Polymorphic variants in the dopamine receptor D2 in women with endometriosis-related infertility

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Abstract. Data suggests that dopamine receptor *DRD2* gene variants may contribute to hyperprolactinemia and that they may be risk factors for endometriosis-related infertility. The purpose of the present study was to determine whether nucleotide variants of the *DRD2* gene may be associated with infertility related to endometriosis. Five *DRD2* SNPs, rs1800497, rs6277, rs2283265, rs4245146 and rs4648317, which are located in different blocks of linkage disequilibrium, were studied in 151 cases and 381 controls. No significant differences between *DRD2* rs1800497, rs6277, rs2283265, rs4245146 and rs4648317 genotype, allele nor haplotype frequencies were observed in women with endometriosis-related infertility compared with the control group. The present results did not confirm *DRD2* gene variants to be genetic risk factors for endometriosis-related infertility.

Introduction

The frequency of endometriosis among infertile women diagnosed by laparoscopic examination ranges from 20 to 50% (1). Patients with endometriosis-related infertility frequently display increased blood plasma levels of prolactin (1). It has been hypothesized that hyperprolactinemia may result in endometriosis-related infertility and that fertility may be restored by prolactin suppression (1,2). Increased levels of prolactin result in anovulation, by blocking estrogen receptor function in the hypothalamus (3). The effect of raised levels of prolactin on the ovary may also reduce affinity of LH receptors in the corpus luteum and decrease the biosynthesis of progesterone, leading to anovulation and suppression of follicular maturation (3). Furthermore, prolactin may contribute to the pathogenesis of endometriosis by supporting angiogenesis (4), which initiates and enhances endometrial lesions (5).

Estrogen supports the proliferation of anterior pituitary lactotroph cells, and induces prolactin gene transcription and protein release from the anterior pituitary gland (6). By contrast, the hypothalamus exerts a tonic inhibitory action against prolactin via the excretion of dopamine from the portal vessels of the pituitary (6). There are two subfamilies of dopamine receptors: DRD1, which stimulates adenylyl cyclase activity; and DRD2, which inhibits the activity of this enzyme (7). The adenohypophysis primarily expresses the DRD2 dopamine receptor (7). Dopamine binds to DRD2 in the pituitary lactotrophs and decreases the level of intracellular cyclic adenosine monophosphate, which in turn inhibits prolactin secretion (8).

Data suggests that *DRD2* gene variants may contribute to hyperprolactinemia (9,10). Furthermore, it has been demonstrated that the *DRD2* single nucleotide polymorphism (SNP), 3438C>T (rs6277), at proline codon in exon 7, is associated with an increased risk of moderate/severe peritoneal endometriosis in women with infertility (11). In order to evaluate whether *DRD2* gene variants are genetic risk factors for endometriosis-related infertility in women from a Polish population, the rs1800497, rs6277, rs2283265, rs4245146 and rs4648317 SNPs, which are located in different blocks of linkage disequilibrium (LD), were selected for further investigation.

Materials and methods

Patients and controls. Peripheral blood samples from females with endometriosis-related infertility and fertile controls, were obtained from the Gynecologic and Obstetrical University Hospital, Division of Reproduction at Poznań University of Medical Sciences (Poznań, Poland). The studied population was divided into two groups: Those with endometriosis and infertility (151), and a fertile control group (381) (Table I). The following inclusion criteria for infertile women with endometriosis were used: No anatomical changes in the reproductive tract, no hormonal treatment, a minimum 1 year of infertility and a current desire to achieve conception. The exclusion criteria were as follows: Male factor infertility, polycystic ovary syndrome (PCOS), mechanical distortion of the endometrial cavity by fibroids and bilateral tubal occlusion. All

