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Research article

Association between *GPER* gene polymorphisms and GPER expression levels with cancer predisposition and progression

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ABSTRACT

Estrogen is a female sex steroid hormone that plays a significant role in physiological functions. Evidence suggests that estrogen-signaling pathways are closely linked to cancer development and progression. The novel G protein-coupled estrogen receptor (GPER or GPR30) has been shown to influence cancer predisposition and progression, although results of related studies remain equivocal. Thus, this meta-analysis aimed to estimate the relationship between *GPER* gene polymorphisms and GPER expression levels, with cancer predisposition and progression. The pooled results showed that two *GPER* polymorphisms, rs3808350 and rs3808351, were significantly associated with cancer predisposition, especially in the Asian population, but no significant association was detected for rs11544331. In parallel, we also found that cancer aggressiveness and progression correlated with rs3808351 and GPER expression in cancerous tissues. Altogether, our findings suggest that GPER plays a pivotal role in cancer pathogenesis and progression. We suggest that rs3808350 and rs3808351 may be used as a prospective biomarker for cancer screening; while rs3808351 and GPER expression can be used to examine the prognosis of patients with cancer. Further biological studies are warranted to confirm our findings.

1. Introduction

Estradiol (E_2) is a major form of estrogen and displays pleiotropic steroid function that play regulatory roles in many physiological processes [1, 2]. Biosynthesis of E_2 is determined by the conversion of testosterone by a rate-limiting enzyme, aromatase (CYP19A1) [1, 2, 3, 4, 5, 6]. E_2-mediated effects are modulated through both genomic and non-genomic pathways by the nuclear and membrane estrogen receptor (ER), respectively [2]. Recent reports have suggested a pivotal role of E_2 in both the development and malignant progression of multiple cancers [7]. Several meta-analysis have demonstrated that cancer risk is associated with the polymorphism of ER-alpha (*ER*α) [8], but not ER-beta (*ER*β) [9]. However, the role of membrane ERs, such as the G protein-coupled estrogen receptor (GPER), with cancer pathogenesis remains elusive.

GPER has been identified as a novel ER, and is a seven-transmembrane domain protein that is structurally distinguished from the classical ERα and ERβ [10]. GPER mediates rapid E_2-induced non-genomic signaling events, resulting in long-term transcriptional changes and a broad range of response among a large variety of cell types [10, 11]. Such evidence was supported by the expression of GPER in various human tissues, including lung, heart, brain, liver, skeletal muscle, and lymphoid tissues [12]. Additionally, E_2 exerts ten times higher binding capacity to GPER than ERα [13], implying a critical role of GPER in regulating normal physiological functions.

GPER overexpression has been reported in several hormone-dependent malignancies, including cancers of the breast, ovaries, and endometrium [10]. The upregulation of GPER is also evident in seminoma and lung cancer [10, 14]. Additionally, GPER overexpression has also been associated with poor treatment outcomes such as lowered efficacy of primary endocrine treatment in breast cancer patients [15] and poor-prognosis of endometrial cancers, uterine carcinosarcoma, and endometriosis [16]. The finding indicates that GPER expressed in ERα/β-negative breast cancer could induce the expression of connective tissue growth factor (CTGF) [17], and thus binding of E_2 to GPER for cell proliferation and migration. Hence, several studies have been proposed to identify novel GPER ligands with specific antiproliferative effects against estrogen-based malignancies [18, 19].

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Single nucleotide polymorphisms (SNPs) are variations in the genomic sequence that could potentially result in modifications of gene expression level as well as protein structure, level, and function [17]. The expression level of *GPER* mRNA is possibly affected by its polymorphism [20]. Although several SNPs have been identified in the *GPER* gene, only three were reported to have higher biological relevance with human neoplasms, which are rs3808350, rs3808351, and rs11544331 [10]. However, the role of *GPER* polymorphism in cancer remains inconclusive as shown by different results in various studies [10, 13, 16, 17]. Therefore, this meta-analysis was conducted in order to understand the role of GPER with cancer predisposition and progression.

2. Methods

2.1. Literature search and data extraction

A meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [21]. A literature search was conducted in MEDLINE and EMBASE using keywords such as "GPER/GPR30", "polymorphisms", "immunohistochemistry", "expression/level", and "cancer", singularly and in combination. The literature search was updated until July, 2020. The inclusion criteria of studies were as follows: (1) evaluating the association between *GPER* rs3808350, rs11544331, and rs3808351 polymorphisms and cancer predisposition, (2) conducted with a case-control design, and (3) evaluating GPER expression level (immunohistochemistry) and cancer progression. Data were extracted as follows: (1) name of the first author, (2) year of publication, (3) type of cancer, (4) the number of cases and controls, (5) number of genotypes in cases and controls, (6) number of haplotypes of rs3808350/rs3808351/rs11544331 in cases and controls, and (7) number of patients with GPER+/– or high/low.

2.2. Statistical analysis

Meta-analysis for each gene polymorphism was performed for two or more studies, as previously described [3, 4, 5, 6, 22, 23, 24, 25]. Genotypic frequency of *GPER* gene polymorphism was tested for deviation from the Hardy–Weinberg equilibrium (HWE) in the control subjects if HWE was not reported. The genetic association was examined using different genetic models, including allelic (a vs. A), recessive (aa vs. Aa + AA), dominant (aa + Aa vs. AA), over dominant (Aa vs. aa + AA), homozygous (aa vs. AA), and heterozygous (Aa vs. AA) models [5, 22, 23, 24, 25, 26, 27, 28, 29, 30]. The associations between *GPER* gene polymorphisms or GPER expression levels with cancer predisposition and progression were calculated by the pooled odds ratio (OR) and 95% confidence interval (CI). Heterogeneity among studies was evaluated using Q test and I^2 statistic. A significant Q-statistic ($p < 0.10$) indicated heterogeneity across studies. The I^2 values indicated no (0–24.9%), low (25–49.9%), moderate (50–74.9%), or high (75–100%) heterogeneity. The random-effect model (REM) was used if heterogeneity existed; otherwise, the fixed-effect model (FEM) was used [31, 32, 33, 34, 35, 36, 37]. Subgroup analysis was conducted by stratifying based on ethnicity, type of cancer, and localization of GPER expression. In addition, we also evaluated the association between rs3808351 and tumor size, as well as the involvement of haplotypes rs3808350/rs3808351/rs11544331 with cancer predisposition. Potential publication bias was assessed by Begg's funnel plots and Egger's regression test. Begg's funnel plot was applied if the pooled effect size consisted of 10 or more studies. The Newcastle Ottawa Scale (NOS) was adopted to assess the quality of the case-control study, with a score of 8–9 for all included studies, indicating a low risk of bias (Supplementary Table 1). A sensitivity analysis was performed by sequentially omitting each study one at a time, and the results remained unchanged (data not shown), implying the robustness and stability of the findings. A quantified result of $p < 0.05$ was indicative of statistical significance.

