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ORIGINAL ARTICLE

Sexual Function

The 5-HT$_{2C}$ receptor gene Cys23Ser polymorphism influences the intravaginal ejaculation latency time in Dutch Caucasian men with lifelong premature ejaculation

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It has been postulated that the persistent short intravaginal ejaculation latency time (IELT) of men with lifelong premature ejaculation (LPE) is related to 5-hydroxytryptamine (HT)$_{2C}$ receptor functioning. The aim of this study was to investigate the relationship of Cys23Ser 5-HT$_{2C}$ receptor gene polymorphism and the duration of IELT in men with LPE. Therefore, a prospective study was conducted in 64 Dutch Caucasian men with LPE. Baseline IELT during coitus was assessed by stopwatch over a 1-month period. All men were genotyped for Cys23Ser 5-HT$_{2C}$ receptor gene polymorphism. Allele frequencies and genotypes of Cys and Ser variants of 5-HT$_{2C}$ receptor gene polymorphism were determined. Association between Cys/Cys and Ser/Ser genotypes and the natural logarithm of the IELT in men with LPE were investigated. As a result, the geometric mean, median and natural mean IELT were 25.2, 27.0, 33.9 s, respectively. Of all men, 20.0%, 10.8%, 23.1% and 41.5% ejaculated within 10, 10–20, 20–30 and 30–60 s after vaginal penetration. Of the 64 men, the Cys/Cys and Ser/Ser genotype frequency for the Cys23Ser polymorphism of the 5-HT$_{2C}$ receptor gene was 81% and 19%, respectively. The geometric mean IELT of the wildtypes (Cys/Cys) is significantly lower (22.6 s; 95% CI 18.3–27.8 s) than in male homozygous mutants (Ser/Ser) (40.4 s; 95% CI 20.3–80.4 s) (P = 0.03). It is concluded that Cys23Ser 5-HT$_{2C}$ receptor gene polymorphism is associated with the IELT in men with LPE. Men with Cys/Cys genotype have shorter IELTs than men with Ser/Ser genotypes.

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INTRODUCTION

According to the International Society for Sexual Medicine lifelong premature ejaculation (LPE) is defined as an ejaculation that occurs within about 1 min after penetration in the majority of sexual encounters, with an inability to delay ejaculation and with associated negative personal consequences such as bother and avoidance of sexual activity.[1] In 1998, Waldinger *et al.*[2] postulated that the intravaginal ejaculation latency time (IELT) of less than 1 min in men with LPE is influenced by genetic factors and associated with disturbed central serotonin (5-HT (5-hydroxytryptamine)) neurotransmission, hypersensitivity of 5-HT$_{1A}$ receptors and/or hypofunction of 5-HT$_{2C}$ receptors. Notably, due to an absence of selective 5-HT$_{1A}$ and 5-HT$_{2C}$ receptor ligands for safe human usage, this hypothesis has so far not been confirmed.[3] However, recent stopwatch-mediated genetic research of the IELT in men with LPE has provided indications that gene polymorphisms of the 5-HT transporter (5HTT) and the 5-HT$_{1A}$ receptor are associated with the duration of the IELT. For example, by measuring the IELT with a stopwatch in 89 Dutch men with LPE, Janssen *et al.*[4] have shown that 5-HTTLPR polymorphism is associated with the IELT duration. Of these men who ejaculated within 1 min after vaginal penetration, men with LL genotype had a 100% and 90% shorter IELT than men with SS and SL genotypes, respectively (P = 0.027).[4] However, there were no significant differences between these men and a control group of 92 Dutch Caucasian men with regard to 5-HTT polymorphism alleles and genotypes.[4] Using the same stopwatch method of associating the IELT duration with gene polymorphism, Janssen *et al.*[5] have recently shown that men with LPE and with the CC genotype of the C (1019) G polymorphism of the 5-HT$_{1A}$ receptor gene, also ejaculate statistically significantly faster than men with GC and GG genotype. Up to now the stopwatch method for genetic research as applied by Janssen *et al.*[4,5] has not been used by other researchers. Instead, other research groups have attempted to investigate the question whether the frequency of certain genotypes of genetic polymorphism in men with LPE differs from those in a control group. For example, two questionnaire studies by Jern *et al.*[6] and Zuccarello *et al.*[7] confirmed the finding of Janssen *et al.*[4] that there is no association in 5-HTTLPR polymorphism between men with LPE and a control group. In contrast, three other studies[8-10] reported a higher SS genotype

