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The Progesterone Receptor PROGINS Polymorphism Modifies The Estradiol To Progesterone Ratio And The Risk Of Endometriosis

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Abstract
Endometriosis is a multifactorial steroid-dependent hereditary disease associated with chronic pain, inflammation and a high degree of disability. The condition is associated with high estrogen production and low progesterone levels. Genetic variations in both the estrogen and progesterone receptors are thought to contribute to the disease. Genetic investigations of both types of receptors have thus far produced mixed results. We have recently shown that endometriosis is associated with the ESR1 gene polymorphisms rs9340799 and rs2234693 and higher serum levels of estradiol. In the current study we extend these findings further by showing that these polymorphisms are associated with increased estradiol to progesterone ratio and increased risk of endometriosis, both of which are attenuated by the progesterone receptor PROGINS polymorphism.
Keywords: Endometriosis, Progesterone Receptor, ESR1, PGR, progesterone, rs9340799, rs2234693, rs1042838, PROGINS, AluIns, C-reactive protein, Interleukin 6.

INTRODUCTION

Endometriosis is a chronic, estrogen-dependent pelvic inflammatory disease characterized by extra-uterine growth of endometrial tissue. This hereditary condition usually manifests in the formation of scars and adhesions, pelvic pain, dysmenorrhea, dyspareunia, dysuria, and infertility [1]. The condition is very common, affecting 5-10% of women of reproductive age [2], with great economic and healthcare burdens.The unknown etiology of endometriosis is believed to involve many genetic factors with small effect size (Fung and Montgomery, 2018; Vassilopoulou *et al.*, 2019). Endometriosis is characterized by elevated levels of estrogen production and lower progesterone levels and the estrogen and progesterone receptors were among the first candidate genes to be evaluated for evaluated risk of single-nucleotide polymorphism (SNP)-associated endometriosis. The actions of estrogen are mediated through the estrogen receptors ESR1 and ESR2 whereas two isoforms of the progesterone receptor PGR-A and PGR-B mediate the actions of progesterone. The latter are two ligand-dependent transcription factors that are identical except for an additional 165 amino acids in the N-terminal of the B isoform. Ligand-binding is followed by dimerization, translocation to the nucleus, and binding to progesterone-response elements in the promoter regions of target genes to modulate their expression. The two receptors have distinct functional activities. In the uterus , the A isoform is required to antagonize the proliferative effects of the B isoform and estrogen.PGR gene polymorphisms that alter the PGR-A to PGR-B ratio could modify the risk for endometriosis. Several PGR gene polymorphisms have been investigated, among which PROGINS that involves the 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 (6). Further characterization of this insertion lead to the discovery of three single nucleotide polymorphisms (SNPs) in strong to complete linkage disequilibrium with the insertion, a coding V660L in exon 4 (rs1042838), a silent H770H in exon 5 (rs1042839), and a coding S344T (rs3740753) (7-9). Romano et al. showed that the Alu insertion in intron G affects gene expression and RNA stability whereas the V660L substitution (rs1042838) reduces the response to progesterone (10). The PROGINS polymorphism has been implicated in several sex hormone-related diseases such as recurrent abortions (11), uterine leiomyomas

(12), migraine (13), and breast, uterine, and ovarian cancers (14). With respect to endometriosis results have been inconsistent. Whereas earlier studies suggested an association with endometriosis (15-18) this was not confirmed by later studies (19-25).

Here we report a case-control study, in which we investigated the relation between endometriosis, the PGR PROGINS variants AluIns and rs1042838, the ESR1 variants rs9340799 and rs2234693, and the estradiol to progesterone ratio. Our results suggest that the PROGINS AluIns polymorphism could modify both the estradiol to progesterone ratio and the risk of endometriosis. The AluIns variant was detected in 20% of control alleles and 9% of patients alleles (OR= 2.53, 95%CI=1.09-5.87, p=0.03). Increased frequency of the ESR1 variants is associated with increasing estradiol to progesterone ratio and elevated risk of endometriosis and that both are attenuated in the presence of the PROGINS AluIns variant.

