



Title	PCR amplification of alleles at locus D17S5: population genetic study in Hong Kong Chinese and detection of allelic loss in patients with hepatocellular carcinoma
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The strength of linkage disequilibrium between two vitamin D receptor polymorphisms varies by ethnicity. S. A. Ingles¹, R. W. Haile¹, B. E. Henderson¹, L. N. Kolonel², G. Nakaichi¹, C.-Y. Shi⁴, M. C. Yu¹, R. K. Ross¹, G. A. Coetzee². Departments of Preventive Medicine¹ & Urology², Norris Comprehensive Cancer Center, University of Southern California School of Medicine. ³Cancer Research Center of Hawaii, University of Hawaii, Honolulu, ⁴Department of Community, Occupational, and Family Medicine, National University of Singapore.

To evaluate the adequacy of a commonly used BsmI RFLP as a marker of the vitamin D receptor (VDR) locus, we genotyped 583 individuals from 4 ethnic groups for this marker, as well as for a polymorphic site in the 3' untranslated region (3'UTR) of this gene. At the latter site, we identified 12 alleles, A₁₃ to A₂₄, of a poly-A microsatellite located approximately 1 kb upstream from the 3' end of the 3.2 kb 3'UTR. Allele size followed a bimodal distribution with distinct short (A₁₃-A₁₇) and long (A₁₈-A₂₄) allele populations. Poly-A allele frequency differed by ethnicity, with the frequency of short alleles being highest in non-Hispanic whites (41%), intermediate in African-Americans and Hispanics (29% and 31%, respectively), and lowest in Asians (14%). In each of the four ethnic groups, both the BsmI and the poly-A markers were in Hardy-Weinberg equilibrium, and some degree of linkage disequilibrium was observed with coupling between BsmI and short poly-A alleles and between BsmI and long poly-A alleles. The strength of the linkage disequilibrium varied by ethnicity, with departures from complete disequilibrium producing disagreement between the BsmI and poly-A genotypes. Genotypic disagreement was lowest in non-Hispanic whites (7%), intermediate in Asians and Hispanics (16% and 19%, respectively), and highest among African Americans (37%), indicating that BsmI is not a good marker for the VDR 3'UTR genotype in all populations.

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Overlapping genetic susceptibilities in IDDM and Cystic Fibrosis Complicated by Diabetes (CF/DM): Benefit of dual quantitative assessments in related diseases. L.J. Krueger¹, D.S. Holsclaw, Jr.¹, H.L. Dorkin² and M. Carrington³. Dept of Pediatrics¹, Med. College of PA & Hahnemann University, Philadelphia, PA; Div. of Pediatric Pulmonology and Allergy², Tufts University SOM, Boston, MA & Biological Carcinogenesis and Development Program³, National Cancer Institute, FCRCDC, Frederick, MD.

The incidence of CF complicated by diabetes (CF/DM) is much higher than that found in Type 1 insulin-dependent diabetes mellitus (IDDM) in the general population (12% versus 0.1%). In our previous study [J. Clin Immunol. 14(6):353-358, 1994], the incidence DQα and DQβ genotypes in the CF/DM population (n=26) were in disequilibrium compared to the normal control and CF/non-DM populations (n=42). In a pt.-matched, total ascertainment study of CF/DM, an increased allele frequency of the Asp⁵⁷ allele, DQB1*0201 was determined (40.4% versus 28.0% for CF/DM and CF/non-DM). The IDDM protective Asp⁵⁷ alleles were lower in the CF/DM versus CF/non-DM (p ≤ 0.025) or normal controls (p ≤ 0.008). One interpretation of the MHC results underscores a potential mechanistic conflict between CF/DM (a non-autoimmune disorder) and IDDM (an autoimmune disease). By assessing other known diabetogenic loci, this interpretation may be tested.

However, identifying susceptibility genes in multifactorial diseases is difficult and even more difficult in CF/DM because of limiting pedigree size. In this ongoing multicenter trial (10 National CF Clinical Centers) of CF/DM using a matched-design [n=139 CF/DM (1x) and n=300 CF/non-DM (2X)], we hope to establish that the investigation of related diseases will not only confirm the identity of candidate IDDM susceptibility genes, but may provide fresh insight into the diabetogenic process encoded by these genes.

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A combination of HLA-DQA1 codon 52 and HLA-DR4 confers susceptibility to insulin-dependent diabetes mellitus. S.P. Lin¹, Y.J. Lee¹, F.S. Lo¹ and J.G. Chang². Dept of Pediatrics, Mackay Memorial Hospital, Taipei, and ²Dept of Molecular Medicine, Taipei Municipal Jen-Ai Hospital, Taipei, Taiwan.

To date, more than twelve separate chromosome regions have been implicated in the development of human type 1 diabetes mellitus (IDDM). A major part of the genetic susceptibility to this disease in humans has been mapped to the human leukocyte antigen (HLA) class II region (DR, DP, and DQ). We, therefore, analysed the HLA-DQA1 52 and HLA-DR4 between IDDM children and healthy old control subjects. The method involved the selective amplification of a DNA fragment from the HLA-DQA1 and HLA-DR4 gene by using the mutagenic primers. After PCR, we can accurately obtain the results after enzyme digestion and electrophoresis. Sixty-seven IDDM patients and 69 nondiabetic control subjects were analysed using this method. Statistical analysis was evaluated using χ^2 tests with Yates correction when appropriate. About the result, please see the tables. We concluded that susceptibility is conferred by DQA1 52 (Arg) as well as DR4. Individuals with two DQA1 52 (Arg) alleles and DR4 homozygous or heterozygous did not have more relative risk for disease. Therefore, DQA1 52 (Arg) and DR4 alleles are independent risk factors. We suggest that other genes in this region may be responsible for the disease.