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frequency in men with LPE compared with a control group. But as the latter three studies were not in Hardy-Weinberg equilibrium (HWE)—most probably due to technical laboratory insufficiencies of polymerase chain reaction (PCR) interpretation—their results are not considered to be reliable.[11–13] In a previous questionnaire study in a large Finish cohort of twins, Jern *et al.*[14] did not find an association of 5-HT_{1A} receptor gene polymorphism C(-1019) G and the ELT. With regard to the 5-HT_{2C} receptor in relation to PE, two studies have previously been performed.[14,15] Luo *et al.*[15] reported that compared to a control group, men with LPE and with G-697C polymorphism of the 5-HT_{2C} receptor gene, have an increased odds for PE. On the other hand, based on a retrospective self-reported measure of the ejaculation time in 1399 male twins, Jern *et al.*[14] reported no association of G-697C polymorphism of the 5-HT_{2C} receptor and the self-reported measure of the ejaculation time.

In the current study in men with LPE, we investigated whether the 5-HT_{2C} receptor gene Cys23Ser polymorphism is associated with the duration of the IELT by using a stopwatch to measure the IELT.

MATERIALS AND METHODS

Patients and assessments

Included were 64 men who were actively seeking drug treatment for LPE at the Outpatient Department of Neurosexology of HagaZiekenhuis in the Netherlands. The included men came from all parts of the Netherlands. They were not recruited by advertisement and none of them was reimbursed for their participation. None of them used or had ever been using drugs, such as selective serotonin reuptake inhibitors or clomipramine, for the treatment of LPE. IELT was defined as the time between the start of vaginal penetration and the start of intravaginal ejaculation.[16] LPE was defined according to the International Society for Sexual Medicine definition.[1]

All patients included were heterosexual men, aged 20–60 years. In order not to exclude men with particular psychological difficulties related to PE, a stable relationship with a female partner was not required. However, it was required that during the 1-month period of IELT assessments, intercourse should have taken place with the same woman. Patients were not permitted the use of condoms, topical local anesthetic creams or sprays, or excessive consumption of alcohol within 5 h prior to intercourse. Exclusion criteria included erectile dysfunction, alcohol or substance abuse, mental disorders, physical illnesses affecting ejaculatory functioning, concomitant medications, a history of sexual abuse reported by the patient and/or his partner, serious relationship problems, pregnancy of the partner or the desire to become pregnant in the near future, a history of very low intercourse frequency, a history of 100% anteportal ejaculation and the possibility of dangerous situations arising at work in the case of paroxetine induced side effects.

Patients attended the Outpatient Department approximately 1 month before the start of daily selective serotonin reuptake inhibitor treatment (first baseline assessment), on the day before treatment (second baseline assessment) and at the end of 10 weeks of daily selective serotonin reuptake inhibitor treatment.

At the first visit, patients were interviewed individually by the last author and asked for an independent estimation of the IELT. A stopwatch and instructions on how to measure the IELT with a stopwatch were provided. The patients measured the IELT at home over the following 4 weeks. The female partners had to handle the stopwatch. It was advised not to have interrupted intromission or to change the usual way of frequency of intercourse. If intercourse took place more than once at the time of IELT measurement, only the first incident was included.

All laboratory testing, including blood sampling and genetic testing, were conducted by the first author. The study was conducted without any involvement of a pharmaceutical industry. All laboratory facilities and test materials were granted by the participating laboratory. Written informed consent was obtained from all patients. The study was approved by the Hospital Medical Ethical Committee and was conducted in accordance with the Declaration of Helsinki of 1975, as revised in 1983.

