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Commentary

Is Angiotensin I-Converting Enzyme a "Master" Disease Gene?

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ABSTRACT

Clustering of diseases has been appreciated by health insurers and epidemiologists for some time. Co-morbidity suggests shared pathways of disease. It is by now well agreed that common diseases have a strong genetic component. Here we present evidence that the angiotensin I-converting enzyme (ACE) deletion/deletion (*D*/*D*) genotype is associated with a large number of common adult diseases, including cardiovascular disease, cancer, and psychiatric disease. Since the ACE *D*/*D* genotype has been shown to be associated with increased levels of tissue ACE expression at the protein level, these data suggest that overactivity of ACE may be involved in the pathogenesis of many seemingly unrelated diseases. These results suggest a broad pattern of relatedness of common diseases, as well as the utility of effective ACE inhibition in their treatment and, perhaps, prevention.

INTRODUCTION

SINCE THE DISCOVERY of the insertion/deletion (*I*/*D*) polymorphism in the angiotensin I-converting enzyme (ACE) gene, and the demonstration in Northern European Caucasians that plasma ACE concentrations are twice as high in deletion/deletion (*D*/*D*) compared with insertion/insertion (*I*/*I*) homozygotes,[1] there has been considerable interest in its potential clinical associations. Taken altogether, however, results are conflicting as to whether the *D* allele, or the *D*/*D* genotype in particular, is significantly associated with diseases such as left ventricular hypertrophy;[2–10] ischemic or idiopathic dilated cardiomyopathy;[11,12] hypertension;[4,5,13–25] restenosis after percutaneous transluminal coronary angioplasty;[26–29] myocardial infarction;[15,30–34] coronary artery disease;[15,30,32,35–44] obesity;[5,14,19] glucose intolerance;[45,46] complications of diabetes mellitus such as nephropathy[47–53] and retinopathy;[48,50,53–55] hypertension[56] and atherosclerotic coronary artery disease;[53,57,58] progression of renal insufficiency;[59] IgA nephropathy;[60,61] sarcoidosis;[62] carotid artery thickness in normal subjects;[16,63] and stroke.[64]

The frequency of the ACE *D*/*D* genotype has been reported to vary with age,[19,65] and the strength of its association with disease may depend on gender.[31] There appears to be ethnic, and perhaps disease-associated, variability in whether or not plasma ACE concentration is correlated with ACE *I*/*D* genotype; in normal

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Caucasians, it was,[1,14] but in a small group of normotensive African-American children,[14] and in hypertensive Japanese adults,[23] it was not.

One possible explanation for the extreme variability in results so far may be the relatively small sample sizes examined.[66] The evaluation of a single polymorphism may require a fairly large sample size ($n > 150$),[66] especially for common diseases that appear to be polygenic. If many genes are involved in the pathogenesis of a disease, then the smaller the contribution any one polymorphism is likely to make to the disease, and the larger the sample size required to avoid a type II error.

Replication also heightens the credibility of a disease association. In addition to genotyping independent samples within the same ethnic group, multiple ethnic groups can be sampled. A disease-associated genomic polymorphism that occurs in multiple ethnic groups may represent an essential step in pathogenesis.

In this study we genotyped three patient populations to assess possible clinical associations of the ACE D/D genotype. Data are presented on a total of 6,414 inpatients and outpatients seen at two indigent care hospitals in St. Louis, expanding on previous data.[67] We also present results from 3,959 hemodialysis patients from the southeastern United States.

METHODS

This study was approved by the Human Studies Committees at the St. Louis VA Medical Center ("StLVA"), St. Louis Regional Medical Center ("Regional"), and REN, a dialysis company with 40 dialysis units throughout the southeastern United States. Informed consent was not required by the Human Studies Committees since only discarded, anonymized blood samples were used.

Table 1 briefly describes the study populations. The first patient population was drawn from StLVA. It consisted of a series of 1,686 consecutive inpatients admitted to the Medical and Surgical Services of StLVA in the 3-month period from December 21, 1993 to March 31, 1994, representing 13% of annual hospital admissions; and 2,660 outpatients from the Medicine, Renal, Diabetes, Hypertension, Neurology, and Peripheral Vascular Disease Clinics

Table 1. Patient Populations

	WM	*WF*	*BM*	*BF*	*HM*	*HF*	*Other*	*Totals*
StLVA								
Consecutive inpatients								
Total	1,058	28	578	12			10	1,686
No PCR product	8	0	3	1				
Median age (years)	65.4	54.9	64.7	45.8				
Median BMI	26.0	26.2	24.1	26.9				
Outpatients								
Total	1,641	40	1,093	30			22	2,826
No PCR product	30	1	26	0				
Median age (years)	66.6	53.3	66.2	45.3				
Median BMI	27.5	27.8	26.7	27.9				
Regional inpatients								
Total	182	162	785	896			43	2,068
No PCR product	7	3	21	24				
Median age (years)	46.4	49.9	46.3	53.6				
Median BMI	26.5	29.3	25.0	29.1				
REN (hemodialysis patients)								
Total	873	678	919	966	197	199	127	3,959
No PCR product	24	15	31	26	2	1		
Median age (years)	66.4	65.8	53.2	61.3	59.7	60.9		
Median BMI	23.2	23.3	23.5	24.8	24.6	24.6		

WM, white male; WF, white female; BM, black male; BF, black female; HM, Hispanic male; HF, Hispanic female; BMI, body mass index (kg/m^2).

seen between March 7, 1994 and July 26, 1995, representing 9% of the approximately 30,000 outpatients seen annually at StLVA.

The second study population consisted of 2,068 consecutive inpatients at Regional during the 5-month period from mid-April 1994 to mid-November 1994. These two hospital-based patient populations are referred to as "StL" in subsequent tables.

The third study population consisted of REN's entire population of 3,959 hemodialysis patients, whose samples were collected in March 1995. This population is referred to as "REN" in subsequent tables.

Patient charts were read and clinical data abstracted from March 1993 through March 1996 by individuals unaware of the patient's genotype. In particular, 1-year follow-up on hemodialysis patients was available, allowing identification of dialysis patients who had died in the interval since their blood sample was collected in March 1995.

Anticoagulated blood (1–5 ml) was obtained from the Hematology Laboratory of each institution after a clinician-ordered test ("complete blood count") had been performed, but before the sample was to be routinely discarded. Generally, blood samples were kept at room temperature for up to 12 h after venipuncture, and then stored at 4°C for up to 16 weeks. ACE I/D genotyping was performed by someone blinded to the patient's clinical data, using the primers and conditions described by Rigat et al.[68] Since the insertion fragment (490 bp) is amplified less efficiently than the smaller deletion fragment (190 bp), 3% dimethyl sulfoxide was included,[69] as well as an *Alu* insertion-specific antisense primer, 5′ GTTTTAGCCGGGATGGTCTCGA 3′, as kindly suggested by Dr. K. Chiu. The three primers resulted in bands of 490 and 290 bp for the insertion fragment and 190 bp for the deletion fragment, and allowed unambiguous assignment of the ACE I/D genotype in every case in which polymerase chain reaction (PCR) product was obtained. Approximately 3% (342 of 10,373) of samples failed to yield a PCR product. Clinical information and genotype were entered at separate times into a spreadsheet (FileMaker Pro), and unadjusted χ^2 values were calculated. The level of statistical significance was taken as $p < 0.05$.

RESULTS

To confirm our laboratory's ability to genotype a population correctly, the parents of 82 French control families [Centre d'Etudes des Polymorphismes Humaines (CEPH)] were genotyped at the ACE I/D locus. The ACE D/D frequency was 25.6% (42 of 164), in good agreement with other Caucasian control groups.[8,13,14,18,22,25,34,35,37]

For African-Americans, there is no agreement as to the frequency of the ACE D/D genotype among control subjects. Duru et al.[13] cited a frequency close to that of American and European Caucasians (25%), but this is based on a sample size of only 37 individuals. Rutledge et al.[70] found a D/D frequency of 49% among 40 control subjects. The D/D frequency among African-American controls is likely to be intermediate between these two values, since the ACE D/D frequency of Nigerians without dis-

Table 2. ACE *I/D* Genotyping Results: Patient "Controls"

	White	*Black*	*Hispanic*
Total	1,844	1,042	396
No PCR product	33	24	3
Male	100%	100%	49.7%
Median age (years)	63.8	53.6	60.2
Median BMI	23.2	23.3	23.5
Source	StLVA + Regional	StLVA + Regional	REN
D/D	456 (25.2%)	337 (33.1%)	101 (25.7%)
I/D	945 (52.3%)	509 (50.0%)	187 (47.6%)
I/I	410 (22.7%)	172 (16.9%)	105 (26.7%)

BMI, body mass index (kg/m^2).

