A Common Copy Number Variation on Chromosome 6 Association With the Gene Expression Level of Endothelin 1 in Transformed B Lymphocytes From Three Racial Groups

Yan V. Sun, PhD; Patricia A. Peyser, PhD; Sharon L.R. Kardia, PhD

Background—Previous studies indicate that the endothelin system is involved in hypertension, heart failure, atherosclerosis, chronic kidney disease, and diabetes. To explore the potential genetic effects of copy number variations (CNVs) on the endothelin system, which underlie these diseases, we studied the association of genome-wide CNVs with gene expression levels of 7 genes involved in the endothelin system using independent HapMap subjects including 90 Asians (45 Han Chinese and 45 Japanese), 60 whites, and 60 blacks.

Methods and Results—For each subject, the genome-wide variations were measured using the Affymetrix 6.0 chip that includes measurements of 906 000 single-nucleotide polymorphisms and 946 000 CNV probes. The gene expression profiles of the transformed B lymphocytes were measured for the same subjects. Among the 210 subjects, we identified 1529 CNV regions on 22 autosomes. By testing the association between CNVs and the gene expression levels in each racial group using linear regression, we identified 4 statistically significant CNV associations in all 3 groups ($\alpha=0.05$). The strongest association was between a 66 kbp CNV region located on chromosome 6 and endothelin-1 (EDN1) expression. The effects of the CNV-EDN1 association in the 3 racial groups were in the same direction and explained 7% to 14% of the variation in EDN1 expression.

Conclusions—Although the biological function of the chromosome 6 CNV is unclear, the significant and consistent association found in 3 racial groups suggests that CNVs may contribute to variation in underlying risks of common disease through their effects on key molecular signaling pathways. (Circ Cardiovasc Genet. 2009;2:483-488.)

Key Words: hypertension ■ heart failure ■ atherosclerosis ■ endothelin system

Although a number of GWA studies to date have identified SNP loci associated with cardiovascular disease (CVD), the association between CNVs and CVD has not been investigated widely and is less understood. CNVs are suggested to affect CVD and its clinical phenotypes. One approach to assess the role of CNVs in CVD susceptibility is to focus on candidate genes. Endothelin-1 (EDN1) is a well-studied candidate gene for CVD. EDN1 was firstly isolated and cloned as a novel vasoconstrictor in 1988. Human EDN1 is located on chromosome 6 and encodes a 21-amino acid peptide. Besides vasoconstriction, EDN1 also contributes to the vasodilation, oxidative stress, inflammation, and fibrogenic processes through the endothelin system. EDN1 is believed to be an important molecule contributing to the pathogenesis of hypertension, heart failure, atherosclerosis, chronic kidney disease, and diabetes. Importantly, several SNPs in the endothelin system genes have been shown to have functional relevance and association with cardiovascular phenotypes and/or diseases.

In this study, we used available data from HapMap subjects to estimate CNV associations with gene expression levels of 7 endothelin system genes, including EDN1, endothelin-2 (EDN2), endothelin-3 (EDN3), endothelin converting enzyme...
1 (ECE1), endothelin converting enzyme 2 (ECE2), endothelin receptor type A (EDNRA), and endothelin receptor type B (EDNRB) in 3 racial groups (Asians, whites, and blacks). The goal of the study was to identify associations between CNVs and gene expression levels that were consistent across the 3 racial groups.

Methods

Sample and Data

Two hundred and seventy subjects in 3 racial groups were available from the HapMap project for this study. All 270 subjects were used to identify the specific CNV regions (described later). We used the 210 unrelated HapMap subjects from 3 racial groups to examine the association between CNVs and the expression level of genes in the endothelin system. There were 60 unrelated subjects from Utah; these individuals represent the US white population with Northern and Western European ancestry (parents in 30 trios). There were 60 unrelated subjects collected from the Yoruba people in Nigeria (parents in the 30 trios). Forty-five unrelated Han Chinese in Beijing, China, and 45 unrelated Japanese in Tokyo, Japan, were collected for the Asian group. All subjects gave specific consent for their inclusion in the HapMap project.18

The mRNA gene expression data for the HapMap samples were obtained from Wellcome Trust Sanger Institute. Gene expression profiles of the 7 endothelin system genes, EDN1, EDN2, EDN3, ECE1, ECE2, EDNRA, and EDNRB, were identified using their unique mRNA RefSeq identifiers from the microarray annotation file. The quantification and normalization of the gene expression data were described in a previous report.3

