## Appendix: Glimpses of the Catalogue for Transmission Genetics in Arabs

### Name
Essential Hypertension

### Alternative Names
EHT  
Primary Hypertension

### WHO International Classification of Diseases
Diseases of the circulatory system > Hypertensive diseases

### OMIM Number
145500

### Mode of Inheritance
Multifactorial

### Gene Map Locus

### Description
Essential hypertension is blood pressure that is consistently higher than normal when no cause for the high blood pressure can be found. Essential (or primary) hypertension is a frequent pathology (10% to 40% of the population, depending on the age group) causing significant cardiovascular morbidity and mortality. About 90-95% of patients with high blood pressure have essential hypertension. Among the many complications related to essential hypertension, a large percentage of patients develop a left ventricular as a physiological adaptation to high blood pressure.

Unlike secondary hypertension, there is no known cause of essential hypertension. However, there are several factors that can increase blood pressure, such as the amount of blood pumped by the heart, size and condition of the arteries, water and salt content of the body, condition of the kidneys, nervous system, hormone levels, and or blood vessel tone in the body. This later could be mediated by enhanced sympathetic activity or by increased circulating levels of angiotensin II. Other factors that lead to essential hypertension include stress, being overweight, smoking, alcohol use, a diet high in salt, heredity, gender, age and race.

### Molecular Genetics
Essential hypertension is a multifactorial genetic disease resulting from complex interactions between multiple environmental and genetic factors. Many familial studies have shown the partially inherited aspect of the disorder. According to estimates, 20 to 40% of blood pressure variance have a genetic origin. Variations in a variety of genes have shown an association with hypertension in some studies, but these associations are often not reproducible in studies of other populations. Candidate genes include angiotensinogen, angiotensin receptor-1, adducin, adrenergic receptors, and the human guanine nucleotide-binding protein beta-3 subunit gene. The product of the later gene is involved as a modulator or transducer in various transmembrane signaling systems, by integrating signals between receptors and effector proteins.

As a key enzyme of the renin-angiotensin-aldosterone system, the renin gene (REN) is a good candidate quantitative trait locus that may be implicated in the molecular etiology of essential hypertension. Among mixed reports on the subject, a REN MboI restriction fragment length polymorphism has been shown to be significantly associated with a family history of hypertension in a Japanese population. To date, however, there is no genetic variant with strong enough effect to be used for predictive purposes.

### Epidemiology in the Arab World

#### Egypt
El-Tagi et al. (1982) described the incidence, pathogenesis and management of hypertension in 1600 pregnant women admitted to El-Hussein University Hospital, Cairo, in 1980. A total of 100 women had pregnancy related hypertension. Twenty five subjects (1.56%) had essential hypertension. Termination of pregnancy occurred only in 2 patients, one with severe pre-eclampsia and the other with severe essential hypertension. Caesarean section was done in 12 patients, 7 of them for hypertension and in the remaining 5 for other reasons. Management of hypertension at the hospital consisted of 3 approaches: 1) rest in bed and sedation such as pethidine, valium or Algrafan; 2) a combination of sedatives and hypotensives such as Brinerdin, Serpasil and Aldomet; and 3) a combination of sedatives, hypotensives and diuretics.
Association of essential hypertension with the human angiotensin-converting enzyme gene: In 1997, Frossard et al. (1997a) studied an insertion/deletion polymorphism in the human angiotensin-converting enzyme (ACE) gene amongst United Arab Emirates (UAE) nationals from the Abu Dhabi Emirate. There was a lack of association between the I/D allele marker system and clinical diagnosis of essential hypertension, suggesting that variations of the angiotensin-converting enzyme gene do not play a major role in the determination of elevated blood pressure in this Arab population. This agrees with results reported on other ethnic groups. In 2003, Saeed Mahmood and colleagues assessed the value of genotyping the ACE G2350A polymorphism in a retrospective case-control study for a putative association with essential hypertension in the UAE population. Polymerase chain reaction and restriction endonuclease analyses were used to investigate a sample population of 254 Emirati, comprising 136 normotensive controls, and 118 patients with clinical diagnoses of essential hypertension. Detailed analysis revealed that the ACE G/G 2350 genotype was positively associated with essential hypertension. According to the literature, this was the first association study of the ACE G2350A polymorphism with essential hypertension. Saeed Mahmood et al. (2003) concluded that this positive result might indicate that ACE could be a quantitative trait locus for essential hypertension as originally thought.

