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POSITIVE ASSOCIATION BETWEEN *SRA1* RS801460 VARIANT AND PROLIFERATIVE TYPE OF BENIGN BREAST DISEASE WITH ATYPIA IN UKRAINIAN FEMALES

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***Aim*: To investigate the association between *SRA1* rs801460 and rs10463297 variants and proliferative type of benign breast disease with atypia development in Ukrainian females. *Materials and Methods*: 83 individuals diagnosed with proliferative type of benign breast disease with atypia and 115 without atypia were enrolled in the study. The rs801460 and rs10463297 variants genotyping was performed using polymerase chain reaction-restriction fragment length polymorphism analysis. Hematoxylin and eosin, toluidine blue and van Gieson's picrofuchsin methods were used for sections staining. *Results:* It was revealed that *SRA1* rs801460-variant is associated with proliferative type of benign breast disease with atypia development both before and after adjustment for risk factors (age, body mass index, age of menarche, oral contraceptives intake and burdened history of breast cancer). The risk for mentioned disease in the individuals with rs801460 TT-genotype is 2.2 times higher (confidence interval 1.010–4.800; $p = 0.047$) than in individuals with the CC and CT genotypes. No link between *SRA1* rs10463297 and proliferative type of benign breast disease with atypia occurrence in Ukrainian females was found. *Conclusion*: The present study specified that *SRA1* rs801460, but not rs10463297, can be the strong genetic predictor for benign breast disease with atypia in Ukrainian females.**
***Key Words*: benign breast disease, SRA, single nucleotide variant.**

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Breast cancer (BC) is the most commonly occurring cancer in women and the second most common cancer overall [1]. Many BC survivors need rehabilitation because of physical, psychological and social dysfunctions [2]. Consequently, it is essential to improve early diagnosis focusing on detection of pre-malignant lesions of the breast.

Benign breast disease (BBD) is a group of benign mammary conditions, some of which can lead to the BC development. It includes nonproliferative lesions, proliferative lesions without atypia, and proliferative lesions with atypia [3]. The latter are of the highest BC risk. Based on the aberrations of normal development and involution (ANDI) concept, the BBD origin is related to the normal breast physiology encompassing the entire spectrum of benign conditions from mild to severe abnormality [4, 5].

It is considered that estrogen may contribute to the BC development, for instance, because of enhancing breast cell proliferation. The effects of estrogen are mediated via two estrogen receptor (ER) subtypes, ERα and ERβ [6]. These nuclear receptors expressed in the mammary tissue are capable to modulate the transcription activity of target genes [7, 8]. Only a part of breast cells contains ER while the rest are receptor-negative. Clarke *et al*. [9] showed that proliferating cells are receptor-negative and located near the receptor-positive cells. Accordingly, estrogen can modulate receptor-positive cells activity that stimulates proliferation through the paracrine signaling.

The steroid receptor RNA activator (SRA) is the long non-coding RNA (lncRNA) that also can act via the ERα- and ERβ-receptors. It is a coactivator of steroid receptors, such as ER, androgen receptor, glucocorticoid receptor (GR) and progesterone receptor. This lncRNA is encoded by the *SRA1* gene, which is 8027 bp in length and located on 5q31.3 chromosome. It consists of 5 exons and 4 introns (NC_000005.10) [10]. Lanz *et al*. [11, 12] found that transgenic mice with human SRA-overexpression exert an abnormal breast development. Histopathology showed ductal ectasia, ductal-epithelial hyperplasia, focal metaplasia and intraductal proliferation. Therefore, SRA may be associated with the proliferative type of BBD development.

In our previous article, we found *SRA1* rs801460-variant to be associated with the development of thyroid nodules in Ukrainian females with proliferative type of BBD without atypia [13]. The aim of the present research was to explore the possible link between *SRA1* rs801460 and rs10463297 single nucleotide variants (SNVs) and proliferative type of BBD with atypia development in the Ukrainian females.