The genotyping data for the 270 HapMap subjects were produced and distributed by Affymetrix using the Genome-Wide Human SNP Array 6.0 platform. The CNV genotype data for the 210 HapMap subjects were merged with their gene expression data using the anonymous, unique identifiers. Before CNV analysis, the Contract QC (CQC) value was calculated for each chip (Affymetrix 6.0) for each of the 270 HapMap subjects using Affymetrix Genotyping Console. All of the studied chips passed the CQC threshold of 0.4, which is recommended by Affymetrix for controlling genotyping quality.

Copy Number Variation Analysis

Two different approaches were applied to identify CNV. For the first approach, the copy number analysis module in HelixTree was used to process the Affymetrix raw intensity files (.CEL) and generated a common reference genome with a normal number of copies, using all 270 HapMap subjects. Then the log-ratio was calculated for each probe (both SNP probes and copy number probes) on each microarray compared with the reference genome. HelixTree implements a dynamic programming based algorithm,9,20 which exhaustively searches through all possible cutpoint positions to find an optimal segmentation of the log-ratios for each measured subject. A multi-variation method implemented in HelixTree segments log-ratios across all subjects simultaneously, finding general copy number regions that may be similar across all subjects (HelixTree manual of copy number analysis module). For a given subject, the mean of the log-ratios within each segment for that subject are used as independent variables to identify the CNV associations with a dependent variable.

The second approach used the Affymetrix Genotyping Console 3.0.1 to generate a reference genome for comparing copy numbers and was generated using all 270 raw intensity files (.CEL files) from the human SNP 6.0 array (Affymetrix Genotyping Console 3.0.1 User Manual). Using the common reference genome for comparions, the intensity ratio of each probe (both SNP probe and copy number probe) on each array was calculated. The boundaries of the common CNV segments were determined using the predefined CNV regions.21 A hidden Markov model was used to call the copy number state (ie, the number of DNA copies, 2 for a diploid genome like human) for each identified CNV. Genotype calls for the common CNVs (observed in multiple unrelated subjects) were determined using the Canary algorithms.21 The chromosomal boundaries and the copy number state were exported and used in the association analysis of gene expression levels.

Statistical Analysis

Population genetic parameters for CNVs (copy number states) were calculated, including minor allele frequencies (MAFs), genotype frequencies, and a χ² test for departures from expectations under Hardy-Weinberg equilibrium for the 210 unrelated subjects in 3 racial groups. Summary statistics for CNVs and linear regression models were generated using the statistical software R. Single CNV associations with gene expression levels were evaluated in each racial group separately using standard linear regression models. For CNV associations with P value <0.05 in all 3 racial groups, we pooled the 210 HapMap subjects from all racial groups after testing for heterogeneity (described later) and performed the CNV association analysis. To estimate the relationship between the associated CNVs and SNPs, we tested the additive effect of SNPs associated with gene expression levels in the pooled sample.

For the CNV and SNP association tests conducted on the pooled sample of 3 racial groups, and on the sample of each of the 3 racial groups, we used the principal component (PC) analysis to adjust for the population stratification.22 The top 10 PCs of the 752 286 autosomal SNPs (MAF >0.05 and call rate >95%) were calculated within each race and in the pooled sample. The PCs significantly associated with the gene expression levels were used as covariates in the multiple regression model of testing CNV associations. In the CNV association analysis of EDN1 gene expression within each racial group, none of top 10 PCs is significantly associated with the outcome and no PC was used to adjust the linear regression model within each racial group.

All regression analyses were performed with the mean log2ratio of each CNV fragment as the independent variable. The null hypothesis of no CNV effect was evaluated by testing whether the regression coefficients were significantly different from zero. The CNV genotypes (copy number states exported from Affymetrix Genotyping Console 3.0.1 using Canary) were also used as independent variables in regression analysis to confirm the findings. In the CNV genotype test, we assumed an additive model of the DNA copy number effect for each CNV. All tests were 2-sided and the α level was set to 0.05.

