ITGB7 GENE POLYMORPHISM AND CHRONIC GVHD AFTER THE ALLOGENEIC HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Ambruzova Z[1], Mrazek F[1], Raida L[2], Faber E[2], Stahelova A[1], Indrak K[2], Petrek M[1]

[1] Laboratory of Immunogenomics and Proteomics, Dept of Immunology &
[2] Dept. of Haematooncology;
Medical Faculty of Palacky University and University Hospital, Olomouc, Czech Republic.

Introduction

- **graft-versus-host disease** (GVHD) is the most serious complication of the allogeneic haematopoietic stem cell transplantation (aHSCT) and substantially influences its outcome
- **migration and distribution of activated donor T cells** to the recipient mucosal sites and parenchymal target organs of the recipient is important for development of GVHD
- **Integrin alpha-4/beta-7** (Peyer patches-specific homing receptor LPAM-1) is an adhesion molecule that mediates lymphocyte migration and homing to gut-associated lymphoid tissue (GALT)
- Integrin alpha-4/beta-7 **interacts with the cell surface adhesion molecule MAdCAM-1** which is normally expressed by the vascular endothelium of the gastrointestinal tract
- *MADCAM1* gene variants have already been associated with the risk of chronic GVHD in Czech population [1]

[1] Ambruzova Z et al. Possible impact of *MADCAM1* gene single nucleotide polymorphisms to the outcome of allogeneic hematopoietic stem cell transplantation. *Human Immunology 2009; 70(6):457-60.*

Rationale and Aim

to investigate if there is a possible relationship (association) between:

***ITGB7* gene SNP** (rs1554753)

acute or chronic GVHD

overall survival or transplant-related mortality (TRM)

Investigated subjects

87 aHSCT pairs

Age – median (range)		**Donor type**	
Patients	44 (18-61)	Related	70
Donors	40 (18-69)	Unrelated	17
Recipient gender		**Cell source**	
Female	37	PBSC	86
Male	50	Bone marrow	1
Diagnosis		**Acute GVHD**	
Acute leukaemia (AML, ALL)	43	Grade 0-I	53
Chronic leukaemia (CML, CLL)	15	Grade II	23
Non-Hodgkin lymphoma	14	Grade III	4
Other	15	Grade IV	8
Conditioning regimen		**Chronic GVHD**	
Non-myeloablative	48	None	56
Myeloablative	39	Limited	17
Donor HLA compatibility		Extensive	14
Identical	87		
Mismatched	0		

Methods

1. Genotyping
qRT-PCR with „TaqMan®“ probes (Applied Biosystems, Assay ID C_12055694_10, Fig. 1)

2. Statistics
Conformity to the Hardy-Weinberg equilibrium: Chi-square test
Differences between allele and genotype frequencies: Pearson´s Chi-squared test
Survival analysis: Kaplan-Meier analysis, log-rank test (SPSS software)

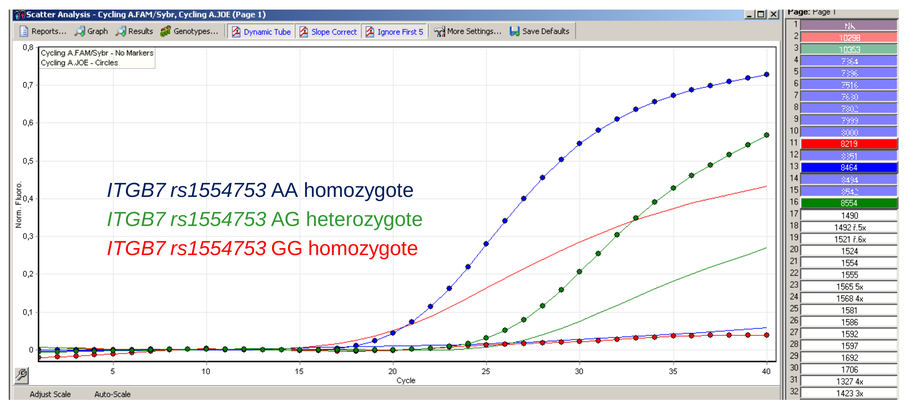

Figure 1: *ITGB7 rs1554753* genotyping by qRT-PCR - interpretation

Results

Analysis of *ITGB7* rs1554753 SNP

- no significant difference in the proportion of *ITGB7* alleles/genotypes between the groups of patients and donors (Tab.1)
- no association of recipient *ITGB7* gene variants with GVHD or survival after aHSCT
- a trend for more frequent chronic GVHD in recipients transplanted with donor possessing at least one *ITGB7* rs1554753*G allele (p=0.08, Fig. 2)