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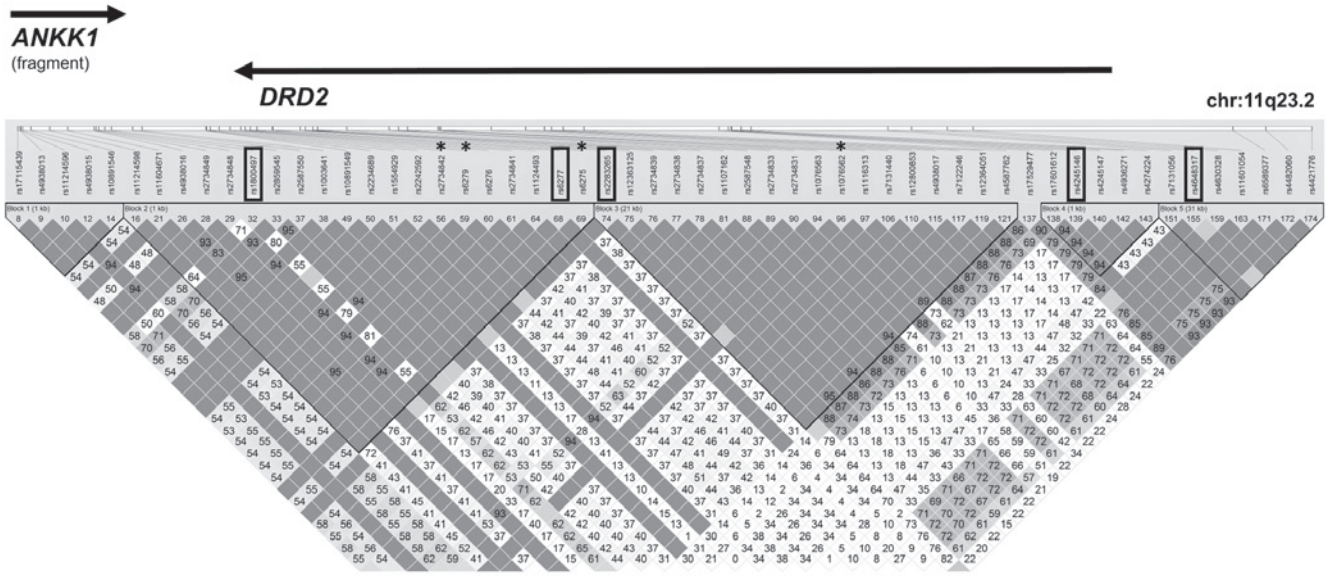

Figure 1. LD plot of HapMap SNPs within the *DRD2* gene region. The plot was generated using genotype data from HapMap CEU samples and the Haploview 4.0 software. The names of the examined SNPs are enclosed in boxes and * corresponds to HapMap-available SNPs cited in the Discussion section. Numbers in the squares indicate the percentage of LD between a given pair of SNPs (D'-values). LD, Linkage Disequilibrium; *DRD2*, dopamine receptor D2.

patients with endometriosis received laparoscopic and histological diagnoses of endometriosis. The stage of endometriosis was evaluated according to the revised classification of the American Society for Reproductive Medicine (rASRM) (12).

All fertile women assigned to the control group were examined for the cause of pelvic pain. However, the laparoscopy evaluation did not demonstrate any pelvic abnormalities. The controls were diagnosed by laparoscopy with varicose veins in the pelvic floor, and exhibited no signs of past or present inflammation. The following inclusion criteria for the fertile controls were used: Regular menses, no anatomical changes in the reproductive tract, no hormonal treatments, and ≥1 child born ≤1 years prior to the laparoscopy (Table I). The exclusion criteria were as follows: Diagnosis of past or present inflammation, pelvic abnormalities, endometriotic lesions and PCOS. Patients and controls were matched by age, and were all Caucasians of Polish descent (Table I). Written and verbal consent was obtained from all participating individuals. The study procedures were approved by the Local Ethical Committee of Poznań University of Medical Sciences.

Table I. Clinical characteristics of patients.

Characteristic	Endometriosis	Controls
Number of patients	151	381
Age in years (range)	32 (21-42)	32 (20-39)
Parity	NA	1 (1-4)
Duration of infertility in years (range)	3 (1-7)	NA
rASRM stage		
Stage I	(n=83)	
Stage II	(n=68)	NA

Data are presented as the median (range). rASRM, revised American society for reproductive medicine classification (12); NA, not applicable.