MATERIALS AND METHODS

Study population. Venous blood of 83 females with proliferative type of BBD with atypia (mean age [±SD] 36.80 ± 8.87) and 115 females with proliferative type of BBD without atypia (mean age 30.43 ± 9.26) as a control was used for the study. The licensed surgeon examined each BBD patient on an outpatient basis. Surgical treatment was performed for all patients at the clinical sites of the Department of Surgery with a Course of Pediatric Surgery and Urology of the Sumy Regional Oncology Center. The Scientific

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Abbreviations used: ANDI – aberrations of normal development and involution; BBD – benign breast disease; BC – breast cancer; BMI – body mass index; CI – confidence interval; ER – estrogen receptor; OR – odds ratio; PCR-RFLP – polymerase chain reaction-restriction fragment length polymorphism analysis; SNV – single nucleotide variant; SRA – steroid receptor RNA activator.

center of pathomorphological researches of the Sumy State University studied each morphological material. Molecular genetic research was conducted in the Scientific Laboratory of Molecular Genetic Research of the Sumy State University. Study involved individuals with atypical proliferative changes in mammary gland and excluded patients with nonproliferative lesions.

Patient assessment, examination and diagnosis were carried out in accordance with the current orders of the Ministry of Health of Ukraine № 690 from 23.09.2009 and № 616 from 03.08.2012, the European Convention of Human Rights and Biomedicine and the Declaration of Helsinki of the World Medical Association on Ethical Principles for Medical Research Involving Human Subjects. All participants provided a written informed consent.

Genotyping of SNVs. Genomic DNA was extracted from the whole venous blood using the GeneJET Whole Blood Genomic DNA Purification Kit (Thermo Fisher Scientific, USA). Genotyping of the *SRA1* rs801460 and rs10463297 SNVs was performed using the polymerase chain reaction-restriction fragment length polymorphism analysis (PCR-RFLP). The reaction mixture for PCR included 5 μL of FastDigest Green Buffer (10X) (Thermo Fisher Scientific, USA), 0.5 μL dNTP Mix (10 mM of each deoxynucleotide) (Thermo Fisher Scientific, USA), 0.75 U DreamTaq DNA Polymerase (5 U/μL) (Thermo Fisher Scientific, USA), 0.1 μL of each primer, 75–100 ng DNA, and bidistilled water added up to 25 μL. The sequences of the specific primers (Yan *et al.* [14]) and PCR conditions are shown in Table 1. Amplification was carried out using Thermocycler GeneAmp PCR System 2700 (Thermo Fisher Scientific, USA).

The reaction mixture on the restriction stage consisted of 2U of restriction enzyme, 0.8 μL of 10X Buffer R (Thermo Fisher Scientific, USA) and bidistilled water added up to 2 μL. The amplification product (6 μL) with the addition of the reaction mixture (2 μL) was incubated at 37 °C for 20 h. *Nsi*I (Thermo Fisher Scientific, USA) was used for restriction analysis of *SRA1* rs801460 SNV. The replacement of cytosine (C) to thymine (T) at the (-)5749th position of the *SRA1* gene leads to the splitting of the amplicon (178 bp) by *Nsi*I into 155 bp and 23 bp fragments. We had only one 178 bp fragment in the presence of cytosine due to the *Nsi*I restriction site loss (Fig. 1). Restriction analysis of the *SRA1* rs10463297-variant was done using *Eco*47I (Thermo Fisher Scientific, USA). *Eco*47I cut the primary amplicon (483bp) into two fragments of 317bp and 166bp in case of thymine to cytosine substitution at the (-)1440th position of the *SRA1* gene. The presence of thymine prevented restriction and the primary amplicon was retained (Fig. 2).

Restriction fragments were separated using horizontal electrophoresis (10 V/cm) with the ethidium bromide (10 mg/mL) addition in 2.5% agarose gel. Ultraviolet transillumination was applied for DNA fragments visualization.

