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Association Of Endometriosis With Polymorphisms Of The Estrogen Receptor Alpha- And Progesterone Receptor Genes Revisited

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Abstract
Endometriosis is a chronic inflammatory disease characterized by increased estrogen activity and progesterone resistance. Genome wide association studies (GWAS) have implicated many single nucleotide polymorphisms (SNPs) in this polygenic inflammatory disease. Historically, however, gene-based approaches investigating a potential role for the estrogen receptor alpha (ESR1) and progesterone receptor (PGR) genes have produced mixed results, leading to the failure to detect a meaningful association. In this minireview we revisit this issue in light of our recent findings, showing that the ESR1 rs2234693 (PvuII) and rs9340799 (XbaI) polymorphisms were associated with endometriosis and that the condition was also associated with increased estradiol to progesterone ratio that was modified by the PGR PROGINS AluIns polymorphism.
Keywords: *Endometriosis, estrogen receptor alpha, ESR1, progesterone receptor, PGR, rs2234693, rs9340799, rs1042838, PROGINS, AluIns, PvuII, XbaI, CA19-9, GWAS.*

INTRODUCTION

Endometriosis is a hereditary condition defined as the growth of endometrium-like tissue outside the uterus, affecting an estimated 5-10% of women of reproductive age (1) and imposing great economic and healthcare burdens (2). The growth occurs mostly on the pelvic peritoneum, rectovaginal septum, and ovaries, and in rare cases in the abdominal wall, diaphragm, pleura, pericardium, and peripheral and central nervous systems (3, 4). Endometriosis is generally thought to result from retrograde menstruation of endometrial cells through the fallopian tubes to reach the abdomino-pelvic cavity where they settle and implant, thereby eliciting an inflammatory response that leads to the formation of scars and adhesions, pelvic pain, dysmenorrhea, dyspareunia, dysuria, and infertility (5, 6). A variant on this theory assumes that endometrial cells reach through the lymph vessels to cause endometriosis in lymphatic nodes and distal locations (7). Alternatively, endometriosis could be caused by coelomic metaplasia, i.e. the transformation of peritoneal epithelium lining under the influence of stimuli (8).

Current diagnosis depends mainly on surgical examination, which is expensive and could mis the disease altogether. Furthermore, the necessary infrastructure and skills for such a procedure could be lacking in undeveloped regions and regions with increased instability due to armed conflicts and/or natural disasters. There is, therefore, a growing need for simple, non-invasive diagnostic tools to facilitate early detection and treatment initiation. Despite great efforts, this has not been achieved yet, mainly because the disease mechanism is still far from clearly understood.

The contribution of genetic factors to the variation in endometriosis has been estimated to be 47%, with the other 53% attributed to unique environmental factors (9). However, endometriosis is a heterogenous condition, involving many genetic factors each with a small effect size (10, 11). This means that very large studies are required to identify genetic factors that can only explain a small fraction of disease variance.

Genetic studies of endometriosis have been performed both at single gene level (SNP analysis) (reviewed in 12) and genome level (genome wide association studies, GWAS) (13; 14). The former is based on assumptions about the etiology of the disease whereas the latter is agnostic to such assumptions. Both approaches have contributed to our current understanding of the underlying biology in endometriosis. In this minireview we focus on association studies of the estrogen receptor 1 alpha (ESR1) and

progesterone receptor (PGR) genes. We also discuss the relevance of progesterone resistance or estrogen dominance (defined here as higher estrogen to progesterone ratio) in light of these genetic changes.

GWAS studies of endometriosis

As of April 24, 2025, the GWAS Catalog (15) contained 598 unique single nucleotide polymorphisms (SNPs) that were associated with endometriosis in 19 curated studies (supplementary info). These associations are distributed across all human chromosomes with an average of 26 SNPs per chromosome and fall either within the coding sequence of, or very close to, 414 different genes (median distance to upstream gene is 48kb and to downstream gene is 61kb). Only half of these genes are protein coding, whereas the rest are either RNA-coding or correspond to pseudogenes. Only eight SNPs are predicted to alter the amino acid sequence of the translation product. This means that virtually all the SNPs that are associated with endometriosis affect regulatory expression mechanisms of target genes. Functionally (Figure 1), besides the expected steroid hormone receptor activity that culminate in DNA-transcriptional activity, and urogenital system development, the associated genes are implicated in cell junction assembly, cell and organ growth, glutamatergic neuron-neuron synapses, heart development, and epithelial tube morphogenesis, which is fundamental to the development of (branching-)organs like brain, lung, liver, kidney, and vasculature (17). It is noteworthy that at pathway level only six of these genes (MAPK9, CDC42, MAP3K4, MAP3K1, ITPR2, PLCB) function in the gonadotropin releasing hormone (GnRH) signaling pathway, which is the key regulator of the reproductive system (18). More often, the associated genes are linked to pathways that connect glycation processes (advanced glycation end products (AGE) and proteoglycans) to dysregulated transcription and inflammation. The top scoring of these pathways is the AGE-RAGE (receptor for AGE) signaling pathway, which activates NF-kB through multiple intracellular signaling pathways involving NADPH oxidase, protein kinase C, PI3K-Akt, and MAPKs (19-21). NF-kB promotes the expression of pro-inflammatory cytokines such as IL-1, IL-6 and TNF-alpha and a variety of atherosclerosis-related genes, including RAGE (22). RAGE, through JAK-STAT-, ERK1/2, and PI3K-Akt-dependent pathways, participates in cell proliferation. Collectively, the results of these intertwined signaling cascades lead to the common microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (heart disease, stroke and peripheral arterial disease) diabetes complications (23). These results identify endometriosis as a steroid-dependent inflammatory disease involving immune system dysfunction (24, 25).

