ANGIOTENSIN CONVERTING ENZYME POLYMORPHISM IN SAUDIS

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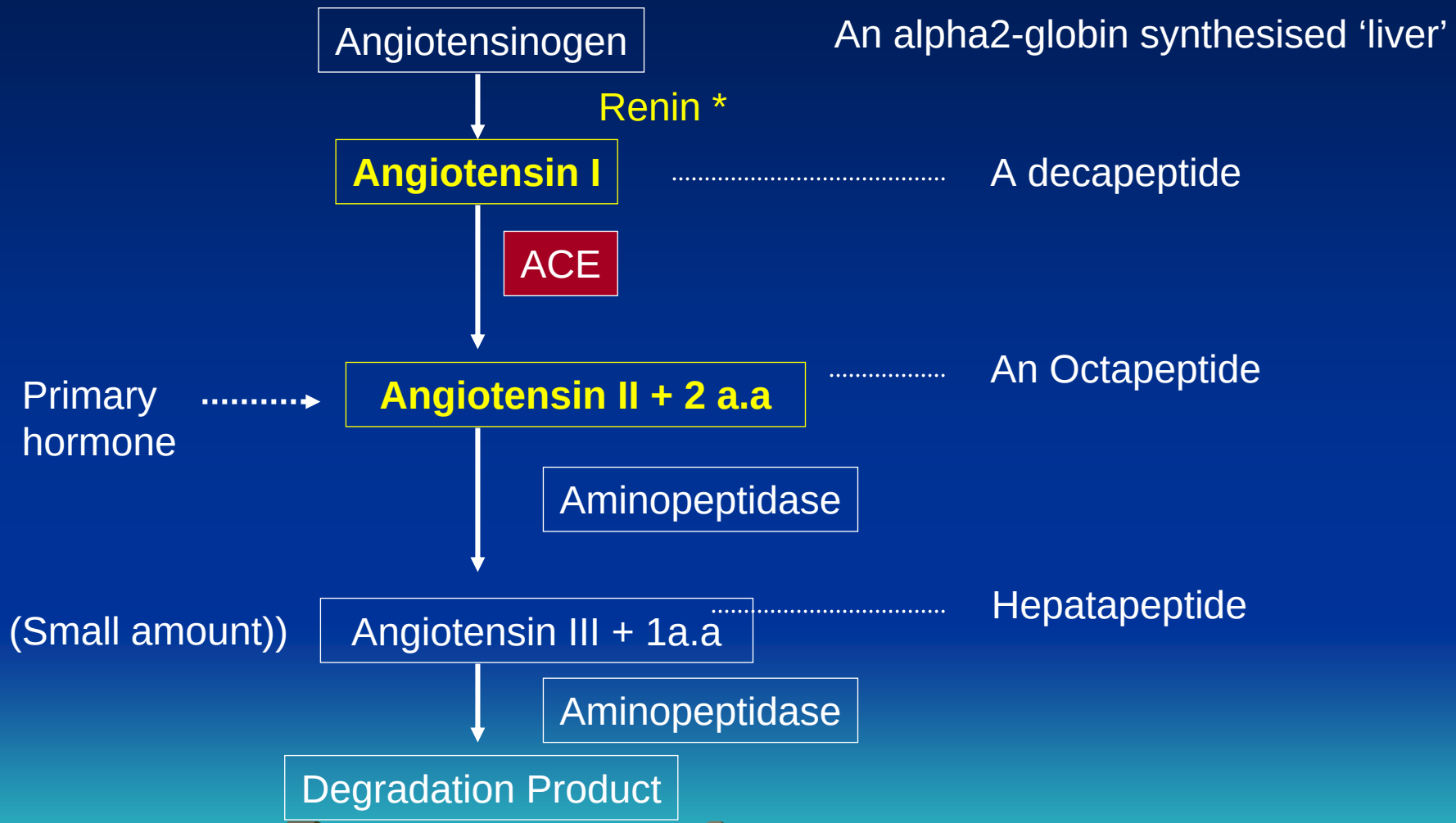
Presentation Outline

- Introduction to ACE- structure and function.
- Genetic aspects of ACE.
- Insertion/deletion polymorphism.
- Studies in Saudis.
- Results in Saudis.
- Comparison of results with other populations.
- Discussion of the results.