Histology. Breast tissue obtained during surgery was used for histology (Fig. 3). Biological material was fixed in 10% phosphate buffered formalin for 48 h and then embedded in paraffin. Paraffin series were sliced at a thickness of 8–10 μm and incubated at 37 °C for 12 h. After deparaffinization, sections were stained with one of the following methods: hematoxylin and eosin, toluidine blue or van Gieson's picrofuchsin.

Statistical analysis. To analyze the possible link between *SRA1* rs801460 and rs10463297 SNVs and proliferative type of BBD with atypia development, informative samples were selected (198 cases). The statistical analysis was performed using Statistical Package for the Social Sciences software (SPSS, version 25.0, Chicago, IL, USA). Continuous variables are presented as the mean ± SD (Kolmogorov–Smirnov test was applied for the distribution normality checking); categorical variables are indicated as absolute

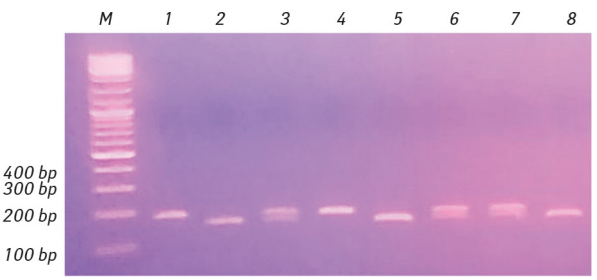

Fig. 1. Results of *SRA1* rs801460 variant restriction analysis. M — molecular marker (bp — base pairs); lanes 1 and 4 — CC-genotype; lanes 3, 6 and 7 — TC-genotype; lanes 2, 5 and 8 — TT-genotype

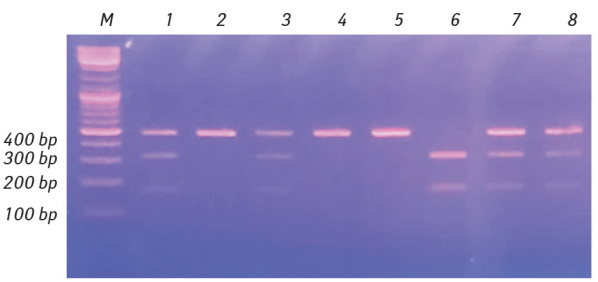

Fig. 2. Results of *SRA1* rs10463297 variant restriction analysis. M — molecular marker (bp — base pairs); lanes 2, 4 and 5 — TT-genotype; lanes 1, 3, 7 and 8 — TC-genotype; lane 6 — CC-genotype

Table 1. PCR conditions for *SRA1* rs801460 and rs10463297 genotyping

SNV	Primer nucleotide sequence	PCR conditions (30 cycles)			Amplicon size
		D	H	E	
rs801460	F: 5`-TTT TTA GTA GAG ACA GGG TTT TGC C-3` R: 5`-ACT CTA CGC CAG ACA ATA TGC TAT G-3`	94 °C – 30 s	63 °C – 45 s	72 °C – 30 s	178 bp
rs10463297	F: 5`-GTC CAT TCT GTC TTC ACT TAG-3` R: 5`-GGT GGC TCT CCT CTA CTT-3`	94 °C – 30 s	56 °C – 45 s	72 °C – 30 s	483 bp

Notes: D – denaturation; H – hybridization; E – elongation; F – forward primer; R – reverse primer; bp – base pairs.

