Genetic Effect on Blood Pressure is Modulated by Age: The HyperGEN Study --- Supplemental Materials

Short Title: Gene-age Interactions in BP

Gang Shi,[1] Chi C. Gu,[1] Aldi T. Kraja,[2] Donna K. Arnett,[3] Richard H. Myers,[4] James S. Pankow,[5] Steven C. Hunt,[6] Dabeeru C. Rao[1,7]

[1]Division of Biostatistics, Washington University School of Medicine, Saint Louis, MO, 63110, USA; [2]Division of Statistical Genomics, Washington University School of Medicine, Saint Louis, MO, 63110, USA; [3]Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, AL, 35294, USA; [4]Department of Neurology, Boston University School of Medicine, MA, 02118, USA; [5]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN, 55454, USA; [6]Cardiovascular Genetics Division, University of Utah School of Medicine, Salt Lake City, UT, 84108, USA; [7]Also Departments of Genetics and Psychiatry, Washington University School of Medicine, Saint Louis, MO, 63110, USA.

Address for Correspondence:

Dr. Gang Shi
Division of Biostatistics
Washington University School of Medicine
Campus Box 8067
660 South Euclid Avenue
St. Louis, MO 63110-1093

Email: gang@wubios.wustl.edu
Phone: (314) 362-3643
Fax: (314) 362-2693

Statistical Analysis

In the traditional variance components approach,[1] the variance covariance matrix ($\mathbf{\Omega}$) among the relatives in a pedigree is typically decomposed as

$$\mathbf{\Omega} = \hat{\mathbf{\Pi}}\sigma^2_g + 2\mathbf{\Phi}\sigma^2_a + \mathbf{I}\sigma^2_e$$

where $\hat{\mathbf{\Pi}}$ is an $n \times n$ matrix whose elements $\hat{\pi}_{ij}$ are estimated allele-sharing proportion between the i th and j th individuals in the pedigree and σ^2_g represents the additive variance due to the QTL. $\mathbf{\Phi} = (\phi_{ij})_{n\times n}$ is a matrix whose elements are kinship coefficients for the pairs of individuals in the pedigree, and $\mathbf{I}$ is an identity matrix of dimension $n \times n$. σ^2_a is the additive polygenic variance, and σ^2_e is the residual environmental variance. We recently generalized the variance components model to include gene-age interactions in the QTL and polygenic effects,[2] i.e., to expand the variance covariance matrices $\hat{\mathbf{\Pi}}\sigma^2_g$ and $2\mathbf{\Phi}\sigma^2_a$ as functions of the ages of the relatives in the pedigree. The variance covariance matrix may be expressed as:

$$\mathbf{\Omega} = \hat{\mathbf{\Pi}} \circ \mathbf{T}(age)\sigma^2_g + 2\mathbf{\Phi} \circ \mathbf{H}(age)\sigma^2_a + \mathbf{I}\sigma^2_e$$

where $\mathbf{T}(age)$, and $\mathbf{H}(age)$ are age trend matrices consisting of normalized age trend functions, and "$\circ$" represents element-wise matrix product. We used Gaussian age trend functions and σ^2_g will represent the maximum variance (maximum over ages) explained by the QTL effect and σ^2_a denotes the maximum polygenic variance. Note that linear[3,4] and exponential[3] functions were proposed to model gene-age interactions, which are applicable to monotonic age trend only. The unimodal Gassian function used in this study is inspired by prior work in cross-sectional[5] and longitudinal[6] data which clearly and consistently demonstrated non-monotonic age trends in genetic effects. To test for linkage, we tested on peak QTL variance σ^2_g. Under the null

hypothesis $\sigma^2_g = 0$, i.e., there is no linkage between QTL and marker, and under the alternative hypothesis there is a tight linkage $\sigma^2_g > 0$. Since σ^2_g is constrained to be nonnegative and the null hypothesis is on the boundary, test statistic follows an asymptotic distribution of $(1/2)\chi_2^2 + (1/2)\chi_3^2$.[7] We computed multi-point IBDs at each marker location by the Genehunter[8] software and conducted likelihood ratio tests using the QTL*trends* package.[2]

