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ORIGINAL ARTICLE

# POLYMORPHISM OF THE *ADRB2* rs1042713 GENE IS NOT ASSOCIATED WITH SPONTANEOUS PRETERM BIRTH: ANALYSES IN A SLOVENIAN SAMPLE AND META ANALYSIS

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## ABSTRACT

The β-2-adrenergic receptor (*ADRB2*) gene has an important impact on smooth muscle relaxation, including the smooth muscles of the uterus. The results of previously published studies of the association between the *ADRB2* rs1042713 polymorphism and spontaneous preterm birth (SPTB) were inconsistent. We evaluated the association between *ADRB2* and SPTB in a case-control association study in a Slovenian sample population and performed a meta analysis of previously published studies. No association was found between the polymorphism in the *ADRB2* gene and SPTB in the Slovenian sample of 98 SPTB patients and 135 controls under dominant [$\chi^2$ = 0.01, $p$ = 0.92, odds ratio (OR) = 1.03, 95% confidence interval (95% CI) = 0.52-2.04), recessive ($\chi^2$ = 0.01, $p$ = 0.92, OR = 0.98, 95% CI = 0.57-1.70) and codominant genetic models ($\chi^2$ = 0.01, $p$ = 0.92, OR = 0.99, 95% CI = 0.59-1.68). The meta analysis of a pooled sample of 404 SPTB patients and 878 controls suggested no association of *ADRB2* polymorphism and SPTB under dominant (OR = 1.12, 95% CI = 0.81-1.54) and recessive genetic models (OR = 0.84, 95% CI = 0.64-1.12). These findings suggest no association between the *ADRB2* rs1042713 gene polymorphism and SPTB. Further association studies with larger sample sizes are needed.

**Keywords:** β-2-Adrenergic receptor (*ADRB2*) gene; Case-control association study; Meta analysis; Risk factor; Spontaneous preterm birth (SPTB).

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## INTRODUCTION

Spontaneous preterm birth (SPTB) is the leading cause of neonatal morbidity and mortality worldwide. Approximately 12.0% of all infants are born preterm in the USA; this figure is 6.0-12.0% in the European Union (EU) [1,2], and 7.6% in Slovenia [3].

Infants born preterm can suffer from lifelong morbidities such as developmental delay, lung disease, vision, and hearing deficits, as well as other neurosensory impairments [4,5]. They are also predisposed to hypertension and diabetes in adult life [6].

The etiology of SPTB is multifactorial. In addition to multiple gestations and assisted reproductive technologies, several environmental contributors to SPTB have been proposed, such as an infection [7,8], maternal smoking during pregnancy [9,10], maternal/fetal stress [11,12], adolescence or advanced maternal age [13], cervical dysfunction [14], decidual thrombosis [15], and metabolic enzyme variation [14]. In about 70.0% of SPTB cases no risk factor can be identified, which makes genetic contribution a likely cause to be considered [16]. The role of genetic predisposition to SPTB is based on epidemiological evidence showing that SPTB tends to recur in families. Mothers with previous preterm deliveries have a significantly increased risk of preterm delivery in subsequent pregnancies [17-20]. Spontaneous preterm birth also occurs across generations and sibships [18,21-23]. The heri-tability of SPTB has been estimated to be in the range of 27.0-36.0% [24,25].

Based on their potential role in pathogenesis, as many as 482 genes have already been tested for genetic association with SPTB (HuGENavigator), however, validation of study results remains challenging [26,27]. One of the most frequently investigated candidate genes is the β-2-adrenergic receptor (*ADRB2*) gene.

β-2-Adrenergic receptors, members of the superfamily of G protein-coupled receptors, mediate the catecholamine-induced activation of the adenylate cyclase signaling cascade, a mechanism that plays an important role in smooth muscle relaxation [28]. They are ubiquitously expressed in numerous human tissues, including smooth muscle cells of the trachea, bronchi, vasculature and the uterus. Uterine contractility is modulated by stimulation of *ADRB2*s with endogenous and exogenous agonists that have a potential to affect cervical tone and resistance to mechanical stretching [29]. Therefore, we hypothesized that genetic variability in the *ADRB2* gene modulates uterine contractility and might be consequently associated with SPTB.

