Common genetic polymorphisms of adenosine A2A receptor do not influence response to regadenoson

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Abstract

Introduction:

Hemodynamic response to regadenoson varies greatly, and underlying mechanisms for variability are poorly understood. We hypothesized that 5 common variants of A2A receptor are associated with altered response to regadenoson.

Methods:

Consecutive subjects (n=357) undergoing resting regadenoson nuclear stress imaging were enrolled. Genotyping was performed using Taqman based assays for rs5751862, rs229838, rs3761422, 2267076 and rs5751876.

Results:

There was no significant difference in heart rate or blood pressure between different genotypes following regadenoson administration. There was also no significant difference in myocardial ischemia detected by nuclear perfusion imaging as defined by summed difference score, or in self-reported side effects among the genotypes tested.

Conclusions:

The common A2A variants studied are not associated with variability in hemodynamic response to regadenoson or variability in detection of ischemia with nuclear perfusion stress imaging.

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Introduction:

Since its FDA approval in 2008, regadenoson has largely replaced adenosine as the principle agent used in pharmacological cardiac stress testing. Regadenoson is an adenosine analogue and selective A2A adenosine receptor agonist which causes vasodilation of arteriolar vascular smooth muscles cells and myocardial hyperemia, leading to the desired cardiac state for myocardial perfusion imaging (MPI). Compared to its predecessor, regadenoson produces hyperemia with more rapid onset (30 seconds) and for a longer time period (two to five minutes) [1]. In addition, the ADVANCE-MPI 1 and 2 randomized trials demonstrated noninferiority for regadenoson to adenosine when comparing efficacy for detection of reversible perfusion defects. Regadenoson was also associated with a decreased overall symptom score (which included dyspnea, chest pain and flushing), attributed to the selective activation of adenosine receptor A2A without acting on adenosine receptors A1, A2B or A3 [2].

Despite the selective activity of regadenoson, there remains considerable inter-patient variability in hemodynamic response and reported side effects associated with its use[3, 4]. We recently reported the association of adenosine monophosphate deaminase-1(AMPD-1) polymorphism with increased incidence of reported adverse effects during regadenoson administration.

Several genetic variants of A2A receptor have been previously described. Single nucleotide polymorphisms (SNP) of A2A have been associated with functional differences in psychiatric and neurological phenotypes [5]. Several A2A variants (rs 5751862, rs2298383, rs3761422) were found to be associated with anxiety related personality scores. In particular rs5751876 has been associated with Gilles de la Tourette syndrome, caffeine

induced anxiety, panic disorder with agoraphobia, and adverse effects in nonacute schizophrenia[6-9]. Levodopa-induced dyskinesis in Parkinson patients was also found to be associated with diplotypes of two A2A variants (rs2298383 and rs3761422)[10]. The pharmacodynamic impact of these common receptor variants with suggested functional phenotype variability on regadenoson response has not been previously examined.

We hypothesized that common A2A receptor polymorphisms are associated with altered hemodynamic response to regadenoson.

Methods

Patients

The study protocol was approved by the institutional review board (IRB) and a written consent was obtained for all patients enrolled.

All subjects who were scheduled for regadenoson nuclear stress testing were eligible for the study. Those who underwent a combination of exercise and nuclear pharmacologic stress testing with regadenoson were excluded from our analysis. Information on medical history, risk factors, and demographics were collected by interview and chart review.

Genotyping

The Qiagen Flexigene DNA Kit #51206 was used for genomic DNA extraction following the protocol for isolation of DNA from 100-500 µl buffy coat (Germantown, USA). SNPs associated with ADORA2A including rs5751862, rs229838, rs3761422, 2267076 and rs5751876 were analyzed using an open array genotyping platform (Life Technologies,

Grand Island, NY, USA) according to the manufacturer's instructions. Amplification of alleles of interest were amplified using sequence-specific primers along with allele-specific TaqMan® probes (Applied Biosystems, Foster City, CA). Individual genotypes were determined using allelic discrimination.

Regadenoson administration

A dose of 0.4 mg of regadenoson was administered through peripheral venous access over a period of ten seconds, followed by a saline flush of five mL over another ten seconds.

Study Measurements

Systolic blood pressure (SBP), and heart rate (HR) were recorded prior to regadenoson infusion, then at one minute, and three minutes following infusion. Self-reported adverse symptoms were recorded. Primary outcomes were change in HR, and change in SBP. Change in HR was defined as the difference between the peak post-administration HR and the baseline HR. Change in SBP was defined as difference of baseline SBP minus 1min or 3min SBP following regadenoson administration.