For those CNVs that were significant in 3 racial groups, we applied 2 methods, Cochran Q test23 and Higgins’s inconsistency test,24 to examine the heterogeneity of the results across the 3 racial groups. Among the 270 HapMap genotyped subjects, we identified 1529 CNV regions on 22 autosomes using copy number analysis module implemented in HelixTree 6.2 software package. We identified statistically significant associations between 4 CNVs and gene expression levels among the endothelin system in each of the 3 racial groups. One CNV region (chromosome 6, 79 025 772 bp to 79 091 892 bp) was associated with EDN1 expression, one CNV region (chromo-
some 2, 86 802 346 bp to 86 807 353 bp) was associated with EDN3 expression, one CNV region (chromosome 7, 3 150 183 bp to 3 150 685 bp) was associated with ECE1 expression, and one CNV region (chromosome 20, 35 480 198 bp to 35 488 136 bp) was associated with EDNRA expression. The respective P values in Asians, whites, and blacks were 0.011, 0.009, and 0.003 for the EDN1 association; 0.011, 0.026, and 0.023 for the EDN3 association; 0.016, 0.039, and 0.008 for the ECE1 association; and 0.027, 0.008, and 0.016 for the EDNRA association.

We focused on the CNV-EDN1 associations, as they represented the most statistically significant findings in this study. The CNV-EDN1 associations are summarized in Table 1. The numbers of CNV regions demonstrating statistically significant associations with EDN1 expression were 77 in Asians, 218 in whites, and 106 in blacks. We repeated the CNV association analysis of EDN1 gene expression using the standardized copy number states called by Affymetrix Genotyping Console 3.0.1. Both methods identified the CNV region (CNV_6q14.1) on chromosome 6 with identical boundaries. The P values are higher when using the discrete log2 ratio. The P values, however, remain statistically significant within each racial group (Table 1). Pooling the samples from the 3 racial groups together yielded highly significant P values for the log2 ratio test and the copy number test with adjustment of population stratification using PC analysis.\(^{22}\) Among the top 10 PCs, the first and second were associated with EDN1 gene expression. In the pooled CNV association test of EDN1 expression, we used these 2 PCs to adjust for population stratification. The P values of CNV_6q14.1 in the multiple regression models were 4.34×10⁻⁵ (log2 ratio test) and 1.15×10⁻⁵ (copy number test). These P values were significant after Bonferroni correction for multiple testing, with adjusted P values of 4.77×10⁻³ (log2 ratio test) and 1.27×10⁻² (copy number test). The results are similar when including the top 10 PCs in the adjustment model (nominal P values are 1.07×10⁻⁵ for log2 ratio test and 2.66×10⁻⁵ for copy number test).

The proportion of variance (R²) explained by this CNV ranges from 0.071 in the Asians to 0.142 in the blacks (log2 ratio test) and from 0.058 in the Asians to 0.121 in the blacks (copy number test). The R² values from the copy number test are slightly smaller than those obtained when using the mean log2 ratio as the independent variable. The R² values between the 2 pooled tests (mean log2 ratio versus CNV state) are comparable (0.146 versus 0.143). Previous studies found that R² values or P values generated in the association test using the log2 ratios or the CNV genotypes are strongly correlated (Pearson correlation coefficients >0.9), indicating that log2 ratios can be used directly.\(^{3}\) In our study, we also found that the linear relationship between CNV_6q14.1 and EDN1 expression is very similar using either log2 ratio or CNV genotype (Figure), and the R² values or P values from the linear regression model are also consistent (Table 1).

In addition, we examined the heterogeneity of the estimated betas of the CNV_6q14.1 association with EDN1 gene expression levels in 3 racial groups, using Cochran Q test\(^{23}\) and Higgins’s inconsistency test.\(^{24}\) The P value of the Cochran Q test was 0.649 and the I² value was 4.6% in the inconsistency test (possible range 0% to 100%, I²<25% indicates low heterogeneity).\(^{24}\) Both tests indicate that no heterogeneity was observed across the CNV_6q14.1-EDN1 association results from 3 racial groups. The beta coefficients for CNV associations are all of the same relative magnitude and direction of association (eg, 0.381 [Asian], 0.427 [white], and 0.609 [black] for the CNV genotype association). We recognize, however, that we may have low power to detect heterogeneity with only 3 groups.

