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Beta2-adrenergic receptor gene polymorphisms as systemic determinants of healthy aging in an evolutionary context

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ABSTRACT

The $Gln^{27}Glu$ polymorphism but not the $Arg^{16}Gly$ polymorphism of the beta2-adrenergic receptor (ADRB2) gene appears to be associated with a broad range of aging-associated phenotypes, including cancers at different sites, myocardial infarction (MI), intermittent claudication (IC), and overall/healthy longevity in the Framingham Heart Study Offspring cohort. The $Gln^{27}Gln$ genotype increases risks of cancer, MI and IC, whereas the Glu^{27} allele or, equivalently, the $Gly^{16}Glu^{27}$ haplotype tends to be protective against these diseases. Genetic associations with longevity are of opposite nature at young-old and oldest-old ages highlighting the phenomenon of antagonistic pleiotropy. The mechanism of antagonistic pleiotropy is associated with an evolutionary-driven advantage of carriers of a derived Gln^{27} allele at younger ages and their survival disadvantage at older ages as a result of increased risks of cancer, MI and IC. The ADRB2 gene can play an important systemic role in healthy aging in evolutionary context that warrants exploration in other populations.

1. Introduction

The etiology of complex phenotypes entails epistatic and gene-environment interactions that makes relevant gene association studies a challenging task. Polymorphisms in the beta2-adrenergic receptor (ADRB2) gene have long attracted the attention of health researchers for their possible multiple physiological and health effects, particularly those involving vascular responses and airway function (Buscher et al., 1999; Contopoulos-Ioannidis et al., 2005; Hindorff et al., 2005; Snyder et al., 2005). ADRB2 is a member of the receptors family that mediates the physiological effects of the hormone epinephrine and the neurotransmitter norepinephrine. Adrenergic stimulation of the ADRB2 influences, for instance, cardiovascular function by regulating vasomotor tone (Guimaraes and Moura, 2001). This function makes ADRB2 an important target in cardiovascular disease therapy. The two most common functional single nucleotide polymorphisms of the ADRB2 gene are rs1042713 (46GA) and rs1042714 (79CG), which result in changes of amino acids at codon 16, Arg to Gly, and at codon 27, Gln to Glu, respectively (George, 2008). Various studies have shown that the role of these polymorphisms is of a broad nature because of their involvement not only in vascular responses but also in pulmonary, endocrine, and central nervous systems functioning (Brodde, 2008a,b). Specifically, the roles of $Arg^{16}Gly$ and $Gln^{27}Glu$ polymorphisms in the pathophysiology of diseases of the heart (Heckbert et al., 2003), hypertension (Puddu et al., 2007), obesity (Jalba et al., 2008), diabetes (Pinelli et al., 2006), asthma (Contopoulos-Ioannidis et al., 2005), Alzheimer disease (Yu et al., 2008), COPD (Matheson et al., 2006), and cancer (Huang et al., 2001) have been studied in different populations.

The pleiotropy of the effects of these genetic variants makes them promising candidates for studies of genetic predisposition to healthy aging (Melzer et al., 2007), which is often defined as life with preserved health and physical, social and mental wellness, independence, and quality of life (Peel et al., 2004). Although a common goal is to determine genetic pathway(s) which could directly modulate senescence (Johnson, 2005), a more realistic strategy is to understand mechanisms involved in the process of development of aging-associated disorders to improve the health of an increasing elderly population in contemporary societies (Hadley and Rossi, 2005; Melzer et al., 2007; Olshansky et al., 2007; Sierra et al., 2008).

Currently, a large number of genetic studies focus on aging per se in model organisms and humans (Vijg and Suh, 2005). Likewise, a large body of studies focus on a single particular disease phenotype (e.g., Brodde, 2008b). Integration of these diverse initiatives in a systematic way could greatly advance studies of the genetics of healthy aging. The problem is that an integrative

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Table 1
Mean age (MA) and standard deviation (SD) for carriers of each genotype of the ADRB2 $Gln^{27}Glu$ or $Arg^{16}Gly$ polymorphism at first FHSO examination, and number of men and women carrying given compound genotypes of the $Gln^{27}Glu$ and $Arg^{16}Gly$ polymorphisms in the sample of the genotyped FHSO participants.