Gene based approaches complement genome wide association studies

At gene level several candidate genes have been investigated for a potential association with endometriosis, including the estrogen and progesterone receptors, which were among the first to be investigated based on the steroid dependence of the condition.

In human, there are three known forms of the estrogen receptor (26), the estrogen receptor alpha encoded by the estrogen receptor 1 gene (ESR1) on chromosome 6 q25.1-q25.2, the estrogen receptor beta encoded by the estrogen receptor 2 gene (ESR2) on chromosome 14 q23.2-q23.3, and the membrane estrogen receptor encoded by the G-protein coupled estrogen receptor 1 gene (GPER1) on chromosome 7 p22.3. ESR1 and ESR2 are nuclear receptors that translate the estrogen signal mainly into slow genomic processes (27-29) whereas the rapid nongenomic effects of estrogen are mediated through GPER1 as well as some variants of ESR1 and ESR2 (29). Upon activation, ESR1 and ESR2 form homo- and heterodimers and bind to DNA to up-regulate or down-regulate target genes. However, ESR1 is the predominant form of the nuclear receptor in the endometrium (30) and possesses higher affinity for estrogen and related steroids (31). Therefore, ESR1 is postulated to be more relevant to estrogen-dependent diseases such as endometriosis.

Of the different variants of the ESR1gene, the two polymorphisms rs2234693 T>C (32, 33) and rs9340799 A>G (34, 35), which ablate, respectively, the PvuII and XbaI restriction sites in intron 1, have been investigated in the context of many steroid-dependent phenotypes, such as bone mineral density (36), breast cancer (37), prostate cancer (38), cardiovascular disease (39), and of course, endometriosis. The two polymorphisms, which could affect regulatory elements involved in transcription and/or stability of the ESR1 gene (40), are associated with estradiol (E2) levels: in postmenopausal women, the variant

alleles of rs2234693 and rs9340799 (respectively, C and G) were associated with an allele-dose-dependent increase in E2 (41, 42).

The progesterone receptor gene (PGR) on chromosome 11 q22.1 encodes two isoforms of the receptor (A and B) that are identical except for an additional 165 amino acids in the N-terminus of the B-isoform. The two isoforms exert reciprocal effects on the expression of target genes: isoform B activates target genes whereas isoform A inhibits both isoform B and target genes (43). Several PGR gene polymorphisms have been investigated, among which PROGINS, which consists of an insertion of an Alu element into intron G between exons 7 and 8 of isoform A of the PGR gene (AluIns) resulting in an increase of 306 bp in the gene product (44), a coding V660L in exon 4 (rs1042838), a silent H770H in exon 5 (rs1042839), and a coding S344T in exon 1 (rs3740753) (45-47). These variants, which are in strong to complete linkage disequilibrium, have been implicated in several sex hormone-related diseases such as recurrent abortions (48), uterine leiomyomas (49), migraine (50), and breast, uterine, and ovarian cancers (51). However, the functional consequences of these variants are largely unknown although some evidence suggests altered gene expression, reduced RNA stability, and reduced response to progesterone (52).The endometrium goes through tightly regulated cycles of growth and withering, characterized by specific alterations in estrogen and progesterone levels (53). During the first half of the period, the luminal layer of the endometrium gradually thickens in response to a gradually increasing estrogen, which induces, among others, genes involved in cell proliferation by binding to estrogen-response elements (ERE) (54) and other motifs in their promoter regions (reviewed in 55). This estrogen-induced activation of proliferative genes is mediated through the estrogen receptors that also induce the expression of the progesterone receptor (56). The activated progesterone receptor now redirects the estrogen-receptors mediated expression of genes towards differentiation instead of proliferation (57).Starting in 1999 with the study by Georgiou and colleagues (58), many groups have investigated the potential association between endometriosis and the sequence variants of the progesterone and estrogen receptors. Table 1 summarizes the findings from 25 association studies of the ESR1 PvuII polymorphism (rs2234693) (58-82), 21 of the ESR1 XbaI polymorphism (rs9340799) (61-71, 76, 77, 80-87), 9 of the PGR PROGINS AluIns polymorphism (88-96), and 4 of the PGR PROGINS rs1042838 polymorphism (85, 96-98). The results from these studies appear to be inconsistent but this is probably due to the typical small sample size, which is inherent to the labor-intensive, usually restriction-fragment length-based, PCR method to detect the polymorphism and the difficulty of obtaining a large patient group in which endometriosis is surgically confirmed. The error in estimating the sample-mean is inversely related to sample size. It follows that a set of small size experiments will have increased variance but, as the number of experiments is increased, the average estimate will approach the true average of the population. A meta-analysis of an adequate number of such experiments would provide a more accurate estimate of the population mean.In this context, several meta-analyses of association studies of endometriosis with ESR1 and PGR polymorphisms have been published but were mostly based on too few datasets (Table 1), and some were biased. For instance, the analyses in Guo et.al. (99) and Hu et. al.(100) misassigned the wild-type and variant forms of rs2234693 in the dataset from Georgiou et. al. (58), leading to the reported lack of association with endometriosis. Similarly, the analyses in Li et. al. (101) and Zhao et. al. (103), who also found no association between rs2234693 and endometriosis, were biased by the results from Kitawaki et. al. (60). In the latter study two reference groups were reported, a relatively large population-based control group (N=179) and a small disease-free group (N=27), consisting of patients with cervical cancer in situ but showing no other gynecological disease or patients with tubal occlusion or adhesion but without endometriosis, adenomyosis or leiomyomata. However, when the dataset from Kitawaki et. al. is excluded or when the larger population-based control group is used as reference a positive association is detected (for the allelic model, respectively, OR1.56(1.03-2.35) and OR1.66(1.08-2.54), in Li et. al. and OR=1.46(1.04-2.05) and OR=1.39(1.00-1.94) in Zhao et. al.). Also, gene variants that are in strong or complete linkage disequilibrium could still be functionally distinct and therefore it might be more appropriate to treat them as such, i.e. not pooling data from related variants (e.g. the ESR1 PvuII and XbaI variants or the PROGINS AluIns and rs1042838 variants).Using random effects model with inverse variance method to compare the odds ratio (OR) of the allelic model in the different studies listed in Table 1, we detect a