3. Results

3.1. Relationship between GPER gene polymorphisms and cancer

For *GPER* gene polymorphisms, a total of 142 articles were screened, among which 11 were reviewed. Six studies were excluded due to not relating to cancer or *GPER* rs3808350, rs11544331, and rs3808351 polymorphisms. Five studies were then included in this meta-analysis [10, 13, 16, 17, 38]. From 5 studies, Chevalier et al. [10] and Giess et al. [17] recruited testicular and breast cancer patients, respectively, while Kasap et al. [16] and Hong et al. [13] enrolled patients with uterine leiomyoma and adenomyosis/uterine leiomyoma/another precancerous lesion of uterine-cervix, respectively. The last included study recruited gynecomastia patients [38], and although it should be noted that some reports have classified the condition as a non-malignant male breast disorder [39], gynecomastia has shown strong association with GPER [38], exhibiting a nearly 10-fold increased risk of breast cancer in men [40]. A total of 1,288 (case: 601, control 687), 5,565 (case: 729, control: 4,836), and 1,294 (case: 610; control: 684) subjects for *GPER* rs3808350, rs11544331, and rs3808351 polymorphisms, respectively, were further analyzed. All studies complied with the HWE except for the study from Chevalier et al. (for rs11544331 and rs3808351) [10]. Details of the retrieved studies are shown in Table 1.

The pooled result of the analyses is shown in Table 2. Overall, there was no significant association between *GPER* rs3808350, rs11544331, and rs3808351 polymorphisms with cancer predisposition in all inheritance models, even when the studies evaluating gynecomastia or/and study deviated from HWE were excluded (Table 2). However, subgroup analyses stratified by ethnicity revealed a significant association between rs3808350 (G vs. A, OR = 1.38, 95%CI = 1.06–1.79, p = 0.015; GG vs. AG + AA, OR = 2.20, 95%CI = 1.42–3.43, p = 0.000 or OR = 2.11, 95% CI = 1.19–3.74, p = 0.010; GG vs. AA, OR = 1.83, 95%CI = 1.10–3.04, p = 0.019; AG vs. AA, OR = 0.51, 95% = CI 0.28–0.95, p = 0.033; Table 2) and rs3808351 (A vs. G, OR = 0.51, 95%CI = 0.34–0.75, p = 0.000; AA vs. GA + GG, OR = 0.34, 95%CI = 0.14–0.78, p = 0.011; AA + GA vs. GG, OR = 0.48, 95%CI = 0.29–0.81, p = 0.006; AA vs. GG, OR = 0.28, 95%CI = 0.11–0.69, p = 0.005; GA vs. GG, OR = 0.56, 95% = CI 0.32–0.98, p = 0.043; Table 2) with cancer predisposition. Ethnicity did not associate with predisposition of cancer for rs11544331 (data not shown). In addition, no association was also observed in any haplotypes of rs3808350/rs3808351/rs11544331 with cancer predisposition (Table 3).

In addition to the association of GPER polymorphism with cancer predisposition, we also evaluated the association between rs3808351 and tumor size (Table 4). The analysis showed that rs3808351 (AA + GA vs. GG, OR = 0.46, 95%CI = 0.28–0.76, p = 0.002; GA vs. GG, OR = 0.46, 95% = CI 0.27–0.79, p = 0.004; Table 5) was associated with smaller tumor size.

3.2. Relationship between GPER expression levels and cancer progression

A total of 204 articles were first screened to evaluate the association between GPER expression levels with cancer progression. After reviewing the title, abstract, and removing duplications, 151 articles were excluded, and 53 articles were then further evaluated. Among them, 33 articles were subsequently removed either because the data cannot be extracted, or the studies did not provide immunohistochemistry results. Finally, 20 articles were included in this meta-analysis [41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60]. The characteristics of the included studies are shown in Table 6.

The meta-analysis results regarding pooled GPER expression levels and cancer progression are shown in Table 7. In brief, no associations were found between GPER expression levels with tumor size, stage, nor

Table 1. Characteristics of individual studies for the association between *GPER* polymorphisms and cancer.

No	Author (year)	Disease	Country/Ethnicity	Sample size		SNP	Definition of allele		*p HWE	Genotype distribution					
				Case	Control		Ref.	Alt.		Case			Control		
										AA	Aa	aa	AA	Aa	aa
1	Korkmaz et al (2014)	Gynecomastia	Turkey/Asian	109	104	rs3808350	A	G	0.5295	37	41	31	44	45	15
2	Chevalier et al (2014)	Testicular cancer	France/Caucasian	89	224				0.6146	45	41	3	82	110	32
3	Hong et al (2019)	Adenomyosis	Korea/Asian	35	34				0.2115	8	12	15	4	20	10
4	Giess et al (2010)	Breast cancer	Germany/Caucasian	257	247				0.4092	100	121	36	96	111	40
5	Kasap et al (2016)	Uterine leiomyoma	Turkey/Asian	111	78				0.8309	41	33	37	27	37	14
1	Korkmaz et al (2014)	Gynecomastia	Turkey/Asian	109	104	rs11544331	C	T	0.0873	61	43	5	66	37	1
2	Chevalier et al (2014)	Testicular cancer	France/Caucasian	223	4,374				**0.0005**	78	43	2	2843	1321	210
3	Hong et al (2019)	Adenomyosis	Korea/Asian	35	34				1	33	2	0	34	0	0
4	Giess et al (2010)	Breast cancer	Germany/Caucasian	251	246				0.5145	146	88	18	128	96	22
5	Kasap et al (2016)	Uterine leiomyoma	Turkey/Asian	111	78				0.5106	44	45	22	23	36	19
1	Korkmaz et al (2014)	Gynecomastia	Turkey/Asian	109	104	rs3808351	G	A	0.4980	36	46	27	52	41	11
2	Chevalier et al (2014)	Testicular cancer	France/Caucasian	100	222				**0.0031**	16	69	15	96	114	12
3	Hong et al (2019)	Adenomyosis	Korea/Asian	35	34				0.0989	27	7	1	19	15	0
4	Giess et al (2010)	Breast cancer	Germany/Caucasian	255	246				0.0545	133	99	23	130	89	27
5	Kasap et al (2016)	Uterine leiomyoma	Turkey/Asian	111	78				0.1432	57	45	9	28	32	18

Alt., alternative allele; Ref., reference allele; SNP, single nucleotide polymorphism; *p for Hardy–Weinberg equilibrium test in controls; A, Wild type; a, mutant type. Bold values indicate statistically significant $p < 0.05$.

grade. Subgroup analysis by ethnicity and cancer type were also performed, yielding similar findings, with the exception of a significant association between GPER expression with higher tumor stage in the Asian population (OR = 2.22, 95% CI = 1.12–4.41, p = 0.022, Table 7). No association was also observed when the analysis was performed based on the localization of GPER (data now shown).