Genotyping. Genomic DNA was obtained from peripheral blood leukocytes using salt extraction. The DNA samples were subsequently genotyped for the 5 SNPs in *DRD2* (Table II and Fig. 1). SNPs were selected using the genome browser of the International HapMap Consortium (http://www.hapmap.org/index.html.en), UCSC (http://genome.ucsc.edu) and dbSNP database (http://www.ncbi.nlm.nih.gov/projects/SNP/). SNPs were selected based on functional significance, location in the distinct LD blocks and minor allele frequency (MAF) of >0.1 in the Caucasian population.

Genotyping of *DRD2* rs2283265, rs4245146 and rs4648317 was conducted by high-resolution melting (HRM) using the HOT FIREPol EvaGreen HRM mix (Solis BioDyne, Tartu, Estonia), on the LightCycler 480 system (Roche Diagnostics, Mannheim, Germany). Evaluation frequency of *DRD2* rs1800497 and rs6277 was performed using polymerase chain reaction (PCR), followed by digestion by the appropriate restriction enzyme (PCR-RFLP), according to the manufacturer's instructions (Fermentas, Vilnius, Lithuania), and 3% agarose separations (Serva, Heidelberg, Germany). The primary sequences and conditions for HRM and PCR-RFLP analyses are presented in Table II. Genotyping quality was evaluated by repeated genotyping of a random selection of 10% of the study population.

Statistical analysis. For each SNP, the Hardy-Weinberg equilibrium (HWE) was assessed using Pearson's goodness-of-fit χ^2 statistic. The differences in the allele and genotype frequencies between cases and controls were determined using standard χ^2 or Fisher tests. Odds ratios (OR) and the associated 95% confidence intervals (95% CI) were also calculated. The data was analyzed under recessive and dominant inheritance models. For the additive inheritance model, SNPs were tested

Table II. Characteristics of polymorphisms genotyped in the data set.

Gene symbol	Chromosome location	rs no.	SNP function	Alleles[a]	MAF[b]	Primers for PCR amplification (5'-3')	Annealing temp. (˚C)	PCR product length (bp)	HRM Melt. temp. (˚C)	RFLP conditions	
										RE	RFL (bp)
ANKK1	chr11:113270828	rs1800497	missense p.Glu713Lys	C/T	0.18	F: CCATCCTCAAAGTGCTGGTC R: ATCTCGGCTCCTGGCTTAGA	61.0	172	NA	*Taq*I	C=153+19 T=172
DRD2	chr11:113283459	rs6277	cds-synon p.Pro319Pro	C/T	0.46	F: TCTCTGGTTTGGCGGGGCTCTC[c] R: GGAACTTGTCCGGCTTTACC	65.0	213	NA	*Dde*I	C=213 T=193+20
DRD2	chr11:113285536	rs2283265	intron	G/T	0.14	F: CACACTCACGTCCCTTCTCA R: GGGCTAGACGCATCAGGTT	61.0	171	75-90	NA	NA
DRD2	chr11:113317973	rs4245146	intron	C/T	0.44	F: CTAGCATGTCATAGCCCTTGC R: ACATCACGGAGCCTGAGC	61.0	193	81-96	NA	NA
DRD2	chr11:113331532	rs4648317	intron	C/T	0.18	F: CTCCCACCAGGATTATGGAC R: CATTGGGCCTTCACTACCTC	61.0	170	80-95	NA	NA

[a]According to the Single Nucleotide Polymorphism database; underline denotes the minor allele in the control samples. [b]MAF from 1000 Genomes project for EUR samples. [c]Underlined letter denotes the modified base necessary for creation of a *Dde*I restriction site. SNP, single nucleotide polymorphism; MAF, minor allele frequency; PCR, polymerase chain reaction; *ANKK1*, ankyrin repeat and kinase domain containing 1; *DRD2*, dopamine receptor D2; RE, restriction enzyme; RFL, restriction fragment length; RFLP, RFL polymorphism; HRM, high resolution melting; Melt. temp, melting temperature; NA, not applicable.

