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Beta-Adrenoceptor Gene Variation and Intermediate Physiologic Traits: Prediction of Distant Phenotype

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Abstract

Intermediate physiological phenotype is the genetic and environmental influence on functional physiological characteristics with direct prognostic relevance to distant, more complex phenotypes such as cardiovascular and metabolic disease. Increasingly available and affordable genotyping techniques have created an explosion of information on candidate gene variation and its relationship to intermediate physiological traits. Variation in beta-adrenoceptor genes is an intense focus of investigation because beta-adrenoceptors are 1) ubiquitous in organ system distribution; 2) integral to a multitude of physiological processes; 3) well-described in cardiovascular and metabolic disease; and 4) major pharmacologic treatment targets. Furthermore, knowledge of functional gene variants in these receptors predates the description of the human genome. This review highlights the influence of common gene variation in the three beta-adrenoceptor subtypes on intermediate physiologic phenotype predictive of cardiovascular disease and obesity. Although further information is needed to replicate this information across populations, this review condenses and summarizes growing trends in specific pleiotropic effects of beta-adrenoceptor polymorphisms, and suggests which variants may be predictive of distant phenotype.

Phenotype is defined as the observable manifestations of a genetic trait, resulting from specific genotypes and their interactions with the environment. Controlling for environmental factors to the extent possible, *intermediate phenotype* may be thought of as the influence of genotype on functional physiological characteristics (Figure 1). Generally, these characteristics would be considered simple, obtainable, and able to be extrapolated to larger populations. In this context, *distant phenotype* is the complex multi-factorial disease that may arise in part from the intermediate phenotype. There is tremendous potential for intermediate phenotyping. Determining a link between candidate gene variation and a physiological outcome in healthy individuals--before development of disease--may allow the prediction of disease risk or perhaps disease protection. Growing information regarding gene variation in adrenoceptors exemplifies this potential.

The sympathetic nervous system plays a key role in blood pressure regulation and metabolism. Beta-adrenoceptor gene variation is an intense area of investigation because beta-adrenoceptors are well-described in organ system distribution, catecholamine-mediated physiological processes, disease states, and treatment targets. Furthermore, description of the gene sequences and the discovery of functional variants in these genes predate description of the human genome. The purpose of this review is to highlight the influence of beta-adrenoceptor gene variation on intermediate phenotypes. The intermediate phenotypes, the relationship with common beta-receptor gene polymorphisms, and the relevant distant phenotypes are summarized in this review and highlighted in Table 1.

ADRB1 and Intermediate Phenotype

The ADRB1 gene is located on chromosome 10q, is intronless, and codes for 477 amino acids. The most studied SNPs in the ADRB1 gene encode for serine or glycine in amino acid 49 (major/minor allele: Ser49/Gly), and arginine or glycine in amino acid 389 (Arg389/Gly). Other nonsynonymous SNPs exist in the ADRB1 gene but are less prevalent, with unknown functional relevance in humans. The Ser49/Gly position is located on the extracellular amino terminus, and the Arg389/Gly is located near the intracellular carboxyl terminus and interacts with the intracellular G_s protein. These SNPs have not been shown to affect agonist binding affinity. Studies in recombinant systems suggest that the Gly49 variant is more susceptible to agonist-promoted down-regulation or desensitization, while the Ser49 variant is resistant to desensitization (Brodde 2008). Recombinant systems and transgenic animal models suggest that the Arg389 variant is associated with augmented response to agonist-mediated stimulation when compared to Gly389 (Brodde 2008), which is consistent with ex vivo stimulation of right ventricle tissue isolated from healthy humans (Liggett *et al.* 2006).

Resting heart rate is an intermediate physiological phenotype with profound implications for the development of cardiovascular disease. Even in healthy individuals, resting heart rate has been shown to be positively correlated with subsequent development of hypertension and cardiovascular disease (Palatini 2007; Hsia *et al.* 2009). The heritability of heart rate is estimated to range from 20 to 40% (Singh *et al.* 1999; Ranade *et al.* 2002). Because the ADRB1 is a major mediator of intrinsic heart rate, it is reasonable to postulate that variation in the ADRB1 gene is associated with resting rate, with implications for development of cardiovascular disease and pharmacogenetic relevance to beta-blocker therapy.

