A Comprehensive Genetic Study on Left Atrium Size in Caribbean Hispanics Identifies Potential Candidate Genes in 17p10

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Background—Left atrial (LA) enlargement is associated with cardiovascular disease and stroke. Genetic factors contributing to the LA dimension are poorly understood. We sought to map susceptibility genes for LA size in a large Dominican family data set and an independent population-based sample from the Northern Manhattan Study.

Methods and Results—One hundred Dominican families comprising 1350 individuals were studied to estimate heritability and map quantitative trait loci for LA size using variance components analysis. LA dimension was measured by transthoracic echocardiography. A polygenic covariate screening was used to identify significant covariates. LA size had a moderate estimate of heritability ($h^2 = 0.42$) after adjusting for significant covariates. Linkage analysis revealed suggestive evidence on chromosome 10p19 (D10S1423, MLOD = 2.00) and 17p10 (D17S974, MLOD = 2.05). Ordered subset analysis found significantly enhanced ($P < 0.05$ for increase of LOD score) evidence for linkage at 17p10 (MLOD = 2.9) in families with lower LDL level. Single nucleotide polymorphisms (n = 223) were used to perform a peak-wide association mapping across 17p10 in 825 NOMAS individuals. Evidence for association were found in NTN1, MYH10, COX10, and MYOCO genes ($P = 0.00005$ to 0.005).

Conclusions—Using nonbiased genome-wide linkage followed by peak-wide association analysis, we identified several possible susceptibility genes affecting LA size. Among them, MYOCO has been shown to serve as a key transducer of hypertrophic signals in cardiomyocytes. Our data support that polymorphisms in MYOCO modify LA size. (Circ Cardiovasc Genet. 2010;3:386-392.)

Key Words: left atrium ■ genetics ■ myocardin ■ MYO10 ■ COX10

Left atrial (LA) enlargement has been associated with increased mortality in high-risk patients with left ventricular dysfunction or atrial arrhythmias, but also in the general population. An enlarged LA is also associated with the development of atrial fibrillation, a strong determinant of ischemic stroke and death. Even among subjects without atrial fibrillation, LA enlargement has been associated with an increased risk of ischemic stroke. We have previously shown an increased stroke risk in subjects with increased LA size, whether measured directly by echocardiography or inferred by electric abnormalities detected on ECG.

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Multiple conditions have been associated with LA enlargement, including mitral valve disease, arterial hypertension, and any condition that increases the left ventricular filling pressures. Elucidating the genetic influences on LA size would help to identify subjects at risk for developing an enlarged LA. In addition, this knowledge is essential for understanding cardiac structure and function at the molecular level and identifying therapeutic targets in the management of LA enlargement.

Little is known about the genetic basis of LA size, with sparse studies mainly among Caucasian populations. Therefore, we estimated the heritability and mapped quantitative trait loci (QTLs) for LA size in Caribbean Hispanic families from the Family Study of Stroke Risk and Carotid Atherosclerosis. To identify the genes underlying the QTLs, we performed a peak-wide association study in an independent sample drawn from the prospective community-based cohort from the Northern Manhattan Study (NOMAS).

Methods

Subjects and Data Collection

Previously, we have reported the detailed ascertainment scheme on NOMAS and the family study. NOMAS participants had never been diagnosed with a stroke, were at least 40 years of age, and resided for at least 3 months in a household with a telephone in

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The online-only Data Supplement is available at http://circgenetics.ahajournals.org/cgi/content/full/CIRCGENETICS.110.938381/DC1.

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Northern Manhattan. A total of 3298 subjects were enrolled between 1993 and 2001. Among them, 1137 individuals with MRI data were genotyped in a genome-wide association study (GWAS) to primarily study subclinical brain phenotypes. Probands in the family study were drawn from the NOMAS. To maximize the genetic component for cardiovascular risk in the families, we used the following criteria to define a qualifying proband: (1) reporting a sibling with a history of myocardial infarction or stroke or (2) having 2 of 3 quantitative risk phenotypes (maximal carotid plaque thickness, left ventricular mass, or homocysteine level above the 75th percentiles in the NOMAS cohort). To have an independent data set for follow up study, probands of the family study were excluded in the fine mapping analysis using NOMAS cohort. All subjects provided informed consent to participate in the study and the study was approved by the institutional review boards of Columbia University, University of Miami, and the National Bioethics Committee and the Independent Ethics Committee of Instituto Oncologico Regional del Cibao in the Dominican Republic.