MATERIALS AND METHODS

Sampling

This is a case-control study performed at the Department of Biochemistry, College of Medicine University of Babylon and Babel Teaching Hospital for Maternity and Children in Hilla city, Iraq in the period January-August 2024. The study involved a total of 50 patients with endometriosis as determined by laparoscopy (mean age: 39.3 ± 4.1) and 50 non-endometriosis controls (mean age: 41.6 ±3.5). The latter group consisted of women who visited the hospital for annual controls and patients who did not possess symptoms of endometriosis. Patients with all types of cancer, diabetes, renal and liver diseases were excluded. The study was approved by the institutional ethics committee. All participants provided informed consent prior to collection of samples.

Measurements

From each subject three ml venous blood was withdrawn in a serum separation gel tube (AFCO, Jordan), centrifugated at 3000 rpm for 20 min, and the separated sera were divided in 2 aliquots that were kept at -20 °C until further analysis. Serum levels of progesterone, CRP and IL-6 were measured by electrochemiluminescence (Cobas 6000) according to manufacturer's protocol.

SNP analysis was performed at ASCo Learning Center, Baghdad, Iraq. Unless otherwise stated, all materials used in the SNP analysis were from Promega, USA. From each subject two ml venous blood was withdrawn in an EDTA tube (AFCO, Jordan), mixed on a shaker at room temperature for ten minutes and frozen at -20 °C until further analysis. Frozen blood samples were thawed and mixed for 15 minutes at room temperature. Genomic DNA was isolated from thawed blood sample using ReliaPrep™ Blood gDNA Miniprep System as per manufacturer's protocol. Isolated DNA was quantified using Quantus Fluorometer (Promega, USA). The PGR gene polymorphisms were investigated by PCR using the following primers (Macrogen, Korea): PROGINES-F GGCAGAAAGCAAAATAAAAAGA, PROGINES-R AAAGTATTTTCTTGCTAAATGTC, rs1042838-F: TGACCAGCACGGGTATAA, rs1042838-R: GACCACTTGACTACTGAAAGAA. PCR amplification was performed with 20µl volumes containing 10µl GoTaq® Green Master Mix (2X); 1µl of each primer (10pmol); 6µl nuclease free water and 2µl of template DNA. PCR cycling was performed with PCR Express (Thermal Cycler, Veriti, USA) with the following program: denaturing at 94oC for 4 min followed by 30 cycles of denaturation at 94°C for 30 sec, annealing at 55°C for 30 sec, and extension at 72°C for 45 sec. A final extension incubation of 7 min at 72°C was included, followed by a 10 min incubation at 4°C to stop the reactions. One fifth of the PCR products were separated on agarose gel and visualized with ethidium bromide staining. The PCR products corresponding with the rs1042838 polymorphism were sequenced using Applied Biosystems 3730XL DNA analyzer (Macrogen, Korea).

Statistical analysis

Odds ratios were calculated with MedCalc (https://www.medcalc.org/calc/chisquared-2way.php). 2x3 Fisher's exact tests were calculated at https://www.cog-genomics.org/software/stats. Meta-analysis was performed at https://metaanalysisonline.com. Two-tailed t-test was used to compare the means of serum levels of progesterone, CRP and IL-6. Results are reported as average ± SE. A $p<0.05$ was defined as statistically significant.

RESULTS

Genetic analysis

In this work we investigated the two PROGINS variants AuIns and rs1042838 to determine their frequencies in the studied population and whether they have similar effects. The frequency of the rs1042838 variant was determined by DNA sequencing of the PCR-amplified gene products whereas the frequency of the PROGINS AluIns variant was determined by PCR, utilizing the specified primers that produce a 479bp fragment for the AluIns variant and a 159bp fragment for the wild-type variant (Fig1 A). At both the genotype and allele levels, the rs1042838 variant was comparable between the patient and control groups (Table 1). In contrast, the AluIns variant was detected in eight patient samples (one homozygous and seven heterozygous) and 16 control samples (four homozygous, and 12 heterozygous), suggesting that this variant was more common in the control group.

Serum levels of progesterone, CRP, and IL-6

The measured serum levels of progesterone (ng/mL), CRP (mg/dL), and IL-6 (pg/mL), divided in ascending quintiles, are summarized in Table 4. In each quintile the average value of the control and the endometriosis samples were calculated and compared by a two-sided t-test. In this way subtle differences could be detected that otherwise would be obscured by the variance in this low-size study. The results shown in Table 4 indicate that progesterone tended to be decreased in all endometriosis samples (4A), CRP was increased in about 60% of endometriosis samples (4B), and IL-6 tended to be decreased in most endometriosis samples (4C). We found no relation between the measured levels of progesterone, CRP, and IL-6 and the two PROGINS variants AuIns and rs1042838.