Reference

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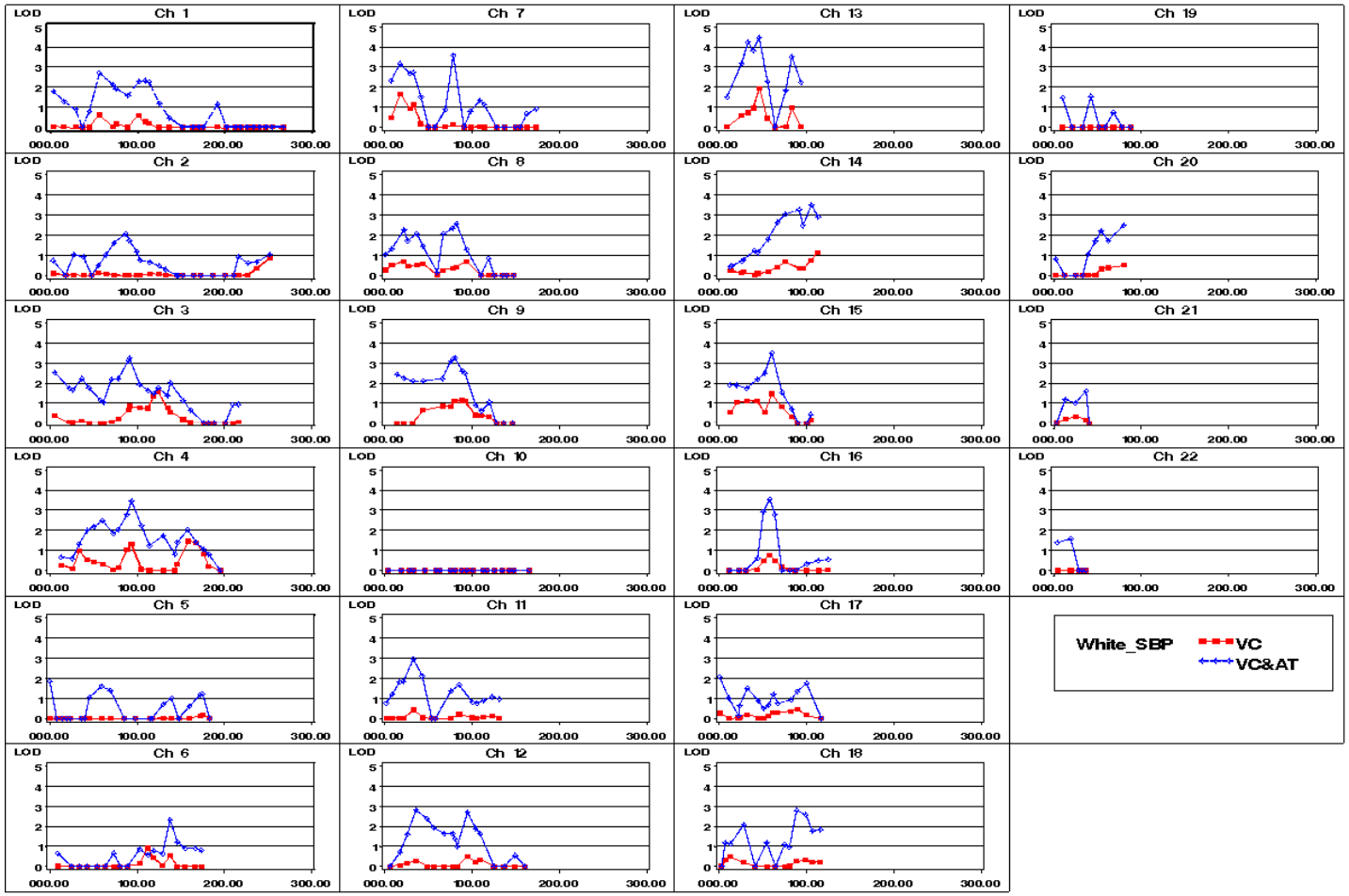

Figure S1. SBP genome-wide linkage results for Caucasians. VC: traditional variance component approach, VC&AT: variance component with age trends.

