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Preliminary Evidence for an Association Between Variants of the Catechol-O-Methyltransferase (*COMT*) Gene and Premature Ejaculation

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ABSTRACT

Background: Studies have suggested that dopamine plays a role in the neurobiological mechanism that triggers ejaculation, leading scientists to hypothesize that dopamine-related genetic polymorphisms could contribute to symptoms of premature ejaculation (PE).

Aim: To investigate associations between dopamine receptor and catechol-O-methyltransferase (COMT; an enzyme involved in the catabolism of dopamine) gene-linked polymorphisms and PE.

Methods: PE status in patient groups was determined by clinical diagnosis performed by a physician specializing in sexual medicine. Self-reported PE symptoms from a validated questionnaire also were reported. Saliva samples were collected from 149 patients with PE and 1,022 controls from a population-based sample. In total, we tested associations between PE and 11 single-nucleotide polymorphisms in the dopamine receptor D1, D2, and D3 genes and in the *COMT* gene.

Outcomes: We found no associations between dopamine receptor gene polymorphisms and PE, but 2 *COMT*-linked loci (rs4680 and rs4818) had significant associations after correction for multiple testing.

Results: 1 *COMT* gene-linked locus that was associated with PE symptoms in the present study, rs4680, is a well-documented functional polymorphism that causes a valine-to-methionine substitution. The other polymorphism, rs4818, is in high linkage disequilibrium with the rs4680 locus, indicating that they capture the same effect. Surprisingly, the rs4680 variant that was statistically significantly more prevalent in the PE group (ie, the valine-encoding allele) has been associated with higher enzymatic activity and therefore lower synaptic dopamine levels.

Clinical Translation: Drugs targeting the dopaminergic system could affect PE symptoms.

Strengths and Limitations: No replication sample was available for the present study; thus, our findings should be interpreted with caution. Moreover, a limitation of our study is the small sample in the context of genetic association studies (although it should be mentioned that genetically informative samples with phenotypic information about PE symptoms are scarce, and most previous genetic association studies of PE have used samples of similar or smaller size). However, our results are plausible: we report an association between one of the most extensively studied and understood genetic polymorphisms in psychiatric research and PE, and our results are in line with the long-standing hypothesis that dopamine influences human ejaculatory function.

Conclusions: We report an association between 2 *COMT* gene-linked loci and PE symptoms, but our results should be treated with caution until independently replicated. **Jern P, Johansson A, Strohmaier J, et al. Preliminary Evidence for an Association Between Variants of the Catechol-O-Methyltransferase (*COMT*) Gene and Premature Ejaculation. J Sex Med 2017;14:1558–1565.**

Key Words: Premature Ejaculation; Gene; Dopamine; *COMT*; Association Study

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INTRODUCTION

Premature ejaculation (PE) is a common—if not the most common—sexual dysfunction in men.[1] By *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* criteria, it is characterized by "a persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within approximately 1 minute following vaginal penetration and before the individual wishes it"; other symptoms include associated distress for at least 6 months for 75% to 100% of all occasions of partnered sexual activity[2] [p. 443]. Recent research reports from studies on humans and animals have suggested that the ejaculatory reflex is under neurobiological control.[3] These findings also have spawned interest in the genetic underpinnings of PE, beginning with single reports describing familial resemblance, indicating that PE might be under at least partial genetic control.[4,5] Recently, twin studies have provided empirical evidence for this hypothesis, suggesting that approximately 30% of the variance in ejaculatory function is under genetic control.[6,7]