The effect of the PROGINS variants

We have recently shown, in the same patient and control groups used in this study, that endometriosis is associated with the two ESR1 gene polymorphisms rs9340799 and rs2234693 and that increased frequencies of these polymorphisms are associated with elevated estradiol levels. We wondered whether there is a relation between the increased levels of estradiol reported earlier, the lower levels of progesterone reported in this study and whether such a relation is influenced by the ESR1 and PGR gene variants. To this end, we compared the estradiol to progesterone ratio in all samples stratified by the gene variant. The results, summarized in Figure 2 for samples stratified by the rs9340799 and AluIns gene variants, show that in the absence of the PGR variant (sample subgroups 1-3), the estradiol to progesterone ratio increases with increasing frequency of the ESR1 variant rs9340799: the average estradiol to progesterone ratio was 72.4 in the wt/wt group, 99.4 in the heterozygous wt/var group, and 245 in the homozygous var/var group. The increase in estradiol to progesterone ratio was accompanied by a 5.8 increase in the odds ratio of endometriosis in the wt/var group (p=0.019) and a 22.2 increase in the var/var group (p=0.0001). However, in the presence of at least one copy of the PROGINS variant (groups 4 to 6) the estradiol to progesterone ratio decreased with increasing copy number of the ESR1 gene variant whereas the odds ratios of endometriosis were reduced. Supplementary figures 1-3 summarize the results obtained with the other combinations (i.e. rs9340799 and rs1042839, rs2234693 and AluIns, and rs2234693 and rs1042839).

DISCUSSION

ROGINS is a compound polymorphism of the PGR gene that consists of a 320-bp PV/HS-1 *Alu* repeat insertion (AluIns) in intron G, downstream of exon 7, and 2 SNPs: a synonymous His770His (rs1042839) and a coding Val660Leu (rs1042838). These three gene variants are in strong/complete linkage disequilibrium (8, 23). An additional coding SNP (Ser344Thr, rs3740753) is also considered part of PROGINS by some researchers in the field (26). The PROGINS variants of PGR could be less responsive to progesterone compared to the wild-type variant because of reduced stability of gene transcript and decreased protein activity (10). Accordingly, the PROGINS polymorphism is envisioned to modify the risk for several steroid-related disorders, but results have mostly remained inconclusive. For example, in breast cancer, research has suggested that the PROGINS polymorphism either increases (27), decreases

(28), or has no effect on the risk factor (29-30). Similarly, PROGINS was associated with endometriosis in some studies (15-18) whereas in some other studies no association was found (19-25).

The results presented in this study suggest that the PGR gene PROGINS variants could modify the estradiol to progesterone ratio and reduce the risk of endometriosis. The PROGINS AluIns variant was more frequently detected in the control group and associated with reduced odds ratio of endometriosis (OR=0.4, 95%CI=0.17-0.92, p=0.03) and higher estradiol to progesterone ratios that decreased with increasing frequencies of ESR1 gene polymorphisms. The frequency of the rs1042838 variant, which is in complete linkage disequilibrium with the AluIns variant, had no effect on the risk of endometriosis (OR=0.8, 95%CI=0.34-2.05, p=0.692) suggesting that the two variants are functionally distinct.

Additional research is warranted to confirm these results in a larger group and to show how the estradiol to progesterone ratio is affected by genetic variants in the estrogen and progesterone receptors.

Declarations

Declaration of interest

The authors declare that they have no competing financial or non-financial interests in relation to the work described.

Ethical approval

This study was conducted in compliance with the ethical principles in the Declaration of Helsinki and was approved by a local ethics committee at the College of Medicine, Babylon University, Hilla, Iraq.

Consent

All subjects enrolled in this study provided informed consent regarding the participation in the study and the publication of the anonymized results prior to collection of samples.

Authors approval:

All authors have seen and approved this study for publication.

Data availability

Data are available at request from the corresponding author.