DQA1	IDDM	f	Control	f	RR	P	DR4	IDDM	f	Control	f	RR	P
Arg/Arg	53	0.79	24	0.35	7.0	<0.05	+/+/-	33(1;32)	0.50	17(3;14)	0.24	3.16	<0.05
Arg/-	13	0.19	35	0.51	NS		-/-	34	0.50	52	0.76	NS	
-/-	1	0.02	10	0.14	NS		Total	67		69			

DQA1 52	DR4	IDDM (n=67)	Control (n=69)	RR	P
Arg/Arg	+/+/-	26	11	3.3	<0.05
Arg/Arg	-/-	27	13	2.9	<0.05
Arg/-	+/+/-	7	6	NS	
Arg/-	-/-	6	29	NS	
-/-	+/+	0	0	NS	
-/-	-/-	1	10	NS	

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Consanguinity and common adult diseases in Israel Arab communities. L. Jaber², T. Shohat¹, J.I. Rotter¹ and M. Shohat¹. ¹Department of Medical Genetics, Rabin Medical Center, Beilinson Campus, Petah Tikva, ²Taybe Children's Medical Center, Taybe Tel Aviv University, Israel and ³Medical Genetics and Birth Defect Center, Cedars-Sinai Medical Center and UCLA, Los Angeles, CA, USA.

While consanguinity has been proven to have a deleterious effect with regard to congenital malformation and rare autosomal recessive diseases, little information exists on its role in multifactorial common adult morbidity. The aim of this study was to investigate the effects of consanguinity on the prevalence of common diseases in adulthood such as diabetes mellitus, myocardial infarction, bronchial asthma and duodenal ulcer. As part of a larger study aiming to investigate the inbreeding coefficient in the Israeli-Arab community, we distributed questionnaires to parents of 4100 second-grade students in 158 randomly chosen schools. Among the 3772 responders (92%), 34.8% of the students' fathers and 31% of their mothers were found to be products of consanguineous matings. There was no difference in the prevalence (males, females) between the offspring of consanguineous versus non-consanguineous matings for diabetes mellitus (consanguinity: 4.3%, 1.5% vs non-consanguinity: 2.9%, 1.6%) myocardial infarction (2.7%, 0.03% vs 2.3%, 0.03%), bronchial asthma (2.4%, 2.0% vs 3.7%, 2.3%) or duodenal ulcer (7.0%, 3.0% vs 7.8%, 2.9%), respectively. This study suggests that even in a population with a high rate of consanguinity, there is no significant increase in the prevalence of these common adult diseases.

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Lack of association of CHRNA4 S248F mutation with epileptic syndromes with presumed genetic etiology. W.L. Lee¹, A.H.N. Tay², P.S. Low³, L.Y. Wong², H.T. Ong³ and U. Rajan⁴. Tan Tock Seng Hospital¹, Institute of Molecular and Cell Biology, National University of Singapore², National University Hospital³, School Health Services⁴.

A missense mutation in the alpha4 subunit of the nicotinic acetylcholine receptor (CHRNA4) has been found to be associated with autosomal dominant frontal lobe epilepsy. In addition, a nonsense mutation in CHRNA4 has been reported to cosegregate with 20q-linked benign neonatal familial convulsions.

As part of an ongoing evaluation of neurotransmitter mutations in epilepsy, we investigated CHRNA4 as a candidate gene for various forms of epilepsies which are thought to be genetic in etiology. A total of 101 patients with one of the following epileptic syndromes were evaluated: benign focal epilepsy of childhood (31), childhood absence epilepsy (26), juvenile absent epilepsy (2), juvenile myoclonic epilepsy (14), photosensitive epilepsy (7), benign familial infantile epilepsy (5), benign familial neonatal convulsions (1), primary generalized epilepsy with generalized tonic-clonic seizures (6). Nine patients had idiopathic epilepsy and strong family history of idiopathic epilepsy.

Genomic DNA from lymphocytes was used in a PCR assay (Steinlein et al, 1995) which allowed for rapid detection of the missense mutation that replaces serine with phenylalanine at codon 248, a highly conserved amino acid residue in the second transmembrane domain. All 101 samples examined failed to show this mutation.

The S248F mutation in CHRNA4 does not appear to be associated with the idiopathic epileptic syndromes examined in this study.

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PCR Amplification of Alleles at Locus D17S5: Population Genetic Study in Hong Kong Chinese and Detection of Allelic loss in patients with Hepatocellular Carcinoma. C.K.Ma¹, S.C.F.Tam¹, S.W.Ng¹, R.M.C.Wong² and A.S.F.Lok³. ¹Dept. of Clinical Biochemistry, ²Virus Unit, Queen Mary Hospital, Hong Kong and ³Dept. of Internal Medicine, University of Michigan, Ann Arbor, U.S.A.

D17S5, a highly polymorphic, variable number of tandem repeat (VNTR) locus, have proven a powerful tool for paternity testing, genetic disease mapping, individual identification in forensic science, and determination of clonality in human tumors. A population genetic study was performed to provide a database for the probability calculation of forensic identification and paternity testing. In addition, the application of the D17S5 locus in detection of loss of heterozygosity (LOH) in chromosome 17p in hepatocellular carcinoma (HCC) was demonstrated. In the population genetic study, a total of 102 genotypes corresponding to 19 alleles were found in a population of 953 Hong Kong Chinese individuals. The most frequent alleles were, 4>1>5>6. The allelic frequency were significantly different from the Caucasian populations (p<0.001). The expected and observed heterozygosity were 89.5% and 90.3% respectively. The discrimination power was 0.98. The chance of exclusion was 0.79. In the LOH study, 46 HCC patients were studied, 39 cases were found informative and 15 have loss of heterozygosity (38.5%).