Echocardiographic Evaluation
Transthoracic echocardiography was performed according to the guidelines of the American Society of Echocardiography. LA size was measured in parasternal long-axis view at end-systole. Measurements were made in triplicate and averaged. Echocardiographic studies were interpreted by researchers blinded to the clinical characteristics. Interobserver variability ranged between 8% and 10%.

Genotyping and Quality Control
As described before,19 DNA from the family study was genotyped at the Center for Inherited Disease Research. Autosomal microsatellite genotypes were used to verify and adjust family structure using the programs PREST.20 Mendelian error checking was performed on the final family structure using Pedcheck.21 DNA from the NOMAS cohort was genotyped using the Genome-Wide Human SNP Array 6.0 chip (AffyMetrix) at the Genotyping Core of the John P. Hussman Institute for Human Genomics at the University of Miami. Samples were excluded if they had call rates below 95%, relatedness, sex discrepancies, or were outliers beyond 6 SD from the mean, based on Eigenstrat analysis. Single nucleotide polymorphisms (SNPs) with severe deviation from Hardy-Weinberg equilibrium (P<10⁻⁷) or a genotyping call rate <95% were also removed using PLINK 1.05.22

Statistics
A polygenic covariate screening as implemented in Sequential Oligogenic Linkage Analysis Routines (SOLAR) was run to screen age, sex, smoking, diabetes, dyslipidemia, hypertension, and body mass index (BMI) to determine significant covariates. An interaction between age and sex was automatically included by SOLAR. A permissive threshold of P<0.1 was used to allow for inclusion of any potentially significant covariates. Hypertension was defined as reported history of high blood pressure, systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of antihypertensive medication. Smoking was defined as never versus ever. Dyslipidemia was defined as a history of hyperlipidemia or total cholesterol > 240 mg/dL. Diabetes was defined as a history of diabetes or fasting blood sugar > 126 mg/dL.

Variation components methodology as implemented in SOLAR was used to estimate heritability and calculate 2-point and multipoint LOD scores.23-25 Because SOLAR requires that quantitative traits have a standard deviation of >0.5 and a residual kurtosis <0.8, LA measurements were natural-log transformed, multiplied by 10. A mixed-effects model that incorporates fixed covariate effects, additive genetic effects, and residual error was used. Heritability is calculated as the proportion of phenotypic variance explained by additive genetic effects while accounting for covariates. Heritability of LA diameter was assessed by itself or after correction for the indices of body size most commonly used in the literature: body surface area (BSA), and height (HT). For QTL mapping, marker-specific IBGs were computed using the David and Weeks Monte Carlo algorithm. Then, marker-specific IBGs were merged to calculate multipoint IBGs using a 1-cM grid. Empirical probability values for LOD scores were calculated based on 10 000 replicates in which a fully informative marker, unlabeled to LA diameter, was simulated and used to compute possible LOD scores.

Ordered subset analysis (OSA) was used to identify a more homogeneous subset of families for linkage analysis.26 First, families were ranked by trait-related quantitative covariates. Then, the family-specific LOD scores were added in order of the increasing or decreasing covariate values of families until the maximum evidence for linkage was achieved. Family orderings (n=10 000) were permuted to generate empirical probability values for the significance of increase in the LOD score from the overall data set to the OSA-identified subset.

The NOMAS cohort included samples from a broader population, and population stratification was assessed using Eigenstrat.27 Linear regression analysis was done in PLINK, using an additive genetic model and adjusting for the independent covariates. A stepwise selection procedure in SAS. As in the family study, the same set of covariates were screened, and any covariate with P<0.10 was kept in the model. Additionally, the top 3 principal components (PCA1, PCA2, and PCA3) as identified by Eigenstrat as well as the number of years between baseline (when risk factor information was collected) and when the echocardiographic measurement was taken were included in the covariate screening. LA measurements were transformed to be consistent with the family analysis.

To correct for multiple testing of SNPs in the peak-wide association mapping, we applied SimpleM.28 In large-scale genetic studies, many SNPs were tested simultaneously, but they are often not independent due to linkage disequilibrium. In the presence of this dependence, the Bonferroni correction will control the Family Wise Error Rate strictly below the nominal level, α. The SimpleM method estimates the number of independent tests such that a standard Bonferroni correction can be applied while maintaining the prescribed level of α.