positive association between endometriosis and the ESR1 polymorphisms rs2234693 (OR=1.29, 95%CI=1.08-1.56) (Figure 2A) and rs9340799 (OR=1.27, 95%CI=1.05-1.55) (Figure 2B) but not with the PGR PROGINS variants AluIns (OR=1.08, 95%CI=0.75-1.56) (Figure 2C) and rs1042838 (OR=0.97, 95%CI=0.83-1.13) (Figure 2D). The data in Figure 2 also show that there is significant heterogeneity in the rs2234693, rs9340799, and PROGINS AluIns datasets (average I2=73%) indicating inconsistent effects in magnitude and/or direction, which could be related to ethnic differences or sample size. Sensitivity analysis, in which the studies are sequentially removed to determine the influence of each study on the pooled OR, shows that the pooled OR is not significantly altered by the removal of any single study (Figure 3). Notably, the ESR1 region 6q25.1-25.2 contains 11 different SNP's that have been linked with endometriosis in five different large-scale GWAS studies (106-110) whereas the PGR region 11q22.1 was significantly associated with endometriosis in only one small-size GWAS study (111). Given the steroid-dependence of the reproductive tract it is highly likely that genetic variants in the progesterone receptor are also of influence on the development of related conditions such as endometriosis but, with respect to the PROGINS variants, the current evidence does not support a consistent effect. These results are in complete agreement with our recent findings (82, 96). Besides confirming the association between endometriosis and the ESR1 polymorphisms rs2234693 and rs9340799, we showed that the two polymorphisms were also associated with elevated serum levels of estradiol and the inflammatory marker CA19-9 such that the two polymorphisms and the two serum markers could identify endometriosis with 91% accuracy (sensitivity=0.92 (95%CI=0.80-0.98), specificity= 0.74 (95%CI=0.60-0.85)) (82). And as indicated above (Table 1 and Figures 2C and 2D), endometriosis was not associated with increased frequencies of the PGR PROGINS variants. Instead, the PROGINS AluIns variant was more frequently detected in the control group and was associated with a reduced odds ratio of endometriosis and higher estradiol to progesterone ratios that decreased with increasing frequencies of ESR1 gene polymorphisms (96 and Figure 4). Notably, the frequency of the rs1042838 variant, which is in complete linkage disequilibrium with the AluIns variant, had a much weaker effect on the risk of endometriosis, suggesting that the two variants are functionally distinct. Collectively, these results suggest that endometriosis is associated with a hormonal imbalance that could be related to the ESR1 and PGR gene variants.

The estrogen-progesterone ratio and endometriosis

Estrogen causes cell proliferation whereas the main effect of progesterone is to increase cell differentiation and maturation while inhibiting proliferation (112). These differential effects can easily be correlated with the two phases of the menstrual cycle, the proliferative follicular, and the secretive luteal, where estrogen predominates in the former and progesterone in the latter. At receptor level, estrogen (estradiol) leads to a general increase of estrogen and progesterone receptors expression whereas a combination of estrogen and progesterone downregulates receptor expression (113). In this context it is important to note that the progesterone receptor is not merely a target gene of estrogen but is also a modifier of estrogen-mediated transcriptional programs: PGR binds to ESR1 to redirects downstream transcription programs, inducing a switch from a proliferative towards a more differentiative state (57). Balanced estrogen and progesterone actions are important to the health of the women's reproduction system (114) and dysregulation of this balance is implicated in many uterine pathologies including endometriosis, infertility, endometrial cancer, uterine leiomyoma, and recurrent pregnancy loss (115).

Progesterone resistance

Endometriosis is characterized by disturbed hormone balance, often termed progesterone resistance or estrogen dominance, i.e. increased estrogen levels at lower levels of- and decreased sensitivity to progesterone (116). The underlying mechanism is not fully understood but may include disturbed PGR signaling, chronic inflammation, epigenetic alterations, altered gene expression, and environmental toxins (116-120).The two isoforms of PGR, A and B, have similar steroid-binding affinities but exert opposing transcriptional activities such that the B isoform functions as activator (e.g. enhances expression of target genes) and the A isoform functions as a repressor, among others of the B-isoform transcriptional activity. The response to progesterone is inversely related to the PGR A to B ratio and the current consensus is that progesterone resistance reflects a PGR A dominant state (115, 119, 121-123). However, as to the cause of progesterone resistance in endometriosis, the underlying mechanism is not clear yet.As