In more than 1,300 individuals of Chinese and Japanese descent from the SAPHIRE study, the Ser49 allele had an additive effect on heart rate, with Ser49 homozygotes having a greater mean HR than Ser49/Gly heterozygotes, who had a greater mean heart rate than Gly49 homozygotes (Ranade *et al.* 2002). Although the cohort included individuals with hypertension, the association of Ser49/Gly with heart rate was significant when accounting for hypertension status and medication use. Furthermore, the Gly389 homozygotes tended to have mean heart rate greater than Arg389/Gly heterozygotes and Arg389 homozygotes (Ranade *et al.* 2002). More recently in the FATE study, 53 SNPs in 46 genes were analyzed in 1468 individuals without cardiovascular disease, and the Arg389/Gly was one of five SNPs associated with resting heart rate, and Gly389 homozygotes had greater heart rate than Gly389/Arg heterozygotes and Arg389 homozygotes (Wilton *et al.* 2008). In the context of distant phenotype, it appears that Gly49 and Arg389 may portend a lower cardiovascular risk due to lower resting heart rate.

Several whole-body exercise trials in healthy humans have been unable to demonstrate an effect of ADRB1 gene variation on chronotropic, inotropic, or pressor response. Due to complex physiological regulation of cardiovascular responses to whole body exercise and the extensive variability in fitness levels, it may be impossible to differentiate variation at one gene but will instead require extensive analysis across multiple sites. In a simpler model of exogenous receptor stimulation, beta-1 agonist infusions in healthy subjects demonstrate a greater heart rate or contractility in Arg389 homozygotes than Arg389/Gly heterozygotes or Gly389 homozygotes (La Rosee *et al.* 2004; Bruck *et al.* 2005b). Although resting heart rate was similar in these genotype groups, one may speculate from the large-scale studies on resting heart rate (mentioned above) that Arg389 may be favorable in disease states (i.e., coronary artery disease, heart failure) where low resting heart rate is desirable, and myocardial adrenoceptor responsiveness (i.e., contractile function) is preserved.

Lipolysis is the process of hydrolysis of triglycerides into free fatty acids, which are released into the circulation as a source of energy production, making triglycerides the major source of stored energy in the body. Catecholamine-mediated activation of beta-receptors stimulates lipolysis and favors a reduction of stored fat. There is evidence that obesity is associated with a resistance to catecholamine-induced lipolysis and that common SNPs in the ADRB1 gene may be important to the development of obesity. In 238 healthy young whites and African-Americans, Gly389 carriers had a higher level of insulin and insulin resistance than non-carriers, and this allele was more prevalent in the subjects with higher BMI (Lima *et al.* 2007). A longitudinal study over 24 years of 1,179 African-American and white men and women found an association with the Gly389 allele and the development of obesity (Ellsworth *et al.* 2005). A longitudinal study enrolled 761 healthy women in Sweden, measured their BMI and followed them for 15 years, and found that the Gly49 genotype was associated with a higher risk toward an increased BMI (Linne *et al.* 2005). These findings are examples of intermediate phenotyping in otherwise healthy subjects that suggest an influence of ADRB1 gene variation on metabolic alteration and propensity toward obesity. However, case-control association studies have been unable to show a greater prevalence of the Gly389 or Gly49 alleles in obesity. Taken together, this is consistent with the idea that highlighting individual SNPs in individuals with established disease may be much more challenging than exploring genetic relevance to intermediate phenotype.

ADRB2 and Intermediate Phenotype

The ADRB2 gene is located on chromosome 5q, is intronless, and codes for 413 amino acids. The most common SNPs in the ADRB2 gene include amino acid position 16 which contains either glycine or arginine (major/minor allele: Gly16/Arg), and amino acid position 27 which contains either glutamine or glutamic acid (Gln27/Glu). Neither the Gly16/Arg SNP nor the Gln27/Glu SNP affect the binding of agonist to the receptor or G-protein coupling. However, genotype does appear to influence the degree of agonist-induced receptor desensitization with Gly16 showing increased agonist induced desensitization compared with Arg16 (Green *et al.* 1994). The presence of Glu27 rather than Gln27 is associated with resistance to desensitization (Green *et al.* 1995). For the common SNPs, linkage disequilibrium dictates that Glu27 homozygotes are nearly always homozygous for Gly16, and Arg16 homozygotes are almost always homozygous for Gln27 (Drysdale *et al.* 2000; Hawkins *et al.* 2006). The *in vitro* impact of these SNPs has been extensively reviewed (Brodde & Leineweber 2005). The uncommon yet functional threonine164/ isoleucine (Thr164/Ile) polymorphism (minor allele frequency ~ 0.02) does alter ligand binding and G-protein coupling. In cells transfected with cDNA that mimic this SNP, the Ile164 receptor displays a lower binding affinity for epinephrine, and functional coupling to G_s - as determined in adenylyl cyclase assays - is significantly depressed as compared to the wild-type receptor (Green *et al.* 1993). Homozygous Ile164 has not been reported in humans.

