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Title: Genetics of detoxification and oxidative stress pathways in COPD

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Body: Cigarette-smoking, although, is the most important risk factor, but only a small percentage of smokers develop symptomatic COPD. Does that mean the genetic predisposition plays a pivotal role? To address this query, we investigated polymorphisms on several genes but restrict here to cytochrome p450 1A1(CYP1A1), CYP1A, CYP2E1, N-acetyl transferase (NAT) and microsomal epoxide hydrolase (mEPHX) of detoxification and cytochrome b-245 alpha (CYBA), glutathione-S-transferase P1 (GSTP1) of oxidative stress pathways in a case-control design. We present data on haplotypes, gene-gene interactions and correlations with clinical and biolevels. Haplotypes 462Val:3801C, 462Val:3801T of CYP1A1, −1293C:7632T, −1293C:9893C, −1293C:9893G and −1293C:7632T:9893C of the CYP2E1, 930G:242C of CYBA ($p<0.05$); 105V-114V of GSTP1 ($p<0.001$) and 113H-139H of mEPHX ($p<0.05$) were over-represented in patients. The same alleles-associated genotype-combinations between genes, GSTP1:CYBA and NAT2*6 and NAT2*7 alleles were prevalent in patients ($p<0.01$). Patients had significantly elevated malondialdehyde (MDA) level and decreased catalase (CAT), glutathione peroxidase (GPx) activities, glutathione (GSH) level (p 0.01). Genotypes, 462Ile/Val+Val/Val, 3801TC+CC of CYP1A1 and 930AG+GG of CYBA associated with increased MDA level, decreased FEV1, CAT activity and GSH level in patients (p 0.05). Likewise genotypes, I105V/V105V, A114V/V114V of GSTP1 and Y113H/H113H of mEPHX associated with increased MDA and decreased GSH levels in patients(p 0.05). Gene polymorphisms affecting the function of proteins cause imbalance of detoxification and oxidative-stress pathways thereby contributing to pathogenesis.