Table 2 summarizes the population genetics of this EDN1 associated CNV. The minor allele (ie, deletion allele) frequency in whites is 0.242, which is much higher than that in Asian (MAF=0.061) and black (MAF=0.075) populations. None of the 3 populations have significant P values from the χ² test of Hardy-Weinberg equilibrium, with an alpha level of 0.05 (Table 2). The EDN1 associated CNV spans 66 kbp on 6q14.1 starting at 79 025 772 bp and ending at 79 091 892 bp (NCBI build 36). This CNV has been previously identified and repeatedly reported in several human CNV studies.\(^{2,25,26}\)

The GWA of 752 277 autosomal SNPs (MAF >5% and call rate >95%) with EDN1 gene expression level was conducted using all 210 unrelated HapMap subjects with adjustment for population stratification by PC analysis.\(^{22}\) The lowest P value among 752 277 SNP tests for the pooled sample is 1.06×10⁻⁶, which is not significant after adjusting for multiple testing (Bonferroni corrected P value is 0.79). Within the flanking region of CNV_6q14.1 (25 kbp upstream and downstream), there are 13 SNPs (5 upstream and 8 downstream) genotyped on the Affymetrix 6.0 array with a MAF >5% and call rate >95%. Their distances and linkage disequilibrium correlations to CNV_6q14.1, and the associations with EDN1 gene expression levels are summarized in supplemental Table 1. The lowest P value among 13 SNPs is 0.006 (rs818269). None of these neighboring SNPs have strong linkage disequilibrium with CNV_6q14.1.

### Table 1. Summary of the Linear Regression Analysis of the Chromosome 6 CNV Associated With EDN1 Expression

<table>
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<tr>
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<th>log2 ratio</th>
<th>CNV State (0,1,2)</th>
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<tr>
<td></td>
<td>β</td>
<td>SE</td>
</tr>
<tr>
<td>Asian (n=90)</td>
<td>0.576</td>
<td>0.222</td>
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<tr>
<td>White (n=60)</td>
<td>0.631</td>
<td>0.234</td>
</tr>
<tr>
<td>Black (n=60)</td>
<td>1.210</td>
<td>0.391</td>
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<tr>
<td>Pooled (n=210)</td>
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<td>0.142</td>
</tr>
</tbody>
</table>

*Adjusted for the population stratification using principal components computed from 752 286 autosomal SNPs.
Discussion

CNVs have been suggested to influence CVD because of their potential biological effects on various CVD candidate genes.\textsuperscript{14} One plausible mechanism is indicated by the effect of CNV on the gene expression levels of given disease candidate genes.\textsuperscript{10} Using unrelated Asians, whites, and blacks from HapMap samples, we investigated the associations between genome-wide CNVs with the gene expression levels of the endothelin system, which includes well-studied candidate genes for hypertension, atherosclerosis, heart failure, chronic kidney disease, and diabetes. In this study, a known deletion variation on chromosome 6 was significantly associated with \textit{EDN1} expression in each of the 3 racial groups considered.

Although there is no known gene overlapped with the identified CNV region on chromosome 6, 4 genes are located within 1 Mbp window from the CNV region, including 5-hydroxytryptamine (serotonin) receptor 1B (\textit{HTR1B}, 796 Kbp upstream), interleukin-1 receptor-associated kinase 1 binding protein 1 (\textit{IRAK1BP1}, 608 Kbp downstream), pleckstrin homology domain interacting protein (\textit{PHIP}, 684 Kbp downstream), and high-mobility group nucleosomal binding domain 3 (\textit{HMGN3}, 942 Kb downstream). Two neighboring blocks within the chromosome 6 CNV, 79033035 bp to 79033306 bp and 79033329 bp to 79033429 bp, are highly conserved among 10 mammalian species (UCSC genome browser). The log-odds score for the 2 blocks are 644 and 272 correspondingly computed by PhastCons,\textsuperscript{27} which is a program for identifying evolutionarily conserved elements in a multiple alignment, given a phylogenetic tree. The log-odds scores range from 0 to 1000 and the higher score indicates more conserved region across species. On the other hand, \textasciitilde60\% of conserved bases in the ENCODE regions are assigned at least 1 molecular function.\textsuperscript{28} The interspecies conservation within the chromosome 6 CNV region suggests plausible biological functions.