Table 3. ACE *I/D* Genotyping Results of Patient Populations from Different Sources

	White				*Black*				*Hispanic*	
	Male		*Female*		*Male*		*Female*		*Male*	*Female*
	StLVA + Regional	*REN*	*StLVA + Regional*	*REN*	*StLVA + Regional*	*REN*	*StLVA + Regional*	*REN*	*REN*	*REN*
Total	2,783	873	228	678	2,377	919	949	966	197	199
No PCR product	58	24	4	15	57	31	25	28	2	1
Median age (years)	65.2	66.4	50.7	65.8	59.4	53.2	52.7	61.3	59.7	60.9
Median BMI	27.0	23.2	29.1	23.3	25.7	23.5	28.9	24.8	24.6	24.6
D/D	773 (28.4%)[1]	300 (35.3%)[2]	69 (30.8%)	199 (30.0%)[1]	787 (33.9%)	337 (38.0%)[3]	306 (33.1%)	334 (35.6%)	44 (22.6%)	57 (28.8%)
I/D	1,354 (49.7%)	375 (44.2%)	114 (50.9%)	342 (51.6%)	1,121 (48.3%)	407 (45.8%)	442 (47.8%)	447 (47.7%)	96 (49.2%)	91 (46.0%)
I/I	598 (21.9%)	174 (20.5%)	41 (18.3%)	122 (18.4%)	412 (17.8%)	144 (16.2%)	176 (19.0%)	157 (16.7%)	55 (28.2%)	50 (25.3%)

BMI, body mass index (kg/m^2).
[1]$p < 0.025$, [2]$p < 0.001$, [3]$p < 0.05$, compared with control group.

ease has been observed to be 35%[71] and 44% (K. Chiu, personal communication). Where it has been measured, African-Americans in urban centers such as Detroit, Oakland, and Pittsburgh have 22–26% Caucasian admixture.[72–74] If we take 35.7% as the ACE D/D frequency in West African control individuals, then the "control" D/D frequency of 33.1% that we arrived at (see below) would suggest 25% Caucasian admixture in our sample of St. Louis African-Americans.

Given the lack of an obvious control group, we chose to perform a disease–disease comparison, using as "control" diseases those (1) without any reported relationship to angiotensin II, (2) in which the D/D frequency for Caucasians was 25%, in agreement with previous Caucasian control groups and our own laboratory's observation using European Caucasian samples, and (3) in Hardy–Weinberg equilibrium. We used the 6,414 St. Louis inpatients and outpatients for this analysis, since there is already abundant evidence for ACE's involvement in end-stage renal disease.[59–61]

The diseases that met these conditions among white males were: type 1 diabetes mellitus (IDDM; $n = 26$), cataracts in patients with type 2 diabetes (NIDDM; $n = 160$), seizure disorder ($n = 145$), peptic ulcer disease ($n = 389$), alcohol abuse ($n = 772$), gastritis ($n = 31$), eczema ($n = 20$), obesity ($n = 125$), and mean triglyceride level above 300 mg/dL ($n = 143$). This yielded a white male control group of 1,811 individuals with the following genotypes: 456 D/D (25.2%), 945 I/D, and 410 I/I (Table 2).

The genotype frequencies of white women were compared with those of the white male control group, since there is no evidence of any gender difference in I and D allele frequencies among healthy controls (CEPH data, not shown).

Among black men, the D/D frequency varied considerably for the same nine diseases: IDDM (36.0%, $n = 25$), cataracts in patients with NIDDM (27.6%, $n = 116$), seizure disorder (36.9%, $n = 214$), peptic ulcer disease (31.7%, $n = 290$), alcohol abuse (33.1%, $n = 1{,}018$), gastritis (24.0%, $n = 50$), eczema (43.8%, $n = 16$), and mean triglyceride level above 300 mg/dL (43.8%, $n = 48$). The average D/D frequency for all nine diseases was 33.1% (589 of 1,777), precisely the D/D frequency for the group of 1,018 ethanol abuse patients (Table 2). Black men with alcohol abuse were therefore used as the comparison disease group ("control") for black male and female patients.

Finally, the reference D/D frequency for Hispanic male and female hemodialysis patients was taken simply as the average of the group (Table 2). This is a conservative choice, since the D/D frequency is elevated among white male and female and black male hemodialysis patients, and tends to be elevated among Hispanic female dialysis patients (Table 3).

The χ^2 statistic was used to determine whether patients with a particular disease deviated significantly in their D/D genotype frequency from the relevant "control" D/D frequency. Disease–disease comparison of the frequencies of all three possible genotypes (D/D, I/D, I/I, with 2 degrees of freedom) almost always yielded the same results as comparison of the two genotype categories, D/D and "I/D plus I/I," with 1 degree of freedom. Thus, any disease–disease difference was due to a difference in D/D frequency, rather than in I/D or I/I frequency.

The population frequency of the ACE D/D genotype appears to vary with age. Among Caucasian centenarians, the ACE D/D frequency was reported to be increased significantly above 25%.[65] However, our data contradicted this result (Table 4). White male patients 80 years or older had a D/D frequency no dif-

Table 4. ACE *D/D* Frequency and Age in White and Black Men

Age	*White men*	*Black men*
≥80 years		
Total	140	177
Unknown	6	4
D/D	37 (27.6%)	69 (39.9%)
I/D	64 (47.8%)	81 (46.8%)
I/I	33 (24.6%)	23 (13.3%)
<40 years		
Total	252	686
Unknown	3	17
D/D	78 (31.3%)[1]	218 (32.6%)
I/D	119 (47.8%)	310 (46.3%)
I/I	52 (20.9%)	141 (21.1%)

[1] $p < 0.05$ versus control group.

TABLE 5. ACE *D/D* ODDS RATIOS (OR): HYPERTENSION AND ITS COMPLICATIONS

	WM		*WF*		*BM*		*BF*		*HM*		*HF*	
	OR	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n
Hypertension												
StL	1.21[1]	857	0.70	47	1.15	877	1.01	234				
LVH by echocardiography												
StL	1.43	86	—		1.22	167	0.65	66				
REN	3.0	10	—		1.07	26	1.2	16	2.0	17[2]		
Atrial fibrillation												
StL	1.24	78	—		0.70	35	0.63	21				
REN	1.19	63	1.67	50	1.32	39	1.26	39	2.0	10[2]		
History of CHF												
StL	1.95[3]	116	—		1.13	164	0.58	54				
REN	1.12	51	1.09	41	1.41	56	2.11[4]	44	2.5	13[2]		
Positive cardiac stress test												
StL	1.13	59	—		0.79	33	—					
Positive cardiac catheterization												
StL	1.20	67	—		1.06	37	—					
REN	2.55[4]	26	1.3	13	0.4	12	1.2	11	—	—		
PTCA												
StL	1.31	37	—		1.4	16	—					
CABG												
StL	1.95[5]	96	—		1.2	16	—					
REN	2.33	25	0.7	16	—		—		—	—		
Myocardial infarction												
StL	1.50[5]	241	1.7	11	1.30	184	1.13	39				
REN	1.76	38	0.59	30	1.01	33	0.67	24	—	—		
Ventricular ectopy (ventricular tachycardia or fibrillation)												
StL	0.9	13	—		—		—					
Chronic renal failure												
StL	1.27	117	—		1.08	175	0.65	33				
End-stage renal disease												
REN	1.18	221	1.20	195	1.07	415	1.36[1]	256	1.55	43	1.52	29
APVD (not otherwise specified)												
StL	1.13	243	—		1.10	184	0.91	42				
REN	1.86[6]	78	1.01	63	0.89	59	1.66	51				
Amputation of toes or legs												
StL	1.9	13	—		0.67	24	—					
REN	2.4	9	—		—		—		—		—	
Revascularization of legs												
StL	1.19	35	—		1.1	17	—					
REN	1.1	11	—		—		—		—		—	

