

SCA 32

FUNCTIONAL POLYMORPHISMS IN THE BETA2 ADRENERGIC RECEPTOR GENE ARE ASSOCIATED WITH ADVERSE OUTCOMES FOLLOWING CARDIAC SURGERY

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Introduction: Substantial variability exists in long-term outcomes after cardiac surgery,[1] influenced by genetic and environmental factors. Four functional single nucleotide polymorphisms (SNPs) have been described in the promoter (-47C/T) and coding region (Arg16Gly, Gln27Glu, Thr164Ile) of the beta2 adrenergic receptor (2AR) gene,[2] resulting in altered receptor expression,[3] regulation, and response to sympathetic stimulation.[4] We tested the association of these 2AR SNPs with the incidence of major adverse cardiac events (MACE – a composite of death, myocardial infarction, and repeat revascularization) following cardiac surgery.

Methods: A total of 2193 patients (1875 white, 378 non-white) were genotyped at the 4 proposed 2AR loci using MALDI/TOF mass spectrometry and pyrosequencing. Patients were prospectively followed-up for a median of 14 months (range 0-95 months). Data were analyzed using a Cox proportional hazard additive genetic model, adjusting for the Hannan risk score[5] and time on CPB, and focusing on point estimates. Haplotypes were explored using the EM-DeCODER program.[6] Death and 1-year incidence of any MACE were used as primary endpoints.

Results: As expected, allele frequencies differed by race; this initial analysis is limited to Caucasians only. The Glu27 allele is associated with increased risk of death after cardiac surgery, with incidence increasing as a function of number of Glu27 alleles (gene-dose effect): Gln27Gln 6.1%, Gln27Glu 8%, Glu27Glu 30% (p=0.02). A trend (p=0.06) of increased risk for 1-year MACE exists for Gly16 carriers: Arg16Arg 5.3%, Gly16Gly 10.2% (Fig.1) The two SNPs are in linkage disequilibrium (Glu27 and Gly16). Three common haplotypes have been identified (Fig.2).

Conclusion: Our findings suggest that specific 2AR SNPs predict adverse outcomes after cardiac surgery and should be considered in outcome predictive models and clinical decision tools incorporating genetic pattern information. This may have important implications in improving prognostication and directing medical decision-making for individual patients.

References

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Fig1

SNP	Aminoacid Subst.	Allele Freq.	Heterozygosity	HR 1yr-MACE	HR Death
-47C/T	Arg/Cys 5'LC	0.39 C	0.45	1	1
		0.61 T		0.86	0.77
46A/G	Arg16Gly	0.38 Arg	0.52	1	1
		0.62 Gly		1.96	1.12
79C/G	Gln27Glu	0.68 Gln	0.62	1	1
		0.32 Glu		2.17	2.82
491C/T	Thr164Ile	0.98 Thr	0.02	1	1
		0.02 Ile		1.54	1.47

Fig.2

Haplotypes				Frequency (SE) n alleles=4386
-47 C/T	46A/G	79C/G	491 C/T	
C	A	C	C	0.001 (0.0004)
C	A	G	C	0.00001 (0.00004)
C	G	C	C	0.07 (0.003)
C	G	C	T	0.0002 (0.0002)
C	G	G	C	0.31 (0.007)
C	G	G	T	0.0001 (0.0001)
T	A	C	C	0.38 (0.007)
T	A	C	T	0.00 (0.00)
T	A	G	C	0.00 (0.00)
T	G	C	C	0.22 (0.006)
T	G	C	T	0.01 (0.001)
T	G	G	C	0.006 (0.001)
T	G	G	T	0.00 (0.00)