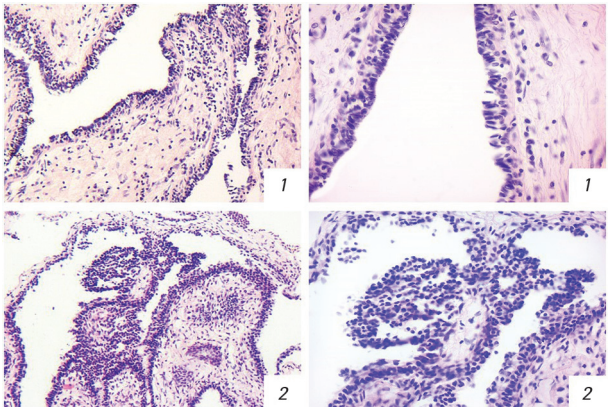

Fig. 3. Simple (1) and atypical (2) intraductal papillomas. H&E, ×200 (left section), ×400 (right section)

number and percentage value. The mean values were compared using two-tailed Student's *t*-test for two and ANOVA for three groups. Bonferroni post hoc test was used for multiple comparisons. Chi square ($\chi 2$) test was used for the comparison of alleles and genotypes frequencies as well as other categorical variables. An odds ratio (OR) and 95% confidence interval (CI) were received from logistic regression for the four models of inheritance: dominant, recessive, overdominant and additive. Multivariable logistic regression was used to increase reliability of the obtained results via adjustment for age, body mass index (BMI), age of menarche, oral contraceptives intake and burdened history of BC. Value $p < 0.05$ was considered significant.

RESULTS

The clinical characteristics of the comparison groups are presented in Table 2. The differences in age ($p < 0.001$) and BMI ($p = 0.016$) were found to be significant. In contrast, the investigated groups were comparable by height ($p = 0.296$), size of the glandular and fibroglandular parts of breast ($p = 0.756$ and $p = 0.364$ respectively), age of menarche ($p = 0.273$), oral contraceptives intake ($p = 0.733$) and burdened history of BC ($p = 0.136$).

The distribution of *SRA1* rs801460 and rs10463297 alleles and genotypes in comparison groups is indicated in Table 3. The frequency of *SRA1* rs801460 genotypes in patients with proliferative lesions with atypia significantly differed from the group without atypia ($p = 0.032$), while the distribution of *SRA1* rs10463297 genotypes was similar between these groups ($p = 0.852$). No significant differences between alleles were found in comparison groups for both SNVs ($p > 0.05$).

The results of *SRA1* rs801460 and rs10463297 genotypic association with proliferative type of BBD with atypia are shown in Table 4. The statistically significant association was found for *SRA1* rs801460-variant in a crude recessive model ($P_c = 0.012$; $OR_c = 2.602$, 95% CI = 1.239–5.462) of inheritance as well as after adjustment for age, body mass index, age of menarche, oral contraceptives intake and burdened history of BC ($P_a = 0.047$; $OR_a = 2.202$, 95% CI = 1.010–4.800). Although mean age of the group with atypia is markedly higher than that of the group without atypia ($p < 0.001$), a significant link remained after adjustment. It supports the genotypic association between *SRA1* rs801460-variant and proliferative type of BBD with atypia development.

DISCUSSION

Estrogen is a steroid hormone that not only controls the development and normal functioning of the mammary gland, but also is involved in the breast tumori-

Table 2. Clinical characteristics of the study population

Parameter	Proliferative lesions with atypia (n = 83)	Proliferative lesions without atypia (n = 115)	*p*
Age, years	36.80 ± 8.87	30.43 ± 9.26	< 0.001
Weight, kg	61.63 ± 10.42	59.09 ± 10.10	0.087
Height, cm	165.65 ± 4.98	166.57 ± 6.81	0.296
BMI, kg/m^2	22.47 ± 3.87	21.26 ± 3.15	0.016
Size of the glandular part of breast (mm)	15.52 ± 2.71	15.36 ± 4.12	0.756
Size of the fibroglandular part of the breast (mm)	19.95 ± 4.48	19.37 ± 4.36	0.364
Age of menarche, years	13.20 ± 1.65	13.45 ± 1.49	0.273
Oral contraceptives intake, n (%)	19 (22.9%)	24 (20.9%)	0.733
Burdened history of BC, n (%)	20 (24.1%)	39 (33.9%)	0.136

Notes: Categorical variables were compared by $\chi 2$ test, continuous variables by *t*-test.

