

# Department of Molecular Medicine, the Institute of Experimental Medicine

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The Department of Molecular Medicine at the Istanbul University, Institute of Experimental Medical Research is the only Molecular Medicine Department in Turkey. It is a 14 years old department but actively working for 12 years. It is an interdisciplinary scientific branch and there are many different projects going on in that department. Masters and Ph.D. programs are offered in the Department of Molecular Medicine under the aegis of the Institute of Health Sciences and 13 students have completed their degrees so far.

**Key words:** Molecular medicine, institution

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## Introduction

The Department of Molecular Medicine at the Istanbul University Institute of Experimental Medical Research is an interdisciplinary scientific branch that analyzes the molecular biology of cells and organisms, particularly from a medical point of view .

Recent advances in molecular and cellular biology have required enormous amounts of research and practice. In all areas of medicine, molecular biology has played a key role and its importance to medical research is increasing every day. It is therefore impossible to disregard this fast-growing area. Biotechnology and molecular biology will certainly play major roles in clarifying the causes of some of the unsolved mysteries of modern medicine, such as heart disease, hypertension, major psychiatric illness, rheumatic disease, and many others. Work in these fields may also help us to gain insight into broader aspects of human biology including devel-

opment, aging, and evolution, adding to the importance and necessity of molecular medical research.

## Postdoctoral and Graduate Student Program

### Graduate students

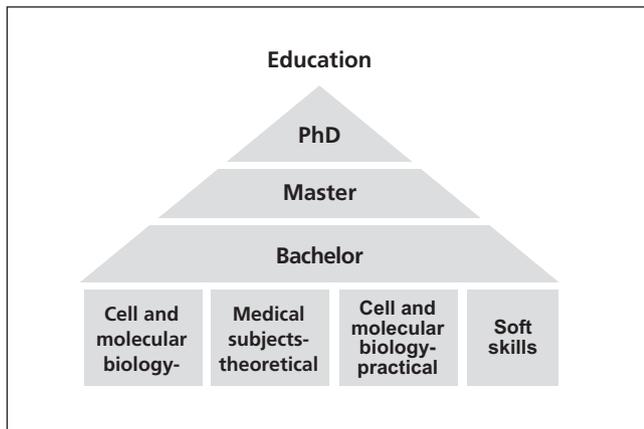
Masters and Ph.D. programs are offered in the Department of Molecular Medicine under the aegis of the Institute of Health Sciences. Graduate students at the department carry out thesis research under the supervision of staff members. Generally, these students have completed their major course work requirements for the M.S. and doctoral

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degrees and are engaged in full-time research. During the past few years, 13 students have worked here, supported by training grants to the University of Istanbul or by investigation research funds from the state. During the past 4 years, six students have completed their degrees in the Department of Molecular Medicine.

The program allows young investigators to develop APOE, ACE, LPL, AGN, CETP, PON1, END1 and MTHFR skills in research methodology and interpretation. It is generally agreed that establishment of high technology in both medicine and biology will help Turkey in becoming a developed state. In other words, the status of a country that exports more than it imports is achieved only by maintaining enough technical knowledge of molecular biology, physiology, biophysics, biochemistry, genetics, and immunology, etc.<sup>1-67</sup>



### Current research overview

The University's Department of Molecular Medicine is involved in many aspects of metabolic diseases that affect several million people worldwide, including atherosclerosis, hypertension, diabetes, and Alzheimer's disease. Another branch of the department is dedicated to cancer research. In all of these areas, research on free oxygen radicals is being conducted, as well as molecular biological analyses of several substances such as apolipoprotein E, angiotensin, angiotensinogen, lipoprotein lipase, and cholesterol ester transfer protein poly-

morphism. In the laboratory the application of molecular biological methods is used to assess the prognosis and treatment of cancer. The main areas in our cancer research include myc protein, casein kinase, p53 protein, and glutathione S-transferase polymorphism.

### Cardiovascular Biology, Hypertension and Diabetes Biology

This group studies the pathogenesis of hypertension and its sequelae, including left ventricular hypertrophy and renal insufficiency.