Combined analysis of *MADCAM1* rs2302217 and *ITGB7* rs1554753 SNPs

- a trend for more frequent chronic GVHD in *MADCAM1* rs2302217 AA homozygous recipients transplanted with donor carrying *ITGB7* rs1554753*G allele in comparison to other combinations of *MADCAM1* and *ITGB7* genotypes (p=0.07, Fig.3)

Table 1: Distribution of *ITGB7* rs1554753 gene polymorphism in aHSCT pairs

ITGB7 rs1554753 A/G		aHSCT pairs	
		Patients (n=87)	Donors (n=86)
Genotypes	AA	53 (0.61)	57 (0.66)
	AG	33 (0.38)	26 (0.30)
	GG	1 (0.01)	3 (0.04)
Alleles	A	139 (0.80)	140 (0.81)
	G	35 (0.20)	32 (0.19)

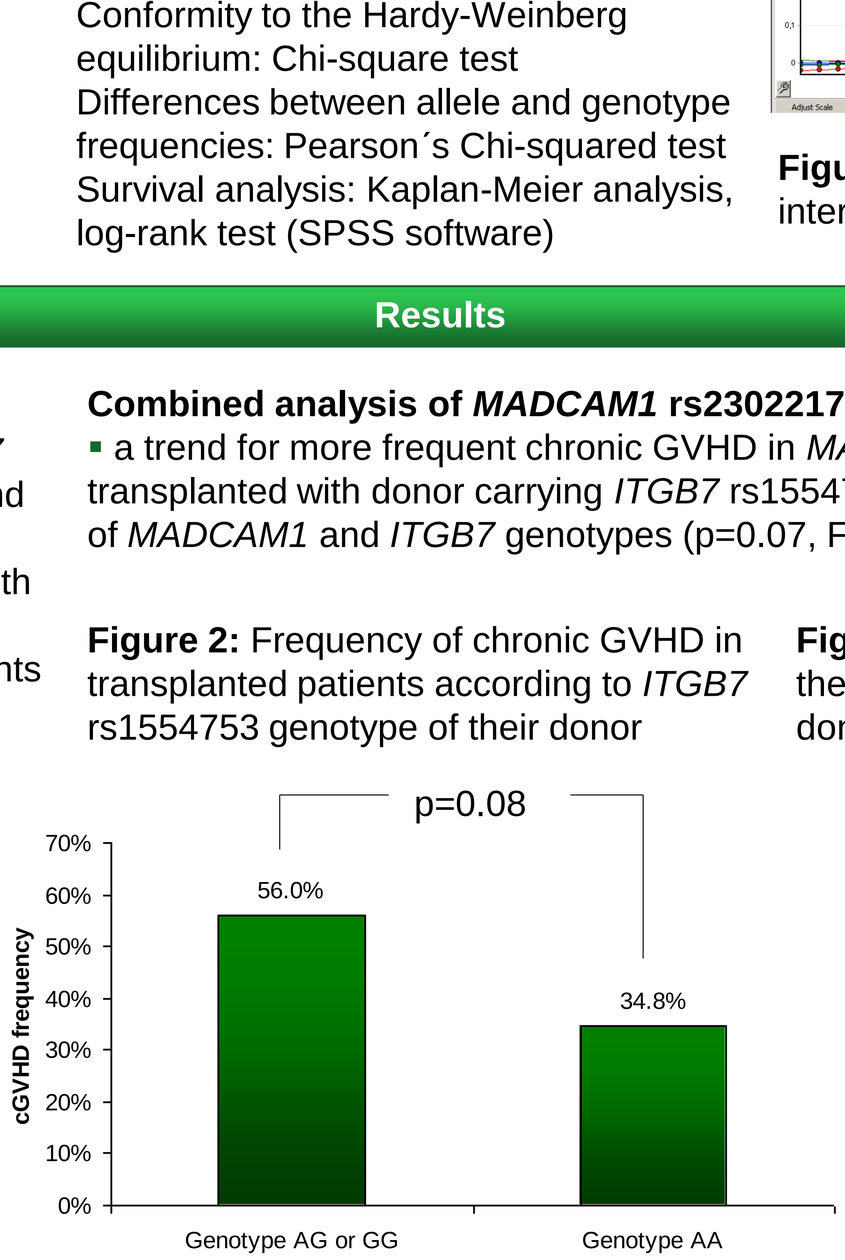

Figure 2: Frequency of chronic GVHD in transplanted patients according to *ITGB7* rs1554753 genotype of their donor