Genotyping (DNA isolation and polymerase chain reaction (PCR) analysis)

Genomic DNA was extracted from 10 ml of ethylenediaminetetraacetic acid (EDTA)-anticoagulated venous blood samples using a standard salting out method protocol. By PCR analysis we investigated the single nucleotide polymorphism (SNP) Cys23Ser. 5HT2C (Cys23Ser): P7 (5'-TTG GCC TAT TGG TTT GGG AAT-3') and P8 (5'-GTC TGG GAA TTT GAA GCG TCC-3'). The underlined nucleotide is a mismatch with the 5HT sequence, creating a restriction site in the PCR product. PCR conditions were as follows: 7 min at 94 °C; 35 cycles of 1 min at 94 °C, 1 min at 50 °C and 1 min at 72 °C and finally 7 min at 72 °C. The size of the amplified product was 104 bp. Then the PCR product (10 μl) was digested with HinfI (Roche) in a total volume of 15 μl for 1 h at 37 °C and subsequently analyzed on a 3% agarose/Tris-borate-ethylenediaminetetraacetic acid gel with ethidium bromide staining. The fragments obtained for the wild-type allele was 104 bp and for the variant allele the fragments were 86 and 18 bp.[17]

Statistical analysis

The mean, median and geometric mean IELT was calculated from stopwatch-determined IELTs. Statistical Package for Social Sciences (SPSS) 19.0 for Windows (Chicago, IL, USA) was used. $P < 0.05$ was considered statistically significant. Analysis of variance (ANOVA) was performed to determine an association between the genotypes and their IELTs.

RESULTS

The study included 64 patients. **Table 1** shows the characteristics of the men with LPE. Of all men the mean ± standard deviation frequency of intercourse during 1 month in the baseline period was 3.3 (±1.3) ranging from 1 to 12 intercourses. Of all men, the majority (96%) ejaculated within 1 min after vaginal penetration. Of all men, 20.0% ejaculated within 10 s, 10.8% within 10–20 s, 23.1% within 20–30 s and 41.5% between 30 and 60 s after vaginal penetration (**Figure 1**).

As seen in our previous studies,[4,18] the IELT distribution in the current study was skewed with geometric mean, median and natural mean IELTs of 25.2, 27.0 and 33.9 s, respectively. Therefore, statistical analysis of IELT was performed after logarithmic transformation.[19]

Table 2 shows the results of the genotyping of the Cys23Ser 5-HT_{2C} receptor polymorphism. As the gene is only located at the X-chromosome, no heterozygotes of the Cys23Ser 5-HT_{2C} receptor polymorphism exist in males. Accordingly, although the number of alleles is twice as high as the genotypes, the distribution of the genotypes is similar to the distribution in alleles, as the alleles do not distribute on heterozygotes in this case.

The geometric mean IELT of the wildtypes (Cys/Cys) in the current group of men is significantly lower than the geometric mean IELT in male homozygous mutants (Ser/Ser) ($P = 0.03$) (**Table 3**).

DISCUSSION

The results of the current study show that wildtypes Cys/Cys of the 5-HT_{2C} receptor gene, which is exclusively located at the X-chromosome, have a statistically significant faster ($P = 0.03$) IELT than men with a mutant genotype (Ser/Ser). In the current study, we did not use a control group,

Table 1: Patient characteristics (*n*=64)

Characteristics	*Value*
Age (year)	
Mean±s.d. (range)	39±9 (20–60)
Age partner (year)	
Mean±s.d. (range)	34±8.5 (21–57)
Nationality (%)	
Dutch (caucasian)	94
Marital status (%)	
Married	46
Relationship but not married	54
No relationship	-
Duration of relation (years)	10
Mean±s.d. (range)	10±7.1 (0.2–29)
Education (%)	
Low	16
Medium	49
High	35

s.d.: standard deviation

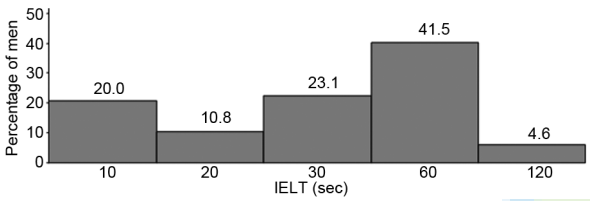

Figure 1: Intravaginal ejaculation latency time distribution in Dutch men with lifelong premature ejaculation.