We examine the genetic predisposition of patients with coronary artery disease (CAD), hypertension, preeclampsia and diabetes mellitus (DM) in Turkish population and intended to determine whether genetic variations at the Apolipoprotein E (apoE), Angiotensin converting enzyme (ACE), Angiotensinogen (AGN), Angiotensin Type 1 Receptor (AT1R), Lipoprotein lipase (LPL), Cholesterol Ester Transfer Protein (CETP), Paraoxonase (PON1), endothelin (END1) and Methylenetetrahydrofolate reductase (MTHFR) locus were determined. Polymerase Chain Reaction (PCR), RFLP (Restriction Fragment Length Polymorphism), and agarose gel electrophoresis techniques were used to determine the apo E genotypes.

In the patients with CAD, the frequencies of Apo E e2, e3, e4 alleles were 0.05, 0.85, 0.10 in CAD patients and 0.6, 0.91, 0.04 in control groups. CETP Msp1 M1 and M2 allele frequencies 0.77, 0.23 and 0.64 and 0.36 in CAD patients control groups respectively. The frequency of Apo e4 ( $p < 0.05$ ) and CETP M1 ( $p < 0.01$ ) alleles were higher than in the control group. Msp M1 ( $p = 0.012$ ) and Apo e4 alleles ( $p < 0.05$ ) were associated with low HDL cholesterol levels in patients group. The distributions of LPL genotype and allele did not differ between the CAD and control groups. The frequencies of DD, ID, and II genotypes of ACE among the patients group were 0.66, 0.19 and 0.14, whereas among the control subjects these were 0.30, 0.38 and 0.32 respectively. The frequency of DD genotype was higher in the patient

group (66.7%) than control subjects (30.3%). Frequencies of PON 192 AA, BB AB and PON 55 LL, MM, and LM genotypes among the patients with CAD were 0.32, 0.15, 0.52; 0.39, 0.05, 0.55, among the control subjects, there were 0.32, 0.09, 0.58; 0.46, 0.06, 0.47, respectively. The gene frequency for the PON1 192/55 polymorphisms were not statistically significant between controls and CAD patients ( $P=NS$ ,  $\chi^2$  test). Distribution of endothelin (END-1) genotypes (AA, GG, AG) in patients with CAD are: 9(15.8%), 21(36.8%), 27(47.4%), and in control subjects: 1(3.1%), 18(56.3%), 13(40.6%) respectively. Patients with END-1 A alleles (AA+AG) had higher serum END-1 levels than patients with GG genotypes (3.41±0.34 pg/ml vs 3.20±0.29 pg/ml,  $p<0.01$ ). The present study demonstrates that the END-1 A alleles may be responsible with high serum END-1 levels and predisposition of coronary artery disease in Turkish patients.

In hypertensive group, the frequencies of DD, ID, and II genotypes of ACE among the patients group were 0.45, 0.09, and 0.54 and among the control subjects were 0.42, 0.20 and 0.38. Carrying of ACE D allele was significantly higher than controls (99.1% vs 80%) ( $p<0.001$ ). AGN M235T TT genotype was found significantly higher in hypertensives than control group (20% vs 2.7%;  $p<0.001$ ). The frequency of AGN T174M M allele was higher in the hypertensive group than control subjects (8.76% vs 4.81%). Carrying of ATR1 C allele was found higher in hypertensives than controls (39.4% vs 25.9%) ( $p=0.054$ ). The frequencies of apo e2, apo e3, and apo e4 alleles were 3.97%, 88.06%, and 7.95% in hypertensive group and 5.5%, 92.0%, and 2.38% in control group. There were about twice as many individuals in the heterozygotes hypertensive group who had apo E as compared to the control group (7.30% vs 2.38%) ( $p=0.07$ ). The hypertensive patients who were carriers of the apo e4 had significantly higher organ damage [left ventricular hypertrophy ( $p<0.001$ ), dilated left atrium ( $p<0.05$ ), retinopathy ( $p<0.05$ )] compared to those who were not carriers of apo e4. In type II diabetes mellitus, the frequency of the MTHFR mutated allele (T) was 31.7%, while 31.1% in the control group. The homozygous muta-

tion (T/T) in the MTHFR gene was identified in 12% of type II diabetes mellitus patients versus in 9.3% of controls. Patients with TT genotype showed a higher prevalence of LVH compared to patients with CC and CT genotypes ( $p=0.01$ ). It was suggested that MTHFR gene C677T mutation was a possible risk factor of the development of LVH in type II diabetic patients. Frequencies of ACE DD, ID, II genotypes were 0.56, 0.36, 0.06 in Type II DM and 0.35, 0.50, 0.15 in Type I DM and 0.36, 0.44, 0.20 in diabetic nephropathy patients. ACE D alleles was significantly higher than control groups ( $p<0.05$ ). Frequencies of PON 192 AA, BB AB and PON 55 LL, MM, and LM genotypes among the patients with

