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REVIEW

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Are β_3-adrenoceptor gene polymorphisms relevant for urology?

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Abstract

Aims: β_3-adrenoceptors (ARs) are an important drug target for the treatment of overactive bladder syndrome (OAB) and are under investigation for other indications. The human β_3-AR gene is polymorphic; an exchange of amino acid tryptophan (Trp) for arginine (Arg) in position 64 of the receptor protein is the most frequent and best-studied polymorphism. A narrative review on the impact of β_3-AR polymorphisms on urological disease and its treatment is presented.

Results: Two out of four studies have reported that the 64Arg allele was found more frequently in subjects with OAB than in healthy controls. A large study in a highly selective population (men undergoing prostatectomy for cancer treatment) did not confirm this. On the other hand, studies examining symptom severity typically found little difference between 64Arg and 64Trp carriers. In vitro studies with endogenously expressed β_3-AR reported a decreased lipolytic response in human adipose tissue. Studies with heterologously expressed receptors sometimes found a decreased responsiveness to agonists including β_3-AR agonists, but others did not confirm that.

Conclusions: The overall evidence points to carriers of the 64Arg genotype expressing fewer and/or hypofunctional β_3-ARs and being associated with the presence of OAB but such findings were only detected inconsistently. If this hypofunctionality exists, the consequences may be of insufficient magnitude to allow a robust detection. Only adequately powered studies comparing responses with a β_3-AR agonist in 64Arg carriers versus wild-type patients can address this.

KEYWORDS
ethnicity, gene polymorphism, overactive bladder syndrome, β_3-adrenoceptor

Abbreviations: BPH, benign prostatic hyperplasia; LUTS, lower urinary tract symptoms; OAB, overactive bladder.

1 | INTRODUCTION

The sympathetic nervous system contributes to the control of lower urinary tract function. The primary sympathetic neurotransmitter, noradrenaline, acts on adrenoceptors (ARs) that are classified into the subfamilies of α_1-, α_2-, and β-ARs, the latter originally proposed to include the two subtypes β_1 and β_2.[1] It had been speculated for decades that a third subtype of β-ARs should exist, partly based on data from the cat urinary bladder that were inconsistent with the classification into β_1- and β_2-ARs.[2] However, the existence of a β_3-AR only became unequivocally established with its cloning in 1989; the human gene is located on chromosomes 8p11 and 8p12.[3] Meanwhile, based on the introduction of mirabegron and vibegron as treatments for overactive bladder syndrome (OAB), the β_3-AR has been established as a validated urological drug target. While under clinical investigation for the treatment of heart failure, no indications for β_3-AR ligands outside of urology have been validated.

It emerged soon after the cloning of the human β_3-AR that the gene encoding it is polymorphic. The first identified single-nucleotide polymorphism is a thymidine to cytosine change at nucleotide position 190 resulting in an exchange of tryptophan (Trp) in amino acid position 64 for an arginine (Trp64Arg; also known as rss4994).[4,5] The Trp64Arg polymorphism is in linkage with other polymorphisms outside the coding region and forms a haploblock consisting of either the Trp haplotype (190t, 1219g, 2135a, 2502g, 3558a plus a nine repeat thymine guanine (TG) dinucleotide length polymorphism) and the Arg haplotype (190c, 1219t, 2135g, 2502c, 3558t plus an eight repeat TG.[6,7] The frequency of the 64Arg allele in Caucasian populations typically is about 8%,[6,8,9] with slightly different values in other ethnicities including Japanese (19%–25%)[10–12] and Pima Indians (31%).[4] Accordingly, homozygous 64Arg carriers are rare (<1% in Caucasians). The Trp64Arg polymorphism appears evolutionarily young as other genotypes were found in Macaque and Chimpanzee.[13]

While other polymorphisms of the human β_3-AR gene have been identified,[14] only the Trp64Arg polymorphism has been studied extensively. Early studies linked it to phenotypes associated with obesity and type 2 diabetes[4,5]; however, neither these associations nor others outside of urology have been confirmed robustly.[15] Reports on a possible role of β_3-AR gene polymorphisms in the regulation of urinary bladder function started emerging about a decade ago.[16] Meanwhile, multiple studies on a possible role have been reported and will be summarized and discussed here.