SOLAR was used to calculate power for the Family Study. Polygenic and linkage models were fitted, keeping the final total genetic heritability constant at 0.42 (estimated in our data set) and assuming a biallelic QTL with a significant frequency of 0.2113 while gridding the effect size of the QTL from 0 to 0.4 in steps of 0.05. For each effect size, 100 replicates were simulated to get LOD scores, which were converted to power. Quanto was used to calculate power for the NOMAS cohort. Assumptions included independence of individuals, minor allele frequency of 0.20, an additive genetic effect, a population mean of 3.62 and standard deviation of 0.12 (estimated in the 825 NOMAS subjects used in the final analysis), and a 2-sided α of 0.005.

Results
We enrolled 100 Dominican families, consisting of 2182 individuals, in our family study. The mean family size was 22±11 members with a range of 4 to 87. LA measurement and genotype were available for 1369 subjects. Because of the significant contribution of mitral regurgitation and low left ventricular ejection fraction to LA size, individuals (n=13) with severe mitral regurgitation or ejection fraction <30% were excluded. Six individuals with outlier LA measurements (beyond 3 SD from the mean) were also removed. Using our final data set, we had >80% power to detect QTLs with heritability estimates >0.19 at a LOD score threshold of 2.0.

Within the NOMAS cohort, 1137 individuals were genotyped in a GWAS. Additional samples were excluded for the following reasons: probands in the family study (n=52), failed genotyping quality control (n=44), sex discrepancy (n=16), relatedness (n=22), outliers based on Eigenstrat analysis (n=5), missing LA phenotype or covariate data (n=127), and mitral valve regurgitation or low left ventricu-
The NOMAS GWAS sample is mainly composed of Hispanics (66.3%). To ensure sufficient statistical power, we used the entire NOMAS GWAS sample (n=825 after data cleaning) adjusting for population stratification. With this data set, we had 90% power to detect a $\beta$ of 0.03 (corresponding to an approximate change of 1 mm from the mean of LA diameter). Table 1 summarizes the sociodemographic, vascular risk factors, and LA diameter in the family data set and the NOMAS GWAS sample used in the final analysis.

Table 2 summarizes the estimates of heritability for LA diameter, LA/BSA, and LA/HT. Age, dyslipidemia and BMI were significant covariates for all 3 LA size measurements ($P<0.1$). Covariates explained 32% of the LA diameter variance (sex and smoking as additional significant covariates), 21% of LA/BSA variance (sex and age-sex interaction as additional significant covariates), and 34% of LA/HT variance (age-sex interaction as additional significant covariates) variance. After adjusting for the significant covariates, the heritability of LA diameter, LA/BSA, and LA/HT were 0.42, 0.35, and 0.34, respectively.

Because the noncorrected LA diameter measurement had the highest estimate of heritability, we focused our QTL mapping on noncorrected LA diameter. Two-point linkage analysis found suggestive evidence (LOD scores $\geq 2.0$) on chromosomes 10 and 17 (Figure 1). Multipoint linkage analysis confirmed evidence for linkage in the 2 regions: 10p19 (MLOD=2.00) and 17p10 (MLOD=2.05) (Table 3). However, neither of them met the criteria for genome-wide significance.

To reduce phenotypic heterogeneity and strengthen the linkage signal, we performed OSA for the 2 promising

<table>
<thead>
<tr>
<th>Trait</th>
<th>Significant Covariates</th>
<th>Variance by Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA diameter</td>
<td>Age X</td>
<td>0.42±0.06</td>
</tr>
<tr>
<td>LA/BSA</td>
<td>Age X</td>
<td>0.35±0.06</td>
</tr>
<tr>
<td>LA/HT</td>
<td>Age X</td>
<td>0.34±0.05</td>
</tr>
</tbody>
</table>

Figure 1. Two-point LOD scores for LA size. Variance components methodology as implemented in SOLAR was used to calculate 2-point LOD scores in 100 Dominican families. LOD scores of 405 microsatellite markers were plotted along all chromosomes.
regions. Quantitative covariates related to LA size variance were used to rank families from high to low (H-L) or low to high (L-H) order. Five covariates, SBP, HDL, LDL, triglycerides, and waist circumference, were used in our OSA. HDL, LDL, and triglycerides were chosen because dyslipidemia significantly contributed to the LA diameter in our Dominican families (Table 2), even though the lipid levels are not traditionally considered as important factors affecting LA size. Among all ranking strategies, significantly enhanced linkage evidence was observed while ordering families by average LDL from L-H on chromosome 17p10 (OSA subset MLOD \(\Delta \) 2.9, \(P \Delta \) 0.0314 for increase of linkage) (Figure 2).