NIDDM were 0.48, 0.10, 0.41; 0.54, 0.03, 0.42; among the control subjects, these were 0.33, 0.09, 0.57; 0.46, 0.06, 0.46, respectively. The gene frequency for the PON1 55/192 polymorphisms in controls and NIDDM patients was not significantly ( $P=NS$ ,  $\chi^2$  test). Our findings showed that the two polymorphisms were associated with PON1 activity, which increased in the order of the AA < AB < BB genotype in the PON1 192 polymorphism and MM < ML < LL genotype in the PON1 55 polymorphism.

In preeclamptic pregnant, we found an association between the genotype II and low ACE activity in preeclamptic women and an association between D allele frequency and preeclampsia. The prevalence of MTHFR TT genotype was found nonsignificant in the preeclamptics. Total homocysteine (t-Hcy) in the plasma of preeclamptics was found increased with regard to healthy pregnant ( $p<0.001$ ). Preeclamptic patients bearing CC genotype (wildtype) had significantly higher homocysteine levels than those with uncomplicated pregnancy ( $p=0.009$ ); which rule out the possibility that the presence of a mutated allele is associated with hyperhomocysteinemia seen in preeclamptics. In membranoproliferative glomerulonephritis (MPGN) patients distribution of PON1 192 genotype (AA, AB, BB) in MPGN patients were 61.1%, 27.8%, 11.1% and in controls 15.1%, 49.1%, 35.8%, respectively. The frequency of AA genotypes was significantly higher in MPGN group (0.611) compared with the

controls (0.151) ( $p= 0.001$ , Fisher exact test). Our results suggest that homozygosity for the A allele seems to be a risk for developing MPGN and may also be associated with the poor prognosis of disease in Turkish children.

In conclusion, these studies in Turkish population demonstrate that the CETP Msp1 and Apo E gene polymorphisms are associated with variations in lipids in patients with CAD and ACE I/D and END1 polymorphisms have an effect on development of CAD, but are not LPL Pvu II and PON1 192/55 polymorphisms. ACE, AGN, ATR1 and Apo E polymorphisms are associated with hypertension and ApoE4 allele is associated with hypertensive organ damage. In addition, MTHFR C677T T mutant allele is associated with cardiovascular symptoms in NIDDM and paraoxonase activities are affected by PON1 polymorphism and NIDDM. Additionally, ACE I/D gene polymorphism is a genetic determinant for the occurrence of preeclampsia but not MTHFR C677T mutation. We showed that preeclampsia is associated with ACE D genotype. Finally, our results suggest that homozygosity for the A allele seems to be a risk factor for developing MPGN and may also be associated with the poor prognosis of disease in Turkish children.

These studies are basis for genetic susceptibility cardiovascular disease and diabetes in Turkish population. 2-13 Angiotensin-I Converting Enzyme Gene Polymorphism In Turkish Type 2 Diabetic Patients. Non insulin dependent diabetes mellitus is often associated with some complications such as nephropathy, retinopathy and neuropathy. Genes of the renin angiotensin system are potential candidate genes for diabetic complications. Therefore we investigated the relationship between Angiotensin Converting Enzyme (ACE) gene polymorphism in type 2 diabetic patients with and without diabetic nephropathy. We studied 75 patients (25 type 2 diabetic patients with nephropathy, 50 type 2 diabetic patients without nephropathy) and 37 healthy controls. Gene polymorphism of ACE was determined by PCR (polymerase chain reaction) amplification using allele-specific primers.