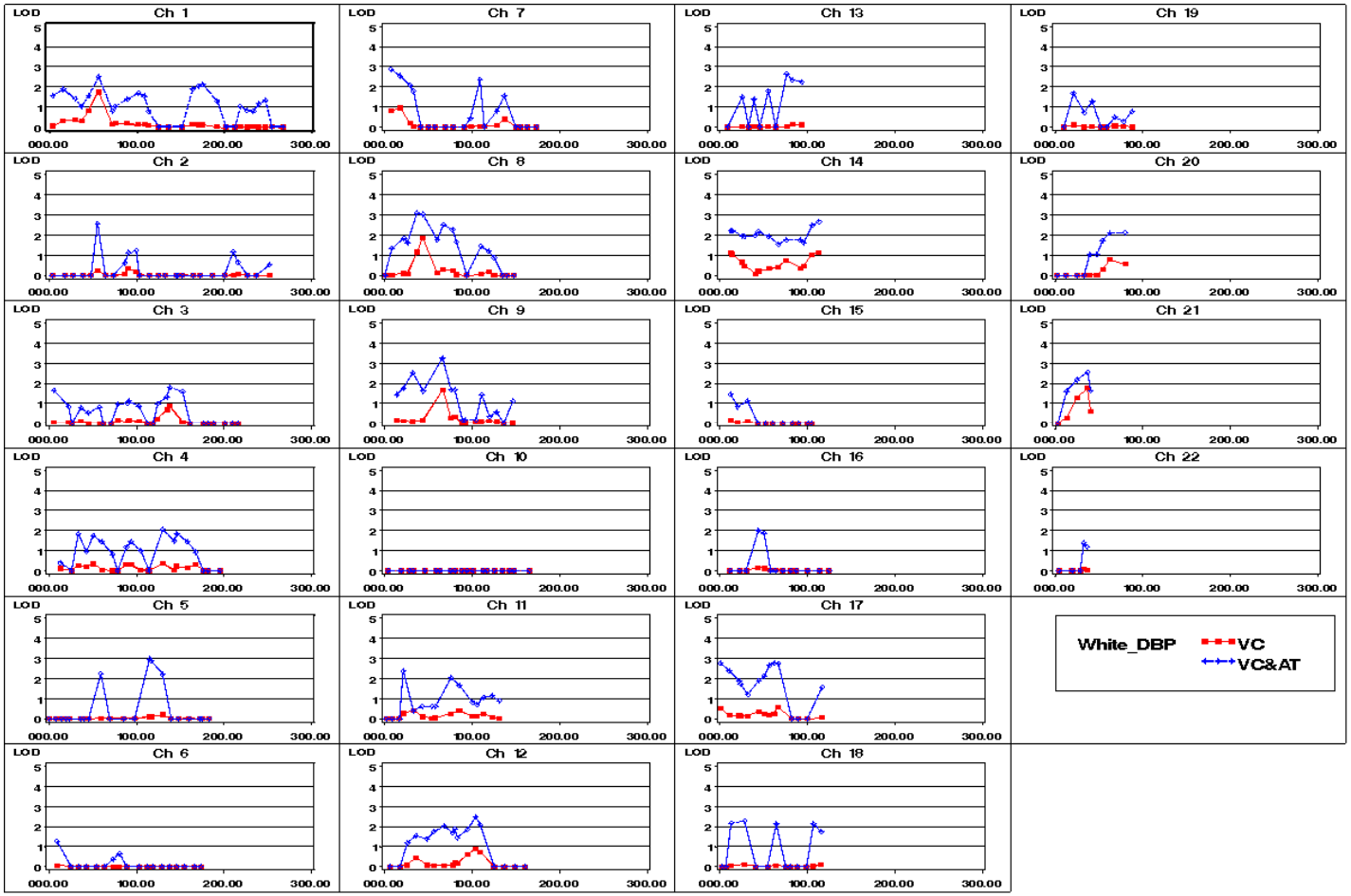

Figure S2. DBP genome-wide linkage results for Caucasians. VC: traditional variance component approach, VC&AT: variance component with age trends.

