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CLINICAL & BASIC RESEARCH

Frequencies of the Arg16Gly, Gln27Glu and Thr164Ile *Adrenoceptor* β_2 Polymorphisms among Omanis

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تكرار التعدد الجيني لمورثات Arg16Gly, Gln27Glu and Thr164Ile في مستقبلات بيتا 2 الأدرينيرجية عند العمانيين

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abstract: ***Objectives:*** This study aimed to assess the distribution of missense mutations in the *adrenoceptor* β_2 (*ADRB2*) gene in an Omani cohort. ***Methods:*** This study was carried out between May 2014 and March 2015 at the Sultan Qaboos University, Muscat, Oman. Blood samples were taken from 316 unrelated Omani subjects. Genotyping for rs1042713 (c.46A>G, p.Arg16Gly), rs1042714 (c.79C>G, p.Gln27Glu) and rs1800888 (c.491C>T, p.Thr164Ile) polymorphisms was performed by real-time polymerase chain reaction using single nucleotide polymorphism (SNP) genotyping assays. The allelic frequencies of these polymorphisms were estimated on the basis of the observed numbers of specific alleles from the genotype data for male and female subjects. The genotype frequencies for each polymorphism were tested for deviation from the Hardy-Weinberg equilibrium. ***Results:*** Gly16 and Glu27 were the most frequent variants found among the cohort (63% and 75%, respectively). The Ile164 variant was not detected in the study population. There was a significant linkage disequilibrium between the rs1042713 and rs1042714 SNPs (r^2 = 0.209; $P \leq 0.001$). The most observed haplotypes were Gly16-Gln27 and Arg16-Gln27 (0.37 and 0.38, respectively). The frequency of Gly16-Glu27 was 0.25, comprising all Glu27 carriers. ***Conclusion:*** The allelic distribution of variants in this Omani cohort was similar to distributions reported among Caucasian populations.

Keywords: beta-2 Adrenergic Receptor; Genetic Polymorphisms; Single Nucleotide Polymorphisms; Allele Frequencies; Genotype; Oman.

الملخص: الهدف: هدف هذا البحث إلى دراسة توزيع الطفرات المغلطة في مورثات مستقبلات بيتا 2 الأدرينيرجية (ADRB2) في مجموعة من العمانيين. **الطريقة:** أجريت الدراسة بين مايو 2014م ومارس 2015م بجامعة السلطان قابوس بمسقط في عمان. تمجمع عينات دم من 316 فرد من العمانيين الغير أقارب. وتمت دراسة نمط التعدد الجيني في مورثات (c.46A>G, p.Arg16Gly) rs1042713، (p.Gln27Glu) rs1042714 (c.79C>G, p.Thr164Ile) and rs1800888 (c.491C>T, بواسطة جهاز تفاعل البلمرة التسلسلي (الوقت الحقيقي) وباستخدام مقايسة التنميط الجيني للتعدد الجيني للنيوكليوتايد الواحد (SNP). وتم تقدير هذه التعددات الجينية بحسب الأرقام الملاحظة من تعدادات الأليات المحددة المتحصل عليها من معلومات الأنماط الجينية في عينات الذكور والإناث في هذا البحث. وقيس انحراف تكراركل تعدد جيني من توازن هاردي–فاينبيرغ. **النتائج:** كانت أكثر المتفاوتات تكرارا هي Gly16 و Glu27 في المجموعة التي تمت دراستها 63% و75%، على التوالي). ولم يوجد متفاوت Ile164 في تلك المجموعة. وكان هنالك اختلال توازن معنوي إحصائيا في الارتباط بين ال (r^2 = 0.209 ; P ≤0.001) rs1042714 SNPs و rs1042713. وكان أكثر نمط فرداني هو في Gly16–Gln27 و Arg16–Gln27 (0.37 و 0.38 على التوالي). وبلغ تواتر Gly16–Glu27، 0.25 ويشمل ذلك حوامل Glu27. **الخلاصة:** كان التوزيع الأليلي لمختلف المتفاوتات في المجموعة العمانية التي درست مشابهة لتوزيعها عند الشعوب القوقازية.

مفتاح الكلمات: مستقبلات بيتا 2 الأدرينيرجية؛ التعدد الجيني؛ التعدد الجيني للنيككليوتايد الواحد؛ تكرارالأليات؛ النمط الجيني؛ عمان.