Association of essential hypertension with the human angiotensin-converting enzyme gene: Frossard et al. (1997b) also studied an insertion/deletion (I/D) polymorphism located in the second intron of the human angiotensin-converting factor (ANF) gene among 232 UAE nationals (112 normotensives and 120 hypertensives) from the Abu Dhabi Emirate, with a view to evaluating the value of this marker in relation to hypertension. Results reveal that genotype frequencies of this I/D marker occur in Hardy-Weinberg proportions (respective genotype frequencies in the overall sample population are: II, 51%; ID, 42%; DD, 7%). No association, however, was evidenced between this dimorphic site and clinical diagnosis of essential hypertension. This suggests that: 1) this I/D polymorphism is not a useful marker to study the relationship between the ANF gene and hypertension in the UAE; and 2) variations of the ANF gene that may be in linkage disequilibrium with this marker do not play a major role in the determination of hypertension in this Arab population. Obineche et al. (2002) carried out a case-controlled study on a group of 151 UAE nationals (62 normotensives and without left ventricular hypertrophy and 89 hypertensives, also with and without left ventricular hypertrophy) with a view to evaluate the value of an insertion/deletion (I/D) polymorphism located in the second intron of the human atrial natriuretic factor gene in relation to left ventricular hypertrophy. Obineche and colleagues found a significant difference in the distribution of the I and D alleles between the two groups. The significant association of the D allele with left ventricular hypertrophy could implicate the involvement of variants of the ANF gene in the determination of left ventricular hypertrophy.

Association of essential hypertension with the human renin gene: Frossard et al. (1998a) described a polymerase chain reaction-based assay for the detection of the REN MboI polymorphic site located in the ninth intron of the gene. MboI genotype distributions were investigated in 331 hypertensive and 279 normotensive subjects from the United Arab Emirates (UAE), a genetically homogeneous ethnic population with no history of smoking or alcohol consumption. A statistically significant association was found between alleles on which the MboI site is present and clinical diagnosis of essential hypertension, indicating that 1) the presence of the MboI site is a marker for susceptibility to hypertension in the UAE (the associated odds ratio is 3.16); and 2) variations of the REN (or of a nearby) gene that may be in linkage disequilibrium with this marker play a role in the development of essential hypertension in the UAE. Later on, Frossard et al. (1999b) found a statistically significant association between alleles on which the BglII site was present and the clinical diagnosis of essential hypertension in the UAE population, and to a lesser extent, in a U.S. Caucasian group that was studied for hypercholesterolemia. Frossard and colleagues (1999b) also postulated that such a genetic influence, which seems to show a recessive mode of inheritance, could also be implicated in raising both systolic and diastolic blood pressures.

Association of essential hypertension with the human angiotensinogen gene: In 1998, Frossard et al. (1998b) assessed the value of genotyping the human angiotensinogen gene in a genetically homogeneous population. They carried out a retrospective, case control study of variants M235T and T174M for putative correlations with cardiovascular diseases among UAE. A sample population of 229 Emirati (119 males and 110 females) was investigated. This comprised groups of controls and patients with clinical diagnoses of essential hypertension, left ventricular hypertrophy, ischaemic heart disease and myocardial infarction. M235T and T174M alleles were determined via assays based on the polymerase chain reaction. T174M showed no correlation with any of the four clinical entities included in this study. T235 alleles, however, occurred more frequently in the essential hypertension group and less frequently in the group of myocardial infarction survivors. Frossard and colleagues (1998b) found that T235 allele frequencies decreased with age, indicating that in the Emirati population, T235 alleles are associated with an increased life span and that this effect could occur through independent mechanisms underlying genetic susceptibilities to both essential hypertension and myocardial infarction.

Association of essential hypertension with the human apolipoprotein B gene: Frossard and Lestringant (1999) used a polymerase chain reaction-based assay to investigate the allele and genotype frequency distributions of the alleles of a hypervariable region located in the
3’ of the human apolipoprotein B (apoB) gene. The analysis of DNA samples of 367 unrelated UAE nationals (201 males and 166 females) revealed the presence of 18 different alleles, ranging from 21 to 55 repeats, making up 51 genotypes occurring in Hardy-Weinberg proportions with a heterozygosity index of 80.9%. This observation leads to the conclusion that this marker is very informative in the Emirati population and may be very useful for UAE-specific DNA fingerprinting as well as to assess the role of the apoB gene in cardiovascular diseases. Frossard et al. (1999a) investigated the associations between genetic variations of the apoB gene and clinical diagnosis of essential hypertension. They compared the distribution of the alleles of a highly polymorphic variable number of tandem repeats localized 3’ to the human apoB gene, the apoB 3’ hypervariable region (HVR), in a group of normotensive and a group of hypertensive individuals. DNA samples from 437 unrelated UAE nationals (215 normotensives and 222 hypertensives) were collected. The apoB 3’ HVR allele and genotype status were determined using a polymerase chain reaction-based assay. The main peak of the distributions occurred at 35 repeats among hypertensives (with a relative frequency of 25.7% versus 19.6% in normotensives) and at 37 repeats among normotensives (28.8% versus 20.3% in hypertensives). Alleles with 21, 23, 25, 49, and 55 repeats are found in hypertensives only (with a combined relative frequency of 7.6%). Frossard et al. (1999a) concluded that variations of the apoB gene, or of a nearby gene, that may be in linkage disequilibrium with these alleles play a role in the development of essential hypertension in UAE nationals.