ANGIOTENSIN CONVERTING ENZYME (ACE)

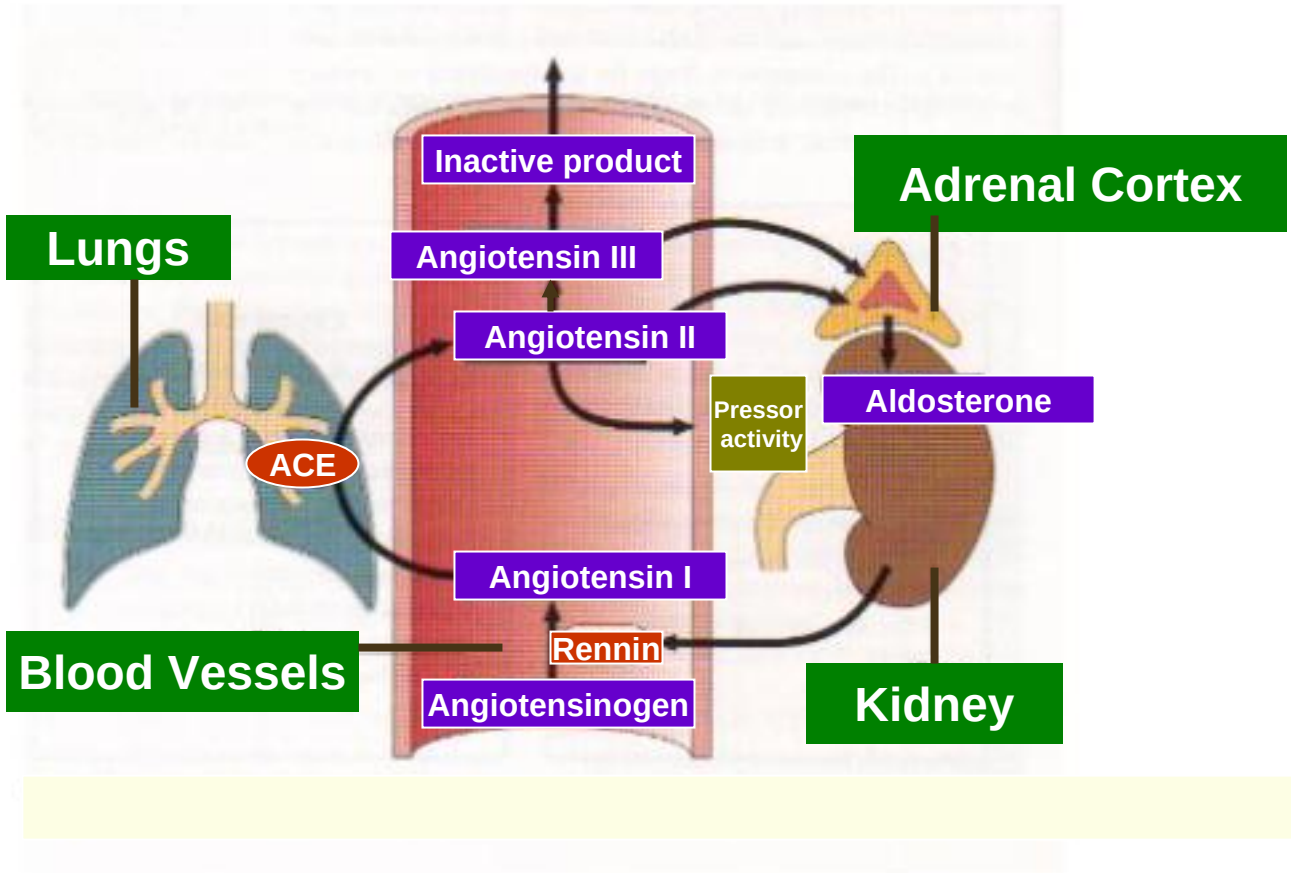
- Zn^{++}-metallopeptidase
- Glycoprotein
- Present in lungs, endothelial cells and plasma.
- Involved in the renin- angiotensin system, which is implicated in regulation of blood pressure and electrolytes.
- Removes two carboxyl terminal amino acids from the decapeptide angiotensin I to form angiotensin II, a vasoconstrictor, that degrades bradykinin, a vasodilator.