Author contributions

Dr. MF Smaism and Dr. NM Sulaiman designed the study, informed the participants, performed the diagnosis and collected the samples. TH Farhood collected the samples, performed the analysis and wrote the article.

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Legends

Table 1: Genotype and allele frequencies of the PROGINS variants rs1042838 and AluIns in endometriosis and control samples.

Table 2: Serum levels (average ± SE), per quintile, of progesterone (ng/mL) (A), CRP (mg/dL) (B), and IL-6 (pg/mL) (C).

Fig.1 Representative PCR products of the PGR gene amplified with primers corresponding to the AluIns (A) and the rs1042838 (B) PROGINS variants. Using the primers specified in Materials and Methods, the Alu insertion in the progesterone receptor gene generates a 479-bp PCR product compared to the 159-bp fragment obtained for the wild type.

Fig. 2A: Estradiol to progesterone ratio in samples stratified by the PROGINS AluIns variant (absent: group 1-3, present: group 4-6) and the ESR1 gene polymorphism rs9340799 (1 and 4: wt/wt, 2 and 5: wt/var, 3 and 6: var/var). B: Summary of data of the different groups in A. OR: odds ratio of endometriosis relative to group 1 for the rs9340799 subgroups (i.e. 2-6) or relative to groups 1-3 for the AluIns positive subgroups (i.e. 4-6).

(Supplementary) Figures 3: Same as in Figure 2, for the combination of rs9340799 and rs1042839.

(Supplementary) Figures 4: Same as in Figure 2, for the combination of rs2234693 and AluIns.

(Supplementary) Figures 5: Same as in Figure 2, for the combination of rs2234693 and rs1042839.

Tables

Table 1

PROGINS rs1042838					
	E (N=50)	C (N=50)	OR	95 % CI	*p* *
wt/wt	38	36	1.23	0.50-3.02	0.65
wt/var	8	11	0.68	0.25-1.85	0.45
var/var	4	3	1.36	0.29-6.43	0.7
wt	84	83	1.08	0.51-2.27	0.85
var	16	17	0.93	0.44-1.96	0.85
PROGINS AluIns					
	E (N=50)	C (N=50)	OR	95 % CI	*p* *
wt/wt	42	34	2.47	0.94-6.46	0.07
wt/var	7	12	0.52	0.18-1.44	0.21
var/var	1	4	0.23	0.03-2.18	0.2
wt	91	80	2.53	1.09-5.87	0.03
var	9	20	0.40	0.17-0.92	0.03

Table 2

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A	Progesterone (ng/mL)			
Prg Quintile	Contr.	Endom.	p	Endom./Contr.
1	0.048±0.001	0.041±0.003	0.0352	0.854
2	0.065±0.002	0.059±0.002	0.0508	0.908
3	0.091±0.004	0.082±0.003	0.0499	0.901
4	0.205±0.028	0.184±0.016	0.5285	0.898
5	4.183±1.164	1.530±0.499	0.0507	0.366

B	CRP (mg/dL)			
CRP Quintile	Contr.	Endom.	p	Endom./Contr.
1	0.064±0.008	0.062±0.011	0.8885	0.969
2	0.141±0.005	0.193±0.018	0.0119	1.369
3	0.206±0.011	0.426±0.022	<0.0001	2.068
4	0.513±0.041	0.647±0.034	0.0213	1.261
5	1.701±0.358	1.078±0.070	0.1046	0.634

C	IL-6 (pg/mL)			
IL-6 Quintile	Contr.	Endom.	p	Endom./Contr.
1	3.75±0.53	6.22±0.66	0.009	1.659
2	9.91±0.43	9.02±0.17	0.0705	0.910
3	12.76±0.34	10.71±0.18	<0.0001	0.839
4	17.13±0.38	13.43±0.35	<0.0001	0.784
5	21.51±0.55	19.70±0.91	0.099	0.916