3.3. Publication biases

Publication biases were examined by Begg's funnel plots and Egger's regression tests. Overall, funnel plots were symmetrical (data not shown) and *p*-values of Egger's regression test greater than 0.05, suggesting that publication biases did not likely influence the results.

4. Discussion

To date, this study is the first to summarize the association between *GPER* gene polymorphisms and GPER expression levels with cancer. The pooled meta-analyses results demonstrated that *GPER* rs3808350 and rs3808351, but not rs11544331, were significantly associated with cancer predisposition, specifically in the Asian population. Patients harbouring the A allele of rs3808351 exhibited a lower risk of developing cancer and displayed smaller tumor size. Moreover, GPER expression levels in cancerous tissues were correlated with higher tumor stage in the Asian population.

Our finding reinforces previous reports that A allele carriers of rs3808350 and rs3808351 exhibit protective effects against uterine leiomyoma and gynecomastia risks in the Turkish population [17, 38]. Similar to our findings, Giess et al. [17] observed that AA and AG genotypes of rs3808351 were correlated with lower tumor stage and grade. Although we did not observe a significant association between rs11544331 and cancer risk, it has been suggested that rs11544331 (P16L) can alter the conformational structure and localization of GPER, resulting in defective GPER function and the aggravated migration of carcinoma cells [61]. We also found no significant relationship between haplotypes of rs3808350/rs3808351/rs11544331 with cancer predisposition, possibly because our analysis was pooled from two studies reporting different cancer type/disease. Considering the potential functional significance of rs3808350 and rs3808351, further studies should try to estimate the relationship between rs3808350 and rs3808351 with cancer in a larger population and other ethnicities to test whether our findings are statistically robust.

Because rs3808350 and rs3808351 are located in the 5′ region of the *GPER* gene (rs3808350 (–642) is located in the 5′-regulatory region, while rs3808351 (+124) is located in the 5′-untranslated region and containing the gene promoter) [10], these polymorphisms may influence the transcription level of GPER. However, no related studies are currently available. Since our results showed that GPER expression in cancerous tissues correlate with the aggressiveness of malignancies and that the A allele of rs3808351 exhibits protective effects against tumor progression in the Asian population, it is reasonable to speculate that the G allele of rs3808351 may be associated with the upregulation of GPER transcription. However, only one study has reported the functional role of *GPER* polymorphisms in relation to post-transcriptional expression. The study reported that only rs10235056 was significantly correlated with *GPER* mRNA expression [20]. Therefore, further studies are still required to reveal the exact molecular mechanism underlying our significant findings.

Although in general we did not find any relationship between expression level and localization of GPER with cancer progression, other studies have reported that GPER overexpression is strongly associated with lower survival rates in several cancer types [43, 54, 55, 59, 60, 62, 63]. Contrastingly, some studies demonstrated that loss of GPER protein corresponds with low *GPER* mRNA and poorer prognosis of endometrial and breast cancer patient [50, 64], possibly due to *GPER* promoter hypermethylation [64]. Moreover, it seems that the localization of GPER in the plasma membrane is responsible for cancer aggressiveness [63]. Thus, in order to evaluate the prognostic value of GPER in cancer patients, GPER protein level, localization, and promoter hypermethylation must be examined simultaneously.

Despite being the first meta-analysis in the field, several limitations of this study should be noted. First, only a limited number of studies were included for meta-analysis of *GPER* gene polymorphisms and cancer. Consequently, further studies are still warranted to test our findings with a larger sample size. Second, because the etiologies of cancer are complex, other genetic and environmental factors need to be addressed and may influence the relationship between *GPER* gene polymorphism, GPER level, and its localization in different cancer types. Hence, publication

Table 2. Meta-analysis for the association between *GPER* polymorphisms and cancer.

