of *ELAC2* in prostate cancer, suggest moderate familial risk, and estimate that risk genotypes in *ELAC2* may cause 2% of prostate cancer in the general population.

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Electronic-Database Information

Accession numbers and URLs for data presented herein are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for prostate cancer [MIM 176807], HPC2/ELAC2 [MIM 605367], Ser-to-Leu change at amino acid 217 [MIM 605367.0001], and Ala-to-Thr change at amino acid 541 [MIM 605367.0002]

GenBank, http://www.ncbi.nlm.nih.gov/Genbank/ (for variant Ser217Leu [AF304370])

References

Lillienfeld AM, Lillienfeld DE (1980) Foundations of epidemiology. 2nd ed. Oxford University Press, New York

Kirkwood BR (1988) Essentials of medical statistics. Blackwell Scientific Publications, Oxford

Rebbeck TR, Walker AH, Zeigler-Johnson C, Weisburg S, Martin AM, Nathanson KL, Wein AJ, Malkowicz SB (2000) Association of HPC2/ELAC2 genotypes and prostate cancer. Am J Hum Genet 67:1014–1019

Rokman A, Ikonen T, Mononen N, Autio V, Matikainen MP, Koivisto PA, Tammela TL, Kallioniemi OP, Schleutker J (2001) ELAC2/HPC2 involvement in hereditary and sporadic prostate cancer. Cancer Res 61:6038–6041

Suarez BK, Gerhard DS, Lin J, Haberer B, Nguyen L, Kesterson NK, Catalona WJ (2001) Polymorphisms in the prostate cancer susceptibility gene HPC2/ELAC2 in multiplex families and healthy controls. Cancer Res 61:4982–4984

Tavtigian SV, Simard J, Teng DH, Abtin V, Baumgard M, Beck A, Camp NJ, et al (2001) A candidate prostate cancer susceptibility gene at chromosome 17p. Nat Genet 27:172–180

Vesprini D, Nam RK, Trachtenberg J, Jewett MA, Tavtigian SV, Emami M, Ho M, Toi A, Narod SA (2001) HPC2 variants and screen-detected prostate cancer. Am J Hum Genet 68:912–917

Wang L, McDonnell SK, Elkins DA, Slager SL, Christensen E, Marks AF, Cunningham JM, Peterson BJ, Jacobsen SJ, Cerhan JR, Blute ML, Schaid DJ, Thibodeau SN (2001) Role of HPC2/ELAC2 in hereditary prostate cancer. Cancer Res 61:6494–6499

Xu J, Zheng SL, Carpten JD, Nupponen NN, Robbins CM, Mestre J, Moses TY, Faith DA, Kelly BD, Isaacs SD, Wiley KE, Ewing CM, Bujnovszky P, Chang B, Bailey–Wilson J, Bleecker ER, Walsh PC, Trent JM, Meyers DA, Isaacs WB (2001) Evaluation of linkage and association of HPC2/ELAC2 in patients with familial or sporadic prostate cancer. Am J Hum Genet 68:901–911

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Regarding "Testing for Population Subdivision and Association in Four Case-Control Studies"

To the Editor:

Ardlie et al. (2002) recently found no evidence for population structure in separate case-control studies of type 2 diabetes and hypertension in U.S. whites and only weak evidence of structure in a case-control study of hypertension in African Americans. These results are consistent with the theoretical results of Wacholder et al. (2000), who found that the magnitude of bias due to unrecognized population stratification is likely to be small under most plausible scenarios. To further evaluate the potential bias due to stratification for these and other conditions, we conducted a series of case-control studies for six common phenotypes in a population-based sample of U.S. adults.