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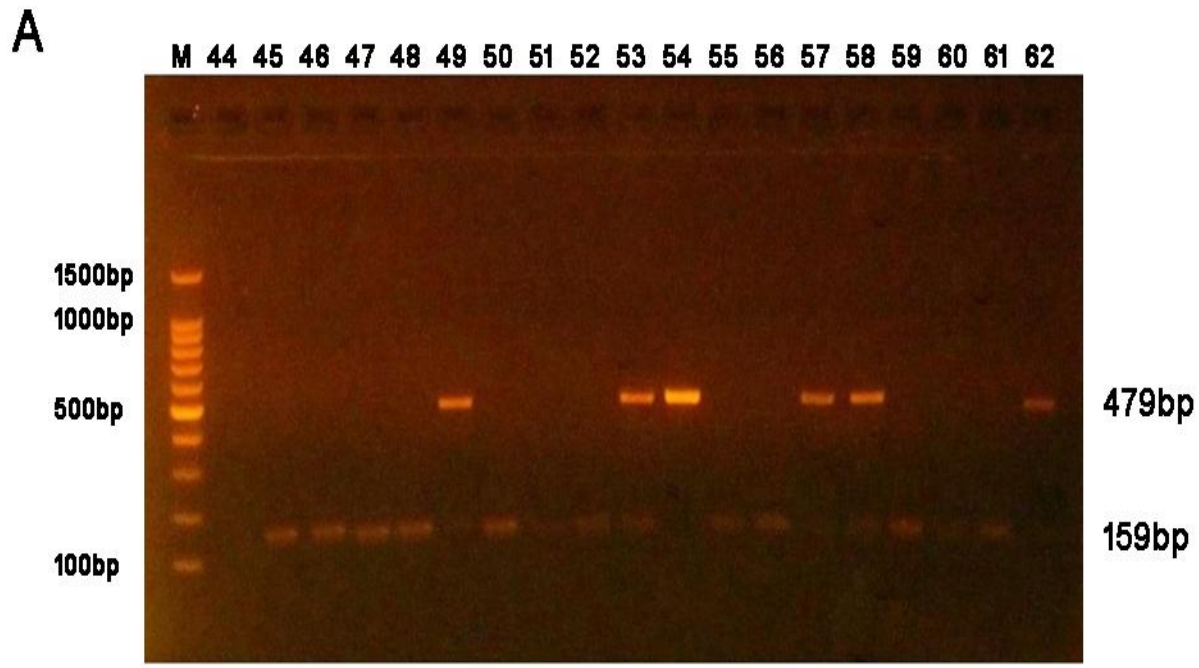
Figure 1



