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LETTER TO THE EDITOR

Premature Ejaculation

Trio-based genome sequencing identifies candidate causal genes in lifelong premature ejaculation

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Dear Editor,

Premature ejaculation (PE) is the most common sexual dysfunction with prevalence rates of 20%–30%.¹ Unfortunately, there are limited treatment options as a result of the lack of knowledge about the pathophysiology of PE.² Although the exact etiology of PE is not clear, it is known that PE is etiologically heterogeneous, with both genetic and environmental factors playing a role.³ Schapiro and Waldinger's study suggested that PE ran in families, with a higher morbidity in the family members of PE patients than that in unaffected individuals.^{4,5} The results of Jern's study indicated that PE is moderately heritable, with an inheritability ratio of 28% in a cohort of 3946 pairs of twins.⁶

Because the patients with lifelong PE suffer from symptoms beginning with the first sexual experience, we proposed that lifelong PE is driven more by genetic predisposition than by environmental factors. In this study, we recruited eight trios (healthy parents and a lifelong PE proband) to explore the genetic predisposition using whole-genome sequencing (WGS). It was also the first time that trio-based genome sequencing had been used to investigate the genetic basis of lifelong PE. In our study, we showed rare inherited novel mutations, *de novo* mutations, and autosomal recessive inherited mutations significantly contributed to lifelong PE.

In this study, all patients were diagnosed with lifelong PE in Tongji Hospital, Huazhong University of Science and Technology (Wuhan, China). Signed informed consent forms were provided by the probands and their parents. The Ethics Committee of Tongji Hospital approved our study (Approval No. 2017s321). The Chinese language version of the PE diagnostic tool (PEDT) was used to diagnose these patients.⁷ The diagnosis of lifelong PE was based on the clinical history of the probands. The intravaginal ejaculation latency time (IELT) of all probands was <1 min from the first sexual experience, indicating the presence of lifelong PE, and their PEDT scores were more than 15.

Through WGS, we identified 741 mutant genes, including 969 missense mutations in eight trios (proband and his unaffected parents). The summary of all mutations is shown in **Table 1**. There were 71 genes containing more than one mutation (**Supplementary Figure 1a**).

Table 1: Summary of total mutations in lifelong premature ejaculation

Trio	Number of mutant gene	Number of missense mutations
H1	109	130
H2	123	143
H3	112	138
H4	40	45
H6	93	100
H7	106	118
H8	122	138
H9	142	157
Total	741	969

Furthermore, we identified 60 mutant genes in more than one trio (**Supplementary Figure 1b**). In eight trios, we identified 63 missense mutations in zinc finger protein 717 (*ZNF717*), a putative transcriptional regulator associated with many diseases, such as growth retardation, intellectual disability, and DiGeorge-like syndrome. Mutant carboxy-terminal domain small phosphatase 2 (*CTDSP2*) was found in all seven trios containing 23 missense mutations. *CTDSP2* is the target gene of microRNA miR-26, and they work together to affect many biological processes, including differentiation of neurons, tumor cell growth, and cell cycle.⁸

In our study, we identified 165 novel mutations in 158 genes (**Table 1**). There were three novel missense mutations in *CTDSP2* found in four trios, including p.Y262C, p.V261L, and p.P250S. We also found a mutant gene, FAT atypical cadherin 4 (*FAT4*), in trios H7 and H8. Badouel *et al.*⁹ reported that *FAT4* affected mouse brain development by regulating neural tube closure and neural progenitor proliferation. Beste *et al.*¹⁰ also reported that *FAT4* affected functional cerebral architecture. Lifelong PE patients cannot control ejaculation, which means that the central nervous system loses control of the ejaculation impulsion. The mutant *FAT4* in our study might impair the central nervous system function of lifelong PE patients, resulting in the lack of control of ejaculation. The relationship between *FAT4* and lifelong PE is worthy of further study to confirm this hypothesis.

Through trio-based genome sequencing, seven inherited autosomal recessive mutations were identified from five trios in our study. All the seven mutations were homozygous in probands and were heterozygous in their unaffected parents. In trio H2, two inherited autosomal recessive mutations, p.L52V in *ZNF717* and p.D201G in cytochrome

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P450 family 4 subfamily F member 3 (*CYP4F3*), were found. *CYP4F3* encodes a member of the cytochrome P450 superfamily of enzymes. CYPs can metabolize both endogenous and exogenous substances, and one of the endogenous substrates of CYPs is neurotransmitters. We conjectured that this mutation in *CYP4F3* might impair the enzyme function, leading to an imbalance in metabolism of neurotransmitters or other substances. The resultant imbalance in these substances might have a negative effect on the control of ejaculation impulsion.

In addition to the rare inherited mutations, we proposed that *de novo* germline mutations might contribute to the genetic architecture of lifelong PE. We found 12 *de novo* single-nucleotide variants (SNVs) in our study. There was an increased trend of the overall *de novo* mutation rate in the lifelong PE patients (1.5 events per proband on average) compared with that in controls (0.74 events per proband on average), with a lifelong PE/control rate ratio of 2.03. Overall, 5 of the 8 probands (62.5%) carried at least one *de novo* mutation, and 3 probands (37.5%) harbored more than two *de novo* mutations.