Secondary outcomes included incidence of symptoms including abdominal pain, headache, nausea, dyspnea, flushing, dizziness and chest pain.

Nuclear myocardial perfusion imaging was analyzed using a standard 17 segment model. Summed stress score (SSS), summed rest score (SRS), and summed difference scores (SDS) were recorded[11].

Statistical Analysis

SPSS software, version 23.0 (IBM, Chicago, IL) was used to perform statistical analyses. A p-value of less than 0.05 was used to define statistical significance. Values reported represent the mean ± standard deviation, unless specified otherwise. All statistical

tests were two-sided. Continuous variables were compared using unpaired two-sided Student's t-tests, and analysis of variance testing (ANOVA) for multiple group testing. Categorical variables were compared using chi-square test. Haploview software was used for haplotype analysis (www.broadinstitute.org/haploview). Linkage disequilibrium (LD) between variants in same gene was expressed as D′ coefficients.

Results

A total of 357 patients underwent regadenoson stress testing and successful genotyping and were included in the study. Genotype distribution was consistent with Hardy-Weinberg equilibrium ($p>0.05$) (Table 1). There was close linkage disequilibrium between rs229838, rs3761422, 2267076 and rs5751876 (Figure 1.)

The mean age was 58 years with 55% being female and majority (71%) Caucasian. Table 2 summarizes the baseline characteristics of the study population.

Genotype distribution for rs5751862 and rs2298383 was significantly different between Caucasian and African-American subjects, with lower prevalence of the minor allele variant among African Americans (Table 2). In addition, carriers of the minor allele variant for rs2298383, rs3761422, rs2267076, and rs5751876 had a higher prevalence of congestive heart failure. Chronic obstructive pulmonary disease was more common in minor allele carriers for rs2267076.

There was no significant difference in incidence of self-reported side effects between non-carriers and carriers of the minor allele variants studied (rs5751862, rs229838, rs3761422, 2267076 and rs5751876) (Table 3.). Symptoms reported included abdominal pain, headache, nausea, dyspnea, flushing, dizziness and chest pain.

Baseline BP and heart rate were not significantly different between genotypes for all variants studied (Table 4.). After regadenoson administration the average rise in heart rate was 29.7 beats/min. Mean change in SBP at 1 min was -2.7±18mmHg and -2.5±19mmHg at 3min. There was no significant difference in change of heart rate or SBP after regadenoson administration between genotypes of variants studied (Table 4).

The summed stress score (SSS) was higher in carriers of the minor allele variant of rs2267076, but not significantly different between different genotypes of rs5751862, rs229838, rs3761422, and rs5751876. The summed resting score (SRS) was also higher in carriers of the minor allele of rs2267076 and rs3761422. However, the summed difference score was not significantly different among any of the genotypes for each of the variant studied.

Since it has been reported that diabetes mellitus enhances A2A receptor response, we have included a subgroup analysis with only non-diabetic subjects[12]. This did not demonstrate any significant difference in baseline and post stress hemodynamic measurements, nor nuclear perfusion scores (supplemental data).

Discussion

Adenosine is an endogenous purine nucleoside that is known to affect cardiac myocyte activity via four structurally related G-protein coupled receptors (ADORA1, ADORA2A, ADORA2B and ADORA3). Levels of adenosine in the blood have been shown to affect heart rate, cardiac conduction impulse, coronary perfusion, remodeling of cardiovascular tissue and cardiac vascular resistance to adverse insult [13]. Thus, the activity of these receptors plays an important role in overall cardiovascular function.

Regadenoson, a selective ADORA2A agonist, has largely replaced adenosine as the primary agent for pharmacologic cardiac stress testing. Certain receptor polymorphisms of ADORA2A have already been linked with various noncardiac conditions [5-9] including caffeine induced anxiety [14], childhood encephalopathy [15] and proliferative diabetic retinopathy [16]. Similarly, rs5751876 was evaluated in the pathogenosis of vasovagal syncope however no association with head-up tilt table test was reported [17]. Also homozygous CC carriers of rs2298383 were shown to have increased expression of ADORA2A receptor mRNA in brain and lymphoblasts [15].