The study population included 444 unrelated adults (231 African Americans and 213 non-Hispanic whites) randomly selected from five U.S. communities as part of the Hypertension Genetic Epidemiology Network (HyperGEN) of the National Heart, Lung, and Blood Institute (NHLBI) Family Blood Pressure Program (Williams et al. 2000). The study was approved by the institutional review boards at each institution, and appropriate informed consent was obtained from human subjects. Phenotypes measured included: (1) obesity (BMI $\geq$ 30), (2) hypercholesterolemia (total plasma cholesterol $\geq$ 240 mg/dl or current use of medications to lower cholesterol), (3) hypertension (systolic blood pressure $\geq$ 140 mmHg, diastolic blood pressure $\geq$ 90 mmHg, or current use of medications to lower blood pressure), (4) diabetes (fasting serum glucose $\geq$ 126 mg/dl, nonfasting glucose $\geq$ 200 mg/dl, self-reported physician diagnosis of diabetes, or current use of hypoglycemic medications), (5) renal dysfunction (serum creatinine $\geq$ sex-specific 90th percentile [1.4 mg/dl in men and 1.1 mg/dl in women]), and (6) cardiovascular disease (self-reported history of heart attack, stroke, or coronary artery bypass surgery). For each

phenotype, those who did not meet the case definition served as control individuals.

We constructed contingency tables and performed χ^2 tests of association for these six phenotypes with each of 368 STR markers typed by the NHLBI Mammalian Genotyping Service at Marshfield, WI (screening set 10). Like Ardlie et al. (2002), we then computed a statistic, χ_s^2, to test for overall differences in allele frequencies between each set of case individuals and control individuals (Pritchard and Rosenberg 1999). To simplify the analysis and ensure that expected values in contingency tables were sufficiently large (> 5) for the classical χ^2 test, we converted each STR marker to a biallelic marker by selecting one index allele for each marker and then collapsing all other alleles for that marker into a single alternative allele. Index alleles for each marker were selected by first choosing alleles with allele frequencies of at least 15% in both African Americans and whites and then selecting the allele that demonstrated the largest absolute difference in allele frequencies between racial groups.

The prevalence of several of the phenotypes differed substantially between racial groups (table 1). In crude analysis pooling both racial groups, the percentage of markers nominally associated ($P < .05$) with each phenotype was higher than expected, under the null hypothesis, for diabetes (8.4%), hypertension (7.9%), renal dysfunction (7.6%), and hypercholesterolemia (5.4%) but not for cardiovascular disease (4.9%) or obesity (4.9%). The summary test for stratification incorporating all 368 markers (i.e., 368 df) was statistically significant for diabetes, renal dysfunction, and hypertension (table 1), indicating overall differences in allele frequencies between case individuals and control individuals. However, after adjustment for race or stratification by race, there was no evidence of cryptic stratification for any of the six phenotypes, with the possible exception of obesity in whites.

Our results provide further evidence that hidden or unrecognized population stratification is unlikely to be a serious threat to the validity of case-control designs that appropriately account for ethnicity in either the design or analysis phase of the study (Wacholder et al. 2000; Ardlie et al. 2002). Because of the large number of markers tested, it is likely that our study was even more sensitive to subtle background genetic differences between case individuals and control individuals than that conducted by Ardlie et al. (2002), which included only 9 STR markers and 35 SNP markers. We think that other factors, such as selection bias, chance, publication bias, gene-environment interactions, and differences in linkage disequilibrium patterns across study populations, are more plausible explanations for inconsistency of results between genetic association studies.

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Table 1

Summary Tests for Population Stratification by Phenotype

	No. of Case Subjects (Prevalence)		All Subjects, Unadjusted		All Subjects, Adjusted for Race		African Americans Only		Whites Only	
Phenotype	African Americans	Whites	χ_s^2	P	χ_s^2	P	χ_s^2	P	χ_s^2	P
Obesity	110 (48%)	82 (39%)	379.5	.33	336.8	.88	329.5	.93	431.9	.01
Hypercholesterolemia	44 (19%)	55 (26%)	401.4	.11	360.9	.59	358.4	.63	362.5	.57
Hypertension	130 (56%)	91 (43%)	456.2	.001	371.9	.43	391.7	.19	384.4	.27
Diabetes	46 (20%)	23 (11%)	507.2	<.001	395.7	.15	373.9	.41	381.4	.30
Renal dysfunction	29 (13%)	11 (5%)	442.5	.005	374.2	.40	388.4	.22	367.6	.50
Cardiovascular disease	30 (13%)	20 (9%)	378.6	.34	373.2	.41	377.1	.36	354.7	.68

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References

Ardlie KG, Lunetta KL, Seielstad M (2002) Testing for population subdivision and association in four case-control studies. Am J Hum Genet 71:304–311