Three main approaches have been used, sometimes combining the first and second approach within one study: First, studies have compared the frequency of the polymorphic allele in populations with urological conditions such as OAB or more generally in those with lower urinary tract symptoms (LUTS), with those in control groups. Second, the severity of symptoms and other urological parameters was compared within OAB/LUTS cohorts between subjects with and without the polymorphism. Finally, the functionality of the polymorphic receptor in response to β-AR agonists including selective β_3-agonists has been tested in native tissue and/or in transfected cells. All three approaches will be discussed here.

2 | ALLELE FREQUENCY IN CONTROL VERSUS DISEASE POPULATIONS

A pilot study compared a mixed population of 27 patients with LUTS (including 16 with neurogenic voiding dysfunction and 7 with benign prostatic hyperplasia [BPH]) to 17 without voiding symptoms but has been published in abstract form only 2 decades ago.[17] Several studies have compared the frequency of the 64Trp and 64Arg alleles with control subjects and LUTS (mostly OAB) patients. A total of 169 healthy women and 49 with OAB from Brazil were of similar age (64 vs. 62 years) and had similar mean parity,[3,7] age at menopause (48 years), and family history of urgency incontinence (12%).[16] However, they differed slightly in ethnicity (49.1% vs. 34.7% whites). Obviously, they also differed markedly in frequency (5.1 vs. 8.2), nocturia (0.67 vs. 3.31), and urgency episodes (0 vs. 3.23) per 24 h, and in OAB-V8 score (0.85 vs. 26.39). The study found a homozygous T allele in 69.8%, heterozygotes in 29.8%, and a homozygous A allele in 0.45% (Table 1). In multiple logistic regression analysis, a positive family history for urgency incontinence (3.23 [95% confidence interval: 1.20–8.71]) and for heterozygotic genotype (3.11 [1.49–6.49]) was associated with a greater probability for having OAB, whereas body mass index was not (1.03 [0.96–1.11]). The Trp64Arg polymorphism was not associated with an increased body mass index.

A second study compared genotype frequency in 101 healthy women and 100 with OAB from Japan.[10] Age (62 vs. 64 years), body weight (53 vs. 54 kg), height (152 vs. 151 cm), and body mass index (23.1 vs. 23.5 kg/m^2) were very similar in both groups. The frequency of the 64Arg allele was 22.8% in healthy women and 47.0% in OAB patients (Table 1). However, carriers of the 64Arg allele

TABLE 1 Frequency of the 64Trp and 64Arg allele and reported descriptive *p* values in control and OAB patients

	64Trp allele		64Arg allele		*p* value
Reference	**Control**	**OAB**	**Control**	**OAB**	
Adult OAB studies					
Ferreira et al.[16]	296	73	42	25	0.0020
Honda et al.[10]	177	148	25	52	<0.0001
Çırakoğlu et al.[9]	144	131	12	13	0.8360
Total adult	617	352	79	90	<0.0001
Pediatric nonneurogenic LUTS studies					
Gurocak et al.[8]	79	84	84	4	0.7424
Total incl. children	696	436	84	94	0.0004

Note: Pooled data from the three original studies were analyzed by a two-sided Fisher's exact test using Prism 9.4.0 (GraphPad Software).

Abbreviations: Arg, arginine; LUTS, lower urinary tract symptoms; OAB, overactive bladder syndrome; Trp; tryptophan.

did not differ from homozygous 64Trp allele carriers in OAB symptom severity (see below).

