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ARTICLE

Studies of the associations between functional β_2-adrenergic receptor variants and obesity, hypertension and type 2 diabetes in 7,808 white subjects

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Abstract
Aims/hypothesis Functional and common Arg16Gly and Gln27Glu polymorphisms have been identified in *ADRB2*, the gene encoding the β_2-adrenergic receptor. These variants have previously been examined for association with obesity, hypertension and diabetes with inconclusive results.
Materials and methods We investigated both of these variants in 7,808 unrelated, middle-aged white people for their association with obesity in a case–control study, quantitative trait analysis and meta-analysis. Moreover, both variants were investigated for their potential influence on measures of hypertension and type 2 diabetes by case–control and quantitative trait analyses.
Results The present study did not find consistent evidence for an association of these β_2-adrenergic receptor variants with obesity or hypertension; neither did the quantitative trait analyses show any effect of the variants on obesity-related traits. However, both the Gly allele of the Arg16Gly variant and the Glu allele of the Gln27Glu variant showed nominal association with systolic blood pressure. Furthermore, there was a nominal association of the Arg16 allele frequency and genotype distribution with type 2 diabetes; however, no influence on quantitative biochemical phenotypes related to type 2 diabetes was found. A nominal association of the Arg/Gly genotype with the metabolic syndrome was also observed (p=0.003). Logistic regression analyses provided no evidence of a synergistic or an additive effect of these variants on obesity, hypertension or diabetes.
Conclusions/interpretation After studying 7,808 middle-aged white subjects, we were unable to demonstrate any consistent associations between two common amino acid polymorphisms of the β_2-adrenergic receptor and obesity, hypertension or type 2 diabetes.

Keywords Adrenergic receptor · Diabetes · Epidemiology · Genetics · Hypertension · Metabolic syndrome · Obesity

Abbreviations

ADRB2	β_2-adrenergic receptor
MABP	mean arterial blood pressure
MAF	minor allele frequency

Introduction

Via the sympathetic nervous system, the β_2-adrenergic receptor is involved in the regulation of metabolism and vascular resistance. Polymorphisms have been identified in this receptor, of which the Arg16Gly and Gln27Glu variants are the most frequent [1]. The Arg16Gly variant has shown increased agonist binding in human fat cells [2] and in Chinese hamster fibroblasts. Furthermore, both polymorphisms have altered agonist-induced downregulation [3].

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A substantial number of studies have previously investigated the association between the Arg16Gly and the Gln27Glu variant and obesity and obesity-related traits. Several of these failed to identify any association [3–9]. Other studies have found significant associations [8, 10, 11], but without a consensus regarding which allele is associated with obesity or related traits.

The same ambiguity is observed when the two variants are examined in relation to hypertension [9, 10, 12–15] and type 2 diabetes [2, 5, 9, 14, 16–18].

Therefore, despite the large number of previous reports of relatively small studies the influence of the Arg16Gly and Gln27Glu variants of *ADRB2*, the gene encoding the β_2-adrenergic receptor, on the risks of obesity, hypertension and type 2 diabetes remains unclear and the purpose of this study was in relatively large-scale analyses of well-characterised traits in Danish white subjects to evaluate a potential impact of the two *ADRB*2 polymorphisms on the prevalence of obesity, hypertension and type 2 diabetes.

Subjects and materials

Patients The *ADRB2* Arg16Gly (rs1042713) and Gln27Glu (rs1042714) variants were genotyped in a total of 7,808 Danish white subjects. The study involved three groups. The first group was a population-based sample (Inter99) of middle-aged Danish white subjects from the greater Copenhagen area sampled at the Research Centre for Prevention and Health [19] (n=6,364; 3,115 men, 3,249 women) aged 46±8 years (mean±SD) and having a BMI of 26.3±4.6 kg/m^2. Of these, 4,520 (71%) had fasting normoglycaemia and NGT, 502 (8%) had IFG, 692 (11%) had IGT, 253 (4%) had screen-detected and untreated type 2 diabetes, and 119 (2%) had known type 2 diabetes. Glucose tolerance status was unknown for 278 participants. The second group were middle-aged glucose-tolerant subjects recruited randomly from the Central Population Registry of Copenhagen county (n=394; 196 men, 198 women) with an age of 62±5 years and BMI of 26.5±4.2 kg/m^2. The third group were type 2 diabetic patients sampled through the outpatient clinic at the Steno Diabetes Center (n=1,050; 636 men, 414 women). The mean age was 59±11 years, mean age of clinical diagnosis 52±11 years, mean BMI 29.4±5.2 kg/m^2 and mean HbA_{1c} 8.1±1.6%.