The LDL-defined subset included 83 families with lower LDL. The average LDL was 105.2 mg/dL for the OSA subset of families and 130.3 mg/dL for the rest of families (data not shown).

To fine-map our most prominent peak, we conducted a peak-wide association study using SNP data from a recent GWAS completed in a sample of the NOMAS cohort; 723,979 SNPs across the whole genome passed quality control. Among them, 2232 SNPs were located within the 1-LOD unit downregion (6.8 to 14.4 megabase) of the 17p10 linkage peak (Figure 3). Significant covariates based on the stepwise selection procedure were used in all analyses and included PCA1, PCA3, age, sex, BMI, hypertension, and years between baseline and echocardiographic measurement. The effective number of independent tests is 763 for the 2232 SNPs surveyed. Using standard Bonferroni correction, the peak-wide significance threshold is \(0.05/763\) \(=\) 0.00007. The top 2 associated SNPs met the peak-wide significance criterion: rs1029659 \(P \leq 0.00004, \beta = 0.024\) in an intergenic region near Cytochrome C Oxidase Protein 10 (COX10) and rs4791774 \(P \leq 0.00005, \beta = -0.021\) in Netrin 1 (NTN1) \(P \leq 0.00005\) (Table 4). Several SNPs with a nominal \(P \leq 0.005\) but not meeting peak-wide significance reside in genes that have been implicated in cardiac hypertrophy, such as LOC100128006/Myocardin and Nonmuscle Myosin Heavy Chain 10 (MYH10) (Table 4). A regional association plot centered around the most significant SNP from each of the 4 genes are provided in the online-only Data Supplement Figure.

The entire NOMAS GWAS sample was used for association analysis to maximize statistical power. However, analyzing a heterogeneous population could introduce substructure bias. To evaluate whether this bias was present in our associations, we did the same analysis in the Dominican subset of the NOMAS GWAS sample. The trends of association are all in the same direction, as indicated by the \(P\) values (Table 4). The probability values are less significant \(P \leq 0.006\) to 0.14, except for the 3 SNPs with minor allele frequency around 0.05, which is expected as we only have 55% power to detect a \(\beta\) of 0.03 in the Dominican subset, compared with >90% power to detect the same effect size in the entire NOMAS GWAS sample.

**Discussion**

Using well-characterized, extended Dominican Republic families and an independent sample from a community-based prospective cohort, we demonstrated that genetic factors explain a moderate proportion of the variance in LA size and mapped a few candidate genes that warrant further study. To

**Table 3. Potential QTLs Mapped for LA Size**

<table>
<thead>
<tr>
<th>Chromosomal Region</th>
<th>Position (cM)</th>
<th>Marker</th>
<th>Maximum LOD Score</th>
<th>(P) Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>10p19</td>
<td>40</td>
<td>D10S1423</td>
<td>1.99</td>
<td>0.00115</td>
</tr>
<tr>
<td>17p10</td>
<td>24</td>
<td>D17S974</td>
<td>2.05</td>
<td>0.0014</td>
</tr>
</tbody>
</table>

*Empirical \(P\) value was calculated based on 10,000 permutations.

**Figure 2.** Multipoint linkage plot for LA size on chromosome 17 in overall families and subset families defined by OSA. OSA has defined a subset of 83 families with lower average LDL on chromosome 17. Multipoint LOD score curve is depicted in the overall families as solid line and in the subset as dashed line.