Zhai et al [18] recently described an association between one common single nucleotide polymporphism (SNP) of ADORA2A (rs4822489) and the severity of congestive heart failure after adjustment for traditional risk factors (OR 1.912, 95% CI = 1.029-3.550) in a northern Chinese population. We did not genotype this particular variant, but we have observed a higher prevalence of congestive heart failure in carriers of the minor allele variant for rs2298383, rs3761422, rs2267076, and rs5751876. Further studies may be indicated to examine the influence of ADORA2A variants in congestive heart failure pathogenesis and phenotypes.

We hypothesized that 5 of the common A2A receptor variants that have been associated with variability in response to adenosine stimulation in non-cardiac phenotypes, would affect hemodynamic response to regadenoson, and possibly influence tolerability and detection of ischemia as defined by summed difference scores during regadenoson nuclear perfusion testing,. However none of the variants were associated with significant differences in reported adverse symptoms, nor significant differences in baseline and post regadenoson hemodynamic variables. Similarly, we could not document a significant

difference in ischemia detected by nuclear perfusion imaging among genotypes. This indicates a low likelihood that the ADORA2A variants studied would be associated with a dampened vasodilator response to regadenoson or decrease in observed perfusion defects seen on nuclear testing. The finding of higher baseline perfusion defects (SRS) in carriers of rs2267076 and rs3761422 could be due to chance, or less likely be an indicator of higher prevalence of chronic ischemic heart disease in carriers of the variant, however there has been no prior data to suggest this. Small fixed perfusion defects are commonly observed with soft tissue attenuation artefacts particularly in obese individuals, which could have contributed to a small difference in SRS. This would be supported by higher body mass index seen in carriers of minor allele variants of rs2267076 and rs3761422 (Table 2).

Conclusion

Our findings suggest that there are no significant differences in hemodynamic response and side effects of regadenoson administration among genotypes of the five ADORA2A variants studied (rs5751862, rs229838, rs3761422, 2267076 and rs5751876). In addition, no significant difference in myocardial ischemia was detected on nuclear stress perfusion imaging with regadenoson among ADORA2A variants studied, indicating that these variants are unlikely to significantly affect regadenoson cardiac stress testing.

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Table 1. Hardy-Weinberg Equilibrium

A2A variants	n (Alleles)			Minor Allele Carriers (Minor Allele Frequency)	P-value
rs5751862	70 (GG)	160 (AG)	109 (AA)	230/339 (0.44)	0.42
rs2298383	84 (CC)	184 (CT)	87 (TT)	268/355 (0.5)	0.7
rs3761422	126 (CC)	177 (CT)	54 (TT)	231/357 (0.4)	0.53
rs2267076	142 (CC)	167 (CT)	46 (TT)	213/355 (0.36)	0.78
rs5751876	72 (TT)	185 (CT)	99 (CC)	257/356 (0.46)	0.39