Patients with diabetes due to known chronic pancreatitis, haemochromatosis, severe insulin resistance, maturity-onset diabetes of the young, maternally inherited diabetes and deafness, and family history of first-degree relatives with type 1 diabetes were excluded before entering the study population. Patients with an insulin requirement within the first year after diabetes diagnosis or a fasting serum C-peptide level ≤150 pmol/l at the time of recruitment were excluded from the category of clinically defined type 2 diabetes (n=48).

Subjects of study groups 1 and 2 underwent a standard 75-g OGTT. Glucose tolerance status was classified according to the 1999 WHO criteria [20]. The metabolic syndrome was classified according to both the 1999 WHO criteria [20] including microalbuminuria and the National Cholesterol Education Program (NCEP) III criteria [21]. Hypertension was defined as mean systolic blood pressure ≥140 mmHg and/or mean diastolic blood pressure ≥90 mmHg and/or current or previous treatment with antihypertensive drugs.

Informed written consent was obtained from all subjects before participation. The study was approved by the Ethical Committee of Copenhagen County and was in accordance with the principles of the Declaration of Helsinki.

Biochemical, anthropometric and physiological measurements These analyses were performed as previously described [22].

Genotyping Genotyping was performed using chip-based matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (DNA MassARRAY; Sequenom, San Diego, CA, USA) of PCR-generated primer extension products as described [23]. The genotyping success rates were 97% (Arg16Gly) and 98% (Gln27Glu) and all genotype groups obeyed Hardy–Weinberg equilibrium. Of 182 samples genotyped in duplicates (for each variant) no genotype discrepancies were observed.

Statistical analysis Fisher's exact test was applied to examine differences in minor allele frequencies (MAFs) and genotype distributions between affected and unaffected subjects. Patients with known type 2 diabetes were excluded from case–control analyses for hypertension and individuals with unknown diabetes status were excluded from case–control analyses for diabetes. Logistic regression with adjustment for sex and age was also used to test for differences in genotype distribution. A general linear model was used to test quantitative variables (or transformed variables) for differences between genotype groups. Quantitative trait analysis was performed only in the Inter99. Patients with known diabetes were excluded from these analyses and patients receiving antihypertensive treatment (n=411) were not included in cardiovascular quantitative trait analyses. Genotype and sex were considered as fixed factors and age and BMI as covariates. Logistic regression analysis including both variants with adjustment for sex and age was also used to test for differences in haplotype distributions. All analyses were performed using the

Statistical Package for Social Science (SPSS, Chicago, IL, USA) version 13.0 and RGui version 2.10. A p value<0.05 was considered to be significant. A meta-analysis of all previously published studies was performed using logistic regression (RGui version 2.10). Homogeneity between studies was tested (Mantel–Haenszel) assuming a general model.

Results

The allele frequencies observed in this study were 38.2% (95% CI 37.4–38.9) for the codon 16 Arg allele and 43.8% (95% CI 43.0–44.5) for the codon 27 Glu allele with some degree of pair-wise linkage disequilibrium (r^2=0.48) between the two variants. For the Arg16Gly and Gln27Glu variants case–control studies of overweight (cut-off value at BMI 25 kg/m^2) and obesity (cut-off value at BMI 30 kg/m^2) showed no significant difference between the two groups in terms of allele frequency or genotype distribution when examined using Fisher's exact test (data not shown). Dichotomisation according to sex and subsequent re-analysis did not change these results (data not shown). Logistic regression with adjustment for age and sex was also performed and gave similar results. Quantitative trait analyses examining the relationship between the variants and phenotypes such as weight, waist and hip circumferences, WHR and BMI also failed to detect an effect of the Arg16Gly and Gln27Glu variants (data not shown).

A meta-analysis was also performed including previously conducted case–control studies of obesity [4–8, 13, 14, 16, 17, 24–27]. These populations differed in ethnicity and sex, although homogeneity between studies was fulfilled (p=0.9). This analysis did not identify any association of the Arg16Gly variant with obesity (data not shown). Thirteen previously performed case–control studies including Europid and Asian individuals examining the association of the Gln27Glu variant with obesity were combined with the present study and analysed in a meta-analysis (Fig. 1). Men and women were analysed together and separately in dominant, recessive and additive models. Homogeneity testing of the overall difference in MAF and genotype distribution between the studies was performed; however, homogeneity was not fulfilled (p=0.01). This analysis also failed to identify any association between the Gln27Glu variant and obesity (Glu/Glu odds ratio=0.92 [0.81–1.04], Gln/Glu odds ratio=1.07 [0.98–1.18]).