The ADRB2 receptor is responsible for vasodilation in the vasculature via the cAMP pathway in smooth muscle cells or by release of nitric oxide (NO) from vascular endothelium (Eisenach *et al.* 2002). The effect of ADRB2 genotype has been investigated for responsiveness to local infusions and systemic infusions. Local infusions of ADRB2 agonists in the brachial artery result in increased vasodilation in Glu27 homozygotes when compared with Gln27 homozygotes (Cockcroft *et al.* 2000) and in Gly16 homozygotes when compared with Arg16 homozygotes (Garovic *et al.* 2003). Venodilatory responses to isoproterenol have also been investigated in isolated hand veins with Gly16 homozygotes exhibiting greater maximal venodilation compared to Arg16 homozygotes; however, this increased response was only present in Gly16 + Glu27 homozygotes and not in Gly16 +

Gln27 homozygotes so this response difference has been attributed to the Glu27 genotype (Dishy *et al.* 2001). In this study it was also found that Arg16 homozygotes demonstrated more rapid agonist-mediated desensitization, and Glu27 homozygotes had increased agonist-mediated vasodilation. Arg16 homozygotes have also been found to have greater desensitization in response to terbutaline after oral terbutaline treatment (Bruck *et al.* 2005a). This is in contrast to the results from *in vitro* studies by Green *et al.* (Green *et al.* 1995) where the Gly16 homozygotes showed greater desensitization. This may be due to the chronic exposure of highly sensitive receptor variants to endogenous agonists causing desensitization prior to exposure of the exogenous agonist to which they do not become further desensitized (Liggett 2002).

ADRB2 gene variation and the response to sympathoexcitation have been evaluated by our group and revealed genotype-dependent differences in response to handgrip, as individuals homozygous for Gly16 had greater increases in heart rate and cardiac output, and a tendency for lower systemic vascular resistance (Eisenach *et al.* 2004; Eisenach *et al.* 2005). The higher heart rate and cardiac output response during handgrip in the Gly16 homozygotes may be due to greater ADRB2-mediated vasodilation by circulating catecholamines in Gly16 homozygotes. To achieve the same pressor response, greater increases in heart rate were needed in the Gly16 subjects. This interpretation is also consistent with the aforementioned studies demonstrating greater ADRB2-mediated nitric oxide-dependent responsiveness in Gly16 subjects (Cockcroft *et al.* 2000; Garovic *et al.* 2003). Furthermore, a study of Brazilian women found that subjects homozygous for Gly16 and Glu27 demonstrated a greater forearm vasodilator response to mental stress and to isometric handgrip, an effect that was no longer present following brachial artery infusion of a beta-blocker (Trombetta *et al.* 2005). Similar to the venodilator responses described by Dishy (2001), these findings were attributed to position 27, as Gly16 + Glu27 subjects had a greater FBF response than Arg16 + Gln27 and Gly16 + Gln27 subjects.