Association of essential hypertension with the human guanine nucleotide-binding protein beta-3 subunit gene: Obineche et al. (2001) investigated the relationship of left ventricular hypertrophy with five candidate genes in a genetically homogenous population group of 213 UAE nationals (98 subjects with left ventricular hypertrophy and 115 age- and sex-matched controls). The study focused on the distributions of genotypes of intragenic markers in the human guanine nucleotide-binding protein beta-3 subunit gene variant; methylene tetrahydrofolate reductase gene; angiotensin converting enzyme gene; and paraoxonase 1 and 2 genes. Of the five candidate gene markers studied, no significant differences in the genotype distribution of the methylene tetrahydrofolate reductase gene; angiotensin converting enzyme gene; or paraoxonase 1 and 2 gene markers were found between the left ventricular hypertrophy and control groups. However, data on the homogenous cohort of Emirati lead Obineche and colleagues to suggest a possible association between the C825T marker of the human guanine nucleotide-binding protein beta-3 subunit gene and left ventricular hypertrophy (p=0.0445).

Association of essential hypertension with other genes: Frossard et al. (2002) evaluated the putative involvement of cytokine gene variants in human essential hypertension. They carried out case-control study on 174 unrelated UAE nationals (81 hypertensives and 93 normotensives) from the Abu Dhabi Emirate. Five candidate genes were targeted: loci-transforming growth factor beta1 (TGF-beta1), interferon gamma (IFN-gamma), epidermal growth factor (EGF), interleukin-1 beta (IL-1beta) and tumour-necrosis factor (TNF-alpha). The distribution of genotypes and alleles of the six following dimorphic variants were assessed: TGF-beta1(*)10(T>C) and TGF-beta1(*)25(G>C), located at codons 10 and 25, respectively, of TGF-beta1; T874A in intron 1 of IFN-gamma; G61A in exon 1 of EGF; TaqI dimorphism at +3962 (exon 5) of IL-1beta; and -308A>G in the promoter of TNF-alpha. These six bi-allelic markers were visualised by methods based on the techniques of amplification refractory mutation system-polymerase chain reaction (for TGF-beta1, IFN-gamma, EGF and TNF-alpha) and by polymerase chain reaction-TaqI restriction endonuclease analysis in the case of IL-1beta. In each of the two groups (normotensives and hypertensives), genotype frequencies of all six markers occurred in Hardy-Weinberg proportions. There were, however, no statistical differences in the allele and genotype frequencies of any of the six markers between the two groups of subjects. There was also no difference in distribution and frequencies of haplotypes constructed with combinations of TGF-beta1(*)10(T>C) and TGF-beta1(*)25(G>C) sites. However, although they do not reach statistical significance (which may be due to the relatively restricted number of subjects included in this study), the distribution differences (in normotensives and hypertensives) observed in the cases of EGF and TNF-alpha reflect trends that could be expected from a mechanistic explanation of the pathways that underlie the patho-physiology of hypertension.

References


Frossard PM, Lestringant GG, Elshahat YI, John A, Obineche EN. An MboI two-allele polymorphism may implicate the human renin gene in primary hypertension. Hypertens Res. 1998a; 21(3):221-5. PMID: 9786608


Frossard PM, Obineche EN, Lestringant GG, Elshahat YI. Association study between the ANF gene and hypertension in a Gulf Arab population. Am J Hypertens. 1997b; 10(11):1308-10. PMID: 9397252


Related CTGA Records
Angiotensin I (OMIM: 106150)
Angiotensin I-Converting Enzyme (OMIM: 106180)
Apolipoprotein B (OMIM: 107730)
Guanine Nucleotide-Binding Protein, Beta-3 (OMIM: 139130)
Natriuretic Peptide Precursor A (OMIM: 108780)
Renin (OMIM: 179820)

Links
http://www.cvphysiology.com/Blood%20Pressure/BP024.htm
http://www.hmc.psu.edu/healthinfo/e/essentialhypertension.htm
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=421

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Genetic Disorders in the Arab World: United Arab Emirates

Name
Epidermolysis Bullosa Letalis

Alternative Names
Epidermolysis Bullosa, Junctional, Herlitz-Pearson Type
Herlitz-Pearson Type Epidermolysis Bullosa
Epidermolysis Bullosa, Junctional, Herlitz Type
Epiligrin

WHO International Classification of Diseases
Congenital malformations, deformations and chromosomal abnormalities > Other congenital malformations

OMIM Number
226700

Mode of Inheritance
Autosomal recessive

Gene Map Locus
18q11.2, 1q32, 1q25-q31

Description
Epidermolysis bullosa is a group of inherited disorders of the epithelial basement membrane zone that manifest with blistering of the skin and mucous membranes after minor trauma. The disease appears to be one of the most frequent monogenic causes of infant mortality among Arabs. The disease is traditionally classified into three groups according to the level of cleavage within the skin: Epidermolysis bullosa simplex results from separation of the skin above the basement membrane, junctional epidermolysis bullosa is caused by blister formation within the basement membrane, and in the dystrophic form of epidermolysis bullosa, blisters appear below the basement membrane. To date, all cases of junctional epidermolysis bullosa have been shown to be transmitted in an autosomal recessive fashion.