SNP	Genetic model	Group	No. of studies	Test of association			Stat. Model	Test of heterogeneity		Publication bias *p*-value (Egger's test)
				OR	95% CI	*p*-value		*p*-value	I^2 (%)	
rs3808350	G vs. A	Overall	5	1.02	[0.72; 1.45]	0.888	Random	0.003	74.50	0.815
		Overall*	4	0.91	[0.64; 1.29]	0.604	Random	0.027	67.14	0.943
		Asian	3	**1.38**	**[1.06; 1.79]**	**0.015**	Fixed	0.548	0	0.357
		Asian*	2	1.22	[0.86; 1.74]	0.252	Fixed	0.595	0	NA
		Caucasian	2	0.74	[0.44; 1.24]	0.268	Random	0.025	79.89	NA
	GG vs. AG + AA	Overall	5	1.20	[0.59; 2.45]	0.602	Random	0.001	77.16	0.840
		Overall*	4	0.99	[0.43; 2.31]	0.996	Random	0.003	77.71	0.837
		Asian	3	**2.20**	**[1.42; 3.43]**	**0.000**	Fixed	0.902	0	0.057
		Asian*	2	**2.11**	**[1.19; 3.74]**	**0.010**	Fixed	0.700	0	NA
		Caucasian	2	0.47	[0.12; 1.81]	0.273	Random	0.036	77.15	NA
	GG + AG vs. AA	Overall	5	0.90	[0.71; 1.13]	0.379	Fixed	0.114	46.18	0.584
		Overall*	4	0.81	[0.63; 1.05]	0.121	Fixed	0.237	29.12	0.403
		Asian	3	1.06	[0.72; 1.57]	0.753	Fixed	0.221	33.66	0.359
		Asian*	2	0.79	[0.46; 1.38]	0.424	Fixed	0.342	0	NA
		Caucasian	2	0.77	[0.44; 1.34]	0.359	Random	0.068	69.93	NA
	GG vs. AA	Overall	5	0.95	[0.44; 2.04]	0.913	Random	0.003	74.06	0.583
		Overall*	4	0.73	[0.32; 1.68]	0.468	Random	0.021	69.04	0.558
		Asian	3	**1.83**	**[1.10; 3.04]**	**0.019**	Fixed	0.355	3.36	0.246
		Asian*	2	1.43	[0.72; 2.86]	0.302	Fixed	0.314	1	NA
		Caucasian	2	0.42	[0.08; 2.05]	0.287	Random	0.018	82.03	NA
	AG vs. AA	Overall	5	0.84	[0.65; 1.08]	0.182	Fixed	0.216	30.81	0.132
		Overall*	4	0.80	[0.61; 1.05]	0.114	Fixed	0.171	40.05	0.080
		Asian	3	0.74	[0.48; 1.15]	0.186	Fixed	0.168	43.81	0.403
		Asian*	2	**0.51**	**[0.28; 0.95]**	**0.033**	Fixed	0.396	0	NA
		Caucasian	2	0.89	[0.66; 1.21]	0.484	Fixed	0.183	43.50	NA
rs11544331	T vs. C	Overall	5	0.91	[0.76; 1.08]	0,299	Fixed	0.204	32.48	0.283
		Overall**	3	0.80	[0.63; 1.01]	0,064	Fixed	0.462	0	0.389
	TT vs. CT + CC	Overall	4	0.76	[0.49; 1.19]	0,244	Fixed	0.234	29.66	0.662
		Overall**	2	0.77	[0.48; 1.24]	0,295	Fixed	0.966	0	0.265
	TT + CT vs. CC	Overall	5	0.93	[0.75; 1.16]	0,555	Fixed	0.205	32.41	0.502
		Overall**	3	0.76	[0.56; 1.03]	0,080	Fixed	0.398	0	0.543
	TT vs. CC	Overall	4	0.68	[0.42; 1.09]	0,114	Fixed	0.214	32.91	0.522
		Overall**	2	0.66	[0.40; 1.11]	0,122	Fixed	0.748	0	0.723
	CT vs. CC	Overall	5	0.97	[0.78; 1.22]	0,854	Fixed	0.252	25.31	0.606
		Overall**	3	0.78	[0.56; 1.08]	0,136	Fixed	0.418	0	0.532
rs3808351	A vs. G	Overall	5	1.07	[0.61; 1.87]	0.809	Random	0.000	89.43	0.657
		Overall**	3	0.68	[0.41; 1.12]	0.135	Random	0.032	70.73	0.481
		Asian	3	0.83	[0.30; 2.27]	0.716	Random	0.000	90.93	0.732
		Asian*	2	0.51	[0.34; 0.75]	**0.000**	Fixed	0.974	0	NA
		Caucasian	2	1.44	[0.65; 3.17]	0.364	Random	0.000	92.33	NA
	AA vs. GA + GG	Overall	5	1.27	[0.49; 3.29]	0.618	Random	0.000	82.14	0.817
		Overall**	3	0.60	[0.37; 0.97]	**0.040**	Fixed	0.103	55.95	0.903
		Asian	3	1.14	[0.17; 7.38]	0.886	Random	0.000	86.74	0.970
		Asian*	2	0.34	[0.14; 0.78]	**0.011**	Fixed	0.174	45.90	NA
		Caucasian	2	1.53	[0.41; 5.71]	0.526	Random	0.007	85.87	NA
	AA + GA vs. GG	Overall	5	1.16	[0.56; 2.38]	0.680	Random	0.000	87.44	0.882
		Overall**	3	0.66	[0.36; 1.21]	0.182	Random	0.054	65.68	0.219
		Asian	3	0.77	[0.26; 2.24]	0.640	Random	0.000	85.67	0.593
		Asian*	2	0.48	[0.29; 0.81]	**0.006**	Fixed	0.571	0	NA
		Caucasian	2	1.98	[0.52; 7.50]	0.313	Random	0.000	93.24	NA
	AA vs. GG	Overall	5	1.56	[0.44; 5.51]	0.484	Random	0.000	88.31	0.798
		Overall**	3	0.54	[0.19; 1.57]	0.263	Random	0.069	62.47	0.995
		Asian	3	1.12	[0.12; 9.73]	0.916	Random	0.000	89.02	0.988
		Asian*	2	0.28	[0.11; 0.69]	**0.005**	Fixed	0.210	36.18	NA
		Caucasian	2	2.42	[0.28; 20.91]	0.419	Random	0.000	93.40	NA
	GA vs. GG	Overall	5	1.15	[0.61; 2.19]	0.653	Random	0.000	82.10	0.728

(*continued on next page*)

Table 2 (*continued*)

SNP	Genetic model	Group	No. of studies	Test of association			Stat. Model	Test of heterogeneity		Publication bias *p*-value (Egger's test)
				OR	95% CI	*p*-value		*p*-value	I^2 (%)	
		Overall**	3	0.73	[0.40; 1.32]	0.307	Random	0.081	60.15	0.001
		Asian	3	0.78	[0.33; 1.81]	0.564	Random	0.020	74.22	0.402
		Asian*	2	0.56	[0.32; 0.98]	**0.043**	Fixed	0.243	26.59	NA
		Caucasian	2	1.93	[0.59; 6.31]	0.271	Random	0.000	90.87	NA

*analysis by excluding Korkmaz et al (2014); **analysis by excluding Korkmaz et al (2014) and Chevalier et al (2014); CI. confidence interval; OR. odds ratio; Stat. model, statistical model. Bold values indicate statistically significant differences between cases and control, $p < 0.05$.

Table 3. Characteristics of individual studies and meta-analysis for the association between rs3808350/rs3808351/rs11544331 haplotypes and cancer risk.

No	Author (year)	Haplotypes	Case		Control		OR (95% CI) [Random]	*p*-value
			Events	Total	Events	Total		
1	Korkmaz et al (2014)	AGC	70	109	87	104	0.55 (0.23–1.34)	0.193
2	Kasap et al (2016)		60	111	45	78		
1	Korkmaz et al (2014)	AGT	9	109	12	104	1.00 (0.58–1.73)	0.990
2	Kasap et al (2016)		30	111	18	78		
1	Korkmaz et al (2014)	AAC	25	109	28	104	0.59 (0.29–1.19)	0.143
2	Kasap et al (2016)		11	111	17	78		
1	Korkmaz et al (2014)	GGC	31	109	34	104	1.87 (0.35–0.89)	0.458
2	Kasap et al (2016)		44	111	10	78		
1	Korkmaz et al (2014)	GGT	8	109	12	104	0.86 (0.49–1.50)	0.598
2	Kasap et al (2016)		25	111	17	78		
1	Korkmaz et al (2014)	AAT	11	109	6	104	1.13 (0.50–2.56)	0.755
2	Kasap et al (2016)		14	111	12	78		
1	Korkmaz et al (2014)	GAC	39	109	20	104	1.64 (0.76–3.54)	0.205
2	Kasap et al (2016)		18	111	12	78		
1	Korkmaz et al (2014)	GAT	25	109	9	104	1.09 (0.14–8.40)	0.930
2	Kasap et al (2016)		20	111	28	78		

CI, confidence interval; OR, odds ratio.