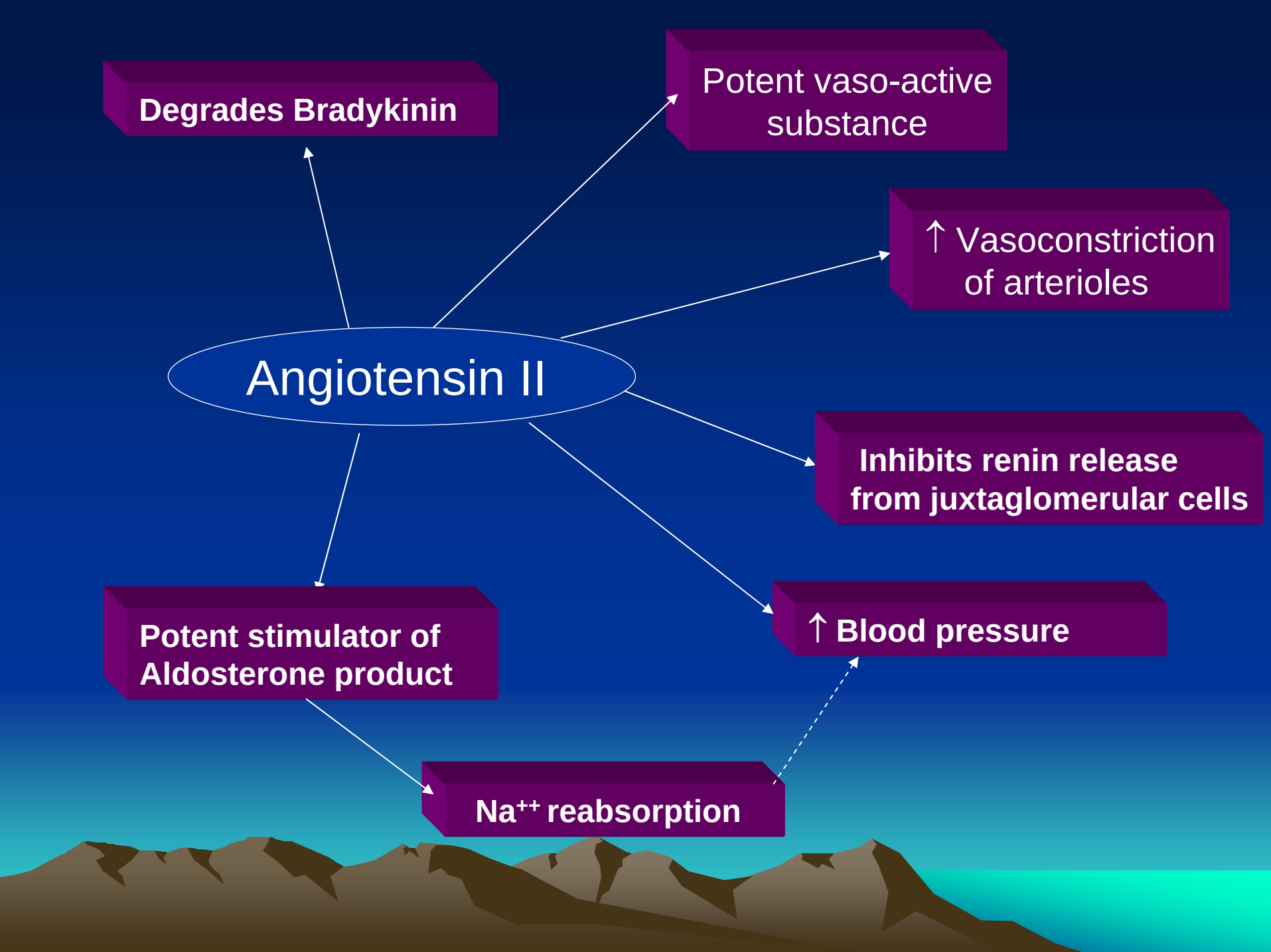
ACTION OF ACE



- **Rennin release is stimulated under influence of any factor that decrease fluid volume (dehydration, decrease bp, fluid or blood loss) or decrease Na+**

Mechanism of Action of ACE

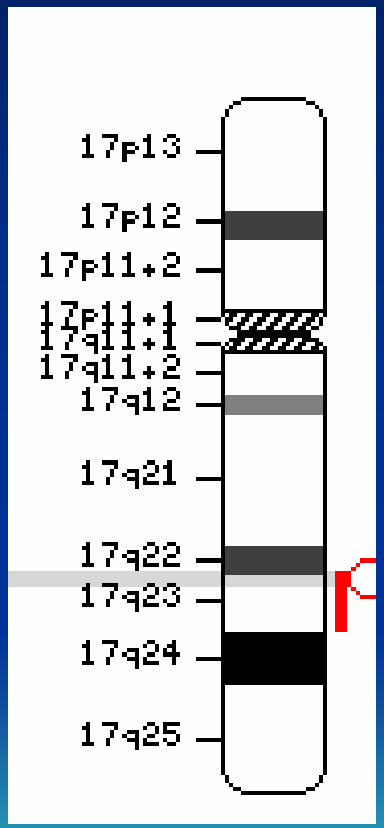



Degrades Bradykinin
Potent vaso-active substance
↑ Vasoconstriction of arterioles
Angiotensin II
Inhibits renin release from juxtaglomerular cells
Potent stimulator of Aldosterone product
↑ Blood pressure
Na++ reabsorption

Other biological functions of ACE

- Involved in:
  - Neuronal Metabolism
  - Hematopoiesis
  - Digestion
  - Reproduction