noted above, estrogen regulates the expression of PGR A. The promoter region of PGR A contains a half-ERE/Sp1 binding site, where ligand-activated ESR1 and additional coregulatory proteins and transcription factors bind to enhance the expression of the receptor (124). In addition, several functional binding sites up to hundreds of kilobases upstream and downstream of the PGR-transcription start site associate with the latter in an estrogen-dependent manner (125, 126), thereby creating a chromatin loop to bind and tether ESR-containing transcription complexes to the promoter region of PGR (127). In turn, PGR modulates ESR1 expression and co-regulates downstream target genes (115, 128, 129).In endometriosis the expression of ESR1 is downregulated whereas the expression of ESR2 (estrogen receptor beta) is upregulated (130-133). Increased expression of ESR2, and PGR A, is associated with hypomethylation of their promoter regions (131, 134) and hypermethylation of the promoter regions of the alternative receptors, ESR1 (132) and PGR B (134, 135). In endometriotic lesions, histones acetylation, which decreases DNA compactness and increases gene activity, was also reduced at the promoter region of many genes known to be downregulated in endometriosis (e.g., HOXA10, ESR1, CDH1, and p21 (WAF1/Cip1) and increased at the promoter region of stereoidogenic factor 1 (SF1), correlating with its reported high expression in lesions (136). SF1, together with the transcription factor GATA6, are sufficient to induce the estradiol synthetic cascade in endometriosis (137). These and other epigenetics findings reviewed in (138) have reshaped our understanding of endometriosis, implicating differential DNA methylation, acetylation and miRNA control thereof in chromatin organization, with consequences for gene expression (132). While essential to our understanding of endometriosis as a hereditary estrogen-dependent, progesterone-resistant chronic inflammatory disease, these insights also manifest the current gap in our understanding of the underlying disease mechanism for these epigenetic phenomena are basically sequence independent and must therefore be reconnected to sequence variation that could be specific for a single gene (e.g. ESR1 and PGR polymorphisms, Figure 4).To summarize, many genes dysregulated in endometriosis are linked to inflammatory and immune responses. GWAS studies have elucidated many pathways linking endometriosis to steroid metabolism and inflammatory and immune responses whereas gene-based approaches have provided insights in the potential association with specific sequence variants of the progesterone and estrogen receptors. Contrary to previous analyses and based on meta-analysis of data from more than 20 studies including recent data from our group, we provide evidence for a positive association between endometriosis and the ESR1 rs2234693 (PvuII, T>C) and rs9340799 (XbaI, A>G) polymorphisms. Our analysis also shows that the PGR PROGINS AluIns and rs1042838 polymorphisms are not associated with increased risk of endometriosis, which is in line with previous analyses. However, the PROGINS AluIns polymorphism could modify the risk of endometriosis induced by the ESR1 polymorphisms. Recent findings have provided a wealth of information regarding the genome-wide epigenetic changes in endometriosis that appear to link progesterone resistance with altered programs of DNA methylation and acetylation. Additional research is needed to confirm these results and to show how sequence variants in one or a few genes cause such profound epigenetic changes.

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Legends

Table 1: Summary of results (sample size, genotype and allele frequencies, odds ratio (OR), 95% confidence interval (95%CI), and chi square p value) from association studies of endometriosis and the ESR1 rs2234693 polymorphism (PvuII) (58-82), the ESR1 rs9340799 polymorphism (XbaI) (61-71, 76, 77, 80-87), the PGR PROGINS AluIns polymorphism (88-96), and the PGR PROGINS rs1042838 polymorphism (85, 96-98). Kitawaki: population-based control group; Christofolini (A): infertile women without endometriosis as control; Christofolini (B): fertile women without endometriosis as control. van Kaam (A): gynecological patients without endometriosis as control; van Kaam (B): population-based control; Farhood[1]: (82); Farhood[2]: (96). Checkmark (✓): included in the corresponding meta-analysis (column header; Guo 2006 (99), Hu 2012 (100), Li 2012 (101), Pabalan 2014 (102), Zhao 2016 (103), Carneiro 2019 (104), Mear 2020 (105)). Exclamation mark (!): caution should be exerted: Guo 2006 (99) and Hu 2012 (100) misassigned the wild-type and variant forms of rs2234693 in the dataset from Georgiou 1999 (58); Li et. al. (101) and Zhao et. al. (103) used the small endometriosis-free cervical cancer- or other gynecological patients (N=27) as control instead of the larger population-based group (N=179); Zhao et al considered the C allele of rs2234693 as the wild-type allele. Country codes: Greece (GR), China (CN), Japan (JP), Korea (KR), Italy (IT), Germany (DE), India (IN), Estonia (EE), USA (US), Brazil (BR), Iraq (IQ), Indonesia (ID), Austria (AT), Iran (IR), Netherlands (NL). Inter: International.

Figure 1: GO analysis (A) and Pathway analysis (B) of endometriosis associated genes identified by genome-wide association studies (GWAS). As of April 24, 2025, the GWAS catalog (15) contained 598 unique SNP's that were associated with endometriosis in 19 curated studies. The SNPs were mapped to 416 unique genes, i.e. SNP-containing genes or nearest upstream and downstream genes if the SNP is intergenic. GO and Pathway analyses of the complete set of 416 genes were performed with the GO Pathway Enrichment Analysis module from SRplot (16), accessed 26 April 2025. The figure depicts the 10 top scoring terms in each category. All significant Pathway and GO terms are provided in the accompanying supplementary info.

Figure 2: Forest plots of individual and total odds ratios (OR) of the association between endometriosis and (A) the ESR1 res2234693 T>C polymorphism, (B) the ESR1 rs9340799 A>G polymorphism, (C) the PGR PROGINS AluIns polymorphism, and (D) the PGR PROGINS rs1042838 polymorphism, based on the allelic models of the studies summarized in Table 1. The weight of each study is indicated by the size of corresponding square. The horizontal lines represent the 95% confidence intervals (CI). Total OR is represented by a black diamond shape, the length of which indicates the 95% CI.

Figure 3: Sensitivity analysis of total odds ratios for the associations in Figure 2. Each individual OR corresponds to the total OR calculated as in Figure 2 but with exclusion of the named study. The total ORs did not change significantly when any single study was omitted, indicating reliability and robustness of the analysis.