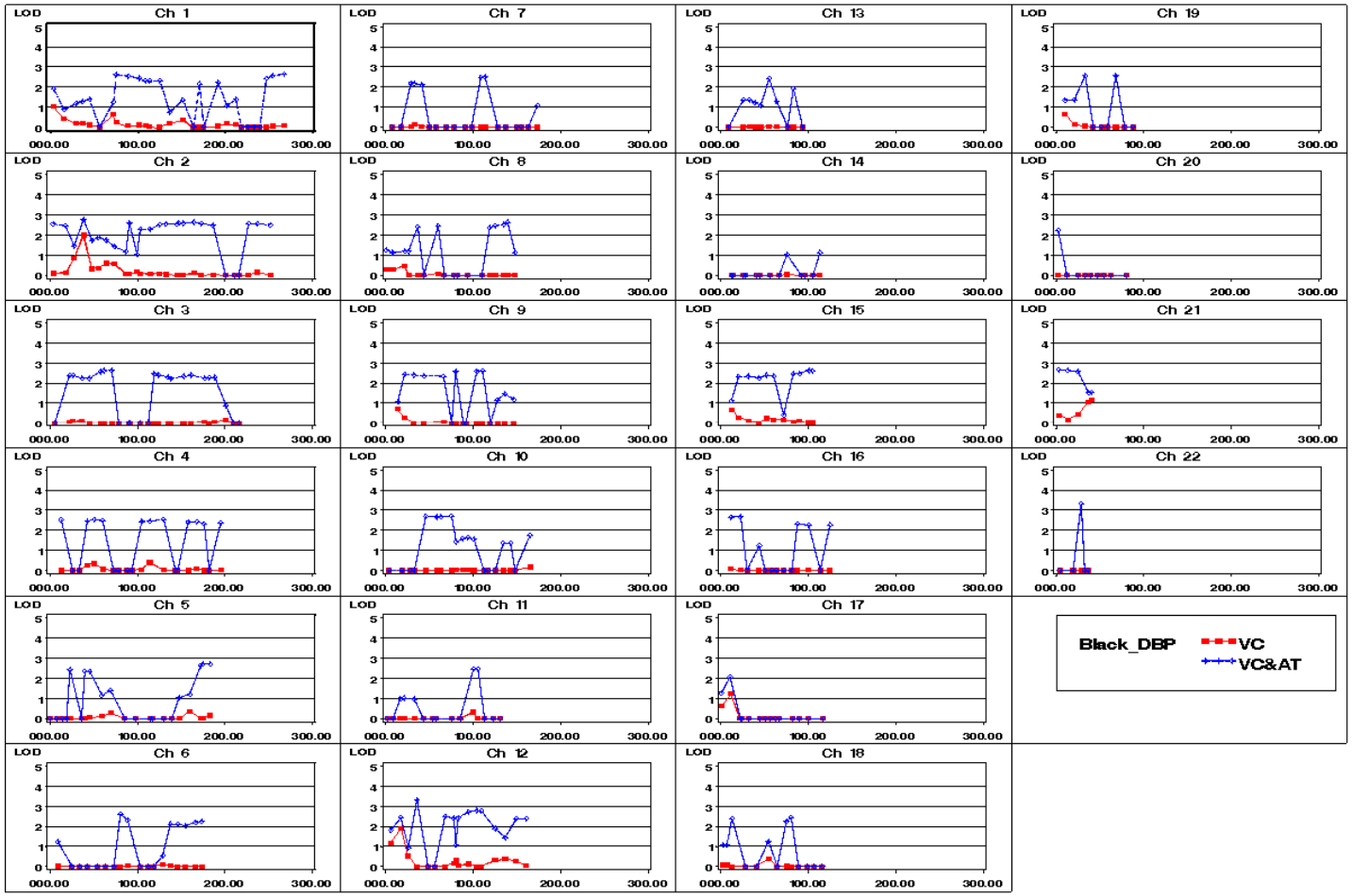

Figure S3. DBP genome-wide linkage results for African Americans. VC: traditional variance component approach, VC&AT: variance component with age trends.