Table 4. Characteristics of individual studies for the association between rs3808351 and tumor size.

No	Author (year)	Sample size		SNP	Definition of allele		*p* HWE	Genotype distribution					
		≥ T2	< T2		Ref.	Alt.		≥ T2			< T2		
								GG	GA	AA	GG	GA	AA
1	Chevalier et al (2014)	56	56	rs3808351	G	A	0.086	2	9	6	8	32	12
2	Giess et al (2010)	104	246				0.9729	67	30	7	61	64	17

Alt., alternative allele; Ref., reference allele; SNP, Single nucleotide polymorphism. *p for Hardy–Weinberg equilibrium test in controls.

bias might affect the accuracy of our pooled studies. Notwithstanding, detailed functional analyses are still needed to uncover the exact molecular mechanisms of the observed significant association between GPER and cancer.

It is notable that rs3808350 and rs3808351 have the potential to be used as a prospective biomarker for cancer, with potential use of rs3808351 in particular as a prognostic marker for cancer progression, particularly in Asians. Thus, future studies should address the possibility

Table 5. Meta-analysis for the association between rs3808351 and tumor size.

SNP	Genetic model	No. of studies	Test of association			Stat. Model	Test of heterogeneity		Publication bias *p*-value (Egger's test)
			OR	95% CI	*p*-value		*p*-value	I^2 (%)	
rs3808351	A vs. G	2	0.79	[0.29; 2.09]	0.637	Random	0.028	79.25	NA
	AA vs. GA + GG	2	0.84	[0.40; 1.74]	0.643	Fixed	0.107	61.37	NA
	AA + GA vs. GG	2	**0.46**	**[0.28; 0.76]**	**0.002**	Fixed	0.180	44.33	NA
	AA vs. GG	2	0.53	[0.23; 1.23]	0.142	Random	0.111	60.47	NA
	GA vs. GG	2	**0.46**	**[0.27; 0.79]**	**0.004**	Fixed	0.292	9.78	NA

CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism; Stat. model, statistical model. Bold values indicate statistically significant differences between ≥ T2 and < T2.

Table 6. Characteristics of individual studies for the association between GPER expression levels and cancer progression.

No	Author (year)	Cancer type	Tumor size ≥2 cm				Tumor stage ≥2				Tumor grade ≥2			
			GPER+/High	Total	GPER–/Low	Total	GPER+/High	Total	GPER–/Low	Total	GPER+/High	Total	GPER–/Low	Total
1	Aiad et al (2014)	Breast cancer	–	–	–	–	–	–	–	–	11	33	6	18
2	Aquino et al (2018)a	Salivary Gland Tumors	–	–	–	–	–	–	–	–	16	26	1	5
	Aquino et al (2018)b	Salivary Gland Tumors	–	–	–	–	–	–	–	–	3	4	14	27
3	Friese et al (2017)a	Cervical cancer	–	–	–	–	96	114	35	42	102	111	38	41
	Friese et al (2017)c	Cervical cancer	–	–	–	–	109	129	22	27	118	125	22	27
4	Heublein (2011)-1	Ovarian Granulosa Cell Tumors	–	–	–	–	1	8	2	7	–	–	–	–
	Heublein (2011)-2	Ovarian Granulosa Cell Tumors	–	–	–	–	1	3	2	12	–	–	–	–
5	Ignatov et al (2011)	Breast cancer	84	183	72	140	–	–	–	–	164	182	126	140
6	Ignatov et al (2013)	Ovarian cancer	–	–	–	–	–	–	–	–	85	103	21	21
7	Ignatov et al (2013)**	Breast cancer	34	65	39	99	84	99	60	65	–	–	–	–
8	Ignatov et al (2018)	Breast cancer	149	352	40	83	–	–	–	–	280	352	74	83
9	Ino et al (2019)*	Uterine cervical adenocarcinoma	–	–	–	–	9	19	1	34	–	–	–	–
10	Kolkova et al (2012)	Ovarian cancer	–	–	–	–	36	50	77	100	48	50	95	100
11	Krakstad et al (2012)*	Endometrial cancer	–	–	–	–	–	–	–	–	68	333	79	141
12	Liu et al (2019)a	NSCLC	–	–	–	–	63	120	8	30	–	–	–	–
	Liu et al (2019)b	NSCLC	–	–	–	–	39	78	32	72	–	–	–	–
13	Luo et al (2011)	Breast cancer	–	–	–	–	–	–	–	–	138	198	10	40
14	Martin et al (2018)a*	Breast cancer	124	327	372	910	132	327	351	910	263	327	775	910
	Martin et al (2018)b*	Breast cancer	111	370	384	864	124	370	348	864	287	370	748	864
15	Samartzis et al (2014)a	Breast cancer	–	–	–	–	99	189	486	789	136	185	680	781
	Samartzis et al (2014)b	Breast cancer	–	–	–	–	313	528	272	450	443	520	373	446
16	Smith et al (2009)*	Ovarian cancer	–	–	–	–	–	–	–	–	39	52	37	82
17	Steiman et al (2013)	Breast cancer	–	–	–	–	21	27	14	21	–	–	–	–
18	Tian et al (2018)*	Gastric cancer	8	26	18	58	17	26	40	58	4	26	33	58
19	Ye et al (2019)*	Breast cancer	–	–	–	–	46	74	127	175	62	73	149	176
20	Yu et al (2014)	Breast cancer	–	–	–	–	48	66	13	30	53	66	23	30

a. cytoplasmic GPER; b. nuclear GPER; c. membrane GPER; *Expression level classified as high/low; **Expression level classified as increase/decrease; 1-Iimunoreactive score; 2-Intensity.

Table 7. Meta-analysis for the association between GPER expression levels and cancer progression.