Abdominal aortic aneurysm										
StL	1.53	50	—	1.1	14	—				
REN	0.4	15	—	1.3	10	—			—	—
Claudication										
StL	1.01	55	—	0.56	37	—				
Leg ulcer										
StL	0.3	13	—		0.79	25	—			
REN	—		—		—		0.9	10	—	—
Transient ischemic attack										
StL	1.24	51	—		1.19	27	—			
REN	3.0	10	—		—		—		—	—
Stroke										
StL	1.10	133	—		1.35	135	1.12	28		
REN	1.58[1]	21	1.22	24	1.12	28	1.35	25	—	—
Positive carotid Doppler										
StL	0.96	41	—		0.2	10	—			
REN	4.5[1]	10	—		—		—		—	—
Deep vein thrombosis										
StL	1.1	18	—		1.35	30	—			
Pulmonary embolism										
StL	—		—		2.0	12	—			
Death within 1 year										
REN	1.32	78	0.82	60	1.39	71	1.42	63	—	—
Frequent de-clotting of vascular access (in hemodialysis patients)										
REN	2.3	16	2.6	13	2.02	20	0.6	17	—	

All patients described here had hypertension but not diabetes. For sample sizes <20, the OR is given to only 2 significant figures to indicate reduced confidence.[66] Dashes indicate insufficient data. StL, patients from StLVA and Regional Hospitals; REN, hemodialysis patients; WM, white males; WF, white females; BM, black males; BF, black females; HM, Hispanic males; HF, Hispanic females; LVH, left ventricular hypertrophy; CHF, congestive heart failure; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; APVD, atherosclerotic peripheral vascular disease.

[1]$p < 0.05$, [3]$p < 0.001$, [4]$p < 0.01$, [5]$p < 0.005$, [6]$p < 0.025$ compared with control group.

[2]Pooled data for men and women combined.

ferent from the control value (27.6% vs. 25.2%), whereas white male patients under 40 years of age had a significantly higher frequency than the control value (31.3% vs. 25.2%, $p < 0.05$), suggesting that the D/D genotype was associated with early mortality.

On the other hand, black male patients 80 years or older tended to have a higher D/D frequency than control (39.9% vs. 33.1%, p = NS), consistent with a mildly protective effect of the D/D genotype. Younger black male patients had essentially the same D/D frequency as the control value (32.6% vs. 33.1%).

The ACE D/D frequency and odds ratio for various diseases are given in Tables 5–19. One possible reason for the observed ethnic difference in the relationship between age and ACE D/D frequency may be the lower D/D frequency for myocardial infarction among blacks as compared with whites (Table 8). This is the case for both hypertension (Table 5) and NIDDM (Table 6).

DISCUSSION

Selecting the appropriate control group is critical in any case-control analysis. The most appropriate control group for a study investigating whether a genomic polymorphism might be associated with any cause of adult mortality would be the total population sampled before the onset of any significant adult mortality. Matching for age does not seem advisable when considering the ACE I/D polymorphism. Unfortunately, such a control group was not available; rather, every blood sample came from a patient whose routine clinical care required at least a complete blood count.

The ACE D/D genotype was hypothesized to be pleiotropic, so this study involved multiple comparisons. Since the proper statistical correction for genetic pleiotropy has not yet been established, and since this study is meant to be exploratory rather than definitive, unadjusted data are reported.

Disease–disease comparison of the frequency of each separate genotype yielded virtually identical results as the frequency of D/D versus "$I/D + I/I$." This suggests that the D/D genotype, rather than merely the D allele, is associated with disease. Recessive behavior of the D allele has been observed by other investigators,[34,75,76] and suggests that there may be a threshold effect which the D/D genotype exceeds, but which the I/D genotype does not. The threshold may refer to the local balance between vasoconstrictors and growth promoters on the one hand, and vasodilators and growth inhibitors on the other.[77] Perhaps sufficient vasodilator (e.g., nitric oxide, prostacyclin) is synthesized and released locally to compensate adequately for the effect of a single D allele on local ACE and angiotensin II levels (a 50% increase over zero D alleles),[1] but not enough vasodilator can be made to compensate fully for the larger effect of two D alleles on local angiotensin II levels (a 100% increase over zero D alleles).[1]

Where linkage analysis of pedigrees has been performed, none of the diseases shown in Tables 5–19 has been linked to markers near the ACE gene on chromosome 17q23. Polymorphisms that are significantly associated with a disease, however, cannot always be identified by linkage analysis of affected pedigree members.[78]

Unadjusted odds ratios are presented in Tables 5–19. The D/D genotype appears to be significantly protective for very few diseases [i.e., myocardial infarction in black female patients with NIDDM, coronary artery bypass grafting in black men with NIDDM, and transmetatarsal/toe amputations in black men with NIDDM (Table 6); stage D (metastatic) prostate cancer and PSA antigen >5 in the presence or absence of prostate cancer in white men (Table 9); and carpal tunnel syndrome in black women on hemodialysis (Table 18)]. There are as yet no reports that ACE inhibition increases the incidence or severity of any of these conditions.

On the other hand, the D/D genotype appears to confer susceptibility to a large number of diseases, for many of which there is already abundant evidence of the usefulness of ACE inhibition. If we limit our attention to disease categories with sample sizes of at least 20 patients, and define an odds ratio of ≥1.15 as conferring susceptibility, then many diseases are positively associated with the D/D genotype (Table 20). Among large patient populations, men and women both had a similar fraction of

TABLE 6. ACE *D/D* ODDS RATIOS (OR): TYPE 2 DIABETES MELLITUS (NIDDM) AND ITS COMPLICATIONS

	WM		*WF*		*BM*		*BF*		*HM*		*HF*	
	OR	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n
NIDDM												
StL	1.18	786	1.25	64	0.96	714	1.02	338				
Myocardial infarction												
StL	1.13	243	1.2	14	0.92	154	0.51[1]	74				
REN	0.99	52	1.34	29	1.35	40	0.99	58	1.9	15	1.2	10
CABG												
StL	1.02	121	0.7	5	0.35[2]	27	0.6	9				
REN	1.92	28	1.49	24	1.0	18 (pooled)	1.3	13	2.3	16 (pooled)		—
PTCA												
StL	0.7	15	—		1.3	10	1.0	6				
REN	—		—		(pooled w/CABG)		0.7	12 (pooled)		(pooled w/CABG)		—
Positive cardiac stress test												
StL	1.05	42	1.0	4	0.95	25	0.6	9				
REN	—		—		(pooled w/CABG)		(pooled w/PTCA)			(pooled w/CABG)		—
Positive cardiac catheterization												
StL	1.06	80	—		1.68	33	0.3	16				
REN	2.23[2]	28	1.22	24	1.1	18	1.24	21		(pooled w/CABG)		—
CHF												
StL	1.24	136	—		1.39	140	0.69	86				
REN	1.60	77	2.50[3]	70	1.27	70	1.32	119	1.5	15	1.24	20
Atrial fibrillation												
StL	1.20	59	—		1.60	34	0.9	13				
REN	2.23	21	2.12	24	3.4[1]	16	1.40	22	—		—	
Chronic renal failure												
StL	1.26	141	—		0.87	180	0.83	86				
End-stage renal disease (hemodialysis)												
REN	1.71[3]	296	1.29	264	1.23	285	1.09	447	0.69	114	0.96	123
APVD (not otherwise specified)												
StL	1.25	294	1.7	11	0.85	230	1.01	69				
REN	2.08[3]	119	1.08	86	1.16	104	1.18	187	1.86	23	0.80	23
Transmetatarsal/toe amputation												
StL	2.06	44	—		0.27[4]	43	—					
REN	1.7	11	—		1.4	15	1.8	19	—		—	
BKA												
StL		(pooled w/AKA)	—		0.67	32	—					
REN	3.4[1]	15	3.0	10	0.79	25	1.08	46	—		—	
AKA												
StL	0.77	34 (pooled w/BKA)			1.40	22	—					
REN	—		—		—		1.7	11	—		—	
Amputation (total)												
REN	2.27[1]	30	2.7	19	0.82	45	1.32	76			0.96	20

