status rooms, we are not able to draw any conclusions from the quantitative data, but as many of the groups showed a clear presence or absence of lesions, we are able to examine the differences between those groups (eg, when a strain shows lesions at 8 weeks of diet in the low-status room and has no lesions after 17 weeks on the atherogenic diet in the high-status room). The presence of lesions in either males or females of 14 inbred strains in the low-status room but not in the high-status room demonstrates that atherosclerosis susceptibility is higher in the room with a lower health status even though mice were on the atherogenic diet.
diet for a shorter time span. We did see some strains (e.g., MOLF and BALB) that developed lesions in the high-status room but not in the low-status room. However, this might be an effect of the duration of the diet.

We also observed differences between males and females within the low-status and high-status rooms. In the low-status room, we saw lesions in C57L, DBA/1, and DBA/2 females but not in males. In the high-status room, we saw lesions in SM, BTBR, SEA, C57BR, SWR, and DBA/1 females but not in males. We made opposite observations for other strains for which only the males were susceptible; this difference depended on the room. SWR mice are interesting because only females developed lesions in the high-status room, whereas only males developed lesions in the low-status room. It is often reported that in mice, females are more susceptible to atherosclerosis than males and that in humans, males are more susceptible. However, our data show that susceptibility depends on the individual inbred strains and their health status. Furthermore, as we did not find any correlation between HDL cholesterol levels and lesions, HDL cholesterol levels are not a major determining factor for the development of atherosclerosis in our inbred strains.

The data that we collected are suitable for genome-wide association mapping, a method similar to human genome-wide association. Performing the analysis for males and females and for the low-status and high-status rooms separately, we conclude that mapping of loci was affected by the health status of the room. Although we were able to map loci for males and females in the low-status room, we did not obtain any results from the high-status room. One way to explain this observation for genes that determine atherosclerosis susceptibility is that in the low-status room, the number of genes is small but relative effects are large, whereas in the high-status room, the number of genes is larger but relative effects are smaller. Our analysis would not have enough power to detect these small effect genes. If this explanation is true, then it would follow

Figure 1. Differences in atherosclerosis susceptibility between mouse rooms. A, Strain distributions for females in the low-status and high-status rooms by log lesion area. B, Males in the low-status and high-status rooms by log lesion area. C, Males and females in the low-status room by log lesion area. D, Males and females in the high-status room by log lesion area. B6 indicates C57BL/6J.
that atherosclerosis susceptibility in the different rooms is determined (in part) by different pathways.

The loci that were mapped in the low-status room differed between males and females, suggesting different pathways. Five of the 7 loci are within the confidence intervals of previously mapped QTL for atherosclerosis, whereas the loci on Chr 2 in females and Chr 6 in males were regions that have never been mapped in any previous studies. When comparing our new QTL with QTL from previously published studies, it would be interesting to consider the health status of each study, whether overlapping QTL were found under similar microbiological conditions, and whether differences among studies can be explained by differences in strains or health status or both. Unfortunately, these data are not available.

The variation in atherosclerosis susceptibility within the same strain and the differences in mapping of loci by genome–wide association analysis between the rooms can be attributed only to the difference in microbiological environment. Although P carinii, P pneumotropica, and H spp. are the only differences that we detected, our microbiological screens are by no means exhaustive, and we cannot rule out the presence of other bacteria or viruses in 1 room and not the other (it is even possible that the high-status room contains a microorganism that is absent in the low-status room). Multiple investigations have shown that infectious agents affect cellular and molecular changes that could contribute to atherogenesis. The development of atherosclerosis is influenced by either (1) infection of the vascular cells or (2) the effects of cytokines or acute phase proteins produced because of infection at nonvascular sites. This causes an activation of the innate immune response and adds to the chronic inflammation that is already present in the atherosclerotic plaque. H pylori is a pathogen that has been found in the human atherosclerotic plaque, but studies have reported both positive and negative roles in CVD development in mice. In a study by Chen et al, it was shown that H pylori infection enhances atherosclerosis in C57BL/6 mice on a high-cholesterol diet. However, another in vivo study performed in C57BL/6 and LDLR-deficient mice demonstrated that H pylori infection does not contribute to the development of atherosclerotic lesion formation.