Table 2. Clinical Variables

A2A variants	rs5751862				rs2298383				rs3761422				rs2267076				rs5751876			
	GG	AG	GG	p-value	CC	CT	TT	p-value	CC	CT	TT	p-value	CC	CT	TT	p-value	TT	CT	CC	p-value
Age (years)	60.1±10.9	59.1 ± 11	57.9 ±10.5	0.38	58.6±10.4	59 ± 11	59.8 ± 10.9	0.76	59.3±10.7	59 ± 10.8	58.5 ± 10.4	0.89	59.0±10.8	58.8 ± 11	59.2 ± 10	0.96	58.6± 10.3	58.9±10.8	59.4± 11	0.88
Males	26/70 (37%)	76/160 (48%)	53/109 (49%)	0.27	36/84 (43%)	89/184 (48%)	39/87 (45%)	0.67	59/126 (47%)	83/177 (47%)	22/54 (41%)	0.71	64/142 (45%)	82/167 (49%)	18/46 (39%)	0.46	32/72 (44%)	83/185 (45%)	46/99 (46%)	0.96
Females	44/70 (63%)	84/160 (52%)	56/109 (51%)		48/84 (57%)	95/184 (52%)	48/87 (55%)		67/126 (53%)	94/177 (53%)	32/54 (59%)		78/142 (55%)	85/167 (51%)	28/46 (61%)		40/72 (56%)	102/185 (55%)	53/99 (54%)	
Caucasian	55/70 (79%)	126/160 (79%)	61/109 (56%)	<0.001	46/84 (55%)	134/184 (73%)	74/87 (85%)	<0.001	85/126 (68%)	129/177 (73%)	41/54 (76%)	0.51	99/142 (70%)	120/167 (72%)	36/46 (78%)	0.53	46/72 (64%)	131/185 (71%)	79/99 (79%)	0.065
African American	13/70 (19%)	33/160 (21%)	45/109 (41%)	<0.001	34/84 (41%)	48/184 (26%)	13/87 (15%)	0.001	41/126 (33%)	44/177 (25%)	10/54 (19%)	0.11	43/142 (30%)	44/167 (26%)	7/46 (15%)	0.13	22/72 (31%)	52/185 (28%)	20/99 (20%)	0.24
Smoking	20/70 (29%)	53/160 (33%)	34/109 (31%)	0.8	27/84 (32%)	53/184 (29%)	27/86 (31%)	0.8	38/126 (30%)	52/176 (30%)	18/54 (33%)	0.87	44/141 (31%)	47/166 (28%)	17/46 (37%)	0.52	23/72 (32%)	56/184 (30%)	30/98 (31%)	0.97
Body Mass Index (kg/m^2)	34.3 ± 7.8	34.3 ± 8.2	36 ± 10.1	0.25	36 ± 9.8	35.1 ± 8.7	32.5 ± 7.8	0.019	33.2 ± 7.6	35.7 ± 9.6	35.4 ± 8.3	0.045	33.3 ± 7.9	35.6 ± 9.6	35.6 ±8	0.07	35.6.6±8.9	35.5±9	32.7± 7.9	0.025
Known Coronary Disease	18/70 (26%)	52/160 (33%)	27/109 (25%)	0.32	17/84 (20%)	58/184 (32%)	27/87 (31%)	0.14	38/126 (30%)	58/177 (33%)	9/54 (17%)	0.07	43/142 (30%)	55/167 (33%)	6/46 (13%)	0.03	16/72 (22%)	56/185 (30%)	29/99 (29%)	0.31
History of stents	16/70 (23%)	38/160 (24%)	18/109 (17%)	0.34	15/84 (18%)	42/184 (23%)	20/87 (23%)	0.62	23/126 (18%)	44/177 (25%)	10/54 (19%)	0.33	26/142 (18%)	44/167 (26%)	6/46 (13%)	0.08	14/72 (19%)	44/185 (24%)	20/99 (20%)	0.67
Coronary Artery Bypass Graft Surgery	6/70 (9%)	12/160 (8%)	11/109 (10%)	0.76	10/84 (12%)	14/184 (8%)	8/87 (9%)	0.52	13/126 (10%)	15/177 (8%)	6/54 (11%)	0.79	14/142 (10%)	14/167 (8%)	5/46 (11%)	0.84	9/72 (13%)	14/185 (76%)	10/99 (%)	0.45
Prior Myocardial Infarction	10/70 (14%)	36/160 (23%)	23/109 (21%)	0.35	16/84 (19%)	36/184 (20%)	21/87 (24%)	0.63	26/126 (21%)	39/177 (22%)	10/54 (19%)	0.85	30/142 (21%)	36/167 (22%)	8/46 (17%)	0.82	15/72 (21%)	38/185 (18%)	22/99 (22%)	0.95
Congestive Heart Failure	3/70 (4%)	13/160 (8%)	16/109 (15%)	0.05	13/84 (15%)	18/184 (10%)	2/87 (2%)	0.012	5/126 (4%)	19/177 (11%)	10/54 (19%)	0.007	8/142 (6%)	18/167 (11%)	8/46 (17%)	0.048	12/72 (17%)	18/185 (10%)	4/99 (4%)	0.021