Group	No. of studies	OR (95% CI) [Random]	*p*-value
Tumor size ≥ 2 cm			
Overall (GPER+/–)	2	0.80 (0.58–1.10)	0.168
Overall (GPER high/low)	4	0.88 (0.55–1.39)	0.575
Breast cancer (GPER+/–)	3	0.87 (0.51–1.46)	0.590
Breast cancer (GPER high/low)	2	0.80 (0.58–1.10)	0.168
Tumor stage ≥ 2			
Overall (GPER+/–)	11	1.18 (0.85–1.64)	0.326
Overall (GPER high/low)	6	0.87 (0.58–1.31	0.497
Asian (GPER+/–)	3	**2.22 (1.12–4.41)**	**0.022**
Asian (GPER high/low)	3	1.65 (0.38–7.21)	0.505
Caucasian (GPER+/–)	8	0.86 (0.72–1.04)	0.120
Caucasian (GPER high/low)	3	0.85 (0.58–1.20)	0.345
Breast cancer (GPER+/–)	4	1.15 (0.69–1.92)	0.595
Breast cancer (GPER high/low)	4	0.80 (0.59–1.09)	0.153
Ovarian cancer (GPER+/–)	3	0.78 (0.38–1.61)	0.505
Tumor grade ≥ 2			
Overall (GPER+/–)	12	1.22 (0.68–2.20)	0.507
Overall (GPER high/low)	5	0.54 (0.25–1.17)	0.117
Caucasian (GPER+/–)	10	0.94 (0.56–1.60)	0.829
Caucasian (GPER high/low)	4	0.69 (0.31–1.55)	0.368
Breast cancer (GPER+/–)	5	1.06 (0.44–2.54)	0.894
Ovarian cancer (GPER+/–)	2	0.49 (0.05–5.12)	0.549

Bold values indicate statistically significant $p < 0.05$.

of *GPER* polymorphisms can be used as an early detection marker for malignancies in clinical settings. Altogether, our findings indicate that GPER plays a crucial role in cancer pathogenesis and progression.

Declarations

Author contribution statement

Zulvikar Syambani Ulhaq: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Gita Vita Soraya, William Ka Fai Tse: Analyzed and interpreted the data; Wrote the paper.

Alvi Milliana: Contributed reagents, materials, analysis tools or data.