Among the numerous neurotransmitters that have been implicated in the regulation of ejaculation, serotonin (eg, [8]) is the most prominent followed by dopamine (DA)[9,10] and oxytocin.[11,12] The influence of DA on ejaculation has been shown in studies on animals that were administered dopaminergic drugs systemically.[13] There is substantial evidence to support the involvement of DA in the process that leads to ejaculation. For example, DA receptor agonists stimulate,[14] whereas antagonists delay,[15] ejaculation in rats. In rodents, DA plays a role in an important integrative region for the control of sexual behavior, the medial preoptic area of the hypothalamus. In this region, DA increases shortly before and during copulation and is involved in the facilitation of other processes related to mating.[13,16,17] In rodents, the DA receptors, which include D1-like and D2-like receptors, play a key role. Although D1-like receptors have been suggested to increase copulation rate and erection, D2-like receptors are relevant for the central regulation of the ejaculatory process.[18–20] Particularly the D3 subtype of the D2-like receptors seems to be important for latency and refractory time after ejaculation, because blockade of this receptor subtype prolongs the 2 processes in rodents.[10,15]

In the human brain, ejaculation also has been shown to activate DA-rich regions.[21] Thus, to explore genetic factors of PE affecting the availability of DA, variations in genes that could influence dopaminergic neurotransmission are of interest. Among those are, for example, DA receptors, the DA transporter, and the catechol-O-methyltransferase (*COMT*) gene, which plays a role in the degradation of DA. The DA receptor 2-like family of receptors, in particular the receptor subtype D3, has been hypothesized to play a key role in the central regulation of ejaculation.[10] 2 studies that investigated associations between dopaminergic genetic polymorphisms and ejaculatory function focused on the *DAT1* microsatellite in the DA transporter gene. Santtila et al[22] analyzed saliva samples from a population-based sample of 1,290 Finnish men and reported increased symptoms of PE in homozygous carriers of the 10-repeat allele. Safarinejad[23] conducted a case-control study involving 270 men with and 266 men without a PE diagnosis and reported that the 9-repeat allele was more prevalent in patients with PE. Because the 9- and 10-repeat alleles constitute the vast majority of the genetic variation at this locus (eg, 99.8% carried some combination of 9- and/or 10-repeat alleles in the study by Santtila et al[22]), these results are conflicting.

To our knowledge, no candidate gene study has yet investigated the DA receptor genes or the *COMT* gene (http://www.ncbi.nlm.nih.gov/gene/1312). The *COMT* gene codes for an enzyme that is involved in the catabolism of DA. A functional single-nucleotide polymorphism (SNP) in the *COMT* coding gene, rs4680 (also known as Val108/158Met polymorphism) is one of the most extensively studied genetic polymorphisms in psychiatric genetics. It causes a valine (Val)-to-methionine (Met) mutation,[24] which has been shown to regulate enzymatic activity so that the Val variant causes DA to be catabolized at a rate of 3 to 4 orders of magnitude higher than the Met variant,[25,26] resulting in lower and higher, respectively, synaptic DA levels.[27] The higher enzymatic activity associated with the Val allele has been hypothesized to cause an improvement in dopaminergic transmission by a U-shaped function (eg, [28]; see also http://www.snpedia.com/index.php/Rs4680 for a summary of studies investigating rs4680). The D2 or D3 receptor agonist enhances ejaculatory behavior in rats, and blockade of D3 receptors with an antagonist prolongs ejaculation.[20] Therefore, we hypothesized that the *COMT* Val108/158Met variant would be associated with PE.

In summary, DA-related genes constitute interesting candidate genes for PE. Based on previous research reports, we tested associations between 11 SNPs in genes coding for DA-1 and DA-2–like family receptors (DA receptor D1 and receptors D2 and D3, respectively) and for *COMT* using a case-control design. 2 variants, rs4680 in *COMT* and rs6280 in *DRD3*, were included because they constitute putatively functional amino acid exchanges.

METHODS

149 men who had visited a specialist in sexual medicine and were diagnosed with and treated for PE and 1,022 controls were included in the analysis. Genetic association tests were conducted using a case-control design, in which those who had been diagnosed with PE by a physician were tested against a control group. (To provide descriptive statistics, variables measuring PE symptoms in the PE and control groups were calculated and presented separately; Table 1). Data collection from patients with PE and controls took place in 2012. 419 individuals who had sought treatment for PE at 2 clinics in Finland and who had been entered in the 5th author's patient registry were contacted. PE status in the PE group had been established through diagnosis by a physician who specialized in sexual medicine (Fellow of the