Clinical and genetic heterogeneity are characteristic of junctional epidermolysis bullosa. Two major clinical variants of this epidermolysis bullosa subtype have been described: the moderately severe non-Herlitz junctional epidermolysis bullosa characterized by localized to generalized blistering, nail dystrophy, scarring alopecia, and mucosal involvement; and the Herlitz type of junctional epidermolysis bullosa, associated with extensive skin and mucosal blistering, nail dystrophy, exuberant granulation tissue, enamel defects, and a high perinatal mortality resulting from overwhelming infections and respiratory complications.

The junctional epidermolysis bullosa subtype, generalized atrophic benign epidermolysis bullosa, is characterized by life-long blistering, resulting in cutaneous atrophy, diffuse scarring alopecia, pigmenary changes, and nail and tooth abnormalities.

Molecular Genetics
The genetic basis of all major clinical variants of epidermolysis bullosa has been delineated. Specific mutations have been demonstrated in 10 different genes expressed within the dermoepidermal adhesion zone, with at least six different genes being involved in the pathogenesis of junctional epidermolysis bullosa. Herlitz junctional epidermolysis bullosa has been shown to be associated with mutations in one of the 3 laminin-5 genes (LAMB3, LAMA3, LAMC2), resulting in premature termination of protein translation, or reduced levels of mRNA transcripts resulting from non-sense-mediated mRNA decay. Non-Herlitz junctional epidermolysis bullosa cases have also been assigned to mutations within the laminin-5 genes.

The current mutation detection strategy followed in the United States and Europe entails analysis of patient samples for the recurrent mutations in LAMB3 followed by sequential screening of LAMB3, LAMC2, and finally LAMA3.

The observation of reduced type XVII collagen/bullous pemphigoid antigen 2 expression in the skin of generalized atrophic benign epidermolysis bullosa patients led to the identification of causative mutations within the gene encoding this protein. Other clinical cases of generalized atrophic benign epidermolysis bullosa were shown to be caused by mutations affecting laminin-5-encoding genes.

Epidemiology in the Arab World
Saudi Arabia
Nakano et al. (2002) identified two consanguineous families originating from Saudi Arabia with non-Herlitz junctional epidermolysis bullosa. Affected members of both families were analyzed for mutations in LAMB3, LAMA3, and LAMC2 genes. Both patients turned out to be homozygous for the Q46X mutation in the LAMC2 gene. Nakano et al. (2002) further investigated the genealogic relationship between the two unrelated families and found out that both originated from a Bedouin tribe of the Empty Quarter that is now split between Saudi Arabia and the United Arab Emirates.
Sudan
Nakano et al. (2002) identified a consanguineous family originating from Sudan with generalized atrophic benign epidermolysis bullosa. The affected member of the family presented with milia over his face. Immunofluorescence studies performed on frozen skin sections indicated lack of staining for type XVII collagen. The affected child in the family was analyzed for mutations in LAMB3, LAMA3, LAMC2, and COL17A1 genes. The child turned out to be homozygous for the R1226X mutation in the COL17A1 gene.

United Arab Emirates
Nakano et al. (2002) identified a consanguineous family originating from the United Arab Emirates with non-Herlitz junctional epidermolysis bullosa. The affected child in the family was analyzed for mutations in LAMB3, LAMA3, and LAMC2 genes. The child turned out to be heterozygote for two mutations, Q1083X and 1296insA, in the LAMB3 gene. The Q1083X mutation has been found in Haifa in Palestine. Interestingly, the two grandmothers of the affected child originated from that village. Nakano et al. (2002) quoted the presence of two different mutations in the affected child to emphasize the fact that the presence of consanguinity does not preclude compound heterozygosity.

Yemen
Nakano et al. (2002) identified a consanguineous family originating from Yemen with non-Herlitz junctional epidermolysis bullosa. The affected child in the family was analyzed for mutations in LAMB3, LAMA3, and LAMC2 genes. The child turned out to be homozygous for the 1942delG aberration in the LAMB3 gene.

References

Related CTGA Records
N/A

Links
http://www.emedicine.com/ped/topic696.htm
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=305

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