ACE GENE

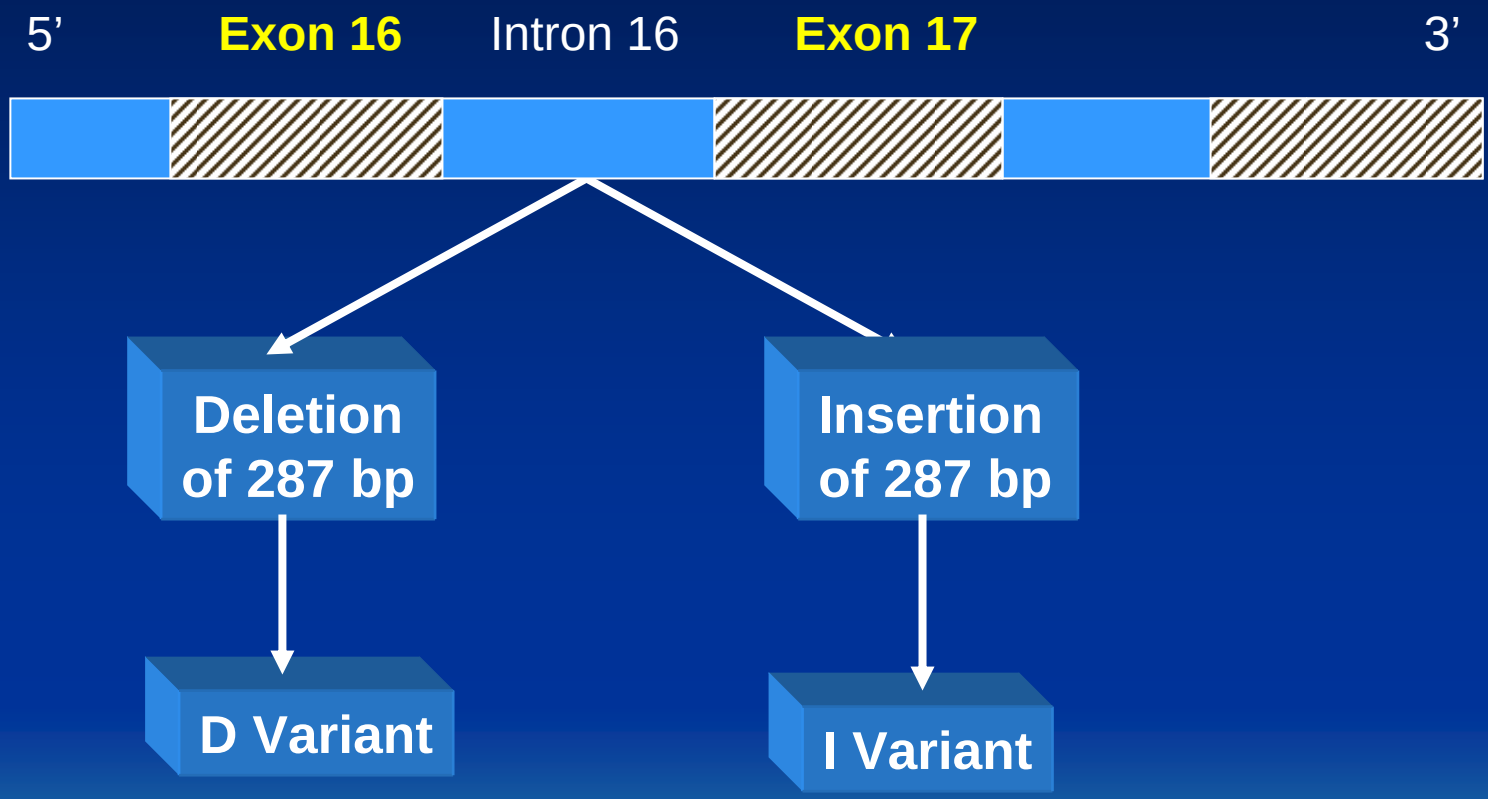


- Located on chromosome 17 (17q 23-q24).
- Has 26 exons and 25 introns.
- Exhibits extensive polymorphism in different populations.
- Insertion/deletion (I/D) polymorphism in intron 16 reported in many studies may be linked to hypertension and cardiovascular disease and obesity development.