A total of 78 controls (39 men and women each) and 72 OAB patients (37 women and 35 men) from Turkey were comparable in age (about 61 years) and body mass index (32 and 29 kg/m^2 in women and men, respectively).[9] The frequency of the 64Arg allele was about 8%, that is lower than in the Brazilian or Japanese study but similar in control subjects and OAB patients (7.7% vs. 9.0%; Table 1). A fourth study looked at 34 toilet-trained children 5 years and older with nonneurogenic LUTS (72% females) from Turkey in comparison to 42 age-matched controls.[8] It found a comparable allele frequency in children with and without LUTS (Table 1) with the overall incidence of the 64Arg allele being similar to that reported in the adult cohort from Turkey.

When the allele frequencies from these four studies were pooled, the 64Arg allele was found in 10.8% of healthy controls and 17.7% of OAB patients (Table 1; descriptive $p = 0.0004$ in a two-sided Fisher's exact test). This did not differ a lot when only the three studies with adult OAB patients were considered (Table 1). A similar conclusion had been reached by meta-analysis only considering the Brazilian and Japanese data[18] or those plus the pilot study.[19] While these pooled data support the hypothesis that the 64Arg allele is more frequent in OAB patients than healthy controls, interpretation is limited by the fact that the available studies are based on different ethnicities, and except for those from Turkey were based on females only. Moreover, it cannot be excluded that a publication bias against studies not confirming a higher incidence of the 64Arg allele exists.

A fifth study genotyped 376 men with localized prostate cancer undergoing robot-assisted prostatectomy in a single center in Japan of which 129 carried the 64Arg alle (114 heterozygous and 15 homozygous) and 247 did not.[11] The authors defined the presence of OAB by taking a muscarinic receptor antagonist or a β_3-AR agonist and BPH by taking an α_1-AR antagonist, phosphodiesterase type 5 inhibitor, and/or 5α-reductase inhibitor. By this definition 25% of homozygous 64Trp carriers and 21% of 64Arg carriers had BPH and 1% in each group had OAB and both groups were pooled for analysis. This yielded a prevalence of 64Arg carriers of 35.4% (99/280) in the non-LUTS and 31.3% (30/96) in the LUTS group (Table 1). While this study represents the largest group for a comparison of genotype prevalence in those with and without LUTS, it is difficult to compare to the other studies. First, it is the only all-male group, and the underlying prostate cancer in all participants may have biased the findings. Second, the definition of LUTS based on medication history is distinct from the definitions applied in the other studies; it may be problematic because most patients with LUTS are not currently or ever have been under medical treatment. Third, it did not provide information on how many of the 64Arg carriers in each group were homo- or heterozygous. This is a pity because a study of this magnitude has the potential to change the conclusions from Table 1.

3 | ASSOCIATION OF POLYMORPHISMS WITH DISEASE SEVERITY

Five-clinical studies have explored whether the genotype of the β_3-AR is associated with greater LUTS, some of them also having looked at genotype frequency in health and disease (see Section 2). One study genotyped 1015 Dutch men with BPH/LUTS from a single academic center and compared homozygous and heterozygous 64Arg carriers with homozygous 64Trp carriers for 32 parameters.[6] This included age, several parameters from pressure-flow studies (compliance, bladder capacity, Q_{max}, P_{det} at Q_{max}, urethral resistance, and Schäfer number), free flow studies (Q_{max}, voided volume, and residual volume), the International Prostate Symptom Score (total, voiding, and storage subscores, each individual question including the quality-of-life question), the Madsen–Iversen score (total and each individual question), prostate volume, and prostate-specific antigen (PSA). The 64Arg allele was found in 137 subjects (including 6 homozygotes) yielding an allele

frequency of 7%. Almost all parameters were similar in homozygous and heterozygous 64Arg as compared with homozygous 64Trp carriers. For instance, compliance as the parameter presumably closest related to β_3-AR function in the bladder was 13.59 versus 14.88 ml/cmH_2O. The only possible exception was prostate volume which was 39.3 ml in the 64Arg carriers as compared with 44.1 ml in the homozygous 64Trp carriers ($p = 0.023$). However, this difference is no longer statistically significant after multiple comparison adjustments and was not mirrored by a difference in PSA; perhaps even more important is that a difference in the prostate volume of <5 ml most likely is of limited biological relevance and no biologically plausible hypothesis exists why the β_3-AR polymorphism should be associated with a smaller prostate volume.