The frequencies of ACE DD, ID and II genotypes among the patients with type 2 diabetic patients

48%, 42%, 10% and in control subjects were 27%, 60%, 13% respectively. Carrying DD genotype in Type 2 diabetic patients without nephropathy 1.77 times increased than control subjects ( $p<0.05$ ). There is no significant correlation between diabetic nephropathy and ACE gene polymorphism. But we found that ACE DD genotype increased significantly in Type 2 diabetic patients compared to control subjects ( $p<0.05$ ).

Association between Apo B signal peptide gene polymorphism and NIDDM. Non-insulin-dependent diabetes mellitus (NIDDM) is a heterogeneous disorder resulting from interactions of numerous genetic and environmental factors. Direct linkage between glucose and lipid metabolism is hypothesized to account for altered lipid profiles in diabetic individuals and a growing understanding of apolipoprotein and lipid metabolism is shedding new light on the pathophysiology of NIDDM. A critical role in blood lipid metabolism is played by apoprotein B (Apo B) and genetic variations in this protein are thought to be associated with susceptibility to cardiovascular disease among diabetic individuals. We aimed to investigate whether there is any relation between polymorphism of the Apo B gene and NIDDM in the Turkish population. In our study, frequency of the SP-24 allele was higher in the NIDDM group than the control subjects ( $p.0.01$ ). The results of our study support the hypothesis that the SP-24/24 genotype of signal peptide gene is a linkage marker for an underlying aetiological mutation that confers a risk for the development of NIDDM and is detectable in subjects previously unidentified by a history of classic risk factors. The numbers in our study are relatively small and thus may be open to dispute, but a relationship between the SP-24 allele and NIDDM is strongly indicated and further studies are warranted.

Is there a role of angiotensin-converting enzyme gene polymorphism in the failure of arteriovenous femoral shunts for hemodialysis? In humans, thrombosis and neointimal hyperplasia are the major factors responsible for prosthetic graft occlusion. Previous studies suggest that the renin-angiotensin system is one of the key enzymes in the vascular sys-

tem and has been implicated in the pathogenesis of thrombosis and neointimal hyperplasia. We conducted a case-control study to determine the frequency of the different angiotensin-converting enzyme (ACE) genotypes among the patients who had PTFE graft implantation for hemodialysis access. Between 1997 and 1999, 30 graft implantations were performed. Twelve individuals (40%) developed thrombotic complications, 8 of the 12 patients had ACE ID polymorphism, and 2 patients had DD and 2 patients had II polymorphism. The ID polymorphism was significantly more frequent in the thrombosed arteriovenous (A-V) grafts than in non thrombosed A-V grafts ( $\chi^2 = 7.57$  and  $p = 0.02$ ). Overall, the frequency of the D and I alleles was 66.6 and 33.3%, respectively. In conclusion, ID polymorphism of the ACE gene plays an important role in the pathogenesis of vascular access thrombosis in subjects undergoing hemodialysis for chronic renal failure.

## Molecular Oncology

Analysis of L-myc gene polymorphism in Breast, Gastric, Lung and and Thyroid cancer. We examined patients with lung, breast, gastric and thyroid cancer to determine whether genetic variations in L-myc gene were associated with higher susceptibility to the afore mentioned diseases. Polymerase Chain Reaction (PCR), Restriction Fragment Length Polymorphism (RFLP), Agarose Gel Electrophoresis Techniques were used to determine the L-myc genotypes in patient and control groups. The results were evaluated using SPSS 7.5 statistical software. Shown below are the conclusions from our research regarding the investigated genetic factors and their association as predisposition factors with the diseases of cancer. These studies in Turkish lung cancer patients demonstrate that the L-myc gene polymorphism is not associated with smoking status, cancer susceptibility or prognosis, and especially increased risk of metastasis either to the lymph nodes or to other organs. According to these results, we found no significant difference both in the distribution of the LL, LS and SS genotypes and in the allelic frequencies between the patient group and

the control group. Our data concerning age, sex, size of tumours, histological type of tumours showed no significant association with L-myc genotype. However, a higher frequency of L-myc S-allele in the epidermoid carcinomas compared to other histological groups was found, although this difference was not statistically significant. In our group of gastric cancer patients, there was a significant difference in the distribution of both L-myc genotypes ( $p=0.004$ ) and allele frequencies ( $p=0.005$ ) between patients with gastric cancer and control groups.

