B – Data Analysis and Bioinformatics in Medical Genetics

B01 ALLELIC FREQUENCIES OF GENETIC VARIANTS ASSOCIATED WITH BONE MARROW DENSITY, IN TURKISH POPULATION

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Introduction: Osteoporosis is a complex disease, which prevalence markedly increases with aging. The disease characterized by increased risk of bone fracture and reduction in skeletal mass. Population based studies indicates contribution of genetic traits to disease, besides of hormonal, nutritional and lifestyle factors. In this study, we investigated single nucleotide polymorphisms, to access allelic frequency of genetic variation associated with osteoporosis.
Materials and methods: Genotyping were carried out in a large sample group (n = 500), using MALDI_TOF based mass spectrometry. Genes, significantly associated with differences in BMD and/or fracture risk in multiple replication studies were included and sequence variants, IL-6_rs**1800795,** TNF-alfa_rs**1800629**, IL-6_rs**1800796**, VDR_rs**1544410**, Col1A1_rs**1800012**, VDR_rs**2228570**, VDR_rs**731236**, were analyzed according to manufacturer's protocol of Sequenom hME platform.
Results: Genotype and allele frequencies were calculated and compared with other populations. Genotyping results were consistent with the Hardy-Weinberg equation. Some genotypes, causing susceptibility to osteoporosis, were found to be frequent in the screened group.
Conclusion: The application of genomics tools and concepts on an individual level may provide more useful and person-specific knowledge for preventing disease. To determine the prevalence of genetic factors in the population may contribute to the development of more precisely and safely healthcare systems that target individuals rather than general public.
Key words: Genetics of complex diseases, susceptibility to osteoporosis, genetic factors and BMD

B02 MULTIFACTOR DIMENSIONALITY REDUCTION (MDR) ANALYSIS FOR GENETIC MODELING OF COMPLEX DISEASES

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Introduction: The nature of coronary artery disease (CAD) as a complex trait involves multiple genetic and environmental interactions. The objective of our study is to predict a genetic model for CAD using MDR method; a non-parametric data-mining approach.
Materials and Methods: Early onset CAD patients (n = 102), (n = 90) and controls (n = 102), (n = 90) respectively for two separate studies were included. Interactions among 5,10 MTHFR C677T, PAI-1 4G/5G, eNOS 3-27bp repeat polymorphisms for the first study and 5,10 MTHFR C677T, PAI-1 4G/5G, eNOS 3-27bp repeat, ACE-I 287bp Alu repeat, PON1 Gln192Arg polymorphism for the second study were evaluated. MDR analysis was performed to identify a model of CAD based on genetic and conventional risk factors in both studies. Statistical significance of MDR was determined using permutation test and was accepted at p value less than 0.05.
Results: The best model of CAD was the two-locus model with two genes, but it failed to reach a statistical significance (p = 0.24) in the first study. However in the second study, MDR analysis detected a significant model with four genes (prediction success approximately 61%, p = 0.03). When conventional risk factors were included, a different model with similar prediction was achieved with three genes.
Conclusion: MDR analysis can provide complex trait models at much smaller sample sized compared with single locus association studies. Our results suggest although it is difficult to characterize high order epistasis among genes and environmental factors, it is a more powerful approach to study complex traits as CAD. Future studies should focus on making inferences about biological epistasis from statistical epistasis.

B04 THE ADAPTATION OF DENSITOMETRIC ANALYSIS TO DIFFERENTIAL DISPLAY GELS OFFERS WELL-MATCHED RESULTS WITH MICROARRAY

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Differential Display (DD), also known as DD-PCR or DDRT-PCR, is one of the major tools in interpreting gene expression patterns. With its simplicity, DD methodology also offers reproducibility, comparison of all mRNA species in the cell populations of interest, and isolation of corresponding cDNA. A number of different protocols have been evolved from basic DD starting since the day it was invented. Our approach basically relies on quantification of the DD results, thus making them calculable. In our ongoing study, which is actually on papillary thyroid carcinomas (PTC), we have taken advantage of the idea that measuring the intensity of gels via software which is also widely used in western blot gels. The gel images were first adjusted for analysis using GIMP (an open-source image editing software) and gel bands were measured using ImageJ (a public domain software developed by National Institutes of Health). Using the integrated density (ID) values that calculated by ImageJ software, we found a number of gene expression differences between groups (Student-Newman-Keuls test). One of the genes which was previously associated with PTC by others using microarray was ZFP36L2 (TIS11D) gene. Other studies found 2.2-fold decrease and 2.5-fold increase in 2 different groups of samples. In our study, quantification of gel bands showed that our data regarding ZFP36L2 gene were very similar to microarray results. Despite the speculations over DD because of its high false-negative rates, our data demonstrated that DD can give reliable results as microarray.