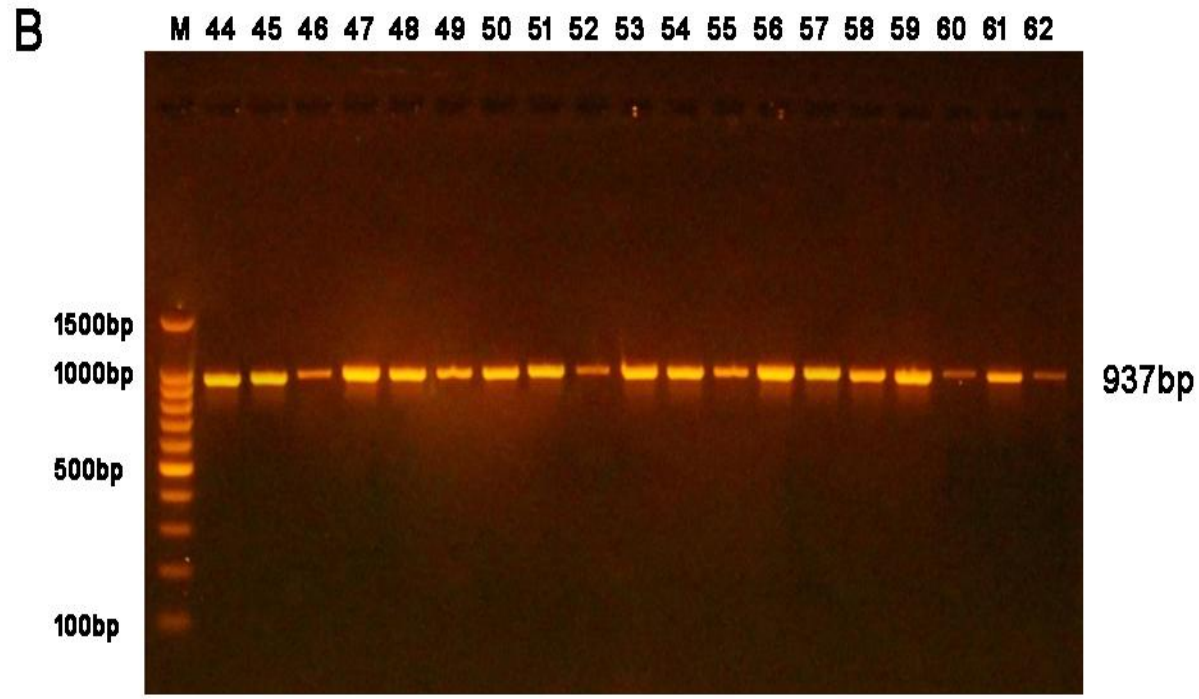


Figure 2

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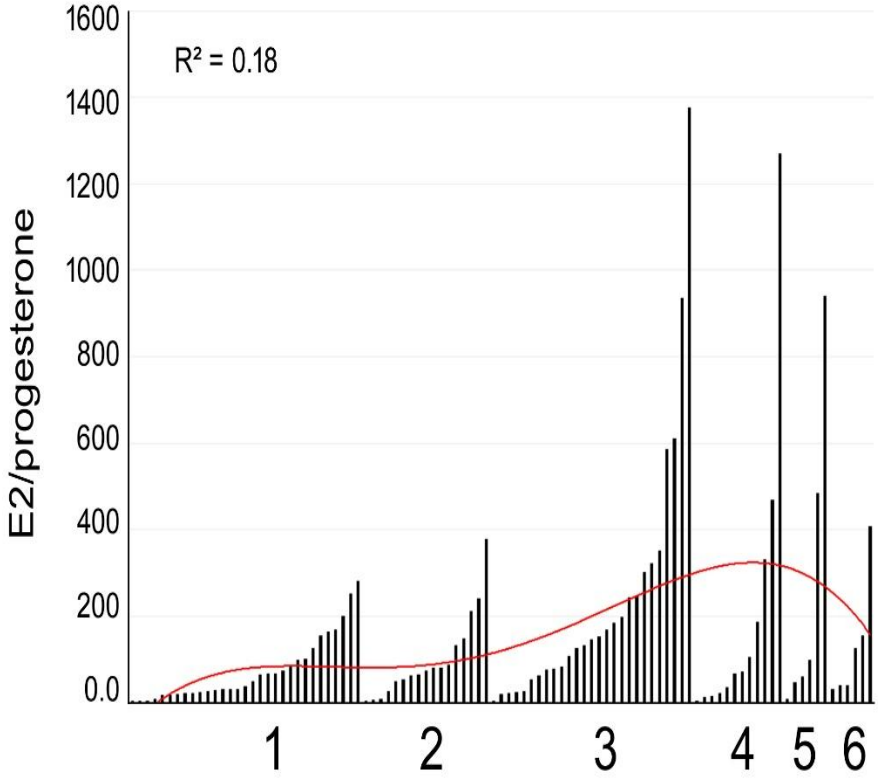
A



B

	1	2	3	4	5	6
PROGINS AluINs	-	-	-	+	+	+
rs9340799	wt/wt	wt/var	var/var	wt/wt	wt/var	var/var
Average E2/progesterone	72.4	99.4	245.024	214.9	272.22	132.707
OR	ref	4.5	8.6	0.2	1.2	4.9
95%CI	ref	1.3-15.8	2.6-28.2	0.0-2.0	0.2-7.9	0.8-31.6
p	ref	0.020	0.000	0.178	0.833	0.096
OR	ref			0.4		
95%CI	ref			0.16-1.09		
p	ref			0.073		