Several association studies have linked *ADRB2* polymorphism rs1042713 and SPTB, but the results were found to be inconsistent [30-33]. Selected polymorphism is a missense polymorphism that results in amino acid change R (Arg)→G(Gly). To address the role of *ADRB2* in SPTB, we conducted a two-stage study. First, we designed a case-control study, where we investigated whether maternal single nucleotide polymorphism of *ADRB2* rs1042713 is associated with the risk of SPTB in the Slovenian population. Second, we carried out a meta analysis to systematically review the association of *ADRB2* rs1042713 with SPTB, including the results of this and previously published case-control studies.

## MATERIALS AND METHODS

**Case-Control Association Study in the Slovenian Population.** Participants of the study all signed a written informed consent. The Republic of Slovenia National Medical Ethics Committee approved the study.

**Definition of SPTB and Inclusion Criteria for the SPTB Cases.** We included healthy mothers with singleton pregnancies who delivered after a spontaneous onset of labor (SPTB) before completed 37 weeks' gestation. Gestational age was determined by the last menstrual period and confirmed by an ultrasound examination in the first trimester. Cases with known risk factors for SPTB (*e.g.,* diabetes, hypertension, kidney disease, autoimmune conditions, infections, uterine malformations and complications during pregnancy) or neonates born with congenital anomalies or evidence of infection were excluded. All analyzed subjects were of Caucasian origin. Additional information on maternal characteristics is shown in Table 1.

**Study Sample in the Case-Control Association Analyses.** We conducted a case-control study including 98 female patients with SPTB and 135 female controls who gave birth at the Division of Obstetrics and Gynecology, University Medical Centre in Ljubljana, Slovenia. Controls were age-matched healthy mothers who delivered after an uncomplicated pregnancy after 37 weeks and delivered a neonate with appropriate-for-gestational-age birth weight (Table 1).

**Genotype Analyses.** Genomic DNA was isolated from peripheral blood leukocytes using standard procedures. Real-time polymerase chain reaction (PCR) method performed on a 7000 Sequence Detection System (Applied Biosystems, Foster City, CA, USA) using KASPar SNP genotyping chemistry carried out genotyping of the single nucleotide polymorphism (SNP). The PCR reaction mix of 8 μL final volume consisted of 3 μL of DNA sample, 4 μL of reaction mix 2X, 0.11 μL assay mix and 0.89 μL $H_2O$. The protocol for PCR amplification was as follows: initial denaturation step at 94 °C for 15 min., then 10 cycles of denaturation at 94 °C for 20 seconds, followed by 5 seconds at 57 °C or 61 °C, 10 seconds at 72 °C, 10 seconds at 94 °C, 20 seconds at 57 °C or 61 °C, and final extension at 72 °C for 40 seconds. The allelic discrimination analysis was performed using SDS Software Version 1.2 (Applied Biosystems). Genotype assignment was performed and interpreted independently by two investigators.

**Statistical Analyses.** We analyzed the significance of associations between allelic and genotype frequencies

**Table 1.** Characteristics of 98 mothers with SPTB and 135 controls.

| Parameters | SPTB | Controls | *p* Value |
|---|---|---|---|
| Mean maternal age (years) | 30.20 ± 4.59 | 30.10 ± 3.92 | 0.28 |
| Smoking during pregnancy % (*n*) | 8.3 (8) | 2.9 (4) | 0.15 |
| Previous SPTB % (*n*) | 12.4 (12) | 4.3 (6) | 0.08 |
| *In vitro* fertilization % (*n*) | 4.1 (4) | 1.4 (2) | 0.31 |
| Urogenital infections % (*n*) | 7.2 (7) | 4.3 (6) | 0.35 |
| High blood pressure % (*n*) | 7.2 (7) | 4.3 (6) | 0.35 |
| Stressful events during pregnancy % (*n*) | 3.1 (3) | 4.3 (6) | 0.50 |