Table 3. Distribution of genotypes and alleles in comparison groups

Gene	SNV		Proliferative lesions with atypia		Proliferative lesions without atypia		χ^2	*p*
			n	%	n	%		
SRA1	rs801460	Genotypes						
		CC	26	31.3	39	33.9		
		CT	35	42.2	62	53.9	6.902	0.032
		TT	22	26.5	14	12.2		
		Alleles						
		C	87	52.4	140	60.9	2.821	0.093
		T	79	47.6	90	39.1		
	rs10463297	Genotypes						
		TT	30	36.14	46	40.0		
		TC	48	57.83	62	53.9	0.320	0.852
		CC	5	6.03	7	6.1		
		Alleles						
		T	108	65.1	154	67.0	0.155	0.694
		C	58	34.9	76	33.0		

Notes: Categorical variables were compared by χ^2 test.

Table 4. Analysis of *SRA1* rs801460 and rs10463297 genotypic association with proliferative type of BBD with atypia development

SNV	Model	P_c	OR_c (95% CI)	P_a	OR_a (95% CI)
rs801460	Dominant	0.702	1.125 (0.615–2.057)	0.911	0.964 (0.506–1.836)
	Recessive	0.012	2.602 (1.239–5.462)	0.047	2.202 (1.010–4.800)
	Over-dominant	0.104	0.623 (0.353–1.102)	0.094	0.595 (0.324–1.093)
	Additive[1]	0.614	0.847 (0.444–1.616)	0.406	0.747 (0.375–1.487)
		0.044	2.357 (1.024–5.426)	0.171	1.849 (0.767–4.460)
rs10463297	Dominant	0.582	1.178 (0.658–2.110)	0.797	0.921 (0.493–1.722)
	Recessive	0.985	0.989 (0.303–3.232)	0.514	0.659 (0.189–2.302)
	Over-dominant	0.584	1.172 (0.663–2.072)	0.941	1.023 (0.556–1.883)
	Additive[1]	0.572	1.187 (0.655–2.151)	0.898	0.959 (0.506–1.817)
		0.885	1.095 (0.318–3.771)	0.508	0.643 (0.174–2.380)

Notes: P_c – crude *P* value; OR_c – crude odds ratio; P_a – *P* value adjusted for age, body mass index, age of menarche, oral contraceptives intake and burdened history of BC; OR_a – adjusted odds ratio.

[1]Upper row in the additive inheritance model – comparison between Aa and AA genotypes; lower row – between aa and AA genotypes.

genesis. Lanz *et al.* [8] in 1999 discovered lncRNA SRA as a 'novel transcriptional coactivator'. It is intergenic with the core region length of 687 bp and has 3 human isoforms [8, 11]. The *SRA1*, steroid receptor RNA activator 1 gene, is located on 5q31.3 chromosome. It is 8027 bp in length, includes 5 exons and 4 introns (NC_000005.10) [10] and encodes a protein, called steroid receptor RNA activator protein [11].

SRA was found to be up-regulated in breast, uterus and ovary. lncRNA SRA is a coactivator of steroid receptors (ER, androgen receptor, progesterone receptor, glucocorticoid receptor), as well as other types of nuclear receptors and transcription factors [11]. It can coactivate the hormone-independent activation domain AF-1 of ERα and ligand-dependent activation domain AF-2 of ERα and ERβ. To mediate full activation, SRA needs the presence of serine-118 in the AF-1. E2 (17-beta-estradiol) induces serine-118 residue phosphorylation by itself or indirectly through the mitogen-activated protein kinase pathway activation that is necessary for SRA functioning [15, 16]. Activated ER receptors stimulate ER-negative cells proliferation through the paracrine signaling [9].

It can be assumed that one nucleotide substitution may lead to a change in the level of *SRA1* expression that affects cell proliferation and predisposes to BBD development. Unfortunately, there are no studies devoted to the association analysis between *SRA1* variants and BBD development. The only known study is that by Yan *et al*. [14] who found that rs10463297 TC-genotype is associated with an increased BC risk in comparison with CC-genotype. In contrast, logistic regression analysis for *SRA1* rs801460 did not show any significant link with BC development. In addition, both SNVs were significantly associated with ER positivity status.