**Figure 3.** Peak-wide association test on chromosome 17p10. SNPs \((n = 2232)\) were used for a peak-wide association analysis on the chromosome 17p10 1-LOD unit down region. Each dot represents an association test using an additive genetic model in the NOMAS cohort. Genes that have SNPs with probability value \(< 0.005\) are displayed as a short vertical bar with gene symbol on top.
our knowledge, this is the first comprehensive genetic study on LA size among Caribbean Hispanics. The most significant finding is for rs1029659 close to COX10. The protein product of COX10 is part of the cytochrome C oxidase (COX), which is essential for energy homeostasis. Defects in COX could lead to cardiac hypertrophy to compensate for the insufficient energy supply. A patient with missense mutations in both alleles of COX10 gene has been reported. One of the clinical symptoms for the patient is severe hypertrophic cardiomyopathy. Another peak-wide significant finding is in NTN1. The protein product of the gene belongs to a family of laminin-related secreted proteins, and it is thought to be involved in axon guidance and cell migration during development and angiogenesis. NTN1 could contribute to the enlargement of left atrium through its angiogenic activity.

Strong evidence for association ($P=0.00017$) was found at LOC100128006, which is next to Myocardin (MYOCD) and codes an antisense RNA for MYOCD. As a coactivator of serum response factor (SRF), MYOCD regulates cardiac gene expression and smooth muscle cell differentiation. Another gene that displayed strong evidence of association ($P<0.005$) is MYH10, which encodes a nonmuscle myosin heavy chain and is expressed in the heart. Mice with heart-specific ablation of MYH10 were born with enlarged cardiac myocytes and developed cardiomyopathy. The susceptibility genes in 17p10 appear to be implicated in heart structure in general. However, we did not find evidence for linkage in this region for left ventricular mass (LVM). We evaluated the association between the significant SNPs in Table 4 and LVM in the NOMAS cohort (data not shown). Except the SNP (rs7212848, $P=0.003$) near MYOCD, none of them are significantly associated with LVM, which suggests that these genes have different effects on LA size and LVM. The significant association between MYOCD and LVM further supports that the gene is a master regulator of cardiac smooth muscle differentiation and lineage as shown in previous in vitro studies.

Two published studies have examined the heritability of LA size. In the Tecumseh Offspring Study, parent-children correlation for LA size was 0.19 ($P=0.007$). This correlation is approximately equal to a heritability of 38%, which is comparable to our results. In the Framingham Heart Study, the estimate of heritability for LA diameter was 25%. A few studies have investigated association between LA size and polymorphisms in candidate genes. Most of the examined genes are associated with the renin-angiotensin system and results have been conflicting, which can probably be attributed to insufficient power in each study.

In contrast to candidate gene studies, a genome-wide approach, such as the one used in this study, has the potential to identify new genes and new pathways. Using 100 000 SNPs, the Framingham Heart Study reported suggestive evidence for linkage on chromosome 13q31.1 (MLOD = 2.55) for LA diameter. Using 402 microsatellite markers, we did not detect any evidence for linkage in this region, which might be related to the relative lower resolution or the unique ethnic population used in our study.

Recently, a metaanalysis of GWAS on cardiac structure measurements was conducted by the EchoGen consortium. Although no SNP was associated with LA size at the genome-wide significant level ($P=5\times10^{-7}$), the strongest association was found in SMG-6 ($P=9\times10^{-7}$), about 4.3 megabases away from our 17p10 peak. The Affymetrix 6.0 chip used in our study includes 60 SNPs in SMG-6. Only rs12451892 was marginally ($P=0.02$, data not shown) associated with LA diameter, but it would not survive multiple testing correction. There are several possible explanations as to why we did not robustly replicate the finding at SMG-6: It could be related to the different ethnic groups studied or the limited statistical power in our study.

Arterial hypertension is a well-described risk factor for enlarged LA size. However, we found that hypertension did not contribute to LA size significantly in the Family Study ($P=0.2$) when we evaluated all traditional covariates. One possible explanation is that age served as surrogate for hypertension in our model. This notion was supported by the
observation that hypertension became significant when age was not included in the covariate screening model.

There are several strengths of our study. First, the extended families provided substantial statistical power. Second, the echocardiographic assessment was performed by the same investigators adopting a common protocol assuring consistent phenotyping of the quantitative trait. Third, the genome-wide approach followed by high-resolution fine-mapping in an independent cohort allowed us to evaluate the genetic contribution to LA size through the whole genome.