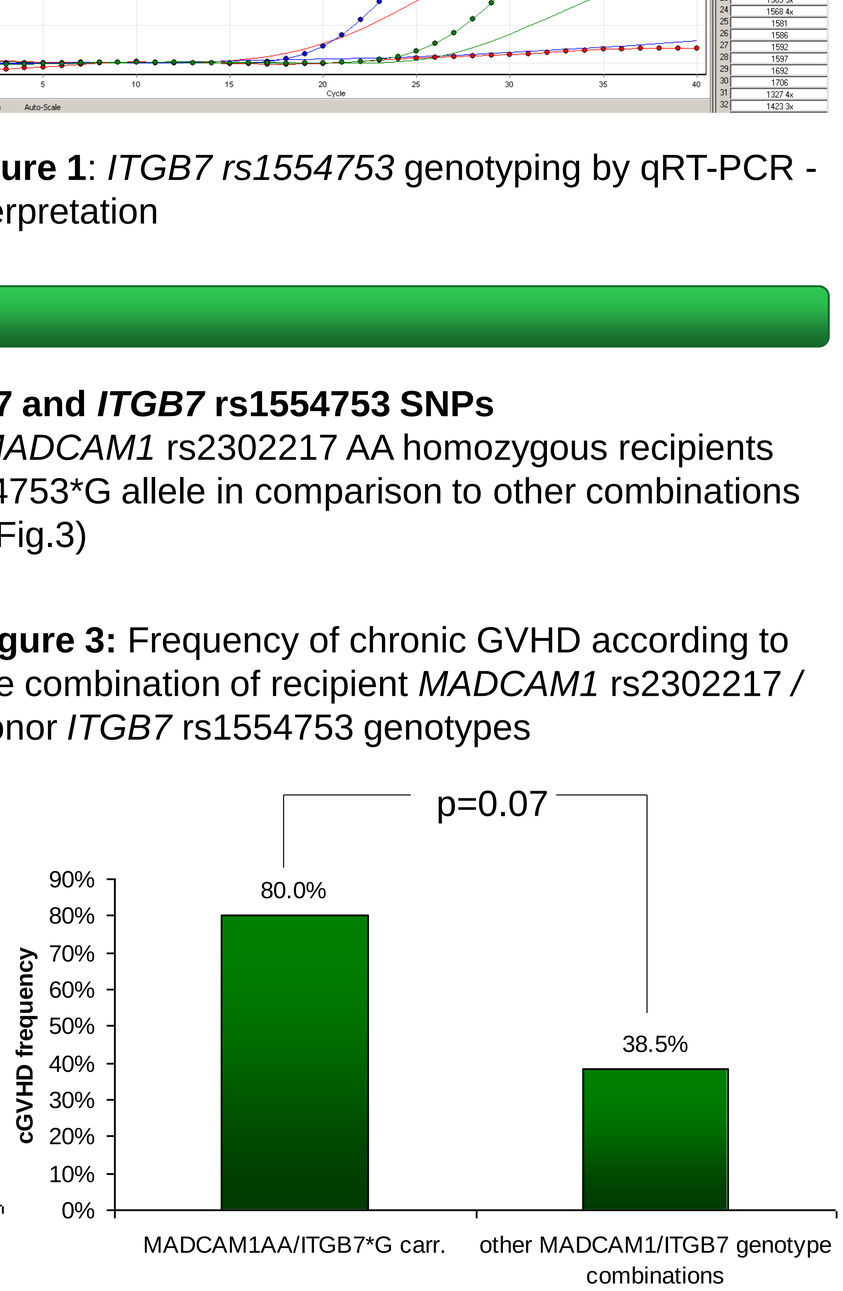

Figure 3: Frequency of chronic GVHD according to the combination of recipient *MADCAM1* rs2302217 / donor *ITGB7* rs1554753 genotypes

Conclusion

- *ITGB7* gene (Integrin alpha-4/beta-7) polymorphisms in donor may be associated with the risk of chronic GVHD, possibly in synergy with particular *MADCAM1* genotype
- replication of our data and/or assessment of functional relevance of *ITGB7* gene variants for aHSCT outcome has to be confirmed in substantially larger cohorts of donor-recipient aHSCT pairs

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