In patients with breast cancer, the frequency of S allele was significantly higher in breast cancer patients than in normal individuals ( $p<0.01$ ). No correlation was observed between the presence of L-myc S allele and several parameters in the history of each patient or characteristic of tumors. We also studied 138 patients of whom 47 had multi nodular goiter, 13 follicular cancer, 69 papiller cancer against a control group of 109 healthy individuals. We found no significant difference in the distribution of LL, LS, SS genotypes among these groups. However, the frequency of S allele was significantly higher in follicular thyroid cancer patients than in patients with multinodular goiter ( $p=0.04$ ). Testing several genetic polymorphisms, simultaneously has the potential to identify individuals with an extremely high risk of developing cancer. This has profound implications for prevention since such high-risk individuals may be screened intensively as well as potentially treated with several preventive approaches. These studies constitute the basis for genetic susceptibility to lung, breast, gastric and thyroid cancer in Turkish patients.

GST M1 and CYP1A1 gene polymorphism and daily fruit consumption in Turkish patients with non-small cell lung carcinomas. In the present study we explored the association between genetic polymorphisms of CYP1A1 and GST M1 and non-small cell lung cancer ( $n=55$ ) and controls ( $n=60$ ), in Turkish subjects. We used PCR methods and enzyme restriction for determining polymorphism. We found that CYP1A1 mutant variant (Ile/Val) was more highly expressed in Turkish patients and controls than in other Caucasian populations. Our find-

ings were similar to Far Eastern populations (32.7% for patient group, 43.1% for controls). In despite of the similarity between the groups regarding GST M1 polymorphism, in the patient group, patients with GST M1 null genotype had a statistically significant positive history of exposure to carcinogens other than smoking, such as asbestos, petrochemicals and/or other chemicals ( $p=0.01$ ). The patients, who had CYP 1A1 mutant variant, had increased risk of adenocarcinoma ( $p=0.046$ ) of lung (8 out of 18 patients) and 6 of them also had GST M1 (-) gene variants together. The patients who consumed less fruit daily had a greater risk of epidermoid carcinoma of lung ( $p=0.019$ ). However this study showed that there were no differences between the patient and control groups regarding genetic polymorphism of genes.

The Apolipoprotein E e4 allele is not a risk factor for Turkish Breast Cancer Patients. Many studies have shown that apolipoprotein E (ApoE) is a potential inhibitor of cell proliferation so it is also thought to have a considerable role in antioxidant activity and thus in tumor growth and proliferation. ApoE has three common isoforms, E2, E3 and E4, coded by three variant alleles, e2, e3, and e4; the presence of different isoforms is reported to affect tumor growth and proliferation at different levels. Our study was designed to determine whether Apo E polymorphism is associated with breast cancer and tumor cell proliferation.

ApoE polymorphism was studied in 32 breast cancer patients (mean age  $56.9 \pm 10.73$ ; age range 32-74 years) and 20 healthy subjects. Healthy persons without any malignancy were selected for the control group (mean age  $54.3 \pm 12.01$ ; age range 32-74 years). The diagnosis of breast cancer was established by mammography, ultrasonography and pathological examination. The samples were collected before any chemotherapeutic or radiation therapy treatment had been started DNA was isolated from the blood leukocytes in 10 ml EDTA by the method of Miller et al. Apo E genotyping was carried out by the Apo E genotyping Kit (Roche, Germany) which allows the detection of point mutations in codon 112 and 158 of the human

apolipoprotein E gene using the light cycler instrument.

During cycling, the hybridization probes hybridize the specific PCR product at the annealing temperature and fluorescence is monitored on the light cycler channel. All results come out to checking channel 2 and 3 when the test run completed on the light cycler. Channel 2 after color compensation allows genotyping of codon 112 and channel 3 allows genotyping of codon 158. This result shows that the allelic frequency for E2 is 3.1% for e3 95.3% and for e4 1.6% in the breast patient group and that the allelic frequency, in the control group was e2 is 0%, e3 100% and for e4 0%. We could find no significant difference between allelic frequencies in breast cancer patients and in the control group.

We conclude that the apolipoprotein e4 allele is not a risk factor for breast cancer in Turkish patients.

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