Similarly, the two *ADRB2* variants were analysed for a possible association with hypertension. Neither variant showed any difference in allele frequency or genotype distribution between the hypertensive and normotensive participants when the analyses were conducted among men and women separately or combined (data not shown). In addition, logistic regression with adjustment for age, sex and BMI did not detect an effect of the variants. Quantitative trait analyses (systolic, diastolic and mean arterial blood pressure [MABP]) were performed showing that both variants have a significant association with systolic blood pressure among women. The Arg/Arg genotype of the Arg16Gly variant was associated with a decreased systolic blood pressure (Table 1) and the Glu allele of the Gln27Glu variant was associated with an increased systolic blood pressure (Table 1). These effects were reflected in the MABP, which was also significantly associated with the variants (Table 1).

The relationship between the variants and type 2 diabetes was evaluated. For both variants, glucose-tolerant individuals were compared with individuals having known diabetes, with individuals having known or screen-detected diabetes, and with individuals having IGT, IFG, screen-detected diabetes or known diabetes. When glucose-tolerant individuals were compared with individuals having known diabetes the Arg allele of the Arg16Gly variant was more frequent among diabetic individuals (p=0.03). Likewise, the genotype distribution was significantly different when using Fisher's exact test (p=0.01) and logistic regression with adjustment for sex and age (p=0.05, odds ratio=1.12, CI 1.00–1.25) (Table 2). When comparing glucose-tolerant individuals with screen-detected and known diabetes

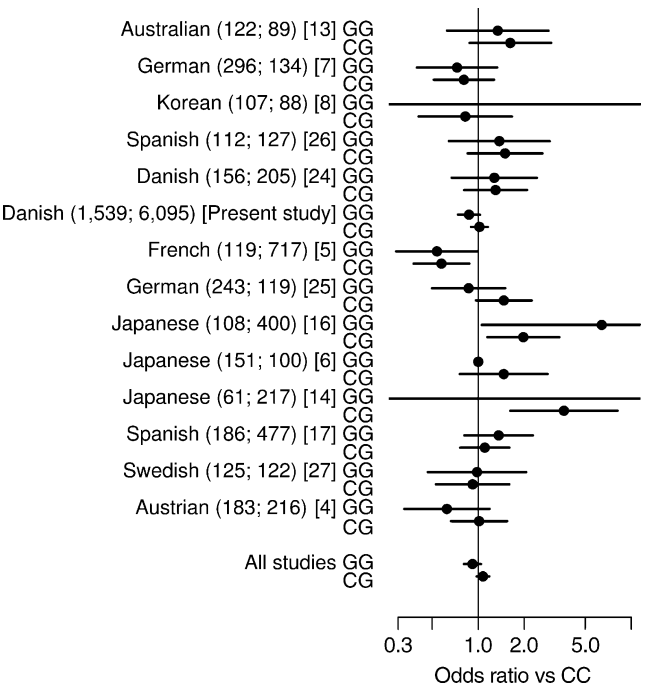

Fig. 1 Estimated risk (95% CIs) of having obesity when carrying the *ADRB2* Glu allele of the Gln27Glu polymorphism in a meta-analysis of data from published case–control studies [4–8, 13, 14, 16, 17, 24–27] and from the present investigation and assuming a general model. The values in parentheses represent the numbers of cases and controls, respectively, of the individual study

Table 1 Blood pressure characteristics (means±SD) of 2,914 middle-aged Danish white women subjects stratified according to *ADRB2* Arg16Gly and the *ADRB2* Gln27Glu genotype

	Arg16Gly				Gln27Glu			
	Gly/Gly	Arg/Gly	Arg/Arg	*p* value	Gln/Gln	Gln/Glu	Glu/Glu	*p* value
n	1,140	1,349	415	–	885	1,432	597	–
Age (years)	45±8	46±8	45±8	–	45±8	45±8	45±8	–
BMI (kg/m^2)	25.5±4.8	25.5±4.9	25.5±5.3	0.9	25.4±5.0	25.6±4.9	25.5±4.9	0.7
Blood pressure (mmHg)								
Systolic	125.6±17	125.8±17	123.4±15	0.02	124.1±16	125.9±17	126.0±17	0.01
Diastolic	79.0±11	79.6±11	78.4±10	0.2	78.5±10	79.5±11	79.1±11	0.1
MABP	94.5±12	95.0±12	93.4±11	0.05	93.7±11	95.0±12	94.7±12	0.03