Advances in Knowledge

- *This study explores the distribution of the major missense mutations of the adrenoceptor β_2 (ADRB2) gene in the Omani population.*
- *The p.Arg16Gly and p.Gln27Glu variants occurred most frequently among this Omani cohort.*

Application to Patient Care

- *Variations in the ADRB2 gene can affect responses to drug actions, thereby impacting diseases in which ADRB2 plays a role, such as asthma, obesity and hypertension. The results of this study could therefore be of importance for the clinical management of these diseases.*

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Genetic variation in the human β_2-adrenergic receptor (β_2AR) has been the subject of much experimental and pharmacoclinical research, especially in the treatment of asthma. Initially cloned, sequenced and reported by Kobilka *et al*., β_2AR encodes a 413 amino acid protein belonging to the family of G-protein coupled receptors.[1] The receptor is the product of the 1,242-base pair intronless *adrenoceptor* β_2 (*ADRB2*) gene located on the long arm of chromosome 5 (q31.q32).[1] *ADRB2* has been linked to asthma, asthma-related phenotypes and diseases such as hypertension and obesity.[2–5] β_2AR is expressed in different types of cells in the lung, including airway smooth muscle cells, the vascular endothelium, alveolar walls, immune cells and presynaptic cholinergic nerve terminals.[6]

Reihsaus *et al*. described nine single nucleotide polymorphisms (SNPs) in the coding region of *ADRB2*.[7] Four of these SNPs were nonsynonymous mutations leading to changes in the amino acid sequence: rs1042713 (c.46A>G, p.Arg16Gly), rs1042714 (c.79C>G, p.Gln27Glu), rs1800888 (c.491C>T, p.Thr164Ile) and rs1141370 (c.100G>A, p.Val34Met). The first three of the nonsynonymous SNPs demonstrated *in vivo* functional effects on the receptor activity.[7] The rs1800888 and rs1141370 SNPs were infrequent and found only in the heterozygous state. Arg16Gly and Glyn27Glu were the most common nonsynonymous polymorphisms reported in the *ADRB2* gene.[7] The Arg16Gly polymorphism is the most common and functionally relevant SNP at the amino terminus of the receptor; it occurs with allelic frequencies of between 67–72% in different populations.[8] The frequency of the Gln27Glu polymorphism is approximately 29% in Caucasian populations.[7] The Thr164Ile polymorphism, which is located in the fourth transmembrane domain of β_2AR, exhibits an allelic frequency of 2–5% in Caucasian populations; however, it has only been reported in the heterozygous state so far.[7]

Allelic frequencies of *ADRB2* polymorphisms, especially the SNPs in the coding region, have been studied in different ethnic groups. Studies on African American, European American, Saudi, Southwest Asian, Kenyan and Chinese populations all show inter-ethnic variation in the frequency of Gln27Glu and Arg16Gly polymorphisms.[9,10] Since β_2AR is an important target for many asthma drugs, these variations in the frequency of *ADRB2* genotypes may influence disease susceptibility and drug responses in different populations.[11] Jamil *et al*. reported that the prevalence of asthma in the USA was lower among Arabs in comparison to non-Middle Eastern Caucasians, independent of environmental factors.[12] This further suggests the role of ethnic-specific gene-environment interactions in the predisposition to asthma. Therefore, the current study aimed to determine the frequencies of alleles and haplotypes of major missense mutations in the *ADRB2* gene in an Omani cohort.

Methods

This study was carried out between May 2014 and March 2015 at the Sultan Qaboos University (SQU), Muscat, Oman. A total of 316 unrelated Omani subjects were recruited either as volunteers from the community or from patients visiting the Family Medicine & Community Clinic at SQU Hospital for regular medical check-ups. The inclusion criteria for the subjects were Omani nationality and an age of ≥35 years old. A minimum sample size of 261 was calculated based on 5.5% precision, 5% type I error and the reported proportion of Gln27Glu in a Caucasian population (0.29).[8]