Figure 4: E2/progesterone ratio is associated with the ESR1 polymorphism and modified by the PGR PROGINS AluIns polymorphism. A: The samples in (96) sorted ascendingly according to the

E2/progesterone ratio, classified in PROGINS AluIns wt and variants groups, and subclassified according to the number of ESR1 rs9340799 variant alleles. With increasing ESR1 rs9340799 variant allele dose, the E2/progesterone ratio increased in the absence of the PROGINS AluIns polymorphism (wt), and decreased in the presence of the PROGINS AluIns polymorphism. The trend is indicated by the 2nd-order fit line (red line). The PROGINS rs1042838 polymorphism had a much weaker effect (96). B: the samples in A, sorted ascendingly according to the E2/progesterone ratio, and separated in control and endometriosis groups. Endometriosis is associated with higher E2/progesterone ratio and increased frequency of the ESR1 rs9340799 variant allele (allelic model OR=6.15, 95%CI=3.31-11.40, p<0.0001), whereas the control was associated with lower E2/progesterone ratio and increased frequency of the PGR PROGINS AluIns variant allele (allelic model OR=2.53, 95%CI=1.09-5.87, p=0.03). Similar results were obtained for the combination of ESR1 rs2234693 and PGR PROGINS AluIns polymorphisms (96).

Table 1

							Case					Control							Meta-analysis						
							Genotype			Allele		Genotype			Allele											
	Source	Year	Country	Reference	# Case	# Control	wt/wt	wt/var	var/var	wt	var	wt/wt	wt/var	var/var	wt	var	OR (95% CI)	p	Guo 2006	Hu 2012	Li 2012	Pabalan 2014	Zhao 2016	Carneiro 2019	Mear 2020
ESR1 rs2234693 (PvuII)	Georgiou	1999	GR	58	57	57	2	28	27	32	82	16	26	15	58	56	2.65 (1.53-4.60)	0.001	✓!	✓!	✓		✓!		
	Fu	2001	CN	59	50	50	22	22	6	66	34	17	23	10	57	43	0.68 (0.39-1.21)	0.192			✓		✓!		
	Kitawaki	2001	JP	60	109	179	36	59	14	131	87	65	71	43	201	157	0.85 (0.60-1.20)	0.353	✓	✓	✓!		✓!		✓
	Fu	2002	CN	61	63	41	25	26	12	76	50	27	11	3	65	17	2.52 (1.32-4.78)	0.005			✓		✓!		
	Wang	2004	JP	62	121	172	48	49	24	145	97	47	88	37	182	162	0.75 (0.54-1.05)	0.098	✓	✓	✓		✓!		
	Ding	2005	CN	63	85	105	29	49	7	107	63	40	53	12	133	77	1.02 (0.67-1.55)	0.937			✓		✓!		
	Dong	2005	CN	64	65	107	42	16	7	100	30	46	49	12	141	73	0.58 (0.35-0.95)	0.031			✓		✓!		
	Huang	2005	CN	65	85	90	23	49	13	95	75	42	39	9	123	57	1.70 (1.10-2.64)	0.017			✓		✓!		
	Kim	2005	KR	66	180	165	73	84	23	230	130	66	67	32	199	131	0.86 (0.63-1.17)	0.332			✓		✓!		✓
	Song	2005	CN	67	49	50	19	21	9	59	39	16	22	12	54	46	0.78 (0.44-1.36)	0.378			✓		✓!		
	Luisi	2006	IT	68	13	48	0	6	7	6	20	15	27	6	57	39	4.87 (1.79-13.23)	0.002			✓				
	Renner	2006	DE	69	98	98	58	20	20	136	60	53	29	16	135	61	0.97 (0.64-1.50)	0.913		✓	✓		✓!		
	Shan	2006	CN	70	40	52	16	15	9	47	33	19	24	9	62	42	1.04 (0.57-1.88)	0.906			✓		✓!		
	Hsieh	2007	CN	71	112	110	27	68	17	122	102	60	44	6	164	56	2.45 (1.64-3.66)	<0.0001		✓	✓		✓!		
	Zhang	2007	CN	72	78	81	31	32	15	94	62	48	29	4	125	37	2.23 (1.37-3.63)	0.001			✓		✓!		
	Govindan	2009	IN	73	110	115	5	32	73	42	178	29	32	54	90	140	2.72 (1.78-4.18)	<0.0001		✓	✓		✓!		
	Xie	2009	CN	74	214	160	62	122	30	246	182	64	76	20	204	116	1.30 (0.97-1.75)	0.083		✓	✓		✓!		
	Li	2010	CN	75	107	80	31	61	15	123	91	32	38	10	102	58	1.30 (0.85-1.98)	0.221			✓				
	Sun	2010	CN	76	60	56	18	33	9	69	51	22	23	11	67	45	1.10 (0.65-1.86)	0.720			✓		✓!		
	Chen	2011	CN	77	56	78	25	21	10	71	41	31	38	9	100	56	1.03 (0.62-1.71)	0.905			✓		✓!		
	Lamp	2011	EE	78	150	199	35	76	39	146	154	59	102	38	220	178	1.30 (0.97-1.76)	0.084		✓			✓!		
	Trabert	2011	US	79	255	558	81	129	45	291	219	173	280	105	626	490	0.96 (0.78-1.19)	0.716					✓!		
	Gu	2012	CN	80	57	106	20	28	9	68	46	33	63	10	129	83	1.05 (0.66-1.67)	0.833					✓!		
	Paskulin	2013	BR	81	98	134	26	54	18	106	90	38	69	27	145	123	1.00 (0.69-1.45)	0.996					✓!		✓
	Farhood[1]	2025	IQ	82	50	50	5	29	16	39	61	31	15	4	77	23	5.24 (2.83-9.69)	<0.0001							
	Fu	2002	CN	61	63	41	30	24	9	84	42	24	14	3	62	20	1.55 (0.83-2.90)	0.170			✓		✓		
	Wang	2004	JP	62	122	171	78	38	6	194	50	103	56	12	262	80	0.84 (0.57-1.26)	0.405			✓		✓		
	Ding	2005	CN	63	85	105	51	31	3	133	37	53	44	8	150	60	0.70 (0.43-1.11)	0.131			✓		✓		
	Dong	2005	CN	64	65	107	41	19	5	101	29	76	26	5	178	36	1.42 (0.82-2.45)	0.209			✓		✓		
	Huang	2005	CN	65	85	90	42	38	5	122	48	50	36	4	136	44	1.22 (0.76-1.96)	0.421			✓		✓		
	Kim	2005	KR	66	180	165	125	50	5	300	60	112	45	8	269	61	0.88 (0.60-1.31)	0.531			✓		✓		
	Song	2005	CN	67	49	50	27	17	5	71	27	21	25	4	67	33	0.77 (0.42-1.42)	0.405			✓		✓		
	Luisi	2006	IT	68	13	48	1	6	6	8	18	22	22	4	66	30	4.95 (1.94-12.65)	0.001			✓			✓	