Multiple forms of ACE

- Exists:
  - as two isoenzymes:
    - Somatic
    - Germinative (testicular)
  - as a soluble form and membrane bond form
  - as several allelic forms
    - Insertion/deletion polymorphism

I / D Polymorphism of ACE Gene *



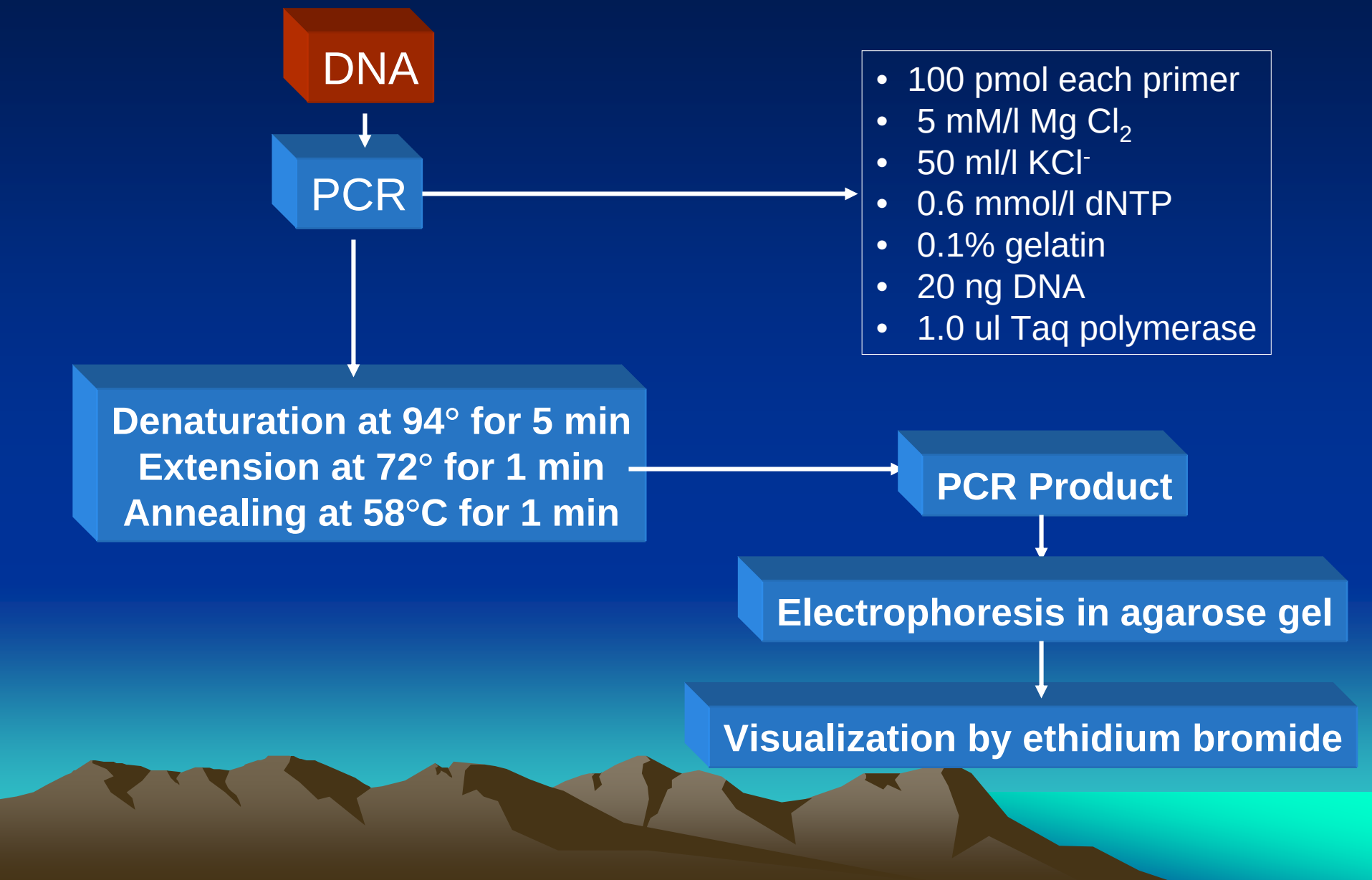
* - No effect on the structure and function of ACE.
- Influence level of ACE in blood

Investigation of ACE gene Polymorphism in Saudis

Objectives

- To determine the allele frequency of ACE gene I/D alleles in Saudi population.
- To compare the frequency in Saudis with those in other populations.
- To investigate the frequency in patients with and with diabetes mellitus.
- To investigate the frequency in NIDDM patients with renal disease with those without renal disease.