In contrast to the vascular response to local infusions of receptor agonists, systemic infusion studies reveal either no difference between genotypes (Bruck *et al.* 2003; Eisenach *et al.* 2006) or greater systemic vasodilation in Arg16 homozygotes compared with Gly16 homozygotes (Gratze *et al.* 1999; Hoit *et al.* 2000; Snapir *et al.* 2003). The difference between local infusion studies revealing Gly16 and Glu27 homozygotes demonstrating greater vasodilation and systemic infusion studies showing greater vasodilation in Arg16 or Arg16 + Gln27 homozygotes is likely due to the impact of counter-regulatory baroreflex activation and the compensation of this reflex for augmented vasodilation in Gly16 or Glu27 carriers. To investigate the discrepancy between regional and systemic vasodilation, we recently administered an ADRB2 agonist (terbutaline) during baroreflex inhibition with the ganglionic blocking agent trimethaphan. Participants were healthy adults grouped according to homozygous haplotypes Arg16 + Gln27, the rare Gly16 + Gln27, and Gly16 + Glu27. Once baroreflex inhibition was established and blood pressure was restored (increased) to baseline levels, the systemic vascular resistance tended to be influenced by haplotype, and was significant for position 16, such that Gly16 homozygotes had a lower SVR response to terbutaline than Arg16 homozygotes (Hesse *et al.*, 2010, in submission). This provides further evidence that Gly16 and possibly Glu27 is associated with greater ADRB2-agonist mediated vasodilation when compared to Arg16 and Gln27.

ADRB2 genotype may have an association with ventricular function. In normotensive humans, the Gly16 homozygotes were found to have greater fractional shortening, ejection fraction, midwall shortening and stress-corrected midwall shortening compared to both heterozygotes and Arg16 homozygotes using echocardiography (Tang *et al.* 2003). This difference was independent of various confounders such as age, sex, ethnicity, heart rate, body mass index, systolic blood pressure, left ventricular end-diastolic dimension, and field

center. Moreover, Gly16 homozygotes have greater cardiac output and stroke volume at rest compared with Arg16 homozygotes, as measured by the open-circuit acetylene wash-in method (Snyder *et al.* 2006b). During low- and high intensity exercise, the Gly16 homozygotes again have a greater cardiac output and stroke volume compared with Arg16 homozygotes (Snyder *et al.* 2006a).

Investigation into the effect of ADRB2 SNPs on bronchodilation in healthy subjects during exercise revealed no difference between Gly16 homozygotes and Arg16 homozygotes, except in the post-exercise recovery phase when the Arg16 homozygotes returned to baseline more quickly indicating a more rapid reduction in bronchodilation (Snyder *et al.* 2006a). Many large-scale human studies have examined ADRB2 genotype and asthma. As with cardiovascular disease, the pathogenesis of asthma is heterogeneous and multifactorial. The impact of the ADRB2 genotype in asthma has yet to be fully elucidated, and consideration of ADRB2 haplotype may add further insight into the effect of genetic variation at positions 16 and 27 on bronchodilation and may be a contributing factor to the existence of seemingly conflicting data. An excellent review of the impact of ADRB2 genotype on bronchodilation both at the cellular level and in human studies is by Johnson (Johnson 2006).

The ADRB2 is also present on adipose cells and mediates lipolysis. The Gly16/Arg allele has been shown to affect lipolysis with variation according to gender. Obese women homozygous for Arg16 have demonstrated a blunted increase in circulating free fatty acids, glycerol and decreased fat oxidation after stimulation by isoprenaline while obese men who were Arg16 homozygotes had a blunted increase in free fatty acids but no difference in glycerol or fat oxidation (Jocken *et al.* 2007). These findings seem consistent with regional vascular infusion studies that demonstrate blunted ADRB2-mediated vasodilation in Arg16 + Gln27 homozygotes compared to Gly16 and/or Glu27 homozygotes.

Similar to ADRB1 gene variants, case-control association studies in obesity have not been able to consistently replicate a causative ADRB2 allele. A study of overweight and obese Scandinavian women did not find an association between ADRB2 haplotype and BMI; however, there was a strong association between haplotype and ADRB2 receptor sensitivity and lipolysis rates (Eriksson *et al.* 2004). Receptor sensitivity to noradrenaline and noradrenaline-induced lipolysis rates were highest in adipose tissue for the few individuals who were homozygous for Gly16 + Gln27. The lowest sensitivity and agonist induced lipolysis rates were found in those who were homozygous for Arg16 and Gln27. The individuals who were homozygous Gly16 and Glu27 had receptor sensitivities and lipolysis rates that were intermediate to the other groups.