Table 1 (continued)

ESR1 rs9340799 (Xt	Renner	2006	DE	69	98	98	62	25	11	149	47	60	26	12	146	50	0.92 (0.58-1.46)	0.726			✓		✓	✓	
	Shan	2006	CN	70	40	52	19	18	3	56	24	29	18	5	76	28	1.16 (0.61-2.22)	0.646			✓		✓	✓	
	Hsieh	2007	CN	71	112	110	30	64	18	124	100	37	71	2	145	75	1.56 (1.06-2.29)	0.023			✓		✓	✓	
	Xie	2009	CN	74	214	160	112	92	10	316	112	110	40	10	260	60	1.54 (1.08-2.19)	0.018			✓		✓	✓	
	Li1	2010	CN	75	107	80	56	46	5	158	56	55	20	5	130	30	1.54 (0.93-2.53)	0.093			✓			✓	
	Sun	2010	CN	76	60	56	41	18	1	100	20	34	21	1	89	23	0.77 (0.40-1.50)	0.449			✓		✓	✓	
	Chen	2011	CN	77	56	78	36	18	2	90	22	44	32	2	120	36	0.81 (0.45-1.48)	0.501			✓		✓	✓	
	Trabert	2011	US	79	256	558	123	105	28	351	161	254	244	60	752	364	0.95 (0.76-1.19)	0.639					✓	✓	
	Gu	2012	CN	80	57	106	33	19	5	85	29	64	40	2	168	44	1.30 (0.76-2.23)	0.334					✓	✓	
	Paskulin	2013	BR	81	98	134	27	55	16	109	87	71	54	9	196	72	2.17 (1.47-3.21)	0.000					✓	✓	
	Eldafira	2021	ID	86	83	76	22	33	28	77	89	32	28	16	92	60	1.77 (1.13-2.77)	0.012							
	Proestling	2024	AU	87	149	86	63	64	22	190	108	31	43	12	105	67	0.89 (0.61-1.31)	0.558							
	Farhood[1]	2025	IQ	82	50	50	10	14	26	34	66	33	10	7	76	24	6.15 (3.31-11.4)	<0.0001							
PGR AluIns	Wieser	2002	AT	88	95	107	65	27	3	157	33	91	15	1	197	17	2.44 (1.31-4.54)	0.005		✓		✓			✓
	Lattuada	2004	IT	89	131	127	89	39	3	217	45	100	26	1	226	28	1.67 (1.01-2.78)	0.047		✓		✓			✓
	De Carvalho	2007	BR	90	121	281	85	35	1	205	37	221	60	0	502	60	1.51 (0.97-2.35)	0.067		✓		✓			
	Govindan	2007	IN	91	100	108	95	5	0	195	5	102	6	0	210	6	0.90 (0.27-2.99)	0.860		✓		✓			
	Gimenes	2010	BR	92	148	179	139	8	1	286	10	158	19	2	335	23	0.51 (0.24-1.09)	0.081				✓			
	Christofolini (A)	2011	BR	93	201	80	181	19	1	381	21	68	11	1	147	13	0.62 (0.30-1.28)	0.197							✓
	Christofolini (B)	2011	BR	93	201	206	181	19	1	381	21	181	22	3	384	28	0.76 (0.42-1.35)	0.347		✓		✓			
	Costa	2011	BR	94	54	45	36	17	1	89	19	38	5	2	81	9	1.92 (0.82-4.49)	0.131		✓		✓			✓
	Ataei	2016	IR	95	86	86	73	9	4	155	17	75	10	1	160	12	1.46 (0.68-3.16)	0.334							
	Farhood[2]	2025	IQ	96	50	50	42	7	1	91	9	34	12	4	80	20	0.40 (0.17-0.92)	0.031							
PGR rs1042838	Van Kaam (A)	2007	NL	97	70	101	46	21	3	113	27	74	26	1	174	28	1.48 (0.83-2.65)	0.181				✓			✓
	Van Kaam (B)	2007	NL	97	70	93	46	21	3	113	27	66	24	3	156	30	1.24 (0.70-2.20)	0.458				✓			
	Near	2011	Inter	98	343	5339	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.94 (0.76-1.16)	0.560							
	Trabert	2011	US	79	256	557	189	58	10	436	78	389	149	19	927	187	0.89 (0.67-1.18)	0.413				✓			
	Farhood[2]	2025	IQ	96	50	50	38	8	4	84	16	36	11	3	83	17	0.93 (0.44-1.96)	0.849							