Table 2: Results of genotyping testing of the Cys23Ser 5-HT$_{2C}$ receptor polymorphism

Allele/genotype	*Count*	*Frequency (%)*
Wildtype (Cys/Cys)	52	81
Mutant (Ser/Ser)	12	19
Sum	64	100

Table 3: Natural logarithm of intravaginal ejaculation latency time per genotype in men with lifelong premature ejaculation

Genotype	*n*	*Mean Ln IELT (s.d.)*	*Mean geometric IELT (s, 95% CI)*
Wildtype (Cys/Cys)	52	3.1 (0.7)	22.6 (18.3–27.8)
Mutant (Ser/Ser)	12	3.7 (1,1)	40.4 (20.3–80.4)
Total	64	3.2 (0.8)	25.2 (20.4–31.1)

CI: confidence interval; s.d.: standard deviation; IELT: intravaginal ejaculation latency time

but compared the genotype frequencies of the 5-HT$_{2C}$ receptor gene polymorphism with the European HapMap-CEU population,[20] consisting of 120 men and women, in which the allele distribution was 15.8% Ser/Ser and 84.2% Cys/Cys. Although this is not a Dutch reference population, but a European population, the genotype frequency of the current cohort of men does not deviate from the European population. Notably, although, Luo *et al.*,[15] did not use our method of comparing the IELT duration values of each single patient with 5-HT$_{2C}$ receptor gene polymorphism, he did find an association of Cys23Ser 5-HT$_{2C}$ receptor polymorphism with LPE by comparing the frequency of genotypes with the frequency of these genotypes in a Han Chinese population. However, as noted, we did not find such an association with the European HapMap-CEU population.

Although the current study shows an association of 5-HT$_{2C}$ receptor Cys23Ser polymorphism and the IELT duration in men with LPE, it remains unknown whether 5-HT$_{2C}$ receptor Cys23Ser polymorphism is in the same way associated with the IELT duration in the general male population. For that purpose, very large population-based stopwatch studies or male twin studies are recommended. However, in a retrospective questionnaire study in Finnish twins, Jern *et al.*[14] did not find an association of Cys23Ser 5-HT$_{2C}$ receptor polymorphism with the ELT duration, as measured by a questionnaire.

By using our method of stopwatch measurement of the IELT in men with LPE and comparing gene polymorphisms with the IELT duration in the same group of men, the current study shows that there is an association of the IELT duration and Cys23Ser 5-HT$_{2C}$ receptor gene polymorphism. By using the same method, we have previously also found an association of the IELT duration in men with LPE with polymorphism of the 5-HTTLPR gene and the C (1019) G polymorphism of the 5-HT$_{1A}$ receptor.[4,5] However, our findings of three genetic polymorphism associations with the IELT duration in an exclusive group of men with LPE by using a stopwatch to prospectively and exactly measure the IELT duration have previously not been found in a large cohort of Finnish twins in which the ELT was retrospectively assessed by the use of a questionnaire.[6,14]

More studies are needed in a large cohort of men with LPE and a control group with well-controlled PCR analysis in order to replicate and confirm the robustness of the current outcome data indicating an association of Cys23Ser 5-HT$_{2C}$ receptor gene polymorphism and the IELT duration in men with LPE. Nevertheless, it is intriguing to note that the studies of Janssen *et al.*[4,5] including the current study and the animal studies[21–23] that formed the basis for the hypothesis of Waldinger *et al.*[2] provide (preliminary) indications that the persistent short IELTs of men with LPE may be associated with central 5-HT neurotransmission and central 5-HT$_{1A}$ and 5-HT$_{2C}$ receptor functioning, as mirrored by the associations of their gene polymorphisms with the IELT duration.

