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Title: Identifying genetic susceptibility to isoniazid- induced hepatitis

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Body: Isoniazid (INH)- induced hepatitis can be fatal. The identification of risk genotypes offers the possibility of therapy individualization and may decrease the frequency of this complication. This study aimed to evaluate the association of polymorphisms of genes involved in INH metabolism or related with hepatocyte response to chemical-induced stress, with the susceptibility to INH-induced hepatitis. Materials and methods: A total of 109 treated tuberculosis patients, were studied. Ten polymorphisms of NAT2 were genotyped by sequencing; polymorphisms of CYP2E1 (rs6413432 and rs2031920) and ABCB11 (rs2287622) were analyzed by PCR - RFLP assay and homozygous for GSTM1 and GSTT1 deletions were identified by PCR multiplex. Results: Clinical variables such as age, alcoholic habits or previous hepatitis, were not associated with the occurrence of INH-induced hepatitis. Slow acetylators (52.3%) identified by NAT2 genotyping were significantly more prone to develop hepatotoxicity (p = 0.01; OR = 3; 95% CI = 1.23-7.35). Polymorphisms of CYP2E1, GSTM1 and GSTT1 were not associated with the phenotype. For ABCB11 polymorphism, homozygous for variant Ala had increased risk of developing hepatotoxicity (OR = 2.1; 95% CI = 0.9-5), though not reaching statistical significance. This effect was more evident for females than for males (OR = 2.19; CI = 0.45-10.58). Conclusion: NAT2 genotyping contributes to identify susceptible patients to INH-induced hepatitis. Prospective studies will define genotyping contribution to the reduction of this infrequent but fearsome complication. Polymorphism in ABCB11 gene deserves further investigation, especially among women.