TABLE 6. ACE *D/D* ODDS RATIOS (OR): TYPE 2 DIABETES MELLITUS (NIDDM) AND ITS COMPLICATIONS (CONT'D)

	WM		*WF*		*BM*		*BF*		*HM*		*HF*	
	OR	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n
Revascularization of legs												
StL	1.62	34	—		0.7	12	—					
Abdominal aortic aneurysm												
StL	1.4	15	—		—		—					
REN	—		—		—		8.1[2]	5				
Claudication												
StL	1.46	79	—		0.92	32	—					
Leg ulcer												
StL	1.43	80	—		0.98	86	—					
REN	2.41[1]	38	0.85	36	0.65	41	1.33	58	—		—	
Transient ischemic attack												
StL	2.03	32	—		1.4	17	—					
REN	—		—		—		1.0	12	—		—	
Stroke												
StL	1.25	135	—		0.96	118	—					
REN	2.08[2]	34	0.65	28	1.89	31	1.14	69	—		—	
Diabetic retinopathy												
Not otherwise specified												
StL	0.66	22	—		0.89	23	1.05	47				
REN	2.15[2]	31	1.04	50	0.89	36	1.28	90	0.85	22	0.6	17
Background												
StL	1.32	127	—		1.25	102	—					
Preproliferative												
StL	0.99	20	—		1.59	25	—					
Proliferative												
StL	1.55	35	—		0.87	20	—					
Diabetic macular edema												
StL	1.10	50	—		1.07	29	—					
Laser photocoagulation												
StL	1.01	55	—		0.94	38	—					
REN	—		1.9	13(pooled)	1.55	30(pooled)	0.88	33(pooled)	—		—	
Cataracts												
StL	1.02	160	—		0.77	116	1.14	36				
REN	1.78	24	0.87	22	1.77	30	1.88[1]	58	—		—	
Neuropathy												
Not otherwise specified												
StL	1.10	63	—		1.76	43	1.3	13				
REN	2.03[2]	32	0.6	18	1.2	19	0.60	26	1.78	21	1.2	10
Feet												
StL	1.16	82	—		1.04	59	0.5	16				
REN	—		1.3	13	0.8	18	1.23	37	—		—	

Gastroparesis												
StL	1.6	17	—		1.01	24	0.6	14				
REN	—		0.71	26	0.87	20	0.97	30	—		—	
Autonomic												
StL	2.6	15	—		0.7	12	—					
REN	—		—		—		1.4	10	—		—	
Neurogenic bladder												
StL	1.0	8	—		—		—					
Impotence												
StL	0.90	86	N/A		1.06	76	N/A					
REN	—		N/A		0.9	10	N/A					
Deep vein thrombosis												
StL	2.12	24	—		0.7	19	—					
Pulmonary embolism												
StL	2.5	11	—		7.1[4]	9	—					
Death within 1 year												
REN	2.29[3]	115	1.07	83	1.10	65	1.24	92	1.53	26	0.92	29
Frequent de-clotting of vascular access (hemodialysis patients)												
REN	1.5	12	0.8	14	1.4	10	1.71	24	—		—	
cf. Frequent de-clots/no NIDDM												
REN	2.3	16	2.6	13	2.02	20	0.6	17	—		—	

All patients described here have NIDDM. See Table 5 for abbreviations. AKA, above-the-knee amputation; BKA, below-the-knee amputation.
[1]$p < 0.025$, [2]$p < 0.05$, [3]$p < 0.001$, [4]$p < 0.005$ compared with control group.

Table 7. ACE *D/D* Odds Ratios (OR): Type 1 Diabetes (IDDM) and Its Complications

	WM		*WF*		*BM*		*BF*		*HM*		*HF*	
	OR	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n
IDDM												
StL	1.04	27	—		1.13	25	2.57[1]	25				
Retinopathy												
StL	0.74	20	—		3.4	8	1.0	9				
REN	2.43	20	1.7	14	1.3	13	1.3	13	2.3	9	—	
Neuropathy												
StL	1.39	22	—		1.2	8	2.0	8				
REN	4.16[1]	24	1.2	17	1.0	15	1.08	20	—		—	
APVD (not otherwise specified)												
StL	1.91	23	—		2.0	6	5.1[1]	7				
REN	3.0[2]	16	1.9	14	3.5[1]	11	0.8	14	—		—	
End-stage renal disease												
REN	2.09[1]	46	1.62	34	1.11	31	0.95	50	0.8	14	0.7	15

All of these patients have IDDM. See Table 5 for abbreviations.
[1]$p < 0.05$, [2]$p < 0.025$ compared with control group.

D/D-associated diseases (Table 20). Combining genders revealed three distinct population patterns (Table 21), suggesting that the ACE *D/D* genotype is associated with more diseases among Caucasians than Hispanics, and with more diseases among Hispanics than African-Americans. This is consistent with population history, in which Hispanics represent the admixture of whites, blacks, and Amerindians (who are genetically similar to Asians).

The odds ratio for hypercholesterolemia and atherosclerotic coronary artery disease is on the order of 1.7. The similar but rather unimpressive odds ratios usually seen for ACE *D/D*[66] (including this study) suggest that ACE may be one of several dozen genes involved in each disease. The larger the odds ratio, assuming an adequate sample size,[66] the more important ACE may be for causation of the disease in question, and the smaller the number of additional interacting genotypes that may exist.

Given the large number of common diseases associated with the *D/D* genotype, we hypothesize that ACE overactivity is important in their pathogenesis. That ACE inhibition can have a large clinical effect in diseases in which the ACE *D/D* odds ratio is only modestly elevated[80] suggests at least two possibilities. One is that another polymorphism within the ACE gene exists with much higher odds ratios than the *I/D* locus. This seems unlikely for two reasons. The first is that at least 17 polymorphisms, covering a region of 5.6 centiMorgans (~5–6 million bases), are in strong linkage disequilibrium with the *I/D* locus[81] (i.e., the *I* and *D* alleles represent extended haplotypes rather than a single locus). The second reason is that the ACE gene has been extensively studied for over a decade, and no more explanatory polymorphism than the *I/D* locus has been described. The possibility of there being another polymorphism within the ACE gene with a higher odds ratio for disease seems very unlikely.

The more attractive possibility is that ACE is an early rate-limiting step for multiple disease pathways (Fig. 1). The clinical effectiveness of inhibiting ACE suggests that it functions early in pathogenesis. Diseases, like the cell biological protein pathways upon which they are based, involve "cascades" of linked steps (proteins) with amplification typical of each step. The most credible way that a single drug could effectively inhibit a multistep cascade is if the target of the drug acts at a very early step in the disease pathway, before amplification steps have occurred with recruitment of many additional proteins (i.e., targets of additional drugs).