Diabetes	27/70 (39%)	74/160 (46%)	43/109 (39%)	0.41	34/84 (41%)	83/184 (45%)	31/87 (36%)	0.33	53/126 (42%)	73/177 (41%)	25/54 (46%)	0.8	60/142 (42%)	67/167 (40%)	22/46 (48%)	0.64	32/72 (44%)	79/185 (43%)	38/99 (38%)	0.69
Hypertension	54/70 (77%)	135/160 (84%)	81/109 (74%)	0.11	64/84 (76%)	153/184 (83%)	61/87 (70%	0.045	94/126 (75%)	146/177 (82%)	41/54 (76%)	0.22	108/142 (76%)	138/167 (83%)	35/46 (76%)	0.31	55/72 (76%)	155/185 (84%)	70/99 (71%)	0.033
Atrial Fibrillation or Flutter	7/70 (10%)	22/160 (14%)	16/109 (15%)	0.65	9/84 (11%)	23/184 (13%)	13/87 (15%)	0.70	17/126 (14%)	24/177 (14%)	5/54 (9%)	0.69	20/142 (14%)	21/167 (13%)	5/46 (11%)	0.84	6/72 (8%)	27/185 (15%)	13/99 (13%)	0.4
COPD or Emphysema	18/70 (26%)	28/160 (18%)	25/109 (23%)	0.31	25/84 (30%)	31/184 (17%)	18/87 (21%)	0.054	20/126 (16%)	36/177 (20%)	17/54 (31%)	0.06	29/142 (20%)	29/167 (17%)	16/46 (35%)	0.036	19/72 (26%)	37/185 (20%)	19/99 (19%)	0.46
Asthma	12/70 (17%)	32/160 (20%	24/109 (22%)	0.73	20/84 (24%)	33/184 (18%)	18/87 (21%)	0.53	26/126 (21%)	33/177 (19%)	12/54 (22%)	0.82	29/142 (20%)	32/167 (19%)	12/46 (26%)	0.59	16/72 (22%)	38/185 (21%)	19/99 (19%)	0.89
Stroke	3/70 (4%)	20/160 (13%)	7/109 (6%)	0.07	9/84 (11%)	17/184 (9%)	6/87 (7%)	0.68	11/126 (9%)	17/177 (10%)	4/54 (7%)	0.88	12/142 (9%)	15/167 (9%)	3/46 (7%)	0.87	5/72 (7%)	20/185 (11%)	7/99 (7%)	0.46
Cancer	5/70 (7%)	17/160 (11%)	11/109 (10%)	0.71	9/84 (11%)	15/184 (8%)	11/87 (13%)	0.49	16/126 (13%)	15/177 (8%)	5/54 (9%)	0.47	17/142 (12%)	14/167 (8%)	5/46 (11%)	0.57	7/72 (10%)	17/185 (9%)	11/99 (11%)	0.87
Hyperlipidemia	49/70 (70%)	109/160 (68%)	70/109 (64%)	0.69	55/84 (66%)	131/184 (71%)	54/87 (62%)	0.29	78/126 (62%)	123/177 (69%)	40/54 (74%)	0.2	90/142 (63%)	113/167 (68%)	37/46 (80%)	0.1	52/72 (72%)	129/185 (70%	61/99 (62%)	0.26
Peripheral Vascular Disease	6/70 (9%)	18/160 (11%)	14/109 (13%)––	0.68	8/84 (10%)	20/184 (11%)	11/87 (13%)	0.81	16/126 (13%)	20/177 (11%)	4/54 (7%)	0.59	17/142 (12%)	20/167 (12%)	3/46 (7%)	0.55	5/72 (7%)	22/185 (12%)	13/99 (13%)	0.41
Beta Blocker	31/70 (44%)	76/160 (48%)	51/109 (47%)	0.9	37/84 (44%)	86/184 (47%)	44/87 (51%)	0.69	61/126 (48%)	84/177 (47%)	25/54 (46%)	0.99	67/142 (47%)	80/167 (48%)	21/46 (46%)	0.96	34/72 (47%)	87/185 (47%)	46/99 (46%)	0.99
Calcium Channel Blocker	17/70 (24%)	50/160 (31%)	31/109 (28%)	0.56	24/84 (29%)	55/184 (30%)	21/87 (24%)	0.61	32/126 (25%)	54/177 (31%)	14/54 (26%)	0.58	39/142 (28%)	48/167 (29%)	11/46 (24%)	0.81	21/72 (29%)	55/185 (30%)	24/99 (24%)	0.6
ACE/ARB	33/70 (47%)	73/160 (46%)	48/109 (44%)	0.92	41/84 (49%)	80/184 (43%)	38/87 (44%)	0.7	57/126 (45%)	79/177 (45%)	27/54 (50%)	0.78	61/142 (43%)	77/167 (46%)	23/46 (50%)	0.68	36/72 (50%)	87/185 (47%)	41/99 (41%)	0.5