SPTB: spontaneous preterm birth.

and disease status using the $\chi^2$ test. Odds ratios (ORs) and their respective 95% confidence intervals (95% CIs), were calculated to compare allelic and genotype distribution in patients and controls. To provide an additional quality step of the genotyping process we calculated the $\chi^2$ goodness-of-fit tests for deviation of genotype distribution from those predicted by Hardy-Weinberg equilibrium. The investigated associations were regarded as significant when they reached $p \leq 0.05$. The R statistical language (version 3.0) was used to perform the analyses.

To calculate the power of the study DSS Researcher's Toolkit (https://www.dssresearch.com/Knowledge Center/toolkitcalculators/statisticalpowercalculators.aspx) was utilized. Calculations showed that our power to detect a significant result in the presence of the actual genotype relative risk equal to at least 2.0 was 85.8% when taking into account the sample size, the significance threshold of 0.05, and the risk genotype frequency of 15%.

**Meta Analyses.** A literature search to find potential eligible studies of the association between *ADRB2* rs1042713 and SPTB was conducted in PubMed (National Center for Biotechnology Information, January 1966-December 2016), Scopus (December 2016), Google Scholar (December 2016), and HugeNavigator (December 2016). We limited our search to articles in the English language. Keywords searched included: (*ADRB2* or β-2-adrenergic receptor gene or polymorphisms) AND (preterm birth or preterm labor). The AND operator was used to create various combinations of selected terms. Studies were selected and reviewed by two independent authors who reached a consensus on all of the items.

**Study Selection and Data Extraction.** We included human studies meeting following criteria: ***1)*** a genotype of *ADRB2* rs1042713 and ***2)*** case-control study in which genotyping was carried out for the group of SPTB cases and control group; ***3)***, SPTB defined as <37 weeks' gestation; ***4)*** control group defined as women who gave birth after 37 weeks' gestation. For each study included in the meta analysis, we extracted authors, year of publication, study population geographic origins, number of SPTB cases and controls, SPTB definition, an occurrence of preterm premature rupture of membranes (PPROM), inclusion criteria for control women, and genotype count for SPTB cases and controls.

We classified subjects into three genotypes: AA, GA and GG. Then pooled effect was calculated for the dominant genetic model (GA+GG *vs.* AA) and recessive genetic model (AA+GA *vs.* GG) in the *ADRB2* rs1042713 polymorphism. Cochrane's Q and $I^2$ tests were used to assess heterogeneity between the studies, with the null hypothesis that there is no difference in findings of primary studies. Heterogeneity was considered significant when $p < 0.1$ for Cochrane's Q statistics. Random effect model (der Simonian-Laird) was applied upon the detection of heterogeneity; otherwise, fixed effect model (Maentel-Haenszel) was used. The random effect model takes into account diversity of included studies due to intra-study sampling errors and inter-study variances, while the fixed effect model assumes that the observed variations between studies are caused by chance alone. Publication bias was assessed by Funnel plot. The asymmetry of the Funnel plot was analyzed with the Egger's test. The analysis was carried out with the R statistical language (version 3.0).