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Additional information

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References

[1] Z.S. Ulhaq, Brain aromatase modulates cardiac functions in embryonic zebrafish, Int. J. Vet. Sci. Med. 7 (2019) 31–34.
[2] Z.S. Ulhaq, M. Kishida, Brain aromatase modulates serotonergic neuron by regulating serotonin levels in zebrafish embryos and larvae, Front. Endocrinol. 9 (2018) 230.
[3] Z.S. Ulhaq, C.P. Garcia, Estrogen receptor beta (ESR2) gene polymorphism and susceptibility to dementia, Acta Neurol. Belg. (2020) 1–3.
[4] Z.S. Ulhaq, The association between genetic polymorphisms in estrogen receptor genes and the risk of ocular disease: a meta-analysis, Turk. J. Ophthalmol. 50 (2020) 216–220.
[5] Z.S. Ulhaq, The association of estrogen-signaling pathways and susceptibility to open-angle glaucoma, Beni-Suef Univ. J. Basic Appl. Sci. 9 (2020) 7.
[6] Z.S. Ulhaq, Update on "associations of estrogen receptor alpha gene polymorphisms with type 2 diabetes mellitus and metabolic syndrome: a systematic review and meta-analysis, Horm. Metab. Res. Horm. Stoffwechselforschung Horm. Metab. 52 (2020) 67–70.
[7] N.J. Rothenberger, A. Somasundaram, L.P. Stabile, The role of the estrogen pathway in the tumor microenvironment, Int. J. Mol. Sci. 19 (2018).
[8] Z. Zhang, C. Zhang, Y. Li, Z. Zhao, S. Yang, Association between ERα Gene Pvu II Polymorphism and Breast Cancer Susceptibility, Medicine (Baltimore), 2018, p. 97.
[9] Z. Li, X. Yang, R. Zhang, D. Zhang, B. Li, D. Zhang, Q. Li, Y. Xiong, No association between estrogen receptor-B Rs4986938 and cancer risk: a systematic review and meta-analysis, Iran, J. Public Health 48 (2019) 784–795.
[10] N. Chevalier, R. Paul-Bellon, P. Camparo, J.-F. Michiels, D. Chevallier, P. Fénichel, Genetic variants of GPER/GPR30, a novel estrogen-related G protein receptor, are associated with human seminoma, Int. J. Mol. Sci. 15 (2014) 1574–1589.
[11] Y. Peng, G. Liang, Y. Pei, W. Ye, A. Liang, P. Su, Genomic polymorphisms of G-Protein Estrogen Receptor 1 are associated with severity of adolescent idiopathic scoliosis, Int. Orthop. 36 (2012) 671–677.
[12] A.M. Kvingedal, E.B. Smeland, A novel putative G-protein-coupled receptor expressed in lung, heart and lymphoid tissue, FEBS Lett. 407 (1997) 59–62.
[13] D.G. Hong, J.Y. Park, G.O. Chong, Y.H. Lee, H.J. Lee, J.U. Shinn, Y.S. Lee, W.J. Seong, Transmembrane G protein-coupled receptor 30 gene polymorphisms and uterine adenomyosis in Korean women, Gynecol. Endocrinol. Off. J. Int. Soc. Gynecol. Endocrinol. 35 (2019) 498–501.
[14] V.R. Jala, B.N. Radde, B. Haribabu, C.M. Klinge, Enhanced expression of G-protein coupled estrogen receptor (GPER/GPR30) in lung cancer, BMC Canc. 12 (2012) 624.
[15] T. Ignatov, O. Treeck, T. Kalinski, O. Ortmann, A. Ignatov, GPER-1 expression is associated with a decreased response rate to primary tamoxifen therapy of breast cancer patients, Arch. Gynecol. Obstet. 301 (2020) 565–571.
[16] B. Kasap, N.Ö. Turhan, T. Edgünlü, M. Duran, E. Akbaba, G. Öner, G-protein-coupled estrogen receptor-30 gene polymorphisms are associated with uterine leiomyoma risk, Bosn. J. Basic Med. Sci. 16 (2016) 39–45.
[17] M. Giess, C. Lattrich, A. Springwald, R. Goerse, O. Ortmann, O. Treeck, GPR30 gene polymorphisms are associated with progesterone receptor status and histopathological characteristics of breast cancer patients, J. Steroid Biochem. Mol. Biol. 118 (2010) 7–12.
[18] F. Aiello, G. Carullo, F. Giordano, E. Spina, A. Nigro, A. Garofalo, S. Tassini, G. Costantino, P. Vincetti, A. Bruno, M. Radi, Identification of breast cancer inhibitors specific for G protein-coupled estrogen receptor (GPER)-Expressing cells, ChemMedChem 12 (2017) 1279–1285.
[19] Full text (n.d.), https://journals.plos.org/plosmedicine/article/file?id=10.1371/journal.pmed.1001835&type=printable. (Accessed 10 November 2020).
[20] W. Zhang, F. Yang, J. Luo, F. Chen, J. Gu, X. Guan, A novel GPR30 rs10235056 A>G polymorphism associated with post-transcriptional regulation in lymphoblastoid cell lines, Biomark. Biochem. Indic. Expo. Response Susceptibility Chem. 19 (2014) 417–423.
[21] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, PRISMA Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, PLoS Med. 6 (2009), e1000097.
[22] Z.S. Ulhaq, G.V. Soraya, Anti-IL-6 receptor antibody treatment for severe COVID-19 and the potential implication of IL-6 gene polymorphisms in novel coronavirus pneumonia, Med. Clin. (2020).
[23] Z.S. Ulhaq, G.V. Soraya, Roles of IL-8 -251A/T and +781C/T polymorphisms, IL-8 level, and the risk of age-related macular degeneration, Arch. Soc. Esp. Oftalmol. 3 (1) (2020).
[24] Z.S. Ulhaq, C.P. Garcia, Inflammation-related gene polymorphisms associated with Parkinson's disease: an updated meta-analysis, Egypt, J. Med. Hum. Genet. 21 (2020) 14.
[25] Z.S. Ulhaq, Genetic polymorphisms associated with Age-related macular degeneration, Int. J. Retina. 3 (2020).
[26] Z.S. Ulhaq, Vitamin D and its receptor polymorphisms are associated with glaucoma, J. Fr. Ophtalmol. (2020) 1009–1019.
[27] Z.S. Ulhaq, G.V. Soraya, Budu, L.R. Wulandari, The role of IL-6-174 G/C polymorphism and intraocular IL-6 levels in the pathogenesis of ocular diseases: a systematic review and meta-analysis, Sci. Rep. 10 (2020) 17453.
[28] Z.S. Ulhaq, The association between genetic polymorphisms in estrogen receptor genes and the risk of ocular disease: a meta-analysis, Turk. J. Ophthalmol. 50 (2020) 216–220.
[29] Z.S. Ulhaq, C.P. Garcia, Estrogen receptor beta (ESR2) gene polymorphism and susceptibility to dementia, Acta Neurol. Belg. (2020) 1–3.
[30] Z.S. Ulhaq, Comment on the assessment of "Association of interleukin-6 gene polymorphisms and glaucoma: systematic review and meta-analysis, Eur. J. Ophthalmol. (2020), 1120672120962049.
[31] Z.S. Ulhaq, G.V. Soraya, Aqueous humor interleukin-6 levels in primary open-angle glaucoma (POAG): a systematic review and meta-analysis, Arch. Soc. Espanola Oftalmol. 95 (2020) 315–321.
[32] Z.S. Ulhaq, Chemokine IL-8 level in aqueous humor of open-angle glaucoma: a meta-analysis, Arch. Soc. Espanola Oftalmol. 95 (2020) 114–119.
[33] G.V. Soraya, Z.S. Ulhaq, Crucial laboratory parameters in COVID-19 diagnosis and prognosis: an updated meta-analysis, Med. Clin. 155 (2020) 143–151.
[34] Z.S. Ulhaq, G.V. Soraya, Interleukin-6 as a potential biomarker of COVID-19 progression, Med. Maladies Infect. 50 (2020) 382–383.
[35] G.V. Soraya, Z.S. Ulhaq, Interleukin-6 levels in children developing SARS-CoV-2 infection, Pediatr. Neonatol. 61 (2020) 253–254.
[36] Z.S. Ulhaq, G.V. Soraya, F.A. Fauziah, Recurrent positive SARS-CoV-2 RNA tests in recovered and discharged patients, Rev. Clin. Esp. (2020).
[37] Z.S. Ulhaq, G.V. Soraya, The prevalence of ophthalmic manifestations in COVID-19 and the diagnostic value of ocular tissue/fluid, Graefes Arch. Clin. Exp. Ophthalmol. Albrecht Von Graefes Arch. Klin. Exp. Ophthalmol. 258 (2020) 1351–1352.
[38] H.A. Korkmaz, T. Edgünlü, E. Eren, K. Demir, E.D.P. Çakir, S.K. Çelik, B. Özkan, GPR30 gene polymorphisms are associated with gynecomastia risk in adolescents, Horm. Res. Paediatr. 83 (2015) 177–182.
[39] C.B. Niewoehner, A.E. Schorer, Gynaecomastia and breast cancer in men, BMJ 336 (2008) 709–713.
[40] L.A. Brinton, J.D. Carreon, G.L. Gierach, K.A. McGlynn, G. Gridley, Etiologic factors for male breast cancer in the U.S. Veterans Affairs medical care system database, Breast Canc. Res. Treat. 119 (2010) 185–192.
[41] K. Friese, B. Kost, A. Vattai, F. Marmé, C. Kuhn, S. Mahner, C. Dannecker, U. Jeschke, S. Heublein, The G protein-coupled estrogen receptor (GPER/GPR30) may serve as a prognostic marker in early-stage cervical cancer, J. Canc. Res. Clin. Oncol. 144 (2018) 13–19.
[42] S. Tian, N. Zhan, R. Li, W. Dong, Downregulation of G Protein-Coupled estrogen receptor (GPER) is associated with reduced prognosis in patients with gastric cancer, Med. Sci. Monit. Int. Med. J. Exp. Clin. Res. 25 (2019) 3115–3126.
[43] S. Ye, Y. Xu, J. Li, S. Zheng, P. Sun, T. Wang, Prognostic role of GPER/Ezrin in triple-negative breast cancer is associated with menopausal status, Endocr. Connect. 8 (2019) 661–671.
[44] S.G. Martin, M.N. Lebot, B. Sukkarn, G. Ball, A.R. Green, E.A. Rakha, I.O. Ellis, S.J. Storr, Low expression of G protein-coupled oestrogen receptor 1 (GPER) is associated with adverse survival of breast cancer patients, Oncotarget 9 (2018) 25946–25956.