Another all-male study compared LUTS according to genotype in 376 men undergoing robot-assisted radical prostatectomy in a single center in Japan, of which 129 carried the 64Arg alle (114 heterozygous and 15 homozygous) and 247 did not.[11] The two groups were similar in age, PSA, prostate size, Gleason score, and the prevalence of concomitant hypertension (47% vs. 50%), diabetes (12% vs. 15%), BPH (25% vs. 21%), and OAB (1% each). In the overall group, 64Arg carriers had slightly greater postvoid residual (PVR) 47 ± 53 versus 58 ± 77 ml, $p = 0.04$) but similar Q_{max}, Q_{ave}, voided volume, voided time, and 1-h pad test. Within the subgroup of men with no history of LUTS ($n = 281$), Q_{ave} (10 ± 4 vs. 9 ± 3 ml/s, $p = 0.03$) and voiding time were slightly elevated (29 ± 15 vs. 33 ± 17 s, $p = 0.04$), whereas Q_{max}, voided volume, PVR, and 1-h pad test was similar across genotypes. Given the number of comparisons and the absence of multiple comparison adjustments in the calculation of p-values, the few observed differences appear to be neither statistically convincing nor clinically meaningful.

Two other studies were performed in cohorts of OAB patients. In a study with 100 women with OAB from Japan, 64Arg carriers and homozygous 64Trp carriers exhibited a similar number of micturitions (12.3 vs. 11.4), urgency episodes (4.42 vs. 4.29), urgency incontinence episodes per 24 h (2.37 vs. 2.32), and the number of subjects with urgency incontinence (34/53 vs. 27/47) was similar.[10] Another study looked at 78 controls and 72 OAB patients from Turkey with a similar representation of both genders in both groups.[9] Median frequency of daytime and of nighttime micturitions was very similar in homozygous 64Trp carriers, homozygous 64Arg carriers, and heterozygotes. The median OAB symptom scores in the three groups were 15, 17, and 10, respectively. The lower value in the heterozygous group not only failed to reach statistical significance with the given sample size and variability ($p = 0.617$); more importantly, it would not be plausible why heterozygotes should have a numerically much lower value than both homozygous groups.

Finally, a fifth study performed videourodynamic measurements of 34 toilet-trained Turkish children older than 5 years of age with nonneurogenic LUTS and analyzed them by genotype.[8] The voiding dysfunction symptom score was numerically higher in homozygous 64Trp carriers than heterozygotes (7.8 ± 9.5 vs. 5.8 ± 10.3), whereas bladder volume was similar in both groups (179 ± 89 vs. 180 ± 67 ml). However, this is difficult to interpret because the variability was large and the sample size small, and no statistical analysis was reported for either outcome. While each of the five studies had specific strengths and weaknesses, no LUTS-related parameter exhibited a consistently greater severity associated with genotype at the β_3-AR locus.

4 | IN VITRO STUDIES

While the above data are of physiological interest, the key question with therapeutic relevance is whether 64Arg carriers respond differently to β_3-AR agonists such as mirabegron and vibegron. However, the available evidence is largely limited to in vitro studies. These have been based either on measurements in isolated cells from genotyped subjects[7,12,20] or in cell lines transfected with polymorphic receptors.[14,21–24] These approaches differ conceptually: native cells and tissues contain the full gene of the polymorphic receptor, that is, the polymorphic site in the coding region and those linked to it outside the coding region and forming a haploblock and potentially involved in gene expression.[6,7] In contrast, cell lines transfected with constructs encoding the wild-type or polymorphic variant of the receptor only look at the polymorphism in the coding region, possibly affecting receptor function at the molecular level. However, they intrinsically cannot detect whether the linked polymorphisms outside the coding region may have affected the expression level of the receptor and thereby its overall responsiveness.