Table III. Association of polymorphic variants of the *DRD2* gene region with the risk of endometriosis.

Gene	rs no.	Alleles[a]	Genotypes cases[b]	Genotypes controls[b]	P_{trend} value	$P_{genotypic}$ value	$P_{allelic}$ value	$OR_{dominant}$ (95% CI)[c]; P-value	$OR_{recessive}$(95% CI)[d]; P-value
ANKK1	rs1800497	C/T	99/46/6	263/100/18	0.619	0.599	0.605	1.171 (0.785-1.746); 0.440	0.835 (0.325-2.145); 0.707
DRD2	rs6277	C/T	37/76/38	95/208/78	0.435	0.480	0.451	1.023 (0.661-1.585); 0.917	1.306 (0.838-2.036); 0.237
DRD2	rs2283265	G/T	102/45/4	260/103/18	0.797	0.489	0.791	1.032 (0.690-1.545); 0.877	0.549 (0.183-1.649); 0.342[e]
DRD2	rs4245146	C/T	52/74/25	116/205/60	0.622	0.587	0.636	0.833 (0.558-1.244); 0.372	1.062 (0.637-1.768); 0.819
DRD2	rs4648317	C/T	110/32/9	265/100/16	0.778	0.369	0.765	0.852 (0.560-1.296); 0.453	1.446 (0.625-3.348); 0.387

[a]Underline denotes the minor allele in the control samples. [b]Order of genotypes: DD/Dd/dd (d is the minor allele in the control samples). [c]Dominant model: dd+Dd vs. DD (d is the minor allele). [d]Recessive model: dd vs. Dd+DD (d is the minor allele). [e]Fisher exact test. *ANKK1*, ankyrin repeat and kinase domain containing 1; *DRD2*, dopamine receptor D2; OR, odds ratio; CI, confidence interval.

Table IV. Haplotype analysis of SNPs genotyped in the *DRD2* gene region.