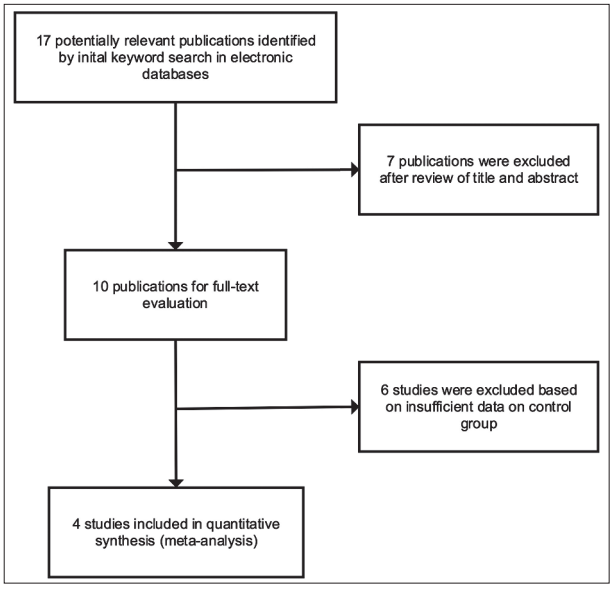


**Figure 1.** Flowchart of study selection process in the meta analysis.

## RESULTS

**Case-Control Association Study in the Slovenian Population.** Cases and controls did not differ in any demographic characteristic or recognized risk factor for SPTB. The history of a previous SPTB was more frequent in the SPTB group (12.4%) in comparison to controls (4.3%), however, the difference did not reach statistical significance (Table 1).

Genotype frequencies of investigated polymorphisms were in accordance with those predicted by the Hardy-Weinberg equilibrium in the group of patients and in the control group. Genotype and allelic distribution of the *ADRB2* polymorphism of the 98 SPTB patients and 135 controls are shown in Table 2. The ADRB2 rs1042713

genotypes were not found to be associated with the risk of SPTB in the Slovene population under any of the investigated models, dominant, recessive, and codominant (Table 3).

**Meta Analyses.** The initial keyword search identified 17 articles (Figure 1). Four previously published case-control studies were included after a review together with added results of our case-control study based on characteristics summarized in Table 4. Therefore, five studies met inclusion criteria with a total of 404 SPTB cases and 878 term controls.

**Association of Genotype and Phenotype.** Cochrane's Q test and $I^2$ test showed that there was no evidence of heterogeneity across all studies under the recessive genetic model, while moderate heterogeneity was present under the dominant genetic model. We found that there was no significant association of *ADRB2* rs1042713 polymorphism with SPTB under the dominant (AA+GA *vs*. GG) or recessive (GG *vs*. AA+GA) genetic models (Figure 2). We analyzed the asymmetry of the funnel plot with Egger's test and found no evidence for publication bias.

**Table 2.** Genotype and allelic distribution of the *ADRB2* rs1042713 polymorphism of the 98 SPTB patients and 135 controls.

| **Parameters** | **Genotype Frequencies *n* (%)** | | | | | **Allele Frequencies (*n*) %** | | | |
|---|---|---|---|---|---|---|---|---|---|
| | AA | GA | GG | *p* Value | $\chi^2$ | A | G | *p* Value | $\chi^2$ |
| SPTB cases | 17 (17.3) | 48 (49.0) | 33 (33.7) | 0.99 | 0.01 | 65 (42.0) | 81 (42.0) | 1.0 | 0 |
| Controls | 24 (18.0) | 66 (49.0) | 45 (33.0) | | | 90 (58.0) | 111 (58.0) | | |

SPTB: spontaneous preterm birth.

**Table 3.** Association of *ADRB2* rs1042713 with SPTB under different genetic models.

| **Genetic Model** | | **$W_{SPTB}$ *vs.* $W_C$** | | |
|---|---|---|---|---|
| | | OR (95% CI) | *p* Value | $\chi^2$ |
| Dominant | GA+GG *vs*. AA | 1.03 (0.52-2.04) | 0.92 | 0.01 |
| Recessive | AA+GA *vs*. GG | 0.98 (0.57-1.70) | 0.92 | 0.01 |
| Codominant | AA+GG *vs*. GA | 0.99 (0.59-1.68) | 0.92 | 0.01 |

SPTB: spontaneous preterm birth; OR: odds ratio; 95% CI: confidence interval; $W_{SPTB}$: SPTB women; $W_C$: control women.

