INPLASY PROTOCOL

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Corresponding author:
Liu Xiaoqiang

xiaoqiangliu1@163.com

Author Affiliation:
Tianjin medical university general hospital.

Support: **Zhao Yi-Cheng Medical Science.**

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None declared.

Association of polymorphisms in estrogen receptors with non-obstructive azoospermia and severe oligospermia

Chen, C[1]; Wang, SR[2]; Zhang, AQ[3]; Liu, L[4]; Zhang, ZX[5]; Niu, S[6]; Song, YX[7]; Pan, Y[8]; Liu, XQ[9].

Review question / Objective: **This meta-analysis aimed to study the association between PvuII (rs2234693, 397T>C), XbaI (rs9340799, 351G>A), AluI (1730G>A, rs4986938) and RsaI (1082G>A, rs1256049) polymorphisms and spermatogenic failure.**
Condition being studied: **Estrogen receptors (ERs) gene play key roles in the male and female reproduction. Non-obstructive azoospermia (NOA) and severe oligospermia (SOL) are the most severe and complex condition of male infertility. Some studies have researched the association between ERs polymorphisms and male infertility. But few studies of ER α and ER β SNPs in patients with NOA or SOL. However, the results of this association remain inconsistent.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 October 2022 and was last updated on 09 October 2022 (registration number INPLASY2022100034).

INTRODUCTION

Review question / Objective: **This meta-analysis aimed to study the association between PvuII (rs2234693, 397T>C), XbaI (rs9340799, 351G>A), AluI (1730G>A, rs4986938) and RsaI (1082G>A, rs1256049) polymorphisms and spermatogenic failure.**

Rationale: **The literature in PubMed, Medline, Embase, Web of Science, Cochrane Library, China Science and Technology Journal Database, WanFang data and China National Knowledge Infrastructure databases were systematically searched, and a meta-analysis was conducted to investigate the the association between polymorphisms in**

estrogen receptors polymorphisms and spermatogenic failure.

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METHODS

Search strategy: The keywords used were: "male infertility", "azoospermia", "non-obstructive azoospermia", "severe oligospermia", "spermatogenic failure ", "polymorphism", "estrogen receptors", "ER", "ESR", "ER α", "ER β", "PvuII", "397T>C", "rs2234693", "XbaI", "rs9340799", "AluI", "1730G>A", "rs4986938", "RsaI", "1082G>A", and "rs1256049", all combinations of the terms were also searched.

Participant or population: Non-obstructive azoospermia (NOA) and severe oligospermia (SOL, sperm concentration < 5×106/ml) affects approximately 1% of general men and 10% of infertilemen. And normal male.

Intervention: Not applicable.

Comparator: Not applicable.

Study designs to be included: Observational study.

Eligibility criteria: The main inclusion criteria were: (1) study design is case-control study; (2) the study must research the connection between the PvuII, XbaI, AluI and RsaI polymorphisms and NOA and/or SOL; (3) have enough data of genotype frequencies that could calculate the odds ratio (OR) and 95% confidence interval (CI); (4) the inclusion of patients was done according to the World Health Organization 2010 guideline diagnosis parameter; (5) the control group complies with Hardy-Weinberg equilibrium (HWE). The main exclusive criteria were: (1) study have not enough data for analysis, such as meta-analysis or review articles, expert opinions, case reports and studies of animals or cells; (2) the control group does not comply with HWE; (3) studies could not extract detailed data and contact the corresponding authors failed; (4) low-quality study.

Information sources: PubMed, Medline, Embase, Web of Science, Cochrane Library, China Science and Technology Journal Database, WanFang data and China National Knowledge Infrastructure databases were searched without language restrictions.

Main outcome(s): The ER α XbaI and ER β RsaI polymorphisms are associated with the risk of NOA and SOL.

Quality assessment / Risk of bias analysis: The Newcastle-Ottawa quality assessment scale (NOS) was applied to assess literature quality. The score of > 7 was classified as a high quality study. Publication bias was tested by the Egger's and Begg's test. HWE in the controls was analyzed by STATA 12.0 (STATA Corporation College Station, TX, USA) and GraphPad Software (San Diego, USA). Data of meta-analysis was analyzed by STATA 12.0 (STATA Corporation, TX, USA).

Strategy of data synthesis: OR and 95% CI were used to test the association between the PvuII, XbaI, AluI and RsaI polymorphisms in the ERs gene and the risk of NOA and/or severe oligospermia. We used five genetic models to calculate the pools OR: (1) allelic model: A vs. a; (2) recessive model: AA vs. Aa + aa; (3) dominant model: AA + Aa vs. aa; (4) heterozygote comparison: Aa vs. aa; (5) homozygote comparison: AA vs. aa. $p<0.05$ was considered statistically significant.
Heterogeneity was tested by the Chi-square based Q test, and Higgins I2 statistic. An I2 < 50% indicated that no heterogeneity existed and the fixed effects

model (FEM) was used; otherwise the random-effects model (REM) was used.

Subgroup analysis: To study the association of polymorphisms in ERs and risks of spermatogenic failure in different ethnicities and different degrees of spermatogenic failure. Subgroup analyses based on different degrees of disease types (NOA and SOL) and by different races were conducted.

Sensitivity analysis: Sensitivity analyses were used to estimate the stability of the results.

Country(ies) involved: China.

Keywords: estrogen receptor, spermatogenic failure, non-obstructive azoospermia, severe oligospermia, meta-analysis.

Contributions of each author:
Author 1 - Chen Cheng.
Author 2 - Wang Shangren.
Author 3 - Zhang Aiqiao.
Author 4 - Liu Li.
Author 5 - Zhang Zhexin.
Author 6 - Niu Shuai.
Author 7 - Song Yuxuan.
Author 8 - Pan Yang.
Author 9 - Liu Xiaoqiang.