Three studies have been reported with the endogenously expressed receptor, all using lipolytic responses to β-AR agonists in isolated human omental adipocytes as indicators of receptor responsiveness (Table 2). After a pilot study found a comparable potency of CGP 12 177 in 64Arg carriers and homozygous 64Trp carriers (−log EC_{50} 8.2 vs. 8.8),[20] this was investigated in more detail in a study with a greater sample size.[7] While the potency of the β_1-selective dobutamine and the β_2-selective terbutaline was comparable in both groups, the potency of the

TABLE 2 Outcomes of in vitro studies on β_3-adrenoceptor Trp64Arg polymorphism

Reference	Model	Phenotype	Outcome 64Arg allele
Studies in native tissue			
Li et al.[20]	Human omental adipocytes	Lipolysis to CGP 12 177	Comparable potency of CGP 12 177
Hoffstedt et al.[7]	Human omental adipocytes	Lipolysis to isoprenaline, dobutamine, terbutaline, and CGP 12 177	No change for isoprenaline, dobutamine, and terbutaline but reduced potency for CGP 12 177
Umekawa et al.[12]	Human omental adipocytes	Lipolysis to isoprenaline, CGP 12 177, and L-755 507	No change for isoprenaline or CGP 12 177; reduced potency and efficacy for L-755 507
Studies in transfected cells			
Candelore et al.[21]	Chinese hamster ovary cells	cAMP response to isoprenaline, adrenaline, noradrenaline, BRL 37 344, and CGP 12 177	Unchanged efficacy and potency
Pietri-Rouxel et al.[22]	Chinese hamster ovary and human embryonic kidney cells	cAMP response to isoprenaline, adrenaline, noradrenaline, and CGP 12 177	Reduced efficacy
Kimura et al.[23]	Mouse 3T3-L1 cells	cAMP response to isoprenaline, adrenaline, noradrenaline, and L-755 507	Reduced efficacy and potency
Isogaya et al.[4]	Monkey COS-7 cells	cAMP response to CGP 12 177	Unchanged efficacy and potency
	Human JEG-3 cells	cAMP response to isoprenaline and CGP 12 177	Increased efficacy upon co-expression of adenylyl cyclase type III, but unchanged efficacy upon coexpression of Types I, II, and VI
Vrydag et al.[13]	Human embryonic kidney cells	cAMP response to isoprenaline, CGP 12 177, mirabegron, and FK 4664	Unchanged efficacy and potency

Abbreviations: Arg, arginine; Trp; tryptophan.

atypical β_3-AR agonist CGP 12 177 was lower by about one log unit. While the former two studies had been performed in a Caucasian population, a third study was reported based on a Japanese population.[12] The potency and efficacy of isoprenaline and CGP 12 177 were comparable in homozygous 64Trp carriers and homozygous and heterozygous 64Arg carriers, but both potency and efficacy of the β_3-selective agonist L755-507 were lower in 64Arg as compared with homozygous 64Trp carriers. Finally, an in vivo study in humans with local isoprenaline infusion found similar glycerol concentrations in homozygous 64Arg and 64Trp carriers.[25] While the studies agree that responses to isoprenaline and β_1- or β_2-selective agonists are not affected by genotype at the β_3-AR locus, they differ in conclusions on the β_3-AR agonists. These studies largely agree that lipolytic responses to β_3-AR agonists are reduced in 64Arg carriers, the data, particularly those obtained with CGP 12 177, are not easy to interpret for two reasons. First, CGP 12 177 is a high-potency antagonist at β_1- and β_2-AR, an non-orthotoic agonist at β_1-AR in high concentrations, and a partial agonist at β_3-AR.[26] Moreover, lipolytic effects in adult human adipose tissue typically are considered to occur largely independent of β_3-AR.[27]