Steps involved in the study of ACE gene polymorphism in Saudis



ACE GENE POLYMORPHISM – RESULTS IN SAUDIS

Electrophoretic pattern of the I / D variants of ACE gene

Genotype and Allele frequency of I / D alleles of ACE in Saudi population

Population investigated	Genotype Prevalence			Allele frequency	
	II	ID	DD	I	D
Male	0	46	54	0.23	0.77
Female	2.6	42	55.3	0.237	0.763
Total	1.14	44.3	54.5	0.233	0.767

ACE genotype and allele frequency Saudi NIDDM patients and controls

Population investigated	Genotype Prevalence			Allele frequency	
	II	ID	DD	I	D
NIDDM					
Male	0	40.6	59.4	0.203	0.726
Female	6.0	48.0	46.0	0.30	0.70
Control					
Male	0	46.0	54.0	0.23	0.77
Female	2.6	42.0	55.4	0.237	0.763

ACE genotype and allele frequency in Saudi NIDDM patients with & without renal disease

Population investigated	Genotype Prevalence			Allele frequency	
	II	ID	DD	I	D
NIDDM with nephropathy	8.6	37.1	54.3	0.271	0.728
NIDDM without nephropathy	2.13	61.06	46.8	0.276	0.723

Comparison of Saudi results with those in other populations

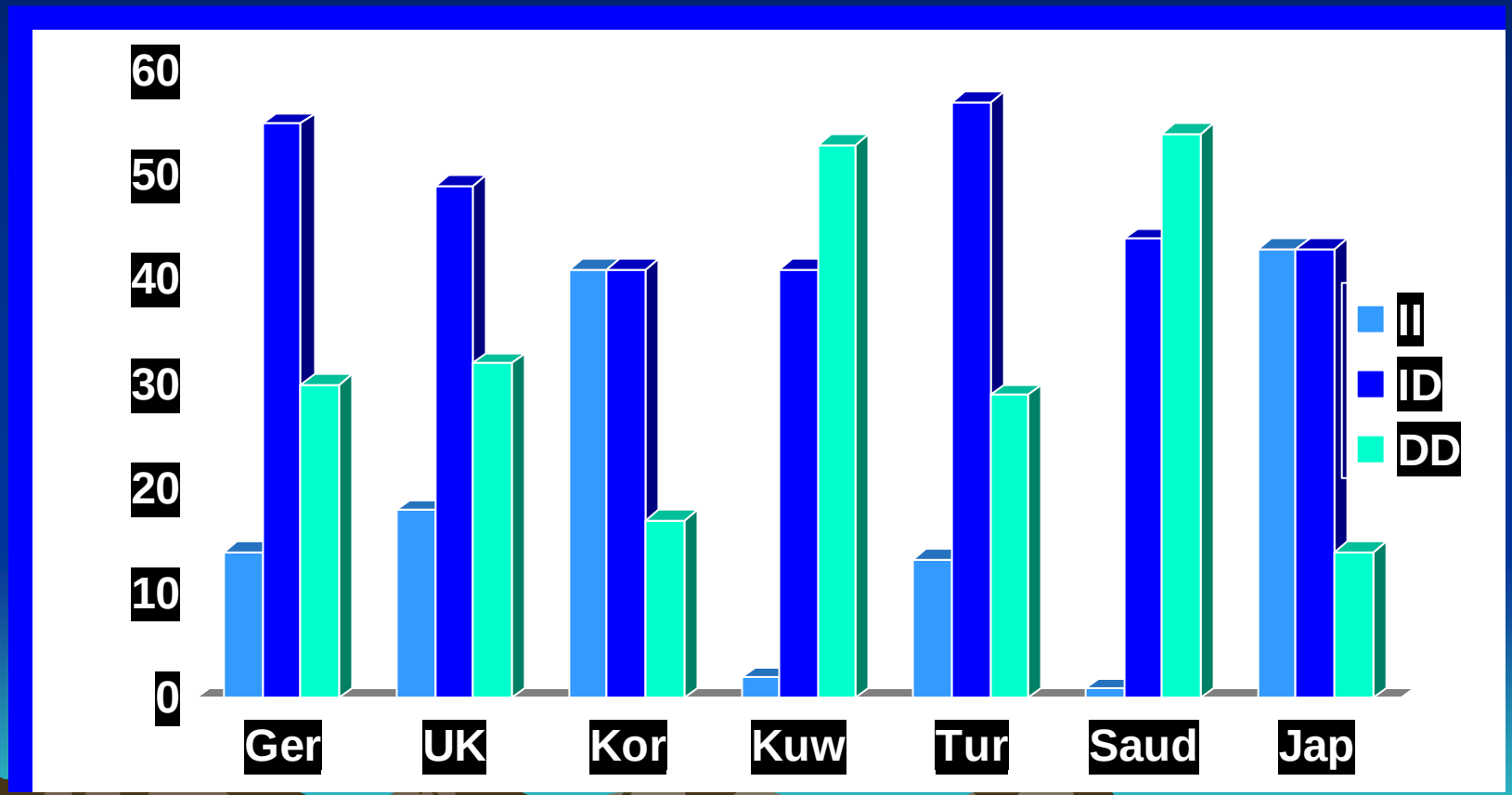
I/D Polymorphism of ACE in different populations