	Men					Women				
	MA (years)	SD (years)	$Gln^{27}Gln$	$Gln^{27}Glu$	$Glu^{27}Glu$	MA (years)	SD (years)	$Gln^{27}Gln$	$Gln^{27}Glu$	$Glu^{27}Glu$
MA (years)			37.2	36.4	35.0			35.5	36.3	36.4
SD (years)			9.3	10.2	9.5			8.9	9.7	10.1
$Arg^{16}Arg$	36.9	8.9	103	0	0	36.5	8.7	101	2	0
$Arg^{16}Gly$	36.8	10.1	113	235	2	35.3	9.4	125	236	0
$Gly^{16}Gly$	35.7	9.8	33	151	144	36.6	9.9	32	140	148

approach requires rich data on health and longevity, which are typically collected in longitudinal studies. A majority of genetic studies of disease phenotypes address particular illnesses, as mandated by the current health care paradigm. These studies often use case-control designs, which prevent rigorous investigation of pleiotropic genetic effects because of the limited number of measured phenotypes. The other problem facing studies of pleiotropic effects is that they can be more susceptible to the effects of other genes (epistasis) or non-genetic factors (gene-environment interaction) – which can partly explain disagreements in replications of the results.

In this study, we focus on the effects of common polymorphisms of the ADRB2 gene, $Arg^{16}Gly$ and $Gln^{27}Glu$, on the probability of staying free of cancer and cardiovascular diseases, as well as on association of these polymorphisms with overall and healthy longevity and survival. Phenotypic and genotypic information are assessed for participants of the longitudinal Framingham Heart Study Offspring (FHSO) cohort that has been followed up for about 36 years.

2. Data and methods

2.1. The FHSO phenotypic data

The FHSO cohort of respondents aged 5–70 years residing in Framingham, MA was launched in 1971–1975 with a focus on biological descendants ($N = 3514$), their spouses ($N = 1576$), and on adopted offspring ($N = 34$) of the participants of the original Framingham Heart Study (FHS) cohort (Dawber, 1980; Gail and Johnson, 1989) resulting in a total sample of $N = 5124$ subjects; 52% women (Govindaraju et al., 2008; Kannel et al., 1979). The publicly released limited-access FHSO data available for this study have phenotypic information assessed at six FHSO examinations performed in 1971–1975, 1979–1982, 1984–1987, 1987–1990, 1991–1995, and 1996–1997. The study participants have been followed for the occurrence of certain aging-associated diseases, with emphasis on cardiovascular diseases (CVDs) and cancer, and death through 2007. Onsets of CVDs and cancers were assessed at regular examinations at the FHS clinic and from medical records from outside clinics and hospitalization.

2.2. Aging-associated phenotypes and risk factors

We selected CVDs and cancers as the most common aging-associated diseases which were studied on their associations with common variants of the ADRB2 gene. Skin cancers were disregarded in this study. An overall longevity phenotype was defined as reaching a certain old age at the end of the follow-up period (i.e., in 2007) or at date of death. For the purpose of the study (see Section 3.3), cut-offs between long and short life were left flexible ranging from the youngest possible age (when too few individuals died before the cut-off age) to the oldest possible age (when there are too few individuals reaching the cut-off age). Individuals who survived cut-off ages were considered as long-living (LL) individuals compared to those who died before or on the cut-off age; called as short-lived (SL) individuals. A healthy longevity phenotype was considered if LL individuals did not develop cancer and/or CVDs.

2.3. ADRB2 polymorphisms in the FHSO

DNA was collected for living participants of the FHSO in the late 1980s and through 1990s (Cupples et al., 2007). Genotyping of about 1900 offspring (mainly unrelated) subjects was performed under the Cardio-Genomics program (http://cardiogenomics.med.harvard.edu/projects/p5/assoc-results) that focused on selected candidate genetic markers of cardiovascular development (a review of genotyped resources in the FHS and FHSO can be found in (Govindaraju et al., 2008; Levy et al., 2006)). Two common $Arg^{16}Gly$ and the $Gln^{27}Glu$ polymorphisms of the ADRB2 gene were selected for this study because of their documented *multiple* physiological and health effects (see Section 1) that warrants exploration of their systemic effect. The released data have information on the $Arg^{16}Gly$ and the $Gln^{27}Glu$ polymorphisms for 1565 (784 women) subjects. All genotyped members (but one) of the FHSO cohort participated in the 1st (1971–1974) and the 6th (1996–1997) examinations. There were 147 deaths (93 deaths occurred among men) in this sample that occurred after the 6th examination.