Polymorphism	Haplotype	Frequency		χ^2	P-value	p_{corr} value[a]
		All individuals	Case, control			
rs1800497_rs6277	CT	0.484	0.473, 0.488	0.199	0.656	0.949
	CC	0.333	0.333, 0.333	0.000	0.993	1.000
	TC	0.152	0.170, 0.145	1.032	0.310	0.635
	TT	0.031	0.024, 0.033	0.638	0.425	0.791
rs6277_rs2283265	TG	0.492	0.487, 0.495	0.055	0.815	0.994
	CG	0.327	0.336, 0.324	0.143	0.706	0.971
	CT	0.158	0.167, 0.155	0.247	0.619	0.945
	TT	0.023	0.011, 0.027	2.643	0.104	0.265
rs2283265_rs4245146	GC	0.450	0.448, 0.450	0.006	0.937	1.000
	GT	0.370	0.376, 0.367	0.074	0.786	0.984
	TC	0.129	0.143, 0.123	0.737	0.391	0.742
	TT	0.052	0.033, 0.059	2.918	0.088	0.193
rs4245146_rs4648317	CC	0.426	0.442, 0.419	0.482	0.488	0.861
	TC	0.403	0.392, 0.408	0.221	0.639	0.951
	CT	0.152	0.147, 0.153	0.066	0.797	0.986
	TT	0.019	0.018, 0.020	0.022	0.882	0.999
rs1800497_rs6277_rs2283265	CTG	0.479	0.473, 0.482	0.071	0.790	1.000
	CCG	0.323	0.328, 0.321	0.049	0.824	1.000
	TCT	0.153	0.173, 0.145	1.366	0.243	0.616
	TTT	0.014	0.005, 0.018	2.638	0.104	0.324
	TTG	0.014	0.016, 0.013	0.147	0.701	0.998
rs6277_rs2283265_rs4245146	TGC	0.261	0.249, 0.265	0.296	0.587	0.993
	TGT	0.231	0.238, 0.229	0.105	0.746	0.998
	CGC	0.188	0.198, 0.185	0.243	0.622	0.995
	CGT	0.139	0.138, 0.139	0.002	0.964	1.000
	CTC	0.119	0.139, 0.112	1.546	0.214	0.579
	CTT	0.039	0.028, 0.043	1.332	0.248	0.649
	TTT	0.013	0.005, 0.016	2.027	0.155	0.416
rs2283265_rs4245146_rs4648317	GTC	0.358	0.365, 0.355	0.102	0.750	1.000
	GCC	0.311	0.318, 0.309	0.093	0.760	1.000
	GCT	0.137	0.129, 0.140	0.241	0.624	0.999
	TCC	0.113	0.123, 0.109	0.414	0.520	0.979
	TTC	0.046	0.028, 0.053	3.296	0.070	0.207
	TCT	0.016	0.020, 0.015	0.347	0.556	0.987
	GTT	0.013	0.012, 0.014	0.085	0.771	1.000
rs1800497_rs6277_rs2283265_rs4245146	CTGC	0.257	0.245, 0.261	0.278	0.598	0.996
	CTGT	0.223	0.228, 0.221	0.067	0.795	1.000
	CCGC	0.188	0.197, 0.185	0.197	0.657	0.998
	CCGT	0.135	0.131, 0.136	0.056	0.813	1.000
	TCTC	0.116	0.141, 0.106	2.588	0.108	0.252
	TCTT	0.037	0.033, 0.039	0.186	0.666	0.998
rs6277_rs2283265_rs4245146_rs4648317	TGTC	0.219	0.230, 0.214	0.296	0.586	1.000
	TGCC	0.215	0.213, 0.216	0.012	0.911	1.000
	CGTC	0.138	0.133, 0.140	0.086	0.769	1.000
	CTCC	0.105	0.120, 0.100	0.935	0.333	0.927
	CGCC	0.099	0.107, 0.096	0.263	0.608	1.000
	CGCT	0.084	0.087, 0.082	0.073	0.787	1.000
	TGCT	0.051	0.041, 0.055	0.792	0.374	0.951
	CTTC	0.036	0.025, 0.040	1.405	0.236	0.785
	CTCT	0.014	0.017, 0.013	0.309	0.579	1.000
	TTTC	0.012	0.004, 0.015	1.961	0.161	0.609
rs1800497_rs6277_rs2283265	CTGCC	0.213	0.211, 0.214	0.013	0.910	1.000
_rs4245146_rs4648317	CTGTC	0.211	0.218, 0.208	0.125	0.724	1.000
	CCGTC	0.133	0.124, 0.136	0.263	0.608	1.000

Table IV. Continued.

Polymorphism	Haplotype	Frequency		χ^2	P-value	p_{corr} value[a]
		All individuals	Case, control			
	TCTCC	0.103	0.122, 0.096	1.619	0.203	0.706
	CCGCC	0.101	0.107, 0.099	0.159	0.691	1.000
	CCGCT	0.083	0.086, 0.081	0.073	0.788	1.000
	CTGCT	0.050	0.042, 0.053	0.544	0.461	0.994
	TCTTC	0.034	0.030, 0.036	0.264	0.608	1.000
	TCTCT	0.014	0.018, 0.013	0.537	0.464	0.994

[a]P-value calculated using permutation test and a total of 1,000 permutations. SNP, single nucleotide polymorphism; *DRD2*, dopamine receptor D2.

for association with endometriosis using the Cochran-Armitage trend test (13). In order to adjust for the multiple testing, the Bonferroni correction was employed. A haplotype-based association analysis was performed using the Haploview software (http://www.broadinstitute.org/mpg/haploview; Broad Institute, Cambridge, MA, USA). P-values for both global and individual tests of haplotype distribution between cases and controls were calculated. Statistical significance was assessed using the 1,000-fold permutation testing with a cut-off of <0.05.