We therefore hypothesize that ACE is a "master" disease gene. Since there can only be a limited number of origins, there can be only a limited number of such susceptibility genes that are shared by many common diseases. In-

TABLE 8. ACE *D/D* ODDS RATIOS (OR): CARDIOLOGY

	WM		*WF*		*BM*		*BF*		*HM*		*HF*	
	OR	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n
Atrial fibrillation												
StL	1.21	193	0.9	9	1.10	79	0.67	40				
REN	1.19	63	1.67	50	1.32	39	1.26	39	2.0	10[1]		
Supraventricular tachycardia												
StL	1.40	25 (w/REN)	—		0.9	10	1.7	13 (w/REN)				
REN	(pooled w/StL)		—		0.4	13	(pooled w/StL)		—		—	
Ventricular ectopy												
StL	0.95	33	—		1.4	15 (w/REN)	—					
REN	1.7	11	0.6	6	(pooled w/StL)		—		—		—	
Pacemaker												
StL	1.31	49	—		2.0	16	1.6	9				
REN	1.7	11	1.2	17	0.5	10	0.7	15	—		—	
Aortic valve replacement												
StL	1.49	21	—		1.1	17 (w/REN)	—					
REN	2.0	10	—		(pooled w/StL)		—		—		—	
Aortic stenosis												
StL	0.89	26	—		2.0	14	—					
REN	1.1	11	—		(pooled w/StL)		—		—		—	
Aortic regurgitation												
StL	0.83	32	—		1.74	26	—					
REN	—		—		2.0	2	—		—		—	
Mitral valve replacement												
StL	1.9	13 (w/REN)	—		0.9	10 (w/REN)	—					
REN	(pooled w/StL)		2.0	5	(pooled w/StL)		—		—		—	
Mitral regurgitation												
StL	1.22	24	—		0.56	23	—					
REN	—		0.7	5	0.4	6	—		—		—	
Mitral stenosis												
StL	6.0	3	—		0.7	4 (w/REN)	—					
REN	—		—		(pooled w/StL)		—		—		—	
Dilated cardiomyopathy												
StL	1.24	126	1.4	19	0.93	149	0.75	81				
REN	1.83	76	1.53	47	1.08	69	1.19	54	1.2	10	1.0	8
Death within 1 year												
REN	1.84[2]	254	1.09	190	1.15	162	1.27	179	1.58	34	1.13	32
Myocardial infarction												
StL	1.26[3]	648	1.27	30	1.10	393	0.78	129				
REN	1.21	107	1.01	67	1.10	79	0.88	96	1.45	24	1.6	14
CHF												
StL	1.49[4]	323	1.4	19	1.19	342	0.65	152				
REN	1.44[5]	156	1.72[2]	128	1.34	138	1.37	183	1.86	23	1.31	32

TABLE 8. ACE *D/D* ODDS RATIOS (OR): CARDIOLOGY (CONT'D)

	WM		*WF*		*BM*		*BF*		*HM*		*HF*	
	OR	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n
APVD												
StL	1.18	710	1.09	26	1.00	474	0.97	130				
REN	1.87[2]	254	1.25	176	1.13	178	1.24	256	1.45	36	0.89	34
Stroke												
StL	1.14	354	0.9	18	1.10	289	0.82	97				
REN	1.64[5]	73	0.97	57	1.40	66	1.08	100	2.4	11	2.2	7
Frequent de-clotting of vascular access (hemodialysis patients)												
REN	1.81	37	1.41	31	1.67	31	1.15	44	0.5	7	2.9	8
Deep vein thrombosis												
StL	1.42	71	—		1.14	61	1.08	23				
Pulmonary embolism												
StL	1.49	27	—		3.36[6]	24	0.7	8				

Patients are presented without regard to whether their underlying disease is diabetes or hypertension. See Table 5 for abbreviations.
[1]Pooled data for men and women combined.
[2]$p < 0.001$, [3]$p < 0.025$, [4]$p < 0.005$, [5]$p < 0.05$, [6]$p < 0.01$.

TABLE 9. ACE *D/D* ODDS RATIOS (OR) OF COMMON CANCERS

	WM		*WF*		*BM*		*BF*		*HM*		*HF*	
	OR	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n
Lung cancer												
StL	1.11	103	0.4	8 (w/REN)	1.79[1]	51	1.2	16 (w/REN)				
<50 pk-yrs	1.4	16	—		1.66	20	—					
>65 pk-yrs	0.79	38	—		1.4	12	—					
REN	0.6	6	(pooled w/StL)		0.7	4	1.3	18 (pooled w/StL)	—		—	
Colon polyps												
StL	1.25	91	0.9	13 (w/REN)	0.98	40	1.1	17				
REN	—		(pooled w/StL)		0.3	16	0.4	17	—		—	
Colon cancer												
StL	1.25	81	0.7	15 (w/REN)	1.20	51	1.35	20				
REN	3.0	10	(pooled w/StL)		0.9	10	1.35	20	—		—	
BPH												
StL	1.42[2]	452	N/A		1.08	316	N/A					
REN	1.11	42	N/A		0.67	28	N/A		—		N/A	
Transurethral resection of the prostate for BPH												
StL	1.74[3]	222	N/A		1.23	137	N/A					
REN	0.63	23	N/A		0.7	8	N/A		—		N/A	
Prostate cancer												
StL	1.13	178	N/A		1.19	172	N/A					
Stage A	—		N/A		0.5	5	N/A					
Stage B	0.4	19	N/A		1.85	23	N/A					
Stage C	—		N/A		0.9	10	N/A					
Stage D	0.13[2]	23	N/A		0.91	29	N/A					
PSA antigen												
<5, + prostate cancer												
StL	1.45	58			0.74	41						
>5, + prostate cancer												
StL	0.39[1]	43			1.44	61						
>10, + prostate cancer												
StL	0.12[4]	25			1.27	44						
>15, + prostate cancer												
StL	0.16[1]	20			1.18	38						
<5, no prostate cancer												
StL	1.26	330			1.08	205						
>5, no prostate cancer												
StL	0.51[1]	64			1.03	83						
>10, no prostate cancer												
StL	0.6	18			1.28	36						
>15, no prostate cancer												
StL	—				1.24	21						
Prostate cancer												
REN	1.65	28	N/A		2.3	15	N/A		—		N/A	

TABLE 9. ACE *D/D* ODDS RATIOS (OR) OF COMMON CANCERS

	WM		*WF*		*BM*		*BF*		*HM*		*HF*	
	OR	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n
Skin cancer (not otherwise specified)												
StL	1.35	115	0.4	16 (w/REN)	—		—					
REN	1.5	9	(pooled w/StL)		—		—		—		—	
Melanoma (StL + REN)	0.7	10	3.0	2	—		—		—		—	
Basal cell cancer												
StL	2.36[2]	52	—		—		—					
REN	6.0	3	1.5	6	—		—		1.4	2[5]		
Pancreatic cancer	2.0	10	(StL + REN pooled)[5]		2.1	8	(StL + REN pooled)[5]					
Liver cancer	1.5	3	(StL + REN pooled)[5]		8.1[4]	5	(StL + REN pooled)[5]					
Multiple myeloma	1.5	12	(StL + REN pooled)[5]		1.24	21	(StL + REN pooled)[5]					
Myelodysplastic syndrome												
StL	4.0	7[5]			—		—		—		—	
Lymphoma (total)	1.58	23	(StL + REN pooled)[5]		0.9	10	(StL + REN pooled)[5]		—		—	
Non-Hodgkin's lymphoma	1.7	14	(StL + REN pooled)[5]		—		—		—		—	
Hodgkin's lymphoma	1.2	7	(StL + REN pooled)[5]		—		—		—		—	
Renal cell cancer												
StL	1.57	26	—		1.7	13	1.2	8 (w/REN)				
REN	2.6	15	1.1	11	0.5	15	(pooled w/StL)					
Ear-nose-throat cancer												
StL	1.32	65	—		1.56	39	1.0	9				
<50 pk-yr	0.3	11	—		1.0	15						
>65 pk-yrs	1.49	21	—		5.0[1]	7	(>50 pk-yr)					
Bladder cancer												
StL	2.15[2]	62	—		0.7	12	0.7	4 (w/REN)				
<50 pk-yr	0.6	12	—									
>65 pk-yrs	1.9	13	—									
REN	1.8	8	—									
Leukemia	1.58	23	(StL + REN pooled)[5]		2.4	11	(StL + REN pooled)[5]					
Chroic leukemia												
CML + CLL	1.98	20	(StL + REN pooled)[5]		4.0	9	(StL + REN pooled)[5]					
CLL	3.6[1]	11	(StL + REN pooled)[5]									
Fibrocystic breast disease												
StL			1.0	4			1.6	9				
Breast cancer												
StL			0.2	16			0.93	51				
REN			1.2	14			0.56	23				
Cervical cancer	N/A		0.6	6 (StL + REN pooled)			2.4	16 (StL + REN pooled)				
Esophageal cancer												
StL	8.9[2]	8	—		0.6	14[5]						
Uterine fibroids												
StL	N/A		—		N/A		0.81	35	N/A		—	

See Table 5 for abbreviations. BPH, benign prostatic hyperplasia; CML, chronic myelogenous leukemia; CLL, chronic lymphocytic leukemia; pk-yr, pack years of cigarettes smoked; N/A, not applicable.