Values of BMI were cube root transformed before statistical analysis. Values were adjusted for age, sex and BMI (where appropriate), and were calculated assuming an additive (*p*) model

MABP is calculated as ([2×diastolic blood pressure]+[systolic blood pressure])/3

patients (cases=1,325; controls=4,739) and with IGT, IFG, screen-detected diabetes patients and known diabetes patients (cases=2,491; controls=4,739) no association of the variants was present (data not shown). Stratifying the data according to sex revealed only a borderline association of the Arg16Gly variant with genotype distribution among men with known diabetes compared with glucose-tolerant men (p=0.05). Quantitative traits related to the pathogenesis of diabetes such as fasting levels of plasma glucose and serum insulin and C-peptide and levels of plasma glucose and serum insulin and C-peptide after oral glucose ingestion as well as homeostasis model assessment of insulin resistance were examined for association with Arg16Gly and Gln27Glu variants. The Arg16Gly did not show any consistent effect on the examined quantitative traits (data not shown). For the Gln27Glu variant, plasma glucose levels 2 h after an oral glucose load appeared to be increased by the Glu allele (Gln/Gln=6.13±2.01, Gln/Glu=6.19±2.07, Glu/Glu=6.37±2.39 mmol/l; p=0.03).

The Arg16Gly variant did show an association between the genotype distribution and metabolic syndrome defined according to WHO 1999 criteria [20] (p=0.003). When stratifying according to sex this association was only observed among men and not among women. This variant did not show an association with the metabolic syndrome defined according the NCEP III [21]. The Gln27Glu variant was not associated with the metabolic syndrome regardless of definition criteria (data not shown).

Finally, logistic regression analysis examining the combined effect of the two variants was performed for hypertension, diabetes and obesity for men and women together and separately. However, there were no combined effects of the variants on hypertension, diabetes or obesity (data not shown).

Table 2 MAF and genotype distribution of the *ADRB2* Arg16Gly variant and the *ADRB2* Gln27Glu variant in glucose-tolerant individuals (NGT) and patients with known type 2 diabetes and in individuals with the metabolic syndrome (MetS) according to WHO criteria [20] and individuals without any components of the metabolic syndrome (Non-MetS)

	NGT	Diabetes	*p* value (NGT vs diabetes)	Non-MetS	MetS	*p* value (Non-Mets vs MetS)
Arg16Gly						
n	4,739	1,052	–	1,826	2,013	–
Gly/Gly	1,853 (39)	361 (34)	–	741 (41)	736 (37)	–
Arg/Gly	2,212 (47)	538 (51)	0.01[a]	811 (44)	1,004 (50)	0.003[a]
Arg/Arg	674 (14)	153 (15)	–	274 (15)	273 (13)	–
MAF (95% CI)	37.6 (36.6–38.5)	40.1 (38.0–42.2)	0.03[b]	37.2 (35.6–38.8)	38.5 (37.3–40.0)	0.25[b]
Gln27Glu						
n	4,771	1,117	–	1,838	2,080	–
Gln/Gln	1,472 (31)	364 (33)	–	568 (31)	664 (32)	–
Gln/Glu	2,338 (49)	553 (50)	0.2[a]	899 (49)	1,025 (49)	0.5[a]
Glu/Glu	961 (20)	200 (18)	–	371 (20)	391 (19)	–
MAF (95% CI)	44.6 (43.6–45.6)	42.7 (40.6–44.7)	0.09[b]	44.6 (43.0–46.2)	43.4 (41.9–44.9)	0.3[b]

Data are number of subjects in each genotype group (% of each group) and MAF in % (95% CI)

The *p* values were calculated using Fisher's exact test and are stated for [a] the genotype distribution and [b] the allele frequency

Discussion

The Arg allele frequency of the *ADRB2* Arg16Gly variant (38%) was similar to previously identified allele frequencies [2, 4, 5]. The present case–control study, quantitative trait analysis and meta-analysis did not provide evidence of an impact of the variant on obesity, which is consistent with previously performed case–control studies [2, 4–9]. Previous studies have suggested sex differences [16]. Therefore, the case–control and the quantitative trait study analysed the sexes separately as well as combined, although without any influence on the results.