B05 AUTOZYGOSITY SEARCH IN A TURKISH FAMILY WITH SCOLIOSIS, BLINDNESS, AND ARACHNODACTYLY

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Scoliosis, blindness, and arachnodactyly syndrome **(OMIM ID612445)** has been described by Dundar *et al*. in a family with parental consanguinity. The 29-year-old male proband had scoliosis, arachnodactyly of both fingers and toes, and progressive visual loss and strabismus. His 33-year-old brother had severe kyphoscoliosis, arachnodactyly of fingers and toes, and was bilaterally blind. His 39-year-old sister had only eye findings. Late father, 60-year-old, had mild scoliosis, blindness, and arachnodactyly. Mother and 2 more brothers were normal while 2 sisters had mild scoliosis. Parents were first cousin. In this report we present the strategy employed to determine the gene locus responsible for the syndrome. Whole genome SNPs were scanned using 250 K Affymetrix Arrays. Runs of homozygosity shared by two affected brothers and segregating in the entire pedigree with different combinations due to unclear affected status of some siblings were visually evaluated. Two and multiple-point LODscore analyses were performed by easyLINKAGEplus v5.08. Five homozygous blocks over 2 Mb shared by two affected brothers were found to be segregating with phenotype in 2 affected and 3 unaffected siblings and in mother whose phenotypes were unequivocal. The longest homozygous block in this first analysis was found to be on the 14th chromosome between 67817621bp (rs7148416) and 82508151bp (rs17117757). When another sister with positive eye findings was added to the analysis, this region was narrowed down to between 67817621bp (rs7148416) and 75657598bp (rs11626830) for which a maximum LODscore of 2.3956 was calculated with two-point analysis.

Sequence analysis of the *LTBP2* gene located on this region is currently under examination.

B06 HETEROZYGOSITY FREQUENCIES OF THE STR MARKERS IN TURKISH POPULATION, WHICH ARE COMMONLY USED IN CHIMERISM ANALYSIS

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Recently, Short Tandem Repeat (STR) markers have been commonly used in the posttransplant detection of donor cells (chimerism analysis), elimination of maternal contamination in prenatal diagnosis and biological identity detection. This method is reliable, inexpensive, fast and sensitive to show very low level chymeric situations or contaminations. The aim of this study is to reveal the informativeness of the STR markers used in a commercially available widely used chimerism analysis kit ([AmpF*ℓ*STR® Identifiler® PCR Amplification Kit (Applied Biosystems)]. The study included 100 healthy bone marrow transplant donors whose molecular analyses were performed in Molecular Genetics Laboratory of Ege University, Faculty of Medicine Department of Medical Genetics. The STR markers analyzed were D3S1358, vWA, FGA, D8S1179, D21S11, D18S51,D5S818, D13S317, D7S820, D19S433, THO1, D16S539, CSF1PO, TPOX, D2S1338.

Results: The highest heterozygosity rate (89%) was found for the STR marker *D18S51*. The heterozygosity rates for the other STR markers are as follows: 82% for *D7S820*, 80% for *D3S1358*, 82% for *D8S1179*, 84% for *D21S11*, 82% for *TH01*, 82% for *D13S317*, 82 for *D16S539*, 85 for % *D2S1338*, 77% for *D19S433*, 82% for *vWA*, 78% for *FGA*, 65% *CSF1PO*, 59% for *TPOX*, 72% for *D5S818*. In conclusion except two STR markers (CSF1PO and TPOX), the heterozygosity rates of STR markers included in the kit were found to be efficient to reveal the chimeric cases and to identify the biological identity in our population.