[1]$p < 0.05$, [2]$p < 0.005$, [3]$p < 0.001$, [4]$p < 0.025$.

[5]Pooled data for men and women combined.

TABLE 10. ACE *D/D* ODDS RATIOS (OR) OF PULMONARY DISEASES

	WM		*WF*		*BM*		*BF*		*HM*		*HF*	
	OR	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n
COPD												
StL	1.29[1]	645	1.24	34	1.01	292	0.88	79				
<50 pk-yr	1.09	153	0.7	11 (w/REN)	0.90	94	1.32	38				
>50 pk-yr	1.42[1]	229	0.5	13	1.08	80	0.9	13				
REN	1.66	67	0.48	38	0.74	45	1.31	28	1.5	9[2]		
Asthma												
StL	0.74	55	1.72	30	0.97	93	0.82	125				
REN	3.6[3]	11	0.8	14	1.3	18	1.19	27	0.5	7[2]		
Pulmonary hypertension												
StL	1.39	22	1.0	8 (w/REN)	1.08	20	—					
REN	1.2	7	(pooled w/StL)		0.5	10	1.4	15	—		—	
Obstructive sleep apnea												
StL	0.93	67	1.2	7 (w/REN)	1.01	33	0.7	12				
Cigarette abuse												
<1 ppd												
StL	1.38	60	2.4	9 (w/REN)	0.98	227	0.96	103				
REN	3.0	4	(pooled w/StL)		—		—		—		—	
>1 ppd												
StL	1.33	623	0.99	44	1.04	266	1.43	53				
REN	1.5	9	—		—		—		—		—	
<30 pk-yr												
StL	1.04	350	1.55	35	1.03	544	1.02	206				
REN	2.5	11	—		—		—		—		—	
>30 pk-yr												
StL	1.25	748	1.21	45	1.01	442	0.86	94				
>50 pk-yr												
StL	1.43	489	1.05	23	0.96	209	0.95	25				
>75 pk-yr												
StL	1.43	295	—		1.27	83	—					
>100 pk-yr												
StL	1.35	109	—		1.13	25	—					
>125 pk-yr												
StL	1.32	52	—		0.9	10	—					
Deep vein thrombosis												
StL	1.42	71	0.3	10 (w/REN)	1.14	61	1.08	23				
Pulmonary embolism												
StL	1.49	27	—		3.36[4]	24	0.6	13 (w/REN)				

See Table 5 for abbreviations. COPD, chronic obstructive pulmonary disease; pk-yr, pack-years of cigarettes smoked; ppd, packs per day.
[1]$p < 0.025$; [3]$p < 0.05$, [4]$p < 0.005$.
[2]Pooled data for men and women combined.

TABLE 11. ACE *D/D* ODDS RATIOS (OR) OF ENDOCRINOLOGIC DISEASES

	WM		*WF*		*BM*		*BF*		*HM*		*HF*	
	OR	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n
Gout												
StL	1.39	141	—		0.77	195	1.35	25				
REN	1.59	43	4.0[1]	14	0.93	54	1.21	40	0.9	17[2]		
Hypothyroidism												
StL	0.89	39	0.6	19	1.71	24	0.6	23				
REN	—		2.2	19	—		2.0	14	—		—	
Obesity												
StL	1.02	125	0.6	19	0.97	102	1.01	59				
REN	0.6	6	—		0.8	7	1.01	21	—		—	
BMI												
>35												
StL	1.18	228	1.30	56	1.15	182	1.06	201				
REN	1.40	25	1.43	43	0.91	42	1.08	72	—		—	
>30												
StL	1.13	702	1.73[3]	88	1.04	502	1.04	343				
REN	1.33	71	1.29	99	1.27	124	1.08	192	—		—	
<20												
StL	0.95	202	1.1	18	1.26	271	0.83	79				
REN	1.64[1]	132	1.57[1]	156	1.16	175	1.01	150	—		—	
Cholesterol												
>200 mg/dL												
StL	1.14	767	1.22	62	1.03	602	0.89	273				
REN	1.72[4]	128	1.59[4]	195	1.05	112	0.93	254	1.53	26	1.09	51
<200 mg/dL												
StL	1.21	751	1.07	65	1.03	738	1.06	256				
REN	1.59[5]	702	1.15	447	1.27[1]	758	1.20	670	0.73	168	1.21	142
<150 mg/dL												
StL	1.17	232	0.57	25	1.25	286	1.20	94				
REN	1.76[5]	315	1.25	152	1.25	361	1.17	204	0.55	81	0.57	55
>250 mg/dL, triglycerides >300 mg/dL (mixed hyperlipidemia)												
StL	0.80	61	1.2	7	1.8	19	2.0	10				
REN	0.2	14	1.75	27	3.2[3]	18	0.9	16	—		1.2	7
<150 mg/dL, triglycerides <150 mg/dL												
StL	1.53	47	0.6	19	1.12	143	1.03	80				
REN	1.70[5]	242	1.15	111	1.18	295	1.17	161	0.51	53	0.62	34
Triglycerides												
>300 mg/dL												
StL	1.00	143	1.0	8	1.57	48	1.8	7				
REN	1.55[6]	99	1.12	84	2.33[3]	28	1.19	54	—		—	
>250 mg/dL												
StL	0.96	180	2.0	15	1.36	82	1.12	28				
REN	1.73[4]	144	1.04	131	1.88[3]	58	1.40	93	—		—	
>200 mg/dL												
StL	1.09	253	1.58	23	1.12	126	1.16	71				
REN	1.62[5]	230	1.14	223	1.41	124	1.39	174	—		—	
<200 mg/dL												
StL	1.39[3]	290	1.08	80	1.08	560	0.93	433				
REN	1.64[5]	607	1.34[3]	427	1.20[6]	754	1.07	757	—		—	
<150 mg/dL												
StL	1.37	194	0.95	59	1.05	454	0.94	364				
REN	1.58[5]	466	1.12	282	1.11	595	1.09	615	—		—	
Hyperparathyroidism												
Primary StL	1.2	7	—		0.6	13	—					
Tertiary REN	1.0	8	0.9	9	2.4	11	0.7	8	—		—	
Renal osteodystrophy												
REN	0.7	5	0.3	12	1.1	17	0.5	10	—		—	
Paget's disease												
StL	—		—		1.5	7	—					
Osteoporosis												
StL	0.3	10	2.0	5 (w/REN)	—		2.0	5 (w/REN)	—		—	

See Table 5 for abbreviations. BMI, body mass index (kg/m^2).
[1]$p < 0.01$, [3]$p < 0.025$, [4]$p < 0.005$, [5]$p < 0.001$, [6]$p < 0.05$.
[2]Pooled data for men and women combined.

TABLE 12. ACE *D/D* ODDS RATIOS (OR) OF GASTROENTEROLOGIC DISEASES

	WM		*WF*		*BM*		*BF*		*HM*		*HF*	
	OR	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n
Alcoholic hepatitis												
StL	0.90	60	—		0.81	84	1.4	12				
REN	—		—		0.5	5	—		—		—	
Alcoholic cirrhosis												
StL	0.94	83	1.5	3 (w/REN)	1.07	84	1.8	15				
Alcoholic pancreatitis												
StL	0.74	45	—		0.94	60	1.2	19				
REN	—		2.1	12	—		1.52	28	—		—	
Esophageal varices												
StL	0.6	18	—		0.5	15	2.0	4				
Ascites (and alcoholic cirrhosis)												
StL	0.3	11	—		1.7	13	1.2	8				
Gastro-esophageal reflux disease												
StL	1.50[1]	191	1.27	20 (w/REN)	0.94	85	0.87	30				
REN	0.9	13		(pooled w/StL)	2.3	17	1.6	16	—		1.9	5
Hiatal hernia												
StL	1.17	166	1.3	10	0.81	56	0.60	26				
REN	2.0	15	2.4	9	2.0	10	0.67	20	—		—	
Peptic ulcer disease												
StL	0.98	382	0.99	24	0.94	290	0.77	80				
REN	1.38	63	0.79	38	0.87	63	1.59	50	1.3	13	0.6	6
Esophagitis												
StL	1.27	20	—		0.7	12	—					
REN	0.5	7	—		—		0.4	6	—		—	
Gastritis												
StL	1.03	31	1.1	15 (w/REN)	0.64	50	1.08	20				
REN	1.5	18	0.9	9	1.1	14	1.15	22	—		—	
Cholecystectomy												
StL	1.13	149	1.27	40	0.99	55	1.94[1]	53				
REN	2.14[1]	43	1.53	50	0.8	17	1.14	47	1.0	4	0.4	8
Diverticulosis												
StL	0.44[2]	62	—		0.69	47	1.1	14				
REN	1.30	23	2.06	22	1.4	17	1.64	29	—		—	
Diverticulitis												
StL	2.4	18	—		0.7	8	1.6	9				
REN	1.0	4	—		—		—		—		—	
Irritable bowel syndrome												
StL	2.3	14	1.0	4 (w/REN)	4.0	3	2.0	2				
Inflammatory bowel disease												
StL	1.3	13	2.2	7 (w/REN)	1.2	8	1.4	5				
REN	1.8	8		(pooled w/StL)	—		—		—		—	