Figure 3

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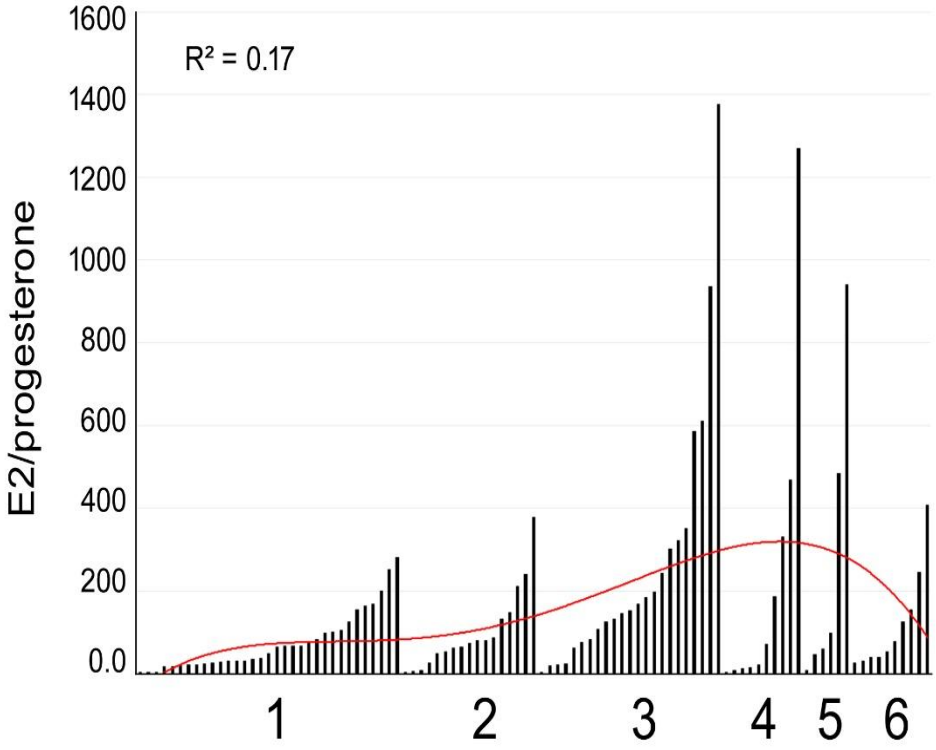
A



B

	1	2	3	4	5	6
PROGINS rs1042838	-	-	-	+	+	+
rs9340799	wt/wt	wt/var	var/var	wt/wt	wt/var	var/var
Average E2/progesterone	74.1	99.4	270.219	238.1	272.22	119.684
OR	ref	5.7	11.3	0.8	1.6	12.5
95%CI	ref	1.6-20.5	3.2-40.1	0.1-4.5	0.2-10.2	2.2-71.4
p	ref	0.007	0.000	0.781	0.641	0.005
OR	ref			0.8		
95%CI	ref			0.34- 2.05		
p	ref			0.692		

Figure 4

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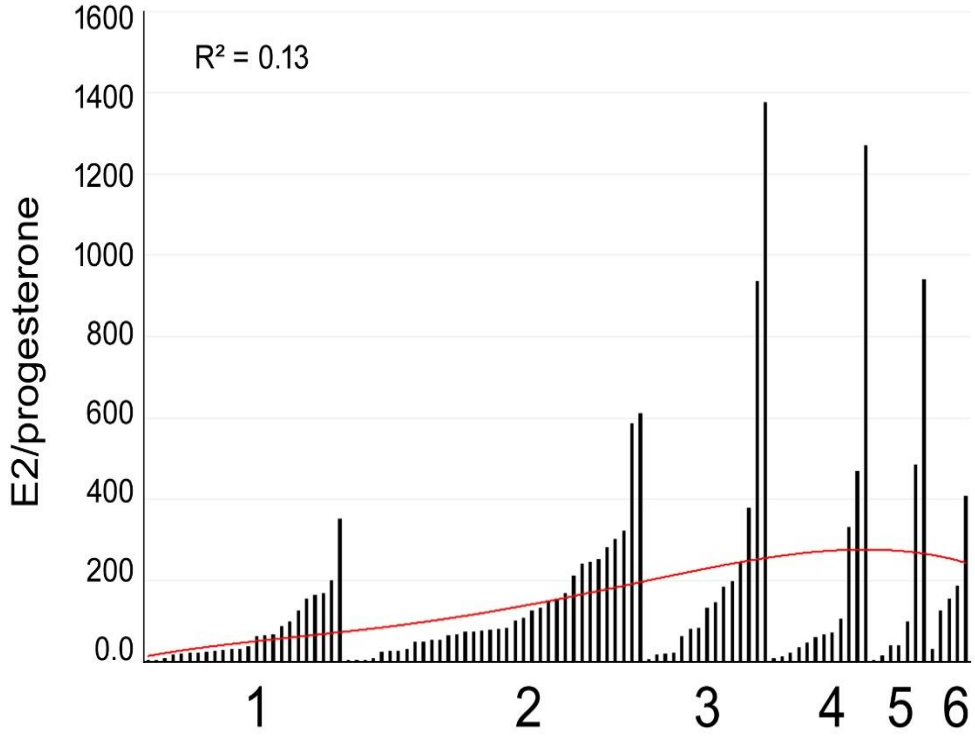
A