BBD includes premalignant lesions that can lead to the BC development [4]. Therefore, it is interesting to determine the influence of *SRA1* rs801460 and rs10463297 variants on the development of proliferative lesions with atypia.

The essence of rs801460-variant is the replacement of cytosine by thymine at the (-)5749th position of the *SRA1* gene [10]. According to 1000 Genomes Project phase 3 browser [17], the minor T allele frequency is 0.43 in general population, 0.48 in European, 0.51 in Ad Mixed American, 0.22 in African, 0.56 in East Asian and 0.48 in South Asian. The polymorphic site rs10463297 is located in the *SRA1* second intron as well, as rs801460 SNV, and leads to thymine/cytosine conversion at (-)1440th position. The minor C allele frequency is 0.33 in general population, 0.40 in European, 0.42 in Ad Mixed American, 0.01 in African, 0.51 in East Asian and 0.43 in South Asian [17].

The obtained results on the link of *SRA1* rs801460 and rs10463297 variants with proliferative type of BBD with atypia showed that only the rs801460 locus is associated with the occurrence of the mentioned disease in Ukrainian females. Regardless of the adjustment for risk factors, it was found that the risk of proliferative lesions with atypia development in subjects with TT-genotype is 2.2 times higher than in individuals with CC and CT genotypes. This is the first evidence of the association between *SRA1* gene variants and BBD occurrence in Ukrainian females. The comparatively small number of patients enrolled into the present study is a significant limitation. Hence, future case-control studies involving more patients are essential.

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ПОЗИТИВНИЙ ЗВ'ЯЗОК МІЖ *SRA1* RS801460-ВАРІАНТОМ ТА ПРОЛІФЕРАТИВНИМ ТИПОМ ДОБРОЯКІСНОЇ ДИСПЛАЗІЇ МОЛОЧНОЇ ЗАЛОЗИ З АТИПІЄЮ СЕРЕД УКРАЇНСЬКИХ ЖІНОК

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Мета*:** Дослідити зв'язок між *SRA1* rs801460- та rs10463297-варіантами та виникненням проліферативного типу доброякісної дисплазії молочної залози з атипією серед українських жінок. ***Матеріали та методи*:** У цьому проєкті проводилося дослідження 83 пацієнток з проліферативним типом доброякісної дисплазії молочної залози з атипією та 115 — без атипії. Метод полімеразної ланцюгової реакції з аналізом довжини рестрикційних фрагментів (PCR-RFLP) було використано для генотипування rs801460- та rs10463297-варіантів. Гематоксилін та еозин, толуїдиновий синій та пікрофуксин за Ван Гізоном використовували для фарбування зразків. ***Результати*:** У ході дослідження було виявлено зв'язок *SRA1* rs801460-варіанту з розвитком проліферативного типу доброякісної дисплазії молочної залози з атипією як до, так і після виконання поправки на фактори ризику (вік, індекс маси тіла, вік менархе, прийом оральних контрацептивів та обтяжений анамнез щодо раку молочної залози). Ризик виникнення цього захворювання для rs801460 TT-генотипу є у 2.2 рази вищим (довірчий інтервал 1.010–4.800; $p = 0.047$), ніж для осіб із CC- and CT-генотипами. У той же час не було виявлено зв'язку між *SRA1* rs10463297-варіантом та розвитком проліферативного типу доброякісної дисплазії молочної залози з атипією серед українських жінок. ***Висновок: У цьому дослідженні випадок-контроль показано, що саме *SRA1* rs801460, а не rs10463297, може бути генетичним предиктором розвитку доброякісної дисплазії молочної залози з атипією серед українських жінок.

***Ключові слова*:** доброякісна дисплазія молочної залози, SRA, однонуклеотидний варіант.