Results

Prevalence of the DRD2 rs1800497, rs6277, rs2283265, rs4245146 and rs4648317 SNPs in patients with endometriosis-related infertility. The distribution of the *DRD2* rs1800497, rs6277, rs2283265, rs4245146 and rs4648317 SNP genotypes did not display deviation from the HWE in either the patient or control groups (P>0.05). The number of genotypes, in addition to the ORs and 95% CI intervals for these SNPs are stated in Table III. *DRD2* rs1800497, rs6277, rs2283265, rs4245146 and rs4648317 SNP association was observed in neither the dominant nor recessive inheritance models of endometriosis-related infertility. The lowest P-values of the trend test were observed for *DRD2* rs6277 in women with endometriosis-related infertility (ptrend=0.435).

Association of *DRD2 haplotypes with endometriosis-related infertility*. Haplotype analysis of the *DRD2* rs1800497, rs6277, rs2283265, rs4245146 and rs4648317 SNPs did not reveal these polymorphisms to be risk factors for endometriosis-related infertility (Table IV). The lowest global P=0.070, p_{corr}=0.207, refers to haplotypes comprising *DRD2* rs2283265, rs4245146 and rs4648317 (Table IV).

Discussion

Dopamine receptors are members of the G protein-coupled receptors and contain seven transmembrane domains. The *DRD2* gene is situated on chromosome 11q and encodes the D2 subtype of the dopamine receptor. Previously, a number of genetic studies have demonstrated the significance of SNPs located in the *DRD2* gene in various neurological and psychiatric disorders, including severe alcoholism, schizophrenia, migraine, post-traumatic stress disorder and addictive disorders (14,15). Furthermore, Hansen *et al* (10) showed that *DRD2* gene rs6275 was a genetic risk factor for hyperprolactinemia.

Recently, Bilibio *et al* (11) demonstrated an association between *DRD2* rs6277 and endometriosis in infertile women from the Brazilian population (11). The authors also suggested that this polymorphism may lead to a defect in post-receptor signaling, causing a mild upregulation of prolactin serum levels. Thus, prolactin may promote angiogenesis of ectopic endometrial implants (11). However, in the present study, no association between *DRD2* rs1800497, rs6277, rs2283265, rs4245146 and rs4648317 SNPs and endometriosis-related infertility was observed. The differences in the effect of *DRD2* polymorphisms on the development of endometriosis-related infertility in the current study may be due to racial heterogeneity, the small study population, or distinct environmental factors.

To date, the genetic variants of *DRD2* have been shown to be involved in the pharmacokinetics and pharmacodynamics of antipsychotic drugs, which may produce varying effects on prolactin secretion (9,16-23). The *DRD2*/ankyrin repeat and kinase domain containing 1 *(ANKK1)* Taq1A polymorphism (rs1800497) is situated in the *ANKK1* gene, which is downstream from *DRD2* and creates two allelic variants, A1 and A2 (17,18). The *DRD2/ANKK1* rs1800497 A1 allele, is linked to a reduced density of *DRD2* in the striatum (17,18). Patients with the A1 allele, who were currently receiving antipsychotics, displayed hyperprolactinemia, compared with individuals without this allele (9,19,20). Aklillu *et al* (21) observed that carriers of the A1/A1 genotype exhibited an increase in prolactin level at 2 h following treatment with an antipsychotic drug. The *DRD2* Taq1A SNP also produced an effect on prolactin levels, when induced by atypical antipsychotic drugs in healthy volunteers (22). In addition to these findings, clinical trials have also shown that the *DRD2* rs2734842, rs1076562, rs6275 and rs6279 SNPs are associated with hyperprolactinemia during antipsychotic treatment (23,24).

Despite the association of *DRD2* SNPs with hyperprolactinemia and infertility, the present study failed to demonstrate an association between the selected SNPs and endometriosis-related infertility. In conclusion, the current

study requires replication in a larger study population, with varying ethnicity and environmental exposures, for example to different pollutants and toxins, in order to confirm or refute the association between these SNPs and endometriosis-related infertility.

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