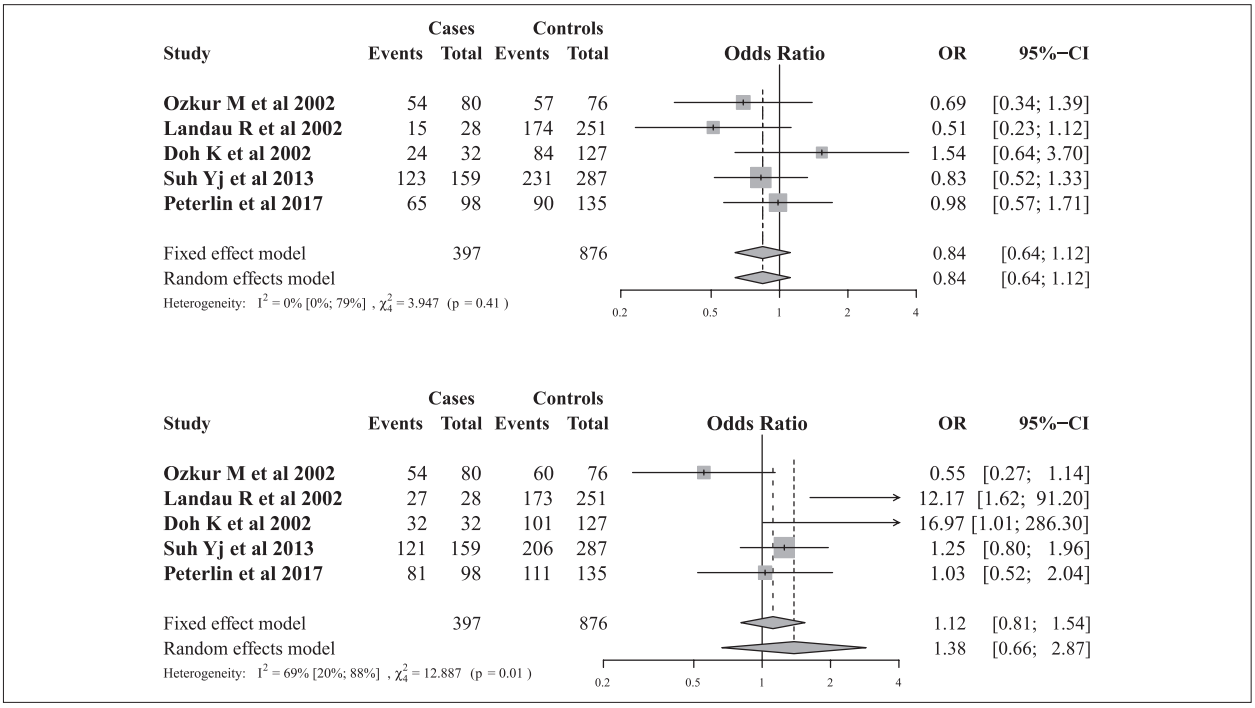


**Figure 2.** Forest plots for the association between the *ADRB2* rs1042713 polymorphism and SPTB risk in recessive and dominant genetic models.

**Table 4.** Characteristics of studies included in the meta analysis.

| Refs. | Year | Country | Population | PPROM Excluded | SPTB Cases Criteria | Case Sample Size | Control Criteria | Control Group Size |
|---|---|---|---|---|---|---|---|---|
| this study | 2017 | Slovenia | Caucasian | no | GA <37 | 98 | GA >37 | 135 |
| [30] | 2013 | Korea | Asian | no | GA <37 | 166 | GA >37 | 289 |
| [31] | 2004 | Hungary | Caucasian | no | GA <37 | 32 | GA >37 | 127 |
| [33] | 2002 | Turkey | Caucasian | yes | GA <37 | 80 | GA >37 | 76 |
| [32] | 2002 | USA | Hispanic | no | GA <37 | 28 | GA >37 | 251 |

PPROM: preterm premature rupture of the membranes; SPTB: spontaneous preterm birth; GA: gestational age.