Pritchard JK, Rosenberg NA (1999) Use of unlinked genetic markers to detect population stratification in association studies. Am J Hum Genet 65:220–228

Wacholder S, Rothman N, Caporaso N (2000) Population stratification in epidemiologic studies of common genetic variants and cancer: quantification of bias. J Natl Cancer Inst 14:1151–1158

Williams RR, Rao DC, Ellison RC, Arnett DK, Heiss G, Oberman A, Eckfeldt JH, Leppert MF, Province MA, Mockrin SC, Hunt SC (2000) NHLBI family blood pressure program: methodology and recruitment in the HyperGEN network. Ann Epidemiol 10:389–400

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The ABCA4 Gene in Autosomal Recessive Cone-Rod Dystrophies

To the Editor:

Recently, Maugeri et al. (2000) reported on the screening of the *ABCA4* gene in 5 patients with autosomal recessive cone-rod dystrophies (CRD) and 15 patients with sporadic CRD originating from Germany and the Netherlands. The identification of mutations in 13/20 patients (65%) led the authors to speculate that "Mutations in the *ABCA4* (*ABCR*) gene are the major cause of autosomal recessive cone-rod dystrophy."

The present study was undertaken to evaluate the prevalence of *ABCA4* mutations in a cohort of 55 patients affected with autosomal recessive or sporadic CRD.

Within the huge family of inherited retinal dystrophies, the CRD phenotype indicates a specific form of retinal degeneration in which the cone degeneration appears early in life with a central involvement of the retina, followed by a degeneration of rods several years later (Klevering et al. 2002). This particular form of retinal dystrophy has long been regarded as "inverse retinitis pigmentosa" (RP) and can be misdiagnosed as macular dystrophy in the first stages of the disease.

Indeed, the main symptoms at onset of the disease are decrease of visual acuity, loss of color discrimination, and photophobia. The b-wave of the photopic ERG (cone response) is severely reduced, although the b-wave of the scotopic ERG is still normal. As the disease progresses, nyctalopia, progressive peripheral visual field deficit, and decreasing scotopic electroretinogram (ERG) amplitudes are observed.

Four genes (*CRX* [MIM 602225], *GUCY2D* [MIM 600179], *GCAP1* [MIM 600364], and *HRG4* [MIM 604011]) and two loci have been implicated in autosomal dominant CRD (*CORD5* [MIM 600977] and *CORD7* [MIM 603649]), whereas two other loci were reported for autosomal recessive CRD (*CORD9* [Danciger et al. 2001] and *CORD8* [MIM 605549]) and one for X-linked CRD (*RPGR* [MIM 312610]).

Conversely, the *ABCA4* gene, which was identified in 1997 as the Stargardt-causing gene, was later recognized as responsible for some forms of RP (RP19) and some CRD, depending on the nature of the *ABCA4* mutations and on the remaining protein activity (Allikmets et al. 1997; Martinez-Mir et al. 1997; Cremers et al. 1998; Gerber et al. 1998; Rozet et al. 1998, 1999).

Sixty-one individuals affected with CRD and 40 healthy relatives belonging to 55 families of various origin were recruited from genetic and ophthalmologic consultations. In 29/55 families, the disease was undoubtedly inherited as an autosomal recessive condition—23 multiplex families (11/23 consanguineous) and six simplex patients born to consanguineous parents. In the 26/55 remaining families, the patients were simplex cases. The time course of the disease was determined by interviewing at least one patient per family and, whenever possible, all affected siblings of the family. Minimal criteria for inclusion in the study were initial cone dysfunction and subsequent progressive peripheral disease.

In one affected patient per family, we screened for mutations the 50 exons of the *ABCA4* gene, as well as the flanking intronic sequences, using denaturing high-pressure liquid chromatography. On the basis of the secondary structure of each exon, the screening was performed at 1 or 2 temperatures (mutation detection rate estimated to be at least 0.98). Exons showing a shift were directly sequenced.

Sixteen different mutant alleles were identified in 13/55 patients (i.e., 23.6% of all cases). Among these 13 patients, 2 were homozygotes (from two consanguineous families), 4 were compound heterozygotes, and 7 were