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Replication Study and Meta-Analysis of Human Nonobstructive Azoospermia in Japanese Populations[1]

Youichi Sato,[2,4,5] Timothy Jinam,[4,6] Teruaki Iwamoto,[7] Aiko Yamauchi,[5] Issei Imoto,[8] Ituro Inoue,[6,9] and Atsushi Tajima[3,8]

[5]*Department of Pharmaceutical Information Science, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima, Tokushima, Japan*
[6]*Division of Human Genetics, Department of Integrated Genetics, National Institute of Genetics, Mishima, Shizuoka, Japan*
[7]*Center for Infertility and IVF, International University of Health and Welfare Hospital, Nasushiobara, Tochigi, Japan*
[8]*Department of Human Genetics, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima, Tokushima, Japan*
[9]*Division of Molecular Life Science, School of Medicine, Tokai University, Isehara, Kanagawa, Japan*

ABSTRACT

Recently, a Chinese genomewide association study (GWAS) identified four autosomal single-nucleotide polymorphism (SNP) loci as being significantly associated with risk factors for nonobstructive azoospermia (NOA; $P < 5 \times 10^{-8}$). In the present study, we performed a replication study on two Japanese cohorts from different institutions in order to evaluate whether SNP loci are associated with NOA. The four SNPs (rs12097821, rs2477686, rs10842262, and rs6080550) reported in the Chinese GWAS were genotyped in 490 NOA patients and 1167 controls. To assess the significance of the associations between each of the four SNPs and NOA in the Japanese population, the association results for the two cohorts were combined by meta-analysis. In the meta-analysis, the combined per-allele odds ratios (ORs) for the four SNPs and their respective 95% confidence intervals (CIs) were as follows: rs12097821, OR = 1.10 (CI = 0.89–1.37); rs2477686, OR = 1.11 (CI = 0.87–1.43); rs10842262, OR = 1.11 (CI = 0.94–1.32); and rs6080550, OR = 0.96 (CI = 0.76–1.21). None of the SNPs was significantly associated with NOA ($P > 0.05$). However, three of four SNPs (rs12097821, rs2477686, and rs10842262) showed associations in the same direction in Japanese men as those reported in the Chinese GWAS. To determine whether the four SNPs are genetic risk factors for NOA, the effect sizes of NOA risk factors require further investigation using larger independent sets of case-control samples of populations, including Japanese and Chinese populations.

Japanese population, nonobstructive azoospermia, replication study

INTRODUCTION

Infertility is a major problem worldwide that affects approximately 10% of couples, and roughly half of these cases are due to male-factor etiology [1, 2]. The main cause of male infertility is spermatogenic failure such as nonobstructive azoospermia (NOA) and oligozoospermia. Deletions in the azoospermia factor (*AZF*) regions on the long arm of the Y chromosome, which are prevalent in 10%–15% of male infertility patients, result in spermatogenic failure and severely reduce sperm concentrations [3, 4]. Polymorphisms in certain genes, such as the deleted-in-azoospermia-like (*DAZL*) [5], androgen receptor (*AR*) [6–9], estrogen receptor (*ER*)α [10–12], 5-methylenetetrahydrofolate reductase (*MTHFR*) [13–15], and ADP-ribosyltransferase 3 (*ART3*) [16, 17] genes, have been reported to be associated with male infertility. However, studies of genetic associations frequently produce inconsistent results among different populations. For example, the T54A polymorphism in the *DAZL* gene was found to be associated with NOA in Taiwanese populations [5] but not in Italian [18], Caucasian [19], Japanese [20], or Indian populations [21]. In addition, between-study differences have been observed in the associations between CAG repeat number polymorphisms in the *AR* gene and male infertility, and some studies have even reported significant associations [9, 22–25], whereas others obtained nonsignificant results [26–28]).

Recently, a genomewide association study (GWAS) conducted on Chinese men indicated that common variants located near the *PRMT6* (rs12097821 at 1p13.3), *PEX10* (rs2477686 at 1p36.32), and *SOX5* genes (rs10842262 at 12p12.1) were associated with NOA (rs12097821, OR = 1.25; rs2477686, OR = 1.39; and rs10842262, OR = 1.23). Single-nucleotide polymorphism (SNP) rs6080550 at 20p13 (*SIRPA-AIRPG*) also exhibited a significant association (OR = 1.27) with NOA in a combined analysis, although the association was not replicated in the second stage of validation [29]. To increase our understanding of the genetic risk factors for male infertility, we conducted a replication study to assess whether the four

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[2]Correspondence: Youichi Sato, Department of Pharmaceutical Information Science, Institute of Health Biosciences, The University of Tokushima Graduate School, 1-78-1 Sho-machi, Tokushima 770-8505, Japan. E-mail: youichi.sato@tokushima-u.ac.jp
[3]Correspondence: Atsushi Tajima, Department of Human Genetics, Institute of Health Biosciences, The University of Tokushima Graduate School, 3-18-15 Kuramoto, Tokushima 770-8503, Japan.
E-mail: tajima.atsushi@tokushima-u.ac.jp
[4]These authors contributed equally to this work.

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