Table 1 shows mean age for samples of men and women stratified by the selected polymorphisms, as well as the number of individuals with a given compound genotype. Men with $Glu^{27}Glu$ genotype are somewhat younger (significantly with conventional tests and non-significantly with adjustment for multiple comparisons) than men with the $Gln^{27}Gln$ genotype. There are no other significant differences between mean ages. The $Arg^{16}Gly$ and $Gln^{27}Glu$ polymorphisms are in modest linkage disequilibrium (LD) with $r^2 = 0.41$ (evaluated using Haploview, v. 4.1 (Barrett et al., 2005)). As a result, the Arg^{16} allele is tightly linked to the Gln^{27} allele (but not vice versa) and the Glu^{27} allele is tightly linked to the Gly^{16} allele (but again not vice versa) (Table 1). Both polymorphisms are in Hardy–Weinberg equilibrium with $p = 0.78$ ($Arg^{16}Gly$) and $p = 0.86$ ($Gln^{27}Glu$).

2.4. Analyses

The Cox proportional hazards regression model was used to evaluate the relative risks (RRs) of death and incidence of the selected diseases as well as probability of staying free of a given disease (“survival patterns”) within the follow-up period through 2007 for carriers of the $Arg^{16}Gly$ and $Gln^{27}Glu$ polymorphisms. Associations of these polymorphisms with longevity-related phenotypes were evaluated using the logistic regression.

The analyses were first performed with adjustment for sex (when necessary) and age. Then the models were adjusted for such potential effect-mediators as systolic (SBP) and diastolic (DBP) blood pressures (mm Hg), smoking (ever smoked), diabetes, body-mass index (BMI; kg/m^2), total cholesterol (TC) and high-density lipoprotein (HDL) cholesterol (mg/100 ml) (Jalba et al., 2008; Petrone et al., 2006; Pinelli et al., 2006; Puddu et al., 2007). The absolute values of SBP, DBP, TC, and HDL were used in the regression models with increments of 10 mm Hg for SBP and DBP, and 10 mg/100 ml for TC and HDL cholesterol. BMI was categorized using the U.S. federal guidelines (Flegal et al., 2005) as underweight ($<18.5\ kg/m^2$), normal weight ($18.5–24.9\ kg/m^2$), overweight ($25–29.9\ kg/m^2$), and obesity ($>30\ kg/m^2$). Diabetes (present or absent) was defined if the study participant was under treatment with insulin/oral hypoglycemics or the level of fasting blood glucose $\geq$140 mg/dL (i.e., according to the WHO-1985 guidelines). Both types of analyses provided qualitatively similar results with slightly better estimates in the analyses with full adjustment.

Our analyses show that the $Gln^{27}Glu$ polymorphism is more relevant to diseases than the $Arg^{16}Gly$ polymorphism. Therefore, we present the results for the $Gln^{27}Glu$ polymorphism and show potential mediating/modulating role of the $Arg^{16}Gly$ polymorphism by evaluating the effect of six common compound genotypes of these two polymorphisms (i.e., excluding rare $Arg^{16}Gly/Glu^{27}Glu$ and $Arg^{16}Arg/Gln^{27}Glu$ genotypes; see Table 1).

Given prior evidences on the associations of the $Gln^{27}Glu$ and $Arg^{16}Gly$ polymorphisms with various aging-related phenotypes including those studied in this paper (see Section 1) and very limited number of independent tests, Type I sampling error is unlikely to be an issue for our analyses. Consequently, correction for multiple comparisons was not carried out. We note that robustness of our findings is further justified by the pleiotropic effect of the $Gln^{27}Glu$ polymorphism (revealed in this study) as well as by a hypothesized role of the ADRB2 polymorphisms in cardiovascular development (see Section 2.3) and by the candidate-gene-focused genotyping technique that offsets potential problems relevant to genome-wide technologies (Ziegler et al., 2008).

3. Results

3.1. The $Gln^{27}Glu$ polymorphism and health risks

Fig. 1A shows the highly significant protective role of the $Glu^{27}Glu$ homozygous genotype against cancer (all sites but skin) for men and women combined. To ascertain that this effect is not an artifact of biased attrition of the FHSO cohort before the blood