Table 3. Symptoms during Regadenoson administration

		≥1 Symptoms			≥3 Symptoms		
		Percentage (actual)	Odds Ratio (95% CI)	p-value	Percentage (actual)	Odds Ratio (95% CI)	p-value
rs5751862	Carriers Minor Allele	198/230 (86%)	1.6 (0.86-2.9)	0.14	53/230 (23%)	1.3 (0.75-2.34)	0.33
	Non Carriers	87/109 (80%)			20/109 (18%)		
rs2298383	Carriers Minor Allele	226/268 (84%)	1.03 (0.5-2)	0.93	62/268 (23%)	1.14 (0.623-2.086)	0.2
	Non Carriers	73/87 (84%)			18/87 (21%)		
rs3761422	Carriers Minor Allele	197/231 (85%)	1.16 (0.64-2.1)	0.63	57/231 (25%)	1.55 (0.9-2.7)	0.12
	Non Carriers	105/126 (83%)			22/126 (18%)		
rs2267076	Carriers Minor Allele	180/213 (85%)	1.05 (0.6-1.9)	0.86	51/213 (24%)	1.18 (0.71-2)	0.54
	Non Carriers	119/142 (84%)			30/142 (21%)		
rs5751876	Carriers Minor Allele	217/257 (84%)	0.97 (0.51-1.8)	0.92	62/257 (24%)	1.34 (0.75-2.4)	0.32
	Non Carriers	84/99 (85%)			19/99 (19%)		

Table 4. Hemodynamic Response to Regadenoson Administration and Nuclear Perfusion Imaging

rs5751862				p values			
	(GG)	(AG)	(AA)	GG vs AG	GG vs AA	AG vs AA	ANOVA
Baseline Heart Rate	69.5±13.5	71.3±12.6	72.7±13	0.99	0.32	1.0	0.27
Heart Rate Change	29.7±11.1	28.8±14.9	29.5±13	1.0	1.0	1.0	0.99
Baseline Systolic Blood Pressure	137±21.7	136±22.8	136±20.7	1.0	1.0	1.0	0.98
Systolic Blood Pressure Change 1min	-2.8±22	-2.8±16	-1.6±15	1.0	1.0	1.0	0.73
Systolic Blood Pressure Change 3min	-0.6±18	-3.2±20	-2.5±19	1.0	1.0	1.0	0.58
Summed Stress Score (SSS)	1.56±3.41	2.57±5.27	3.29±5.66	0.52	0.08	0.77	0.09
Summed Resting Score (SRS)	1.39±3.47	1.83±4.98	2.73±5.51	1.0	0.25	0.45	0.18
Summed Difference Score (SDS)	0.57±1.62	0.88±1.6	1.03±2.09	0.67	0.3	1.0	0.25

rs2298383				p values			
	(CC)	(CT)	(TT)	CC vs CT	CC vs TT	CT vs TT	ANOVA
Baseline Heart Rate	72.0±12.7	71.9±13.3	69.8±13	1.0	0.78	0.65	0.41
Heart Rate Change	30.1±13.8	29.6±14.5	29.6±10.7	1.0	1.0	1.0	0.95
Baseline Systolic Blood Pressure	138±19.5	137±23.1	134±21	1.0	0.56	0.6	0.34
Systolic Blood Pressure Change 1min	-3.6±15	-2±16	-2.4±22	1.0	1.0	1.0	0.82
Systolic Blood Pressure Change 3min	-1.6±20	-1.6±19	-4.9±17	1.0	1.0	1.0	0.41
Summed Stress Score (SSS)	2.80±5.43	3.02±5.36	2.00±4.08	1.0	0.92	0.38	0.3
Summed Resting Score (SRS)	2.53±5.35	2.17±5.1	1.49±3.79	1.0	0.52	0.87	0.37
Summed Difference Score (SDS)	0.77±1.71	1.06±1.96	0.93±1.87	0.77	1.0	1.0	0.45