Population	Prevalence (%) of genotype			Allele frequency	
	II	ID	DD	I	D
Germany	14.1	55.4	30.4	0.418	0.582
UK	18.4	49.2	32.0	----	-----
Korean	41.0	41.0	17.0	0.551	0.449
Kuwait	2.0	41.0	52.9	0.25	0.75
Turkey	13.3	57.3	29.4	0.507	0.493
Saudi	1.14	44.3	54.5	0.233	0.767
Japan	43.0	43.0	14.0	0.58	0.42

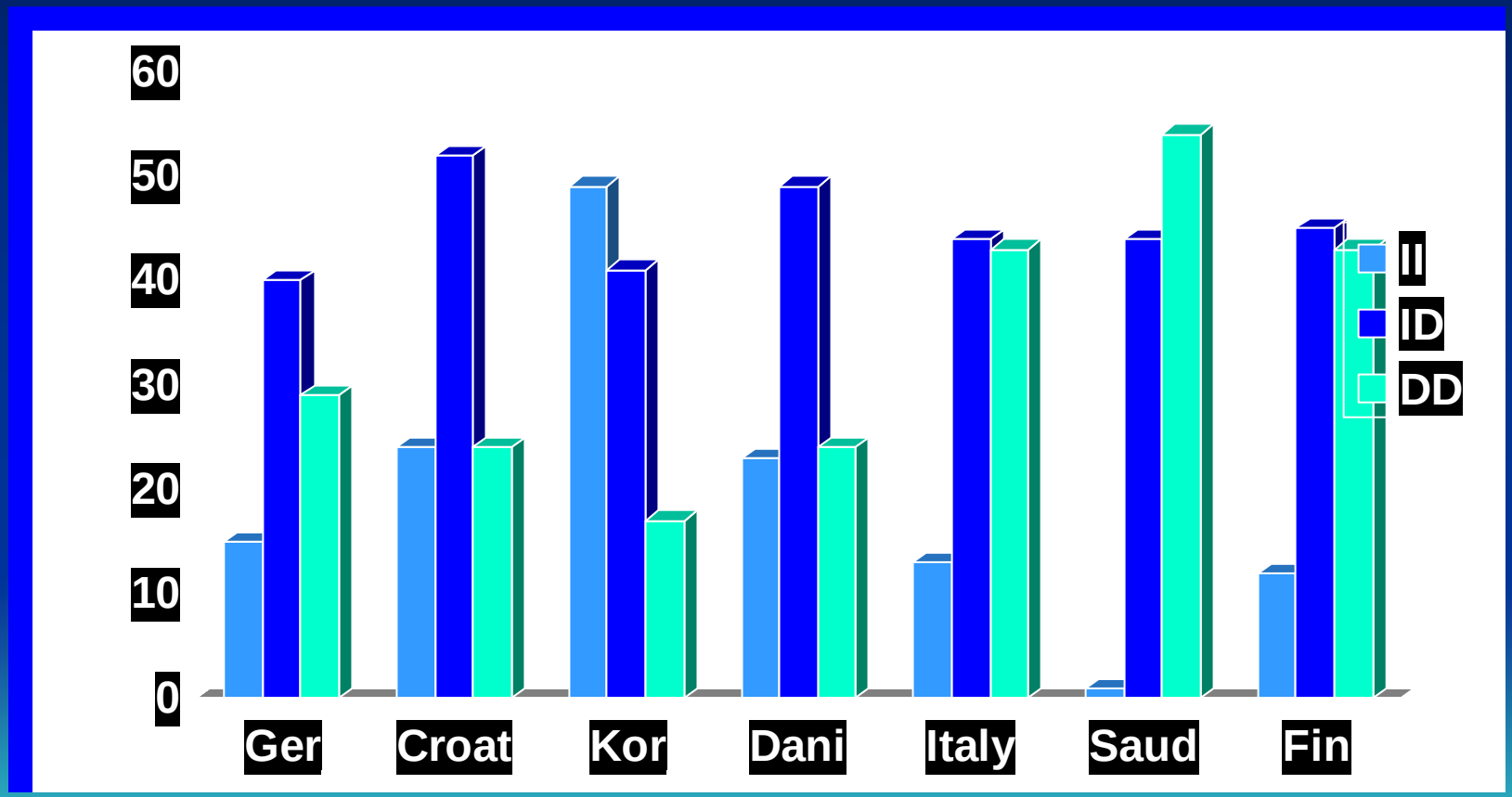
I/D Polymorphism of ACE in different populations (contd)

Population	Prevalence (%) of genotype			Allele frequency	
	II	ID	DD	I	D
Greece	15.0	40.0	29.0	0.42	0.58
Croatia	24.0	52.0	24.0	0.5	0.5
Denmark	23.4	49.7	24.7	0.487	0.513
Italy	13.1	44.1	42.8	------	------
Saudis	1.14	44.3	54.5	0.233	0.767
Finland	12.0	45.0	43.0	0.35	0.65