[45] C. Liu, Y. Liao, S. Fan, X. Fu, J. Xiong, S. Zhou, M. Zou, J. Wang, G-Protein-Coupled estrogen receptor antagonist G15 decreases estrogen-induced development of non-small cell lung cancer, Oncol. Res. 27 (2019) 283–292.
[46] T. Ignatov, M. Claus, N. Nass, J. Haybaeck, B. Seifert, T. Kalinski, O. Ortmann, A. Ignatov, G-protein-coupled estrogen receptor GPER-1 expression in hormone receptor-positive breast cancer is associated with poor benefit of tamoxifen, Breast Canc. Res. Treat. 174 (2019) 121–127.
[47] E.P. Samartzis, A. Noske, A. Meisel, Z. Varga, D. Fink, P. Imesch, The G protein-coupled estrogen receptor (GPER) is expressed in two different subcellular localizations reflecting distinct tumor properties in breast cancer, PloS One 9 (2014), e83296.
[48] T. Ignatov, C. Weißenborn, A. Poehlmann, A. Lemke, A. Semczuk, A. Roessner, S.D. Costa, T. Kalinski, A. Ignatov, GPER-1 expression decreases during breast cancer tumorigenesis, Canc. Invest. 31 (2013) 309–315.
[49] Z. Kolkova, V. Casslén, E. Henic, S. Ahmadi, A. Ehinger, K. Jirström, B. Casslén, The G protein-coupled estrogen receptor 1 (GPER/GPR30) does not predict survival in patients with ovarian cancer, J. Ovarian Res. 5 (2012) 9.
[50] C. Krakstad, J. Trovik, E. Wik, I.B. Engelsen, H.M.J. Werner, E. Birkeland, M.B. Raeder, A.M. Øyan, I.M. Stefansson, K.H. Kalland, L.A. Akslen, H.B. Salvesen, Loss of GPER identifies new targets for therapy among a subgroup of ERα-positive endometrial cancer patients with poor outcome, Br. J. Canc. 106 (2012) 1682–1688.
[51] H.-J. Luo, P. Luo, G.-L. Yang, Q. Peng, M.-R. Liu, G. Tu, G-protein coupled estrogen receptor 1 expression in primary breast cancers and its correlation with clinicopathological variables, J. Breast Cancer. 14 (2011) 185–190.
[52] T. Ignatov, S. Modl, M. Thulig, C. Weißenborn, O. Treeck, O. Ortmann, A. Zenclussen, S.D. Costa, T. Kalinski, A. Ignatov, GPER-1 acts as a tumor suppressor in ovarian cancer, J. Ovarian Res. 6 (2013) 51.
[53] G. Aquino, F. Collina, R. Sabatino, M. Cerrone, F. Longo, F. Ionna, N.S. Losito, R. De Cecio, M. Cantile, G. Pannone, G. Botti, Sex hormone receptors in benign and malignant salivary gland tumors: prognostic and predictive role, Int. J. Mol. Sci. 19 (2018).
[54] Y. Ino, T. Akimoto, A. Takasawa, K. Takasawa, T. Aoyama, A. Ueda, M. Ota, K. Magara, Y. Tagami, M. Murata, T. Hasegawa, T. Saito, N. Sawada, M. Osanai, Elevated expression of G protein-coupled receptor 30 (GPR30) is associated with poor prognosis in patients with uterine cervical adenocarcinoma, Histol. Histopathol. 35 (2020) 351–359.
[55] H.O. Smith, H. Arias-Pulido, D.Y. Kuo, T. Howard, C.R. Qualls, S.-J. Lee, C.F. Verschraegen, H.J. Hathaway, N.E. Joste, E.R. Prossnitz, GPR30 predicts poor survival for ovarian cancer, Gynecol. Oncol. 114 (2009) 465–471.
[56] A. Ignatov, T. Ignatov, C. Weissenborn, H. Eggemann, J. Bischoff, A. Semczuk, A. Roessner, S.D. Costa, T. Kalinski, G-protein-coupled estrogen receptor GPR30 and tamoxifen resistance in breast cancer, Breast Canc. Res. Treat. 128 (2011) 457–466.
[57] H.A. Aiad, M.M.A. Wahed, N.Y. Asaad, M. El-Tahmody, E. Elhosary, Immunohistochemical expression of GPR30 in breast carcinoma of Egyptian patients: an association with immunohistochemical subtypes, APMIS 122 (2014) 976–984.
[58] T. Yu, M. Liu, H. Luo, C. Wu, X. Tang, S. Tang, P. Hu, Y. Yan, Z. Wang, G. Tu, GPER mediates enhanced cell viability and motility via non-genomic signaling induced by 17β-estradiol in triple-negative breast cancer cells, J. Steroid Biochem. Mol. Biol. 143 (2014) 392–403.
[59] S. Heublein, D. Mayr, K. Friese, M.C. Jarrin-Franco, M. Lenhard, A. Mayerhofer, U. Jeschke, The G-protein-coupled estrogen receptor (GPER/GPR30) in ovarian granulosa cell tumors, Int. J. Mol. Sci. 15 (2014) 15161–15172.
[60] J. Steiman, E.A. Peralta, S. Louis, O. Kamel, Biology of the estrogen receptor, GPR30, in triple negative breast cancer, Am. J. Surg. 206 (2013) 698–703.
[61] M. Pupo, A. Bodmer, M. Berto, M. Maggiolini, P.-Y. Dietrich, D. Picard, A genetic polymorphism repurposes the G-protein coupled and membrane-associated estrogen receptor GPER to a transcription factor-like molecule promoting paracrine signaling between stroma and breast carcinoma cells, Oncotarget 8 (2017) 46728–46744.
[62] H.O. Smith, K.K. Leslie, M. Singh, C.R. Qualls, C.M. Revankar, N.E. Joste, E.R. Prossnitz, GPR30: a novel indicator of poor survival for endometrial carcinoma, Am. J. Obstet. Gynecol. 196 (2007) 386, e1–e9; discussion 386.e9-11.
[63] M. Sjöström, L. Hartman, D. Grabau, T. Fornander, P. Malmström, B. Nordenskjöld, D.C. Sgroi, L. Skoog, O. Stål, L.M.F. Leeb-Lundberg, M. Fernö, Lack of G protein-coupled estrogen receptor (GPER) in the plasma membrane is associated with excellent long-term prognosis in breast cancer, Breast Canc. Res. Treat. 145 (2014) 61–71.
[64] C. Weissenborn, T. Ignatov, N. Nass, T. Kalinski, S. Dan Costa, A.C. Zenclussen, A. Ignatov, GPER promoter methylation controls GPER expression in breast cancer patients, Canc. Invest. 35 (2017) 100–107.