Despite the rarity of Thr164/Ile, important vascular and metabolic effects have been described. In two studies of healthy individuals, presence of the minor allele (Ile164) has been shown to be associated with blunted ADRB2-mediated venodilation in phenylephrine pre-constricted hand veins (Dishy *et al.* 2004; Bruck *et al.* 2005a). Another study found decreased heart rate and inotropic response to systemic terbutaline in healthy Thr164/Ile heterozygotes (Brodde *et al.* 2001). For lipolysis, individuals with the Ile164 SNP showed a 6-fold increase in the lipolytic EC(50) for terbutaline demonstrating decreased receptor function (Hoffstedt *et al.* 2001) consistent with the cardiac and vascular findings.

ADRB3 and Intermediate Phenotype

The ADRB3 gene is located on chromosome 8p and codes for 396 amino acids. Of the beta-adrenoceptors, the ADRB3 is considered most relevant to lipolysis and thermogenesis, and the functional relevance of ADRB3 gene variants in other tissue beds is the least known.

The ADRB3 gene contains a SNP that encodes either tryptophan or arginine (Trp64/Arg). This polymorphism does not appear to influence the response to agonists such as isoprenaline or noradrenaline (Vrydag *et al.* 2009). However, when omental adipocytes were studied for response to the ADRB3 selective agonist L-755,507 the Arg64 homozygotes and the Trp64Arg heterozygotes demonstrated decreased responsiveness compared with Trp64 homozygotes. Lipolysis in response to isoproterenol and CGP12177 was not different among the genotypes (Umekawa *et al.* 1999).

Presence of the minor allele (Arg64) appears to alter cholesterol levels and may influence obesity and insulin resistance. Post-menopausal Danish women with the Arg64 allele had decreased high density lipoprotein (HDL) levels (Dunajska *et al.* 2008) which is partially consistent with higher LDL levels associated with the Arg64 allele in Japanese men and women (Kotani *et al.* 2008). Taken together, the Arg64 allele appears to confer a less desirable metabolic profile including increased cholesterol and LDL levels and decreased HDL levels, which may increase the risk for cardiovascular disease.

Conflicting evidence exists regarding the influence of the Trp64/Arg SNP on the development of obesity. A large study from the U.K. did not find an association between BMI and Trp64/Arg; however, a meta-analysis of 97 studies found that the SNP was associated with BMI in East Asians, but not Europeans (Kurokawa *et al.* 2008). Higher BMI, weight and fat mass were found in subjects with Arg64 when a group of obese Caucasians was studied (de Luis *et al.* 2008). Gjesing and colleagues found that in a group of Danish subjects Arg64 was not associated with an increased risk for obesity, but it was associated with an increased risk for Type 2 diabetes, increased insulin resistance and higher plasma glucose levels after glucose ingestion (Gjesing *et al.* 2008). This difference was also noted in another study of postprandial plasma lipid levels which showed higher fasting and postprandial triglyceride levels, fasting plasma glucose levels and fasting plasma immunoreactive insulin levels in subjects with the Arg64 gene (Ueno *et al.* 2007). Gender differences in the effect of the Trp64/Arg polymorphism on metabolism have also been studied. Japanese men who were heterozygous for Trp64/Arg had decreased rates of fat oxidation compared with Trp64 homozygotes. This study did not find any difference in fat oxidation based on genotype among Japanese women (Morita *et al.* 2009). Investigation of the influence of the Arg64 SNP on the risk for development of metabolic syndrome (MS) showed no increased risk of MS in post-menopausal women in one study (Dunajska *et al.* 2008) while another study found an increased risk for MS development in obese males only (Zhu *et al.* 2008). The ADRB3 receptor genotype appears to have some influence in the development of obesity and appears to impact insulin resistance and possibly the development of diabetes, however, it appears that there are ethnic as well as gender differences in the impact of genotype on these conditions.

What conclusions can be drawn from the recent explosion of information regarding the influence of beta-adrenoceptor gene variation on intermediate physiological traits? As summarized in Table 1, it appears that for ADRB1, the Ser49 and Gly389 alleles may contribute to lower resting heart rate and myocardial responsiveness to agonist-mediated stimulation, which may therefore be detrimental in heart disease. For ADRB2, the Arg16 and Gln27 alleles appear to harbor unfavorable characteristics in cardiovascular and pulmonary health, due to blunted indices of cardiac function, vasodilation, and perhaps postexercise bronchodilation. For intermediate characteristics in the development of obesity, Gln27 may be associated with a lower rate of lipolysis. For the rare Thr164/Ile, considerable evidence in healthy humans suggests that presence of the minor allele is associated with blunted cardiac, vasodilator, and lipolysis responses to ADRB2-mediate stimulation. For ADRB3, perhaps the most consistent findings in metabolic and obesity physiology markers involve the beneficial or protective effect of the wild type allele, while the minor allele

(Arg64) is implicated in the characteristics predictive of obesity. It deserves mention that these conclusions deserve further replication because of the potential for undiscovered interactions among genes, and the unique aspects of evolutionary diversity among specific ethnic and racial populations.