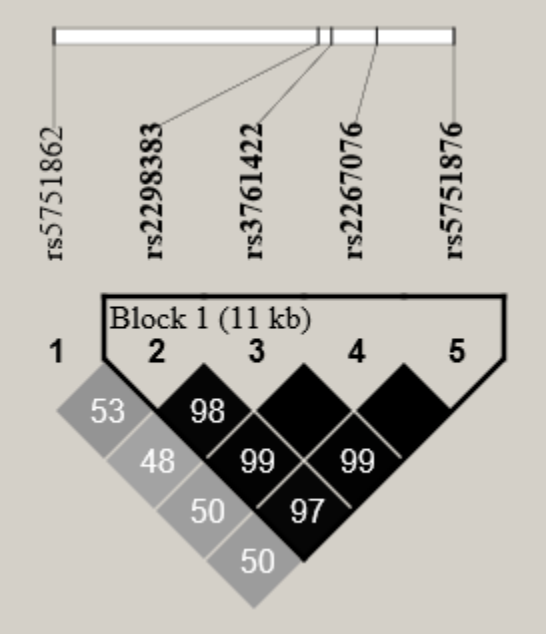
rs3761422				p values			
	(CC)	(CT)	(TT)	CC vs CT	CC vs TT	CT vs TT	ANOVA
Baseline Heart Rate	69.9±12.7	72.0±13.6	73.1±12.1	0.48	0.38	1.0	0.22
Heart Rate Change	29.6±10.7	30.4±15.2	27.8±13.3	1.0	1.0	0.69	0.48
Baseline Systolic Blood Pressure	136±22	136±22.1	140±20.8	1.0	0.85	1.0	0.59

Systolic Blood Pressure Change 1min	-3.1±18	-1.2±17	-5±16	1.0	1.0	0.53	0.38
Systolic Blood Pressure Change 3min	-3.6±17	-1.2±17	-1.5±18	1.0	1.0	1.0	0.74
Summed Stress Score (SSS)	1.85±3.68	3.17±5.69	3.24±5.89	0.09	0.29	1.0	0.07
Summed Resting Score (SRS)	1.21±3.27	2.44±5.48	2.83±5.64	0.1	0.13	1.0	0.047
Summed Difference Score (SDS)	0.91±1.88	0.95±1.86	0.92±1.88	1.0	1.0	1.0	0.98

rs2267076				**p values**			
	(CC)	(CT)	(TT)	CC vs CT	CC vs TT	CT vs TT	ANOVA
Baseline Heart Rate	70.1±13	72.4±13.5	72.3±11.3	0.35	0.99	1.0	0.26
Heart Rate Change	30.2±11.6	30.0±14.8	28.2±13.5	1.0	1.0	1.0	0.66
Baseline Systolic Blood Pressure	135±21.7	137±22.3	138±21.3	1.0	1.0	1.0	0.78
Systolic Blood Pressure Change 1min	-2.8±19	-1.5±17	-4.5±16	1.0	1.0	1.0	0.62
Systolic Blood Pressure Change 3min	-3±18	-2.3±20	-1.7±19	1.0	1.0	1.0	0.91
Summed Stress Score (SSS)	1.81±3.49	3.51±6.69	3.02±4.68	0.02	0.56	1.0	0.024
Summed Resting Score (SRS)	1.16±3.14	2.81±6.35	2.73±5.2	0.02	0.24	1.0	0.018
Summed Difference Score (SDS)	0.85±1.74	0.94±1.86	0.89±1.8	1.0	1.0	1.0	0.92

rs5751876				**p values**			
	(TT)	(CT)	(CC)	TT vs CT	TT vs CC	CT vs CC	ANOVA
Baseline Heart Rate	71.5±12.2	72.3±13.3	69.5±13.2	1.0	0.92	0.25	0.22
Heart Rate Change	29.1±13.8	30.5±14.7	28.8±9.5	1.0	1.0	0.94	0.55
Baseline Systolic Blood Pressure	140±20.9	136±22.0	134±22.4	0.52	0.27	1.0	0.22
Systolic Blood Pressure Change 1min	-4.6±15	-1.2±17	-2.2±21	0.61	1.0	1.0	0.45
Systolic Blood Pressure Change 3min	-2.8±18	-1±20	-4±16	1.0	1.0	0.67	0.46
Summed Stress Score (SSS)	3.28±5.8	2.93±5.4	1.91±3.91	1.0	0.26	0.34	0.17
Summed Resting Score (SRS)	2.88±5.66	2.18±5.19	1.44±3.63	0.97	0.2	0.7	0.18
Summed Difference Score (SDS)	0.87±1.79	0.99±1.9	0.78±1.83	1.0	1.0	1.0	0.64

Figure 1. Linkage Disequilibrium



Legends:

Figure 1.

Shades of grey and numbers indicate extent (D') of linkage disequilibrium (LD) with haploblock assignment. (black/empty box: D'=1).