The Gln27Glu variant was also examined in a case–control study, a quantitative trait analysis and a meta-analysis for its potential impact on obesity. All three studies failed to demonstrate any significant effect of this variant. The allele frequencies of the variant (44%) is in line with previously identified allele frequencies [18, 24, 25]. The reported case–control studies have presented ambiguous results with either allele being associated with obesity. The disparity could be due to associations with other disease-causing variants, interaction with other genetic variants or environmental influences.

To examine possible additive or synergistic effects of the two variants, haplotype analyses within the *ADRB2* locus have been reported. Most studies find that there was no significant association between haplotypes and obesity [4, 10]. In the present study we examined the combined effect of the Arg16Gly and Gln27Glu variants in relation to obesity using regression analysis. There was no effect of the two variants on overweight or obesity, or when individuals having a BMI >30 kg/m^2 were compared with individuals having BMI <25 kg/m^2. Therefore, based on the present analyses there is no evidence that the Arg16Gly or Gln27Glu variants (separately or combined) exert a major impact on the pathogenesis of obesity in the examined study samples.

The present case–control study examining the effect of the Arg16Gly and Gln27Glu variants on hypertension was negative, which is in accord with previous reports [10, 12]. An Italian study observed a higher prevalence of hypertension among carriers of the Arg allele when individuals below 50 years of age were analysed independently [9]. In the present study, individuals below 50 years of age were therefore examined in a separate case–control study; however, this did not influence the results. Furthermore, different definitions of hypertension have been used in different studies; however, when applying criteria for hypertension comparable to those in previous reports there was still no impact of either of the variants. In studies of quantitative traits the Gly allele carriers had increased systolic blood pressure and the Glu allele carriers of the Gln27Glu variant had an increase in systolic blood pressure. These associations were weak and when considering adjustment for multiple testing these associations become insignificant; however, both observations are consistent with earlier findings [10, 15].

Investigators have examined the effect of the two variants combined; however, no clear picture has emerged [9, 12]. In the present logistic regression analysis for the two variants combined there was no indication of an effect of the variants on hypertension.

The Arg16Gly and Gln27Glu variants were examined for their relationship with type 2 diabetes. The Arg allele of the Arg16Gly variant did associate, although weakly, with known type 2 diabetes (p=0.03) and the Gly/Gly genotype was most predominant among control subjects (p=0.01). This association was not present when patients also included screen-detected type 2 diabetic patients or individuals having IGT and IFG. The quantitative trait analyses did not indicate any consistent influence of the variant on traits related to diabetes. The Gln27Glu variant did not associate with type 2 diabetes in the present case–control study. Likewise, the quantitative trait study did not indicate a consistent influence of the Gln27Glu variant on diabetes-related traits. However, it was observed in the present study that the Glu allele is associated with an increased 2-h post-load plasma glucose concentration among men, which was also observed in a Spanish study of 666 individuals [17]. It should be kept in mind that both of these associations are weak and when considering adjustment for multiple testing they become insignificant. However, as both variants may exert a minor influence we examined if there was a collective effect of the two *ADRB2* variants on type 2 diabetes prevalence. In this analysis there was no combined impact of the Arg16Gly and the Gln27Glu polymorphisms. Other haplotype analyses including the two variants have been conducted but no clear picture has emerged [8, 9].

In order to further explore the relationship between these variants and phenotypes related to the function of the receptor in blood pressure regulation and lipolysis, case–control studies were performed examining the association with the metabolic syndrome. An association was identified between the Arg16Gly genotype and the metabolic syndrome defined according to WHO 1999 criteria [20]. As a previous study found an association between the variant and the metabolic syndrome only among men [28], sex stratification was also performed in the present study. In agreement with the previous study the association with the metabolic syndrome was only seen among men. This association was, however, not found with the metabolic syndrome defined according to NCEP III [21], and therefore the above-mentioned association is cautiously interpreted.

In conclusion, it seems unlikely that Arg16Gly and Gln27Glu polymorphisms of *ADRB2* are major contributors to the pathogenesis of obesity, hypertension or type 2 diabetes. However, the Arg16Gly variant is possibly associated with the metabolic syndrome especially among

men. In order to elucidate the full effect of variants in the *ADRB2* locus resequencing is required with subsequent tagging of identified single-nucleotide polymorphisms (SNPs) and association studies performed on the tag SNPs.

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Duality of interest The authors declare that there is no duality of interest for this study.

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