Three other CNVs were also associated with gene expression levels of \textit{EDN3}, \textit{ECE1}, and \textit{EDNRA}. Taken together, these associations demonstrate a possible impact of CNVs on CVD, chronic kidney disease, and diabetes through the endothelin system, although further epidemiological studies are needed to confirm the potential relationships between the CNVs and these complex common diseases.

In this study, the gene expression profile was measured in transformed B lymphocytes. Therefore, the CNV association

\begin{table}[h]
\centering
\caption{Population Genetics of the Chromosome 6 CNV Associated With \textit{EDN1} Expression}\\
\begin{tabular}{lcccccc}
\hline
Genotype & Copy No. 0 & Copy No. 1 & Copy No. 2 & MAF & HWE P \\
\hline
Asian (n=90) & 1 & 9 & 80 & 0.061 & 0.223 \\
White (n=60) & 2 & 25 & 33 & 0.242 & 0.289 \\
Black (n=60) & 0 & 9 & 51 & 0.075 & 0.530 \\
\hline
\end{tabular}
\end{table}
may not be generalized to other cell types or tissues because of potential cell-type and tissue specific gene expression. Because of the high heritability of many gene expression levels, studying CNV association with gene expression in transformed B lymphocytes can be an essential approach to understanding the molecular mechanisms between CNV and disease traits through examining the intermediate gene expression traits.

For CNV analysis, data quality needs to be carefully controlled to guard against false CNV calls. In Affymetrix Genotyping Console, the CQC value was calculated for each chip (Affymetrix 6.0) for each of the 270 HapMap subjects. The CQC values of the chips from the 210 unrelated HapMap subjects range from 1.0 to 3.7 with a mean of 2.6. All of the chips passed the CQC threshold of 0.4, which is recommended by Affymetrix for controlling genotyping quality. These high-quality chip results were used in the CNV analysis.

CNV association studies show promise as a complement to the current GWA studies using SNPs to identify disease loci on the human genome.10 Because the CNVs have large base-pair coverage on the human genome,2 their functional roles in human disease development are substantial. At least one thousand human CNVs have been characterized and validated in recent years2,25,29 and more will be discovered with improved technology.30 Unlike the SNPs, CNVs tend to have differential boundaries across individuals.30 This property of CNV limits the current population studies with the more conserved CNVs with common boundaries among individuals. The advancement of technology in both CNV measurements and CNV calling algorithms21 will improve our understanding of the boundaries, origins, and distributions of human CNVs, as well as our knowledge of their functional roles in human diseases. The ongoing GWA studies provide a unique opportunity to study the genome-wide CNV association with CVD and other common human diseases. These high-quality chip results were used in the CNV analysis.

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Disclosures
None.

References
Copy number variation (CNV) may influence cardiovascular disease risk through potential biological effects on various cardiovascular disease candidate genes. One plausible mechanism is an effect of CNV on gene expression levels of candidate genes. We studied the association between 1529 CNV regions on 22 autosomes and gene expression levels of 7 genes in the endothelin system. The endothelin system is implicated in hypertension, heart failure, atherosclerosis, chronic kidney disease, and diabetes. Two hundred seventy subjects from 3 racial groups in the HapMap project had mRNA gene expression data for endothelin-1, endothelin-2, endothelin-3, endothelin converting enzyme 1, endothelin converting enzyme 2, endothelin receptor type A, and endothelin receptor type B and genotype data from the Affymetric 6.0 chip. Gene expression was measured in transformed B lymphocytes. The strongest association was between a 66 kbp CNV region on chromosome 6 and endothelin-1 expression. This CNV explained between 7% and 14% of the variation in endothelin-1 expression in the 3 racial groups. Because CNVs have large base-pair coverage in the human genome, their functional roles in development of human disease are substantial. Importantly, ongoing genome wide association studies provide the opportunity to study genome wide CNV association with candidate genes to help expand our understanding of the genetic architecture of cardiovascular disease and identify high-risk individuals as well as targets for prevention and therapeutic interventions.
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**SUPPLEMENTAL MATERIAL**

Supplemental Table 1. Summary of SNPs in the flanking region of CNV_6q14.1.

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<th>Chr.</th>
<th>Position (bp)</th>
<th>Allele</th>
<th>EDN1 Expression Assoc. P</th>
<th>Distance to CNV_6q14.1 (bp)</th>
<th>LD with CNV_6q14.1 (R²)</th>
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