TABLE 12. ACE *D/D* ODDS RATIOS (OR) OF GASTROENTEROLOGIC DISEASES (CONT'D)

	WM		*WF*		*BM*		*BF*		*HM*		*HF*	
	OR	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n
Inguinal hernia repair												
StL	1.44[1]	46	3.0	4 (w/REN)	2.0	16	—					
Viral hepatitis A												
StL	5.2[3]	11	—		0.9	16	0.5	5				
REN	—		—		0.8	7	—		—		—	
Viral hepatitis B												
StL	1.39	22	—		1.08	40	0.5	11				
REN	1.5	6	—		2.0	18	1.0	12	—		—	
Viral hepatitis C												
StL	0.52	40	—		1.05	91	0.5	15				
REN	1.3	10	—		1.35	45	2.7	14	—		—	

See Table 5 for abbreviations.
[1]$p < 0.025$, [2]$p < 0.05$, [3]$p < 0.005$.

TABLE 13. ACE *D/D* ODDS RATIOS (OR) OF NEUROLOGIC DISEASES

	WM		*WF*		*BM*		*BF*		*HM*		*HF*	
	OR	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n
Alzheimer's disease												
StL	0.52	20	—		1.5	14	1.4	10 (w/REN)				
Multi-infarct dementia												
StL	1.72	30	—		0.94	41	2.0	8 (w/REN)				
REN	—		—		1.4	5	(pooled w/StL)		—		—	
Dementia (not otherwise specified)												
StL	0.87	44	—		1.32	48	2.8	12				
REN	3.4[1]	15	0.7	5	1.0	12	1.3	18	—		—	
Parkinson's disease												
StL	1.05	42	3.0	6 (w/REN)	2.3	17	1.6	9 (w/REN)				
REN	5.9[2]	9	(pooled w/StL)		1.4	5	(pooled w/StL)		—		—	
Multiple sclerosis												
StL	1.9	13	—		8.2[1]	5	1.0	6 (w/REN)				
Migraine headaches												
StL	0.6	18	1.2	7 (w/REN)	0.7	15	1.2	16				
Headaches (not migrainous)												
StL	1.2	14	—		1.52	21	1.3	13				
Seizure disorder												
StL	1.02	145	1.3	10	1.18	214	1.33	63				
REN	1.98	25	0.59	30	0.95	44	0.94	60	1.2 10[3]			
Hearing loss												
StL	2.6[4]	17 (w/REN)	—		5.0[4]	7 (w/REN)	—					

See Table 5 for abbreviations.
[1]$p < 0.025$, [2]$p < 0.005$, [4]$p < 0.05$.
[3]Pooled data for men and women combined.

TABLE 14. ACE *D/D* ODDS RATIOS (OR) OF PSYCHIATRIC DISEASES

	WM		*WF*		*BM*		*BF*		*HM*		*HF*	
	OR	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n
Bipolar affective disorder												
StL	2.85[1]	49	1.2	7 (w/REN)	1.4	15 (w/REN)	0.3	8 (w/REN)				
Schizophrenia												
StL	1.27	87	—		0.89	85	0.8	11 (w/REN)				
Depression												
StL	1.22	343	1.62	34	0.90	176	0.89	85				
REN	1.61	54	0.97	53	1.35	30	1.95[2]	57	—		—	
Anxiety												
StL	1.10	96	0.9	17 (w/REN)	0.7	20 (w/REN)	0.9	19 (w/REN)				
Drug abuse												
Not otherwise specified												
StL	0.71	26	4.0	7 (w/REN)	0.83	55	0.6	9 (w/REN)				
REN	2.1	12	(pooled w/StL)		1.01	27	1.84	20 (all REN drug abuse pooled)				
Cocaine												
StL	1.03	62	1.8	8	1.08	290	0.90	62				
REN	—		—		1.85	46	1.7	11	—		—	
Heroin												
StL	1.19	28	4.0	7	1.23	119	0.59	22				
REN	—		—		8.1[1]	15	—					
Marijuana												
StL	1.52	65	1.5	6	0.98	144	0.89	36				
REN	—		—		1.2	8	—					
Alcohol abuse												
StL	1.01	774	1.24	34	1.00	1,018	1.00	148				
REN	1.49	21	—		1.06	67	0.77	29	—		—	

See Table 5 for abbreviations.
[1]$p < 0.001$, [2]$p < 0.025$.

TABLE 15. ACE *D/D* ODDS RATIOS (OR) OF RENAL DISEASES

	WM		*WF*		*BM*		*BF*		*HM*		*HF*	
	OR	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n
Kidney stones												
StL	1.16	64	2.2	14 (w/REN)	1.52	21	2.0	8 (w/REN)				
REN	1.3	10	(pooled w/StL)		—		(pooled w/StL)		—		—	
Membranous glomerulonephritis												
StL + REN	0.8	14	4.0	7	0.9	19	3.1	5	—		—	
IgA glomerulonephritis												
StL + REN	2.1	12	4.0	7	>5	3	1.0	3	—		—	
Obstructive uropathy												
StL + REN	1.98	25	1.0	4	0.76	22	—		—		—	
Acquired renal cystic disease												
REN	—		0.4	9	2.5	18	1.6	9	4.3	5[1]		
Membranoproliferative glomerulonephritis												
StL + REN	1.5	3	3.0	4	1.4	5	—		—		—	
Amyloidosis												
StL + REN	1.0	4	—		—		—		—		—	
Autosomal dominant polycystic kidney disease												
StL + REN	1.25	27	—		1.0	6	—		—		—	
Systemic lupus erythematosus												
StL	0.7	5 (w/REN)	—		1.0	9 (w/REN)	2.0	8				
REN	(pooled w/StL)		1.91	23	(pooled w/StL)		1.01	42	1.4	6[1]		
Focal segmental glomerulosclerosis												
StL	1.04	27 (w/REN)	—		2.0	18	—					
REN	(pooled w/StL)		1.5	12	1.12	28	0.6	31	1.2	7[1]		
HIV-associated nephropathy												
StL	—		—		0.8	7	—					
REN	—		—		2.49[2]	29	2.0	8	—		—	

See Table 5 for abbreviations.
[1]Pooled data for men and women combined.
[2]$p < 0.025$.

TABLE 16. ACE *D/D* ODDS RATIOS OF OPHTHALMOLOGIC DISEASES

	WM		*WF*		*BM*		*BF*		*HM*		*HF*	
	OR	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n
Cararacts												
Total												
StL	1.14[1]	353	3.5[2]	13	0.95	228	1.08	46				
REN	1.31	49	1.29	45	1.46	50	1.89[3]	93	1.0	12	1.9	10
In patients with NIDDM												
StL	1.02	160	3.0	6	0.77	116	1.14	36				
REN	1.78	24	0.87	22	1.77	30	1.88[2]	58	1.1	11	1.9	10
In patients without NIDDM												
StL	1.26	191	4.0	7	1.18	111	0.3	7				
REN	0.66	22	1.98	20	1.1	17	2.29[2]	32	—		—	
Glaucoma												
StL	1.56[1]	119	0.8	14 (w/REN)	1.13	186	1.08	40				
REN	2.0	10	(pooled w/StL)		1.2	16	0.9	16	1.0	4[4]		

See Table 5 for abbreviations.
[1]$p < 0.05$, [2]$p < 0.025$, [3]$p < 0.005$.
[4]Pooled data for men and women combined.