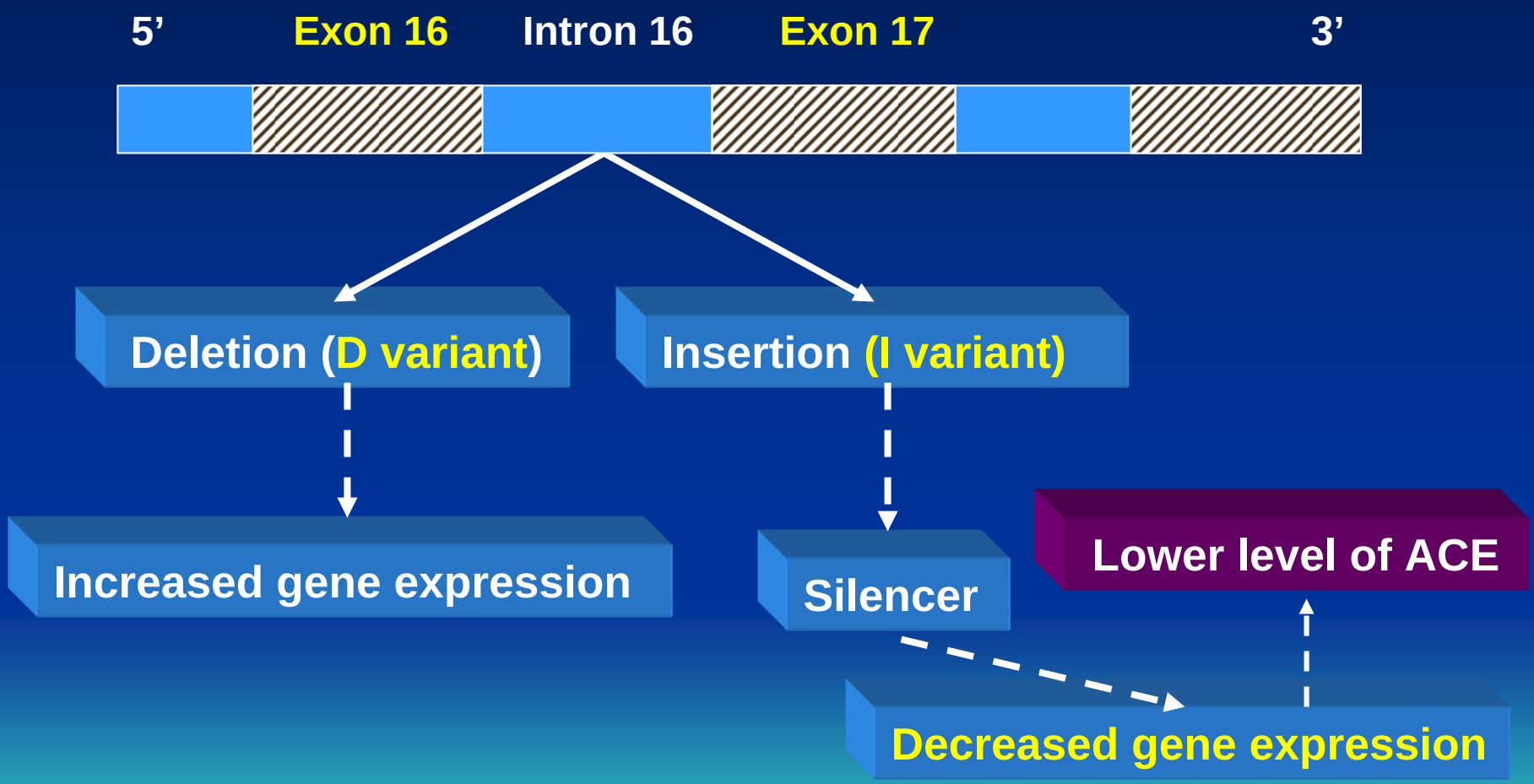
Comparison of frequency of DD allele of ACE gene in different populations



Comparison of frequency of DD allele of ACE gene in different populations



I/D Polymorphism of ACE Gene



Conclusions

- The deletion (D) allele occurs at a high frequency in Saudis, similar to the reports from Kuwait.
- The frequency of D allele is significantly higher, while I allele is significantly lower compared to several other populations.
- The D allele is associated with elevated level of ACE in plasma– Does this have any clinical consequences in Saudis have yet to be determined.
- Increased frequency of DD genotype and D allele is not seen in Saudi diabetic patients. This may be due to the fact that D allele occurs at a high frequency even in normal individuals. NIDDM patients with renal disease do not show any significant differences in the frequency, but have elevated creatinine level.