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### Role of xenobiotic and drug resistance genes in acute myeloid leukemia

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**Introduction:** Genetic polymorphisms that affect drug resistance in AML include variants of Phase 1 and Phase 2 metabolizing genes. Furthermore, drug resistance in AML frequently involves over expression of ABC transport proteins and altered expression of apoptotic genes.

**Objectives:** To analyze the association of polymorphisms in xenobiotic/drug metabolizing genes (*GSTM1*, *GSTT1*, *GSTP1*, *CYP1A1*, *EPHX1*, and *SULT1A1*) and p53 codon 72 gene polymorphism in 131 adult patients of AML and 199 healthy controls by PCR-RFLP method. Further, the expression of drug resistance genes (*MDR1*, *MRP1*, *LRP*, *BCRP*, *GSTP1* and *DHFR*) and apoptosis (p53, BCL-2, Survivin) was determined by real time RT-PCR in 45 adult patients of AML.

**Result:** The main effect of each SNP assessed for the risk using conditional logistic regression model showed no significant association with AML risk. In multifactor dimensionality reduction (MDR), the best four locus model (P53, EPHX1 exon3, CYP1A12A, and SULT1A1) had TA of 58.08% (CVC =10/10), however lost significance in permutation testing of p-values. In CART analysis, combinations of *GSTM1* present, *CYP1A12C* AA or GG, *EPHX1* exon3 TC, and *EPHX1* exon4 AA or GG genotype strongly enhanced the risk of AML (OR=5.89; 95% CI=1.40–26.62; P=0.01). Real-time PCR results showed that *MDR1* expression was significantly associated with the expression of CD34 marker (p=0.002). The expression of *MDR1* (3.56±2.23) and BCL-2 (3.43±1.77) was significantly higher in non-responder patients who did not respond to induction chemotherapy compared to responders (1.71±3.09, p=0.001 and 2.19±1.06, p=0.02).

**Conclusion:** The study showed the clinical relevance of *MDR1* and BCL-2 in drug resistance and an importance of high order gene-gene interaction of xenobiotic gene SNPs in AML risk.

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