A limitation of the current study is that not all polymorphisms of the 5-HT$_{2C}$ receptor gene have been investigated. For that purpose, genotyping of the whole 5-HT$_{2C}$ receptor gene is required. Such a study in men with LPE has so far not been published. Another limitation of the current study is the relatively low number of participants. However, our number of 64 males does not differ from the average number of male and female patients investigated in other studies on 5-HT$_{2C}$ receptor polymorphism. For example, in five studies[24-28] on major depression and bipolar disorder, the average number of male and female participants was 67 (range 42–98). Notably, of these five studies, three studies reported an association between Cys23Ser polymorphism and major depression or bipolar disorder.[24-28] However, in order to avoid any misunderstanding such association does not mean that LPE is in any way associated with major depression or bipolar disorder. Moreover, at the moment genetic research of lifelong and acquired PE is only meant for scientific purposes and therefore is not part of daily practice to evaluate and diagnose PE.[29]

CONCLUSIONS

The current study shows evidence that 5-HT$_{2C}$ receptor gene Cys23Ser polymorphism is associated with the IELT duration in men with LPE. Men with Cys/Cys genotype have statistically shorter IELTs than men with Ser/Ser genotype. The current study adds to our previously stated hypothesis that apart from 5-HTTLPR polymorphism, the IELT in men with LPE is also influenced by other genetic polymorphism of the serotonergic system.

AUTHOR CONTRIBUTIONS

PKCJ conceived the study, its design and coordination, sampled blood from the patients, carried out the genetic analysis, performed the statistical analysis and drafted the manuscript. RVS participated in a part of the genetic analysis. BO participated in drafting the manuscript. MDW recruited and examined the patients, conceived the study, its design and coordination and drafted the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