Figure 1

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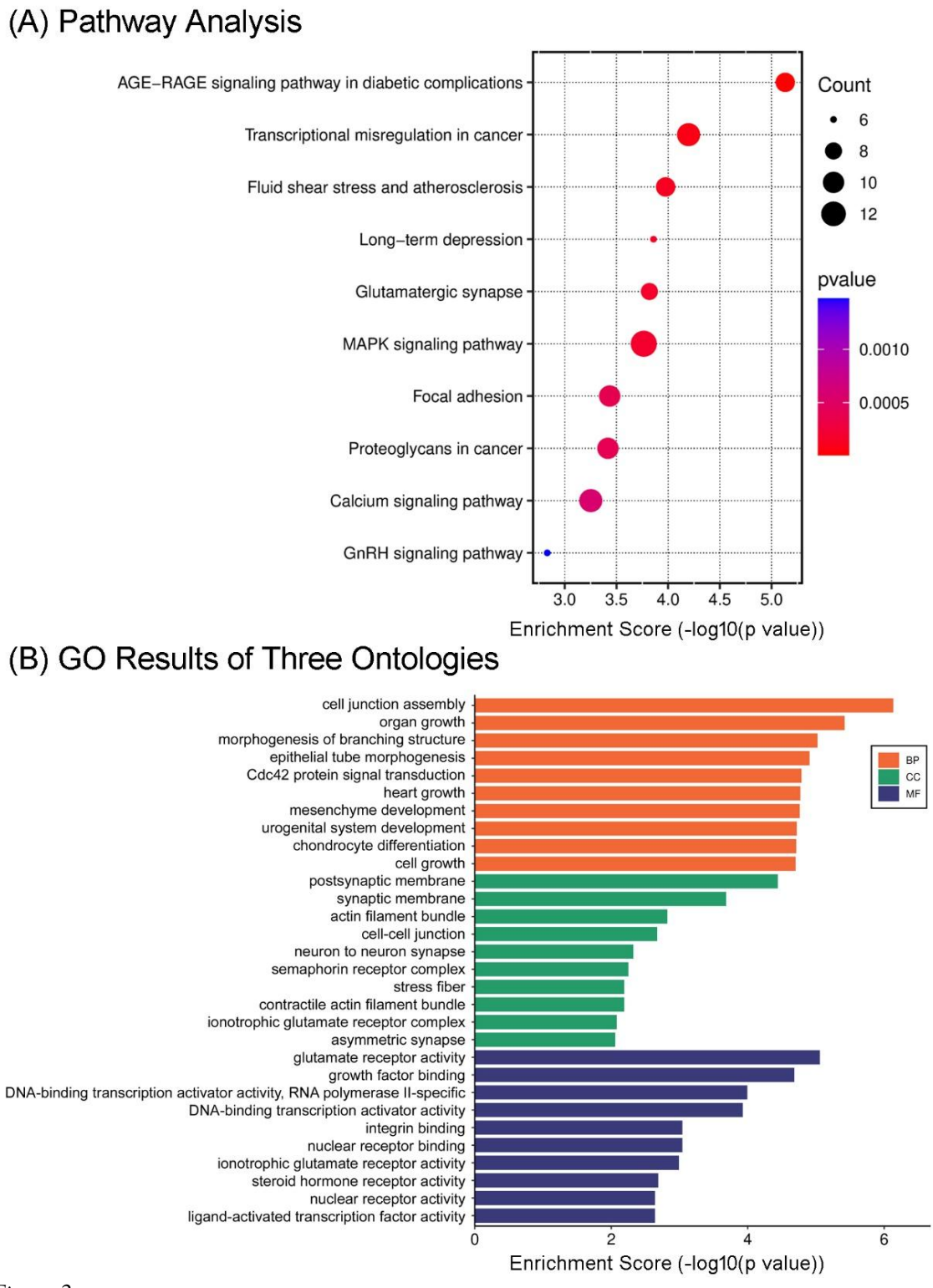