We also acknowledge several limitations. We used LA diameter instead of volume, which is considered a more accurate measure of the atrial size, especially in the case of asymmetrical enlargement. However, the determination of LA volume is more time-consuming and may be less reproducible than a linear measurement of a single LA diameter, which has been shown to have good intraobserver and interobserver concordance. The consistency of phenotype measurement in a large cohort is critical to the genetic study of quantitative traits, which might outweigh the lack of accuracy for the current study. Another weakness is the possibility that other covariates or confounders may not have been accounted for. In an attempt to gain cleaner estimates of the genetic influence on LA size, we included the most known risk factors associated with LA size. We did not collect clinical data on atrial fibrillation (AF) duration. The uncertain contribution of AF to our results is another limitation of the study although the effect of AF duration is likely to be small, given the low occurrence (about 6% in the Family Study and 2% in the NOMAS samples) of AF (based on baseline questionnaire). Finally, to reduce heterogeneity and increase our power to map the QTLs, we restricted our linkage study to Dominican families with strong genetic burden for vascular diseases. As a result, our findings should not be directly generalized to other populations.

In conclusion, we have mapped several potential genes that influence LA size. It is clear that hemodynamic factors play a very important role in inducing LA enlargement. Although hemodynamic and other acquired factors have long been considered the major determinants of atrial size, the emerging inherited contribution to atrial arrhythmias suggest that there may be an underlying diathesis, further supported by our work. Our findings suggest that the hemodynamic factors may converge in a couple of common pathways that mediate LA enlargement, and the genes identified in our study may serve as a point of convergence. Alternatively, our data may suggest that patients with the genetic variations are predisposed to LA size change, rendering them particularly susceptible to the hemodynamic factors. Further studies are warranted to evaluate the contribution of these genetic variants to LA size.

Acknowledgments

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Disclosures

None.

References


22. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Maller J, Sklar P, de Bakker PI, Daly MJ, Sham PC. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet.* 2007;81:559–575.


**CLINICAL PERSPECTIVE**

Left atrial (LA) enlargement is associated with increased mortality, ischemic stroke, atrial fibrillation, and other adverse cardiovascular outcomes. Although hemodynamic factors have long been considered the major determinants of atrial size, the emerging inherited contribution to atrial arrhythmias suggests that there may be underlying genetic determinants of atrial size also. Identifying genetics factors contributing to LA size may help identify individuals at risk of developing LA enlargement and perhaps its adverse sequel. In addition, understanding the genetic determinants may facilitate the identification of therapeutic targets for the management of LA enlargement. Using well-characterized, extended families and an independent sample from a community-based prospective cohort, we evaluated the genetic correlates of LA size. Our data demonstrate that genetic factors explain a moderate proportion of variance in LA size and indicate that several genes on chromosome 17p10 may influence LA size. Among the potential candidate genes identified, Myocardin (*MYOC*) has been shown to be a key transducer of hypertrophic signals in cardiomyocytes in vitro. Our study is consistent with the notion that genetic variations in *MYOC* may modify LA size. Large-scale genetic studies and additional functional studies are warranted to further evaluate the contribution of genetic variants in the identified loci to interindividual variation in LA size.
A Comprehensive Genetic Study on Left Atrium Size in Caribbean Hispanics Identifies Potential Candidate Genes in 17p10
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Supplementary Figure: Regional association plot with recombination rate on the four candidate genes.

The graphs are centered around the most significant SNP from each of the four genes reported in Table 4 and extend 200 – 300 KB on either side, as far as it takes to at least cover the whole gene. The \( r^2 \) values (linkage disequilibrium between the most significant SNP and the rest of SNPs in the region) are calculated in NOMAS cohort, and the recombination rates are based on CEU HapMap data.
rs1029659 ( CEU )

Chromosome 17 position (hg18) (kb)

13600 13800 14000

Observed (-logP)

0 2 4 6 8

Recombination rate (cM/Mb)

rs1029659

P=3.55e-05

0.8 0.5

r^2

COX10  CDRT15
rs4791774 (CEU)

Chromosome 17 position (hg18) (kb)

Observed (-logP)

Recombination rate (cM/Mb)

rs4791774

P=4.68e-05

CCDC42
LOC388333
FLJ35773
PIK3R5
PIK3R6
NTN1
STX8
rs7212848 (CEU)

Chromosome 17 position (hg18) (kb)

Recombination rate (cM/Mb)

-logP

rs7212848

P=0.0001669

r²

MYOCD

RICH2
rs7223040 ( CEU )

Chromosome 17 position (hg18) (kb)

Observed (-logP)

Recombination rate (cM/Mb)

rs7223040

P = 0.0008766

ODF4
KRBA2
RPL26
NDEL1
MYH10
CCDC42
LOC388333