## DISCUSSION

In the case-control association study in the Slovenian population and meta-analysis of previous studies, we did not find any evidence of an association between SPTB and *ADRB2* rs1042713. In the Slovenian population case-control association study, we also did not find any difference in *ADRB2* rs1042713 polymorphism allele and genotype distribution between SPTB and controls. The arginine (A allele) at rs1042713 was reported to be associated with reduced downregulation of gene expression and reduced desensitization of ADRB2 leading to a change in the responsiveness to circulating endogenous β-agonists shown in Figure 3 [34,35]. Thus, it was suggested that down-regulation of *ADBR2* could play a role in the timing of labor, especially as ADRB2 agonists in some cases appear to prevent preterm delivery [36,37].

This led us, and other authors, to investigate the association between the *ADRB2* rs1042713 polymorphism and SPTB. While case-control association studies conducted in the Hungarian and Hispanic populations proposed that homozygosity for *ADRB2* rs1042713 (AA genotype) protects against SPTB [31,32], our study and studies in the Korean and Turkish populations have not found any evidence of genotype AA effect on SPTB [30,33]. Both studies reporting an association between *ADRB2* rs1042713 polymorphism and preterm birth (PTB) had small sample sizes, especially in the group of patients suffering from PTB, which leads to a lower statistical power to detect small effects of the studied polymorphism. The results of the studies could also be influenced by ethnical diversity among the participants.

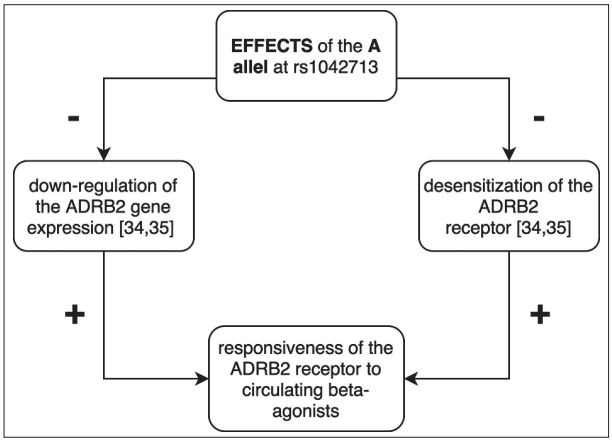


**Figure 3.** Effects of the *ADRB2* rs1042713 A allele on the ADRB2 receptor.

The results of genetic association studies quite frequently fail to be reproduced in subsequent studies, either because the original findings are false-positive reports, or because the small genetic effects were not detectable [38]. Large sample sizes or meta-analysis are required in order to identify the small genetic effects of polymorphisms [39]. A meta analysis is a statistical tool that enables objective, quantitative synthesis of research findings, thus overcoming the problem of a small sample size and the inadequate statistical strength of genetic association studies [40].

To further investigate the role of the *ADRB2* rs1042713 polymorphism and SPTB we performed a meta analysis of four previously published case-control association studies and our study [30,33]. The evidence for association was found neither under the recessive nor dominant genetic models.

Alternatively, the previously published meta analysis of three reports, including both studies that found association [31,32] and studies by Ozkur *et al.* [33] and Dolan *et al.* [41], suggested a nominally significant association. Our study has some limitations. On the one hand, the study in the Slovenian population had limited power to detect small effects of the studied polymorphism. On the other hand, the size of studies included in the meta analysis was small and of heterogeneous genetic background. Additionally, we found evidence of moderate heterogeneity under the dominant genetic model in our meta analysis. We only included studies in the English language; therefore, we might have missed potential association studies linking *ADRB2* rs1042713 to SPTB.

In conclusion, both the association study in the Slovenian population and meta analysis showed no evidence of an association between *ADRB2* rs1042713 and SPTB. Further larger association studies on the topic are needed to reach a more definite conclusion.

**Declaration of Interest.** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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