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I/D Ace Gene Polymorphism Distribution in the World and Human Prehistoric Migrations

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Introduction

The angiotensin I-converting enzyme (ACE) gene converts the inactive decapeptide angiotensin I into the vasoactive peptide Angiotensin II that plays a key role in the regulation of blood pressure, electrolyte balance and blood volume homeostasis (Renin-Angiotensin-Aldosterone System, RAAS). The ACE gene is located on chromosome 17q23,is 21 kD and comprises 26 exons and 25 introns.
The ACE plasma levels show a great variability among individuals and in 1990 Rigat and collegues identified a polymorphism that consists of an Insertion (I) or a Deletion (D) of a 287 bp *Alu* sequence within the intron 16 of the ACE gene (Rigat et al., 1990). It's a common polymorphism withethnic differences in its distribution. There are three possible genotypes: Insertion/Insertion (I/I), Insertion/Deletion (I/D) and Deletion/Deletion (D/D).

Materials and Methods

In order to investigate the world distribution of this gene polymorphism, *PubMed* was used to search for case-control studies in which the I and D allele frequencies were determined in different populations of the world. 186 research papers of this type were found. Then, data related to control samples, belonging to ethnic groups historically established in a given geographical area, were extrapolated (i.e. the populations already living in that geographical area before 1492 AD).
The I/D ACE gene allele frequencies of 55.324 individuals belonging to 86 different populations were analyzed in this work and related to the Paleolithic migration pattern (data derived from mitochondrial DNA and Y-chromosomal DNA analysis).

Results

Observing the I/D ACE alleles distribution map in the world we can see a longitudinal effect (Fig.1): the I allele frequency, very low in Eastern Africa and Middle East,

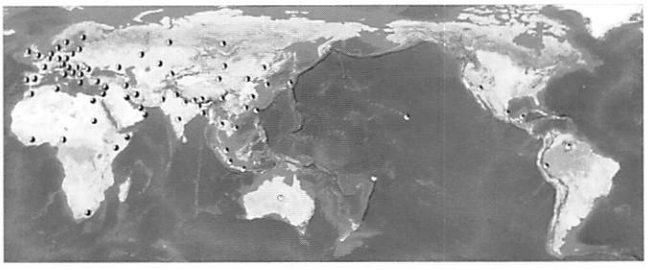

Fig. 1. *I/D ACE alleles distribution map in different populations of the world (D allele: black; I allele: white).*

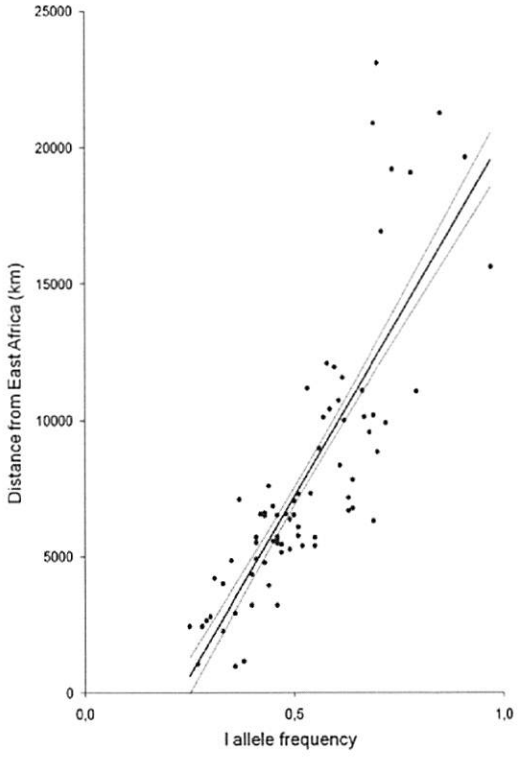

Fig.2. *The I allele frequency is positively correlated with the distance from East Africa (Pearson's R= 0,823; p<0,001).*

tends to increase in proportion to the longitude. Eastern Africa and Australia are the poles of the I/D ACE gene polymorphism. Comparing the I/D ACE gene polymorphism distribution map with maps showing the migratory routes of human populations in the late Paleolithic (60–12 kya) we can see that I allele presents the highest

frequencies in those populations that have faced the longer migrations, reaching the most distant lands: the I allele average frequency in Southeast Asian populations is 0,72, among Native Americans varies from 0,61 (Mexican Nahuas)to 0,85 (Venezuela's Yanomami) and reaches the value of 0,97 among Australian Aboriginal people. In addition, the I allele frequency is positively correlated with distance from East Africa (Pearson's R=0,823; P<0,001) (Fig. 2).

Discussion

Alu insertions are very informative markers for the study of human populations and unlike other biallelic polymorphic systems the ancestral state and the direction of mutagenesis for each *Alu* locus are always known. In the case of ACE gene, D allele is known to be the ancestral form while I allele is the most recent variant of the gene. Some researchers have found an association between the I allele of ACE gene and better performance in sports that require endurance. The I allele, for instance, seems to be more common in high-altitude mountaineers and between runners there is an increasing frequency of the I allele with distance run (Myerson *et al.*, 1999).
Williams and colleagues observed that, after a training period, there is a greater improvement of the muscular performance in the II genotype compared to the DD genotype. The lower ACE enzyme activity associated with the II genotype may raise local concentrations of nitric oxide, which in turn may improve the efficiency of mitochondrial respiration and hence contractile function in both cardiac and skeletal muscle (Williams *et al.*, 2000).

Conclusions

The results of this study reveal a 'longitude effect': the I allele frequency, very low in East Africa and in the Middle East, tends to increase in direct proportion to the longitude, reaching the highest values in populations that have faced the longest migrations during the Paleolithic era (Pearson's R = 0.823, P <0.001).
In normal situations, when peripheral tissues receive adequate oxygen and nutrients intake, the better muscular efficiency, linked to the presence of the I allele, may not be necessary and may not represent a benefit. But in extreme metabolic stress conditions, I allele carrier may have an adaptive advantage. Situations like these could easily have occurred during the long migrations of the Paleolithic era where physical resistance to fatigue and poor availability of food may have been a selective pressure for the evolution of the characteristic distribution of the I/D ACE gene polymorphism in the populations of Southeast Asia, Oceania and Americas.

References

Myerson S., Hemingway H., Budget R., Martin J., Humphries S., Montgomery H. 1999. Human angiotensin I-converting enzyme gene and endurance performance. *J. Appl. Physiol.*, Oct, 87(4): 1313-1316.

Rigat B., Hubert C., Alhenc-Gelas F., Cambien F., Corvol.P, Soubrier F. 1990. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. *J. Clin. Invest.*, 86(4): 1343-1346.

Williams A.G., Rayson M.P., Jubb M., World M., Woods D.R., Hayward M., Martin J., Humphries S.E., Montgomery H.E. 2000. The ACE gene and muscle performance. *Nature*, Feb. 10,403(6770): 614.