REFERENCES

1 McMahon CG, Althof SE, Waldinger MD, Porst H, Dean J, *et al*. An evidence-based definition of lifelong premature ejaculation: report of the International Society for Sexual Medicine (ISSM) ad hoc committee for the definition of premature ejaculation. *J Sex Med* 2008; 5: 1590-606.
2 Waldinger MD, Berendsen HH, Blok BF, Olivier B, Holstege G. Premature ejaculation and serotonergic antidepressants-induced delayed ejaculation: the involvement of the serotonergic system. *Behav Brain Res* 1998; 92: 111–8.
3 Waldinger MD. Risk factors in premature ejaculation: the genetic risk factor. In: Jannini EA, McMahon CG, Waldinger MD, editors. Premature Ejaculation: From Etiology to Diagnosis and Treatment. Italia: Springer-Verlag; 2013. p. 111–23.
4 Janssen PK, Bakker SC, Rethelyi J, Zwinderman AH, Touw DJ, *et al*. Serotonin transporter promoter region (5-HTTLPR) polymorphism is associated with the intravaginal ejaculation latency time in Dutch men with lifelong premature ejaculation. *J Sex Med* 2009; 6: 276-84.
5 Janssen PK, van Schaik R, Zwinderman AH, Olivier B, Waldinger MD. The 5-HT_{1A} receptor gene C (1019) G polymorphism influences the intravaginal ejaculation latency time in Dutch Caucasian men with lifelong premature ejaculation. *Pharmacol Biochem Behav* 2014.
6 Jern P, Eriksson E, Westberg L. A reassessment of the possible effects of the serotonin transporter gene linked polymorphism 5-HTTLPR on premature ejaculation. *Arch Sex Behav* 2013; 42: 45–9.
7 Zuccarello D, Ghezzi M, Pengo M, Forzan M, Frigo AC, *et al*. No difference in 5-TTLPR and Stin2 polymorphisms frequency between premature ejaculation patients and controls. *J Sex Med* 2012; 9: 1659–68.
8 Safarinejad MR. Polymorphisms of the serotonin transporter gene and their relation to premature ejaculation in individuals from Iran. *J Urol* 2009; 181: 2656–61.
9 Ozbek E, Tasci AI, Tugcu V, Ilbey YO, Simsek A, *et al*. Possible association of the 5-HTTLPR serotonin transporter promoter gene polymorphism with premature ejaculation in a Turkish population. *Asian J Androl* 2009; 11: 351–5.
10 Luo SW, Wang F, Xie ZY, Huang XK, Lu YP. Study on the correlation of the 5-HTTLPR polymorphism with premature ejaculation in Han Chinese population. *Beijing Da Xue Xue Bao* 2011; 43: 514–8.
11 Waldinger MD, Janssen PK, Schweitzer DH. Re: Polymorphisms of the serotonin transporter gene and their relation to premature ejaculation in individuals from Iran. *J Urol* 2009; 182: 2983.
12 Waldinger MD, Janssen PK, Schweitzer DH. Hardy Weinberg equilibrium in genetic PE research remains critical to avoid misinterpretation. *Asian J Androl* 2009; 11: 524; 9: e88031
13 Janssen PK, Olivier B, Zwinderman AH, Waldinger MD. Measurement errors in polymerase chain reaction are a confounding factor for a correct interpretation of 5-HTTLPR polymorphism effects on lifelong premature ejaculation: a critical analysis of a previously published meta-analysis of six studies. *PLoS ONE* 2014; 9: e88031.
14 Jern P, Westberg L, Johansson A, Gunst A, Eriksson E, *et al*. A study of possible associations between single nucleotide polymorphisms in the serotonin receptor 1A, 1B, and 2C genes and self-reported ejaculation latency time. *J Sex Med* 2012; 9: 866-72.
15 Luo S, Lu Y, Wang F, Xie Z, Huang X, *et al*. Association between polymorphisms in the serotonin 2C receptor gene and premature ejaculation in Han Chinese subjects. *Urol Int* 2010; 85: 204–8.
16 Waldinger MD, Hengeveld MW, Zwinderman AH. Paroxetine treatment of premature ejaculation: a double-blind, randomized, placebo-controlled study. *Am J Psych* 1994; 151: 1377-9.
17 Lappalainen J, Zhang L, Dean M, Oz M, Ozaki N, *et al*. Identification, expression, and pharmacology of a Cys23-HT2C receptor gene (HTR2C). *Genomics* 1995; 27: 274-9.
18 Waldinger MD, Hengeveld MW, Zwinderman AH, Olivier B. An empirical operationalization study of DSM-IV diagnostic criteria for premature ejaculation. *Int J Psychiatry Clin Pract* 1998; 2: 287-93.
19 Waldinger MD, Zwinderman AH, Olivier B, Schweitzer DH. Geometric mean IELT and premature ejaculation: appropriate statistics to avoid overestimation of treatment efficacy. *J Sex Med* 2008; 5: 492-9.
20 dbSNP Short Genetic Variations. Available from: ww.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=6318 [Last accessed date on 2014 Jan 03].
21 Ahlenius S, Larsson K, Svensson L, Hjorth S, Carlsson A, *et al*. Effects of a new type of 5-HT receptor agonist on male rat sexual behavior. *Pharmacol Bioch Behav* 1981; 15: 785-92.
22 Foreman MM, Love RL, Hall JL. Effects of LY237733, a selective 5-HT2 receptor antagonist, on copulatory behavior of male rats. *Society Neurosci Abstracts* 1988; 14: 374.
23 Berendsen HH, Broekkamp CL. Drug-induced penile erections in rats: indications of serotonin1B receptor mediation. *Eur J Pharmacol* 1987; 135: 279-87.
24 Lerer B, Macciardi F, Segman RH, Adolfsson R, Blackwood D, *et al*. Variability of 5-HT2C receptor cys23ser polymorphism among European population and vulnerability to affective disorder. *Mol Psychiatry* 2001; 6: 579–85.
25 Oruc L, Verheyen GR, Furac I, Jakovljevic M, Ivezic S, *et al*. Association analysis of the 5-HT2C receptor and 5-HT transporter genes in bipolar disorder. *Am J Med Genet* 1997; 74: 504–6.
26 Gutierrez B, Fananas L, Arranz MJ, Valles V, Guillamat R, *et al*. Allelic association analysis of the 5-HT2C receptor gene in bipolar affective disorder. *Neurosci Lett* 1996; 212: 65–7.
27 Frisch A, Postilnick D, Rockah R, Michaelovsky E, Postilnick S, *et al*. Association of unipolar major depressive disorder with genes of the serotonergic and dopaminergic pathways. *Mol Psychiatry* 1999; 4: 389–92.
28 Vincent JB, Masellis M, Lawrence J, Choi V, Gurling H, *et al*. Genetic association analysis of serotonin system genes in bipolar affective disorder. *Am J Psychiatry* 1999; 156: 136–8.
29 Jannini EA, Maggi M, Lenzi A. Evaluation of premature ejaculation. *J Sex Med* 2011; 8 Suppl 4: 328-34.

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