**Table 3. Results of the Genome-Wide Analysis**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Chr</th>
<th>Locus Start</th>
<th>Locus End</th>
<th>P Value</th>
<th>Genes in Interval</th>
<th>QTL Strains</th>
<th>QTL Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>1</td>
<td>108 137 026</td>
<td>108 799 193</td>
<td>3.4×10⁻⁹</td>
<td>Kdsr, Bcl2, Serpinb5, Phlp1, Vps4b</td>
<td>B6×129</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>53 791 464</td>
<td>53 903 686</td>
<td>1.0×10⁻⁸</td>
<td>Cplv</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>67 543 894</td>
<td>67 957 095</td>
<td>3.4×10⁻⁹</td>
<td>Bnip3l, Ppp2r2a, Ebf2</td>
<td>B6×FVB</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>109 951 892</td>
<td>110 501 333</td>
<td>4.0×10⁻⁷</td>
<td>Cdc34, Bbox1, Fibn, Slc5a12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>7</td>
<td>85 652 862</td>
<td>85 927 942</td>
<td>2.6×10⁻⁷</td>
<td>Ntrk3, Gm9885, Mrps11</td>
<td>B6×A</td>
<td>Ath3⁰⁷</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>58 022 123</td>
<td>58 291 010</td>
<td>2.5×10⁻⁷</td>
<td>Slc12a2, Fen2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>42 044 028</td>
<td>42 195 636</td>
<td>3.0×10⁻⁷</td>
<td>Mms19, Ubtd1, Ankrd2, Hoga1, Mom4, Phk2a</td>
<td>B6×FVB</td>
<td>16</td>
</tr>
</tbody>
</table>

Chr indicates chromosome; QTL, quantitative trait loci. Loci were only found using the mice with the lower health status; B6, C57BL/6J.
Overall, previous data provide conflicting results on the role of *H pylori* in atherogenesis. Although the previous data from various studies are conflicting, the influence of *H* spp. on the pathogenesis of atherosclerotic plaque formation in different inbred strains of mice in our study is certainly a possibility. Although less commonly considered, it is also possible that the immune response caused by these bacteria exert a protective effect in some strains but not others, thus contributing to the differences seen within the strains between the different rooms.

In conclusion, we surveyed atherosclerotic lesions in inbred strains of mice in 2 animal rooms with different health statuses. The intent of this large study was to investigate development of atherosclerotic lesions in different genetic backgrounds under different microbiological conditions and to subsequently identify loci that regulate predisposition to atherosclerosis. We

<table>
<thead>
<tr>
<th>Chr</th>
<th>Peak, Mb</th>
<th>LOD</th>
<th>95% CI</th>
<th>Induction</th>
<th>Sex</th>
<th>Cross</th>
<th>HighAllele</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>105</td>
<td>5.0</td>
<td>75–135</td>
<td>Apoe&lt;sup&gt;−/−&lt;/sup&gt;</td>
<td>M+F</td>
<td>(B6. Apoe&lt;sup&gt;−/−&lt;/sup&gt;x129. Apoe&lt;sup&gt;−/−&lt;/sup&gt;)F2</td>
<td>129</td>
<td>15</td>
</tr>
<tr>
<td>163</td>
<td>6.8</td>
<td>151–173</td>
<td>Apoe&lt;sup&gt;−/−&lt;/sup&gt;</td>
<td>M+F</td>
<td>(B6. Apoe&lt;sup&gt;−/−&lt;/sup&gt;x129. Apoe&lt;sup&gt;−/−&lt;/sup&gt;)F2</td>
<td>129</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>163</td>
<td>(2.3)</td>
<td>160–194</td>
<td>Apoe&lt;sup&gt;−/−&lt;/sup&gt;</td>
<td>M+F</td>
<td>(B6. Apoe&lt;sup&gt;−/−&lt;/sup&gt;xFVB. Apoe&lt;sup&gt;−/−&lt;/sup&gt;)F2</td>
<td>?</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>6.8</td>
<td>161–164</td>
<td>Ath diet</td>
<td>F</td>
<td>B×H and CxB RI</td>
<td>B6</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>180</td>
<td>(2.3)</td>
<td>160–194</td>
<td>Apoe&lt;sup&gt;−/−&lt;/sup&gt;</td>
<td>M+F</td>
<td>(B6. Apoe&lt;sup&gt;−/−&lt;/sup&gt;xFVB. Apoe&lt;sup&gt;−/−&lt;/sup&gt;)F2</td>
<td>?</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

Chr indicates chromosome; Ath diet, atherogenic diet; HF diet, high-fat diet; unpub, unpublished; B6, C57BL/6J.
observed that a small percentage of inbred strains developed lesions and that susceptibility was dependent on sex and the health status of the room in which the mice were kept. Genome-wide association mapping using the data from our strain surveys demonstrate that mapping results are not only dependent on sex, with different loci mapped in males and females, but also on health status of the animal room. Therefore, health status is an important factor in genetic studies for atherosclerosis and should be a consideration in the experimental design.

Acknowledgments

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Disclosures

None.

References


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Supplemental Material

supplemental figure I
Supplemental Material

supplemental figure II

female low

male low

female high

male high