Multiple studies have explored signal transduction responses (cAMP formation) in cells transfected with the wild-type and polymorphic variant of the human β_3-AR (Table 2). These have employed mouse, hamster, and monkey-derived but also human cell lines and reported contradictory results. The earliest study found unchanged potency and efficacy for isoprenaline, adrenaline, noradrenaline, the mixed β_2/β_3-AR agonist BRL 37 344, and for CGP 12 177.[21] Unchanged potency and efficacy were also reported for CGP 12 177[24] and for isoprenaline, CGP 12 177 and the β_3-selective agonists mirabegron and FK 4664.[14] One study in human JEG-3 cells reported complex findings: The efficacy of isoprenaline and CGP 12 177 was unchanged when coexpressed with Types I, II, and VI adenylyl cyclase but increased when coexpressed with Type III adenylyl cyclase.[24]

On the other hand, two studies reported a reduced potency and/or efficacy for isoprenaline, adrenaline, noradrenaline, and CGP 12 177[22] and for isoprenaline, adrenaline, noradrenaline, and L-755-507.[23]

Taken together these data are not consistent, but there is a trend that the 64Arg allele may lead to a hypofunctional receptor, particularly when the entire polymorphic receptor including its noncoding parts is present. Other than the limited consistency of the findings, other factors also limit conclusions. First, none of the reported studies was based on sample size calculations, that is, we do not know whether it was adequately powered to detect effects of potentially relevant magnitudes. Second, the effects of a coding polymorphism may be specific for some agonists as each compound may have a distinct binding pocket in the receptor.[28] Third, several studies with heterologous expression of the polymorphic receptors were done in host cells of nonhuman origin. Thus, it is possible that those cells lack the correct machinery to reflect changes in receptor function.

5 | CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

Two out of four studies have reported that the 64Arg allele was found more frequently in subjects with OAB than in healthy controls. Ethnic differences between populations being studied may at least partly explain these conflicting observations. On the other hand, studies examining symptom severity found little difference between 64Arg and 64Trp carriers. These findings could be interpreted either as a lack of effect of the polymorphic β_3-AR or that it is associated with the presence but not the severity of LUTS—a proposition that is difficult to explain mechanistically. If the presence of the 64Arg allele was associated with OAB, this would imply that the receptor encoded by this allele is hypofunctional, that is, produces less relaxation of the bladder. Studies with endogenously expressed receptors in adipose tissues are compatible with this idea, whereas those with heterologously expressed receptor variants are too inconsistent to allow robust conclusions.

The only study type that could unequivocally tell us whether the polymorphisms in the human β_3-AR gene are relevant would be an adequately powered clinical trial in which therapeutic responses to a β_3-AR agonist such as mirabegron or vibegron were compared across genotypes. Given that the 64Arg allele is not very frequent, such studies would presumably require screening >1000 participants to have meaningful statistical power. One small clinical study from Turkey has explored a related question. It compared changes in voiding dysfunction symptom score and bladder volume upon treatment with oxybutynin in homozygous 64Trp and heterozygous 64Arg carriers.[8] While both parameters were improved upon treatment in the 64Trp carriers, changes in 64Arg carriers were smaller and did not reach statistical significance with the given sample size. As the lack of statistical significance with a small sample size can have several reasons, a design in which the extent of improvement is compared with genotypes may be more appropriate. Of note, the lack of a meaningful effect on therapeutic responses regarding symptom scores cannot necessarily be extrapolated to other outcome parameters such as bladder enlargement or fibrosis. Given the state of the evidence, other research directions such as a role for metabolic syndrome may be more promising in unraveling the pathophysiology of OAB.

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CONFLICT OF INTEREST

Martin C. Michel is a consultant to Astellas related to the β_3-adrenoceptor agonist mirabegron. He has been a consultant to and shareholder of Velicept, a company clinically developing the β_3-adrenoceptor agonist solabegron.

DATA AVAILABILITY STATEMENT

Not applicable for a review manuscript.

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