Table 17. ACE *D/D* Odds Ratios (OR) of Allergic, Immunologic, and Infectious Diseases

	WM		*WF*		*BM*		*BF*		*HM*		*HF*	
	OR	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n
Allergy to penicillin or sulfa												
StL	3.3[1]	17	—		0.8	7	—					
Allergic sinusitis												
StL	1.86[2]	52	—		1.17	30	0.8	11				
Allergic rhinitis												
StL	0.9	17	6.0	3	1.4	5	0.8	7				
HIV												
StL	1.6	17	—		1.35	50	3.0	10				
REN	—		—		2.59[3]	33	2.0	8	—		—	
AIDS												
StL	0.9	9	—		1.26	26	1.5	7 (w/REN)				
REN	—		—		8.1[4]	15	(pooled w/StL)		—		—	
Tuberculosis												
StL	1.13	29	—		1.68	44	1.4	5				
Pelvic inflammatory disease												
StL	N/A		—		N/A		1.2	11				

See Table 5 for abbreviations. N/A, not applicable.
[1]$p < 0.01$, [2]$p < 0.05$, [3]$p < 0.005$, [4]$p < 0.001$.

dividual diseases are likely to be distinguished by additional genetic polymorphisms that confer organ specificity; these remain to be determined.

Since ACE inhibitors have superior, although not yet fully explained, clinical efficacy, and an established safety profile, our data suggest many additional disease targets for the therapeutic use of ACE inhibitors. Furthermore, since the ACE *D/D*-associated diseases described here are largely age-dependent, it may be possible to lower all-cause morbidity and even mortality, especially for individuals with the ACE *D/D* genotype, by the early, perhaps even presymptomatic, administration of an ACE inhibitor. Whether ACE inhibition increases the incidence or severity of diseases with a "protective" *D/D* odds ratio (e.g., ≤ 0.60) remains to be seen. On balance, however, more good than harm seems likely to come from ACE inhibition at the population level (Table 21).

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Table 18. ACE *D/D* Odds Ratios (OR) of Rheumatologic and Orthopedic Diseases

	WM		*WF*		*BM*		*BF*		*HM*		*HF*	
	OR	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n
Systemic lupus erythematosus												
StL	0.7	6 (w/REN)	1.0	4	1.2	8 (w/REN)	1.6	18				
REN	(pooled w/StL)		1.91	23	(pooled w/REN)		0.92	42	1.0	6[1]		
Rheumatoid arthritis												
StL	1.19	28	1.1	11 (w/REN)	2.0	14	0.8	7				
REN	—		(pooled w/StL)		—		1.5	7	—		—	
Osteoarthritis ("degenerative joint disease")												
StL	1.16	720	1.66	53	1.11	485	0.93	204				
REN	1.23	58	1.80[2]	61	1.22	53	1.14	72	0.7	5	2.9	10
Total knee replacement												
StL	1.27	20	0.7	5 (w/REN)	0.9	10	—					
Hip replacement												
StL	1.05	42	1.5	6 (w/REN)	1.13	25	2.0	4 (w/REN)				
REN	3.0	4	(pooled w/StL)		—		(pooled w/StL)		—		—	
Degenerative disc disease												
StL	0.7	71	3.0	4 (w/REN)	0.79	32	0.9	10 (w/REN)				
Carpal tunnel syndrome												
StL	0.96	37	0.66	22 (w/REN)	0.5	15	1.1	17				
REN	1.1	11	(pooled w/StL)		0.9	13	0.35[3]	62	—		—	
Scleroderma												
StL + REN	—		3.0	2	—		4.0	3	—		—	
Sarcoidosis												
StL	1.0	4	—		0.8	14 (w/REN)	0.8	14 (w/REN)				

See Table 5 for abbreviations.
[1]Pooled data for men and women combined.
[2]$p < 0.05$, [3]$p < 0.005$.

Table 19. ACE *D/D* Odds Ratios (OR) of Dermatologic Diseases

	WM		*WF*		*BM*		*BF*		*HM*		*HF*	
StL	*OR*	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n	*OR*	n
Eczema	0.99	20	—		1.6	16	1.0	3[1]				
Psoriasis	1.49	21	—		0.5	5						

WM, white male; WF, white female; BM, black male; BF, black female; HM, Hispanic male; HF, Hispanic female.
[1]Pooled with REN.

Table 20. Number of Disease Categories for Which ACE *D/D* Is a Susceptibility [Odds Ratio (OR) ≥1.15] Versus a Protective (OR ≤0.60) Genotype

	WM	*WF*	*BM*	*BF*	*HM*	*HF*
Number of disease categories	219	78	196	132	14	13
Number of diseases with						
OR ≥1.15	157 (71.7%)	46 (59.0%)	79 (40.3%)	50 (37.9%)	9 (64.3%)	4 (30.8%)
OR ≤0.60	8 (3.7%)	4 (5.1%)	4 (2.0%)	7 (5.3%)	3 (21.4%)	1 (7.7%)

WM, white male; WF, white female; BM, black male; BF, black female; HM, Hispanic male; HF, Hispanic female. Only diseases with sample sizes of at least 20 patients were considered.

Table 21. Clinical Role of ACE *D/D* Genotype Different Ethnic Groups

Number of diseases	*Whites*	*Blacks*	*Hispanics*
To which *D/D* predisposes	203 (68.4%)	129 (39.3%)	13 (48.1%)
Against which *D/D* protects	12 (4.0%)	11 (3.4%)	4 (14.8%)

Shown are the numbers of diseases with a sample size of ≥20, for which *D/D* either predisposes to, or protects from, disease. Data are from Table 20, pooling both genders.
$p < 0.001$, whites versus blacks; $p < 0.05$, blacks versus Hispanics; $p < 0.025$, whites versus Hispanics.

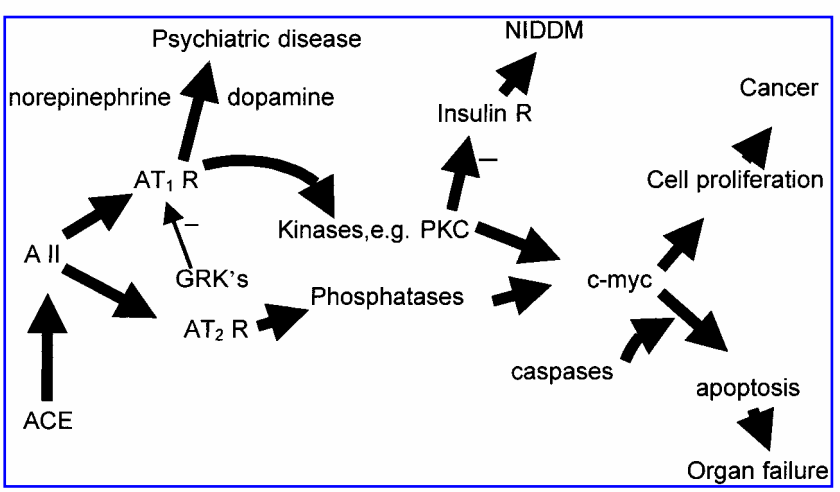

FIG. 1. Hypothetical scheme for ACE at the origin of many common diseases. AII, angiotensin II; AT_1R, angiotensin II type 1 receptor; AT_2R, angiotensin II type 2 receptor; GRKs, G-protein receptor kinases; "norepinephrine" and "dopamine" refer to the synthesis, release, transport, and reuptake proteins for these neurotransmitters; PKC, protein kinase C; Insulin R, insulin receptor, down-regulated by PKC (see White et al.[79]). The AT_1R appears to be involved in vasoconstriction, interaction with catecholamines such as norepinephrine and dopamine, inhibition of the insulin receptor, and stimulation of cell proliferation, whereas the AT_2R appears to mediate apoptosis through phosphatases such as mitogen-activated protein kinase phosphatase-1 (see Gallinat et al.[82]).

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