Blood was collected from all participants for the purposes of DNA extraction. Genomic DNA was isolated from 200 µL of whole blood using a DNA kit (QIAGEN GmbH, Hilden, Germany) according to the protocols provided by the manufacturer. Genotyping for the rs1042713, rs1042714 and rs1800888 SNPs was performed by real-time polymerase chain reaction using SNP genotyping assays (TaqMan®, Applied Biosystems, Thermo Fisher Scientific Inc., Wilmington, Delaware, USA) according to the manufacturer's instructions.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), Version 20.0 (IBM Corp., Chicago, Illinois, USA). Data were compiled by genotype and the derived allelic frequencies were estimated based on the observed numbers of the specific alleles from the genotype data for male and female subjects. The genotype frequencies for each polymorphism were tested for deviation from the Hardy-Weinberg equilibrium (HWE) using a Chi-squared goodness-of-fit analysis with one degree of freedom. Haplotypes were constructed from the combination of both polymorphisms. Frequencies were inferred using PHASE 2.1.1 software (Matthew Stephens Laboratory, Department of Human Genetics, University of Chicago, Chicago, Illinois, USA).[13,14]

Ethical permission to conduct this study was obtained from the Medical Research & Ethics Committee of the College of Medicine & Health Sciences at SQU (MREC #284-A). All participants gave informed consent before inclusion in the study.

Table 1: Genotype distributions of *adrenoceptor* β_2 genetic polymorphisms by gender among an Omani cohort (N = 316)

SNP	n (%)		*P* value
	Male (n = 129)	Female (n = 187)	
rs1042713 G>A			0.937
GG	54 (41.9)	77 (41.2)	
AG	56 (43.4)	80 (42.8)	
AA	19 (14.7)	30 (16.0)	
rs1800888 C>T			-
CC	129 (100.0)	187 (100.0)	
CT	0 (0.0)	0 (0.0)	
TT	0 (0.0)	0 (0.0)	
rs1042714 C>G			0.715
CC	70 (54.3)	109 (58.3)	
CG	49 (38.0)	67 (35.8)	
GG	10 (7.8)	11 (5.9)	

SNP = single nucleotide polymorphism.

Table 3: Observed and expected genotype distributions and allelic frequencies of the *adrenoceptor β-2* gene among an Omani cohort (N = 316)

SNP	n (%)		95% CI	HWE	*P* value
	Observed	Expected			
rs1042713 G>A				1.88	0.171
GG	131 (41.5)	125.3 (39.7)	34.4–45.1		
AG	136 (43.0)	147.4 (46.6)	41.2–52.2		
AA	49 (15.5)	43.3 (13.7)	10.3–18.0		
rs1800888 C>T				-	-
CC	316 (100.0)	316 (100.0)	-		
CT	0 (0.0)	0 (0.0)	-		
TT	0 (0.0)	0 (0.0)	-		
rs1042714 C>G				0.14	0.708
CC	179 (56.6)	177.8 (56.3)	50.8–61.7		
CG	116 (36.7)	118.5 (37.5)	32.2–42.8		
GG	21 (6.6)	19.8 (6.3)	3.6–8.9		

SNP = single nucleotide polymorphism; CI = confidence interval; HWE = Hardy-Weinberg equilibrium.

Table 2: Allelic frequencies and percentages of *adrenoceptor β-2* genetic polymorphisms among an Omani cohort (N = 316)

SNP	Allelic frequency	Allelic percentage
rs1042713 GA	0.63/0.37	63/37
rs1800888 CT	1.00/0.00	100/0
rs1042714 CG	0.75/0.25	75/25

Table 4: Haplotype frequencies and linkage disequilibrium pattern of *adrenoceptor β-2* genetic polymorphisms (rs1042713/rs1042714) among an Omani cohort (N = 316)

Haplotype	n	Frequency	Linkage		
			R^2	χ^2	*P* value
GG	158	0.25	0.209	127.54	≤0.001
GC	240	0.38			
AG	0	0.00			
AC	233	0.37			

Results

Among the Omani cohort, there were 129 male and 187 female subjects. The overall mean age was 46.0 ± 8.0 years, with a mean age of 45.0 ± 9.0 years for males and 46.0 ± 7.9 years for females (*P* = 0.291). Three variants of the *ADRB2* gene were genotyped: rs1042713 (p.Arg16Gly), rs1042714 (p.Gln27Glu) and rs1800888 (p.Thr164Ile). No significant differences were observed in the genotype frequencies between genders [Table 1]. The rare rs1800888 SNP was not detected in the cohort; all individuals were homozygous for the wild-type allele. Gly16 and Gln27 were the most frequent variants in the study population (63% and 75%, respectively), with average frequencies of 0.63 and 0.75, respectively [Table 2]. The *P* values for observed and expected genotype frequencies of the rs1042713 and rs1042714 SNPS were 0.171 and 0.708, respectively, with no deviation from the HWE distribution. Allelic frequencies for the rs1042713, rs1800888 and rs1042714 SNPs were 0.63/0.37, 1.00/0.00 and 0.75/0.25, respectively [Table 3].

