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DETERMINATION OF THE RELATIONSHIP BETWEEN GENOTYPES AND CHROMOSOMAL ABERRATION FREQUENCIES IN A NORMAL POPULATION.

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Individual differences in cancer susceptibility may be attributed in part to genetic differences in the genes which code for enzymes involved in metabolic activation and detoxification of environmental procarcinogens. Polymorphisms of certain genes functioning in this manner (CYP2D6, CYP1A1, CYP2E1, NAT1, NAT2, GSTT1, GSTM1) have been linked to an increased risk of some cancers. An increased level of genomic instability, often reflected as an increase in chromosomal aberrations (CA), has also been associated with an elevated risk of cancer. Accurate polymorphism frequency determinations for these genes in a normal population is needed to establish whether these frequencies are different in a diseased population. In this work, analyses are being performed on over 100 normal individuals, ranging from 0 to 80 years of age, to determine CA frequency and genotypes. Individual exposure and health data have also been obtained from all individuals in the study. These analyses will provide a baseline frequency for the various gene polymorphisms in a normal (mainly Caucasian) population, and will determine whether a relationship between the CA frequency and certain polymorphisms and or genotypes exists. In addition the interaction between environmental exposures (such as smoking), genotypes and CA frequencies are being examined. At present 24 individuals have been genotyped for GSTT1, GSTM1 and CYP2D6(T) and their CA frequencies determined. Genotype frequencies of 21% for GSTT1 null, 46% for GSTM1 null, 29% for GSTM1 A, 21% for GSTM1 B, 4% for GSTM1 A,B, and 0% for CYP2D6(T) have been determined from the small sample analyzed to date. We plan to extend our genotype analysis to include the remaining CYP2D6 polymorphisms, CYP2E1, CYP1A1, NAT1 and NAT2. Work performed under the auspices of the US DOE by LLNL contract No. W-7405-ENG-48.