A Genome-Wide Affected Sibpair Linkage Analysis of Hypertension: The HyperGEN Network


Results are reported here from a genome-wide linkage analysis of hypertension in a large sample of hypertensive (affected) sibpairs (650 African American and 915 white sibpairs) recruited by the HyperGEN Network of the National Heart, Lung and Blood Institute (NHLBI) Family Blood Pressure Program (FBPP). Analysis using MAPMAKER/SIBS suggests one interesting region with a LOD score of 2.08 at 63 cM from the p telomere on chromosome 2 in the African American sibpairs, which may harbor hypertension susceptibility genes. Am J Hypertens 2003;16:148–150 © 2003 American Journal of Hypertension, Ltd.

Key Words: Linkage, hypertension, genetics.

Hypertension is a significant risk factor for many cardiovascular, cerebrovascular, and renal diseases that affects approximately one in four Americans across all major ethnic groups. Hypertension-associated diseases constitute a major public health burden. Although genetic mutations have been identified for rare forms of hypertension such as Liddle’s syndrome, multiple etiologies involving interactions among genes and environments complicate the genetic dissection of more prevalent forms of hypertension. The impact of hypertension varies among ethnic groups. It is more prevalent, strikes earlier, and is associated with more severe complications in African Americans than in any other ethnic group. Therefore, identification of genes with pronounced effects that contribute to the risk of hypertension constitutes a priority, as this may enable early identification of individuals at high risk, development of more efficacious treatments tailored for patients, and targeted prevention strategies.

Because so many intermediate pathways contribute to interindividual variability in blood pressure (BP) and hypertension, variations in a large number of genes potentially influence these complex traits. Therefore, the detectable impact of any one gene is probably subdued as its effect is likely transmitted across many intervening pathways, thus complicating their detection. Genome-wide investigations constitute an important approach to gene finding for common chronic diseases. Here we present the results from one large-scale genome-wide linkage study called the HyperGEN Network.

Methods
Study Population

The Hypertension Genetic Epidemiology Network (HyperGEN) is a constituent multicity network participating in the National Heart, Lung and Blood Institute (NHLBI) Family Blood Pressure Program (FBPP). HyperGEN recruited two types of participants (hypertensive sibships and random samples of subjects) in African Americans and whites. Recruitment of the study participants, including the hypertensive probands, was carried out at five field centers (FC) based largely on ongoing population-based studies. The study protocols and the

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Dedicated to the late Roger Williams, an outstanding cardiovascular geneticist, for his visionary leadership until his tragic death on September 2, 1998.

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process for obtaining informed consent were approved by the
Institutional Review Committees at the FC.\textsuperscript{3} In all,
HyperGEN recruited and characterized a total of 1142
white hypertensive subjects from 480 sibships, yielding a
total of 992 self-reported sibpairs, and a random sample of
472 biologically unrelated white participants. Likewise, it
recruited and characterized a total of 1261 African American
hypertensive subjects from 596 sibships yielding a
total of 826 self-reported sibpairs, and a random sample of
446 biologically unrelated African Americans. This report
is based on the entire sample. Overall, the study was
designed to have 80% power or better under ideal condi-
tions to detect linkage as long as the trait locus accounts
for at least one-third of the affected individuals.

All the samples described, involving a total of 992 +
826 = 1818 sibpairs, have been characterized fully for a
variety of phenotypes\textsuperscript{3} including hypertension. Genoty-
ping has been carried out on all the hypertensive sibs and
a subset of the random samples (213 whites and 231 African
Americans). The random samples are used to estimate
ethnicity-specific allele frequencies for the purpose of
estimating allele sharing identical-by-descent (IBD) by a
sibpair. In recruiting hypertensive sibs, persons with hy-
pertension diagnosed after 60 years of age and those with
type I diabetes were excluded. Type II diabetics were not
excluded.

**Diagnostic Algorithm**

HyperGEN was designed to increase statistical power by
recruiting sibships preferentially with severe hyperten-
sives (those with stage 2 or higher of the Sixth Report of
the Joint National Committee classification, namely sys-
tolic BP ≥160 or diastolic BP ≥100 mm Hg; or the use of
two or more antihypertensive medications). Nearly 80% of
the sibships in each race group are severe, and the remain-
ing are mild sibships.

**Genotyping**

Genome-wide scan was performed by the Mammalian
Genotyping Service (MGS) in Marshfield using a standard
panel of approximately 391 anonymous markers. Using
the marker data, we have performed extensive quality
checks for parentage errors and misinheritance, and cre-
tated cleaned datasets before carrying out the genome-wide
linkage analysis. The cleaned dataset included a total of
1565 sibpairs.

**Genetic Analysis**

Using the cleaned datasets, genome-wide multipoint link-
age analysis of the hypertension phenotype was performed
using MAPMAKER/SIBS.\textsuperscript{4} All possible sibpairs were
used without any weighting. Marker order and map loca-
tions were deduced from the Marshfield map. Linkage
evidence is expressed in terms of likelihood scores (LOD).

