Germline genetic variants in *VDR*, *RFC* and *IL15* genes are associated with minimal residual disease in pediatric B-cell precursor ALL

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BACKGROUND & OBJECTIVES

Minimal residual disease (MRD) is the most significant prognostic factor in acute lymphoblastic leukemia (ALL).

We aimed at identification of host genetic variants associated with MRD in patients with pediatric ALL.

DESIGN & METHODS

- **159 patients** treated according to ALL-IC-BFM 2002 & 2009 protocols
- **23 genetic variants** potentially involved in: metabolism of drugs used in ALL; anti-tumor immunity and MRD-associated variants revealed by Genome-Wide Association Study
- Genotyping by: High Resolution Melting, TaqMan Genotyping Assays, PCR and PCR-RFLPF
- **MRD assessment at day 15, day 33 and week 12** by flow cytometry or real-time quantitative polymerase chain reaction
- 10^{-4} cut off level used to identify high vs. low/negative MRD levels

Gene Symbol	Gene Name	Involement	rs Identifier	Polymorphism Type	Genotyping Method
Loci Selected Based on Candidate Gene Approach					
MDR1	Multidrug Resistance Protein 1	drug transport (nonspecific)	rs3789243 rs2235046 rs1045642	SNP	HRM
VDR	Vitamin D (1,25- Dihydroxyvitamin D3) Receptor	transcriptional regulation of gene expression	rs2228570 rs1544410		
NR3C1	Nuclear Receptor Subfamily 3, Group C, Member 1 (Glucocorticoid Receptor)	transcriptional regulation of gene expression	rs6198		
			rs41423247	SNP	TagMan
GSTP1	Glutathione S-Transferase Pi 1	xenobiotic metabolism	rs1695	SNP	HRM
GSTM1	Glutathione S-Transferase Mu 1		gene deletion	gene deletion	multiplex PCR
GSTT1	Glutathione S-Transferase Theta 1				
CCR5	Chemokine (C-C Motif) Receptor 5	migration of T cells and macrophages	**rs333**	585del32	PCR
TPMT	Thiopurine S-Methyltransferase	thiopurine drugs metabolism	**rs1142345** **rs1800460**	SNP	HRM
MTHFR	Methylenetetrahydrofolate Reductase (NAD(P)H)	drug targets	rs1801133		
TYMS	Thymidylate Synthetase		rs3474033	tandem repeats (TSER*2 / TSER*3)	PCR-RFLP
			rs3474033	SNP (TSER*3G>C)	
RFC	Reduced Folate Carrier Protein	drug transport (specific)	rs1051266	SNP	
Loci Selected Based on Association with MRD in Genome Wide Association Study					
IL15	Interleukin 15	stimulation of T cells and NK cells	**rs10519613**	SNP	HRM
intergenic	---	---	**rs3862227**	SNP	TagMan
NALCN	Sodium Leak Channel, Non Selective	ion channel transport	**rs7992226**		
CCDC85C	Coiled-Coil Domain Containing 85C	prabable role in cortical development	**rs11160533**		
intergenic	---	---	**rs4888024**		
intergenic	---	---	**rs9871556**		

RESULTS

MRD-associated polymorphic variants

VDR (rs1544410) MRD at day 15
RFC (rs1051266) MRD at day 33
IL15 (rs10519613) MRD at day 33

Risk for MRD-positivity

OR=2.37, 95%CI=1.07-5.21, *P*=0.03; A allele
OR=1.93, 95%CI=1.05-3.52, *P*=0.03; A allele
OR=2.30, 95%CI=1.02-5.18, *P*=0.04; A allele

Additive effect of carrying risk alleles on the risk of MRD-positivity

RFC* & *IL15 MRD at day 33

OR=3.94, 95% CI=1.28-12.11, *P*=0.024 (2 vs.1 risk alleles) ; **OR=6.75**, 95% CI=1.61-28.39, *P*=0.012 (2 vs.0)

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CONCLUSIONS

Germline variation in genes related to pharmacokinetics of anti-leukemic drugs and to anti-tumor immunity is associated with MRD and might help improve risk assessment in ALL.

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