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Dissertation

Title	***GENETIC POLYMORPHISM OF CYTOCHROME P1-450A2 (CYP1A2) AND N-ACETYLTRANSFERASE2-(NAT2) AMONG EMIRATIS***
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Abstract	Brief introduction: There are limited studies on CYP1A2 and NAT2 polymorphisms among Emiratis. Aims: This study aims to determine CYP1A2 and NAT2 alleles and genotypes and correlate these genotypes with caffeine metabolism phenotypes among Emiratis. Methods: After obtaining informed consent, five hundred and eighty one non-smoker subjects were given 300ml of caffeinated soft drink and were asked to provide a buccal swab and a urine sample two hours later. TaqMan Real Time PCR, PCR-RFLP, DNA sequencing were performed to determine CYP1A2 and NAT2 alleles and genotypes. Phenotyping was carried out by analysing the caffeine metabolites using HPLC analysis. Results: We found that 1.4%, 16.3% and 82.3% of the recruited subjects were slow, intermediate and rapid CYP1A2 metabolisers, respectively. Only 1.4% of the subjects were homozygotes for CYP1A2 mutant alleles while 16.1% were heterozygotes and 82.5% were homozygotes for the CYP1A2 wild type genotype. Therefore, the frequency of the wild type genotype CYP1A2*1A/*1A was 0.825 followed by CYP1A2*1A/*1C and CYP1A2*1A/*1K, with frequencies of 0.102 and 0.058, respectively. The degree of phenotype/genotype concordance was 81.6%. The CYP1A2*1C/*1C and CYP1A2*3/*3 genotypes showed the lowest phenotype status. With regards to NAT2, we found that 78.5%, 19.1% and 2.4% of the subjects were slow, intermediate and rapid NAT2 acetylators, respectively, with 77.4% being homozygote or heterozygote for NAT2 mutant alleles and 18.4% and 4.2% were heterozygote and homozygote for the NAT2 wild type genotypes, respectively. The most common genotypes found were NAT2*5B/*7B, NAT2*5B/*6A, NAT2*7B/*14B and NAT2*4/*5B with frequencies of 0.255, 0.135, 0.105 and 0.09, respectively. The degree of phenotype/genotype concordance was equal to 96.2%. The NAT2*6A/*6A, NAT2*6A/*7B, NAT2*7B/*7B, NAT2*5A/*5B and NAT2*5A/*5A genotypes were found to be associated with the lowest 5-Acetylamino-6-Formylamino-3-Methyluracil/1-Methylxanthine (AFMU/1X) ratios. Significant contributions: The majority of the studied Emiratis are slow NAT2 acetylators with implications for the prescription of medications that are metabolised by this enzyme. In addition, a small percentage of Emiratis have slow CYP1A2 enzyme activity which again should be taken into consideration when prescribing medications that are partially metabolised by this enzyme. In Emirati population, the frequency of the CYP1A2*1A and NAT2*5 alleles were the highest relative to other alleles frequencies. Moreover, Individuals who carried NAT2*6A/*6A, NAT2*6A/*7B, NAT2*7B/*7B, NAT2*5A/*5B, NAT2*5A/*5A, CYP1A2*1C/*1C or CYP1A2*3/*3 genotypes might be at high risk of toxicity with some drugs and some diseases compared to others as these genotypes are associated with the slowest phenotype status. Consequently, genetic testing is recommended prior to prescribing medications that are largely metabolized by CYP1A2 or NAT2. Gap filled: This is the first detailed study of CYP1A2 and NAT2 alleles and genotypes among Emiratis.