Figure 2

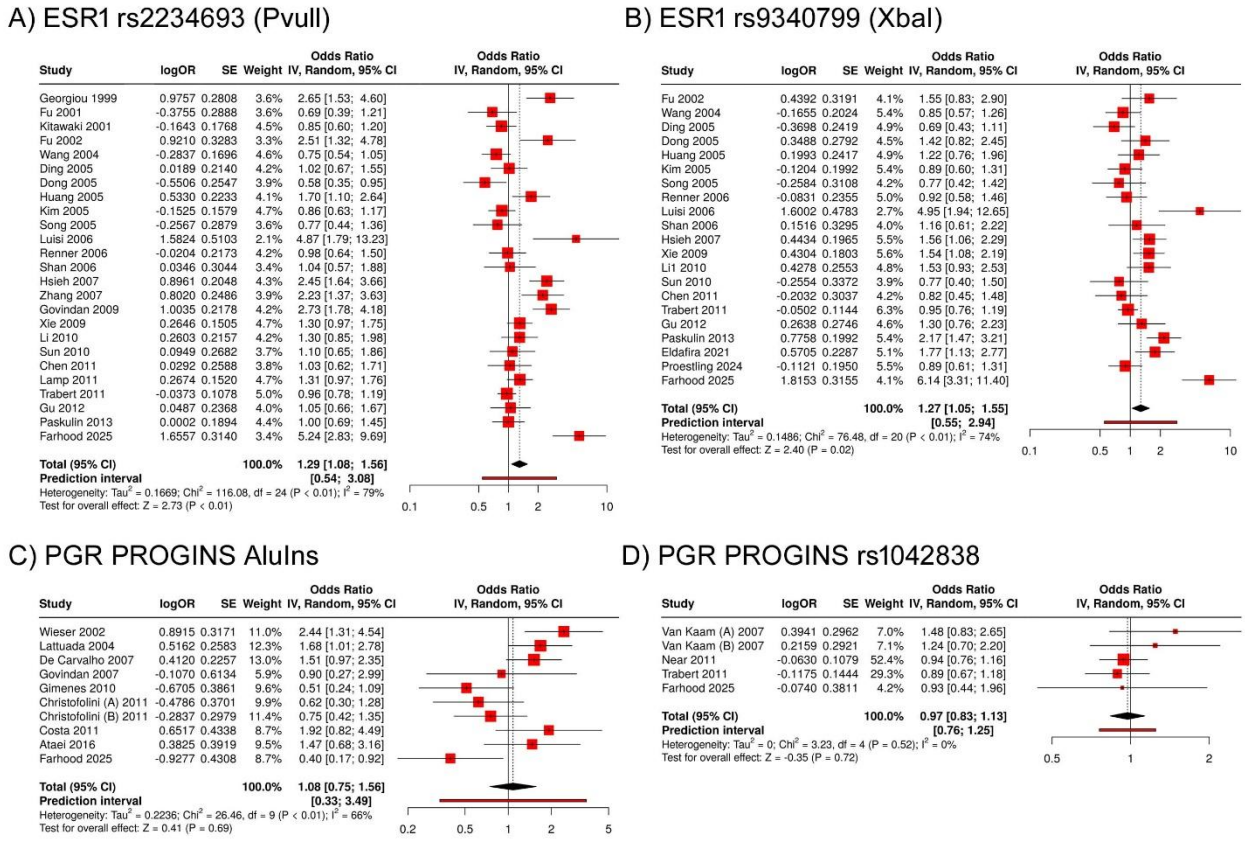
A) ESR1 rs2234693 (PvuII)
B) ESR1 rs9340799 (XbaI)
C) PGR PROGINS AluIns
D) PGR PROGINS rs1042838

Figure 3

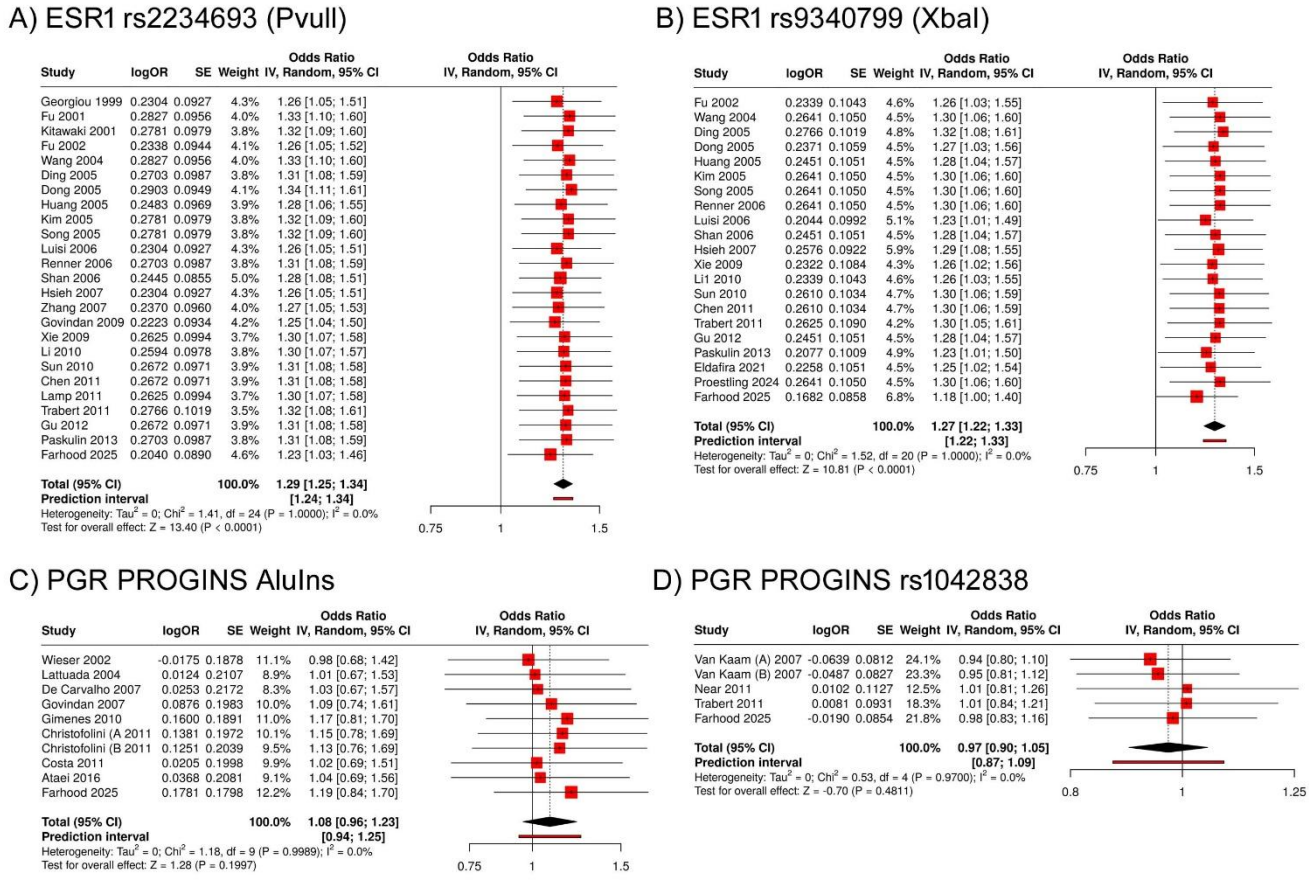
A) ESR1 rs2234693 (PvuII)
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Figure 4