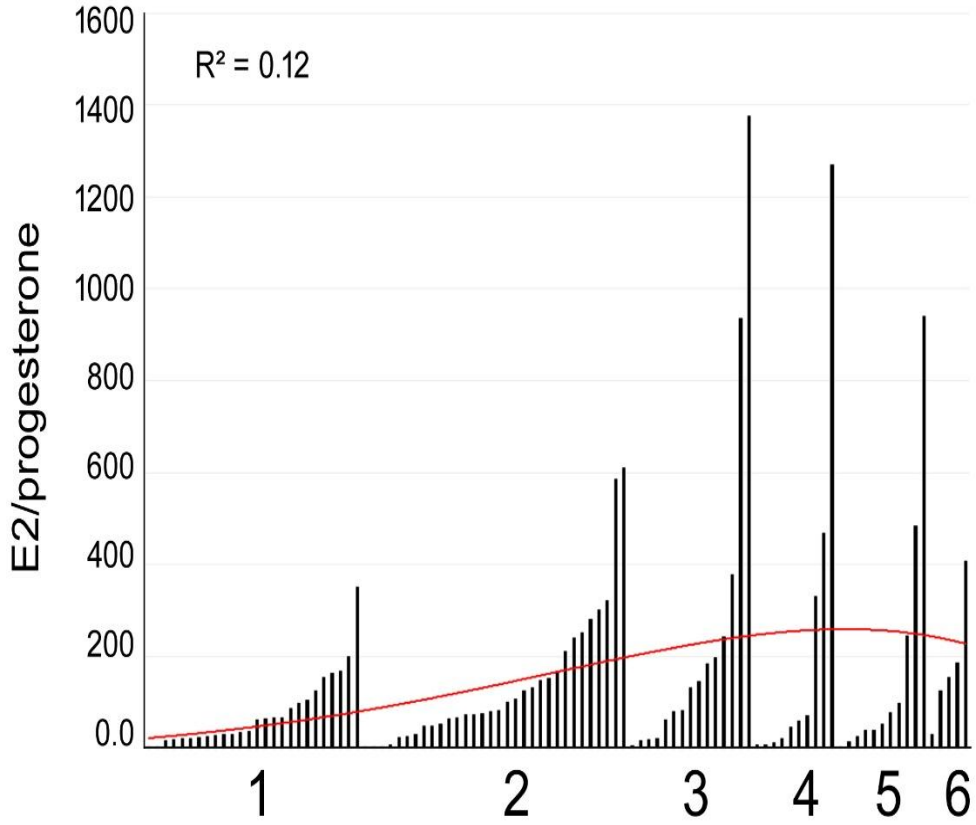


B

	1	2	3	4	5	6
PROGINS AluINs	-	-	-	+	+	+
rs2234693	wt/wt	wt/var	var/var	wt/wt	wt/var	var/var
Average E2/progesterone	74.9	135.6	257.985	207.6	230.61	180.545
OR	ref	11.4	20.0	0.5	3.8	20.0
95%CI	ref	3.1-41.1	3.8-105.1	0.0-4.6	0.6-23.7	1.7-229.5
p	ref	0.000	0.000	0.694	0.160	0.016
OR	ref			0.4		
95%CI	ref			0.16-1.09		
p	ref			0.073		

Figure 5

A



B

	1	2	3	4	5	6
PROGINS rs1042838	-	-	-	+	+	+
rs2234693	wt/wt	wt/var	var/var	wt/wt	wt/var	var/var
Average E2/progesterone	76.8	140.1	257.985	229.3	183.17	180.545
OR	ref	16.9	30.7	1.9	9.2	30.7
95%CI	ref	4.1-69.5	5.4-175.8	0.3-13.6	1.7-49.9	2.5-373.6
p	ref	0.000	0.000	0.516	0.010	0.007
OR	ref			0.8		
95%CI	ref			0.34-2.05		
p	ref			0.692		

Figure 6