There was a significant linkage disequilibrium between the rs1042713 and rs1042714 SNPs (R^2 = 0.209; *P* ≤0.001). Random segregation of alleles showed that the Arg16 allele did not occur together with Glu27, as shown in the distribution of the AG haplotype. The most observed haplotypes in the cohort were Gly16-Gln27 (GC) and Arg16-Gln27 (AC) with frequencies of 0.38 and 0.37, respectively. The frequency of Gly16-Glu27 (GG) was also common (0.25), comprising all Glu27 carriers [Table 4].

Table 5: Comparative analysis of allelic frequencies of Gly16 (rs1042713) and Gln27 (rs1042714) polymorphisms in various ethnic groups reported in the literature

Author and year of study	Population	Frequency of polymorphism		Total sample size
		Gly16	Gln27	
Maxwell *et al.*[9] 2005	Saudi	0.53	0.83	100
Maxwell *et al.*[9] 2005	Ghanaian	0.47	0.90	100
Maxwell *et al.*[9] 2005	Kenyan	0.43	0.91	100
Maxwell *et al.*[9] 2005	Sudanese	0.57	0.84	52
Maxwell *et al.*[9] 2005	Filipino	0.46	0.91	78
Maxwell *et al.*[9] 2005	Chinese	0.41	0.93	99
Xie *et al.*[10] 1999	African American	0.51	0.79	123
Maxwell *et al.*[9] 2005	Southwest Asian	0.46	0.84	99
Maxwell *et al.*[9] 2005	Scottish	0.59	0.54	100
Kato *et al.*[17] 2001	Japanese	0.51	0.93	1,681
Ehrenborg *et al.*[18] 2000	Swedish	0.59	0.62	180
Hall *et al.*[19] 2006	British	0.64	0.55	8,018
Hamdy *et al.*[16] 2002	Egyptians	0.43	0.76	240
Aynacioglu *et al.*[15] 1999	Turkish	0.60	0.68	104
Ramasy *et al.*[20] 1999	Australian	0.54	0.60	332
Xie *et al.*[10] 1999	American Caucasian	0.62	0.58	212
Candy *et al.*[21] 2000	South African	0.52	0.83	123
Present study	Omani	0.63	0.75	316
Mean of all populations ± SD	-	0.53 ± 0.07	0.77 ± 0.14	-

SD = standard deviation.

Discussion

In the current study, Gly16 and Gln27 were the most common alleles among the Omani cohort. There were no differences in the genotype frequencies between genders, suggesting random selection; this was further supported by the lack of deviation from the HWE distribution. Previous research in different populations has suggested inter-ethnic differences in *ADRB2* gene polymorphisms. The allelic frequencies of two SNPs (rs1042713 and rs1042714) in the current Omani cohort were compared with those of various ethnic groups reported in the literature [Table 5].[9,10,15–21] Gly16 and Gln27 polymorphisms occur with high allelic frequency in Caucasian populations;[7,8] the frequencies of Gly16 and Gln27 polymorphisms in the current Omani cohort were similar. However, regardless of population, the frequency of the Gln27 variant showed higher inter-ethnic variation than the Gly16 variant (standard deviation: 0.14 versus 0.07).

The haplotype distributions in the population of the current study were similar to those reported in a previous study of the Turkish population.[15] There is strong linkage disequilibrium between SNPs in the *ADRB2* gene since limited sets of haplotypes are observed in different ethnic groups. Drysdale *et al.* reported three common haplotypes in Caucasians and four common haplotypes in African Americans based on 13 *ADRB2* SNPs.[22] Examinations of the results of genetic association studies between *ADRB2* and diseases like asthma should take into account differences in genotype frequencies between populations and the existence of the strong linkage disequilibrium between *ADRB2* SNPs.

Variations in the *ADRB2* gene affect patient responses to drug actions; therefore, these variations could be of importance for the clinical management of diseases in which β_2AR plays a role, such as asthma, obesity and hypertension. Inter-ethnic differences in this receptor have been proposed to explain differences in responses to drugs such as terbutaline, isoproterenol and albuterol.[23]

Conclusion

The present study provides further evidence of inter-ethnic differences in *ADRB2* gene polymorphisms. The allelic distribution of variants in this Omani population was similar to distributions reported in Caucasian populations.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

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