We performed Gene Ontology (GO) analyses of mutant genes including biological process (BP), cellular component (CC), and molecular function (MF), as shown in **Supplementary Figure 1c–1e**, to find genes or signal pathways associated with lifelong PE. There were three BP-GO analysis items containing 6 genes, including positive regulation of secretion by cell (GO:1903532), regulation of mitotic cell cycle phase transition (GO:0090559), and positive regulation of secretion (GO:0051047). We could find six CC-GO analysis items with three genes involved, and nine MF-GO analysis items stood out. Our GO analyses results might provide the evidence of the relationship between secretion regulation and lifelong PE. In reported research, ejaculation could be regulated by the secretion and function of serotonin, dopamine, oxytocin, leptin, and vasopressin. It was suggested that the further study of the underlying causal mechanism of lifelong PE should focus on the regulation of secretion. Thus, we performed the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of mutant genes to explore which signal pathway might be involved in lifelong PE (**Supplementary Figure 1f**). Unfortunately, the most relative item in our study was protein digestion and absorption (hsa04974), which seemed to have little relationship with lifelong PE.

In summary, we performed a trio-based study to genetically dissect lifelong PE using genome sequencing and identified candidate-associated genes or biological processes. However, we need a multicenter cohort study combined with functional experiments to better investigate the genetic factors of lifelong PE. Nevertheless, the discovery of these candidate genes provided insight into lifelong PE development and etiology, which expands our current understanding of lifelong PE. Furthermore, our data may contribute to the future study of causal mechanisms underlying lifelong PE and provide new targets for its treatment.

AUTHOR CONTRIBUTIONS

QL and JHL designed the study. DQW, YTJ, LL, JXW, YHN, ZT, YWC, and JNG carried out the follow-up reviews and participated in clinical data collection. DQW and YTJ performed genome sequencing analysis. DQW drafted the article. QL and TW revised the article. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

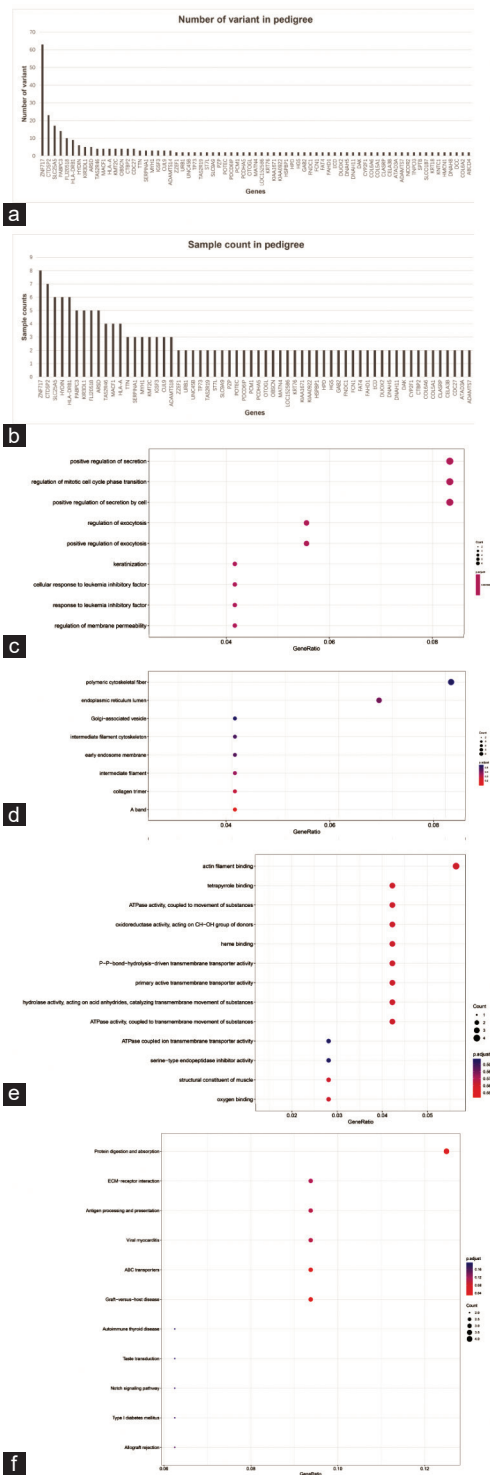
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Supplementary Figure 1: Summary of detected mutant genes from eight trios. (a) number of variants in detected mutant genes. There are 71 detected genes containing more than one mutation. More than 10 mutations were identified in *ZNF717*, *CTDSP2*, *SLC25A5*, and *PABPC3*. (b) Sample counts of detected genes in our study. We identified 60 mutant genes in more than one trio. All eight trios carried mutant *ZNF717*. (c-e) GO analyses of mutant genes identified in lifelong PE. There are GO analyses of biological process, cellular component, and molecular function from the top down. (f) KEGG analysis of mutant genes identified in lifelong PE. *ZNF717*: zinc finger protein 717; *CTDSP2*: carboxy-terminal domain small phosphatase 2; *SLC25A5*: solute carrier family 25 member 5; *PABPC3*: poly(A) binding protein cytoplasmic 3; GO analyses: Gene Ontology analyses; PE: premature ejaculation; KEGG analysis: Kyoto Encyclopedia of Genes and Genomes analysis.