**Results**

The results from multipoint linkage analyses are pre-
sented as LOD score plots (http://www.biostat.wustl.edu/
hypergen/results.html). This analysis yielded only one in-
teresting region with a LOD score >1.5, which was loca-
ted at 63 cm from the p telomere on chromosome 2 in
the African American sibpairs (a maximum LOD score of
2.08). The evidence on chromosome 2 was decidedly
lacking in the whites (with a maximum LOD score of only
0.24 at that location).

Assuming that severity (severe–severe sibpairs) or
early age at diagnosis of hypertension (by age 55 years)
would enhance any true signal, we carried out analyses of
those groups. The primary finding on chromosome 2p
shows consistency across groups, although none lead to a
dramatic increase in the LOD score (see Fig. 2 on the web
site). The group of severe sibships lead to a slight im-
provement in the maximum LOD score (from 2.08 to
2.26). Table 1 summarizes all LOD scores >1.0 by group,
chromosome, and ethnicity, which shows a few more
potentially interesting genomic regions in specific groups.

**Discussion**

As reported here, a genome-wide linkage scan with 1565
hypertensive (affected) sibpairs (650 African American
and 915 white) has produced only one potentially inter-
esting finding on chromosome 2p (at 63 cm from p telo-
mere with a maximum LOD score of 2.08 in the African
American sample, with little evidence in the white sam-
ple), which reflects the general difficulty in finding genes
for complex diseases like hypertension. The lack of con-
sistency of evidence between the two ethnic groups should
not be construed as indicative of different genes predis-
posing the two ethnic groups to hypertension. It is possible
that the latent hypertension genes have the same or similar
function in both ethnic groups, with perhaps different gene
frequencies, so that the at-risk allele for a given gene is
less prevalent in one ethnic group than the other. Alterna-
tively, it is possible that there are important determinants
(either genetic or environmental) that interact with the
predisposing genes in different ways in the two popula-
tions. It is conceivable that the genes express themselves
only in interaction with at-risk lifestyles that may be more
prevalent in one ethnic group.

Numerous other studies have sought to identify genes
for hypertension and BP. Four previous genome-wide
scans are particularly noteworthy for the sampling designs
used, or for the relatively large sample sizes, or for con-
sistency with our primary finding here. Krushkal et al\textsuperscript{5}
have reported a genome-wide scan for systolic BP using
highly discordant white sibpairs and identified four
genomic regions of potential interest (on 2p, 5q, 6q, and
15q). Xu et al\textsuperscript{6} have reported the results of a genome-wide
scan for BP using a very large sample of Chinese sibpairs,
with five informative findings on chromosomes 3, 11, 15,
16, and 17. A genome-wide linkage scan of the Quebec Family Study also found a quantitative trait locus (QTL) for systolic BP on chromosome 2p (97 cM) with a LOD score of 2.28. Atwood et al. also found a QTL at this same marker in the San Antonio Heart Study. This makes our finding on 2p more interesting, although these findings span a broad region on 2p. However, in multipoint genome-wide analyses, it is important to remember that such findings are quite sensitive to the exact genetic map used for IBD computations, potentially leading to shifts in the regions inferred.

These results may provide a basis for identifying the underlying trait genes. The DNA sequence variants in the candidate genes and expressed sequence tags in these regions are candidates for contributing to hypertension risk, and possibly to interindividual variation in BP. HyperGEN is currently pursuing candidate genes in the 2p region identified. Identification of the exact functional mutations may suggest novel mechanisms for BP regulation and the development of hypertension that could suggest new therapies.

On the face of etiologic heterogeneity, analysis of appropriate groups can enhance gene finding. Strategies that enable investigators to sort families into relatively more homogeneous groups are extremely desirable. Pooling data from multiple studies can provide large sample sizes necessary for splitting the aggregate data, in turn, into multiple relatively homogeneous groups. We believe that such a lumping and splitting strategy is a reasonable one that is, in general, capable of enhancing gene finding.

Acknowledgments

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References


Table 1. Summary of potentially interesting linkage results (LOD scores exceeding 1.0)

<table>
<thead>
<tr>
<th>Group</th>
<th>Chromosome</th>
<th>Maximum LOD score</th>
<th>Location (cM)*</th>
<th>Chromosome</th>
<th>Maximum LOD score</th>
<th>Location (cM)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sibpairs (650 AA and 915 white)</td>
<td>2</td>
<td>2.08</td>
<td>63</td>
<td>17</td>
<td>1.05</td>
<td>34</td>
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<tr>
<td></td>
<td>4</td>
<td>1.08</td>
<td>156</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sibpairs in severe sibships (569 AA and 810 white)</td>
<td>1</td>
<td>1.41</td>
<td>125</td>
<td>1</td>
<td>1.29</td>
<td>136</td>
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<tr>
<td></td>
<td>2</td>
<td>2.26</td>
<td>61</td>
<td></td>
<td></td>
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<tr>
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<td>4</td>
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<td>153</td>
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<tr>
<td></td>
<td>7</td>
<td>1.23</td>
<td>29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sibpairs in severe sibships with diagnosis by age 55 (548 AA and 716 white)</td>
<td>1</td>
<td>1.22</td>
<td>125</td>
<td>1</td>
<td>1.41</td>
<td>136</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.65</td>
<td>61</td>
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<td>7</td>
<td>1.18</td>
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</table>

AA = African American.

* Location specifies the genetic map location from p-terminal.