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Figure 1.

The study paradigm for evaluating intermediate phenotype in healthy individuals. The physiological phenotype is measured while accounting for the interaction among genetic variation and environmental influence. The physiological characteristics in question have direct relevance to the development of complex distant phenotype such as heart disease and obesity.

Table 1

Selected examples of common intermediate physiological traits in healthy individuals that may be predictive of future disease or distant phenotype

“Undesirable” Intermediate Phenotype	<u>Adrenoceptor Polymorphism</u>			Distant Phenotype
	Beta-1	Beta-2	Beta-3	
Higher Resting HR	Ser49 Gly389			Cardiovascular disease
Blunted Inotropic, Chronotropic Response to Systemic Agonist	Gly389	Ile164		Cardiovascular disease
Blunted Regional Limb Vasodilation		Arg16 Gln27 Ile164		Hypertension, Cardiovascular disease
Reduced Regional and Systemic Vasodilator Response to Sympathoexcitation		Arg16 Gln27		Hypertension, Cardiovascular disease
Decreased Ventricular Ejection Fraction, Cardiac Output, Stroke Volume		Arg16		Cardiovascular disease, Fitness?
Blunted Post-exercise Bronchodilation		Arg16		Asthma
Increased BMI	Gly49 Gly389	Gly16	Arg64	Obesity
Lower Rate of Lipolysis		Arg16 Gln27 Ile164	Arg64	Hyperlipidemia, Decreased High Density Lipoprotein, Metabolic Syndrome
Insulin Resistance	Gly389		Arg64	Diabetes

Table 2

Allele frequency of highlighted polymorphisms by race/ethnic population.

Gene	Nucl. Position	Amino Acid Position	Major Allele	Minor Allele	Popn.	Major Freq.	Minor Freq.
<i>a</i> ADRB1	145A>G	Ser49/Gly	A: Ser	G: Gly	A-A	0.85	0.15
					As	> 0.9	< 0.1
					Cauc	0.9	0.1
					H-L	0.9	0.1
<i>b</i> ADRB1	1165G>C	Arg389/Gly	C: Arg	G: Gly	A-A	0.47	0.53
					As	0.8	0.2
					Cauc	0.7	0.3
					H-L	0.8	0.3
<i>c</i> ADRB2	46A>G	Arg16/Gly	G: Gly	A: Arg	A-A	0.6	0.4
					As	0.5–0.6	0.4–0.5
					Cauc	0.65	0.35
					H-L	0.65	0.35
<i>d</i> ADRB2	79C>G	Gln27/Glu	C: Gln	G: Glu	A-A	0.8	0.2
					As	0.9	0.1
					Cauc	0.5	0.5
					H-L	0.8	0.2
<i>e</i> ADRB2	491C>T	Thr164/Ile	C: Thr	T: Ile	A-A	1.0	
					As	1.0	
					Cauc	0.98	0.02
					H-L	-	
<i>f</i> ADRB3	190T>C	Trp64/Arg	T: Trp	C: Arg	A-A	0.9	0.1
					As	-	
					Cauc	0.85	0.15
					H-L	0.9	0.1

Nucl., nucleotide; Popn., population based on race/ethnicity; Freq., frequency; A-A, African-American; As, Asian; Cauc, Caucasian; H-L, Hispanic-Latino; dash (-) indicates data not reported or available on reference websites. Information for each polymorphism was obtained by searching the reference SNP (rs) number on the NCBI Reference Assembly. Frequencies are overall approximations based on multiple genotype database submissions for each polymorphism listed in the respective websites, verified on March 3, 2010. The respective web addresses were as follows:

^a http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=1801252

- ^b http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=1801253
- ^c http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=1042713
- ^d http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=1042714
- ^e http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=1800888
- ^f http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=4994